Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Colorectal Cancer (Part 1 of a 3-Part Series)

Wednesday, January 19, 2022

10:15 PM – 11:45 PM ET

Faculty

Kristen K Ciombor, MD, MSCI
Cathy Eng, MD
Pashtoon M Kasi, MD, MS
Christopher Lieu, MD
Alan P Venook, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

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

Cathy Eng, MD
Professor of Medicine
Co-Leader, VICC Gastrointestinal Cancer Research Program
David H Johnson Chair in Surgical and Medical Oncology
Co-Director, GI Oncology
Director, VICC Young Adults Program
Co-Chair, NCI Gastrointestinal Steering Committee
Vanderbilt University Medical Center
Nashville, Tennessee

Pashtoon M Kasi, MD, MS
Director, Colon Cancer Research
Director, Liquid Biopsy Research
Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine
Englander Institute for Precision Medicine
Division of Hematology and Medical Oncology
NewYork-Presbyterian Hospital/Weill Cornell Medicine
New York, New York

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

RTP
RESEARCH TO PRACTICE

Faculty

Alan P Venook, MD
The Madden Family Distinguished Professor of
Medical Oncology and Translational Research
Shorenstein Associate Director, Program Development
Helen Diller Family Comprehensive Cancer Center
University of California, San Francisco
San Francisco, California

Moderator
Neil Love, MD
Research To Practice
Miami, Florida

RTP
RESEARCH
TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Gastroesophageal Cancers (Part 2 of a 3-Part Series)

Thursday, January 20, 2022
9:15 PM – 10:45 PM ET

Faculty

Yelena Y Janjigian, MD
Eric Van Cutsem, MD, PhD
Harry H Yoon, MD

Moderator

Samuel J Klempner, MD

RTP
RESEARCH
TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Hepatobiliary Cancers (Part 3 of a 3-Part Series)

Friday, January 21, 2022
9:15 PM – 10:45 PM ET

Faculty

Ghassan Abou-Alfa, MD, MBA
Richard S Finn, MD
Robin K Kelley, MD

Moderator

Tanios Bekaii-Saab, MD

RTP
RESEARCH TO PRACTICE

Clinicians in the Meeting Room

Networked iPads are available for you to

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

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

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 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.

RTP RESEARCH TO PRACTICE

Virtual Zoom Clinicians

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

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

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

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

RTP
RESEARCH
TO PRACTICE

About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based 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**

RTP
RESEARCH
TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Colorectal Cancer (Part 1 of a 3-Part Series)

Wednesday, January 19, 2022

10:15 PM – 11:45 PM ET

Faculty

Kristen K Ciombor, MD, MSCI
Cathy Eng, MD
Pashtoon M Kasi, MD, MS
Christopher Lieu, MD
Alan P Venook, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Agenda

Module 1 – Current and Future Role of Therapies Targeting BRAF and HER2 in Metastatic Colorectal Cancer (mCRC) — Dr Venook

Module 2 – Integration of Immune Checkpoint Inhibitors into the Management of mCRC — Dr Eng

Module 3 – Selection and Sequencing of Therapy for Patients with Multiregimen-Refractory mCRC — Dr Ciombor

Module 4 – Other Considerations in the Management of Colorectal Cancer; Promising Investigational Strategies — Dr Lieu

ASCO GI 2022 Colorectal Clinical Investigator Survey Respondents

Ghassan Abou-Alfa, MD, MBA

Thomas A Abrams, MD

Dirk Arnold, MD, PhD

Tanios Bekaii-Saab, MD

Jordan D Berlin, MD

Kristen K Ciombor, MD, MSCI

Dustin Deming, MD

Cathy Eng, MD

Tim Greten, MD

J Randolph Hecht, MD

Andrew E Hendifar, MD

Paulo M Hoff, MD

Pashtoon Kasi, MD, MS

Christopher Lieu, MD

Jeffrey A Meyerhardt, MD, MPH

Aparna Parikh, MD

Stacey M Stein, MD

Eric Van Cutsem, MD, PhD

Alan P Venook, MD

RTP RESEARCH TO PRACTICE

How would you generally compare the time you have spent learning about new oncology trial results, guideline interpretation, et cetera in the past 2 years to before the pandemic?

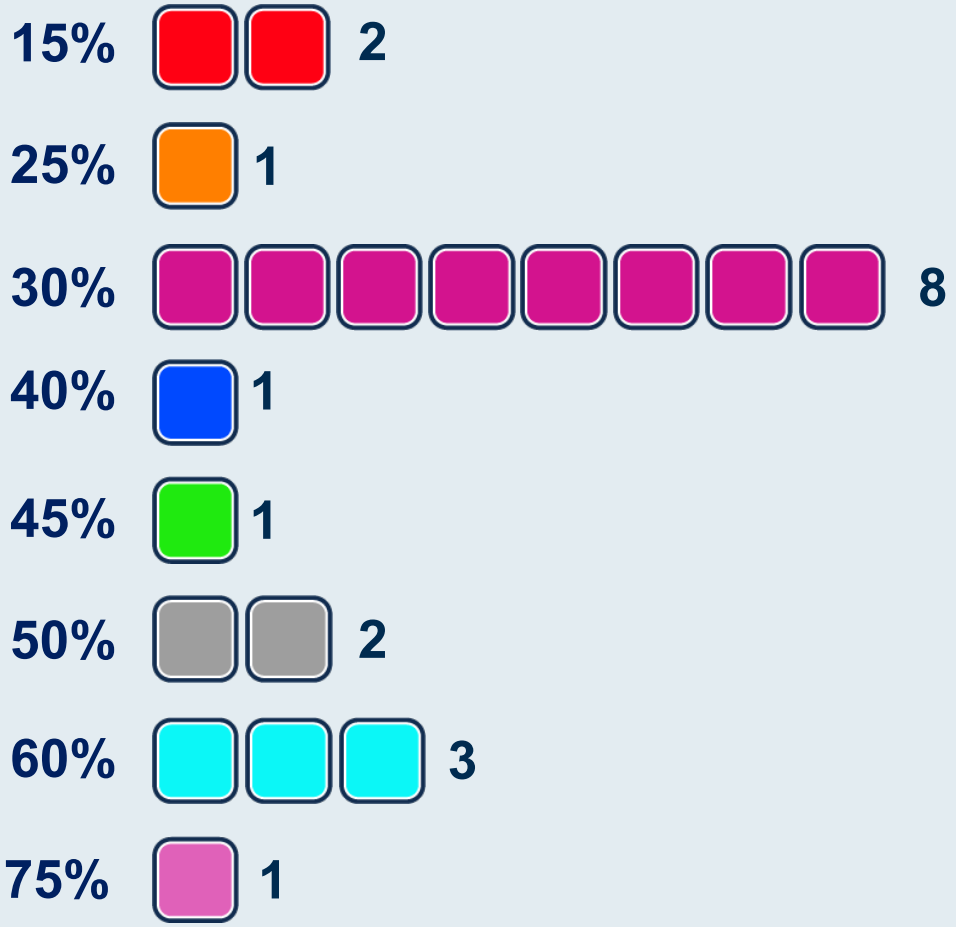
1. About the same
2. More the past 2 years
3. More before the pandemic

How would you generally compare your knowledge level about new oncology trial results, guideline interpretation, et cetera now (ie, in the past 2 years) to before the pandemic?

1. About the same
2. More the past 2 years
3. More before the pandemic

RTP
RESEARCH
TO PRACTICE

In your practice, approximately what proportion of new patients whom you evaluate with colorectal cancer (CRC) are under the age of 50?



Median: 30%
Range: 15%-75%

Survey of US-based clinical investigators

What is your primary hypothesis for the increased incidence of CRC in younger patients in recent years?

- Western lifestyle
- Multifocal etiology
- Lifestyle primarily and potential effect on microbiome
- Increasing obesity, change in diet/lifestyle exposures
- Combination of genetic and environmental/lifestyle factors
- Microbiome
- Diet
- Environmental exposure to carcinogens. Patients require screening at a younger age
- Environmental and lifestyle (obesity/diet) microbiome
- Better screening and recognition. True increased incidence secondary to dietary risk factors
- Microbiome changes

MODULE 1: Current and Future Role of Therapies Targeting BRAF and HER2 in Metastatic Colorectal Cancer — Dr Venook

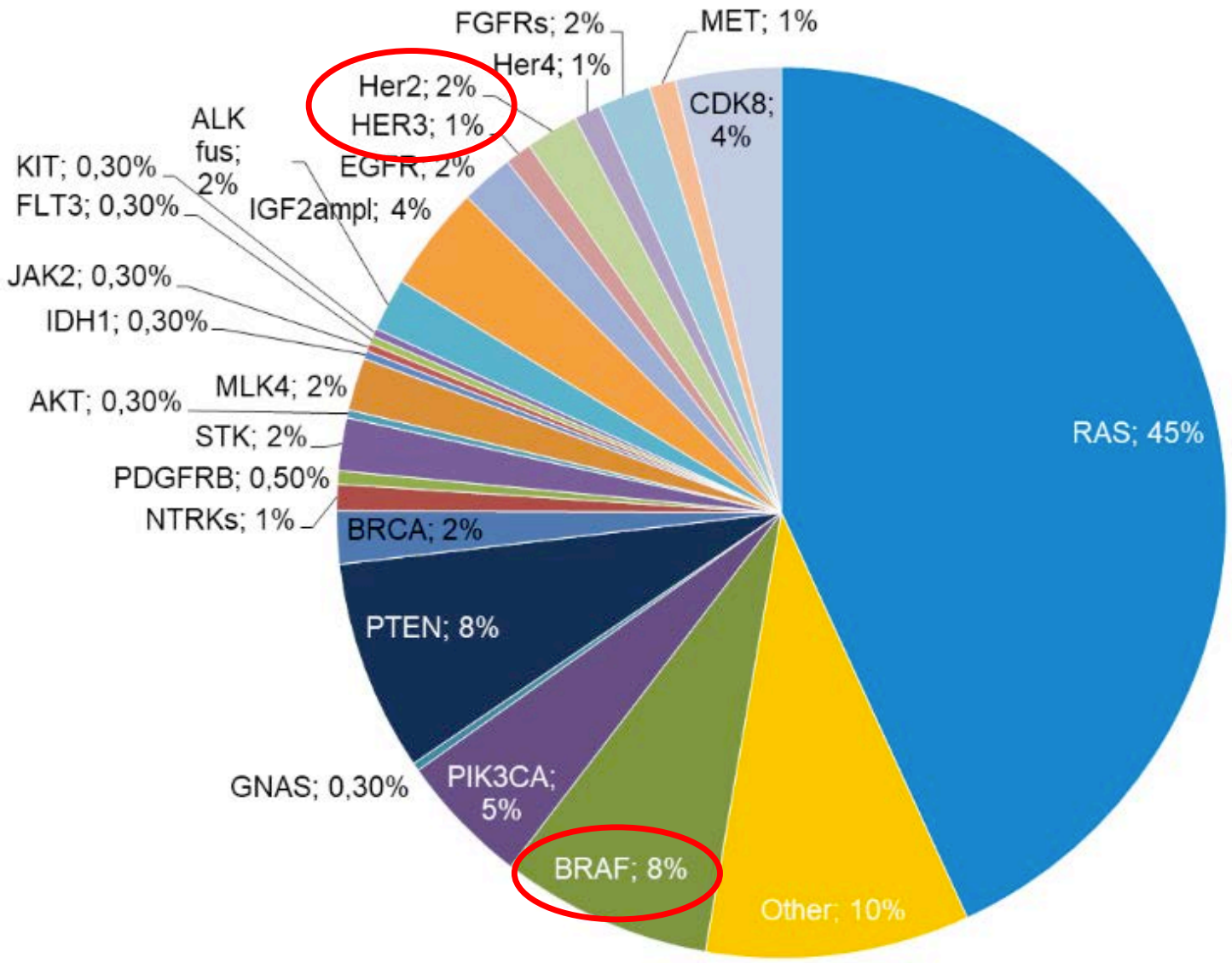
RTP
RESEARCH
TO PRACTICE

CURRENT and FUTURE ROLE OF THERAPIES TARGETING BRAF AND HER-2 IN METASTATIC COLORECTAL CANCER

ALAN P VENOOK, MD

UNIVERSITY OF CALIFORNIA, SF

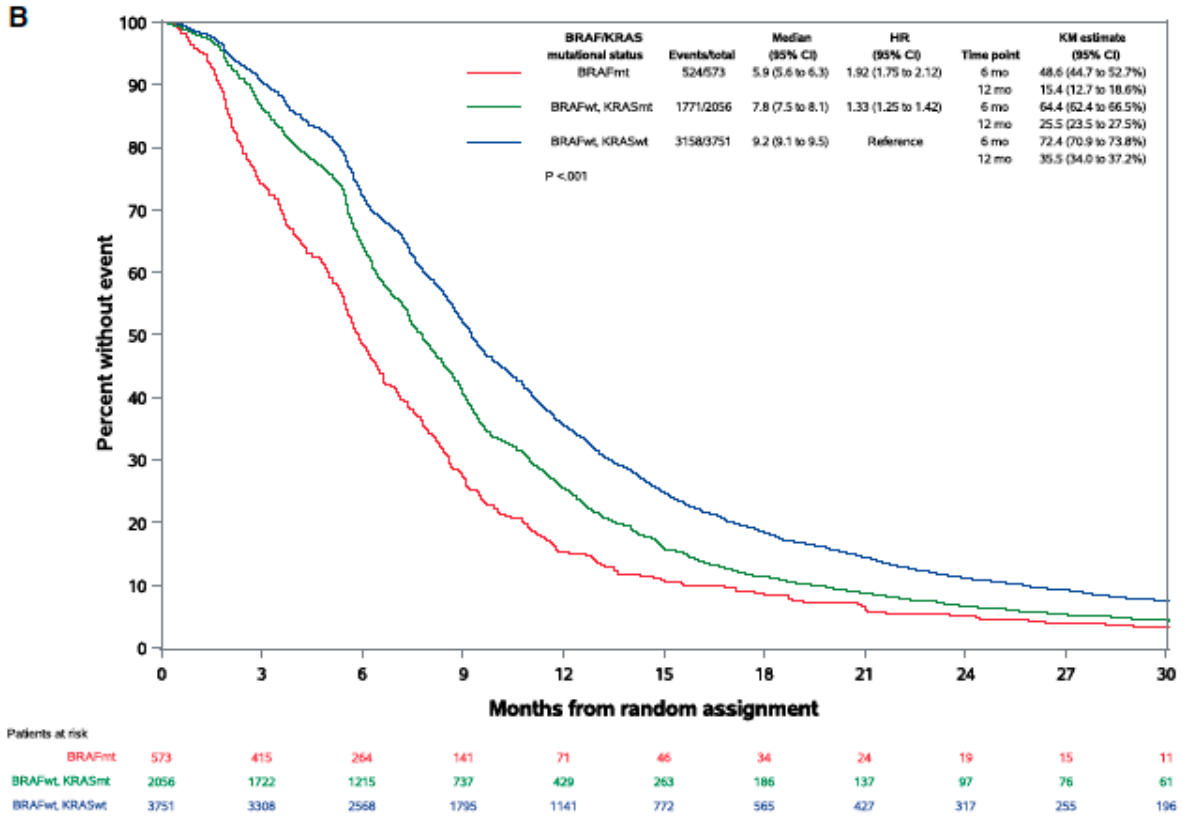
Gene Mutations / Fusions in Colorectal Cancer



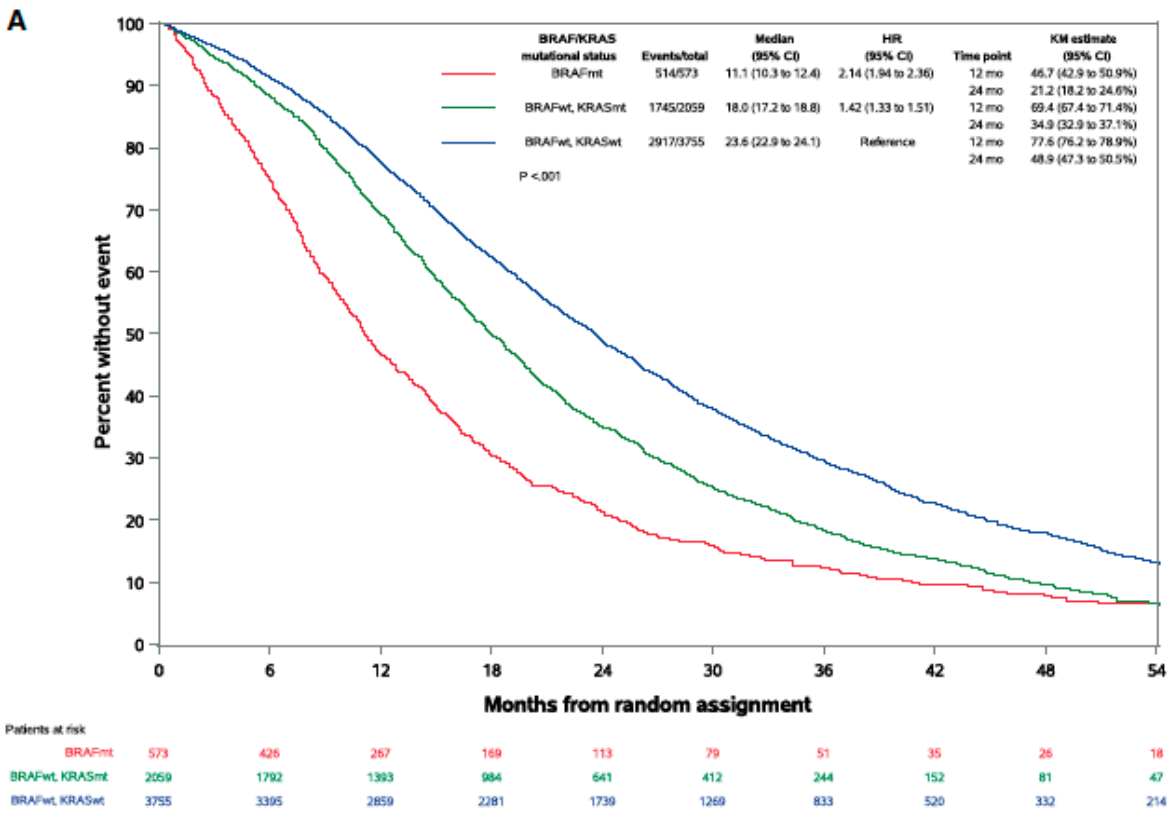
Impact of *BRAF ^{V600E} mt* in 1st-line Metastatic Colorectal Cancer

N = 573 / 6380 (9%)

PFS

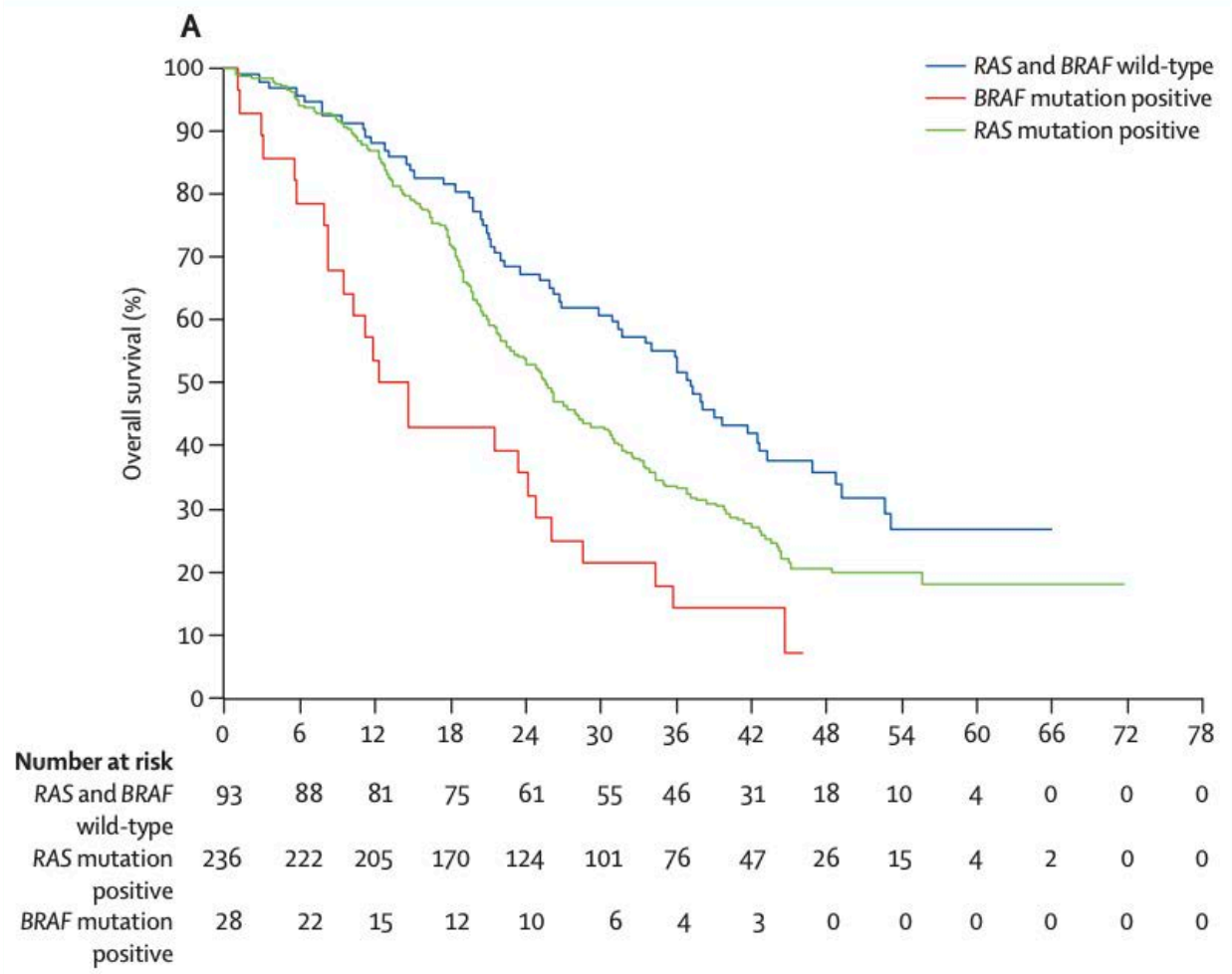


OS



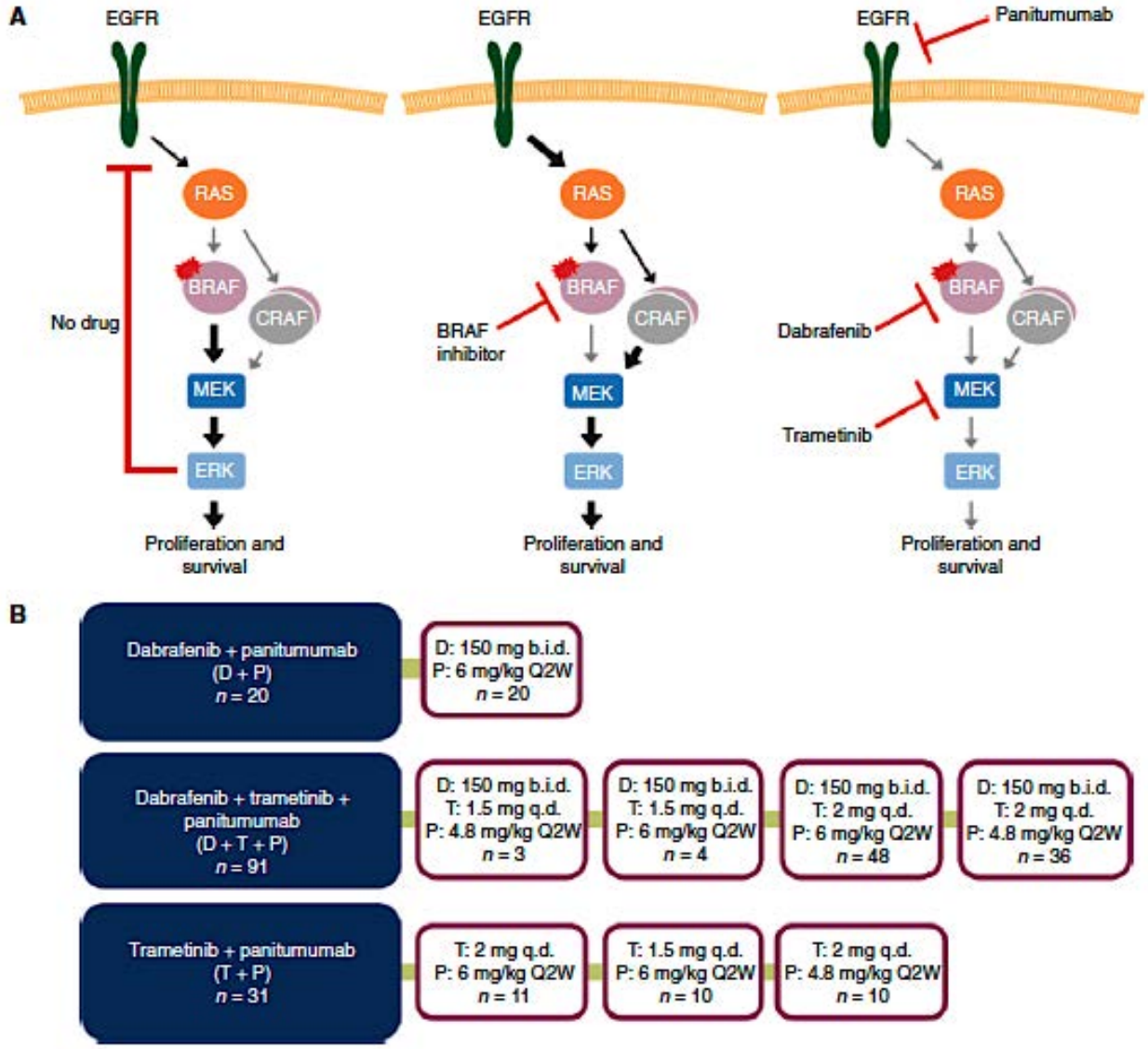
ARCAD Database
Cohen et al, J Natl Canc Inst, 2022

TRIBE: Mutational status and Overall Survival
FOLFOXIRI / BEV



Cremolini et al, Lancet Oncol, 2015

Multiple Pathway Inhibition

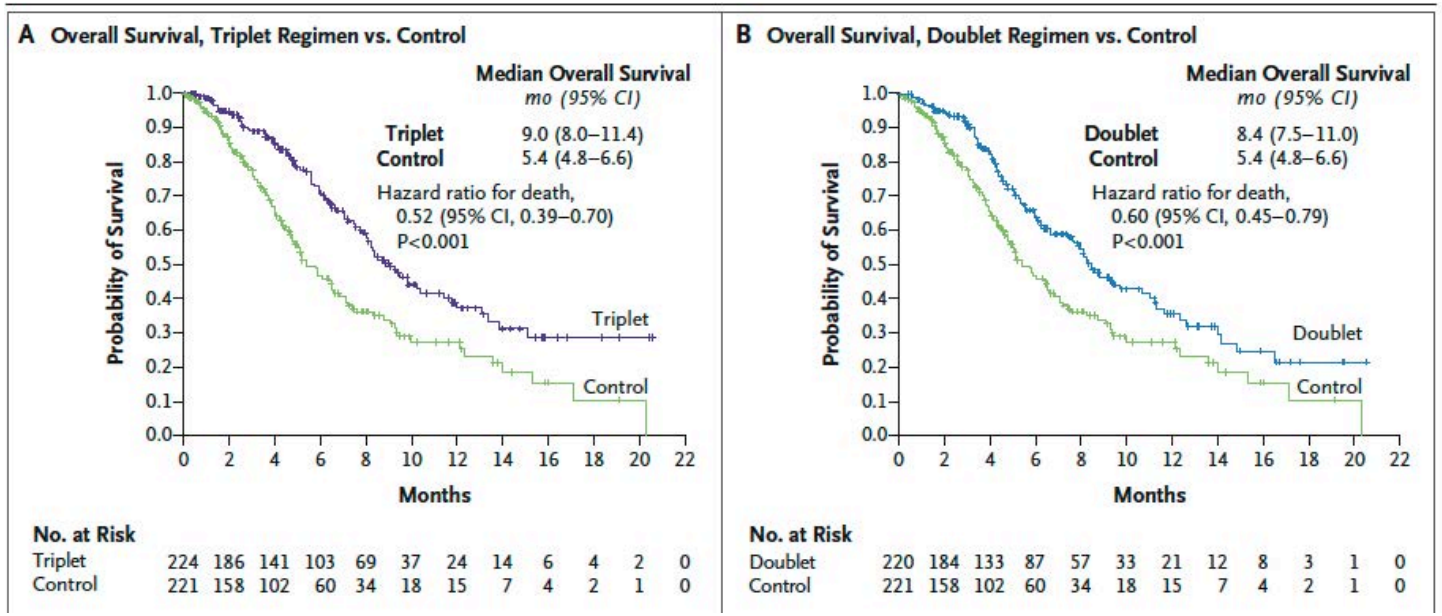


Corcoran et al, Canc Discov, 2018

Encorafenib, Binimetinib, and Cetuximab in *BRAF* V600E–Mutated Colorectal Cancer

New Engl J Med, 2019

S. Kopetz, A. Grothey, R. Yaeger, E. Van Cutsem, J. Desai, T. Yoshino, H. Wasan, F. Ciardiello, F. Loupakis, Y.S. Hong, N. Steeghs, T.K. Guren, H.-T. Arkenau, P. Garcia-Alfonso, P. Pfeiffer, S. Orlov, S. Lonardi, E. Elez, T.-W. Kim, J.H.M. Schellens, C. Guo, A. Krishnan, J. Dekervel, V. Morris, A. Calvo Ferrandiz, L.S. Tarpgaard, M. Braun, A. Gollerkeri, C. Keir, K. Maharry, M. Pickard, J. Christy-Bittel, L. Anderson, V. Sandor, and J. Tabernero



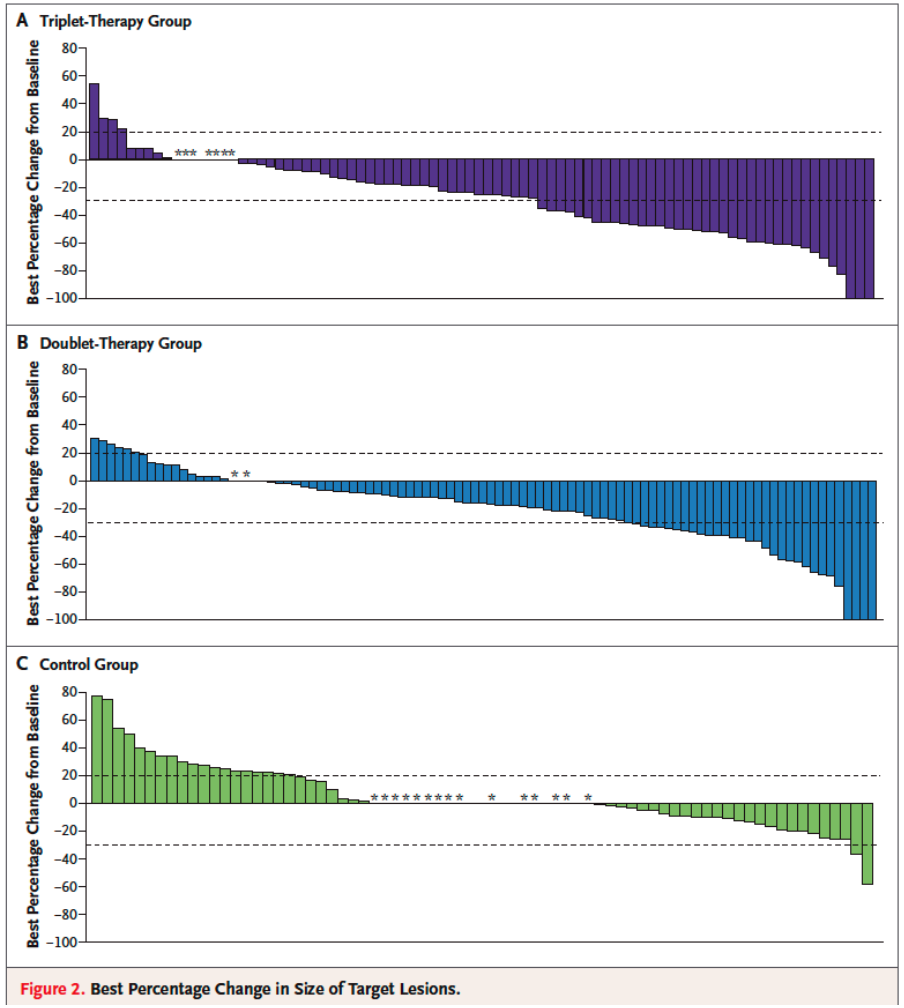
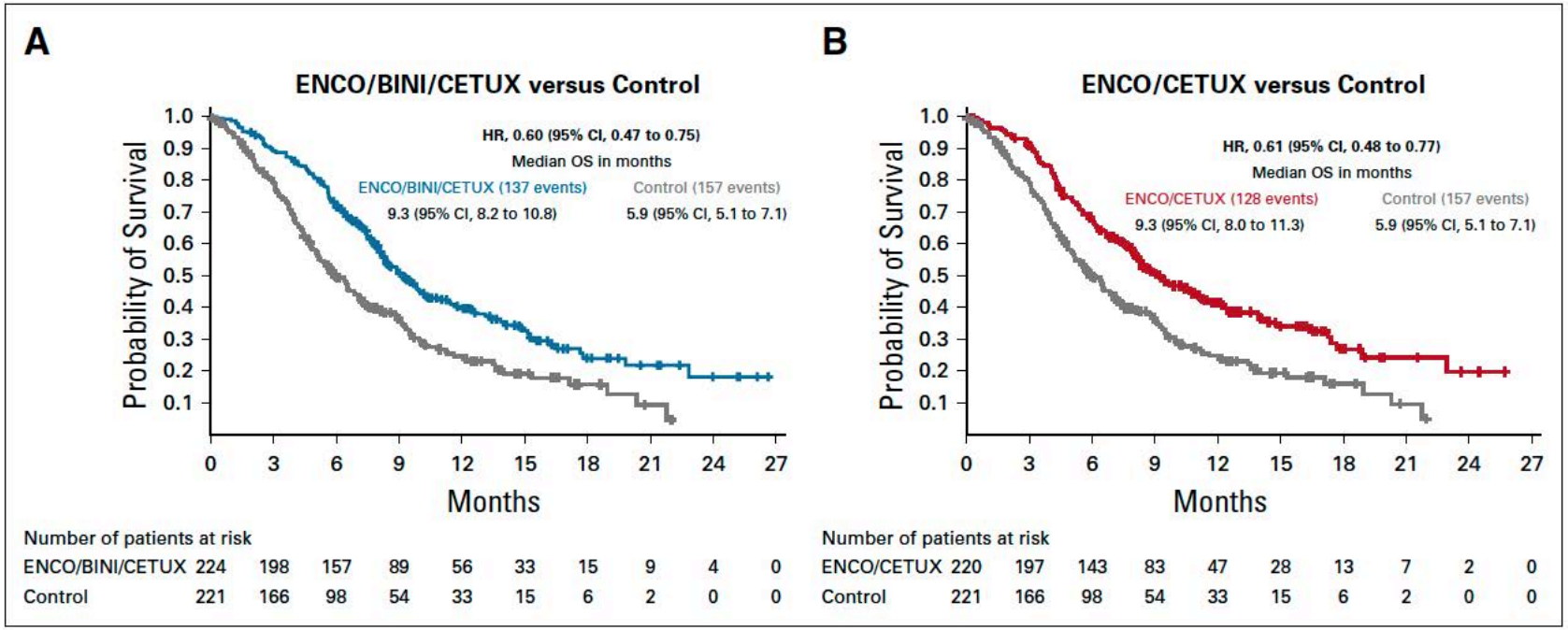


Figure 2. Best Percentage Change in Size of Target Lesions.

Encorafinib /Cetuximab: Standard 2nd-line



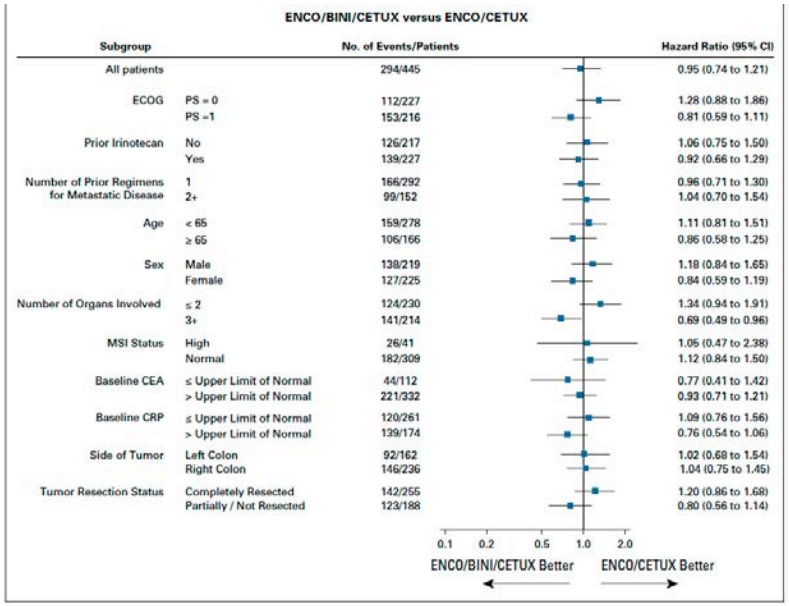


FIG 1. Overall survival results. (A) ENCO/BINI/CETUX versus control. (B) ENCO/CETUX versus control. ENCO/BINI/CETUX, encorafenib, binimetinib plus cetuximab; ENCO/CETUX, encorafenib plus cetuximab; HR, hazard ratio; OS, overall survival.

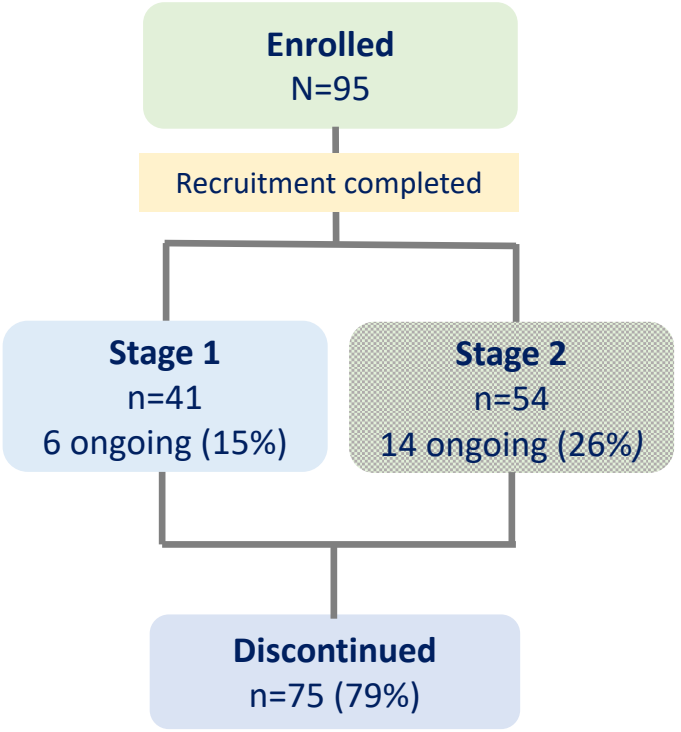
Tabernero et al, J Clin Oncol, 2021

ANCHOR CRC: Phase II study in 1L *BRAF*^{V600E}-mutant mCRC

Two-stage study design[1]

Patient population N=90	Stage 1 n=40#	Stage 2* n=50	Treatment continued until	Follow up
• mCRC • *BRAF*^{V600E} mutation • Untreated in metastatic setting • No prior treatment with any RAF inhibitor, MEK inhibitor, or anti-EGFR inhibitor • ECOG PS 0/1	Encorafenib + binimetinib + cetuximab	Encorafenib + binimetinib + cetuximab	• Disease progression • Unacceptable toxicity • Consent withdrawal	Patients followed up for survival every 3 months

Main analysis on 90 patients



- PD, n=48 (64%)
- Adverse events, n=16 (21%)
- Physician decision, n=6 (8%)
- Other, n=5 (7%)

Primary objective and endpoint: cORR (investigator-assessed)
H0 rejection if lower limit of the 95% CI for cORR ≥30% (≥37 confirmed responses in 90 patients)
Secondary endpoints: PFS, OS, safety, QoL, PK

#Futility analysis; *Stage 2 enrolment only after ≥12 responses observed in Stage 1. cORR, confirmed objective response rate; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRC, metastatic colorectal cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; QoL, quality of life.

1. Grothey A, et al. *Annals Oncol*. 2019;30(suppl 4):P-400.

ClinicalTrials.gov Identifier: NCT03693170

Courtesy Eric Van Cutsem
ESMO GI, 2021

Primary endpoint met* with cORR of 48%

Investigator's assessment	Patients (N=92[#]), n (%)
cORR	**44 (47.8)**
95% CI	**37.3—58.5**
Best overall confirmed response	
CR	0
PR	44 (47.8)
SD	37 (40.2)
PD	5 (5.4)
Not evaluable	6* (6.5)

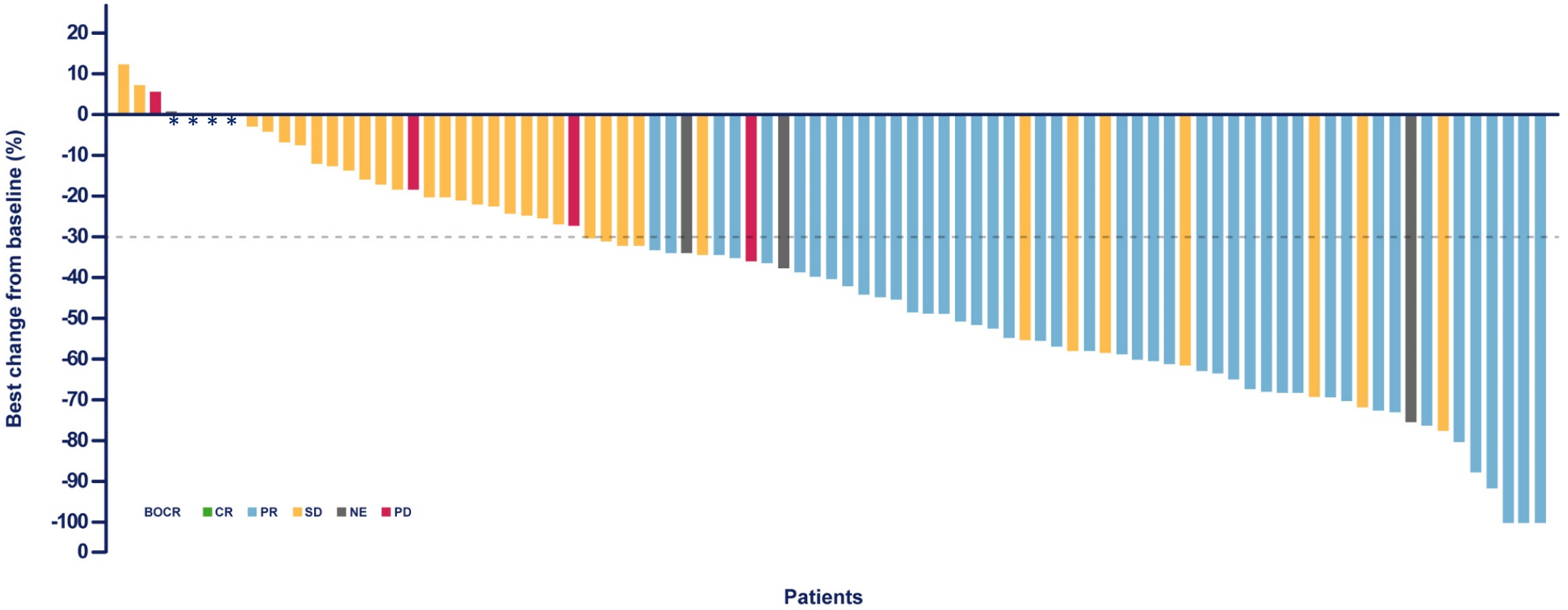
DCR = 88%

*Primary endpoint met with a lower limit of the 95% CI exceeding 30%

[#]3 patients have been excluded from the efficacy analysis as the *BRAF* mutation was not confirmed/indeterminate by central laboratory.
*3 patients with no adequate post-baseline assessment.
1 patient with new antineoplastic therapy started before first post-baseline assessment.
2 patients with unconfirmed CR,PR or SD with first adequate assessment <6 weeks.
cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease.

Best percentage change in tumor measurements

Investigator's assessment, patients evaluable for efficacy (N=92[#])



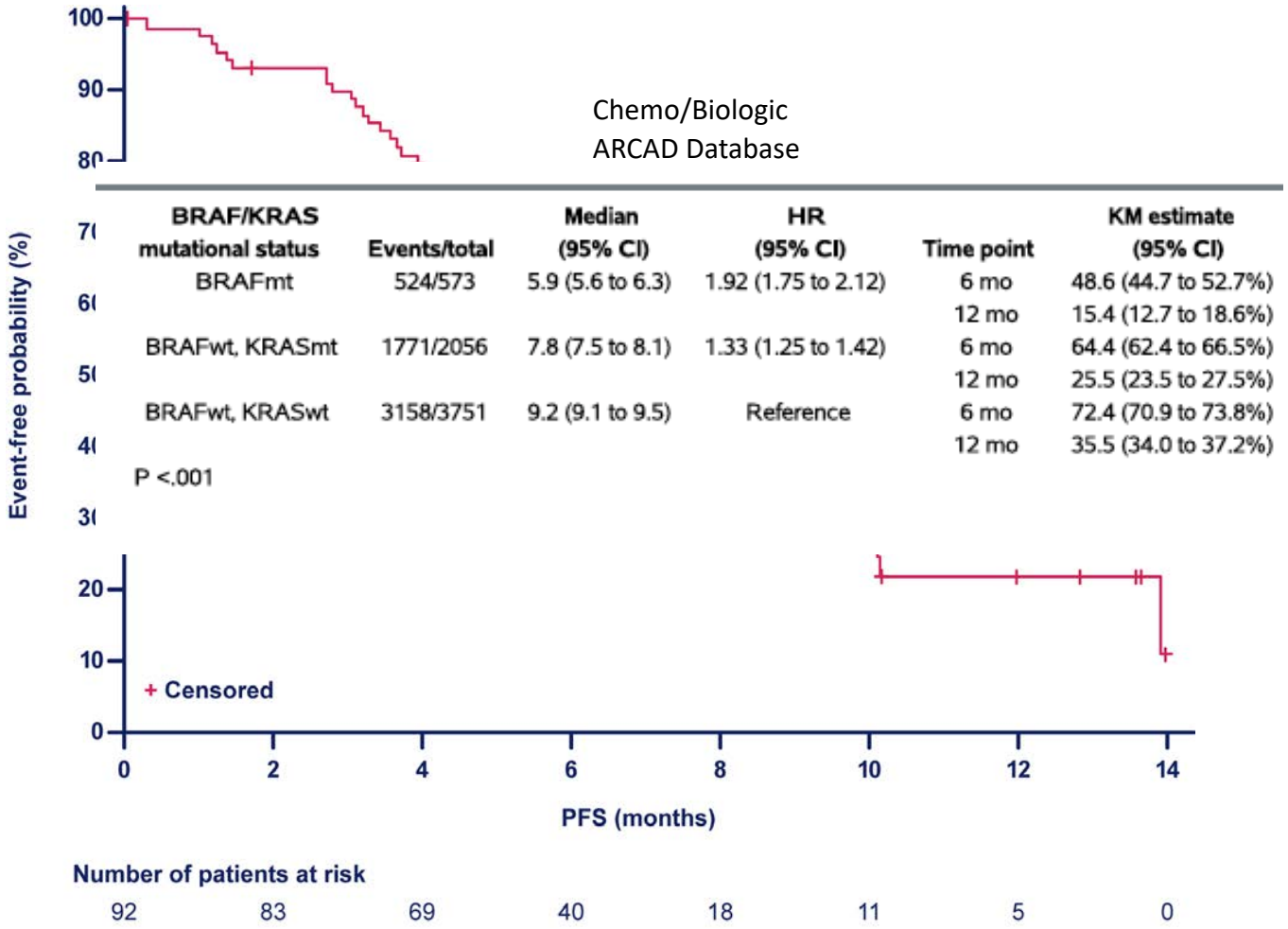
2 patients with BOCR equal to NE are not presented in the plot because they do not have post-baseline tumor diameters.
1 patient with BOCR equal to PD is not presented in the plot because one target lesion was not evaluable and the sum of longest diameters cannot be calculated at the unique post-baseline evaluation.

[#]3 patients have been excluded from the efficacy analysis as the *BRAF* mutation was not confirmed/indeterminate by central laboratory.
*4 patients with the best percentage change from baseline equal to 0% have their BOCR equal to stable SD.

BOCR, best overall confirmed response; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Progression-free survival

Investigator's assessment, median follow-up: 4.86 months



	Encorafenib + binimetinib + cetuximab
Local PFS	N=92[#]
Number of events	61 (66.3%)
Median PFS (months)	**5.8**
95% CI	**4.6—6.4**

[#]3 patients have been excluded from the efficacy analysis as the *BRAF* mutation was not confirmed by central laboratory.
CI, confidence interval; PFS, progression-free survival.

Most patients able to receive active subsequent therapies

Median (range) time to subsequent therapy: 6.9 (5.9–8.4) months

Antineoplastic treatment	Encorafenib + binimetinib + cetuximab N=95, n (%)
Patients with ongoing study treatment	20 (21.1)
Patients with at least one monotherapy/combination of antineoplastic therapy since study treatment discontinuation	41 (43.2)
Oxaliplatin-based doublet ± bevacizumab	21 (22.1%)
FOLFOXIRI ± bevacizumab	12 (12.6)
Immunotherapy	2 (2.1)
Encorafenib + binimetinib + cetuximab	1 (1.1)
Others*	5 (5.3)
Patients who did not receive subsequent antineoplastic therapy	34 (35.8)
unknown	18 (18.9)
Death	14 (14.7)
Withdrawal	2 (2.1)

*5-fluorouracil (5-FU) (n=1), FOLFOX/cetuximab (n=1), bevacizumab (n=1), capecitabine (n=1), oxaliplatin/bevacizumab (n=1). FOLFOXIRI, oxaliplatin, irinotecan, 5-FU, and leucovorin.

Overall safety summary

Duration of exposure, median (range), months	
Encorafenib	4.96 (0.09–15.40)
Binimetinib	4.67 (0.07–14.95)
Cetuximab	4.96 (0.23–15.15)

Relative dose intensity, median (range), %	
Encorafenib	95.4 (31–100)
Binimetinib	93.3 (3–100)
Cetuximab	93.8 (5–109)

	Any grade N=95, n (%)
Any AE	**94 (98.9)**
Any serious AE	49 (51.6)
Any AE leading to dose interruption or dose reduction of at least one study drug	71 (74.7)
Any AE leading to discontinuation of ≥1 study drug	23 (24.2)
Any AE leading to death[#]	3 (3.2)

AE, adverse event; n, number of patients with an AE.
[#]AE leading to death: intestinal obstruction (not related to treatment), acute renal failure (suspected to be treatment related), pneumonitis (suspected to be treatment related).

BREAKWATER study design

An open-label, multicenter, randomized phase 3 study of 1st line encorafenib plus cetuximab with or without chemotherapy versus standard of care therapy in patients with metastatic *BRAF* V600E-mutant mCRC

Safety lead-in

Patients with *BRAF*^{V600E} mutant mCRC with 0 to 1 prior regimens in the metastatic setting

Phase 3

Patients with *BRAF*^{V600E} mutant mCRC and no prior systemic therapy in the metastatic setting

Encorafenib + cetuximab + mFOLFOX6
N=30
Encorafenib + cetuximab + FOLFIRI
N=30

Dosages
- Encorafenib, 300 mg PO QD
- Cetuximab, 500 mg/m^2 IV Q2W
- FOLFOX,full dose IV Q2W
- FOLFIRI, full dose IV Q2W

Randomize 1:1:1*

Arm A**
Encorafenib + cetuximab, N=290

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

Control arm §
Physician's choice: FOLFOX, FOLFIRI, FOLFOXIRI, CAPOX, all ± anti-VEGF antibody, N=290

PRIMARY ENDPOINTS
PFS (BICR) Arm A vs Control
AND
PFS (BICR) Arm B vs Control
(BICR, blinded independent central review)

KEY SECONDARY ENDPOINTS
OS Arm A vs Control
AND
OS Arm B vs Control

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

BREAKWATER STUDY

*Stratified by: ECOG PS 0 v. 1, Region US/Canada v. Western Europe v. ROW
**Same dosing as SLI; $^{\beta}$FOLFOX or FOLFIRI based on SLI results; § No crossover.
ClinicalTrials.gov Identifier: NCT04607421

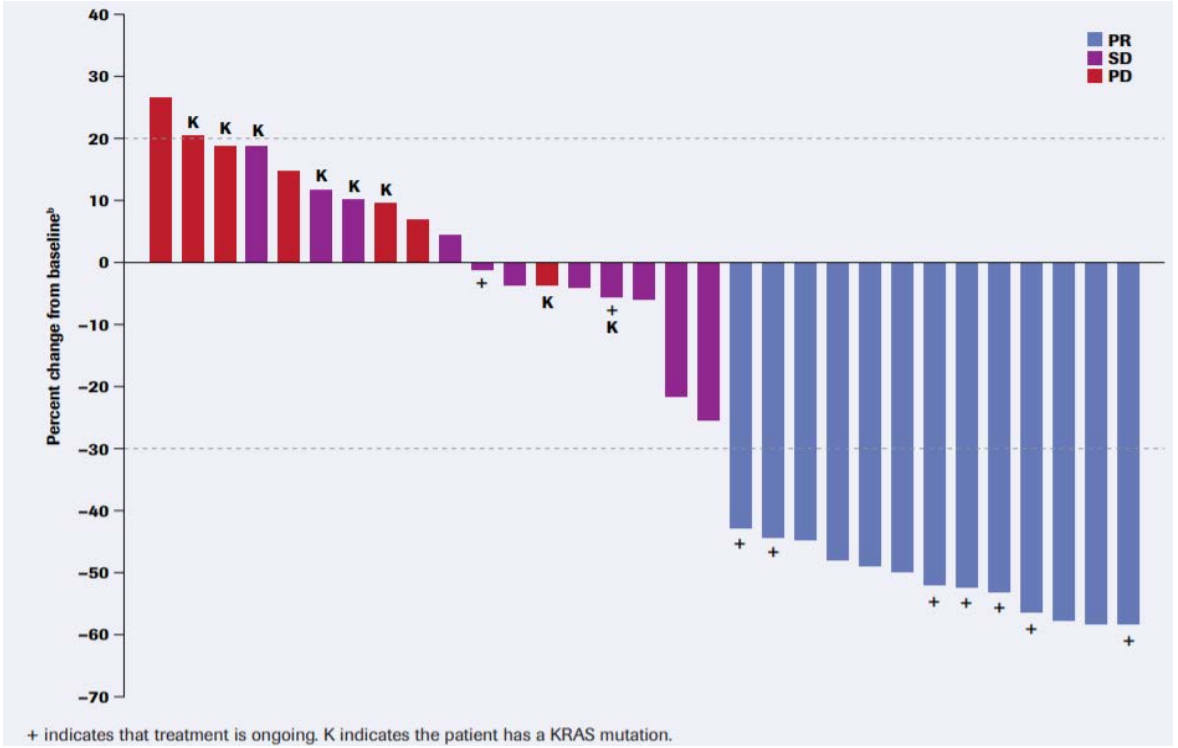
PRINCIPLES OF PATHOLOGIC REVIEW

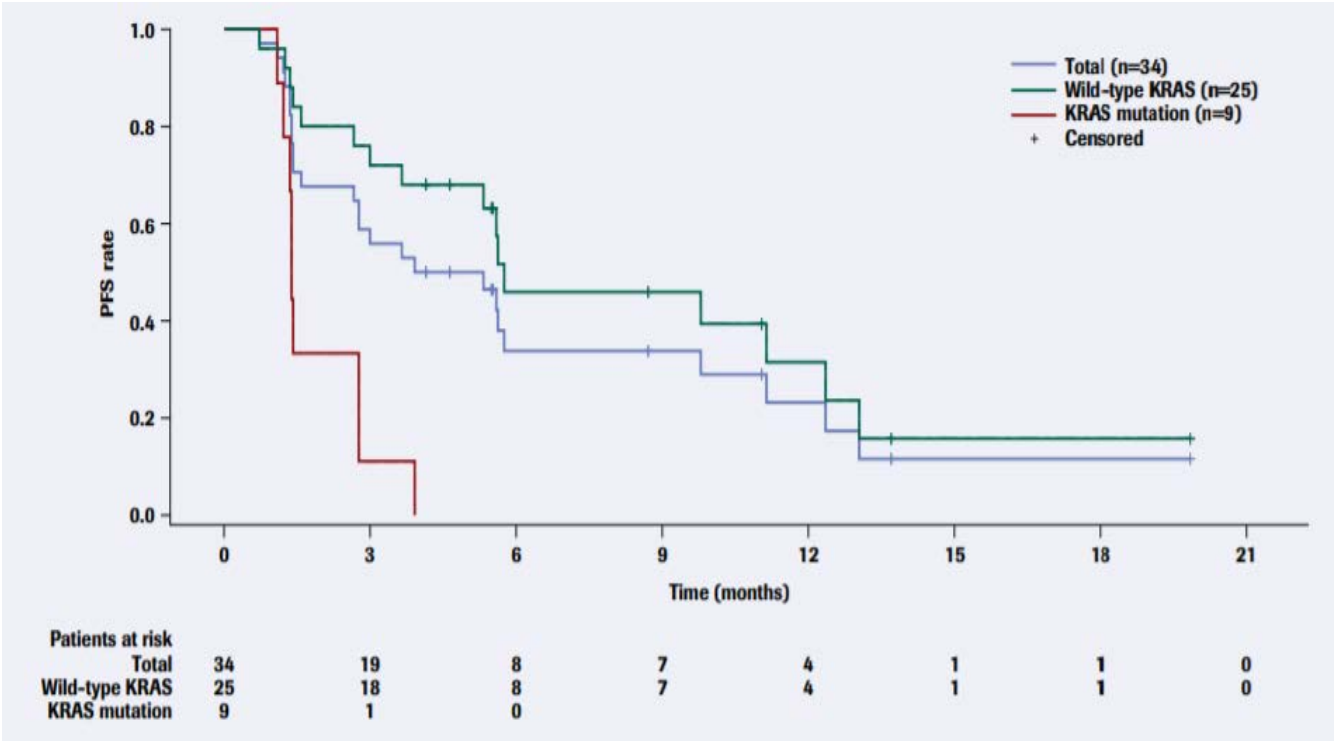
HER2 Testing

- **Diagnostic testing is via immunohistochemistry, fluorescence in situ hybridization (FISH), or NGS.**
- **Positive by immunohistochemistry is defined as: 3+ staining in more than 50% of tumor cells. 3+ staining is defined as an intense membrane staining that can be circumferential, basolateral, or lateral. Those that have a HER2 score of 2+ should be reflexed to FISH testing.[62-64] HER2 amplification by FISH is considered positive when the HER2:CEP17 ratio is ≥2 in more than 50% of the cells.[62-64] NGS is another methodology for testing for HER2 amplification.[65]**
- **Anti-HER2 therapy is only indicated in HER2-amplified tumors that are also *RAS* and *BRAF* wild type.**

MY PATHWAY: Trastuzumab /Pertuzumab in HER-2 amplified mCRC

N = 34 patients



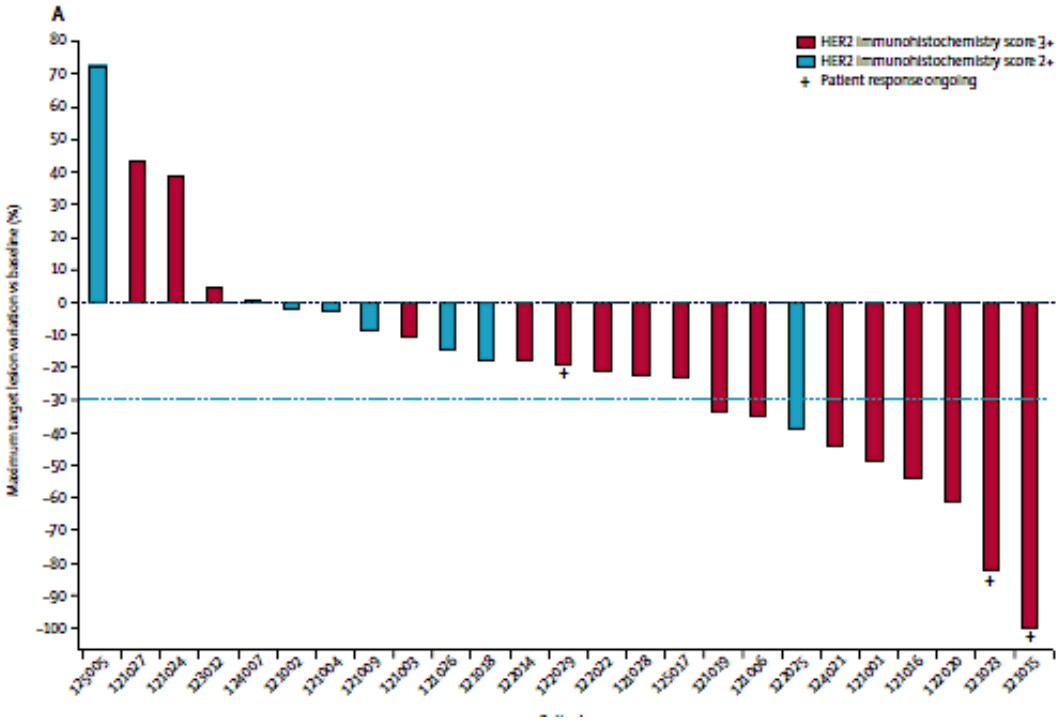


Hurwitz, H. GI ASCO 2018

Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, *KRAS* codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial

Screen
N = 914

Her-2 +
N = 46



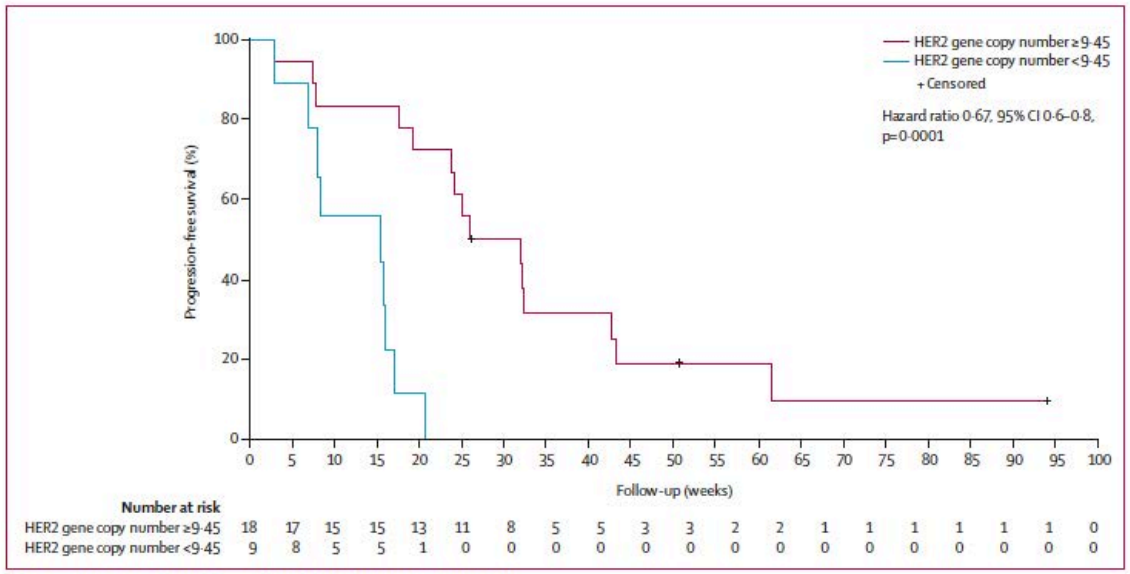
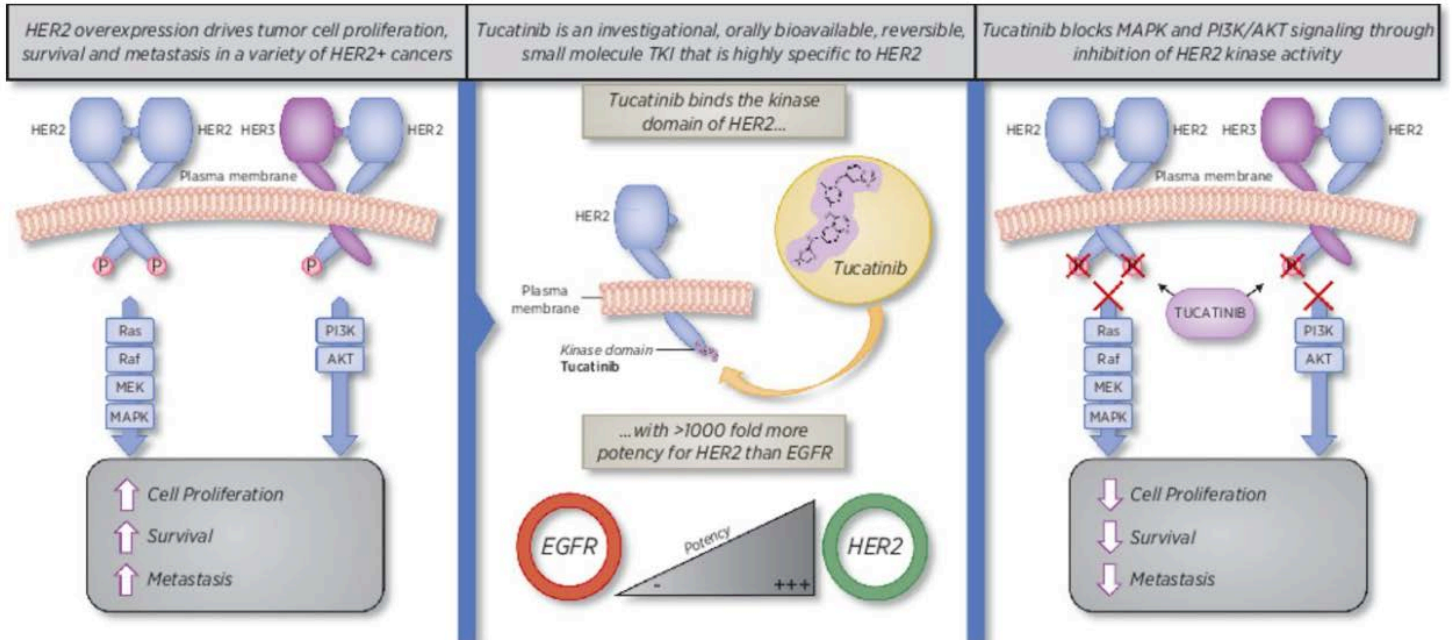


Figure 2: **Progression-free survival by *HER2* gene copy number variation**
Data from three patients, who remained in follow-up for progression-free survival at the time of data cutoff, were censored.

Sartore-Bianch et al, Lancet Oncol, 2016

Tucatinib / Trastuzumab in mCRC



- This trial is designed to evaluate the efficacy and safety of tucatinib in combination with trastuzumab in patients with HER2+ mCRC
- Interim analysis of the initial 26 patients enrolled in MOUNTAINEER demonstrated an objective response rate (ORR) of 52.2% (12 partial response [PRs] in 23 evaluable patients), median duration of response of 10.4 months, with a median progression-free survival (PFS) of 8.1 months and a median overall survival (OS) of 18.7 months.

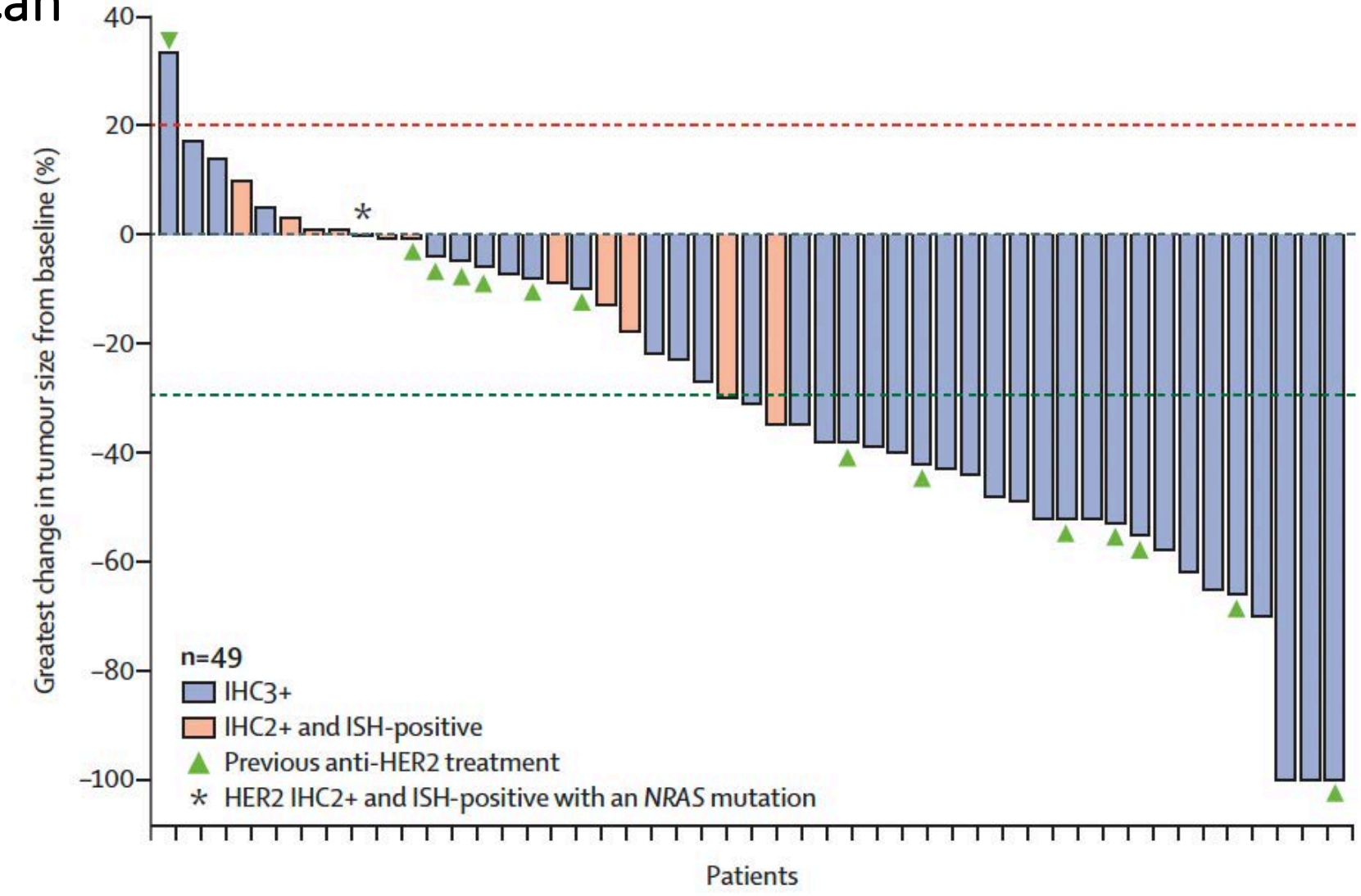
Strickler at al, ASCO, 2021

DESTINY-CRC01: Trastuzumab Deruxtecan in HER2-Expressing Metastatic Colorectal Cancer — Select Baseline Characteristics

	Cohort A (HER2-positive; n=53)	All patients (n=78)
ECOG performance status		
0	37 (70%)	49 (63%)
1	16 (30%)	28 (36%)
2	0	1 (1%)
Sum of target lesions, cm	8·4 (5·3–13·5)	8·8 (5·3–12·1)
Primary tumour site		
Left*	47 (89%)	70 (90%)
Right†	6 (11%)	8 (10%)
Microsatellite status‡		
Stable	43 (81%)	62 (80%)
Unknown	10 (19%)	16 (21%)
RAS wild type‡§	52 (98%)	77 (99%)
BRAF^{V600E} wild type‡	53 (100%)	77 (99%)

	Cohort A (HER2-positive; n=53)	All patients (n=78)
HER2 status¶		
IHC3+	40 (76%)	40 (51%)
IHC2+ and ISH-positive	13 (25%)	13 (17%)
IHC2+ and ISH-negative	0	7 (9%)
IHC1+	0	18 (23%)
Number of previous therapies	4 (3–5)	4 (3–6)
Previous treatment		
Irinotecan	53 (100%)	78 (100%)
Fluoropyrimidines‖	53 (100%)	78 (100%)
Oxaliplatin	53 (100%)	78 (100%)
Cetuximab or panitumumab	53 (100%)	77 (99%)
Bevacizumab	40 (76%)	62 (80%)
Anti-HER2 agents**	16 (30%)	16 (21%)

DESTINY-CRC01: Antitumour activity in patients with HER2-positive metastatic colorectal cancer (cohort A) receiving trastuzumab deruxtecan



Siena S et al, Lancet Oncol, 2021.

DESTINY-CRC01: Clinical response for patients with HER2-positive metastatic colorectal cancer (cohort A) treated with trastuzumab deruxtecan

	Cohort A (HER2-positive; n=53)
Confirmed ORR by ICR, % (95% CI)	45·3 (31·6–59·6)
Complete response	1 (2%)
Partial response	23 (43%)
Stable disease	20 (38%)
Progressive disease	5 (9%)
Non-evaluable*	4 (8%)
Confirmed ORR by investigator, % (95% CI)	45·3 (31·6–59·6)
Complete response	0
Partial response	24 (45%)
Stable disease	19 (36%)
Progressive disease	6 (11%)
Non-evaluable*	4 (8%)
Disease control rate, % (95% CI)	83·0 (70·2–91·9)
Median duration of response by ICR, months (95% CI)	NE (4·2–NE)

Siena S et al, Lancet Oncol, 2021.

DESTINY-CRC01: Interstitial Lung Disease

All Patients (N=86)	n (%)
Grade 1	0
Grade 2	4 (4.7)
Grade 3	1 (1.2)
Grade 4	0
Grade 5	3 (3.5)[a]
Any Grade/Total	8 (9.3)[b,c]

Adjudicated drug-related ILDs:

- Median time to adjudicated onset was 61.0 days (range, 9-165 days)
- 8 of 8 patients received corticosteroids
- 4 patients with grade 2 recovered and 1 patient with grade 3 did not recover (later died due to disease progression)
- Median time from adjudicated onset date to initiation of steroid treatment in the 8 ILD cases was 3.5 days, (range 0-50)

Grade 5 ILDs:

- In the 3 fatal cases adjudicated as drug-related ILD, onset was from 9 days to 120 days (median: 22 days); and death occurred 6-19 days after diagnosis (median: 6 days)

Updated ILD/pneumonitis guidelines recommend to monitor for symptoms, interrupt or discontinue T-DXd, conduct imaging (as clinically indicated), and start steroids as soon as ILD is suspected.

Yoshino et al, ASCO, 2021

DESTINY-CRC01: Treatment-Emergent adverse events occurring in >10% of patients

	Grade 1–2	Grade 3	Grade 4	Grade 5
Nausea	42 (54%)	5 (6%)	0	0
Decreased appetite	26 (33%)	0	0	0
Fatigue	25 (32%)	1 (1%)	0	0
Vomiting	22 (28%)	1 (1%)	0	0
Diarrhoea	21 (27%)	1 (1%)	0	0
Anaemia	18 (23%)	10 (13%)	1 (1%)	0
Platelet count decreased	16 (21%)	5 (6%)	2 (3%)	0
Alopecia	15 (19%)	0	0	0
Constipation	11 (14%)	0	0	0
Asthenia	10 (13%)	0	0	0
Neutrophil count decreased	9 (12%)	12 (15%)	5 (6%)	0
Cough	9 (12%)	0	0	0
Oedema peripheral	9 (12%)	0	0	0
Pyrexia	9 (12%)	0	0	0
Hypokalaemia	8 (10%)	4 (5%)	1 (1%)	0

Siena S et al, Lancet Oncol, 2021.

BRAF and HER-2 Targeted Treatment mCRC

BRAF V600E mt

- Encorafenib / Cetuximab standard 2nd-line
- 1st-line ANCHOR trial: yet to be determined if favorable results

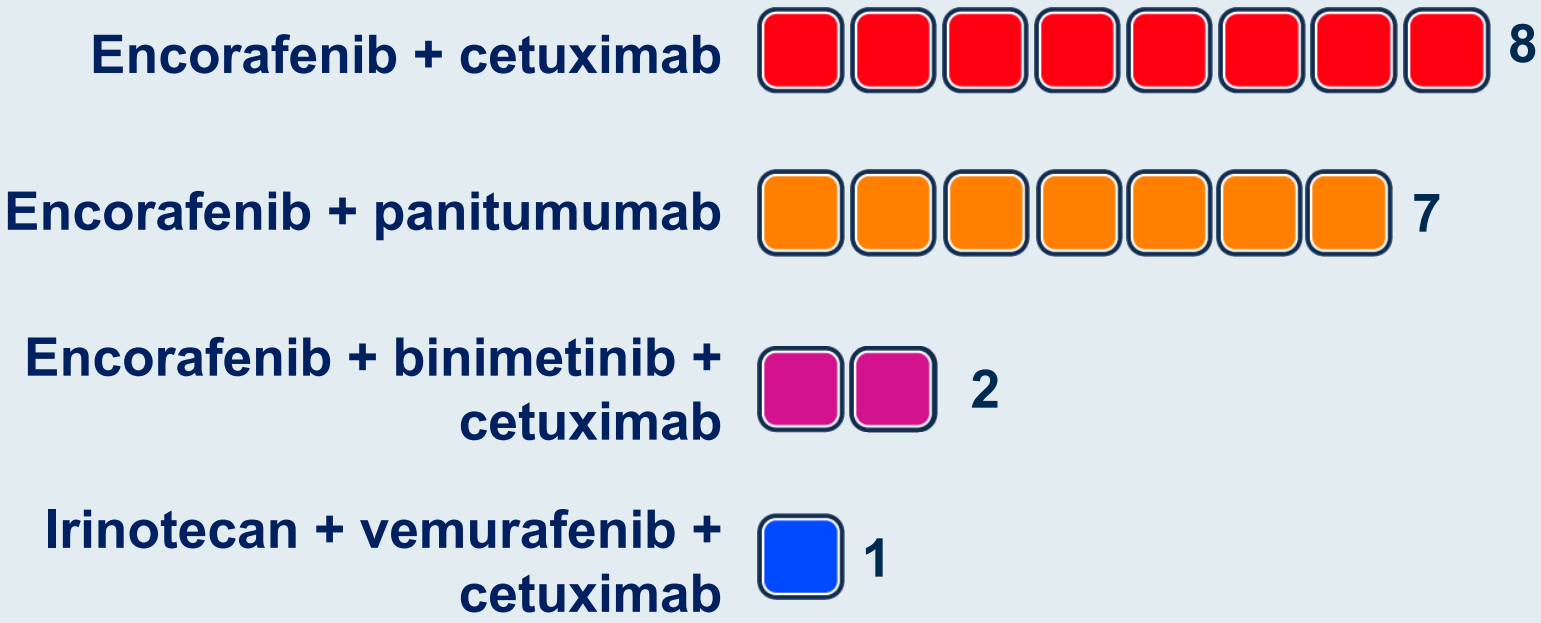
HER-2 amplification

- Variety of combinations with activity in subsequent line
- Trastuzamab/Deruxtecan promising but unique toxicity

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

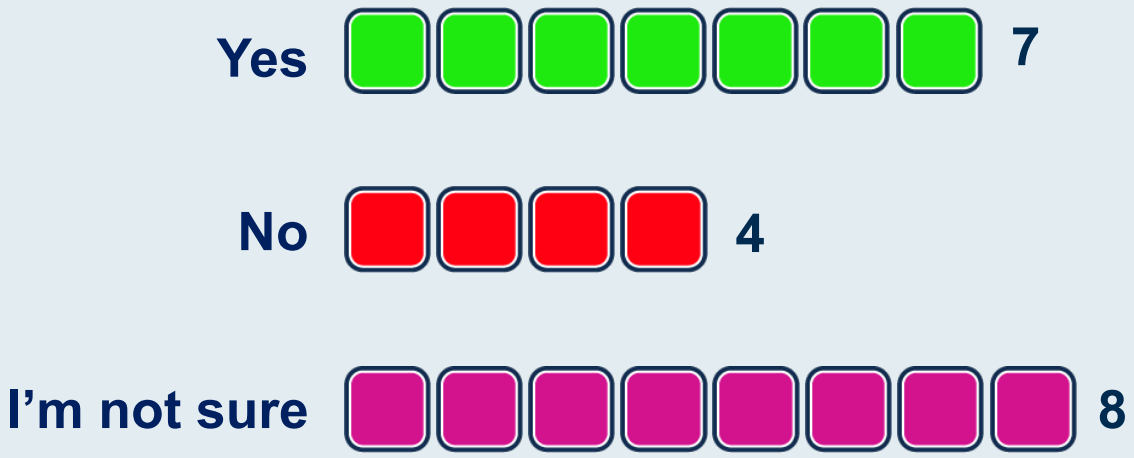
Survey of US-based clinical investigators

For a patient with mCRC with a BRAF V600E mutation to whom you would administer BRAF-targeted therapy, what would be your preferred treatment?



Survey of US-based clinical investigators

Based on currently available data and your own clinical experience, do you believe that there are subsets of patients with mCRC with a BRAF V600E mutation who might derive greater benefit from triplet (eg, encorafenib/binimetinib/EGFR antibody) versus doublet (eg, encorafenib/EGFR antibody) targeted therapy?



Survey of US-based clinical investigators

In general, what is your usual third-line treatment for a patient with pan-RAS wild-type, microsatellite-stable (MSS) mCRC with a BRAF V600E mutation who has experienced disease progression on first-line FOLFOX/bevacizumab and second-line encorafenib/cetuximab?

Survey of US-based clinical investigators

MODULE 2: Integration of Immune Checkpoint Inhibitors into the Management of mCRC — Dr Eng

Integration of Immune Checkpoint Inhibitors into the Management of mCRC

VANDERBILT-INGRAM CANCER CENTER

Cathy Eng, MD, FACP, FASCO

David H. Johnson Chair in Surgical and Medical Oncology

Professor of Medicine, Hematology and Oncology

Co-Director, GI Oncology

Co-Leader, Gastrointestinal Cancer Research Program

Director, Young Adults Cancer Program

Co-Chair, NCI GI Steering Committee

January 19, 2022

Contact Info: cathy.eng@vumc.org

Twitter: @cathyengmd

FB: cathy eng-mdcancer

www.youngadultswithcancer.org

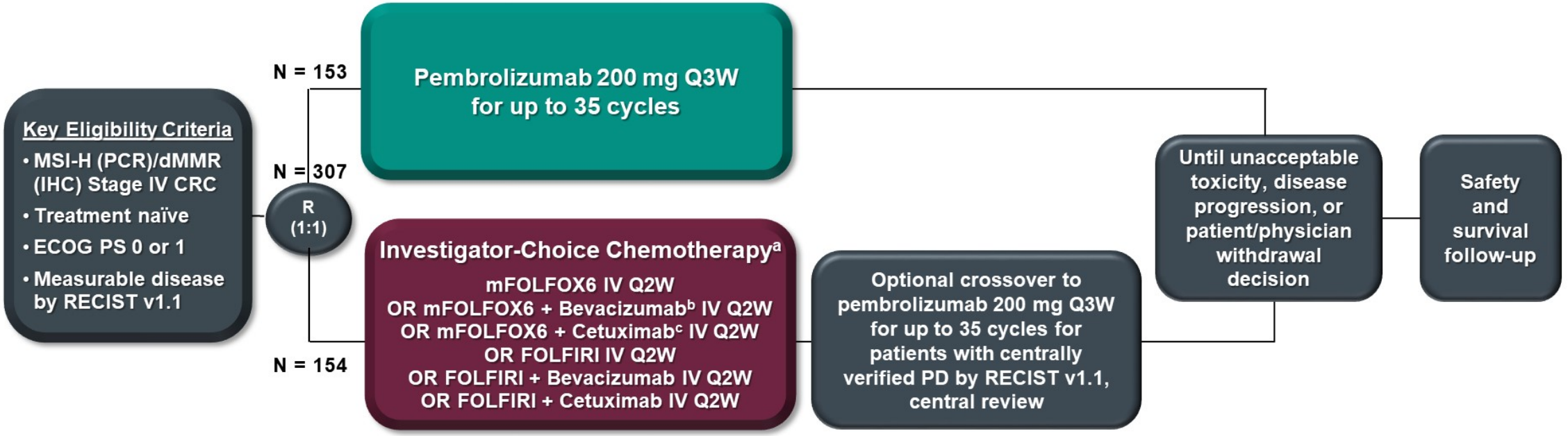
Discussion Points:

- Key efficacy and safety results from the Phase III KEYNOTE-177 study of pembrolizumab versus chemotherapy for microsatellite instability (MSI)-high/mismatch repair-deficient (dMMR) mCRC
- Available efficacy and safety findings with nivolumab/ipilimumab for patients with previously untreated MSI-high/dMMR mCRC
- Clinical trial findings defining the optimal incorporation of pembrolizumab, nivolumab and nivolumab/ipilimumab for patients with progressive MSI-high/dMMR mCRC
- Early results with immune checkpoint inhibitors in combination with other systemic approaches (eg, chemotherapy, targeted therapy) for MSI-high/dMMR advanced CRC
- Biologic rationale for and available data with immune checkpoint inhibition in microsatellite-stable mCRC

VANDERBILT-INGRAM CANCER CENTER

MSI-H Colorectal Cancer

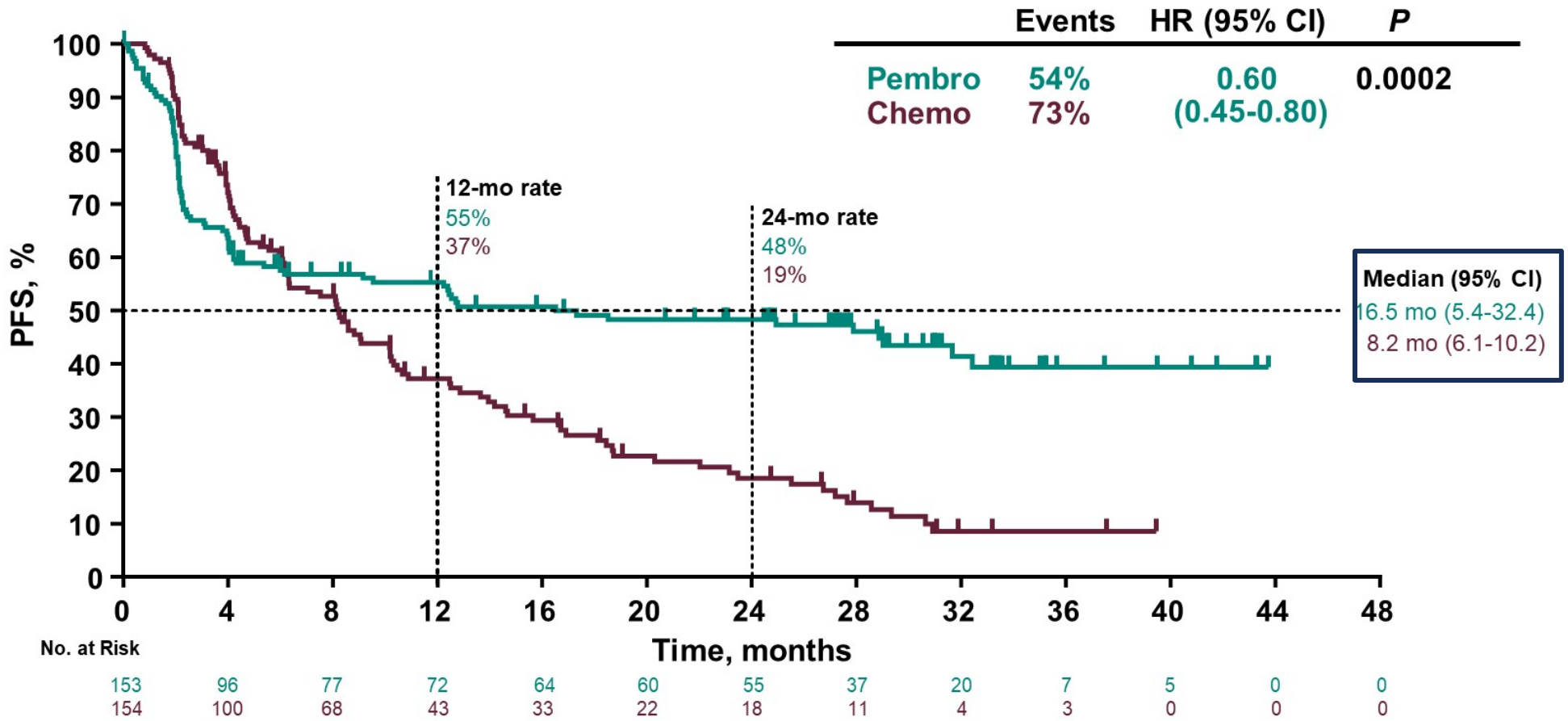
KEYNOTE-177 Study Design (NCT02563002)



- Dual-Primary endpoints: PFS per RECIST v1.1 per blinded independent central review (BICR) and OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, safety
- Exploratory endpoints: DOR per RECIST v1.1 by BICR, PFS2, HRQoL
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

Andre et al; NEJM 2020

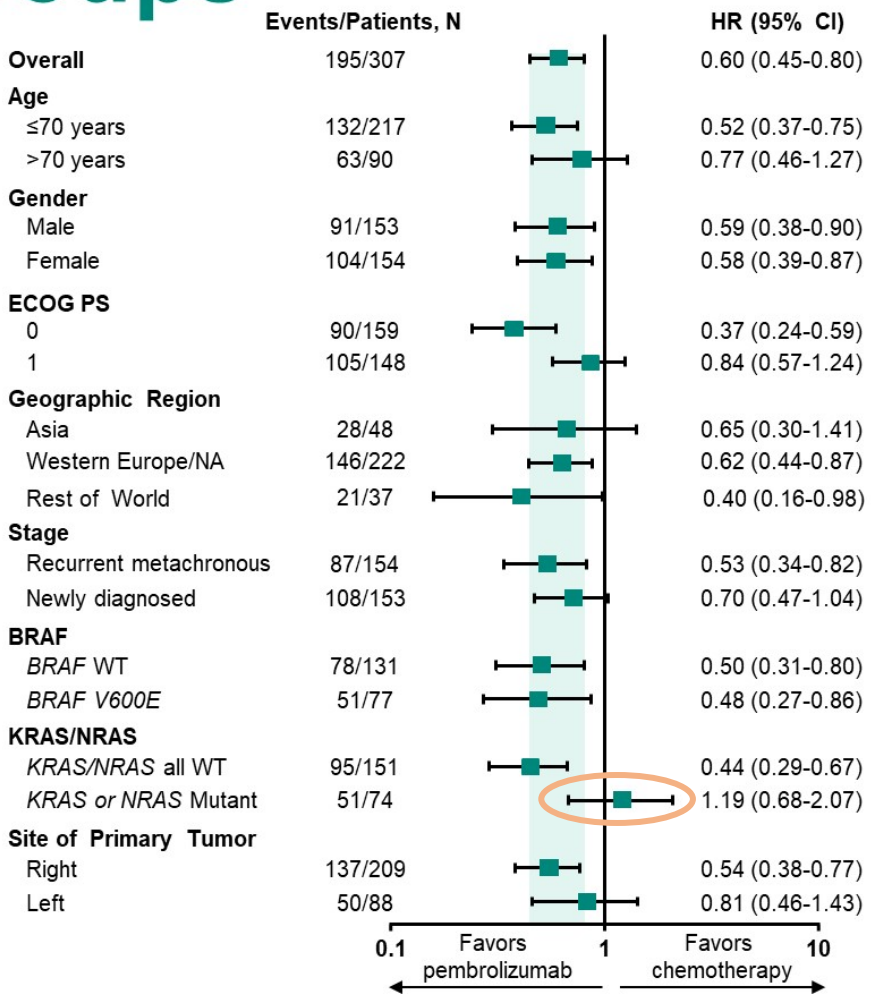
Progression-Free Survival



Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

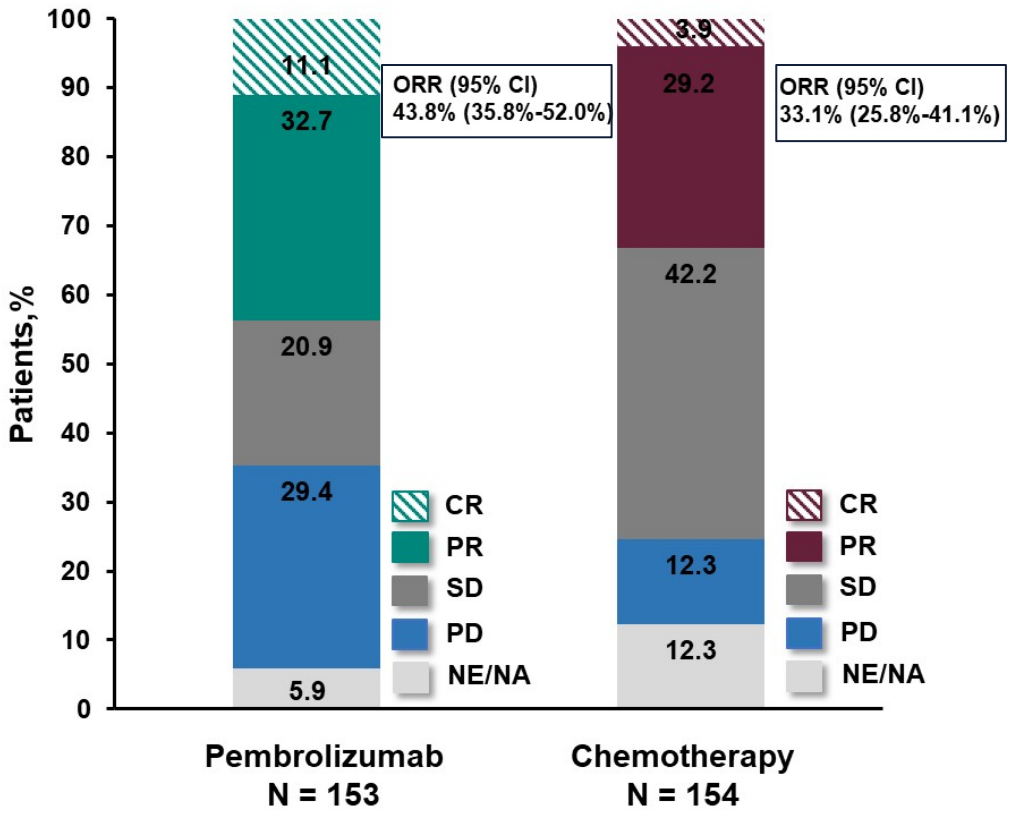
Andre et al; NEJM 2020

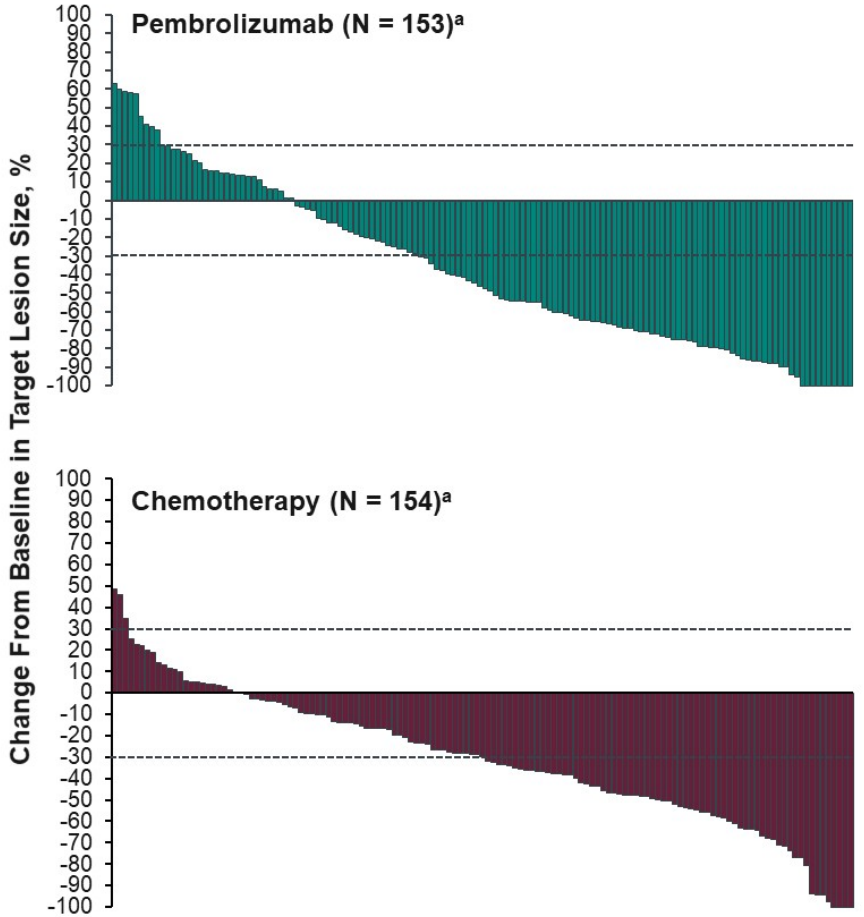
Progression-Free Survival in Key Subgroups



NA, North America; Data cut-off: 19Feb2020.

Summary of Best Anti-Tumor Response





9 (6%) patients in the pembrolizumab arm and 19 (12%) in the chemotherapy arm were not evaluable (NE) or had no assessment (NA); [a]104 of 138 (75%) evaluable patients in the pembrolizumab arm and 111 of 135 (82%) evaluable patients in the chemotherapy arm had a reduction from baseline in target lesion size. Evaluable patients include those with ≥1 post-baseline target lesion imaging assessment in the intention-to-treat population; Data cut-off: 19Feb2020.

Final Results: Cross Over and Subsequent Therapy

- 56 of 154 (**36%**) patients in the chemotherapy arm crossed over to receive pembrolizumab after confirmed disease progression
  - 37 additional patients received anti-PD-1/PD-L1 therapy outside of the study for an effective crossover rate of **60%** in the ITT

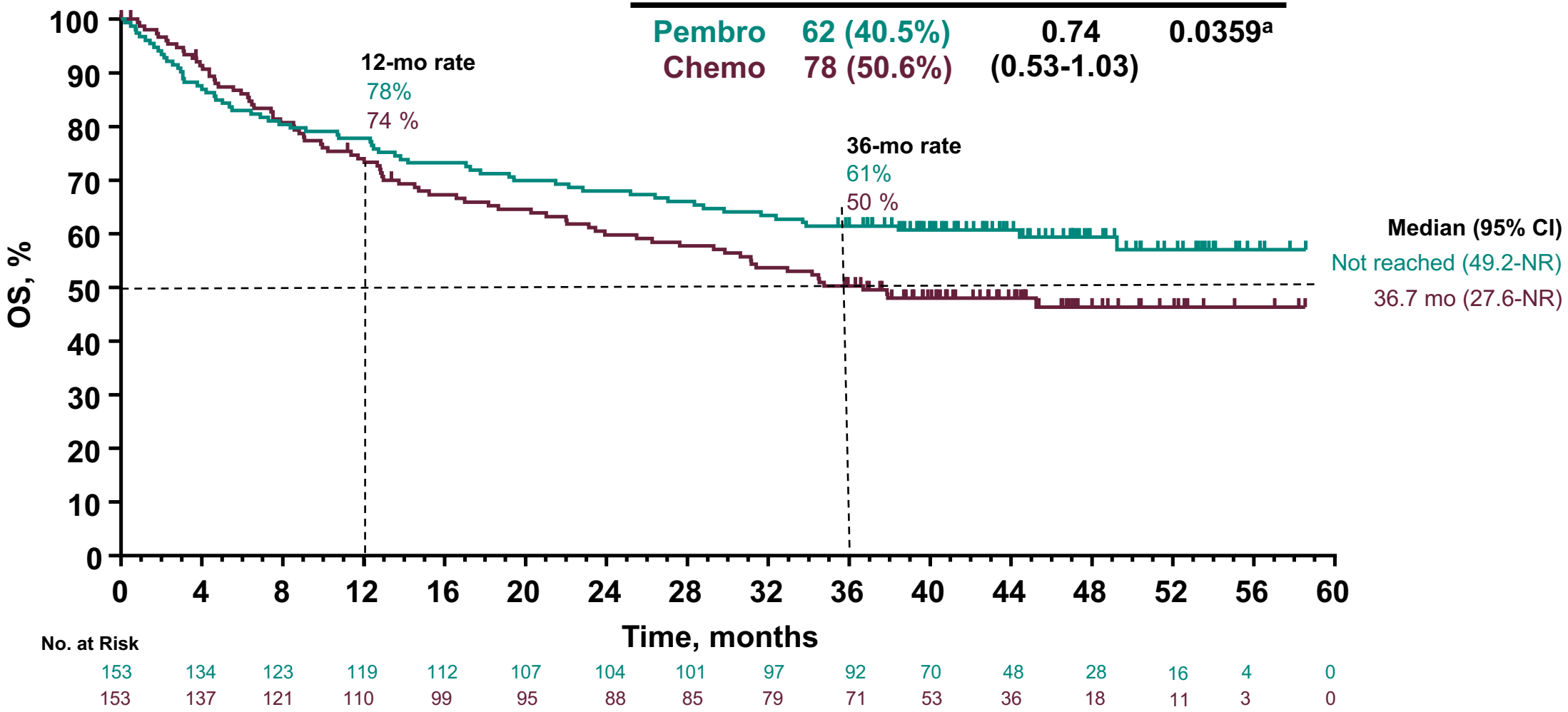
	Pembrolizumab N = 153	Chemotherapy N = 154
Any anti-PD-1/PD-L1 therapy, n (%)	14 (9.2)	93 (60.4)
On protocol therapy - pembrolizumab[a]	8 (5.2)	56 (36.4)
Off protocol therapies	6 (3.9)	37 (24.0)
Any non-anti-PD-1/PD-L1 therapy, n (%)	38 (24.8)	28 (18.2
Chemotherapy	35 (22.9)	20 (13.0)
VEGF inhibitor	22 (14.4)	13 (8.4)
EGFR inhibitor	9 (5.9)	5 (3.2)
Nucleosoide analog/thymidine phosphorylase inhibitor	2 (1.3)	2 (1.3)
CTLA-4 inhibitor	0	5 (3.2)
ICOS agonist	1 (0.7)	1 (0.6)
LAG-3 inhibitor	1 (0.7)	0
TIM3 inhibitor	1 (0.7)	1 (0.6)
Vaccine/viral therapy	0	2 (1.3)

Andre et al; NEJM 2020

[a]Including 2nd course treatment for patients randomized to pembrolizumab arm. Data cut-off: 19Feb2021.

Overall Survival

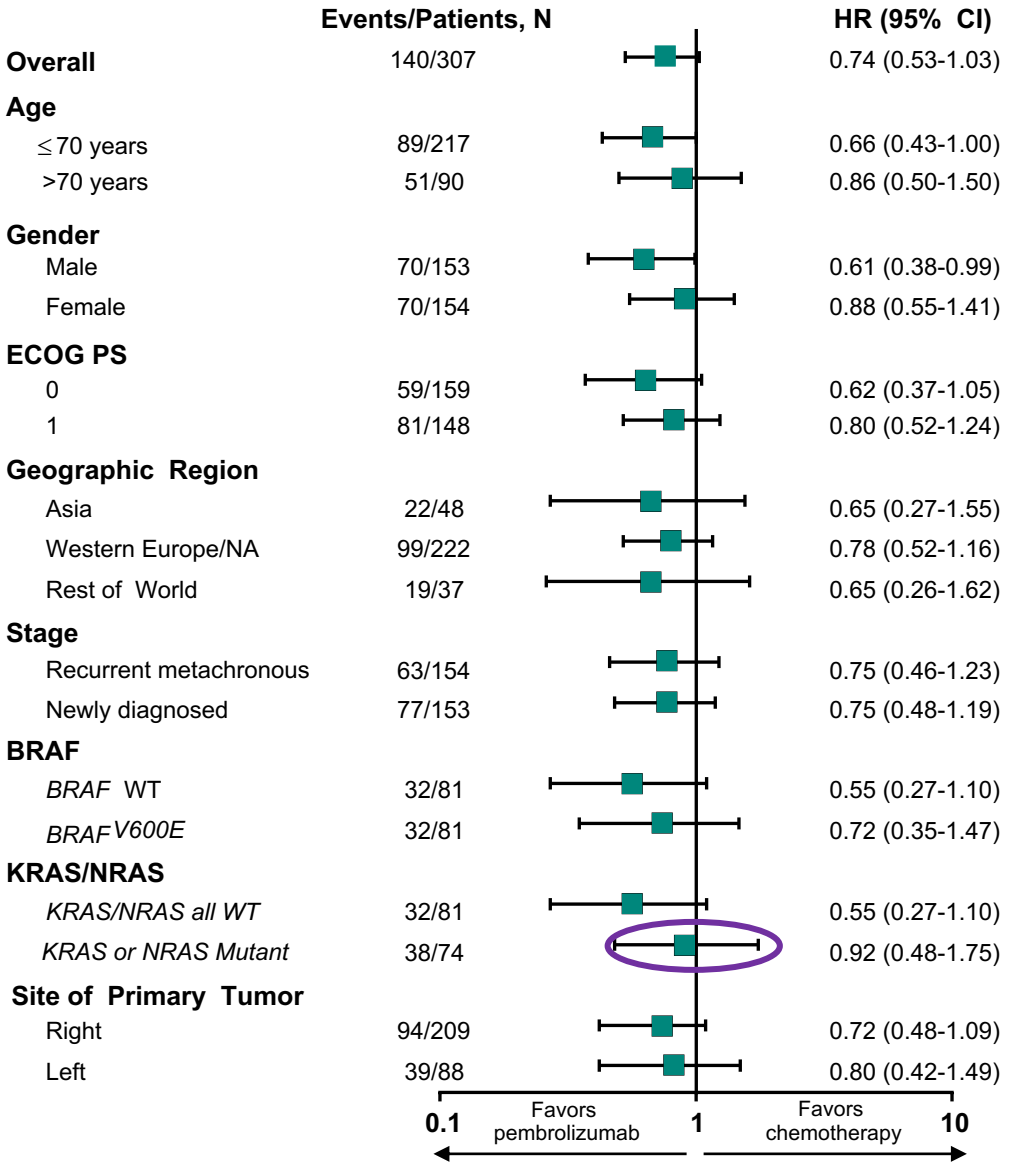
	Events, n (%)	HR (95% CI)	*P*
Pembro	62 (40.5%)	0.74	0.0359[a]
Chemo	78 (50.6%)	(0.53-1.03)	



[a]**Pembrolizumab was not superior to chemotherapy for OS as one-sided α > 0.0246. Pre-specified sensitivity analyses to adjust for crossover effect by rank-preserving structure failure time model and inverse probability of censoring weighting showed OS HRs of 0.66 (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38).** Data cut-off: 19Feb2021.

Andre et al; NEJM 2020

OS in Key Subgroups



Andre et al; NEJM 2020

Summary and Conclusions (1)

- Pembrolizumab versus chemotherapy provided statistically superior PFS as first-line therapy for patients with MSI-H mCRC
  - Pembrolizumab versus chemotherapy met the criteria for superiority in PFS at IA2[1]
  - Superiority was not formally tested at final analysis
- Fewer treatment-related adverse events observed with pembrolizumab versus chemotherapy: grade ≥3 treatment-related events (22% vs 66%)[1]
- Pembrolizumab monotherapy provided clinically meaningful improvements in HRQoL versus chemotherapy in this population[1]
  - Limitations include open label trial and PROs as exploratory end points
  - Results are mostly limited to treatment period in first line
- Treatment with pembrolizumab versus chemotherapy is associated with a non-statistically significant reduction in mortality
  - HR for OS: 0.74 (*P* = 0.0359; did not meet threshold for significance)
  - High crossover rate from chemotherapy to anti-PD-1/PD-L1 therapies in second line of 60%

1. André T et al; *N Eng J Med* 2020;383:2207-18.

CheckMate 142 NIVO3 + IPI1 1L cohort study design

- CheckMate 142 is an ongoing, multicohort, nonrandomized phase 2 trial evaluating the efficacy and safety of NIVO-based therapies in patients with mCRC[a]

- Histologically confirmed metastatic or recurrent CRC
- MSI-H/dMMR per local laboratory
- No prior treatment for metastatic disease

→ NIVO3 Q2W + IPI1 Q6W[b]

Primary endpoint:

- ORR per investigator assessment (RECIST v1.1)

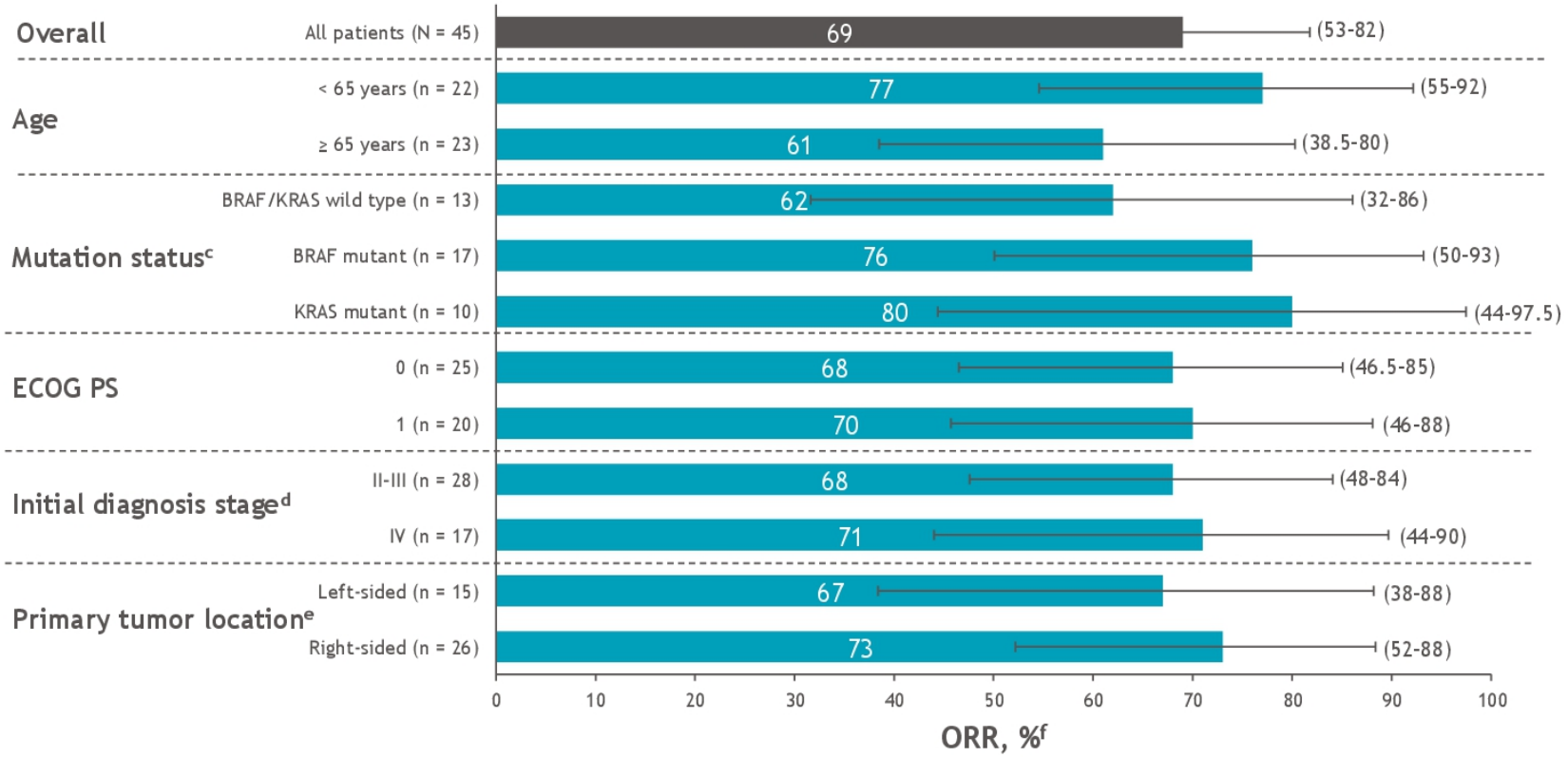
Other key endpoints:

- ORR per BICR, DCR,[c] DOR, PFS, OS, and safety

- At data cutoff (October 2019), the median duration of follow-up was 29.0 months (range, 24.2-33.7)[d]

[a]ClinicalTrials.gov number, NCT02060188. [b]Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end. [c]Patients with CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients. [d]Median follow-up was defined as time from first dose to data cutoff. BICR, blinded independent central review; CR, complete response; CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; NIVO3, nivolumab 3 mg/kg; IPI1, ipilimumab 1 mg/kg; PR, partial response; SD, stable disease.

Objective response rate by subgroup[a,b]



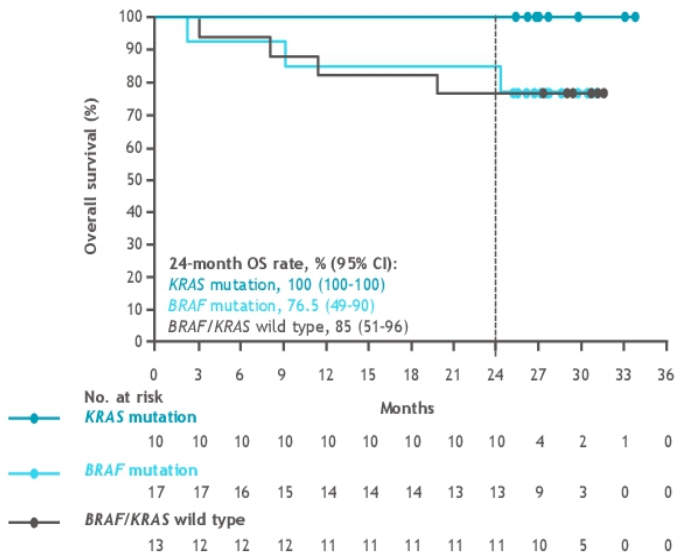
- ORR was generally similar across evaluated subgroups and consistent with that of the overall study population

[a]Median follow-up, 29.0 months. [b]Per investigator assessment. [c]Excluded 5 patients with unknown mutation status. [d]All patients had stage IV disease at study entry. [e]Excluded 4 patients with uncategorized primary tumor location. [f]Error bars and numbers in parentheses indicate 95% CIs; evaluated subgroups had overlapping 95% CIs for ORR.

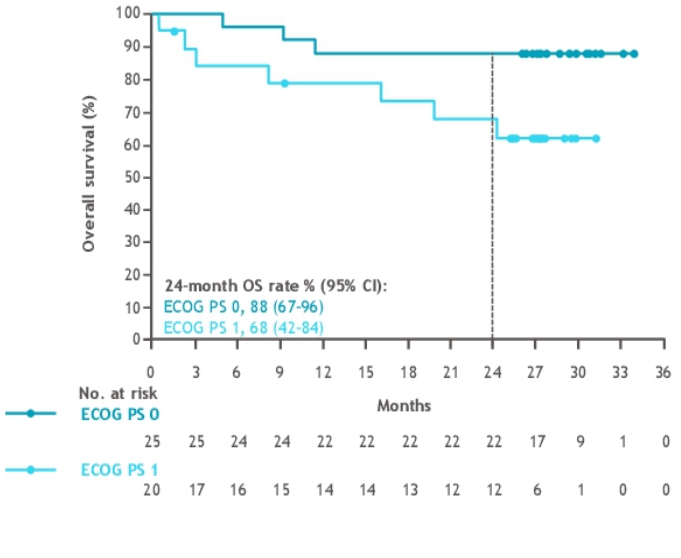
Overall survival by subgroup[a]

- In the overall population, median OS was not reached (95% CI, NE) and the 24-month OS rate was 79% (95% CI, 64.1-88.7)

Mutation status[b]



ECOG PS



OS in other key subgroups

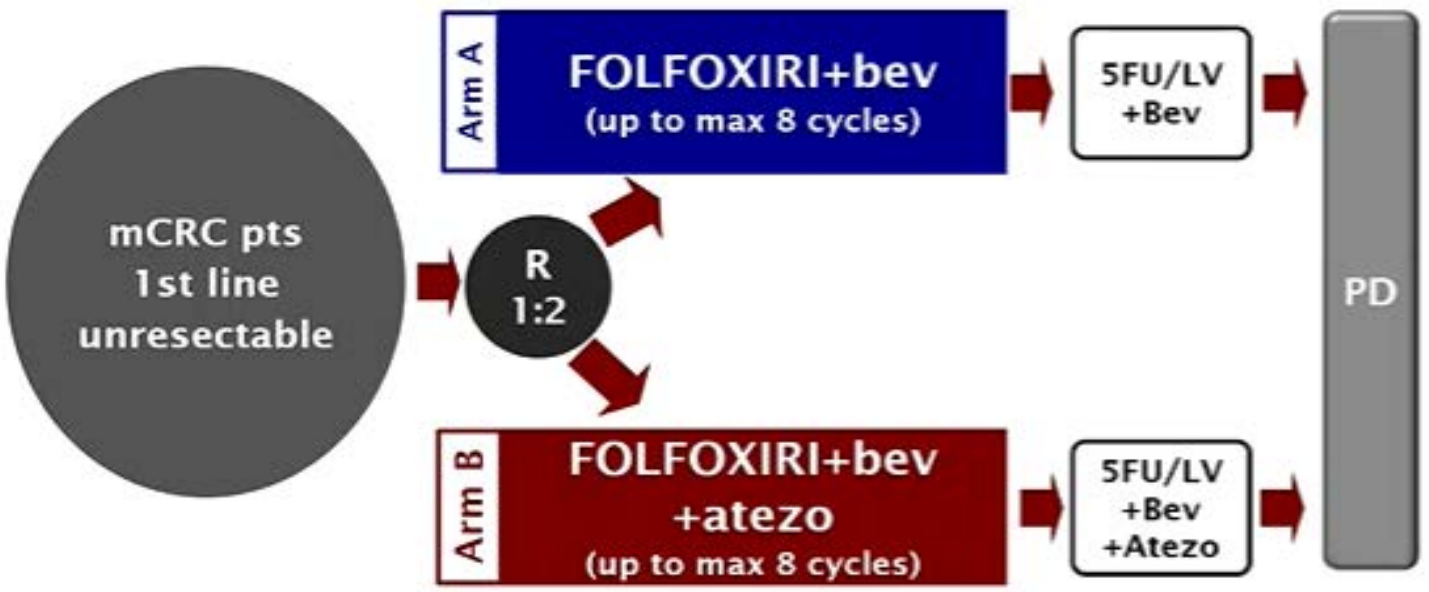
	24-mo rate, % (95% CI)
Age, years	
< 65 (n = 22)	85 (61-95)
≥ 65 (n = 23)	74 (51-87)
Initial diagnosis stage[c]	
II-III (n = 28)	77 (56.5-89)
IV (n = 17)	82 (55-94)
Primary tumor location[d]	
Left-sided (n = 15)	67 (37.5-85)
Right-sided (n = 26)	84 (63-94)

- OS benefit was observed with NIVO3 + IPI1 across all evaluated subgroups and consistent with that of the overall population
- Median OS was not reached in any evaluated subgroup

[a]Median follow-up, 29.0 months. [b]Excluded 5 pts with unknown mutation status. [c]All patients had stage IV disease at study entry. [d]Excluded 4 patients with uncategorized primary tumor location. mo, months; NE, not estimable.

MSI-S Colorectal Cancer

AtezoTRIBE trial



Stratification factors:

- Center
- PS 0 vs 1-2;
- primary tumor location (right vs left or rectum);
- Previous adjuvant CT

Cremolini et al, ESMO, 2021

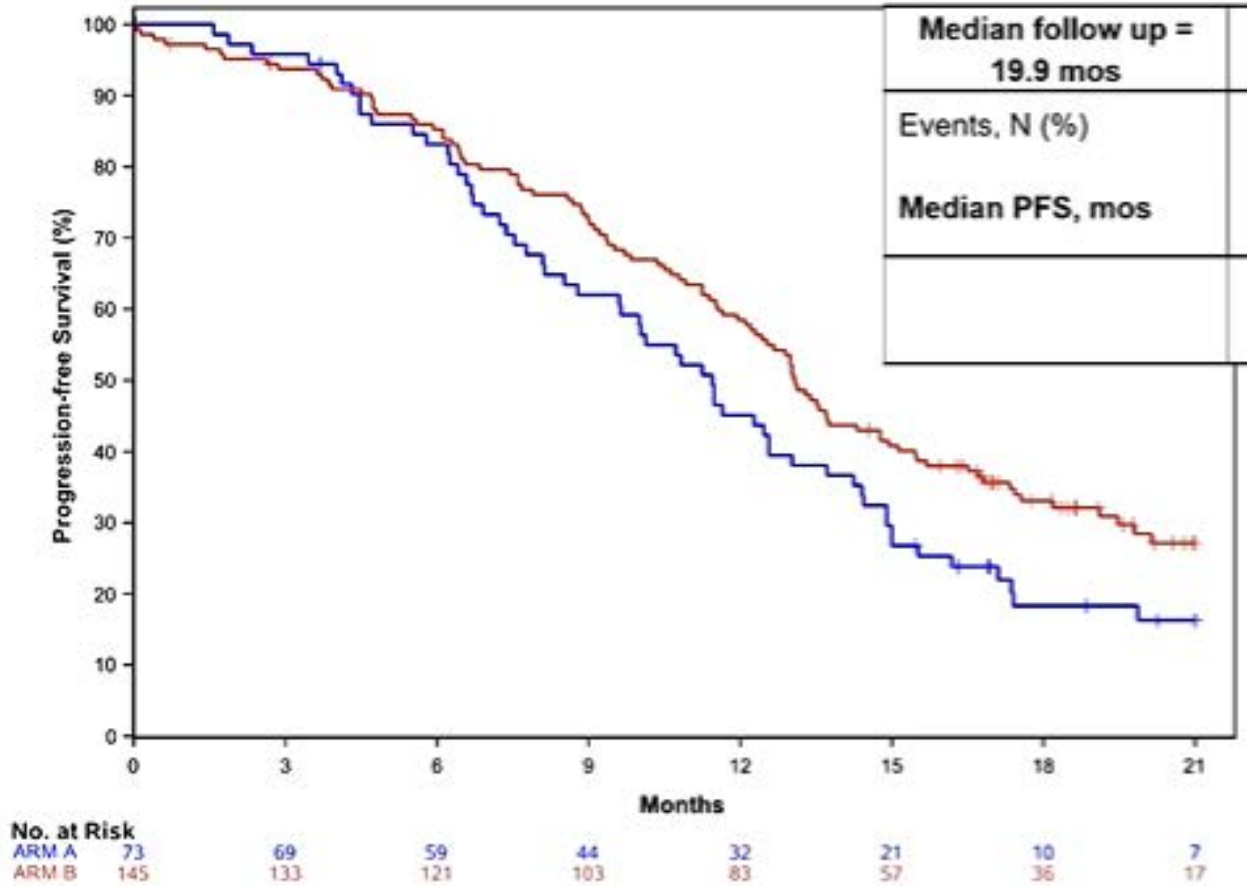
Patients' characteristics – ITT population

Characteristic, % patients	N=218 FOLFOXIRI/Bev N = 73	 FOLFOXIRI/Bev/Atezo N = 145
Gender (M / F)	58 / 42	57 / 43
Median Age (range)	61 (20 – 74)	60 (35 – 75)
ECOG PS (0 / 1-2)	84 / 16	85 / 15
Synchronous Metastases (Y / N)	89 / 11	86 / 14
Prior Adjuvant CT (Y / N)	5 / 95	3 / 97
Number Metastatic Sites (1 / >1)	38 / 62	43 / 57
Liver Only Disease (Y / N)	27 / 78	27 / 78
Primary Tumor Side (right / left)	44 / 56	44 / 56
RAS/BRAF (*RAS* mut / *BRAF* mut / wt / NE)	71 / 14 / 15 / 0	73 / 8 / 16 / 3
Right AND/OR *RAS* mut	75	82
MMR status (pMMR / dMMR*/ NE)	92 / 7 / 1	91 / 6 / 4

* Local evaluation by IHC

Cremolini et al, ESMO, 2021

Primary endpoint: Progression Free Survival



Median follow up = 19.9 mos	FOLFOXIRI/Bev N = 73	FOLFOXIRI/Bev/Atezo N = 145
Events, N (%)	60 (82%)	99 (68%)
Median PFS, mos	11.5	13.1
	HR = 0.69 [80% CI: 0.56-0.85] p=0.012	

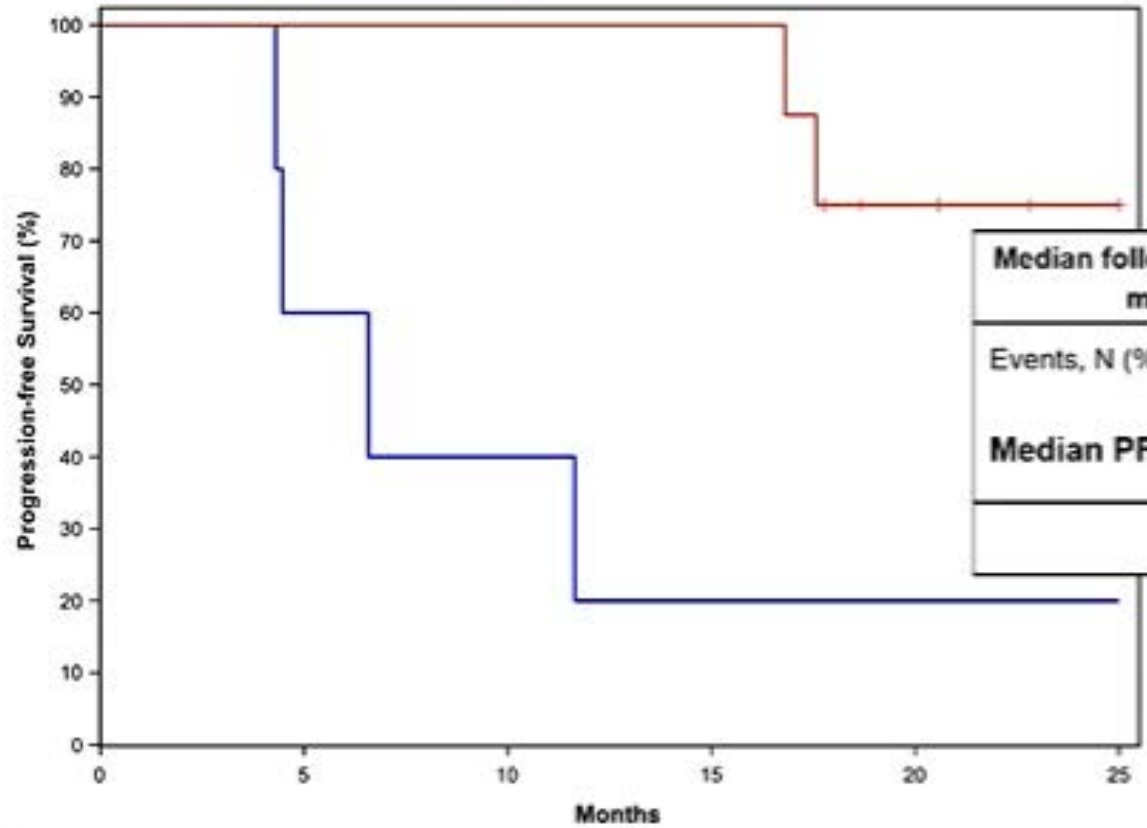
Cremolini et al, ESMO, 2021

Response and Resection Rate

	FOLFOXIRI/Bev N = 73	FOLFOXIRI/Bev/Atezo N = 145	OR [80%CI], p
Complete Response	6%	6%	
Partial Response	59%	53%	
Response Rate	**64%**	**59%**	**0.78 [0.54-1.15], p=0.412**
Stable disease	29%	33%	
Progressive Disease	4%	3%	
Not Assessed	3%	6%	
R0 Resection Rate	**37%**	**26%**	**p=0.175**

Cremolini et al, ESMO, 2021

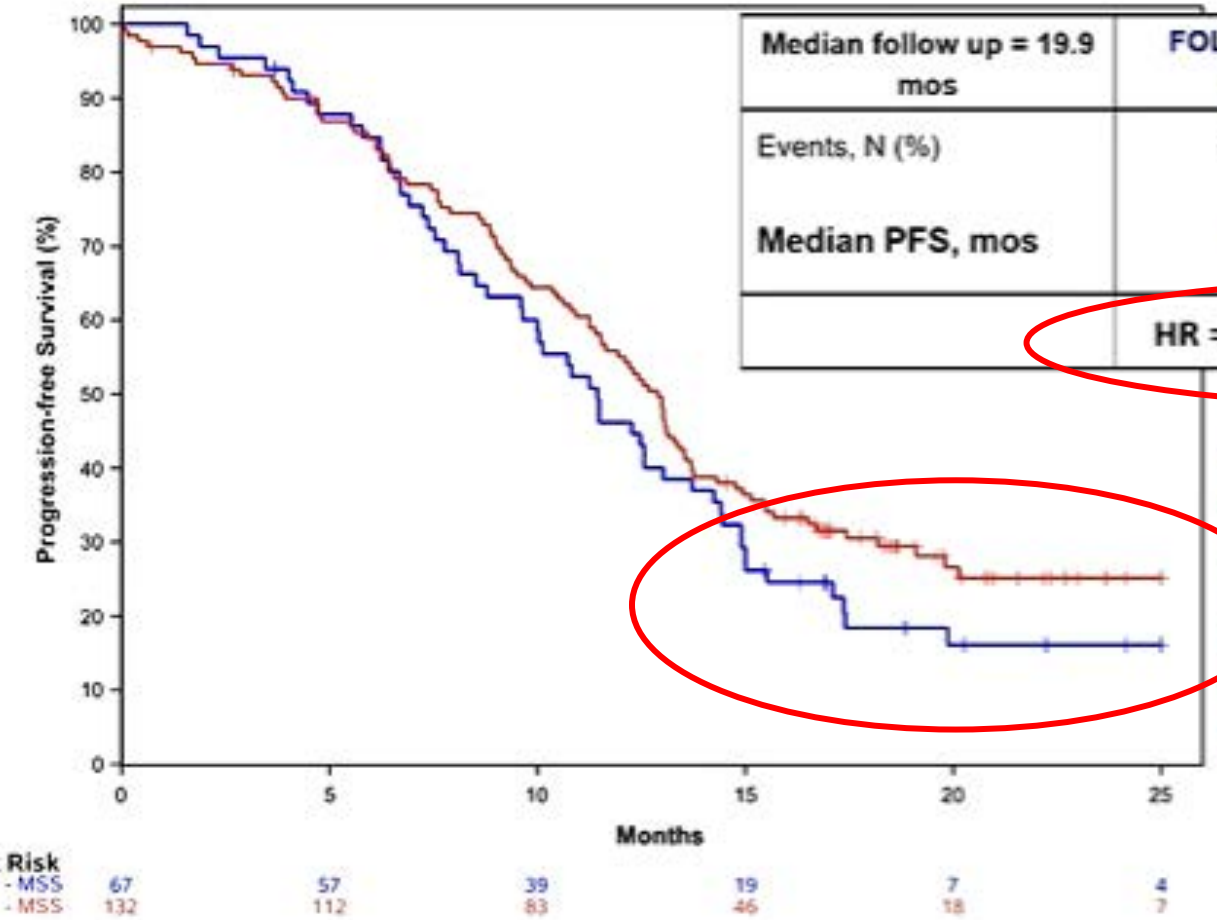
Focus on the dMMR subgroup



Median follow up = 20.6 mos	FOLFOXIRI/Bev N = 5	FOLFOXIRI/Bev/Atezo N = 8
Events, N (%)	5 (100%)	2 (25%)
Median PFS, mos	**6.6**	**NR**
	HR = 0.11 [80% CI: 0.04-0.35] p=0.002	

No. at Risk						
ARM A - MSI-H	5	3	2	1	1	1
ARM B - MSI-H	8	8	8	8	4	2

Focus on the pMMR subgroup



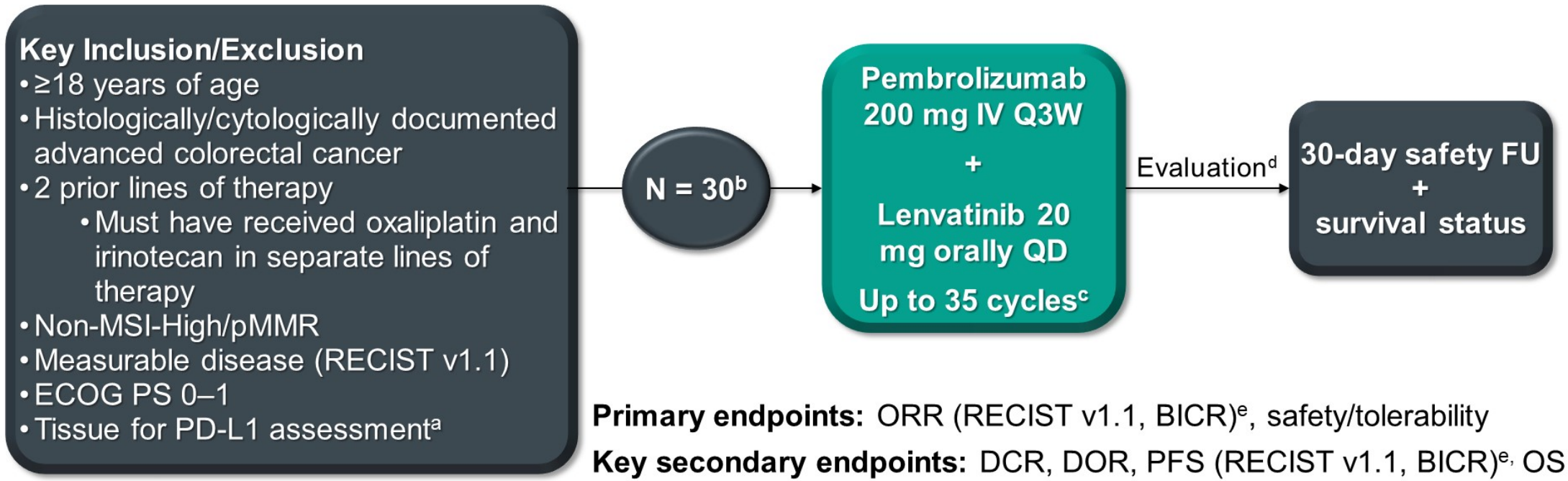
Median follow up = 19.9 mos	FOLFOXIRI/Bev N = 67	FOLFOXIRI/Bev/Atezo N = 132
Events, N (%)	54 (81%)	93 (25%)
Median PFS, mos	**11.4**	**12.9**
	HR = 0.78 [80% CI: 0.62-0.97] p=0.071	

To detect a HR for PFS of 0.66 in favour of arm B

1-sided alpha-error= 0.10; beta-error=0.15
129 events required

Cremolini et al, ESMO, 2021

LEAP-005 (NCT03797326)
Colorectal Cancer Cohort



Primary endpoints: ORR (RECIST v1.1, BICR)[e], safety/tolerability

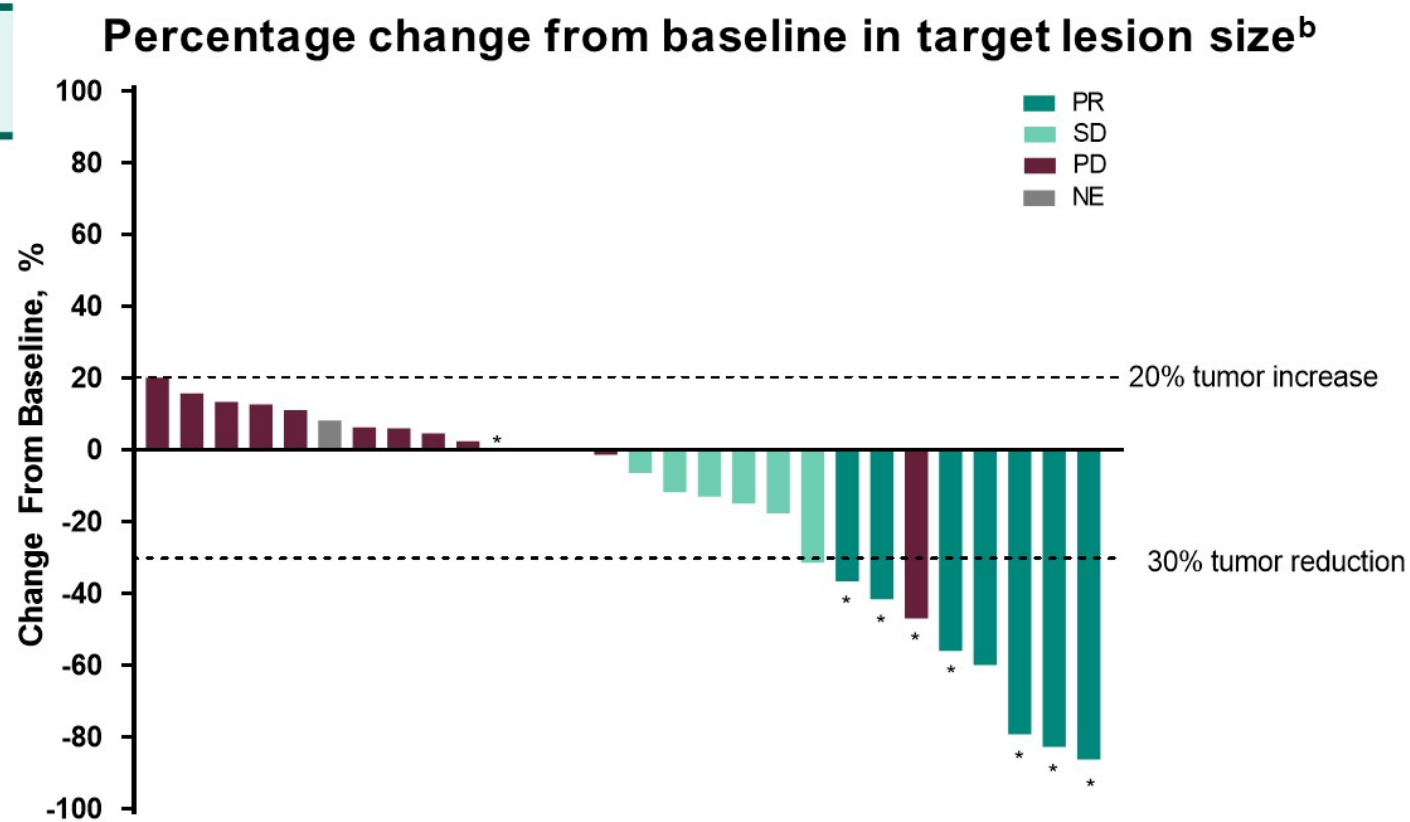
Key secondary endpoints: DCR, DOR, PFS (RECIST v1.1, BICR)[e], OS

Response assessed Q9W until week 54; then Q12W until week 102; then Q24W thereafter

BICR blinded independent central review; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; FU, follow-up; IV, intravenous; MSI, microsatellite instability; OS, overall survival; PFS, progression-free survival; pMMR, proficient mismatch repair; QD, every day; QXW, every X weeks. [a]PD-L1 status assessed centrally using PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA). [b]Initial planned enrollment per cohort; current enrollment, n = 32. [c]With investigator and sponsor approval, patients with disease progression before completing 35 cycles could remain on treatment if they were experiencing clinical benefit without intolerable toxicity; patients experiencing clinical benefit could continue lenvatinib treatment beyond 35 cycles. [d]In interim analysis, if adequate ORR determined, cohort expansion to 100 patients. [e]Response assessed per RECIST v1.1 or iRECIST.

Antitumor Activity
(Confirmed Objective Responses, RECIST v1.1 by BICR)

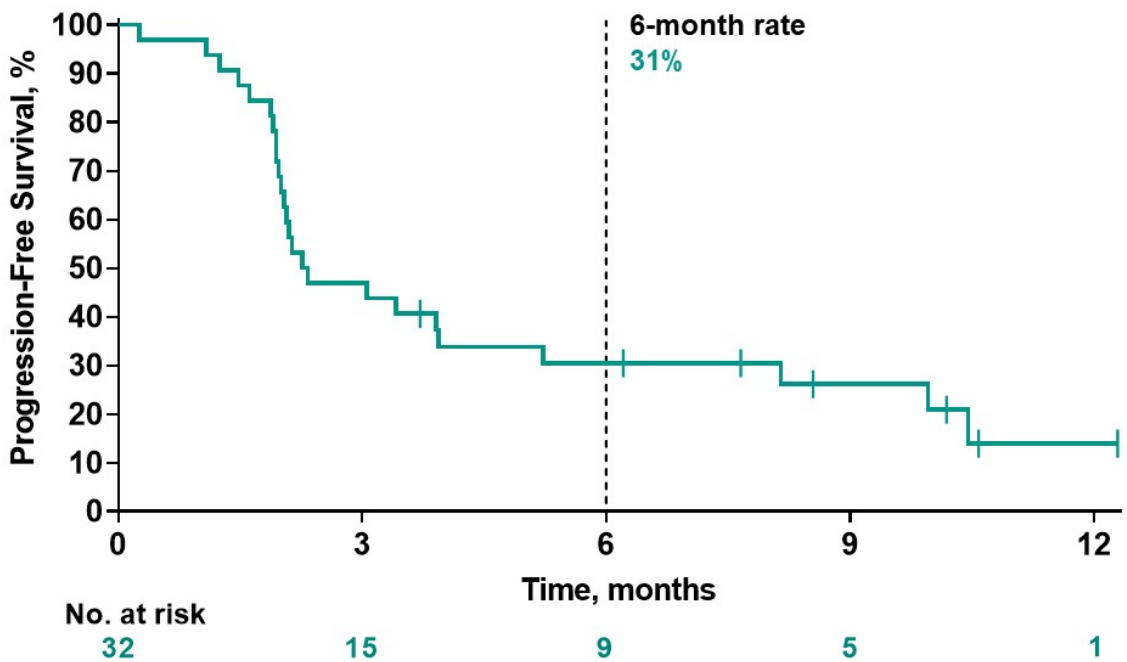
	N = 32
ORR, % (95% CI)	22 (9–40)
DCR,[a] % (95% CI)	47 (29–65)
Best overall response, n (%)	
CR	0
PR	7 (22)[b]
SD	8 (25)
PD	12 (38)
Non-evaluable[c]	1 (3)
No assessment[d]	4 (13)
DOR, median (range), mo	NR (2.1+ to 10.4+)



CI, confidence interval; CR, complete response; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Defined as best overall response of CR, PR or SD. [b]All responders had a PD-L1 CPS score ≥1. [c]Patient had post-baseline imaging and the best overall response was determined to be non-evaluable per RECIST version 1.1. [d]Patient had no post-baseline imaging. *Patient with treatment ongoing.
Data cutoff date: April 10, 2020.

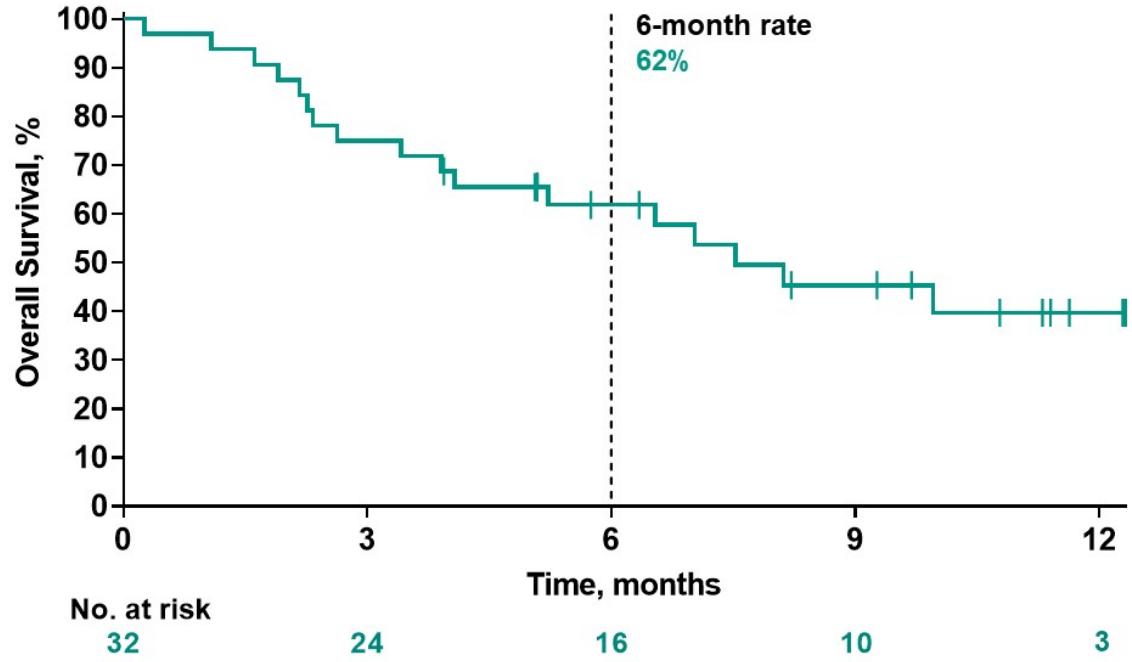
Progression-Free Survival and Overall Survival

Progression-Free Survival[a]



Median (95% CI): 2.3 (2.0–5.2) months

Overall Survival



Median (95% CI): 7.5 (3.9–NR) months

NR, not reached. [a]PFS per RECIST version 1.1 by BICR.
Data cutoff date: April 10, 2020.

MSI-S Colorectal Cancer: Ongoing Trials

Examples of Ongoing Phase I/II Clinical Trials

Study	Phase	N	Eligibility	Model	Treatment Arms	End Points
CheckMate 9N9: NCT03377361	I/II	232	Previously treated Stage IV metastatic colorectal cancer Microsatellite stable status (MSS)	Randomized Parallel	Arm 1: Cohort 1 3rd line: nivolumab + trametinib Arm 1A: Cohort 2 2nd line: nivolumab + ipilimumab + trametinib Arm 1A: Cohort 3 2nd line: nivolumab + ipilimumab + trametinib Arm 1B: Cohort 6 2nd line: nivolumab + ipilimumab + trametinib Arm 2: Cohort 4 3rd line: nivolumab + ipilimumab + trametinib Arm 2: Cohort 5 3rd line: Regorafenib	Dose Limiting Toxicity (DLT), Adverse Events (AE), Serious Adverse Events (SAE), Deaths, Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DOR), Progression-free Survival (PFS), Overall Survival (OS)
Rego/Nivo/Ipi NCT04362839	I	32	Previously treated advanced metastatic or progressive mismatch protenin proficient (pMMR)/MSS adenocarcinoma of colon or rectum; Stage III-Stage IVC Evidence of progression on or after last treatment Known extended RAS and BRAF status	Single Arm	Arm 1: regorafenib PO QD on days 1-21 + nivolumab IV over 30 minutes Q2W, + ipilimumab IV over 30 minutes Q6W Cycles repeat every 28 day for up to 2 years in the absence of disease progression or unacceptable toxicity	DLT, SAE, PFS, DOR, OS, ORR
Cabo/Nivo NCT04963283	II	46	Metastatic or unresectable colorectal adenocarcinoma MSS, microsatellite-low (MSI-L) or have pMMR Known extended RAS and BRAF status	Single Arm	Arm 1: Cabozantinib (40 mg) orally daily + nivolumab (480 mg) IV every 28 days	DCR, ORR, PFS, OS, Safety and Tolerability

NCT04776148: Phase III Lenvatinib (MK-7902/E7080) in Combination With Pembrolizumab (MK-3475) Versus Standard of Care in Participants With Metastatic Colorectal Cancer (MK-7902-017/E7080-G000-325/LEAP-017)

Eligibility:
Unresectable and metastatic colorectal adenocarcinoma

Previously treated with disease progression ***or*** could not tolerate standard treatment

Must **NOT** be microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) by local testing

No presence of malabsorption or other gastrointestinal conditions

Accrual Goal
N = 434

RANDOMIZATION

Arm A: Lenvatinib + pembrolizumab

Pembrolizumab (400 mg) IV on Day 1 of each 6-week cylce
Repeat cycle for up to 18 cycles (approximately 2 years)
+
Lenvatinib (20 mg) oral capsule once daily until progressive disease

Arm B: Standard of care treatment

Regorafenib (160 mg) oral tablet once daily on Days 1 - 21 of each 4-week cycle

or

TAS-102 (trifluridine and tipiracil hydrochloride) (35 mg/m^2) oral tablet twice daily on Day 1-5 + Day 8-12 of each 4-week cycle

FOLLOW-UP

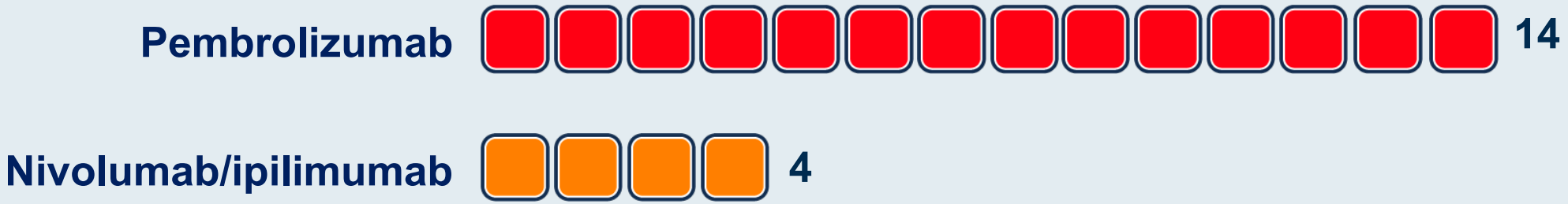
Primary Endpoint:
Overall Survival (OS)

Secondary Endpoints:
Progression Free Survival (PFS), Objective Response Rate (ORR), and Serious Adverse Events (SAE)

Closing Points

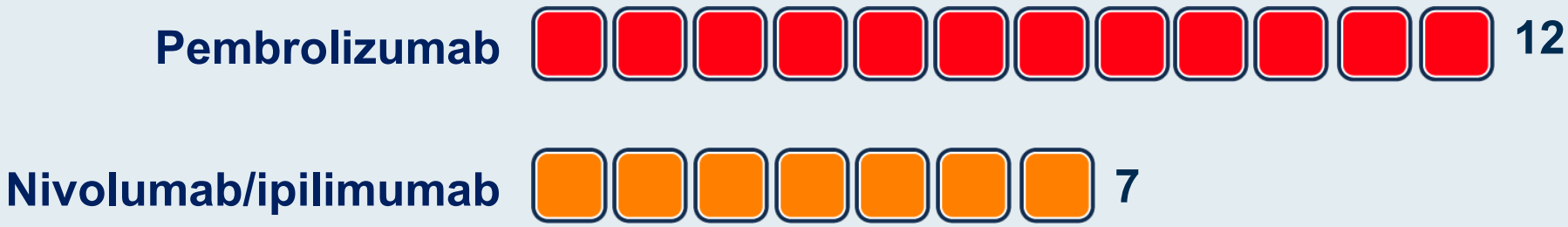
- The role of IO therapy is established in MSI-H/dMMR patients
  - But 1/3 of pts will not respond to IO therapy:
    - Etiology remains unknown and is continues to be evaluated
- MSI-S/pMMR patients historically do not benefit from IO therapy
  - Many trials are underway to evaluate the benefit of IO therapy in combination
- Always enroll to a clinical trial whenever possible!

What is your usual first-line treatment recommendation for a clinically stable 60-year-old patient with left-sided, pan-RAS wild-type, BRAF wild-type, microsatellite instability (MSI)-high mCRC?



Survey of US-based clinical investigators

What is your usual second-line treatment recommendation for a patient with left-sided, pan-RAS wild-type, MSI-high mCRC who responds to first-line FOLFOX/bevacizumab and experiences disease progression after receiving 9 months of maintenance bevacizumab?



Survey of US-based clinical investigators

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

Survey of US-based clinical investigators

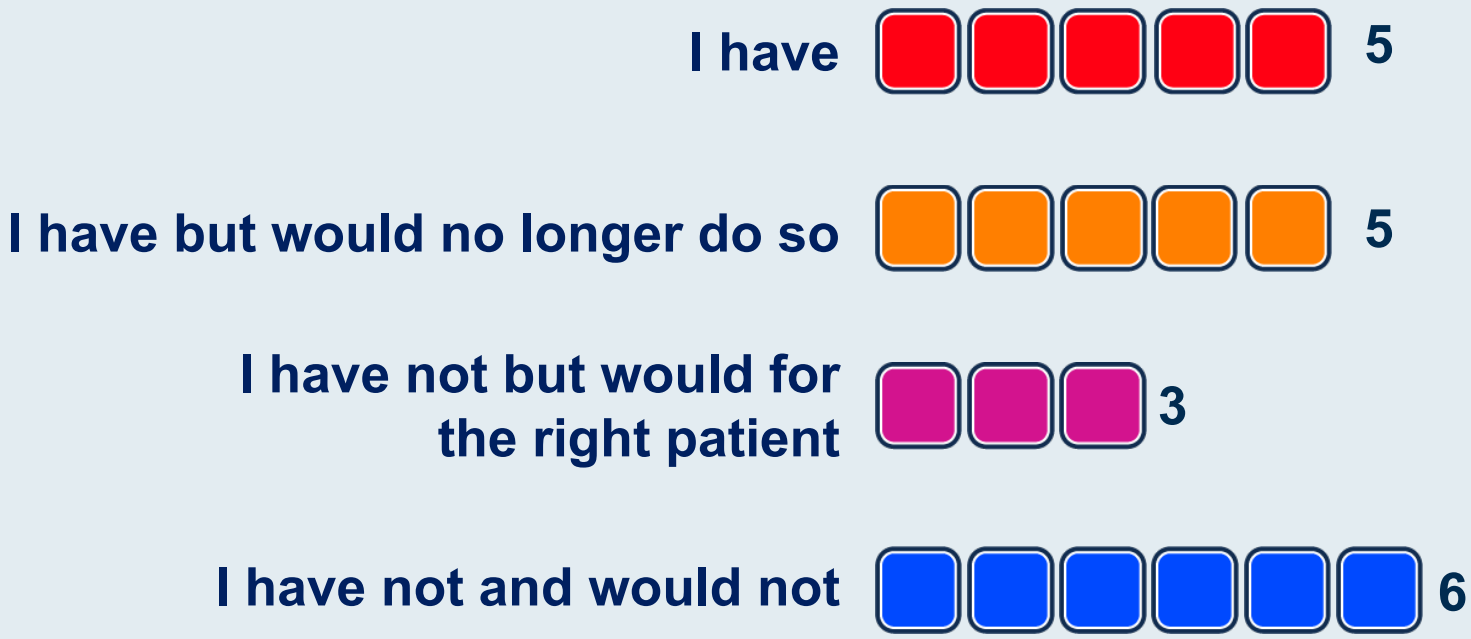
How would you generally sequence HER2-targeted therapy and immunotherapy for a patient with HER2-positive, MSI-high mCRC?

Survey of US-based clinical investigators

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

Survey of US-based clinical investigators

Have you administered or would you administer an immune checkpoint inhibitor to a patient with MSS mCRC outside of a clinical trial?



Survey of US-based clinical investigators

MODULE 3: Selection and Sequencing of Therapy for Patients with Multiregimen-Refractory mCRC — Dr Ciombor

Selection and Sequencing of Therapy for Patients with Multiregimen-Refractory mCRC

Kristen K. Ciombor, MD, MSCI

Vanderbilt-Ingram Cancer Center

January 19, 2022

VANDERBILT UNIVERSITY
MEDICAL CENTER

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

Table 4: Drivers for first-line treatment

many are also valid in later line

Tumour characteristics	Patient characteristics	Treatment characteristics
Clinical presentation:		
Tumour burden	Age	Toxicity profile
Tumour localisation		
Tumour biology	Performance status	Flexibility of treatment administration
RAS mutation status	Organ function	Socio-economic factors
BRAF mutation status	Comorbidities, patient attitude, expectation and preference	Quality of life

Patient and treatment characteristics become even more relevant in later lines

Van Cutsem E, Cervantes A, Arnold D et al, ESMO Consensus 2016 Ann Oncol, July 2016

Anti-EGFR Rechallenge Therapy

- Resistance to anti-EGFR mAbs in RAS wild-type mCRC develops over time
- Emergence of resistant clones:
  - KRAS/NRAS mutant, ERBB2 amp, MET amp, EGFR ectodomain, and others[1-2]
- Without selective pressure from EGFR inhibition, these clones can decay[3]
- Rechallenge with anti-EGFR therapy after prior progression can be effective[4-5]
- How can patients be optimally selected for anti-EGFR rechallenge?

[1]Diaz, *Nature* 2012; [2]Siravegna, *Nat Med* 2015; [3]Parseghian, *Ann Onc* 2019; [4]Santini, *Ann Onc* 2012; [5]Cremolini, *JAMA Onc* 2018

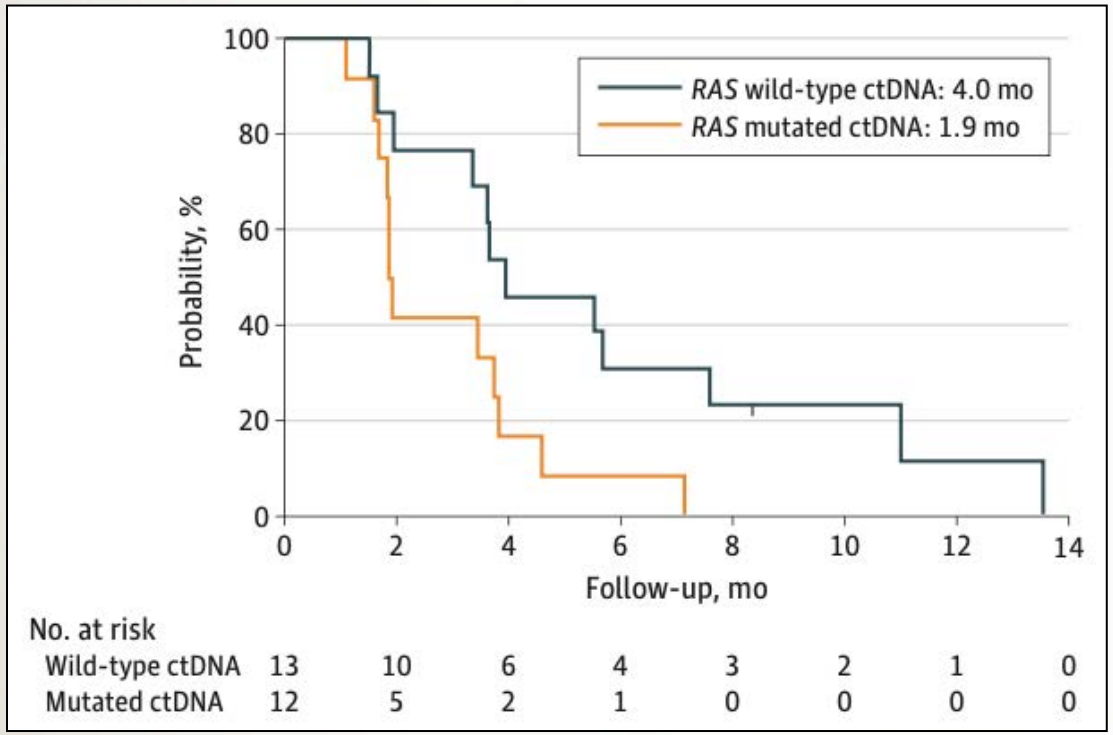
CRICKET: Rechallenge for Pts with *RAS* and *BRAF* WT mCRC with Acquired Resistance to 1L Cetuximab and Irinotecan

- Phase II single-arm Italian study, n = 28
- 3L cetuximab + irinotecan in *RAS/RAF* wt mCRC
  - 1L: Cetuximab + irinotecan-based regimen, at least PR, PFS at least 6 mos
  - 2L: Oxaliplatin + bevacizumab-based regimen
- ORR: 21%, DCR 54%
- No *RAS* mutations found in ctDNA samples of pts who achieved confirmed PR

Cremolini C et al. *JAMA Oncol.* 2019;5(3):343-350

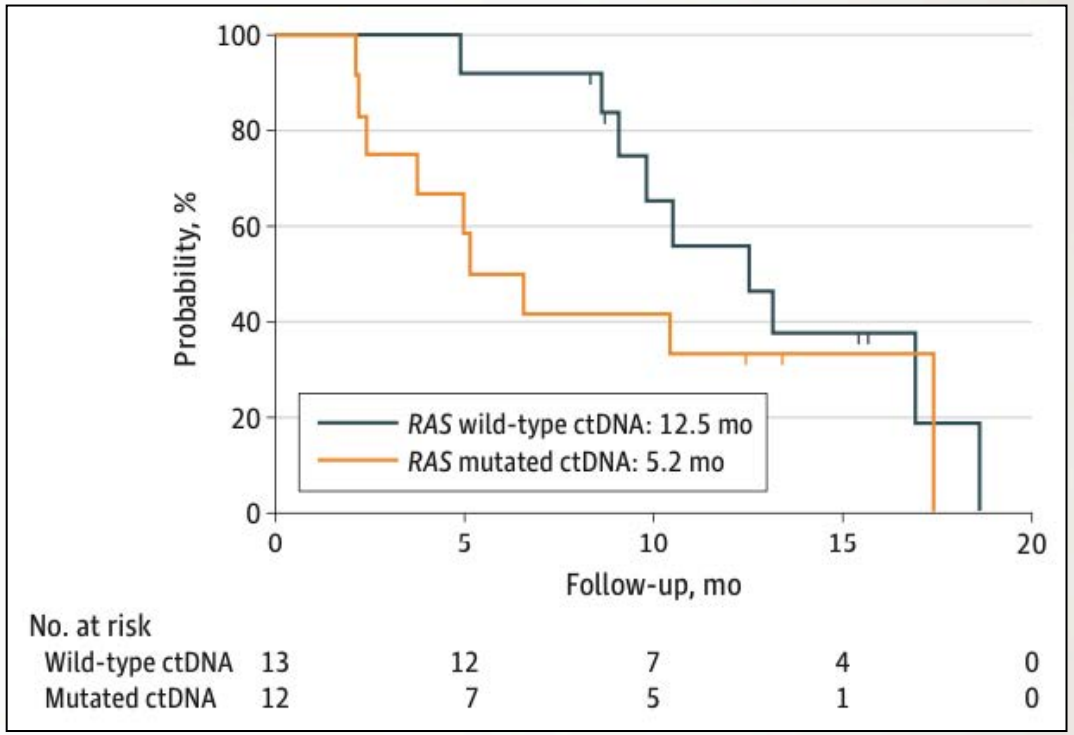
CRICKET Study:
PFS and OS According to *RAS* ctDNA Status

Progression-Free Survival



HR, 0.44 (95% CI, 0.18-0.98; *P* = .03)

Overall Survival



HR, 0.58 (95% CI, 0.22-1.52; *P* = .24)

VANDERBILT UNIVERSITY MEDICAL CENTER

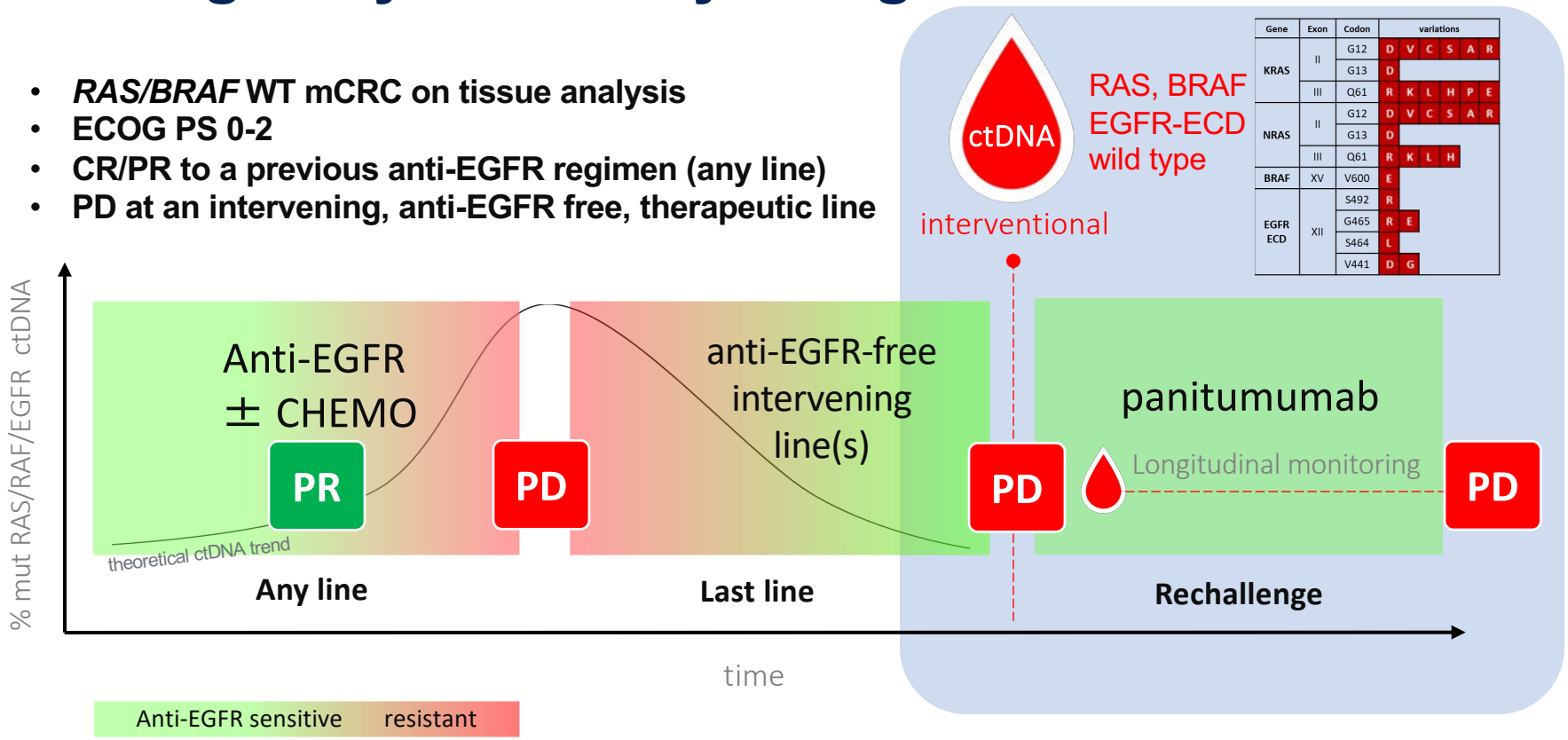
Cremolini C et al. *JAMA Oncol.* 2019;5(3):343-350

CHRONOS

Trial eligibility and study design

- ***RAS/BRAF*** **WT mCRC on tissue analysis**
- **ECOG PS 0-2**
- **CR/PR to a previous anti-EGFR regimen (any line)**
- **PD at an intervening, anti-EGFR free, therapeutic line**

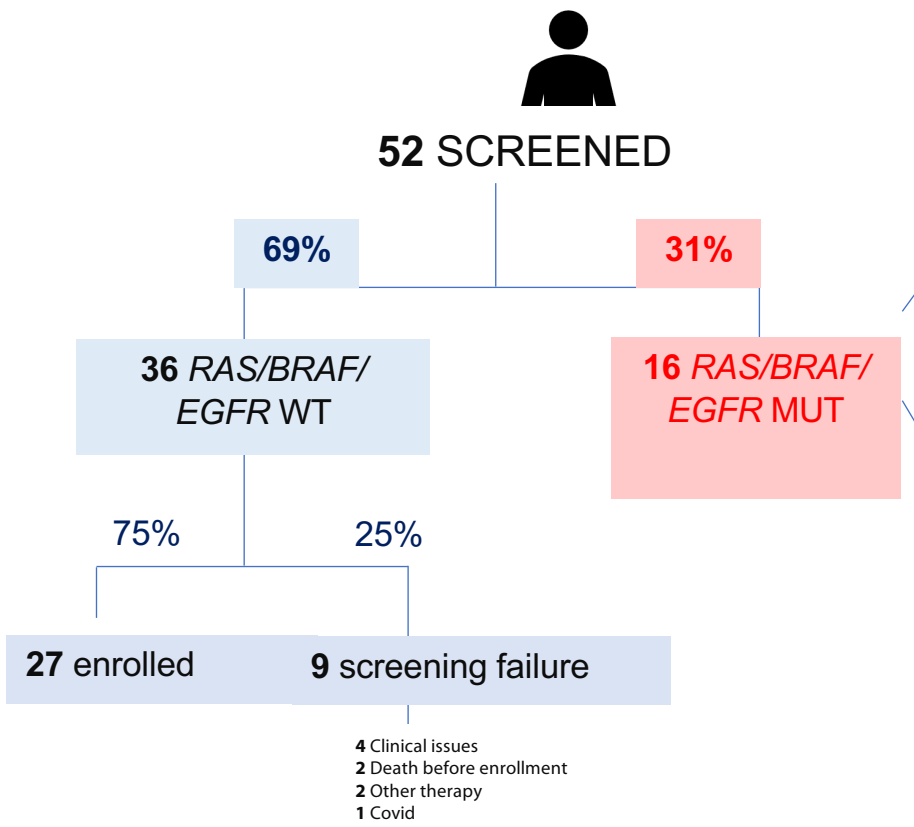
Phase II trial single-stage

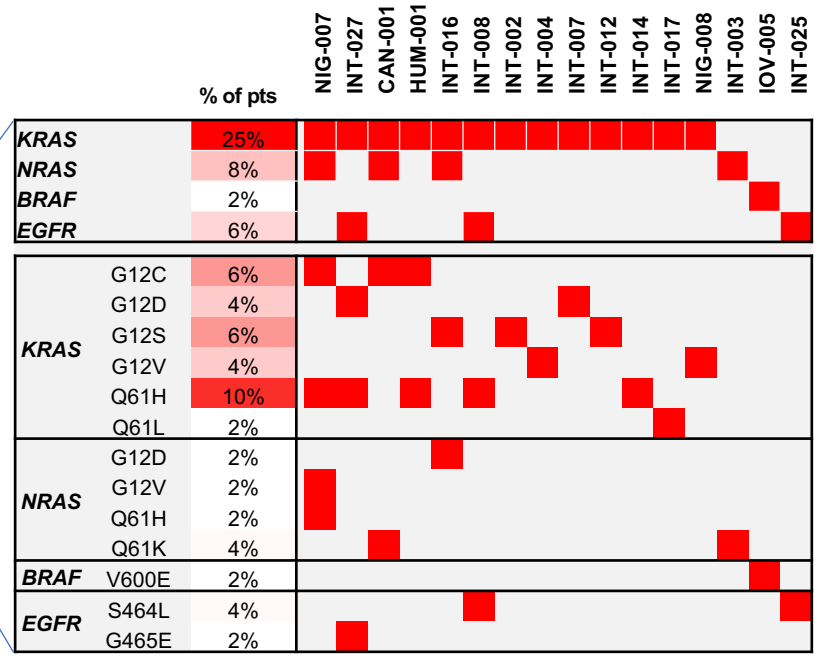


CHRONOS

Molecular screening: results

Liquid biopsy avoids ineffective treatment in 30% of clinically eligible cases



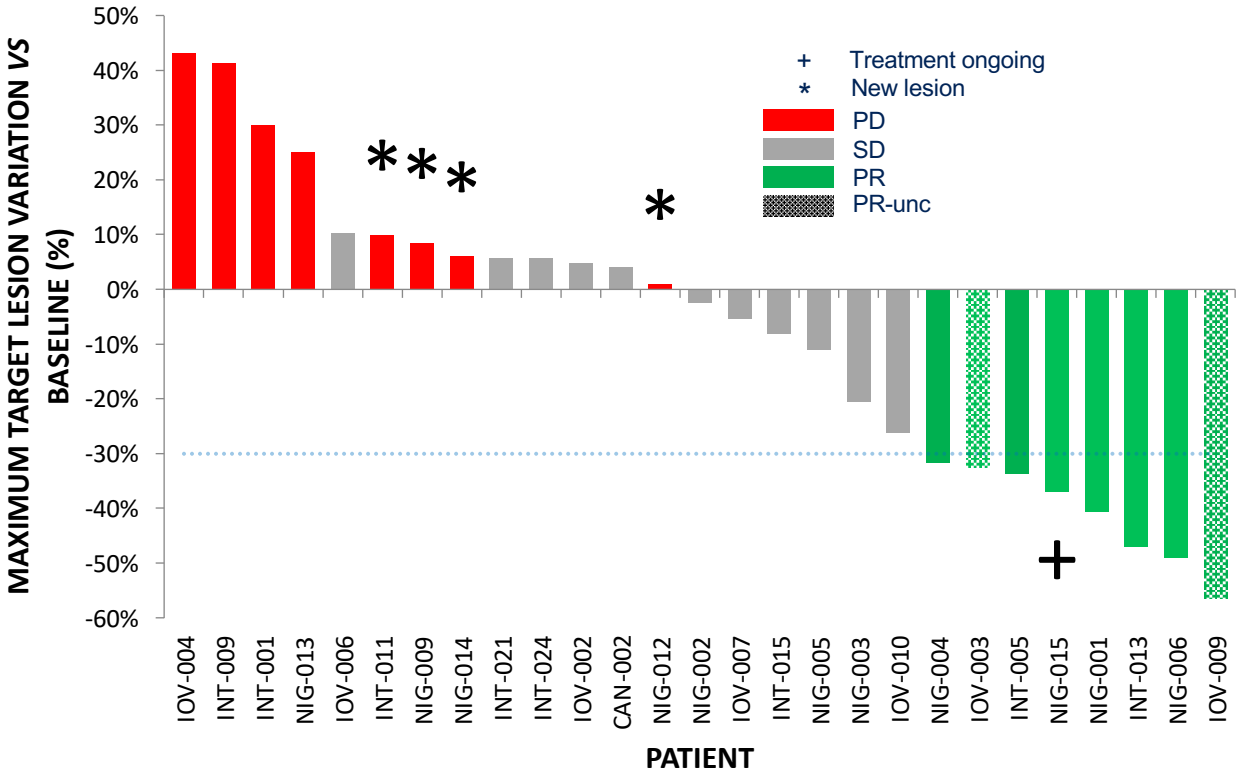


CHRONOS

Objective response rate

Best Response RECIST 1.1 by centralized revision	N	%
Responses (PR+CR)	8	30%
Partial Response	8*	30%
Stable Disease ≥4 mos	9	33%
Stable Disease <4 mos	2	7%
Control of disease (PR+SD≥4 mos)	17	63%
Progressive Disease	8	30%
Total	27	100%

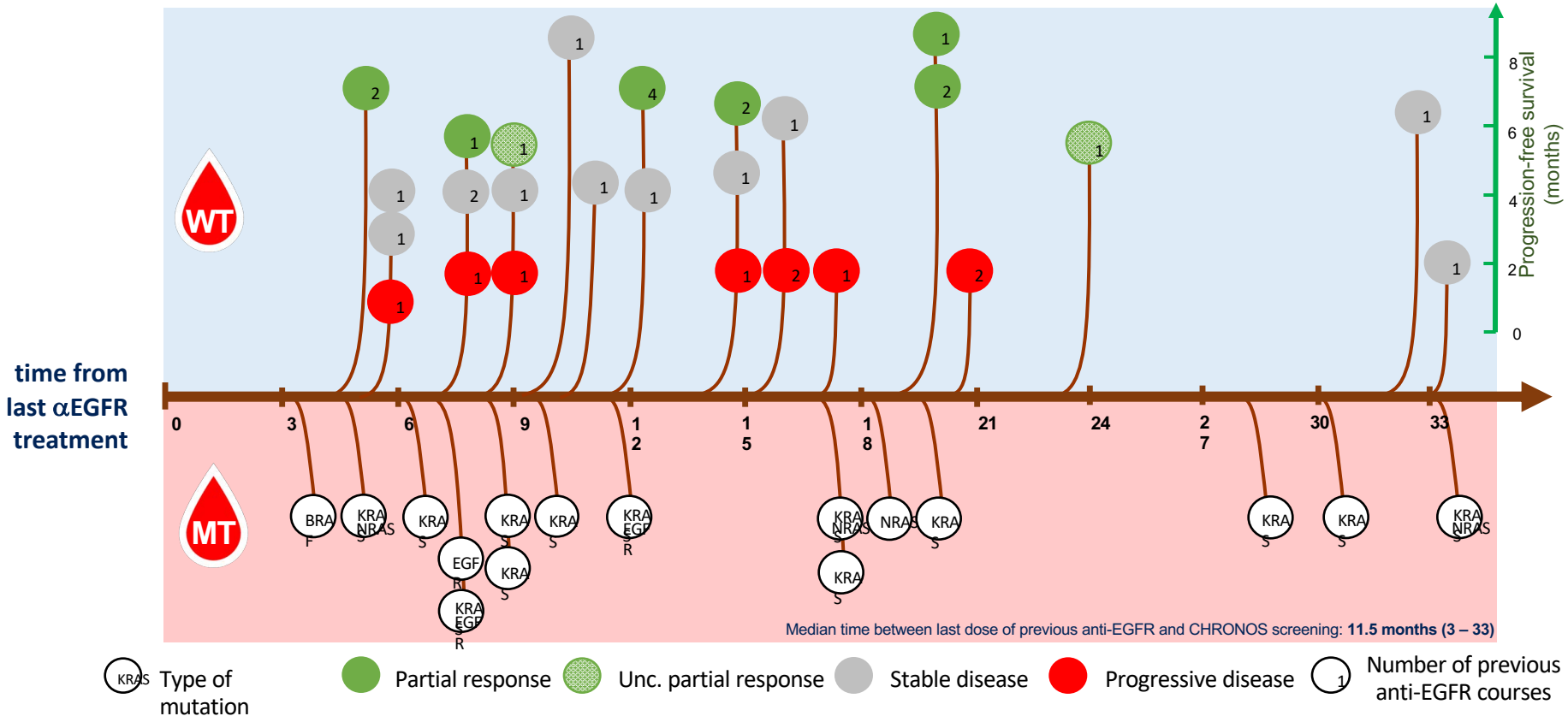
* Two PR were unconfirmed



CHRONOS

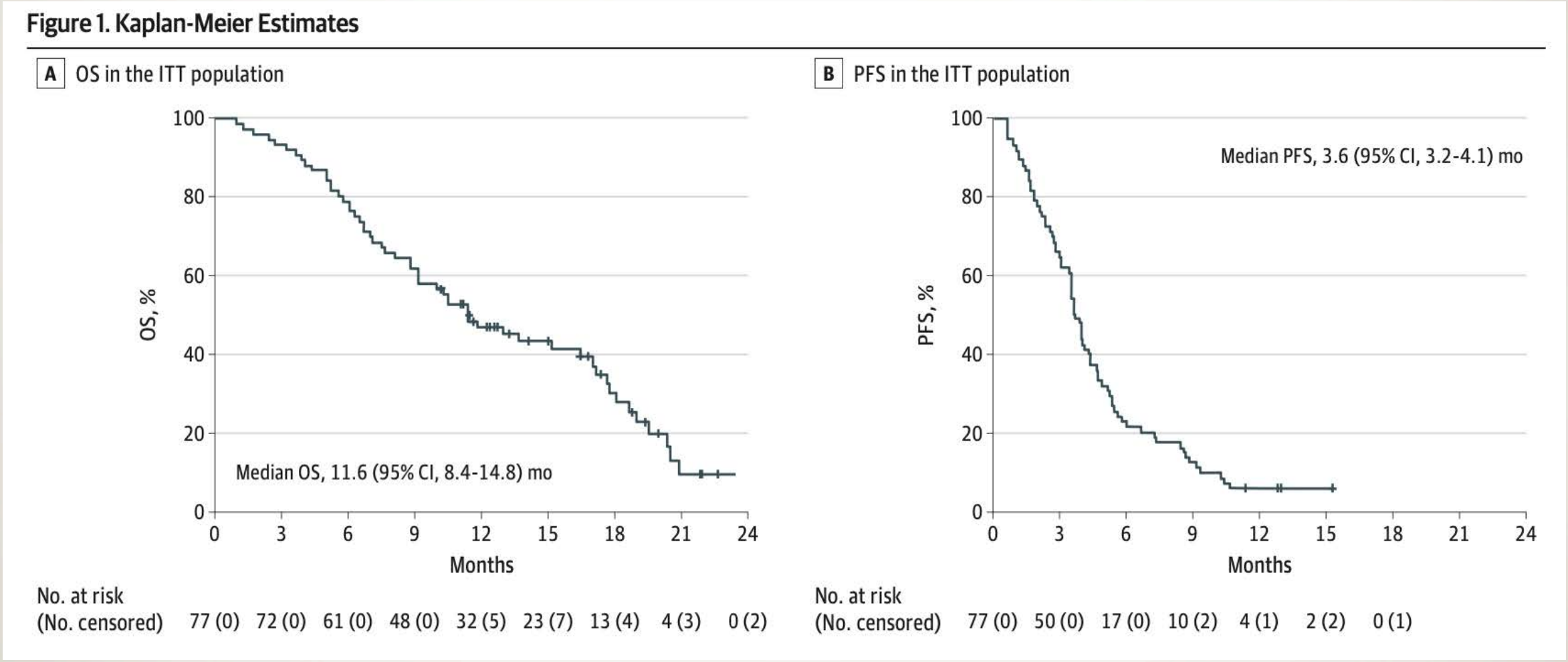
Time after last anti-EGFR and ctDNA *RAS/BRAF/EGFR* status

Presence of resistance-conferring mutations and response are independent of time since last anti-EGFR



CAVE: Phase 2 Cetuximab Rechallenge Plus Avelumab in Pretreated Patients with RAS WT mCRC

Figure 1. Kaplan-Meier Estimates



VANDERBILT UNIVERSITY MEDICAL CENTER

Martinelli E et al. *JAMA Oncol.* 2021

CAVE: Phase 2 Cetuximab Rechallenge Plus Avelumab in Pretreated Patients with RAS WT mCRC

Table. Activity and Efficacy in the Intention-to-Treat Population and in Patients With Plasma Available for ctDNA at Baseline

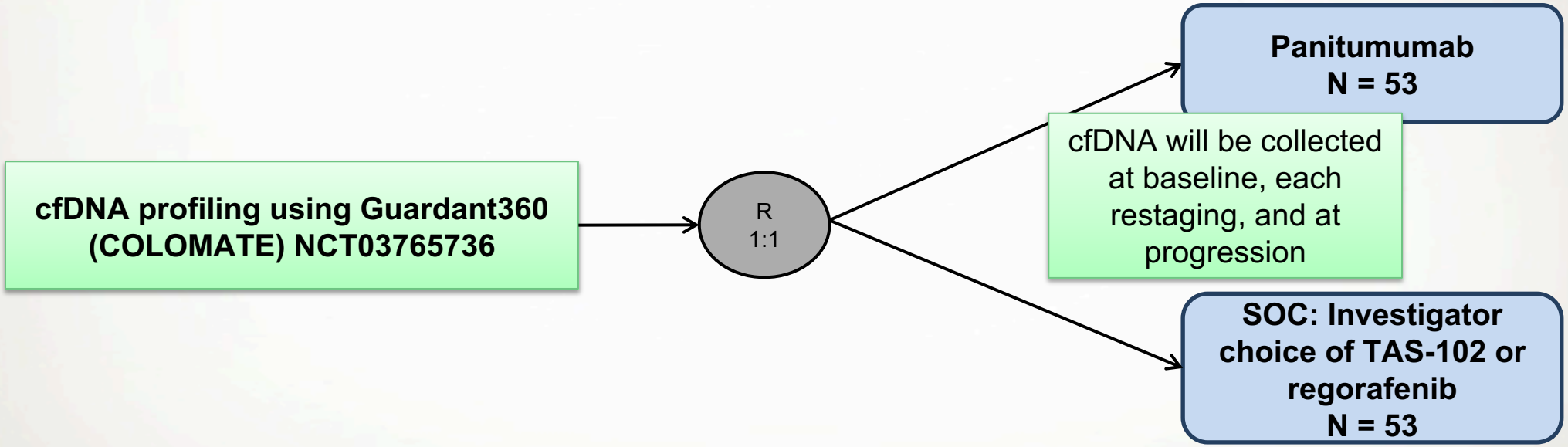
		No. (%) [95% CI]							Median (95% CI), mo	
Variable	No.	CR	PR	ORR	SD	SD >4 mo	PD	DCR	mPFS	mOS
ITT	77	1 (1.3) [0-7]	5 (6.5) [2-14]	6 (7.8) [2.9-16.2]	44 (57.1) [45-68]	28 (36.4) [25.7-48.1]	27 (35) [24-47]	50 (65) [53-75]	3.6 (3.2-4.1)	11.6 (8.4-14.8)
ITT MSS	71	1 (1.4) [0-7.6]	5 (7) [2.3-15.7]	6 (8.5) [3.2-17.5]	40 (56.3) [44-68.1]	24 (33.8) [23-46]	25 (35.2) [24.2-47.5]	46 (64.8) [52.2-75.8]	3.6 (3.3-3.9)	11.6 (8.3-15.0)
Basal ctDNA cohort	67	1 (1.5) [0-8]	4 (6.0) [1.7-14.6]	5 (7.5) [2.5-16.6]	39 (58.0) [45.5-70.2]	25 (37.3) [25.8-50]	23 (34.3) [23.2-46.9]	44 (65.7) [53.1-76.8]	3.9 (3.3-4.5)	13.8 (7.7-19.9)
RAS/BRAF WT	48	1 (2.1) [0.1-11.1]	3 (6.2) [1.3-17.2]	4 (8.3) [2.3-20]	31 (64.6) [49.5-77.8]	21 (43.8) [29.5-58.8]	13 (27.1) [15.3-41.8]	35 (72.9) [58.2-84.7]	4.1 (2.9-5.2)	17.3 (12.5-22)
RAS or BRAF mutant	19	0 (0) [0-17.6]	1 (5.3) [0.1-26]	1 (5.3) [0.1-26]	8 (42.1) [20.3-66.5]	4 (21.1) [6.1-45.6]	10 (52.6) [28.9-75.6]	9 (47.4) [24.4-71.1]	3.0 (2.6-3.5]	10.4 (7.2-13.6)
MSS RAS/BRAF WT	44	1 (2.3) [0.1-12]	3 (6.8) [1.4-18.7]	4 (9.1) [2.5-21.7]	28 (63.6) [47.8-77.6]	18 (40.9) [26.3-56.8]	12 (27.3) [15-42.8]	32 (72.7) [57.2-85]	3.9 (2.8-5)	17.3 (11.2-23.4)

Abbreviations: CR, complete response; ctDNA, circulating tumor DNA; DCR, disease control rate; ITT, intention to treat; mOS, median overall survival; mPFS, median progression free survival; MSS, microsatellite stable; ORR, overall response rate; PD, progression disease; PR, partial response; SD, stable disease; WT, wild type.

VANDERBILT UNIVERSITY MEDICAL CENTER

Martinelli E et al. *JAMA Oncol.* 2021

PULSE: A Randomized, Phase II Open Label Study of PanitUmumab RechaLlenge Versus Standard Therapy after Progression in Patients with Metastatic Colorectal Cancer on Anti-EGFR Therapy (PI: John Strickler)

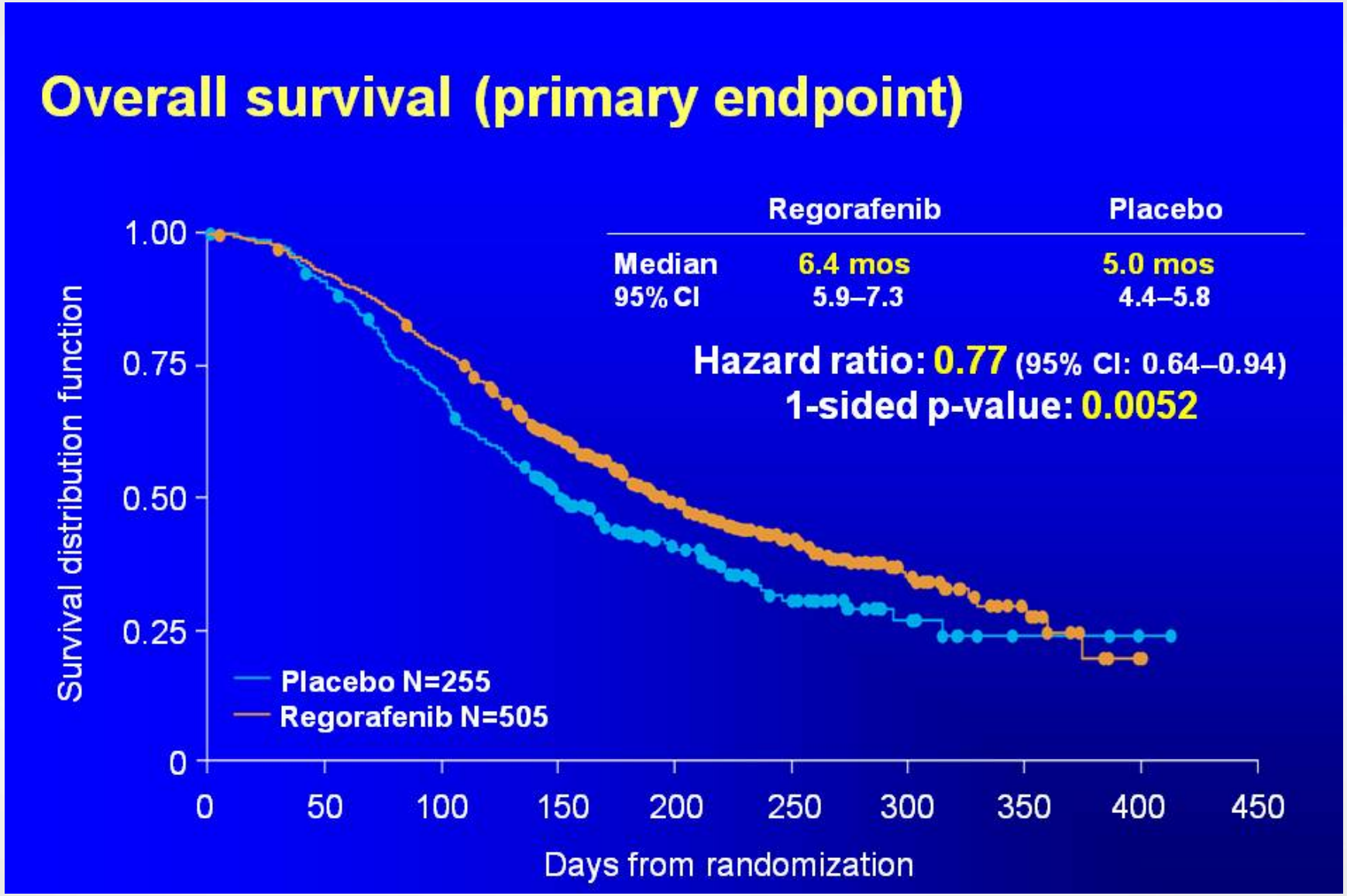


Primary Endpoint: Overall Survival (OS)

VANDERBILT UNIVERSITY MEDICAL CENTER

ACCRU

CORRECT

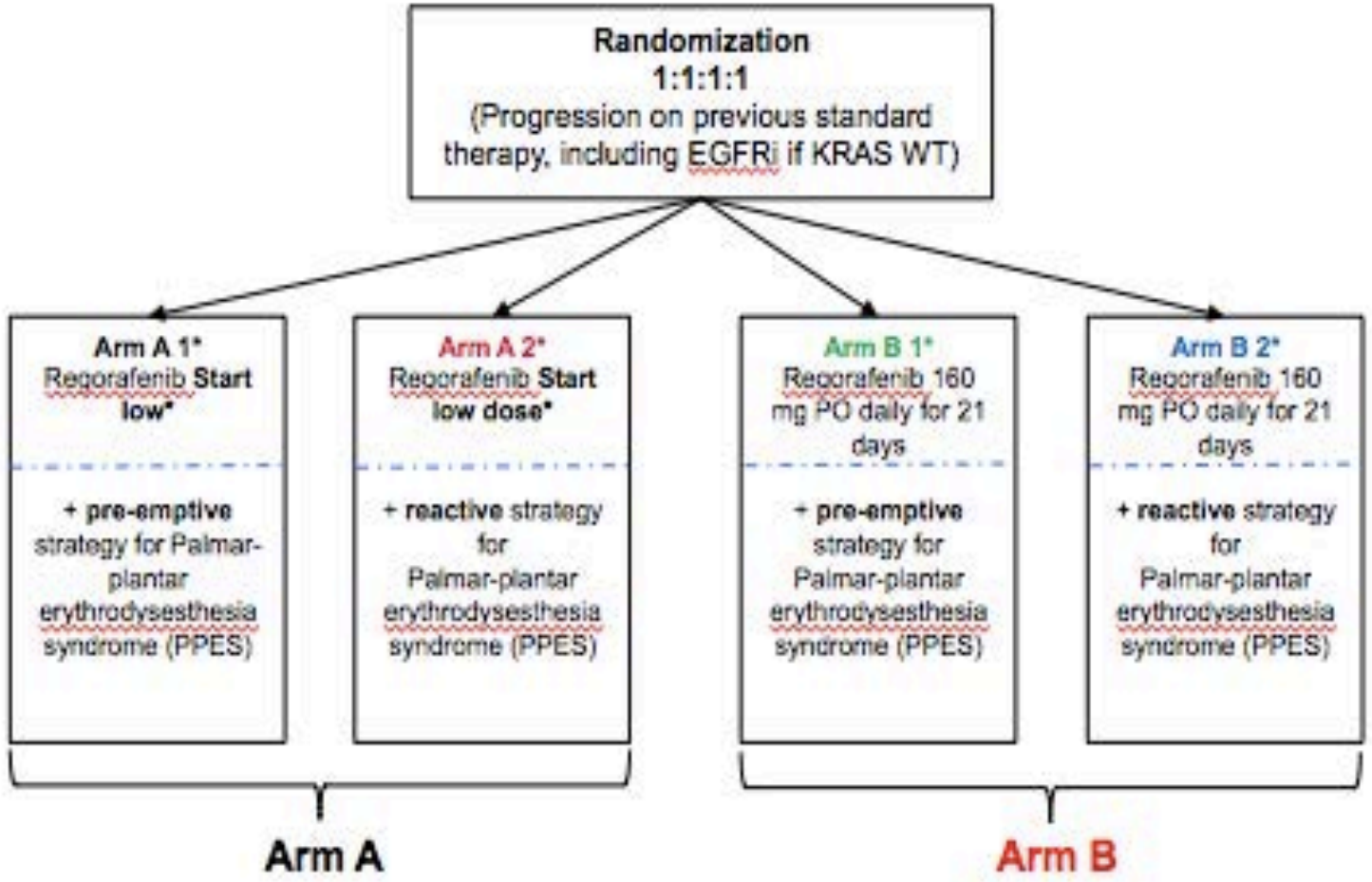


AEs leading to permanent tx discontinuation: 8.2%

VANDERBILT UNIVERSITY MEDICAL CENTER

Regorafenib dose optimization study (ReDOS): Randomized phase II trial to evaluate dosing strategies for regorafenib in refractory mCRC

WEEK of C1		DOSE
1	Starting dose C1	80 mg
2	↓	120 mg
3	End dose C1	160 mg
4		off
WEEK of C2+		**DOSE**
1		160 mg
2		160 mg
3		160 mg
4		off

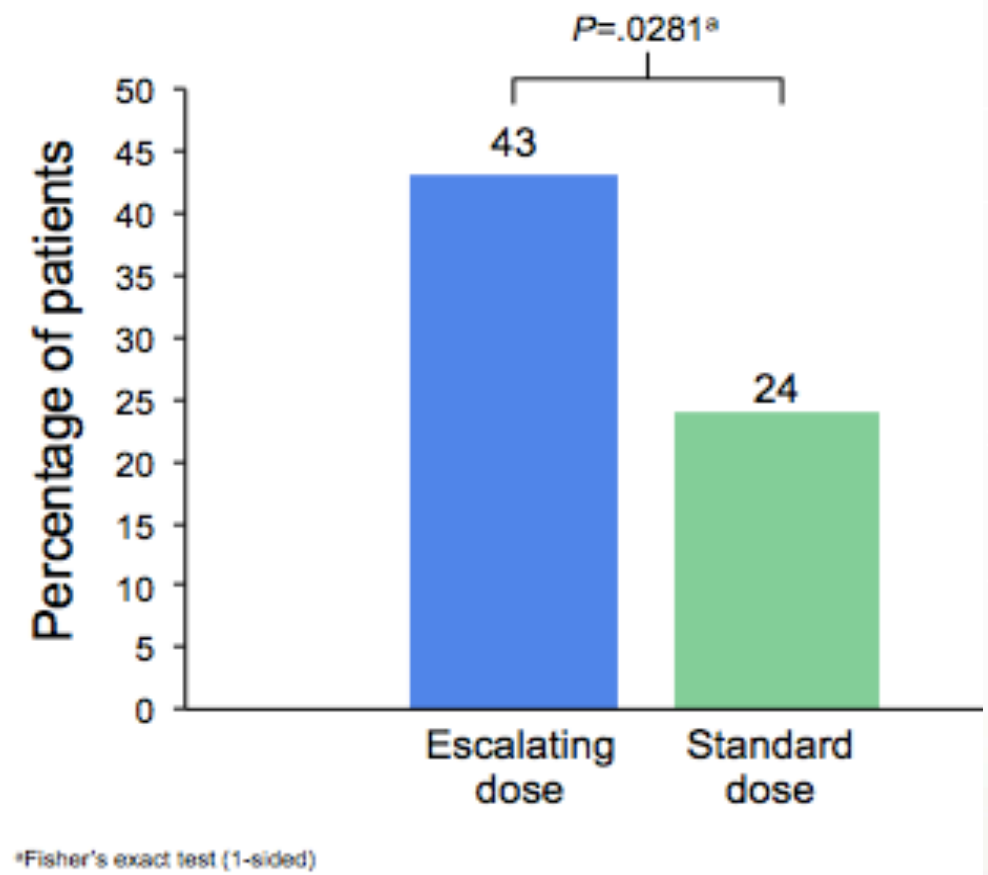


1ary endpoint: proportion of patients who complete 2 cycles of protocol treatment and initiate cycle 3 in arm A and arm B
2ary endpoints: OS, PFS, TTP

Bekaii-Saab T et al, ASCO GI 2018

ReDOS: Regorafenib Dose-Optimization Study

% of Patients Starting Cycle 3 (Primary Endpoint)



	Arm A n=54	Arm B n=62	*P*-Value
Primary Endpoint (patients initiating 3rd cycle)	**43%**	**25%**	**0.028**
mOS (mos)	9	5.9	0.094
mPFS (mos)	2.5	2.0	0.553
% HFSR	15%	16%	n/a
% HTN	7%	15%	n/a
% Fatigue	13%	18%	n/a

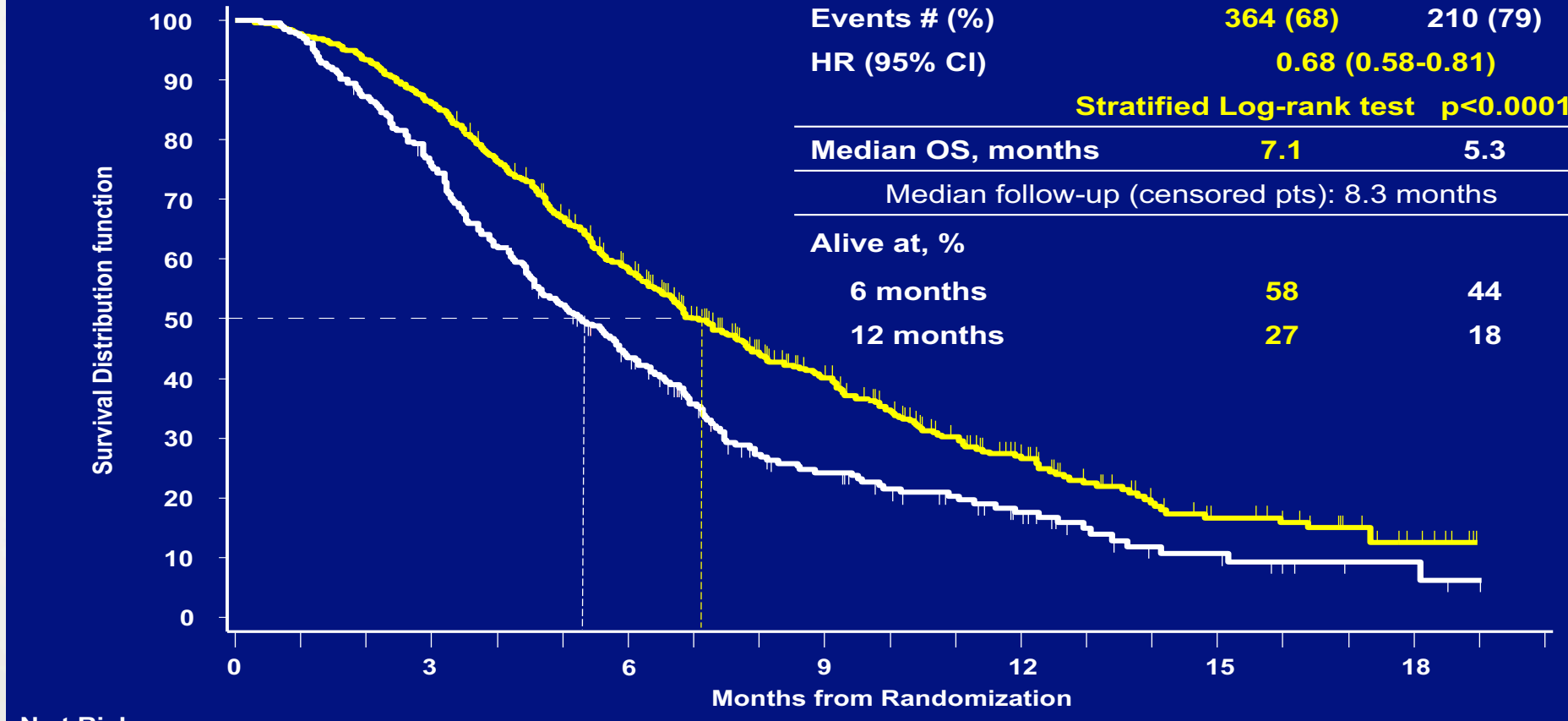
VANDERBILT UNIVERSITY MEDICAL CENTER

Bekaii-Saab T et al, ASCO GI 2018

RECOURSE

Overall Survival

	TAS-102 N=534	Placebo N=266
Events # (%)	364 (68)	210 (79)
HR (95% CI)	0.68 (0.58-0.81)	
	Stratified Log-rank test	p<0.0001
Median OS, months	7.1	5.3
Median follow-up (censored pts): 8.3 months		
Alive at, %		
6 months	58	44
12 months	27	18



N at Risk:

TAS-102	534	459	294	137	64	23	7
Placebo	266	198	107	47	24	9	3

TAS-102 +/- Bev in Refractory mCRC

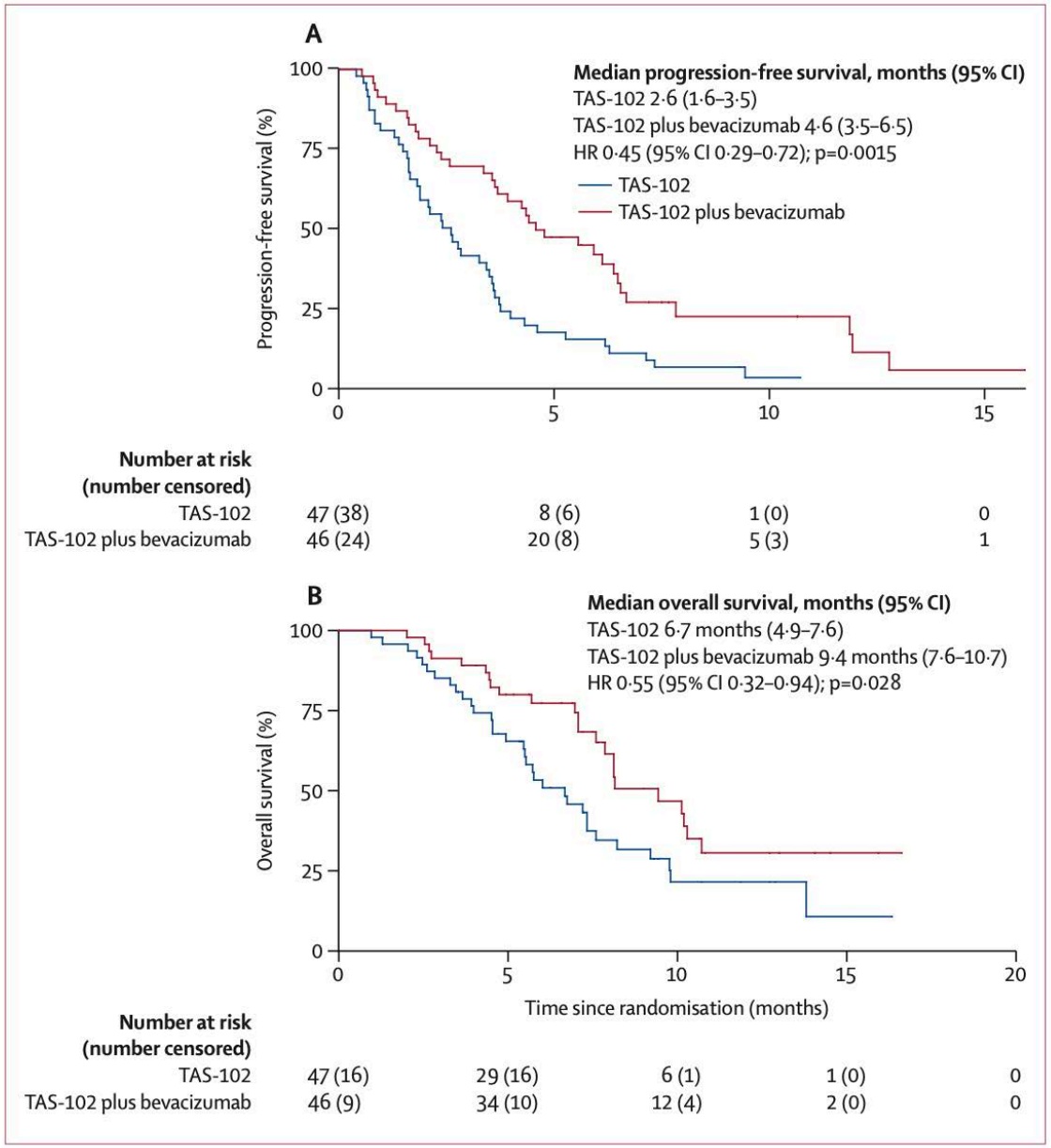


Figure 2: **The efficacy of TAS-102 monotherapy versus TAS-102 plus bevacizumab combination therapy**
(A) Progression-free survival. (B) Overall survial. HR=hazard ratio.

VANDERBILT UNIVERSITY MEDICAL CENTER

Pfeiffer P, *Lancet Oncol* 2020

TASCO1 TRIAL

Phase 2 study evaluating trifluridine/tipiracil + bevacizumab (TT-B) and capecitabine + bevacizumab (C-B) in first-line mCRC patients who are not candidates for intensive therapy.

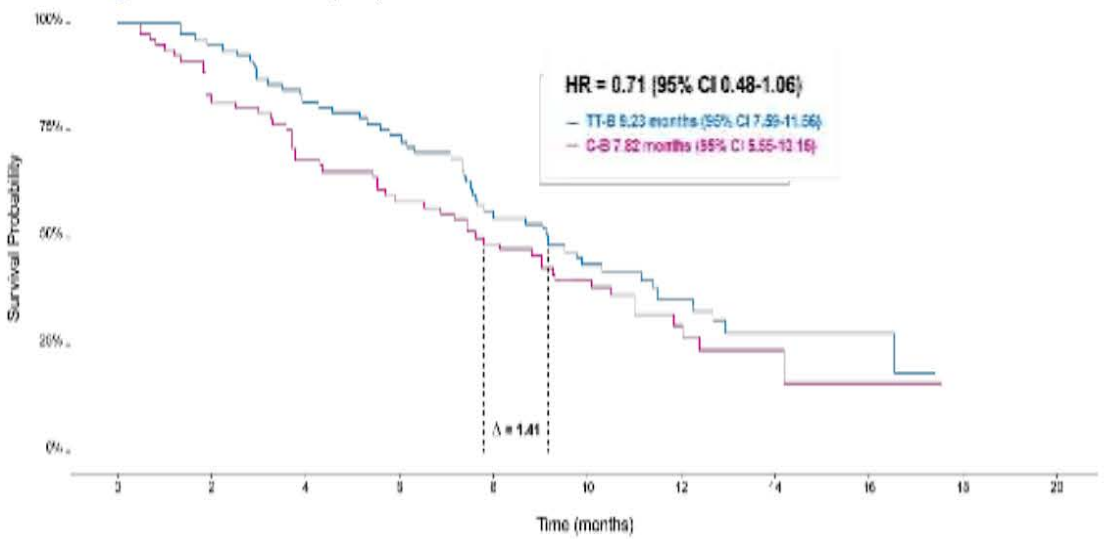
- **N=**153 patients
- **Stratification factors**
  RAS status
  ECOG PS
  Region
- **Primary endpoint: PFS** based on investigator assessment of radiologic images by RECIST 1.1.

  Median PFS (months): 9.23 for TT-B vs 7.82 for C-B (HR, 0.71; 95% CI, 0.48 -1.06).
- **Secondary Endpoint: OS**

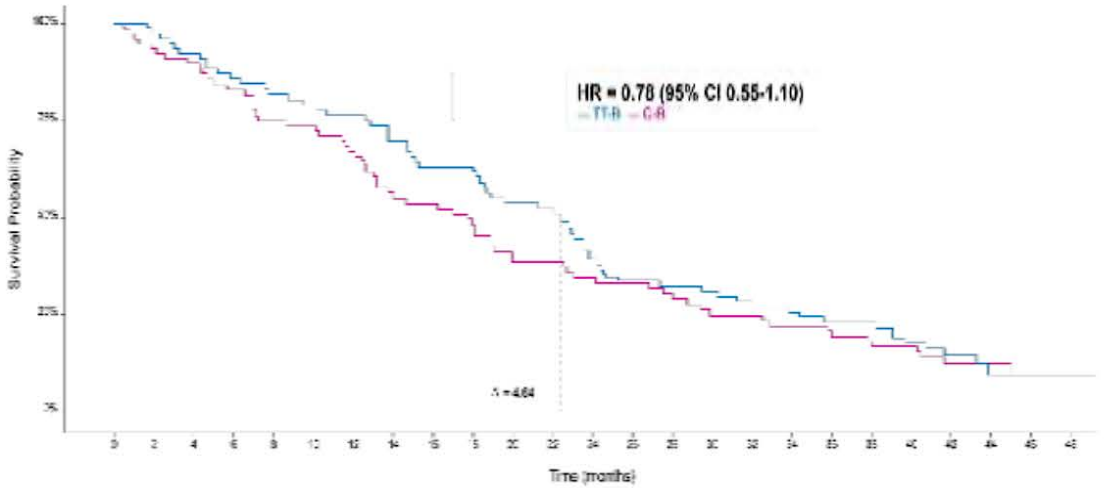
  Median OS (months): 22.31 for TT-B vs 17.67 for C-B (HR, 0.78; 95% CI, 0.32 -0.98).

Van Cutsem E. ASCO GI 2021

Progression-free survival (PFS)



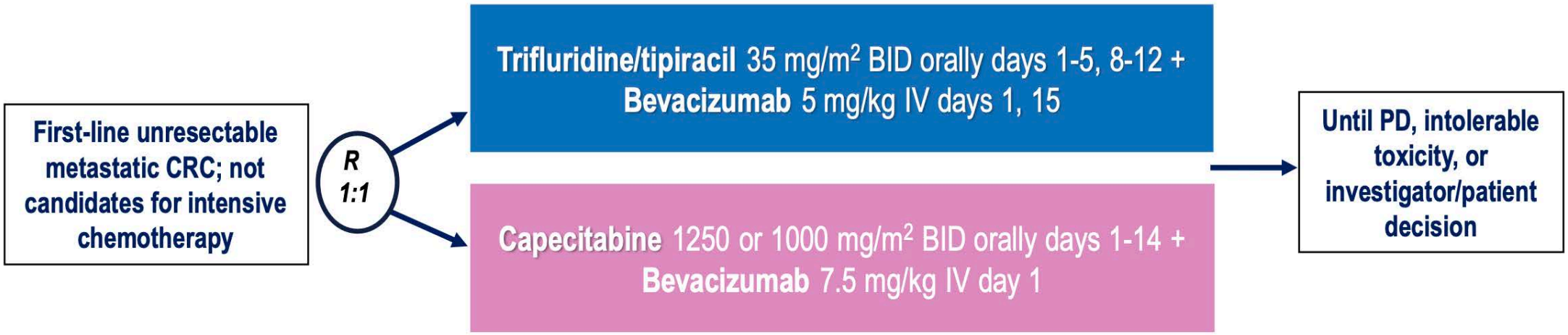
Overall survival (OS)



VANDERBILT UNIVERSITY MEDICAL CENTER

SOLSTICE TRIAL

Open-label, Randomized, Phase 3, Comparative study

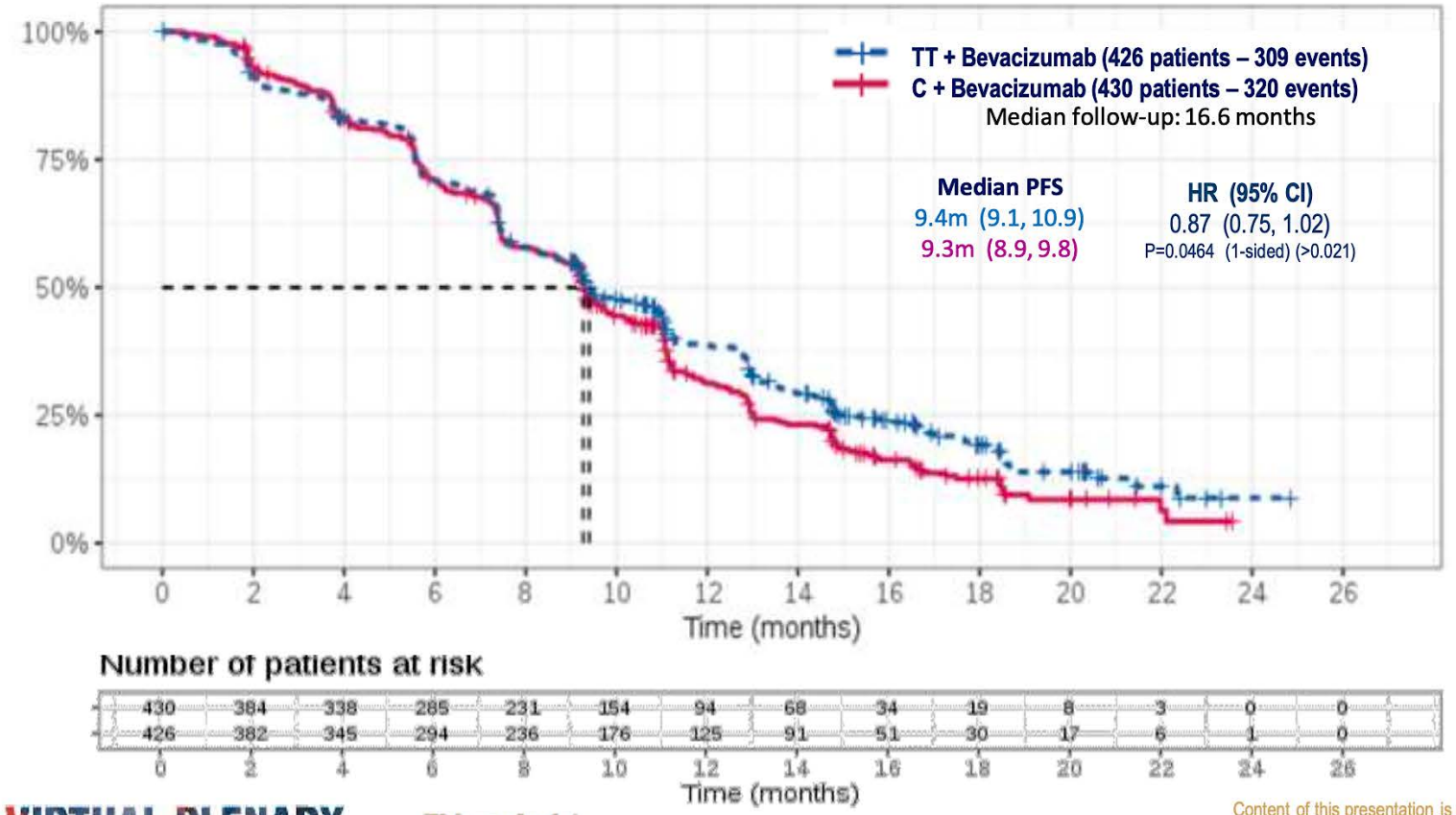


3 stratification factors:

- ECOG performance status (0 vs. 1 vs. 2)
- Tumour localisation (right vs. left)
- Reason for not being candidate to intensive therapy: Clinical condition (ECOG, Comorbidities, Elderly) vs. Non-clinical condition (Low tumour burden, Patient preference, Other)

SOLSTICE

PFS BY INVESTIGATOR'S ASSESSMENT

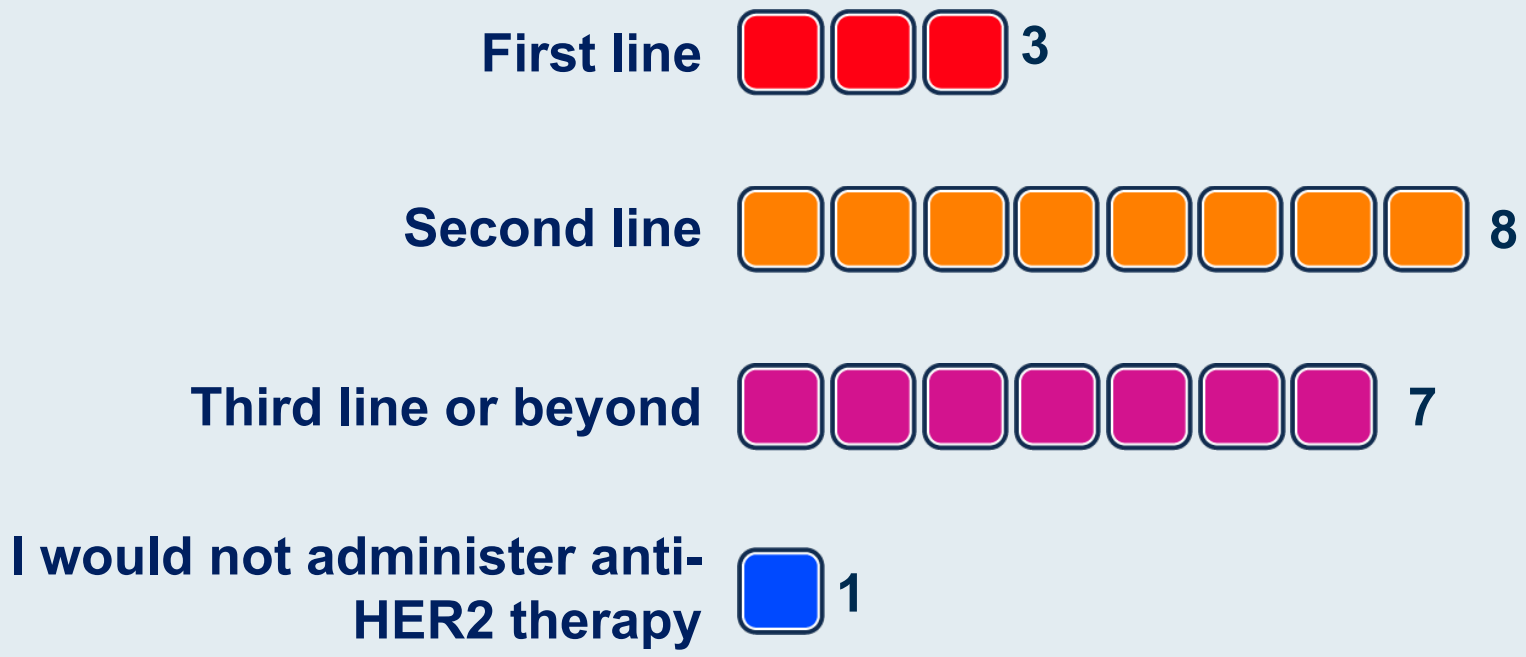


SOLSTICE

TUMOUR RESPONSE BY INVESTIGATOR

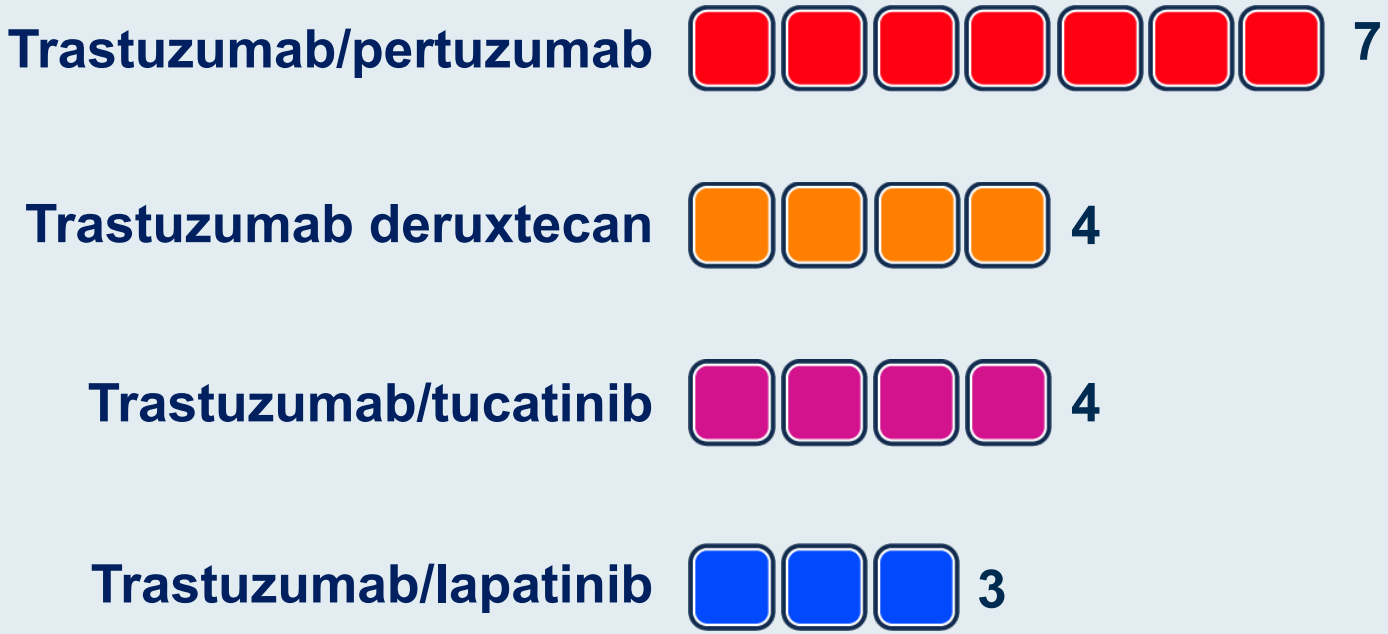
		TT+BEV (n = 426)	C+BEV (n = 430)
Best Overall Response n (%)	CR	6 (1.4)	3 (0.7)
	PR	147 (34.5)	176 (40.9)
	SD	215 (50.5)	187 (43.5)
	PD	40 (9.4)	32 (7.4)
	NE	18 (4.2)	32 (7.4)
Objective Response Rate (CR+PR)	n (%)	153 (35.9)	179 (41.6)
	95% CI	[31.4;40.7]	[36.9;46.5]
Disease Control Rate (CR+PR+SD)	n (%)	368 (86.4)	366 (85.1)
	95% CI	[82.76;89.5]	[81.40;88.4]

Regulatory and reimbursement issues aside, for a patient with HER2-amplified mCRC, in what line of therapy would you generally administer anti-HER2 therapy?



Survey of US-based clinical investigators

For a patient with HER2-amplified mCRC to whom you would administer HER2-targeted therapy, what would be your preferred treatment?

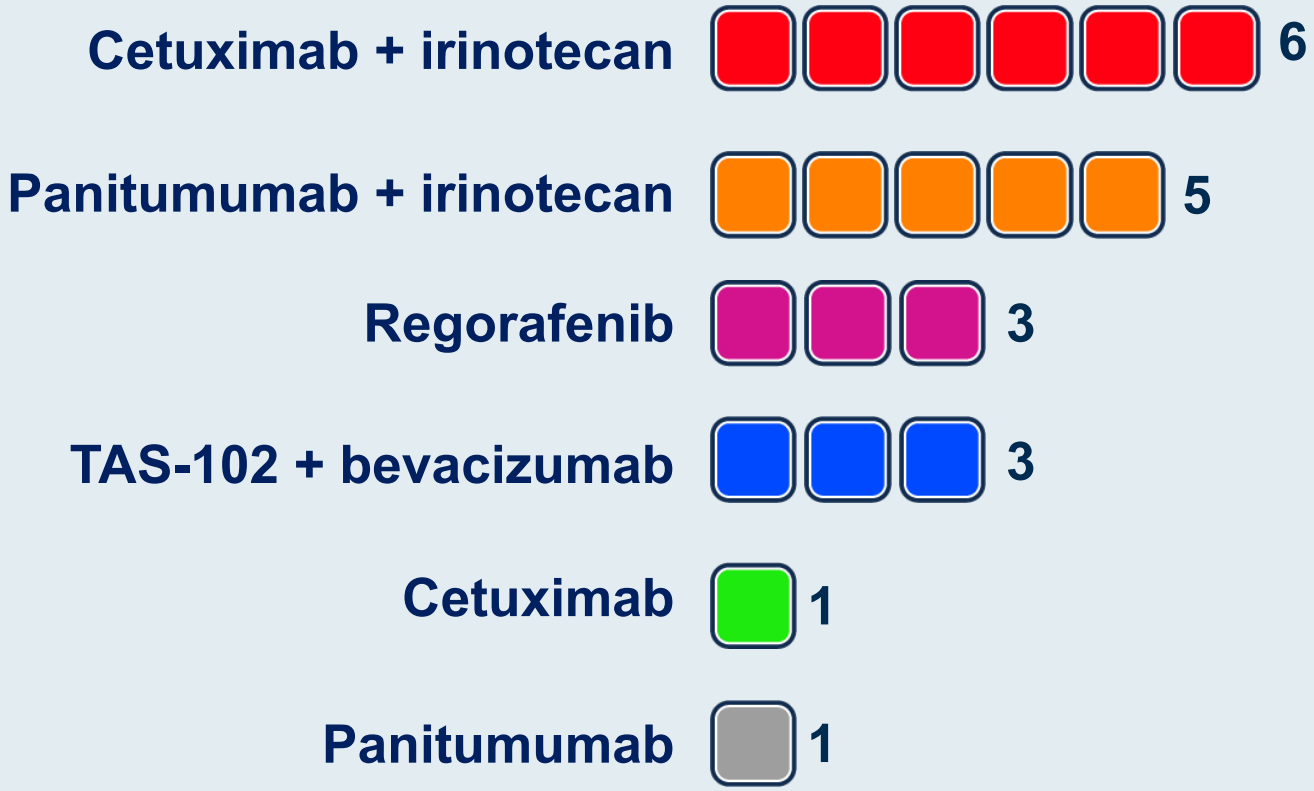


Survey of US-based clinical investigators

In general, do you consider the RAS/RAF status of a patient with HER2-positive mCRC when deciding on the use of anti-HER2 therapy?

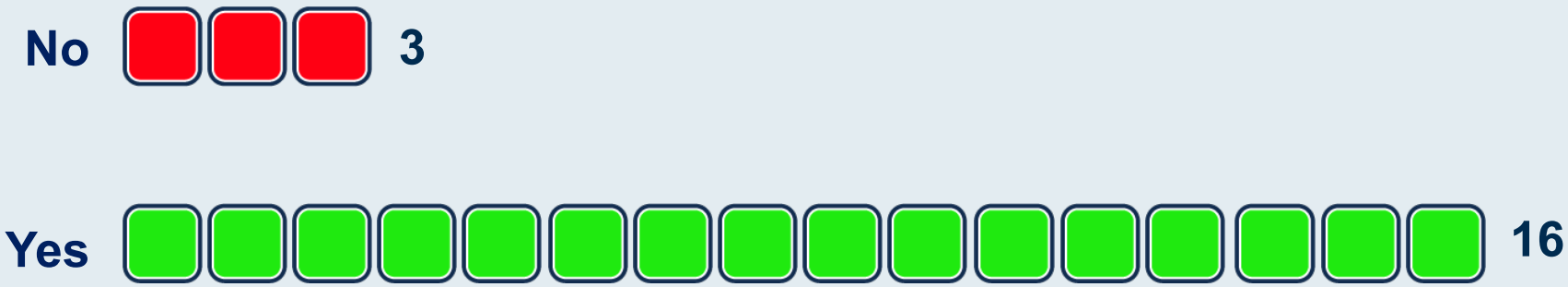
Survey of US-based clinical investigators

A 65-year-old patient with right-sided, MSS, pan-RAS wild-type mCRC receives first-line FOLFOX/bevacizumab and second-line FOLFIRI/bevacizumab and is now experiencing disease progression with a PS of 0. Regulatory and reimbursement issues aside, what would be your most likely third-line treatment recommendation?

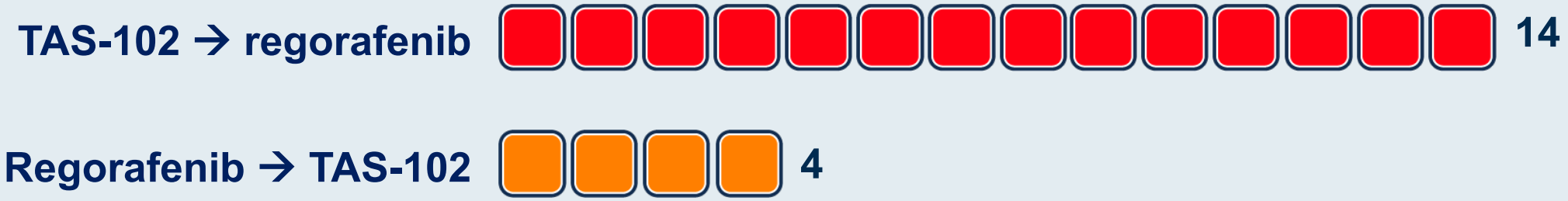


Survey of US-based clinical investigators

For a patient with mCRC who has received EGFR antibody-containing therapy and experienced disease progression, are there any circumstances in which you will rechallenge with the same or a different EGFR antibody later in the treatment course?

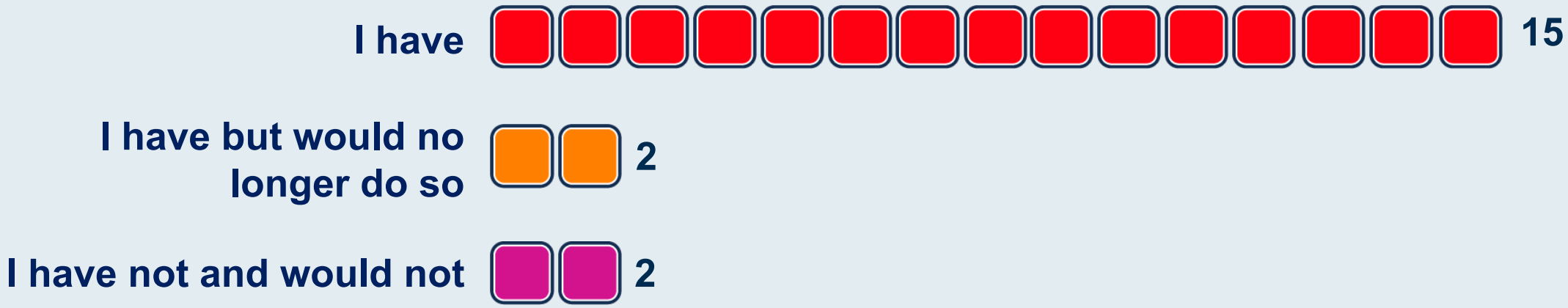


What is your preferred sequence for administering regorafenib and TAS-102 with or without bevacizumab for your patients with multiregimen-relapsed mCRC?



Survey of US-based clinical investigators

Have you used or would you use TAS-102 in combination with bevacizumab outside of a clinical trial setting for a patient with mCRC?



Survey of US-based clinical investigators

MODULE 4: Other Considerations in the Management of CRC; Promising Investigational Strategies — Dr Lieu

RTP
RESEARCH
TO PRACTICE

Cancer Center

NCI-DESIGNATED CONSORTIUM
COMPREHENSIVE CANCER CENTER

Other Considerations in the Management of CRC; Promising Investigational Strategies

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

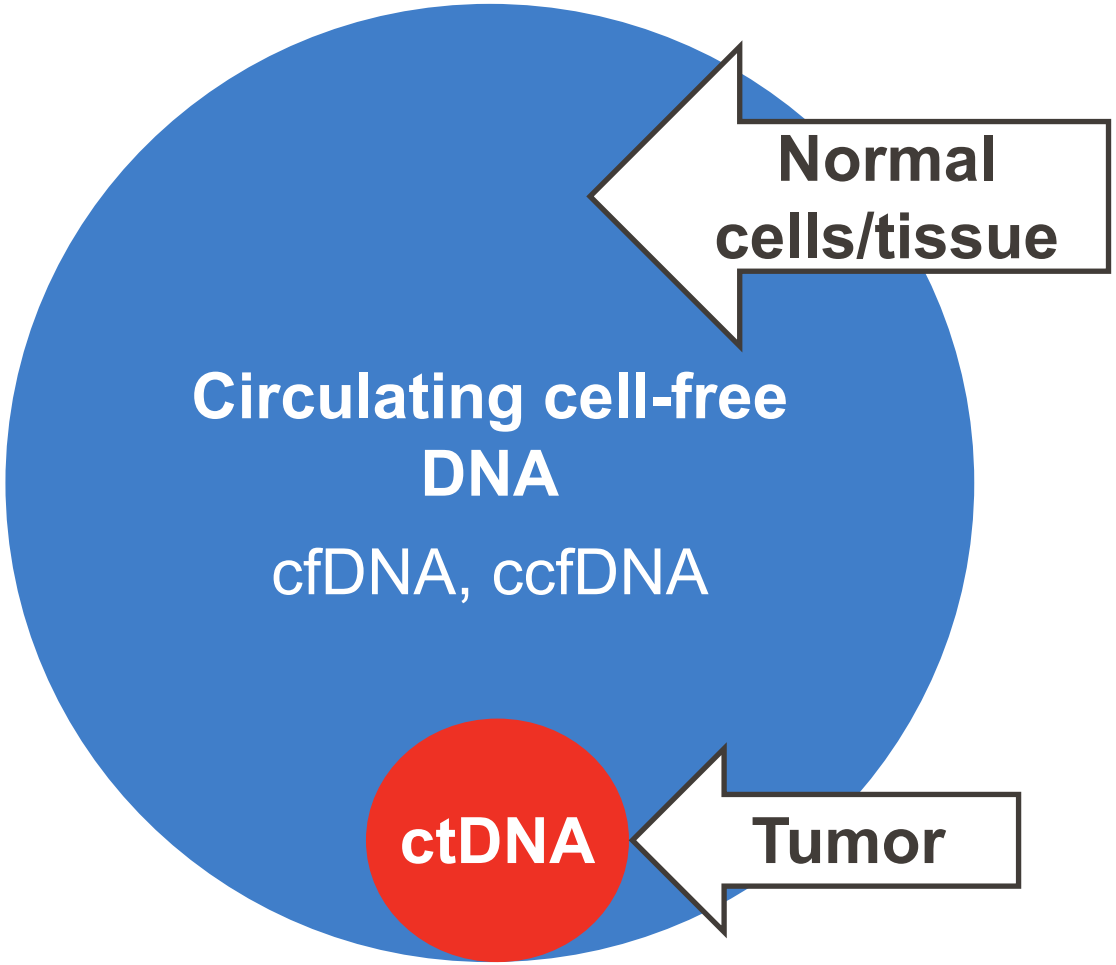
NCI Designated Comprehensive Cancer Center

Topics for Discussion

- Diagnostic testing
  - Minimal Residual Disease (MRD) Monitoring in CRC
- Biomarkers
  - Sidedness in mCRC
- Is KRAS druggable?
  - KRAS G12C inhibitors
- HER3 and mCRC

Minimal Residual Disease and ctDNA

Characteristics and Terminology for Circulating Tumor DNA (ctDNA)



Two Main Ways to Test ctDNA:

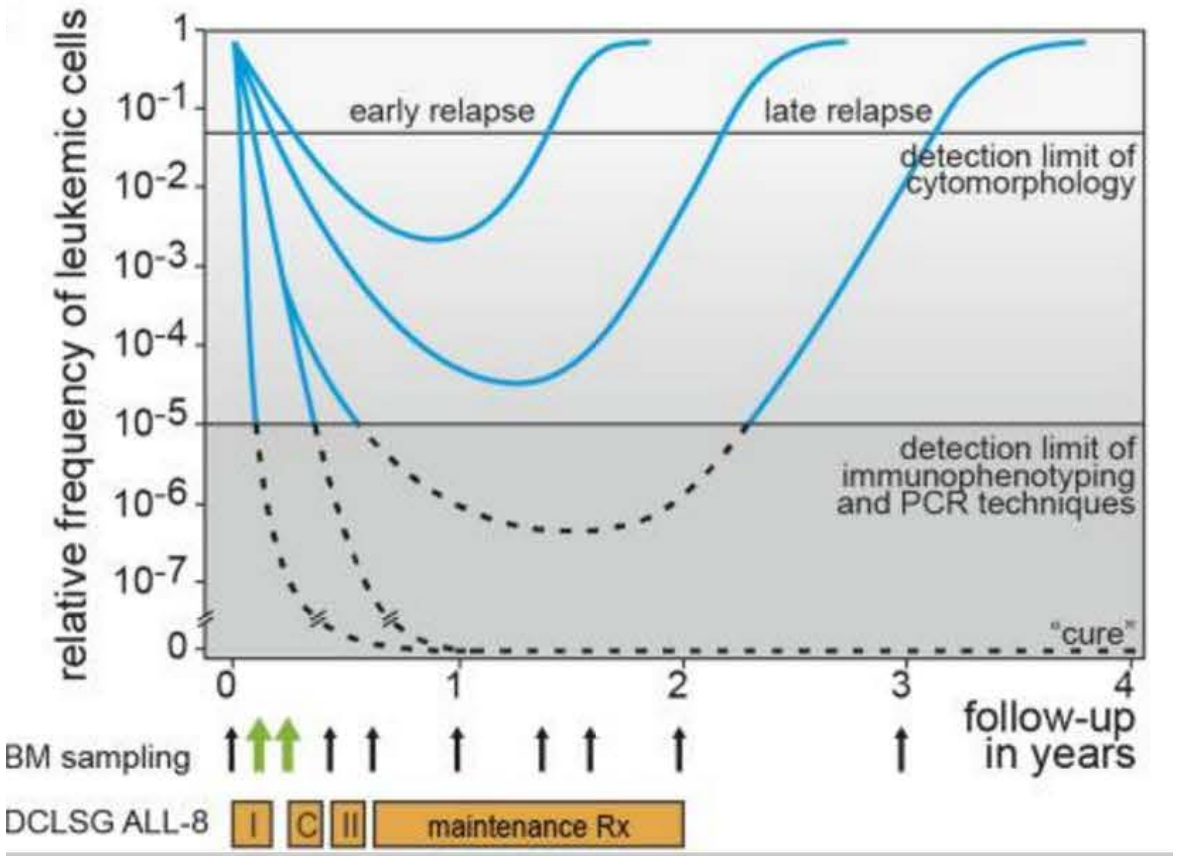
- "Tumor-informed testing"
  - Sequencing the tumor and looking for those mutations
- "Tumor-naïve testing"
  - Casting a wide net and looking for tumor mutations

Initially described by Madel and Metais in 1948
Half-life: ~ 0.5 hours

Chandrananda D et al. *BMC Med Genomics.* 2015;8:29; Wyllie AH. *Nature.* 1980;284(5756):555-556; Mandel P & Metais P. *C R Seances Soc Biol Fil.* 1948;142(3-4):241-243.
Slide courtesy of Scott Kopetz

Minimal Residual Disease: Two Key Points

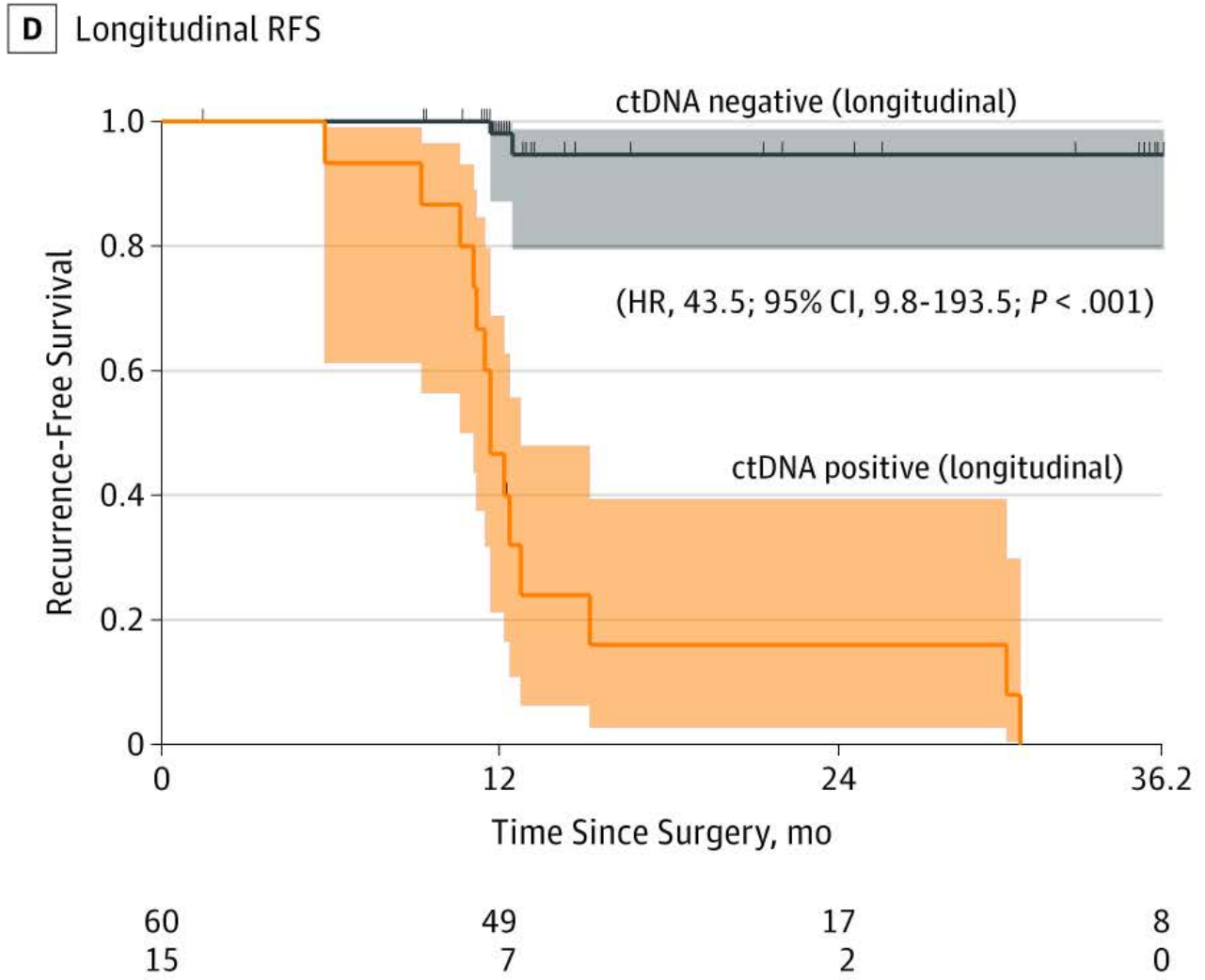
- MRD applications are enabled by very high **positive predictive value** (low false positive) for recurrent disease in patients with ctDNA detected in the “adjuvant” setting
- This is not a marker of high risk for recurrence but **defines molecular persistence of disease**.
  - Stage I-III patients with ctDNA+ after definitive interventions should be considered as a Stage IV minimal residual disease, or Stage IV MRD



Well-established concept in hematologic malignancies

Van Dongen JJ et al. *Blood.* 2015;125(26):3996-4009.

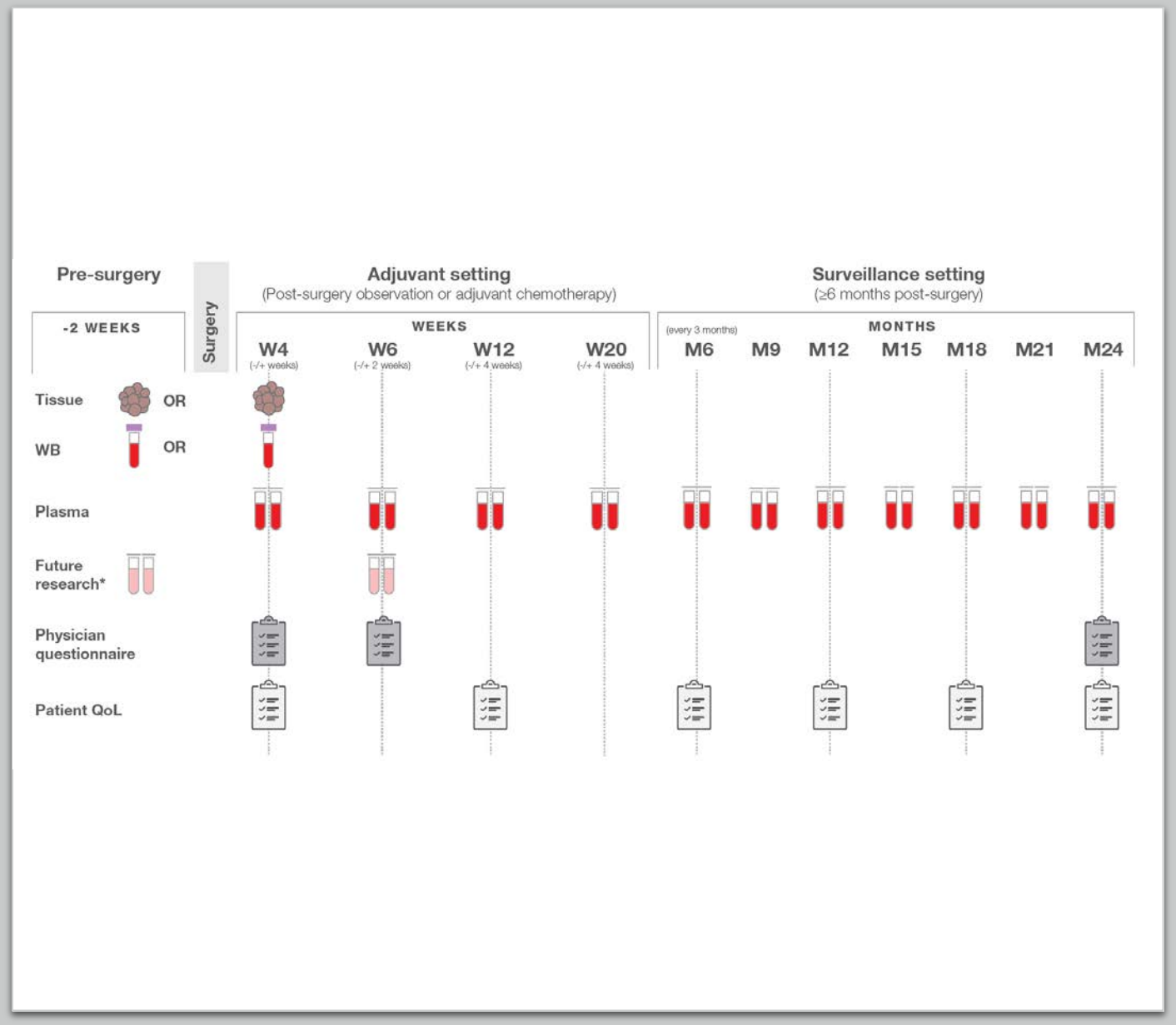
Longitudinal ctDNA and Relapse-Free Survival



Reinert T et al. *JAMA Oncol.* 2019;5(8):1124-1131.

BESPOKE CRC

- Prospective, non-randomized cohort study
- 1,000 patients with Stage II-III CRC tested with Signatera
- Real-world study of MRD-guided treatment

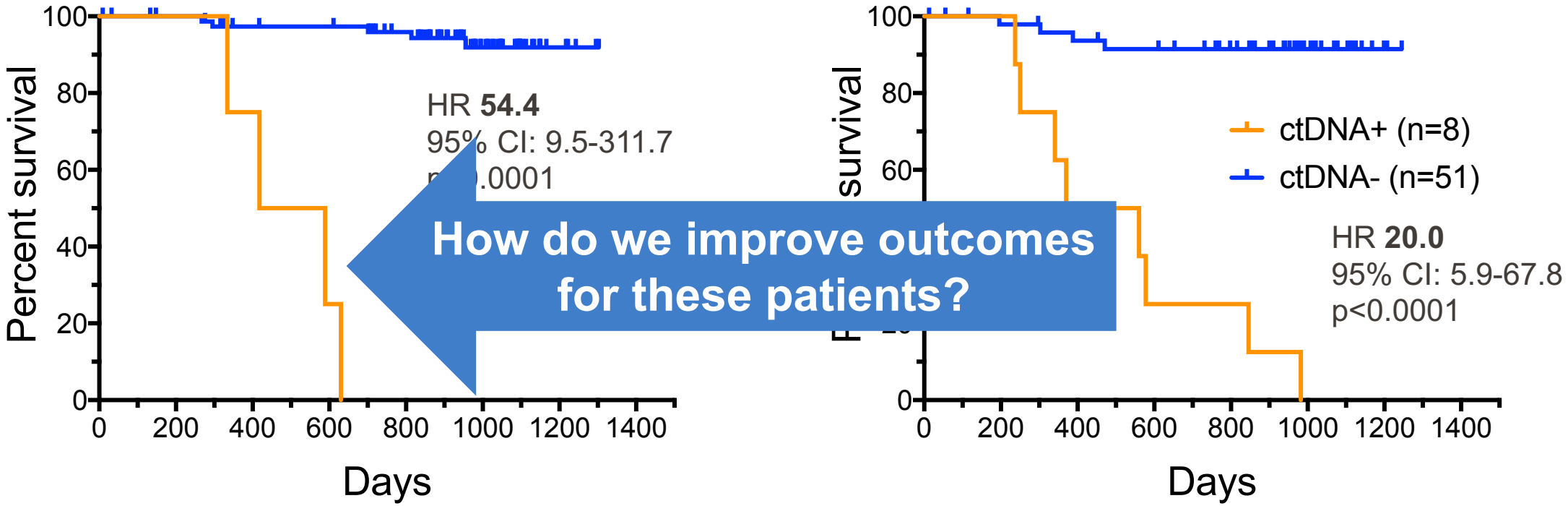


NGS Assay

Assay with 197 genes; at least one mutation detected 99.3% of tumor tissue
57% sensitivity for recurrence; 100% specificity

Stage II (5% prevalence of ctDNA+)

Stage III (16% prevalence of ctDNA+)

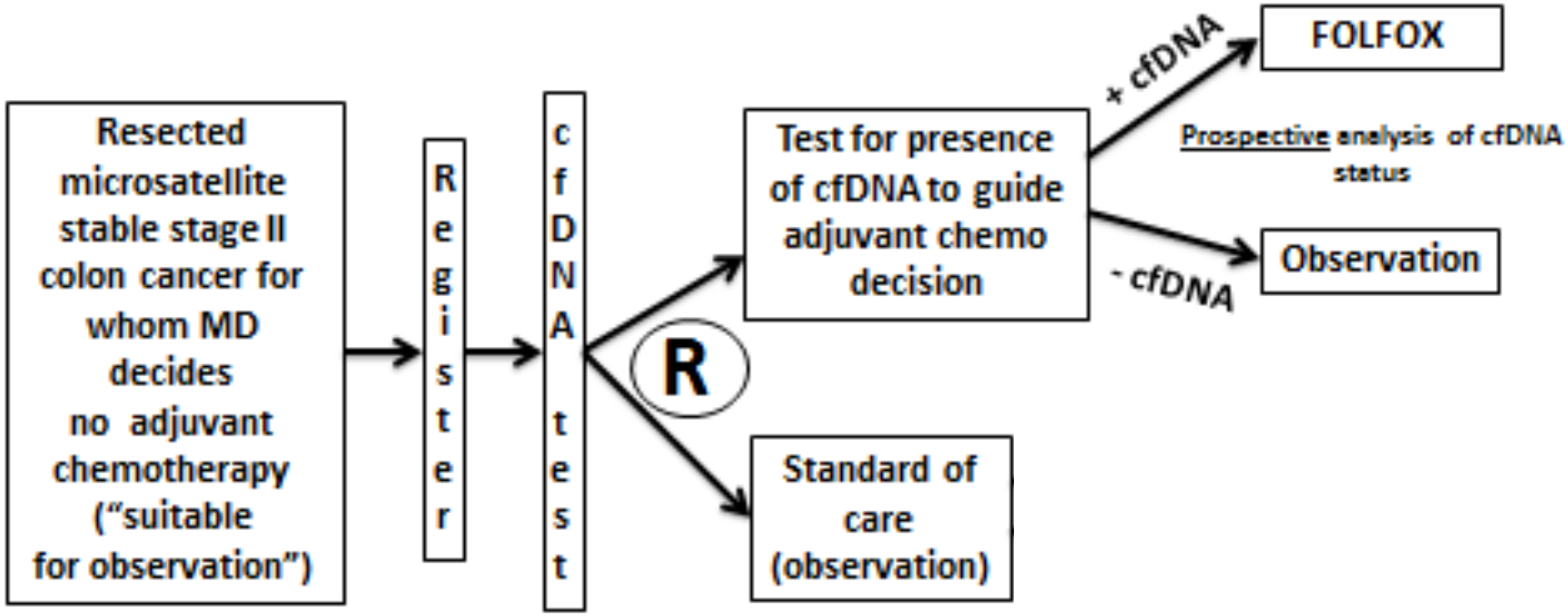


Diehn M et al. ASCO 2017. Abstract 3591.

Stage II Adjuvant Study: NRG-GI005 (COBRA)

Evaluating early intervention for Minimal Residual Dz

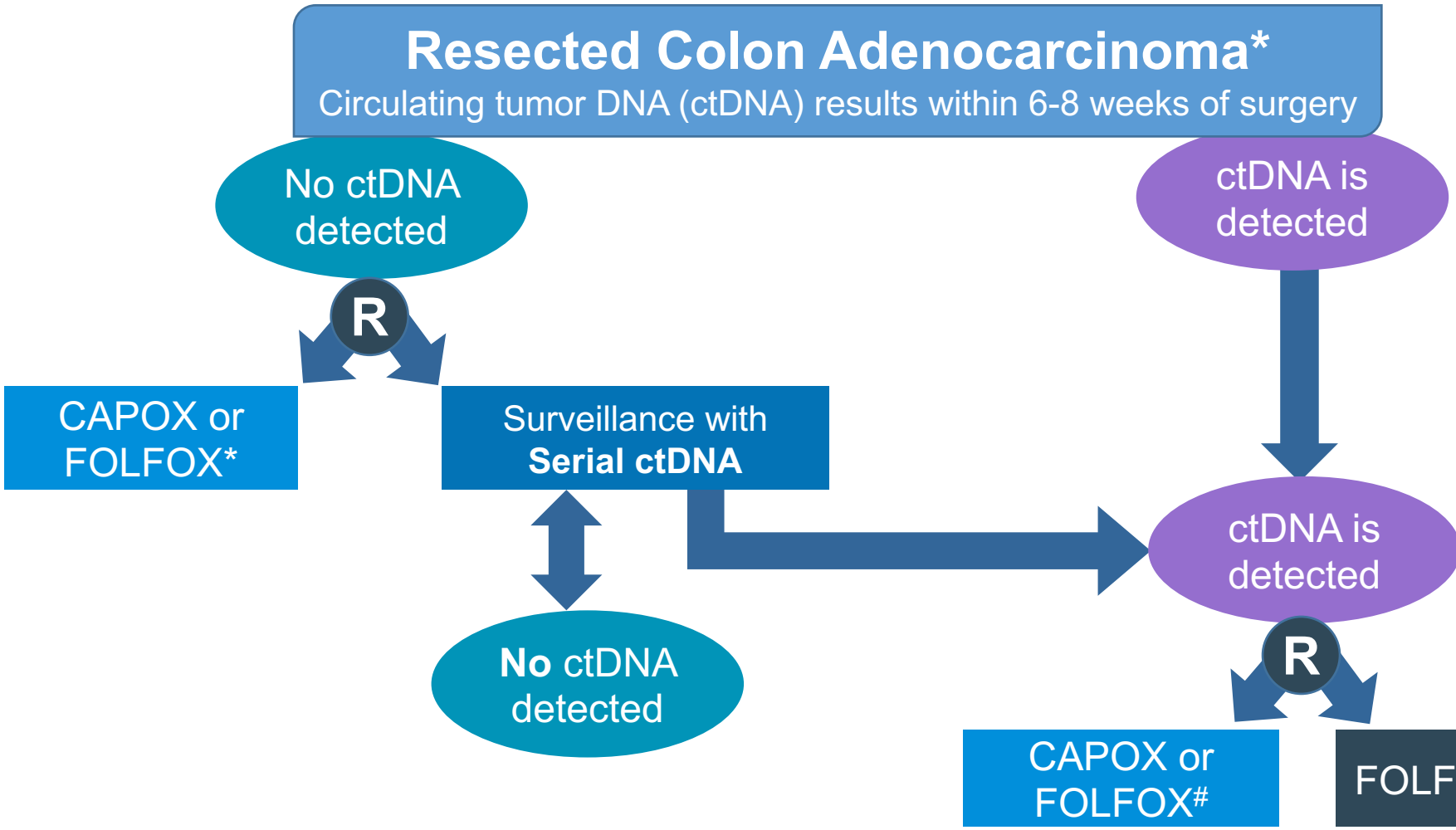
Van Morris



Primary objective: Clearance of cfDNA (to undetectable levels) for patients cfDNA+ at randomization

Morris VK et al. ASCO 2020. Abstract TPS4121.

Morris, Kopetz



***Stage III (T1-3, N1/N1c)**
or
ctDNA +ve Stage II or Stage IIIC

R0 resection
pMMR / MSS

ctDNA Assay: Signatera

PIs:
Arvind Dasari (MDACC – NRG)
Christopher Lieu (UCCC – SWOG)

*: Duration and regimen per physician discretion
#: 6 months duration

NRG-GI008

TAKE HOME POINT:

Detection of ctDNA post-operatively is a poor prognostic sign

Serial monitoring will increase sensitivity

Clinical trials will further guide the use of these assays (prognostic and/or predictive?)

Sidedness: *the cheapest biomarker*

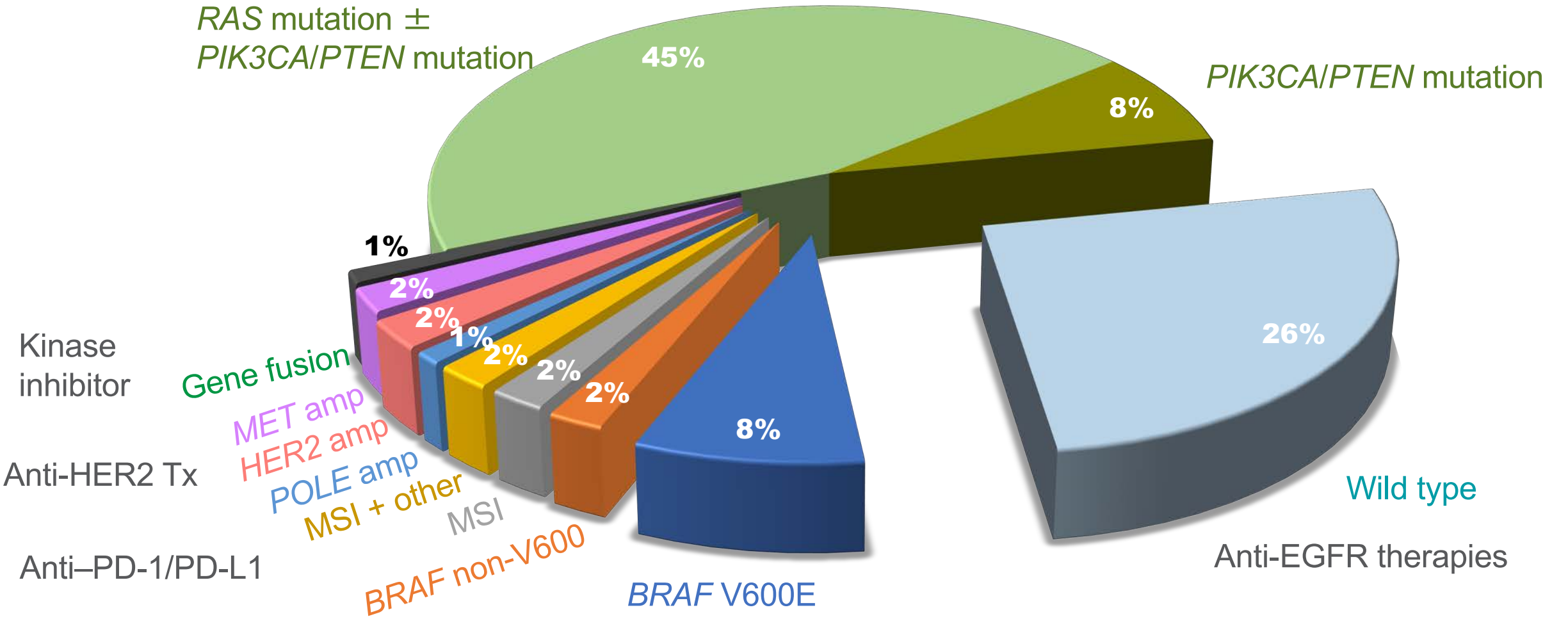
16 FDA-Approved Drugs for Metastatic Colorectal Cancer

"Cytotoxics"	Mechanism
1. 5-Fluorouracil (5-FU)	-> pyrimidine analog
2. capecitabine	-> oral 5-FU pro-drug
3. TAS-102	-> 5-FU drug with metabolism inhibitor
4. irinotecan	-> topoisomerase I inhibitor
5. oxaliplatin	-> 3rd generation platinum

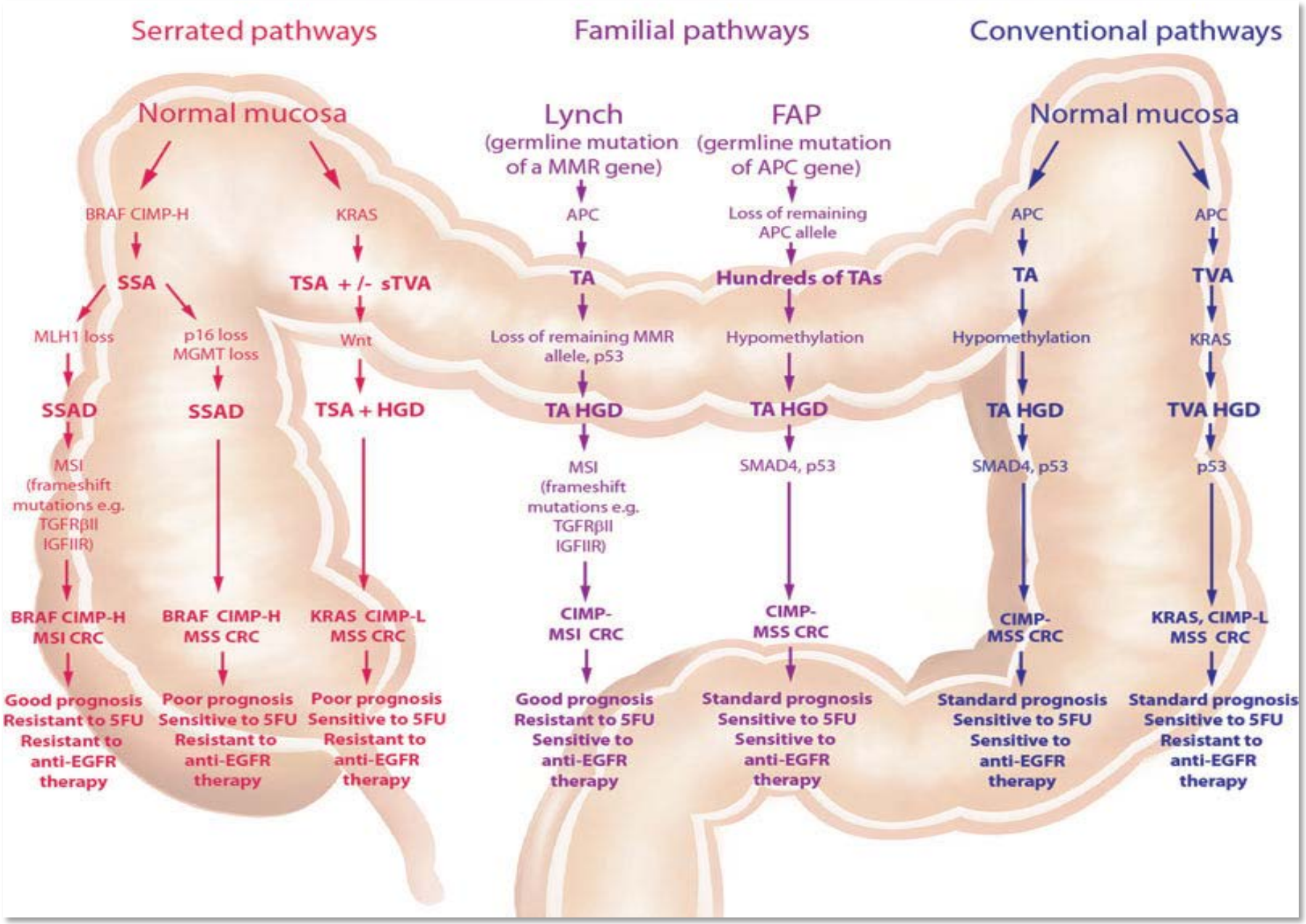
"Biologics/Targeted"	Mechanism
1. cetuximab	-> antibody against EGFR
2. panitumumab	-> antibody against EGFR
3. bevacizumab	-> antibody against VEGF
4. ziv-aflibercept	-> VEGF trap
5. ramucirumab	-> antibody against VEGFR2
6. regorafenib	-> multi-tyrosine kinase inhibitor
7. ramucirumab	-> antibody against VEGFR2
8/9. pembrolizumab/nivolumab	-> antibody against PD-1 (MSI-high only)
10. ipilimumab	-> antibody against CTLA-4 (MSI-high only)
11. encorafenib + cetuximab	-> tyrosine kinase inhibitor against BRAF V600E

VEGF= Vascular Endothelial Growth Factor
EGFR= Epidermal Growth Factor Receptor

Genomic Markers in CRC

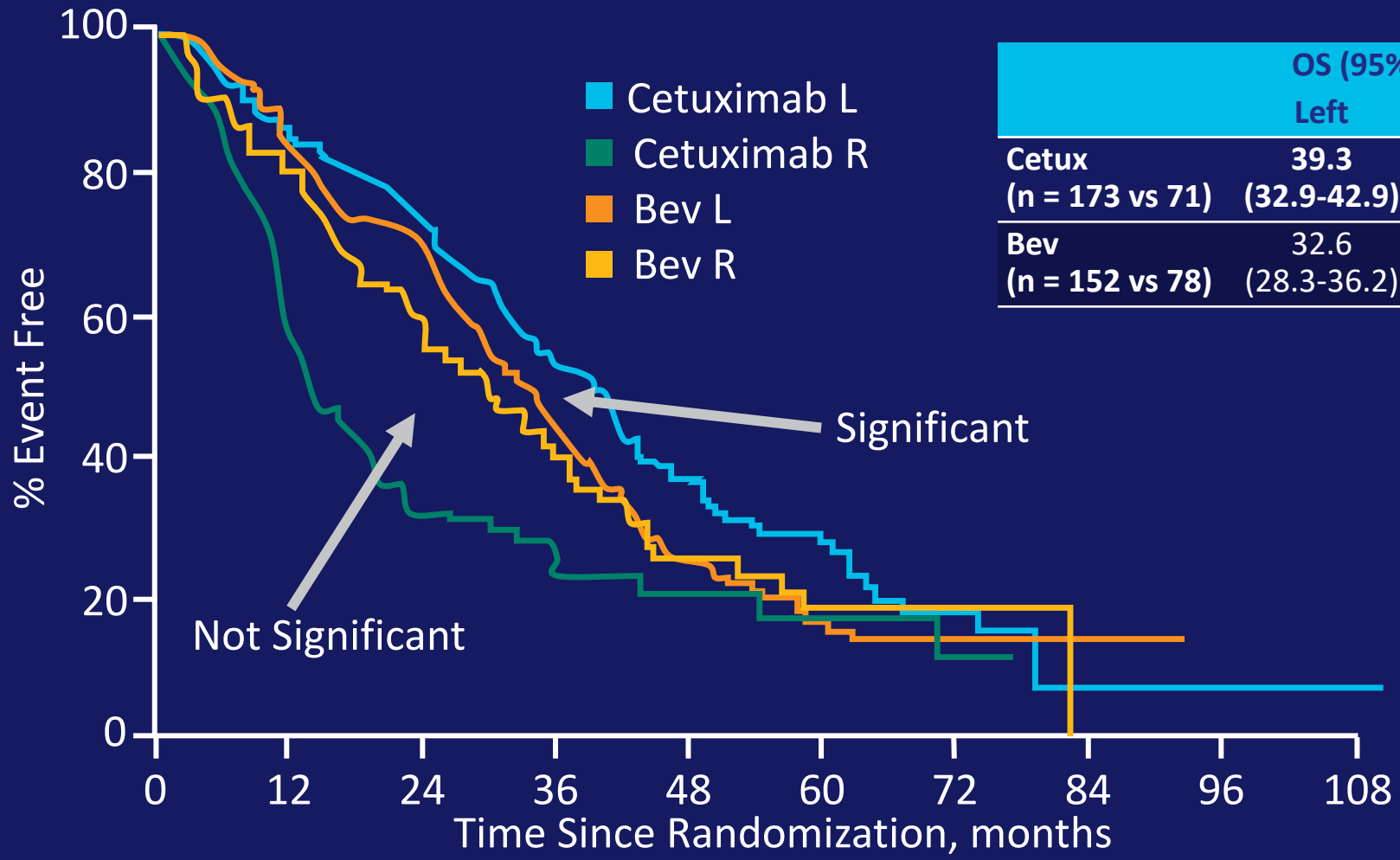


Dienstmann R, et al. *Am Soc Clin Oncol Ed Book*. 2018;38:231-238.



Reprinted with permission from Bettington M, et al. *Histopathology.* 2013;62:367-86.

CALGB/SWOG 80405: OS by Tumor Location (RAS WT)



	OS (95% CI), mos		HR	
	Left	Right	(95% CI)	*P* Value[a]
Cetux (n = 173 vs 71)	**39.3 (32.9-42.9)**	**13.6 (11.3-19.0)**	0.55 (0.39-0.79)	.001
Bev (n = 152 vs 78)	32.6 (28.3-36.2)	29.2 (22.4-36.9)	0.88 (0.62-1.25)	.50

Tx	ΔR vs L, mos
Cetux	25.7
BEV	3.4

[a]Adjusted for biologic, protocol CT, prior adjuvant therapy, prior RT, age, sex, synchronous disease, in place primary, liver metastases.

Venook A, et al. *JAMA*. 2017;317:2392-401.

The "Perfect" Candidate for First-line anti-EGFR therapy

Negative selection (mutually exclusive)

- *KRAS/NRAS/HRAS* exon 2, 3, 4 WT - 55%
- No *BRAF* V600E mutation - 8%
- No HER2 amplification -2.5%

Further exclusion criteria (not mutually exclusive)

- Right-sided cancers 30%

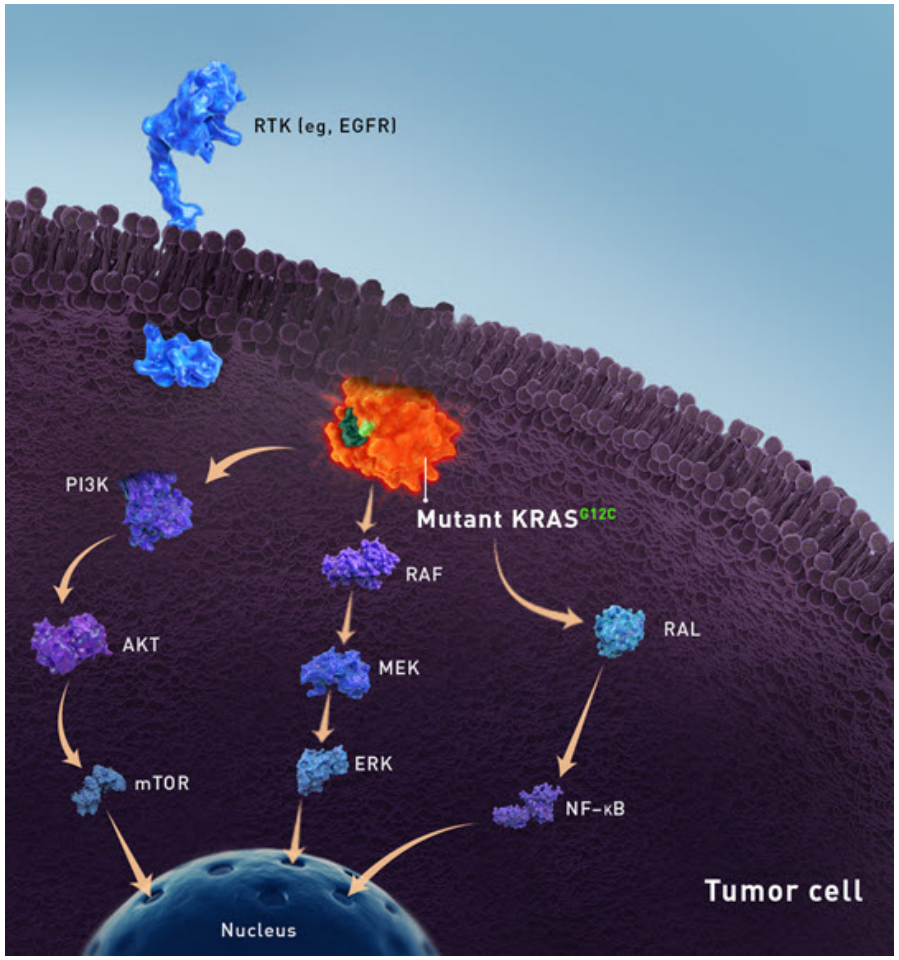
Zhao B, et al. *Oncotarget*. 2017;8:3980-4000.

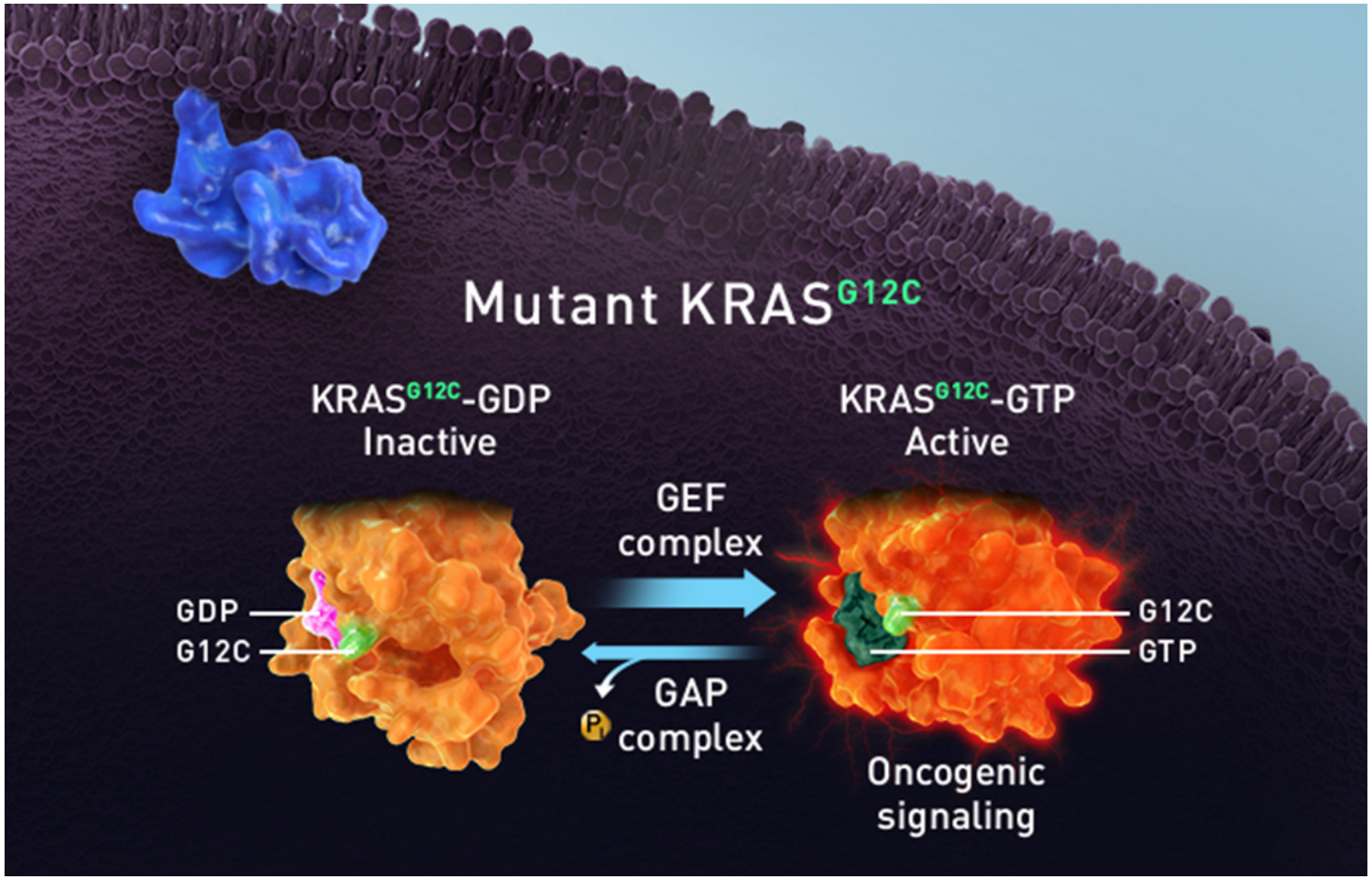
TAKE HOME POINT:

Right-sided colorectal cancers should ***not*** receive anti-EGFR therapy in the frontline setting regardless of RAS mutational status

KRAS G12C Mutations in mCRC

KRAS has historically been “undruggable”

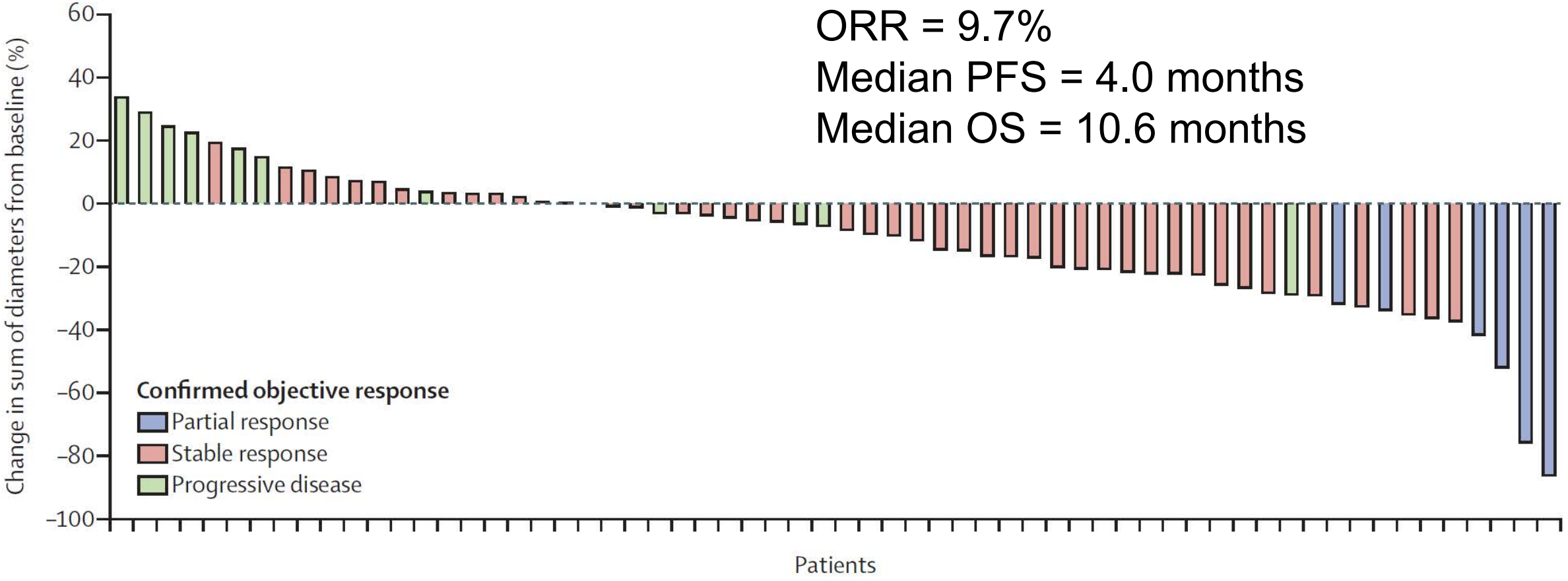




https://www.amgenoncology.com/targets/kras.html

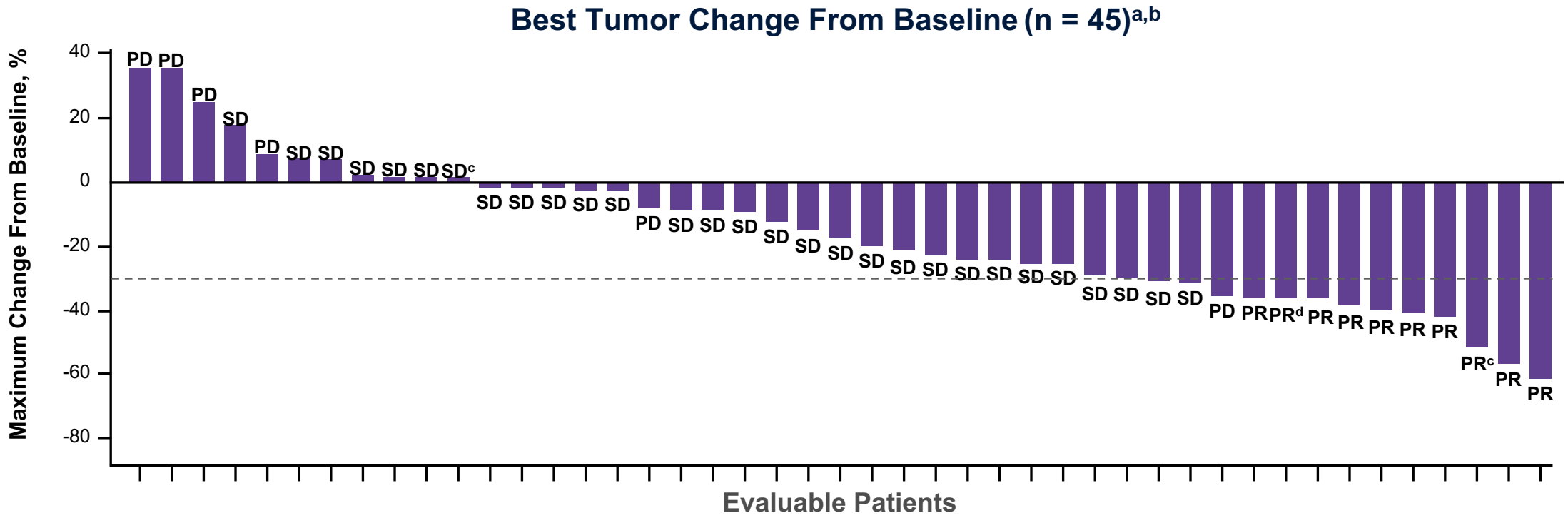
Sotorasib and Adagrasib: First to Inhibit "Undruggable" *KRAS* – Targeting *KRAS* G12C!

Sotorasib:
ORR = 9.7%
Median PFS = 4.0 months
Median OS = 10.6 months



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

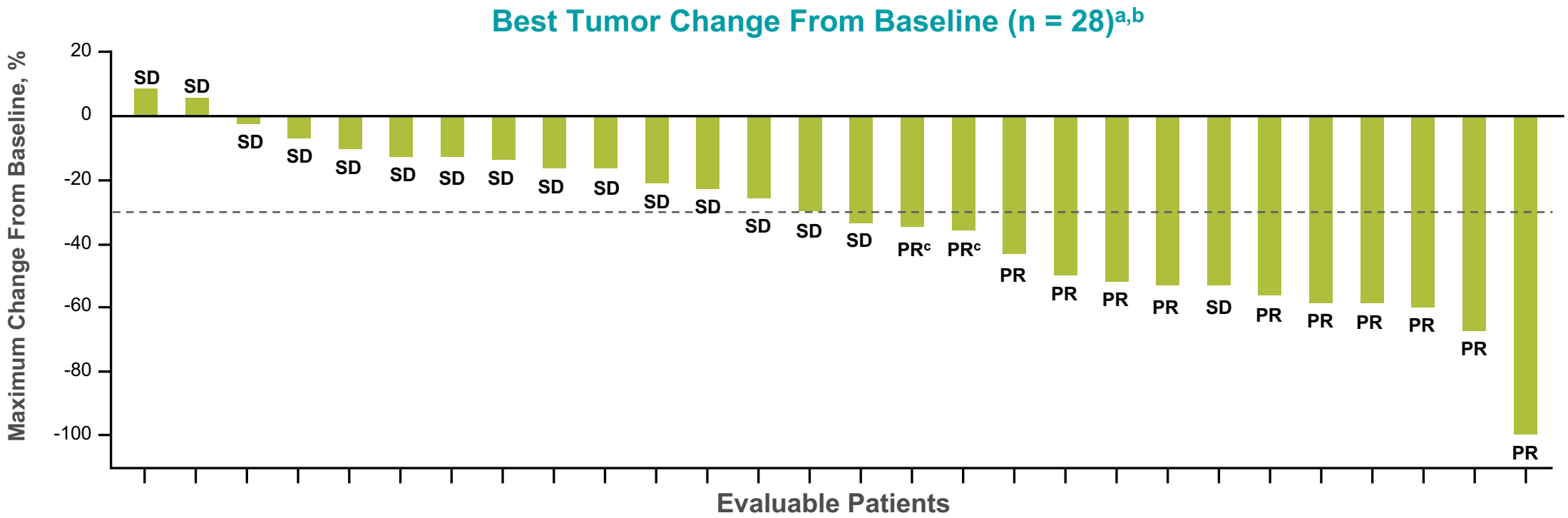
Adagrasib Targeting *KRAS*^{G12C} in Patients With CRC



- Response rate was 22% (10/45), including 1 unconfirmed PR
- SD was observed in 64% (29/45) of patients
- Clinical benefit (DCR) was observed in 87% (39/45) of patients
- No apparent association between response rate and molecular status was shown in an exploratory analysis[e]

[a]All results are based on investigator assessments. [b]Evaluable population (n = 45) excludes 1 patient who withdrew consent prior to the first scan. [c]Phase I/Ib. [d]At the time of the 25 May 2021 data cutoff, the patient had uPR. [e]Molecular status (*BRAF* V600E mutation, MSI-H or dMMR, *EGFR* amplification, *TP53* mutation, *PIK3CA* mutation) includes patients with conclusively evaluable test results.
Data as of 25 May 2021 for monotherapy (median follow-up: 8.9 months).
Weiss J, et al. ESMO 2021. Abstract LBA6.

Adagrasib + Cetuximab in Patients With Advanced CRC



- Response rate was 43% (12/28), including 2 unconfirmed PRs
- SD was observed in 57% (16/28) of patients
- Clinical benefit (DCR) was observed in 100% (28/28) of patients
- No apparent association between response rate and molecular status was shown in an exploratory analysis[e]

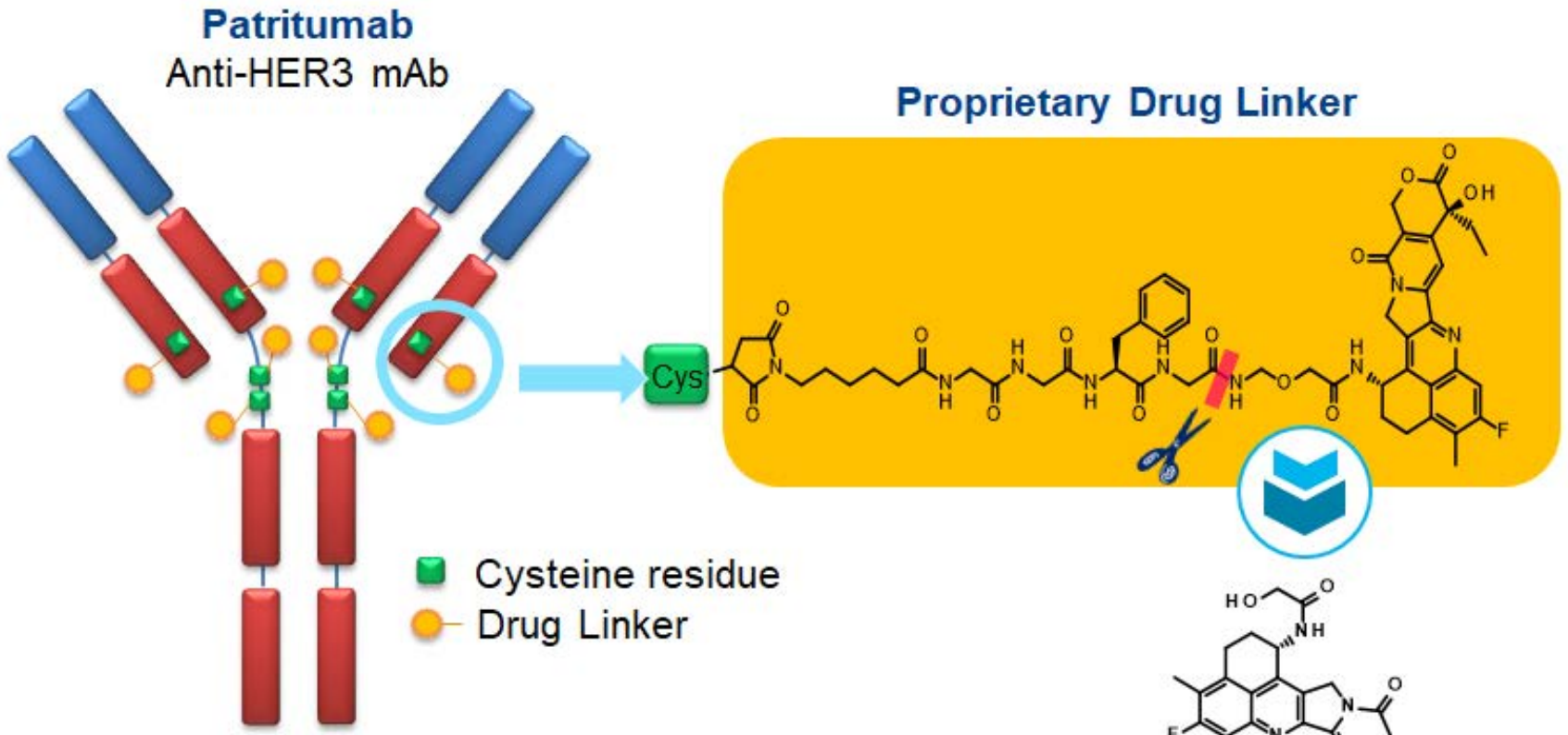
[a]All results are based on investigator assessments. [b]Evaluable population (n = 28) excludes 4 patients who withdrew consent prior to the first scan. [c]At the time of the 9 July 2021 data cutoff, 2 patients had uPRs. [e]Molecular status (*BRAF* V600E mutation, MSI-H or dMMR, *EGFR* amplification, *TP53* mutation, *PIK3CA* mutation) includes patients with conclusively evaluable test results.
Data as of 9 July 2021 (median follow-up: 7 months).
Weiss J, et al. ESMO 2021. Abstract LBA6.

TAKE HOME POINT:

Treatment for KRAS G12C mutated mCRC is evolving, and initial data is promising – particularly in combination with anti-EGFR therapy

Is HER3 a potential target in mCRC?

U3-1402 – anti-HER3 ADC



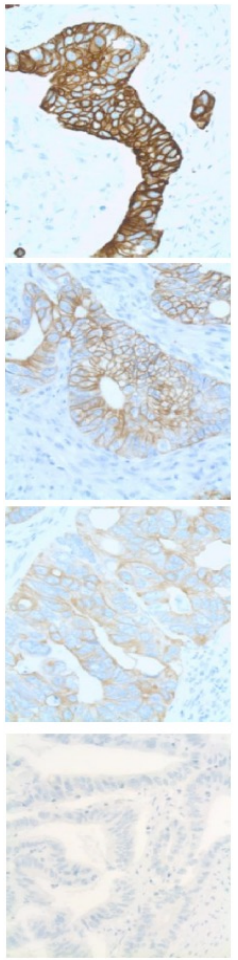
Conjugation Chemistry
The linker is connected to cysteine residues of the antibody

Proprietary Payload (DXd)
DX-8951 derivative
(topoisomerase I inhibitor)

Masuda N, et al. SABCS 2018 poster.

What is the expression rate of HER3 in CRC?

Study	Testing Modality	Cutoffs	Stage of CRC	Tissue Tested	Sample Size	Proportion
Ledel 2014 24300455	IHC (DAKO)	10% Membranous	II/III	Primary	236	3+ = 42% 2+ = 28% 0/1+ = 30%
Ledel 2014 24300455	IHC (DAKO)	10% Membranous	III	Lymph Nodes	102	3+ = 56% 2+ = 20% 0/1+ = 24%
Seo 2015 25739551	IHC (DAKO)	10% Membranous Or Cytoplasmic	All Stages	All tissue	364	3+ = 18% 2+ = 50% 0/1+ = 32%
Styczen 2015 25915155	IHC (Spring Bioscience)	10% ToGA	IV	Liver	208	3+ = 45% 2+ = 30% 0/1+ = 25%
Styczen 2015 25915155	IHC (Spring Bioscience)	10% ToGA	IV	Primary	22	3+ = 64% 2+ = 9% 0/1+ = 27%



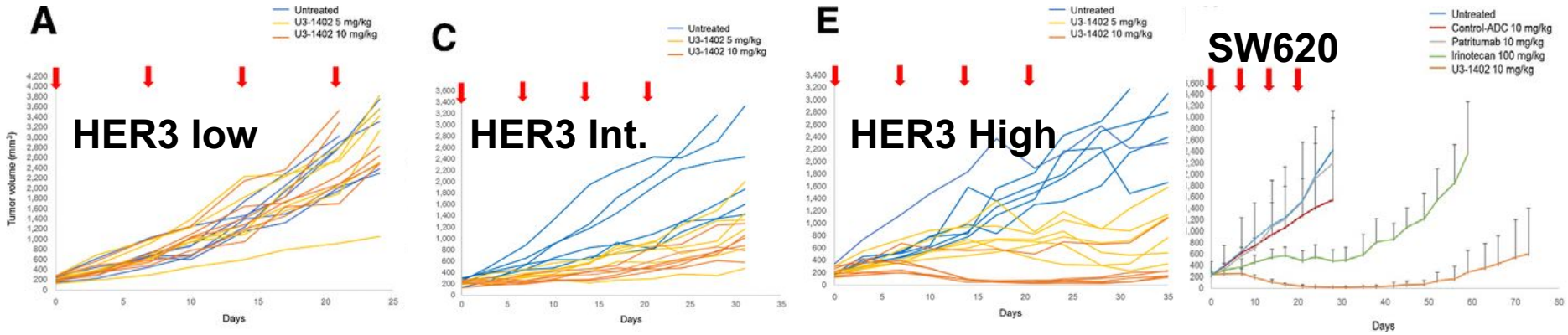
45%

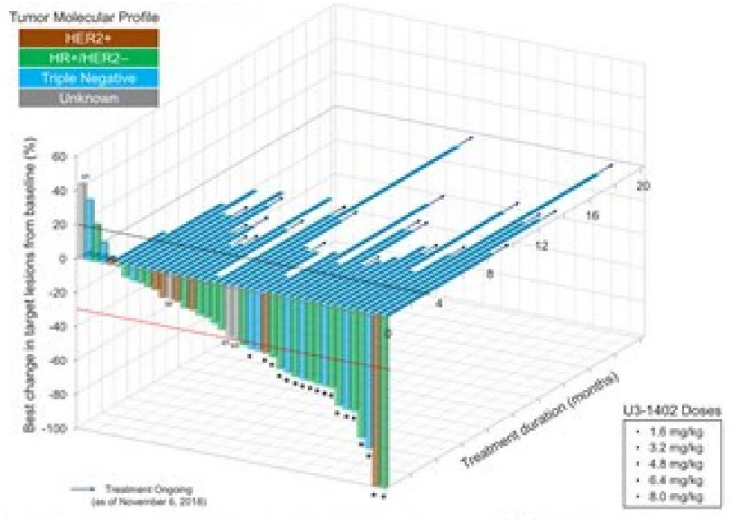
25%

30%

Slide courtesy of Kanwal Raghav, MD and Scott Kopetz, MD

Preliminary Data on Efficacy of U3-1402 in breast cancer





U3-1402 in HER3-overexpressing mBC (N = 42):

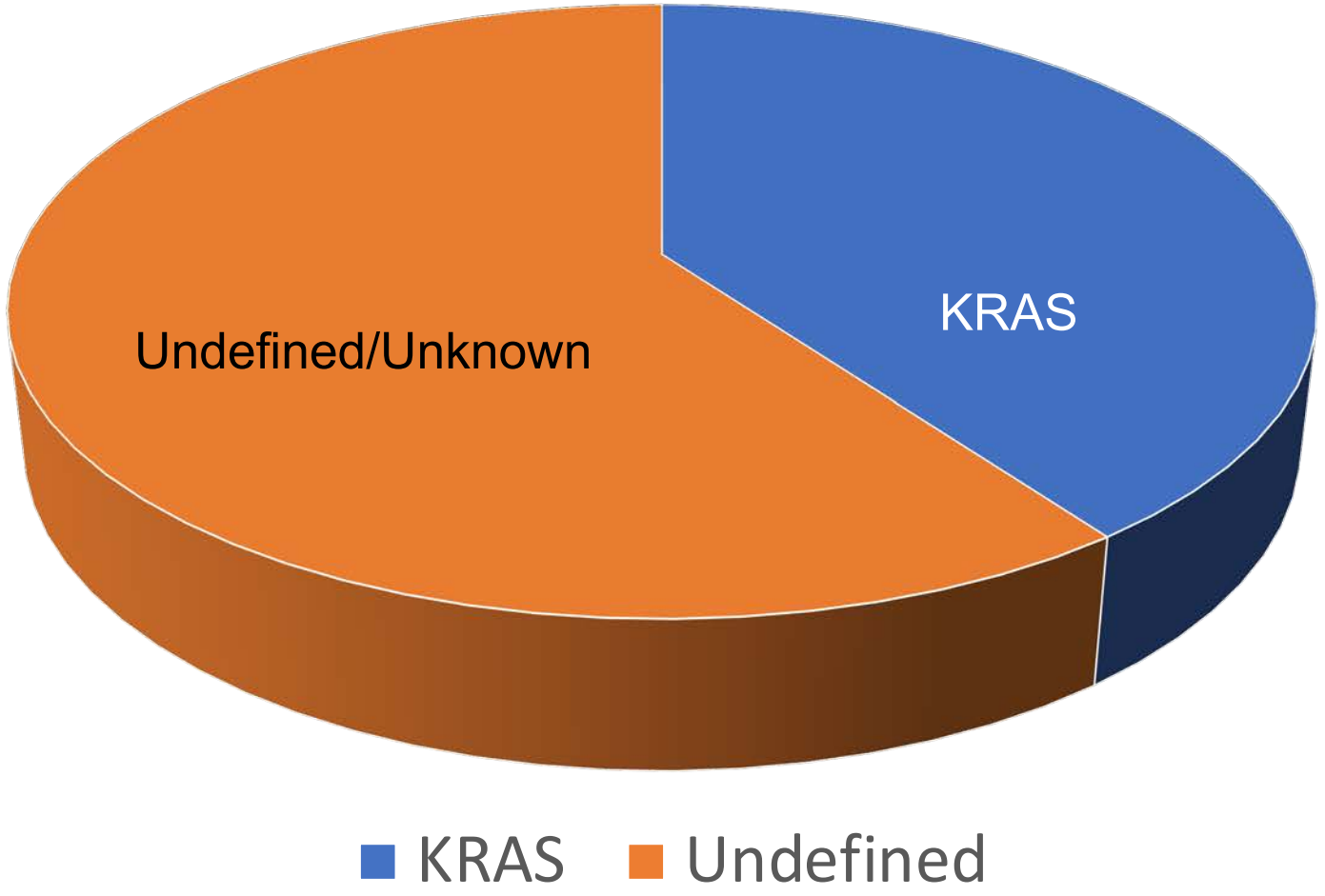
- ORR ~ 46.3%
- DOR ~ NR
- DCR ~ 90.1%
- PFS ~ 8.3 months

Grade ≥3 TEAEs: 61.9%

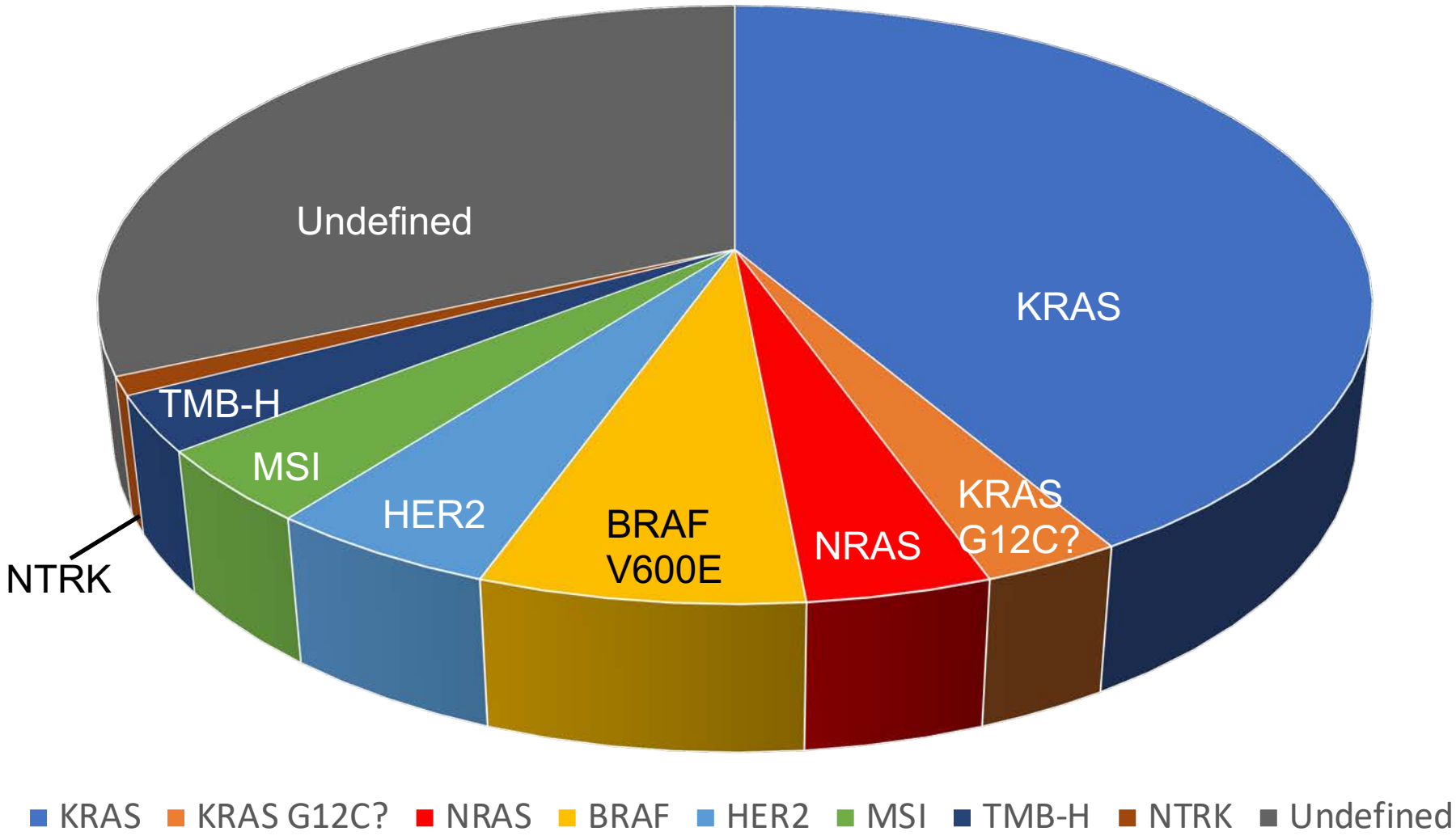
- Nausea (4.8%)
- Thrombocytopenia (33.3%)
- Anorexia (7.1%)
- Neutropenia (26.2%)
- Leukopenia (19.0%)

Masuda SABCS 2018; Koganemaru MCT 2019

Snapshot of Molecularly-Directed Therapy for mCRC (2011)



Snapshot of Molecularly-Directed Therapy for mCRC (2021)



Final Thoughts

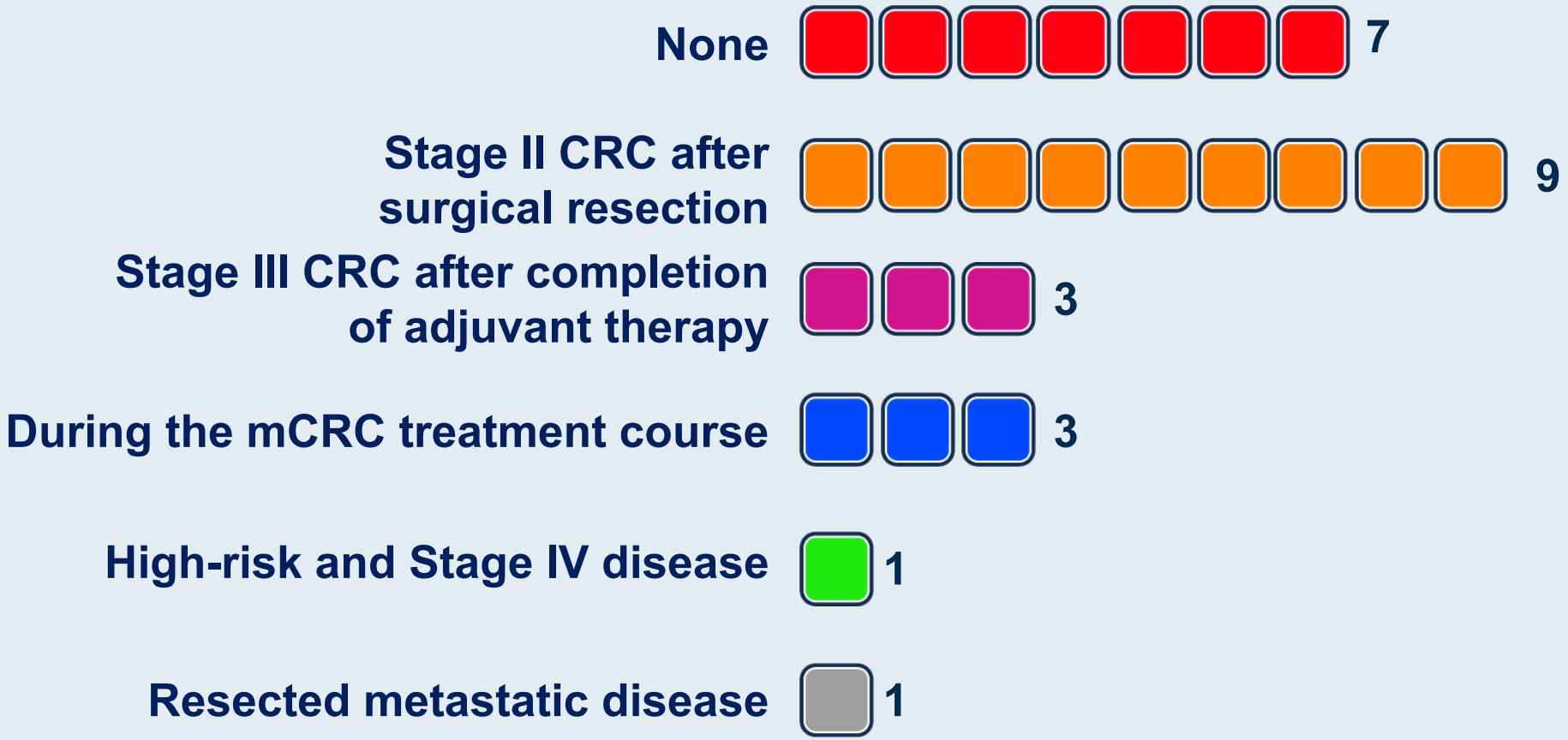
- Minimal Residual Disease: ctDNA data is exciting
  - Is the data purely prognostic, or is it ACTIONABLE?

- Sidedness in metastatic CRC
  - Patients with right-sided primaries should not be treated with anti-EGFR therapy in the frontline setting
    - Is therapy effective in the refractory setting?

- Is KRAS druggable?
  - Evolving data with G12C inhibitors particularly in combination with cetuximab

- HER3 ADC shows promising activity in breast cancer
  - Is efficacy translatable to mCRC?

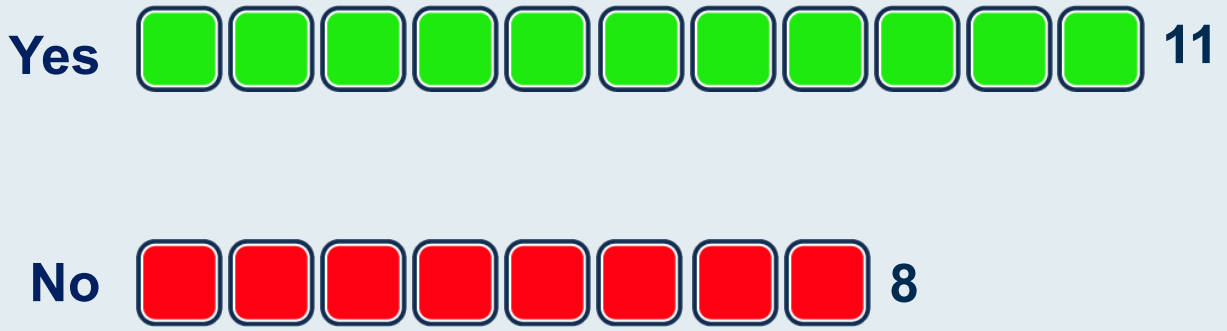
In general, in which settings, if any, do you order a circulating tumor DNA (ctDNA) assay for your patients with CRC outside of a clinical trial? (Select all that apply.)



In general, when using a ctDNA assay for a patient with CRC, which assay do you order?

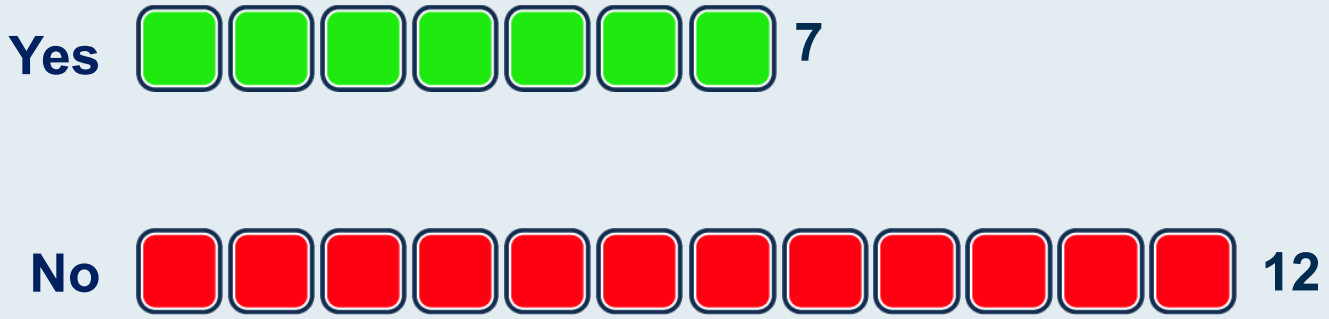
Survey of US-based clinical investigators

In general, do you use the results of ctDNA assays to inform treatment decisions for your patients with CRC outside of a protocol setting?

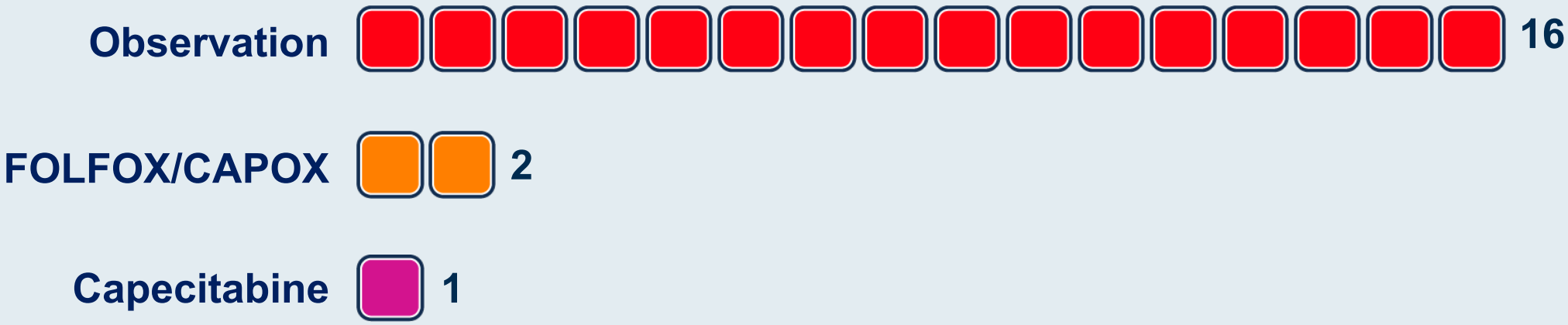


Survey of US-based clinical investigators

A 65-year-old patient presents with Stage II CRC with no high-risk features and undergoes R0 resection. Would you order a ctDNA assay to inform the decision regarding adjuvant chemotherapy?

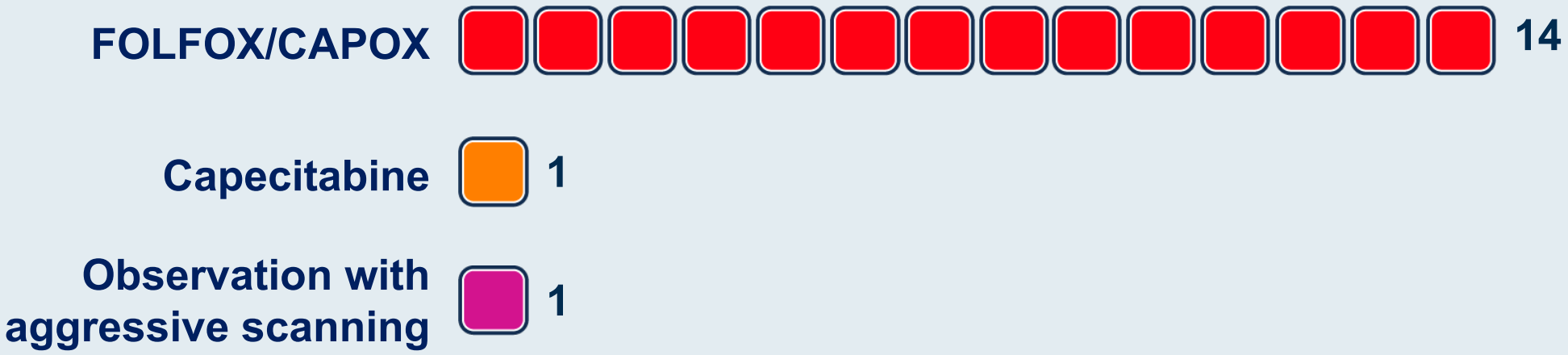


A ctDNA assay is ordered for the patient in the previous scenario and returns negative for the presence of ctDNA. What would be your approach to adjuvant therapy?



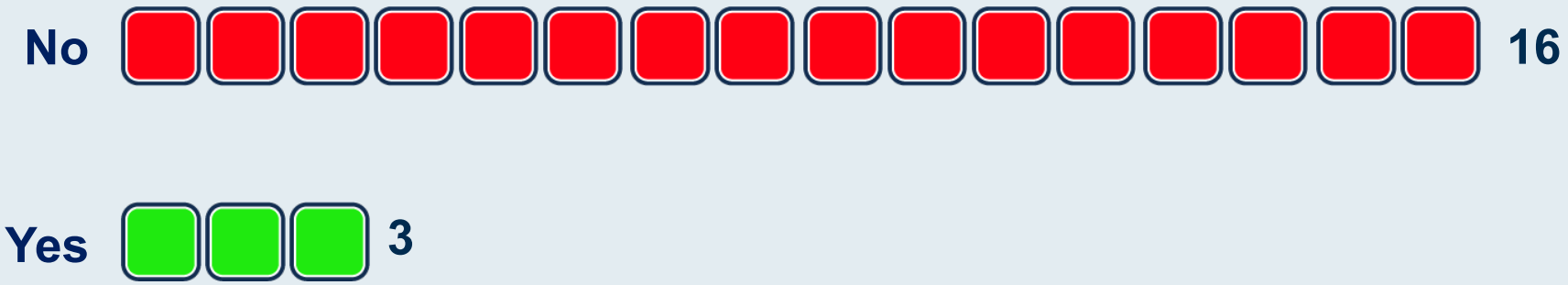
Survey of US-based clinical investigators

A ctDNA assay is ordered for the patient in the previous scenario and returns positive for the presence of ctDNA. What would be your approach to adjuvant therapy?



Survey of US-based clinical investigators

A 65-year-old patient presents with low-risk Stage III (T2N1) CRC and undergoes R0 resection. Would you order a ctDNA assay to inform the decision regarding adjuvant chemotherapy?



Survey of US-based clinical investigators

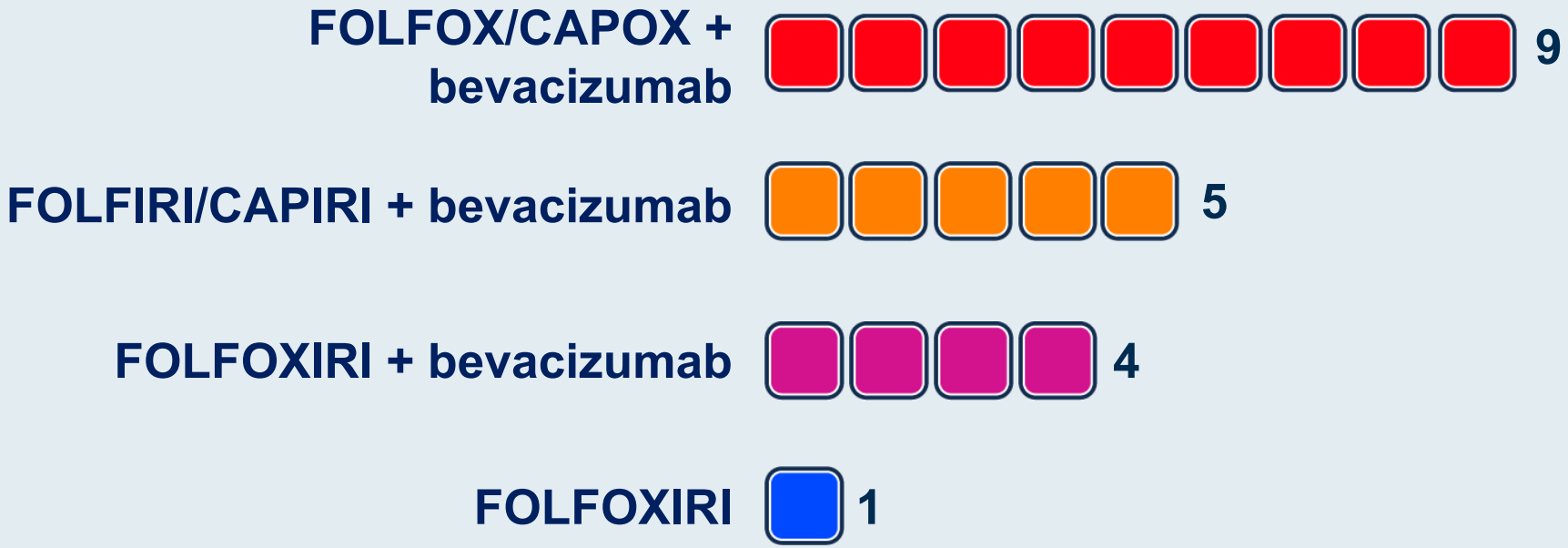
A ctDNA assay is ordered for the patient in the previous scenario and returns negative for the presence of ctDNA. What would be your approach to adjuvant therapy?

Survey of US-based clinical investigators

A ctDNA assay is ordered for the patient in the previous scenario and returns positive for the presence of ctDNA. What would be your approach to adjuvant therapy?

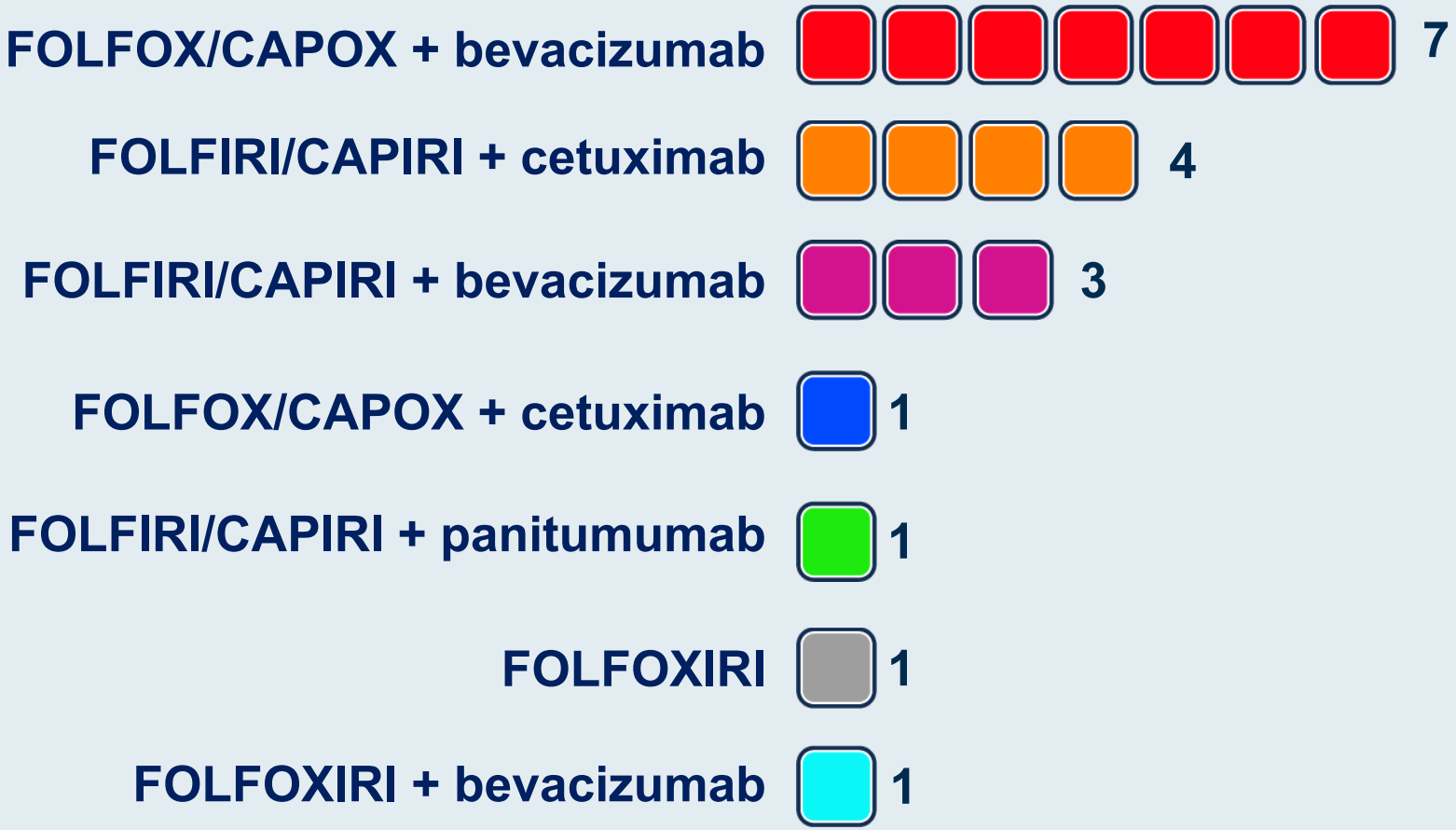
Survey of US-based clinical investigators

What is your usual first-line treatment recommendation for a clinically stable 60-year-old patient with right-sided, MSS, pan-RAS wild-type, BRAF wild-type mCRC?



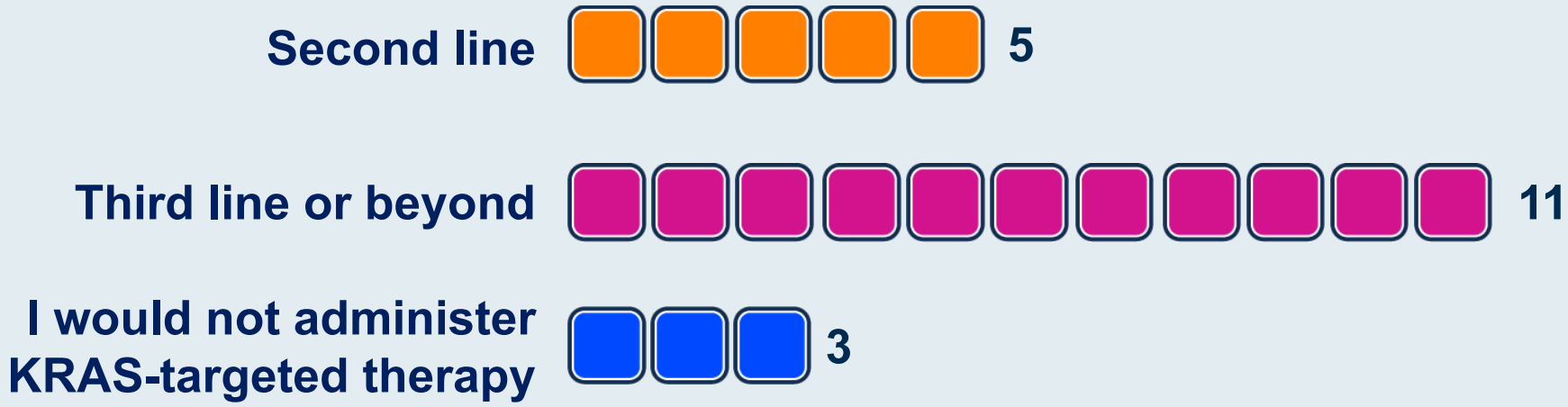
Survey of US-based clinical investigators

What is your usual first-line treatment recommendation for a clinically stable 60-year-old patient with left-sided, MSS, pan-RAS wild-type, BRAF wild-type mCRC?



Survey of US-based clinical investigators

Regulatory and reimbursement issues aside, for a patient with mCRC with a KRAS p.G12C mutation, in which line of therapy would you generally administer KRAS-targeted therapy (eg, sotorasib)?



Survey of US-based clinical investigators

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Gastroesophageal Cancers (Part 2 of a 3-Part Series)

Thursday, January 20, 2022
9:15 PM – 10:45 PM ET

Faculty

Yelena Y Janjigian, MD
Eric Van Cutsem, MD, PhD
Harry H Yoon, MD

Moderator

Samuel J Klempner, MD

RTP
RESEARCH
TO PRACTICE

Thank you for attending!

CME Credit Information

For those participating in person today, please remit your CME credit form as you exit the meeting room.

For all others, a CME credit link will be provided in the chat room at the conclusion of the program.

RTP
RESEARCH
TO PRACTICE