Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

CME/MOC, NCPD and ACPE Accredited

Saturday, October 11, 2025
7:15 AM – 12:30 PM ET

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — Breast Cancer: *Drs Burstein, Goetz, McArthur and Nanda*

Module 2 — Prostate Cancer: *Drs Antonarakis and M Smith*

Module 3 — Colorectal Cancer: *Drs Lieu and Strickler*

Module 4 — Diffuse Large B-Cell Lymphoma and Follicular Lymphoma: *Drs Lunning and S Smith*

Colorectal Cancer Faculty

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

John Strickler, MD
Professor of Medicine
Associate Director, Clinical Research – GI
Co-Leader, Molecular Tumor Board
Duke University
Durham, North Carolina

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Cancer Center

NCI-DESIGNATED CONSORTIUM
COMPREHENSIVE CANCER CENTER

Current and Future Role of Immune Checkpoint Inhibitors in the Management of Colorectal Cancer

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

NCI
Designated Comprehensive Cancer Center

Topics for Discussion

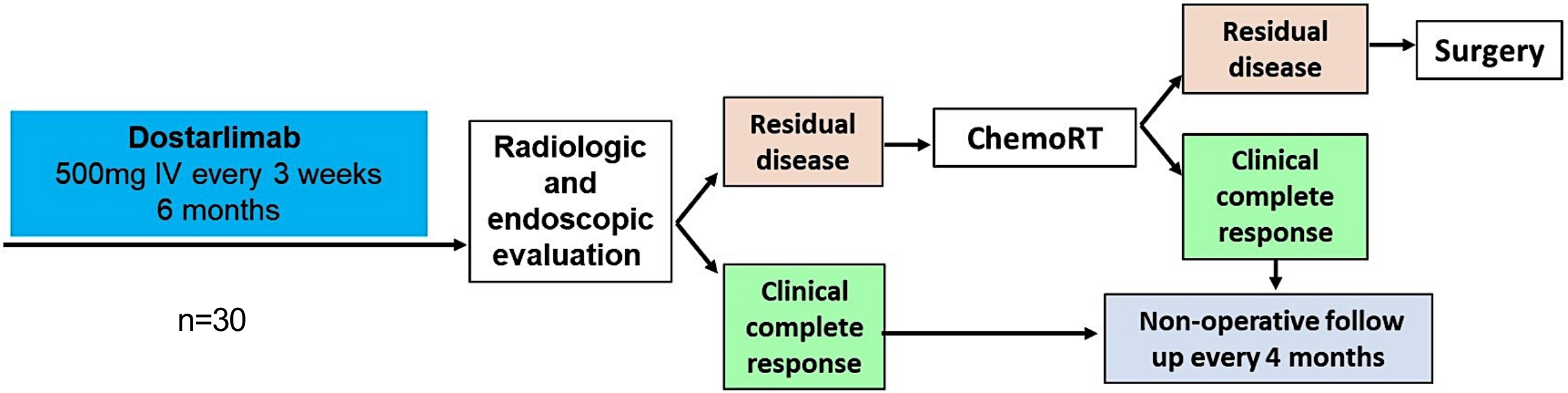
- Neoadjuvant and adjuvant immune checkpoint inhibitors for MSI-H/dMMR colon and rectal cancers
  - *Should immunotherapy go first, or after surgery?*

- Immunotherapy in the first-line setting for MSI-H/dMMR colorectal cancer
  - *Is doublet better than single-agent?*

- Immunotherapy for MSS/pMMR metastatic colorectal cancer

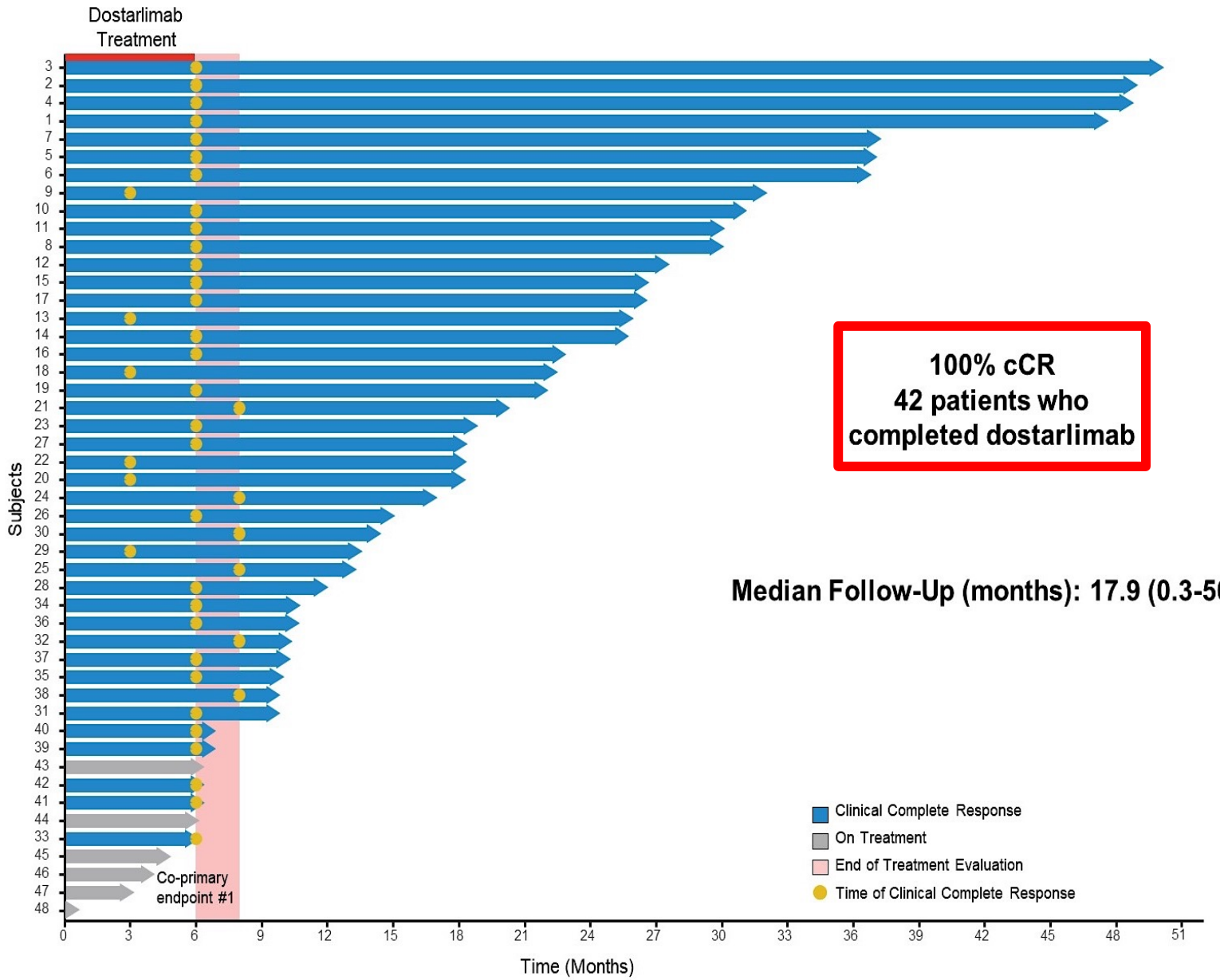
Immune checkpoint inhibitors for patients with non-metastatic rectal cancer

Dostarlimab for MSI-H Stage II-III Rectal Cancer



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

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



100% cCR
42 patients who completed dostarlimab

Median Follow-Up (months): 17.9 (0.3-50.5)

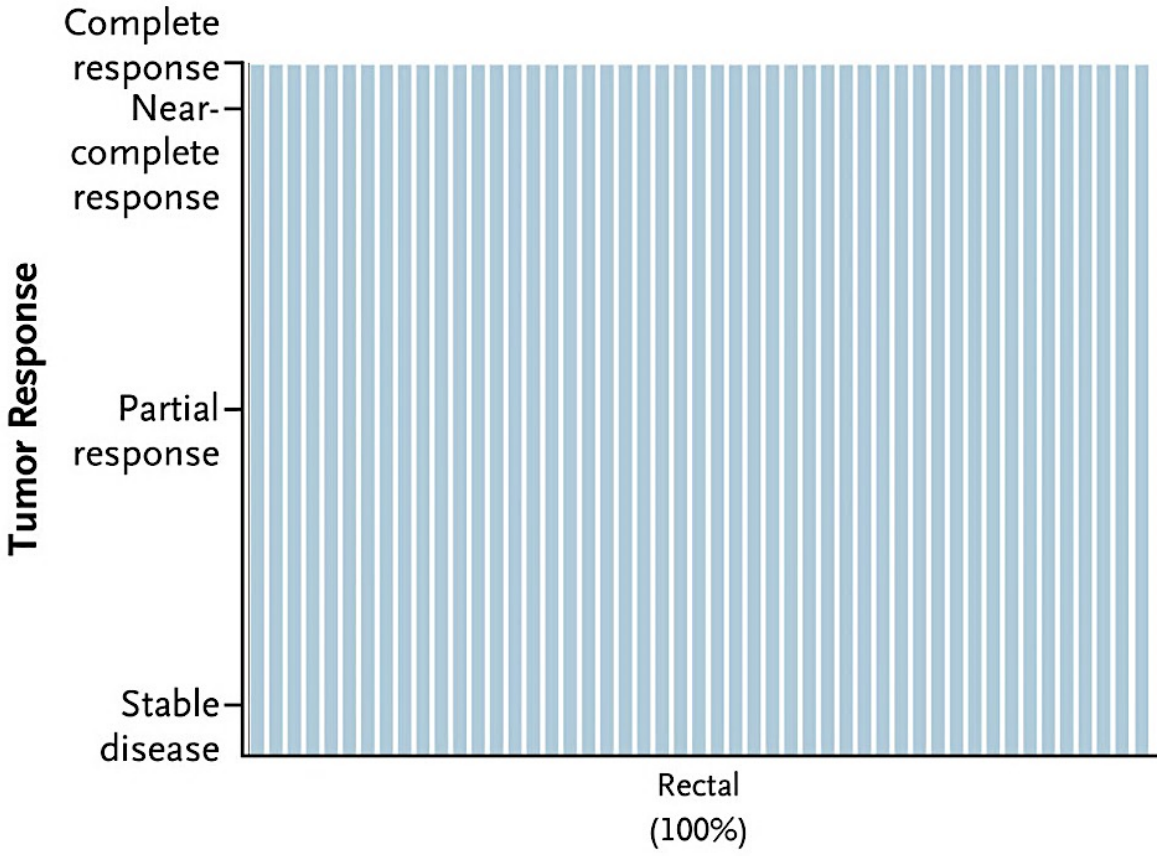
Most Common AEs

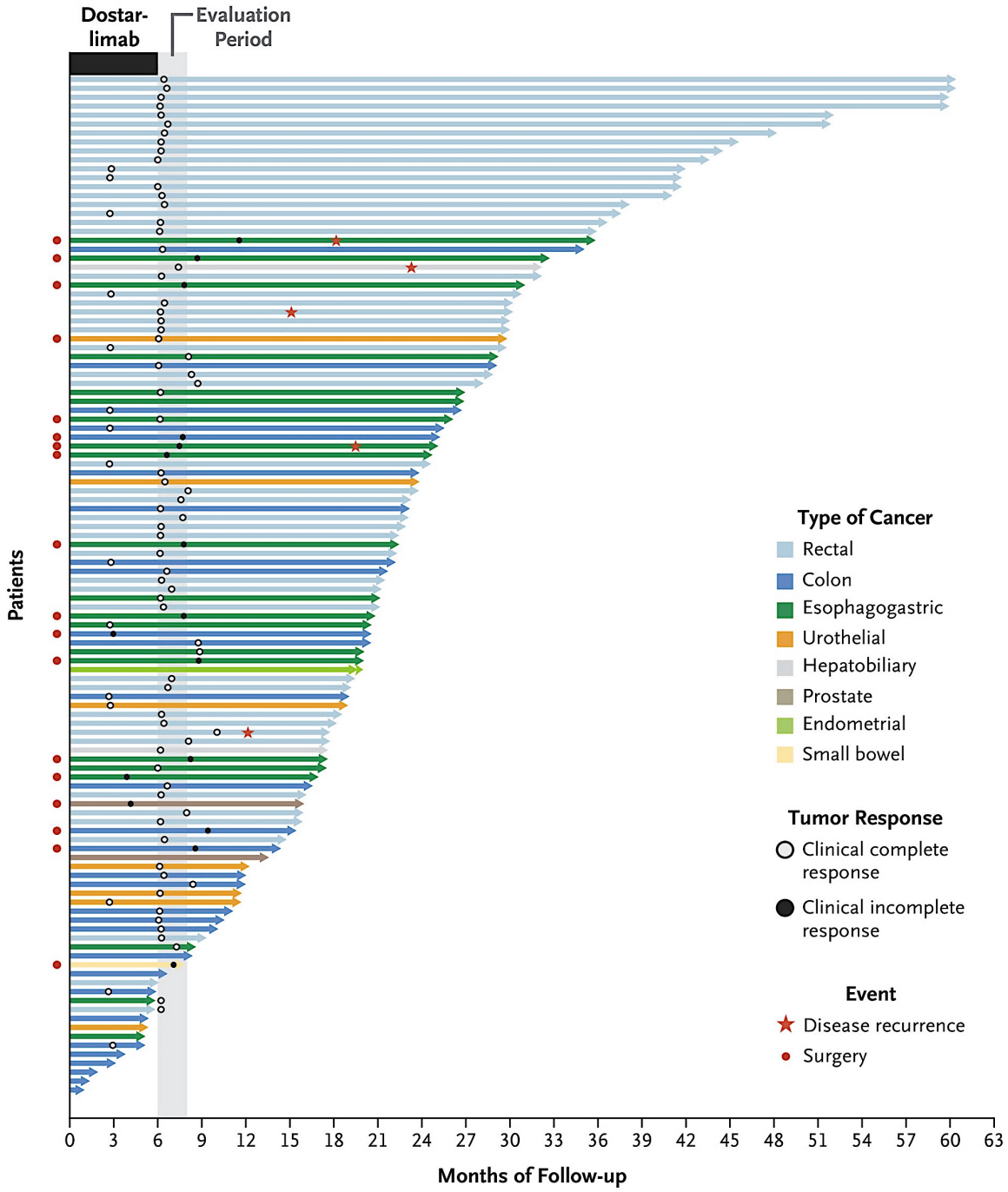
	All Grades	Grade 3 or 4
Dermatologic -no.(%)		
Pruritus	6 (13)	0 (0)
Rash / dermatitis	10 (21)	0 (0)
Gastrointestinal-no.(%)		
Diarrhea	4 (9)	0 (0)
Nausea	4 (9)	0 (0)
Constitutional-no.(%)		
Fatigue	5 (11)	0 (0)
Fever	3 (6)	0 (0)
Endocrine-no.(%)		
Hypothyroidism	5 (11)	0 (0)

Cercek A et al. NEJM 2022, Cercek A et al. ASCO 2024;Abstract LBA3512

Dostarlimab for MSI-H Stage II-III Rectal Cancer

Updated data (2025)





Cercek A et al. *N Engl J Med* 2025.

Take Home Points:

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

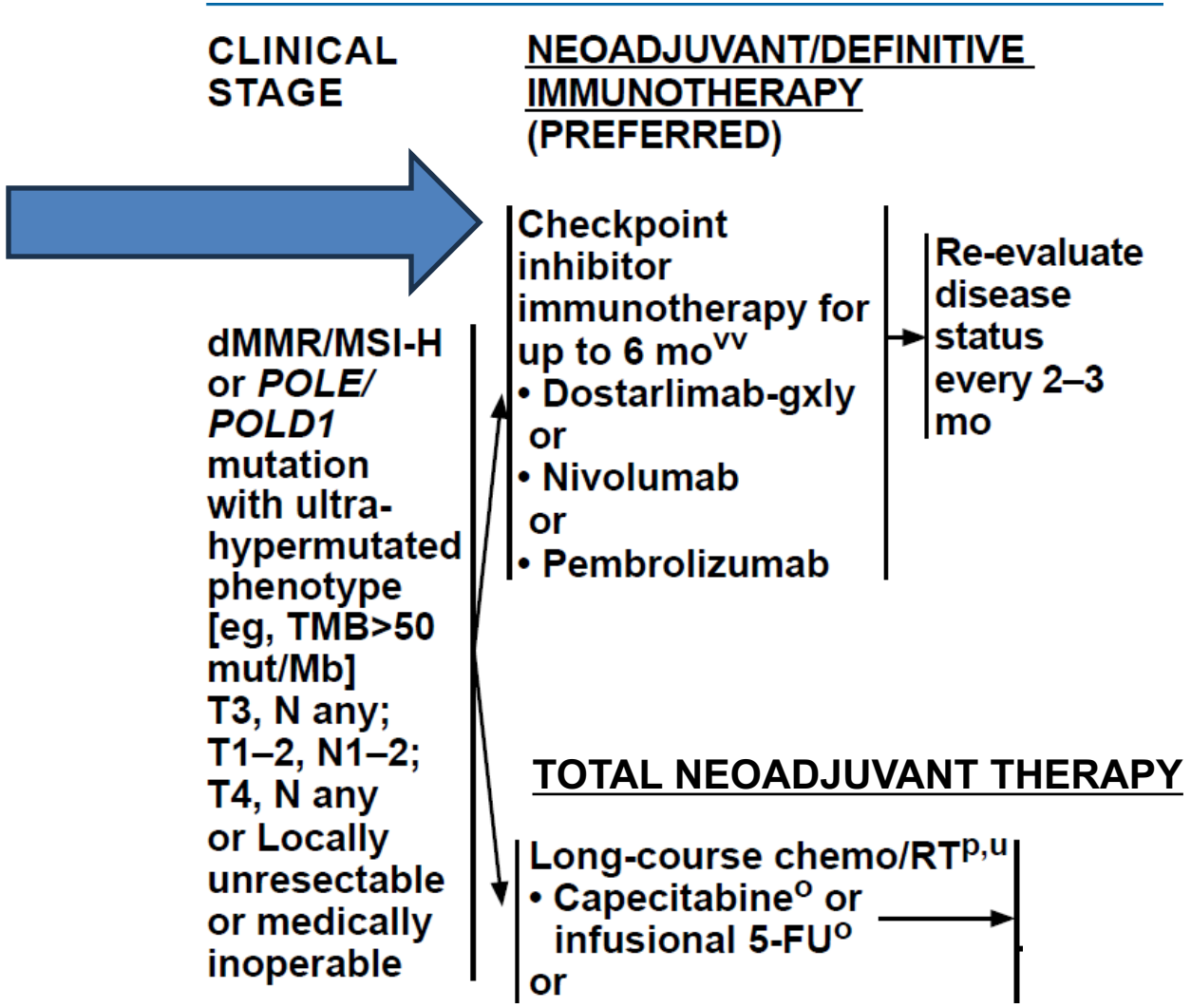
QUESTIONS:

What about stage I rectal cancer?

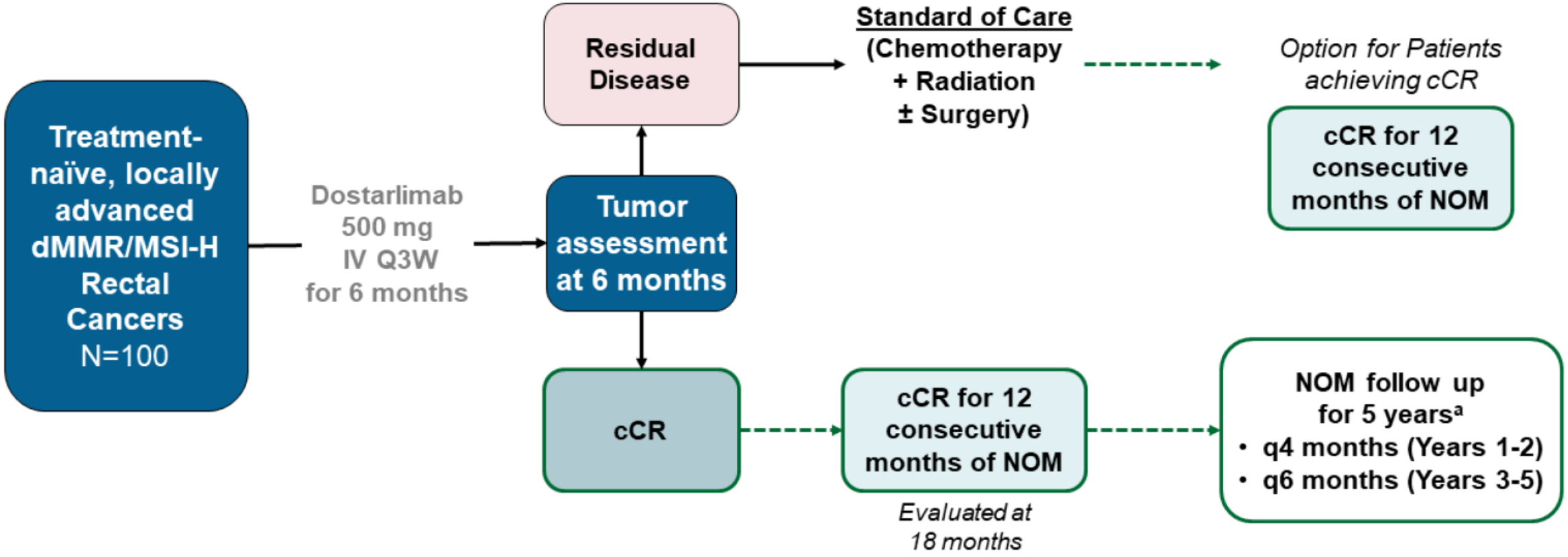
Should we be using nivo/ipi?

Does pCR mean cure?

What is the impact of immunotherapy on pMMR/MSS rectal cancer?



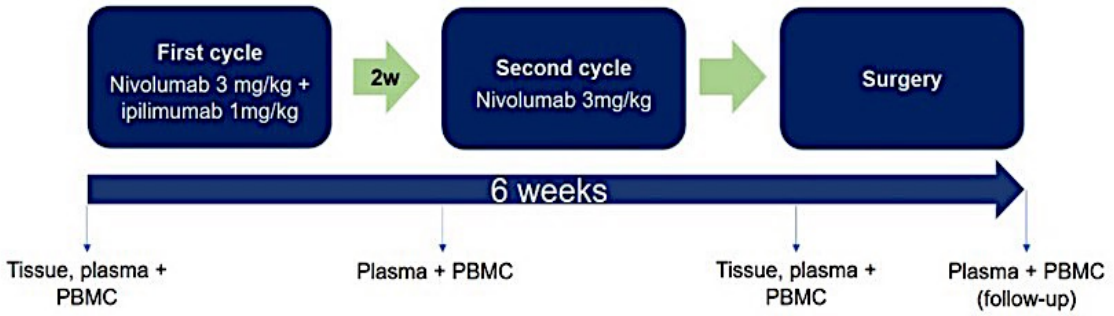
AZUR-1: Dostarlimab in dMMR/MSI-H Locally-Advanced Rectal Cancer



NCT05723562

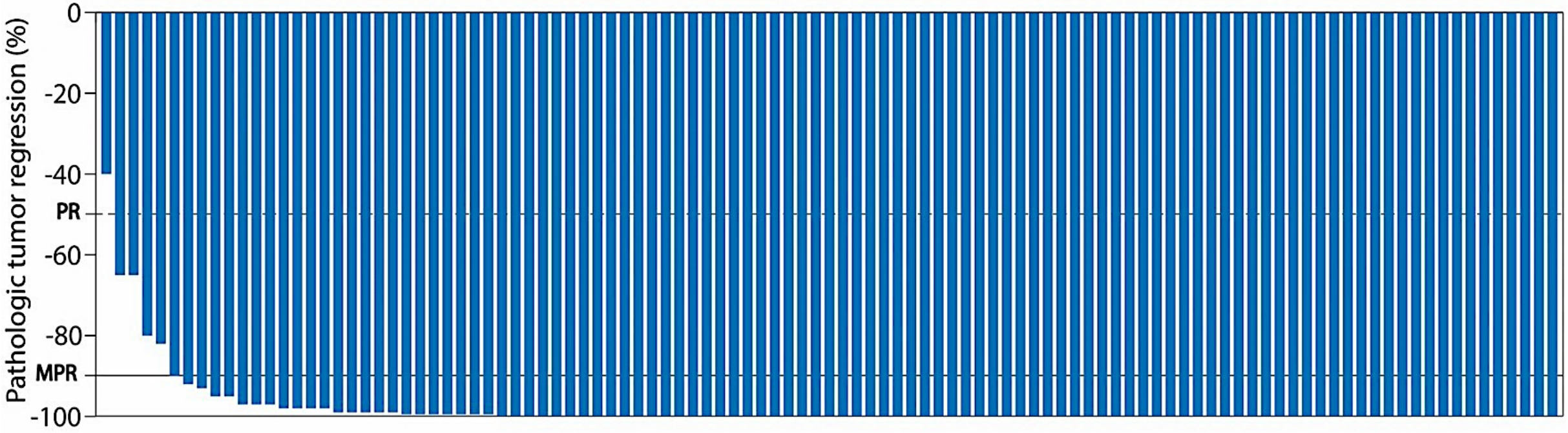
Immune checkpoint inhibitors for patients with non-metastatic colon cancer

NICHE-2 Study: Nivo/Ipi dMMR colon cancer



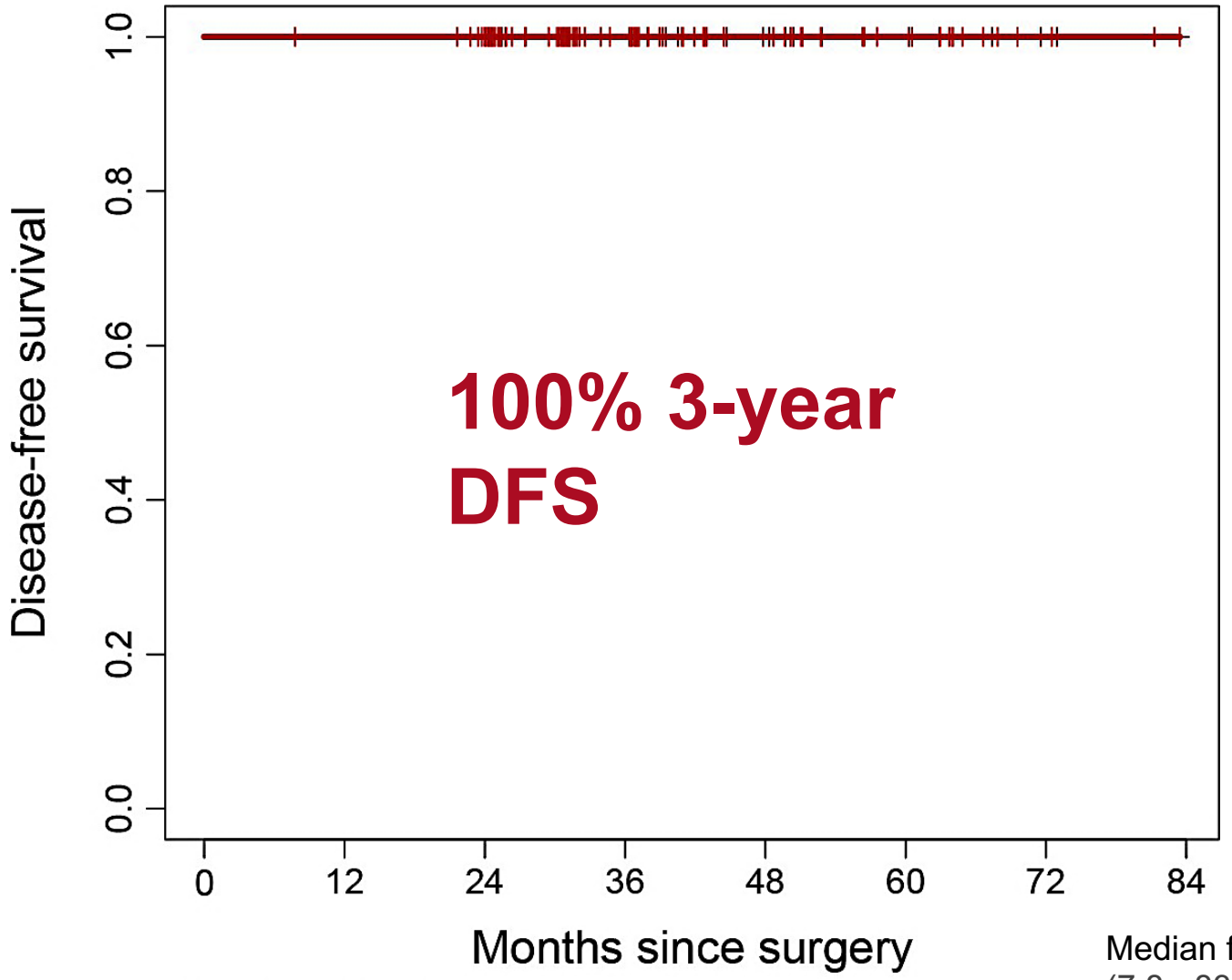
In locally advanced MMR-deficient colon cancers

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



Chalabi M et al. ESMO 2022;Abstract LBA7

Results – 3-year disease-free survival 100%



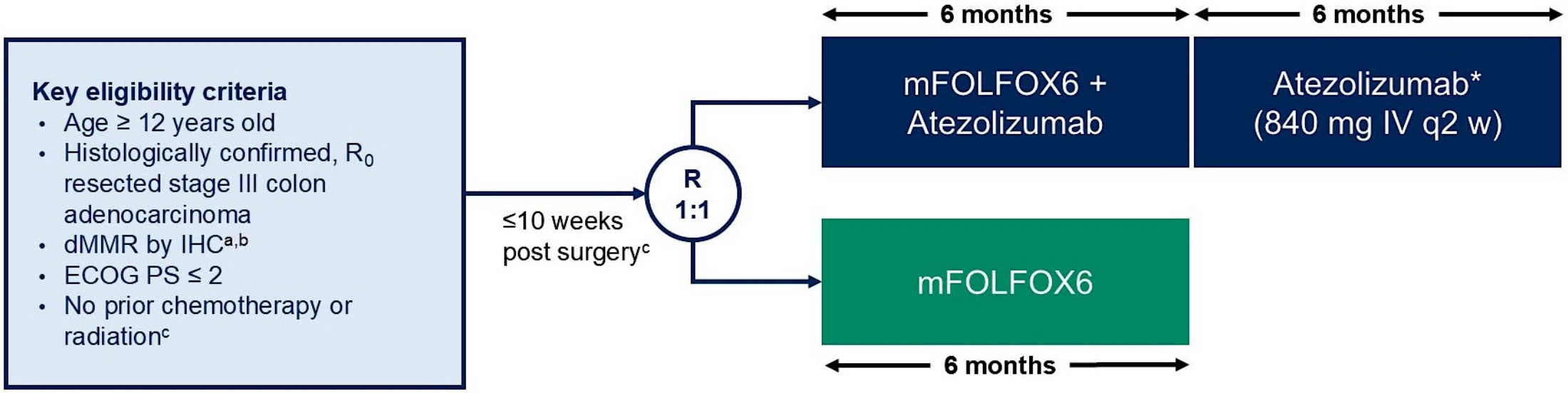
Median follow-up after surgery: 36.6 months (7.8 - 83.4)

Chalabi M et al. ESMO 2024;Abstract LBA24

BARCELONA 2024 ESMO congress

Data cut-off: 11 September 2024

ATOMIC: addition of atezolizumab to standard chemotherapy for dMMR/MSI-H colon cancer

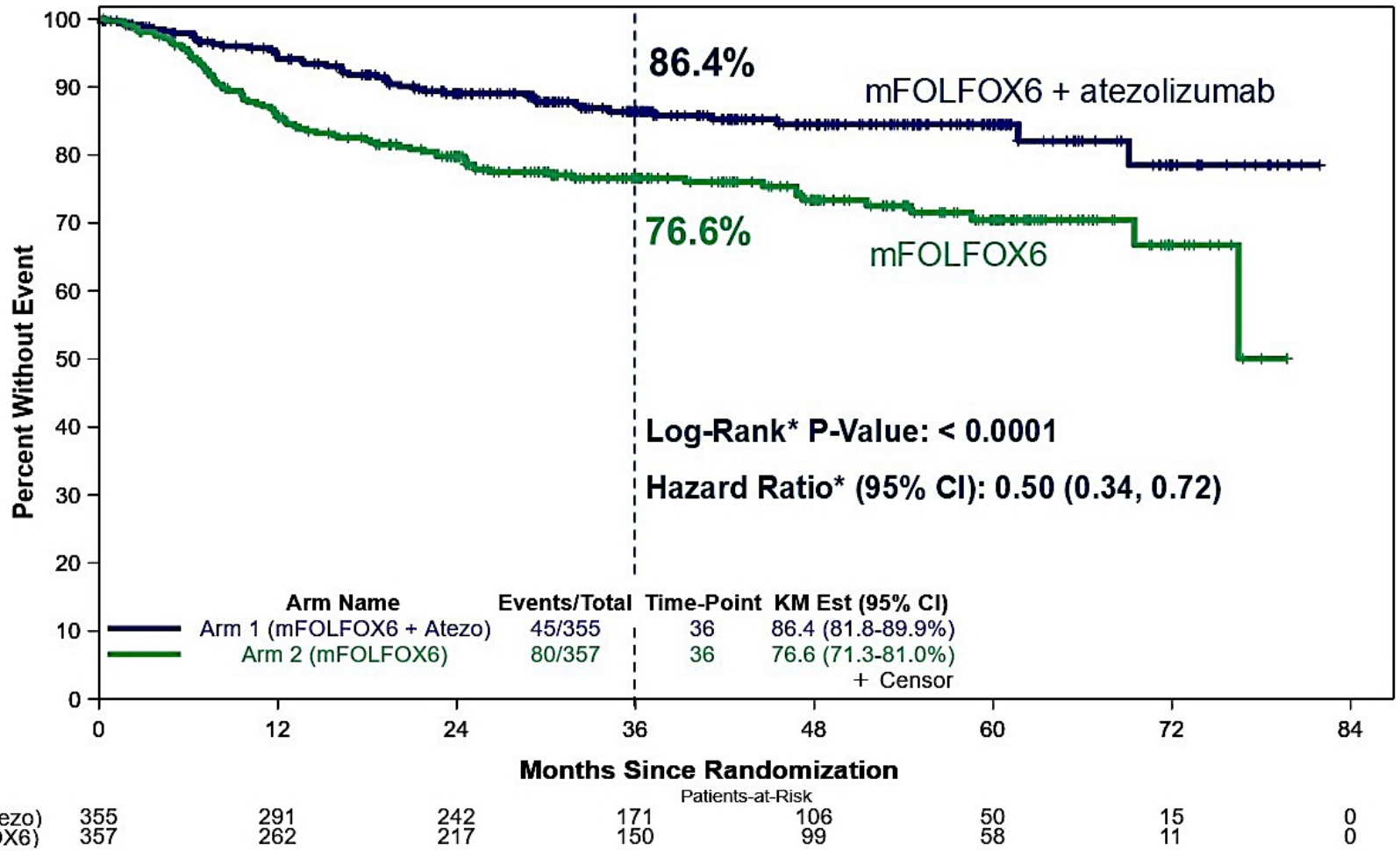


[a] **dMMR by immunohistochemistry (IHC) locally or at site-selected reference laboratory. Retrospective central confirmation of dMMR also performed.**
[b] Lynch syndrome included.
[c] One cycle of mFOLFOX6 prior to randomization permitted.

*Atezolizumab (anti-PD-L1)

NCT02912559

Primary Endpoint: DFS



Patients-at-Risk

Arm 1 (mFOLFOX6 + Atezo)	355	291	242	171	106	50	15	0
Arm 2 (mFOLFOX6)	357	262	217	150	99	58	11	0

Confirmed dMMR by central reference laboratory: Log-Rank P-Value: 0.0007, Hazard Ratio (95% CI): 0.53 (0.36, 0.79)

*Stratified by randomization factors

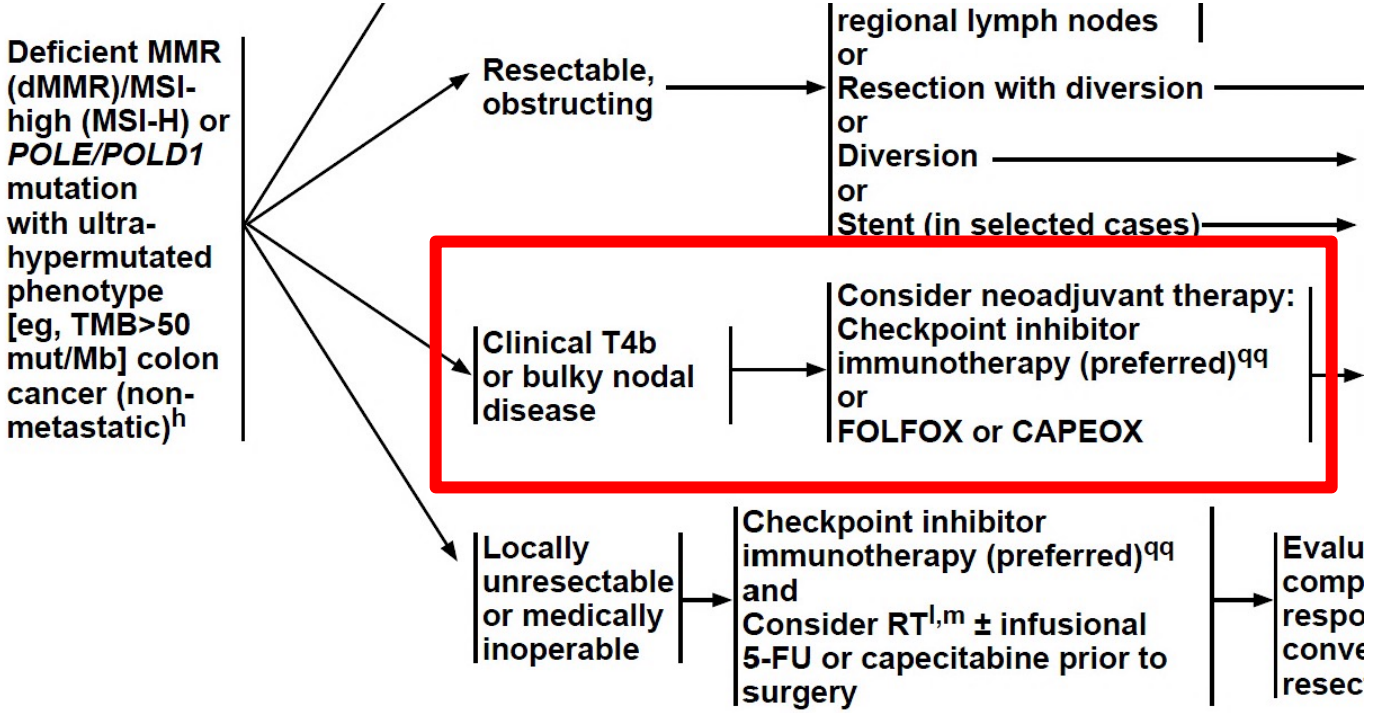
Median follow-up = 37.2 mos

Sinicrope FA et al. ASCO 2025;Abstract LBA1

Take Home Points:

Neoadjuvant immune checkpoint inhibition should be considered for high-risk disease (T4b/bulky nodal disease) colon cancer

FOLFOX/atezolizumab is the new standard in patients not receiving neoadjuvant therapy!

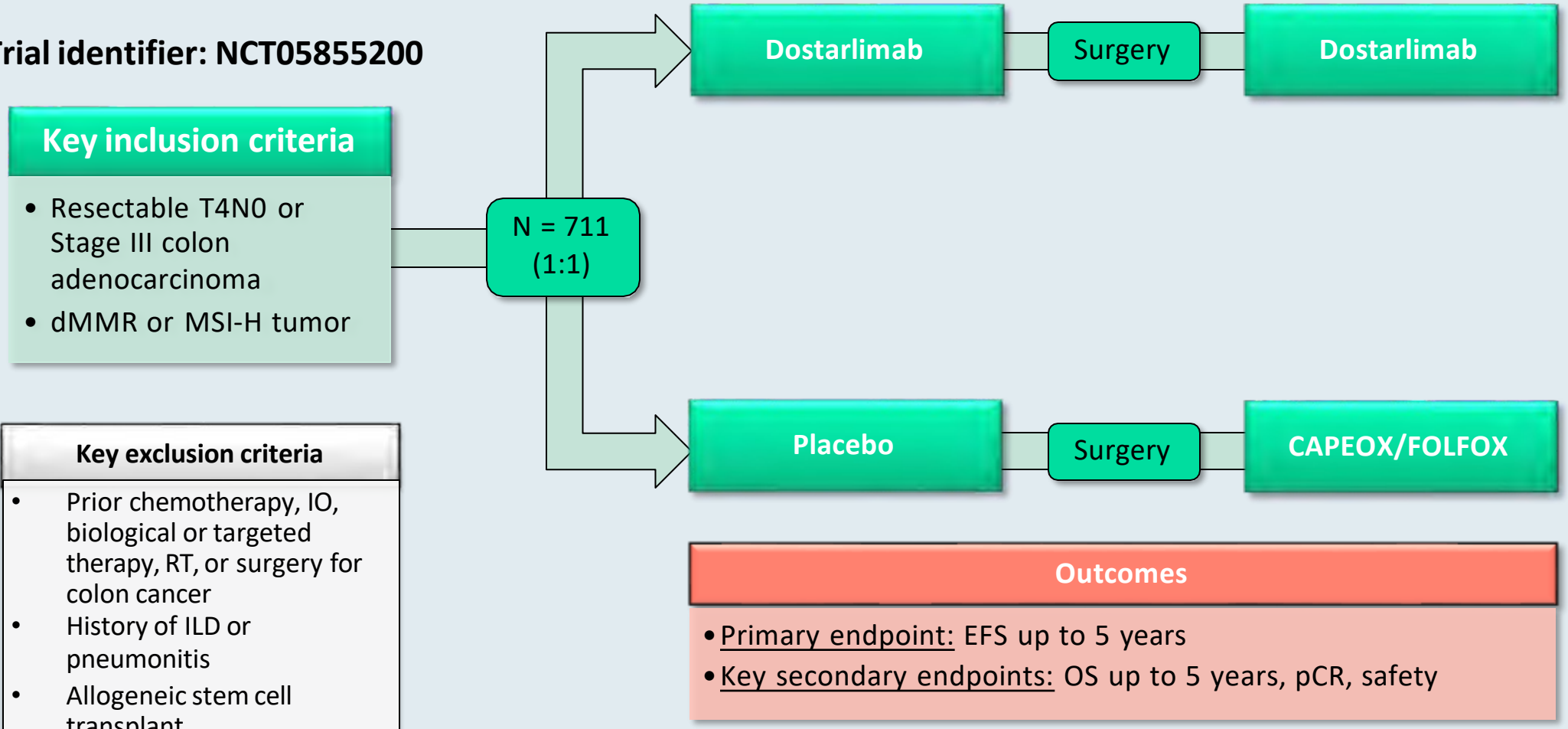


QUESTIONS:

- Should we consider non-operative management for MSI-H/dMMR colon cancer?
- Are serial colonoscopies better or worse than a hemicolectomy?
- What is the best duration of immunotherapy prior to resection?
- Is there a role for immunotherapy in pMMR/MSS colon cancer?

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

Trial identifier: NCT05855200



Key exclusion criteria

- Prior chemotherapy, IO, biological or targeted therapy, RT, or surgery for colon cancer
- History of ILD or pneumonitis
- Allogeneic stem cell transplant
- Any major surgery or injury within 28 days of enrollment

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

www.clinicaltrials.gov. Accessed January 2024.

AZUR-4: randomized study of neoadjuvant dostarlimab plus CAPEOX vs CAPEOX in untreated T4N0 or stage III in pMMR/MSS colon cancer

[a]Dostarlimab solution for infusion will be administered as a dose of 500 mg Q3W beginning on day 1 of each 21-day cycle for 4 cycles. [b]Oxaliplatin will be administered as an infusion with dose of 130 mg/m² Q3W on day 1 of each 21-day cycle for 4 cycles. Capecitabine will be administered as an oral agent for 14 days of a 21-day cycle with a dose of 1000 mg/m² BID for 4 cycles. [c]At least 3 and no more than 6 (+2) weeks after last dose of neoadjuvant chemotherapy.

Primary Endpoints:

- **Major pathological response (≤ 10% residual viable tumor)**
- **Safety**

Secondary Endpoints:

- **Primary tumor resection exclusion**
- **Pathological response**

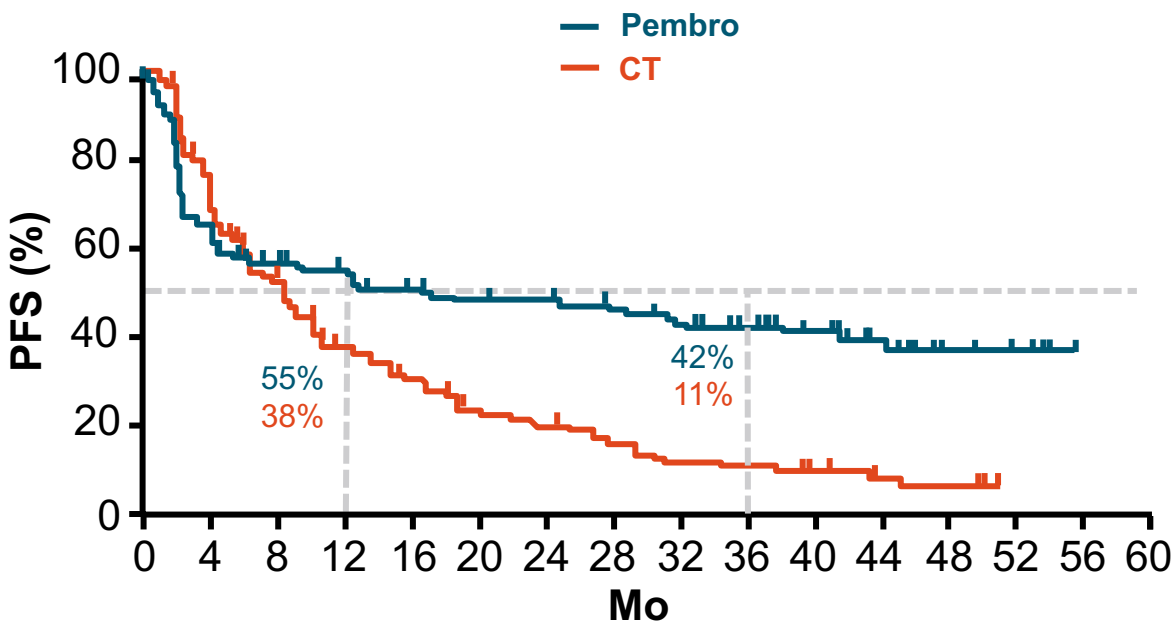
Rasschaert G et al. ASCO 2025;Abstract TPS3649

Immunotherapy in the first-line treatment of mCRC

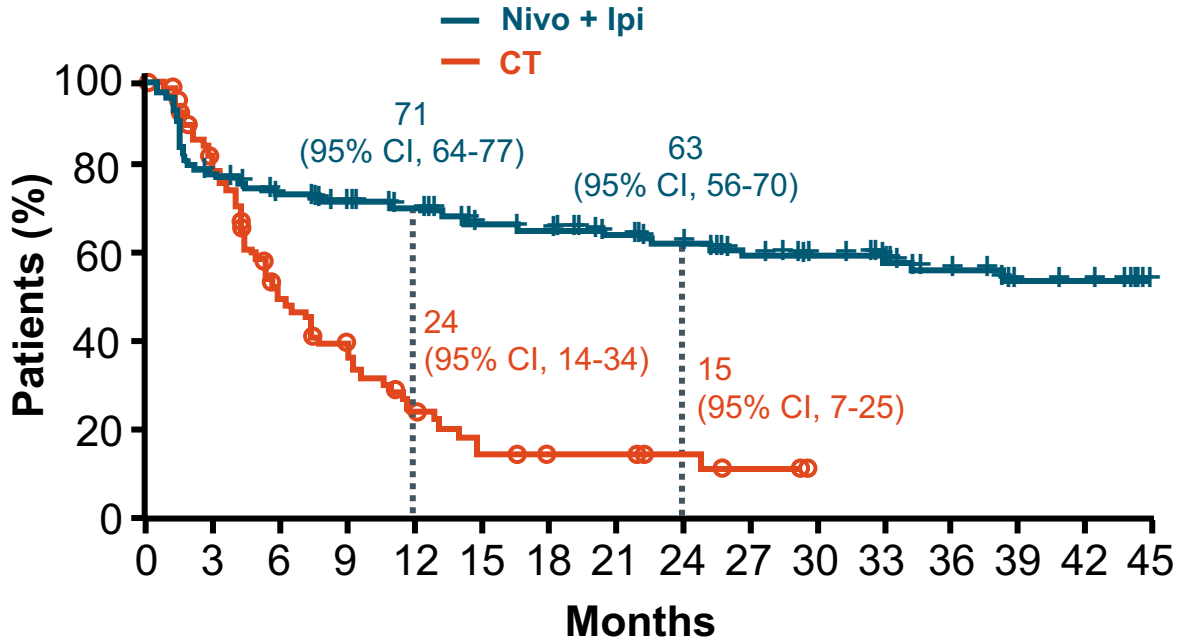
MSI-H/dMMR

Phase III RCTs of Immunotherapy vs Chemotherapy as First-Line Therapy for dMMR/MSI-H mCRC

KEYNOTE-177



Checkmate 8HW



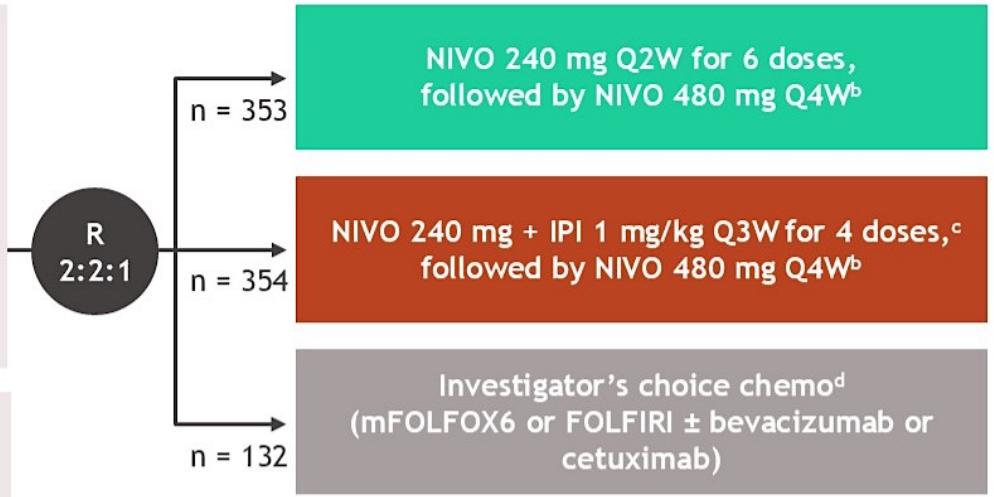
André T et al. ASCO 2021;Abstract 3500. André T et al. *N Engl J Med.* 2024;391(21):2014-2026.

CheckMate 8HW study design

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

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

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



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

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

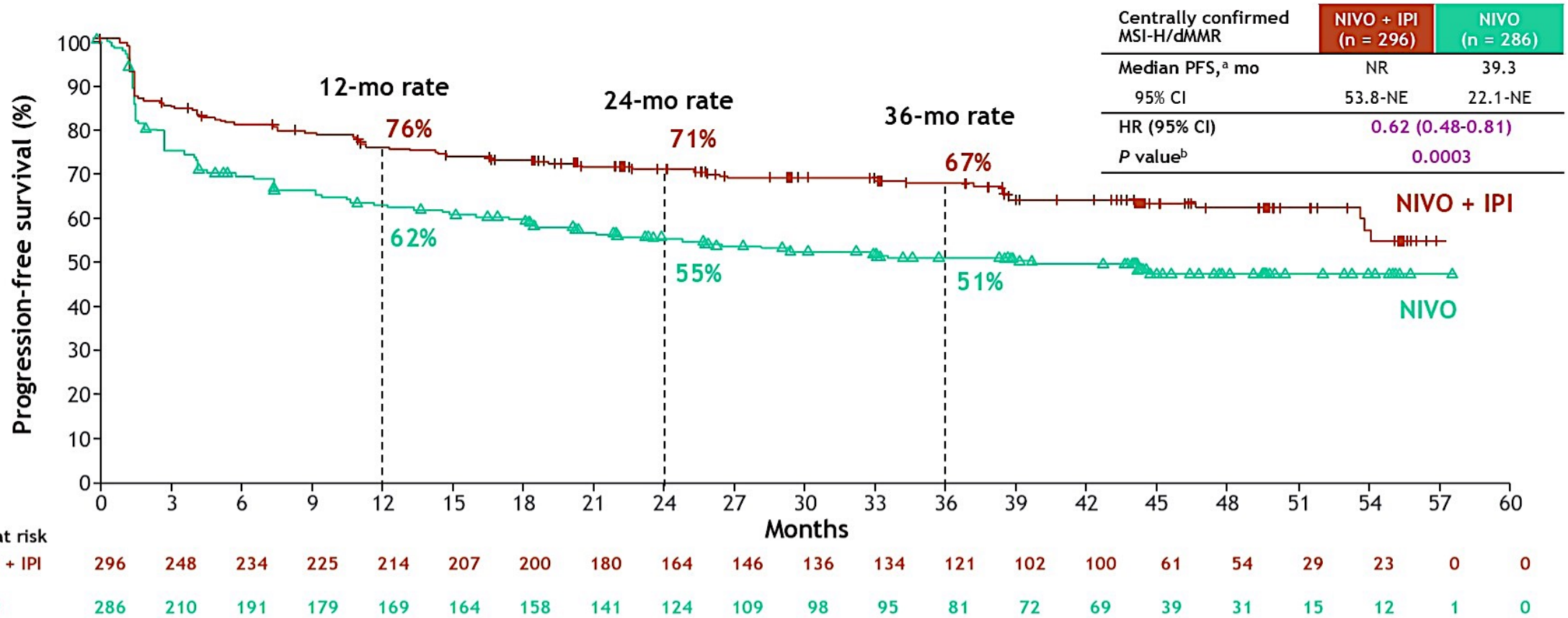
Other select endpoints:
- Safety
- PFS2; ORR by BICR[f]; HRQoL; OS

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

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients can continue NIVO treatment upon early IPI discontinuation. [d]Patients receiving investigator's choice of chemo are eligible to receive NIVO + IPI upon progression (crossover treatment). [e]Confirmed using either immunohistochemistry and/or polymerase chain reaction-based tests. [f]Evaluated using RECIST v1.1. [g]Time between randomization and data cutoff among all randomized patients across all 3 treatment arms.

Lenz HJ et al. ASCO 2024. Abstract 3503.

Progression-free survival: NIVO + IPI vs NIVO (all lines)



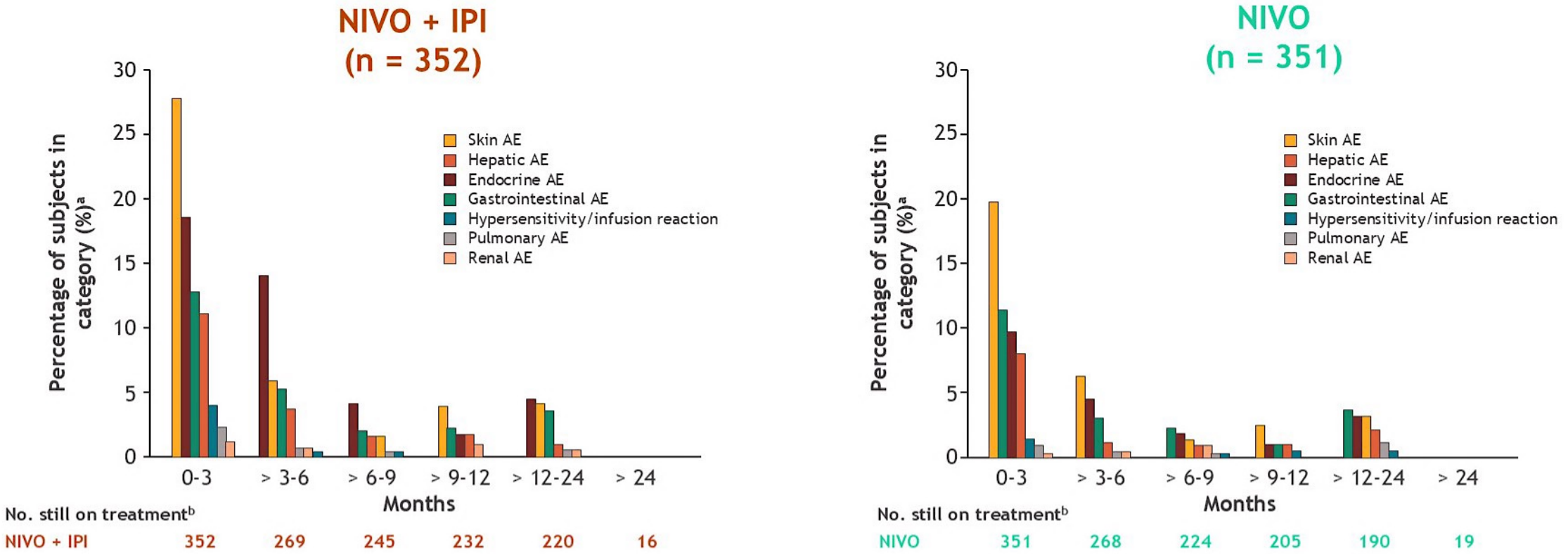
Centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 296)	NIVO (n = 286)
Median PFS,[a] mo	NR	39.3
95% CI	53.8-NE	22.1-NE
HR (95% CI)	0.62 (0.48-0.81)	
P value[b]	0.0003	

- NIVO + IPI demonstrated statistically significant and clinically meaningful PFS benefit vs NIVO in patients with centrally confirmed MSI-H/dMMR mCRC across all lines of therapy
  - PFS benefit with NIVO + IPI vs NIVO was consistent in all randomized patients (mPFS: 54.1 vs 18.4 months; HR, 0.64 [95% CI, 0.52-0.79])

[a]Per BICR. [b]Boundary for statistical significance, $P < 0.0095$.

Andre T et al. ASCO GI 2025. Abstract LBA143.

Emergence of TRAEs with potential immunologic etiology over time



- The majority of any-grade TRAEs with potential immunologic etiology[c] in the NIVO + IPI and NIVO groups emerged within the first 6 months of treatment across organ categories
  - Frequencies were generally comparable between the two treatment groups, except skin and endocrine TRAEs were more frequent with NIVO + IPI

[a]Includes events reported between first dose and 30 days after last dose of study treatment. Patients with ≥ 1 any grade event in a given category were counted only once in the time interval corresponding to the first event. Patients with multiple events from different categories within the same time interval were counted once in each category. Proportion of patients in each category is based on the patients still on treatment for the respective time interval. [b]Number of patients still receiving treatment is identified at the beginning of each respective time interval. [c]TRAEs with potential immunologic etiology that require frequent monitoring/intervention.

Lenz HJ et al. ASCO 2025. Abstract 3501.

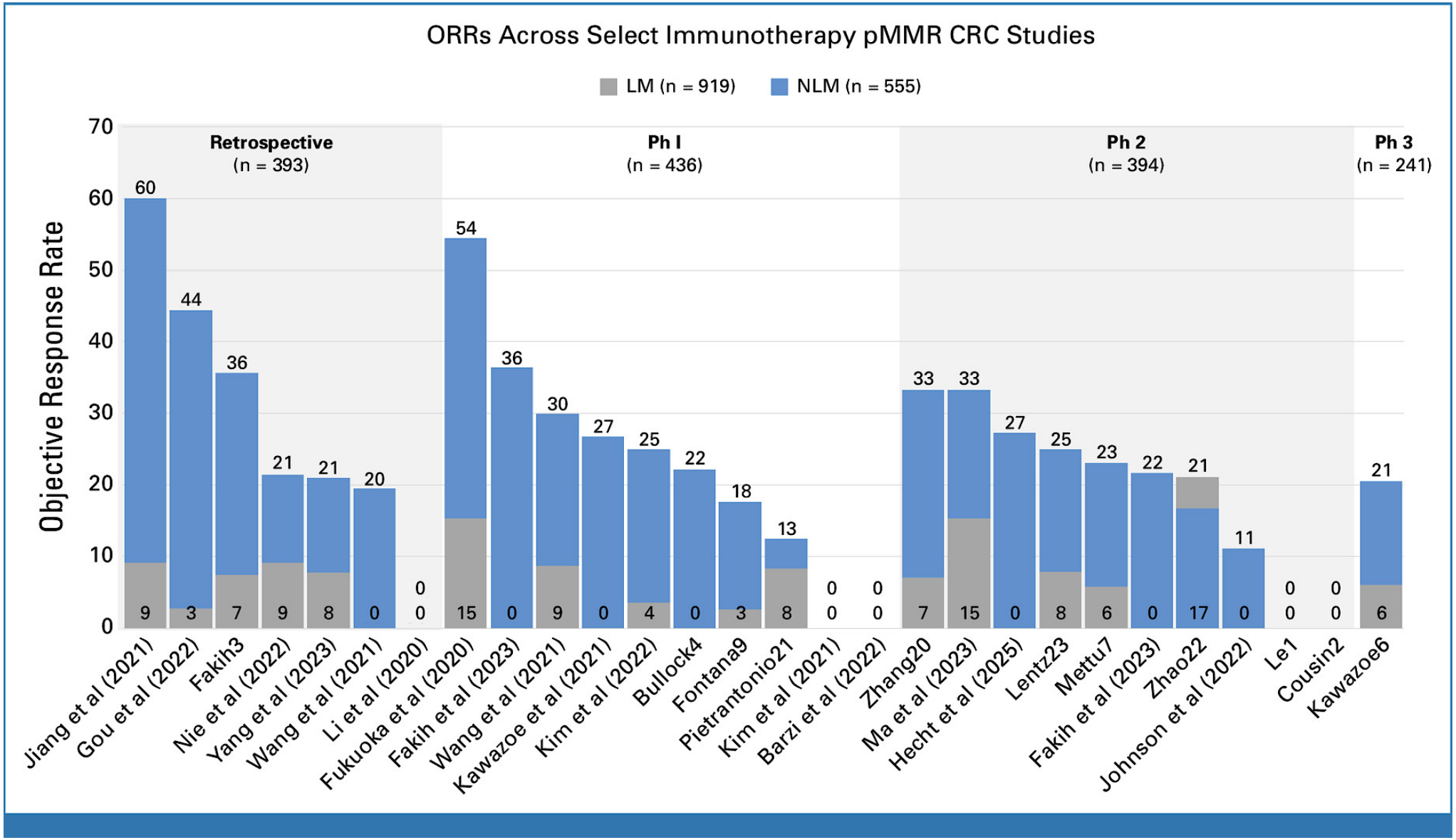
TAKE HOME POINT:

Patients with mCRC and MSI-H and/or dMMR should receive immunotherapy in the frontline setting

In eligible patients, strongly consider dual immunotherapy with nivolumab and ipilimumab

Is there a role for immunotherapy in pMMR/MSS mCRC?

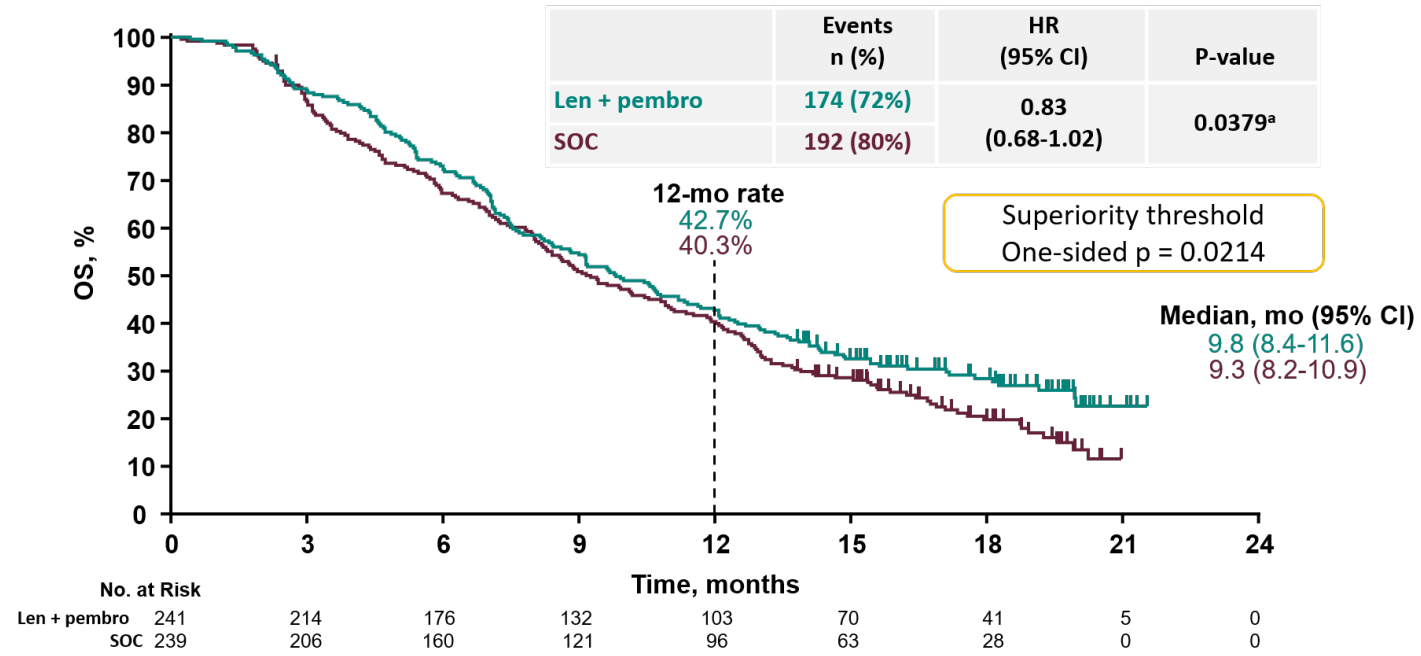
Response Rates in non-liver vs liver mCRC



Beiter ER et al. *J Clin Oncol* 2025

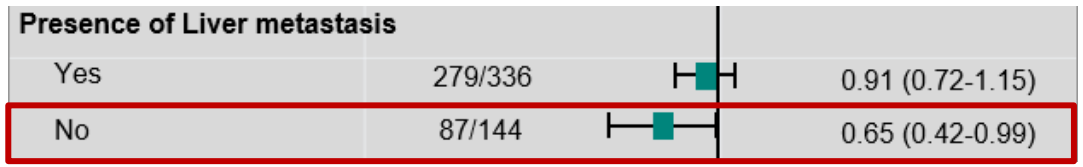
LEAP-017: Lenvatinib/Pembro

Characteristics, n (%)	Lenvatinib + Pembrolizumab N = 241	SOC N = 239
Presence of liver metastases		
Yes	168 (69.7)	168 (70.3)
No	73 (30.3)	71 (29.7)

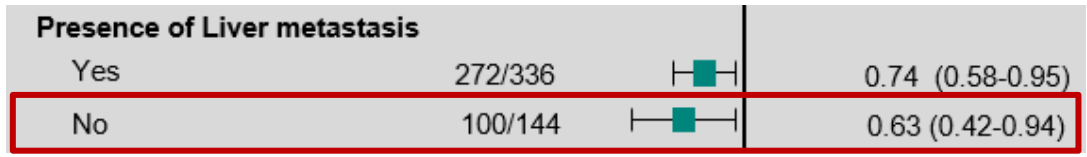


Primary Endpoint OS: NEGATIVE

OS



PFS



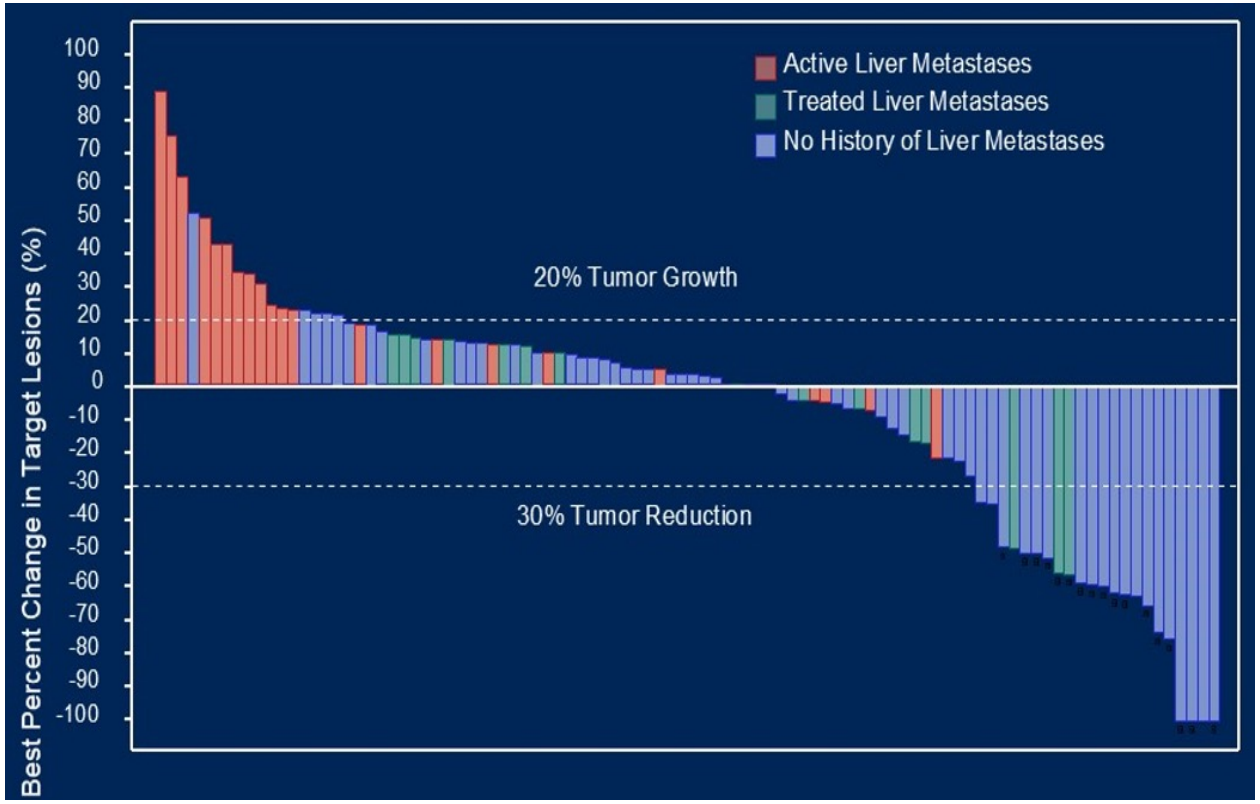
RR

Kawazoe A et al. 2023 ESMO World GI Cancer Congress. Abstract LBA-5
Kawazoe A et al. J Clin Oncol. 2024 Aug 20;42(24):2918-2927.

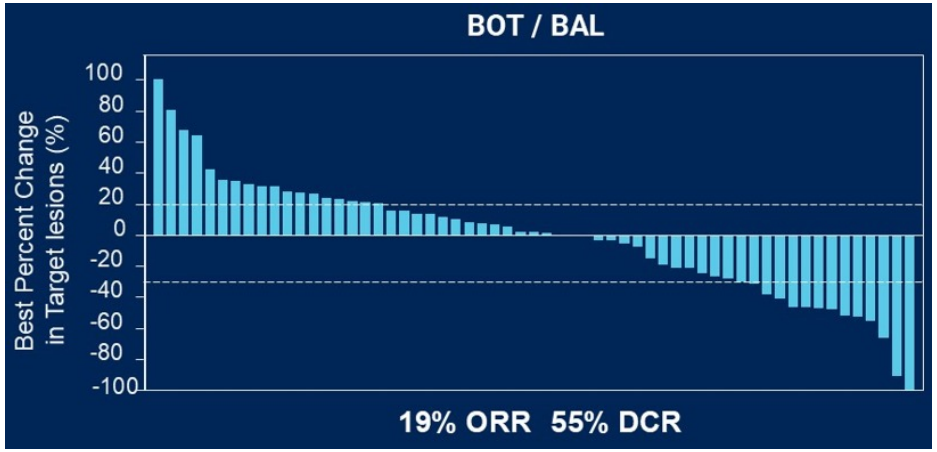
Botensilimab + Balstilimab in Non-liver Met pMMR mCRC

Fc-enhanced CTLA-4 Inhibitor (BOT) and PD-1 Inhibitor (BAL)

Phase 1 Trial

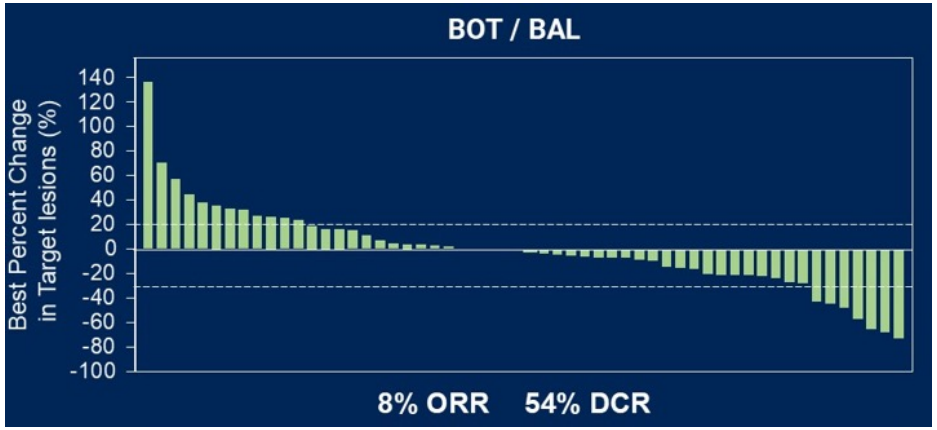


Randomized Phase 2 Trial



BOT 75mg

Non-liver met mCRC



BOT 150mg

Bullock AJ et al. *Nat Med*. 2024;30(9):2558-2567. Fakih M et al. ASCO GI 2025; Abstract 23.

STELLAR-303: Phase 3 Randomized, Open-Label Study of Zanzalintinib (XL092) With Atezolizumab vs Regorafenib in mCRC

Patient population

- MSS/MSI-low CRC
- Must have received SOC for mCRC and radiographically progressed/be refractory or intolerant to these therapies
- Progression during treatment or within 4 months of most recent therapy

N = ~874#

R 1:1

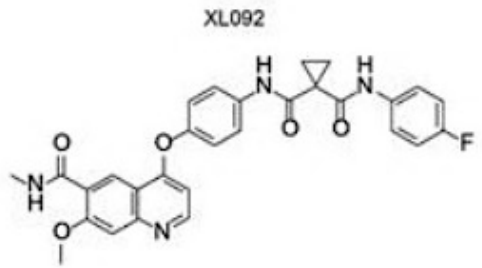
Zanzalintinib + Atezolizumab
Zanzalintinib orally daily + atezolizumab IV every 3 weeks

Regorafenib
Orally daily, 3 weeks on, 1 week off

Co-Primary Endpoint
• OS in all & NLM patients
Key Secondary Endpoints
• PFS by investigator • ORR by investigator • DOR by investigator

#Enrollment of patients with liver metastases will be capped at approximately 524

XL092



Kinase	Kinase Inhibition
MET	3.0 ± 0.27
VEGFR2	15.0 ± 0.95
AXL	5.8 ± 0.38
MER	0.6 ± 0.054
TYRO3	NA

Saeed A et al. *Future Oncol*. 2024;20(24):1733-1743.

STELLAR-303: Phase 3 Randomized, Open-Label Study of Zanzalintinib (XL092) With Atezolizumab vs Regorafenib in mCRC

Zanzalintinib in Combination with an Immune Checkpoint Inhibitor Improved Overall Survival in STELLAR-303 Phase 3 Pivotal Trial in Patients with Metastatic Colorectal Cancer

June 22, 2025

PDF Version

– Zanzalintinib in combination with atezolizumab demonstrated a statistically significant reduction in risk of death versus regorafenib in intent-to-treat population –

TYRO3	NA

Saeed A et al. *Future Oncol*. 2024;20(24):1733-1743.

https://ir.exelixis.com/news-releases/news-release-details/exelixis-announces-zanzalintinib-combination-immune-checkpoint

TAKE HOME POINT:

STELLAR-303: Phase 3 Randomized, Open-Label Study of Zanzalintinib (XL092) With Atezolizumab vs Regorafenib in mCRC

Stay tuned!

Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

CME/MOC, NCPD and ACPE Accredited

Saturday, October 11, 2025
7:15 AM – 12:30 PM ET

RTP
RESEARCH
TO PRACTICE

Nivolumab plus Ipilimumab vs Nivolumab Monotherapy for Microsatellite Instability-High/Mismatch Repair-Deficient (MSI-H/dMMR) Metastatic Colorectal Cancer (mCRC): New Results from CheckMate 8HW

Lonardi S et al.

ESMO 2025;Abstract LBA29.

PROFFERED PAPER| MONDAY, OCTOBER 20 | 8:30 CEST

Zanzalintinib plus Atezolizumab (zanza + atezo) vs Regorafenib (rego) in Patients (pts) with Previously Treated Metastatic Colorectal Cancer (mCRC): Primary Overall Survival (OS) Analysis from the Randomized, Open-Label, Phase 3 STELLAR-303 Study

Saeed A et al.

ESMO 2025;Abstract LBA30.

PROFFERED PAPER| MONDAY, OCTOBER 20 | 9:25 CEST

Questions from General Medical Oncologists

- **A 42-year-old patient with locally advanced MSI-H rectal cancer is responding dramatically to neoadjuvant dostarlimab. If they achieve a complete clinical response, should surgery be deferred entirely?**
- **Should we use dostarlimab as neoadjuvant therapy for MSI-H rectal cancer, or is pembrolizumab OK?**

Questions from General Medical Oncologists

- When, if at all, should we be recommending neoadjuvant IO for MSI-H colon cancer? If we are going to use this approach, should it be single-agent or dual checkpoint inhibition?
- Should we use adjuvant IO in Stage II MSI-high colon cancer?
- Can we get away without chemotherapy in the adjuvant setting for MSI-H colon cancer?
- Can ctDNA monitoring post-surgery help determine which patients benefit from adding atezolizumab?

Questions from General Medical Oncologists

- **Are you typically using dual checkpoint inhibition or anti-PD-1/PD-L1 monotherapy as first-line treatment for metastatic MSI-H CRC?**

Questions from General Medical Oncologists

- **Should we stop pembrolizumab after 2 years in MSI-H mCRC?**
- **What do we know about POLE mutations in mCRC?**
- **What is the current and future role of IO (+ TKI?) in MSS metastatic disease? Do you think the upcoming ESMO presentation of zanzalintinib in combination with atezolizumab will change practice?**

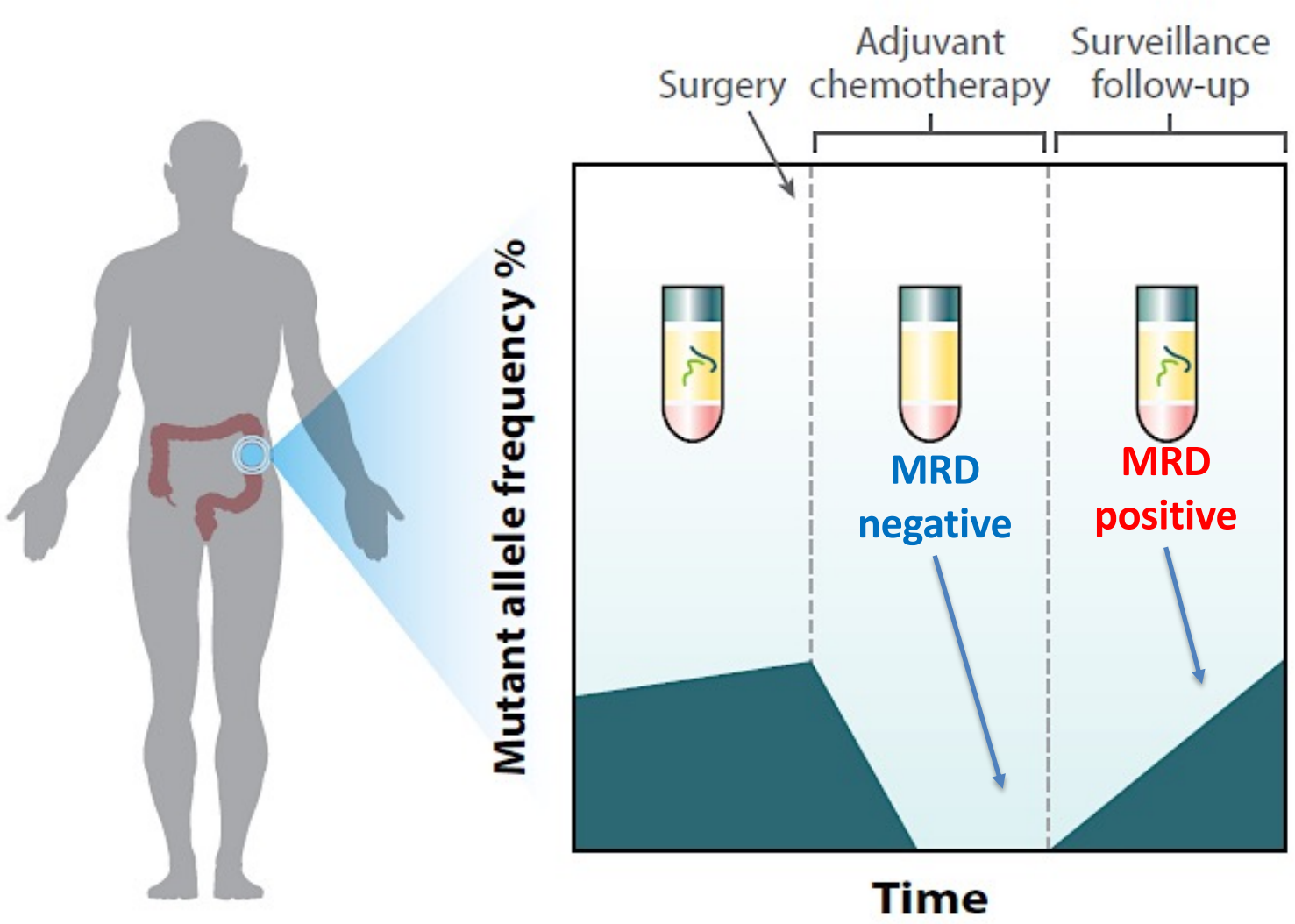
Questions from General Medical Oncologists

- **Can patients with MSI-H mCRC who receive pembrolizumab be treated with ipilimumab/nivolumab in the second line?**
- **How would you approach a patient with mCRC that is MSI-H and BRAF-positive? Would you use IO or targeted therapy with chemotherapy first?**

Other Biomarker-Based Strategies for Patients with Colorectal Cancer

John Strickler, MD
Professor of Medicine
Duke University
October 11, 2025

Defining Minimal Residual Disease (MRD)



ctDNA detection techniques

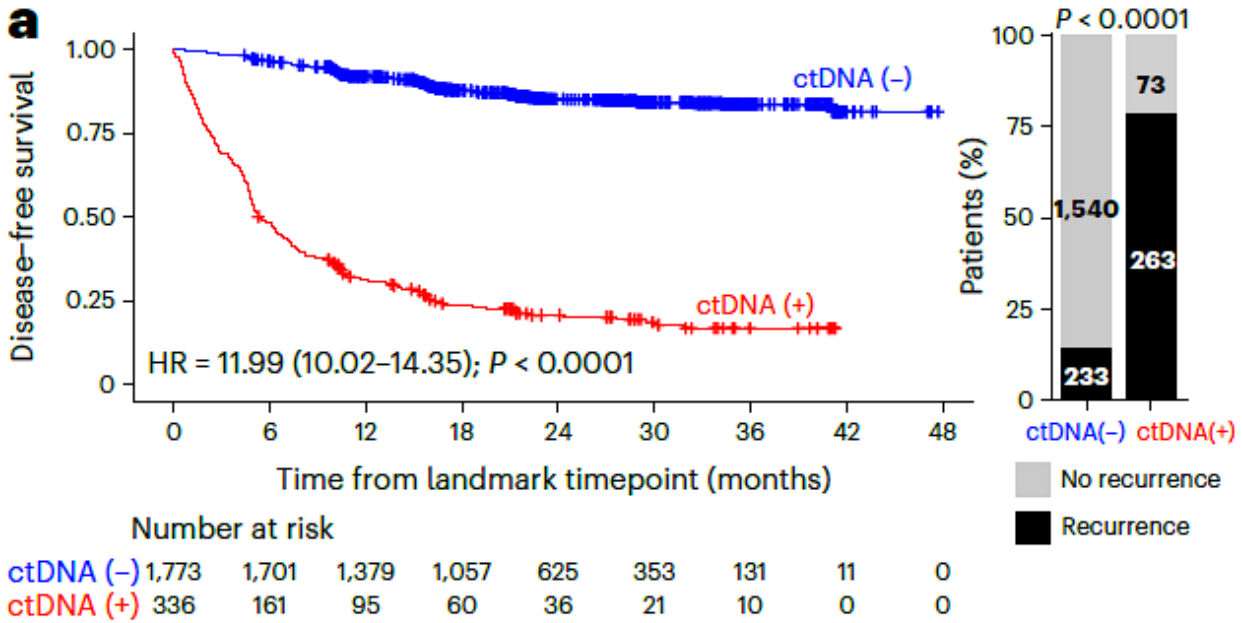
- Tumor informed
- Plasma only

Morris and Strickler, Annu Rev Med. 2021. 72:399–413.

MRD status after surgery is strongly prognostic

GALAXY Study: Tumor-informed MRD testing after resection in patients with stage II-IV CRC (n=2,109)

Disease-free survival

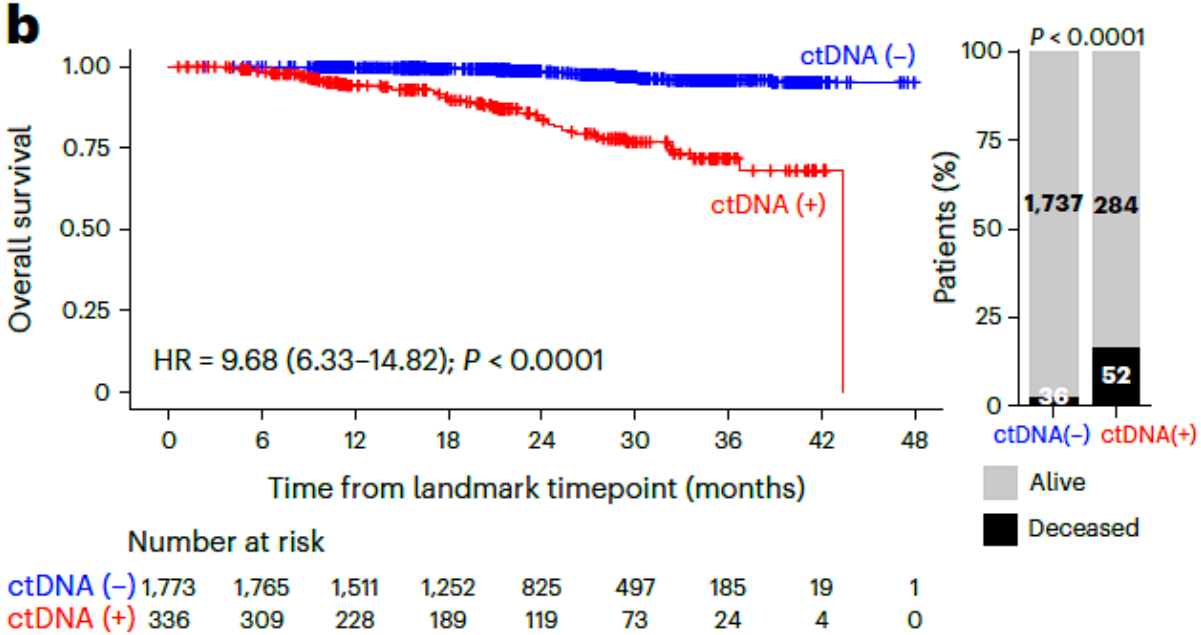


Number at risk

ctDNA (–)	1,773	1,701	1,379	1,057	625	353	131	11	0
ctDNA (+)	336	161	95	60	36	21	10	0	0

ctDNA status	Negative	Positive
Events %	13.14 (233/1773)	78.27 (263/336)
24M-DFS % (95% CI)	85.10 (83.20–86.9)	20.57 (16.14–25.37)
30M-DFS % (95% CI)	84.10 (82.0–86.0)	18.50 (14.0–23.40)
36M-DFS % (95% CI)	83.50 (81.20–85.60)	16.70 (12.10–21.90)
mDFS (mo)	NR	5.34 (4.83–6.70)

Overall survival



Number at risk

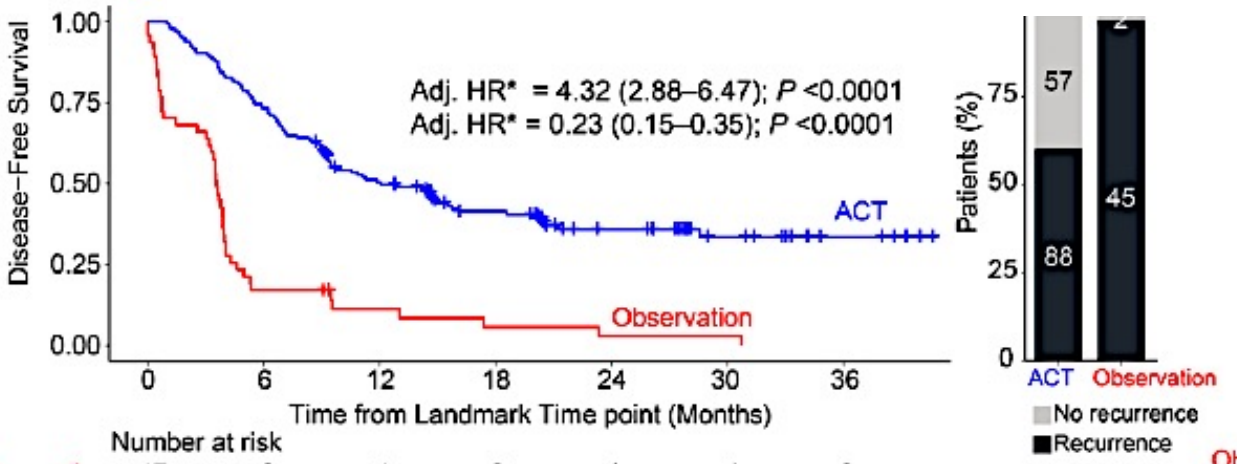
ctDNA (–)	1,773	1,765	1,511	1,252	825	497	185	19	1
ctDNA (+)	336	309	228	189	119	73	24	4	0

ctDNA status	Negative	Positive
Events %	2.03 (36/1773)	15.48 (52/336)
24M-OS % (95% CI)	98.50 (97.70–99.10)	83.65 (77.84–88.06)
30M-OS % (95% CI)	96.80 (95.40–97.80)	76.90 (69.80–82.50)
36M-OS % (95% CI)	96.0 (94.30–97.20)	71.80 (63.40–78.60)
mOS (mo)	NR	43.40 (NR–NR)

Nakamura et. al., Nature Medicine (2024) 30, 3272–3283

GALAXY: Adjuvant chemotherapy for high-risk stage II/III disease

a High-risk stage II/III: MRD+

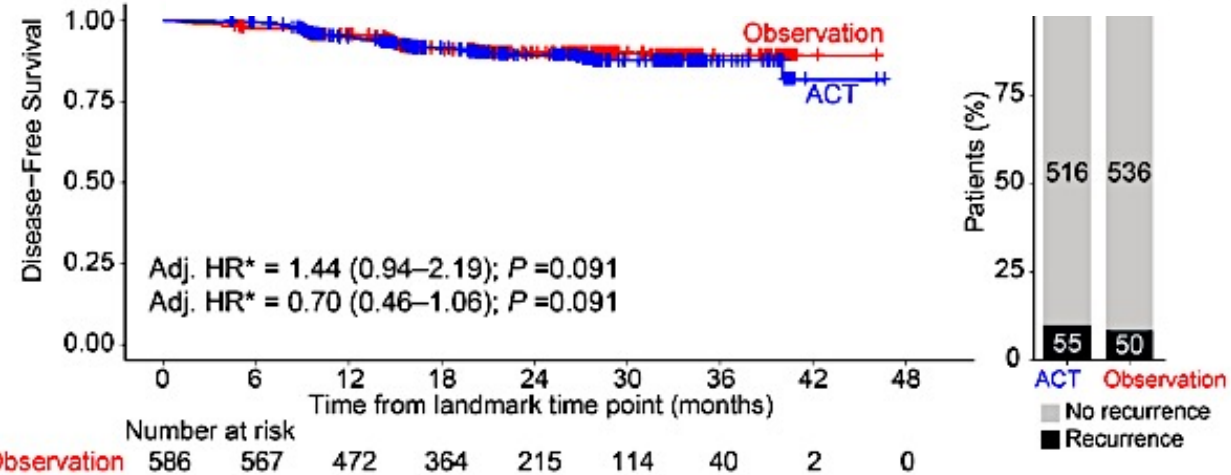


Number at risk

Observation	47	8	4	2	1	1	0
ACT	145	106	68	46	25	14	6

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)

b High-risk stage II/III : MRD-



Number at risk

Observation	586	567	472	364	215	114	40	2	0
ACT	571	562	459	358	216	115	39	2	0

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

Nakamura et. al., Nature Medicine (2024) 30, 3272–3283

DYNAMIC Study Design

Stage II Colon Cancer

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

Plasma Collections
Week 4 + 7 post-op

R
2:1

ctDNA-Guided Management

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

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

Standard Management

Adjuvant treatment decisions based on conventional clinico-pathologic criteria

Endpoints

Primary
- RFS rate at 2 years

Key Secondary
- Proportion receiving adjuvant chemo

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

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

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

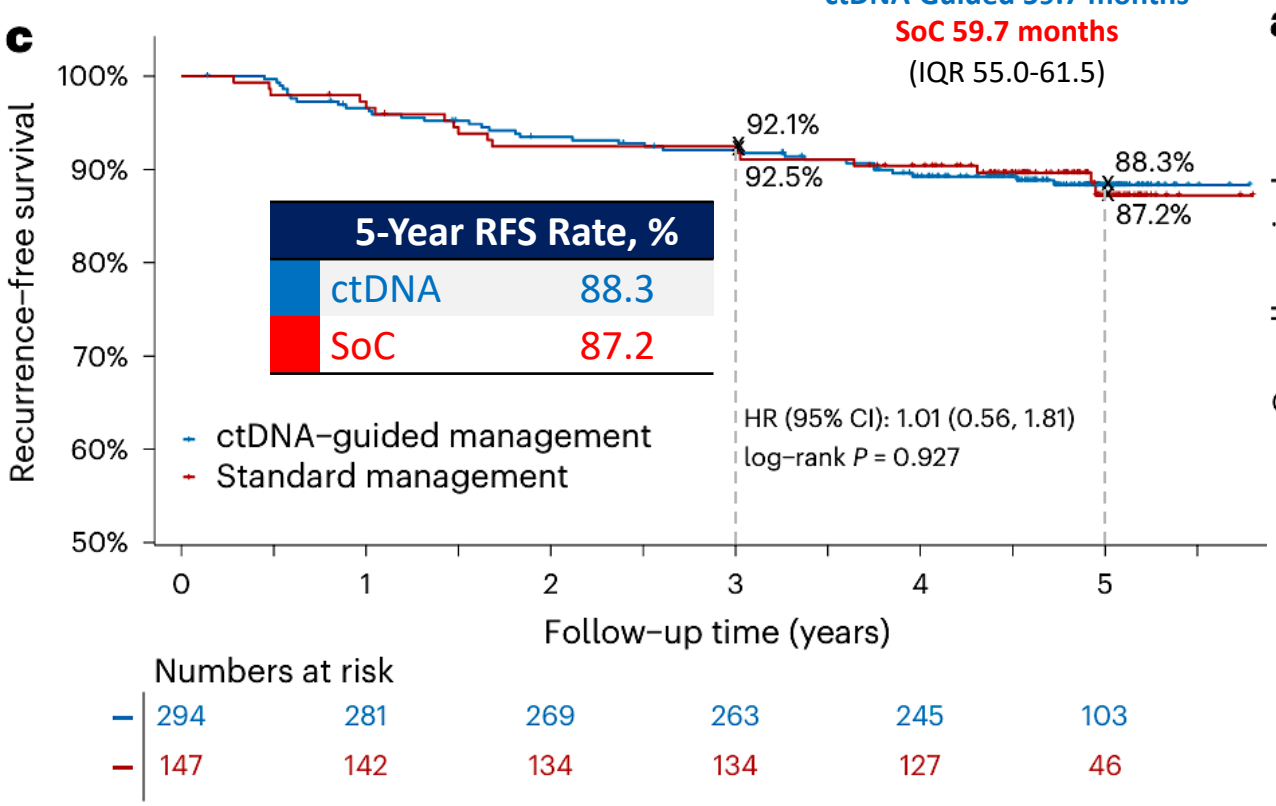
Tie et al., N Engl J Med 2022;386:2261-72.Presented at 2022 ASCO Annual Meeting

DYNAMIC: Updated 5-year RFS and Overall survival

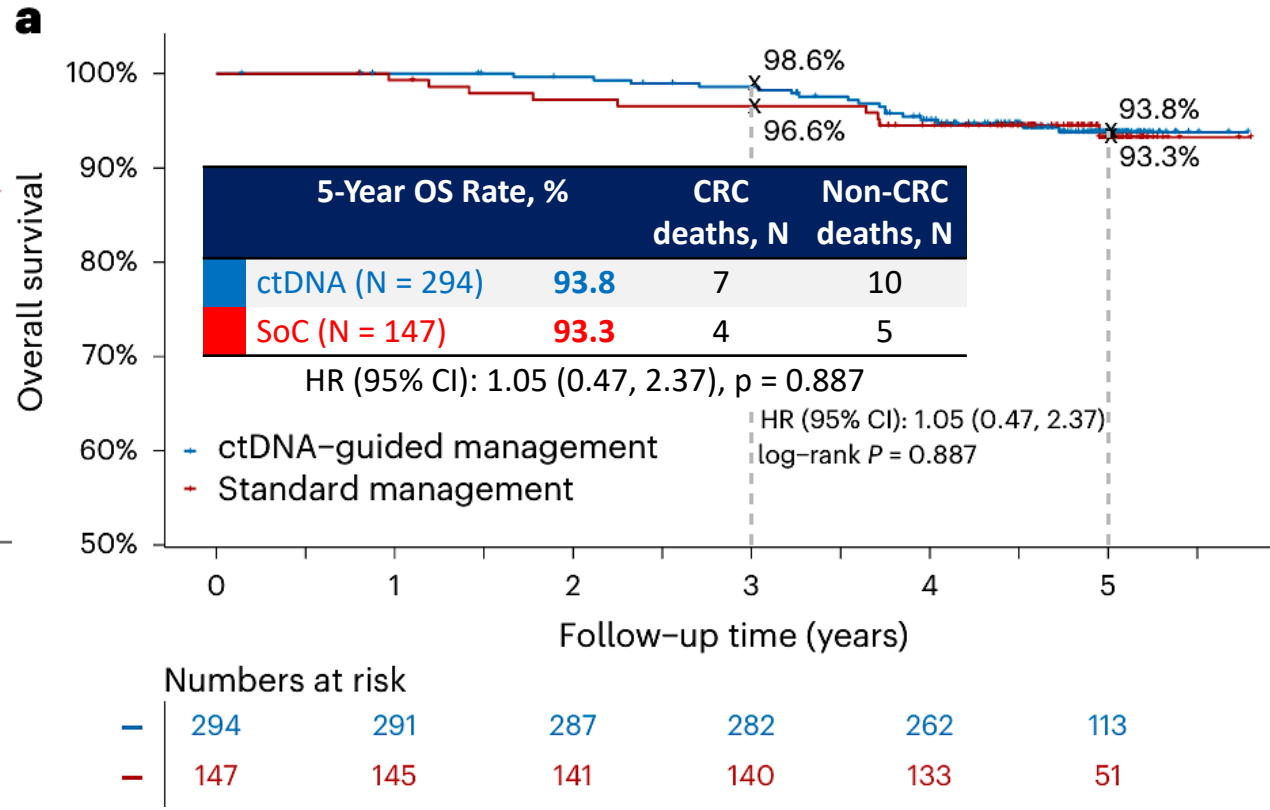
Updated 5-Year RFS Analysis

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)



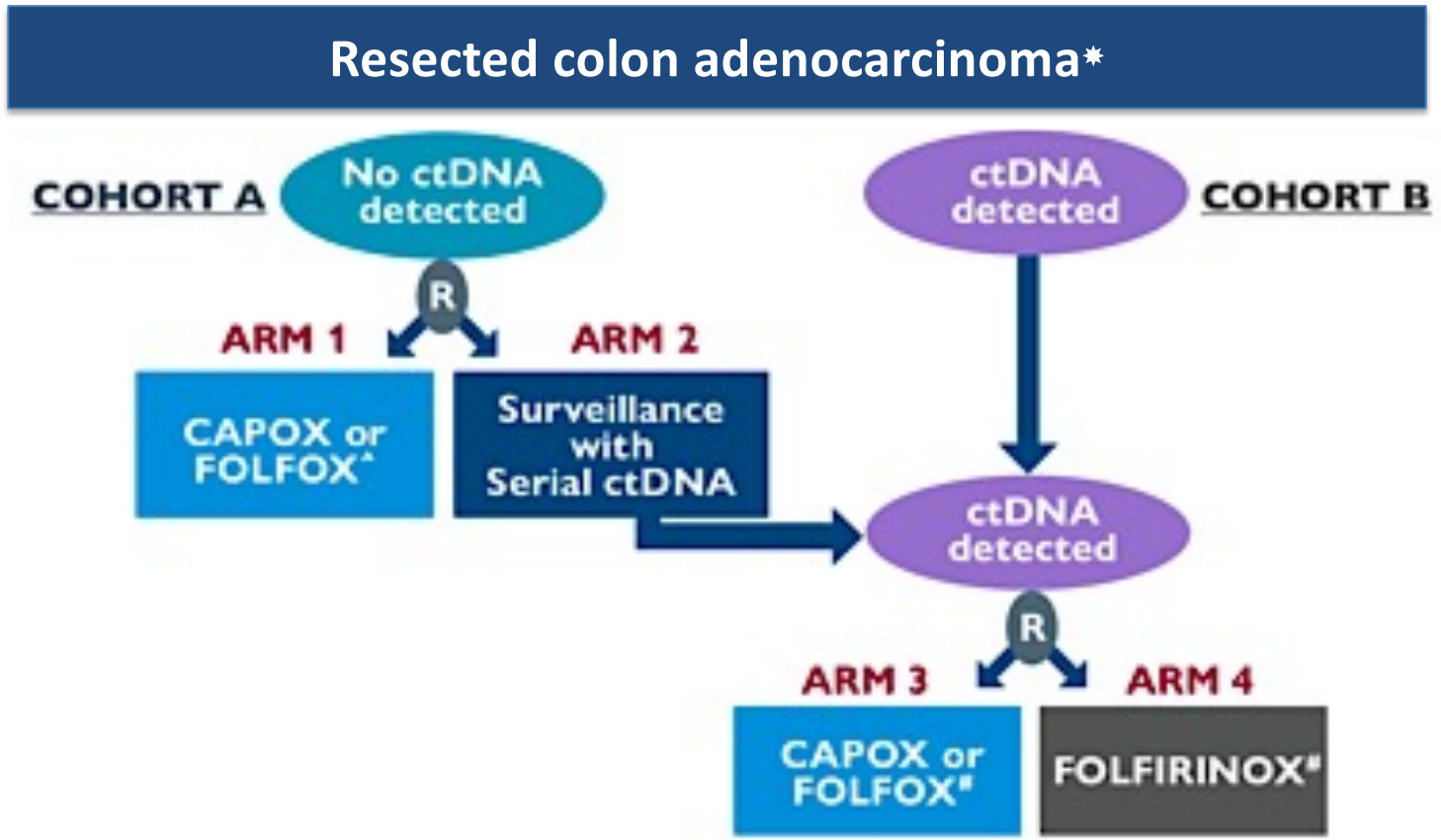
Overall Survival



- **ctDNA-guided MRD-based adjuvant therapy significantly reduced the proportion of patients receiving postoperative adjuvant therapy compared to SOC based on conventional clinicopathological factors, while demonstrating non-inferiority in 5-year RFS/OS.**

Tie J, et al. Nature Medicine 2025

CIRCULATE-US (NRG-GI008)



Primary endpoints

Cohort A: ctDNA negative

- Phase II: Time to ctDNA+
- Phase III: DFS

Cohort B: ctDNA positive

- Phase II/III: DFS

Study size: 1,750-1,912

Joint analysis with Circulate-Japan

Study PIs: Arvind Dasari (MDACC-NRG) and Christopher Lieu (UCCC-SWOG)

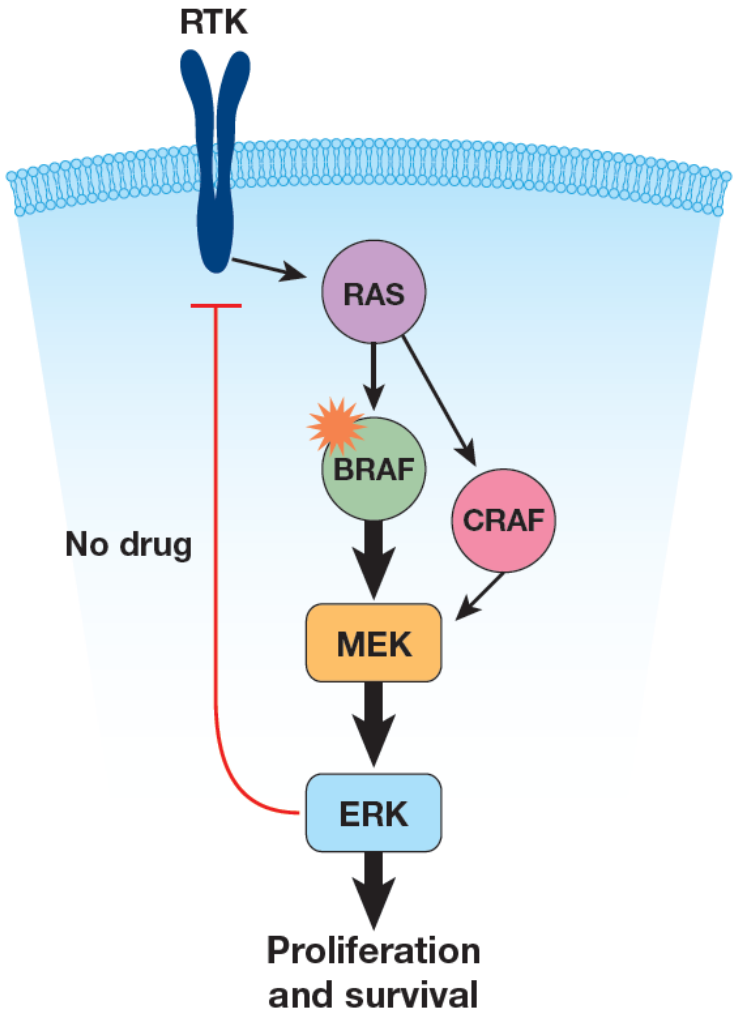
- * Stage IIB, IIC, or any stage III colon cancer post-R0 resection
- Arm 2 pts who become ctDNA +ve may cross-over to Cohort B
- ^ Duration and regimen per MD discretion
- # Duration of therapy 6 mos.
- Randomization in both arms 1:1
- Stratification factors: 5FU vs cape, Stage (II/IIIA vs IIIB vs IIIC, Cohort A), Initial post-op ctDNA status (+ vs -, Cohort B).

Lieu et. al., J Clin Oncol 42, 2023 (3_suppl; TPS243). Presented at ASCO GI 2024

MRD monitoring for CRC: Key points

- MRD testing is a validated prognostic tool
- Observational data demonstrates no advantage for adjuvant chemo in patients with MRD negative stage II/III colon ca
- For stage II colon ca, MRD could be considered a “tie-breaker” for adjuvant chemotherapy
- MRD testing might have utility in patients who have resection of metastatic lesions
- Prospective trials are ongoing to explore the clinical utility of escalation and de-escalation strategies

BRAF^{V600E} in metastatic CRC

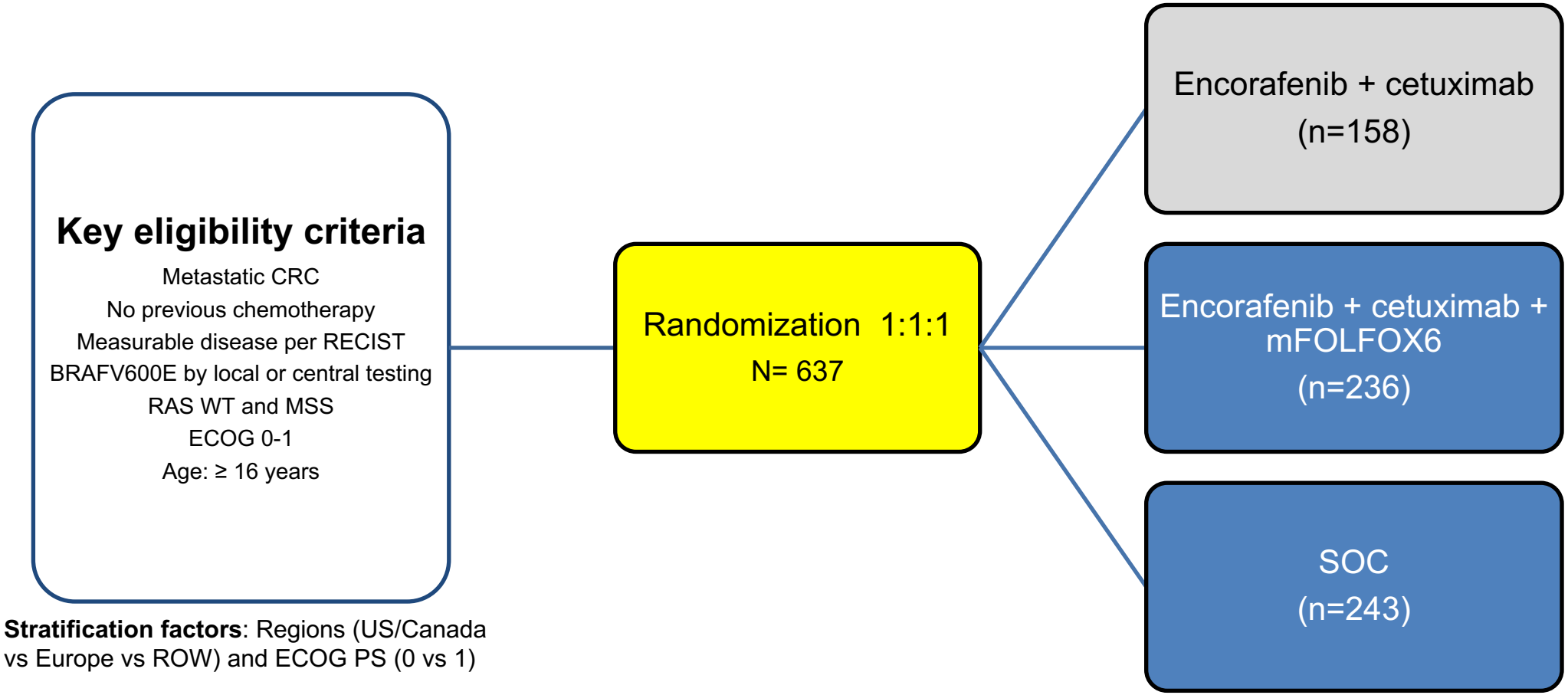


- ~7% of CRC
- Advanced age
- More common in women
- Right-sided
- Poor prognosis
- 30% are MSI-H
- Limited benefit from anti-EGFR Ab
- For 2L+ mCRC, encorafenib + cetuximab is superior to SOC – FDA approved 4/2020

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

BREAKWATER: Study Design

Phase 3, randomized, open-label, multicenter study for 1L treatment of BRAF V600E-mutant mCRC (NCT04607421)



Stratification factors: Regions (US/Canada vs Europe vs ROW) and ECOG PS (0 vs 1)

Dual primary endpoints: PFS and ORR by BICR (EC+ mFOLFOX6 vs SOC)
Key secondary endpoint: Overall survival (EC + mFOLFOX6 vs SOC)

Kopetz et. al., Nat Med. 2025 Mar;31(3):901-908. Presented at ASCO GI 2025

BREAKWATER: 1L EC + mFOLFOX6 vs SOC

	Encorafenib + Cetuximab + mFOLFOX6 (N= 236)	SOC (N= 243)	HR (95% CI)	*P*-value[a]	Encorafenib + Cetuximab (N= 158)
ORR[b]	65.7%	37.4%			45.6%
PFS[b], months (95% CI)	12.8 (11.2-15.9)	7.1 (6.8-8.5)	0.53 (0.407-0.677)	<0.0001	6.8 (5.7-8.3)
OS, months (95% CI)	30.3 (21.7-NE)	15.1 (13.7, 17.7)	0.49 (0.375-0.632)	<0.0001	19.5 (17.6-22.5)

[a] one-sided stratified log rank test
[b] By BICR

Elez et. al., NEJM 2025 DOI: 10.1056/NEJMoa2501912
Presented at ASCO 2025

BREAKWATER: Safety Summary

Patients, n (%)	EC n=153	EC + mFOLFOX6 n=232	SOC n=229
Duration of treatment, median (range), weeks	27.0 (2.0-153.6)	49.8 (1.3-161.9)	25.9 (2.0-150.0)
All causality			
TEAE	149 (97.4)	232 (100)	227 (99.1)
Grade 3 or 4 TEAE	65 (42.5)	189 (81.5)	153 (66.8)
Grade 5 TEAE	4 (2.6)	10 (4.3)	10 (4.4)
Serious TEAE	46 (30.1)	107 (46.1)	89 (38.9)
TEAE leading to permanent discontinuation of any study treatment	20 (13.1)	62 (26.7)	40 (17.5)
TEAE leading to dose reduction of any study treatment	16 (10.5)	152 (65.5)	124 (54.1)
TEAE leading to dose interruption of any study treatment	63 (41.2)	212 (91.4)	168 (73.4)
Treatment-related			
AE related to any drug	136 (88.9)	232 (100)	217 (94.8)
Grade 3 or 4 TRAE	24 (15.7)	177 (76.3)	134 (58.5)
Grade 5 TRAE	0	0	1 (0.4)[a]
Serious AE related to any drug	10 (6.5)	45 (19.4)	50 (21.8)

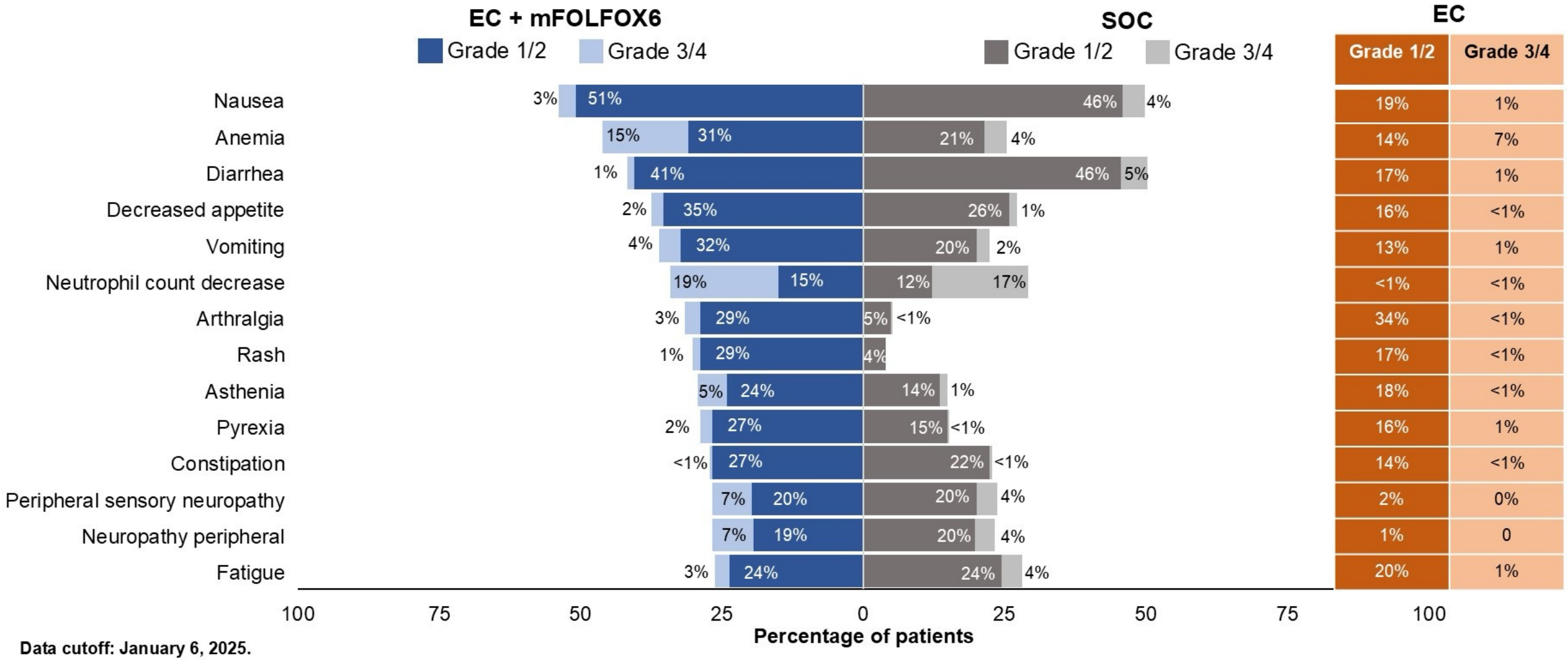
Data cutoff: January 6, 2025.

[a]**Sepsis (preferred term).**

AE, adverse event; EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; SOC, standard of care; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Elez et. al., NEJM 2025 DOI: 10.1056/NEJMoa2501912
Elez et al. ASCO 2025;Abstract LBA3500

BREAKWATER: Most frequent all-causality TEAEs



Data cutoff: January 6, 2025.

[a]Frequency is based on the EC + mFOLFOX6 arm.

EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; SOC, standard of care; TEAE, treatment-emergent adverse event.

Elez et. al., NEJM 2025 DOI: 10.1056/NEJMoa2501912
Elez et al. ASCO 2025;Abstract LBA3500

BRAF V600E: Key points

- *BRAF*^{V600E} mutations are associated with poor prognosis and EGFR resistance
- 1L Encorafenib + cetuximab + FOLFOX is the new standard of care for newly diagnosed *BRAF*^{V600E} mutated metastatic CRC
- Rapid biomarker testing at the time of diagnosis of metastatic disease is essential

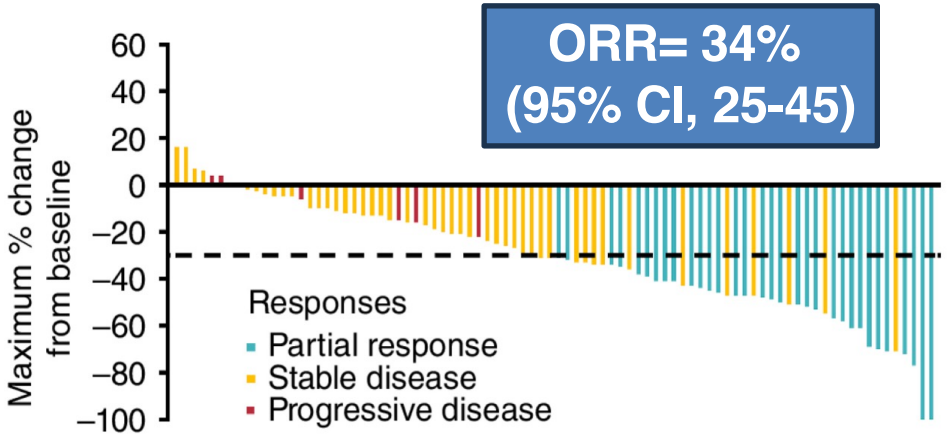
KRAS G12C Inhibitors Have Modest Single-Agent Activity in *KRAS* G12C–Mutant mCRC

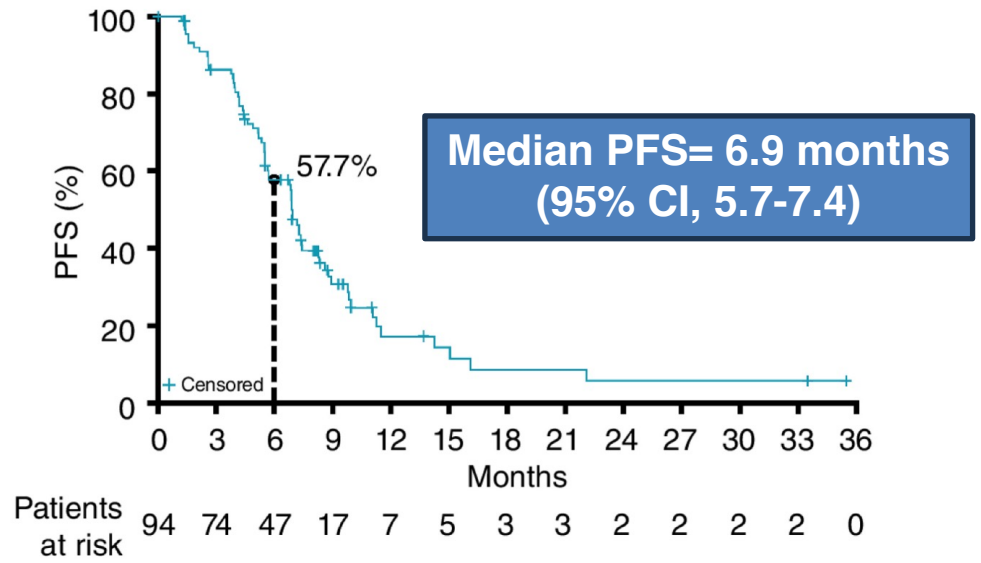
	Adagrasib (n = 43)[a]	Divarasib (n = 55)	Sotorasib (n = 62)
Objective response % (95% CI) per BICR	23 (12-39)	29 (18-43)	10 (4-20)
Median duration of response, mo (95% CI)	4.3 (2.3-8.3)	7.1 (5.5-7.8)	4.2 (2.9-8.5)
Median PFS, mo (95% CI)	5.6 (4.1-8.3)	5.6 (4.1-8.2)	4 (2.8-4.2)
Median OS, mo (95% CI)	19.8 (12.5-23.0)	Not reported	10.6 (7.7-15.6)
AE leading to dose reduction, n (%)	17 (39)	41 (30)[b]	11 (18)[c]
AE leading to discontinuation, n (%)	0 (0)	4 (3)[b]	1 (2)

[a] 1 patient withdrew from study prior to first assessment. [b] Includes all solid tumors treated with divarasib. [c] Includes dose hold.

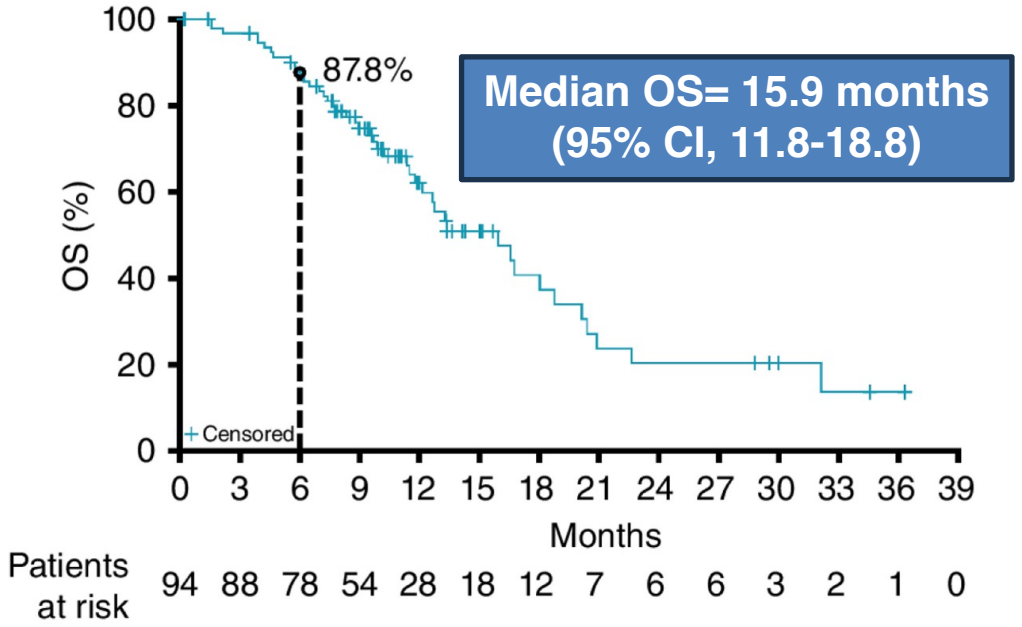
1. Yaeger R et al. *N Engl J Med.* 2023;388:44-54. 2. Sacher A et al. *N Engl J Med.* 2023;710-721. 3. Fakih MG et al. *Lancet Oncol*. 2022;23:115-124.

Adagrasib + cetuximab for *KRAS* G12C–Mutant mCRC





In June 2024, the FDA approved adagrasib + cetuximab for patients with *KRAS* G12C–mutated mCRC



Yaeger et al. *Cancer Discov.* 2024;14:982-993.

Adagrasib + cetuximab for *KRAS* G12C–Mutant mCRC

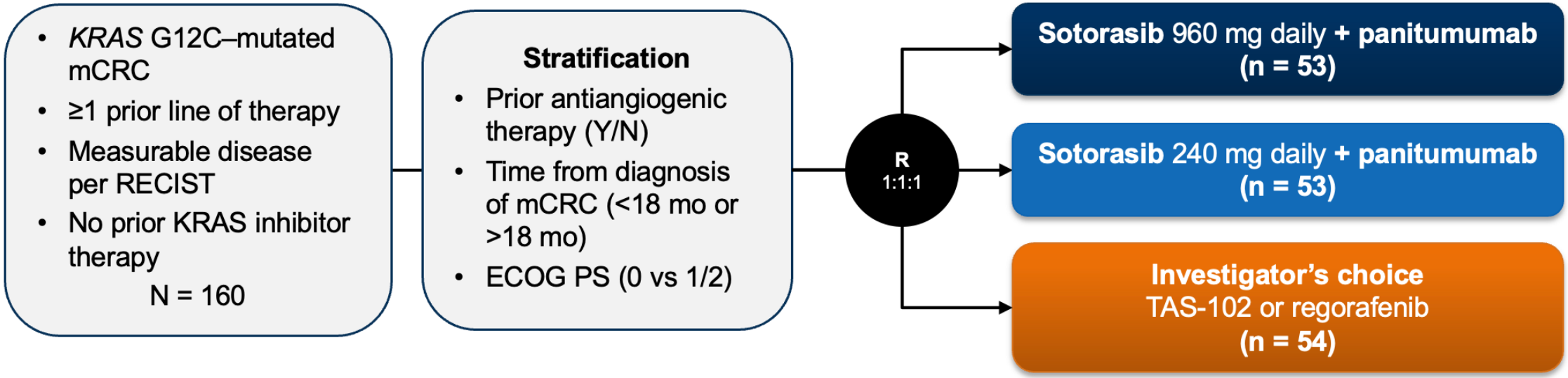
Summary of TRAEs (N = 94)

TRAEs, n (%)	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Any TRAEs	94 (100)	8 (8.5)	60 (63.8)	22 (23.4)	4 (4.3)
Most frequent TRAEs, n (%)					
Nausea	57 (60.6)	35 (37.2)	20 (21.3)	2 (2.1)	0
Vomiting	48 (51.1)	30 (31.9)	18 (19.1)	0	0
Diarrhea	46 (48.9)	31 (33)	14 (14.9)	1 (1.1)	0
Dermatitis acneiform	45 (47.9)	28 (29.8)	15 (16)	2 (2.1)	0
Fatigue	40 (42.6)	23 (24.5)	16 (170)	1 (1.1)	0
Dry skin	32 (34)	24 (25.5)	8 (8.5)	0	0
Hypomagnesemia	27 (28.7)	17 (18.1)	7 (7.4)	2 (2.1)	1 (1.1)
Headaches	25 (26.6)	14 (14.9)	8 (8.5)	3 (3.2)	0
Rash	21 (22.3)	11 (11.7)	8 (8.5)	2 (2.1)	0

- 29% of patients had a dose reduction of adagrasib
- No patients experienced a TRAE leading to discontinuation of adagrasib

Yaeger et al. *Cancer Discov.* 2024;14:982-993.

CodeBreaK300: Sotorasib + panitumumab for *KRAS* G12C–Mutant mCRC



	Sotorasib 960 mg + PMAb (n = 53)	Sotorasib 240 mg + PMAb (n = 53)	Investigator's Choice (n = 54)
Median PFS, mo HR (95% CI; *P*)	**5.6** 0.49 (0.30-0.80; 0.006)	**3.9** 0.58 (0.36-0.93; 0.03)	**2.2** (-;-)
ORR, % (95% CI per BICR)	**26** (15.3-40.3)	**6** (1.2-15.7)	**0** (0-6.6)
Disease control rate, % (95% CI per BICR)	**72** (57.7-83.2)	**68** (53.7-80.1)	**46** (32.6-60.4)

1. Pietrantonio F et al. ESMO 2023. 2. Fakih et al. *N Engl J Med*. 2023;389:2125-2139.

CodeBreaK300: Treatment discontinuation due to TRAEs was rare

	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
Any AE, n (%)	50 (94.3)	51 (96.2)	42 (82.4)
Grade ≥3 event, n (%)	19 (35.8)	16 (30.2)	22 (43.1)
AE leading to sotorasib discontinuation, n (%)	1 (1.9)	1 (1.9)	–
Skin and subcutaneous tissue disorders, n (%)	44 (83.0)	45 (84.9)	11 (21.6)

1. Pietrantonio F et al. ESMO 2023. 2. Fakih et al. *N Engl J Med*. 2023;389:2125-2139.

FOLFIRI + Sotorasib + Panitumumab: ORR and PFS by line of therapy

	1st Line N=40	2nd Line N= 13	3rd Line N= 12	≥ 4th Line N= 15
CodeBreaK 101	Cohort F	Cohort G	Cohort G	Cohort G
ORR	78%	69%	58%	47%
PFS	Not reached	8.3 mo	7.1 mo	8.4 mo

- ORR was numerically higher for those with fewer lines of prior therapy
- Responses were observed regardless of progression on prior irinotecan

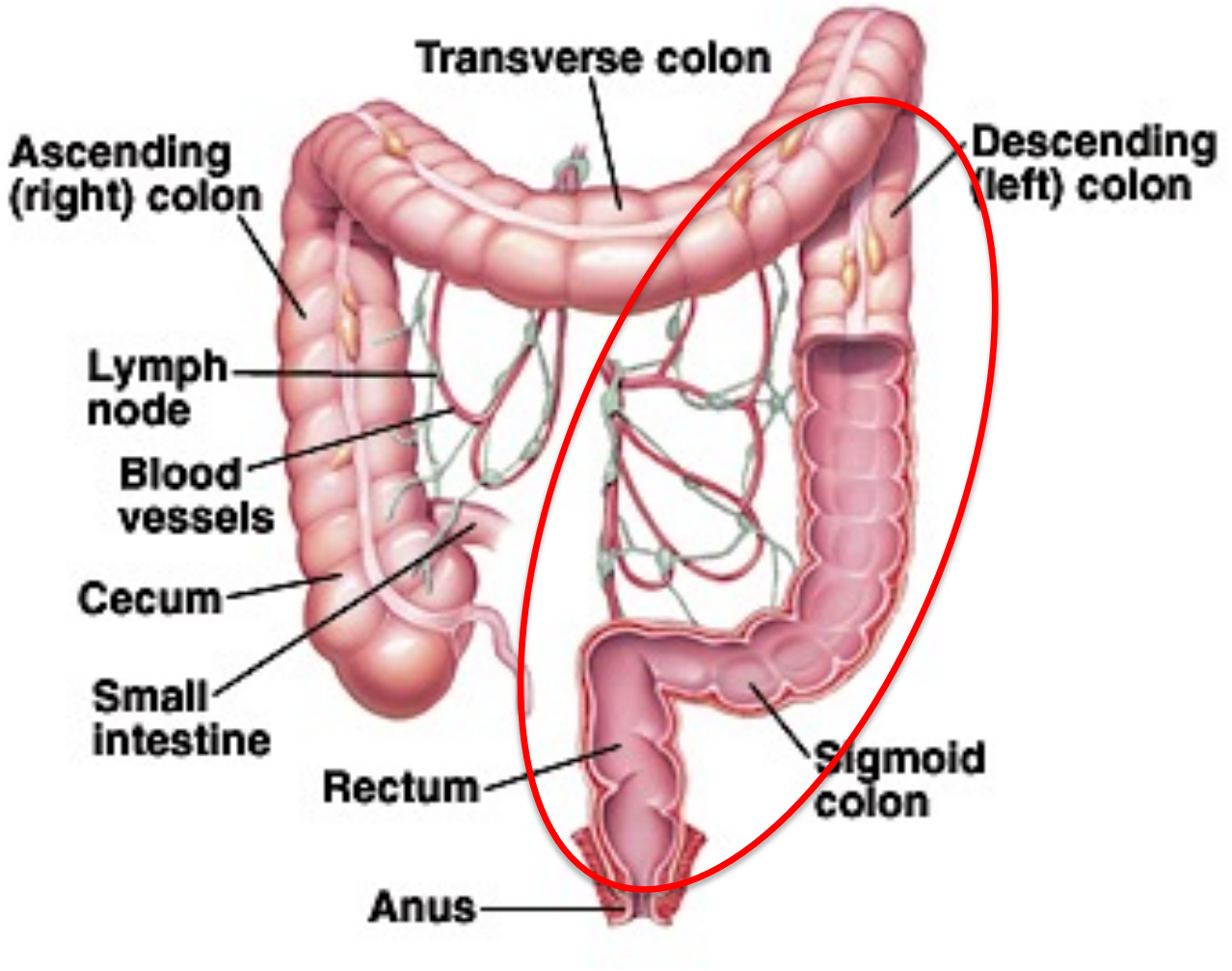
Siena S et al. ESMO 2024;Abstract 505O
Strickler JH et al. ASCO 2025;Abstract 3506

Targeting KRAS: Key points

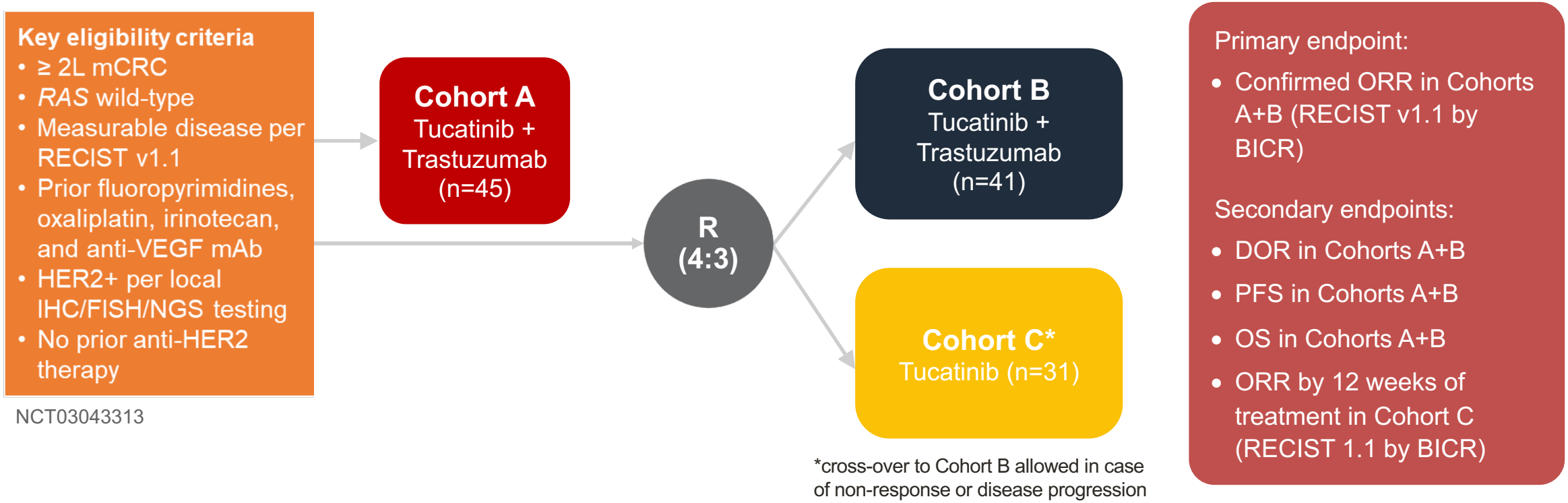
- KRAS G12C inhibitors have limited single agent activity in mCRC – combinations with anti-EGFR Abs are required
- Adagrasib + cetuximab and sotorasib + panitumumab are active and generally well tolerated – now FDA approved
- Future therapeutic strategies for KRAS G12C may combine cytotoxic chemotherapy with targeted therapies

HER2 in Metastatic CRC

- Usually <u>left-sided</u>
- ~ 3% of patients with metastatic CRC
- Enriched in patients with *RAS/ BRAF* WT disease
- Associated with lung, brain metastases
- May drive resistance to EGFR antibodies



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



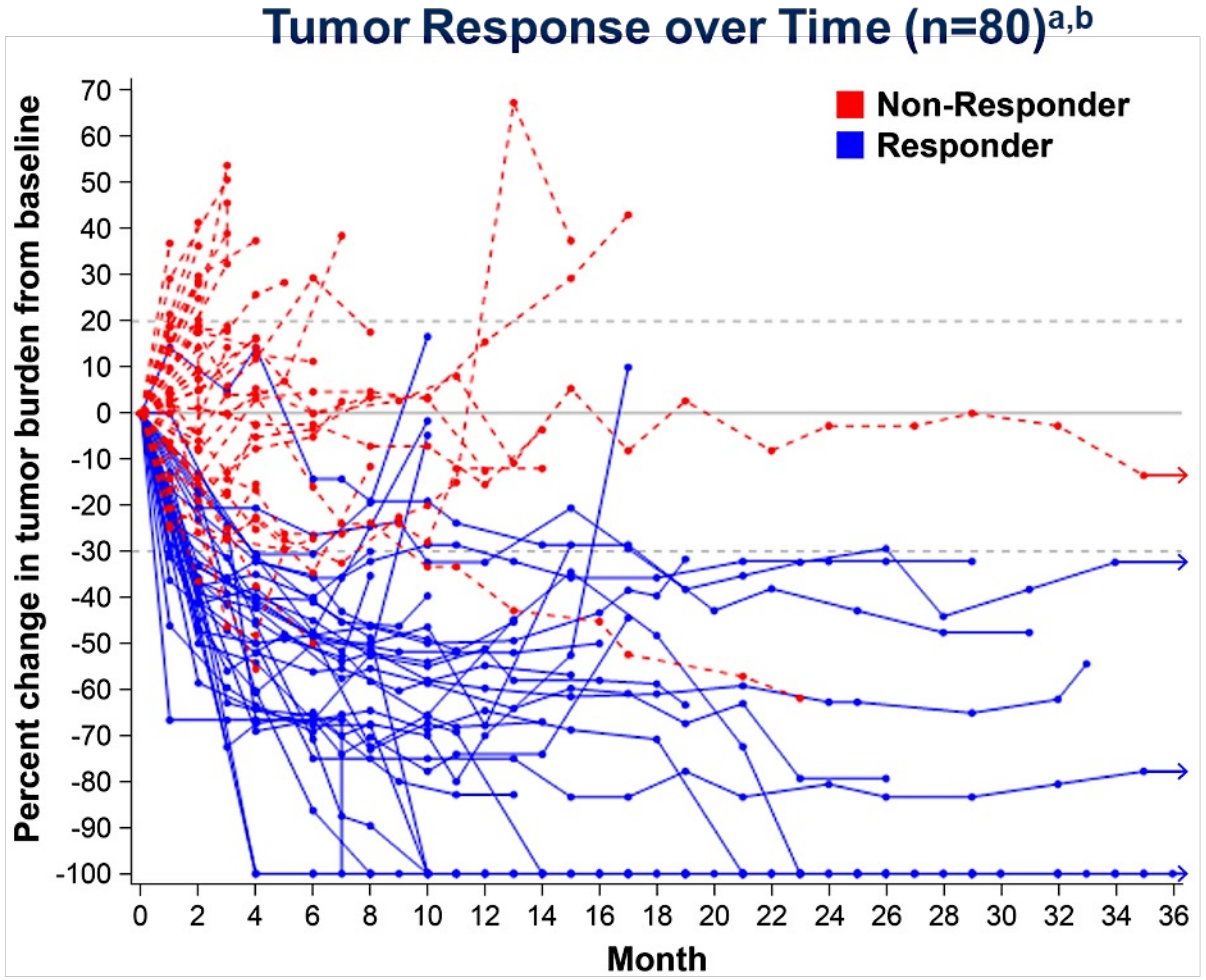
- Tucatinib is an oral, small molecule TKI that targets HER2
- Highly selective for the HER2 receptor
- Selectivity may improve tolerability (skin rash, diarrhea, etc.) compared to non-selective TKIs

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

MOUNTAINEER: Efficacy outcomes for tucatinib + trastuzumab

	Cohorts A+B Final analysis (n=84)
cORR, % (95% CI)	**39.3** (28.8–50.5)
Median DOR, mo (95% CI)	**15.2** (8.9–20.5)
Median PFS, mo (95% CI)	**8.1** (4.2–10.2)
Median OS, mo (95% CI)	**23.9** (18.7–28.3)

- Median follow-up: 32.4 months

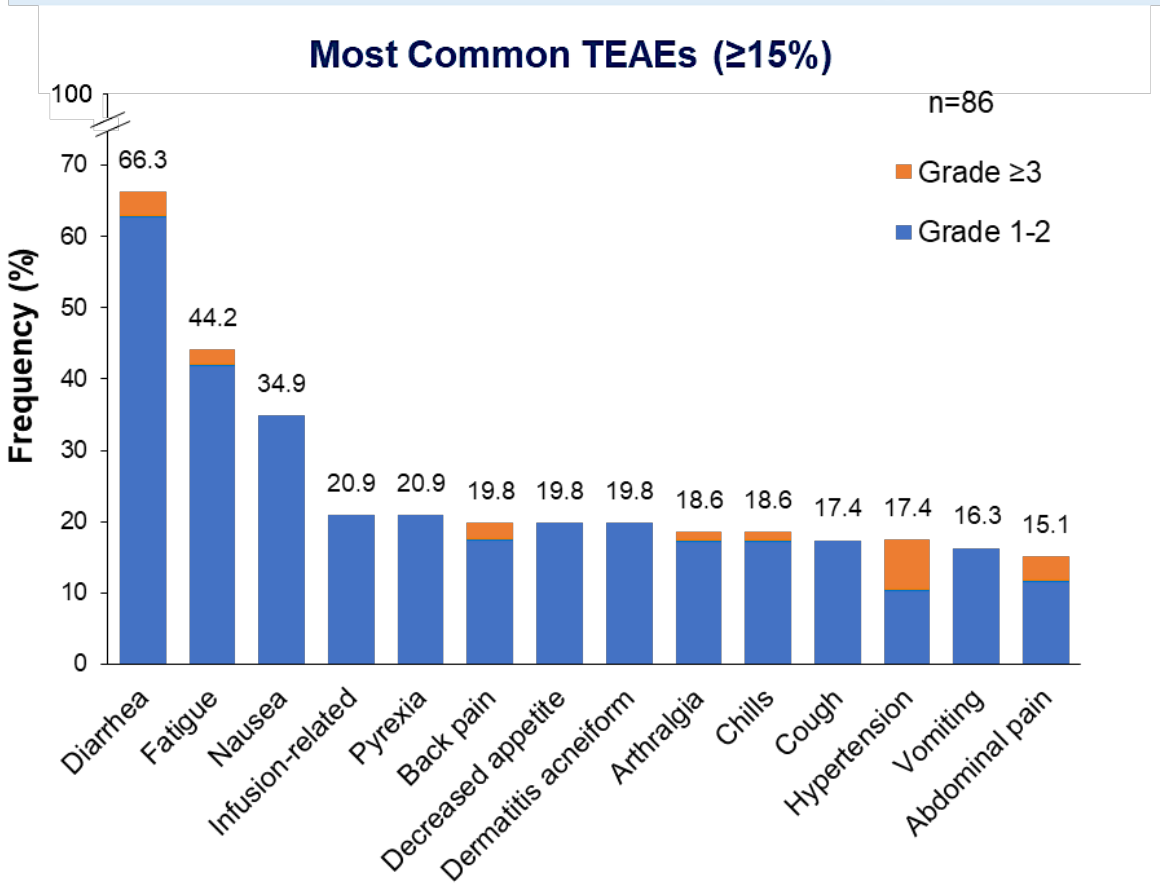


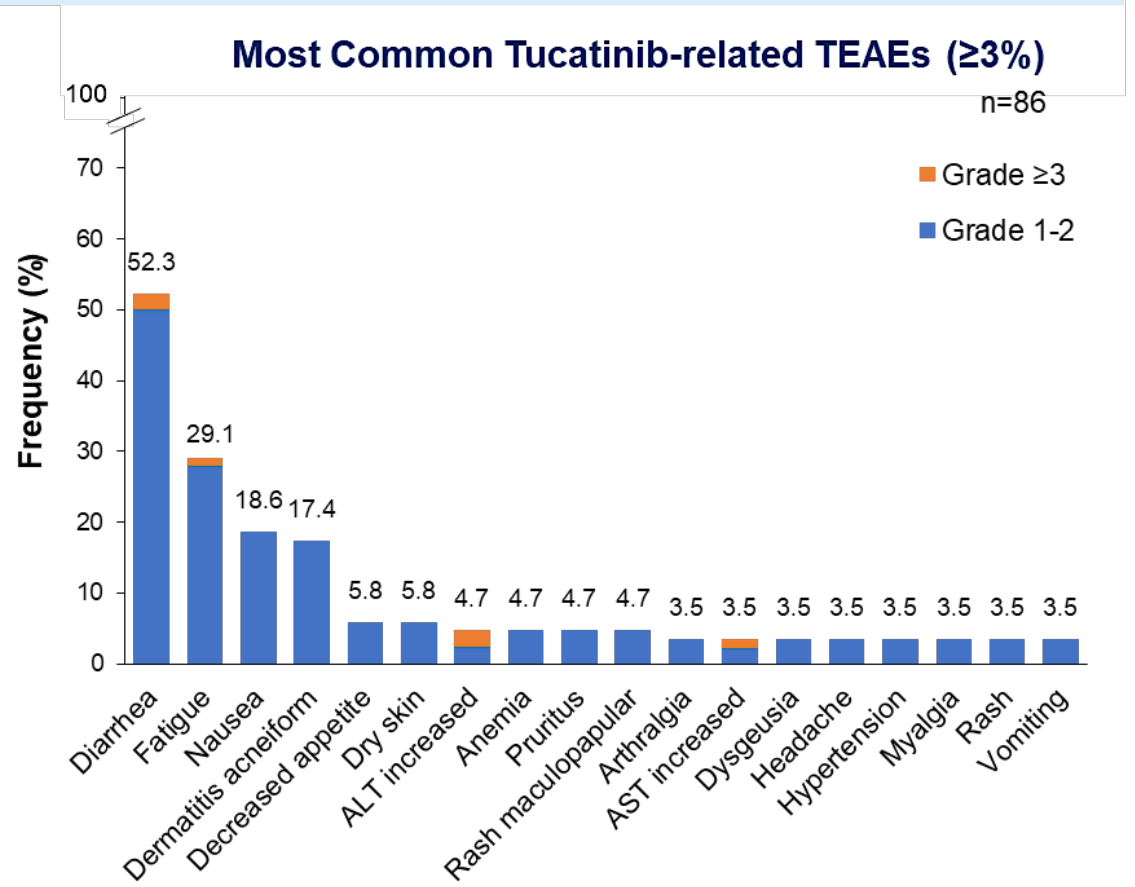
[a] Data up to 36 months are included; [b] Arrows denote treatment duration beyond 36 months.
CI, confidence interval; cORR, confirmed objective response rate; DOR, duration of response; mo, months; OS, overall survival; PFS, progression-free survival.

Strickler JH et al. ASCO 2024;Abstract 3509

MOUNTAINEER: Tucatinib + trastuzumab AE profile

- Majority of TEAEs were low grade, and rates were stable with longer follow-up
- Common TEAEs included diarrhea (66.3%), fatigue (44.2%) and nausea (34.9%)
- Most tucatinib-related TEAEs were of low grade





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

Strickler JH et al. ASCO 2024;Abstract 3509

DESTINY-CRC01: Trastuzumab deruxtecan (T-DXd) for HER2+ mCRC - Efficacy Outcomes

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

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

Data cutoff (Dec 28, 2020)

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

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

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

	5.4 mg/kg Q3W (n = 82)	6.4 mg/kg Q3W (n = 40)
Confirmed ORR, % (95% CI)	37.8% (27.3-49.2)	27.5% (14.6-43.9)
mDOR, months (95% CI)	5.5 months (4.2-8.1)	5.5 months (3.7-NE)
Disease control rate, % (95% CI)	86.6% (77.3-93.1)	85.0% (70.2-94.3)
PFS, months (95% CI)	5.8 months (4.6-7.0)	5.5 (4.2-7.0)
OS, months (95% CI)	13.4 months (12.5-16.8)	NE (9.9-NE)

Raghav K *et al*. 2023 ASCO Annual Meeting; Abstract 3501.
Raghav et al., Lancet Oncol. 2024 Sep;25(9):1147-1162.

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

Adjudicated as drug-related ILD/pneumonitis, n (%)	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 41[a]	Stage 2 n = 42	Total N = 83	Stage 1 N = 39
Any grade	4 (9.8)	3 (7.1)	7 (8.4)	5 (12.8)
Grade 1	1 (2.4)	0	1 (1.2)	2 (5.1)
Grade 2	3 (7.3)	3 (7.1)	6 (7.2)	2 (5.1)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	1 (2.6)

Raghav K *et al*. 2023 ASCO Annual Meeting. Abstract 3501.
Raghav et al., Lancet Oncol. 2024 Sep;25(9):1147-1162.

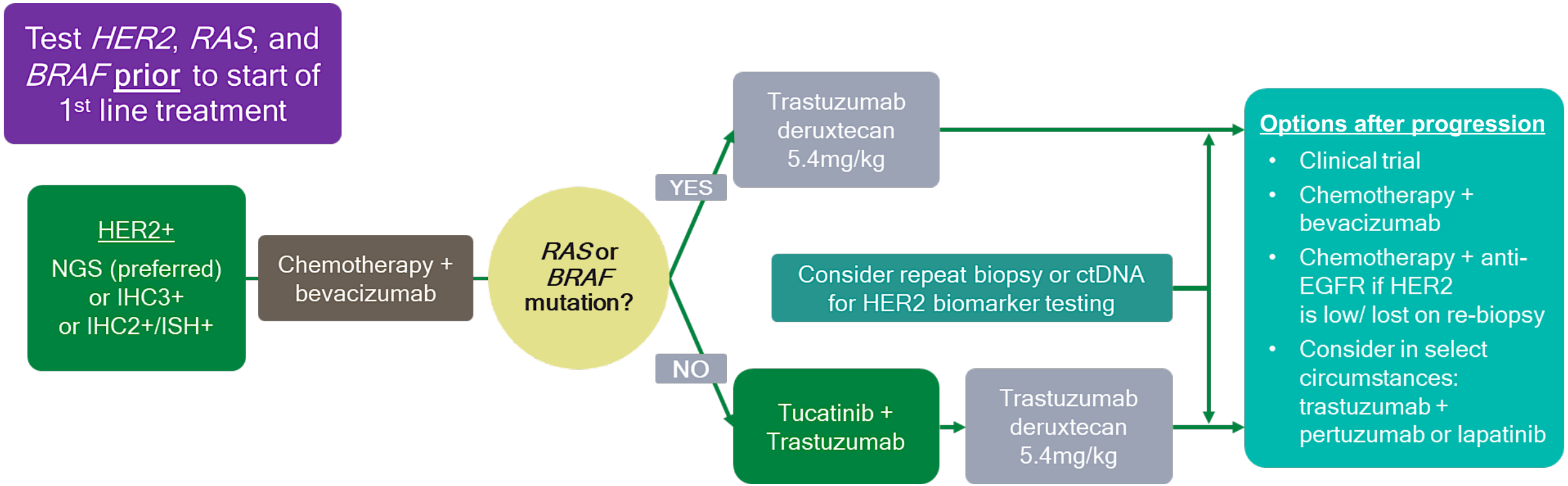
DESTINY-CRC-02: Trastuzumab deruxtecan for HER2+ mCRC - Best ORR (BICR) by T-DXd 5.4 mg/kg Subgroup

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

[a]Based on the exact Clopper-Pearson method for binomial distribution. [b]All RASm responders were IHC 3+. [c]Includes rectum, sigmoid, and descending. [d]Includes cecum, ascending, and transverse.

Raghav K *et al*. 2023 ASCO Annual Meeting. Abstract 3501.
Raghav et al., Lancet Oncol. 2024 Sep;25(9):1147-1162.

How I treat HER2+ metastatic CRC



Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

CME/MOC, NCPD and ACPE Accredited

Saturday, October 11, 2025
7:15 AM – 12:30 PM ET

RTP
RESEARCH
TO PRACTICE

ctDNA-Guided Adjuvant Chemotherapy De-escalation in Stage III Colon Cancer: Primary Analysis of the ctDNA-Negative Cohort from the Randomized AGITG DYNAMIC-III Trial (Intergroup Study of AGITG and CCTG)

Tie J et al.

ESMO 2025;Abstract LBA9.

PRESIDENTIAL SYMPOSIUM III | MONDAY, OCTOBER 20 | 16:52 CEST

Circulating Tumour DNA (ctDNA) Clearance and Correlation with Outcome in the INTERCEPT Colorectal Cancer (CRC) Study

Osterlund O et al.

ESMO 2025;Abstract 732MO.

MINI ORAL| SUNDAY, OCTOBER 19 | 14:50 CEST

Questions from General Medical Oncologists

- **Do you prefer tumor-informed MRD assays versus tumor-naïve assays in early-stage CRC?**
- **Is Signatera the best/only option for ctDNA monitoring?**

Questions from General Medical Oncologists

- **Outside of a clinical trial, how do you utilize ctDNA monitoring in Stage II disease? Stage III disease?**
- **What do you make of the results from the CALGB/SWOG 80702 trial, and are you considering celecoxib for any of your patients?**

Questions from General Medical Oncologists

- **Can ctDNA be used for oligometastatic disease after definitive surgery and NED on scans?**

Questions from General Medical Oncologists

- How do you prevent and manage toxicities with the BREAKWATER regimen?
- What do we know about BRAF inhibition in the adjuvant setting?
- Is there any way to target BRAF non-V600E mutations?

Questions from General Medical Oncologists

- Do I need to retest for HER2 on disease progression in mCRC?
- T-DXd or tucatinib/trastuzumab first for HER2-positive mCRC?
- Would you use T-DXd for HER2-low mCRC?

Questions from General Medical Oncologists

- **Do you prefer sotorasib or adagrasib?**