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

Part 1 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Gastrointestinal Cancers Symposium

Wednesday, January 18, 2023
7:15 PM – 9:15 PM PT

Faculty

Tanios Bekaii-Saab, MD
Scott Kopetz, MD, PhD
John Strickler, MD
Eric Van Cutsem, MD, PhD

Moderator

Kristen K Ciombor, MD, MSCI

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Faculty

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Program Leader, Gastrointestinal Cancer
Mayo Clinic Cancer Center
Consultant, Mayo Clinic in Arizona
Chair, ACCRU Research Consortium
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John Strickler, MD
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Professor of Medicine
Digestive Oncology
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Moderator
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Tanios Bekaii-Saab, MD — Disclosures
Faculty

Consulting Agreements (to Institution)	Arcus Biosciences, Bayer HealthCare Pharmaceuticals, Eisai Inc, Genentech, a member of the Roche Group, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Merck, Merck KgaA, Merus BV, Pfizer Inc, Seagen Inc
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Data and Safety Monitoring Board/Committee	1Globe Health Institute, AstraZeneca Pharmaceuticals LP, Eisai Inc, Exelixis Inc, FibroGen Inc, Merck, Suzhou Kintor
Inventions/Patents	WO/2018/183488 licensed to Imugene, WO/2019/055687 licensed to Recursion
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Scott Kopetz, MD, PhD — Disclosures
Faculty

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John Strickler, MD — Disclosures
Faculty

Advisory Committee	AbbVie Inc, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, GSK, Lilly, Natera Inc, Pfizer Inc, Pionyr Immunotherapeutics, Seagen Inc, Silverback Therapeutics, Takeda Pharmaceuticals USA Inc, Viatris
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Data and Safety Monitoring Board/Committee	AbbVie Inc, BeiGene Ltd, Pionyr Immunotherapeutics
Nonrelevant Financial Relationship	AStar D3

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Eric Van Cutsem, MD, PhD — Disclosures
Faculty

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Research Grants to Institution	Amgen Inc, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Ipsen Biopharmaceuticals Inc, Lilly, Merck KGaA, Merck Sharp & Dohme Corp, Novartis, Roche Laboratories Inc, Servier Pharmaceuticals LLC

Kristen K Ciombor, MD, MSCI — Disclosures
Moderator

Advisory Committee and Consulting Agreements	Incyte Corporation, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Personalis Inc, Pfizer Inc, Replimune, Seagen Inc
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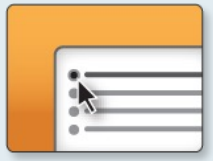
Clinicians in the Meeting Room

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 pre- and postmeeting surveys. 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.

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Clinicians Attending via Zoom

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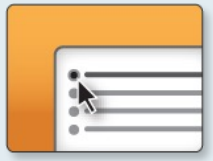

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Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

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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.
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Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Gastroesophageal Cancers

Part 2 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Gastrointestinal Cancers Symposium

Thursday, January 19, 2023
6:15 PM – 7:45 PM PT

Faculty

Yelena Y Janjigian, MD
Zev Wainberg, MD, MSc
Florian Lordick, MD, PhD

Moderator

Samuel J Klempner, MD

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Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Hepatobiliary Cancers

Part 3 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Gastrointestinal Cancers Symposium

Friday, January 20, 2023

6:00 PM – 7:30 PM PT

Faculty

Richard S Finn, MD

Professor Arndt Vogel, MD

Lipika Goyal, MD, MPhil

Moderator

Robin K (Katie) Kelley, MD

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Commercial Support

This activity is supported by educational grants from Bayer HealthCare Pharmaceuticals, Exelixis Inc, Lilly, Natera Inc, and Seagen Inc.

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

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

Part 1 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Gastrointestinal Cancers Symposium

Wednesday, January 18, 2023
7:15 PM – 9:15 PM PT

Faculty

Tanios Bekaii-Saab, MD
Scott Kopetz, MD, PhD
John Strickler, MD
Eric Van Cutsem, MD, PhD

Moderator

Kristen K Ciombor, MD, MSCI

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Agenda

Module 1 – Integration of Therapies Targeting BRAF and HER2 in Metastatic Colorectal Cancer (mCRC) — Dr Strickler

Module 2 – Optimizing the Use of Immune Checkpoint Inhibitors in the Management of mCRC — Dr Ciombor

Module 3 – Evidence-Based Selection and Sequencing of Therapy for Patients with mCRC — Prof Van Cutsem

Module 4 – Promising Agents and Strategies for Patients with mCRC — Dr Bekaii-Saab

Module 5 – The Changing Management Paradigm for Localized CRC — Dr Kopetz

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

Farshid Dayyani, MD, PhD
UCI Chao Family Comprehensive Cancer Center
Orange, California

Philip L Brooks, MD
Northern Light Eastern Maine Medical Center and Lafayette Family Cancer Institute
Brewer, Maine

Victoria Giffi, MD
Meritus Hematology and Oncology Specialists
Hagerstown, Maryland

Jennifer L Dallas, MD
Oncology Specialists of Charlotte
Charlotte, North Carolina

Ranju Gupta, MD
Lehigh Valley Topper Cancer Institute
Bethlehem, Pennsylvania

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Shaachi Gupta, MD, MPH
Florida Cancer Specialists
Lake Worth, Florida

Liudmila N Schafer, MD
Saint Luke's Cancer Institute
Kansas City, Missouri

Namrata I Peswani, MD
Harold C Simmons Comprehensive Cancer Center
Richardson, Texas

Lai (Amber) Xu, MD, PhD
Northwest Oncology & Hematology
Rolling Meadows, Illinois

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MODULE 1: Integration of Therapies Targeting BRAF and HER2 in Metastatic Colorectal Cancer (mCRC) — Dr Strickler

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Case Presentation: A 40-year-old man presenting with MSS rectal cancer and liver metastases

Dr Victoria Giffi (Hagerstown, Maryland)

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QUESTIONS FOR THE FACULTY

Victoria Giffi, MD

"I'm very curious where we are research-wise with patients in the 20- to 40-year-old range getting colorectal cancer, because in the community we are seeing it much more and the American Cancer Society recommendation for having screening colonoscopies at 45 is not catching all of these patients."

- **What is the magnitude of the increase in incidence of CRC in younger people? What are the screening implications?**
- **What is your typical choice of systemic therapy for patients with liver oligometastases, and do you use postoperative "adjuvant" treatment?**
- **If this man were to develop disease progression, what would your likely next systemic regimen be outside of a clinical trial?**

Dr Ranju Gupta
(Bethlehem, Pennsylvania)

A 79-year-old man with HER2-amplified colon cancer and extensive liver metastases

Dr Shaachi Gupta
(Lake Worth, Florida)

A 57-year-old man with KRAS G12S-mutant HER2-amplified colon cancer and lung metastases

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QUESTIONS FOR THE FACULTY

Ranju Gupta, MD

"We had the TAPUR trial from ASCO at our institute, so I gave him the trastuzumab and pertuzumab as part of the trial. He did extremely well and had a partial response…. He is now on trastuzumab deruxtecan. What other anti-HER2 treatments can be used? I know tucatinib was in trials in colon cancer."

- **What are the diagnostic criteria for "HER2-positive" CRC?**
- **Which anti-HER2 regimens have been studied, and when should these be used?**
- **How would you screen this patient on trastuzumab deruxtecan for interstitial lung disease?**
- **What regimen would you consider on progression? (Tucatinib/trastuzumab?)**

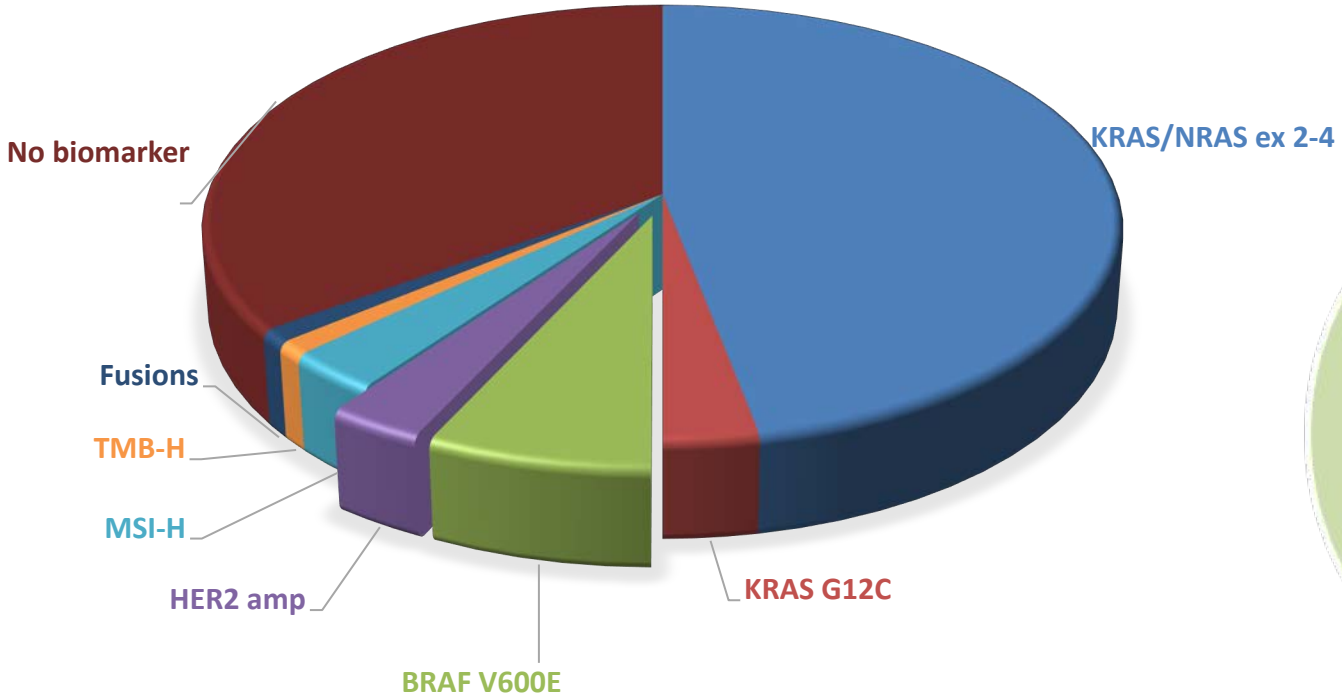
Integration of Therapies Targeting BRAF and HER2 in Metastatic Colorectal Cancer (mCRC)

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

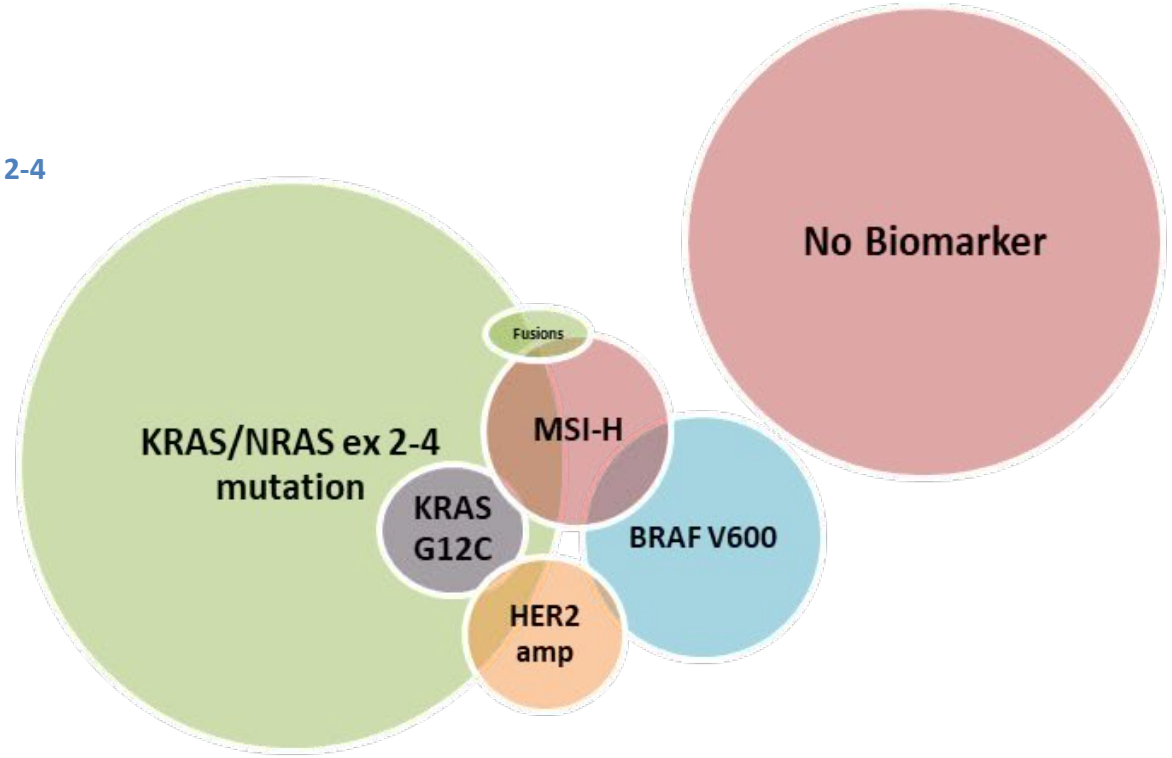
January 18, 2023

Actionable colorectal cancer targets in 2023

Actionable targets… simplified



Actionable targets… reality



ERBB2 (*HER2*) amplification concentrated in patients with RAS/BRAF WT metastatic CRC

Unselected

Dataset	Patients (n)	*ERBB2* amplified
GENIE Cohort v12.1[1]	137,166	2.3%
Foundation Medicine[2]	5,127	3.0%
CARIS Life Sciences[3]	1,226	3.8%
TCGA[4]	615	3.1%

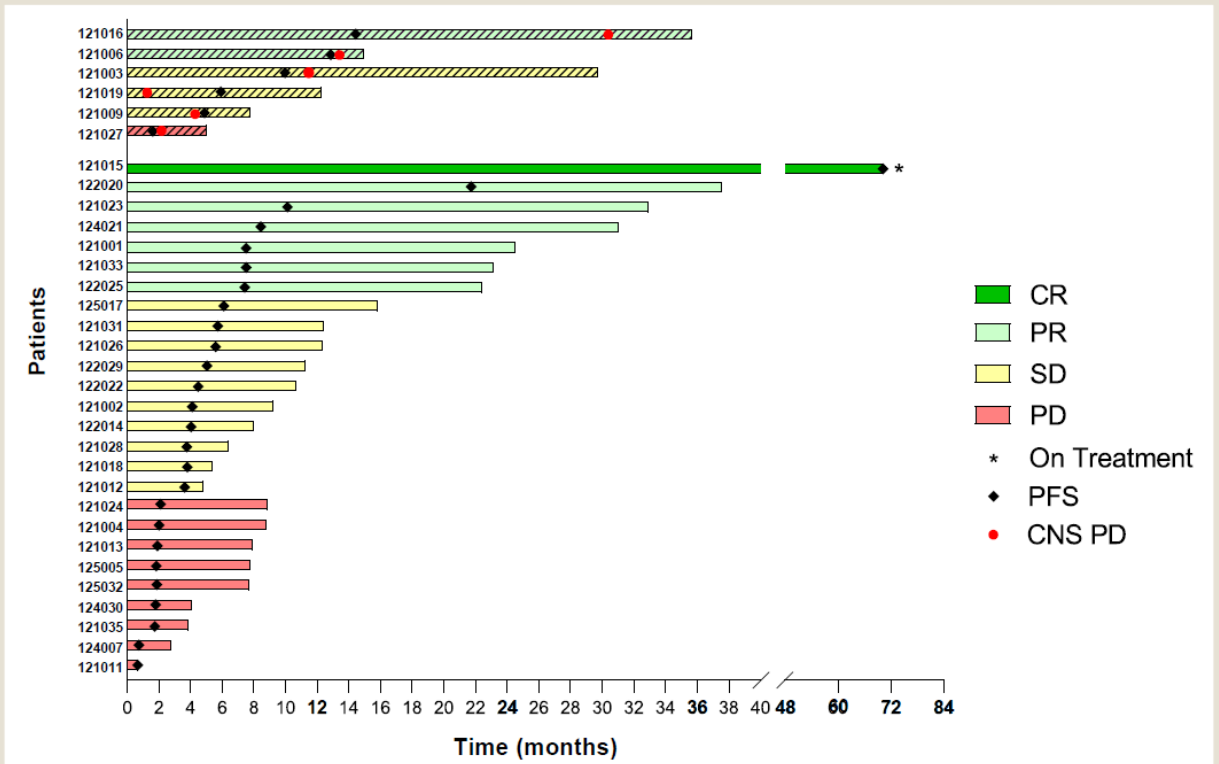
1. Public AACR Project GeNIE cohort
2. J Clin Oncol 34, 2016 (suppl 4S; abstr 630)
3. J Clin Oncol 32, 2014 (suppl; abstr e22200)
4. cbioportal.org

Biomarker enriched

Dataset	Patient sub-group/ (n)	*ERBB2* amplified
HERACLES[1]	914 KRAS exon 2 WT	5.3%
MDACC[2]	98 sequential KRAS/NRAS/BRAF WT	12.2%
Duke University[3]	81 patients with RAS WT mCRC after anti-EGFR (ctDNA)	12.3%

1. Sartore-Bianchi et al., Lancet Oncol, 17(6) 738 - 746 .
2. Raghav et al., J Precision Oncol 2019 31-13.
3. Jia et al., J Clin Oncol 36, 2018 (suppl; abstr 3555)

Long-term clinical outcome of HERACLES-A (trastuzumab + lapatinib) for HER2-positive mCRC



- 7 years of follow-up; 32 patients evaluable
- 28% ORR with 1 patient with 7-year CR
- Median PFS= 4.7 months
- Median OS= 10.0 months

CNS, central nervous system; CR, complete response; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Tosi F et al., Clin Colorectal Cancer 2020

Studies of trastuzumab + pertuzumab for HER2+ mCRC

Trial	N	ORR (95% CI)	Median PFS Months (95% CI)	Median OS Months (95% CI)
MyPathway[1,2]	57 (all RAS) 68 (RAS WT)* 16 (RAS mut)*	32% (20-45) 31% (n/a) 6% (n/a)	2.9 (1.4-5.3)	11.5 (7.7-NE)
TRIUMPH[3]	27 tissue+ 25 ctDNA+	30% (14-50) 28% (12-49)	4.0 (1.4-5.6) 3.1 (1.4-5.6)	10.1 (4.5-16.5) 8.8 (4.3-12.9)
TAPUR[4]	28	25% (11-45)	4.0 (2.6-6.4)	14.0 (7.5-23.9)

* Updated at ASCO 2021 Annual Meeting

ctDNA, circulating tumor DNA; n/a, not available; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; WT, wildtype.

1. Meric-Bernstam et al., Lancet Oncol 2019; 2. Meric-Bernstam et al., J Clin Oncol 39, 2021 (suppl 15; abstr 3004); 3. Nakamura et al., Nature Medicine 27, 2021;
4. Gupta et al., JCO Precision Oncology 2022.

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

Cohort A, N=53 (response assessed by BICR)

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.

Yoshino T et al. Gastrointestinal Cancers Symposium 2022;Abstract 119.

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

(All cohorts, N=78)

	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

- Five (6%) of 78 patients had interstitial lung disease or pneumonitis
  - Grade 2 = 2 patients
  - Grade 3 = 1 patient
  - Grade 5 = 2 patients
- Median time to onset date of interstitial lung disease or pneumonitis was 77 days
- 2 recovered, 1 did not recover and died of disease progression, and 2 died due to the AE

AE, adverse event; HER2+, HER2 gene amplification; mCRC, metastatic colorectal cancer; TEAE, treatment-emergent adverse event.

Siena et al., Lancet Oncol 2021.

DESTINY-CRC01: Trastuzumab deruxtecan for HER2+ mCRC - Subgroup analyses

Cohort A, N=53 (response assessed by BICR)

	N	ORR (%)	95% CI
Cohort A overall	53	45.3	31.6-59.6
HER2 status			
IHC3+	40	57.5	40.9-73.0
IHC2+ and ISH-positive	13	7.7	0.2-36.0
Previous HER2 treatment			
Yes	16	43.8	19.8-70.1
No	37	45.9	29.5-63.1

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.

Yoshino T et al. Gastrointestinal Cancers Symposium 2022;Abstract 119.

DESTINY-CRC01: Adverse Events of Special Interest – ILD/Pneumonitis

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

Adjudicated drug-related ILD/pneumonitis:

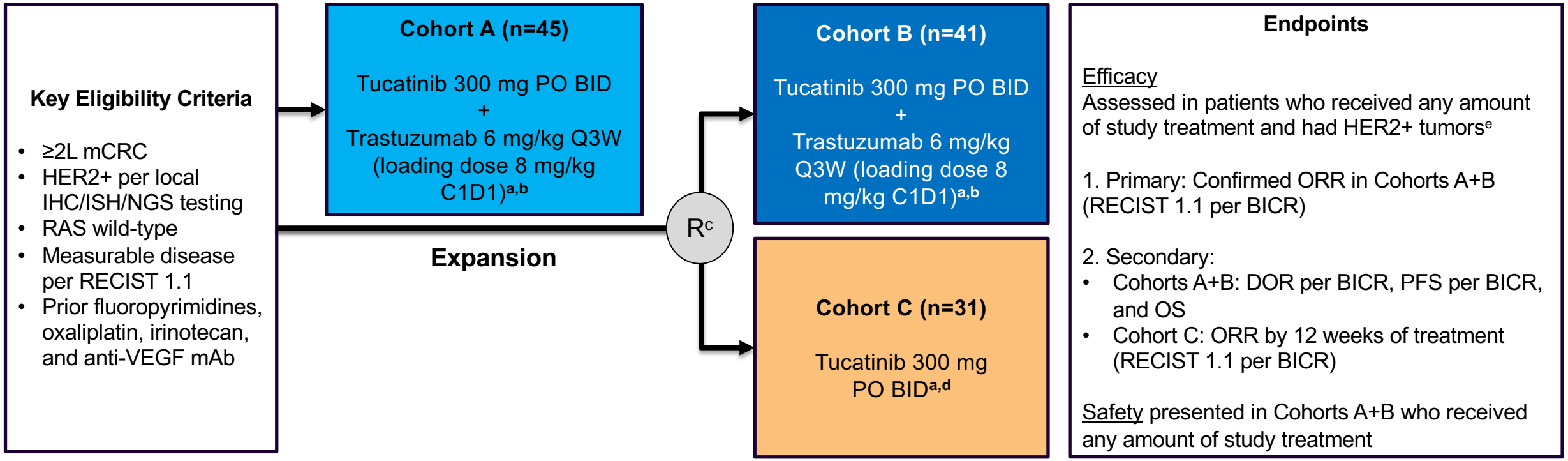
- Median time to adjudicated onset was 61.0 days (range, 9-165)
- 8 of 8 patients received corticosteroids
- 4 patients with grade 2 recovered and 1 patient with grade 3 did not recover (later died due to disease progression)
- Median time from adjudicated onset date to initiation of steroid treatment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

Grade 5 ILD/pneumonitis:

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

Yoshino T et al. Gastrointestinal Cancers Symposium 2022;Abstract 119.

MOUNTAINEER: Global, Open-Label, Phase 2 Trial



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

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

a Each treatment cycle is 21 days; b Patients remained on therapy until evidence of radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or study closure; c Stratification: Left sided tumor primary vs other; d Patients were allowed to cross over and receive tucatinib and trastuzumab if they experienced radiographic progression at any time point or if they had not achieved a PR or CR by week 12; e Patients had HER2+ tumors as defined by one or more protocol required local tests: IHC 3+ (n=46), amplification by ISH (n=36), or amplification by NGS (n=69)

2L+, second line and later; BICR, blinded independent central review; BID, twice a day; C1D1, cycle 1 day 1; CR, complete response; DOR, duration of response; HER2, human epidermal growth receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; PR, partial response; R, randomisation; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; US, United States; VEGF, vascular endothelial growth factor.

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

Tucatinib + Trastuzumab: Efficacy Outcomes

Responses	Tucatinib + Trastuzumab Cohorts A+B n=84
Best overall response per BICR[a], n (%)	
CR	3 (3.6)
PR	29 (34.5)
SD[b]	28 (33.3)
PD	22 (26.2)
Not available[c]	2 (2.4)
cORR per BICR, % (95% CI)[d]	**38.1 (27.7, 49.3)**
cORR per Investigator, % (95% CI)[d]	42.9 (32.1, 54.1)
Median time to objective response per BICR[e], months (range)	2.1 (1.2, 9.8)
DCR[f] per BICR, n (%)	60 (71.4)
Median DOR per BICR, months (95% CI)	**12.4 (8.5, 20.5)**

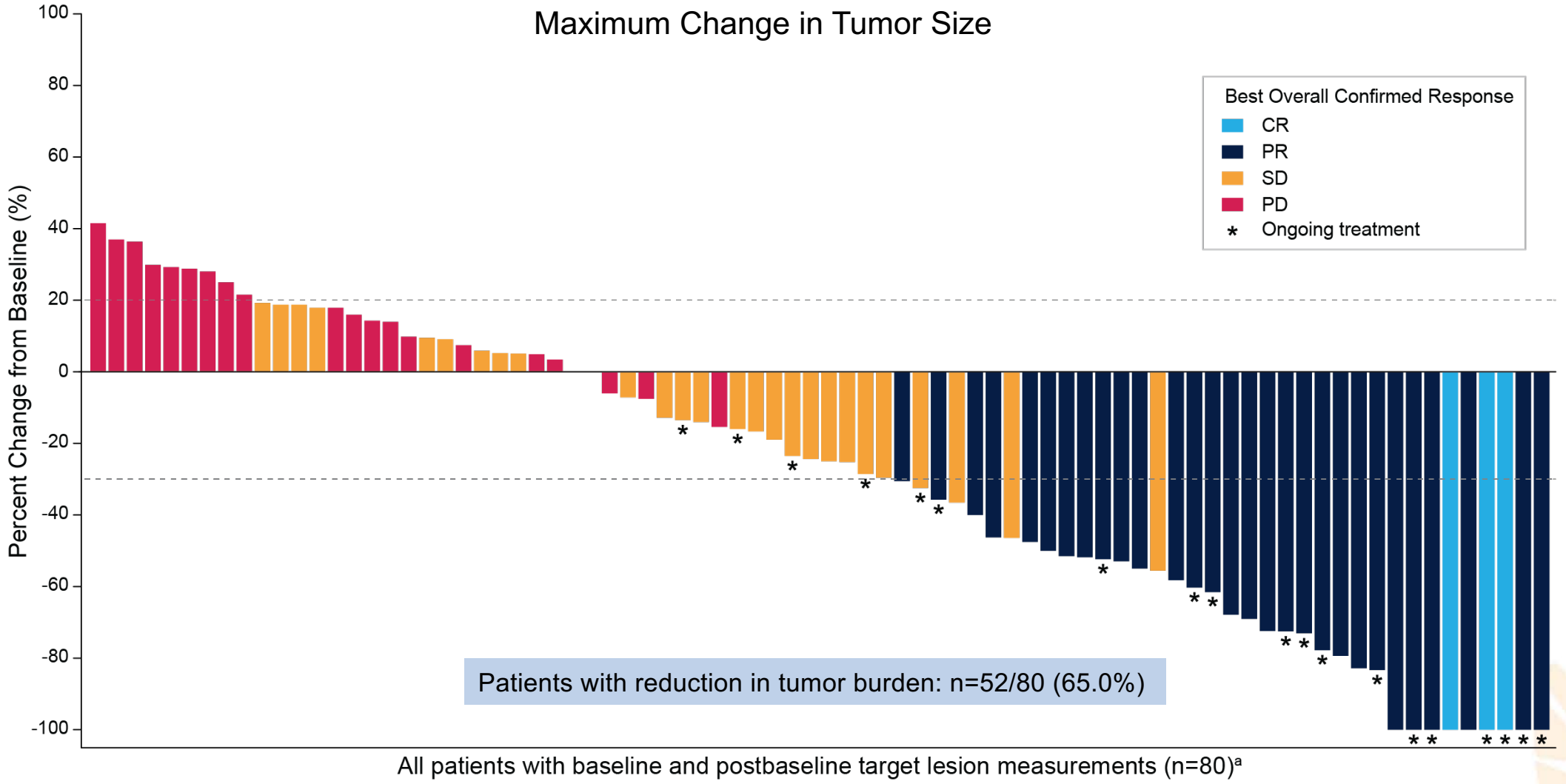
a Confirmed best overall response assessed per RECIST 1.1; b Includes SD and non-CR/non-PD; c Includes patients with no post-baseline response assessment and patients whose disease assessments are not evaluable; d Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934); e Time from the start of study treatment (Cohort A) or date of randomisation (Cohort B) to the first documentation of objective response (CR or PR that is subsequently confirmed); f Defined as sum of CR, PR, and SD

BICR, blinded independent central review; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Data cutoff: 28 Mar 2022

Presented at ESMO World Congress of Gastrointestinal Cancer 2022

Tucatinib + Trastuzumab: Change in Tumor Size



a Four patients who did not have baseline and/or post-baseline target lesion measurements are excluded

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

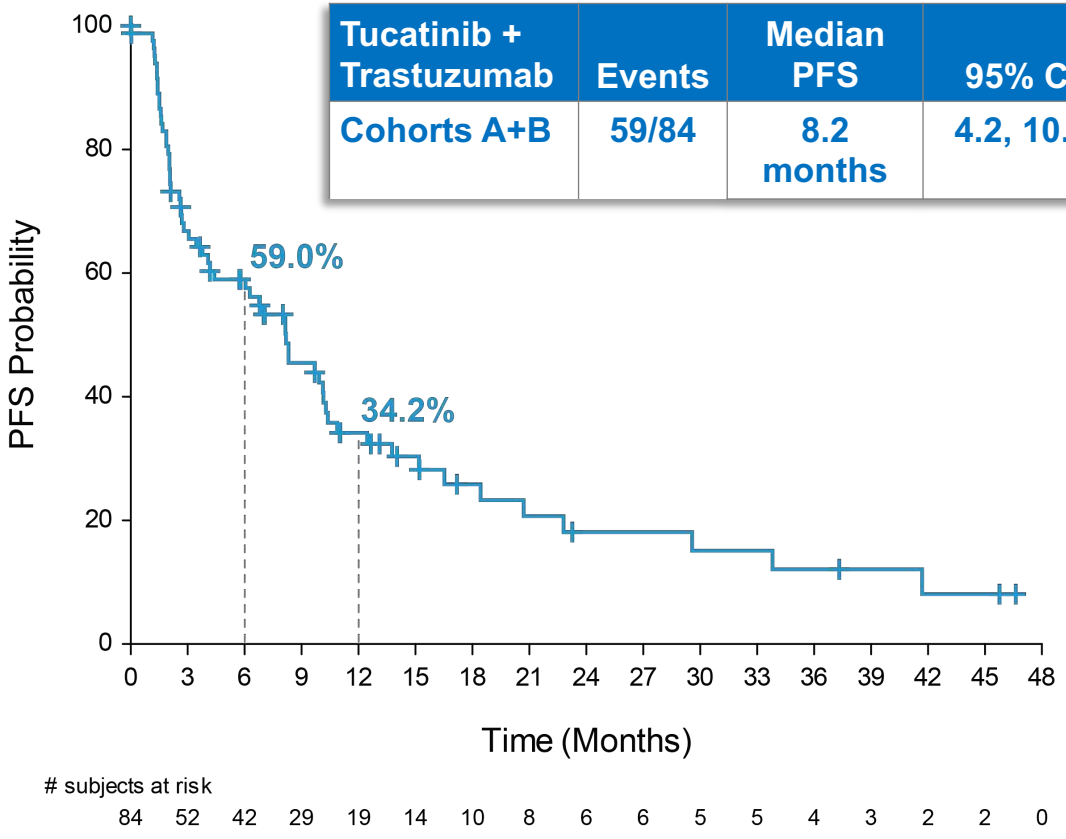
Data cutoff: 28 Mar 2022

Presented at ESMO World Congress of Gastrointestinal Cancer 2022

Tucatinib + Trastuzumab: PFS and OS

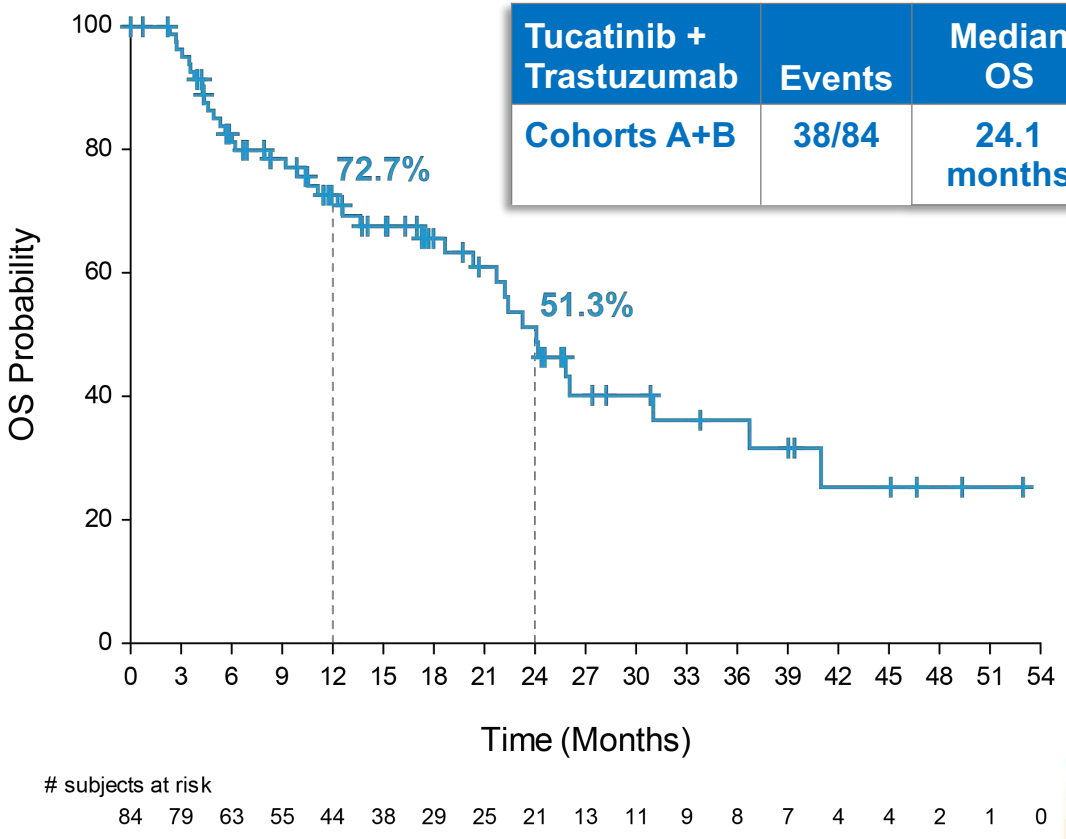
Progression-free Survival per BICR

Tucatinib + Trastuzumab	Events	Median PFS	95% CI
Cohorts A+B	59/84	8.2 months	4.2, 10.3



Overall Survival

Tucatinib + Trastuzumab	Events	Median OS	95% CI
Cohorts A+B	38/84	24.1 months	20.3, 36.7



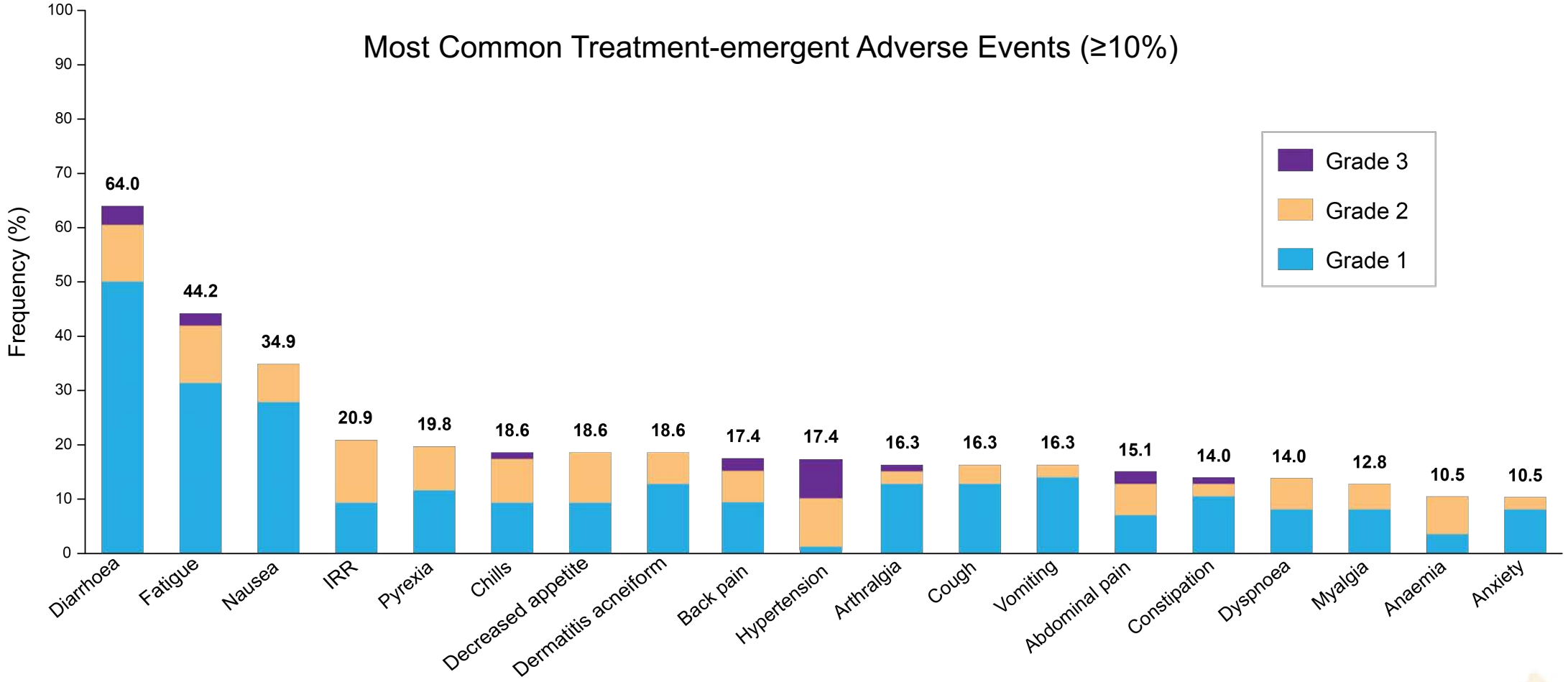
Median follow-up for Cohorts A+B was 20.7 months (IQR, 11.7, 39.0)

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

Data cutoff: 28 Mar 2022

Presented at ESMO World Congress of Gastrointestinal Cancer 2022

Most Common TEAEs (≥10%) for Tucatinib + Trastuzumab



- Most common tucatinib-related AEs (≥10%): diarrhoea (52.3%), fatigue (29.1%), nausea (18.6%), and dermatitis acneiform (17.4%)
  - Grade ≥3 tucatinib-related AEs (≥2%): alanine aminotransferase increase (2.3%) and diarrhoea (2.3%)

AE, adverse event; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.

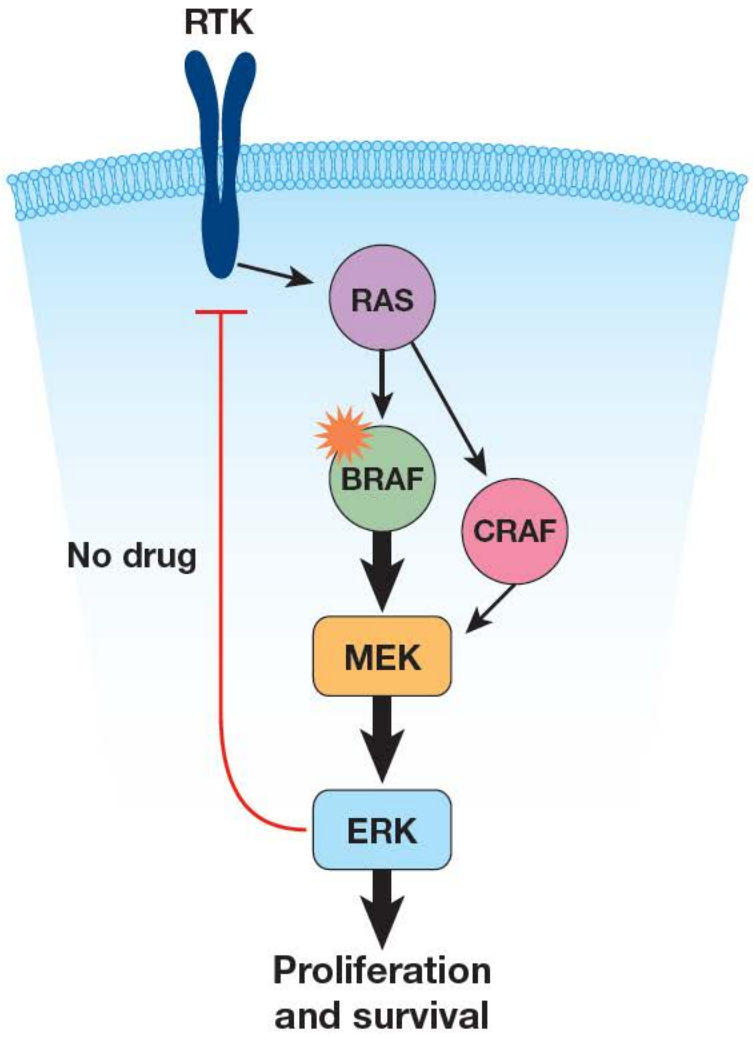
Data cutoff: 28 Mar 2022

Presented at ESMO World Congress of Gastrointestinal Cancer 2022

HER2 in metastatic CRC: Final thoughts

- *HER2* amplification/overexpression is an actionable target in refractory HER2+ mCRC
- Anti-HER2 therapies demonstrate greatest efficacy in biomarker selected HER2+ mCRC patient populations:
  - IHC 3+
  - High gene copy number
  - *KRAS*, *NRAS, PIK3CA*, and *BRAF* wildtype
- Several anti-HER2 therapies have demonstrated efficacy:
  - Trastuzumab + tucatinib has high ORR and DoR with favorable tolerability
  - Trastuzumab deruxtecan has high ORR and retains activity after progression on prior anti-HER2 therapies
- Key considerations: clinical/genomic characteristics, efficacy, and safety profile

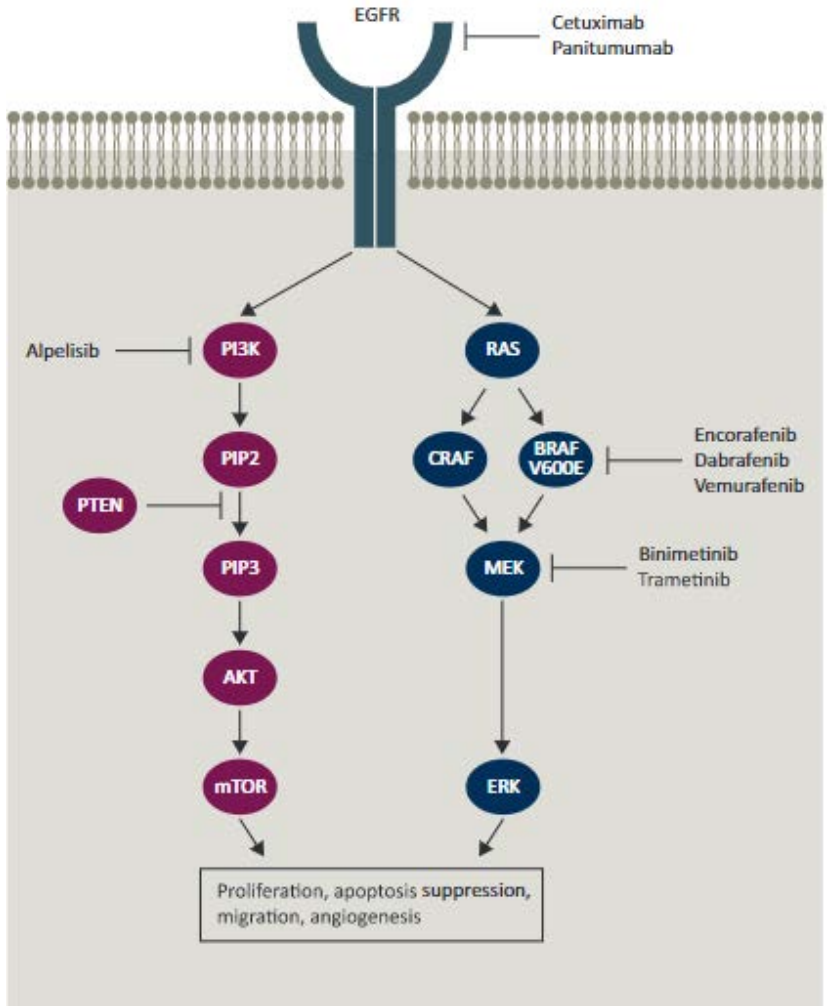
BRAF^{V600E} mutations in metastatic CRC



- ~7% of CRC
- Right sided
- High grade
- ~30% MSI-H
- Poor prognosis
- Limited benefit from anti-EGFR therapy

Source: Strickler *et al.*, Cancer Treat Rev. 2017 Nov;60:109-119.

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



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

Combination therapies	*Patients (N)*	*ORR (%)*	*Median PFS (mos)*
BRAFi + MEKi			
Dabrafenib + Trametinib	43	**12**	**3.5**
BRAFi + anti-EGFR			
Vemurafenib + Cetuximab	27	**4**	**3.7**
Vemurafenib + Panitumumab	15	**13**	**3.2**
Dabrafenib + Panitumumab	20	**10**	**3.5**
Encorafenib + Cetuximab	50	**22**	**4.2**
Encorafenib + Cetuximab	220	**20**	**4.2**
BRAFi + MEKi + anti-EGFR			
Dabrafenib + Trametinib + PMab	91	**21**	**4.2**
Encorafenib + Binimetinib + Cetux	224	**26**	**4.3**

BEACON CRC Phase 3 Study Design

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

Safety Lead-in

ENCORAFENIB + BINIMETINIB + CETUXIMAB
N = 30

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

Phase 3

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)

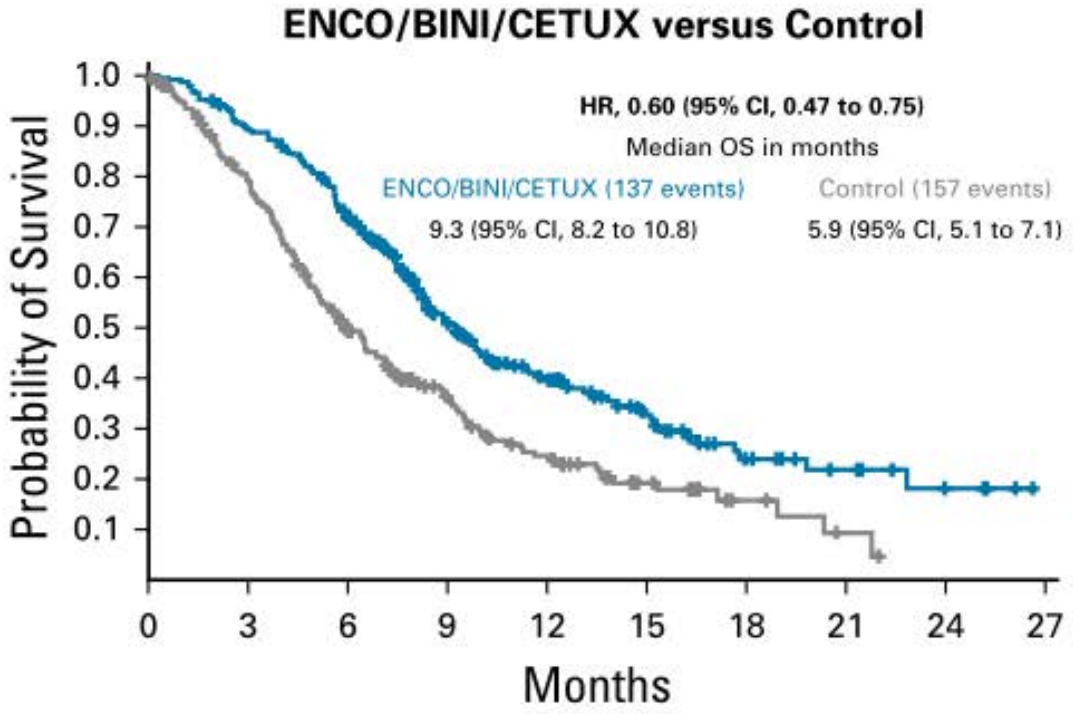
Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved)

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).

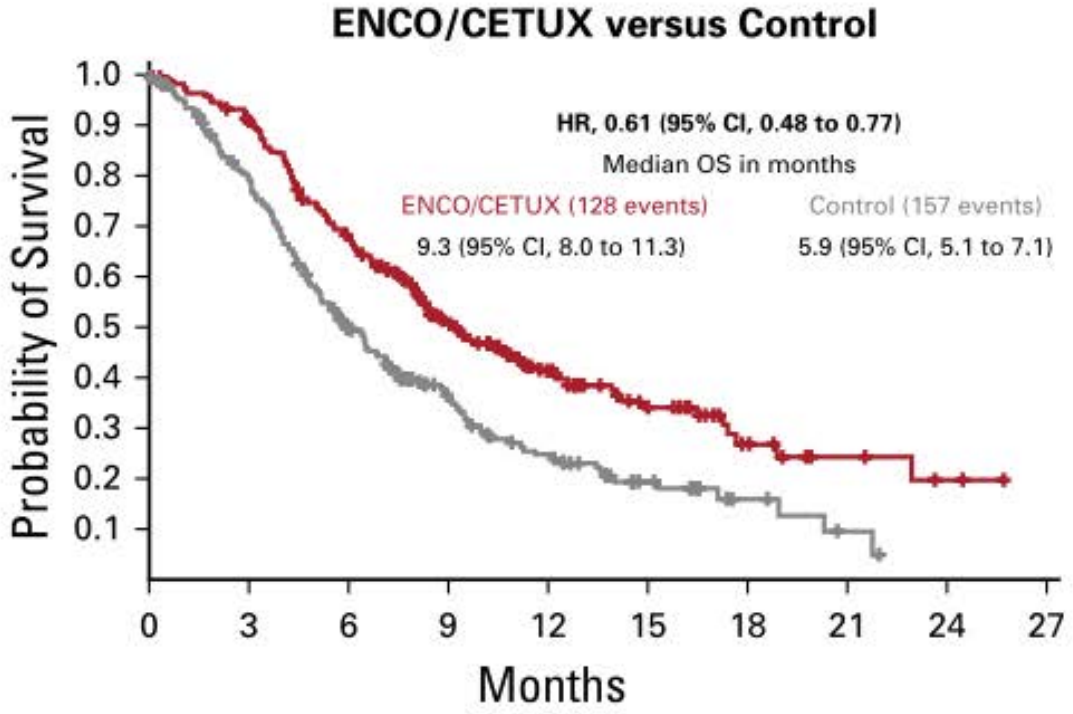
Van Cutsem. JCO. 2019. Taberno. ESMO 2019. LBA32. Kopetz. NEJM. 2019;[Epub]. NCT02928224

BEACON: Overall Survival (updated)
ENCO/BINI/CETUX vs ENCO/CETUX 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



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

Tabernero J, et al. J Clin Oncol. 2021; 39:273-284.

BEACON: Objective Response Rates (updated)

Confirmed Response by BICR	ENCO/BINI/CETUX N=224	ENCO/CETUX N=220	Control N=221
Objective Response Rate[a]	**27%**	**20%**	**2%**
95% (CI)	(21, 33)	(15, 25)	(<1, 5)
Best Overall Response[b]			
Complete Response (CR)	4%	3%	0%
Partial Response (PR)	23%	16%	2%
Stable Disease[c]	48%	56%	29%
Progressive Disease	11%	10%	34%
Non Evaluable by RECIST[d]	14%	15%	32%

BICR=blinded independent central review.

a. Confirmed responses per RECIST 1.1; Objective Response Rate equals the percentage of patients with a complete response or a partial response.

b. Best overall response percentage may not add up to 100% due to rounding.

c. Stable disease includes measurable disease patients who were either stable disease or non-measurable disease patients who were non-complete response/non-progressive disease per RECIST 1. Patients with only non-measurable disease, whose best non-target lesion response was Non-CR/non-PD and did not have any new lesions.

d. This category refers to patients who discontinued the trial regimen because of adverse events or whose disease could not be assessed centrally but who had clinical or radiologic disease progression according to local assessment.

Kopetz et al., J Clin Oncol 38: 2020 (suppl; abstr 4039)

Overall Summary of Safety

Relative dose intensity

- ENCO/BINI/CETUX arm: Encorafenib 91%, Binimetinib 87%, Cetuximab 91%
- ENCO/CETUX arm: Encorafenib 98%, Cetuximab 93%
- Control arm: 74-85%

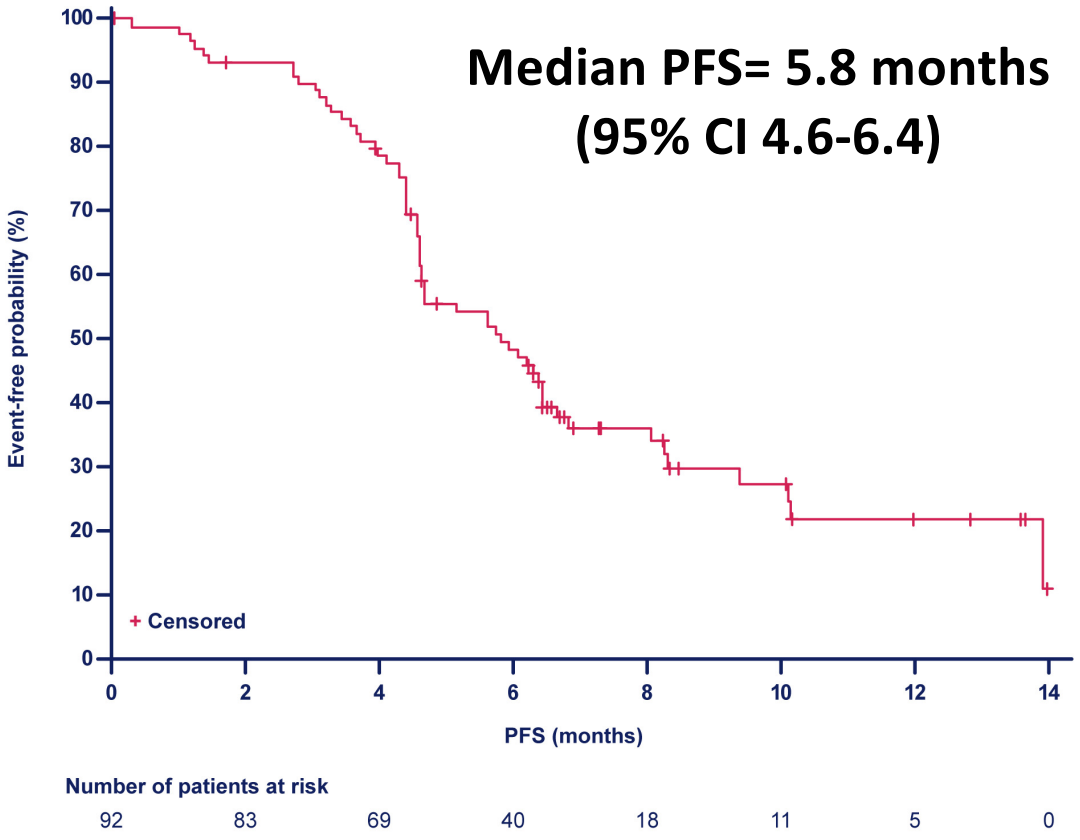
Event	ENCO/BINI/CETUX N=222 Median Duration of Exposure: 21 weeks*	ENCO/CETUX N=216 Median Duration of Exposure: 19 weeks*	Control N=193 Median Duration of Exposure: 7 weeks*
Any event	98%	98%	97%
Grade 3/4 adverse event (AE)	58%	50%	61%
Any serious AE	42%	33%	37%
Any event leading to discontinuation of any one drug	15%	12%	17%
Any event leading to discontinuation of all drugs	7%	8%	11%

*Median duration of exposure calculated using Kaplan-Meier method.

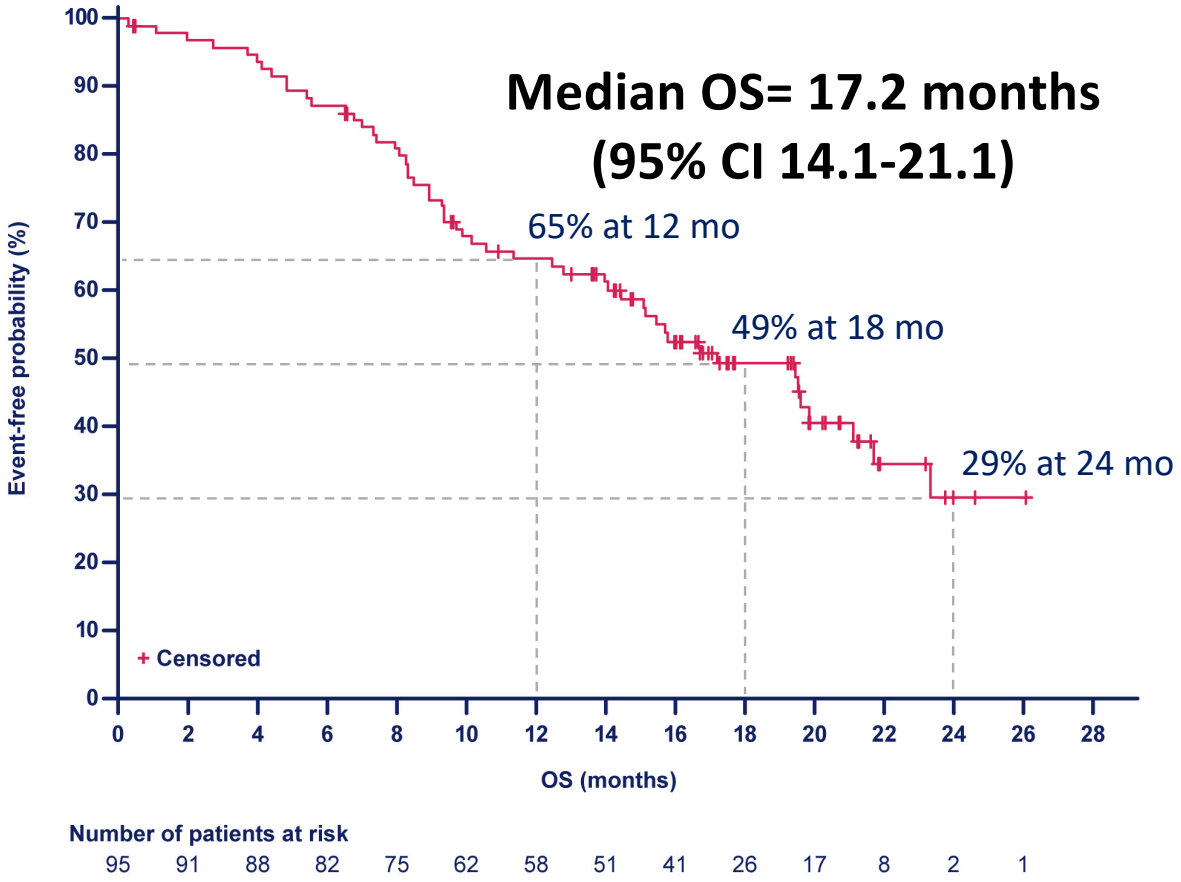
Kopetz et al. N Engl J Med. 2019; 381:1632-1643.
Tabernero J, et al. Ann Oncol. 2019; 30 (suppl_5): v851-v934 (Abstract: LBA32).

ANCHOR CRC trial: Phase 2 trial for adults with previously untreated mCRC with a *BRAF V600E* mutation

Progression-free survival



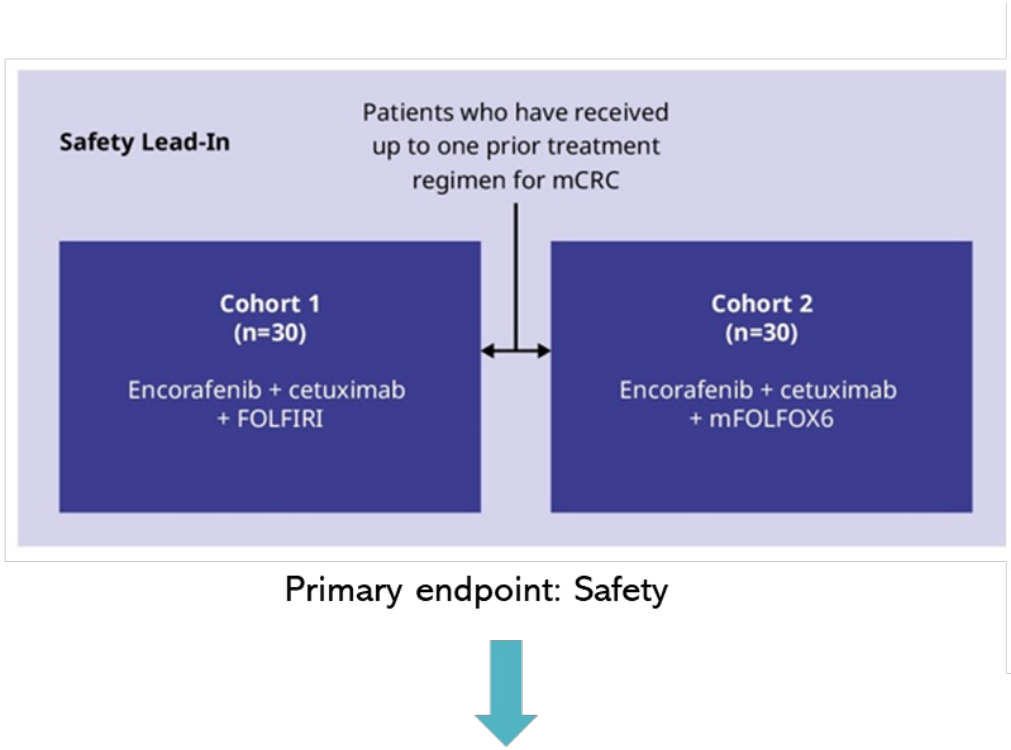
Overall survival



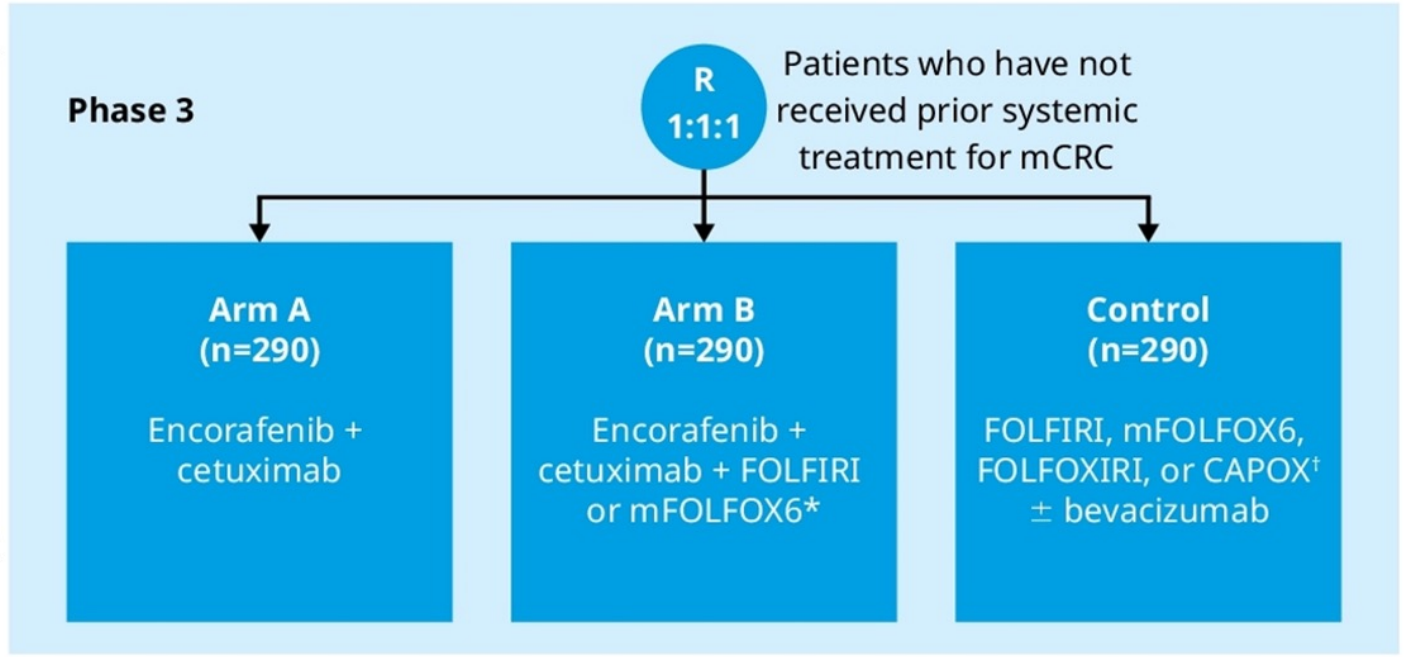
- Investigator assessed cORR was 47.8% (95% confidence interval [CI], 37.3-58.5) and DCR was 88%

Van Cutsem E, et al., ESMO GI 2021, Abstract O-10; Annals of Oncology volume 32 sup 3, S222.

BREAKWATER trial: Phase 3 trial for 1st line treatment of adults with mCRC with a *BRAF V600E* mutation



Primary endpoint: Safety



Primary endpoint: PFS (arm A *versus* control; arm B *versus* control)

Based on data from safety lead-in, BREAKWATER phase 3 will compare encorafenib + cetuximab ± mFOLFOX6 to mFOLFOX6/FOLFOXIRI/CAPOX ± bevacizumab[2]

1. Kopetz S, et al. J Clin Oncol. 2021;39(15_supp) Abstract TPS3619; 2. Kopetz S, et al. J Clin Oncol. 2022;40(4_suppl)134-134.

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)

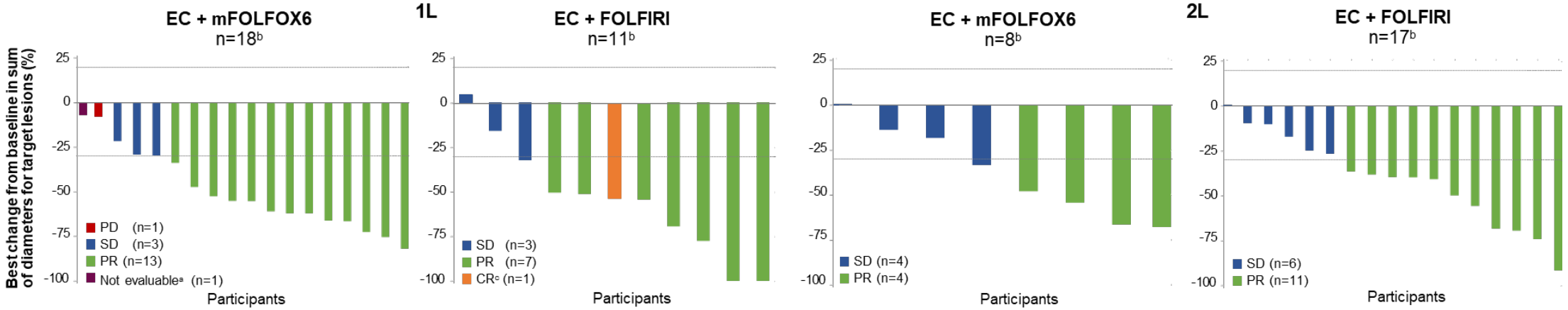
Data cutoff: 16 May 2022

[a]All grade in ≥30% of participants in either the EC + mFOFLOX6 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.

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

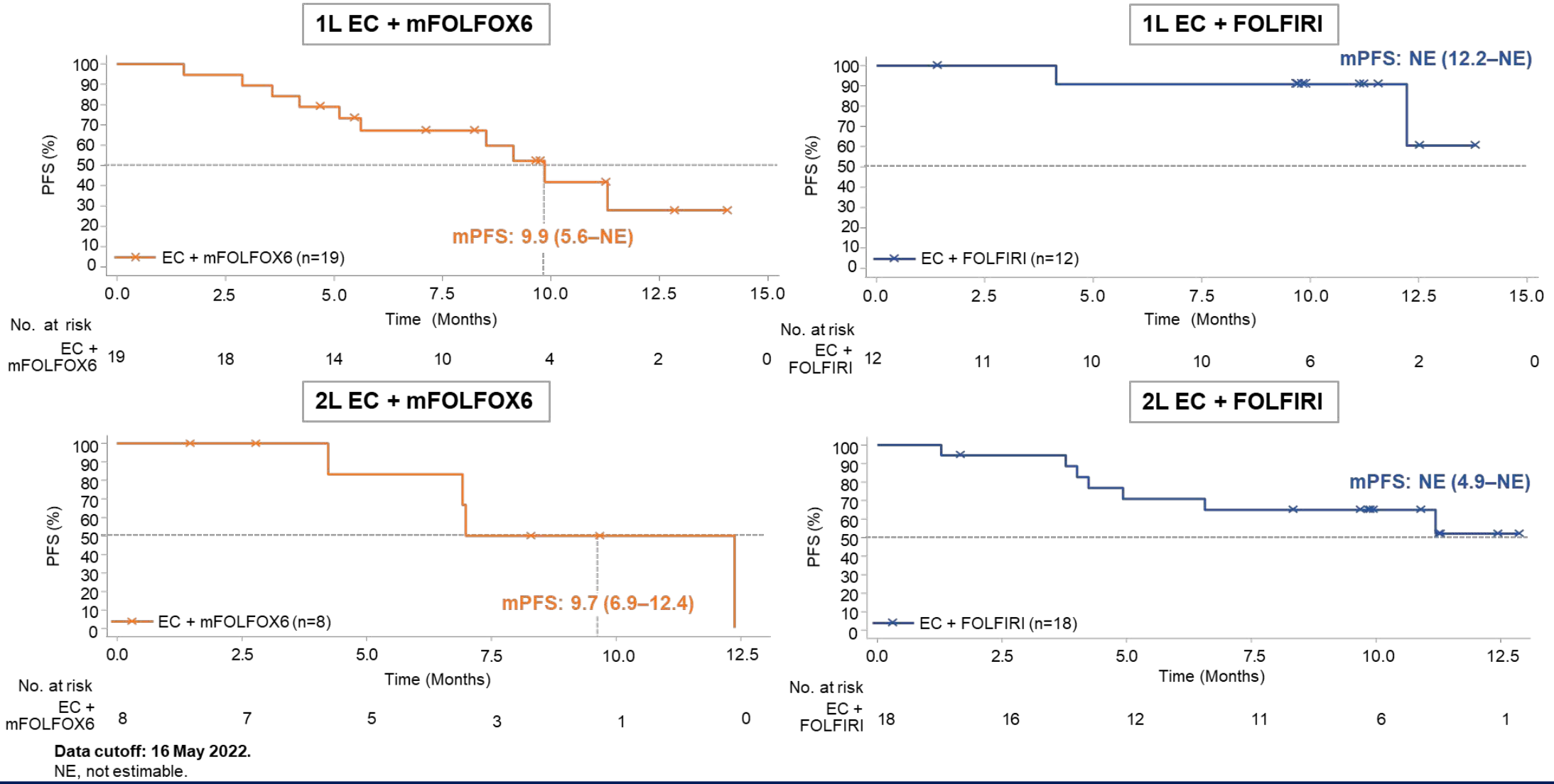
[a]Reasons included SD <6 weeks after treatment start date (1 patient in the EC + mFOLFOX6 arm in the 1L setting) and early death (1 patient in the EC + FOLFIRI arm in the 2L setting). [b]Only includes participants with target lesions at baseline and ≥1 non-missing post-baseline % change from baseline 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.

BRAF^{V600E} mutated metastatic CRC- Final thoughts

- *BRAF*^{V600E} mutations are associated with poor prognosis
- Optimal treatment for *BRAF*^{V600E} metastatic CRC: anti-BRAF + anti-EGFR
  - Addition of MEK inhibitor does not improve PFS, survival, or tolerability
- Current treatment approach for *BRAF*^{V600E} mutated mCRC:
  - 1st line: Chemotherapy + anti-VEGF
  - 2nd line: Encorafenib + anti-EGFR (cetuximab or panitumumab)
- Promising activity was seen in patients receiving encorafenib + cetux + mFOLFOX6/FOLFIRI as 1L/2L therapy
- BREAKWATER is a phase 3 trial exploring 1st line chemotherapy with encorafenib + cetuximab

MODULE 2: Optimizing the Use of Immune Checkpoint Inhibitors in the Management of mCRC — Dr Ciombor

Case Presentation: A 54-year-old man with BRAF V600E-mutant, KRAS/NRAS WT metastatic colon cancer with disease progression on FOLFOXIRI/bevacizumab

Dr Amber Xu (Rolling Meadows, Illinois)

QUESTIONS FOR THE FACULTY

Lai (Amber) Xu, MD, PhD

"How would the expert panel decide on first-line treatment for this man with BRAF V600E-mutant disease? What factors will influence their decision-making? Is there any utility of combining targeted therapy with chemotherapy? How does the panel decide between regorafenib and TAS-102 in this specific case? I would also love to hear how they dose regorafenib."

- **In which situations, if any, should bevacizumab be added to TAS-102, including for a patient like this who received prior first-line bevacizumab?**

Case Presentation: A 67-year-old man with localized unresectable MSI-high carcinoma of the cecum

Dr Farshid Dayyani (Orange, California)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Farshid Dayyani, MD, PhD

"How would you treat this patient with locally unresectable MSI-high colon cancer?

- *Do you give up-front FOLFOX, old school, or do you try to take into account that the patient is MMR-deficient?*
- *Do you include a checkpoint inhibitor? Would you combine it with FOLFOX for at least 2 to 3 months to further shrink the tumor prior to possible resection?*
- *Would you likely use ctDNA in managing this case?"*

Optimizing the Use of Checkpoint Inhibitors in the Management of mCRC

Kristen K. Ciombor, MD, MSCI
Associate Professor of Medicine
Vanderbilt-Ingram Cancer Center
January 18, 2023

VANDERBILT UNIVERSITY
MEDICAL CENTER

Immunotherapy in MSI-H mCRC

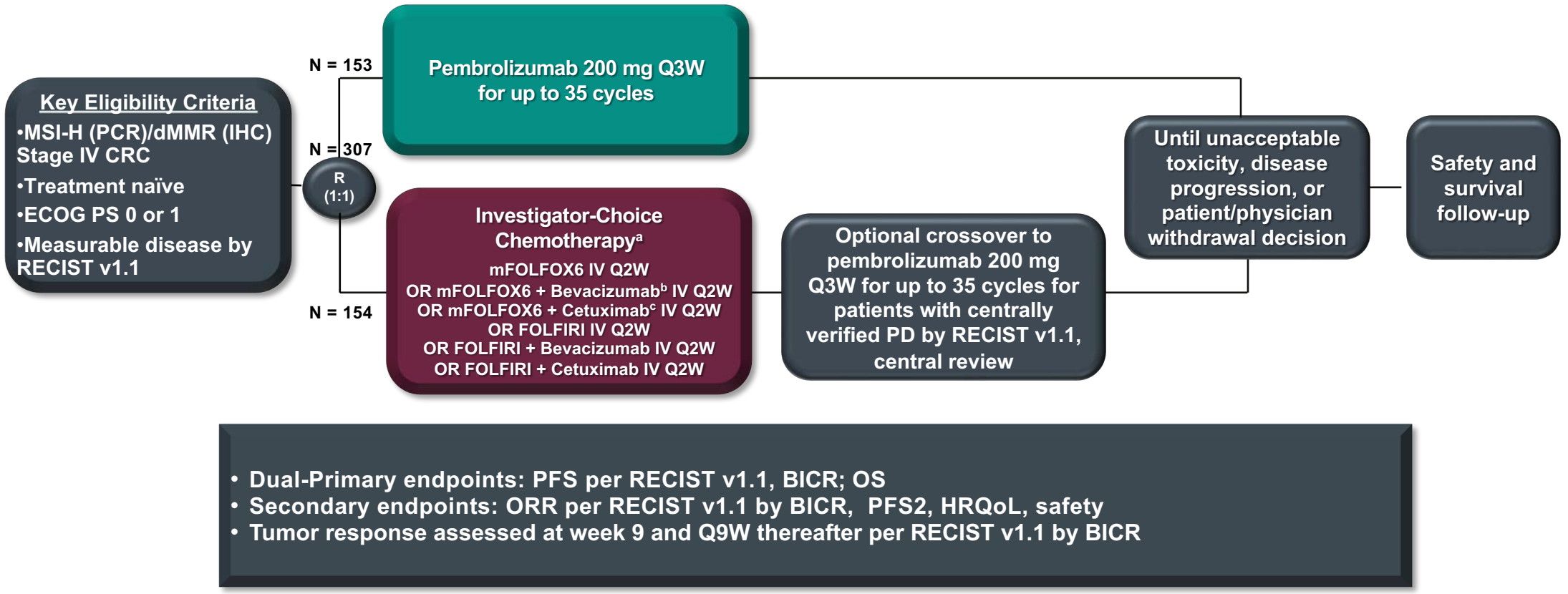
Table 1. Immune checkpoint inhibitors in MSI/dMMR metastatic colorectal cancer.

Clinical Trials	Prior Systemic Treatment	*n*	CR (%)	PR (%)	SD (%)	PD (%)	NE (%)	1-Year PFS Rate (%)	1-Year OS Rate (%)	2-Year PFS Rate (%)	2-Year OS Rate (%)	Median Follow-Up (Months)
Keynote-016 [11]												
Pembrolizumab	≥1	28	11	46	32	4	7	-	-	-	-	8.7
Keynote-164 [12–14]												
Pembrolizumab, cohort A	≥2	61	3	30	18	46	3	34	72	31	55	31
Pembrolizumab, cohort B	≥1	63	8	25	24	40	3	41	76	37	63	24
CheckMate-142 [15–18]												
Nivolumab	≥1	74	9	24	31	31	5	44	-	-	-	21
Nivolumab + Ipilimumab	≥1	119	6	52	28	12	3	71	85	60	74	25.4
Nivolumab + Ipilimumab	0	45	13	56	16	13	2	77	83	74	79	29.0
NIPICOL [19]												
Nivolumab + Ipilimumab	≥2	57	19	40	30	5	3	73	84	-	-	18.1
CD-ON-MEDI4736-1108 [20]												
Durvalumab	≥1	36	22		-	-	-	38			54	29
NCT02227667 [20]												
Durvalumab	≥1	11	27		-	-	-	36				30
GARNET [21]												
Dostarlimab	≥1	69	36		-	-	-	-	-	-	-	-

VANDERBILT UNIVERSITY MEDICAL CENTER

Cohen R, et al. *Cancers (Basel).* 2021;13(5):1149

KEYNOTE-177 Study Design
(NCT02563002)

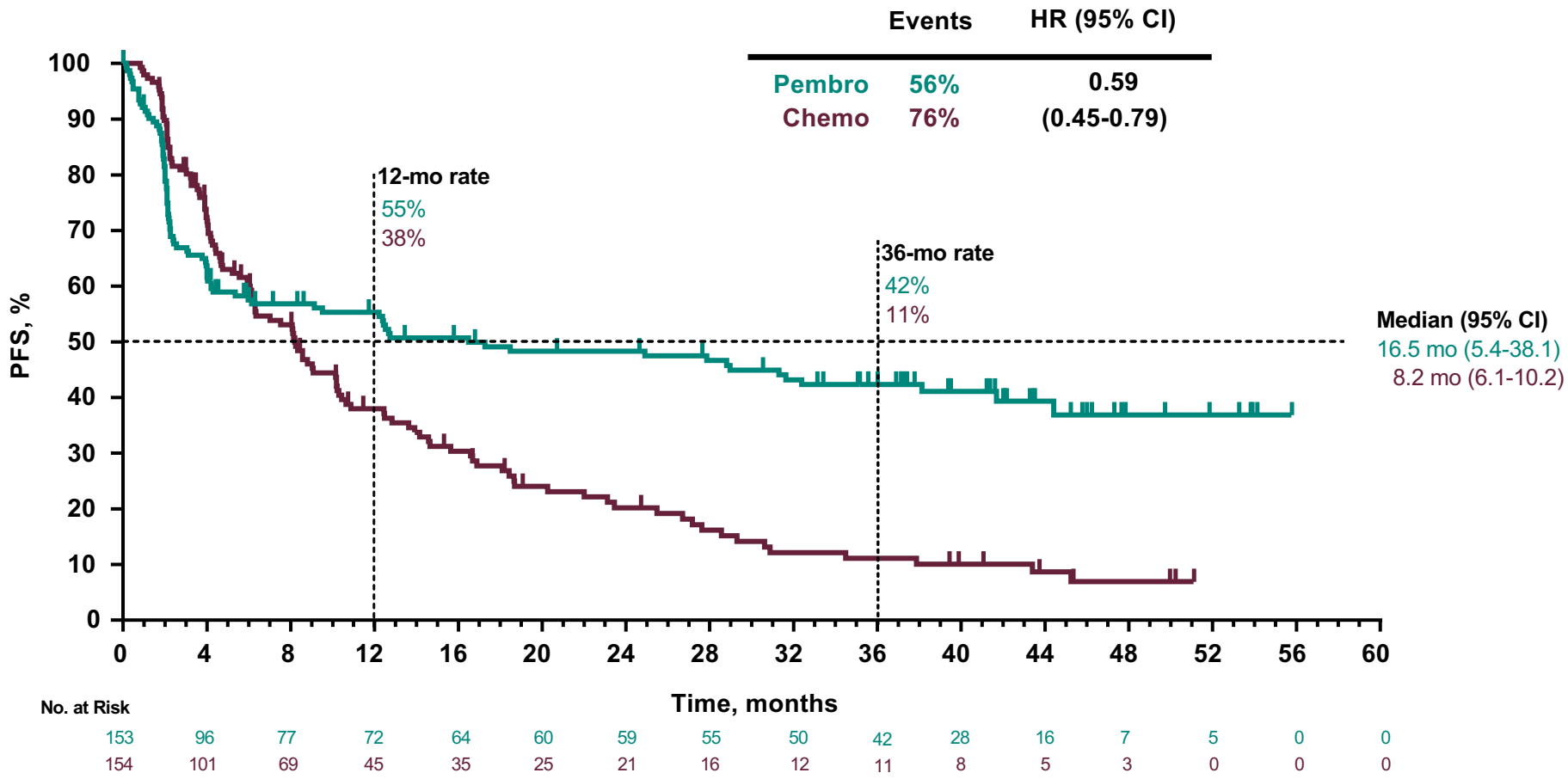


[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400 mg/m2 over 2 hours then 250 mg/mg^2 IV over 1 hour weekly.
BICR, blinded independent central review; IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6, PMS2; PCR: polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

Andre T, ASCO 2021

KEYNOTE-177

Progression-Free Survival



Data cut-off: 19Feb2021.

Andre T, ASCO 2021; Diaz LA Jr et al. *Lancet Oncol* 2022 April 12;23:659-70.

KEYNOTE-177

Antitumor Response

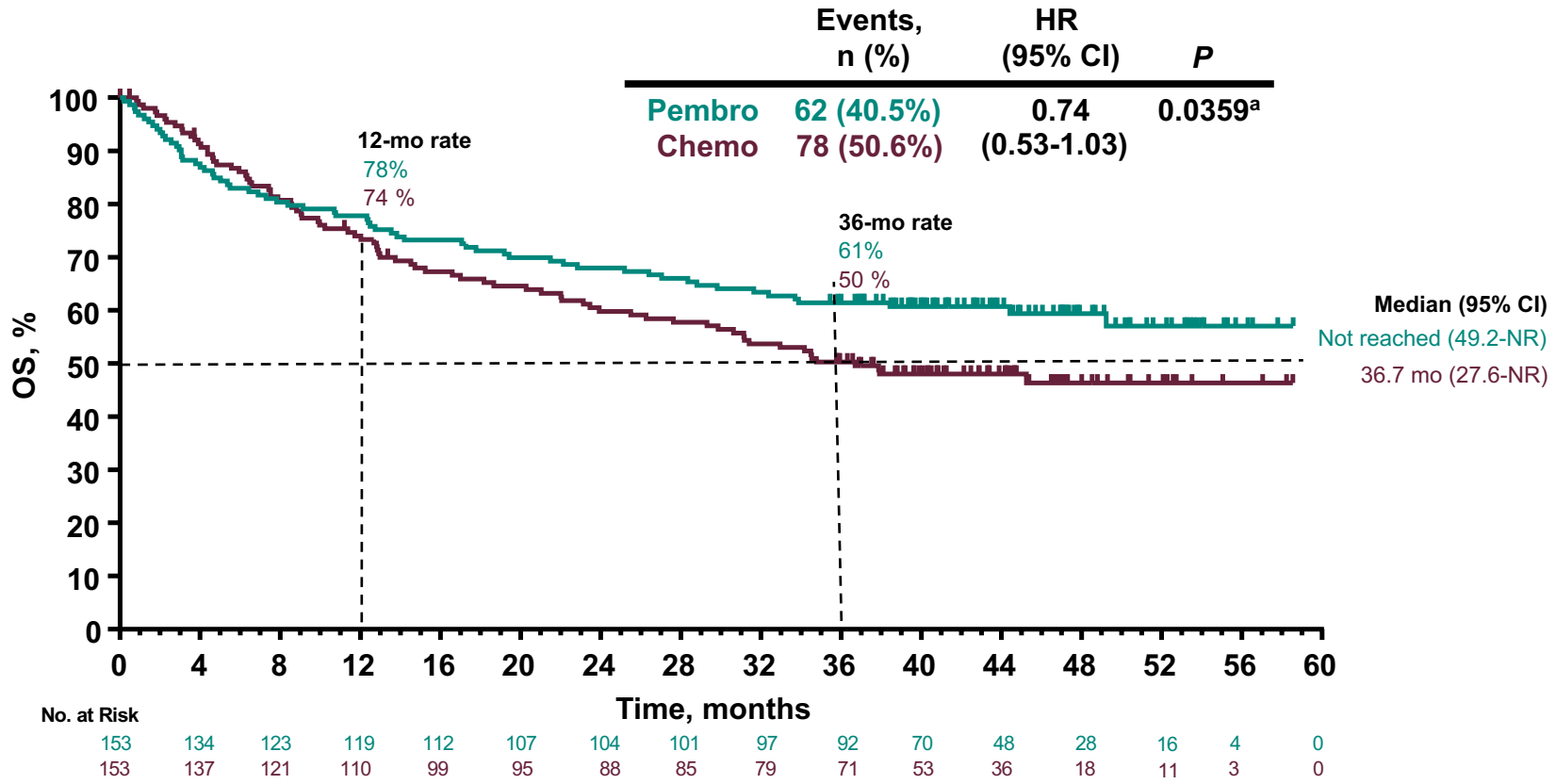
	Pembrolizumab N = 153	Chemotherapy N = 154
ORR, n (%)	**69 (45.1)[a]**	**51 (33.1)**
Best Overall Response, n (%)		
Complete response	20 (13.1)[b]	6 (3.9)
Partial response	49 (32.0)[c]	45 (29.2)
Stable disease	30 (19.6)	65 (42.2)
Disease control rate (CR+PR+SD)	99 (64.7)	116 (75.3)
Progressive disease	45 (29.4)	19 (12.3)
Not evaluable	3 (2.0)	2 (1.3)
No assessment	6 (3.9)	17 (11.0)
Median duration or response (range), mo	NR (2.3+ to 53.5+)	10.6 (2.8 to 48.3+)
≥ 24 months response duration, %	83.5	33.6

[a]ORR 43.8%; [b]CR rate 11.1%; [c]PR rate 32.7% at IA2 (data cut-off 19Feb2020).
Data cut-off: 19Feb2021.

Diaz LA Jr et al. Lancet Oncol 2022 April 12;23:659-70. Andre T, ASCO 2021

KEYNOTE-177

Overall Survival



[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.

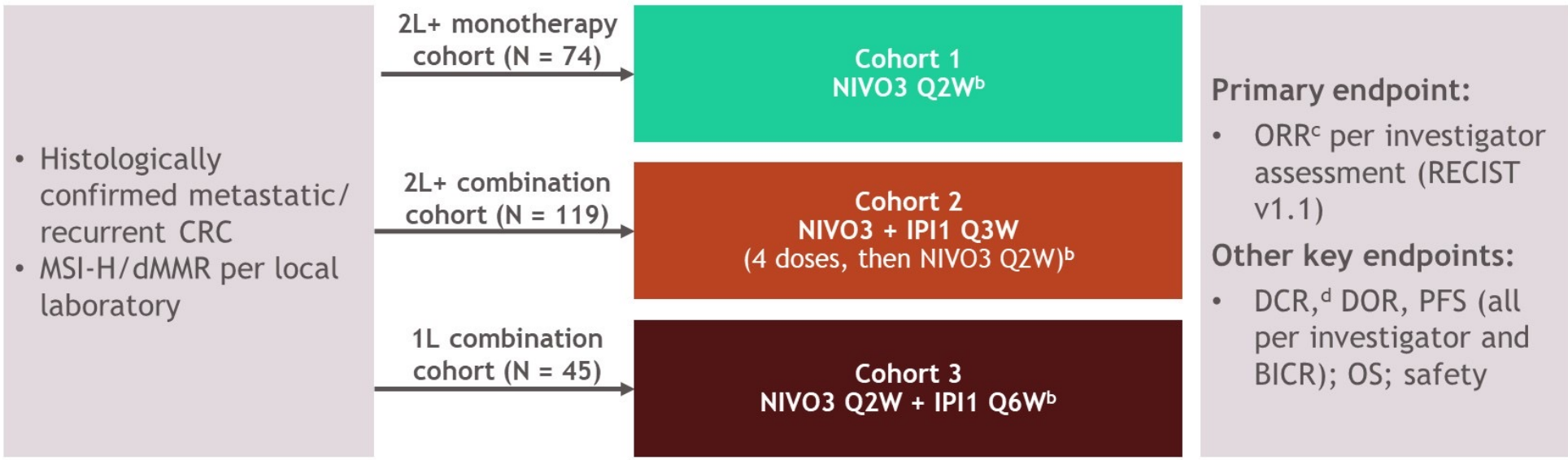
At final analysis, OS with pembrolizumab versus chemotherapy did not meet the one-sided α boundary of 0.025 required for superiority.

Diaz LA Jr et al. *Lancet Oncol* 2022 April 12;23:659-70.

Andre T, ASCO 2021

CheckMate 142[a] cohorts 1-3 study design

- CheckMate 142 is an ongoing, multicohort, non-randomized phase 2 study evaluating the efficacy and safety of NIVO-based therapies in patients with mCRC

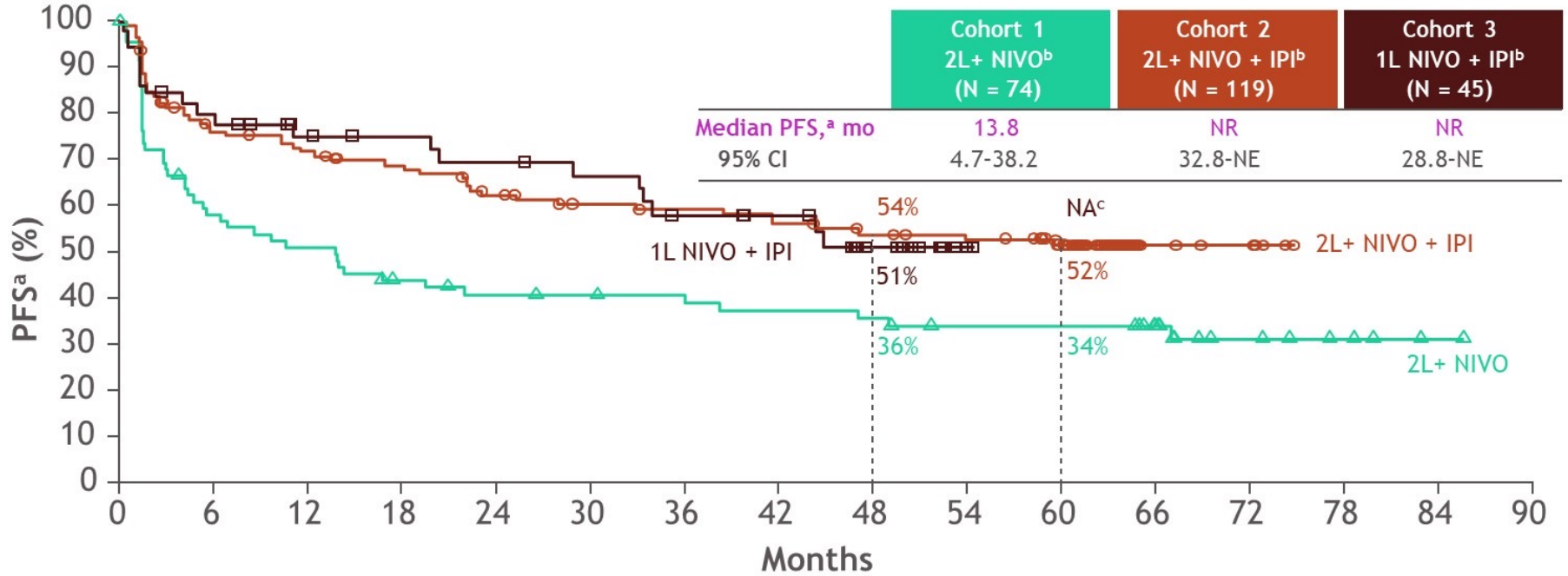


- At data cutoff (September 22, 2021), the median (range) follow-up (time from first dose to data cutoff) was 70.0 (66.2–88.7), 64.0 (60.0–75.8), and 52.4 (47.6–57.1) months for cohorts 1, 2, and 3, respectively

[a]ClinicalTrials.gov number, NCT02060188; [b]Until disease progression, discontinuation due to toxicity, withdrawal of consent, or maximum clinical benefit per investigator. Treatment beyond initial evidence of PD was permitted if the patient tolerated the study drug and benefited from study treatment per investigator assessment; [c]Patients with 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. BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DOR, duration of response; IPI1, ipilimumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Overman M, ASCO 2022

Progression-free survival



No. at risk

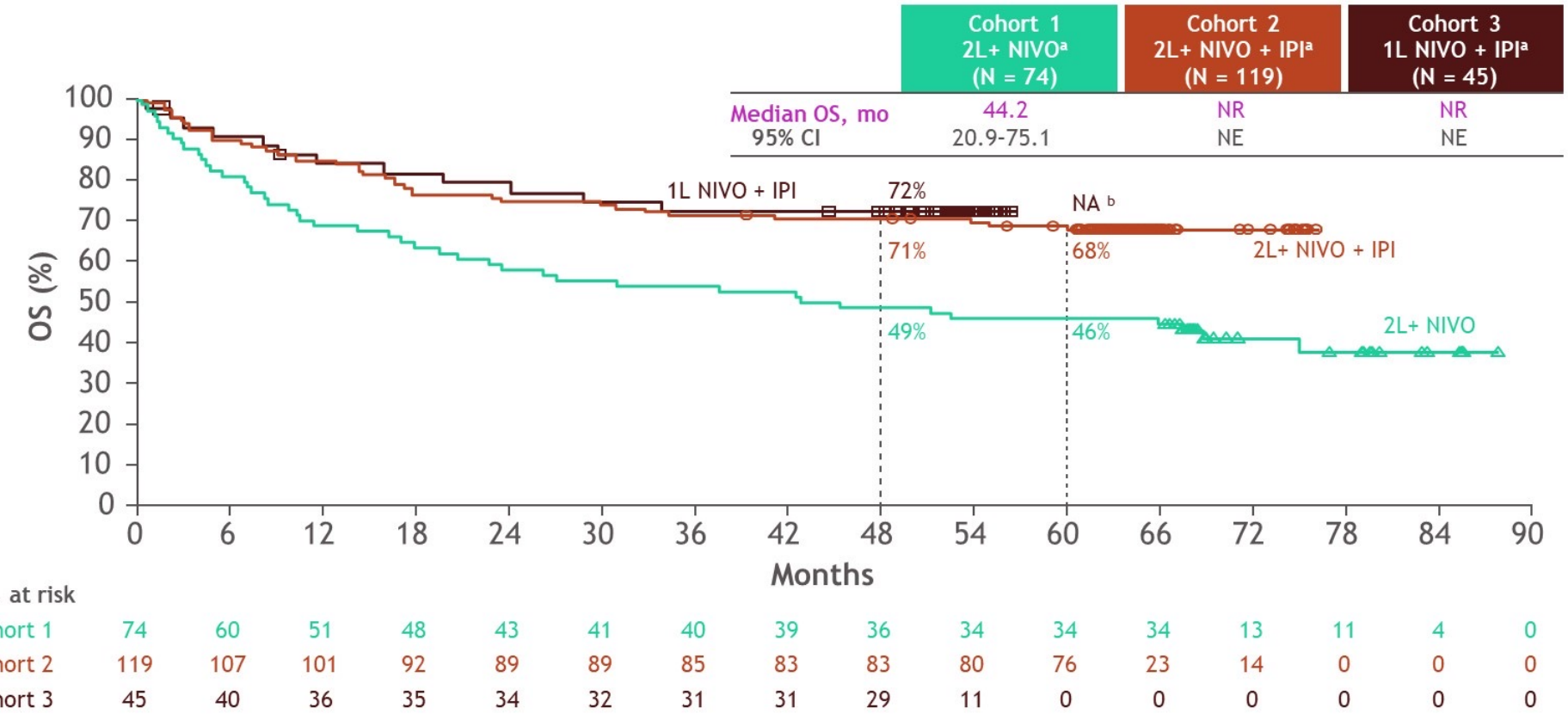
Cohort 1	74	41	36	29	26	25	23	22	21	18	18	14	7	4	1	0
Cohort 2	119	86	80	74	65	59	56	53	49	46	40	7	5	0	0	0
Cohort 3	45	35	29	27	25	23	19	18	10	1	0	0	0	0	0	0

- 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 M, ASCO 2022

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.

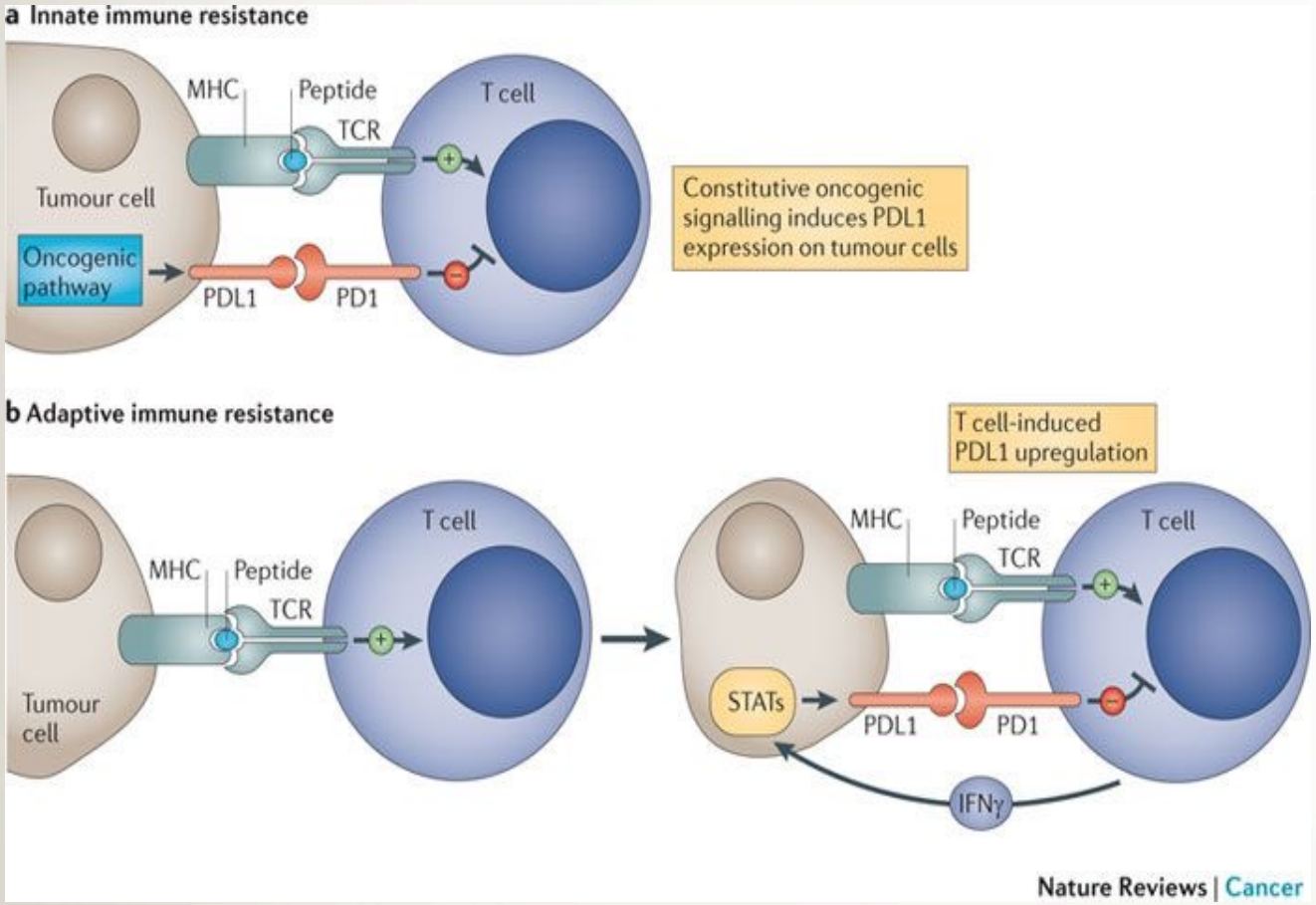
Overman M, ASCO 2022

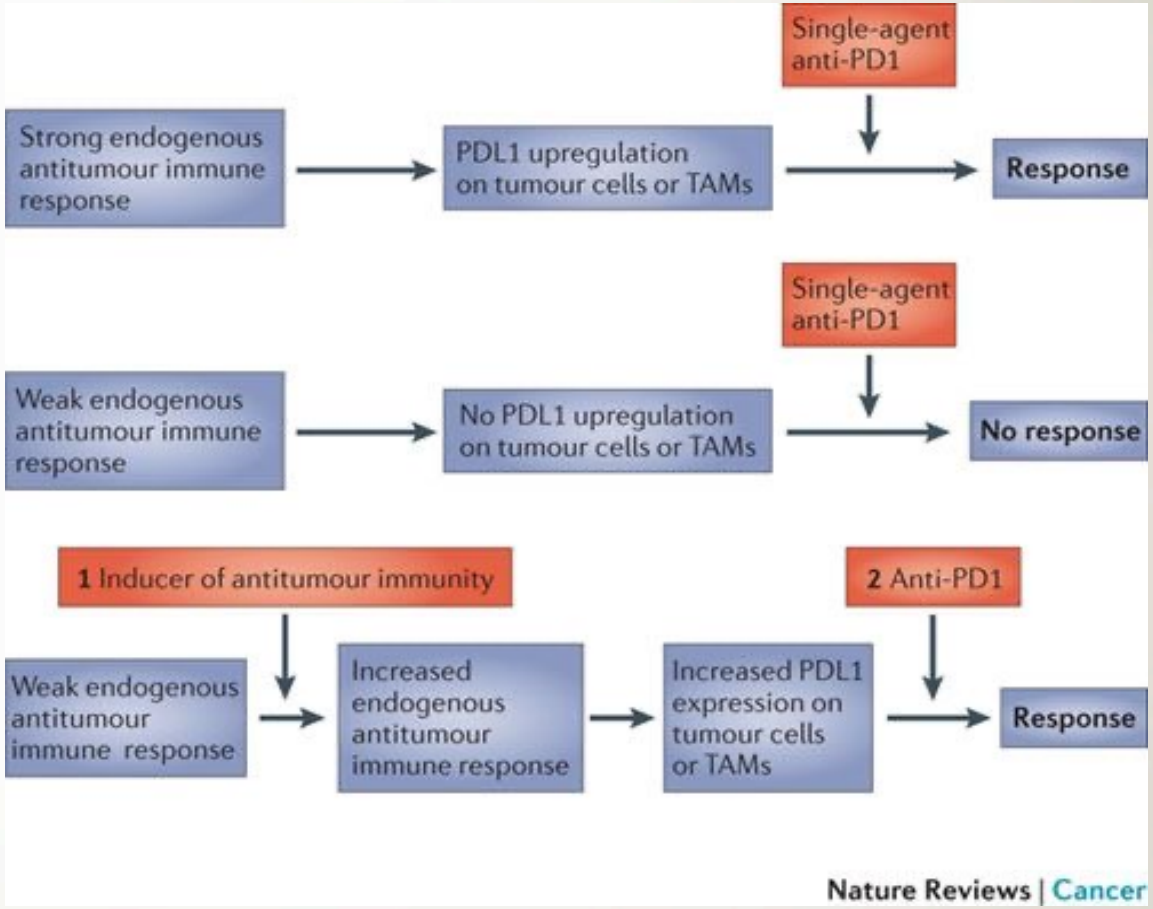
Resistance Mechanisms to Immune Checkpoint Inhibitor Therapy in MSS mCRC

- Low immunogenicity for $CD8^+$ T cell recognition (low tumor mutational burden)
- Defects in antigen presentation machinery
- Overexpression of intrinsic immunosuppressive oncogenic pathways
- Immunosuppressive effects of the tumor microenvironment

Lee JJ, Chu E. *Clin Colorectal Cancer* 2018; 17(4): 258-273

Immune Resistance and Immunotherapy Combinations





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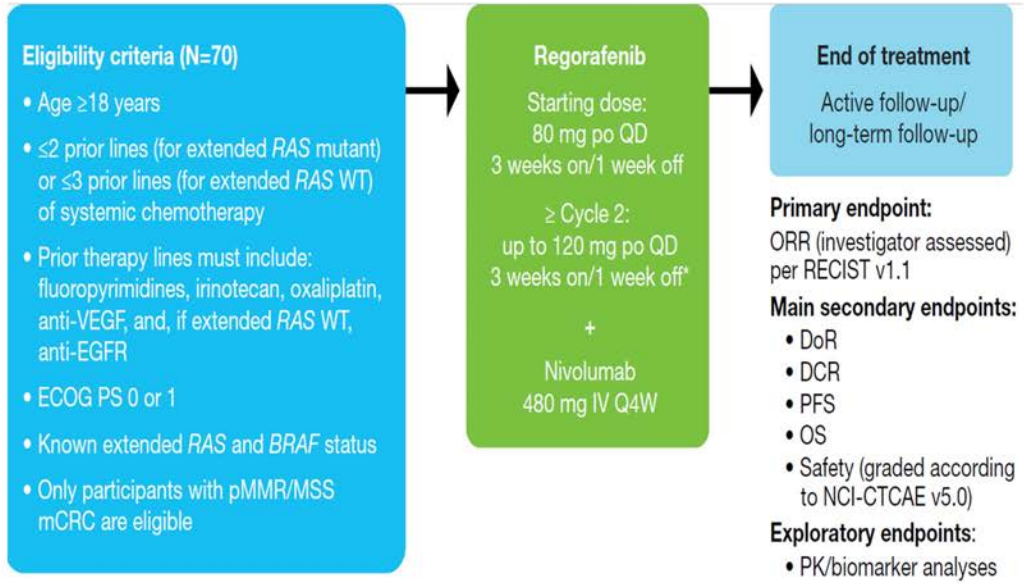
Pardoll D, et al. *Nat Rev* 2012; 12: 252-264

Regorafenib/Nivolumab in MSS mCRC

Study Design (NCT04126733)



Response, n (%)	Without liver metastases (n=23)	With liver metastases (n=47)	All patients (N=70)
Complete response	0	0	0
Partial response	5 (22)	0	5 (7)
Stable disease	8 (35)	14 (30)	22 (31)
Progressive disease	9 (39)	27 (57)	36 (51)
Not evaluable	1 (4)	6 (13)	7 (10)
Objective response rate	5 (22)	0	5 (7)
Disease control rate ≥8 weeks	13 (57)	14 (30)	27 (39)
Median duration of stable disease, weeks	30	21	30

Fakih M, ASCO 2021

ASCO Gastrointestinal Cancers Symposium

Phase I/II study of regorafenib and pembrolizumab in refractory microsatellite stable colorectal cancer

Afsaneh Barzi, Nilofer Azad, Yan Yang, Denice Tsao-Wei, Marwan Fakih, Syma Iqbal, Anthony El-Khoueiry, Priya Jayachandran, Wu Zhang, Rabia Rehman, Heinz-Josef Lenz

Afsaneh Barzi, MD, PhD

Gastrointestinal Cancers Symposium 2022;Abstract 15

Conclusions

- In this large multi-center study, *combination of regorafenib and pembrolizumab in advanced MSS CRC failed to improve PFS.*
- Safety signal is consistent with previously reported data.
- Post-hoc analysis revealed that patients with ***no liver metastasis*** and those with ***prior radiotherapy*** achieved a significantly longer PFS.
  - In multivariate analysis, prior radiotherapy remained a significant predictor of PFS.
  - Additional analysis as well as biomarker discovery for patient subgroups is ongoing.

Barzi A et al. Gastrointestinal Cancers Symposium 2022;Abstract 15.

Pembrolizumab/Lenvatinib in MSS mCRC

LEAP-005 (NCT03797326)

Key Inclusion/Exclusion
- ≥18 years of age
- Histologically/cytologically advanced solid tumor[a]
  - Triple-negative breast (2L/3L)
  - Ovarian (4L)
  - Gastric (3L)
  - Colorectal (non/MSI-H/pMMR) (3L)
  - Biliary tract (2L)
  - Glioblastoma multiforme (2L)
- Measurable disease (RECIST v1.1)
- ECOG PS 0–1
- Tissue for PD-L1 assessment[b]

N = 30[c] → Pembrolizumab 200 mg IV Q3W + Lenvatinib 20 mg orally QD, Up to 35 cycles[d] → Evaluation[e] → 30-Day safety FU + survival status

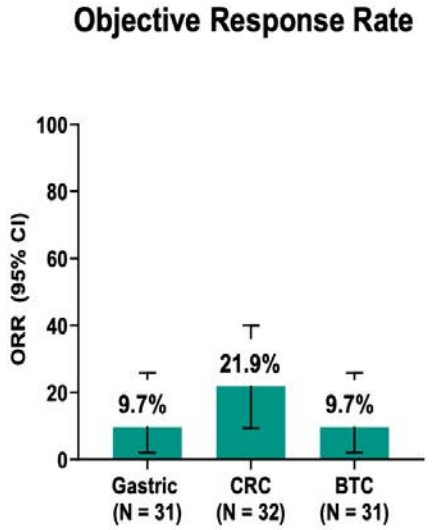
Primary endpoints: ORR (RECIST v1.1 or RANO, BICR)[f], safety/tolerability

Key secondary endpoints: DCR, DOR, PFS (RECIST v1.1 or RANO, BICR)[f]

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

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

	3L Gastric (N = 31)	3L CRC (N =32)	2L BTC (N = 31)
ORR, % (95% CI)	9.7 (2.0–25.8)	21.9 (9.3–40.0)	9.7 (2.0–25.8)
DCR,[a] % (95% CI)	48.4 (30.2–66.9)	46.9 (29.1–65.3)	67.7 (48.6–83.3)
Best overall response, n (%)			
CR	1 (3)	0	0
PR	2 (6)	7 (22)	3 (10)
SD	12 (39)	8 (25)	18 (58)
Non-CR/Non-PD	0	0	0
PD	11 (35)	12 (38)	7 (23)
Non-evaluable[b]	0	1 (3)	2 (6)
No assessment[c]	5 (16)	4 (13)	1 (3)
DOR, median (range), mo	NR (2.1+ to 2.3+)	NR (2.1+ to 10.4+)	5.3 (2.1+ to 6.2)



[a]Defined as best overall response of complete or partial response, or stable disease. [b]Patient had post-baseline imaging and the best overall response was determined to be nonevaluable per RECIST v1.1. [c]Patient had no post-baseline imaging. Data cutoff date: April 10, 2020.

3L CRC: mPFS 7.2 mos (2.0-5.2); 6-month PFS rate: 30.5%

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Lwin Z, ESMO 2020

LEAP-005: Tumor Activity with Lenvatinib and Pembrolizumab in the Colorectal (non-MSI-H/pMMR) Cohort

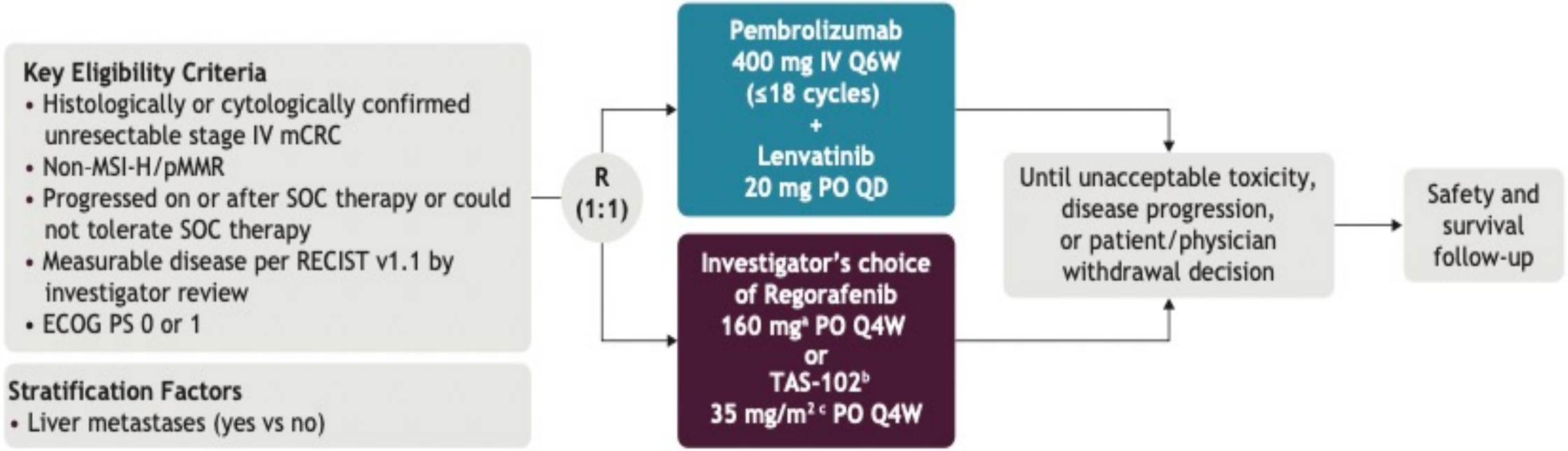
Outcome	Lenvatinib + pembrolizumab (N = 32)
ORR	22%
Disease control rate	47%
Median duration of response	Not reached
Median PFS	2.3 mo
Median OS	7.5 mo

Gomez-Roca C et al. Gastrointestinal Cancers Symposium 2021;Abstract 94.

Pembrolizumab/Lenvatinib in MSS mCRC

- LEAP-017 (NCT04776148) is a global, randomized, open-label, phase 3 trial

Figure 1. LEAP-017 Study Design



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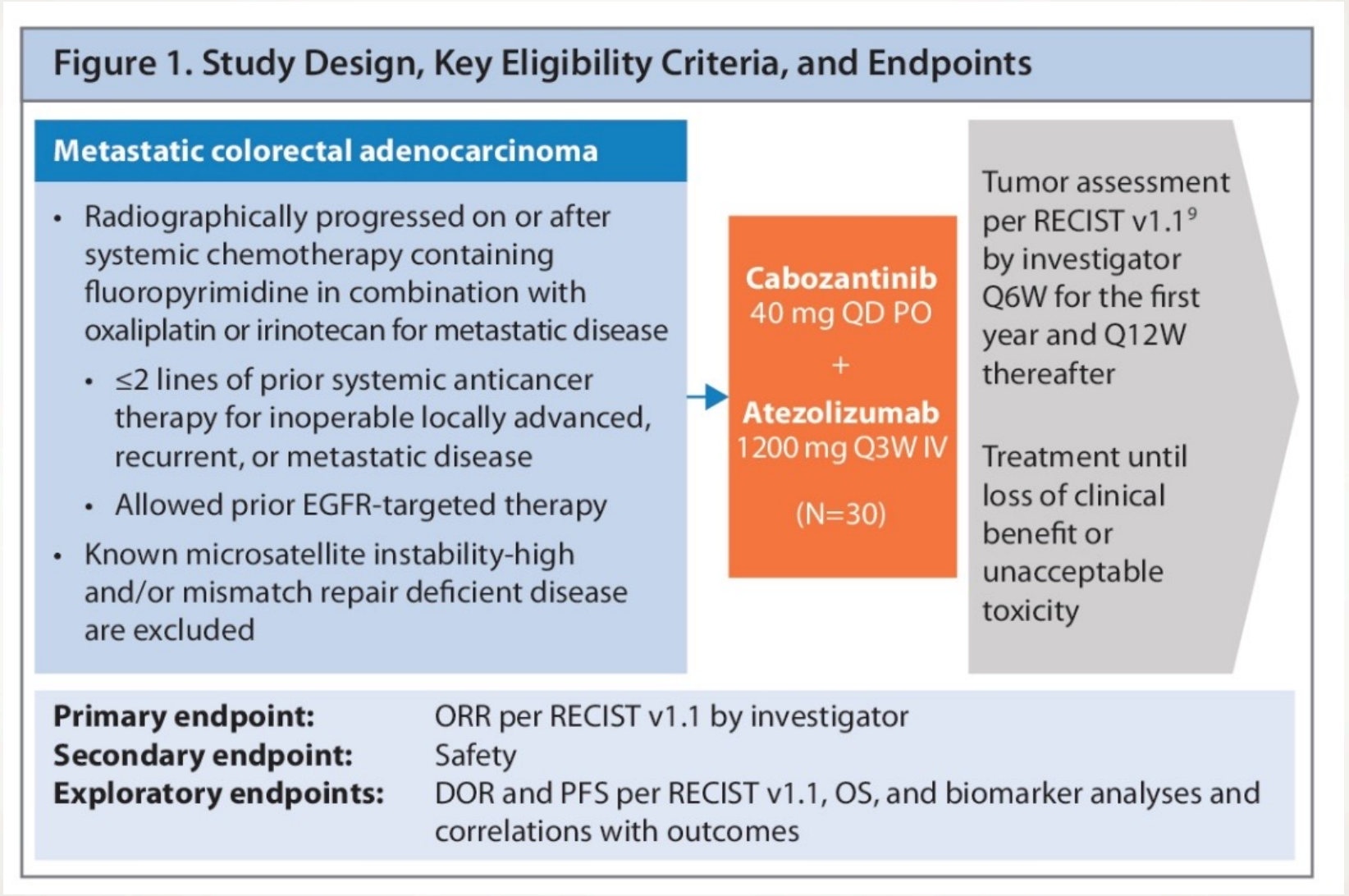
Yoshino T, ESMO 2021

COSMIC-021 mCRC Cohort 16



Abrams T, ASCO GI 2022

COSMIC-021 mCRC Cohort 16

Table 3: Disposition, Exposure, and Safety Summary

	Colorectal cancer cohort (N=31)
Patients on study treatment at data cut-off, n (%)	1 (3)
Duration of exposure, median (range), months	3.0 (0.4 –30.0)
AEs leading to cabozantinib dose reductions, n (%)	14 (45)
AEs leading to cabozantinib dose hold, n (%)	21 (68)
AEs leading to atezolizumab dose delay, n (%)	12 (39)
Discontinuation due to TRAEs, n (%)	
Cabozantinib	2 (6)
Atezolizumab	2 (6)
Any	2 (6)
Both	2 (6)

Table 4: Treatment-Related Adverse Events (TRAEs) Occurring in ≥10%

	Colorectal cancer cohort (N=31)	
	Any Grade	Grade 3/4*
Any TRAE, n (%)	28 (90)	16 (52)
Diarrhea	16 (52)	1 (3)
Fatigue	13 (42)	2 (6)
Nausea	11 (35)	0
Hypertension	6 (19)	3 (10)
Stomatitis	6 (19)	1 (3)
Vomiting	6 (19)	0
ALT increased	5 (16)	0
Amylase increased	5 (16)	1 (3)
Decreased appetite	5 (16)	0
Hypothyroidism	5 (16)	0
Lipase increased	5 (16)	2 (6)
Thrombocytopenia	5 (16)	1 (3)
Dehydration	4 (13)	1 (3)
White blood cell count decreased	4 (13)	0

No grade 5 TRAEs were reported. *Only one grade 4 event (blood creatine phosphokinase increased) was reported.

Table 5: Adverse Events of Special Interest (AESI)*

	Colorectal cancer cohort (N=31)	
	Any Grade	Grade 3/4
Any AESI, n (%)	23 (74)	5 (16)
Hepatitis (diagnosis and lab abnormalities)	12 (39)	1 (3)
Pancreatitis†	8 (26)	3 (10)
Rash	7 (23)	0
Hypothyroidism	6 (19)	0
Colitis	2 (6)	0
Severe cutaneous reactions	1 (3)	0
Rhabdomyolysis	1 (3)	1 (3)

*AESI are potential immune-related AEs for atezolizumab provided by the sponsor and summarized as grouped MedDRA terms irrespective of causality.
†Immune-mediated pancreatitis includes laboratory findings of elevations of lipase/amylase.

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Abrams T, ASCO GI 2022

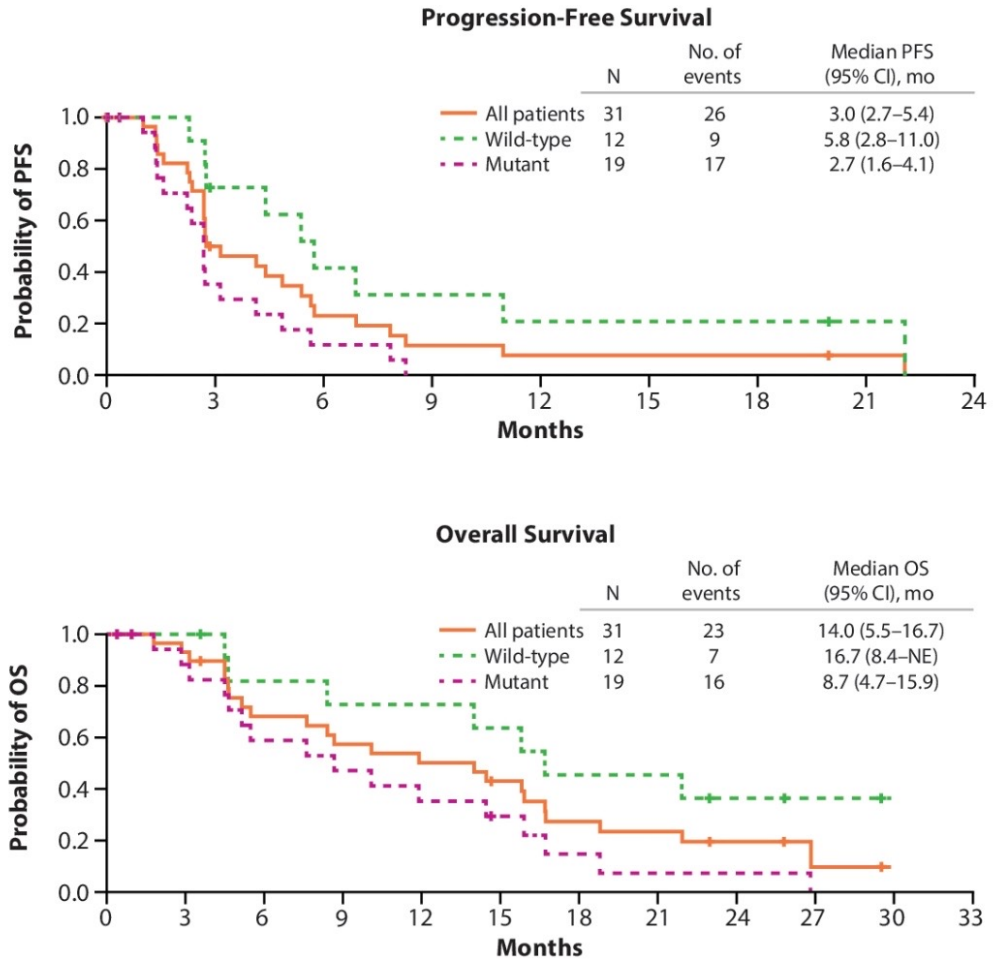
COSMIC-021 mCRC Cohort 16

Table 2: Tumor Response per RECIST v1.1 by Investigator

	All patients (N=31)	Wild-type RAS (n=12)	RAS mutant (n=19)
Best overall response, n (%)			
Confirmed complete response	0	0	0
Confirmed partial response	3 (10)	3 (25)	0
Stable disease	19 (61)	8 (67)	11 (58)
Progressive disease	6 (19)	0	6 (32)
No post-baseline assessments	3 (10)	1 (8)	2 (11)
Objective response rate, n (%)	3 (10)	3 (25)	0
Duration of objective response, median (range), mo	7.6 (4.2–NE)	7.6 (4.2–NE)	NE (NE–NE)
Time to objective response, median (range), mo	2.8 (1.7 –14.5)	2.8 (1.7 –14.5)	NE (NE–NE)
Disease control rate, n (%)	22 (71)	11 (92)	11 (58)

Objective response rate = complete response + partial response.
Disease control rate = complete response + partial response + stable disease.

Figure 2: Kaplan-Meier Analyses of Progression-Free Survival per RECIST v1.1 by Investigator and Overall Survival



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Abrams T, ASCO GI 2022

ASCO Gastrointestinal Cancers Symposium

Phase II trial of cabozantinib (Cabo) plus durvalumab (Durva) in chemotherapy refractory patients with advanced mismatch repair proficient/microsatellite stable (pMMR/MSS) colorectal cancer (CRC): CAMILLA CRC cohort results

Anwaar Saeed, Robin Park, Junqiang Dai, Raed Al-Rajabi, Anup Kasi, Azhar Saeed, Zachary Collins, Kayra Thompson, Lori Barbosa, Kelly Mulvaney, Vanna Manirad, Milind Phadnis, Stephen Williamson, Joaquina Baranda, Weijing Sun

Anwaar Saeed, MD

Associate Professor of Medicine

Associate Director – Early Phase Clinical Trials Program

Kansas University Cancer Center

CAMILLA CRC Cohort

Efficacy

Table 4. Key Efficacy Outcomes	
Overall Population (evaluable patients, N=29)	
ORR [95% CI] (confirmed & unconfirmed PR)	8 (27.6%) [12.73, 47.24]
Confirmed PR [95% CI]	6 (20.7%) [7.99, 39.72]
DCR [95% CI]	25 (86.2%) [68.34, 96.11]
Median PFS [95% CI]	3.8 months [3.4, 6.3]
Median OS [95% CI]	9.1 months [5.8, 21.8]
6-month PFS [95% CI]	10 (34.5%) [17.94, 54.33]
Subgroup analysis: RAS Wild Type (N=12)	
ORR [95% CI]	6 (50.0%) [21.09, 78.91]
DCR [95% CI]	10 (83.3%) [51.59, 97.91]
Median PFS [95% CI]	6.3 months [1.8, NE]
Median OS [95% CI]	21.8 months [4.5, NE]

Figure 2. % of Change from Baseline to Nadir in Sums of Diameters of Target Lesions

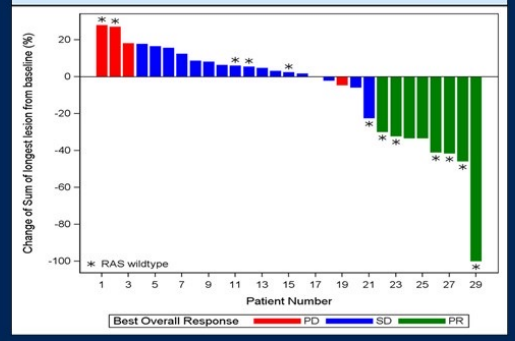


Figure 3. % of Change from Baseline in Sums of Diameters of Target Lesions Over Time

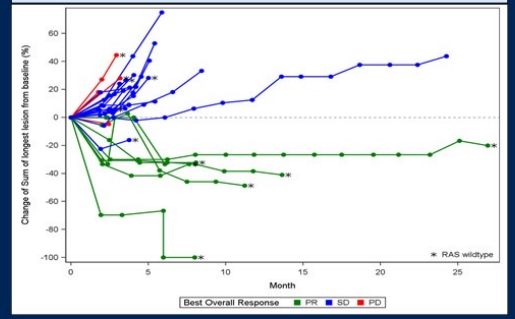
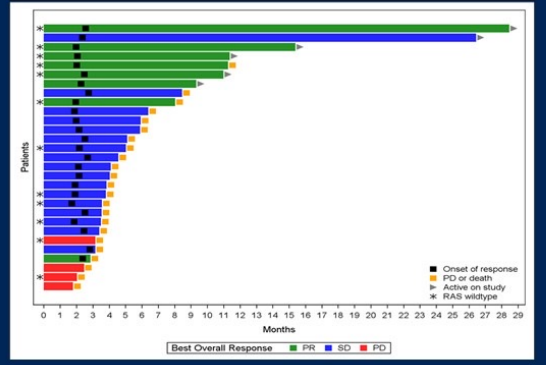


Figure 4. Tumor Response (PR/CR/SD) with Duration by Month



Grade 3+ TRAEs: 31%

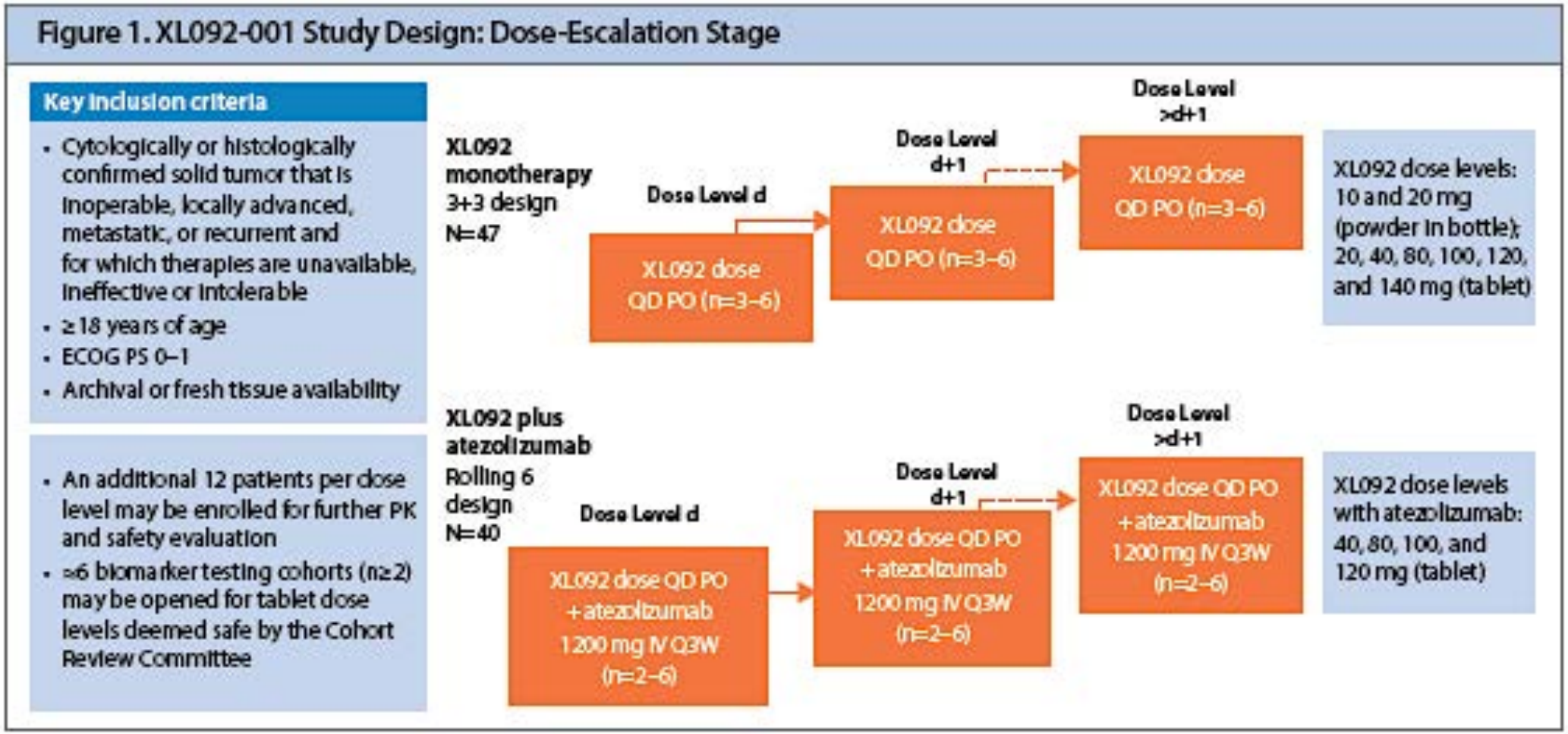
Saeed A, ASCO GI 2022

Cabozantinib versus XL092

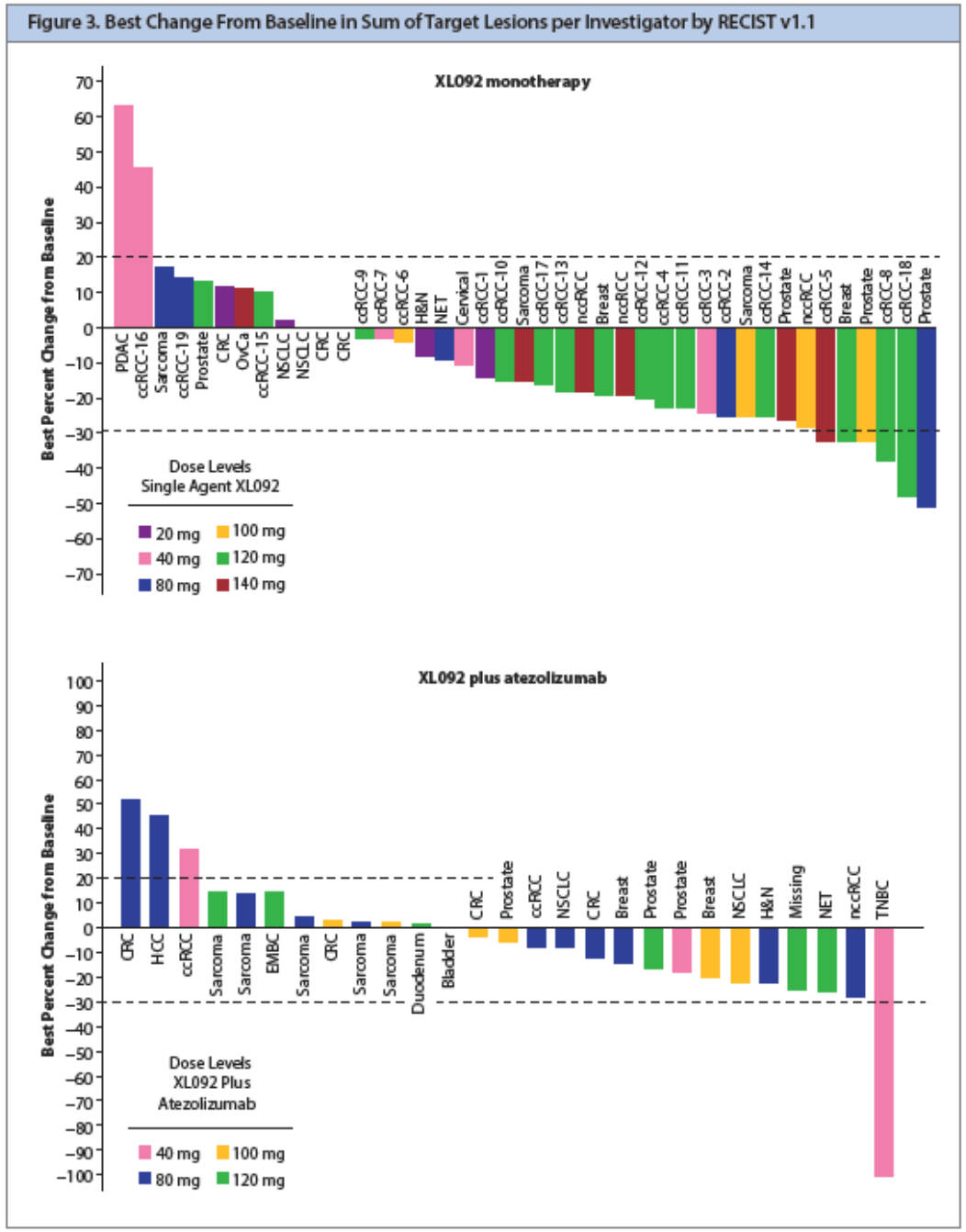
- XL092 = ATP-competitive inhibitor of multiple RTKs (MET, VEGFR2, AXL, MER)
- Higher efficacy with XL092 + immune checkpoint inhibitor in syngeneic tumor models
- PKs from phase I trial showed terminal half-life of 24 hours for XL092 vs. 99 hours for cabozantinib

Hsu J, ENA 2020

STELLAR-001



Sharma M, ESMO 2022



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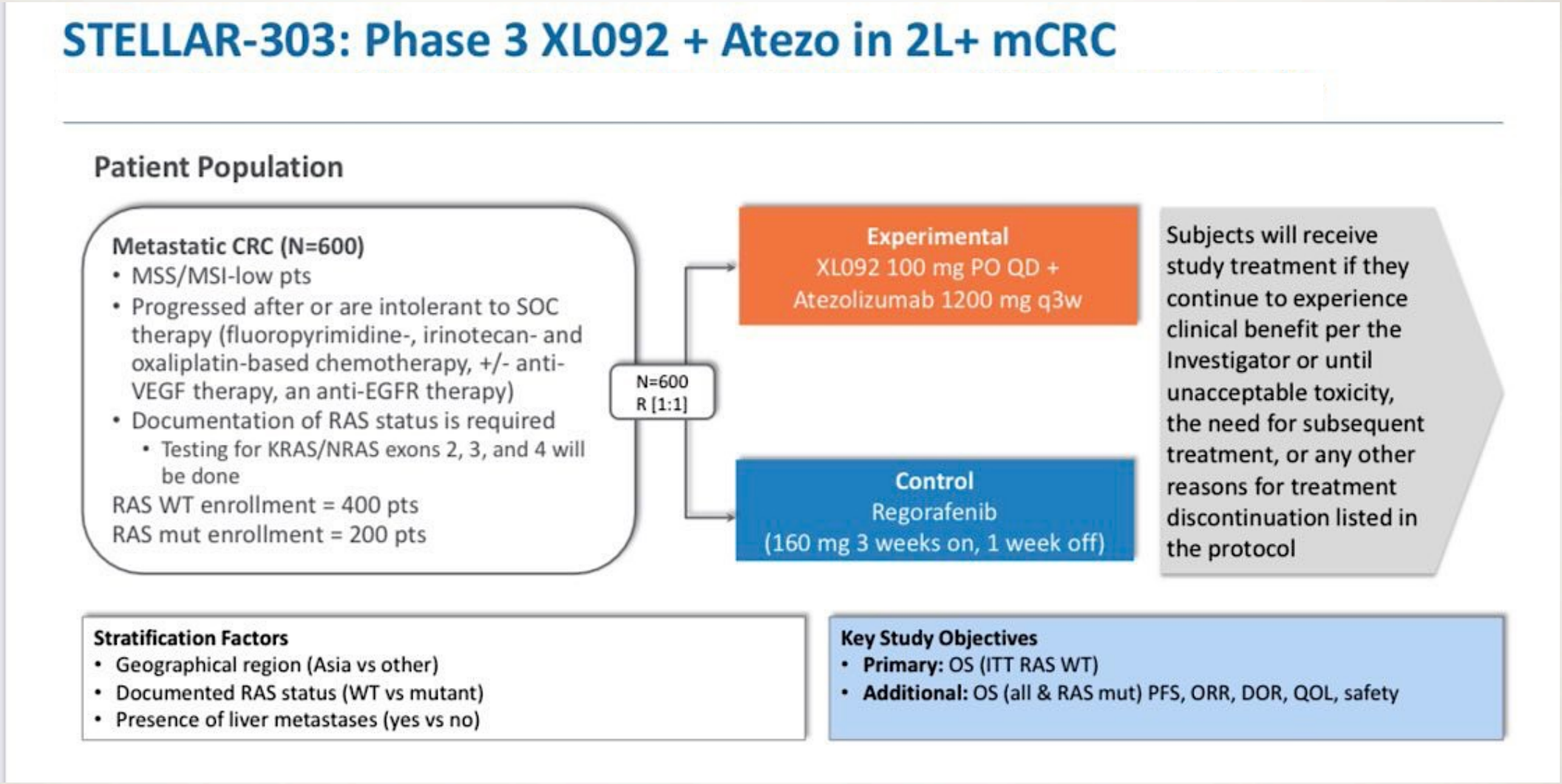
Sharma M, ESMO 2022

STELLAR-303


STELLAR-303: Phase 3 XL092 + Atezo in 2L+ mCRC
Patient Population
Metastatic CRC (N=600)
• MSS/MSI-low pts
• Progressed after or are intolerant to SOC therapy (fluoropyrimidine-, irinotecan- and oxaliplatin-based chemotherapy, +/- anti-VEGF therapy, an anti-EGFR therapy)
• Documentation of RAS status is required
• Testing for KRAS/NRAS exons 2, 3, and 4 will be done
RAS WT enrollment = 400 pts
RAS mut enrollment = 200 pts
N=600
R [1:1]
Experimental
XL092 100 mg PO QD +
Atezolizumab 1200 mg q3w
Control
Regorafenib
(160 mg 3 weeks on, 1 week off)
Subjects will receive study treatment if they continue to experience clinical benefit per the Investigator or until unacceptable toxicity, the need for subsequent treatment, or any other reasons for treatment discontinuation listed in the protocol
Stratification Factors
• Geographical region (Asia vs other)
• Documented RAS status (WT vs mutant)
• Presence of liver metastases (yes vs no)
Key Study Objectives
• Primary: OS (ITT RAS WT)
• Additional: OS (all & RAS mut) PFS, ORR, DOR, QOL, safety

MODULE 3: Evidence-Based Selection and Sequencing of Therapy for Patients with mCRC — Prof Van Cutsem

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 79-year-old man with metastatic rectal cancer and newly diagnosed PMS2-positive Lynch syndrome

Dr Liudmila Schafer (Kansas City, Missouri)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Liudmila N Schafer, MD

"We started him on pembrolizumab, and he actually has been on it since June of last year with stable disease and decreasing CEA. How does the faculty approach variants of unknown significance in MMR-deficient patients and confirmation with germline testing?"

- **Can you explain (at a first-year fellow level) the key biologic and diagnostic issues in MSI-high CRC and Lynch syndrome and other related abnormalities?**
- **What is your usual first-line treatment for MSI-high mCRC? How do tumor bulk, symptoms and age/performance status factor into your decisions?**
- **This patient is doing well on pembrolizumab. The tumor NGS demonstrated mutant TP53 Y220C and KRAS p.G13D. Do these alterations have any clinical relevance?**

RTP RESEARCH TO PRACTICE

Case Presentation: A 54-year-old man with pan-RAS WT metastatic rectal cancer treated with FOLFOX/cetuximab

Dr Warren Brenner (Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Warren S Brenner, MD

"My questions for the investigators are, what are they using in the front-line setting in patients who have left-sided disease, pan-RAS wild-type?

- *Are they using an EGFR inhibitor, or are they still using a VEGF inhibitor such as bevacizumab?*
- *Is disease in the transverse colon considered left-sided or right-sided disease?*
- *Are they using q2wk cetuximab dosing, or are they still using weekly cetuximab dosing?*
- *Should an EGFR inhibitor be combined with FOLFOX or FOLFIRI, and is there any role to combine it with FOLFOXIRI?*
- *Do the investigators ever use 5-FU plus an EGFR inhibitor as a maintenance strategy in patients with left-sided colorectal cancer?*
- *Do they have any pearls about the management of EGFR-related skin toxicity? What about any pearls on the management of oxaliplatin-related peripheral neuropathy?*
- *Are they using preventative strategies for the skin toxicity, such as antibiotics, certain steroid creams or moisturizers, or do they wait for patients to actually develop skin toxicity?"*

RTP RESEARCH TO PRACTICE

UZ LEUVEN

Evidence-Based Selection and Sequencing of Therapy for Patients with mCRC

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Annals of Oncology 0: 1–17, 2017
doi:10.1093/annonc/mdx175
Published online 12 April 2017

SPECIAL ARTICLE

Prognostic and predictive value of primary tumour side in patients with *RAS* wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials†

D. Arnold[1], B. Lueza[2], J.-Y. Douillard[3], M. Peeters[4], H.-J. Lenz[5], A. Venook[6], V. Heinemann[7], E. Van Cutsem[8], J.-P. Pignon[2], J. Tabernero[9], A. Cervantes[10,11] & F. Ciardiello[12*]

- Left sided tumors have a better prognosis than right sided tumors.
- Sidedness is predictive in first line treatment of RAS Wt tumours:
  - Left sided tumors benefit more for anti-EGFR antibodies.
  - Right sided tumors benefit slightly more from bevacizumab

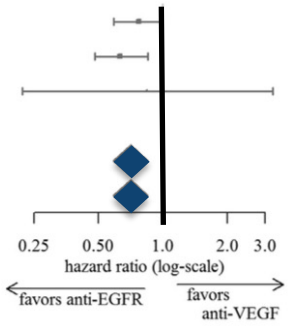
Meta-Analysis of Head to Head Comparisons of anti-EGFR AB vs Bevacizumab

Overall survival

A — **Left-sided mCRC**

study	n	Weight (%)	OS HR	95% CI	P-value
CALGB/SWOG 80405	325	53.8	0.77	(0.59 , 0.99)	
FIRE-3	306	44.2	0.63	(0.48 , 0.85)	
PEAK	107	2	0.84	(0.22 , 3.27)	
Summary (FE)			**0.71**	**(0.58 , 0.85)**	**0.0003**
Summary (RE)			**0.71**	**(0.58 , 0.85)**	**0.0003**

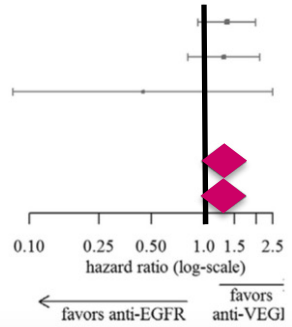
Heterogeneity: I^2 = 0%, 95% CI = (0% , 95.1%)
P-value = 0.575 (χ^2 test)



B — **Right-sided mCRC**

study	n	Weight (%)	OS HR	95% CI	P-value
CALGB/SWOG 80405	149	59.5	1.36	(0.93 , 1.99)	
FIRE-3	88	37.6	1.31	(0.81 , 2.11)	
PEAK	36	2.9	0.45	(0.08 , 2.49)	
Summary (FE)			**1.3**	**(0.97 , 1.74)**	**0.081**
Summary (RE)			**1.3**	**(0.97 , 1.74)**	**0.081**

Heterogeneity: I^2 = 0%, 95% CI = (0% , 99.4%)
P-value = 0.468 (χ^2 test)

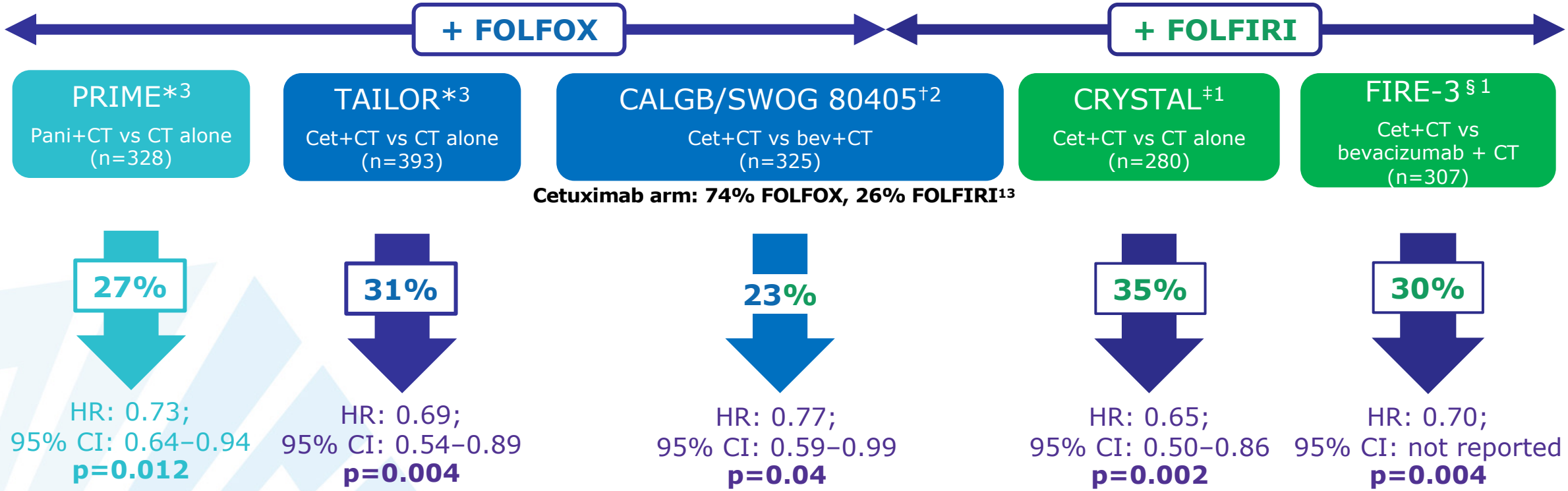


Left-sided primary:
Clear benefit from anti-EGFR agents compared to bevacizumab

Right-sided primary:
Strong trend in favor of bevacizumab

Holch J et al, Eur J Cancer. 2017

Anti-EGFR ab+ CT shows significant mOS benefit vs both FOLFOX and FOLFIRI in left-sided RAS WT mCRC patients in phase III studies



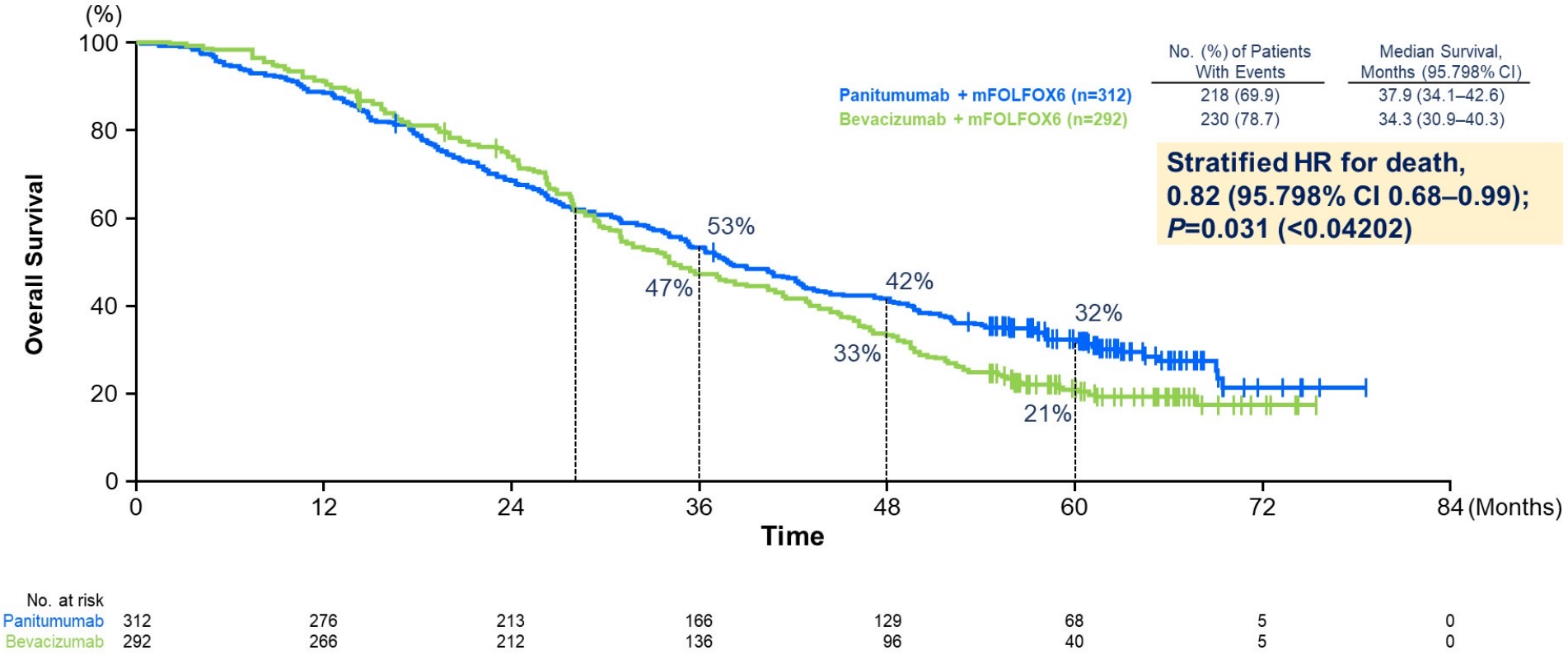
*TAILOR met its primary endpoint of significantly improving PFS in the cetuximab + FOLFOX4 arm vs FOLFOX4 alone in RAS wt mCRC;[3] †CALGB/SWOG 80405 did not meet its primary endpoint of significantly improving OS in the cetuximab + CT arm vs bevacizumab + CT arm in patients with KRAS (exon 2) wt mCRC; ‡CRYSTAL met its primary endpoint of significantly improving PFS in the cetuximab arm vs FOLFIRI arm in KRAS wt mCRC; §FIRE-3 did not meet its primary endpoint of significantly improving ORR based on investigators' read in patients with KRAS (exon 2) wt mCRC.
PFS, progression-free survival.

- 1. Stintzing S, et al. ASCO 2018 (Abstract No. 3508); 2. Venook AP, et al. ESMO 2016. Special session;
- 3. Qin S, et al. J Clin Oncol 2018;36:3031–3039. 4. Van Cutsem E et al, J Clin Onco 2015; 5. Tejpar S... Van Cutsem E, JAMA Onc 2017

Treatment of RAS WT mCRC: FOLFOX + bevacizumab or panitumumab

PARADIGM Trial

Primary Endpoint-1; Overall Survival in Left-sided Population

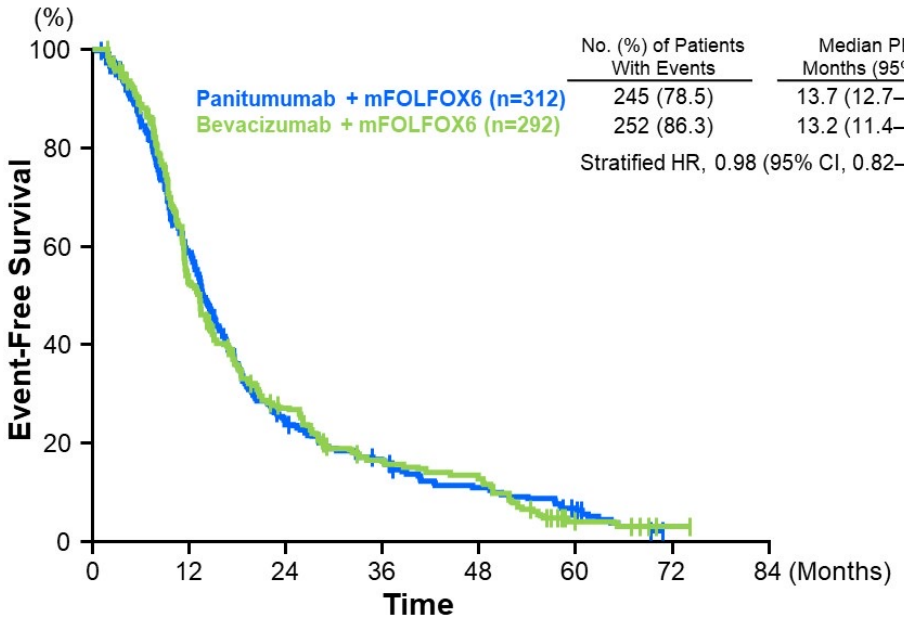


Yoshino T et al, ASCO 2022, LBA1 (presidential session)

Treatment of metastatic CRC: PARADIGM Trial

Progression-free Survival[a]

Left-sided Population

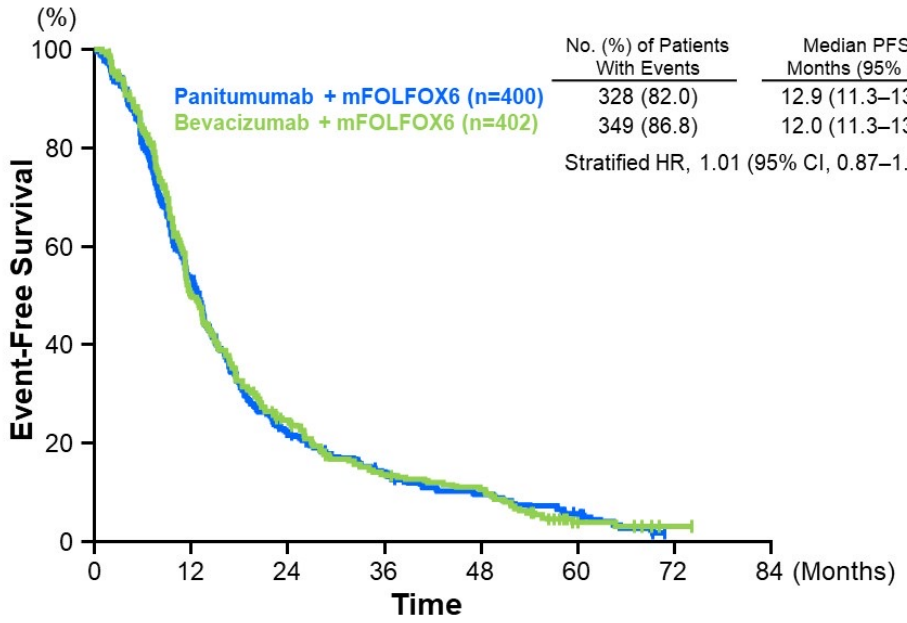


	No. (%) of Patients With Events	Median PFS, Months (95% CI)
Panitumumab + mFOLFOX6 (n=312)	245 (78.5)	13.7 (12.7–15.3)
Bevacizumab + mFOLFOX6 (n=292)	252 (86.3)	13.2 (11.4–14.5)

Stratified HR, 0.98 (95% CI, 0.82–1.17)

No. at risk								
Panitumumab	312	149	59	38	24	13	0	0
Bevacizumab	292	139	67	40	31	5	1	0

Overall Population



	No. (%) of Patients With Events	Median PFS, Months (95% CI)
Panitumumab + mFOLFOX6 (n=400)	328 (82.0)	12.9 (11.3–13.6)
Bevacizumab + mFOLFOX6 (n=402)	349 (86.8)	12.0 (11.3–13.5)

Stratified HR, 1.01 (95% CI, 0.87–1.18)

No. at risk								
Panitumumab	400	179	71	43	28	15	0	0
Bevacizumab	402	182	83	45	35	6	1	0

[a]Patients who underwent curative-intent resection were censored at the last tumor evaluable assessment date before the resection.

Yoshino T et al, ASCO 2022, LBA1 (presidential session)

Other Efficacy Outcomes

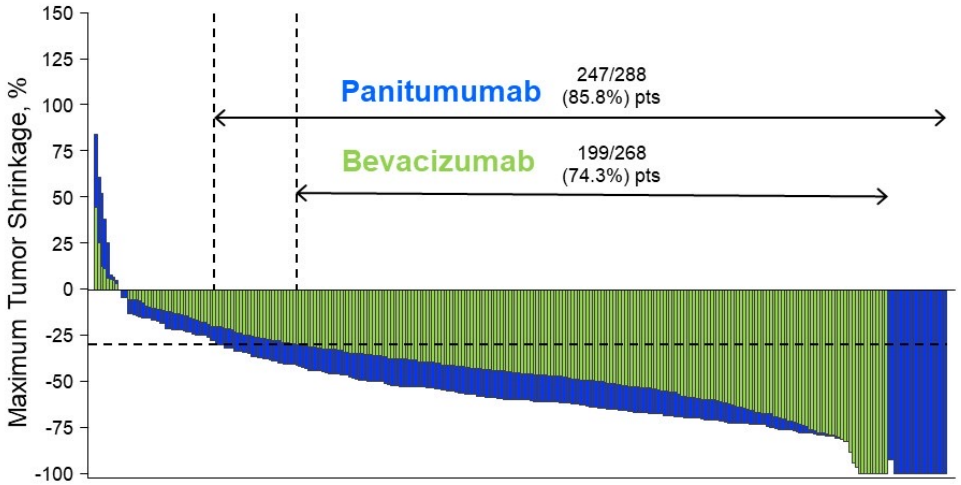
Parameter	Left-sided Population		Overall Population	
	Panitumumab + mFOLFOX6 (n=308)	Bevacizumab + mFOLFOX6 (n=287)	Panitumumab + mFOLFOX6 (n=394)	Bevacizumab + mFOLFOX6 (n=397)
Response rate, % (95% CI)	80.2 (75.3–84.5)	68.6 (62.9–74.0)	74.9 (70.3–79.1)	67.3 (62.4–71.9)
Difference, % (95% CI)	11.2 (4.4–17.9)		7.7 (1.5–13.8)	
DCR, % (95% CI)	97.4 (94.9–98.9)	96.5 (93.7–98.3)	94.9 (92.3–96.9)	95.5 (92.9–97.3)
Median DOR,[a] months (95% CI)	13.1 (11.1–14.8)	11.2 (9.6–13.1)	11.9 (10.5–13.4)	10.7 (9.5–12.2)
R0 rate,[b] % (95% CI)	18.3 (14.1–23.0)	11.6 (8.2–15.9]	16.5 (13.0–20.5)	10.9 (8.1–17.1)

RR, response rate; DCR, disease control rate; DOR, duration of response; R0, curative resection.
[a] DOR was evaluated in patients with complete or partial response.
[b] R0 rate was evaluated in all the patients of efficacy analysis population (left-sided: n=312 for panitumumab and n=292 for bevacizumab; overall: n=400 and 402, respectively).

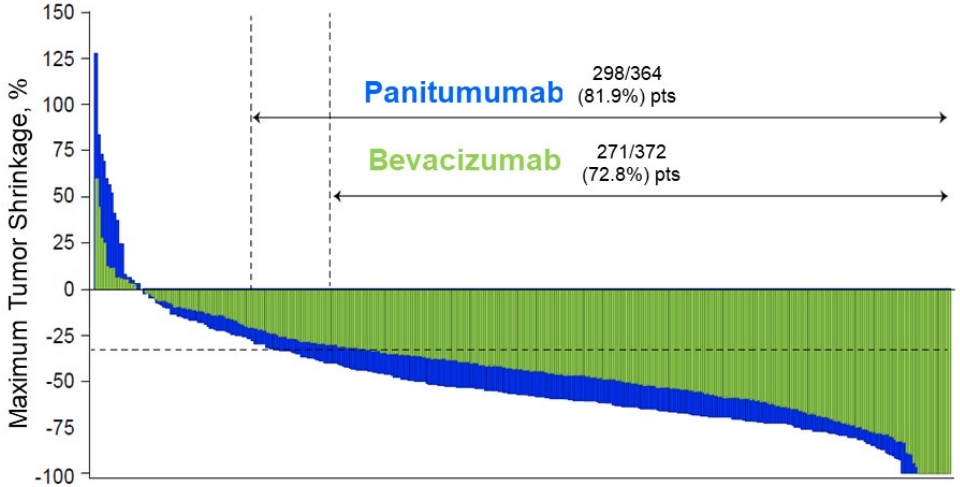
Yoshino T et al, ASCO 2022, LBA1 (presidential session)

Other Efficacy Outcome: Depth of Response

Left-Sided Population



Overall Population



Horizontal dotted line at 30% indicates response per RECIST v1.1.

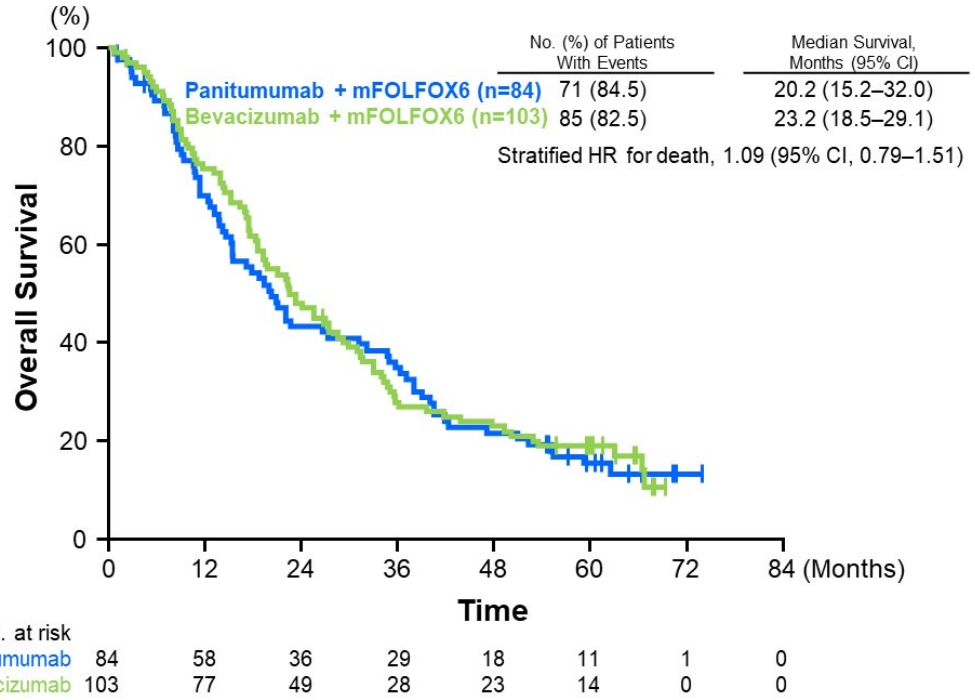
	Left-sided Population		Overall Population	
	Panitumumab + mFOLFOX6 (n=288)	Bevacizumab + mFOLFOX6 (n=268)	Panitumumab + mFOLFOX6 (n=364)	Bevacizumab + mFOLFOX6 (n=372)
Median, %	-59.4	-43.6	-57.3	-43.6

Depth of response was assessed in patients with measurable lesions at baseline.

Yoshino T et al, ASCO 2022, LBA1 (presidential session)

Treatment of metastatic CRC: PARADIGM Trial

OS and Subgroup Analysis in Right-sided Population



Subgroup		Events/Patients: Panitumumab + mFOLFOX6	Events/Patients: Bevacizumab + mFOLFOX6	Hazard Ratio (95% CI)
	Overall*	71/84	85/103	1.09 (0.79-1.51)
Age	20-64 yr	22/26	32/39	1.26 (0.73-2.17)
	65-79 yr	49/58	53/64	0.97 (0.66-1.44)
Sex	Male	37/41	51/61	1.04 (0.68-1.60)
	Female	34/43	34/42	1.08 (0.67-1.74)
ECOG PS	0	54/65	68/82	0.96 (0.67-1.37)
	1	16/18	17/21	1.33 (0.66-2.67)
No. of organs with metastasis	0-1	31/40	30/44	1.27 (0.77-2.10)
	≥2	40/44	55/59	0.94 (0.63-1.42)
Liver metastasis	No	26/35	29/37	0.87 (0.51-1.49)
	Yes	45/49	56/66	1.23 (0.83-1.83)
Organs with metastasis	Liver only	13/14	15/21	1.66 (0.79-3.50)
	Other	58/70	70/82	0.93 (0.66-1.32)
Primary tumor resection	No	30/33	28/30	0.87 (0.51-1.45)
	Yes	41/51	57/73	1.09 (0.73-1.63)

*Stratified Hazard Ratio is shown with 95% CI.

2022 ASCO ANNUAL MEETING #ASCO22

PRESENTED BY: Takayuki YOSHINO, MD, PhD

Yoshino T et al, ASCO 2022, LBA1 (presidential session)

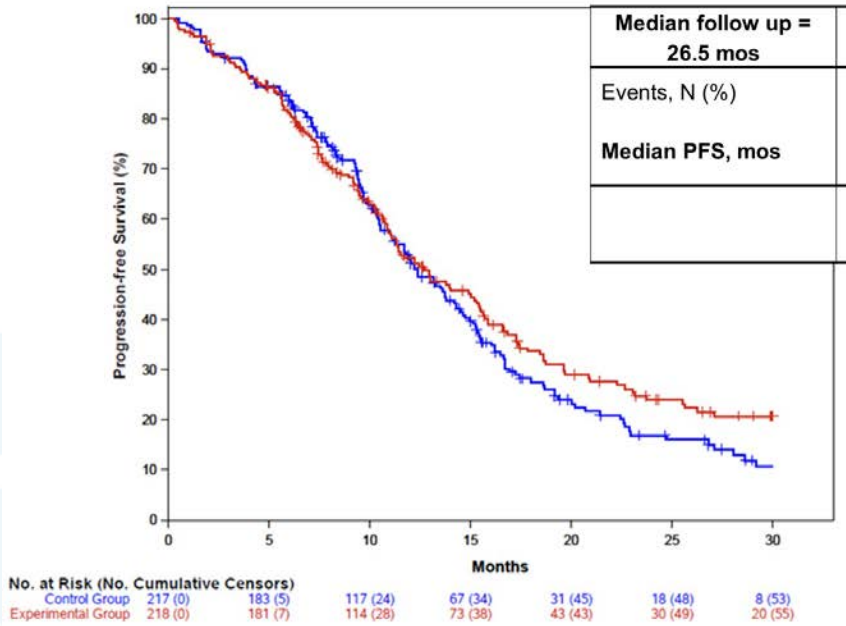
1st line; CT + anti-EGFR vs CT + bevacizumab in left sided RAS wt

	[1] CALGB 80405	[2] PEAK	[3] FIRE3	[4] PARADIGM	[5] STRATEGIC
N RAS wt	325	107	273	604	263
Design	Chemo Cetuxi vs. Chemo Beva	FOLFOX Pani vs. FOLFOX Beva	FOLFIRI Cetuxi vs. FOLFIRI Beva	FOLFOX Pani vs. FOLFOX Beva	FOLFIRI Cetuxi start vs. OPTIMOX Beva → TML strategy
1st endpoint	OS	PFS	RR	OS	DDC
HR for OS	0.77, n.s.	0.84, n.s.	0.71, p<0.001	0.82, p<0.031	0.793, n.s.
Median OS (months)	32.6 vs. 39.3	32 vs. 43.4	28.2 vs. 38.2	34.3 vs. 37.9	34.4 vs. 37.8
				all prospectively planned	left sided 81%

[1]Venook A et al., JAMA 2017 and Arnold D et al, Ann Oncol 2017; [2]Boeckx N et al., Ann Oncol 2017; [3]Heinemann V et al., Br J Cancer 2021; [4]Yoshino T et al., ASCO 2022; [5]Chibaudel B et al., ASCO 2022

Chemo intensity with anti-EGFR

TRIPLETE phase III trial in first line: FOLFOX/panitumumab vs FOLFOXIRI/panitumumab



Median follow up = 26.5 mos	FOLFOX/Pan N = 217	mFOLFOXIRI/Pan N = 218
Events, N (%)	157 (72%)	148 (68%)
Median PFS, mos	12.3	12.7
	HR = 0.88 [95% CI: 0.70-1.11] p=0.277	

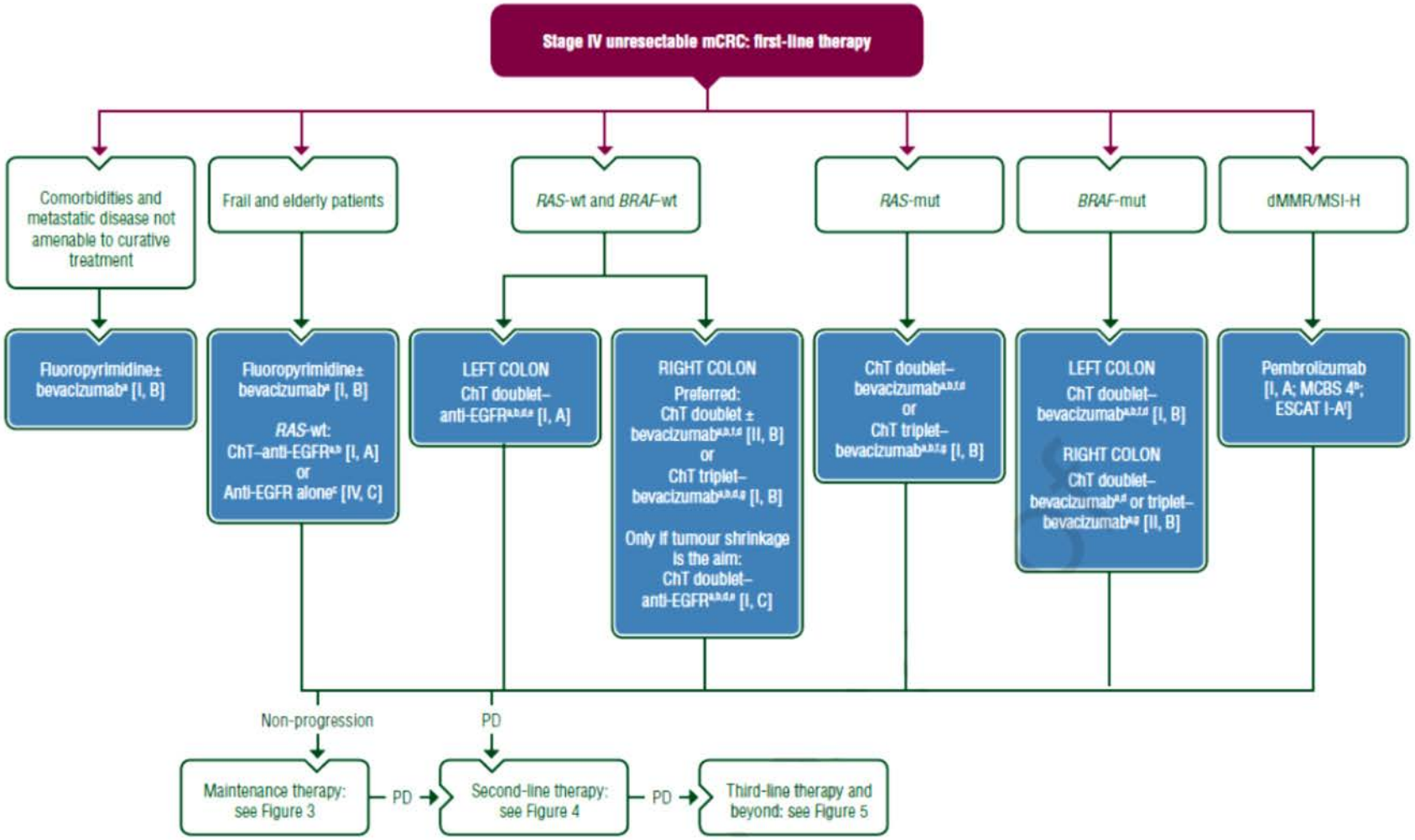
Progression free survival

	FOLFOX/Pan N = 213	mFOLFOXIRI/Pan N = 218
Complete Response	7%	7%
Partial Response	69%	66%
Response Rate	**76%**	**73%**
Stable disease	17%	18%
Progressive Disease	5%	5%
Not Assessed	2%	4%
R0 Resection Rate	**29%**	**25%**

Response rate

Cremolini C et al., ASCO 2022

ESMO guidelines 2022: first line algorithm

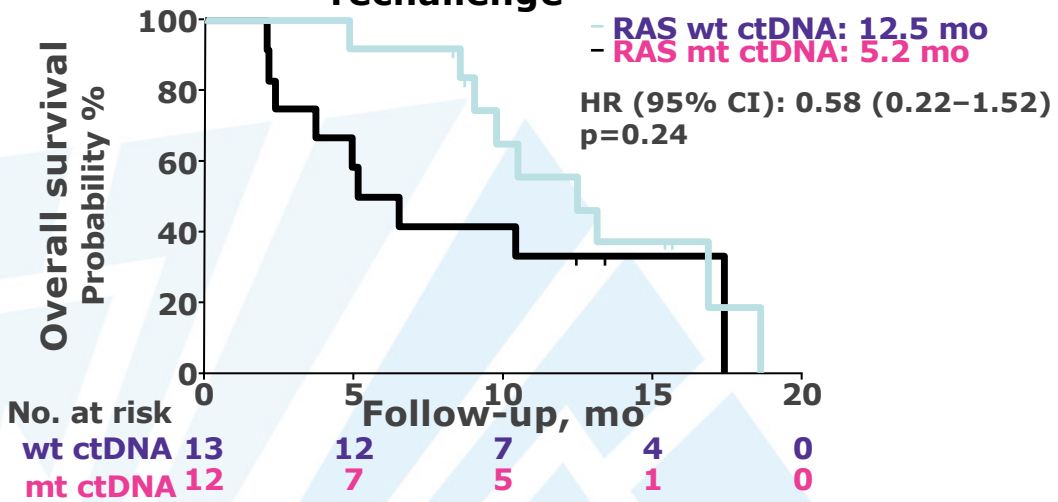


Cervantes A et al, Ann Oncol 2022

CRICKET & CHRONOS Trial: reintroduction with anti-EGFR AB

Genotyping tumor DNA in the blood to direct therapy can be effectively incorporated in the management of advanced CRC

Kaplan-Meier estimates of OS according to RAS and BRAF status at the start of rechallenge[21]



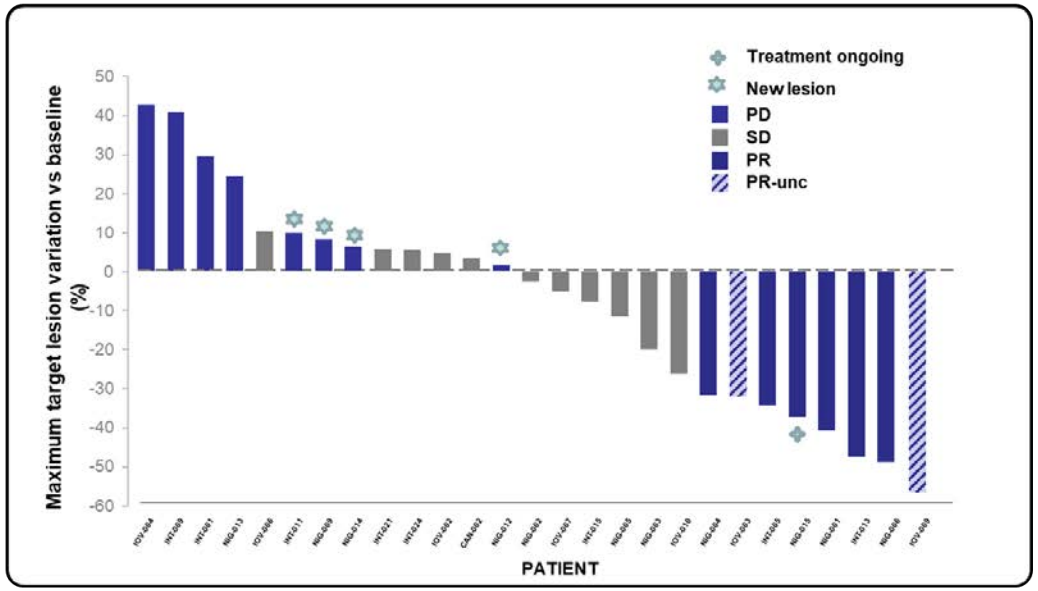
CRICKET trial

Cremolini C, et al. JAMA Oncol 2019;5:343–350.

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 trial

A. Sartore-Bianchi et al, ASCO 2021;Abstract 3506.

CAVE GOIM trial: rechallenge with cetuximab + avelumab

Pre-treated patients with RAS wt mCRC* (N=77)

8 Italian centres

≥3L

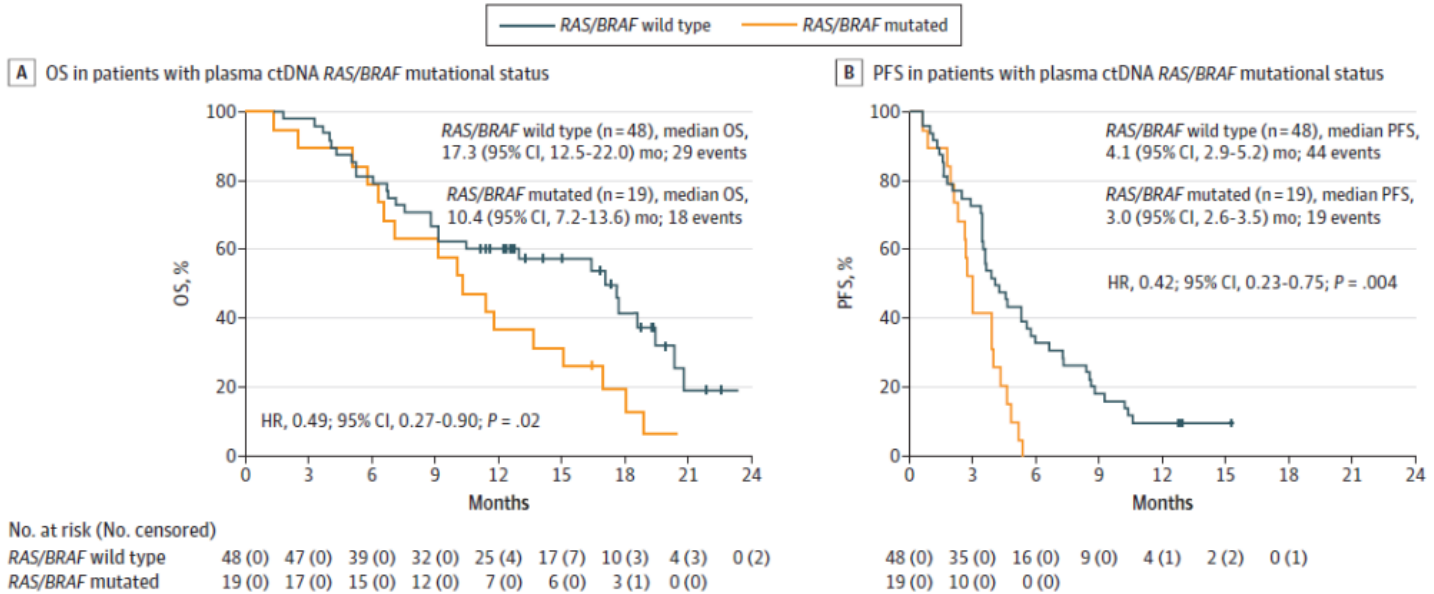
Cetuximab 250 mg/m² + avelumab 10 mg/kg†

Until PD or unacceptable toxicity‡

Key inclusion criteria:

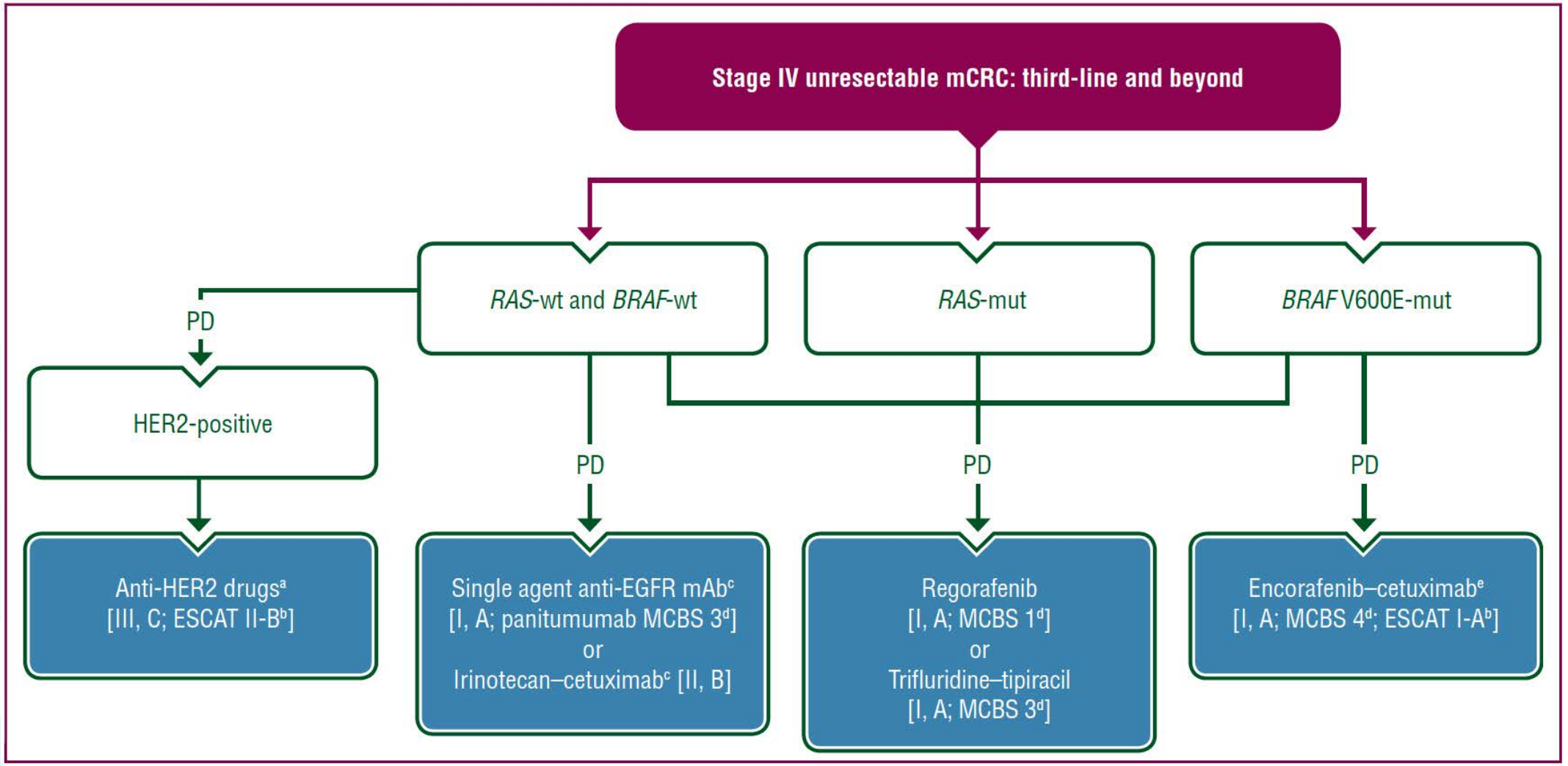
- **1L treatment with anti-EGFR agents + CT, achieving a CR or PR**
- **2L anti-EGFR free interval**
- **ECOG PS 0–1**

Primary endpoint: OS
Secondary endpoints: PFS, ORR, DCR, safety



Martinelli E et al, JAMA Oncol 2021

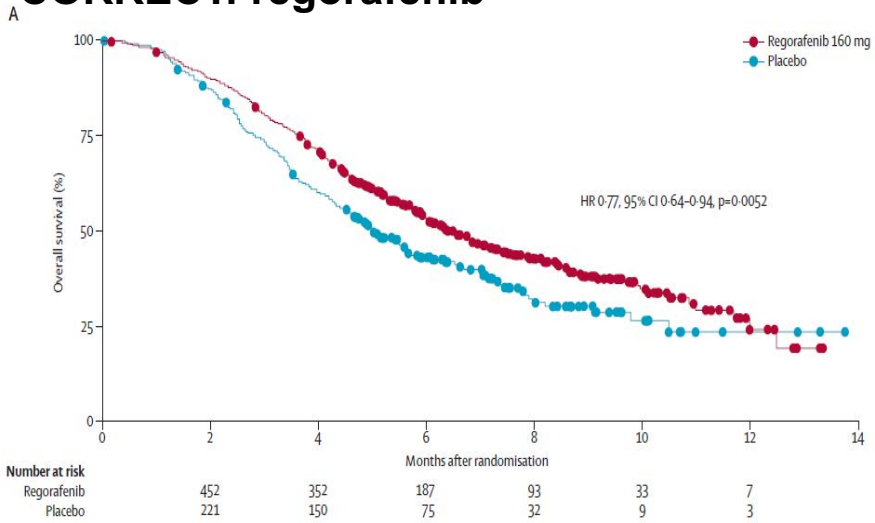
New ESMO Guidelines 2022

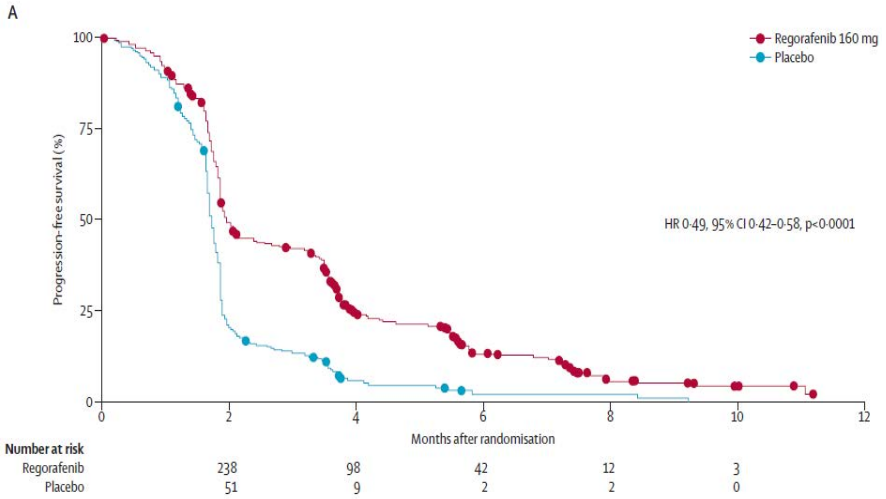


Cervantes A et al, Ann Oncol 2022

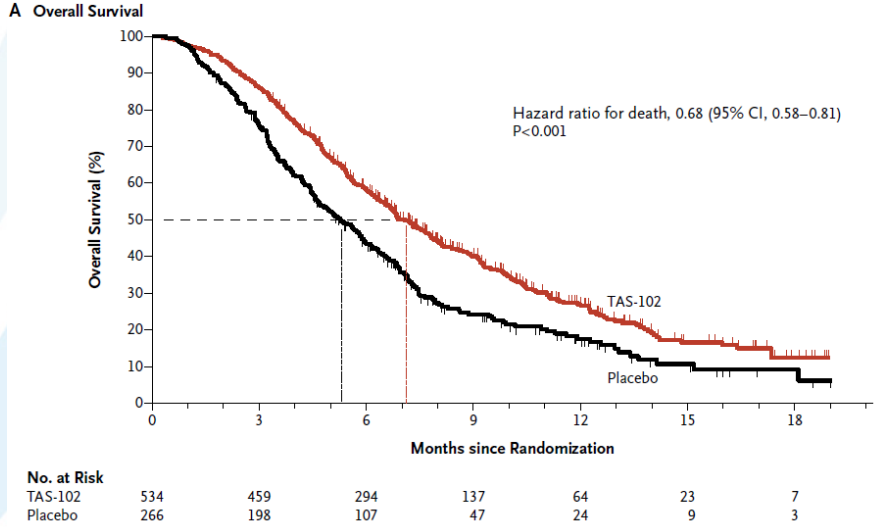
Regorafenib and trifluridine/tipiracil (TAS-102) in refractory mCRC

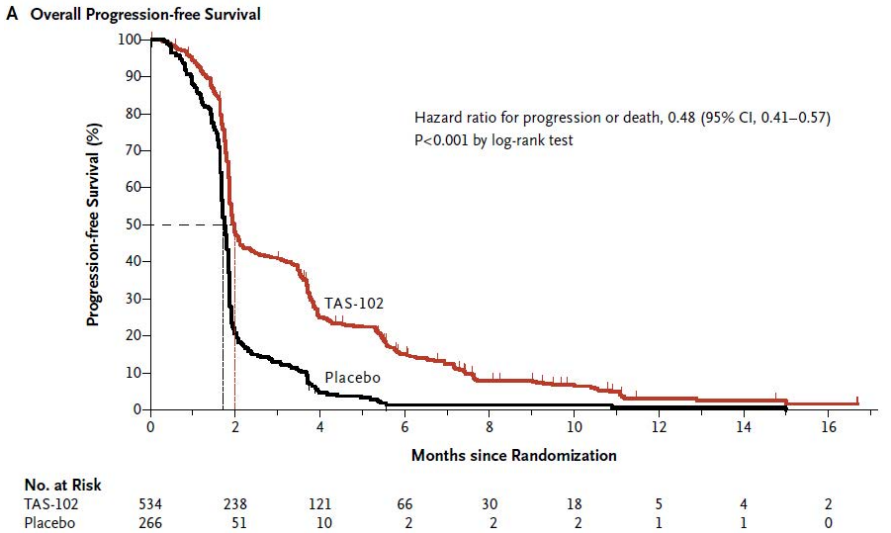
CORRECT: regorafenib





RECOURSE: trifluridine/tipiracil = TAS-102





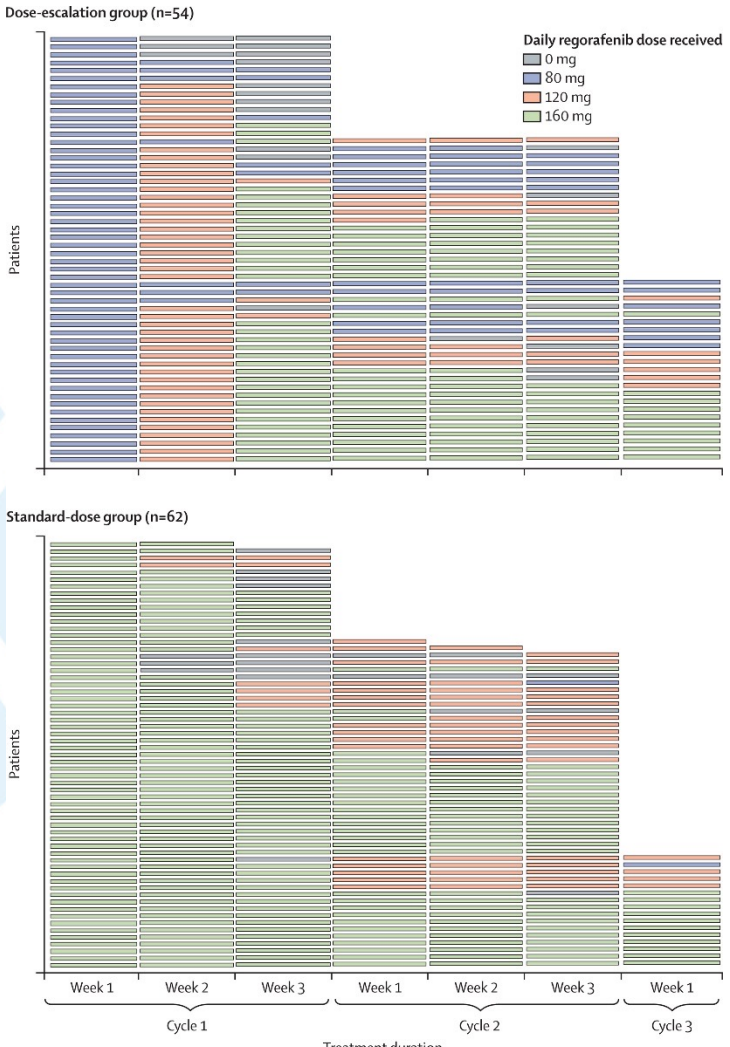
Grothey A, Van Cutsem E et al, Lancet 2013; Mayer R, Van Cutsem E, Ohtsu A et al NEJM, 2015

Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study

Tanios S Bekaii-Saab, Fang-Shu Ou, Daniel H Ahn, Patrick M Boland, Kristen K Ciombor, Erica N Heying, Travis J Dockter, Nisha L Jacobs, Boris C Pasche, James M Cleary, Jeffrey P Meyers, Rodwige J Desnoyers, Jeannine S McCune, Katrina Pedersen, Afsaneh Barzi, E Gabriela Chiorean, Jeffrey Sloan, Mario E Lacouture, Heinz-Josef Lenz, Axel Grothey

Dose escalation arm

Standard dose group



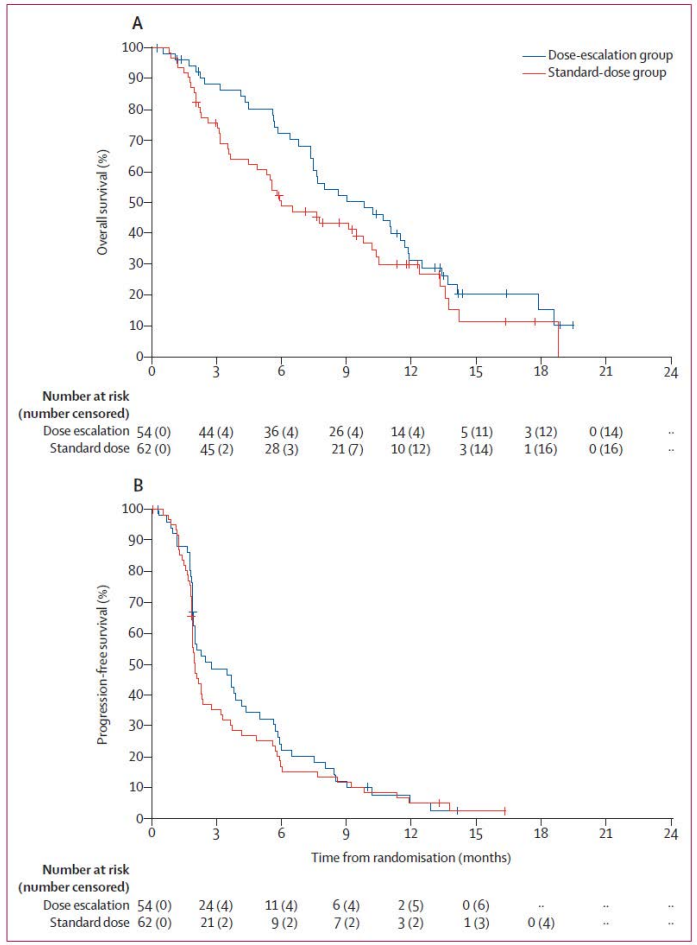


Figure 2: Overall survival (A) and progression-free survival (B) in the dose-escalation and standard-dose groups
Censored patients are marked on the curves with a cross.

The Lancet Oncology 2019: DOI: (10.1016/S1470-2045(19)30272-4)

REARRANGE Study: regorafenib optimal dose seeking

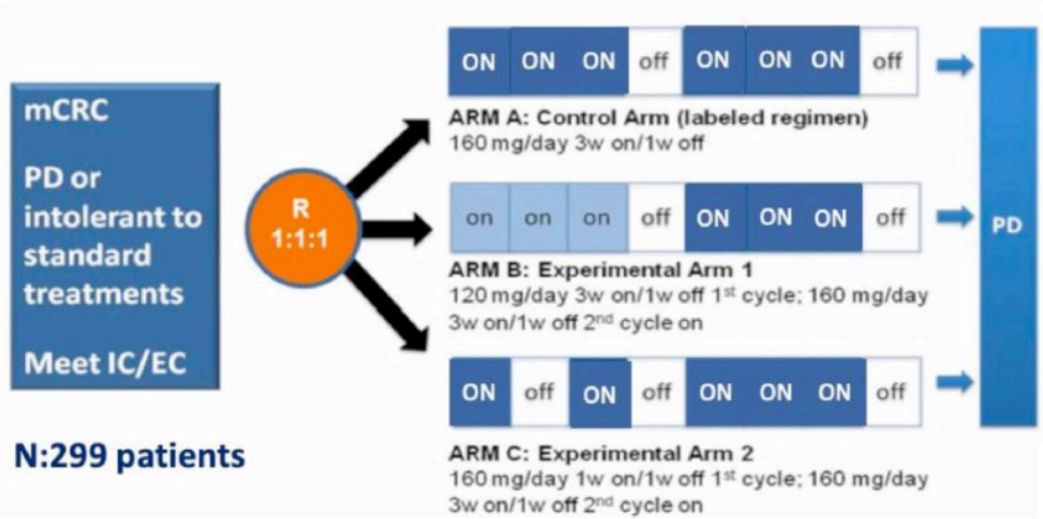
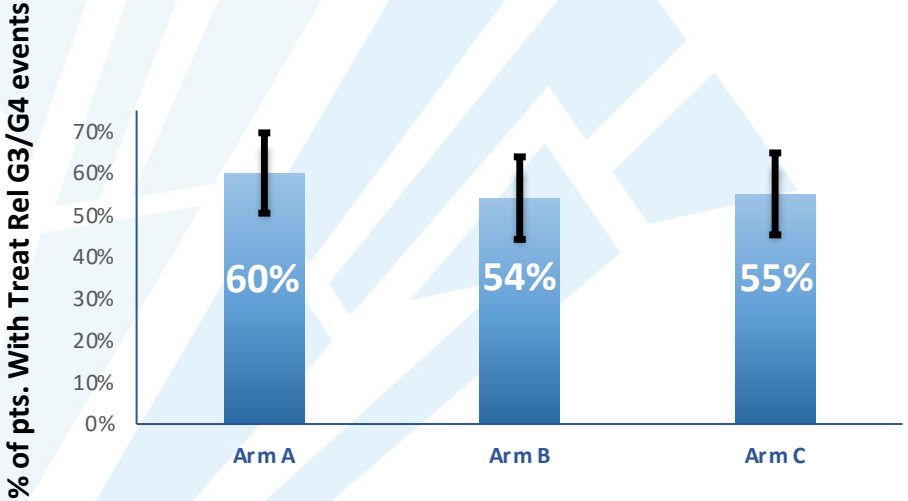


Fig. 1. Trial design.

Primary endpoint:

- **Safety**: % of patients having G3/G4 AEs during the entire course of the treatment



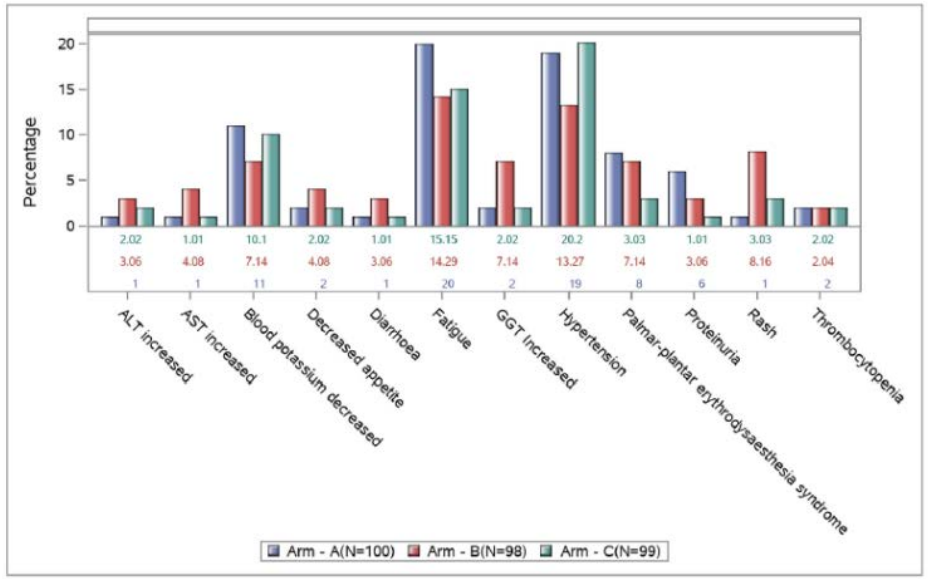
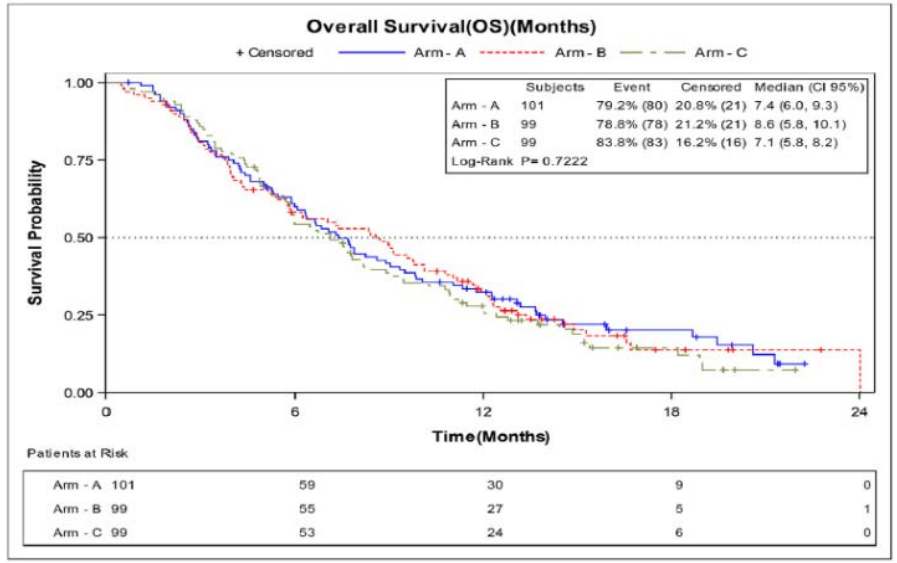


Fig. 3. Treatment-related grade 3-4 adverse events occurring in >2% of patients.



Argiles G et al, Eur J Cancer 2022

Danish phase 2 trial of TAS-102 ± bevacizumab

TAS-102 with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer: an investigator-initiated, open-label, randomised, phase 2 trial

Per Pfeiffer, Mette Yilmaz, Sören Möller, Daniela Zitnjak, Merete Krogh, Lone Nørgård Petersen, Laurids Østergaard Poulsen, Stine Braendegaard Winther, Karina Gravgaard Thomsen, Camilla Qvortrup

Lancet Oncol 2020; 21: 412–20

Published Online January 27, 2020 https://doi.org/10.1016/S1470-2045(19)30827-7

See Comment page 326

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Correspondence to: Prof Per Pfeiffer, Department of Oncology, Odense University Hospital, Odense 5000, Denmark **per.pfeiffer@rsyd.dk**

Summary

Background TAS-102 (trifluridine–tipiracil) has shown a significant overall survival benefit compared with placebo in patients with chemorefractory metastatic colorectal cancer. Inspired by the encouraging results of a small phase 1–2 study, C-TASK FORCE, which evaluated the combination of TAS-102 plus bevacizumab in patients with chemorefractory metastatic colorectal cancer, we aimed to compare the efficacy of TAS-102 plus bevacizumab versus TAS-102 monotherapy in patients receiving refractory therapy for metastatic colorectal cancer .

Methods This investigator-initiated, open-label, randomised, phase 2 study enrolled patients (aged ≥18 years) with metastatic colorectal from four cancer centres in Denmark. The main inclusion criteria were histopathologically confirmed metastatic colorectal cancer refractory or intolerant to a fluoropyrimidine, irinotecan, oxaliplatin, and cetuximab or panitumumab (only for *RAS* wild-type), and WHO performance status of 0 or 1. Previous therapy with bevacizumab, aflibercept, ramucirumab, or regorafenib was allowed but not mandatory. Participants were enrolled and randomly assigned (1:1) in block sizes of two, four, or six by a web-based tool to receive oral TAS-102 (35 mg/m² twice daily on days 1–5 and 8–12 every 28 days) alone or combined with intravenous bevacizumab (5 mg/kg on days 1 and 15) until progression, unacceptable toxicity, or patient decision to withdraw. Treatment assignment was not masked, and randomisation was stratified by institution and *RAS* mutation status. The primary endpoint was investigator-evaluated progression-free survival. All analyses were based on intention to treat. This trial is registered with EudraCT, 2016–005241–23.

Findings From Aug 24, 2017, to Oct 31, 2018, 93 patients were enrolled and randomly assigned to TAS-102 (n=47) or TAS-102 plus bevacizumab (n=46). The clinical cut-off date was Feb 15, 2019, after a median follow-up of 10·0 months (IQR 6·8–14·0). Median progression-free survival was 2·6 months (95% CI 1·6–3·5) in the TAS-102 group versus 4·6 months (3·5–6·5) in the TAS-102 plus bevacizumab group (hazard ratio 0·45 [95% CI 0·29–0·72]; p=0·0015). The most frequent grade 3 or worse adverse event was neutropenia (18 [38%] of 47 in the TAS-102 monotherapy group *vs* 31 [67%] of 46 in the TAS-102 plus bevacizumab group). Serious adverse events were observed in 21 (45%) patients in the TAS-102 group and 19 (41%) in the TAS-102 plus bevacizumab group. No deaths were deemed treatment related.

Interpretation In patients with chemorefractory metastatic colorectal cancer, TAS-102 plus bevacizumab, as compared with TAS-102 monotherapy, was associated with a significant and clinically relevant improvement in progression-free survival with tolerable toxicity. The combination of TAS-102 plus bevacizumab could be a new treatment option for patients with refractory metastatic colorectal cancer and could be a practice-changing development.

Funding Servier.

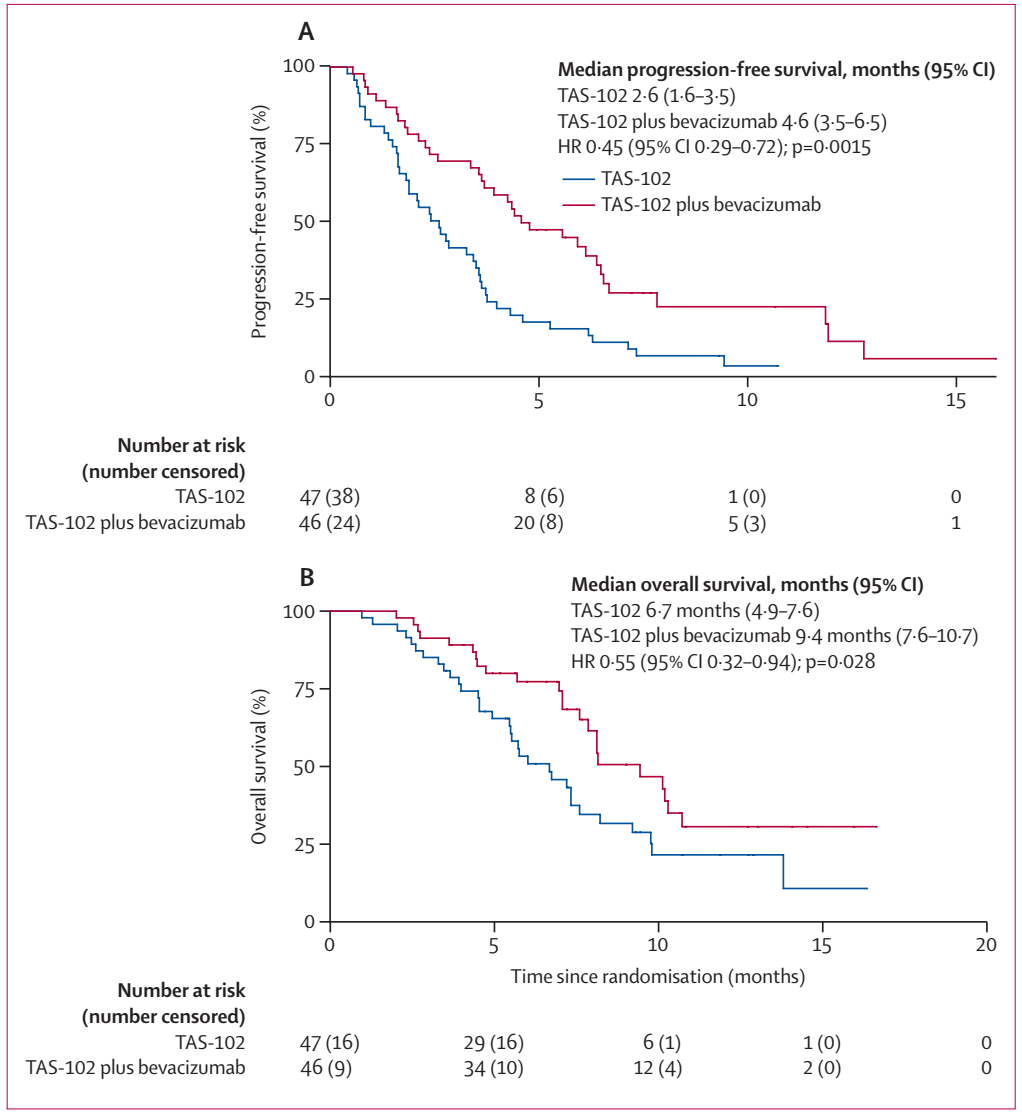
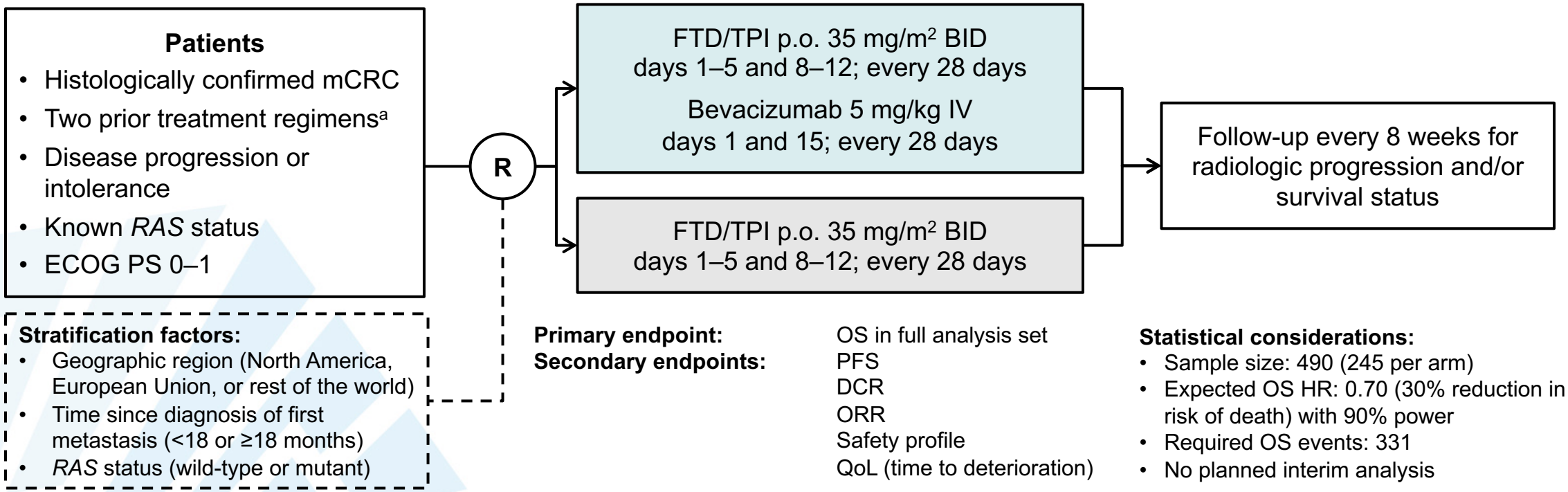


Figure 2: **The efficacy of TAS-102 monotherapy versus TAS-102 plus bevacizumab combination therapy**
(A) Progression-free survival. (B) Overall survial. HR=hazard ratio.

SUNLIGHT study design

- An open-label, randomized, phase 3 study in patients with refractory mCRC (NCT04737187)



Primary endpoint: OS in full analysis set

Secondary endpoints: PFS, DCR, ORR, Safety profile, QoL (time to deterioration)

Statistical considerations:
- Sample size: 490 (245 per arm)
- Expected OS HR: 0.70 (30% reduction in risk of death) with 90% power
- Required OS events: 331
- No planned interim analysis

[a] Prior treatment must have included a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody (not necessarily bevacizumab), and/or an anti-EGFR monoclonal antibody for patients with *RAS* wild-type and could have included (neo)adjuvant chemotherapy if disease had recurred during treatment or within 6 months of the last administration of (neo)adjuvant therapy. BID, twice daily; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; EFGR, epidermal growth factor receptor; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; IV, intravenous; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; p.o., orally; QoL, quality of life; R, randomization; VEGF, vascular endothelial growth factor.

Tabernero J … Van Cutsem E et al, ASCO GI 2023

Trifluridine/Tipiracil plus Bevacizumab for Third-Line Treatment of Refractory Metastatic Colorectal Cancer: The Phase 3 Randomized SUNLIGHT Study

Tabernero J et al.

2023 ASCO Gastrointestinal Cancers Symposium;Abstract 4.

Oral Abstract Session C: Cancers of the Colon, Rectum, and Anus

January 21, 2023

2:00 PM – 2:10 PM ET

MODULE 4: Promising Agents and Strategies for Patients with mCRC — Dr Bekaii-Saab

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 50-year-old woman with KRAS and BRAF WT, HER2-negative T3N1 rectal cancer with liver and lung oligometastases s/p multiple ablations/SBRT and currently receiving FOLFIRI/panitumumab – MSS, pMMR, PD-L1 0%

Dr Jennifer Dallas (Charlotte, North Carolina)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Jennifer L Dallas, MD

"My question for this case is, in this woman with progressive oligometastatic rectal cancer, if she has no evidence of disease after the stereotactic radiation, is there a role for ctDNA testing to help predict recurrence?"

- **What are the most frequent sites of oligometastatic disease, and how do you determine the type of local treatment in common clinical scenarios?**

Case Presentation: A 60-year-old woman with metastatic KRAS G12C-mutant cancer of the sigmoid colon

Dr Philip Brooks (Brewer, Maine)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Philip L Brooks, MD

"The important thing is, she does have a KRAS G12C mutation on NGS. My question is, should I consider sotorasib? Our academic center, which is Dana-Farber, is a 5-hour drive for her, but they are soon going to have a trial of adagrasib and cetuximab. Should I wait for her to get onto the study? Should I do it off study by adding sotorasib to cetuximab?"

- **In what situations should a community-based oncologist consider off-label use of available agents to treat KRAS G12C-mutant CRC? Which agents?**

MAYO CLINIC

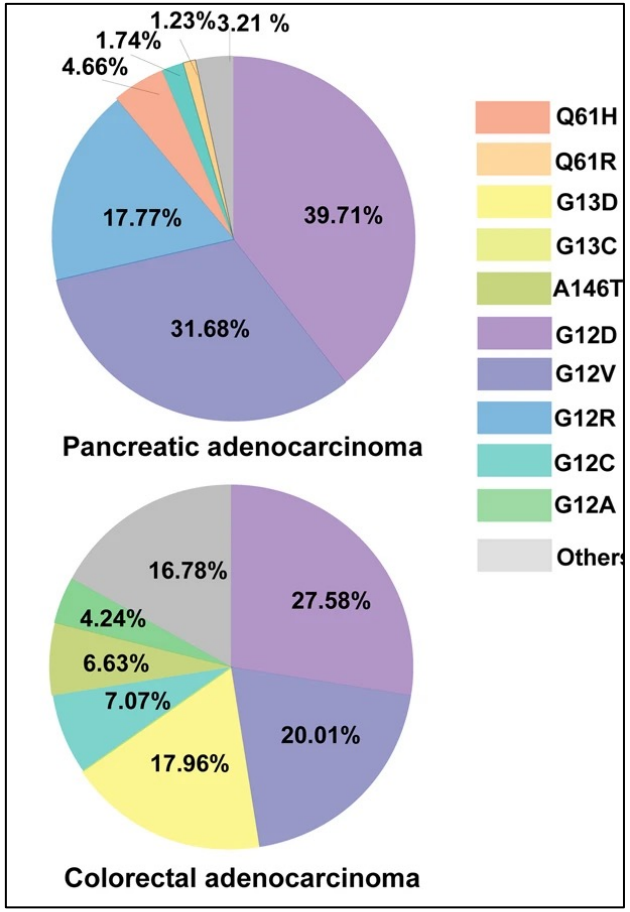
Promising Agents and Strategies for Patients with mCRC

Tanios Bekaii-Saab, MD ,FACP
Professor , Mayo Clinic College of Medicine and Science
Consultant, Mayo Clinic AZ
Chair , ACCRU Consortium

Why Has KRAS Been Considered Undruggable?

- Lack of accessible binding pockets (large hydrophobic pockets difficult to target with small molecule chemistry)
- Toxic effects of indirect KRAS-targeting approaches
- The first signs of the dawn appear on the horizon for one specific mutation, KRAS (G12C). Unlike KRAS (G12D) and KRAS (G12V), KRAS (G12C) can maintain alternative interactions with its downstream effectors through an active cycle between the GDP-bound and GTP-bound states

KRAS Mutation Type in GI Cancers

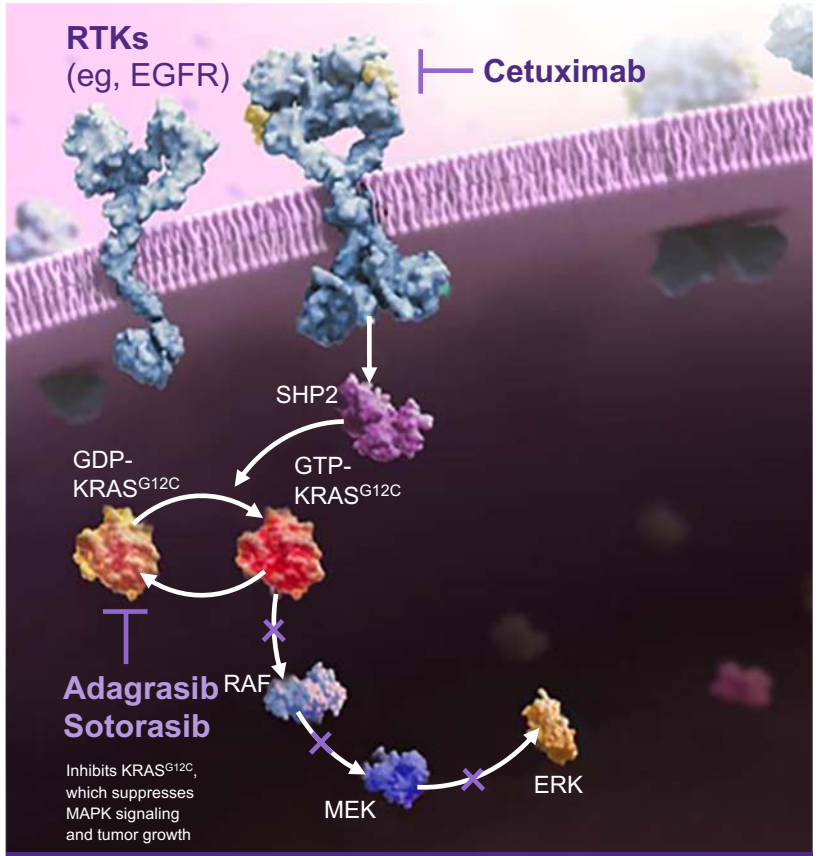


Huang L et al, Signal Transduct Target Ther 2021; 6(1):386

ZMCNNP20221210001 Expire Date 2023/12/10

Background

- KRAS^{G12C} mutations occur in approximately 3–4% of CRC, act as oncogenic drivers, and are a negative predictor of cetuximab efficacy[1–4]
- The KRAS protein cycles between guanosine triphosphate (GTP)-on and guanosine diphosphate (GDP)-off states and has a protein resynthesis half-life of ~24 hours[5,6]
- Adagrasib, a covalent inhibitor of KRAS^{G12C}, irreversibly and selectively binds KRAS^{G12C} in its inactive, GDP-bound state and was optimized for desired properties, including[7]:
  - Long half-life of ~24 hours, dose-dependent PK, and brain penetration
  - Maintaining continuous adagrasib exposure above a target threshold enables inhibition of KRAS-dependent signaling for the complete dosing interval and maximizes antitumor activity
- Sotorasib is another first-in-class, irreversible inhibitor of the KRASG12C protein[8]
- **Combining KRAS G12C inhibitors with an epidermal growth factor receptor (EGFR) inhibitor, may enhance inhibition of KRAS-dependent signaling or overcome adaptive feedback to improve outcomes[9]**



EGFR signaling is implicated in feedback reactivation, providing a rational co-targeting strategy for KRAS-mutant colorectal cancer (CRC)

1. Zehir A, et al. *Nat Med*. 2017;23(6):703-713; 2. Schirripa M, et al. *Clin Colorectal Cancer*. 2020;S1533-0028(20)30067-0; 3. NIH TCGA: *The Cancer Genome Atlas*. February 11, 2021; https://www.cbioportal.org; 4. Modest DP, et al. *Oncology*. 2012;83:241-247; 5. Bos JL, et al. *Cell*. 2007;129:865-877; 6. Shukla S, et al. *Neoplasia*. 2014;16(2):115-128; 7. Hallin J, et al. *Cancer Discov*. 2020;10(1):54-71;8. Lanman BA, et al. J Med Chem. 2020;63:52-65. 9. Tabernero J, et al. Presented at ESMO 23rd World Congress on Gastrointestinal Cancer; June 30-July 3, 2021; virtual

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adagrasib with or without Cetuximab in Colorectal Cancer with Mutated *KRAS* G12C

Rona Yaeger, M.D., Jared Weiss, M.D., Meredith S. Pelster, M.D., Alexander I. Spira, M.D., Ph.D., Minal Barve, M.D., Sai-Hong I. Ou, M.D., Ph.D., Ticiana A. Leal, M.D., Tanios S. Bekaii-Saab, M.D., Cloud P. Paweletz, Ph.D., Grace A. Heavey, B.A., James G. Christensen, Ph.D., Karen Velastegui, B.Sc., Thian Kheoh, Ph.D., Hirak Der-Torossian, M.D., and Samuel J. Klempner, M.D.

KRYSTAL-1 (849-001) Phase 1b/2 CRC Cohorts Study Design

Key Eligibility Criteria

- CRC with a $KRAS^{G12C}$ mutation[a]
- Unresectable or metastatic disease
- Prior systemic treatment for metastatic disease
- No available treatment with curative intent or available standard of care

Phase 1b
CRC Combination

Adagrasib 600 mg BID[b] + cetuximab[c] (n=32)

Phase 2
CRC Monotherapy

Adagrasib 600 mg BID[b] (n=44)

Study Objectives

Phase 1b

- Primary endpoints: safety, RP2D, PK
- Secondary endpoints: ORR (RECIST 1.1), DOR, PFS, OS

Phase 2

- Primary endpoint: ORR (RECIST 1.1)[d]
- Secondary endpoints: safety, DOR, PFS, OS

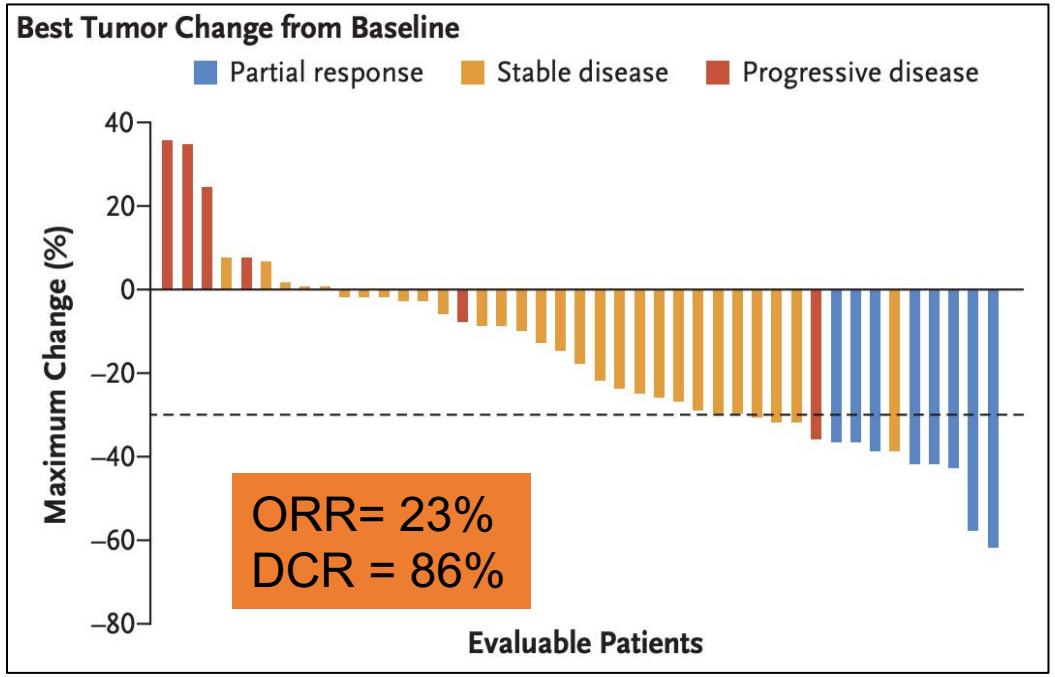
- Previously reported data demonstrated clinical activity of adagrasib monotherapy and adagrasib + cetuximab in patients with previously treated $KRAS^{G12C}$-mutated CRC[10,e]
- Here we report updated data for adagrasib 600 mg BID as monotherapy (Phase 2; median follow-up: 20.1 months) and in combination with cetuximab (Phase 1b; median follow-up: 17.5 months) in patients with previously treated $KRAS^{G12C}$-mutated CRC

[a]$KRAS^{G12C}$ mutation detected in tumor tissue and/or ctDNA per protocol. [b]Capsule, fasted. [c]Cetuximab dosing, 400 mg/m^2 followed by 250 mg/m^2 QW, or 500 mg/m^2 Q2W. [d]Response was analysed in the clinically evaluable population with local radiology review. [e]Previous data were reported for 46 patients (n=2 in Phase 1/1b and n=44 in Phase 2) receiving adagrasib monotherapy (median follow-up: 8.9 months) and 32 patients receiving adagrasib + cetuximab (median follow-up: 7 months)[10]

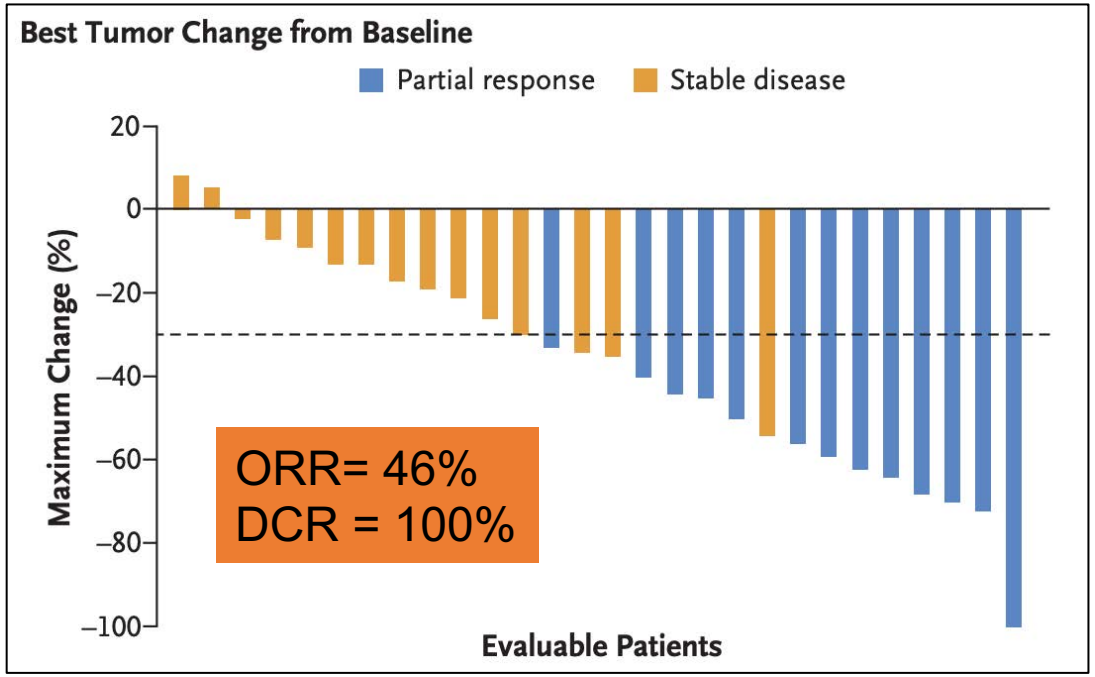
ClinicalTrials.gov. NCT03785249

Best tumor change from baseline

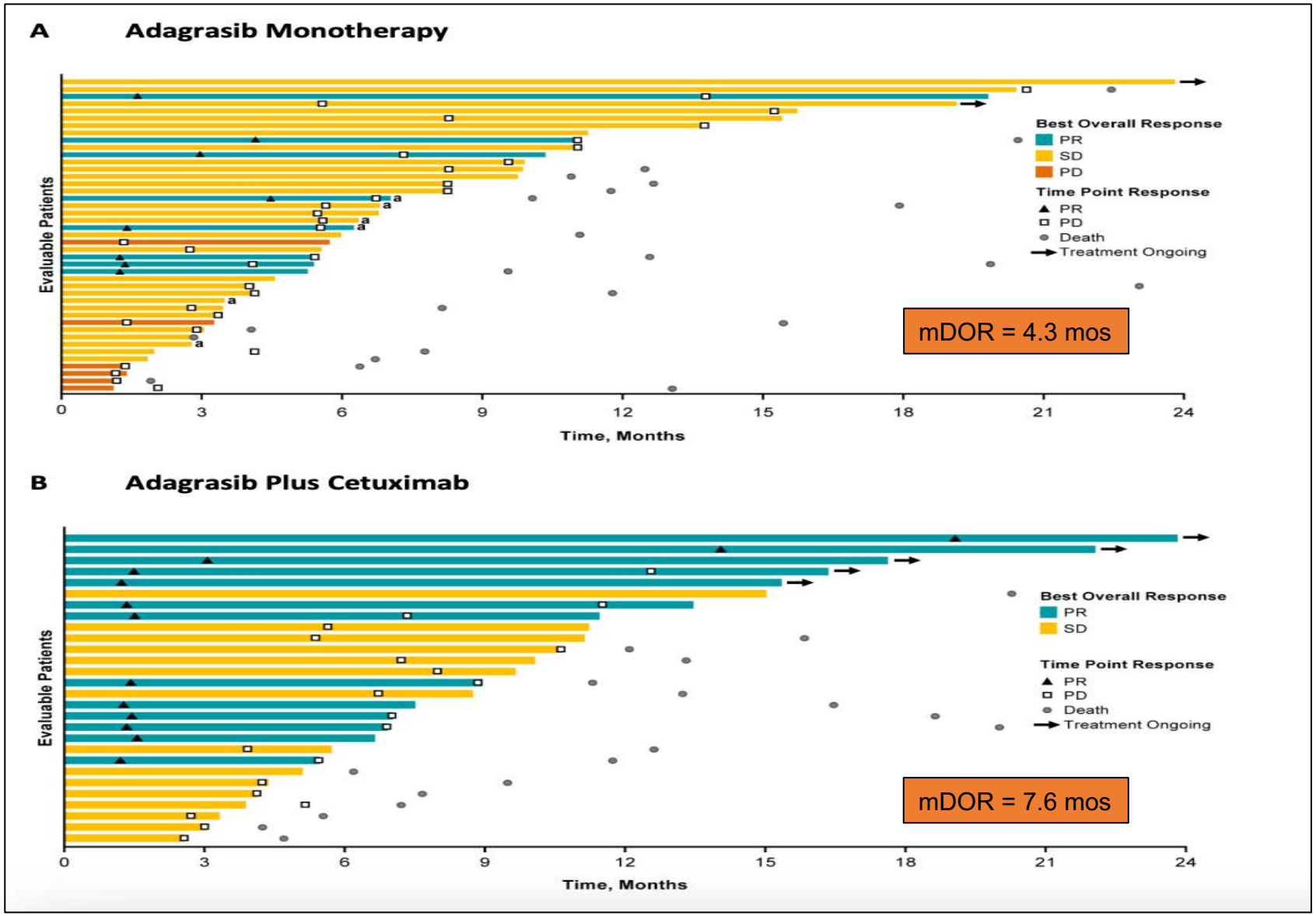
Adagrasib



Adagrasib plus Cetuximab



Time to Response and Duration of Treatment



Overall Summary of Clinical Activity

Variable	Adagrasib Monotherapy (N=43)†	Adagrasib plus Cetuximab (N=28)☼
Objective response§		
Per blinded independent central review — no. of patients	10	13
% (95% CI)	23 (12–39)	46 (28–66)
As confirmed by investigator — no. of patients	8	13
% (95% CI)	19 (8–33)	46 (28–66)
Best overall response — no. (%)		
Complete response	0	0
Partial response	8 (19)	13 (46)
Stable disease	29 (67)	15 (54)
Progressive disease	6 (14)	0
Not evaluable	0	0
Median duration of response — mo	4.3	7.6
95% CI	2.3–8.3	5.7–NE
Median progression-free survival — mo¶	5.6	6.9
95% CI	4.1–8.3	5.4–8.1
Median overall survival — mo¶	19.8	13.4
95% CI	12.5–23.0	9.5–20.1

Summary of Treatment-Related Adverse Events

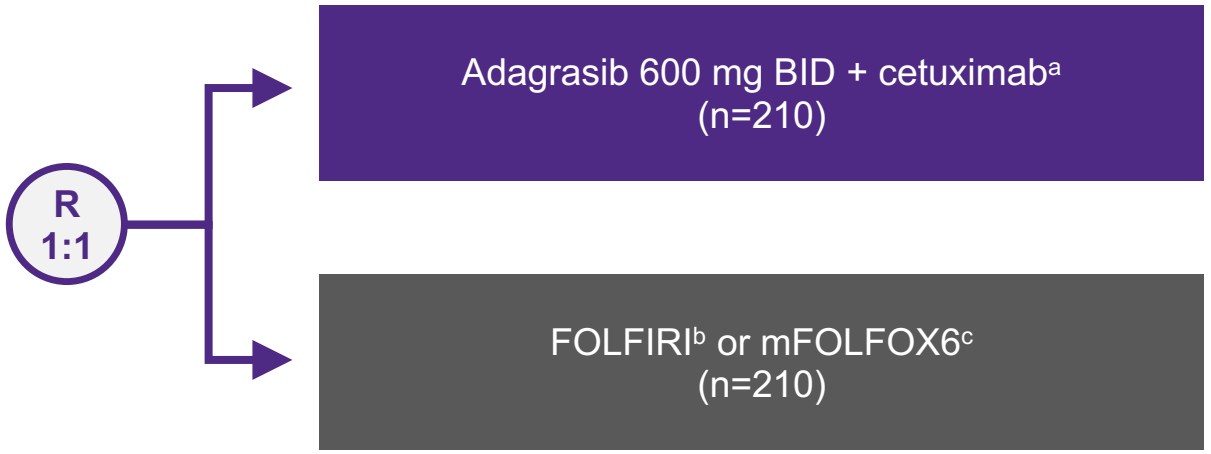
Adverse Event	Adagrasib Monotherapy (N=44)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)				
Any event	41 (93)	10 (23)	16 (36)	13 (30)	2 (5)
Leading to dose discontinuation	0	—	—	—	—
Leading to dose interruption	20 (45)	—	—	—	—
Leading to dose reduction	17 (39)	—	—	—	—
Most frequent events†					
Diarrhea	29 (66)	16 (36)	10 (23)	3 (7)	0
Nausea	25 (57)	15 (34)	10 (23)	0	0
Vomiting	20 (45)	12 (27)	8 (18)	0	0
Fatigue	20 (45)	11 (25)	7 (16)	2 (5)	0
Anemia	7 (16)	2 (5)	1 (2)	4 (9)	0
Prolonged QT interval on ECG	7 (16)	2 (5)	3 (7)	2 (5)	0
Peripheral edema	7 (16)	6 (14)	1 (2)	0	0
Decreased appetite	8 (18)	4 (9)	4 (9)	0	0
Increased ALT	5 (11)	3 (7)	0	2 (5)	0
Increased AST	5 (11)	3 (7)	0	2 (5)	0

	Adagrasib plus Cetuximab (N=32)				
Any event	32 (100)	5 (16)	22 (69)	3 (9)	2 (6)
Leading to dose discontinuation					
Adagrasib	0	—	—	—	—
Cetuximab	5 (16)	—	—	—	—
Leading to dose interruption					
Adagrasib	14 (44)	—	—	—	—
Cetuximab	10 (31)	—	—	—	—
Leading to dose reduction					
Adagrasib	10 (31)	—	—	—	—
Cetuximab	1 (3)	—	—	—	—
Most frequent events†					
Nausea	20 (62)	13 (41)	7 (22)	0	0
Diarrhea	18 (56)	11 (34)	6 (19)	1 (3)	0
Vomiting	17 (53)	13 (41)	4 (12)	0	0
Dermatitis acneiform	15 (47)	11 (34)	3 (9)	1 (3)	0
Fatigue	15 (47)	8 (25)	7 (22)	0	0
Dry skin	13 (41)	11 (34)	2 (6)	0	0
Headache	10 (31)	7 (22)	3 (9)	0	0
Dizziness	8 (25)	4 (12)	4 (12)	0	0
Maculopapular rash	8 (25)	7 (22)	1 (3)	0	0
Stomatitis	7 (22)	5 (16)	1 (3)	1 (3)	0
Dyspepsia	6 (19)	4 (12)	2 (6)	0	0
Hypomagnesemia	6 (19)	3 (9)	3 (9)	0	0
Infusion-related reaction	6 (19)	1 (3)	4 (12)	0	1 (3)

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

Key Eligibility Criteria

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



Anti-VEGF/VEGFR allowed per investigator discretion in comparator arm

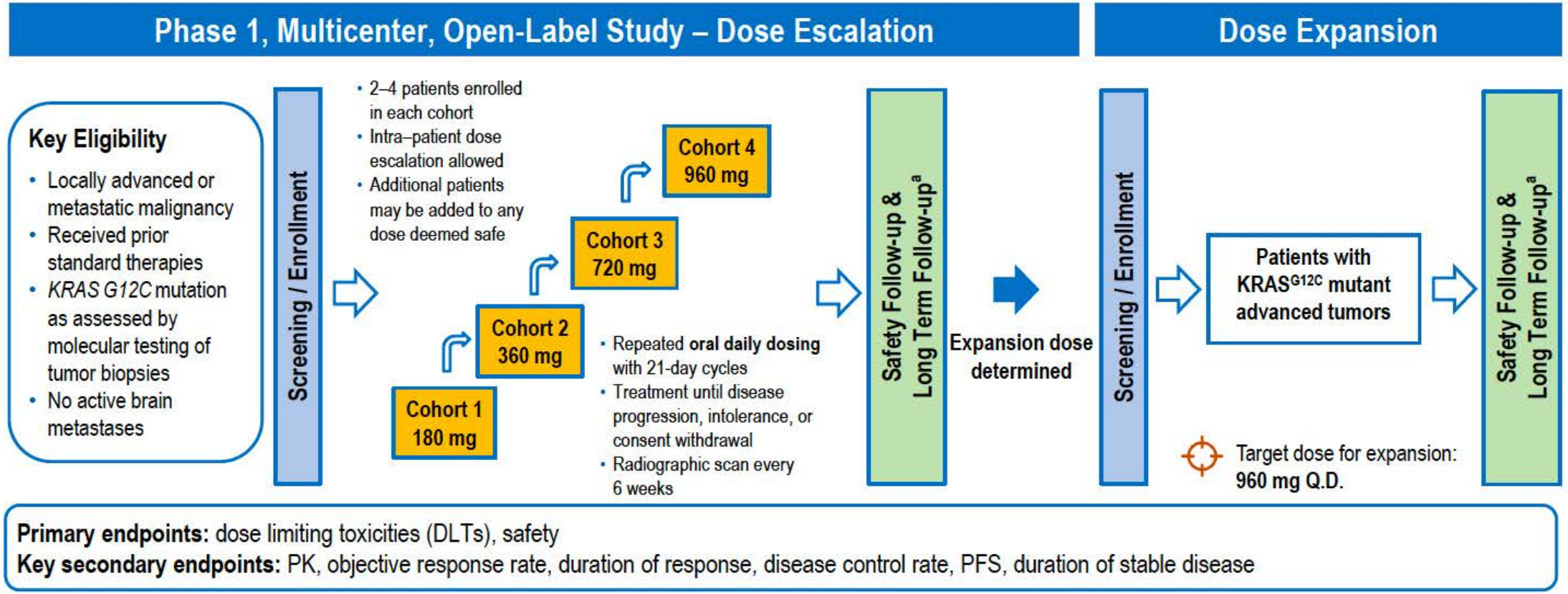
Outcome Measures

Primary: PFS, OS

Secondary: Safety, ORR (RECIST 1.1), 1-year OS, DOR, PK, PROs

[a]Dosing: cetuximab, 500 mg/m^2 Q2W. [b]FOLFIRI Q2W (irinotecan, 180 mg/m^2, 5-FU/LV with fluorouracil given as a 400 mg/m^2 IV bolus followed by a 2400 mg/m^2 dose given as a continuous infusion over 46–48 hours). [c]mFOLFOX6 Q2W (oxaliplatin, 85 mg/m^2, 5-FU/LV, with fluorouracil given as a 400 mg/m^2 IV bolus followed by a 2400 mg/m^2 dose given as continuous infusion over 46–48 hours).
ClinicalTrials.gov NCT04793958.

CodeBreaK 100 : Sotorasib +/- Panitumumab in mCRC



Primary endpoints: dose limiting toxicities (DLTs), safety
Key secondary endpoints: PK, objective response rate, duration of response, disease control rate, PFS, duration of stable disease

[a]30 (+7) days after end of treatment for safety follow-up; every 12 weeks for long term follow-up. PK: pharmacokinetics; PFS: progression-free survival.

Strickler J et al . ESMO GI 2020

CodeBreaK 100: Phase 2 mCRC Results of Sotorasib

	Patients (n=62)
Objective response, n (%; 95% CI)*	6 (9·7%; 3·6–19·9)
Disease control, n (%; 95% CI)†	51 (82·3%; 70·5–90·8)
Best response, n (%)	
Complete response	0
Partial response	6 (10%)
Stable disease	45 (73%)
Progressive disease	11 (18%)
Median time to response, months (IQR)‡	2·0 (1·4–2·8)
Median duration of response, months (IQR)‡	4·2 (2·9–8·5)

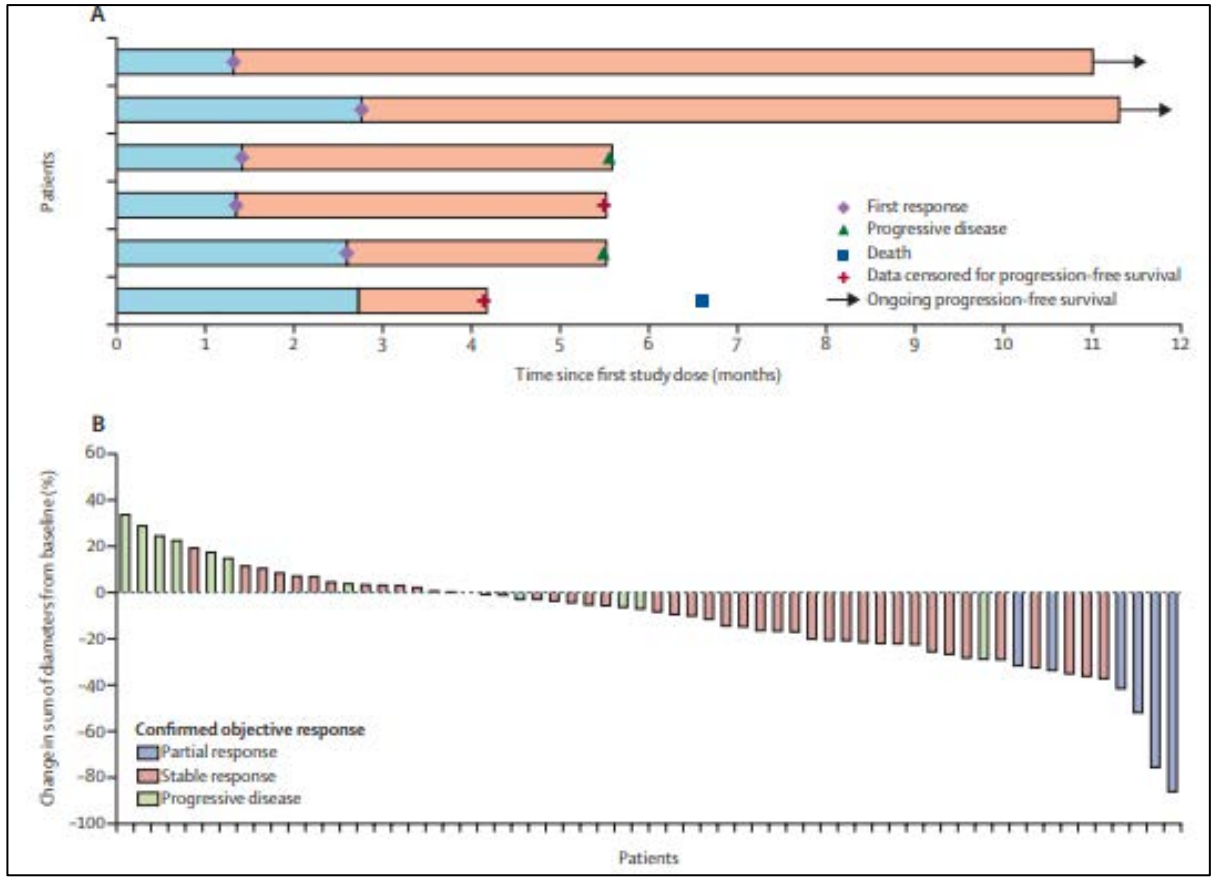
*Objective response was defined as a complete or partial response. †Disease control was defined as a complete response, partial response, or stable disease. ‡Time to response and duration of response were calculated among the six confirmed responders. Kaplan-Meier estimates of the median (95% CI) for duration of response were not calculated given that the analysis had fewer than ten patients. Crude median duration of response is reported.

Table 2: **Tumour response to sotorasib therapy according to independent central review**

	Grade 1–2	Grade 3	Grade 4
Total treatment-related adverse events	27 (44%)	6 (10%)	1 (2%)
Diarrhoea	11 (18%)	2 (3%)	0
Alanine aminotransferase increased	3 (5%)	1 (2%)	0
Aspartate aminotransferase increased	3 (5%)	1 (2%)	0
Fatigue	1 (2%)	1 (2%)	0
Blood cholesterol increased	0	1 (2%)	0
Blood creatine phosphokinase increased	0	0	1 (2%)
Back pain	0	1 (2%)	0
Acute kidney injury	0	1 (2%)	0
Nausea	10 (16%)	0	0

Data are n (%). Treatment-related adverse events are treatment-emergent adverse events that are considered to be related to the investigational product by the investigator. Treatment-related adverse events of grade 1 or 2 occurring in 10% of patients or more, and worse grade is presented. There were no grade 5 treatment-related adverse events.

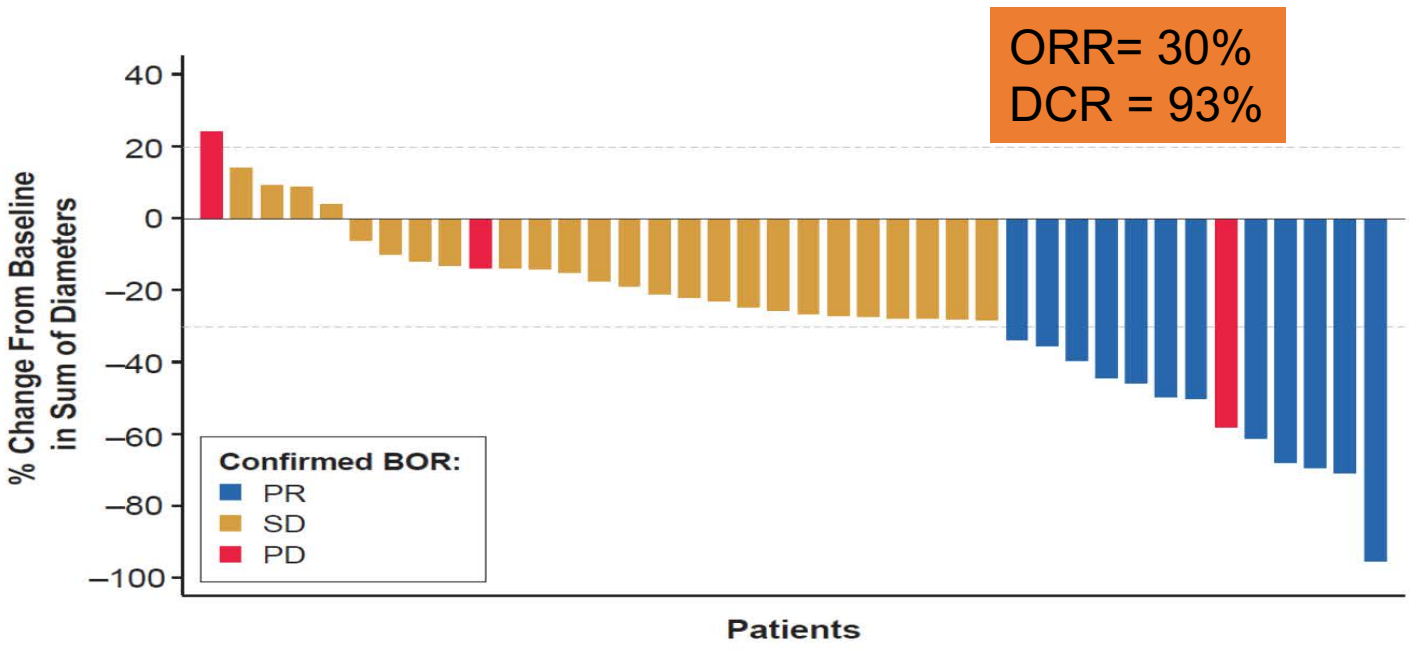
Table 3: **Treatment-related adverse events in the safety population**

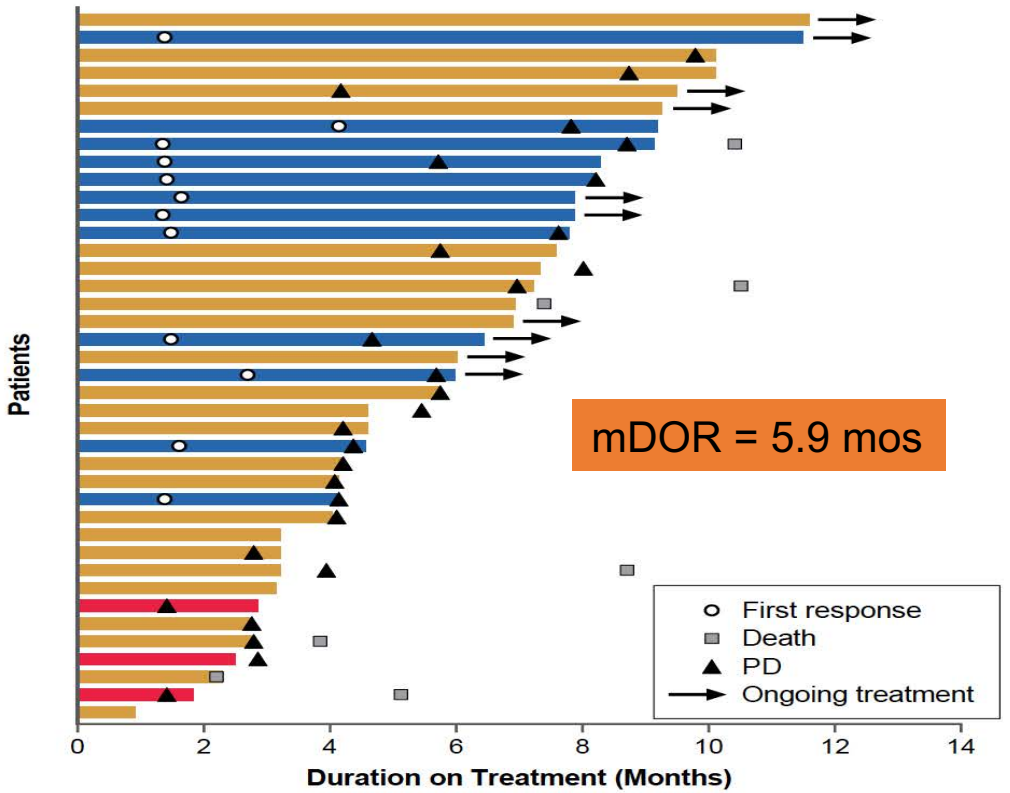


Fakih M et al, Lancet Oncol 2022; 23:115-124.

CodeBreaK101 : Sotorasib + Panitumumab

Tumour Response





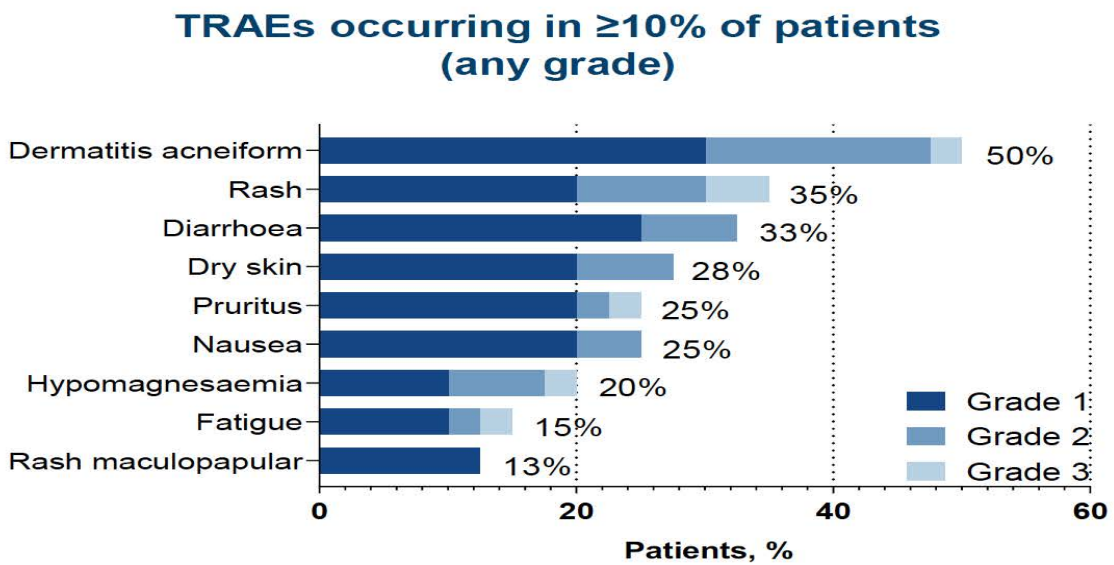
- **Reduction in RECIST target lesions observed in 88% of patients**
- **Median (range) duration of treatment was 5.9 (0.5, 11.3) months, with 25% of patients remaining on treatment**

Kuboki Y et al . ESMO 2022

CodeBreaK101 : Sotorasib + Panitumumab

Treatment-Related Adverse Events (TRAEs)

TRAE	N = 40 n (%)
TRAE, any grade	37 (93)
Attributed to sotorasib	26 (65)
Attributed to panitumumab	37 (93)
Grade 3 TRAE*	9 (23)
Grade 4 TRAE	0
Fatal TRAE	0
TRAE leading to dose interruptions/reductions	
Attributed to sotorasib	6 (15)
Attributed to panitumumab	10 (25)
TRAE leading to discontinuation of either drug	0

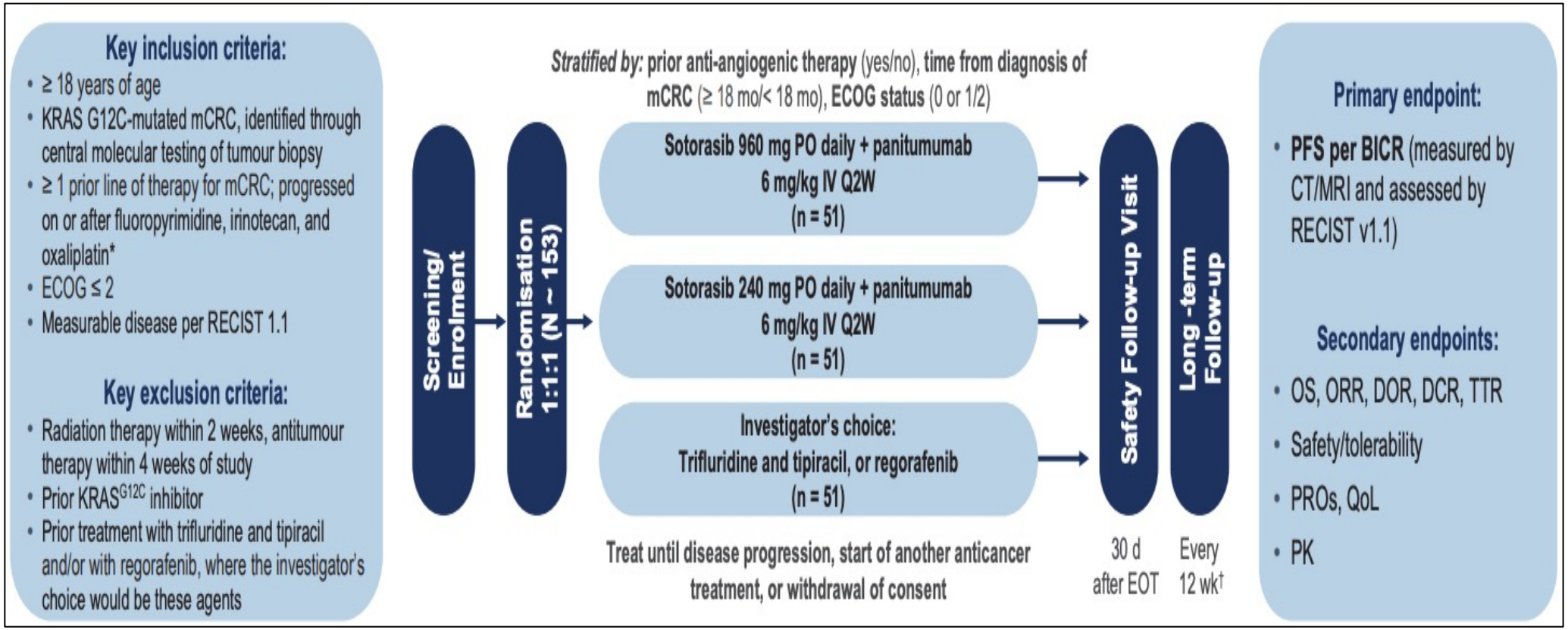


Data cutoff: June 24, 2022.
*Grade 3 TRAEs were rash (n=2, 5%), anaemia, fatigue, peripheral oedema, cellulitis, pustular rash, salmonellosis, skin infection, hypomagnesaemia, malignant neoplasm progression, pulmonary embolism, dermatitis acneiform, and pruritus (n=1 patient each, 3%).

Kuboki Y et al . ESMO 2022

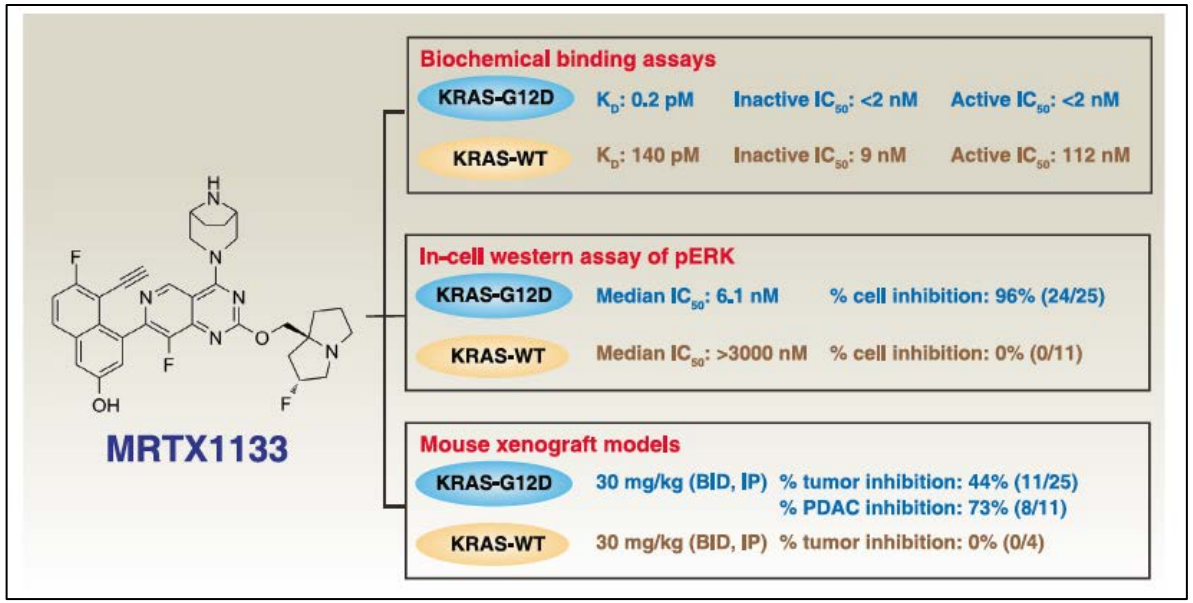
- **Sotorasib/panitumumab was well tolerated; no TRAEs resulted in discontinuation of either drug**
- **TRAEs were consistent with known safety profiles of the individual drugs**

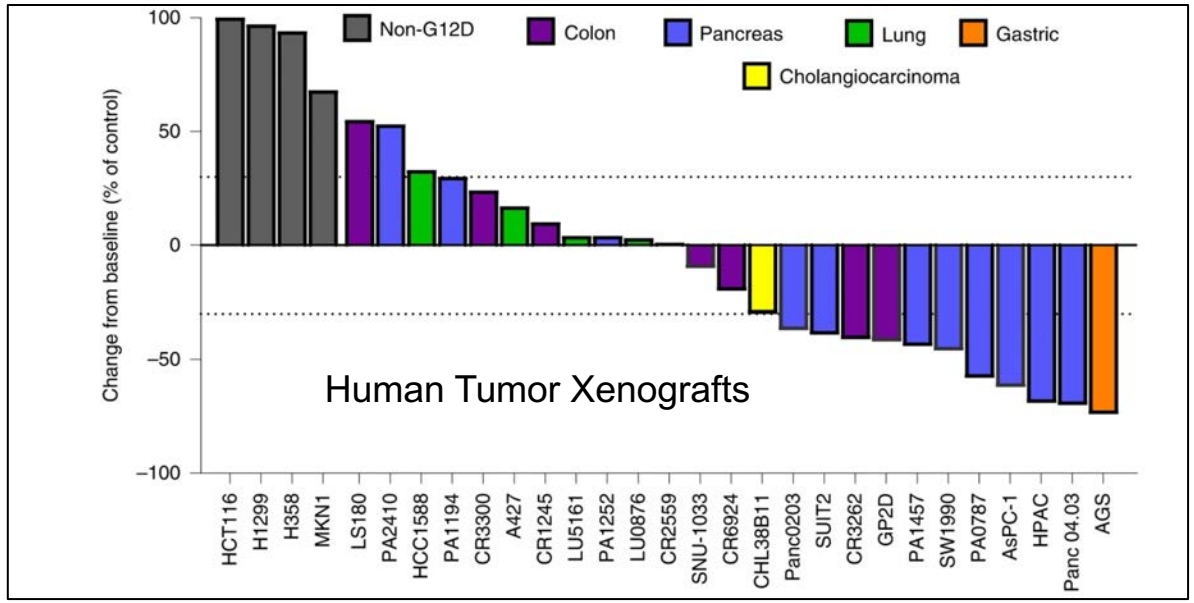
Sotorasib and Panitumumab Versus Investigator's Choice for Participants With Kirsten Rat Sarcoma (KRAS) p.G12C Mutation (CodeBreaK 300)



ClinicalTrials.gov Identifier: NCT05198934

MRTX113 is a selective inhibitor of KRAS-G12D protein

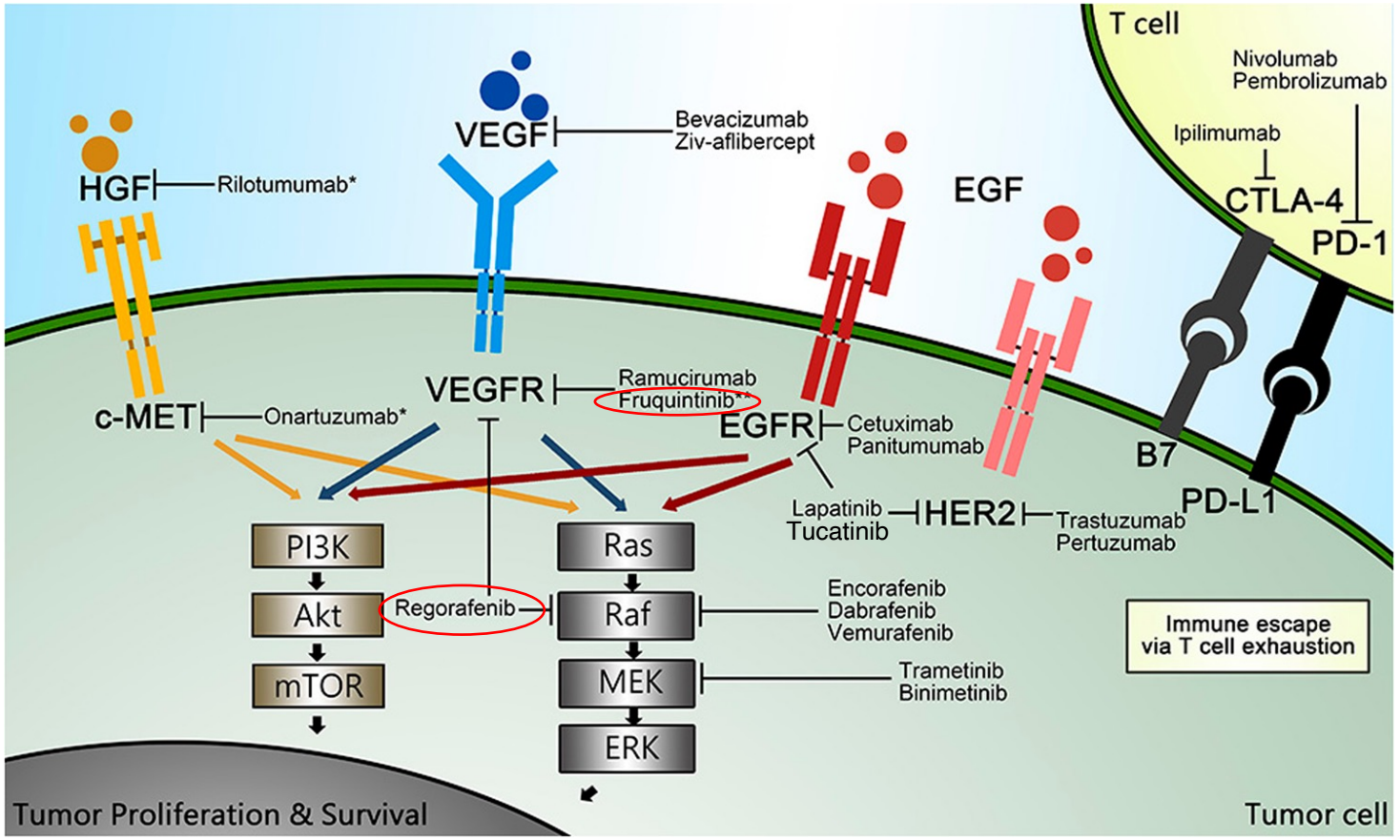




Dang T et al. Cancer Gene Therapy 2022

Hallin J et al . Nature Medicine , 2022

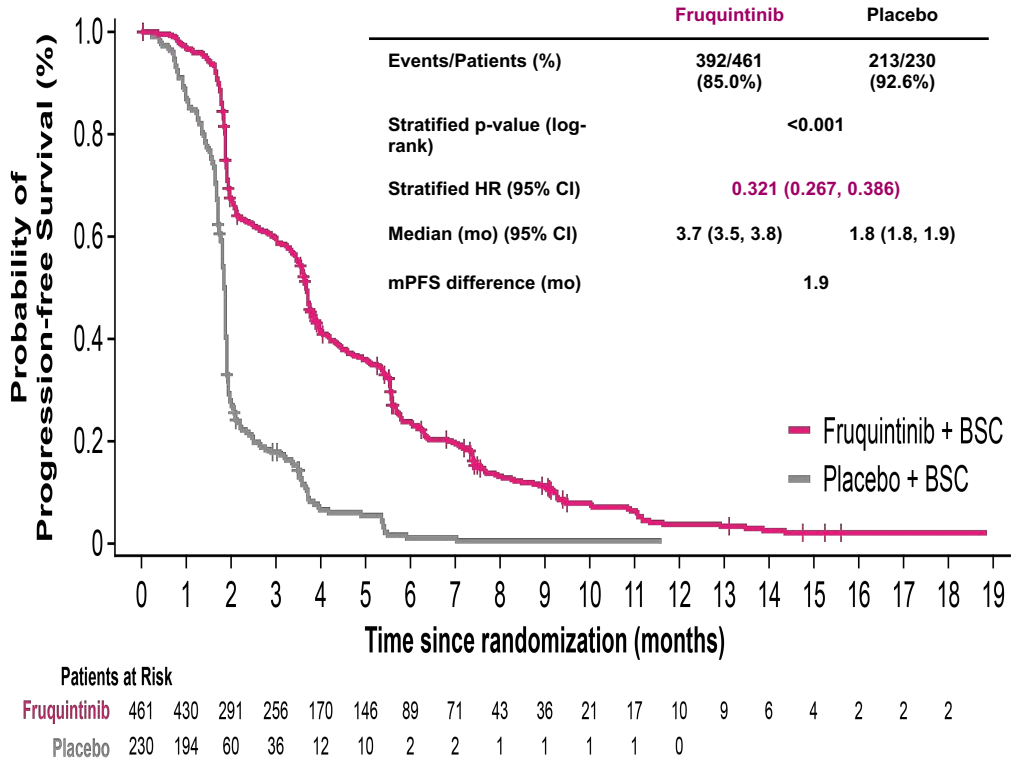
Other Targeted Agents in mCRC



Xie YH et al . *Sig Transduct Target Ther* 2020

FRESCO 2 : Phase III study of fruquintinib in pts with refractory mCRC

Progression Free Survival

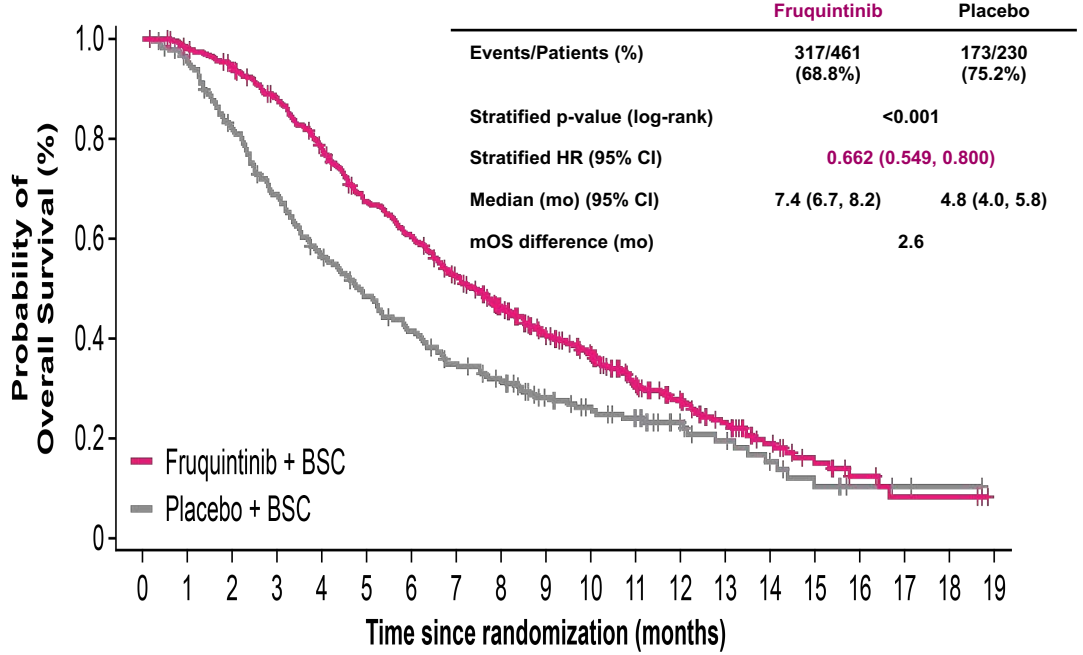


	Fruquintinib	Placebo
Events/Patients (%)	392/461 (85.0%)	213/230 (92.6%)
Stratified p-value (log-rank)	<0.001	
Stratified HR (95% CI)	0.321 (0.267, 0.386)	
Median (mo) (95% CI)	3.7 (3.5, 3.8)	1.8 (1.8, 1.9)
mPFS difference (mo)	1.9	

Patients at Risk

Fruquintinib	461	430	291	256	170	146	89	71	43	36	21	17	10	9	6	4	2	2	2
Placebo	230	194	60	36	12	10	2	2	1	1	1	1	0						

Overall Survival



	Fruquintinib	Placebo
Events/Patients (%)	317/461 (68.8%)	173/230 (75.2%)
Stratified p-value (log-rank)	<0.001	
Stratified HR (95% CI)	0.662 (0.549, 0.800)	
Median (mo) (95% CI)	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)
mOS difference (mo)	2.6	

Patients at Risk

Fruquintinib	461	449	429	395	349	297	266	224	184	143	113	79	58	41	23	14	7	4	4	0
Placebo	230	216	184	153	125	105	89	73	63	45	37	31	20	15	10	6	3	2	1	0

Prior TAS-102 and/or regorafenib	TAS-102	240 (52.1)	121 (52.6)
	Regorafenib	40 (8.7)	18 (7.8)
	Both	181 (39.3)	91 (39.6)

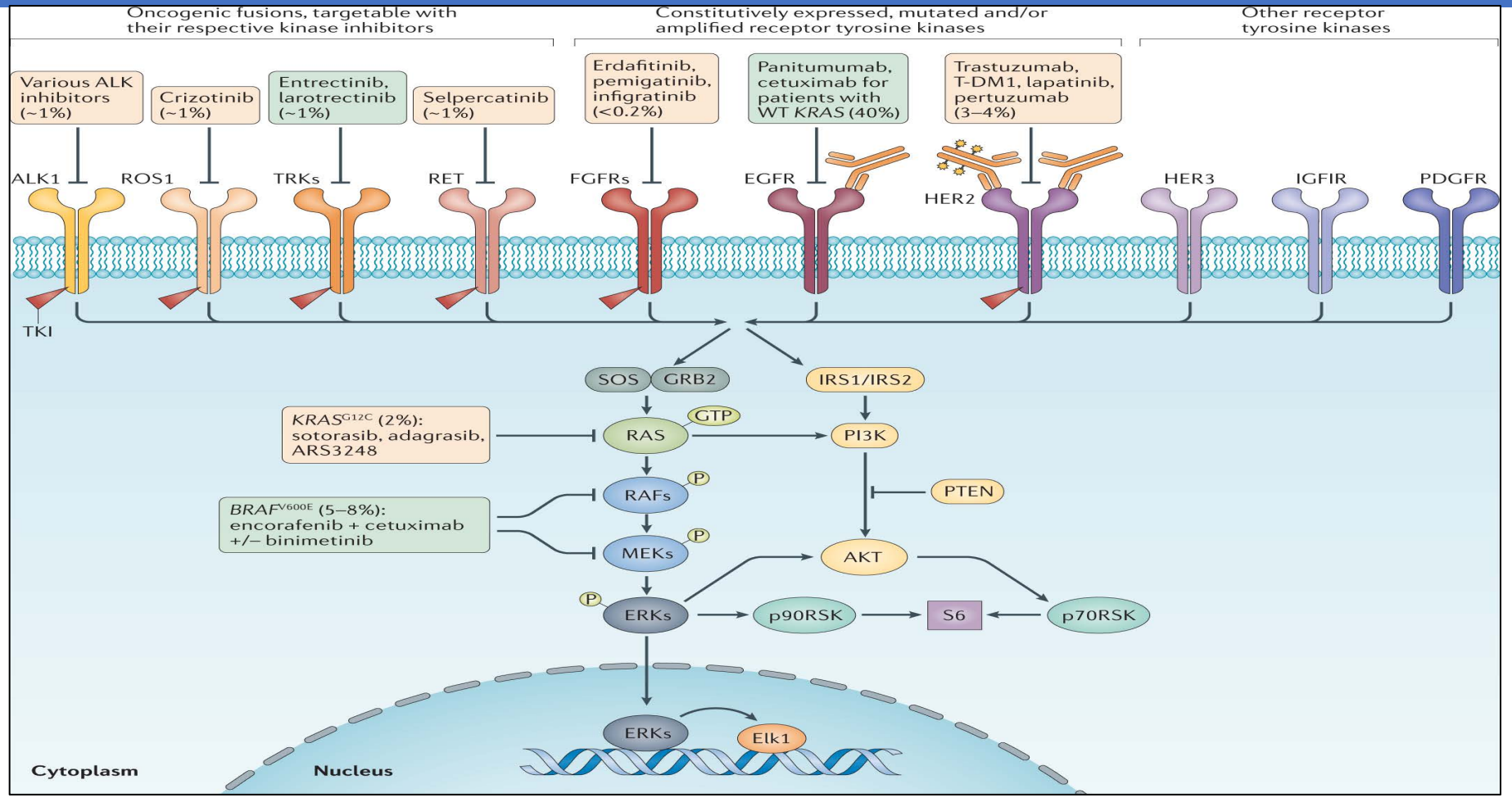
Dasari A et al. ESMO 2022, Presentation LBA25

Most Common TEAEs
(Any Grade ≥ 15% in Either Arm)

TEAE, n (%)	Fruquintinib (N=456)		Placebo (N=230)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Patients with ≥1 TEAE	451 (98.9)	286 (62.7)	213 (92.6)	116 (50.4)
Hypertension	168 (36.8)	62 (13.6)	20 (8.7)	2 (0.9)
Asthenia	155 (34.0)	35 (7.7)	52 (22.6)	9 (3.9)
Decreased appetite	124 (27.2)	11 (2.4)	40 (17.4)	3 (1.3)
Diarrhea	110 (24.1)	16 (3.5)	24 (10.4)	0
Hypothyroidism	94 (20.6)	2 (0.4)	1 (0.4)	0
Fatigue	91 (20.0)	18 (3.9)	37 (16.1)	2 (0.9)
Hand-foot syndrome	88 (19.3)	29 (6.4)	6 (2.6)	0
Abdominal pain	83 (18.2)	14 (3.1)	37 (16.1)	7 (3.0)
Nausea	79 (17.3)	3 (0.7)	42 (18.3)	2 (0.9)
Proteinuria	79 (17.3)	8 (1.8)	12 (5.2)	2 (0.9)
Constipation	78 (17.1)	2 (0.4)	22 (9.6)	0
Dysphonia	74 (16.2)	0	12 (5.2)	0

Dasari A et al. ESMO 2022, Presentation LBA25

Relevant therapeutic targets in metastatic CRC



Di Nicolantoniof et al. *Net Rev in Clin Onc* 2021

MODULE 5: The Changing Management Paradigm for Localized CRC — Dr Kopetz

Case Presentation: A 72-year-old man with 2 synchronous T3N0 cancers of the splenic flexure and cecum who is ctDNA-positive s/p resection

Dr Warren Brenner (Boca Raton, Florida)

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QUESTIONS FOR THE FACULTY

Warren S Brenner, MD

"The number 1 question is, should molecular MRD testing be standard in early-stage disease in order to inform management decisions? Would any of the investigators use molecular testing to potentially avoid chemotherapy in patients who have standard-risk Stage III disease — 1 or 2 positive lymph nodes — especially in older patients? Would they omit chemotherapy if someone were MRD-negative?

- *Is there a role for following MRD results in patients receiving adjuvant chemotherapy to determine length of treatment and possibly escalation or de-escalation of therapy?*
- *Another circumstance where I'm using it is in patients who have had Stage IV colon cancer potentially resected to NED. Are they using it in that situation?"*

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Case Presentation: An 80-year-old man with a Stage II obstructing cancer of the right colon

Dr Namrata Peswani (Richardson, Texas)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Namrata I Peswani, MD

"The patient was post-op when he had his pulmonary embolism. He blamed the capecitabine, but I'm not entirely convinced that it was chemo-related. Maybe it was just his cancer and his surgery that potentially caused it. He doesn't want to continue treatment, but I think having the circulating tumor DNA test would be extremely helpful here. I would love to hear how the experts decide which patient to use the assay on."

- **What are new uses of ctDNA assays being investigated in ongoing clinical trials?**

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

The Changing Management Paradigm of Localized CRC

Scott Kopetz, MD, PhD

Professor and Deputy Chair, GI Medical Oncology, MD Anderson

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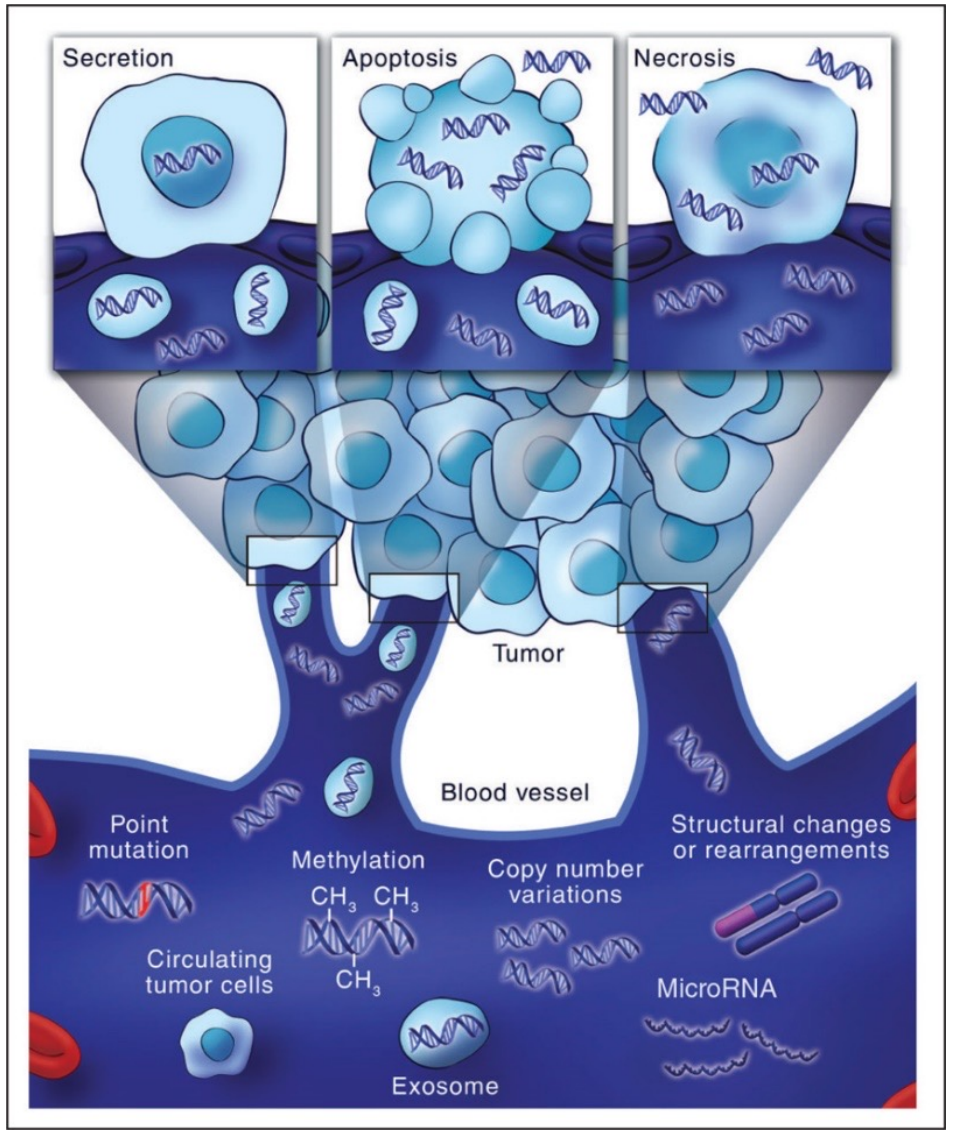
“Liquid Biopsies”: A spectrum of opportunities



Diaz and Bardelli, JCO 2014

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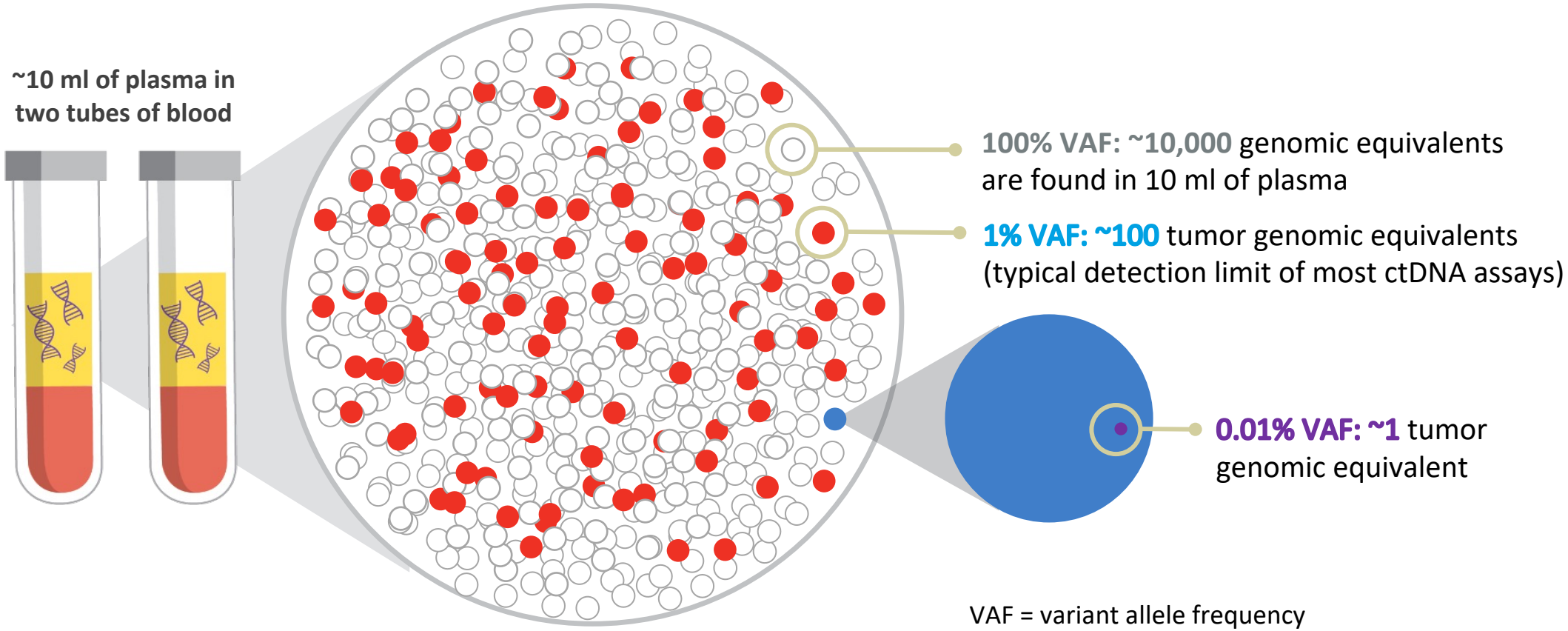
Best performing assays can detect as few as one genomic equivalent in 10 ml of plasma (VAF = 0.01%)



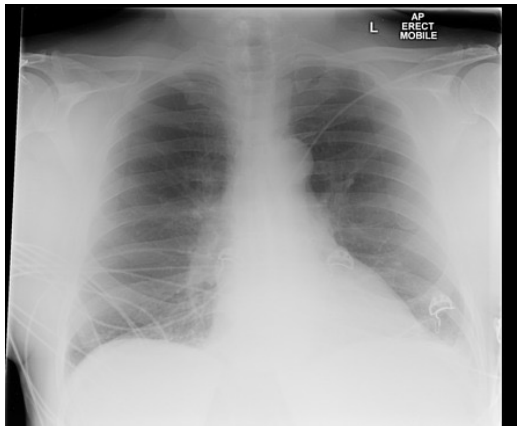
VAF = variant allele frequency

This requires use of a ctDNA assay optimized for minimal residual disease detection

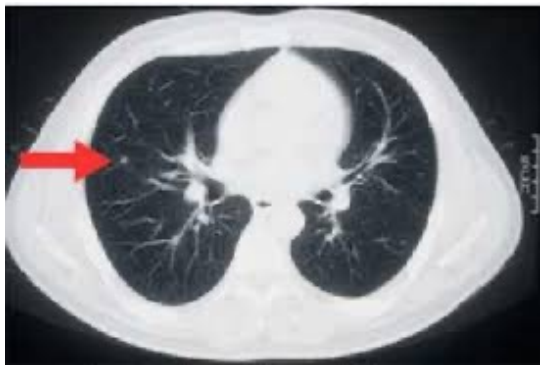
Kopetz GI ESMO '20; Revised from slide of A. Aleshin

Evolution of Tumor Surveillance: Dramatic improvement of sensitivity

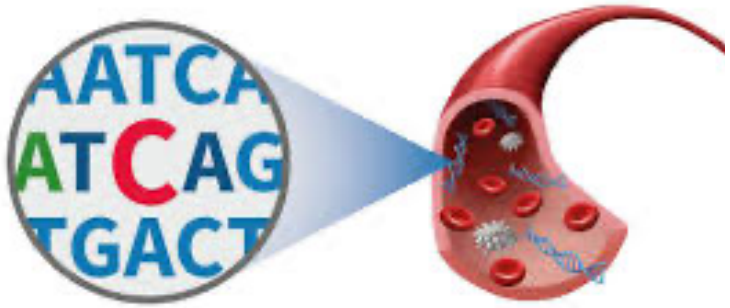
CXR can detect
10^9 cancer cells



CT Scan can detect
10^7 cancer cells



ctDNA can detect
10^5 cancer cells?



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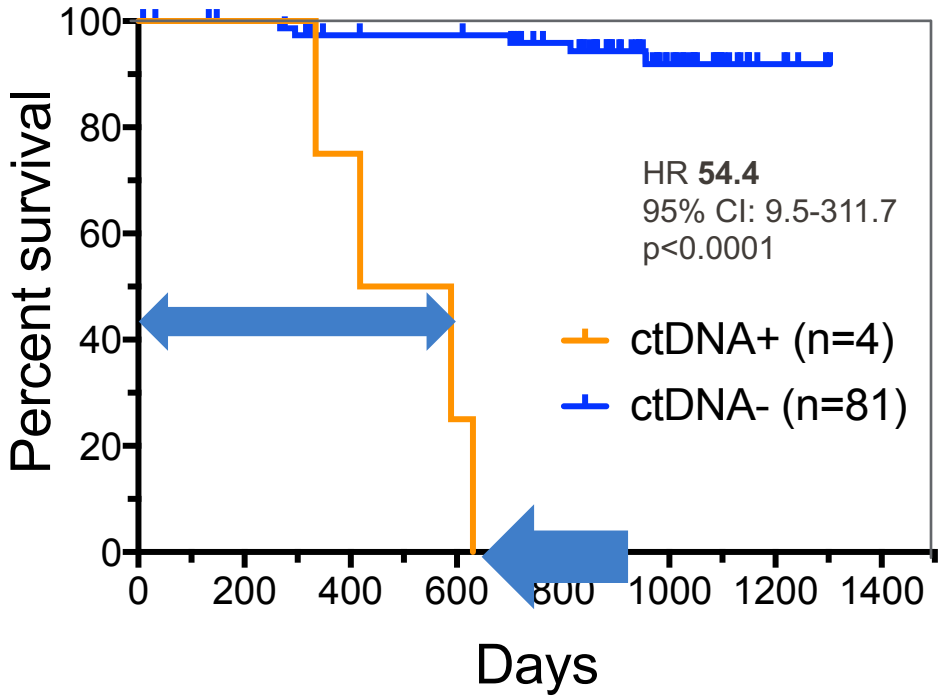
ctDNA can define Minimal Residual Disease after surgery

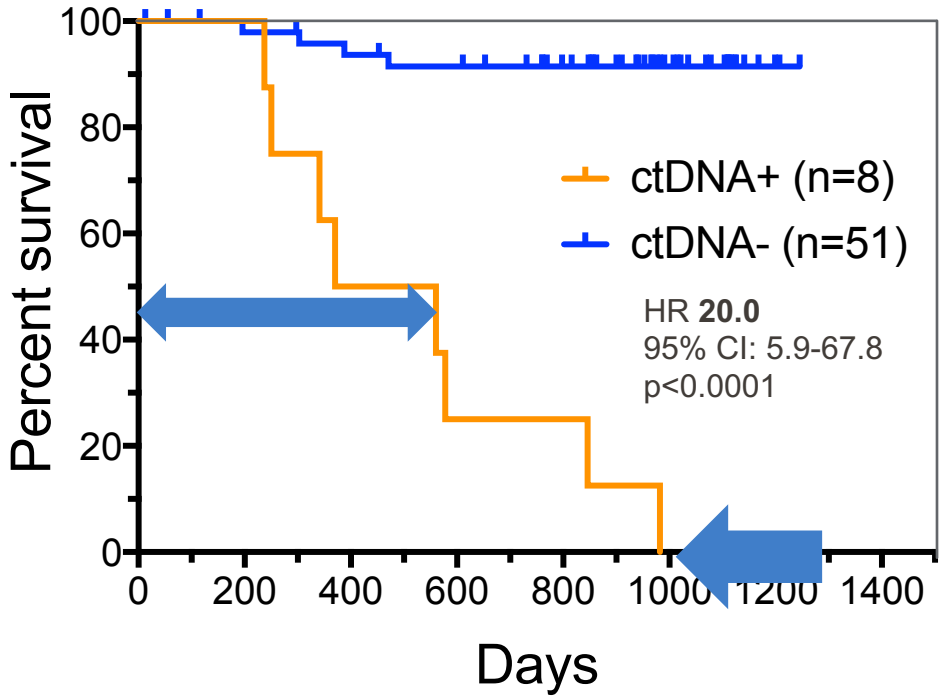
Key features of current ctDNA tests in post-op setting for CRC:

- Near 100% positive predictive value
- Sensitivity ~50-70% for single test
- Lead time between ctDNA+ and radiographic recurrence

Stage II (5% prevalence of ctDNA+)



Stage III (16% prevalence of ctDNA+)



Diehn et al ASCO '17

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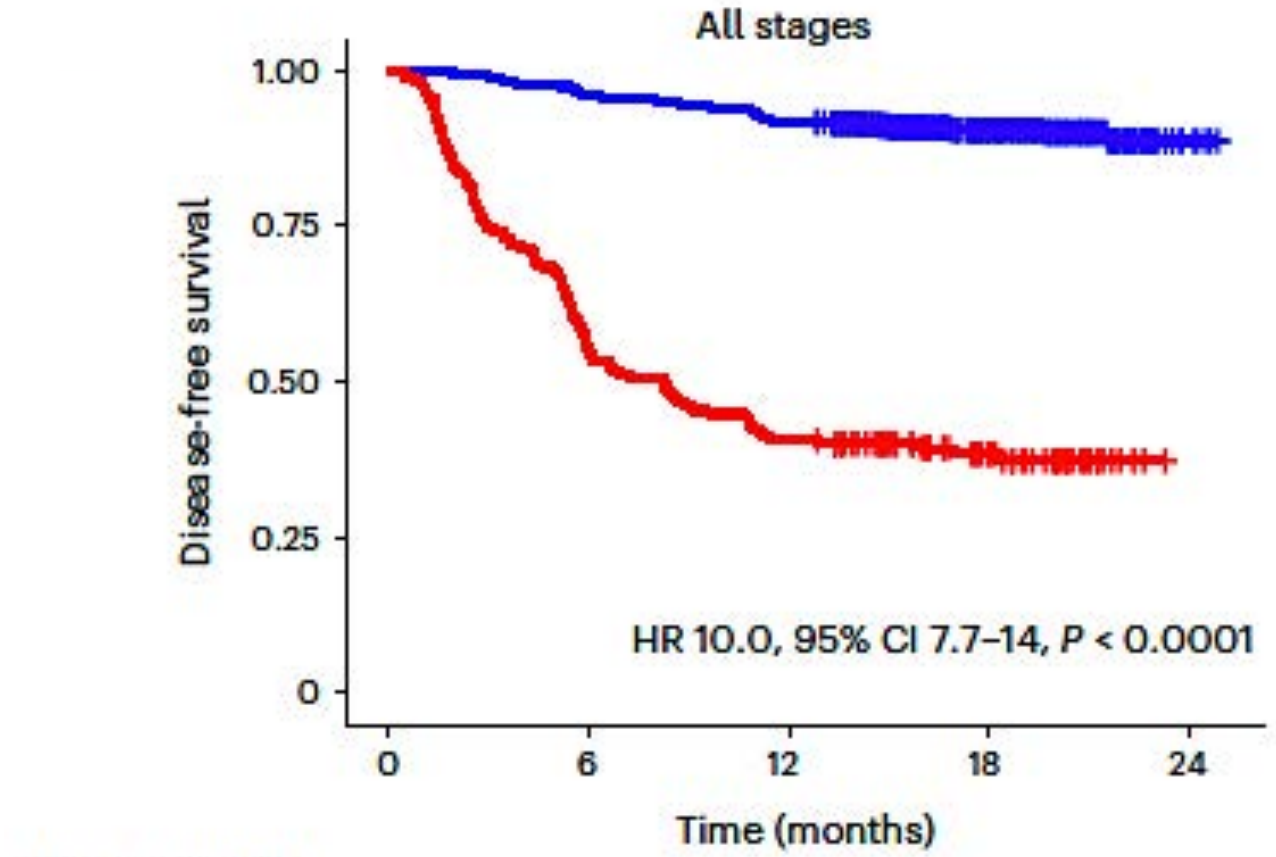
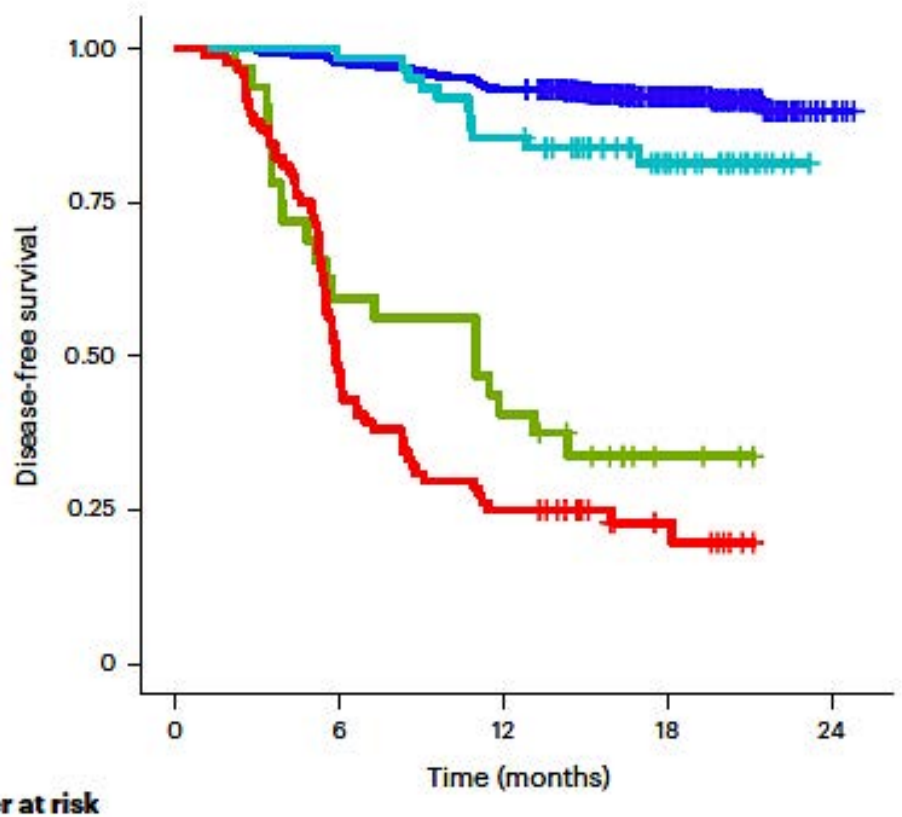
DFS by 4wk post-op ctDNA status



Number at risk					
ctDNA negative	852	819	781	347	5
ctDNA positive	187	104	76	37	0

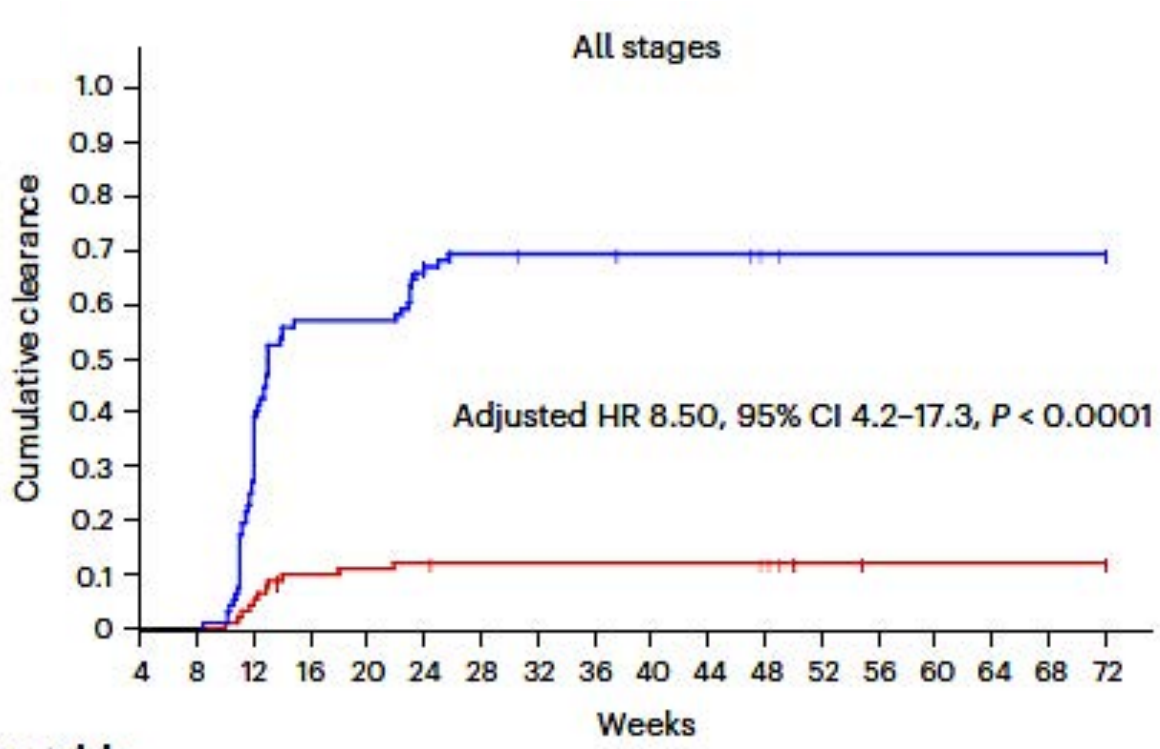
Kotani D et al. Nature Med 2023;Jan 16 [published online].

DFS by ctDNA dynamics 4-12 weeks post-op



Number at risk					
Persistently negative	660	645	616	271	5
Converted positive	32	19	13	3	0
Converted negative	62	61	53	28	0
Persistently positive	84	40	21	7	0

Cumulative ctDNA clearance by adjuvant chemotherapy (ACT) vs observation



Number at risk						
ACT	92	67	30	24	21	21
Observation	90	86	78	77	76	76

Kotani D et al. Nature Med 2023;Jan 16 [published online].

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

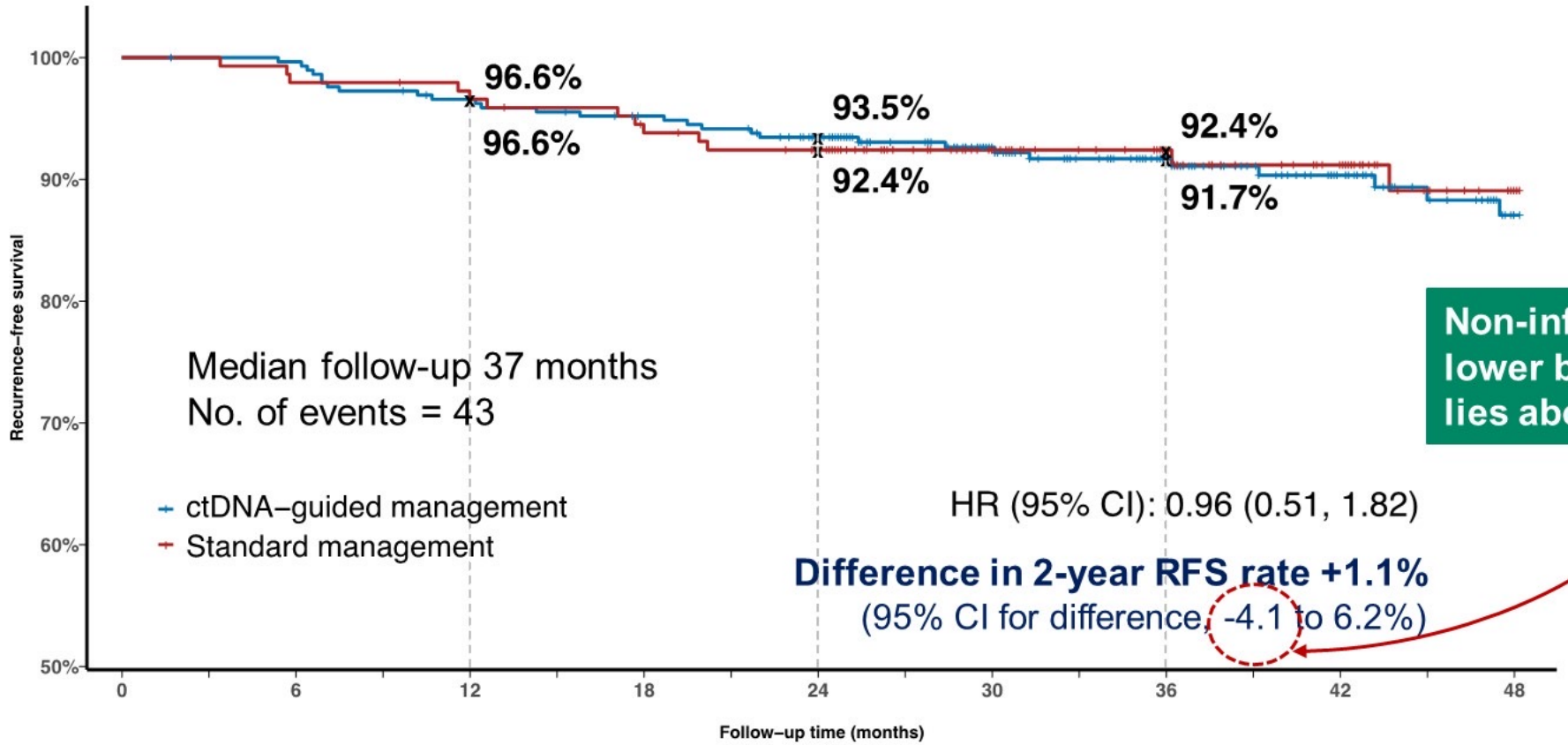
Stratification Factors
- T stage (T3 vs T4)
- Type of participating center (metropolitan vs regional)

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

Adjuvant Treatment Delivery

Treatment Information	ctDNA-Guided N = 294	Standard Management N = 147	P-value
Adjuvant Chemotherapy received, n	45 **(15%)**	41 **(28%)**	0.0017
Chemotherapy regimen received, n Oxaliplatin-based doublet Single agent fluoropyrimidine	 28/45 **(62%)** 17/45 **(38%)**	 4/41 **(10%)** 37/41 **(90%)**	 <.0001
Time from surgery to commencing chemotherapy, median (IQR), days	83 (76, 89)	53 (49, 61)	<.0001
Treatment duration, median (IQR), weeks	24 (19, 24)	24 (21, 24)	0.9318
Completed planned treatment, n	38 (85%)	32 (78%)	0.7036
Percentage of full dose delivered, median (IQR)	78 (56, 100)	84 (64, 100)	0.6194

Recurrence-Free Survival

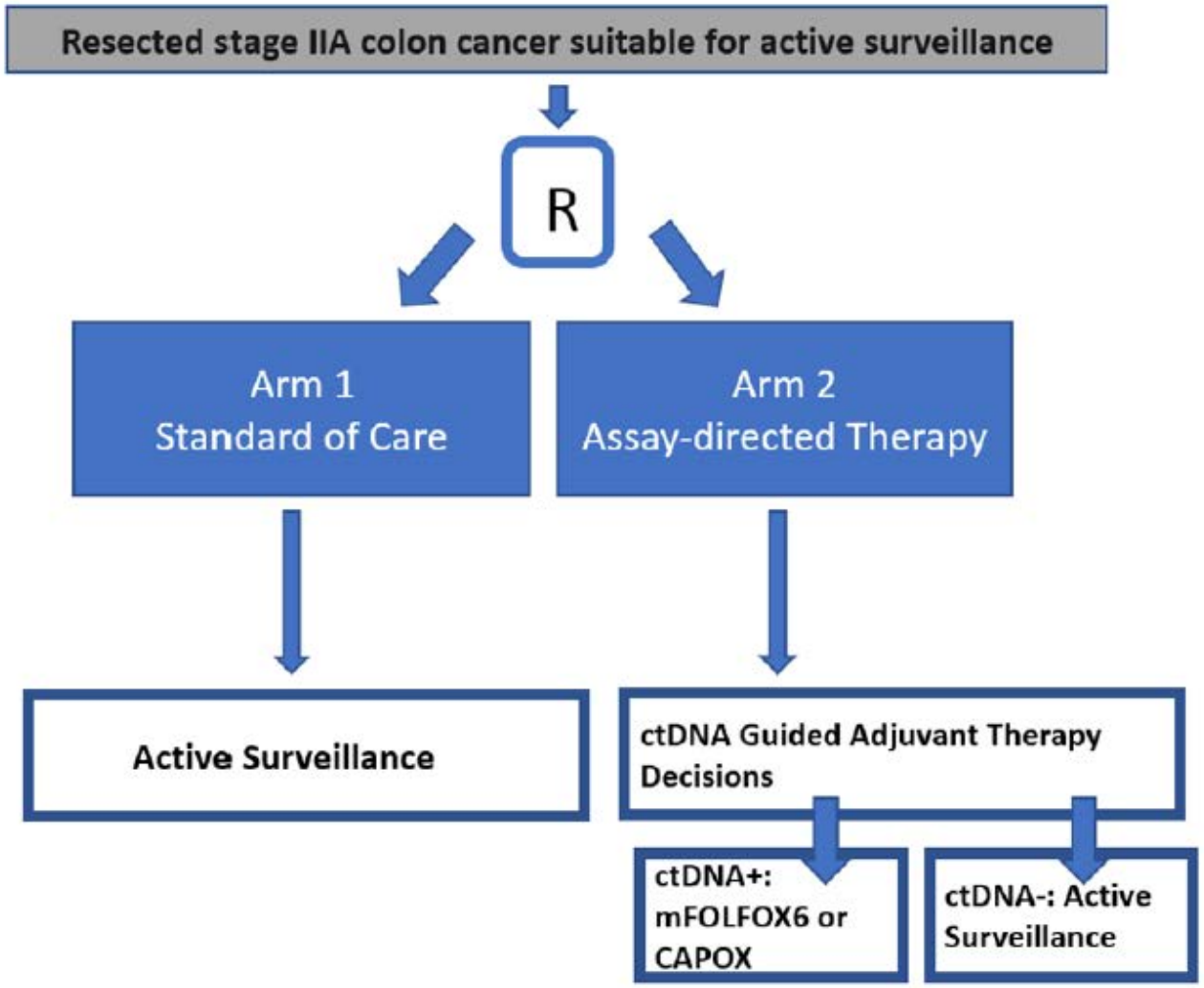


Non-inferiority confirmed: lower bound of 95% CI lies above -8.5%

Numbers at risk

ctDNA-guided	294	292	281	273	259	207	155	109	64
Standard	147	144	142	136	128	97	78	57	33

COBRA: NRG GI-005 (low-risk stage IIA CRC)



- Comparison of outcomes by ctDNA+ status: No chemo vs chemo
- Phase II: ctDNA clearance
- Phase III: RFS
- ctDNA assay: Guardant Reveal

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PI: Van Morris

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SWOG
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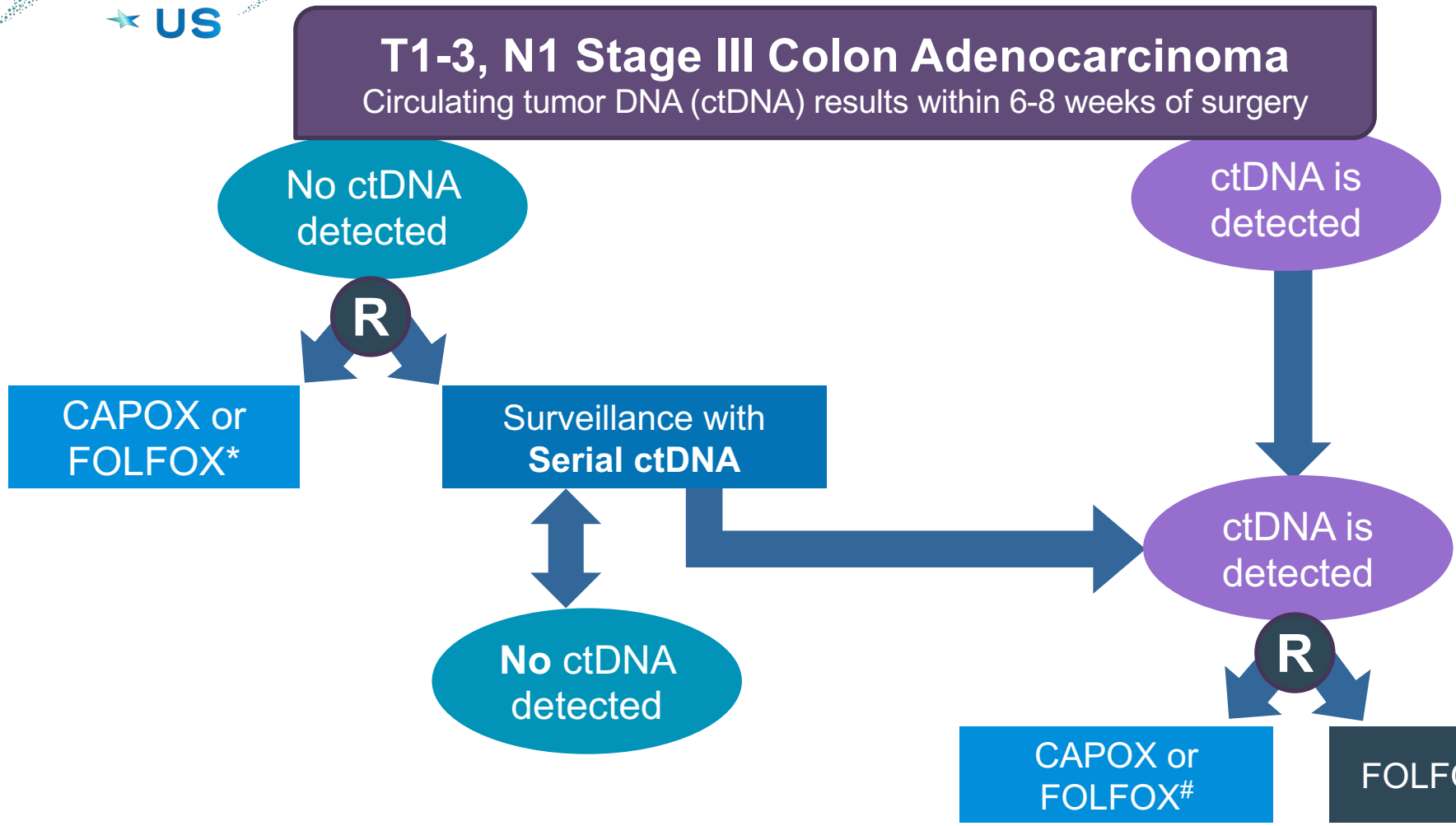

Joint analysis with CIRCULATE-Japan

CIRCULATE Japan

Assay: Signatera

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

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

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Personalized Vaccine Study: BioNTech Study

Patients with **stage IIB/III colon cancer** with detected ctDNA after surgery will be eligible for further evaluation

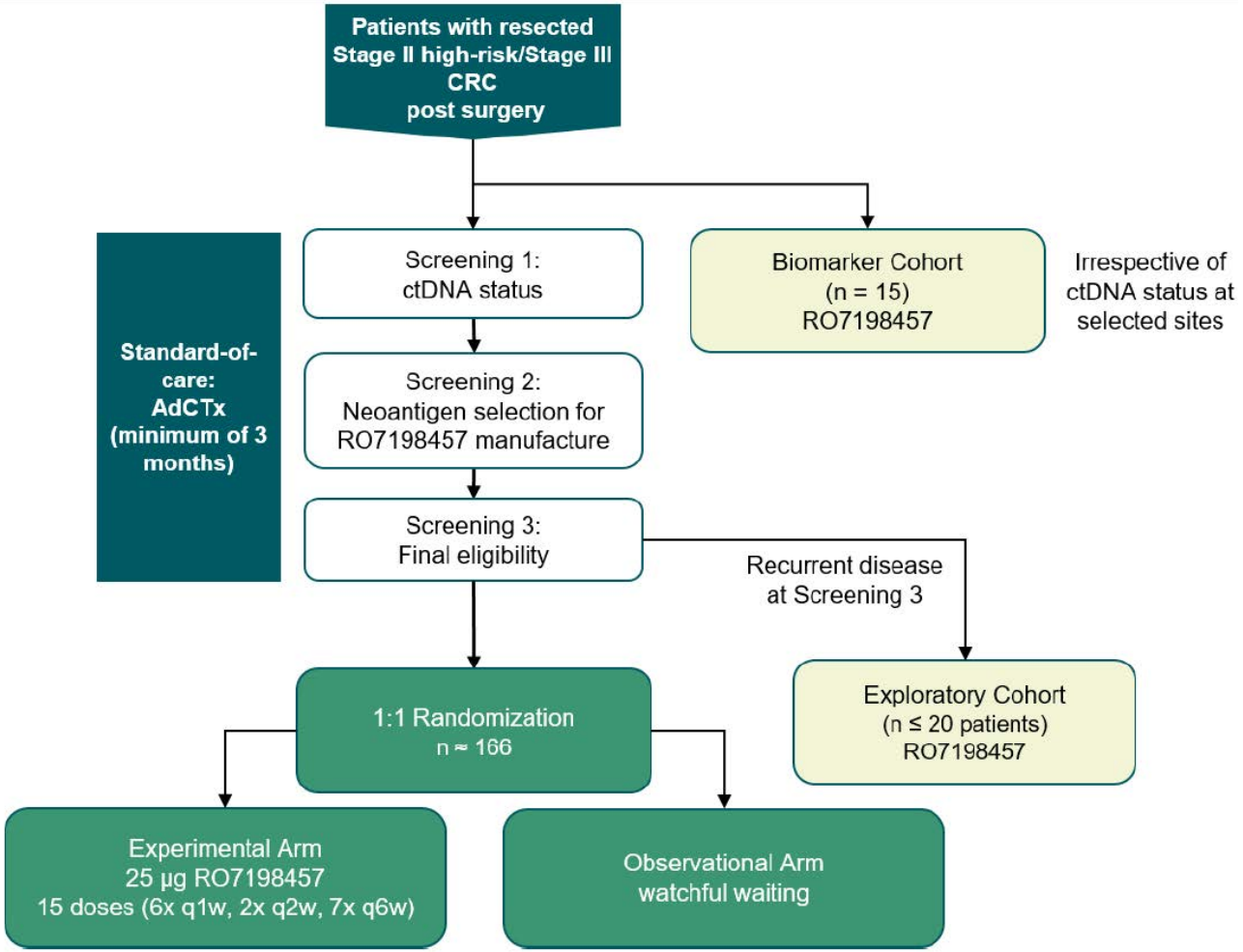
Up to 20 neoantigens predicted from NGS studies using bioinformatics pipeline will be used to create a personalized liposomal mRNA RO7198457 product

Patients on both arms restaged with imaging every 3 months for assessment of recurrence. Plasma collected for qualitative/quantitative ctDNA exploratory assessment.

Primary endpoint: Disease-free survival (DFS)

Key secondary: Change in ctDNA

Sample size: 201 participants



Kopetz, PI

NCT04486378

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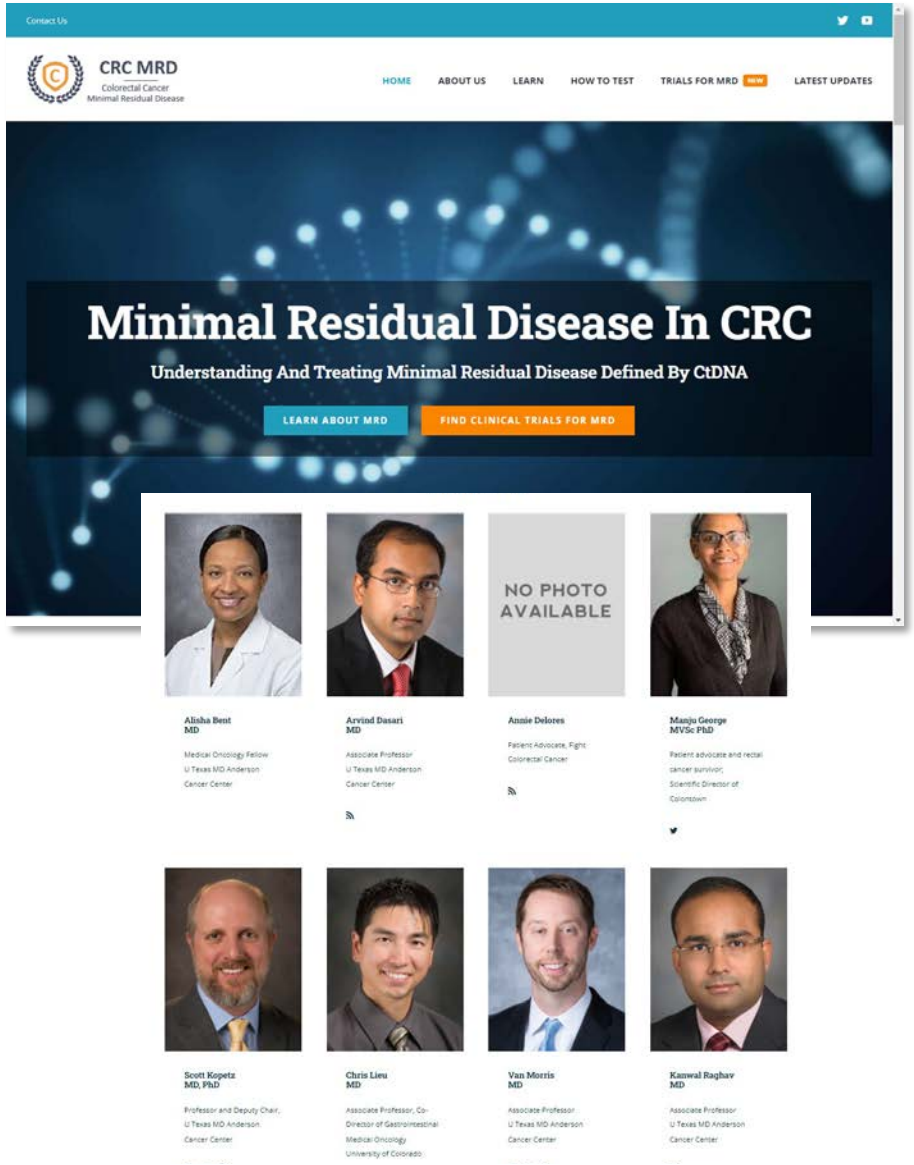
CRCMRD.org: Helping patients find information on clinical trials of MRD

Cord blood NK cells + Cetuximab	NCT05040568
Pembrolizumab or Nivolumab for MSI-H	NCT03803553/NCT03832569
TAS-102 alone or in combination	NCT05343013/ NCT04920032
Exercise +/- Diet, Vit D, Aspirin	NCT05036109 / NCT04589468
Personalized Peptide Vaccine + CD40 + anti-PD1	NCT03803553
Encorafenib, binimetinib, cetuximab in $BRAF^{mut}$	NCT02600949
PD1, CTLA4, Regorafenib	TBD



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Phase 3 ATOMIC Trial (Stage III MSI-H)

N = 700

Eligibility Criteria

- Stage III colon adenocarcinoma with any tumor (Tx-T4, N1-2M0; including N1C) originating or entirely located in colon
- Completely resected tumor
- dMMR
- No residual involved lymph node or metastatic disease at time of registration
- No prior chemotherapy, immunotherapy, biologic, targeted therapy, or radiation therapy; 1 previous cycle of mFOLFOX6 permitted.
- ECOG performance status ≤2
- No known active autoimmune disease or hepatitis B or C

Experimental arm:
mFOLFOX6 with atezolizumab (12 cycles) followed by atezolizumab (6 months)

Control arm:
mFOLFOX6 (12 cycles)

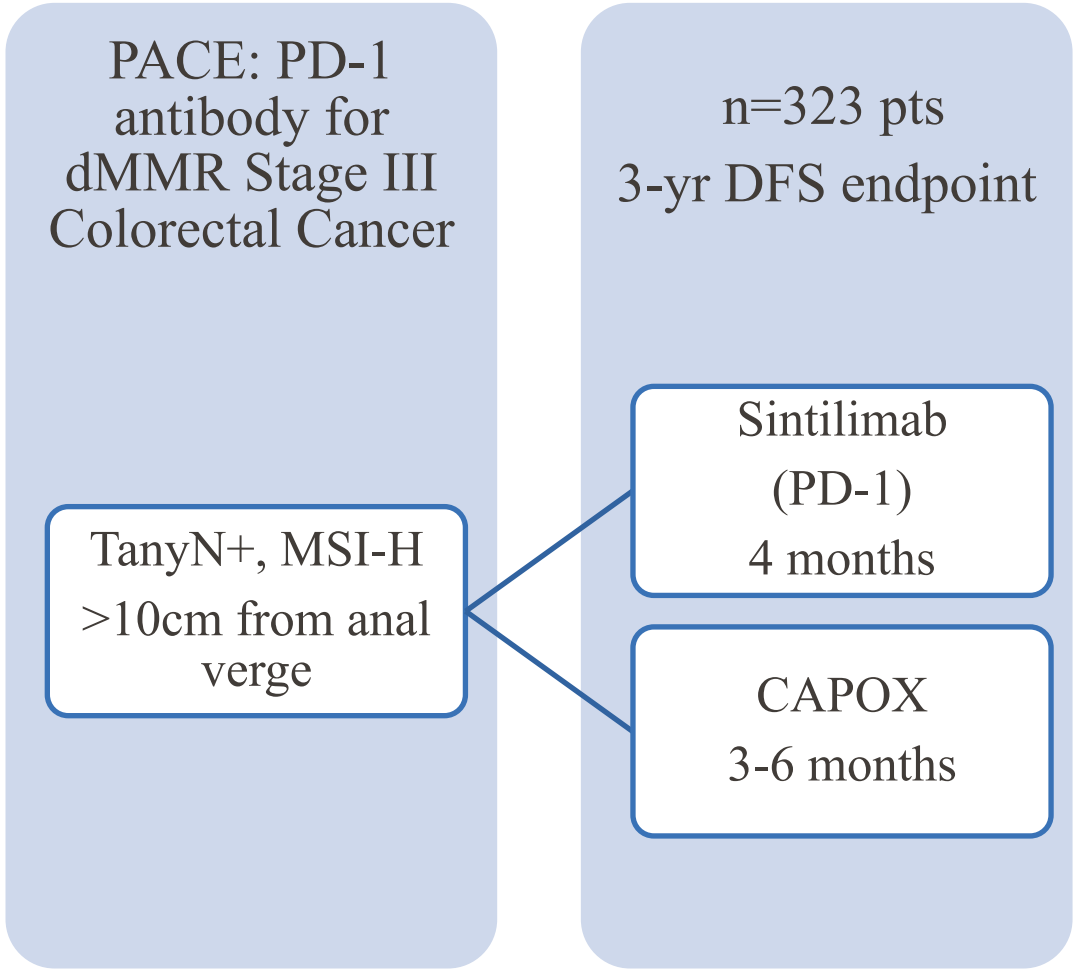
Endpoints:

Primary
DFS

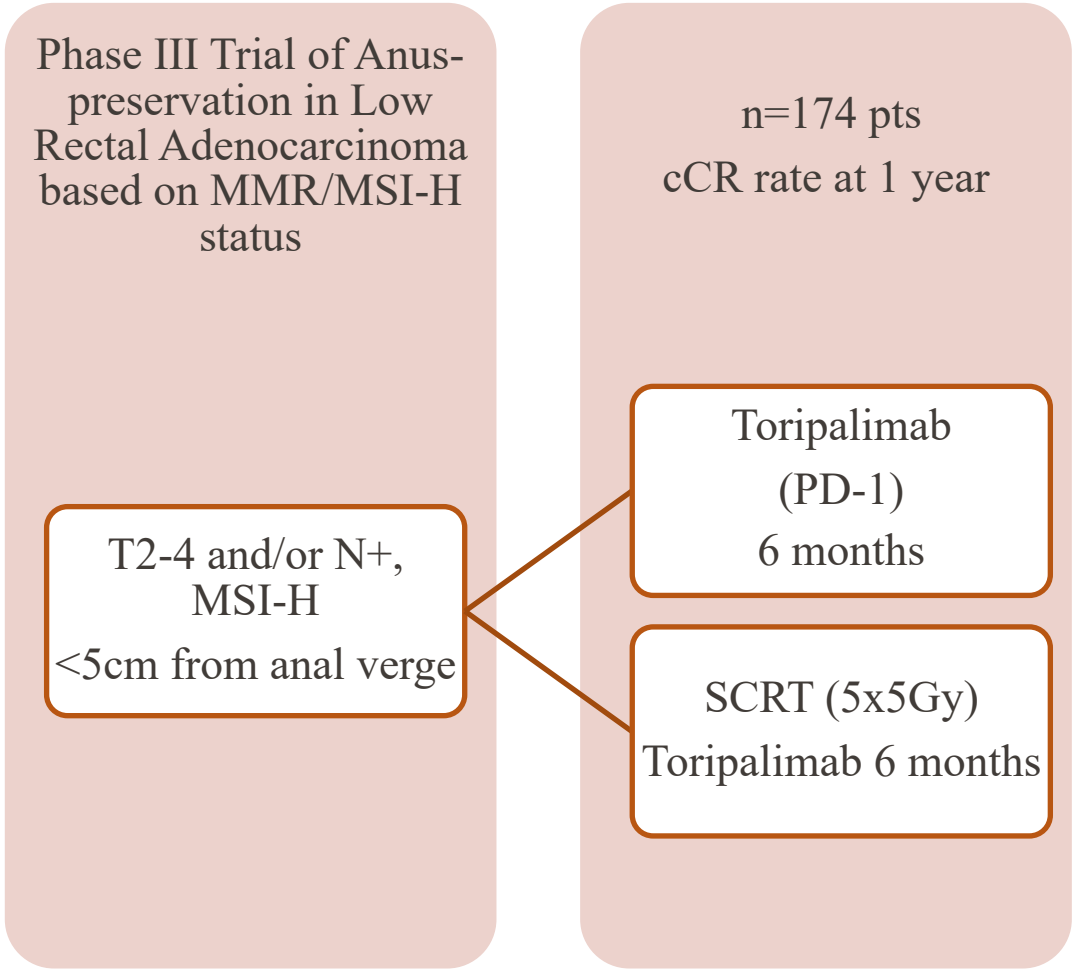
Secondary
OS, AEs

AE indicates adverse event; DFS, disease-free survival; dMMR, DNA mismatch repair; mFOLFOX6, modified leucovorin calcium, fluorouracil, and oxaliplatin; OS, overall survival.

Phase 3 Studies in Stage II / III Colorectal Cancer with MSI-H



NCT05236972



- Additional arm looking at FOLFIRINOX in MSS

NCT05669092

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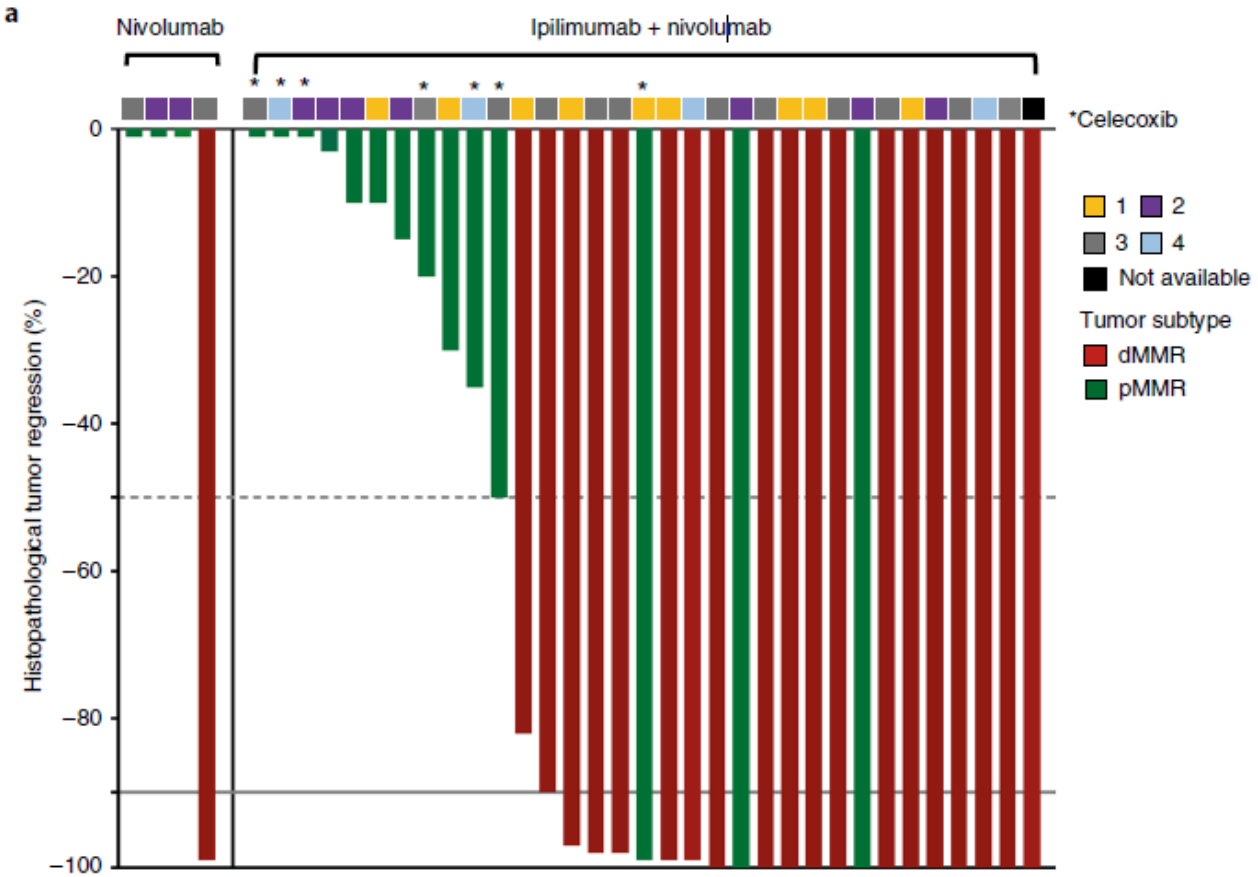
Neoadjuvant: NICHE Clinical Trials Demonstrate Great activity in MSI-H

- Ipilimumab 1mg/kg Day1
- Nivolumab 3mg/kg Day 1 + 15

- Median duration from first tx to surgery 32 days (IQR: 28-35)



- Median duration from first tx to surgery 35 days

Path Response	Patients (N=107)
YES	**106 (99%)**
• Major (<10%)	102 (95%)
• Complete (0%)	72 (67%)
• Partial (10-50%)	4 (4%)
NO	**1 (1%)**

NICHE-2 Clinical Trial

Chalabi et al Nat Med 2020; ESMO 2022

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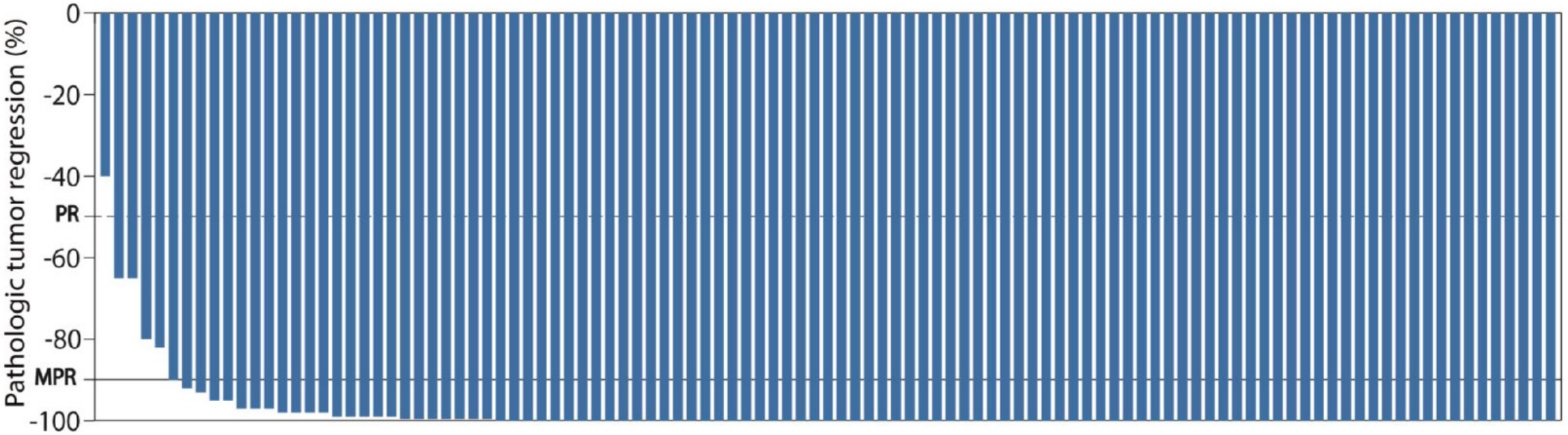
NICHE2 Clinical Trial: High CR in MSI-H



Major pathologic response in 95% of patients; 67% pCR

Chalabi et al ESMO ‘22

See also dostarlimab rectal data with high clinical CR rates, although no pathology responses available.

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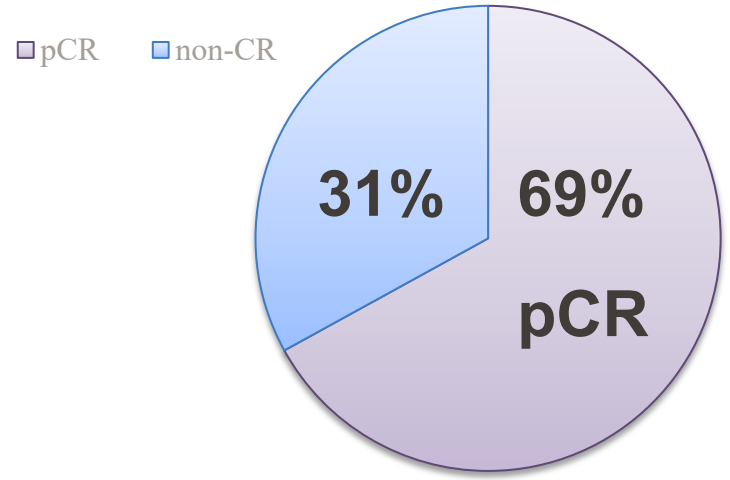
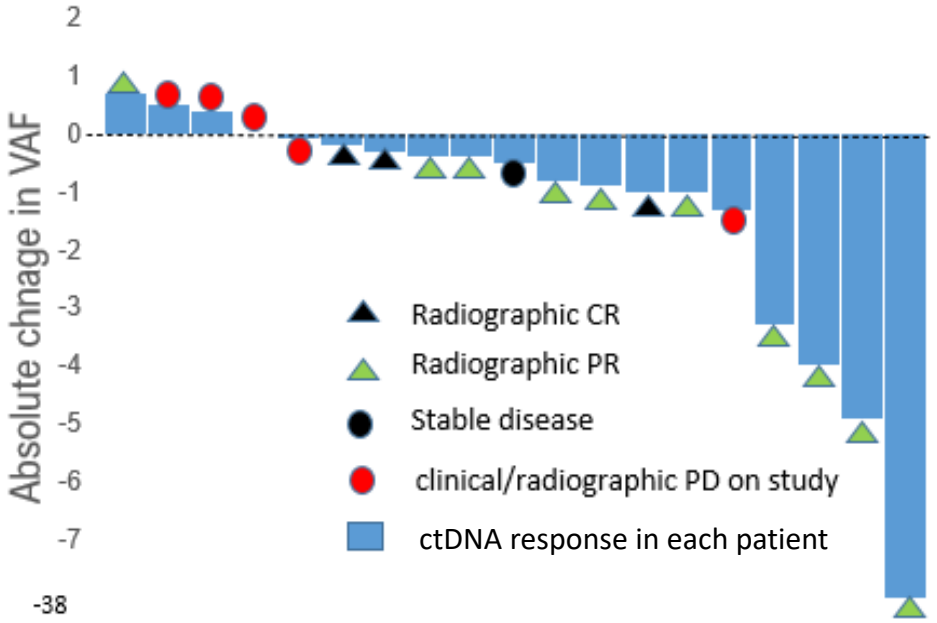
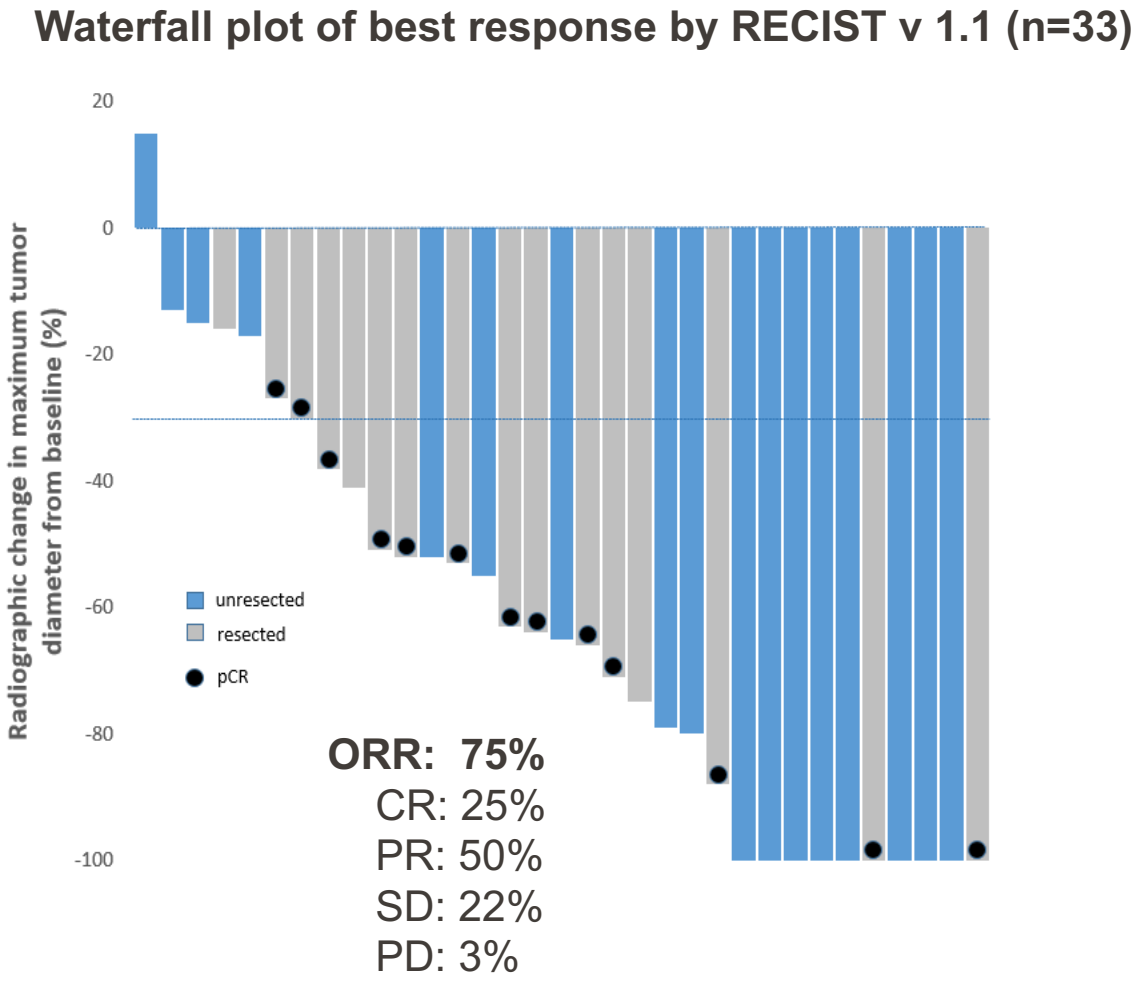
Pembrolizumab Efficacy in Neoadjuvant MSI-H CRC







Ludford and Overman ESMO 2022; JCO '22

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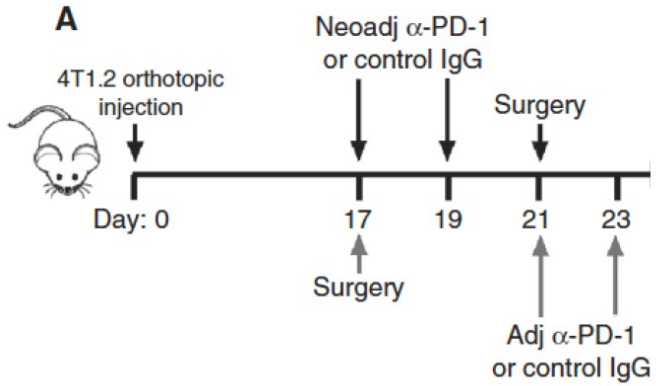
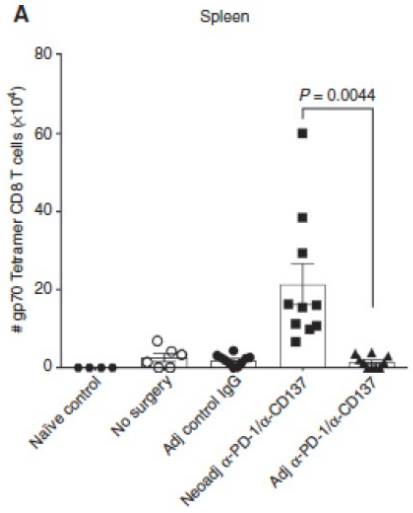
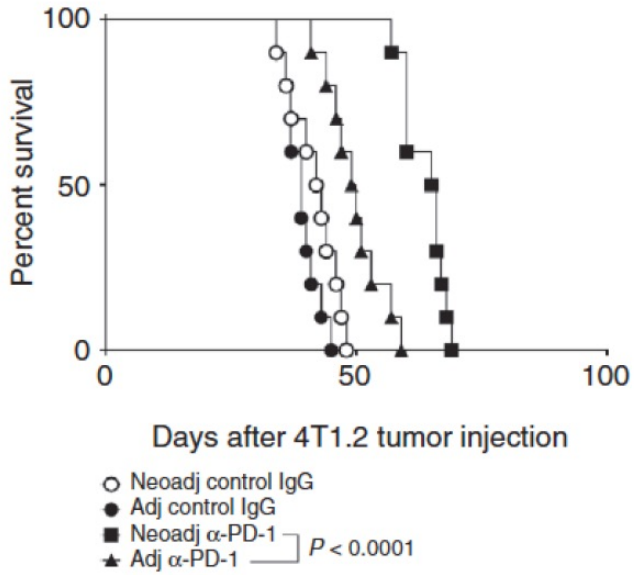
Supportive preclinical and clinical data for neoadjuvant





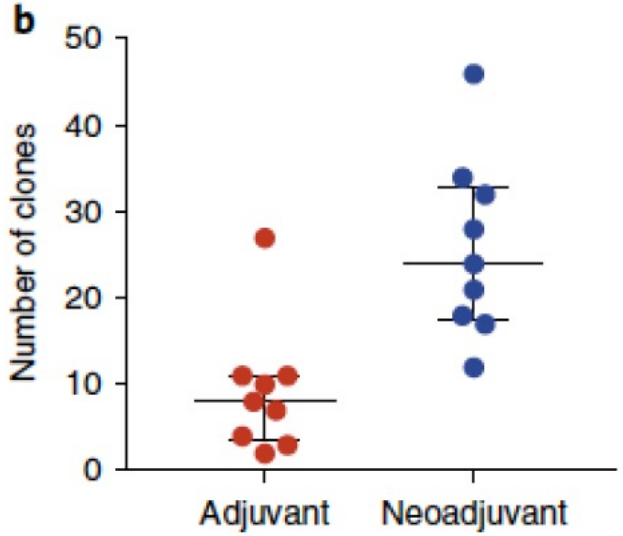


Neoadjuvant produced substantially higher tumor specific T-cell response and improved survival

Liu et al '13

Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma

- 20 patients randomized to 2 cycles prior to, 2 cycles after vs 4 cycles after surgery
- Tumor TCR clones were sequenced and tracked in peripheral blood
- Neoadjuvant vs adjuvant therapy produced greater expansion and increased number of new clones detected



Blank et al '18

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Conclusions

- MRD applications are enabled by very high **positive predictive value** (low false positive) of commercially-available ctDNA for recurrent disease in patients
- Applications in guiding adjuvant therapy are first, but novel therapeutics are being increasingly evaluated in the space
- *In the next several years, ctDNA will dramatically change our approaches to "adjuvant" therapy,* ***but we need to develop the data*** *and understand more about strengths/weaknesses of these strategies before prematurely adopting any new intervention approaches*
- How to utilize PD1 (+/- CTLA4) in neoadjuvant setting remains to be seen and more data is awaited, but potential for organ preservation strategies in MSI-H

Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Gastroesophageal Cancers

Part 2 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Gastrointestinal Cancers Symposium

Thursday, January 19, 2023
6:15 PM – 7:45 PM PT

Faculty

Yelena Y Janjigian, MD
Zev Wainberg, MD, MSc
Florian Lordick, MD, PhD

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.

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