# What Clinicians Want to Know: Biomarker Assessment and Related Treatment Decision-Making for Patients with Colorectal Cancer

*A CME Symposium Held in Conjunction with the 2025 ASCO® Gastrointestinal Cancers Symposium*

**Friday, January 24, 2025**

**6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)**

## Faculty

**Arvind Dasari, MD, MS**

**Van K Morris, MD**

**Jenny Seligmann, MBChB, PhD**

**Eric Van Cutsem, MD, PhD**

## Moderator

**Christopher Lieu, MD**

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# Faculty

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

**Van K Morris, MD**
Associate Professor
Department of Gastrointestinal Medical Oncology
The University of Texas
MD Anderson Cancer Center
Houston, Texas

**Jenny Seligmann, MBChB, PhD**
Professor of Gastrointestinal Cancer
University of Leeds
Leeds, United Kingdom

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

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

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# Dr Dasari — Disclosures
# Faculty

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# Faculty

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# Dr Lieu — Disclosures
# Moderator

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

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Save The Date

# Fourth Annual
# National General Medical Oncology Summit

***A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute***

**Friday to Sunday, February 28 to March 2, 2025**

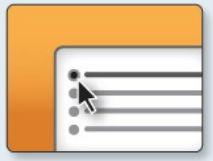
Fontainebleau Hotel, Miami Beach, Florida

**Moderated by Neil Love, MD**

# Clinicians in the Meeting Room

**Networked iPads are available.**

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



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

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

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

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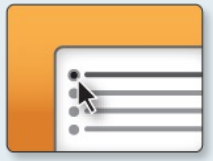
# Clinicians Attending via Zoom

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



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

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

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

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# About the Enduring Program

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

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# Survey of General Medical Oncologists: January 10 – January 16, 2025

***Results available on iPads and Zoom chat room***

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# Agenda

**Module 1:** Optimizing Biomarker Assessment for Patients with Colorectal Cancer (CRC) — Dr Dasari

**Module 2:** Identification and Management of Metastatic CRC (mCRC) with a BRAF V600E Mutation — Dr Morris

**Module 3:** Incorporation of Immune Checkpoint Inhibitors into the Management of MSI-H/dMMR CRC — Dr Seligmann

**Module 4:** Integration of Therapies Targeting HER2 into the Management of mCRC — Prof Van Cutsem

**Module 5:** Biomarker-Based Decision-Making for Patients with mCRC and KRAS G12C Mutations — Dr Lieu

# Agenda

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# Optimizing Biomarker Assessment for Patients with Colorectal Cancer

**Arvind N. Dasari, MD, MS**

**Professor**

**Department of GI Medical Oncology**

**University of Texas MD Anderson Cancer Center, Houston, TX**

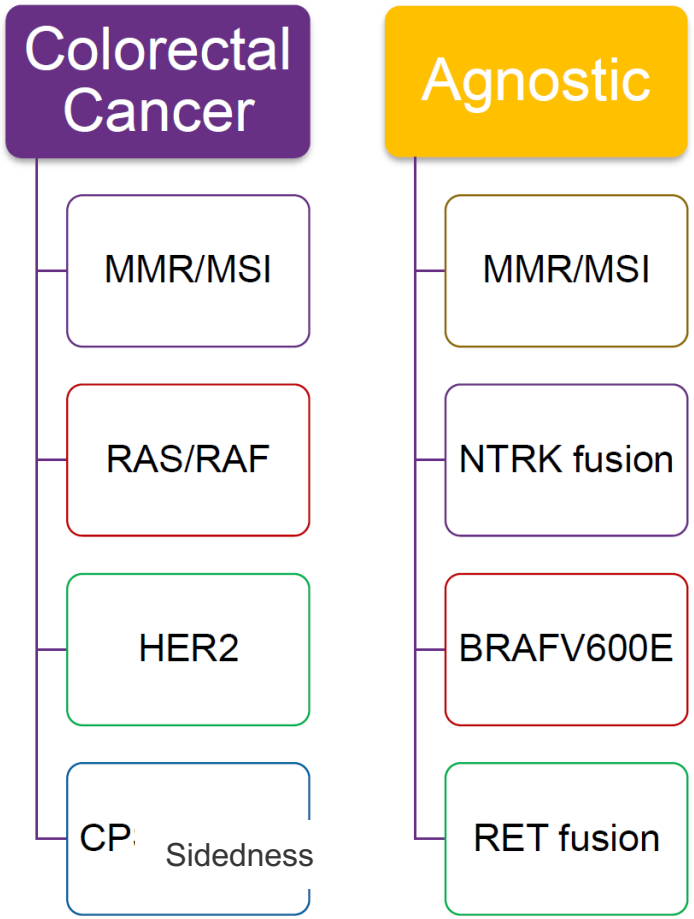
# Agenda

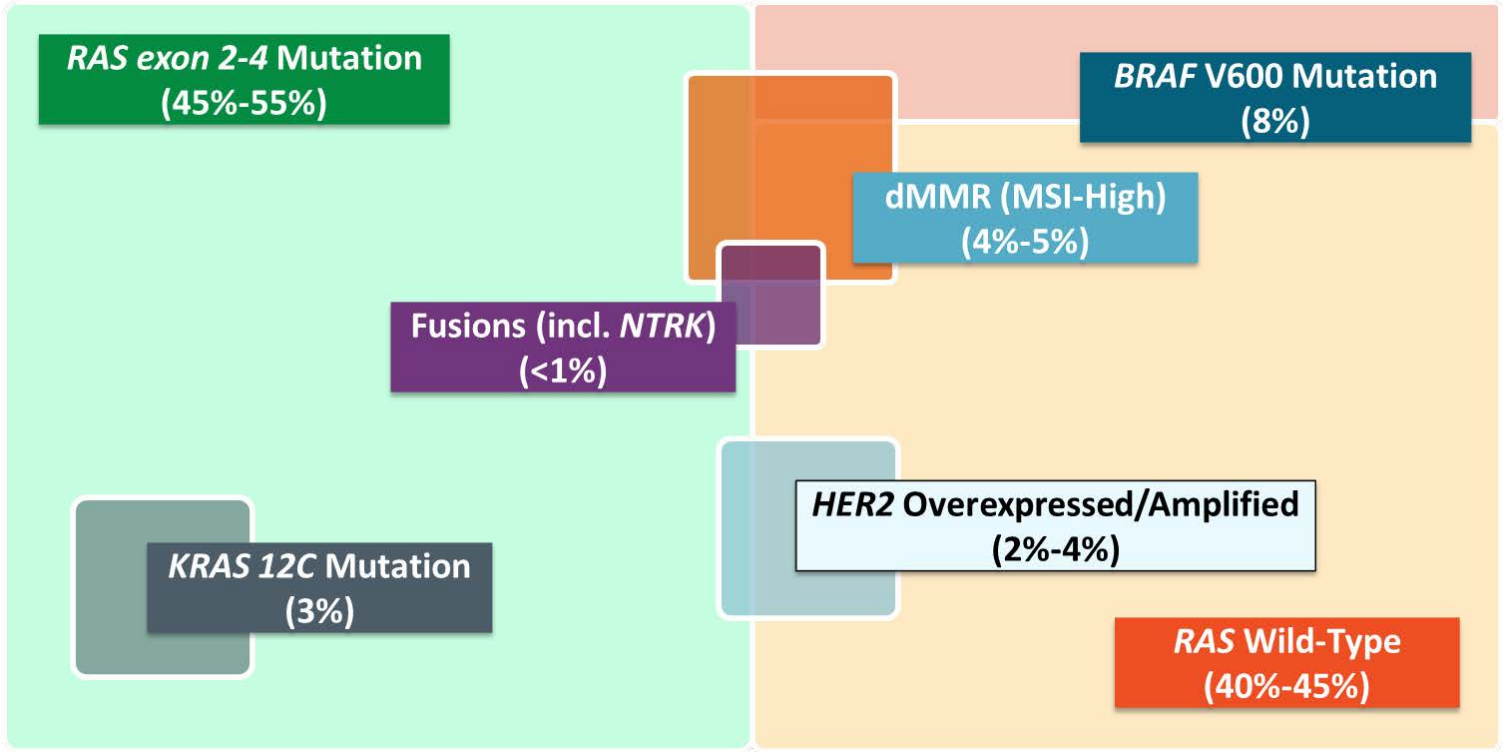
Validated Biomarkers in CRC

ctDNA-based MRD Monitoring in CRC

mCRC, metastatic colorectal cancer; ctDNA, circulating tumor DNA, MRD, minimal residual disease.

# Treatment of mCRC is Defined By Molecular and Clinical Characteristics




NCCN Guidelines. Colon Cancer. V5.2024. www.nccn.org; Eng et al Lancet 2024; 404: 294–310; Slide Acknowledgement: Raghav, MD, Kazmi, MD

# Principles of Biomarker Testing for mCRC

- **Modality & Timing:** Can be performed on tissue (preferred; primary or metastatic) or with blood-based assays.

- **Microsatellite & germline testing:** All patients irrespective of stage at diagnosis or age should be tested for microsatellite instability by IHC or PCR. Germline testing for hereditary conditions should be recommended for < 50 years and discussed with all patients.

- **Mutations:** Extended *RAS, BRAF, POLE, POLD* with NGS

- **Fusions:** May be detected by IHC, DNA or RNA NGS. RNA NGS may be slightly more sensitive than DNA NGS and can also identify irrespective of fusion partner.

- **Her2 AMP:** A) IHC: 3+ staining in more than 50% of tumor cells, or B) FISH: HER2:CEP17 ratio ≥2 in more than 50% of the cells, or C) IHC 2+ and positive on FISH testing, or D) amplification by NGS

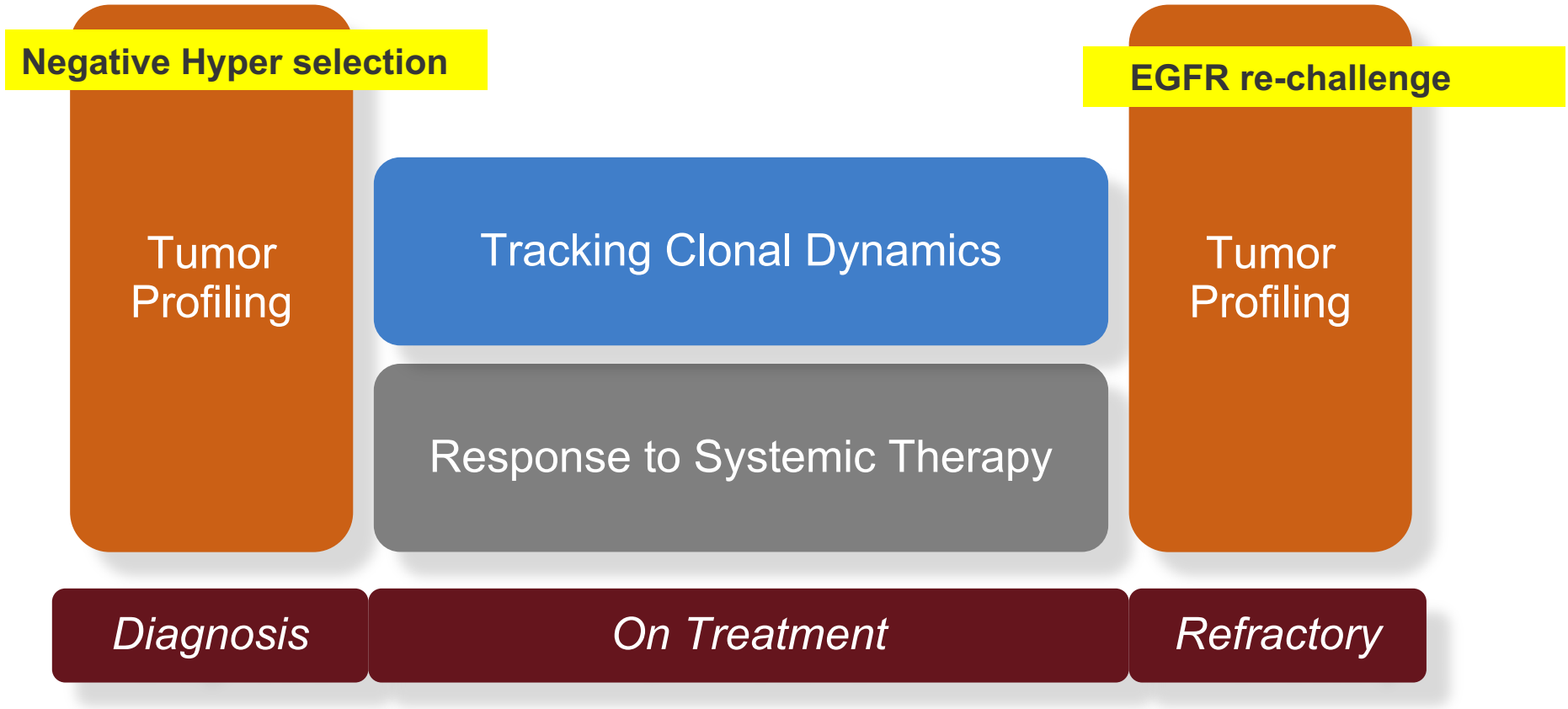
NCCN Guidelines. Colon Cancer. V5.2024. www.nccn.org.

# Genomic Profiling in mCRC

| Molecular Marker | Location / Testing | Frequency in mCRC | Clinical Utility | Line of Therapy |
|---|---|---|---|---|
| MSI / dMMR | IHC and / or PCR | 3-5% | Screening for Lynch syndrome<br>Predictive (+) for immunotherapy | 1st & beyond |
| Extended RAS analysis | KRAS exons 2,3,4<br>NRAS exons 2,3,4 | 50-60% | Predictive (-ve) for EGFR MoAb therapy | 1st & beyond in L sided tumors |
| BRAF mt | V600E – IHC or NGS<br>Atypical - NGS | 7-10% | Poor prognosis<br>Interaction with MSI-H<br>Predictive (+) for anti BRAFV600E therapy | 1st & beyond |
| KRAS G12C | NGS | 2-3% | Predictive (+ve) Anti-KRAS G12C therapies | Refractory |
| POLE POLD1 MT | NGS | 1-2% | High TMB; Predictive (+ve) for immunotherapy | 1st & beyond |
| Her-2neu Amp | IHC and / or FISH, NGS | 3-5% | Predictive (-ve) for EGFR moab<br>Predictive (+ve) for anti-Her2neu rx | Refractory |
| NTRK fusions | IHC, FISH, NGS | < 1% | Predictive (+ve) Anti-NTRK therapies | Refractory |

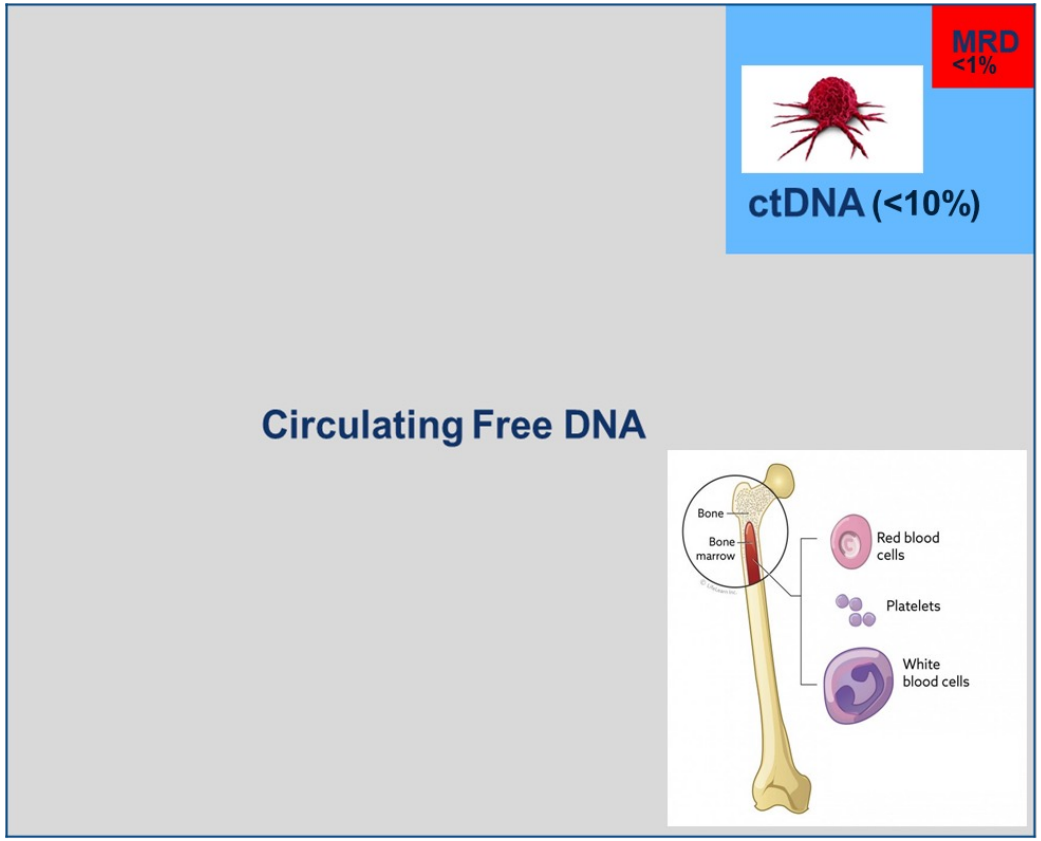
# Liquid Biopsies in mCRC

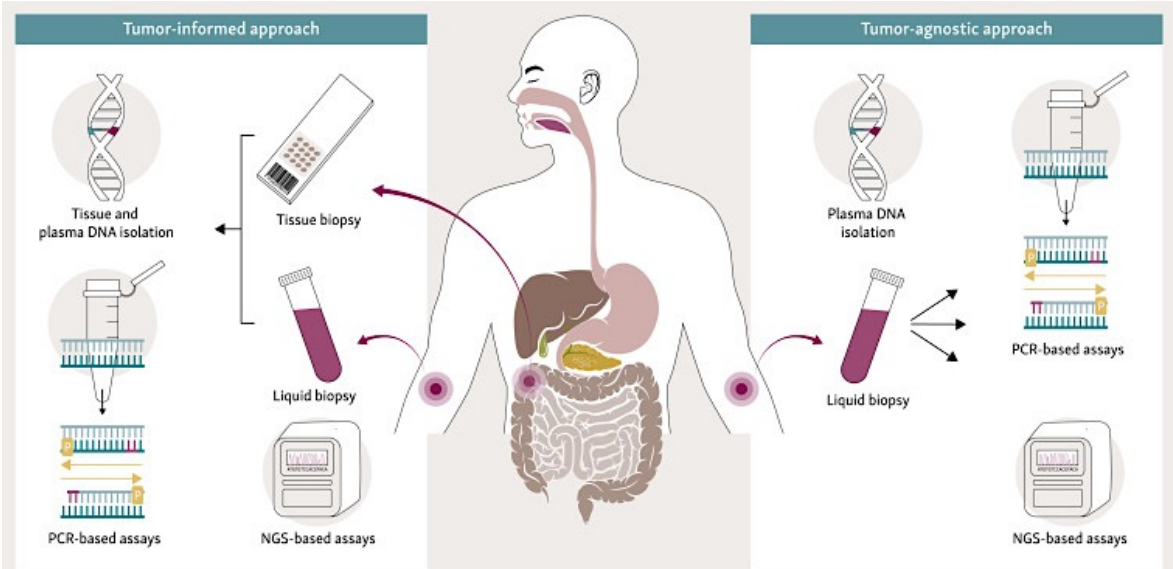
***ctDNA Uses***




***Consider tissue testing if no alterations are detected to avoid false negatives**

# ctDNA as a Marker for MRD & Assays



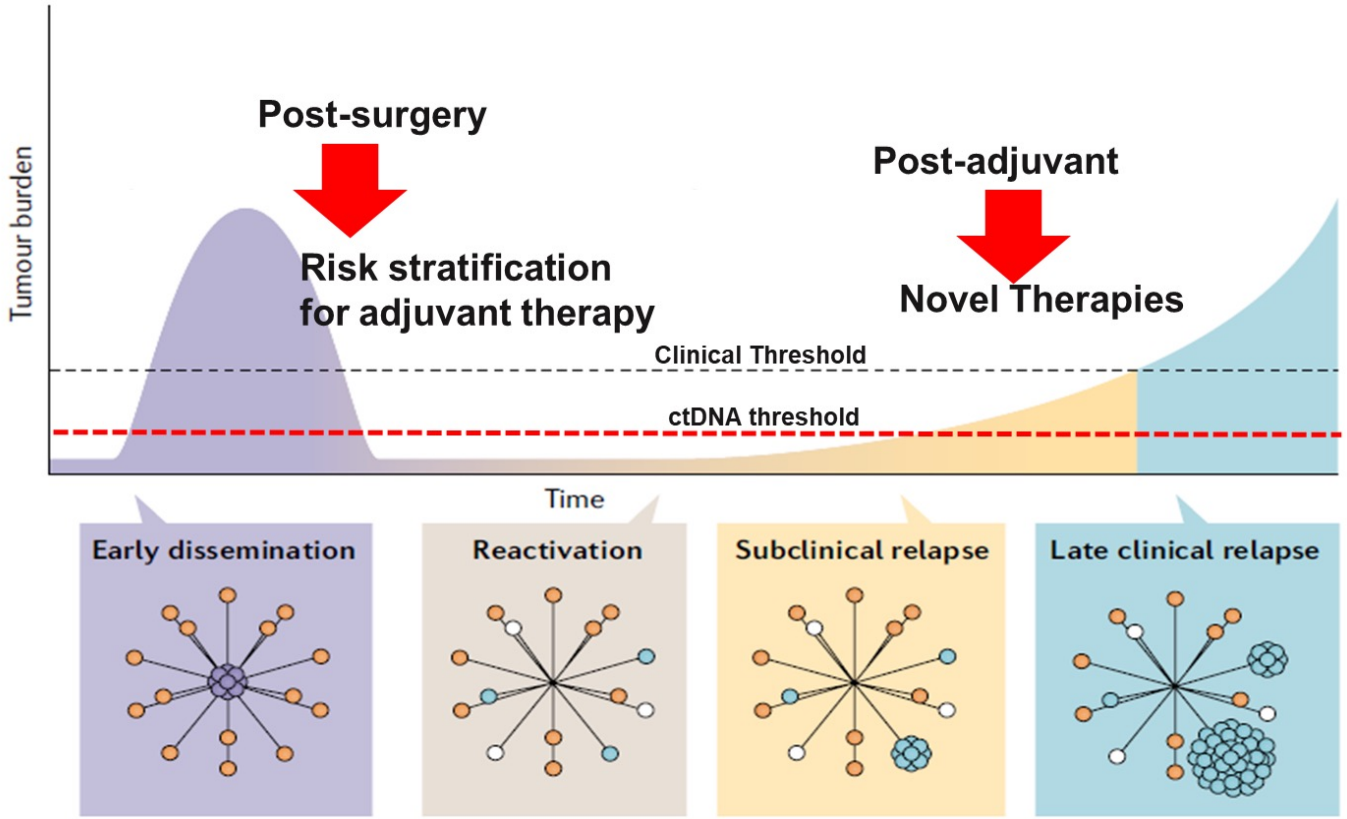

| | TUMOR-INFORMED | TUMOR AGNOSTIC |
|---|---|---|
| **Requires matched tumor tissue?** | Yes | No |
| **Turn-around time adequate for adjuvant chemotherapy window?** | Yes…. | Yes |
| **Gene coverage** | Personalized | Extensive panel including most commonly mutated genes |
| **Correction for CHIP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

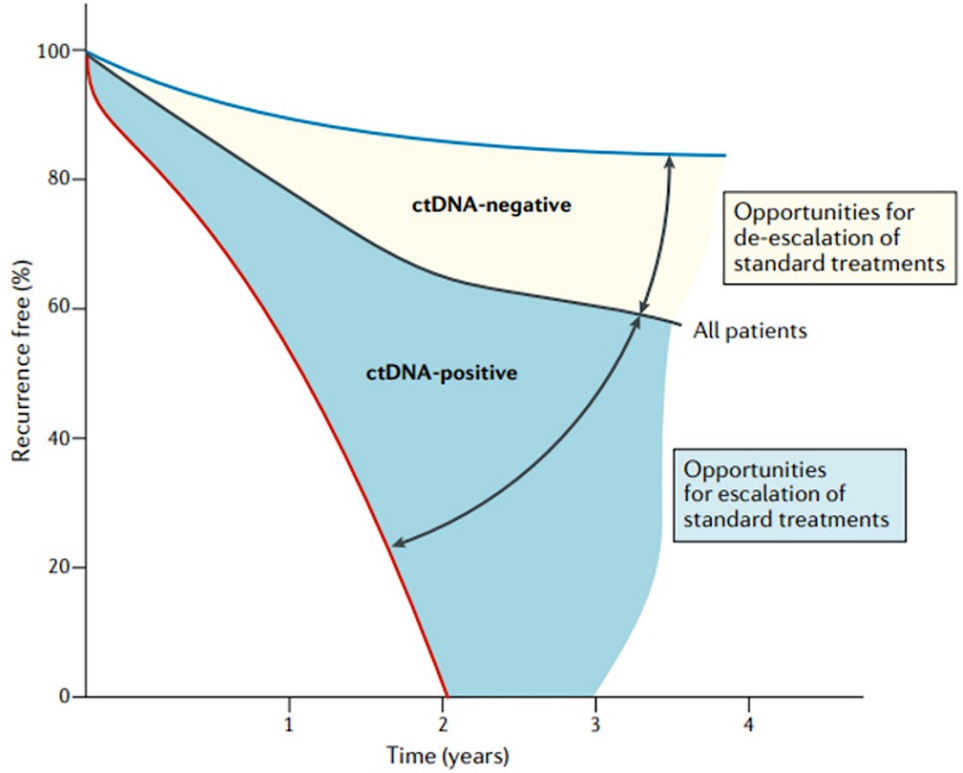
Taieb et al ESMO Gastrointestinal Oncology, 2024

# Clinical Utility of ctDNA Defined MRD

- *High PPV (>95%)*
- *High Specificity (> 95%) for recurrence*

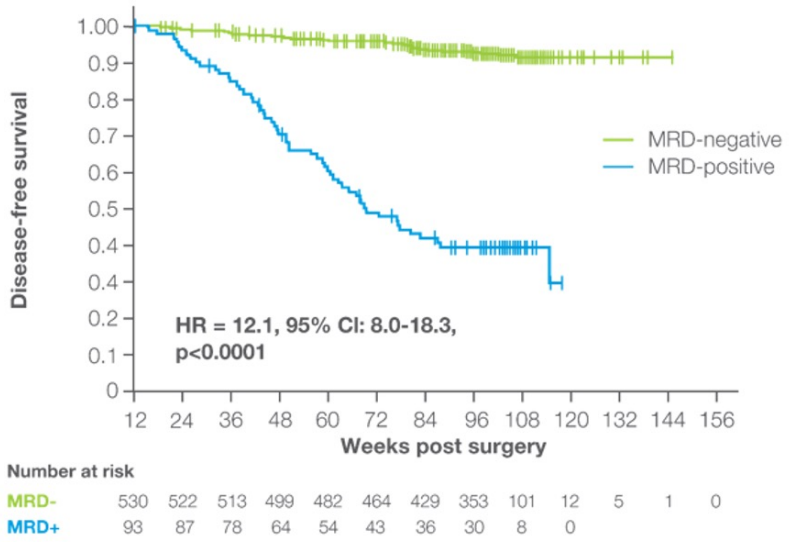
- *Lead time prior to clinical detection*

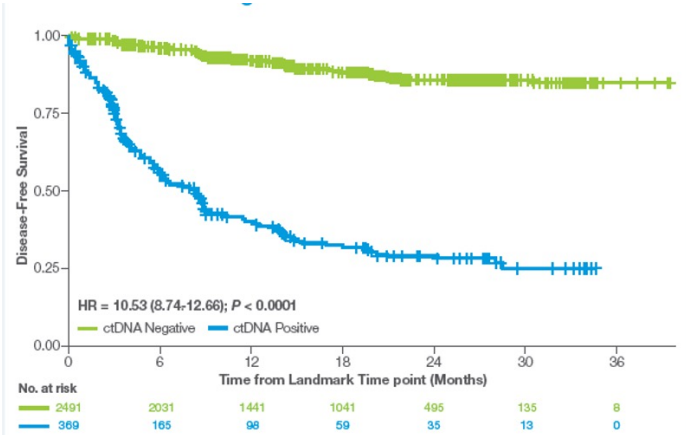



Phan et al, Nat Ca Rev, 2020; Dasari et al, Nat Rev Clin Onc 2020

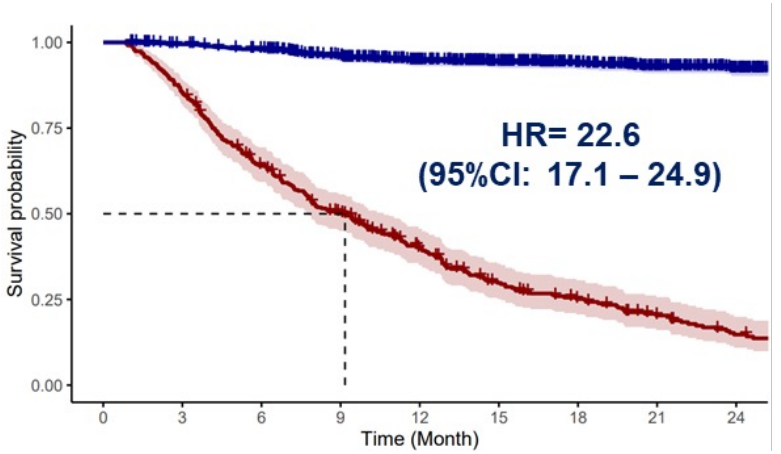
# Data from Observational Studies – MRD is Prognostic




| ctDNA Status | ctDNA Negative | ctDNA Positive |
|---|---|---|
| Events % | 9.4 (235/2491) | 58.8 (217/369) |
| 24M-DFS % (95% CI)** | 85.9 (83.9–87.7) | 28.9 (23.4–34.8) |

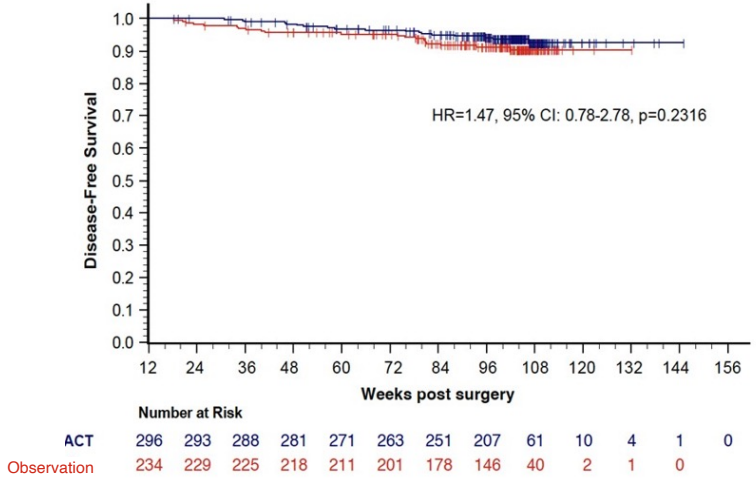
*MRD window: 2-10 weeks post surgery, prior to start of any adjuvant therapy – Landmark 10 weeks post-surgery
**DFS % from landmark time point



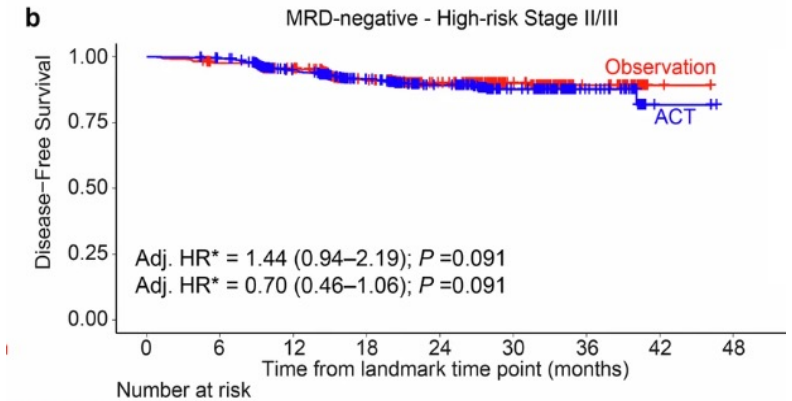

| | BESPOKE | GALAXY | INTERCEPT |
|---|---|---|---|
| n | 627 | 2860 | 1140 |
| Stage | II-IV | II-III | II-IV |
| HR for DFS | 12.1 | 10.5 | 22.6 |

Maddalena, et al ASCO GI 2024
Yukami et al ASCO GI 2024
Kasi et al ASCO GI 2024

# Data from Observational Studies: MRD -ve




| Adjuvant strategy | ACT | Observation |
|---|---|---|
| Numbers of events (%) | 18/296 (6.08) | 20/234 (8.55) |
| 2-year DFS post surgery, % (95% CI) | 93.70 (90.03-96.05) | 90.39 (85.38-93.75) |
| Median DFS post surgery, months (95%) | Not reached | Not reached |

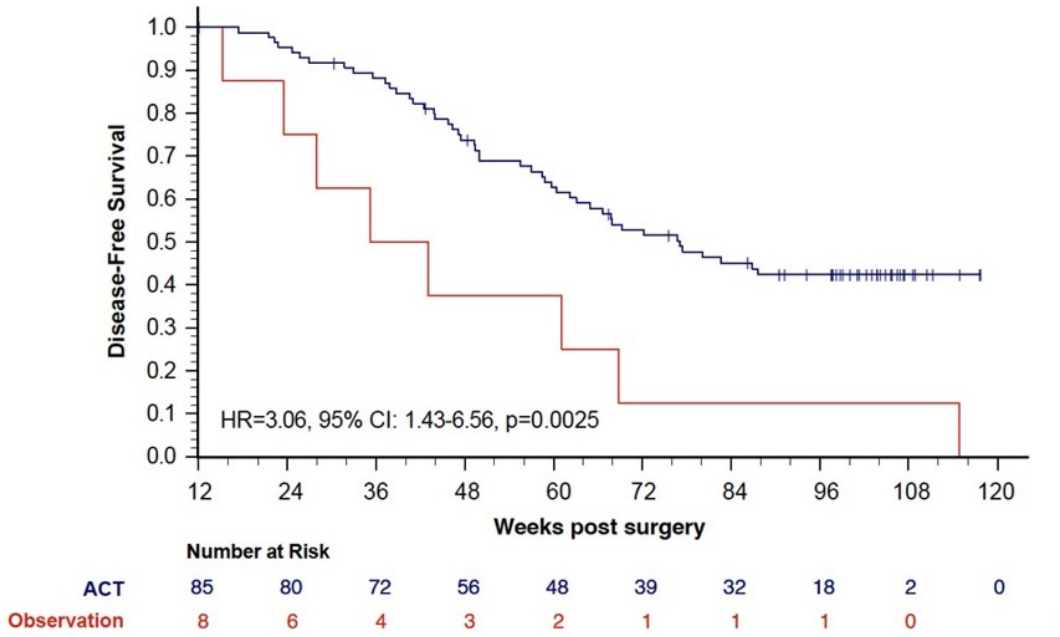


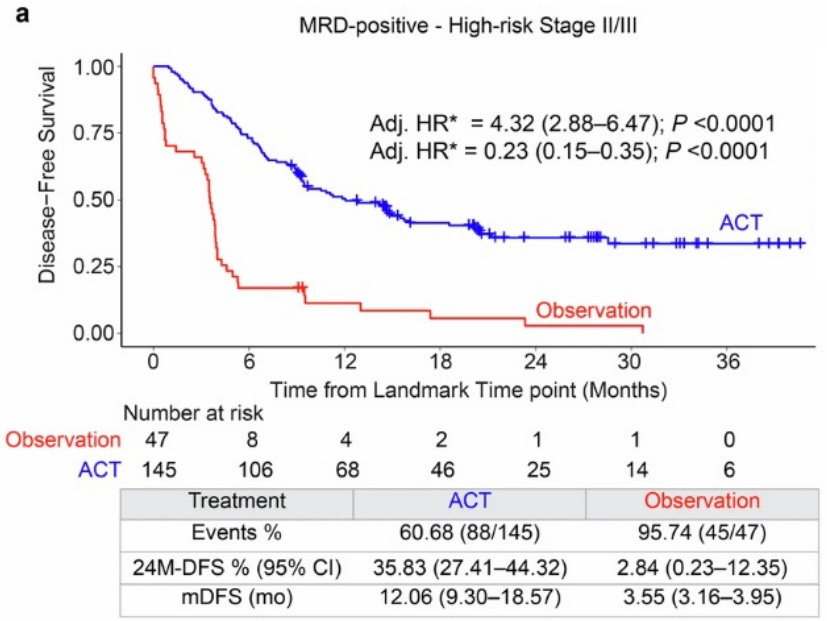

| Treatment | ACT | Observation |
|---|---|---|
| Events % | 9.63 (55/571) | 8.53 (50/586) |
| 24M-DFS % (95% CI) | 89.11 (85.81–91.68) | 89.9 (86.80–92.30) |
| mDFS (mo) | NR | NR |

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

Kasi et al ASCO GI 2024
Nakamura Y, Watanabe J, Akazawa N, et al. Nat Med. 2024;30(11):3272-3283. doi:10.1038/s41591-024-03254-6

# Data from Observational Studies: MRD +ve



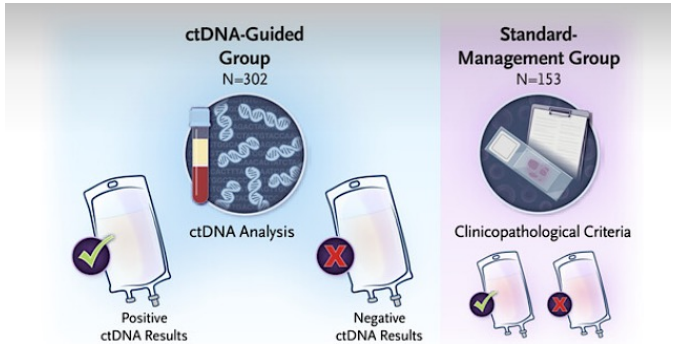



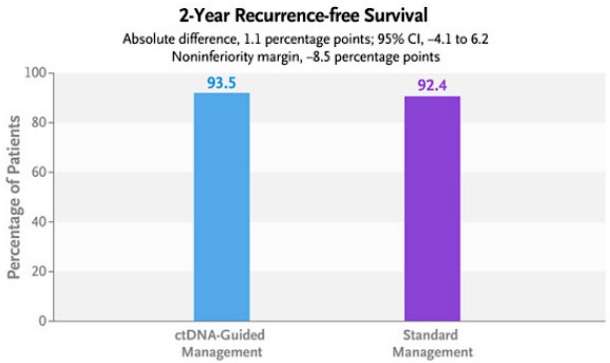

| Treatment | ACT | Observation |
|---|---|---|
| Events % | 60.68 (88/145) | 95.74 (45/47) |
| 24M-DFS % (95% CI) | 35.83 (27.41–44.32) | 2.84 (0.23–12.35) |
| mDFS (mo) | 12.06 (9.30–18.57) | 3.55 (3.16–3.95) |

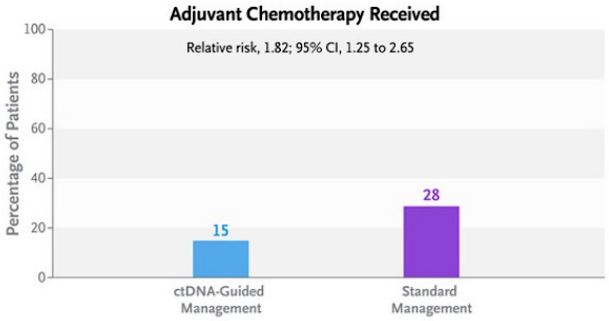
| | BESPOKE | GALAXY |
|---|---|---|
| n | 96 | 192 |
| **2-year DFS (%)** | | |
| With ACT | 42.4 | 35.8 |
| Without ACT | 12.5 | 2.8 |

Yukami et al ASCO 2024
Kasi et al GI ASCO 2024
Nakamura Y, Watanabe J, Akazawa N, et al. Nat Med. 2024;30(11):3272-3283. doi:10.1038/s41591-024-03254-6

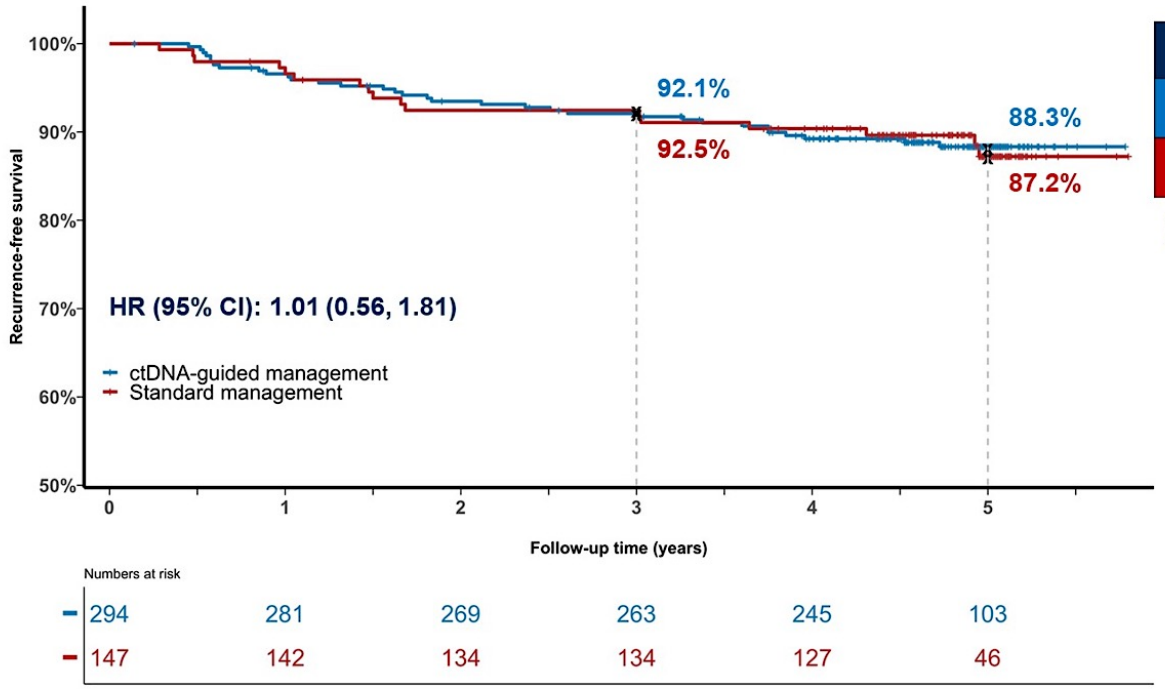
# Data from Randomized Studies: DYNAMIC Trial




## Updated 5-Year RFS Analysis




| 5-Year RFS Rate, % | |
|---|---|
| ctDNA | 88.3 |
| SoC | 87.2 |

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

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

Data cut-off: 17 Jan 2024

2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Jeanne Tie, MBChB FRACP MD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

**Tie et al, N Engl J Med. 2022 Jun 16;386(24):2261-227**
**Tie et al GI ASCO 2024.**

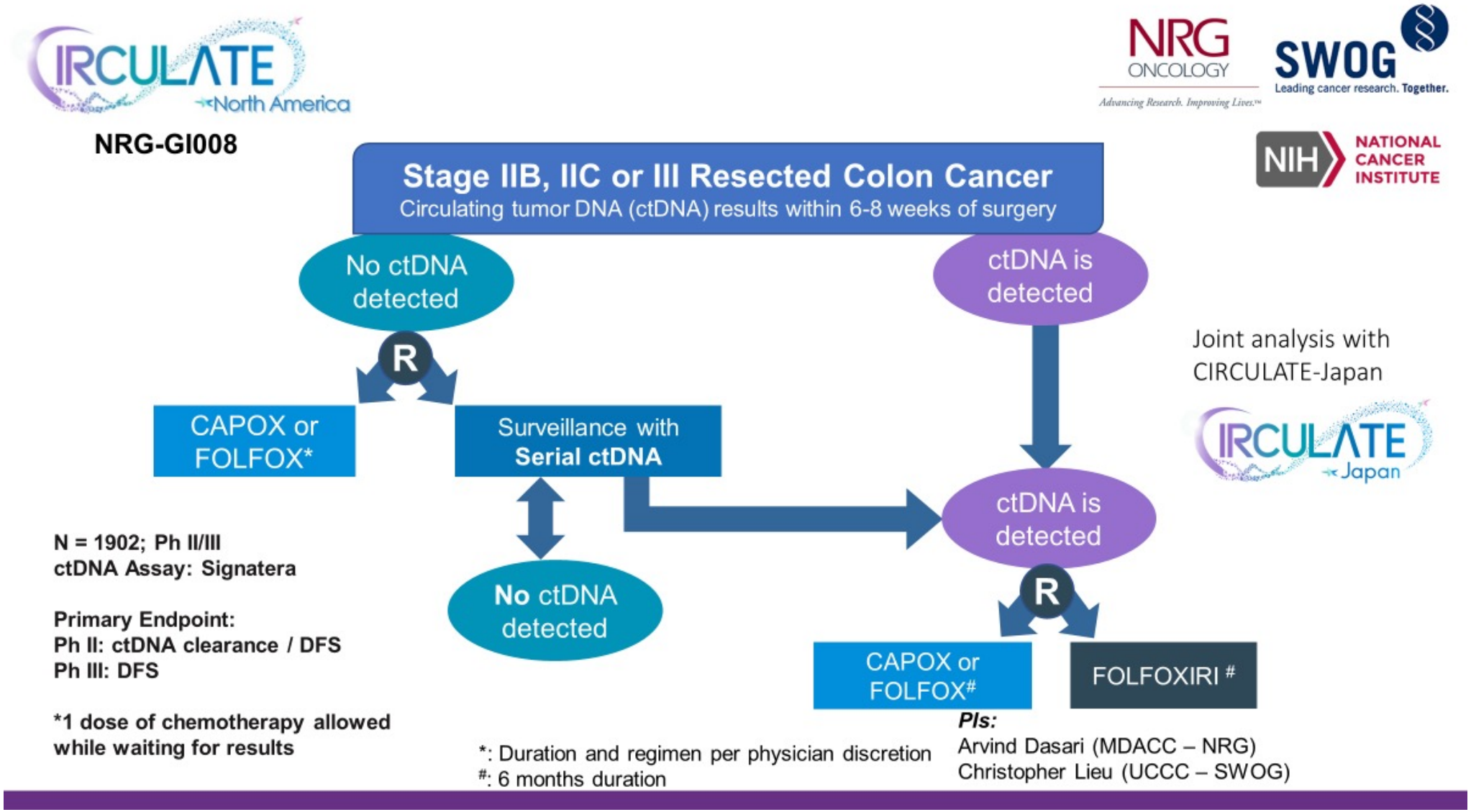
# MRD: Unanswered Questions

- Can adjuvant chemotherapy be de-escalated in higher risk pts (high risk stage II & III)?

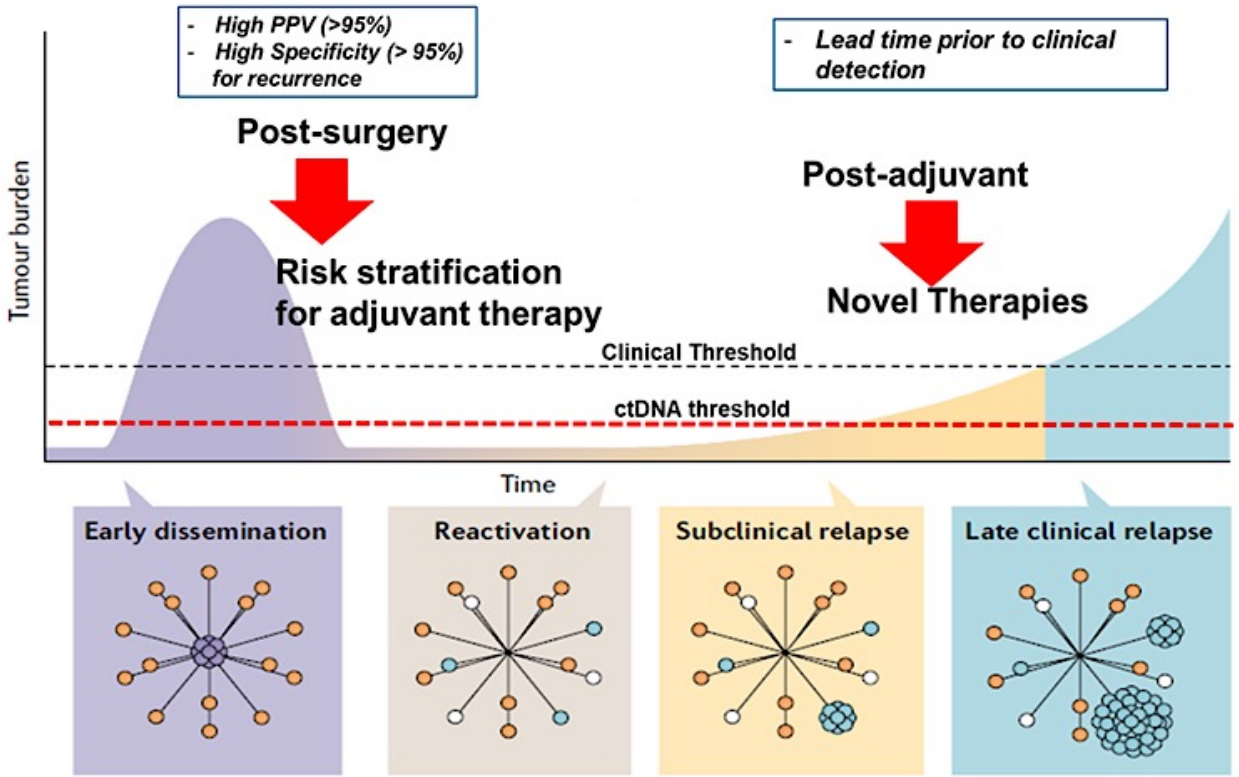
- Role of serial monitoring of ctDNA for de-escalation?

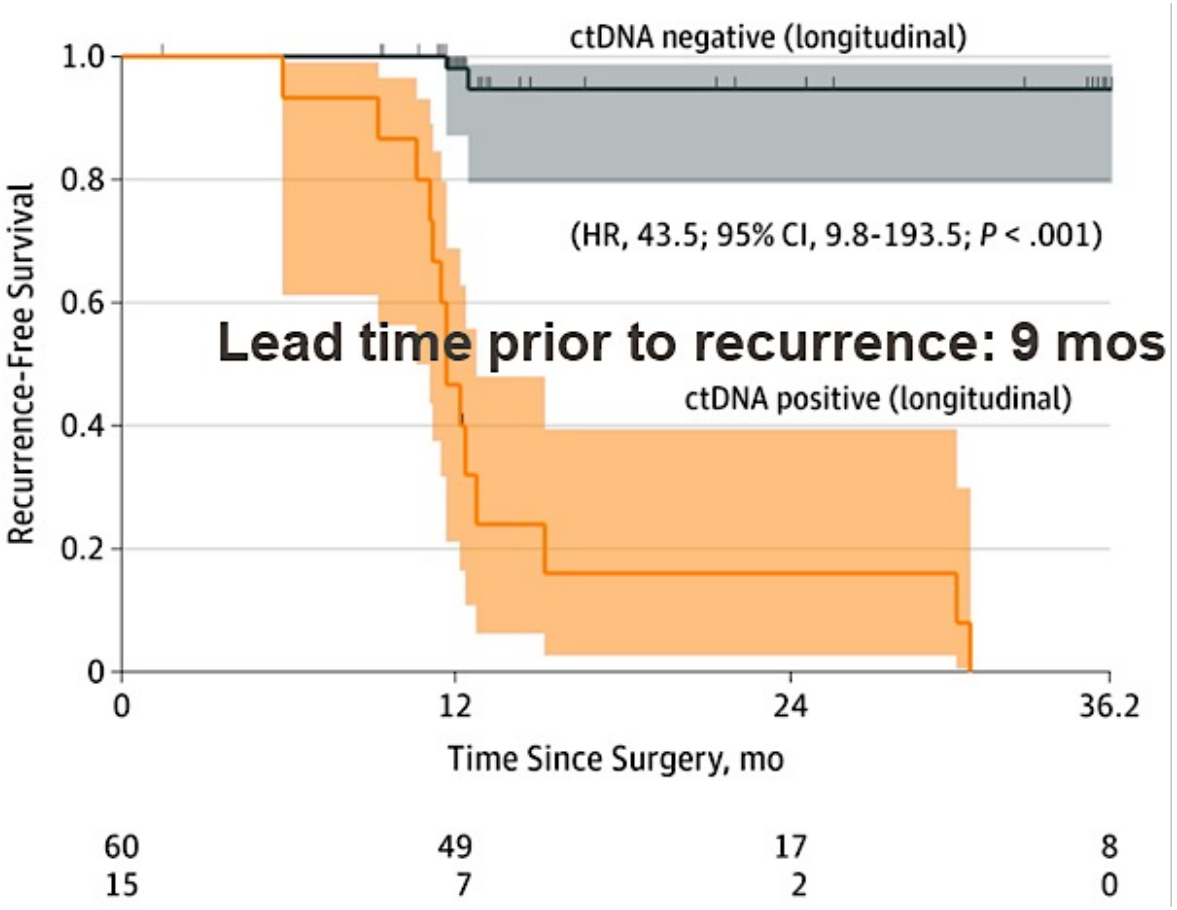
- Escalation of adjuvant therapy in ctDNA+ patients?

# MRD: Unanswered Questions



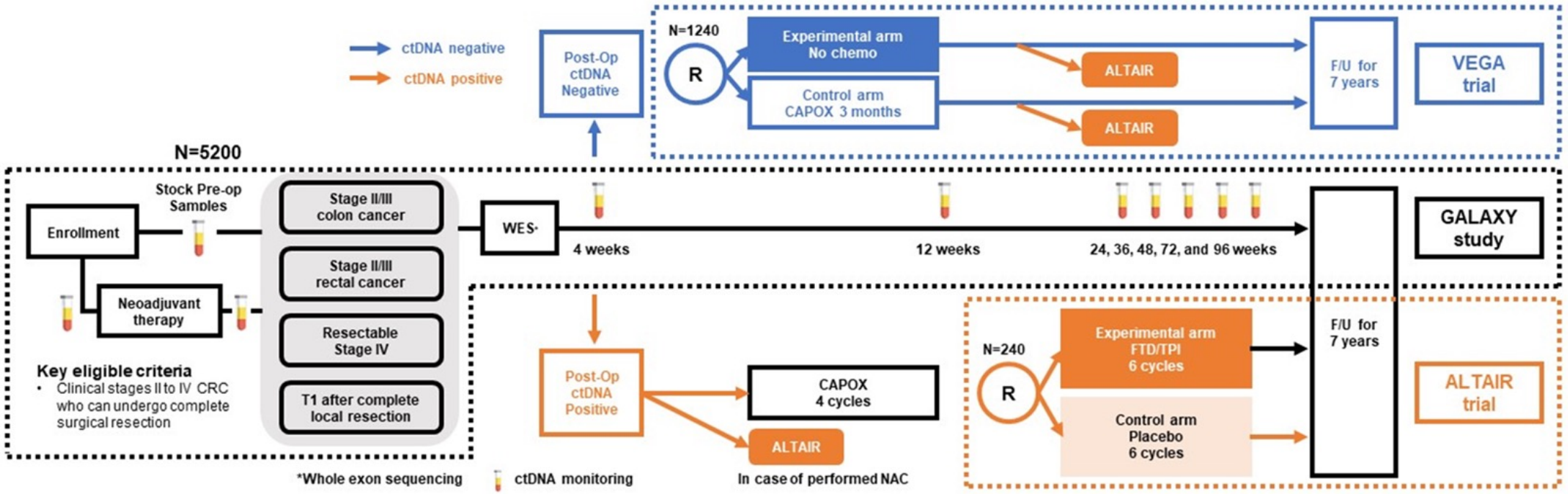
# Clinical Utility of ctDNA Defined MRD



# Clinical Utility of ctDNA Defined MRD – Post Adjuvant Therapy

## ALTAIR Trial




**Clinical trial information: JapicCTI-205363/NCT04457297**

# Clinical Utility of ctDNA Defined MRD – GI ASCO 2025

- **LBA22: A randomized, double-blind, phase III study comparing trifluridine/tipiracil (FTD/TPI) versus placebo in patients with molecular residual disease following curative resection of colorectal cancer (CRC): The ALTAIR study. (*Bando et al*)**

- **LBA14: Prognostic and predictive role of circulating tumor DNA (ctDNA) in stage III colon cancer treated with celecoxib: Findings from CALGB (Alliance)/SWOG 80702. (*Nowak et al*)**

- **Abs 15:  Circulating tumor DNA for detection of molecular residual disease (MRD) in patients (pts) with stage II/III colorectal cancer (CRC): Final analysis of the BESPOKE CRC sub-cohort. (*Shah et al*)**

# Questions from General Medical Oncologists

- Are there any noticeable differences in testing biomarkers from the primary tumor vs from a metastatic site (like liver or lung)?
- What is the role of liquid biopsy in relapsed disease? Would you recommend running tumor mutational analysis at every possible relapse?
- In Stage II colon cancer, should we routinely get initial postop ctDNA to decide on adjuvant therapy, including for historical high-risk populations (obstruction, LVI, perforation)? How often, if at all, should ctDNA be ordered for surveillance?

# Questions from General Medical Oncologists

- **69 yo woman with Stage IIA pT3N0 colon cancer. ctDNA was negative postop but turned positive at 3 months. Would you initiate adjuvant chemo?**
- **73 yo man with Stage IIIA CRC. How strongly would you push for adjuvant chemotherapy for pT2pN1 disease (1/23 nodes) with negative ctDNA? The patient consented to adjuvant CAPOX but is *very* reluctant.**
- **69 yo woman on chemo for Stage IV CRC. The patient requested to discontinue maintenance. How do you use ctDNA to de-escalate treatment?**

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# Questions from General Medical Oncologists

- I have a patient with resected Stage IV CRC (hepatectomy for an isolated liver met). What is the role of ctDNA in surveillance for this patient?
- 66 yo woman got adjuvant FOLFOX for Stage III cancer and during the first cycle developed cardiac arrest. Did not go back on treatment after that and is on surveillance with CEA, imaging and ctDNA. Would you treat based on positive ctDNA irrespective of imaging results?
- What is the utility of ctDNA in organ preservation/nonsurgical management of rectal cancer after TNT?

# Agenda

**Module 1:** Optimizing Biomarker Assessment for Patients with Colorectal Cancer (CRC) — Dr Dasari

**Module 2: Identification and Management of Metastatic CRC (mCRC) with a BRAF V600E Mutation — Dr Morris**

**Module 3:** Incorporation of Immune Checkpoint Inhibitors into the Management of MSI-H/dMMR CRC — Dr Seligmann

**Module 4:** Integration of Therapies Targeting HER2 into the Management of mCRC — Prof Van Cutsem

**Module 5:** Biomarker-Based Decision-Making for Patients with mCRC and KRAS G12C Mutations — Dr Lieu

THE UNIVERSITY OF TEXAS
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Making Cancer History®

# Identification and Management of Patients with mCRC and a *BRAF*$^{V600E}$ Mutation


**Van Morris, M.D.,**

**Associate Professor,**

**Department of Gastrointestinal Medical Oncology**

**1/24/2025**

# Talk Overview

- Review rationale supporting use of BRAF + EGFR blockade for patients with *BRAF*$^{V600E}$ metastatic CRC.

- Discuss breaking data justifying addition of BRAF + EGFR targeted therapies to chemotherapy for patients with *BRAF*$^{V600E}$ metastatic CRC.

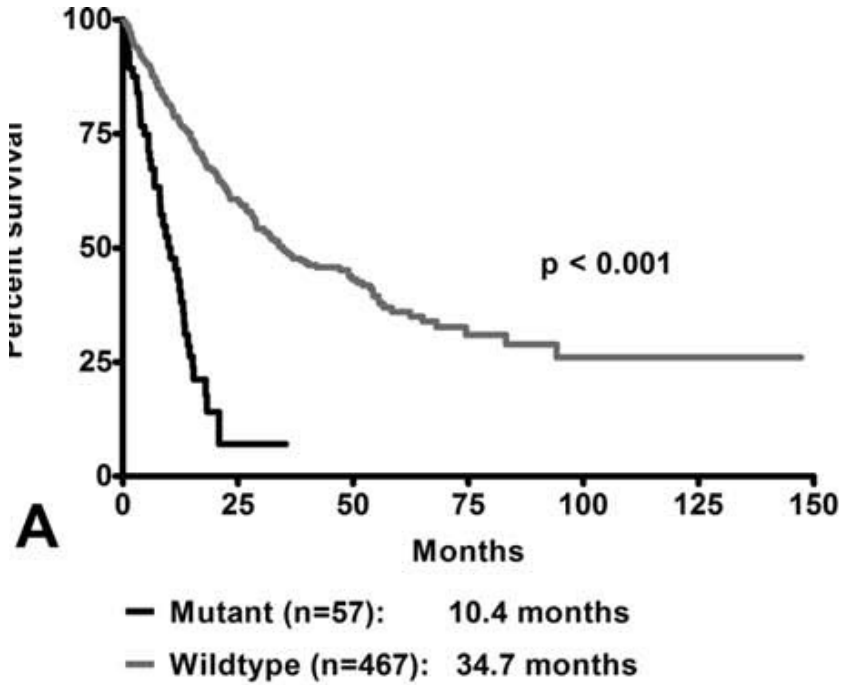
- Highlight promising therapies combining immunotherapy with MAPK blockade as treatment for *BRAF*$^{V600E}$ metastatic CRC.

# BRAF + EGFR blockade as rational therapy for *BRAF*$^{V600E}$ metastatic CRC

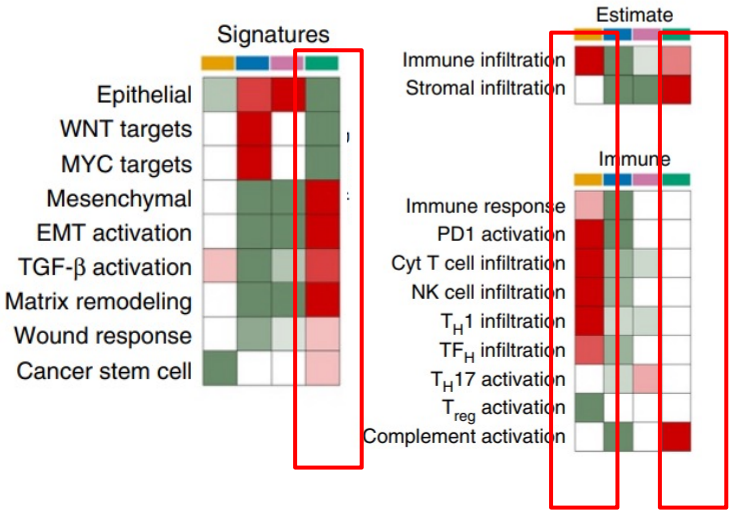
# Clinical and pathologic features important for *BRAF*$^{V600E}$ CRC

- …. with respect to clinical outcomes……
  - -- poor survival outcomes relative to *BRAF*$^{WT}$ pts
  - -- poor responses to systemic chemotherapy
- …. with respect to pathologic characteristics……
  - -- right colon tumors
  - -- T4 primary tumors
  - -- poorly differentiated, mucinous tumors
  - -- dMMR/MSI-H status (25%)
- …. with respect to genome……
  - -- RAS$^{WT}$ tumors
  - -- higher tumor mutation burden
- …. with respect to epigenome……
  - -- hypermethylation/CIMP-high
- …. with respect to transcriptome……
  - -- Consensus molecular subtype (CMS) 1 and 4

**Inferior survival relative to pts w/ *BRAF*$^{WT}$ CRC**

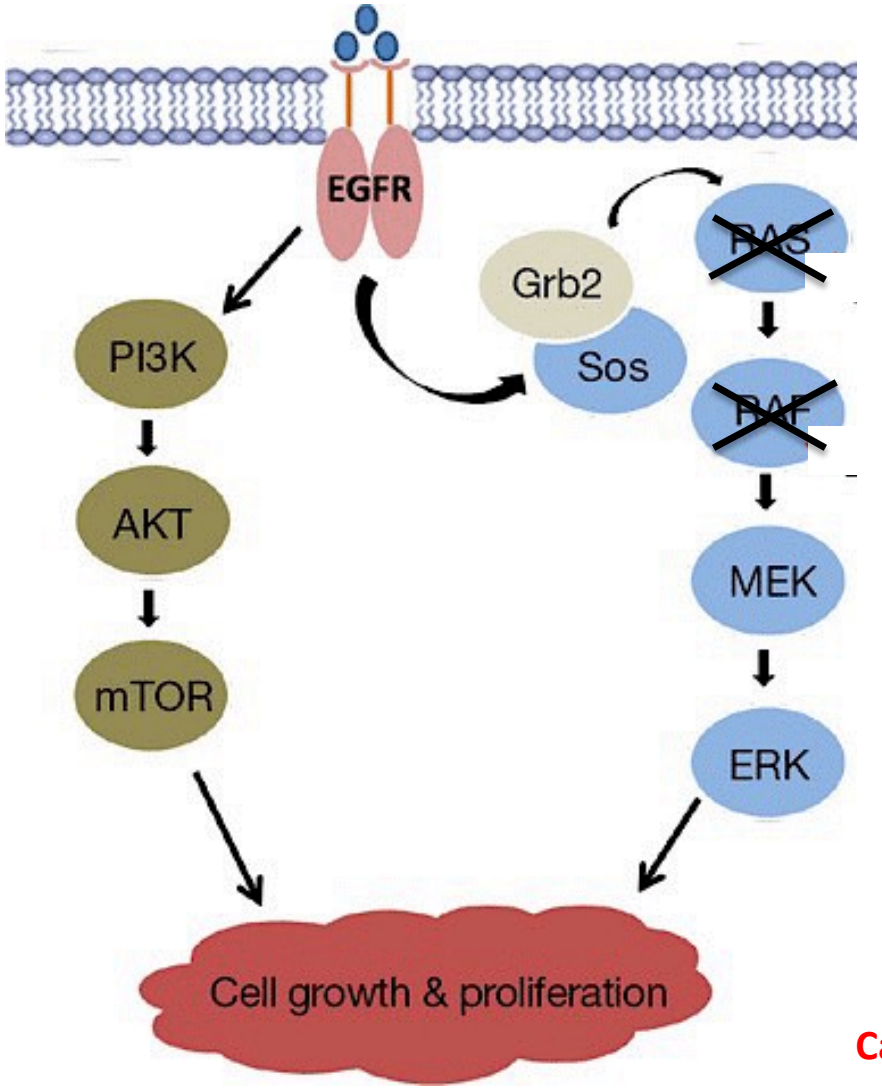



**Unique transcriptome signatures**




Tran et al Cancer 2011, Guinney et al Nat Med 2015

# $BRAF^{V600E}$ as a therapeutic target in clinical oncology



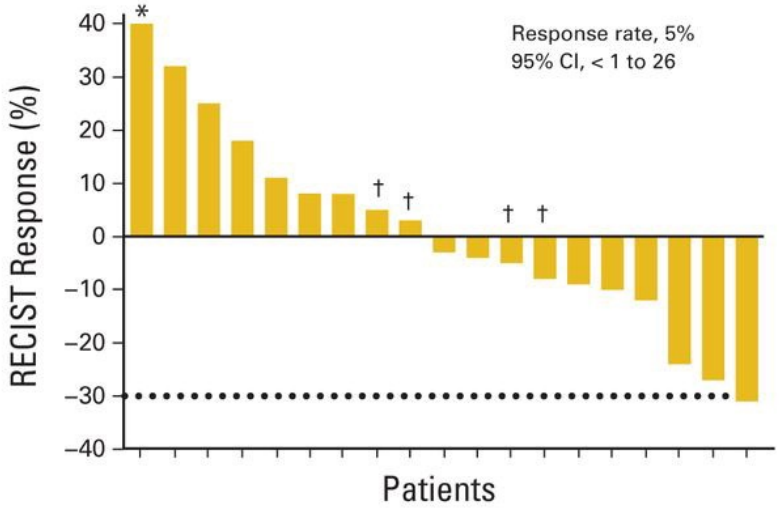

- *$BRAF^{V600E}$* mutations are present in 5-10% of patients with colorectal cancer.
- Activated BRAF perpetuates MAPK activity, leading to cell cycle progression and tumor cell proliferation.
- BRAF inhibitors have activity in metastatic
  - melanoma (RR 34-53%)
  - NSCLC (RR 42%)
  - papillary thyroid cancer (RR 29%)
  - refractory hairy cell leukemia (RR 85-100%)
- BRAF + MEK targeted therapies have activity in
  - metastatic melanoma (RR 64-69%)
  - metastatic NSCLC (RR 67%)

**Can we capitalize on this approach in *$BRAF^{V600E}$* metastatic colorectal cancer?**

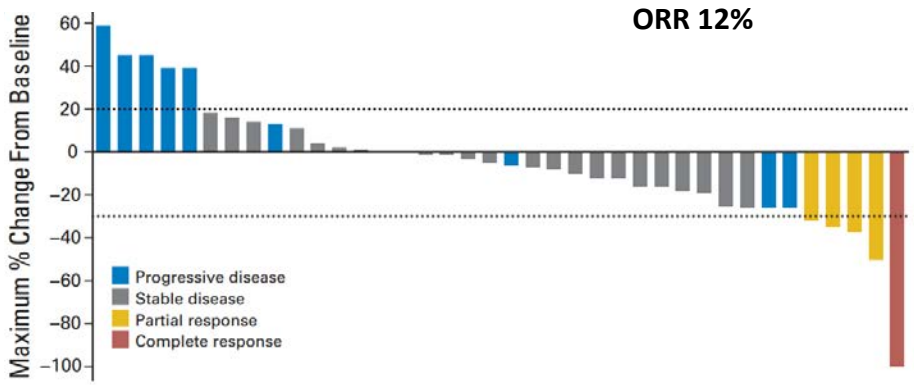
MacArthur et al, Lancet Oncol 2014; Ribas et al Lancet Oncol 2014; Falchook et al Thyroid 2015 Tiacci et al NEJM 2015; Hyman et al NEJM 2015; Gandara et al AILCC 2017

# BRAF +/- MEK inhibitors in *BRAF$^{V600E}$* metastatic CRC: an ineffective approach

**Vemurafenib**




**Dabrafenib + trametinib**

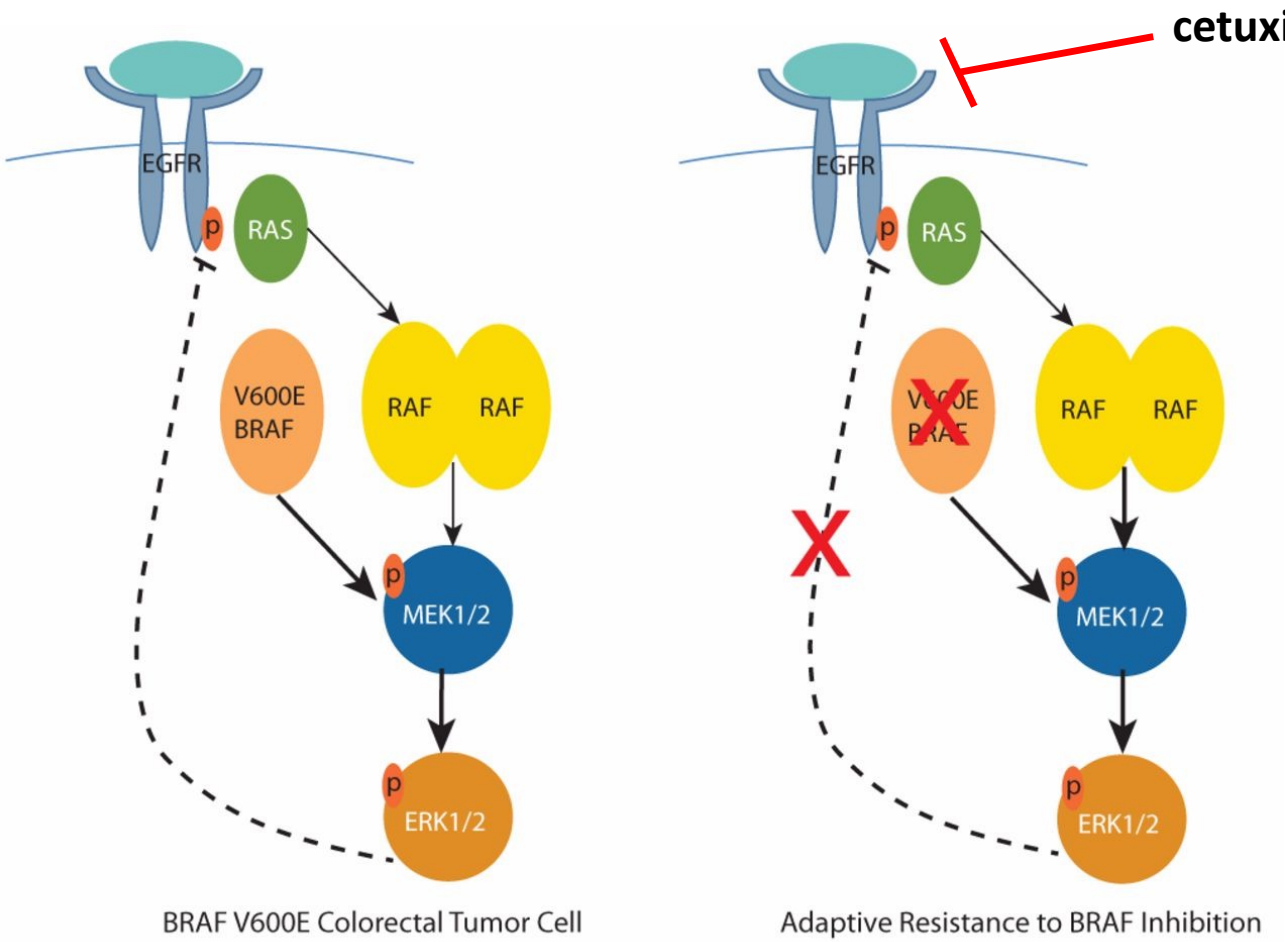



| | N | ORR (%) | mPFS (months) | mOS (months) |
|---|---|---|---|---|
| Vemurafenib | 21 | 5 | 2.1 | 7.7 |
| Dabrafenib | 11 | 11 | NA | NA |
| Encorafenib | 18 | 0 | 4 | NA |
| Dabrafenib + trametinib | 43 | 12 | 3.5 | NA |

**Why are treatment outcomes uniquely different for *BRAF$^{V600E}$* CRC?**

Kopetz S et al JCO 2015; Corcoran RB et al JCO 2015; Falchook GS et al 2012; Gomez-Roca CA et al Annals Oncol 2014

# BRAF inhibition results in EGFR upregulation in CRC



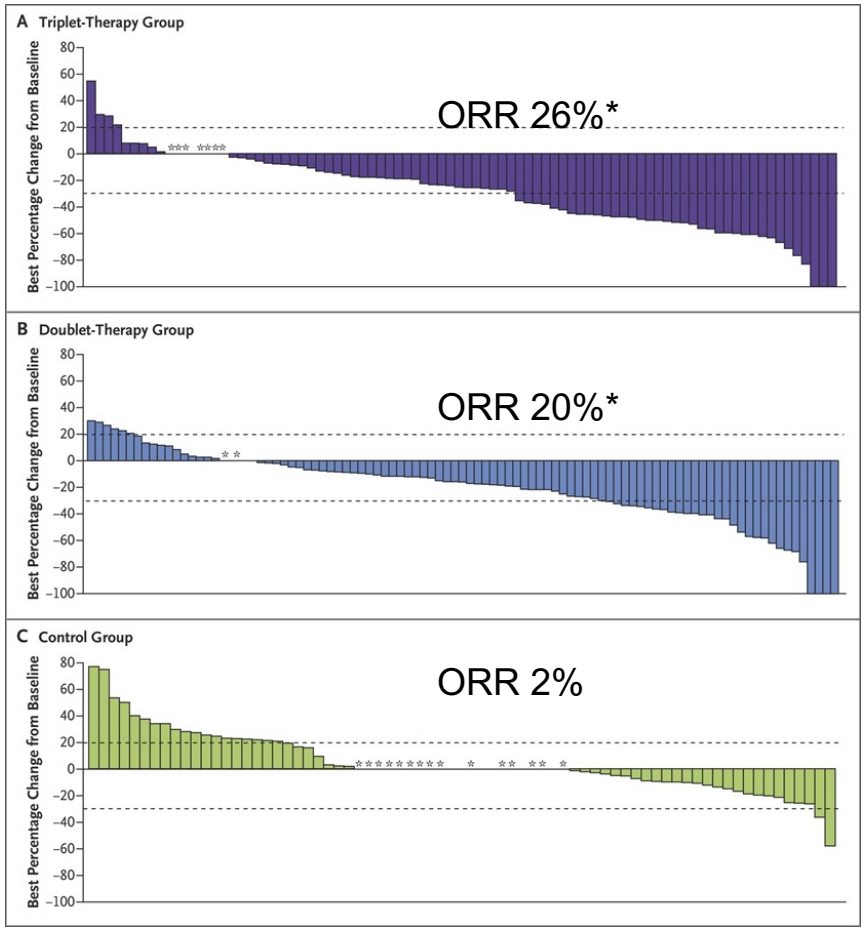

**Blocking BRAF$^{V600E}$ protein alone in CRC cells triggers EGFR activation… which also can be blocked!**

[1]Prahallad et al, Nature 2012. [2]Corcoran RB et el Cancer Discovery. [3]Tian F et al Clin Cancer Research 2012

# BEACON phase III: Improvement in ORR with MAPK-targeted therapies in treatment-refractory setting

**Treatment refractory, *BRAF*$^{V600E}$, *RAS*$^{WT}$ metastatic CRC**

- **Encorafenib + cetuximab + binimetinib**
- **Encorafenib + cetuximab**
- **Irinotecan + cetuximab**




*denotes statistical significance relative to control arm

N=665 (1:1:1 randomization)

Encorafenib 300 mg daily
Binimetinib 45 mg twice daily
Cetuximab 2500 mg/m$^2$ every week

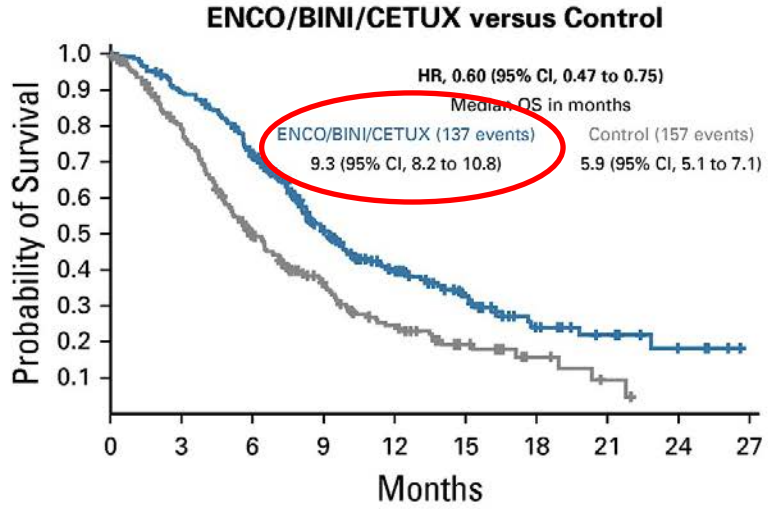
**Endpoints**:

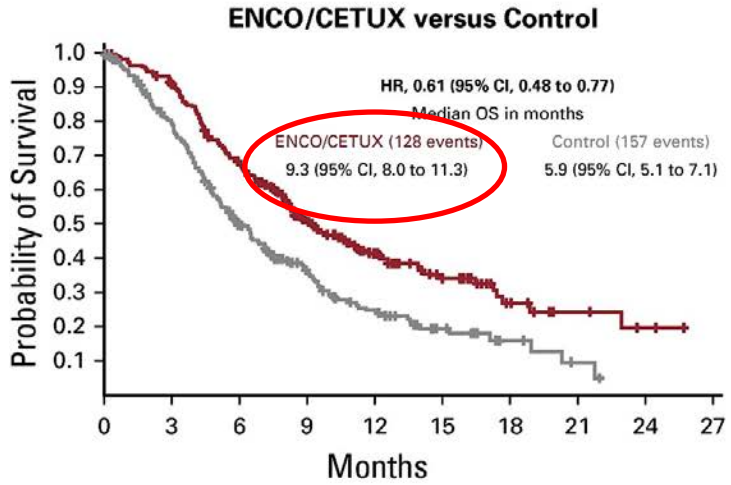
Primary: ORR, OS (triplet vs control)
Secondary: OS (doublet vs control, PFS, DoR, toxicity)

Kopetz S et al, NEJM 2019

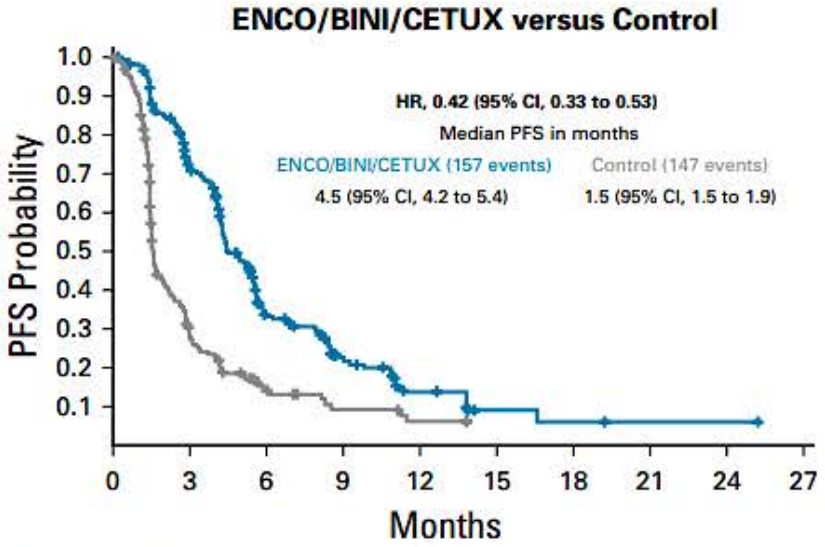
# Survival Outcomes (BEACON)

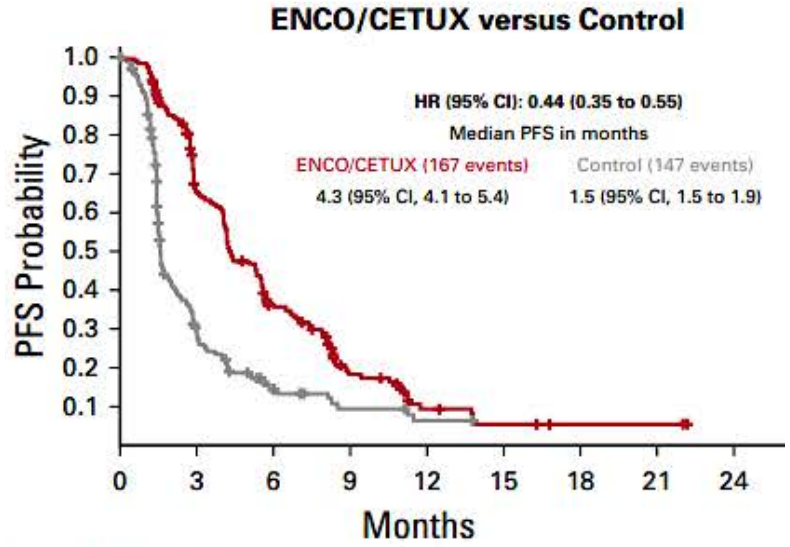
**Overall Survival**




**Progression-free Survival**



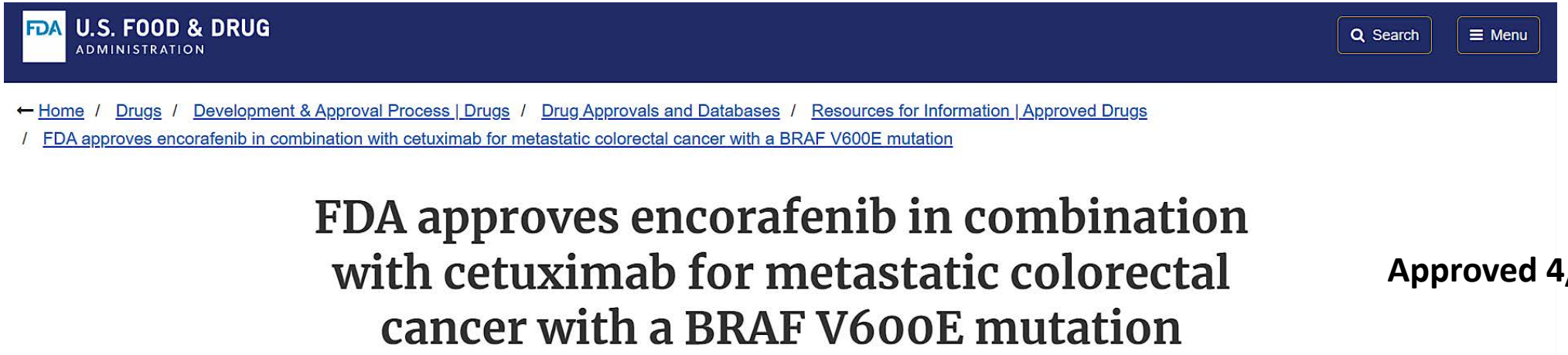

Kopetz S et al, NEJM 2019, Tabernero J et al JCO 2021

# BEACON: Lessons learned with first FDA approval!

For patients with treatment-refractory *BRAF*$^{V600E}$ metastatic CRC,

- Treatment with targeted therapies improves ORR and survival outcomes relative to standard chemotherapy options for metastatic CRC.

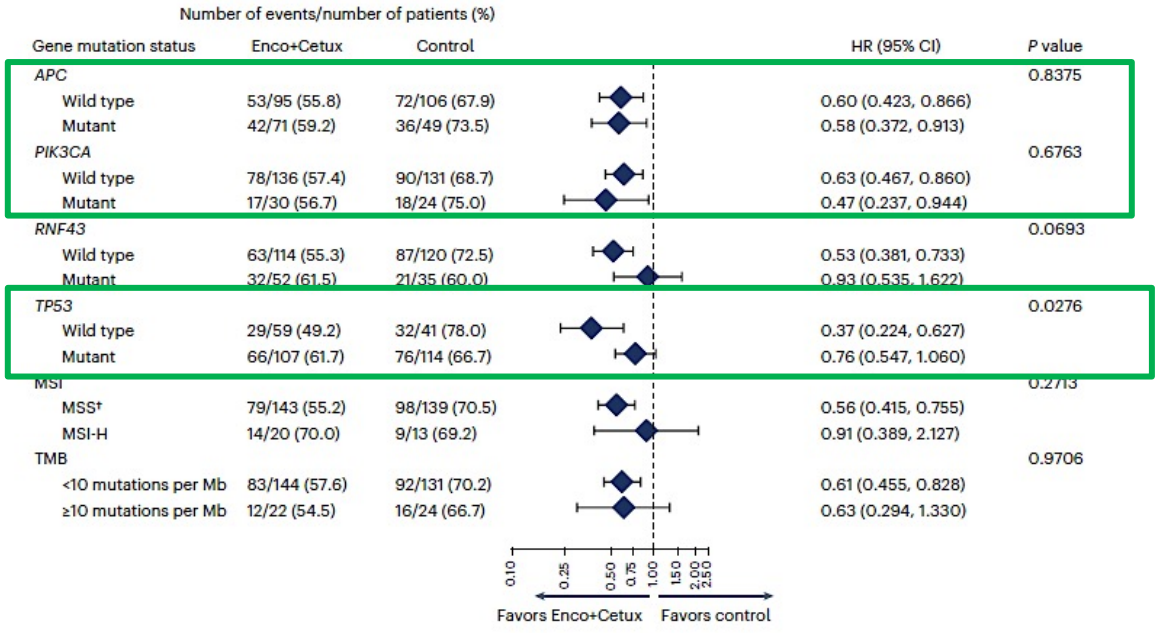
- The addition of a MEK inhibitor does not improve OS relative to encorafenib + cetuximab alone.



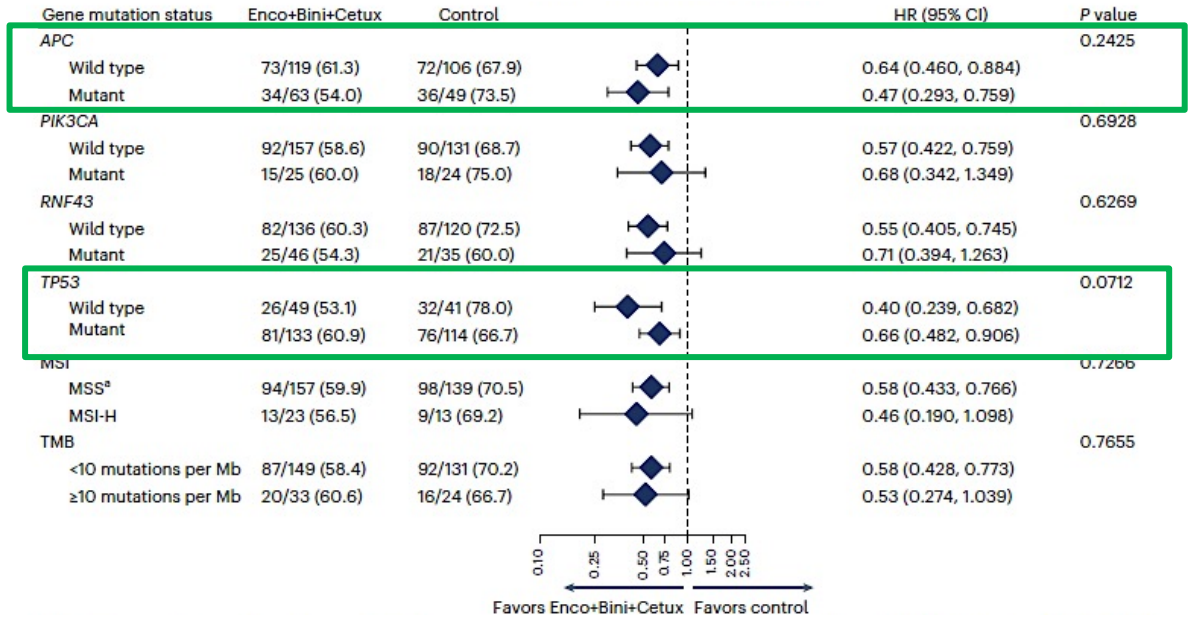

**Approved 4/2020**

# Genomic drivers associated with OS : BEACON

## BRAF + EGFR




## BRAF + EGFR + MEK




- **Wild-type *TP53* status is associated with benefit to encorafenib + cetuximab (trend with addition of binimetinib).**
- ***RNF43* mutation was not associated with benefit to BRAF + EGFR +/- MEK inhibition.**

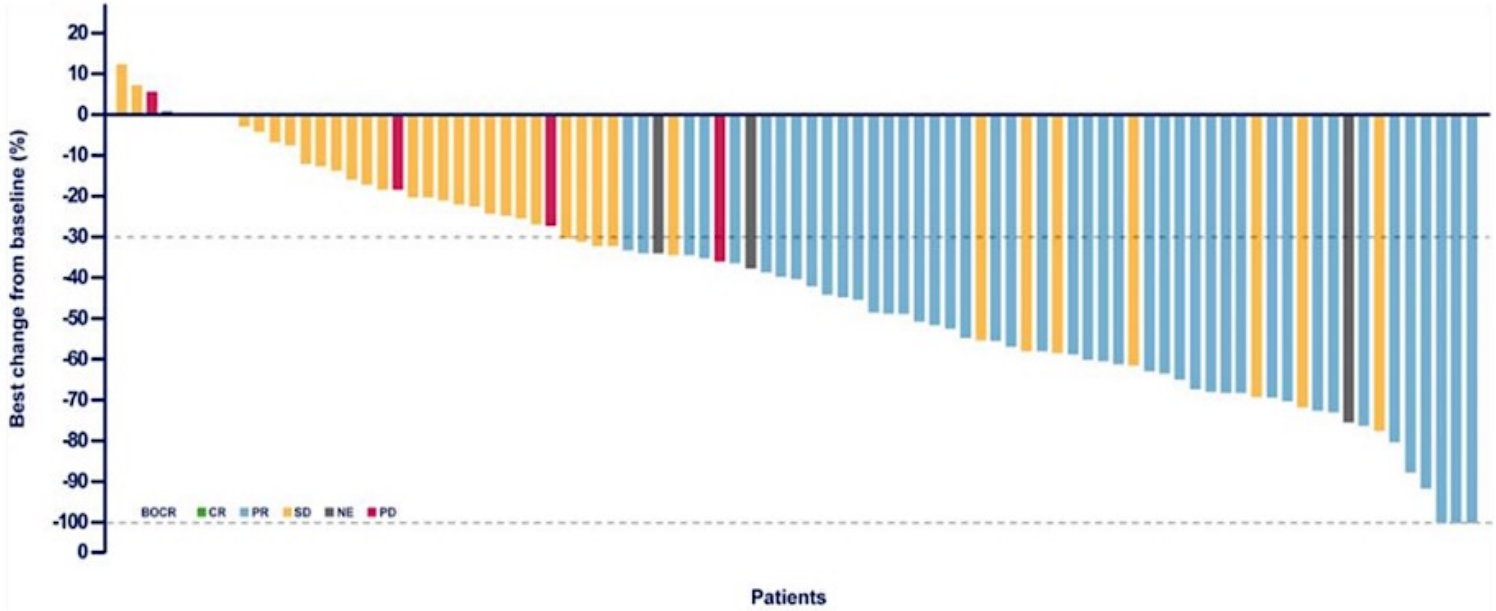
Kopetz S et al Nat Medicine 2024

# ANCHOR phase II trial: moving targeted therapies to the frontline setting for *BRAF*$^{V600E}$ metastatic CRC

- *BRAF*$^{V600E}$ metastatic CRC
- **No prior systemic therapy** for metastatic disease

→ Encorafenib + cetuximab+ binimetinib

**Primary endpoint: overall response**
**N=95**

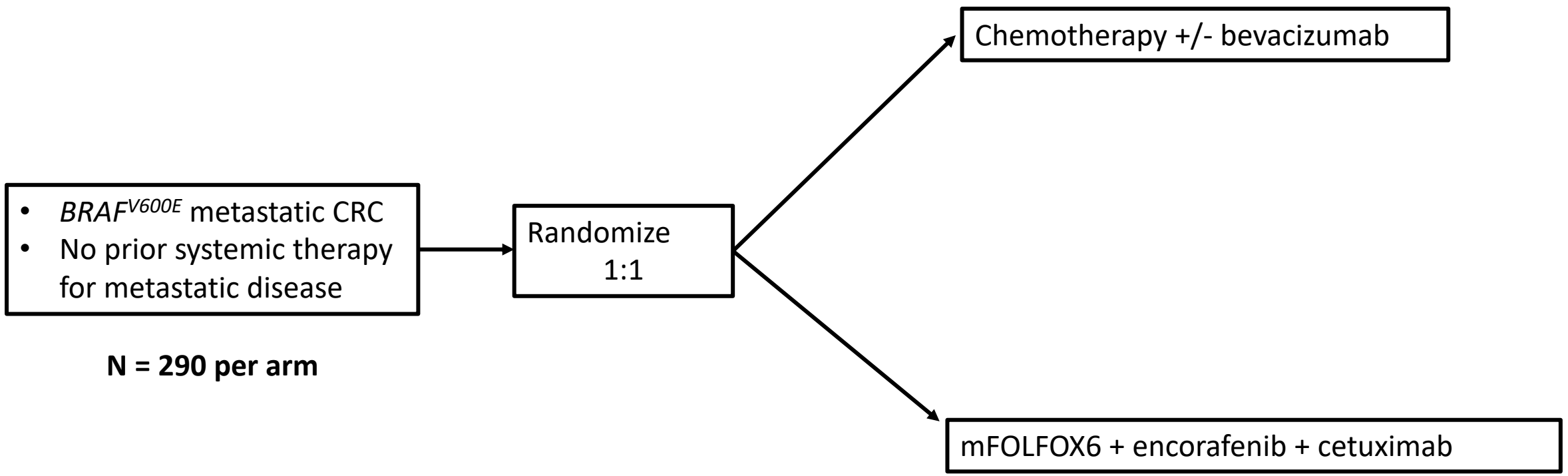



**ORR 48% (95% CI, 37-59)**
DCR 88%

Median DoR: 5.1 months (95% CI, 3.8-8.5)
Median PFS: 5.8 months (95% CI, 4.6-6.6)
Median OS: 18.1 months (95% CI, 14.1-21.1)

Van Cutsem E et al, JCO 2023

# BREAKWATER phase III trial: evaluating BRAF/EGFR blockade as frontline therapy for *BRAF*$^{V600E}$ metastatic CRC




**N = 290 per arm**

**NCT04607421**

# BREAKWATER phase III trial: POSITIVE study for untreated *BRAF*$^{V600E}$ metastatic CRC!!

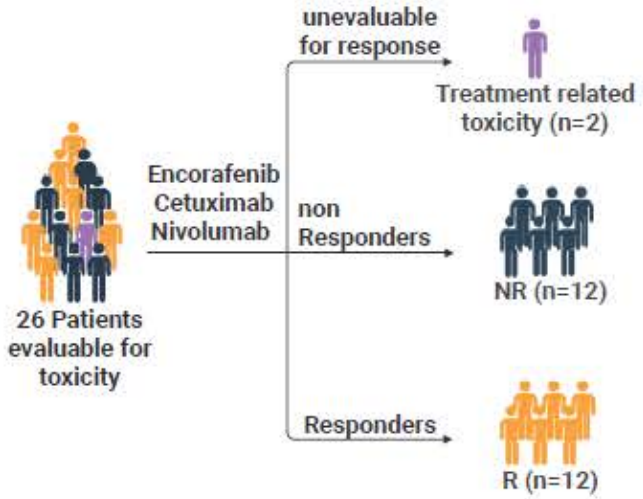
| | Chemotherapy +/- bevacizumab | mFOLFOX6 + encorafenib + cetuximab |
|---|---|---|
| **ORR** | **40%** | **61%** |
| **Duration of response** | **11.1 months** | **13.9 months** |

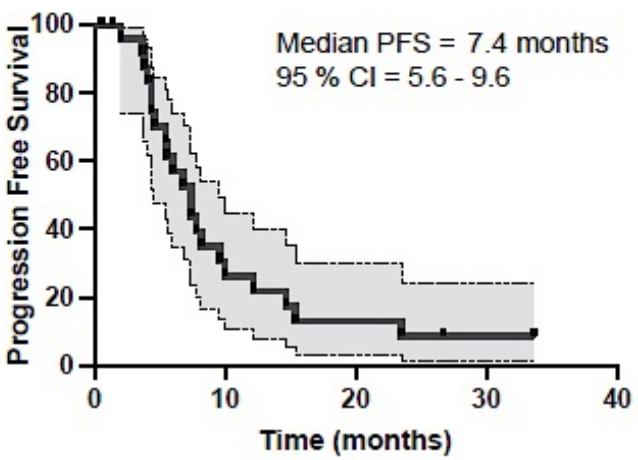

## FDA grants accelerated approval to encorafenib with cetuximab and mFOLFOX6 for metastatic colorectal cancer with a BRAF V600E mutation

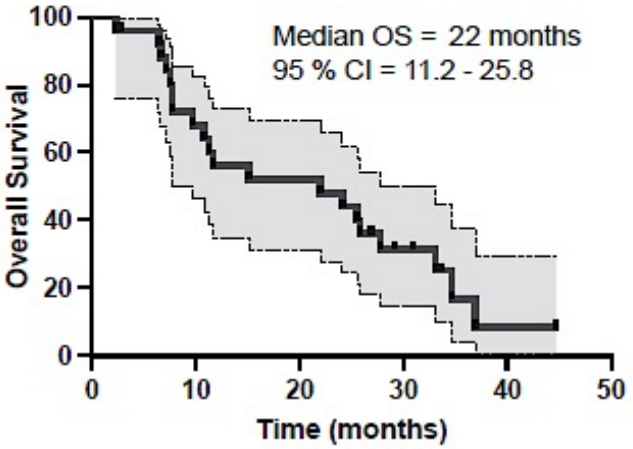
Kopetz S et al ASCO GI 2025

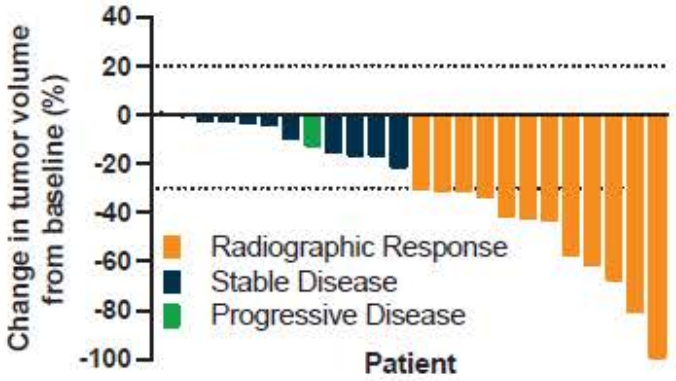
# Immunotherapy as treatment for *BRAF*$^{V600E}$ metastatic CRC

# Phase I/II trial of encorafenib, cetuximab, and nivolumab for MSS, *BRAF*$^{V600E}$ mCRC

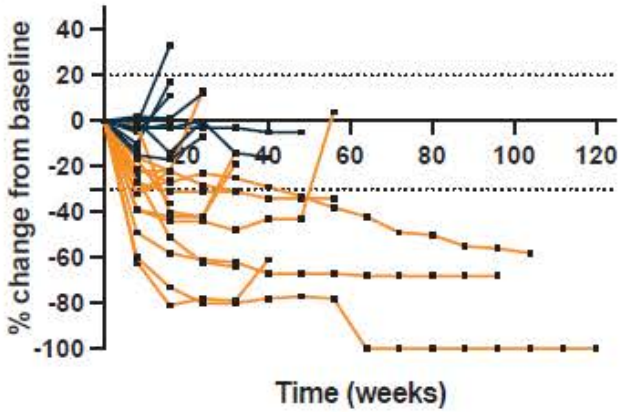


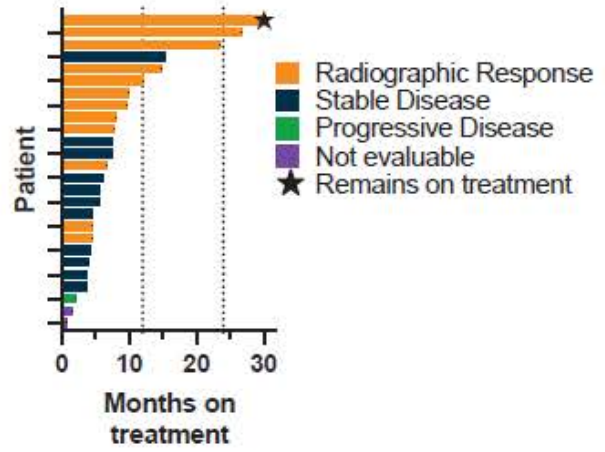



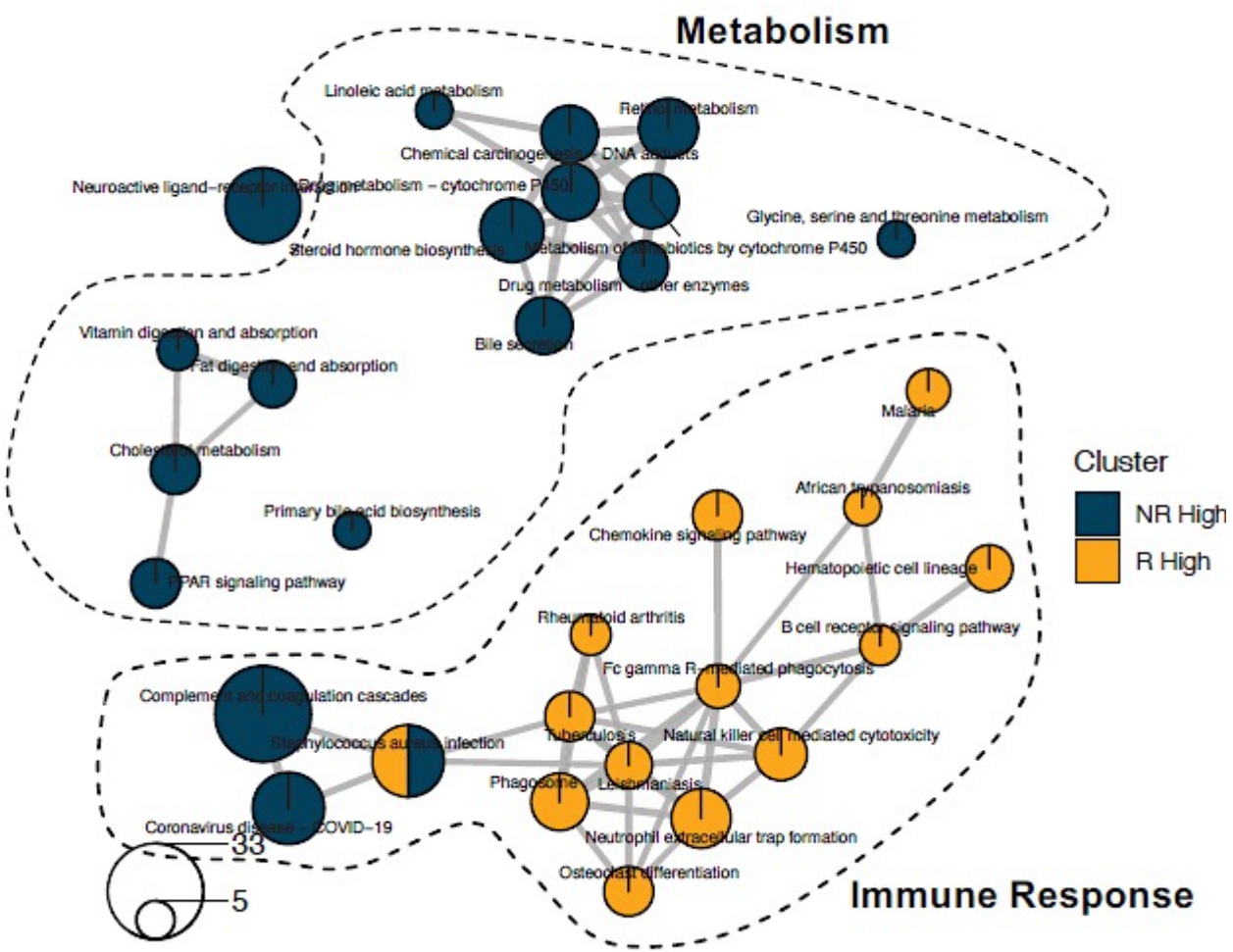

**ORR 50%**
**DCR 96%**

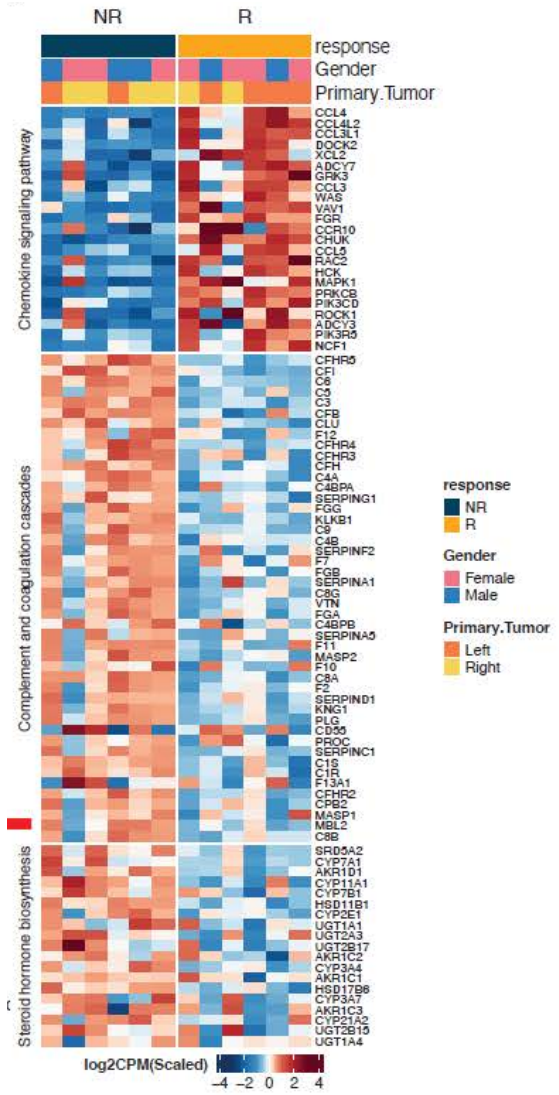



Morris VK et al,, submitted

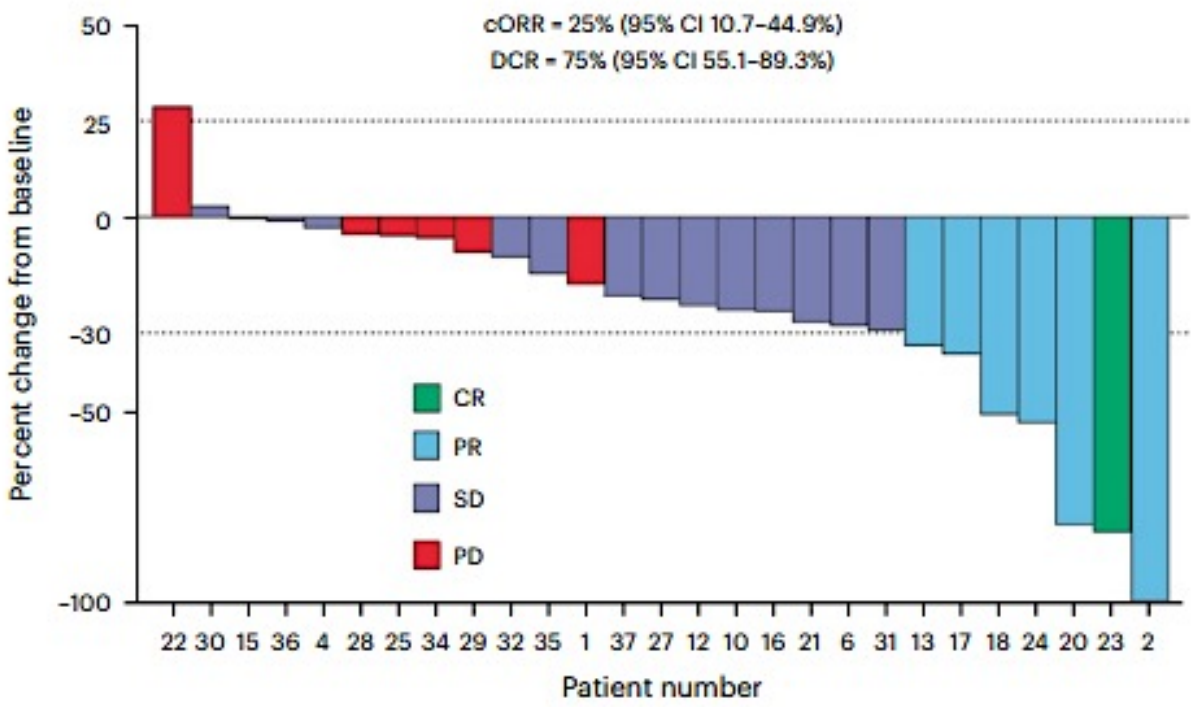
# Differential signatures noted from bulk RNA sequencing of encorafenib, cetuximab, and nivolumab

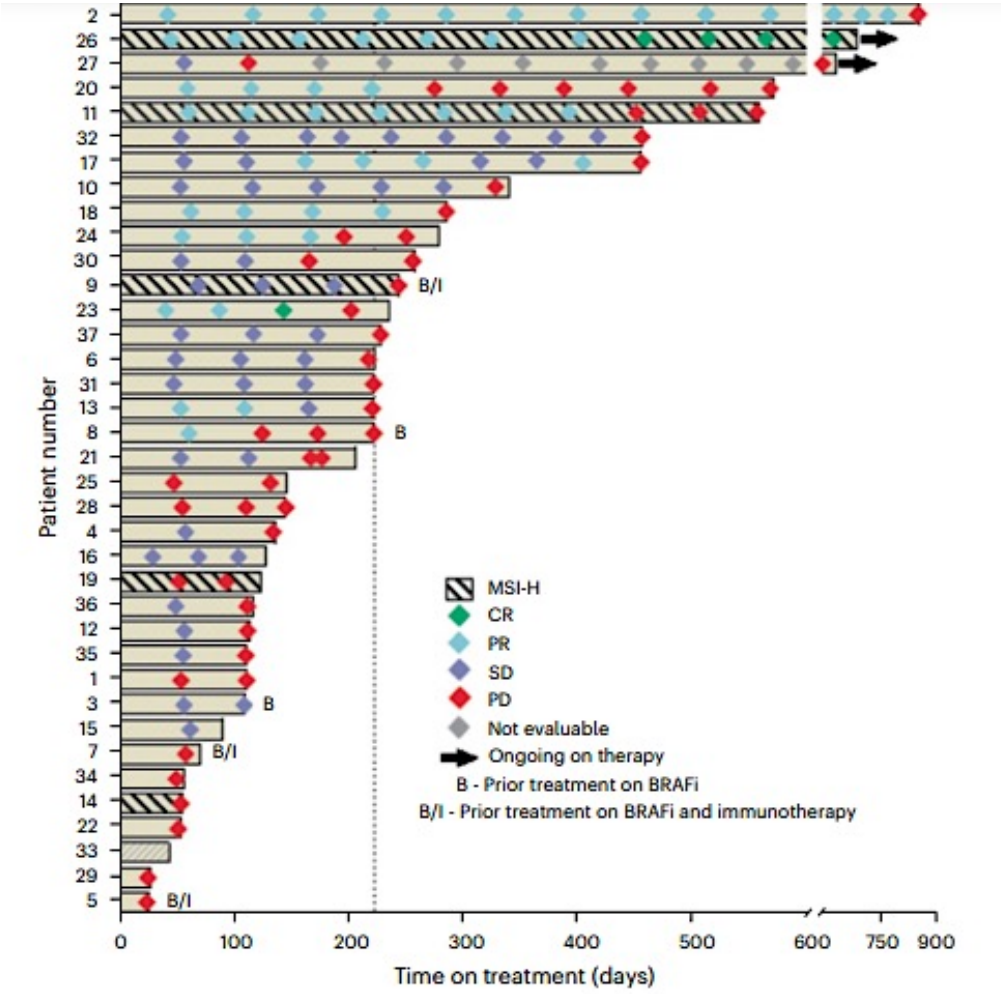



Morris VK et al,, submitted

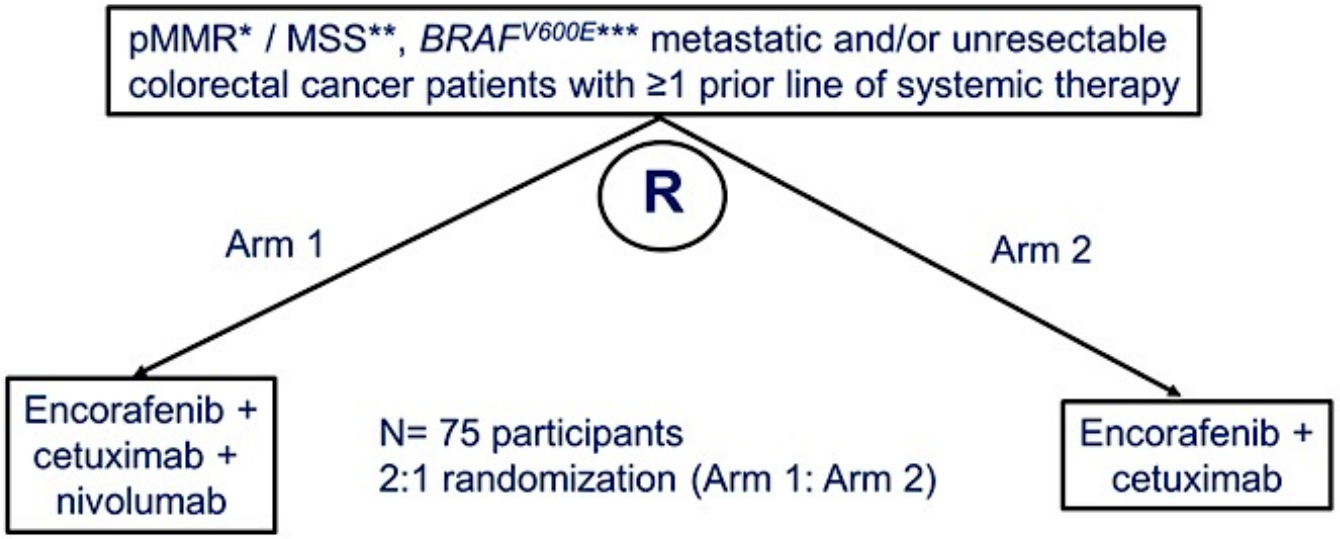
# Phase II trial of dabrafenib, trametinib, and spartalizumab for 2+ line, MSS, *BRAF*$^{V600E}$ mCRC




Tian J et al, Nat Med 2023

# S2107 study schema

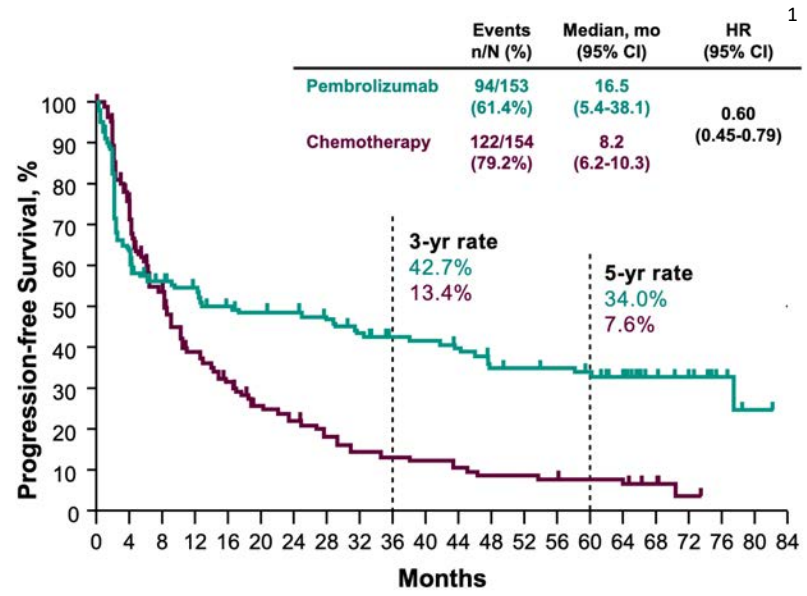



* Proficient mismatch repair (pMMR)
** Microsatellite stable (MSS)
*** An activating missense mutation in codon 600 of exon 15 *B-Raf* proto-oncogene (*BRAF*$^{V600E}$)

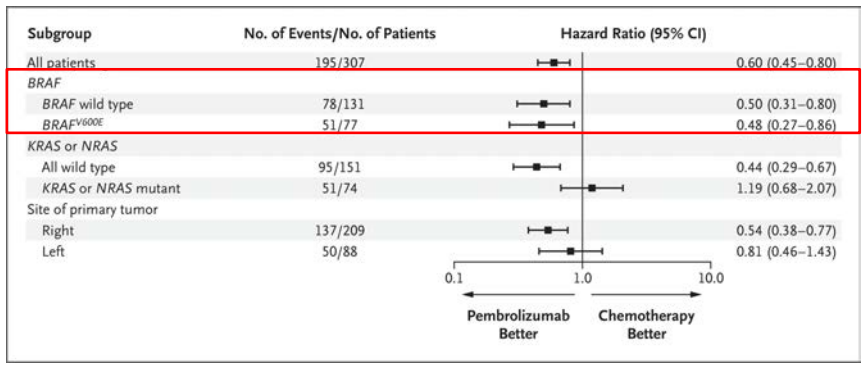
- **Study CNPE 10/1/2024**
- **N=88 patients randomized (84 planned); 1st interim review 9/2024 → primary readout 2025?**

# Immunotherapy for MSI-H/dMMR *BRAF*$^{V600E}$ metastatic CRC

## KEYNOTE-177
### Pembrolizumab vs chemotherapy




[1]




[2]

## CheckMate 8HW
### Nivolumab/ipilimumab vs chemotherapy

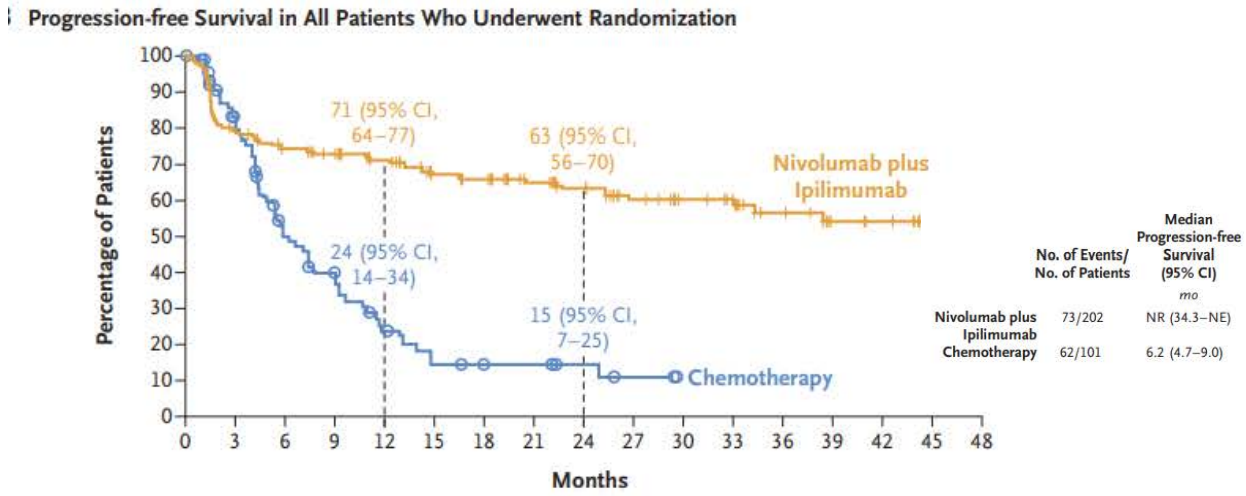
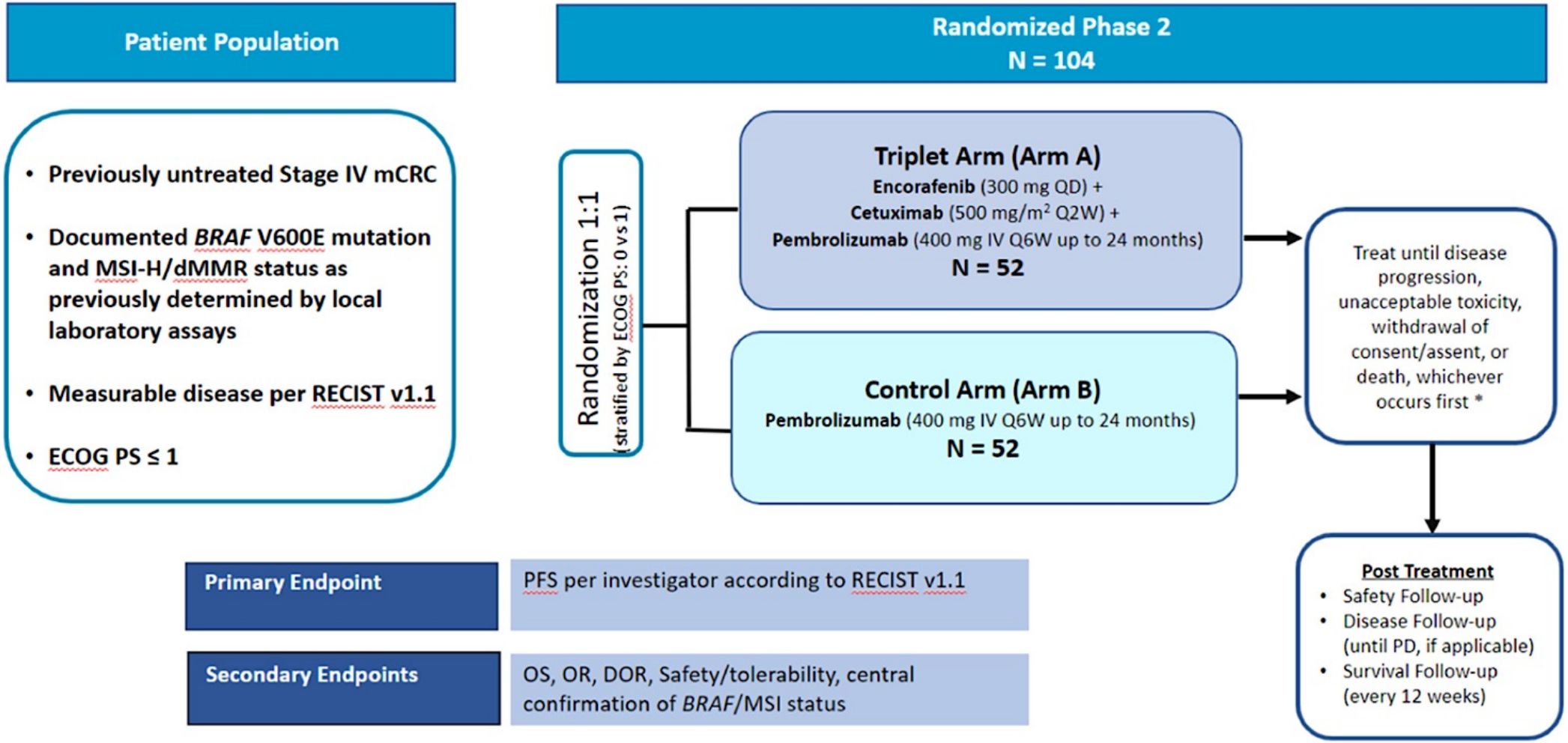



Table 2. Progression-free Survival by Blinded Review in Key Subgroups of Patients with Centrally Confirmed MSI-H or dMMR Metastatic Colorectal Cancer.

| Subgroup | Disease Progression or Death | | 12-Mo Progression-free Survival (95% CI)* | |
|---|---|---|---|---|
| | Nivolumab plus Ipilimumab | Chemotherapy | Nivolumab plus Ipilimumab | Chemotherapy |
| | *no. of events/no. of patients* | | *percentage of patients* | |
| Overall | 48/171 | 52/84 | 79 (72 to 84) | 21 (11 to 32) |
| *BRAF*, *KRAS*, and *NRAS* mutation status | | | | |
| *BRAF*, *KRAS*, and *NRAS* all wild type | 11/41 | 14/17 | 85 (70 to 93) | 0 |
| *BRAF* mutation | 16/50 | 11/22 | 73 (58 to 84) | 34 (12 to 59) |
| *KRAS* or *NRAS* mutation | 9/30 | 9/15 | 76 (56 to 88) | 29 (7 to 56) |
| Unknown | 10/46 | 16/28 | 84 (70 to 92) | 20 (5 to 41) |

[1]Shiu K et al, ESMO 2023; [2]Andre T et al, NEJM 2020; Andre T et al, NEJM 2024

# SEAMARK trial: bringing encorafenib/cetuximab for frontline therapy of MSI-H/dMMR, BRAF$^{V600E}$ mCRC?

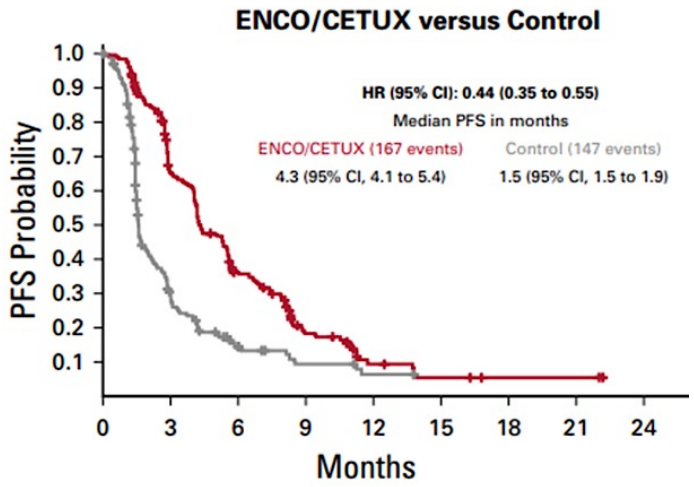



**Study accrual completed 2024.**

NCT05217446

# Emerging clinical considerations for treatment-refractory *BRAF*$^{V600E}$ metastatic CRC

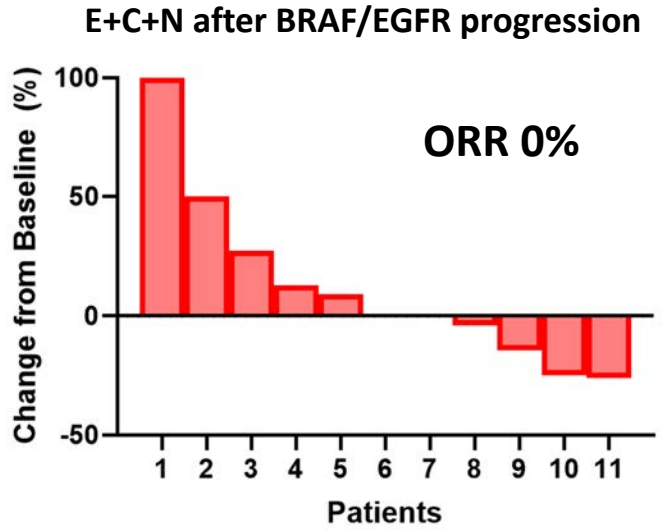
**"I didn't find out about my patient's *BRAF*$^{V600E}$ mutation until they had progressed on FOLFIRI/bevacizumab. Can I use the BREAKWATER regimen of FOLFOX + encorafenib + cetuximab as 2nd line treatment?"**




**NO**

Chemotherapy is not effective in 2nd line+ setting for *BRAF*$^{V600E}$ metastatic CRC. I would recommend encorafenib + cetuximab alone (BEACON).

**"My patient with *BRAF*$^{V600E}$ metastatic CRC has just progressed on encorafenib + cetuximab as 2nd line treatment. Can I just add PD-1 therapy given recent phase II data and keep treating?"**




**NO**

Encorafenib + cetuximab + nivolumab is not effective for *BRAF*$^{V600E}$ metastatic CRC after progression on BRAF + EGFR therapies.

Kopetz et al, NEJM 2019; Pan K et al, ASCO GI 2025

# Conclusions

- For **frontline** therapy of MSS, *BRAF*$^{V600E}$ metastatic colorectal cancer,
  - Addition of encorafenib + cetuximab to mFOLFOX6 numerically improves survival relative to chemotherapy + bevacizumab and is now FDA-approved (BREAKWATER)
  - For patients unable to tolerate chemotherapy, encorafenib + cetuximab + binimetinib has shown promising activity (ANCHOR).

- For **treatment-refractory** therapy of MSS, *BRAF*$^{V600E}$ metastatic colorectal cancer,
  - Encorafenib + cetuximab is FDA-approved for patients with no prior exposure to BRAF+EGFR targeted therapies (BEACON).
  - Early-phase studies show promise of anti-PD-1 therapies to MAPK blockade and are being evaluated in larger studies.

- For **frontline therapy** of MSI-H/dMMR, *BRAF*$^{V600E}$ metastatic colorectal cancer,
  - Pembrolizumab or nivolumab/ipilimumab are effective even when a BRAFV600E mutation is present (KEYNOTE-177; CheckMate 8HW)
  - We are awaiting to see if adding BRAF+EGFR blockade improves survival relative to immunotherapy alone.

- All major advances for this poor prognostic population of patients with metastatic CRC has come from robust clinical trial enrollment, **thanks to the brave patients willing to participate in these clinical trials**.

# Questions from General Medical Oncologists

- In a BRAF mutation-positive mCRC, should we now start with FOLFOX plus encorafenib/cetuximab for everyone, or are there still patients for whom we should start with FOLFIRINOX plus bev and then encorafenib/cetuximab on relapse?
- 65 yo woman with metastatic colon cancer (de novo) with liver mets. She has MSI-H disease and a BRAF V600E mutation. She progressed on first-line pembrolizumab. What would you recommend now — BREAKWATER regimen or encorafenib/cetuximab?

# Questions from General Medical Oncologists

- **Would encorafenib/cetuximab be acceptable as a first-line systemic therapy approach for a 70 y/o man who has had FOLFOX previously for Stage III colon cancer (12 months ago) and has residual neuropathy from that therapy and wishes to avoid 5-FU again?**
- **Can encorafenib/cetuximab be combined with other up-front chemotherapy regimens if a patient isn't a good candidate for FOLFOX?**
- **Some patients respond well to BRAF-targeted therapy and others go right through it. Any clue how to determine who will and who won't respond?**

# Questions from General Medical Oncologists

- If a patient progresses on first-line mFOLFOX6/cetuximab/ encorafenib, what's the optimal second-line therapy?
- 64 yo man with BRAF V600F-positive mCRC. What is the role of BRAF inhibitors for non-V600E mutations?
- 90 yo woman with Stage IV, BRAF V600E-mutated, right-sided colon cancer. What is the QoL data with BRAF-targeted agents in the very elderly?
- Is there data on adjuvant BRAF inhibitors in early-stage colon cancer?

RTP RESEARCH TO PRACTICE

# Agenda

**Module 1:** Optimizing Biomarker Assessment for Patients with Colorectal Cancer (CRC) — Dr Dasari

**Module 2:** Identification and Management of Metastatic CRC (mCRC) with a BRAF V600E Mutation — Dr Morris

**Module 3: Incorporation of Immune Checkpoint Inhibitors into the Management of MSI-H/dMMR CRC — Dr Seligmann**

**Module 4:** Integration of Therapies Targeting HER2 into the Management of mCRC — Prof Van Cutsem

**Module 5:** Biomarker-Based Decision-Making for Patients with mCRC and KRAS G12C Mutations — Dr Lieu

RTP RESEARCH TO PRACTICE

# Incorporation of Immune Checkpoint Inhibitors into the Management of MSI-High (MSI-H)/dMMR CRC

Jenny Seligmann

Professor of Gastrointestinal Cancer

University of Leeds, UK

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# Agenda

- Microsatellite-High (MSI-H)/ deficient mismatch repair (dMMR) colorectal cancer – why are they different?
- Locally advanced rectal and colon cancer
  - Implications of MSI-H status and opportunities for immuno-oncology
- Metastatic colorectal cancer
  - Implications of MSI-H status and opportunities for immuno-oncology
- Future development

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# MSI-H/ dMMR Colorectal Cancer

- Characterised by high tumor mutation burden & increased immunogenicity
  - Germline mutation (eg. Lynch Syndrome)
  - Somatic inactivation (eg. mutation in MLH1 gene)
- NCCN/ ESMO Guidelines advocate testing on all CRC tumours
- Testing usually by immunohistochemistry or by panel testing

**Stage II**

- Prevalence of 20% of CRC
- Mainly infiltrated by activated T-cells (CD8+/Th1)
- Excellent prognosis – better than MSS

**Stage III**

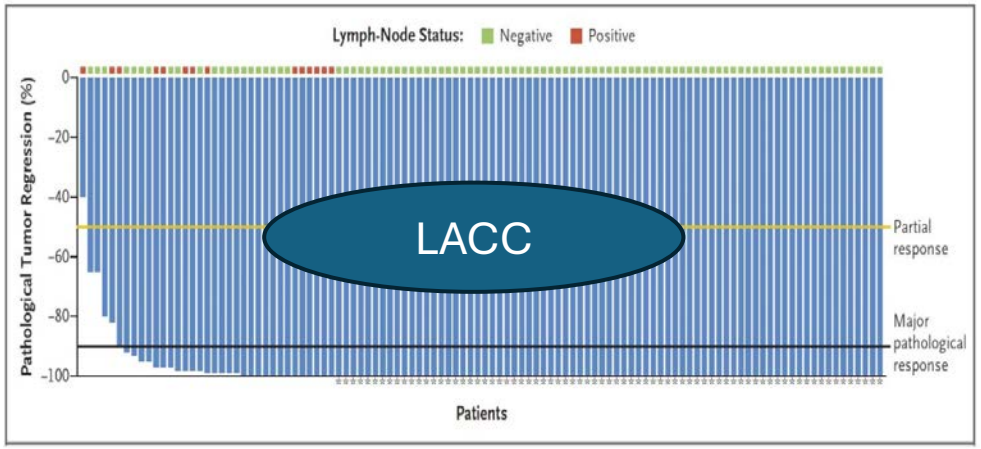
- Prevalence of 15% of CRC
- Infiltrated by T-cells & lymphocytes plus expression of immune checkpoints
- Prognosis similar to MSS

**Stage IV**

- Prevalence of 5% of CRC
- Expression of checkpoint molecules & immune inhibitory molecules lead to anti-tumoral immunity
- Prognosis worse than MSS

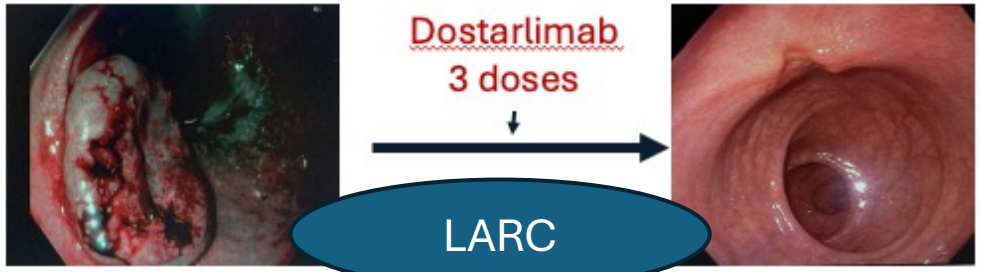
*Marisa L. et al.* The Balance Between Cytotoxic T-cell Lymphocytes and Immune Checkpoint Expression in the Prognosis of Colon Tumors. *J Natl Cancer Inst* (2018) 110(1) Pages F, Lancet 2018; Yoon HH and Sinicrope F, Clin Cancer Research, 2019

# ICIs in the Management of MSI CRC: Paradigm Changes

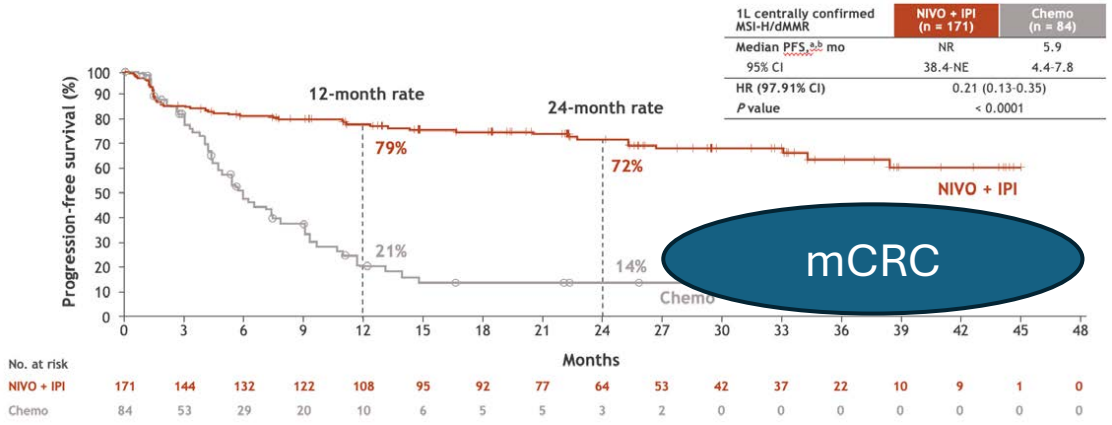



LACC

What are the implications for routine clinical practice in 2025?




LARC




mCRC

Chalabi, Nature Med, 2022; Cercek, NEJM, 2022 ; Andre, NEJM, 2024

# Accumulating evidence for ICI MSI-H LARC

ORIGINAL ARTICLE

## PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.

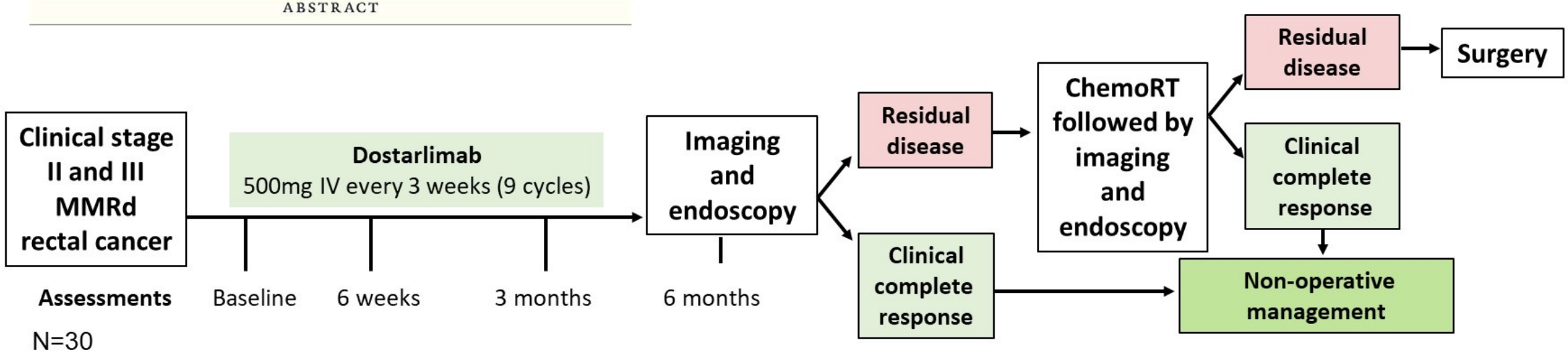
ABSTRACT

**Primary Objectives**

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

**Secondary Objectives**

- Safety and tolerability

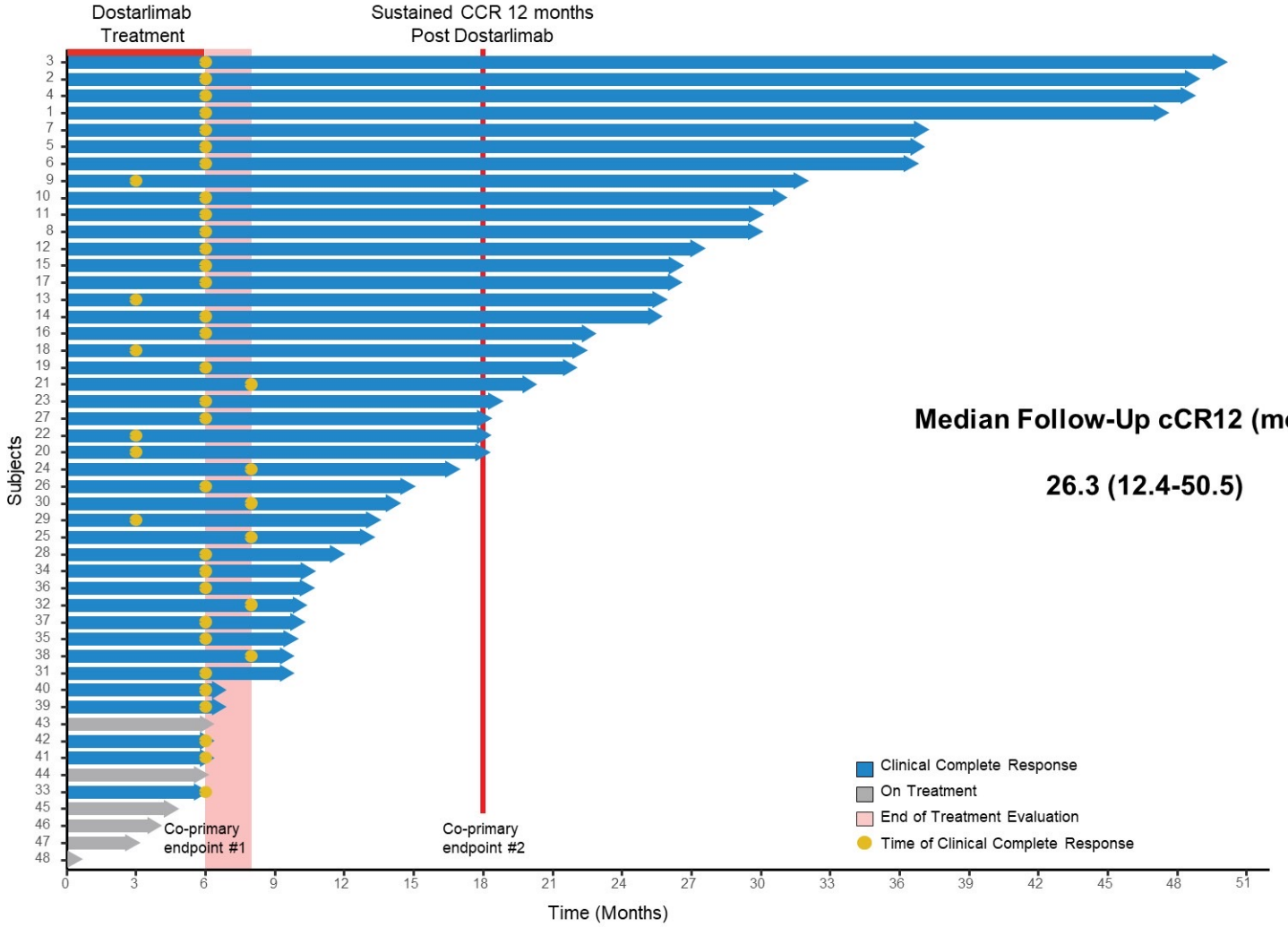



N=30

Simon's two stage minimax

Cercek et al. NEJM 2022

# Accumulating evidence for ICI MSI-H LARC




**Median Follow-Up cCR12 (months):**

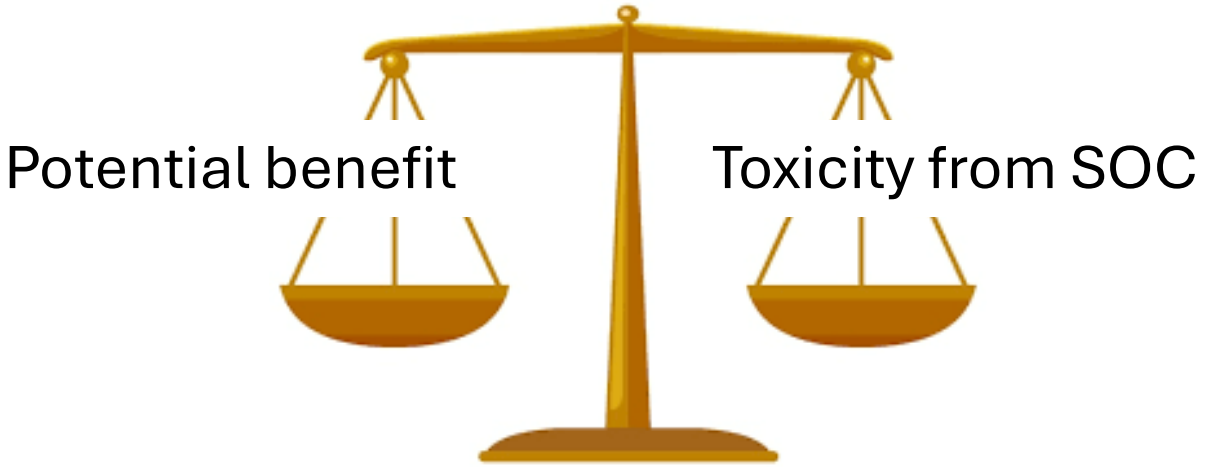
**26.3 (12.4-50.5)**


Cercek, ASCO Annual Meeting, 2024

# Does this data merit practice change?

Limitations of current data:

- Relatively small numbers
- Lack of long term follow up
- Lack of generalizability
- Lack of randomization to current SOC




NCCN guidelines Version 5.2024

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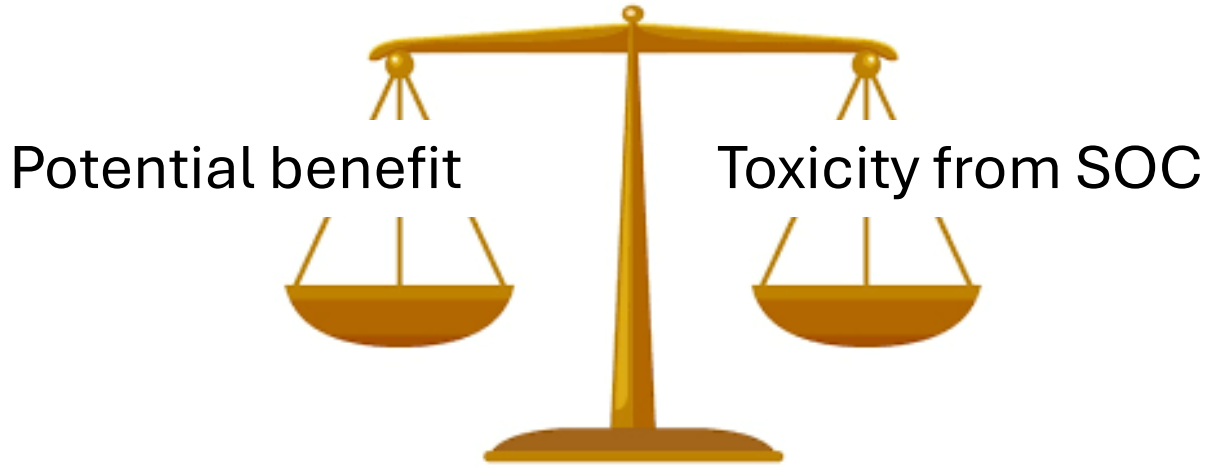
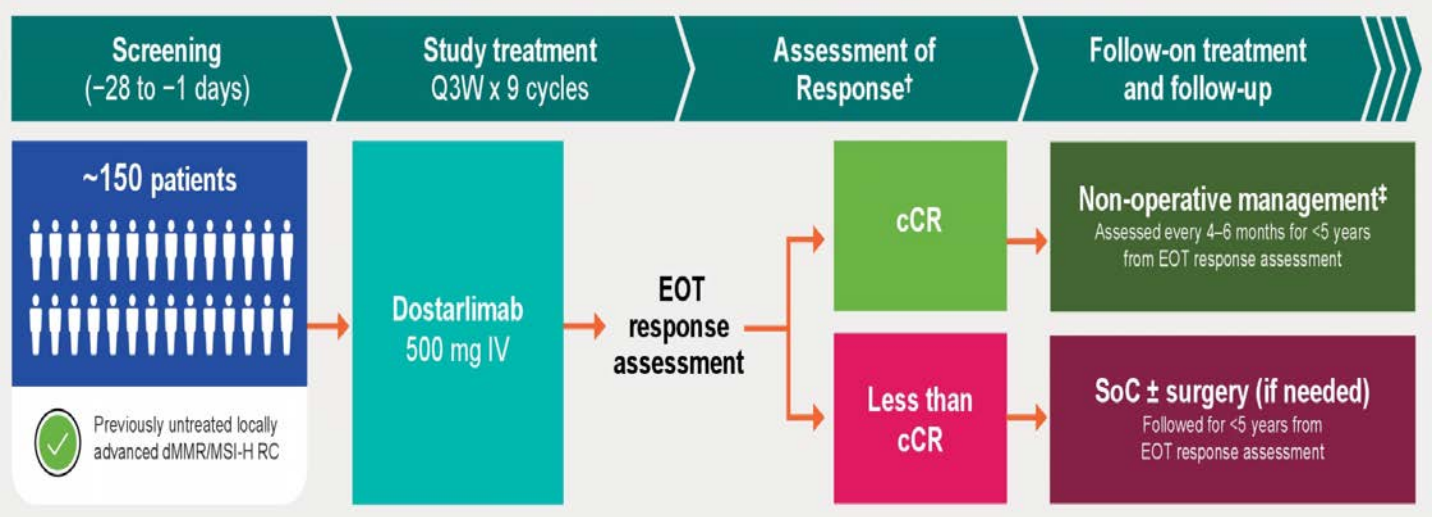



- Global confirmatory study ongoing (AZUR 1)
  - Phase II, single-arm, open-label study of dostarlimab in stage II/III dMMR rectal cancer
- FDA granted breakthrough therapy designation for dostarlimab, following fast-track designation




NCCN guidelines Version 5.2024

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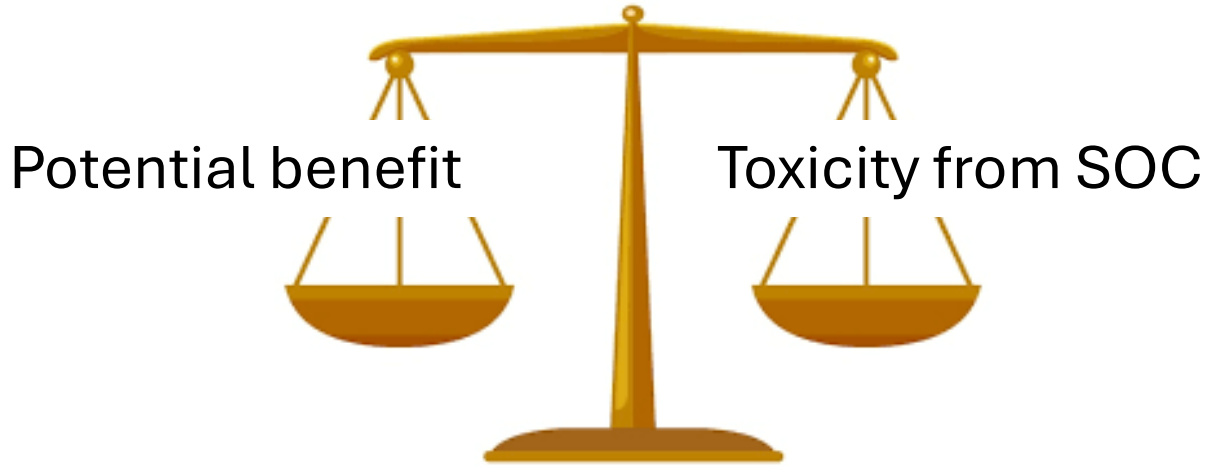


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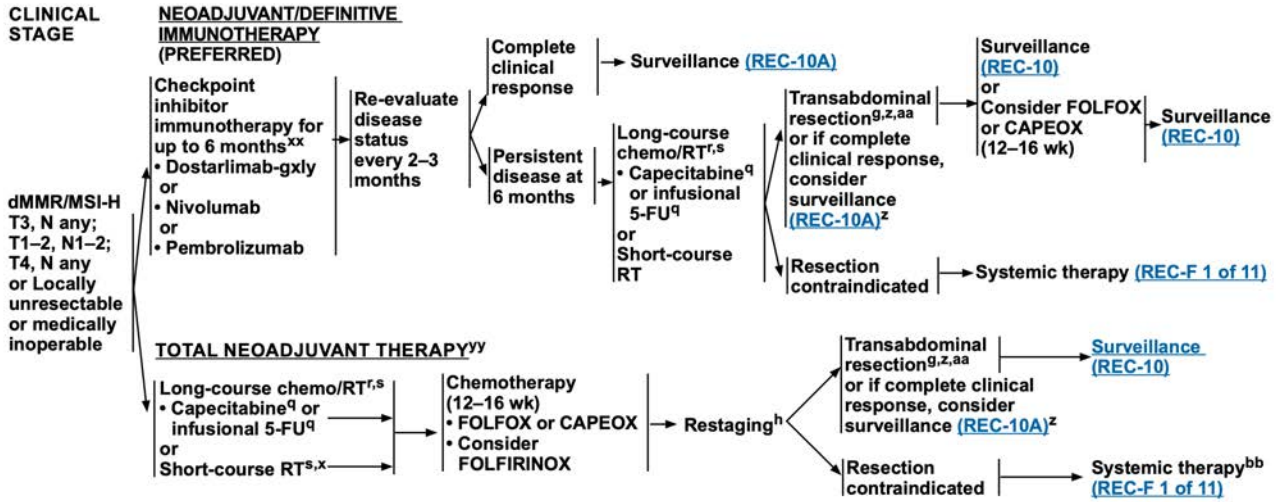


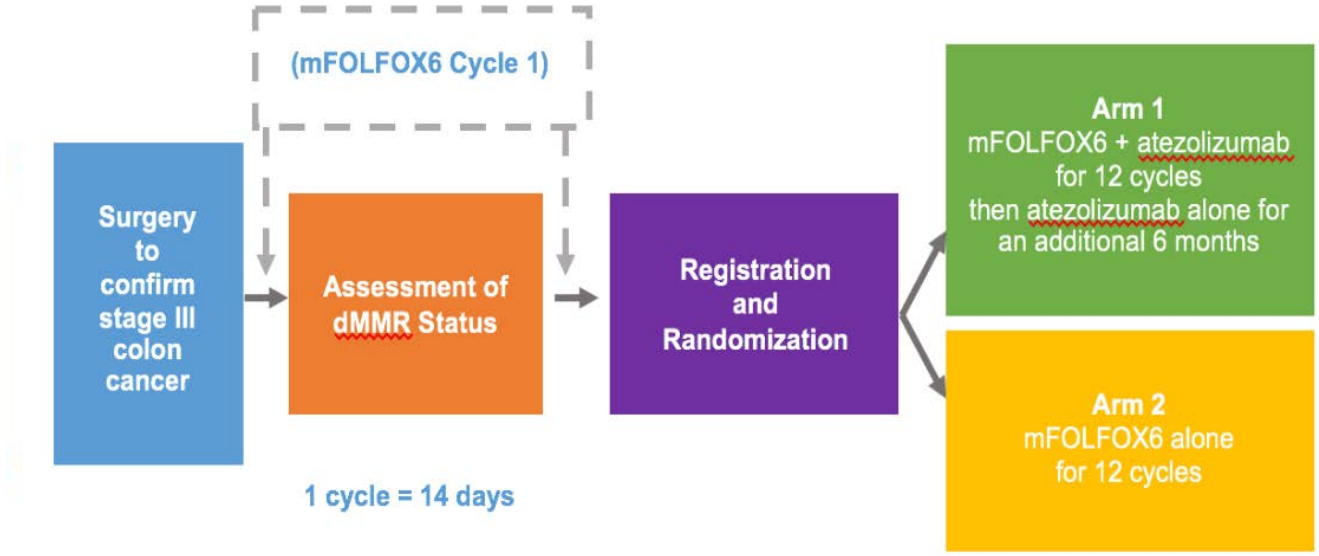

NCCN guidelines Version 5.2024

# Accumulating evidence for ICI in MSI-H LACC

**Stage II Standard of Care:**
Surgical resection then observation

**Stage III Standard of Care:**
Surgical resection then adjuvant OxFp

Atomic Trial: NCT 02912559




Sinicrope, ASCO GI 2019

ORIGINAL ARTICLE

**Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair–Deficient Colon Cancer**

Authors: Myriam Chalabi, M.D., Ph.D., Yara L. Verschoor, M.D., Pedro Batista Tan, M.Sc., Sara Balduzzi, Ph.D., Anja U. Van Lent, M.D., Ph.D., Cecile Grootscholten, M.D., Ph.D., Simone Dokter, M.Sc., +16, and John B. Haanen, M.D., Ph.D. Author Info & Affiliations

Meeting Abstract: 2024 ASCO Annual Meeting I
FREE ACCESS | Gastrointestinal Cancer—Colorectal and Anal | May 29, 2024

**Neoadjuvant treatment of IBI310 (anti-CTLA-4 antibody) plus sintilimab (anti-PD-1 antibody) in patients with microsatellite instability-high/mismatch repair-deficient colorectal cancer: Results from a randomized, open-labeled, phase Ib study.**

Authors: Rui-Hua Xu, Feng Wang, Gong Chen, Meng Qiu, Jinfeng Ma, Haiyi Liu, Xianwei Mo, ... SHOW ALL ..., and Hui Zhou AUTHORS INFO & AFFILIATIONS

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

Huabin Hu, MD † • Prof Liang Kang, MD † • Jianwei Zhang, MD † • Zehua Wu, MD † • Prof Hui Wang, MD •

original reports

**Neoadjuvant Pembrolizumab in Localized Microsatellite Instability High/Deficient Mismatch Repair Solid Tumors**

Kaysia Ludford, MD[1,2]; Won Jin Ho, MD[3]; Jane V. Thomas, MD[2]; Kanwal P.S. Raghav, MBBS[2]; Mariela Blum Murphy, MD[2]; Nicole D. Fleming, MD[4]; Michael S. Lee, MD[2]; Brandon G. Smaglo, MD[2]; Y. Nancy You, MD[5]; Matthew M. Tillman, MD[5]; Carlos Kamiya-Matsuoka, MD[6]; Selvi Thirumurthi, MD[7]; Craig Messick, MD[5]; Benny Johnson, DO[2]; Eduardo Vilar, MD, PhD[8]; Arvind Dasari, MBBS[2]; Sarah Shin, BS[3]; Alexei Hernandez, BS[3]; Xuan Yuan, MD[3]; Hongqui Yang[3]; Wai Chin Foo, MD[9]; Wei Qiao, MS, PhD[10]; Dipen Maru, MD[9]; Scott Kopetz, MD, PhD[2]; and Michael J. Overman, MD[2]

Meeting Abstract: 2024 ASCO Annual Meeting II
FREE ACCESS | Gastrointestinal Cancer—Colorectal and Anal | June 05, 2024

**NEOPRISM-CRC: Neoadjuvant pembrolizumab stratified to tumour mutation burden for high risk stage 2 or stage 3 deficient-MMR/MSI-high colorectal cancer.**

# ?Optimal duration of ICI

| Study | Design | pCR rate |
|---|---|---|
| Xu et al | Sintilimab **4 weeks** | 47.7% |
| **IMHOTEP** | Pembrolizumab **6 weeks** | 46.0% |
| NEOPRISM (n=32) | Pembrolizum… **9 w** | |
| PICC (n=34) | Toripalimab… celecoxib **12 weeks** | 76.5% |
| **IMHOTEP** | Pembrolizumab **12 weeks** | 68.2% |
| Ludford (n=27) | Pembrolizumab **24 weeks** | 79% |

# ?Single vs combination ICI

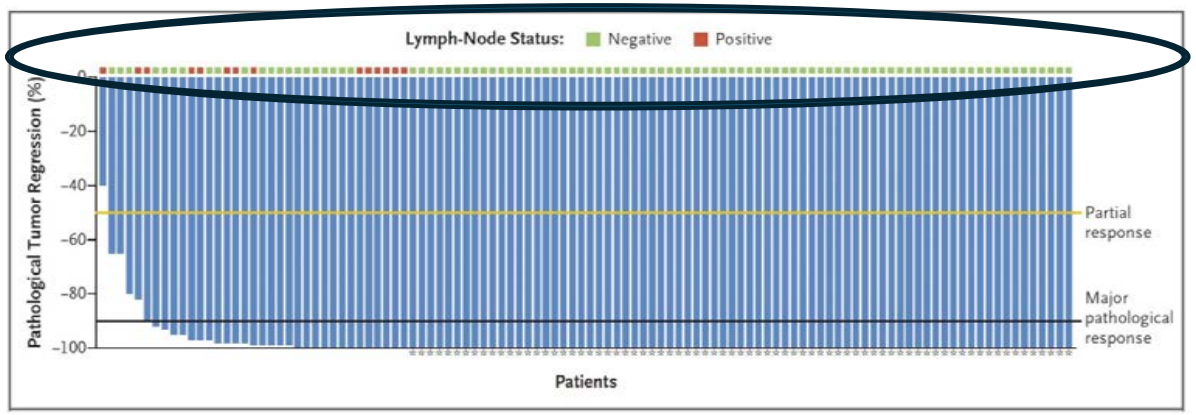
| Study | Design | pCR rate |
|---|---|---|
| PICC | Toripalimab +/- celecoxib (12 weeks) | 76.5% |
| Ludford | Pembrolizumab (24 weeks) | 79% |
| NEOPRISM | Pembrolizumab (9 weeks) | 53% |
| | Pembrolizumab **(6 weeks)** | 46.0% |
| | **(12 weeks)** | 68.2% |
| | …b (4 weeks) | 47.7% |
| NICHE 2 | Nivolumab + ipilimumab (4 weeks) | 68.0% |
| NICHE 3 | Nivolumab + relatlimab (4 weeks) | 68.0% |
| Xu et al | IBI310 + Sintilimab (4 weeks) | 80% |
| Kasi et al | Botensilimab + balstilimab (4 weeks) | 100% |

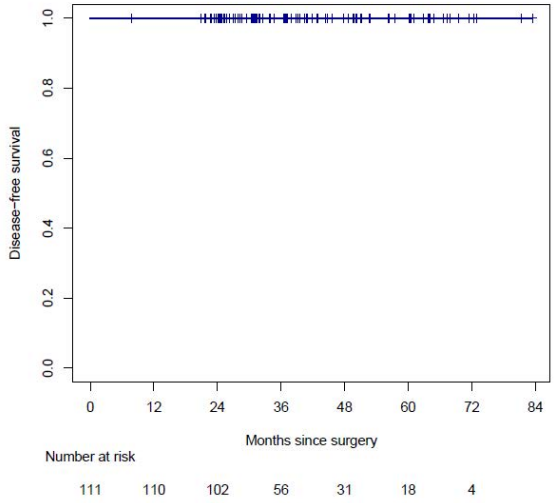
Marked heterogeneity of study designs

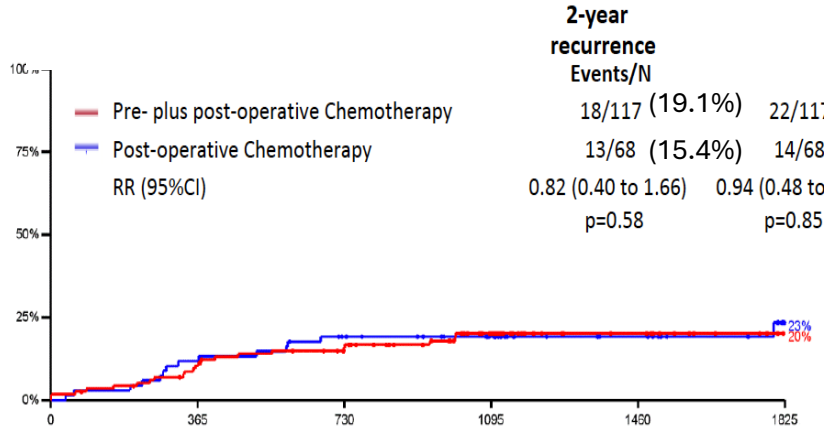
Xu, ASCO Meeting 2024; Shiu, ASCO Meeting 2024; Ludford, JCO, 2023; Hu, Lancet Gastro Hep, 2022; Kasi, ASCO GI Meeting, 2024

# Does short term efficacy translate into long term cancer control?

- Unprecedented 100% recurrence free at 3 years
- Early event in NICHE 3 (1/59 patients)
- 15-20% recurrence in similarly selected patients treated with FOLFOX in FOxTROT trial
- pCR may not be critical for longer term cancer control with surgery




Chalabi, ESMO 2024; de Gooyer, Nature Med, 2024; Morton, JCO, 2023

# Does this data merit practice change?

cT4b tumors

Difficult to achieve R0 resection without multivisceral resection

YES – well represented in NICHE

T3/ T4a tumors

What is the benefit compared with current standard of care?

Compared with post-op chemotherapy, immunotherapy has

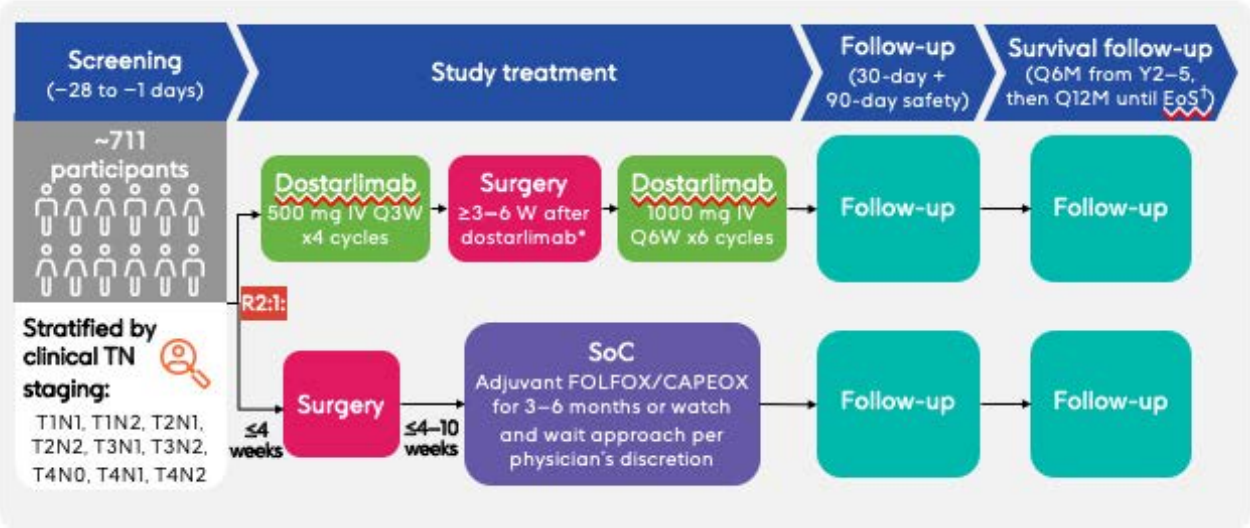
- Improved short-term efficacy
- Is likely to correspond to superior longer term cancer control
- Usually better tolerated


What is needed for regulators?

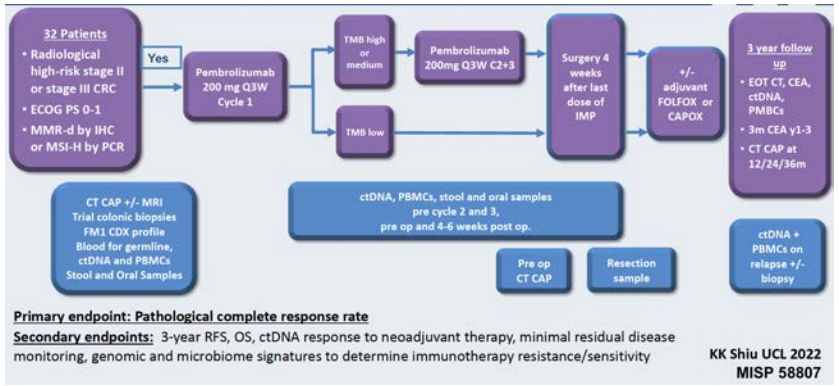
- Design
- Specific population & drugs

# Ongoing trials –neoadjuvant ICI in MSI-H pts

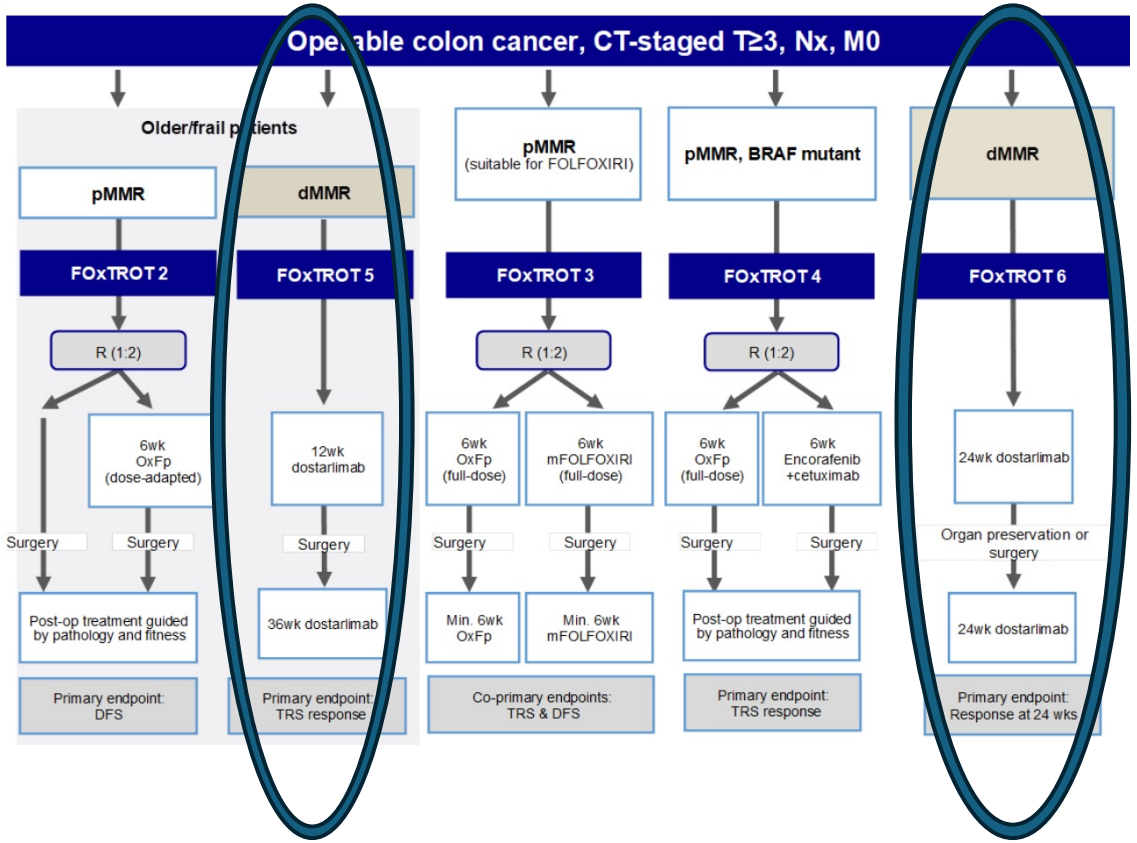
## AZUR-2




## NEOPRISM




## FOxTROT 5 & 6

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# What is the magnitude of risk for emerging safety concerns?

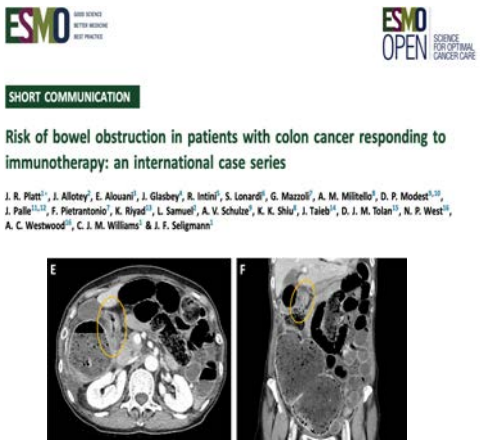
- Risk of grade 5 IO toxicity small but important risk.
- Caution with baseline patient frailty
- Risk of tumor related complications - can be associated with response
- Low grade endocrinopathies can mean life-long treatment
- However, overall good tolerability & completion rates

| Grade 5 AE | Immune-related |
|---|---|
| Sub-occlusive syndrome | No |
| Lung infection / sepsis | No |
| General physical health deterioration | No |
| Septic shock due to inhalation pneumopathy | No |
| **Myasthenia** | **Yes** |

**All 5 patients presented major protocol deviation:**

- Hb <9g/dl
- Peritonitis/tumor perforation with hospitalization during screening period and during 1 month after C1D1
- General health deterioration, undernutrition with hospitalization 4 days after consent form signature
- Severe undernutrition, cognitive disorders & ECOG-PS2 on C1D1
- General health deterioration & EGOG PS2 on C1D1

**and were not included in the *per-protocol* efficacy analysis**




De la Fouchardiere, ESMO Meeting 2024; Gooyer, ESMO Meeting 2024; Chalabi, ESMO Meeting 2024, Platt, ESMO Open 2024

# Decision points in the Treatment pathway

Pathway coordination

1

MDT revi… of diagn… stagin…

PATIENT CHOICE

…gical …ction

2

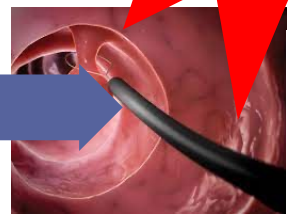
MDT review of post-operative hist… +/- MSI/MMR status

Assessment of post-rx response

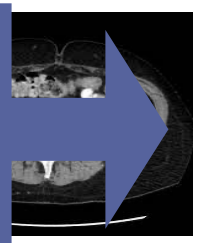
…t

Follow up

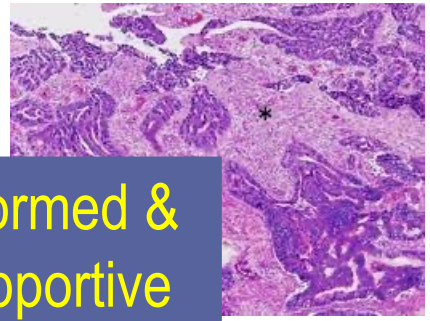
Upfront MMR/MSI

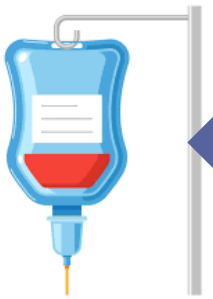


Radiology call on T & N stage



Informed & supportive surgical colleague

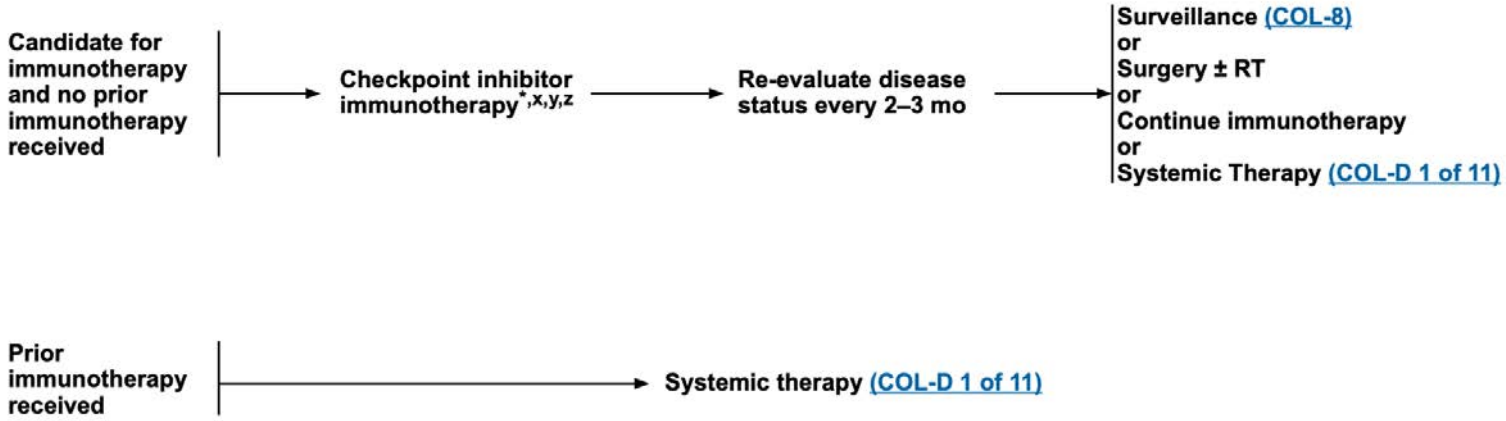




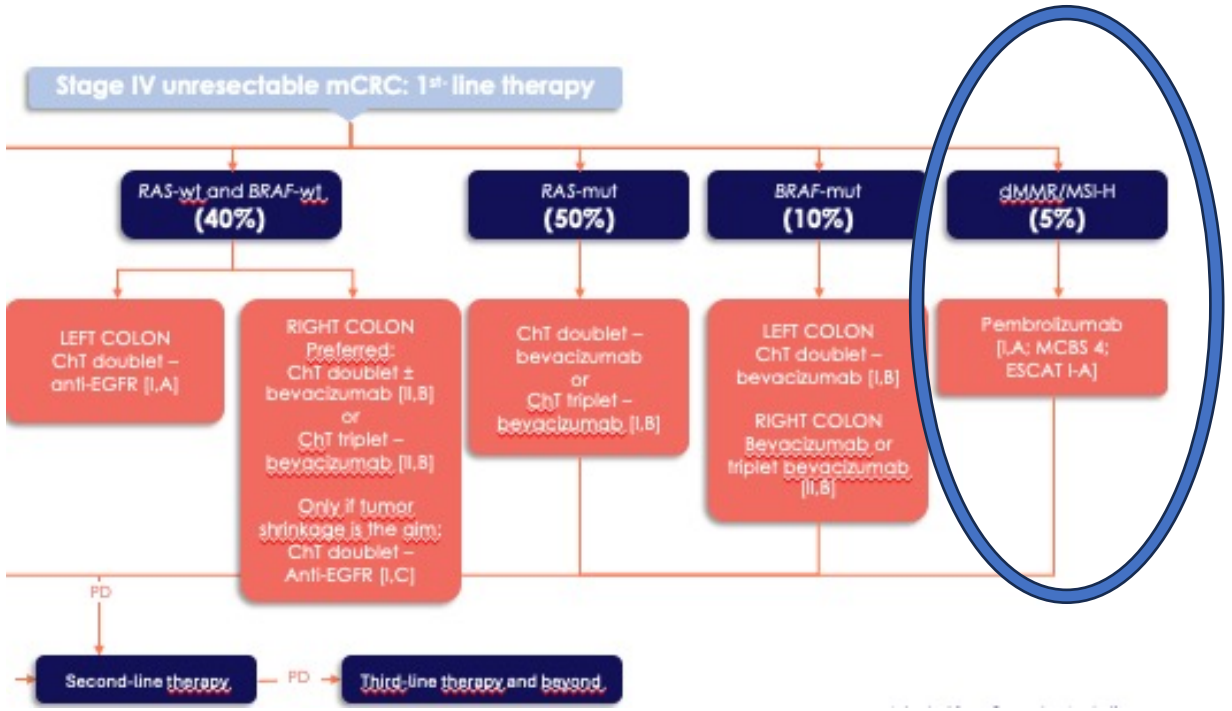
Ability to review & treat rapidly

# Guidelines for use of ICI in mCRC

NCCN Guidelines advanced or metastatic MSI-H or POLE/ POLD mutation
ANY Line of therapy

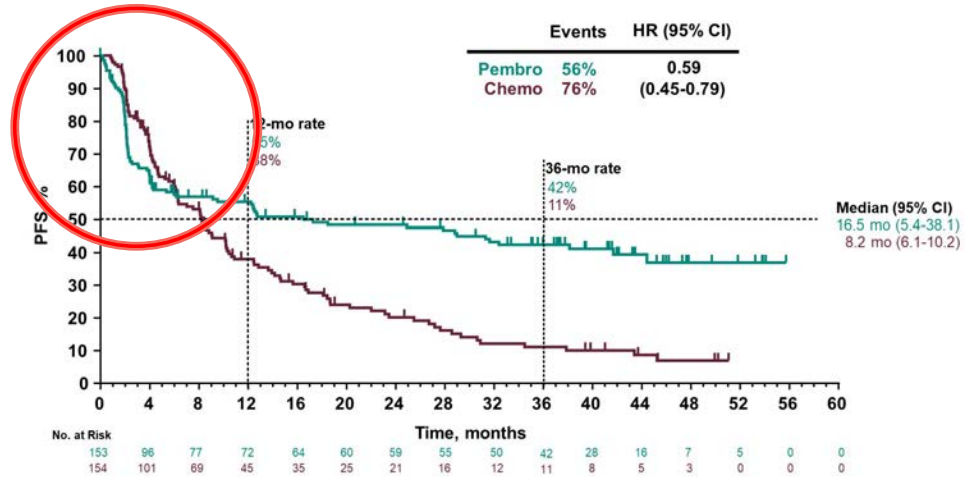


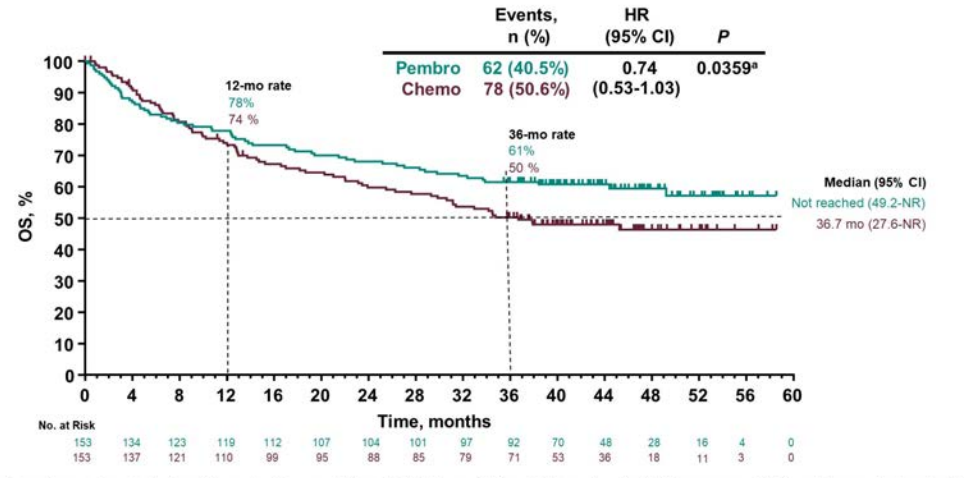

ESMO Clinical Practice Guidelines
ANY Line of therapy

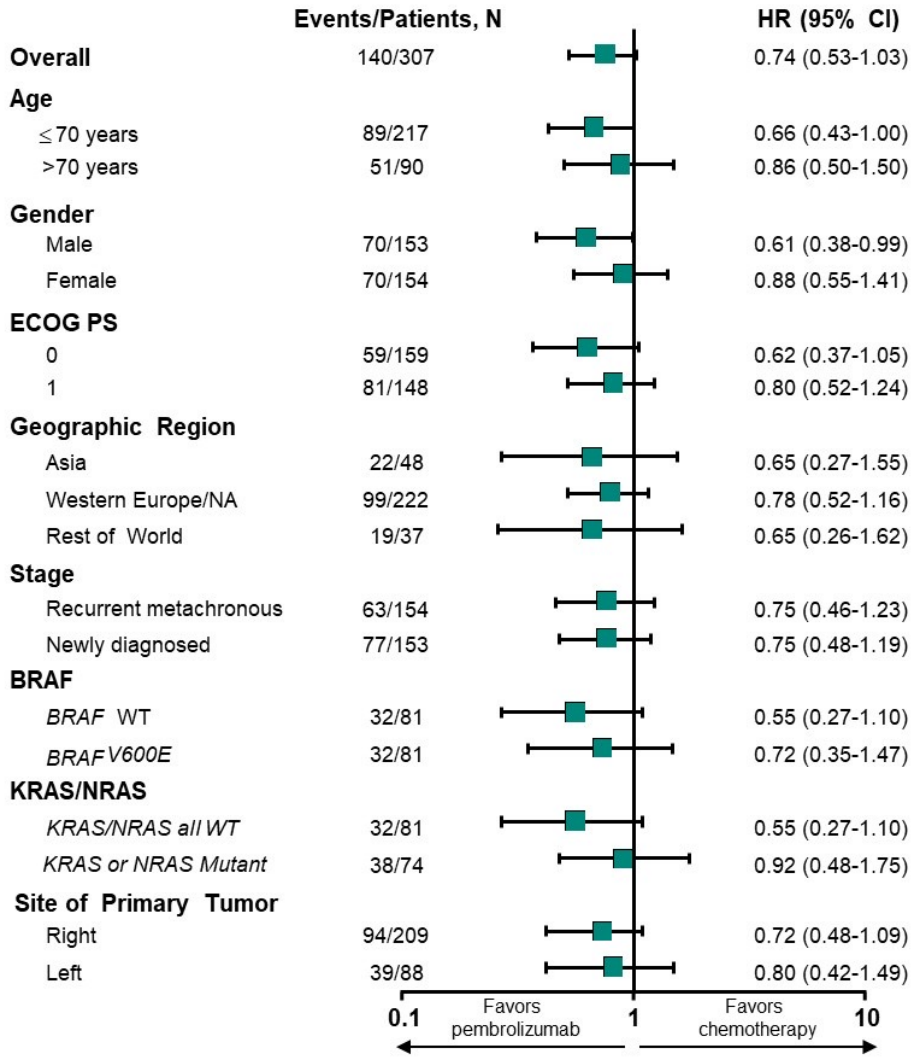



NCCN Guidelines Version 6.2024; Cervantes et al, 2023

# KEYNOTE-177 – Pembrolizumab vs chemotherapy for 1st line treatment of MSI-H mCRC




**1.** André et al., ASCO 2021: #3500. André et al. *New Engl J Med.* 2020;383:2207-2218. Diaz LA Jr et al. *Lancet Oncol*. 2022;23(5):659-670.

# CheckMate 8HW: Nivolumab plus ipilimumab vs chemotherapy for 1st line treatment of MSI-H mCRC

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

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

R 2:2:1

1L setting: n = 2

- NIVO 240 mg Q2W for 6 doses, followed by NIVO 480 mg Q4W[b]
- NIVO 240 mg + IPI 1 mg/kg Q3W for 4 doses, followed by NIVO 480 mg Q4W[b]

1L setting: n = 101

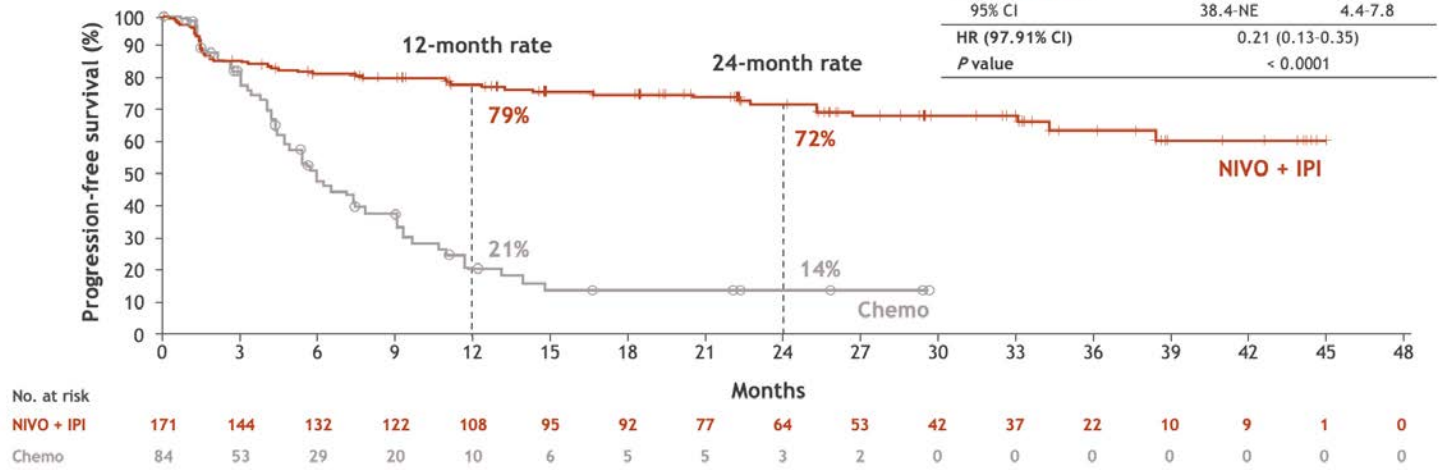
- Investigator's choice chemo[c] (mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab)

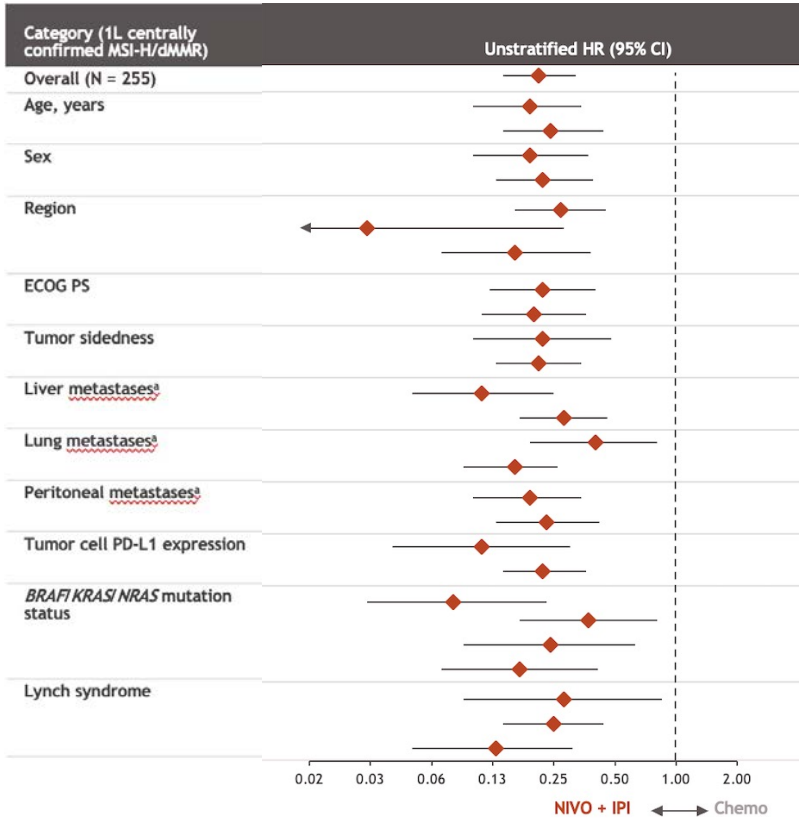
Treatment until disease progression, unacceptable toxicity, withdrawal of consent (all arms), or a maximum treatment duration of 2 years (NIVO and NIVO + IPI arms only)

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

**Other select endpoints:**
- Safety
- OS; ORR by BICR[e]; PFS2 by BICR[e]; PROs

| 1L centrally confirmed MSI-H/dMMR | NIVO + IPI (n = 171) | Chemo (n = 84) |
|---|---|---|
| Median PFS,[a,b] mo | NR | 5.9 |
| 95% CI | 38.4-NE | 4.4-7.8 |
| HR (97.91% CI) | 0.21 (0.13-0.35) | |
| *P* value | < 0.0001 | |




Andre, NEJM, 2024

# First Results of Nivolumab (NIVO) plus Ipilimumab (IPI) versus NIVO Monotherapy for Microsatellite Instability-High/Mismatch Repair-Deficient (MSI-H/dMMR) Metastatic Colorectal Cancer (mCRC) from CheckMate 8HW

Andre T et al.

Gastrointestinal Cancers Symposium 2025;Abstract LBA143.

**ORAL ABSTRACTS | SATURDAY, JANUARY 25 | 1:52 PM PT**

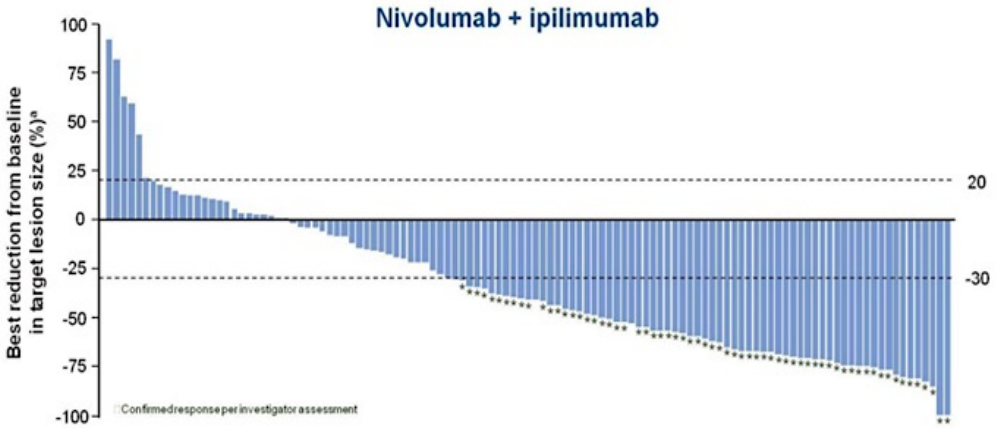
# What is the optimal continuum of care for MSI-H mCRC?

## 1st line management

- Difficult to draw direct comparisons
- Lower discontinuation due to PD with Nivolumab + ipilimumab (19% vs 32.6%)
- Either is better than 1st line chemotherapy
- *The key analysis from CheckMate 8HW will be Nivolumab plus Ipilimumab vs Nivolumab*
- Real world data from other cancers does not show differences in outcomes between pembrolizumab and nivolumab in NSCLC

## Subsequent therapy

- CheckMate 142 tested nivolumab + ipilimumab in previously treated MSI-H mCRC
  - ORR of 65%
  - OS of 71% with 4 year follow up




Andre, NEJM, 2020; Andre NEJM, 2024; Moser, Acta Oncol, 2020; Andre, Ann Onc, 2022

# Unanswered questions & Future Directions for IO in MSI-H mCRC

- Who needs doublet immunotherapy rather than PD-1 alone?
- Who are the early progressors on ICI?
  - Can we identify them upfront?
  - Are they better served with alternative upfront regimen?
  - ?Combination with targeted agent
- Should we resect residual stable disease?
- How do you optimally manage an MSI-H patient post-progression?
- How will the next generation of IO agents change the current landscape?

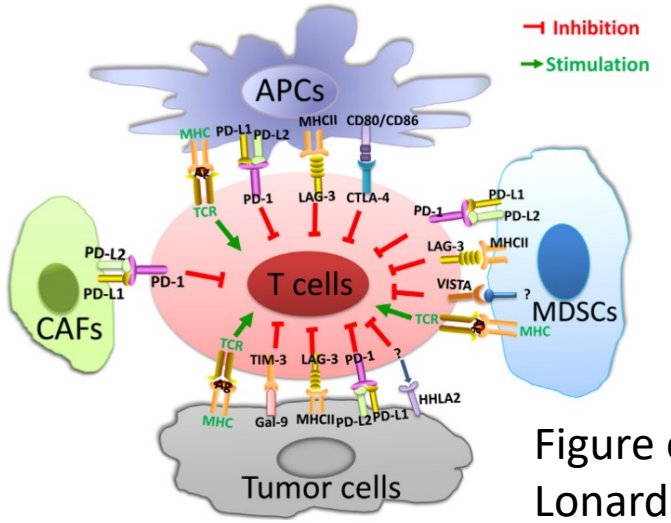
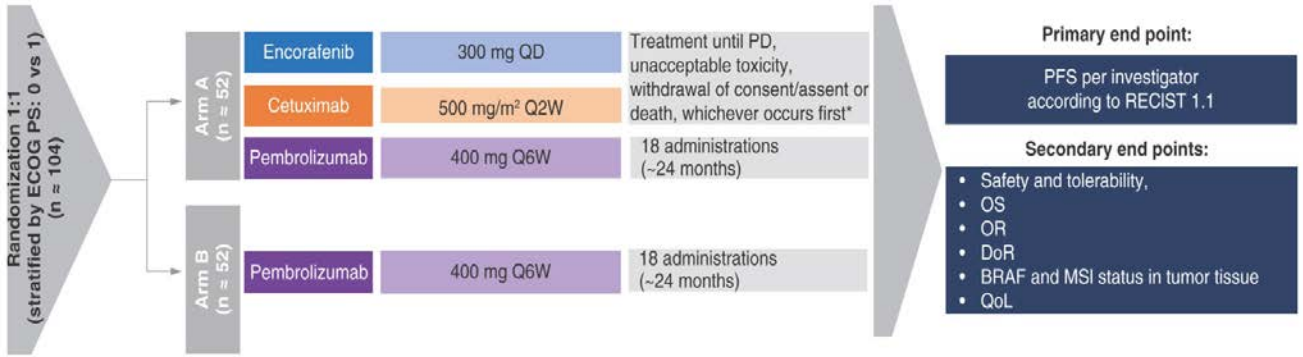



Figure courtesy of Sara Lonardi

SEAMARK TRIAL (BRAF-mutant + MSI-H)




Elez, Future Oncology, 2024

# Conclusions

- Enormous progress made in the treatment of MSI-H CRC which has led to transformative patient benefit

- For MSI-H LARC neoadjuvant ICIs have led to de-escalation of SOC with er
    - Whilst can be used routinely in some areas, AZUR-1 will report generalizability
- For MSI-H LACC the body of evidence is accumulating and is consistent
    - Potential paradigm changing results will be balanced against treating good prognosis patients
    - Current data is unlikely to be sufficient for regulatory approval
- For MSI-H mCRC, upfront ICI treatment clearly superior than chemotherapy
    - Further refinement of patient selection for doublet vs single required
    - Impact of novel agents on primary progressors

# Questions from General Medical Oncologists

- What are the real-world indications for IO in nonmetastatic MSI-H rectal cancer given the small sample size of patients in whom dostarlimab was used but the marvelous responses?
- Is the omission of surgery after neoadjuvant IO for MSI-high rectal cancer now considered SOC?
- Is there any role for neoadjuvant or adjuvant immune checkpoint inhibitor therapy for MSI-high or MMR-deficient Stage II or Stage III colon (as opposed to rectal) cancer? Are any clinical trials available or any data available from clinical trials? Is this strategy endorsed by the experts?

# Questions from General Medical Oncologists

- **Is there a role for combining immunotherapy with chemotherapy in patients with high tumor burden or visceral metastatic disease?**
- **56 yo man with Stage IV MSI-high colon cancer with a CR on pembro but colitis requiring hospitalization and steroids. Now recovered. Would you restart pembro or observe for progression?**
- **67 yo woman with Stage IV MSI-high colon cancer with a PR on pembro but now progressing. Would you opt for ipi-nivo or chemo?**

# Questions from General Medical Oncologists

- When should we use up-front nivo + ipi in Stage IV MSI-high colon cancer?
- For a patient with MSI-H mCRC and Crohn's with a history of fistulae currently well controlled on biologics, would you try IO therapy? What can the gastroenterologist do to help enable this? Any pearls to share?
- 85 yo woman with MSI-high Stage IV CRC. She had single-agent capecitabine first line (NGS was not back). Would you consider switching to pembro as soon as you have MSI-high status back, or would you wait for progression?

# Agenda

**Module 1:** Optimizing Biomarker Assessment for Patients with Colorectal Cancer (CRC) — Dr Dasari

**Module 2:** Identification and Management of Metastatic CRC (mCRC) with a BRAF V600E Mutation — Dr Morris

**Module 3:** Incorporation of Immune Checkpoint Inhibitors into the Management of MSI-H/dMMR CRC — Dr Seligmann

**Module 4: Integration of Therapies Targeting HER2 into the Management of mCRC — Prof Van Cutsem**

**Module 5:** Biomarker-Based Decision-Making for Patients with mCRC and KRAS G12C Mutations — Dr Lieu

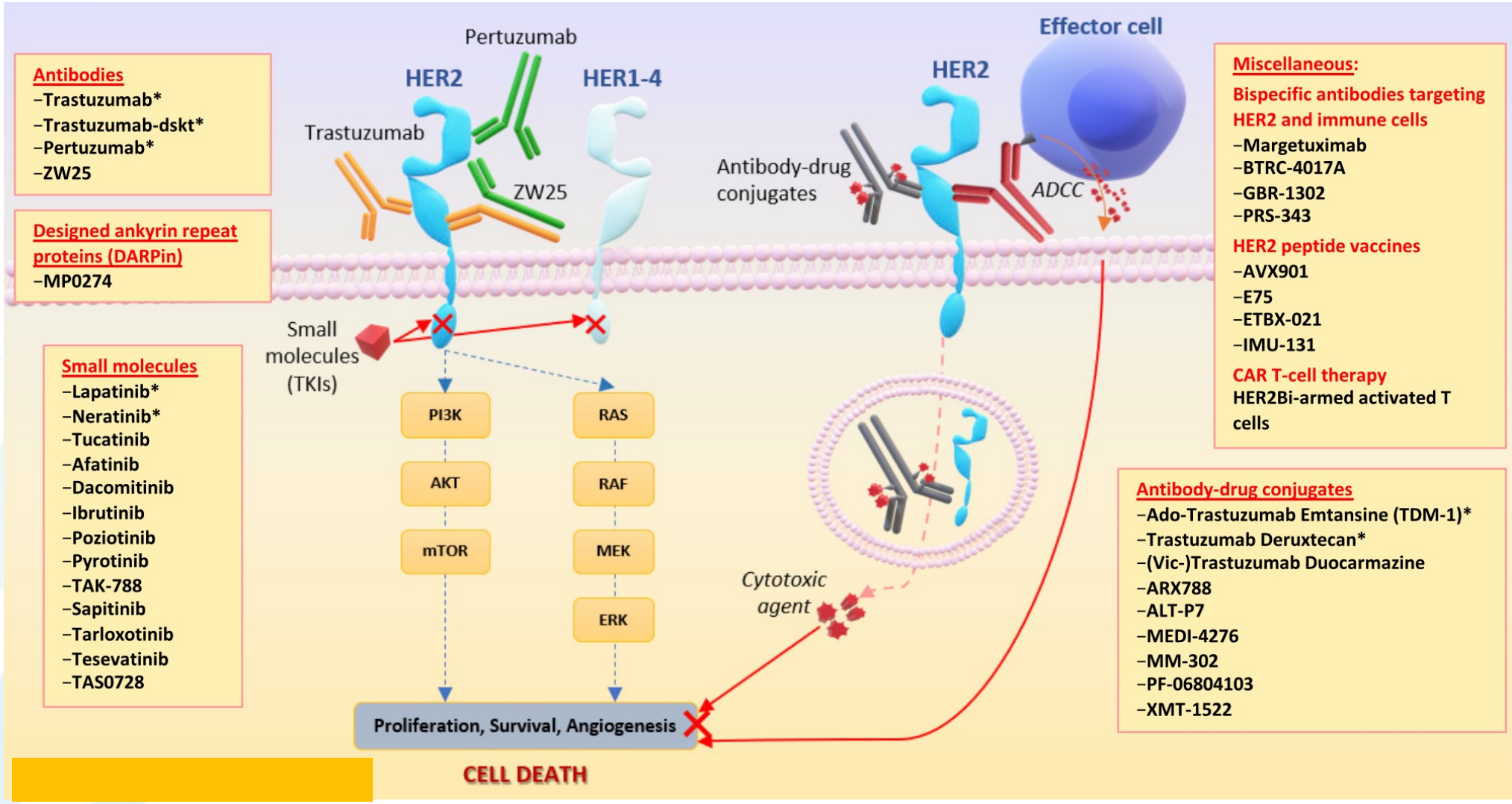
RTP RESEARCH TO PRACTICE

# Integrating of Therapies Targeting HER2 in mCRC

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

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

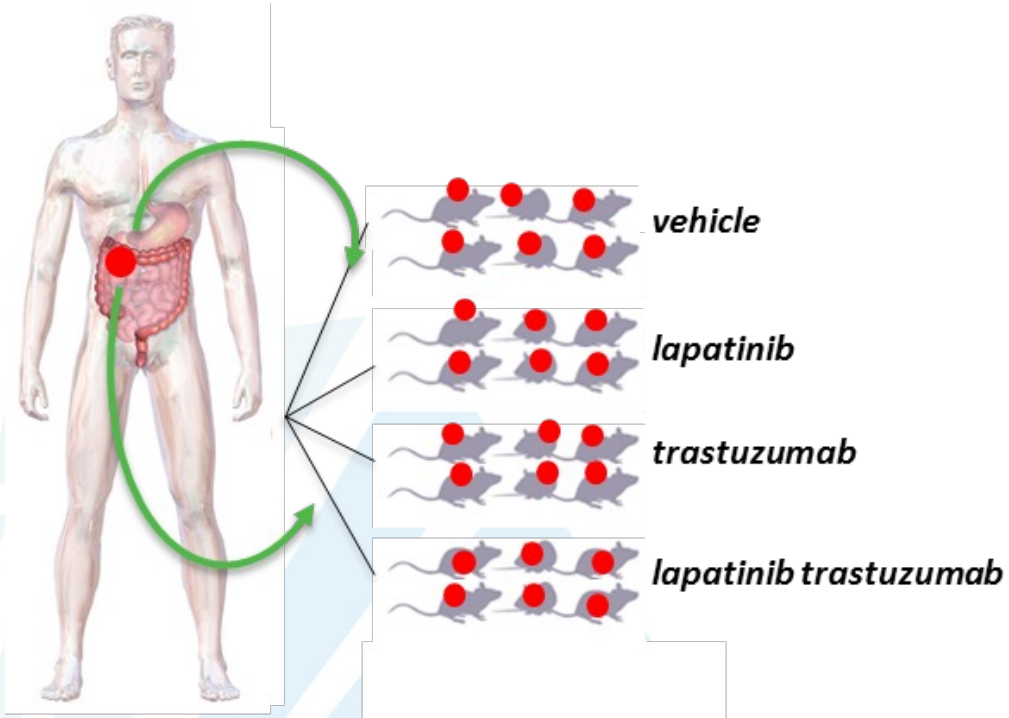
# Novel Anti-HER2 Strategies for GI Tumors



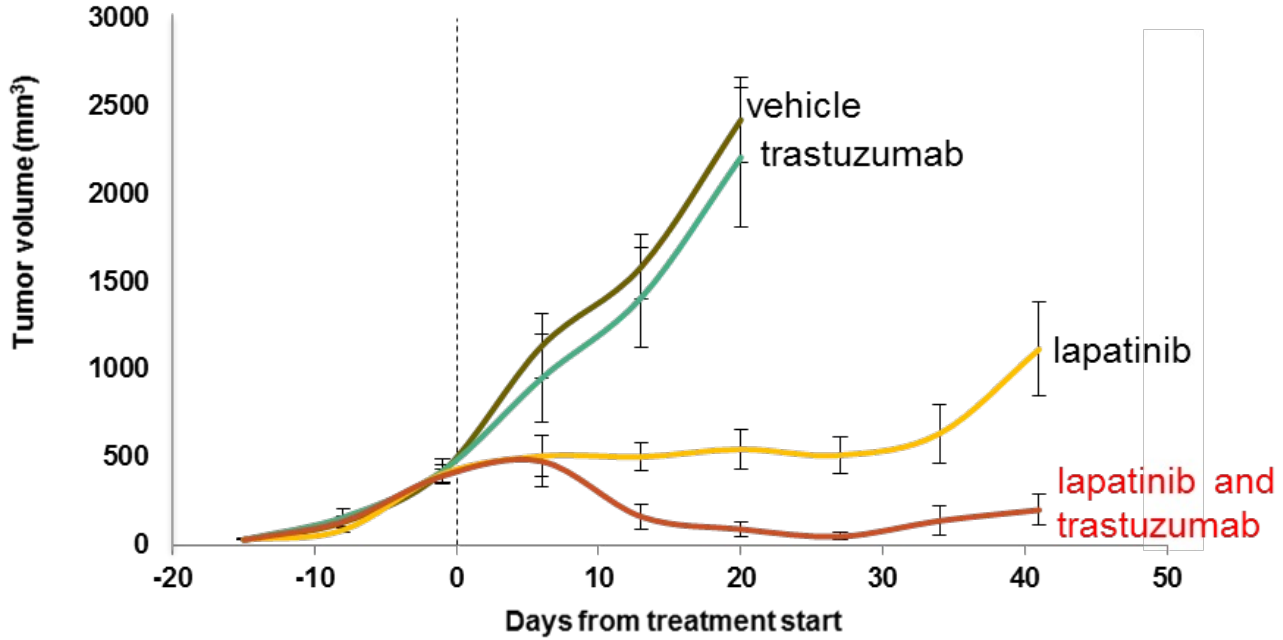

Siena S. et al Cancer Cell 2020

# HER2 amplification as a target in CRC

HER2+ mCRC-PDXs are sensitive to dual HER2-blockade with lapatinib + trastuzumab
but not with either drug alone



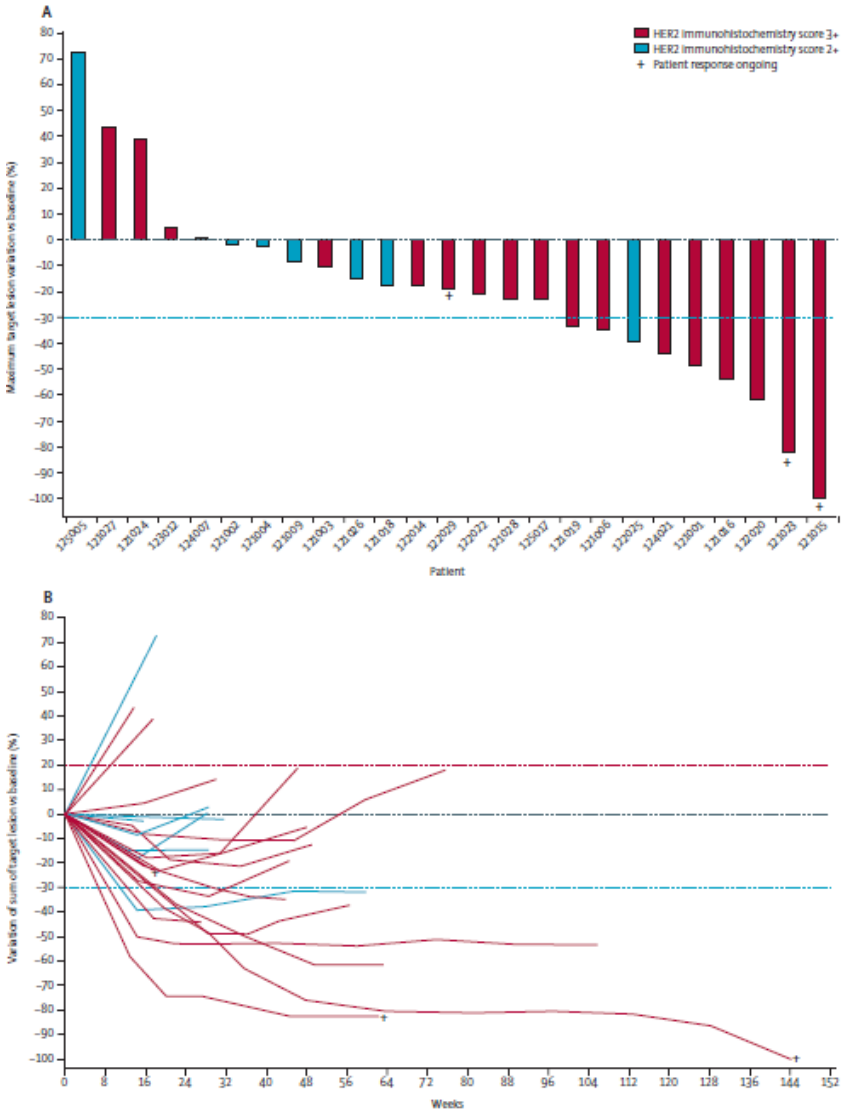

**mCRC patient-derived xenografts**




Bertotti A et al, Cancer Discovery 2011

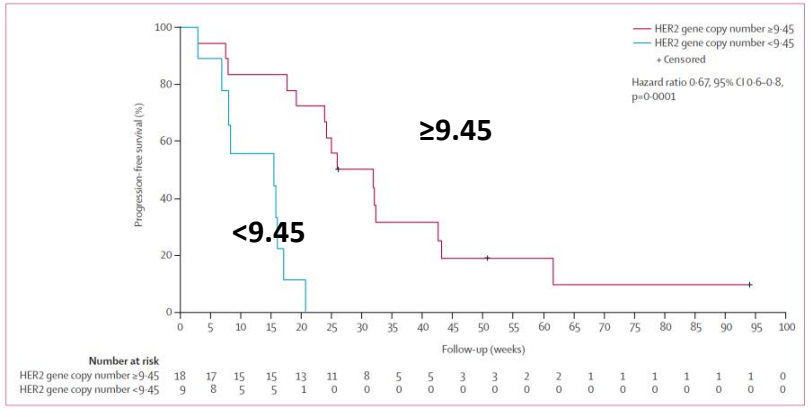
# HER2-targeted therapy in mCRC: HERACLES-A

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



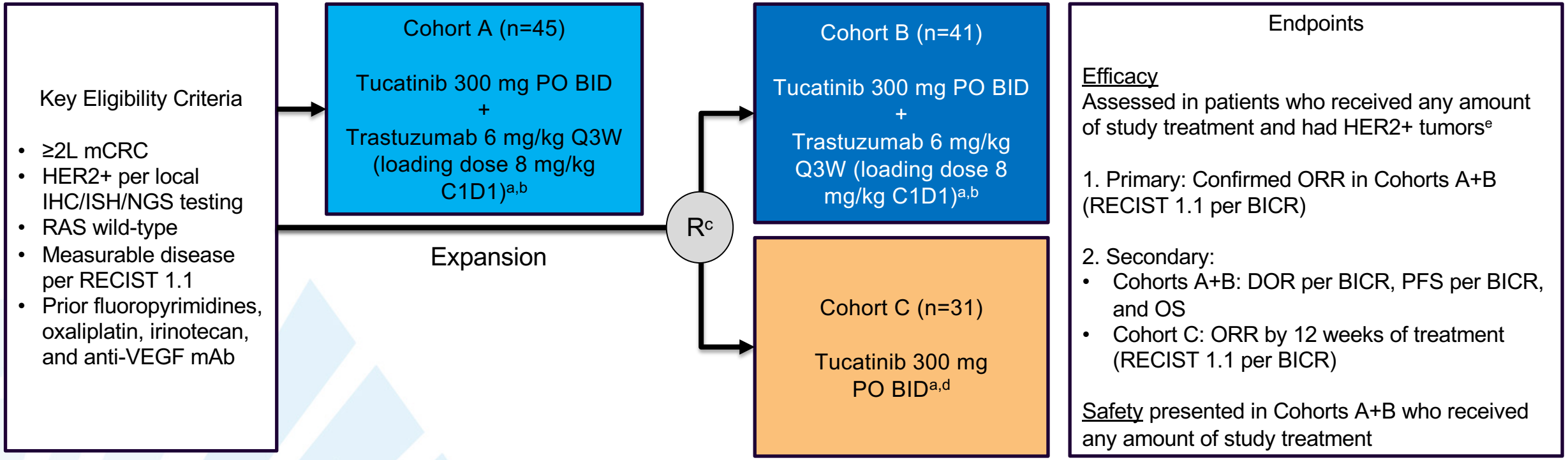

| | |
|---|---|
| Complete response | 1 (4%, −3 to 11) |
| Partial response | 7 (26%, 9 to 43) |
| Objective response | 8 (30%, 14 to 50) |
| Disease control† | 16 (59%, 39 to 78) |
| Duration of response (weeks) | 38 (24 to 94+) |

**PFS according to HER2 GCN**




Sartore-Bianchi A … Siena S, Lancet Oncol 2016

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




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

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

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

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

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

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

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

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

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

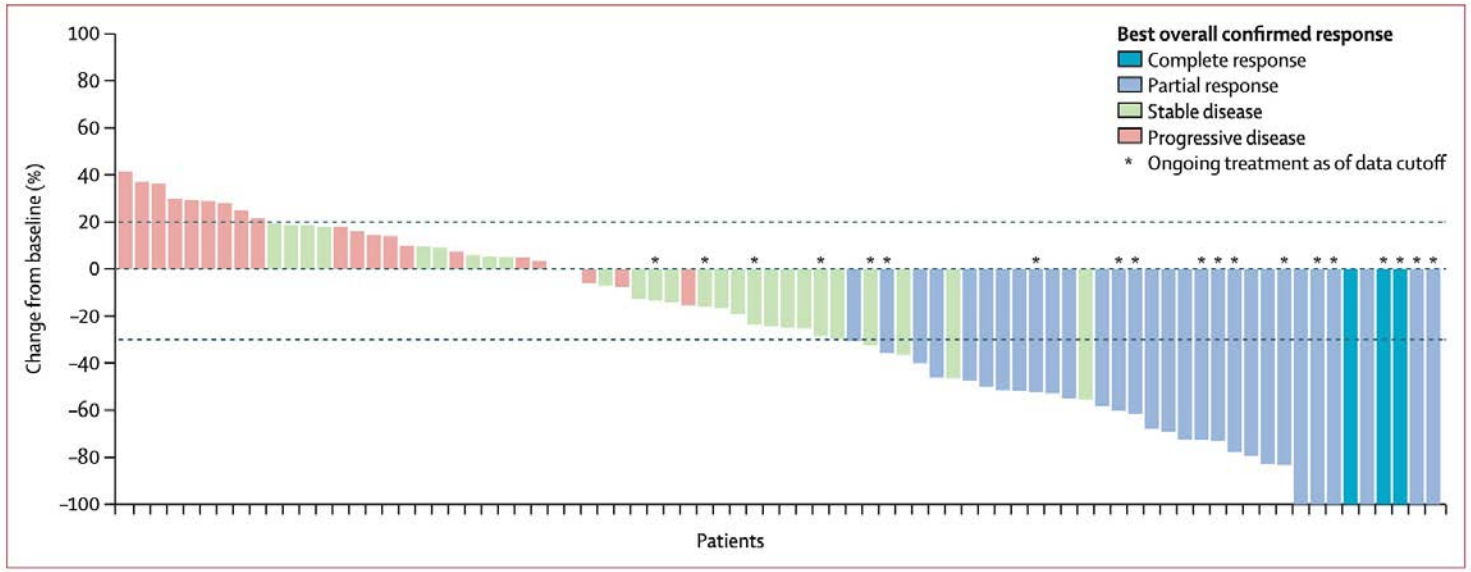



***Figure 2:*** **Anti-tumour activity in patients treated with tucatinib plus trastuzumab with available baseline and post-baseline lesion measurements (n=80)**
Shown are the maximum percentage changes in the sum of the diameters of target lesions per blinded independent central review for all patients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

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

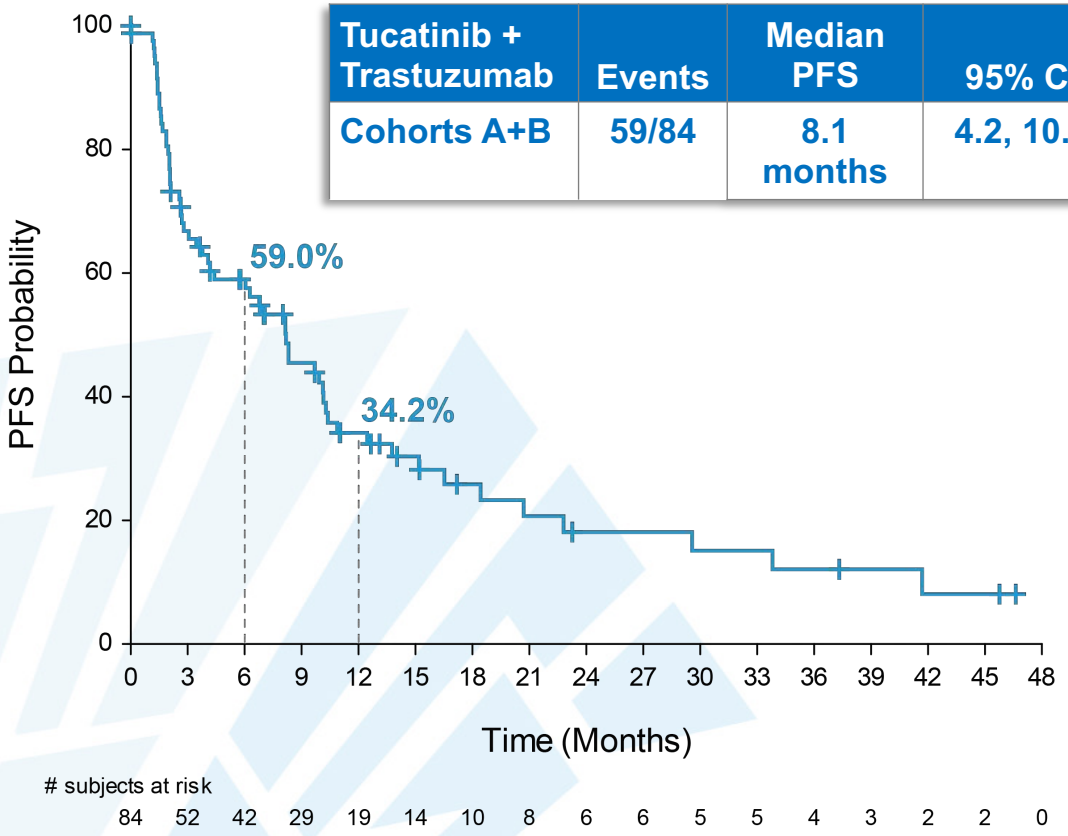
- ✓ **46·7% (95% CI 31·7–62·1; 21 of 45 patients) in those with IHC 3+ tumours,**
- ✓ **20·0% (4·3–48·1; three of 15 patients) in those with IHC 2+ and in-situ hybridisation-positive tumours**
- ✓ **10·0% (0·3–44·5; one of ten patients) in those with HER2-negative tumours**

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

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

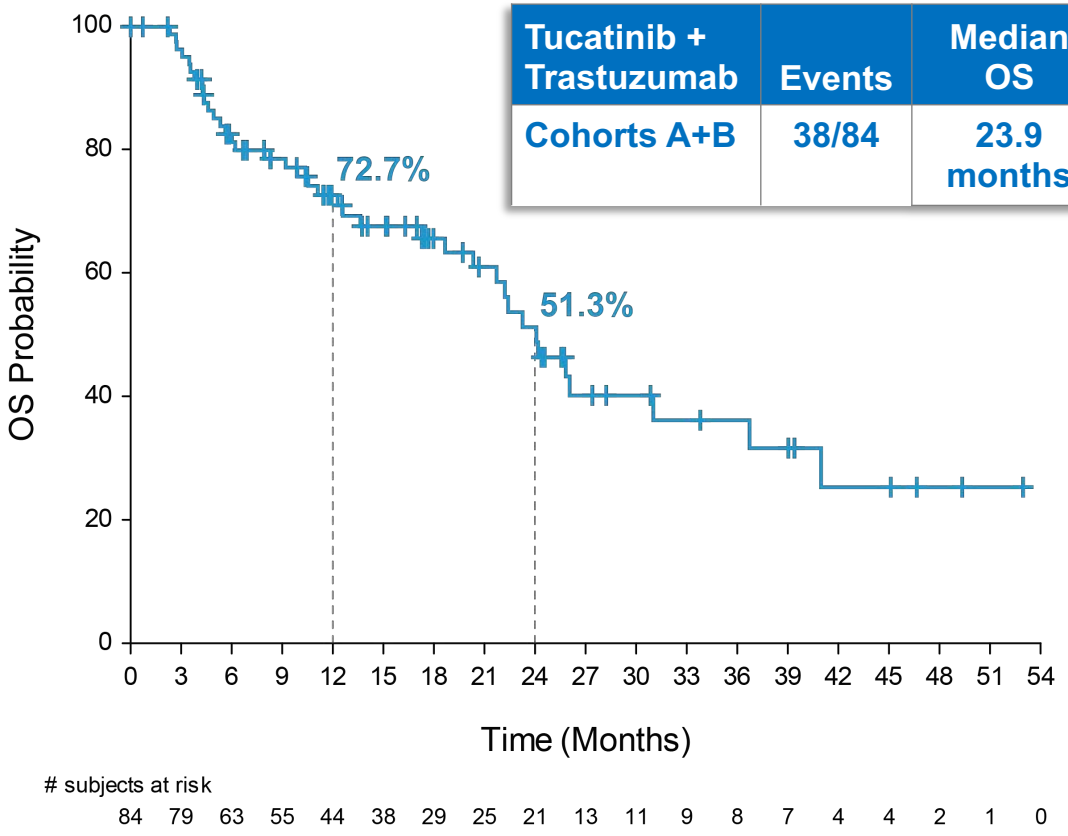
## Progression-free Survival per BICR

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




## Overall Survival

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




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

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

*Data cutoff: 28 Mar 2022*

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

# MOUNTAINEER: Long-term Response (LTR) Analysis

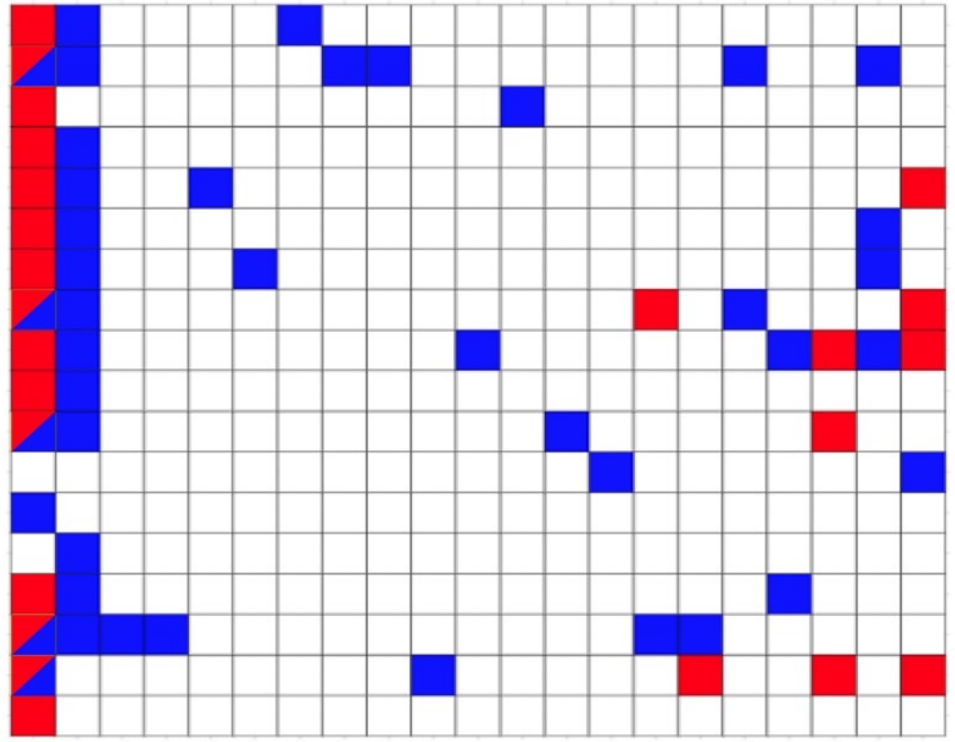
- 23 of 84 (27%) patients[a,b] had LTRs, defined as having >12 months duration of treatment with CR/PR/SD
- LTR status was found among a range of HER2 expression levels
- No evident associations between LTR status and clinicopathologic features, HER2 expression level, or genomic alterations were found

SNV/INDEL | Amplification | SNV/INDEL and amplification

A single blue or red/blue box can represent multiple SNV/INDEL detections in the same gene.

## Tumor biomarker alterations by ctDNA analysis and treatment response

| Treatment lines | HER2 IHC | HER2 copies | HER2:CEN17 ratio | Response | PFS |
|---|---|---|---|---|---|
| 2 | 2+ | 17.3 | 10.8 | CR | 62.7 |
| 2 | 3+ | 16.7 | 7.2 | PR | 48.4 |
| 4 | 3+ | 19.2 | 8.3 | SD | 45.8 |
| 2 | 3+ | 19.7 | 10.4 | CR | 42.1 |
| 2 | | | | PR | 41.7 |
| 1 | 3+ | 14.8 | 5.8 | PR | 30.6 |
| 2 | 3+ | 16.4 | 8 | PR | 22.8 |
| 3 | | | | PR | 22.2 |
| 2 | 3+ | 16.5 | 7.9 | PR | 20.7 |
| 2 | 3+ | 20 | 14.8 | CR | 20 |
| 3 | 3+ | 20 | 9.5 | PR | 18.5 |
| 2 | 3+ | 13.2 | 6 | PR | 15.5 |
| 3 | 2+ | 7 | 2.5 | PR | 15.2 |
| 2 | 2+ | 9.9 | 6.8 | SD | 14.3 |
| 1 | 3+ | 20 | 6.8 | PR | 13.8 |
| 4 | 3+ | 20 | 11.4 | PR | 13.1 |
| 4 | 3+ | 18.5 | 6.8 | PR | 12.6 |
| 2 | 3+ | 17.8 | 12.3 | PR | 12.5 |




[a] 5/23 (22%) with no co-occurring alterations or no ctDNA results available; [b] 18/23 (78%) with co-occurring alterations.
CEN17, centromere of chromosome 17; ctDNA, circulating tumor DNA; CR, complete response; DOR, duration of response; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; INDEL, insertions and deletions; PFS, progression-free survival; PR, partial response; SD, stable disease; SNV, single nucleotide variant.

Strickler JH…Van Cutsem E et al. ASCO 2024; Abstract 3509.

# MOUNTAINEER: Efficacy by Central HER2 Testing Methods

- Clinical efficacy was similar across all 3 central HER2 testing methods

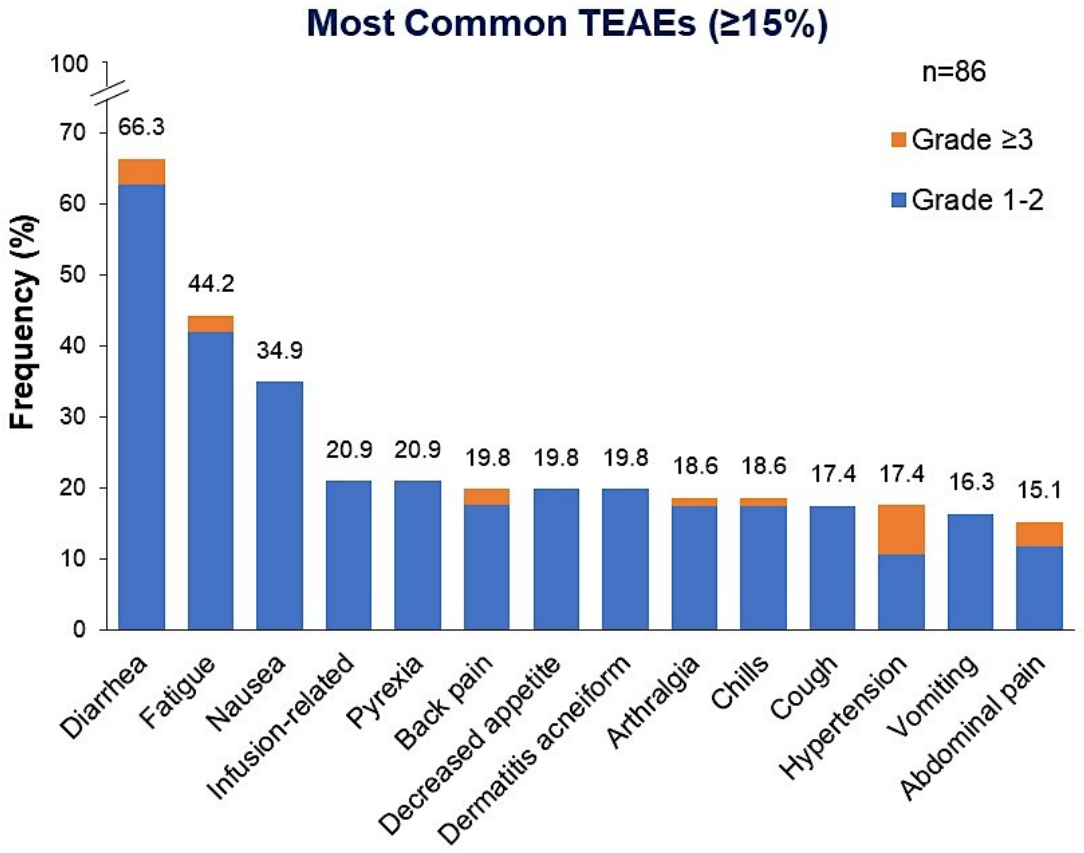
| HER2 results | Tissue IHC/FISH | | Tissue NGS (PGDx) | | Blood NGS (G360) | |
|---|---|---|---|---|---|---|
| | + (n=60) | – (n=10) | + (n=44) | – (n=6) | + (n=59) | ND (n=16) |
| cORR, % (95% CI) | 41.7 (29.1–55.1) | 10.0 (0.3–44.5) | 50.0 (34.6–65.4) | 0 (0–45.9) | 42.4 (29.6–55.9) | 25.0 (7.3–52.4) |
| Median DOR, mo (95% CI) | 16.6 (11.4–25.5) | – | 16.6 (10.6–18.8) | – | 16.6 (8.3–18.8) | 15.2 (11.4–NE) |
| Median PFS, mo (95% CI) | 10.1 (4.2–14.5) | 2.8 (1.2–6.3) | 10.9 (6.8–20.0) | 2.1 (1.3–NE) | 8.1 (3.1–10.3) | 6.3 (2.0–25.5) |

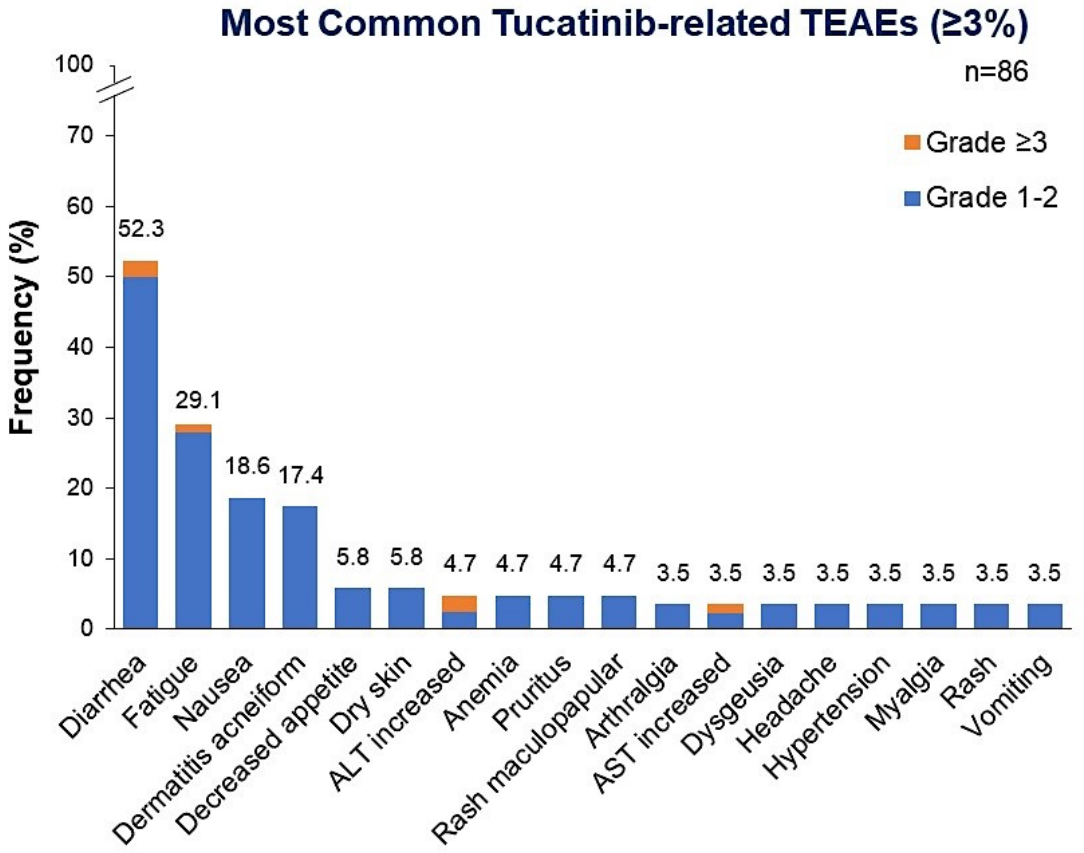
Note: To be included in this analysis, a patient had to have a local HER2+ test and ≥1 central HER2+ test from IHC/FISH, tissue-based NGS, and/or blood-based NGS.

CI, confidence interval; cORR, confirmed objective response rate; DOR, duration of response; FISH, fluorescent in situ hybridization; G360, Guardant360® CDx test; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mo, months; ND, not detected; NE, not estimable; NGS, next-generation sequencing; PFS, progression-free survival; PGDx, PGDx elio tissue complete.

Strickler JH…Van Cutsem E et al. ASCO 2024; Abstract 3509.

# Most Common TEAEs for Tucatinib + Trastuzumab




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

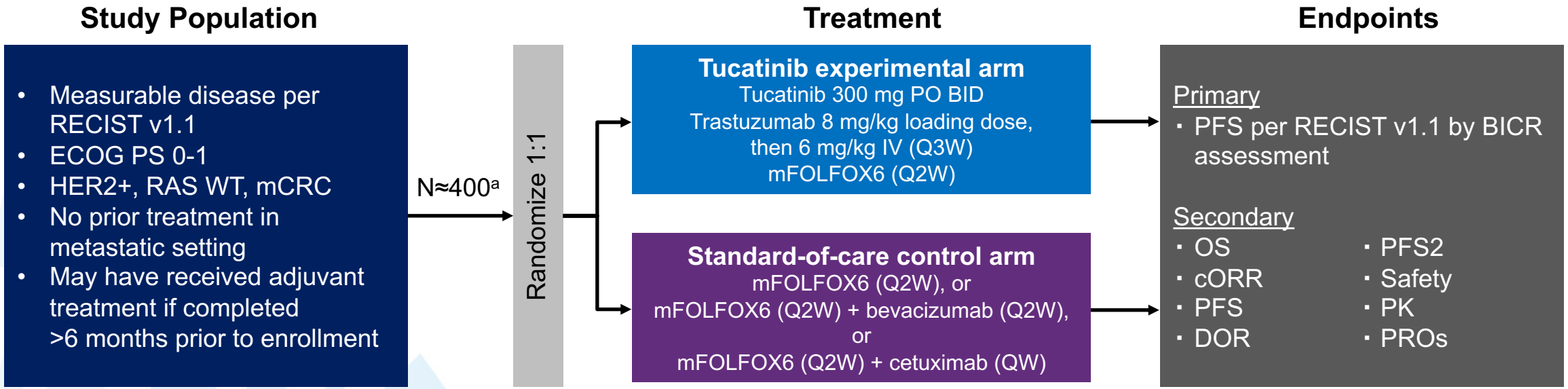
- Most common tucatinib-related AEs: diarrhoea (52.3%), fatigue (29.1%), nausea (18.6%), and dermatitis acneiform (17.4%)
  - Grade ≥3 tucatinib-related AEs (≥3%): alanine aminotransferase increase (2.3%) and diarrhoea (2.3%)

*Data cutoff: 28 Mar 2022*

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

# MOUNTAINEER-03 trial in first line mCRC

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



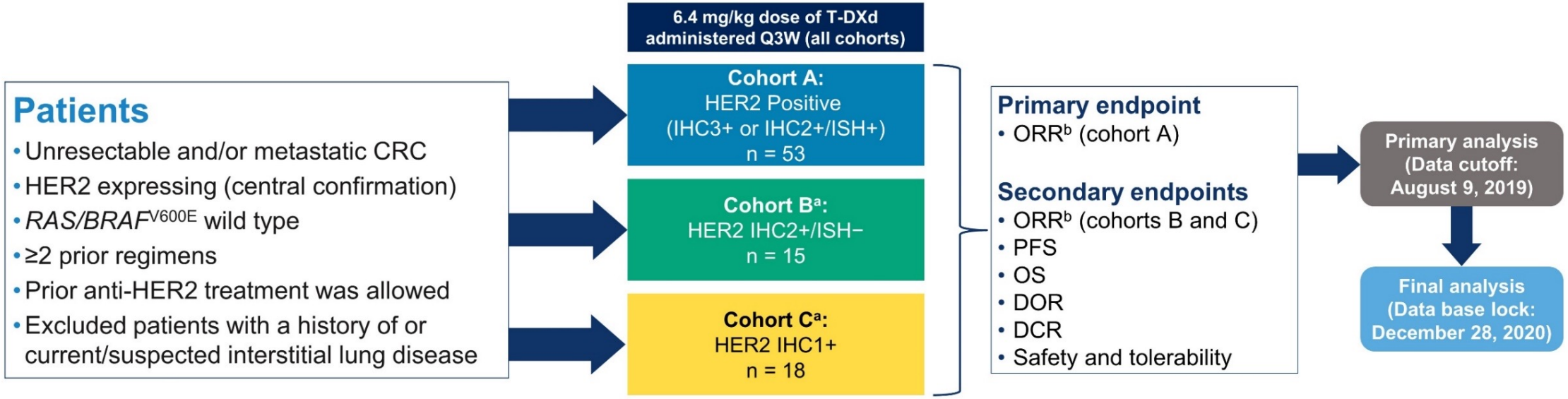

a Stratification by both primary tumor location (left-sided versus all other) and liver metastases (presence or absence)

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

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

# DESTINY-CRC01 Study Design

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




**Primary analysis of cohort A[1]**

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

**Patient disposition at final analysis[c]**

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

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

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

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







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

# DESTINY-CRC01 trial

**Table 3 | Key efficacy endpoints**

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

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

Yoshino T et al, Nat Comm 2023

# DESTINY-CRC01 trial: analysis according to IHC of HER2

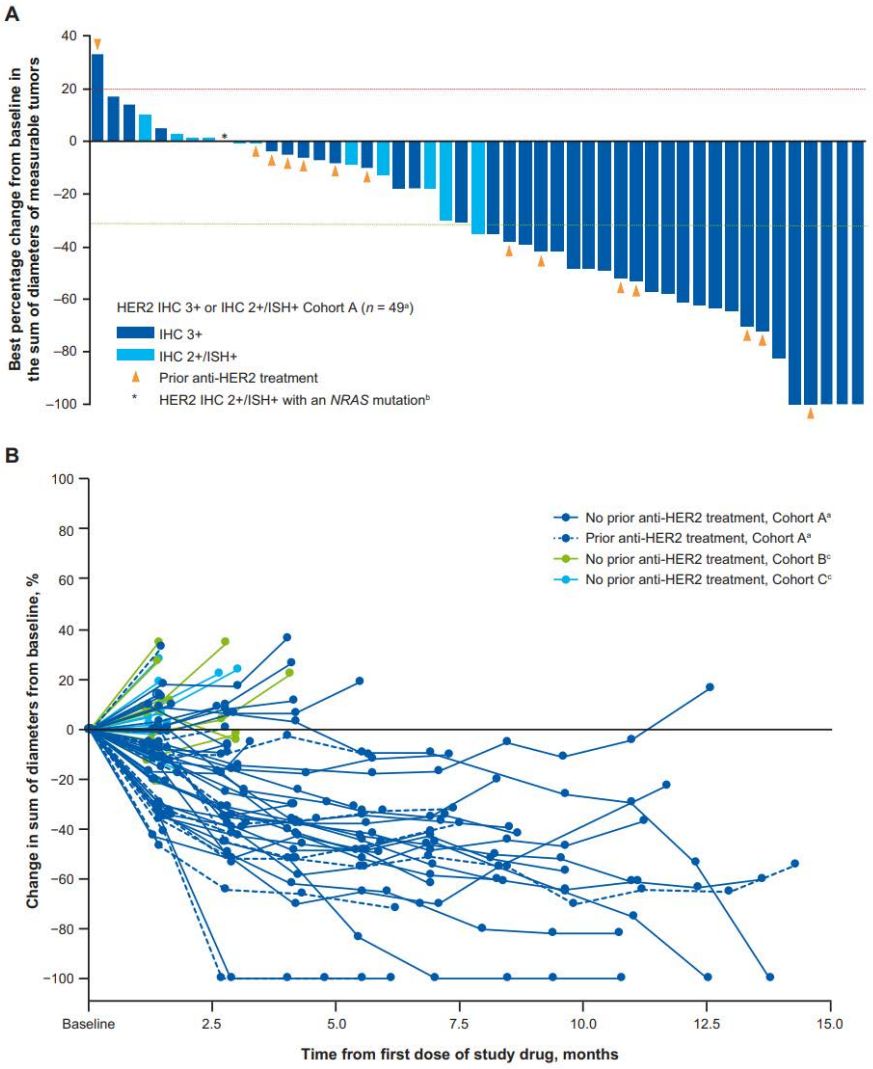
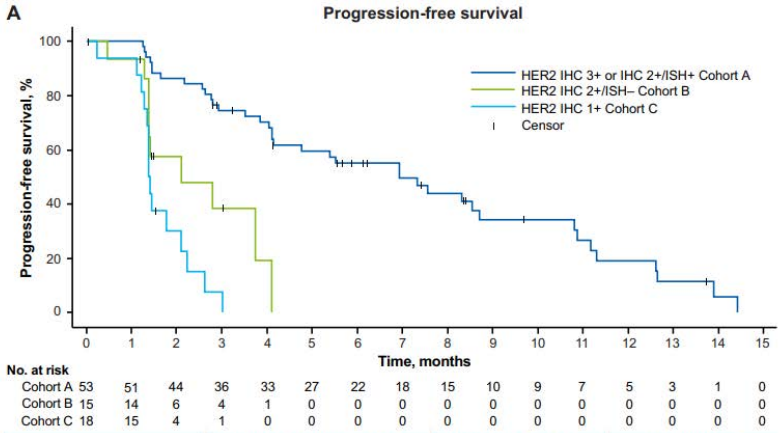
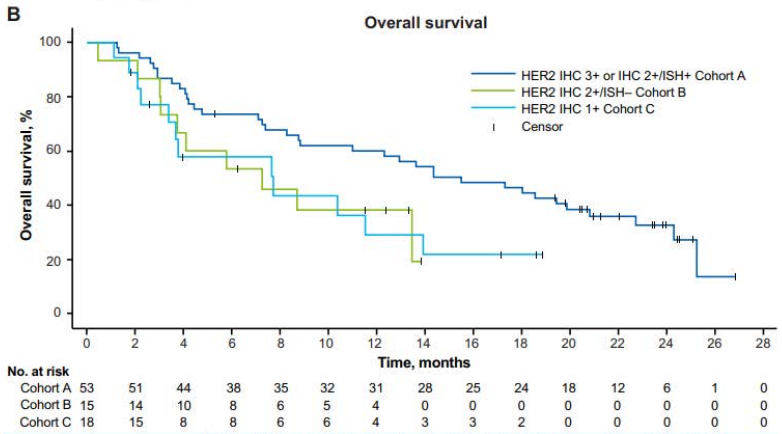



**Fig. 1 | Antitumor activity of trastuzumab deruxtecan. A** Waterfall plot showing the greatest percentage change from baseline in the sum of diameters of measurable tumors in patients with HER2-positive mCRC (cohort A). Each bar represents a patient. The line at 20% indicates progressive disease. The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




| | HER2 IHC 3+ or IHC 2+/ISH+ Cohort A n = 53 | HER2 IHC 2+/ISH– Cohort B n = 15 | HER2 IHC 1+ Cohort C n = 18 |
|---|---|---|---|
| Median progression-free survival (95% CI), months | 6.9 (4.1–8.7) | 2.1 (1.4–4.1) | 1.4 (1.3–2.1) |




| | HER2 IHC 3+ or IHC 2+/ISH+ Cohort A n = 53 | HER2 IHC 2+/ISH– Cohort B n = 15 | HER2 IHC 1+ Cohort C n = 18 |
|---|---|---|---|
| Median overall survival (95% CI), months | 15.5 (8.8–20.8) | 7.3 (3.0–NE) | 7.7 (2.2–13.9) |

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

Yoshino T et al, Nat Comm 2023

# DESTINY-CRC01: Antitumor activity of T-DXd according to baseline HER2 biomarker status

| | | n | ORR (95% CI) | *P* value | Median PFS, months (95% CI) | *P* value | Median OS, months (95% CI) | *P* value |
|---|---|---|---|---|---|---|---|---|
| HER2 status | IHC2+/ISH+ | 13 | 7.7 (0.2-36.0) | 0.003 | 4.1 (1.3-NA) | 0.002 | 11.0 (4.2-14.4) | 0.004 |
| | IHC3+ | 40 | 57.5 (40.9-73.0) | | 8.3 (5.4-10.9) | | 19.9 (8.8-25.3) | |
| HER2 H-score (cutoff = 240) | Below | 27 | 22.2 (8.6-42.3) | 0.001 | 4.1 (2.9-5.5) | 0.007 | 11.0 (4.2-14.4) | <0.001 |
| | Above | 26 | 69.2 (48.2-85.7) | | 8.7 (6.9-12.6) | | 25.3 (12.3-NA) | |
| HER2/CEP17 ratio (cutoff = 6.30) | Below | 18 | 22.2 (6.4-47.6) | 0.019 | 4.1 (1.6-6.9) | 0.170 | 7.4 (4.1-14.4) | 0.023 |
| | Above | 34 | 58.8 (40.7-75.4) | | 8.5 (5.5-11.2) | | 19.9 (12.3-25.3) | |
| HER2 ISH signal (cutoff = 11.25) | Below | 21 | 19.0 (5.4-41.9) | 0.002 | 4.1 (1.4-5.5) | <0.001 | 7.4 (4.1-13.6) | 0.002 |
| | Above | 31 | 64.5 (45.4-80.8) | | 8.7 (6.9-11.3) | | 22.8 (15.5-NA) | |
| Plasma *HER2* Amp | n.d/Ane | 16 | 25.0 (7.3-52.4) | 0.070 | 4.1 (1.6-6.9) | 0.004 | 13.0 (3.5-19.5) | 0.124 |
| | Focal | 36 | 55.6 (38.1-72.1) | | 8.7 (4.1-11.3) | | 19.2 (8.8-25.3) | |
| *HER2* ApCN (cutoff = 30.99) | Below | 28 | 32.1 (15.9-52.4) | 0.050 | 4.1 (2.8-6.9) | <0.001 | 8.8 (4.2-14.4) | <0.001 |
| | Above | 24 | 62.5 (40.6-81.2) | | 10.9 (8.3-12.7) | | 24.3 (18.0-NA) | |
| HER2ECD (cutoff = 23.5) | Below | 27 | 29.6 (13.8-50.2) | 0.023 | 4.1 (2.9-7.3) | 0.136 | 13.6 (4.4-18.6) | 0.317 |
| | Above | 22 | 63.6 (40.7-82.8) | | 8.3 (5.4-11.3) | | 18.2 (7.3-24.3) | |

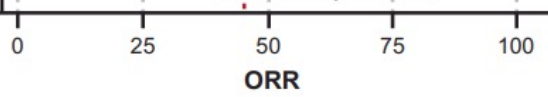


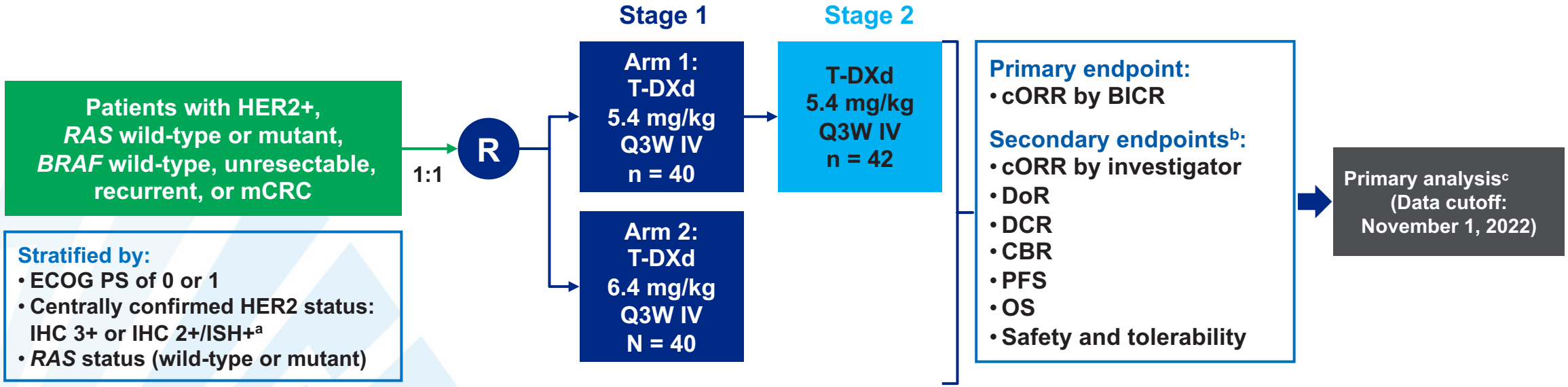

**Fig. 3 | Antitumor activity of T-DXd according to baseline HER2 biomarker status.** Exploratory cutoff values for each HER2 biomarker were defined as the maximum value of the Youden index for ORR. Vertical red dashed line shows the ORR of 45.3% in the overall population for Cohort A. *P* values are based on two-sided Fisher's exact test for ORR and those based on two-sided log-rank test for PFS and OS are shown, without adjustment for multiple comparisons. Error bars represent the 95% CI. The exact *P* values for HER2 H-score for OS, HER2 ISH signal for PFS, *HER2* ApCN for PFS, and *HER2* ApCN for OS were 0.000175, 0.000394, 0.0000168, and 0.0000991, respectively. Amp, amplification; ApCN, adjusted plasma copy number; HER2, human epidermal growth factor receptor 2; HER2ECD, human epidermal growth factor receptor 2 extracellular domain; IHC, immunohistochemistry; ISH, in situ hybridization; NA, not applicable; ND, not determined; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Siena S et al, Nature Comm 2024

# DESTINY-CRC02 Study Design

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

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




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

BICR, blinded independent central review; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; CBR, clinical benefit rate; cORR, confirmed objective response rate; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
Both investigators and patients were blind to treatments.
[a]HER2 status was assessed with the Roche VENTANA HER2 Dual ISH DNA probe cocktail assay (IUO). [b]Exploratory endpoints included best percent change in the sum of diameters of measurable tumors based on BICR and investigator. [c]Primary analysis occurred ≥6 months after the last patient had been enrolled or when all patients discontinued from the study, whichever was earlier.

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

# DESTINY-CRC02: efficacy results

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

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

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

# DESTINY-CRC02: efficacy results in subgroups

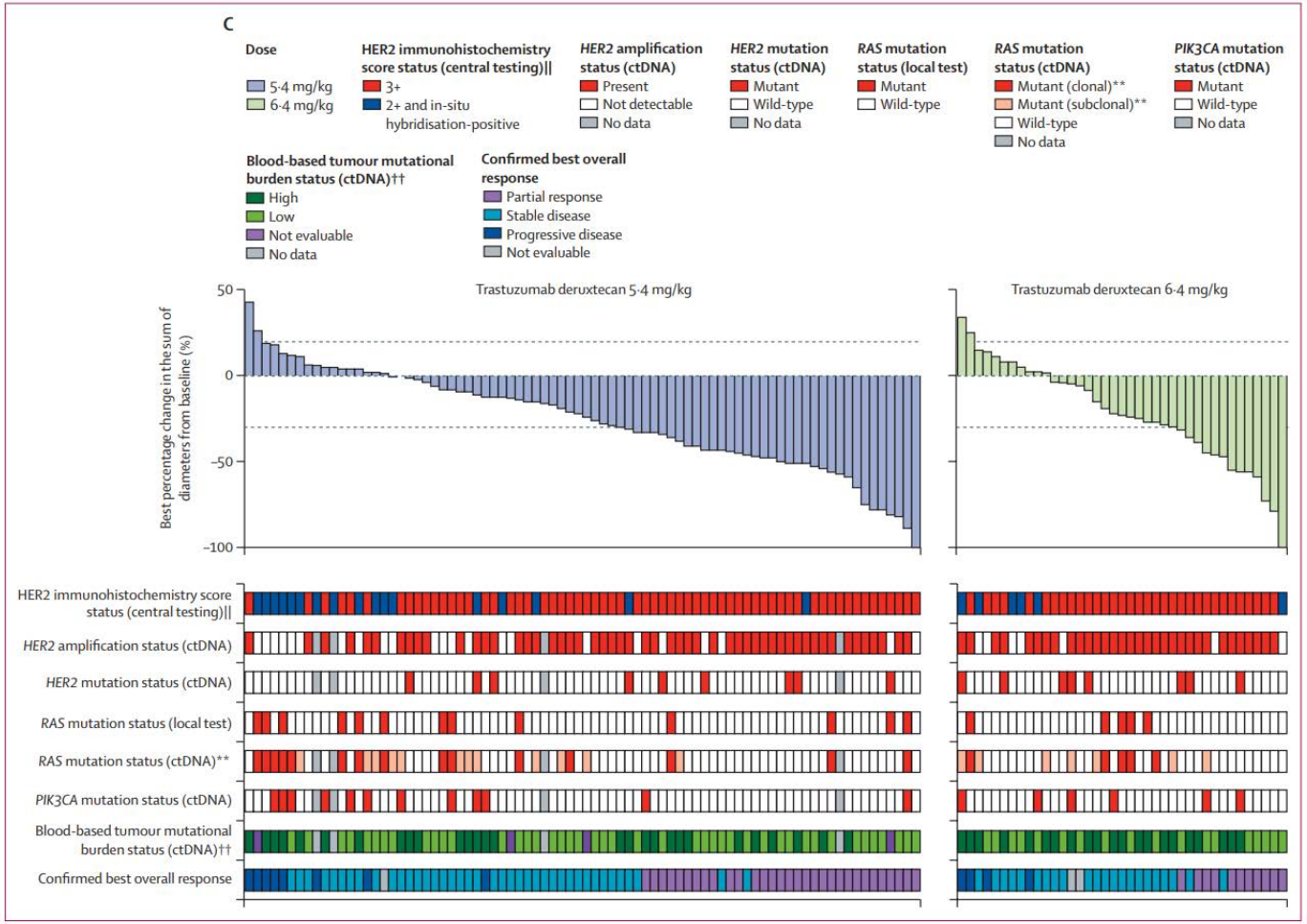



***Figure 2:*** **Subgroup analyses of confirmed objective response rate and best percentage change in the sum of the diameters of all target lesions**
(A) Subgroup analyses of confirmed objective response rate in patients in the trastuzumab deruxtecan 5·4 mg/kg group. (B) Subgroup analyses of confirmed objective response rate in patients in the trastuzumab deruxtecan 6·4 mg/kg group. (C) Percentage change in the sum of diameters by blinded independent central review. Only patients with measurable disease at baseline and at least one post-baseline tumour assessment were included in the figure. Three patients with evaluable ctDNA were not evaluable per Response Evaluation Criteria in Solid Tumours version 1.1 and are not included in the figure. The dashed line at 20% denotes progressive disease and the dashed line at −30% denotes partial response, per Response Evaluation Criteria in Solid Tumours version 1.1. ctDNA=circulating tumour DNA. ECOG=Eastern Cooperative Oncology Group. NA=not applicable. *Based on the exact Clopper-Pearson method for binomial distribution. †Subgroups with fewer than ten patients are reported as NA. ‡Includes rectum, sigmoid, and descending. §Includes caecum, ascending, and transverse. ¶All *RAS*-mutant responders were immunohistochemistry score 3+. ||HER2 status was assessed by central laboratory. ***RAS* mutations were considered clonal if clonality score was ≥0·3 and subclonal if clonality score was <0·3. ††Blood-based tumour mutational burden cutoff was 20 mutations per Mb.

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

# DESTINY-CRC01 and DESTINY-CRC02: adverse events

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

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

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

## Adjudicated drug-related interstitial lung disease or pneumonitis

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

- **Destiny CRC-01:**

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

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

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

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

# HER2-targeted therapies in mCRC

Table 1. HER2-targeted therapies in HER2+ mCRC.

| Clinical trial | Therapies | Patients, N | ORR, % (95% CI) | PFS, months |
|---|---|---|---|---|
| HERACLES-A [17] | Lapatinib + trastuzumab | 32 (response evaluable) | 28 | 4.7 |
| MyPathway [18] | Pertuzumab + trastuzumab | 57[†] (all patients) | 32[†] (20–45) | 2.9 |
| | | 43 (HER2+, *KRAS* WT) | 40 (25–56) | 5.3 |
| | | 13 (HER2+, *KRAS* mutated) | 8 (0.2–36) | 1.4 |
| HERACLES-B [19] | Pertuzumab + T-DM1 | 31 | 9.7 | 4.1 |
| TAPUR [20] | Trastuzumab + pertuzumab | 38 | 25 | 17.2 weeks |
| TRIUMPH [21] | Pertuzumab + trastuzumab | 30 | 30 (14–50) in tissue-positive patients | 4.0 in tissue-positive patients |
| | | | 28 (12–49) in ctDNA-positive patients | 3.1 in ctDNA-positive patients |
| DESTINY-CRC01 [22] | Trastuzumab deruxtecan | 53 | 45.3[‡] | 6.9 |
| MOUNTAINEER [23] | Tucatinib + trastuzumab | 84 (HER2+, *RAS* WT) | 38.1[‡] (27.7–49.3)[§] | 8.2 |
| HER2-FUSCC-G [24] | Trastuzumab + pyrotinib | 11 (ongoing) | 45.5 | 7.8 |

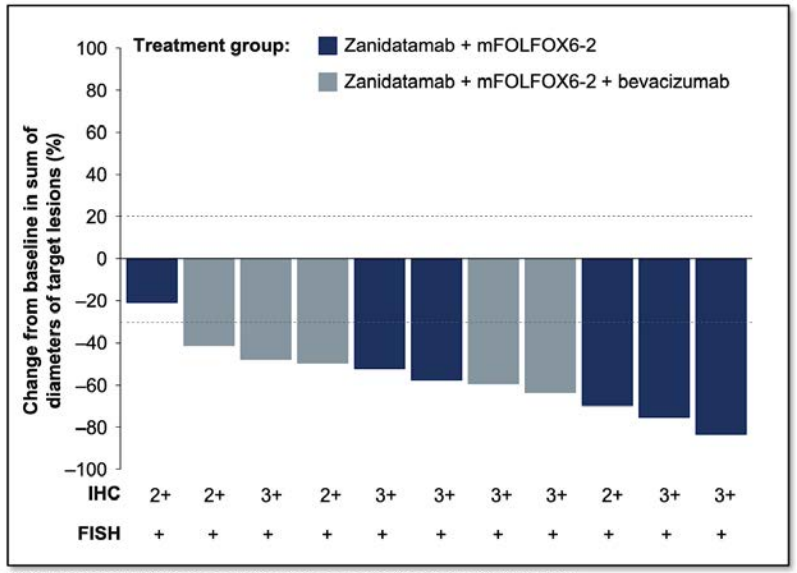
[†]Confirmation was not required; 56/57 patients were tested for *KRAS* status.
[‡]Confirmed ORR.
[§]Two-sided 95% exact CI, computed using the Clopper – Pearson method (1934).
CI: confidence interval; ctDNA: circulating tumor DNA; HER2: human epidermal growth factor receptor 2; ORR: objective response rate; PFS: progression-free survival; T-DM1: ado-trastuzumab emtansine; WT: wild type.

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

# First-Line Zanidatamab + Chemotherapy for HER2-positive mCRC

| | Zanidatamab + mFOLFOX6-2 (n=6) | Zanidatamab + mFOLFOX6-2 + bevacizumab (n=5) | Total (N=11) |
|---|---|---|---|
| **cORR** | | | |
| n (%) | 5 (83.3) | 5 (100) | 10 (90.9) |
| 95% CI | 35.9, 99.6 | 47.8, 100 | 58.7, 99.8 |
| **cBOR, n (%)** | | | |
| CR | 0 (0) | 0 (0) | 0 (0) |
| PR | 5 (83.3) | 5 (100) | 10 (90.9) |
| SD | 1 (16.7) | 0 (0) | 1 (9.1) |
| PD | 0 (0) | 0 (0) | 0 (0) |
| **DCR[b]** | | | |
| n (%) | 6 (100) | 5 (100) | 11 (100) |
| 95% CI | 54.1, 100 | 47.8, 100 | 71.5, 100 |

**Median (range) duration of response:**
Not reached (2.9+-16.7+) months




Dotted lines indicate 20% increase or 30% decrease in sum of diameters of target tumours.

| | Zanidatamab + mFOLFOX6-2 (n=6) | | Zanidatamab + mFOLFOX6-2 + bevacizumab (n=7)[a] | | Total (N=13) | |
|---|---|---|---|---|---|---|
| **Any TEAE, n (%)** | 6 (100) | | 7 (100) | | 13 (100) | |
| **Any TRAE,[b] n (%)** | 6 (100) | | 7 (100) | | 13 (100) | |
| Grade 1-2 | 4 (66.7) | | 4 (57.1) | | 8 (61.5) | |
| Grade 3-4 | 2 (33.3) | | 3 (42.9) | | 5 (38.5) | |
| Grade 5 | 0 (0) | | 0 (0) | | 0 (0) | |
| **Serious TRAE,[b] n (%)** | 1 (16.7) | | 1 (14.3) | | 2 (15.4) | |
| **TRAEs leading to zanidatamab discontinuation, n (%)** | 0 (0) | | 0 (0) | | 0 (0) | |
| **Most common TRAEs,[b,c] n (%)** | **Any grade** | **Grade 3-4** | **Any grade** | **Grade 3-4** | **Any grade** | **Grade 3-4** |
| Diarrhoea | 4 (66.7) | 1 (16.7) | 7 (100) | 2 (28.6) | 11 (84.6) | 3 (23.1) |
| Nausea | 4 (66.7) | 0 (0) | 5 (71.4) | 1 (14.3) | 9 (69.2) | 1 (7.7) |
| Peripheral sensory neuropathy | 4 (66.7) | 0 (0) | 3 (42.9) | 1 (14.3) | 7 (53.8) | 1 (7.7) |
| Fatigue | 1 (16.7) | 0 (0) | 3 (42.9) | 1 (14.3) | 4 (30.8) | 1 (7.7) |
| Infusion-related reaction | 2 (33.3) | 0 (0) | 2 (28.6) | 0 (0) | 4 (30.8) | 0 (0) |
| Stomatitis | 3 (50.0) | 0 (0) | 1 (14.3) | 0 (0) | 4 (30.8) | 0 (0) |
| Ejection fraction decreased | 2 (33.3) | 0 (0) | 1 (14.3) | 1 (14.3) | 3 (23.1) | 1 (7.7) |
| Vomiting | 1 (16.7) | 0 (0) | 2 (28.6) | 1 (14.3) | 3 (23.1) | 1 (7.7) |

Two of 12 DLT-evaluable patients had DLTs (diarrhoea) – 1 in each regimen
- ✓ Diarrhoea resolved with concomitant medication

- Three serious TRAEs in 2 patients
  - ✓ One patient experienced dehydration
  - ✓ One patient experienced colitis and acute kidney injury
- No discontinuations of zanidatamab due to TRAEs and no treatment-related deaths

Rha SY et al. ESMO 2024; Abstract 516MO.

# Strategy in pretreated mCRC, HER2 pos

- **MOUNTAINEER study**
  Tucatinib and trastuzumab works well in *RAS* WT cases with IHC 3+, but also active in IHC2+/ISH+

- Studies in earlier disease are ongoing (e.g. MOUNTAINEER-03)

- **DESTINY-CRC02 Study**
  Recommended dose of T-DXd for mCRC is 5.4 mg/kg
  T-DXd works well in IHC 3+ cases regardless of *RAS* status
  Regardless of prior anti-HER2 therapy

# Questions from General Medical Oncologists

- What is the optimal second-line treatment for HER2+ mCRC — tucatinib/trastuzumab or T-DXd?
- 65 yo woman with Stage IV colon cancer, HER2 IHC 3+, KRAS WT, MSS, BRAF WT, recent h/o DVT and now CHF. How do you use HER2-targeted therapy in patients with cardiac disease, especially if LVEF is less than 45% or with h/o nonischemic or ischemic cardiomyopathy or heart failure with reduced EF?
- 90 yo woman with HER2-positive mCRC. Would you consider first-line anti-HER2 therapy for this patient?

# Questions from General Medical Oncologists

- 66 yo woman with Stage IV HER2-mutant colon cancer. What is the optimal treatment?
- 70 yo man responding to tucatinib and trastuzumab. The patient kept losing weight without any clear reasons. What might be causing this, and what would you recommend?
- HER2 positivity definition — is there any difference in colorectal as opposed to upper GI tract cancer?
- Newly diagnosed HER2 IHC 3+ mCRC with brain mets. Use tucatinib/trastuzumab or T-DXd as initial therapy due to CNS activity?

# Questions from General Medical Oncologists

- **Can CRC metastases have heterogenous HER2 status (eg, a metastasis is positive but the primary is negative)? Also, can HER2 positivity emerge or be lost as we see in breast cancer, resulting in the need for multiple biopsies and retesting?**
- **I have a patient with mCRC, RAS WT, MSS, BRAF-negative, HER2-positive, on second-line tucatinib/trastuzumab after FOLFOX/bevacizumab. He's had an amazing response so far. Should I continue treatment indefinitely until progression or stop at some point if NED? Can I drop the tucatinib at any point and continue the trastuzumab as "maintenance"?**

# Agenda

**Module 1:** Optimizing Biomarker Assessment for Patients with Colorectal Cancer (CRC) — Dr Dasari

**Module 2:** Identification and Management of Metastatic CRC (mCRC) with a BRAF V600E Mutation — Dr Morris

**Module 3:** Incorporation of Immune Checkpoint Inhibitors into the Management of MSI-H/dMMR CRC — Dr Seligmann

**Module 4:** Integration of Therapies Targeting HER2 into the Management of mCRC — Prof Van Cutsem

**Module 5: Biomarker-Based Decision-Making for Patients with mCRC and KRAS G12C Mutations — Dr Lieu**

RTP RESEARCH TO PRACTICE

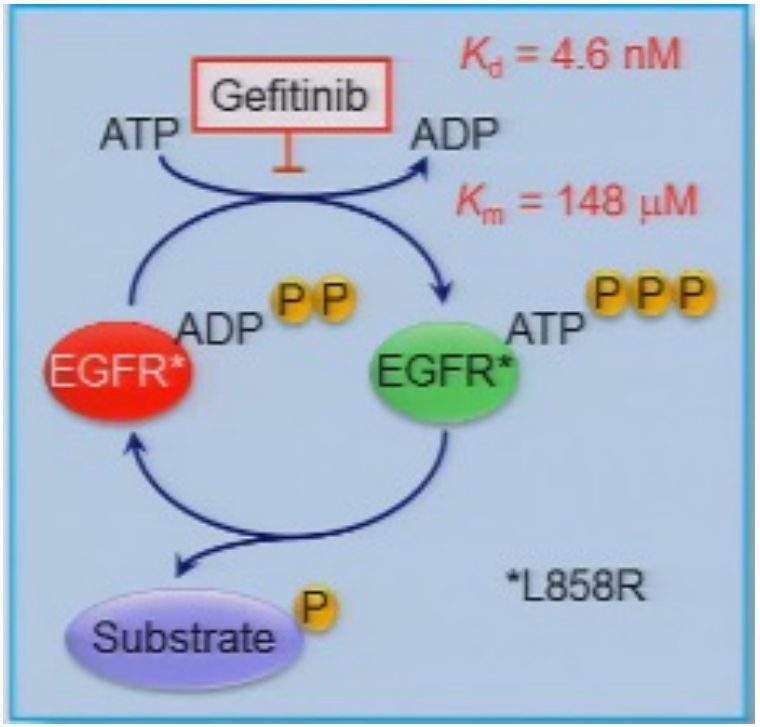
Cancer Center

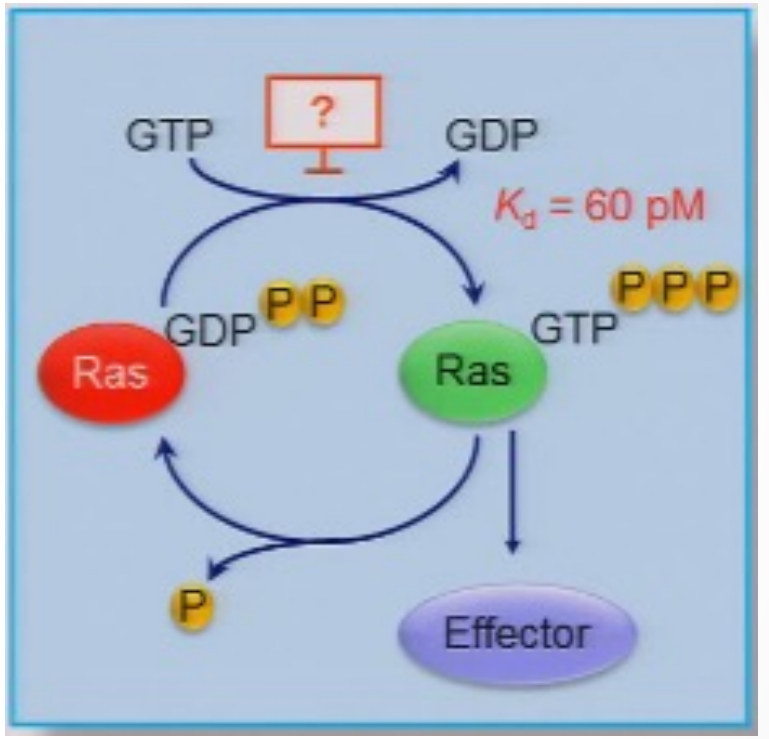
NCI-DESIGNATED COMPREHENSIVE CANCER CENTER

# KRAS G12C Mutations and Biomarker Directed Therapy in Metastatic Colorectal Cancer

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

# Unlike ATP-competitive inhibitors of protein kinases, GTP antagonists of RAS are not feasible

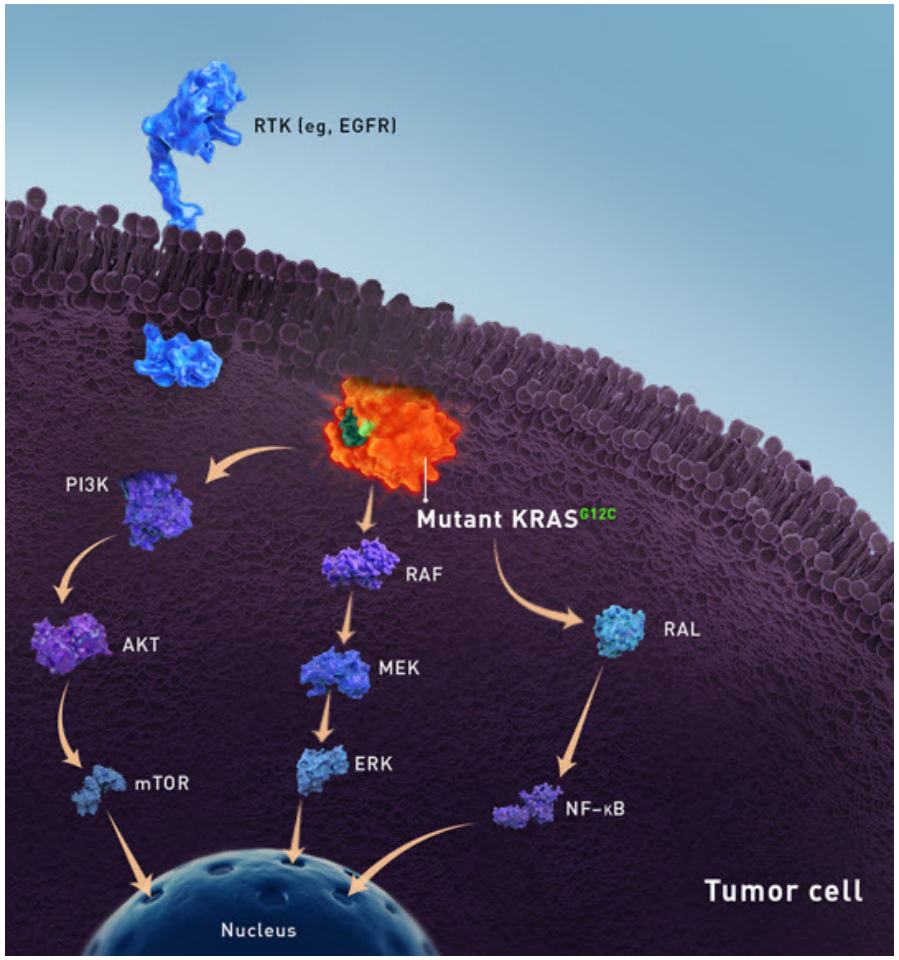


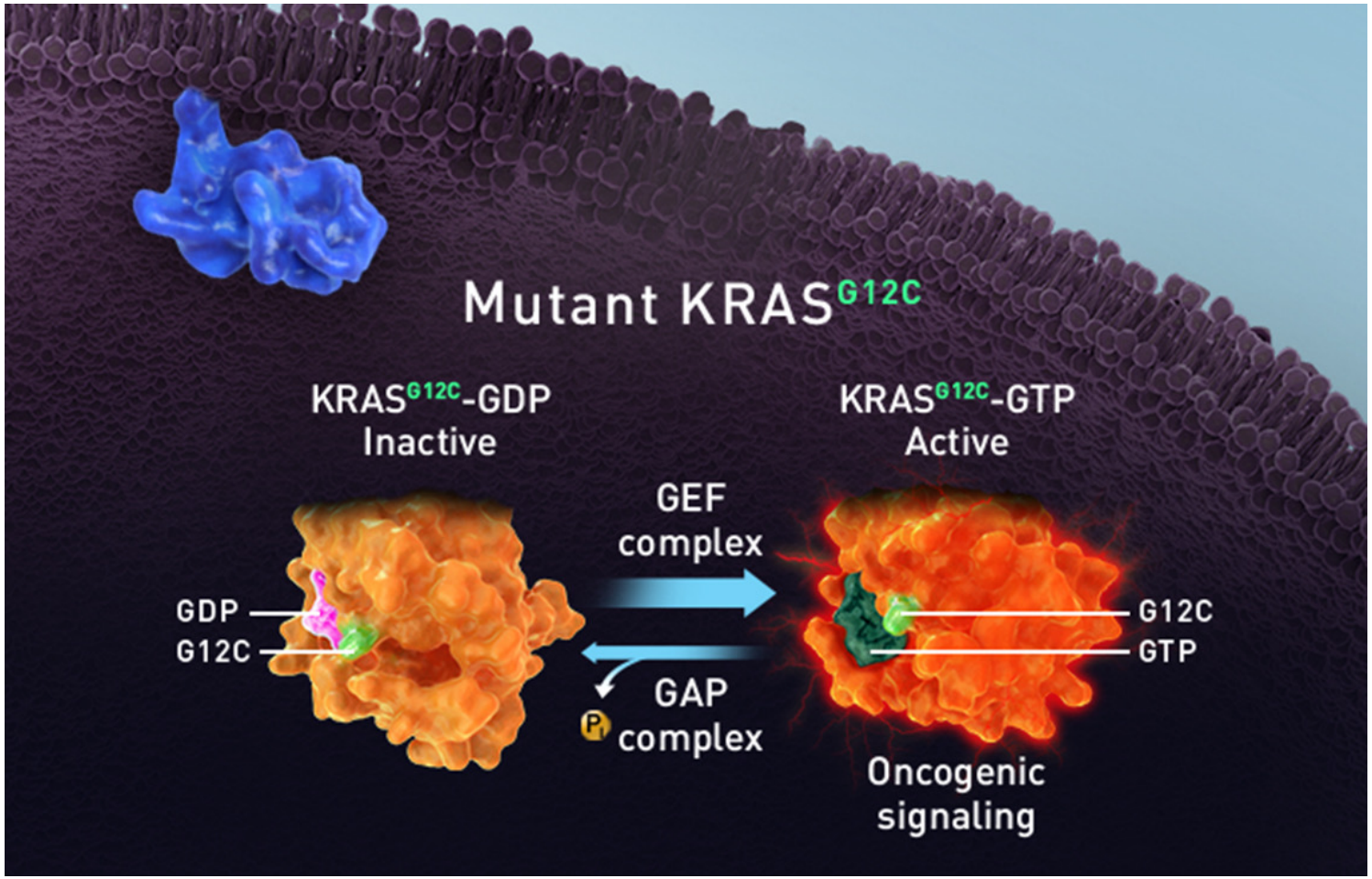




**RAS binds GTP with picomolar affinity**
**(1000 fold higher affinity)**

Channing Der PhD. ASCO GI 2012.

# KRAS has historically been “undruggable”

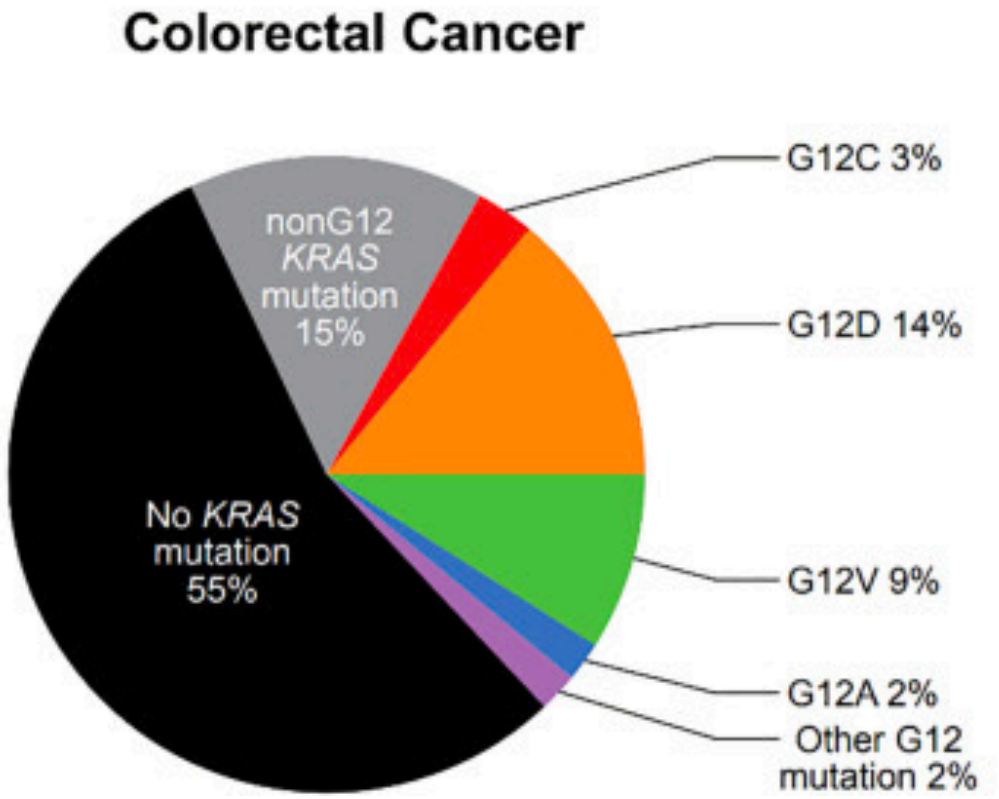


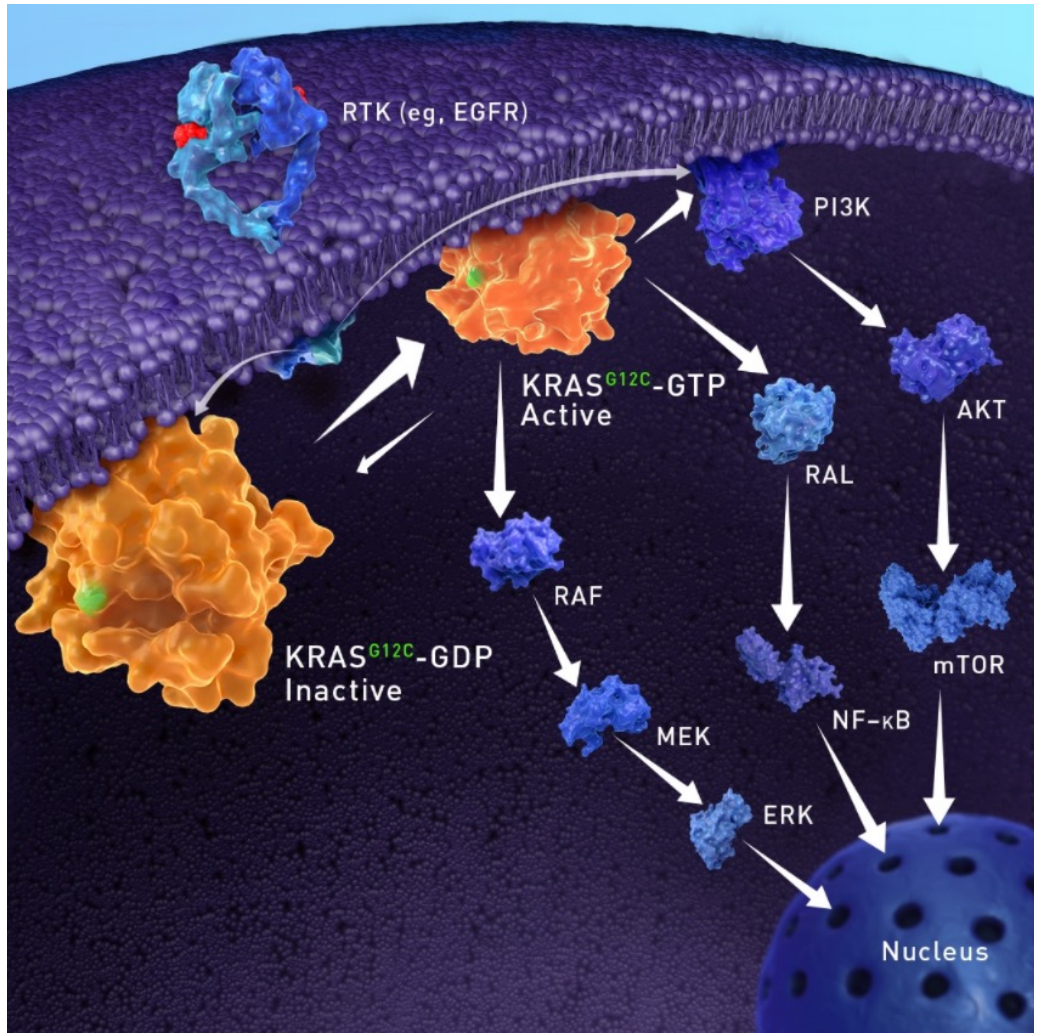




https://www.amgenoncology.com/targets/kras.html

# KRAS G12C Mutations in Colorectal Cancer

$KRAS^{G12C}$ mutations occur in approximately **3-4%** of CRC, act as oncogenic drivers, and are a negative predictor of cetuximab efficacy

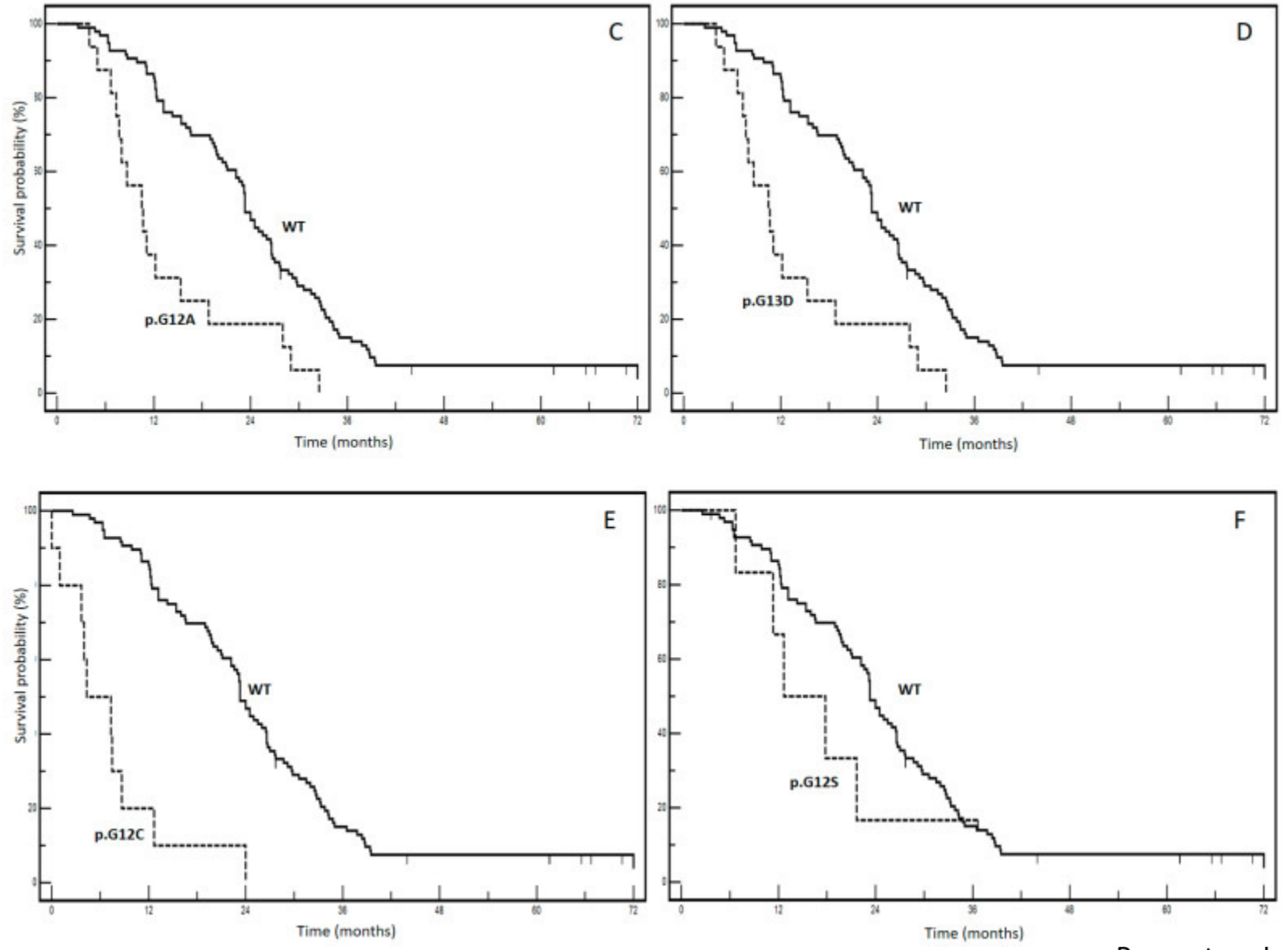



Qunaj et al. Front Oncol. 2023 Sep 15;13:1252516

# KRAS G12C Mutations Appear to Confer a Worse Prognosis

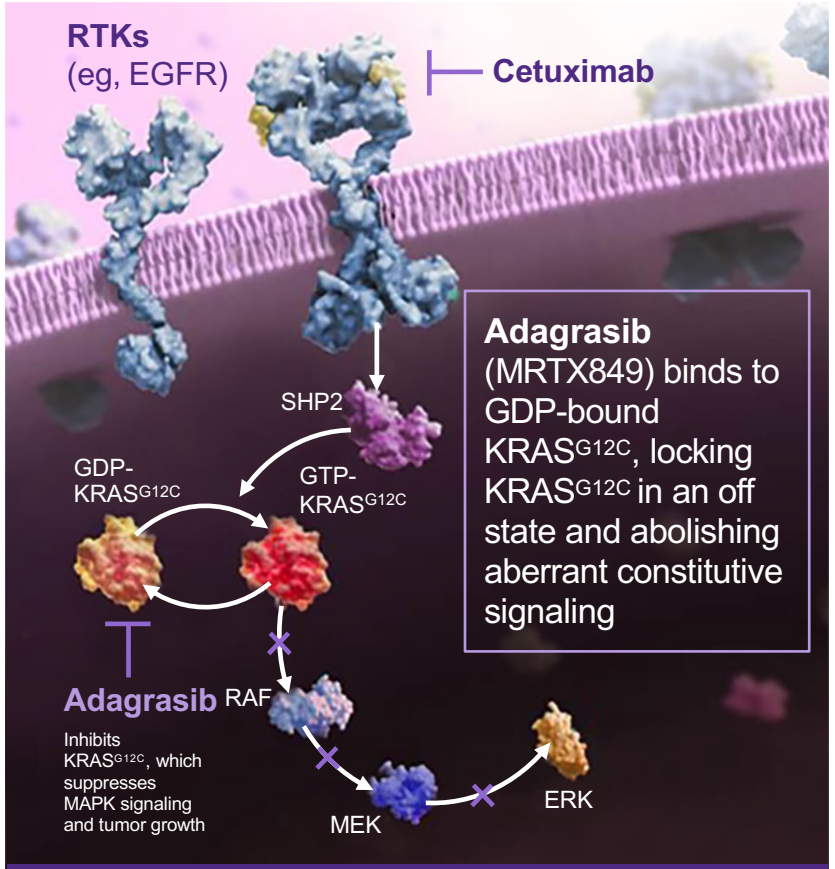
KRAS G12C




Ottaiano et al. *Cancers* 2023;15(14):3579.

# Adagrasib (MRTX849) Is a Differentiated, Selective Inhibitor of KRAS$^{G12C}$

- Adagrasib, a covalent inhibitor of KRAS$^{G12C}$, irreversibly and selectively binds KRAS$^{G12C}$ in its inactive, GDP-bound state
- Maintaining continuous adagrasib exposure above a target threshold enables inhibition of KRAS-dependent signaling for the complete dosing interval and maximizes antitumor activity
- Combining adagrasib with cetuximab, an EGFR inhibitor, may enhance inhibition of KRAS-dependent signaling or overcome adaptive feedback to improve outcomes[8]

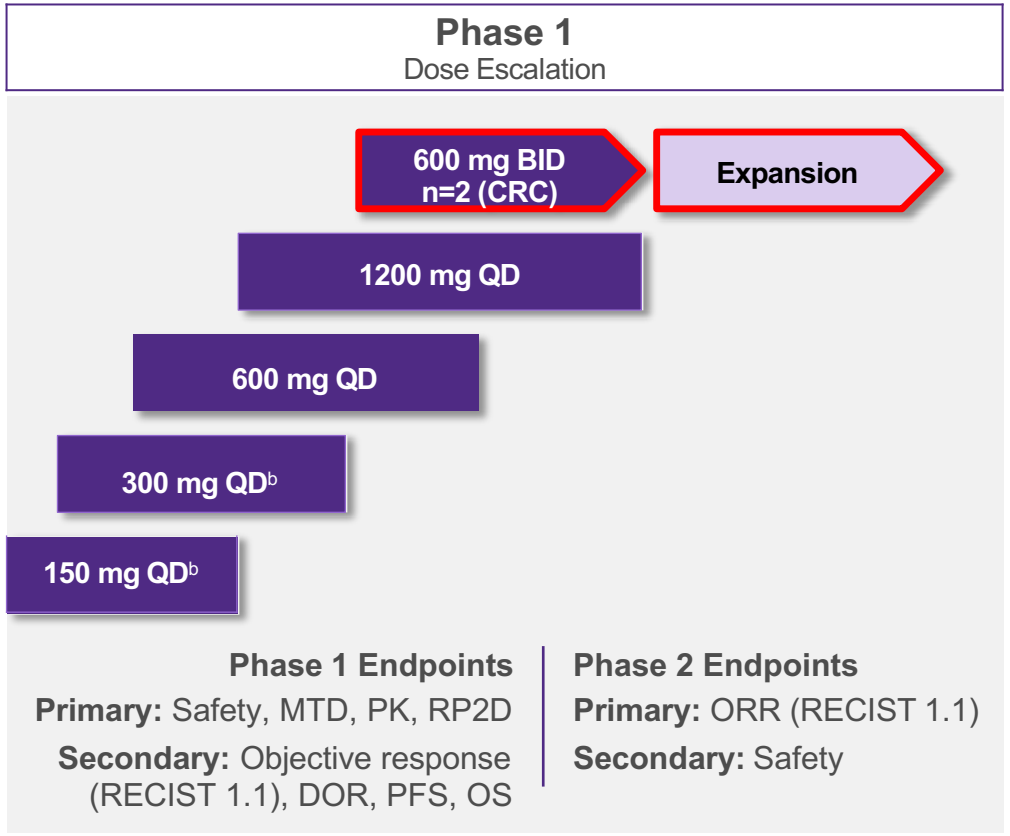



**EGFR signaling is implicated in feedback reactivation, providing a rational co-targeting strategy for KRAS-mutant CRC**

# KRYSTAL-1 (849-001) Study Design

**Key Eligibility Criteria (Up to n=565)**

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

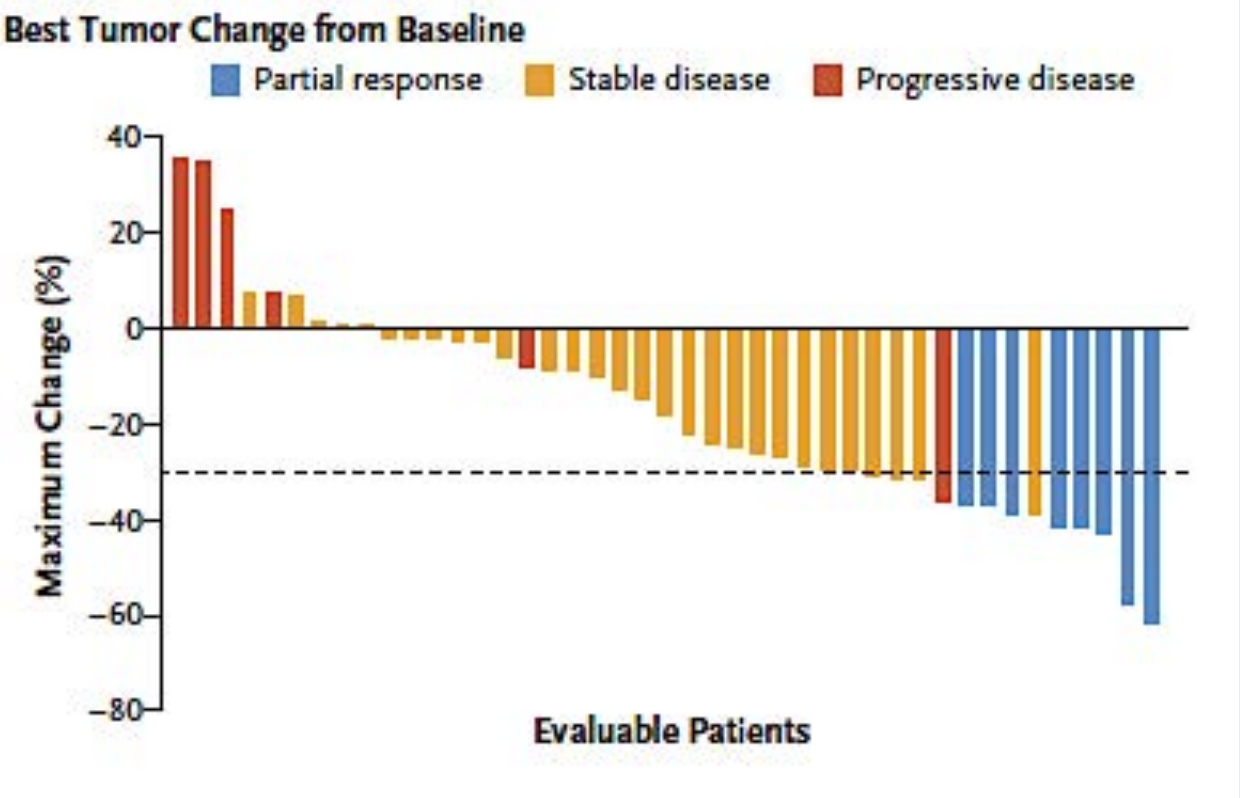



- Previously reported data demonstrated the clinical activity of adagrasib in patients with pretreated CRC with a KRAS$^{G12C}$ mutation[9]
- Here we report preliminary data for adagrasib 600 mg BID as monotherapy (n=2 in Phase 1/1b and n=44 in Phase 2; median follow-up: 8.9 months) and in combination with cetuximab (n=32; median follow-up: 7 months) in patients with pretreated CRC with a KRAS$^{G12C}$ mutation
- Data as of 25 May 2021 (monotherapy), 9 July 2021 (cetuximab combination)

[a]Tissue test and/or ctDNA allowed for Phase 1/1b eligibility. [b]Patients subsequently dose escalated up to 600 mg BID. [c]Patients must have declined 1L systemic therapy. [d]Subjects receiving prior treatment with a KRAS$^{G12C}$ inhibitor not eligible. [e]Subjects receiving prior treatment with a KRAS$^{G12C}$ inhibitor eligible for the Phase 1b adagrasib + cetuximab cohort. [f]Patients who received cetuximab who experienced clinical benefit had the option to continue on adagrasib alone. [g]Cetuximab was administered IV at a dose of 400 mg/m$^2$ followed by 250 mg/m$^2$ QW, or 500 mg/m$^2$ Q2W (Phase 1b). [h]Trial is registrational. [i]KRAS$^{G12C}$ mutation detected in tumor tissue and/or blood. [j]Patients who have stable disease compared to baseline measurements at week 13 or later during treatment with single agent adagrasib are eligible to cross over to adagrasib + cetuximab combination cohort. ClinicalTrials.gov. NCT03785249.

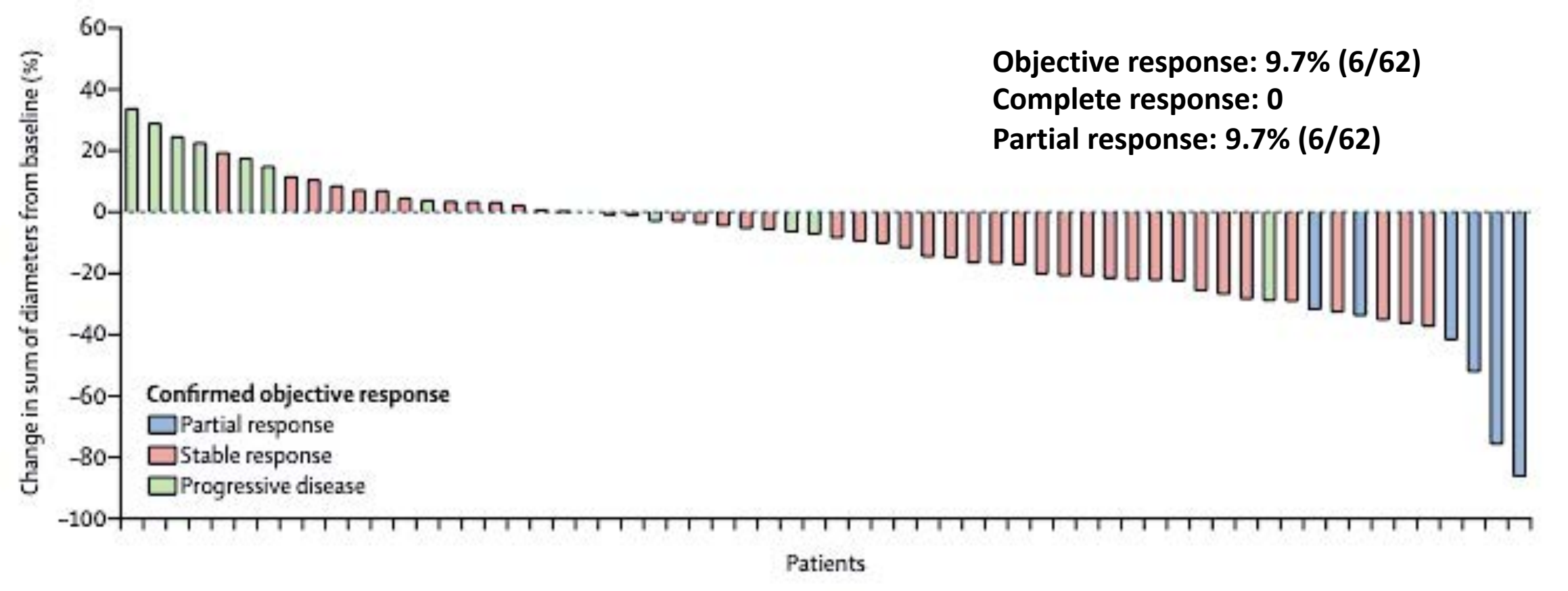
# KRYSTAL-1: Adagrasib Monotherapy for CRC with Mutated KRAS G12C

| Variable | Adagrasib Monotherapy (N=43)† |
|---|---|
| Objective response§ | |
| Per blinded independent central review — no. of patients | 10 |
| % (95% CI) | 23 (12–39) |
| As confirmed by investigator — no. of patients | 8 |
| % (95% CI) | 19 (8–33) |
| Best overall response — no. (%) | |
| Complete response | 0 |
| Partial response | 8 (19) |
| Stable disease | 29 (67) |
| Progressive disease | 6 (14) |
| Not evaluable | 0 |
| Median duration of response — mo | 4.3 |
| 95% CI | 2.3–8.3 |



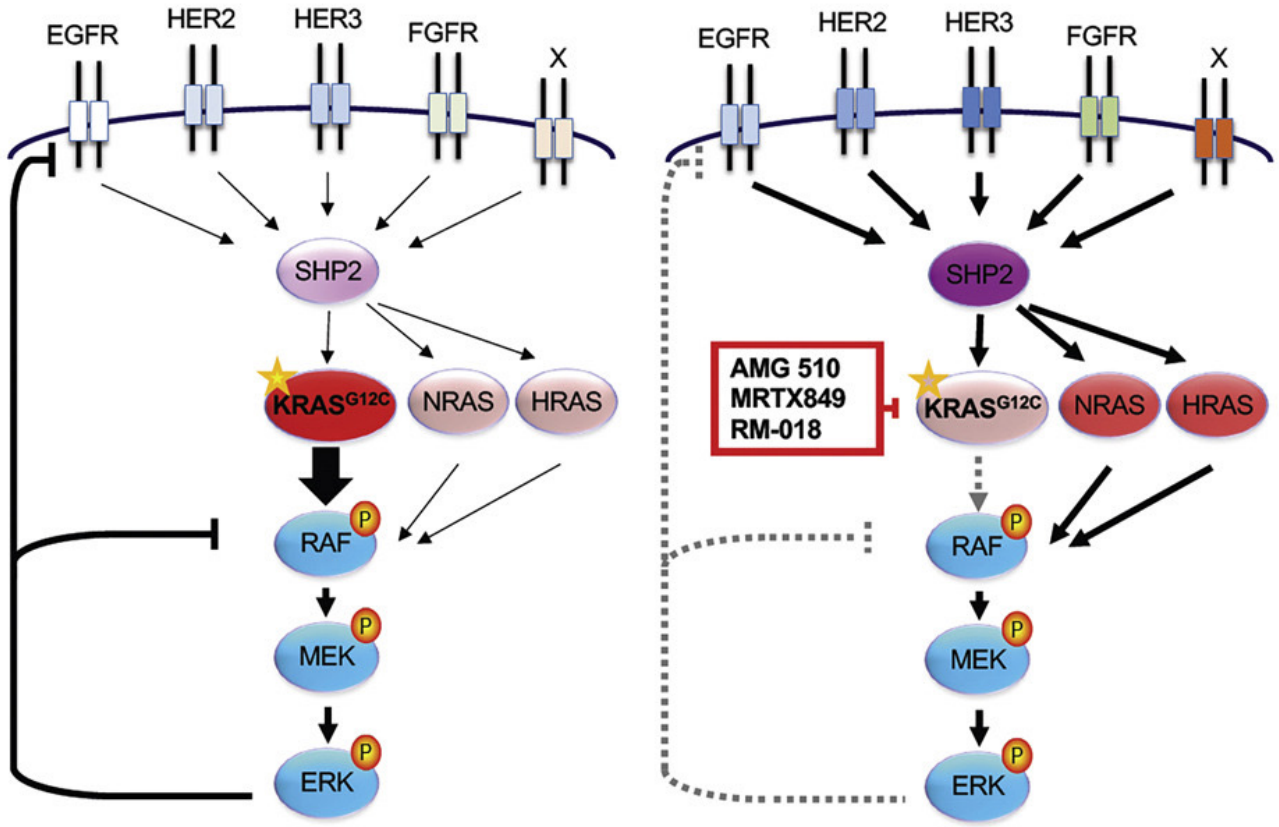

Yaeger R et al. *N Engl J Med* 2023;388:44-54.

# CodeBreaK 100: Sotorasib Monotherapy for CRC with Mutated KRAS G12C




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

# EGFR signaling is the dominant mechanism of CRC resistance to KRAS G12C inhibition



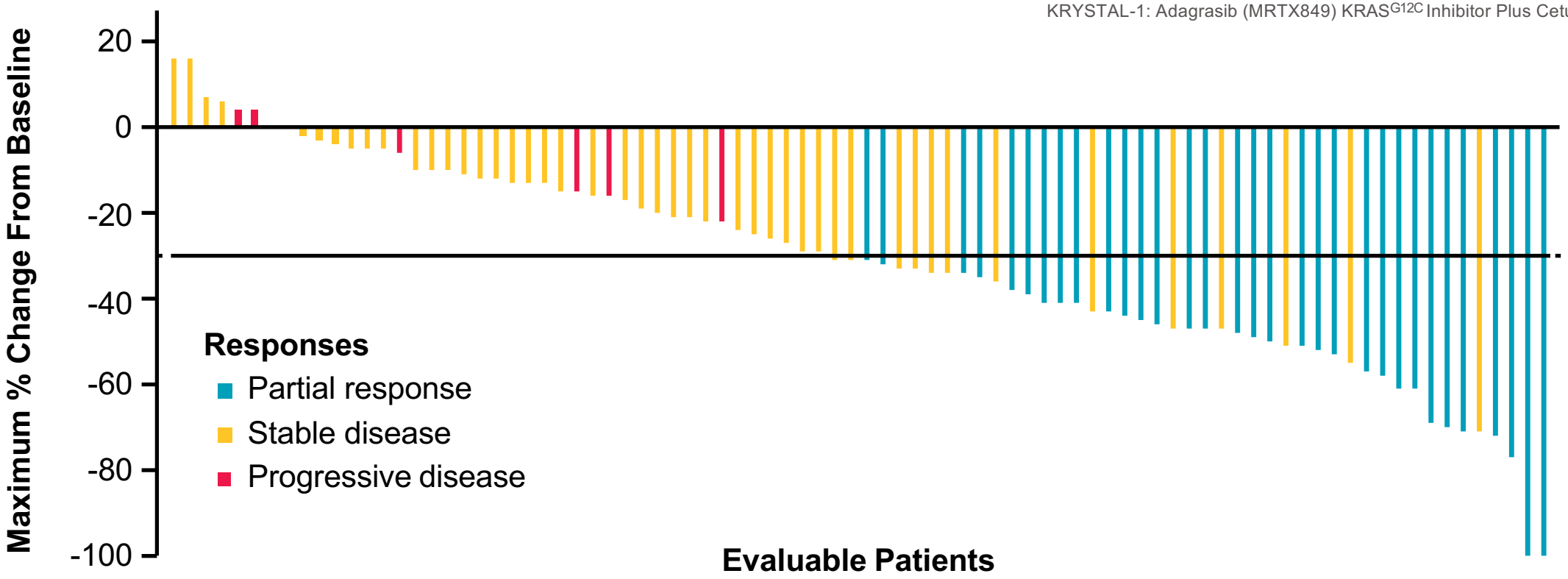

**No inhibitor** **+ inhibitor**

Ryan et al. *Cell Reports* 2022;39(12) 110993.

# Adagrasib and Cetuximab (combination) Best Tumor Change From Baseline

AACR American Association for Cancer Research
ANNUAL MEETING 2024 • SAN DIEGO
APRIL 5-10 • AACR.ORG/AACR24 • #AACR24

KRYSTAL-1: Adagrasib (MRTX849) KRAS$^{G12C}$ Inhibitor Plus Cetuximab in CRC




- Confirmed objective responses were observed in 32/94 patients (34.0%)[a]
- Disease control was observed in 80/94 patients (85.1%)

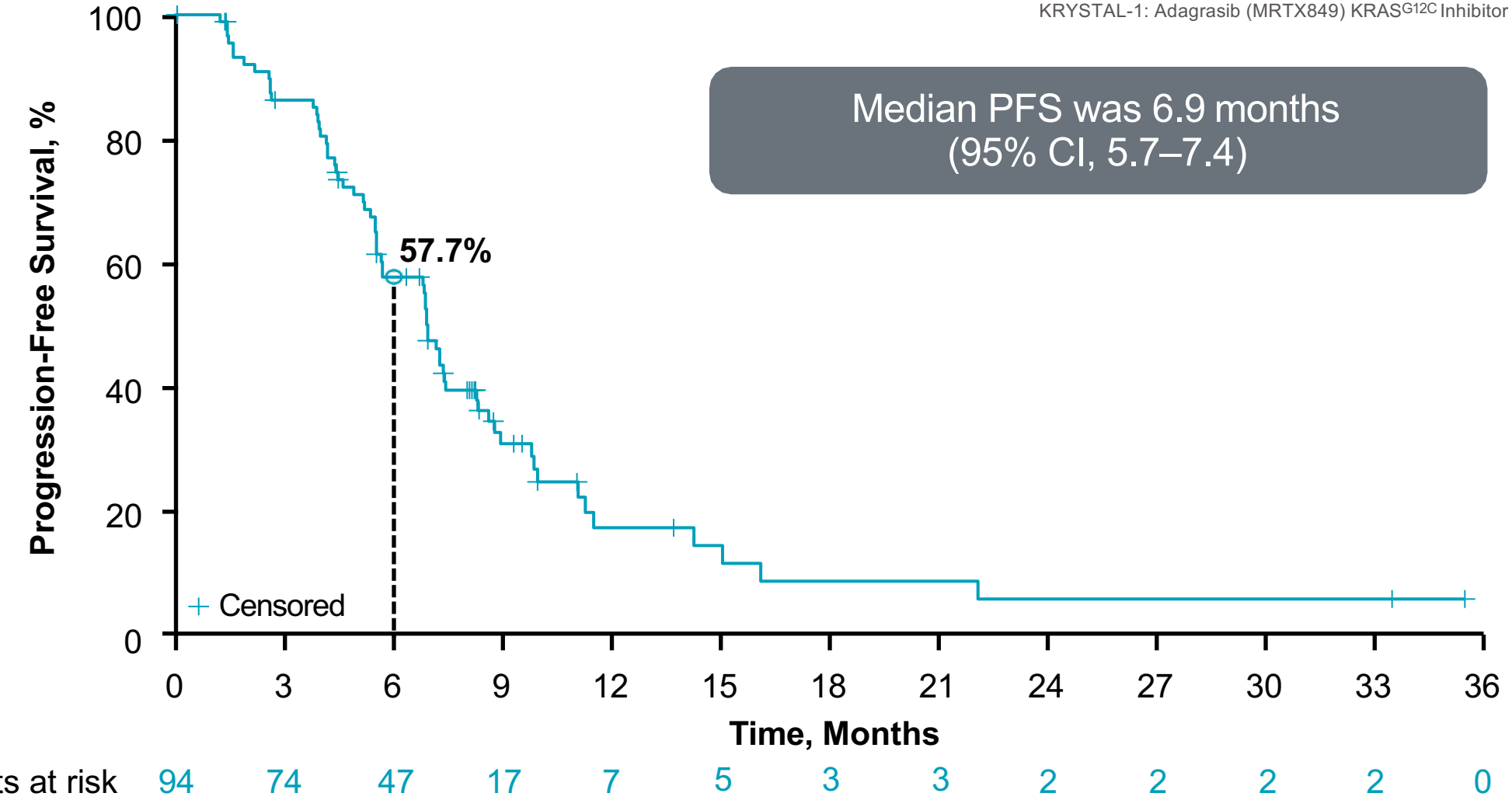
[a]ORR for the Phase 1 portion (n=32) was 43.8%; ORR for the Phase 2 portion (n=62) was 29.0%
All results are based on BICR. Waterfall plot excludes eight patients without any post-baseline scans
Data as of June 30, 2023 (median follow-up 11.9 months)

Kopetz S et al. AACR 2024;Abstract CT013;
Yaeger R et al *Cancer Discov* 2024;14(6):982-93.

# Progression-Free Survival



KRYSTAL-1: Adagrasib (MRTX849) $KRAS^{G12C}$ Inhibitor Plus Cetuximab in CRC



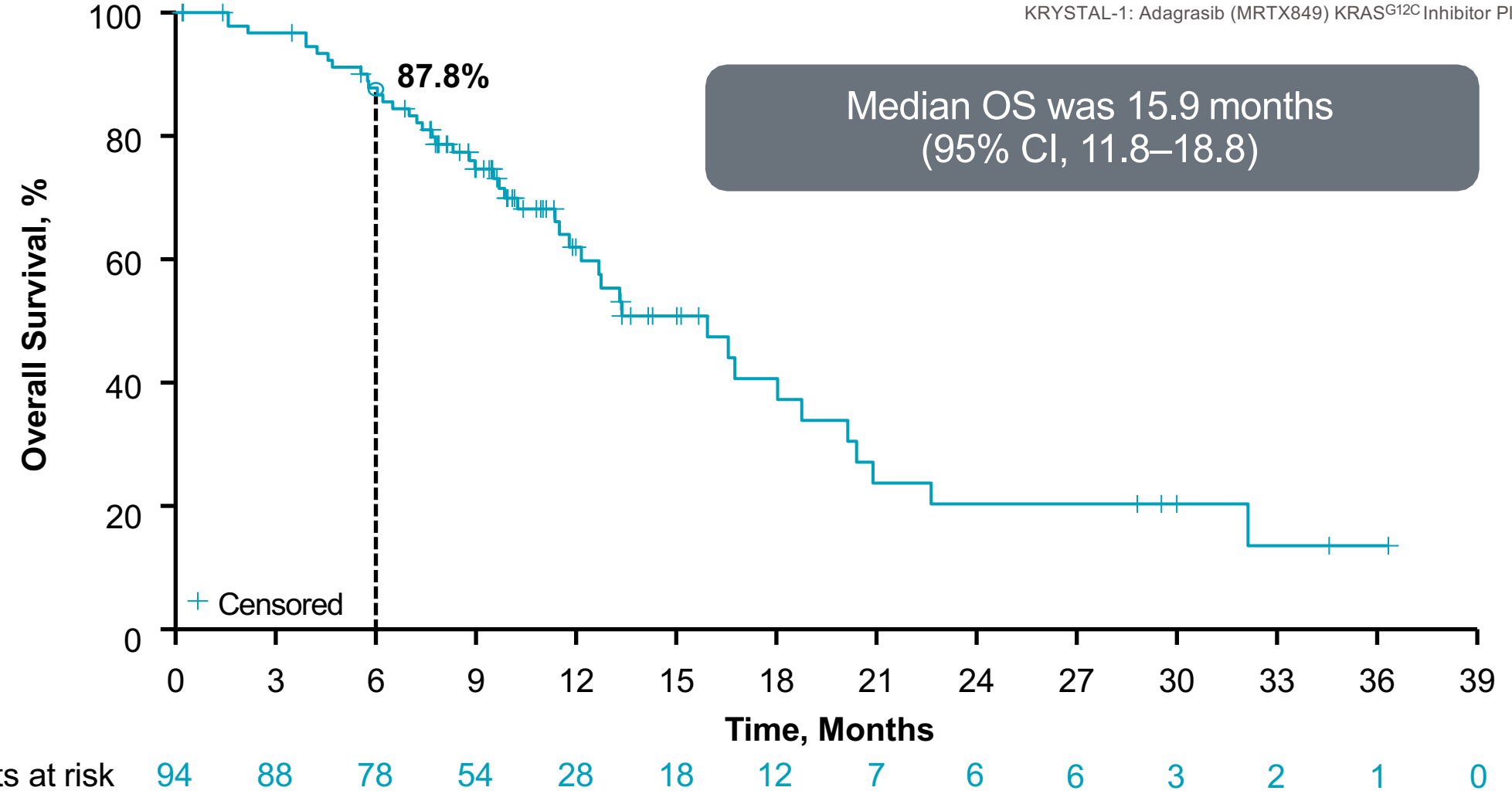

All results are based on BICR
Data as of June 30, 2023 (median follow-up 11.9 months)

Kopetz S et al. AACR 2024;Abstract CT013;
Yaeger R et al *Cancer Discov* 2024;14(6):982-93.

# Overall Survival



KRYSTAL-1: Adagrasib (MRTX849) $KRAS^{G12C}$ Inhibitor Plus Cetuximab in CRC




Median OS was 15.9 months
(95% CI, 11.8–18.8)

Data as of June 30, 2023 (median follow-up 11.9 months)

Kopetz S et al. AACR 2024;Abstract CT013;
Yaeger R et al *Cancer Discov* 2024;14(6):982-93.

# Take Home Point

- Adagrasib and cetuximab (combination) is now approved for metastatic colorectal cancer that has the KRAS G12C mutation

## FDA grants accelerated approval to adagrasib with cetuximab for KRAS G12C-mutated colorectal cancer

Share | Post | Linkedin | Email | Print

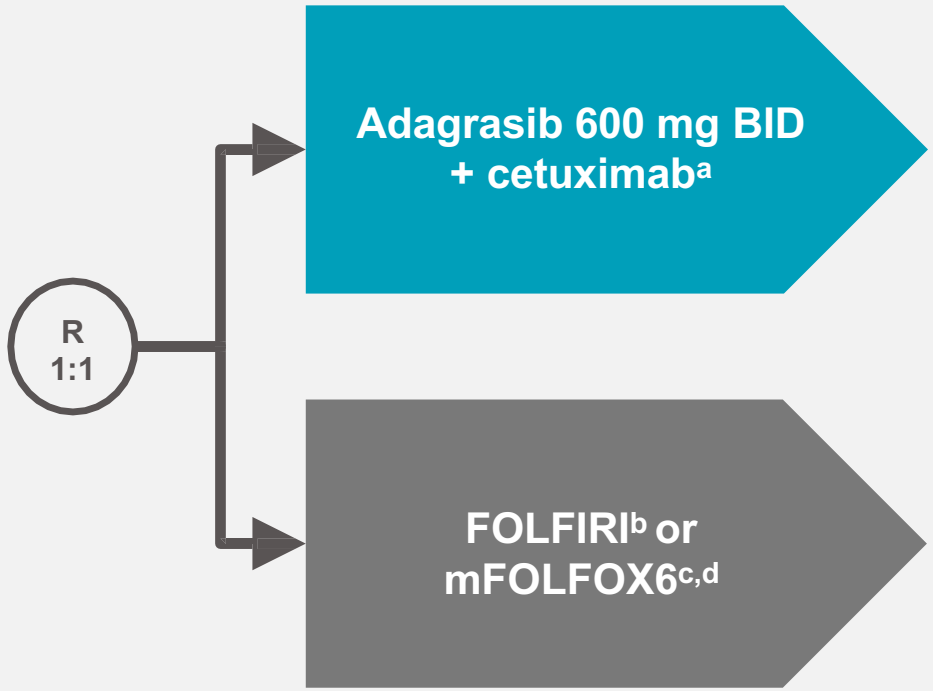
On June 21, 2024, the Food and Drug Administration granted accelerated approval to adagrasib plus cetuximab for adults with KRAS G12C-mutated locally advanced or metastatic colorectal cancer, as determined by an FDA-approved test, who have received prior treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy.

# KRYSTAL-10 (849-010) Phase 3: Study Design

AACR American Association for Cancer Research
ANNUAL MEETING 2024 • SAN DIEGO
APRIL 5-10 • AACR.ORG/AACR24 • #AACR24

**Key eligibility criteria**

- Metastatic CRC with $KRAS^{G12C}$ mutation
- Progression on first-line fluoropyrimidine-based oxaliplatin or irinotecan regimen




**Study objectives**

- Primary endpoints:
  - PFS, OS
- Secondary endpoints:
  - ORR (RECIST 1.1), 1-year OS, DOR, PK, PROs

KRYSTAL-10 is a global, Phase 3, randomized, open-label trial of second-line adagrasib + cetuximab versus chemotherapy in metastatic CRC with $KRAS^{G12C}$ mutation

[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 2,400 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 2,400 mg/m$^2$ dose given as continuous infusion over 46–48 hours).
[d]A VEGF/VEGFR inhibitor may be given per investigator discretion
ClinicalTrials.gov NCT04793958

# CodeBreaK 300 Phase 3 Study Design

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

**Key eligibility criteria**

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

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

**Randomization 1:1:1 (N = 160)**

**Sotorasib 960 mg daily + panitumumab 6 mg/kg 2QW (n = 53)**

**Sotorasib 240 mg daily + panitumumab 6 mg/kg 2QW (n = 53)**

**Investigator's choice: Trifluridine/tipiracil or regorafenib (n = 54)**

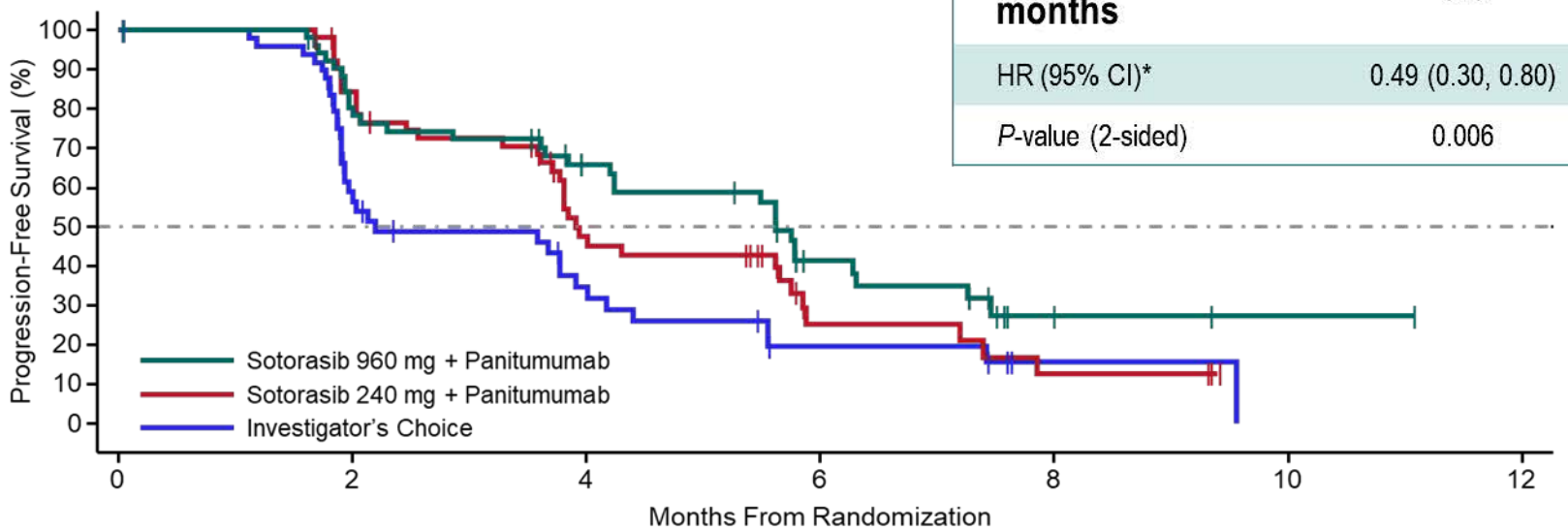
Treat until disease progression, start of another anti-cancer treatment, withdrawal of consent , or intolerance of treatment

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

Fakih et al. *N Engl J Med* 2023;389:2125-2139.

# Primary Endpoint: PFS in Intent-to-Treat Population

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




Number of Patients at Risk:

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

**After a median follow-up of 7.8 months, sotorasib (240 mg and 960 mg) in combination with panitumumab significantly improved PFS by BICR versus investigator's choice**

PFS was tested using stratified log-rank test. *HR is sotorasib 960 mg + panitumumab / investigator's choice therapy, or sotorasib 240 mg + panitumumab / investigator's choice therapy.
BICR, blinded independent central review; HR, hazard ratio; PFS, progression-free survival.

Fakih et al. *N Engl J Med* 2023;389:2125-2139.

# Activity Outcomes

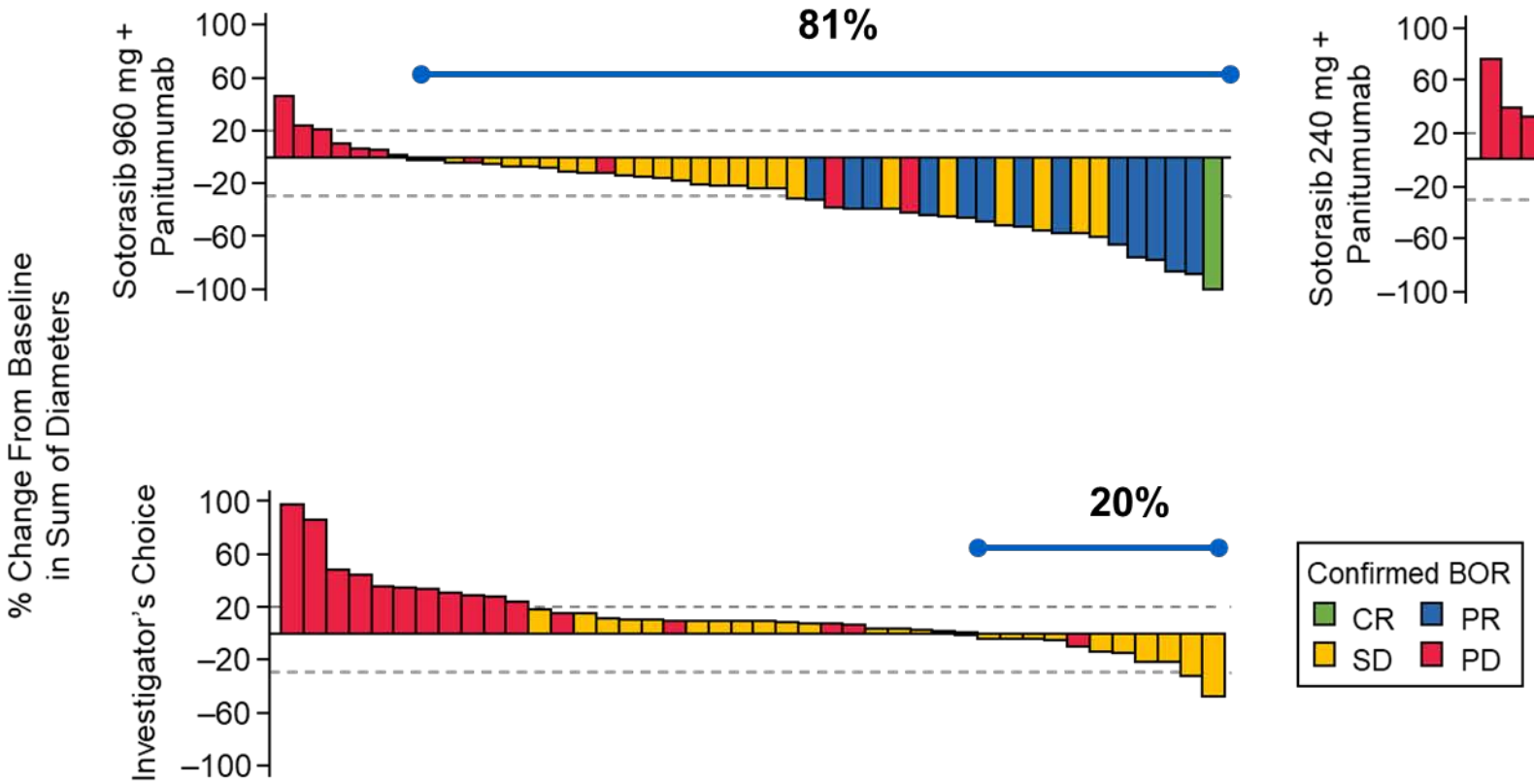
| Response by BICR | Sotorasib 960 mg + Panitumumab (n = 53) | Sotorasib 240 mg + Panitumumab (n = 53) | Investigator's Choice (n = 54) |
|---|---|---|---|
| **ORR, % (95% CI)*†** | 26 (15.3–40.3) | 6 (1.2–15.7) | 0 (0–6.6) |
| Complete response, n (%) | 1 (2) | 0 | 0 |
| Partial response, n (%) | 13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

**ORR and DCR by BICR were higher with sotorasib (960 mg and 240 mg) + panitumumab versus investigator's choice**

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

Fakih et al. *N Engl J Med* 2023;389:2125-2139.

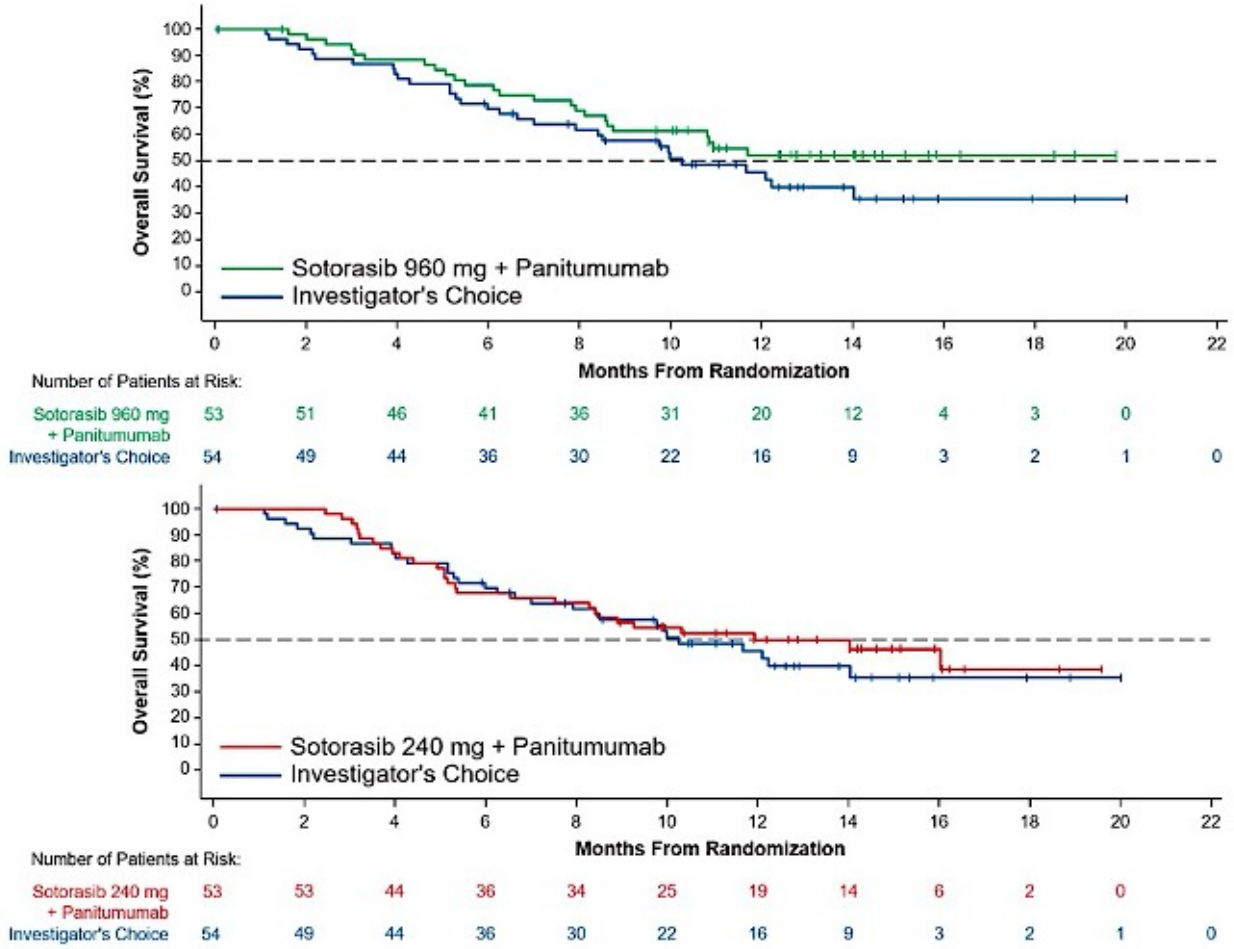
# Tumor Shrinkage From Baseline




**Tumor shrinkage of any level was observed in 81%, 57%, and 20% of patients in sotorasib (960 mg and 240 mg) + panitumumab and investigator's choice arms, respectively**

Fakih et al. *N Engl J Med* 2023;389:2125-2139.

# CodeBreaK 300: Protocol-Specified Final OS in Intent-to-Treat Population




| | Sotorasib 960 mg + Panitumumab (n = 53) | Sotorasib 240 mg + Panitumumab (n = 53) | Investigator's Choice (n = 54) |
|---|---|---|---|
| **Median (95% CI) OS, months*** | NE (8.6–NE) | 11.9 (7.5–NE) | 10.3 (7.0–NE) |
| HR (95% CI)† | 0.70 (0.41–1.18) | 0.83 (0.49–1.39) | – |
| *P*-value (2-sided)‡ | 0.20 | 0.50 | – |
| Number of deaths (%) | 24 (45) | 28 (53) | 30 (56) |

- **After a median follow-up of 13.6 months, sotorasib (240 mg and 960 mg) + panitumumab showed a trend of improved OS versus investigator's choice, with 30% reduction in risk of death for sotorasib 960 mg + panitumumab**

*Estimated using the Kaplan-Meier method, 95% CIs from log-log transformation. †HRs and 95% CIs from stratified Cox proportional hazards model. HR < 1.0 indicates a lower risk and a longer OS for [sotorasib + panitumumab] versus [trifluridine and tipiracil or regorafenib]. ‡*P*-value from stratified log-rank test. Data cutoff, 18 December 2023. CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.

Fakih MG et al. ASCO 2024;Abstract LBA3510.

# FDA Approves Sotorasib with Panitumumab for KRAS G12C-Mutated Colorectal Cancer

## Press Release: January 16, 2025

"On January 16, 2025, the Food and Drug Administration approved sotorasib with panitumumab for adult patients with KRAS G12C-mutated metastatic colorectal cancer (mCRC), as determined by an FDA-approved test, who have received prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

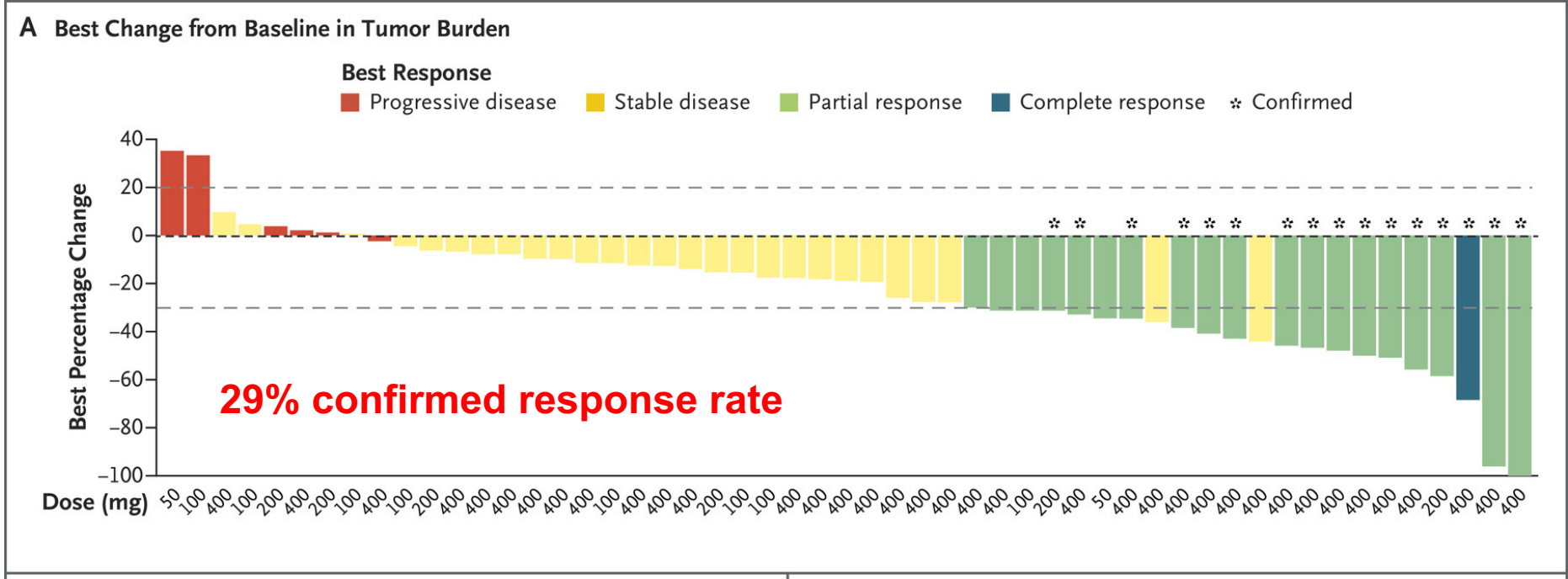
The FDA also approved the therascreen KRAS RGQ PCR Kit (QIAGEN GmbH) as a companion diagnostic device to aid in identifying patients with colorectal cancer whose tumors harbor KRAS G12C mutations and who may be eligible for sotorasib with panitumumab.

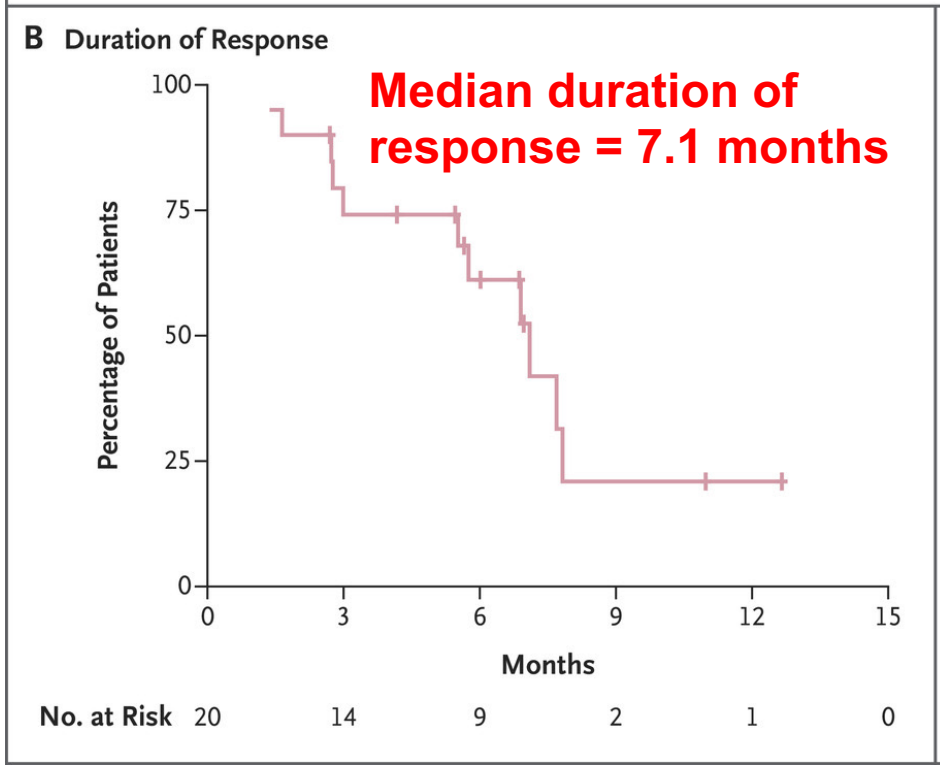
Efficacy was evaluated in CodeBreaK 300 (NCT05198934), a randomized, open-label, controlled trial in patients with KRAS G12C-mutated mCRC who previously received fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy."

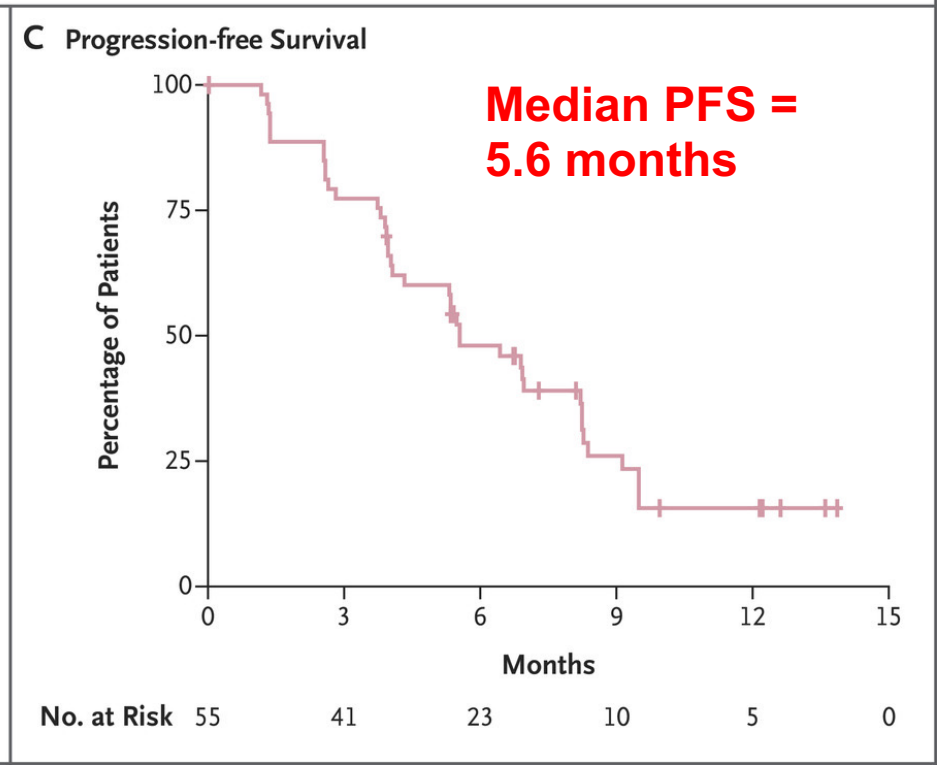
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-sotorasib-panitumumab-kras-g12c-mutated-colorectal-cancer.

RTP RESEARCH TO PRACTICE

# Divarasib in metastatic KRAS G12C mCRC *(n = 55)*




Sacher et al. *N Engl J Med* 2023;389: 710-21.

# Study Schema

**CodeBreaK 101 Subprotocol H phase 1b, multicenter, open-label study*: sotorasib + panitumumab + FOLFIRI in previously treated *KRAS* G12C–mutated mCRC**

**Key eligibility criteria**

- *KRAS* G12C–mutated mCRC, identified through local molecular testing
- No dose reduction or intolerance to prior $KRAS^{G12C}$ inhibitor treatment (Part 1 only)
- $KRAS^{G12C}$ inhibitor-naive (Part 2 only)
- ≥ 1 prior treatment for advanced disease
- No dose reduction or delay due to 5-FU or irinotecan toxicity if previously received

**Part 1: Cohort B**
**Dose exploration†**
**(N = 6)**

**Dose Level 1:**
**Sotorasib: 960 mg PO daily**
**+**
**Panitumumab: 6 mg/kg IV Q2W**
**+**
**FOLFIRI IV Q2W**

**No DLTs were observed and Dose Level 1 was declared the RP2D‡**

**Part 2: Cohort G**
**Dose expansion†**
**(N = 40)**

**Sotorasib: 960 mg PO daily**
**+**
**Panitumumab: 6 mg/kg IV Q2W**
**+**
**FOLFIRI IV Q2W**

**Primary Endpoints:** Safety and tolerability
**Secondary Endpoints:** Anti-tumor efficacy (ORR, DCR, DOR, TTR, PFS per RECIST v1.1, and OS) and PK

*NCT04185883.
†Treatment until disease progression, withdrawal of consent, or end of study.
‡No dose adjustment was needed.

Hong DS, et al. Poster presented at: American Society of Clinical Oncology; June 2-6, 2023; Chicago, IL. Abstract #3513

# Efficacy of Sotorasib + Panitumumab + FOLFIRI

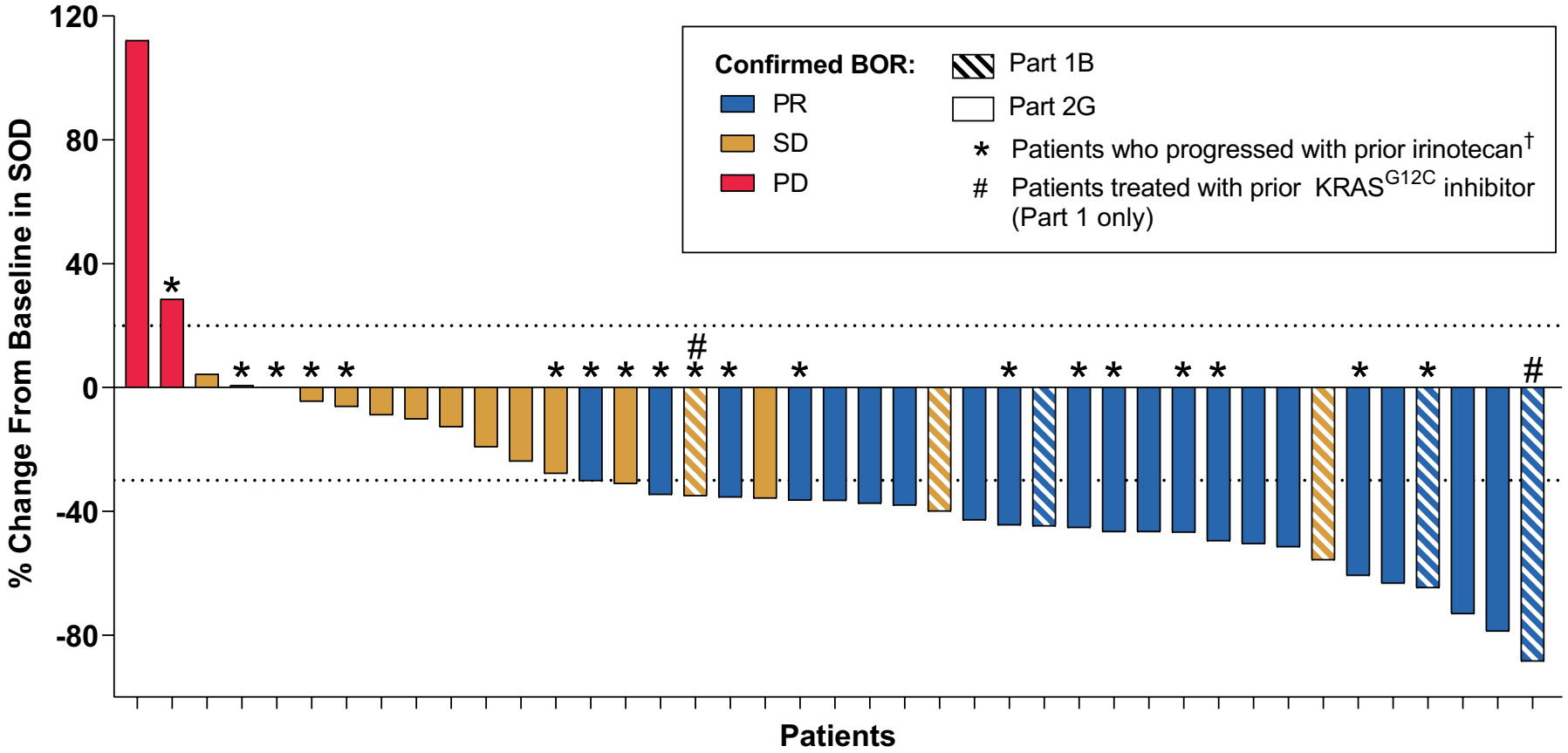
| Response by investigator assessment* | Part 1 Sotorasib + Panitumumab + FOLFIRI (n = 6) | Part 2 Sotorasib + Panitumumab + FOLFIRI (n = 36) | Total (N = 42*) |
|---|---|---|---|
| **ORR confirmed** (95% CI) | 3 (50) (11.8, 88.2) | 20 (56) (38.1, 72.1) | **23 (55)** (38.7, 70.2) |
| CR | 0 | 0 | 0 |
| PR | 3 (50) | 20 (56)† | 23 (55)† |
| SD | 3 (50) | 13 (36) | 16 (38) |
| PD | 0 | 2 (6) | 2 (5) |
| Unavailable | 0 | 1 (3) | 1 (2) |
| **DCR** (95% CI) | 6 (100) (54.1, 100.0) | 33 (92) (77.5, 98.3) | **39 (93)** (80.5, 98.5) |

Data cutoff, April 13, 2023.
The 2 patients treated with prior sotorasib achieved partial response (n = 1) and stable disease (n = 1).
*42 patients enrolled at least 7 weeks before analysis cutoff were included for response summary.
†2 additional patients had unconfirmed partial responses that are awaiting confirmatory scan and not included in these numbers.

- **Confirmed ORR (all partial responses) was 55% (95% CI: 38.7, 70.2) and DCR was 93% (95% CI: 80.5, 98.5), with 2 additional patients with unconfirmed responses awaiting confirmatory scan**

Hong DS, et al. Poster presented at: American Society of Clinical Oncology; June 2-6, 2023; Chicago, IL. Abstract #3513

# Tumor Response: Sotorasib + Panitumumab + FOLFIRI




Data cutoff, April 13, 2023.

†Patients whose disease progressed on prior irinotecan include those with clinical or radiographic progression.

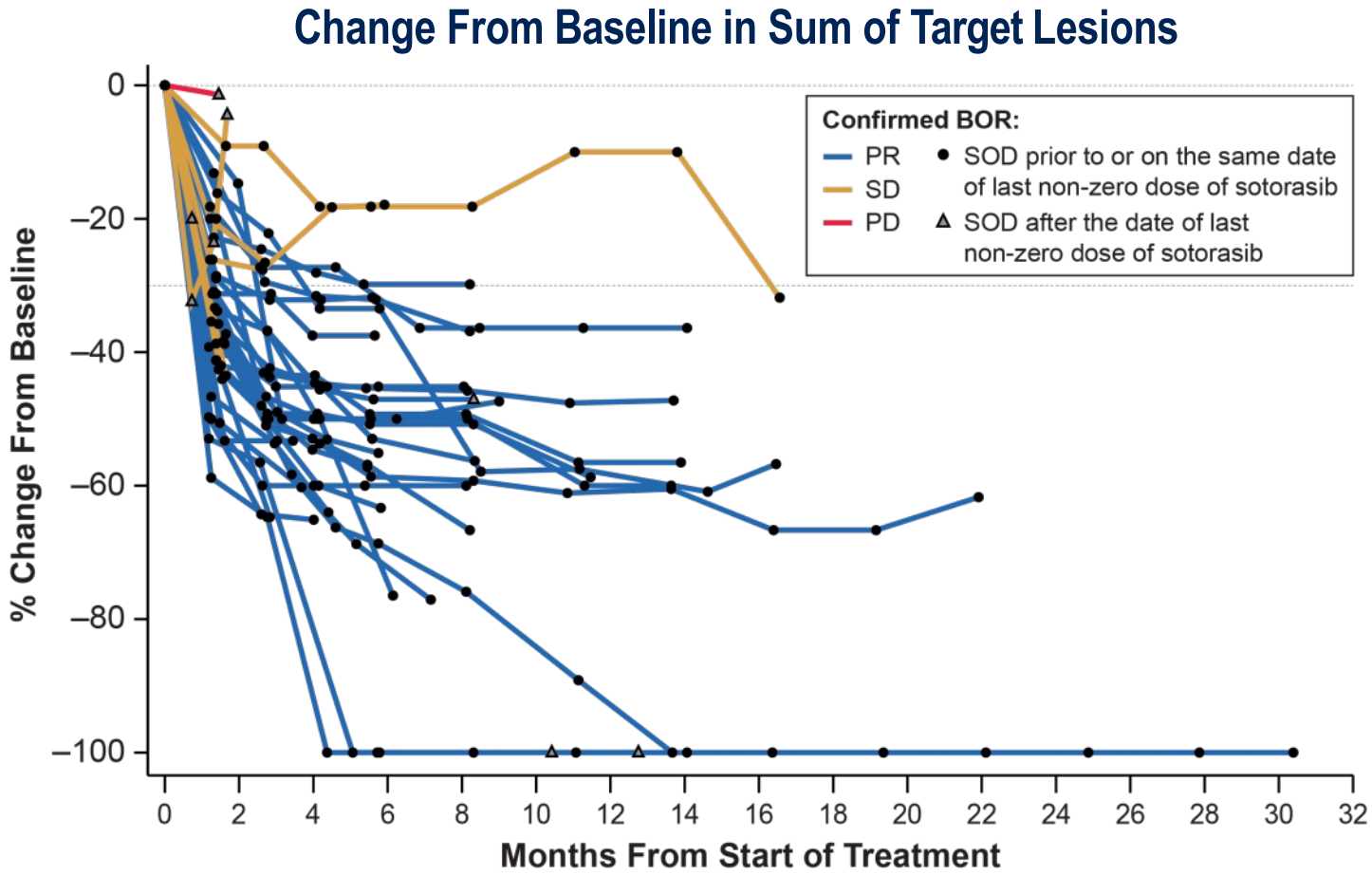
‡42 patients enrolled at least 7 weeks before analysis cutoff were included for response summary; 1 patient with no post-baseline scan is not shown in figure but is included in the denominator.

- **Reduction in RECIST target lesions was observed in 86% of patients‡**

Hong DS, et al. Poster presented at: American Society of Clinical Oncology; June 2-6, 2023; Chicago, IL. Abstract #3513

# Efficacy Summary: Sotorasib + Panitumumab + FOLFIRI

| ORR by Investigator Assessment* | Sotorasib + Panitumumab + FOLFIRI (N = 40) |
|---|---|
| **ORR, n (%)** | 31 (**78**) |
| Complete response† | 0 |
| Partial response | 31 (78) |
| Stable disease | 7 (18) |
| Progressive disease | 1 (3) |
| Not evaluable‡ | 1 (3) |
| **Patients with liver metastasis only, n / N (%)** | 7 / 7 (**100**) |
| **Left-sided tumor, n / N (%)** | 22 / 27 (82) |
| **Right-sided tumor, n / N (%)** | 6 / 10 (60) |




**A total of 38 patients (95%) achieved disease control*, and all patients had reduction in target lesions**

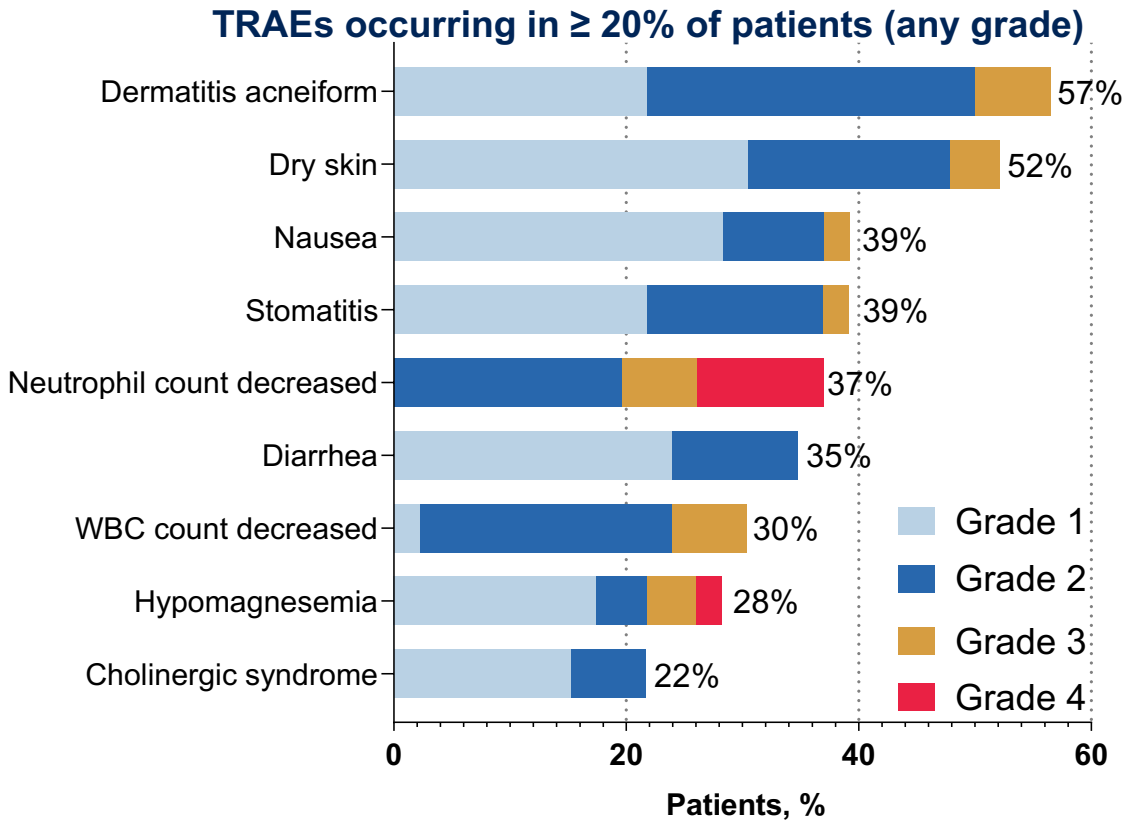
BARCELONA 2024 ESMO congress

Salvatore Siena, MD

Siena et al. ESMO Congress 2024. Annals of Oncology (2024) 35 (suppl_2): S428-S481. 10.1016/annonc/annonc1588

# Safety: Sotorasib + Panitumumab + FOLFIRI

| TRAE | N = 46<br>n (%) |
|---|---|
| TRAE, any grade | 44 (96) |
| Grade 3 | 13 (28) |
| Grade 4* | 7 (15) |
| Serious | 2 (4) |
| Fatal | 0 |
| TRAE leading to ≥ 1 dose interruption/reductions | 34 (74) |
| Attributed to sotorasib | 6 (13) |
| Attributed to panitumumab | 20 (43) |
| Attributed to FOLFIRI (any component) | 30 (65) |
| TRAE leading to discontinuation of ≥ 1 agent | 12 (26) |
| Sotorasib† | 1 (2) |
| Panitumumab | 2 (4) |
| FOLFIRI (any component)‡ | 11 (24) |
| TRAE leading to discontinuation of all agents | 1 (2) |




Data cutoff, April 13, 2023.

*Grade 4 TRAEs were neutrophil count decreased (n = 5, 11%), blood creatine phosphokinase increased (n = 1, 2%), and hypomagnesemia (n = 1, 2%).

†Sotorasib discontinuation was required in 1 patient due to grade 3 alanine aminotransferase increase attributed to all components of treatment.

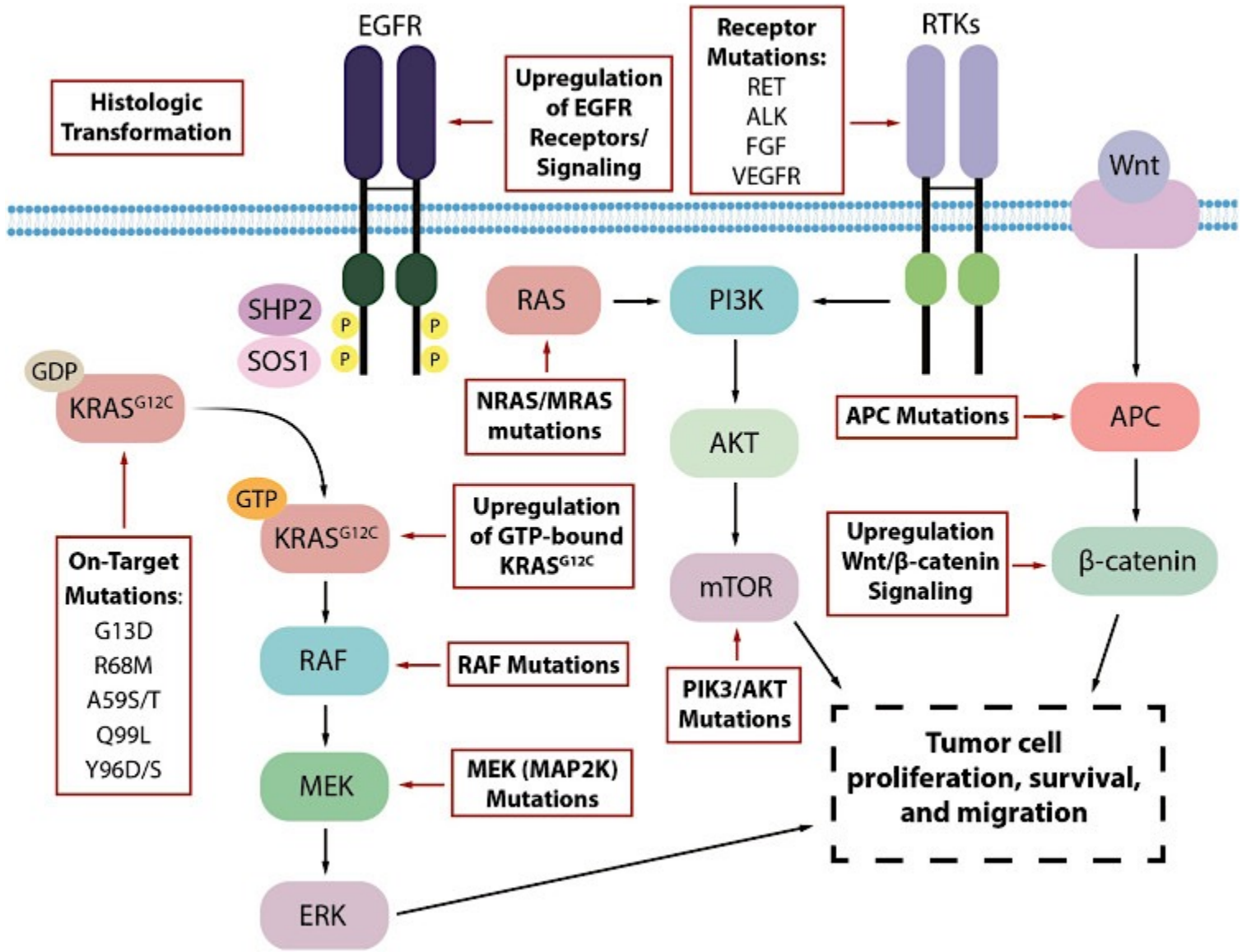
‡The most common component discontinued due to TRAE was 5-FU, occurring in 11 (24%) patients. Discontinuation of 5-FU bolus while continuing 5-FU continuous infusion did not count as discontinuation of one component.

- **No DLTs were observed in dose exploration and sotorasib 960 mg daily, panitumumab 6 mg/kg IV Q2W, and FOLFIRI IV Q2W was determined as the RP2D**
- **Safety findings were consistent with known profiles of sotorasib, panitumumab, and FOLFIRI**

# Take Home Points:

- KRAS G12C is present in approximately 3% of all patients with mCRC
- Emerging data with sotorasib + panitumumab and adagrasib + cetuximab show significant response rates and promising progression-free survival
  - *Both are now FDA-approved regimens for KRAS G12C mutated metastatic CRC*
- Similar results seen with other KRAS G12C inhibitors, and the field is becoming increasingly crowded
- Combinations are well-tolerated, but dermatologic toxicity is seen in over half the patients treated and nausea needs to be managed as well
- Early data with chemotherapy (FOLFIRI) show impressive response rates

# Mechanisms of resistance to KRAS G12C inhibitors




Ji et al. *Onco Targets Ther.* 2022; 15:747-756

# Questions from General Medical Oncologists

- **Can we incorporate KRAS inhibitors into the 1L setting, rather than waiting for 2L/relapse?**
- **Which is the better first-line therapy for a patient with mCRC and a KRAS mutation — chemo plus an EGFR antibody or a KRAS inhibitor plus an EGFR antibody?**
- **How do you decide between adagrasib and sotorasib either as monotherapy or in combination with an EGFR antibody? What about divarasib?**

# Questions from General Medical Oncologists

- **Would you consider using alternate combinations of sotorasib and adagrasib and an EGFR antibody?**
- **How would you sequence targeted treatment for a patient with KRAS G12C-positive, HER2 IHC 3+ mCRC?**
- **34-year-old with mCRC has progressed on FOLFOX, FOLFIRI with bevacizumab. Has KRAS G12C mutation. How would you choose between sotorasib, adagrasib and divarasib? What are the common side effects of these agents as monotherapy or combination with an EGFR inhibitor?**

# Questions from General Medical Oncologists

- **54 yo woman with Stage IV colon cancer and a KRAS G12C mutation. PR on adagrasib and panitumumab but severe cutaneous AEs, despite antibiotics and steroids. Do you ever use dose or schedule modifications to EGFR mAbs in patients with severe cutaneous toxicity?**
- **72 yo woman with Stage IV colon cancer, KRAS G12C, MSS. She is stable on adagrasib plus cetuximab but with nausea issues and fatigue. How would you manage this situation?**

**Thank you for joining us!**
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