RTP Live from Chicago: Investigator Perspectives on Recent Advances and Challenging Questions in the Management of Colorectal Cancer

Monday, June 3, 2024

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

Scott Kopetz, MD, PhD

John Strickler, MD

Moderator

Neil Love, MD

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Faculty

Scott Kopetz, MD, PhD
Professor
Deputy Chair for Translational Research
Department of Gastrointestinal Medical Oncology
Associate Vice President
for Translational Integration
The University of Texas
MD Anderson Cancer Center
Houston, Texas

MODERATOR
Neil Love, MD
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Miami, Florida

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

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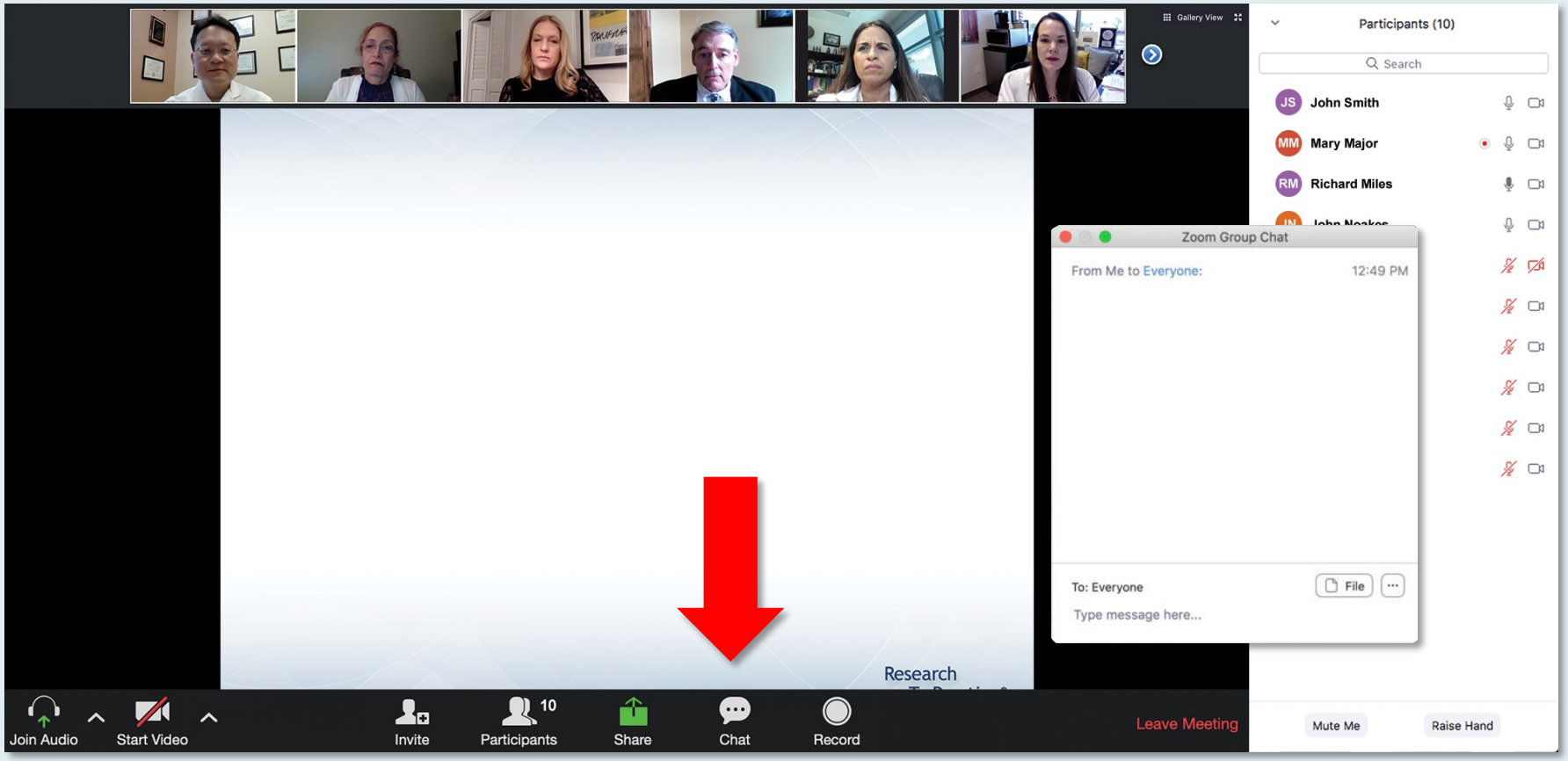
We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

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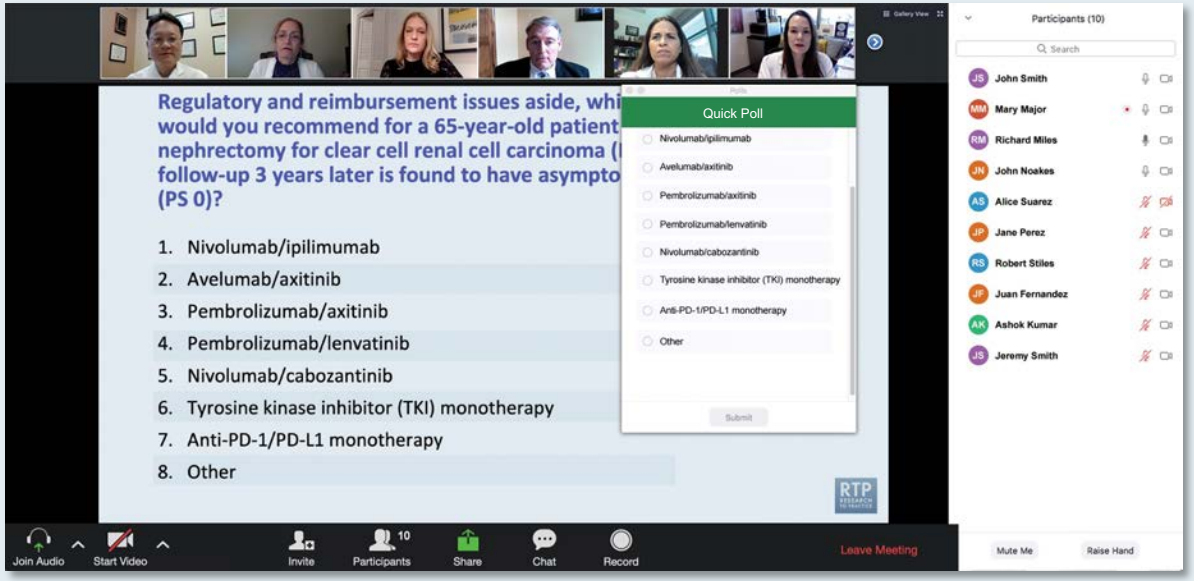
Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys



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ONCOLOGY TODAY

WITH DR NEIL LOVE

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Colorectal Cancer

PROFESSOR THIERRY ANDRÉ, MD
HÔPITAL SAINT-ANTOINE

ARVIND DASARI, MD, MS
THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

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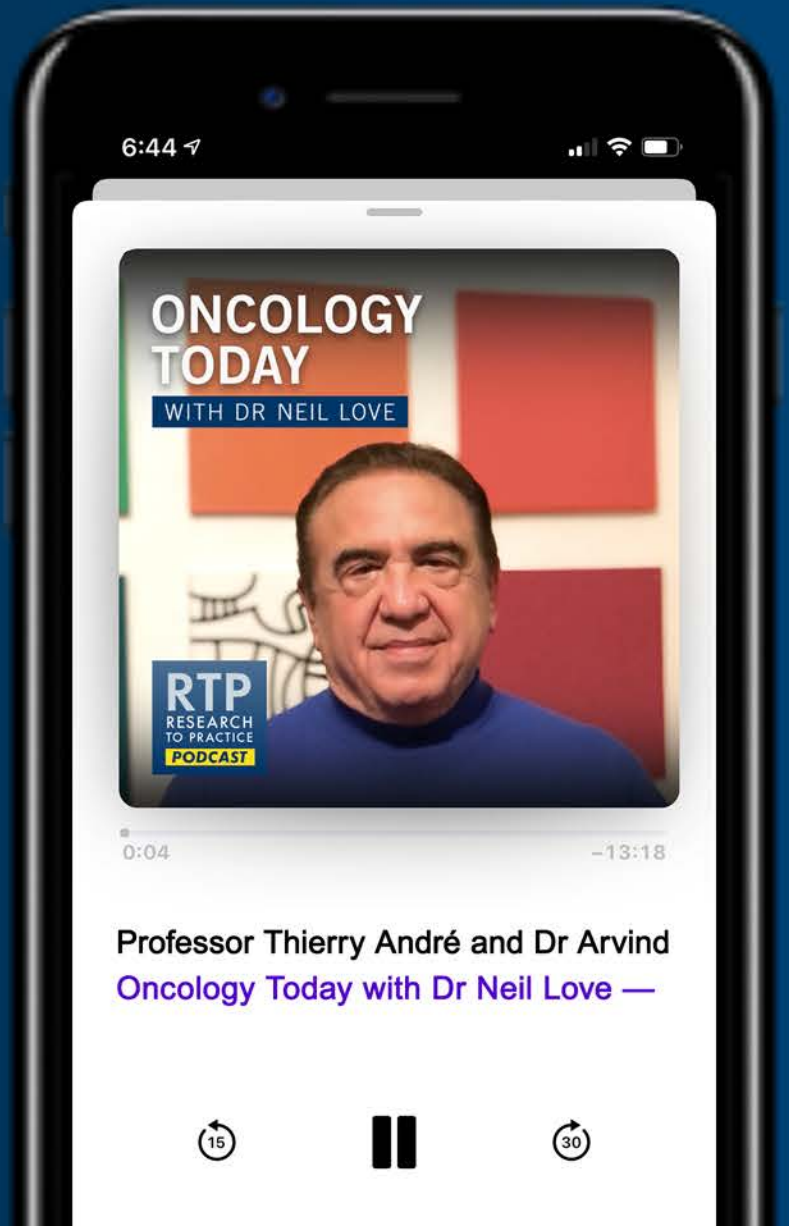

Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2024 ASCO® Annual Meeting

Multiple Myeloma

Sunday, June 2, 2024

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Rafael Fonseca, MD
María-Victoria Mateos, MD, PhD
Elizabeth O'Donnell, MD

LIVE WEBCAST

Colorectal Cancer

Monday, June 3, 2024

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

Scott Kopetz, MD, PhD
John Strickler, MD

Ovarian and Endometrial Cancer

Sunday, June 2, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Floor J Backes, MD
Mansoor Raza Mirza, MD
Ritu Salani, MD, MBA
Angeles Alvarez Secord, MD, MHSc
Brian M Slomovitz, MD

Metastatic Breast Cancer

Monday, June 3, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Aditya Bardia, MD, MPH
Harold J Burstein, MD, PhD
Professor Giuseppe Curigliano, MD, PhD
Sara A Hurvitz, MD, FACP
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2024 ASCO® Annual Meeting

LIVE WEBCAST

Bispecific Antibodies in Lymphoma

Tuesday, June 4, 2024

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

Joshua Brody, MD
Ian W Flinn, MD, PhD
Tycel Phillips, MD

RTP Live from Chicago: Investigator Perspectives on Recent Advances and Challenging Questions in the Management of Colorectal Cancer

Monday, June 3, 2024

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Faculty

Scott Kopetz, MD, PhD

John Strickler, MD

Moderator

Neil Love, MD

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Dr Kopetz — Disclosures
Faculty

Consulting Agreements	Agenus Inc, Amgen Inc, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Carina Biotech, Flame Biosciences, Frontier Medicines, Genentech, a member of the Roche Group, Harbinger Health, Kestrel Therapeutics, Lutris Pharma, Merck, Mirati Therapeutics Inc, Pfizer Inc, Regeneron Pharmaceuticals Inc, Replimune, Revolution Medicines, Roche Laboratories Inc, Tachyon Therapeutics, Tempus, Zentalis Pharmaceuticals
Contracted Research	Amgen Inc, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, BridgeBio, Cardiff Oncology, Daiichi Sankyo Inc, EMD Serono Inc, Genentech, a member of the Roche Group, Guardant Health, Jazz Pharmaceuticals Inc, Lilly, Mirati Therapeutics Inc, Novartis, Pfizer Inc, Sanofi, Zentalis Pharmaceuticals

Dr Strickler — Disclosures
Faculty

Advisory Committees	AbbVie Inc, Agenus Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, GSK, Jazz Pharmaceuticals Inc, Johnson & Johnson Pharmaceuticals, Lilly, Merck, Natera Inc, Pfizer Inc, Regeneron Pharmaceuticals Inc, Sanofi, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Xilio Therapeutics
Contracted Research	AbbVie Inc, Amgen Inc, A*STAR D3, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Curegenix, Daiichi Sankyo Inc, Erasca, Genentech, a member of the Roche Group, GSK, Leap Therapeutics Inc, Lilly, Novartis, Pfizer Inc, Revolution Medicines
Data and Safety Monitoring Boards/Committees	AbbVie Inc, BeiGene Ltd, GSK, Pfizer Inc
Stock Options — Private Company	Triumvira Immunologics

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Dr Love — Disclosures

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Commercial Support

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Agenda

Module 1: Recent Therapeutic Advances in Colorectal Cancer (CRC) — Dr Strickler

Module 2: New Developments in Targeted Therapy for Metastatic CRC — Dr Kopetz

Agenda

Module 1: Recent Therapeutic Advances in Colorectal Cancer (CRC) — Dr Strickler

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Cases from General Medical Oncologists
ctDNA

- **56-year-old woman, Stage IV NED post resection of an oligometastasis to the lung**
- **52-year-old woman, Stage II, negative ctDNA, no adjuvant therapy**
- **65-year-old man, Stage IV, ctDNA initially negative after oligometastasectomy; will continue to monitor for recurrent disease after “adjuvant” mFOLFOX**
- **52-year-old woman, Stage IIIC, ctDNA initially negative but became positive approximately 1 year later; colon cancer therapy deferred despite positive ctDNA because patient is receiving neoadjuvant therapy for triple-negative breast cancer**
- **66-year-old woman, Stage III, ctDNA initially negative; stopped adjuvant chemotherapy after first dose due to myocardial infarction with plan to restart if ctDNA becomes positive**

Survey of US-based general medical oncologists, May 2024.

Cases from General Medical Oncologists
MSI

- **74-year-old man, MSI-high mCRC with a KRAS mutation, received pembrolizumab with a CR, arthralgias**
- **36-year-old woman, MSI-high mCRC, received pembrolizumab with a CR, no tolerability issues**
- **83-year-old woman, MSI-high mCRC, remains NED 3 years after completing 2 years of pembrolizumab, no tolerability issues**

Survey of US-based general medical oncologists, May 2024.

Questions from General Medical Oncologists

- **Pt with poor functional status, initially with Stage I MSI-high colon cancer, resected, no adj tx recommended. Developed unresectable recurrence, s/p pembrolizumab x 6 months. Progression. Other biomarker testing negative. Likely would not tolerate full systemic therapy. Started on capecitabine as a palliative measure. Would investigators choose another oral agent such as fruquintinib or TAS-102 instead?**
- **Do you take into account POLE or POLD1 mutation when deciding about immunotherapy use?**
- **Dual checkpoint vs single-agent checkpoint in patients with MSI-high mCRC?**

Survey of US-based general medical oncologists, May 2024.

Recent Therapeutic Advances in CRC

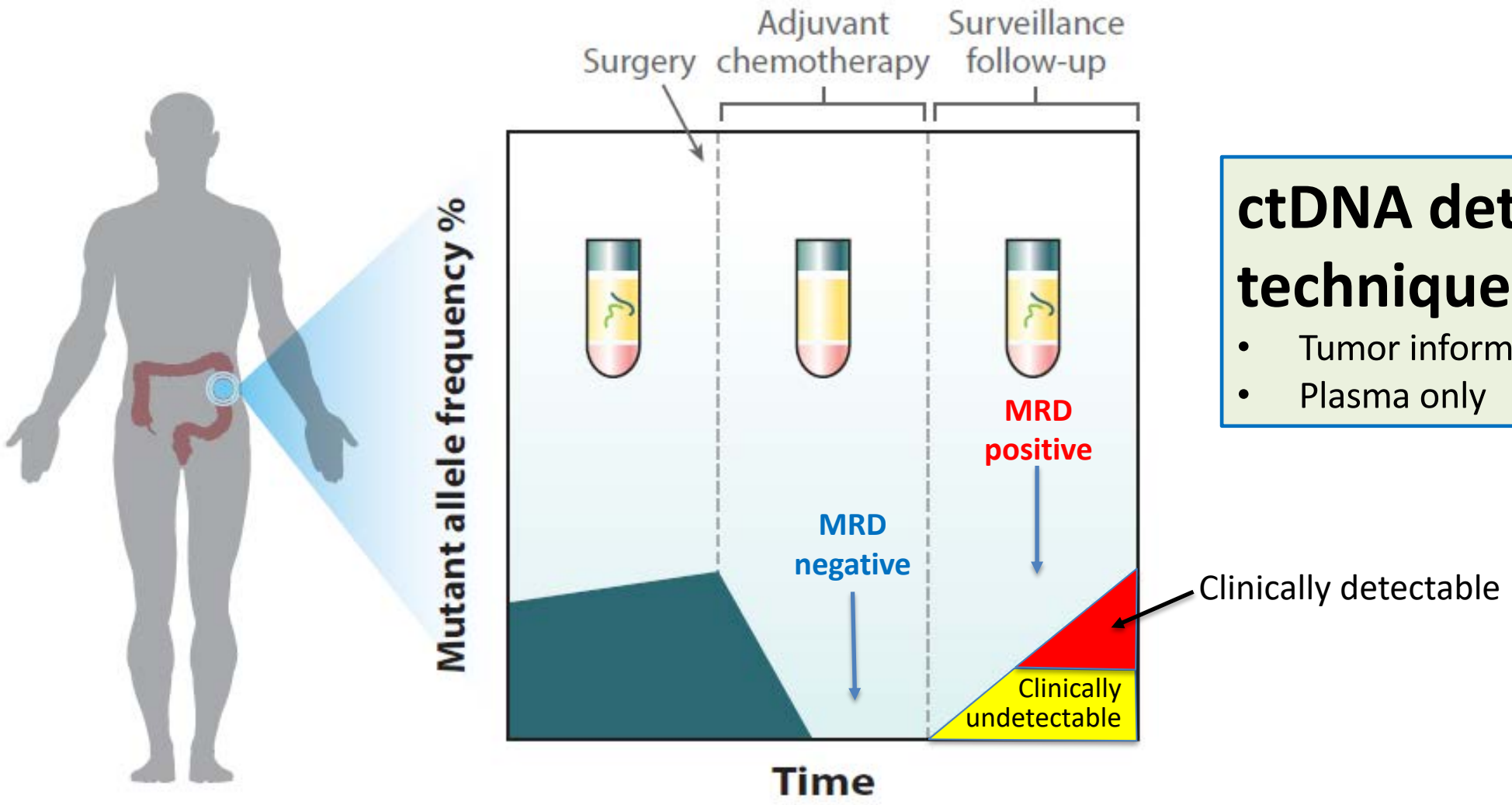
John H. Strickler, MD
Professor of Medicine
Duke University Medical Center

June 3, 2024

Key points

- ctDNA-based molecular residual disease (MRD) monitoring:
  - MRD testing is a validated prognostic tool
  - If MRD+ but no radiologic evidence of disease-- Intensified surveillance/ imaging (MRI liver and/or PET) advised
  - Trials are ongoing to explore escalation/ de-escalation strategies
- Immune checkpoint inhibitors for non-metastatic CRC: impressive data and an emerging SOC option
- CheckMate 8HW establishes ipilimumab + nivolumab as another 1L option for MSI-H metastatic CRC

Defining Minimal Residual Disease (MRD)



ctDNA detection techniques

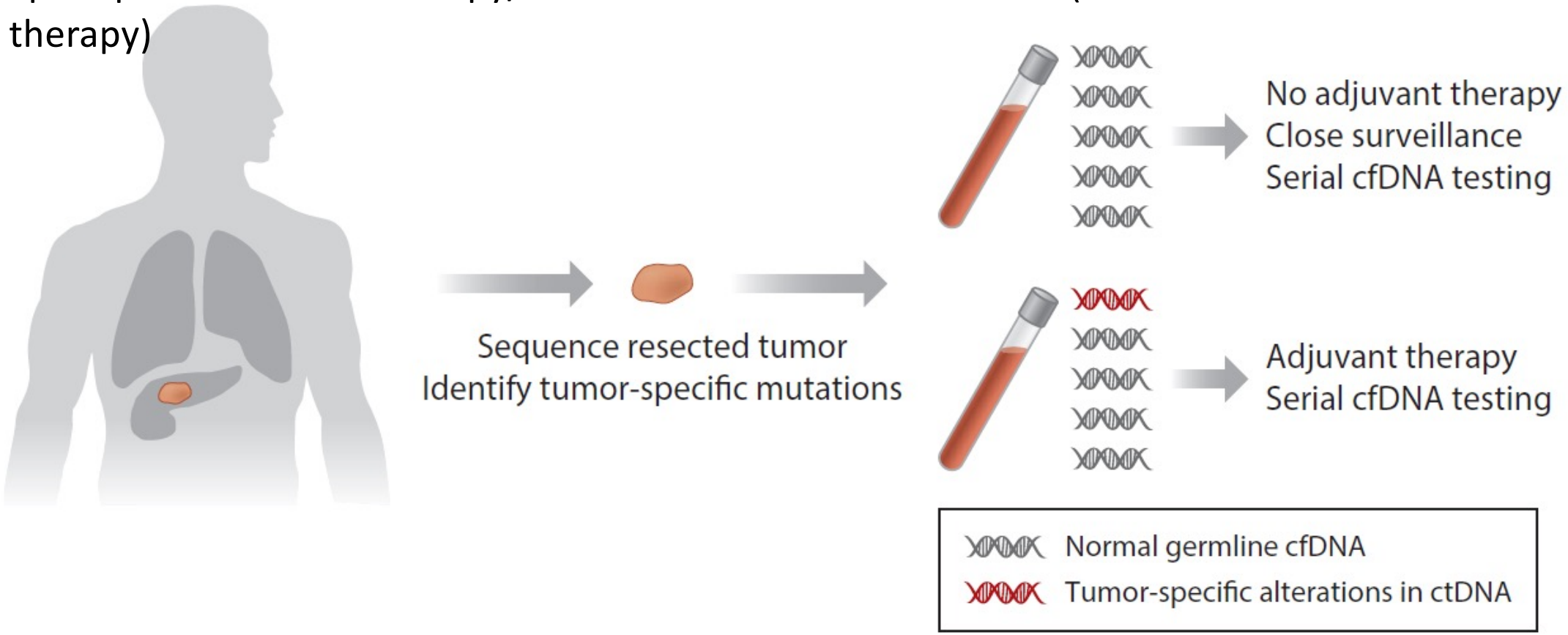
- Tumor informed
- Plasma only

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

Can we integrate MRD into clinical care?

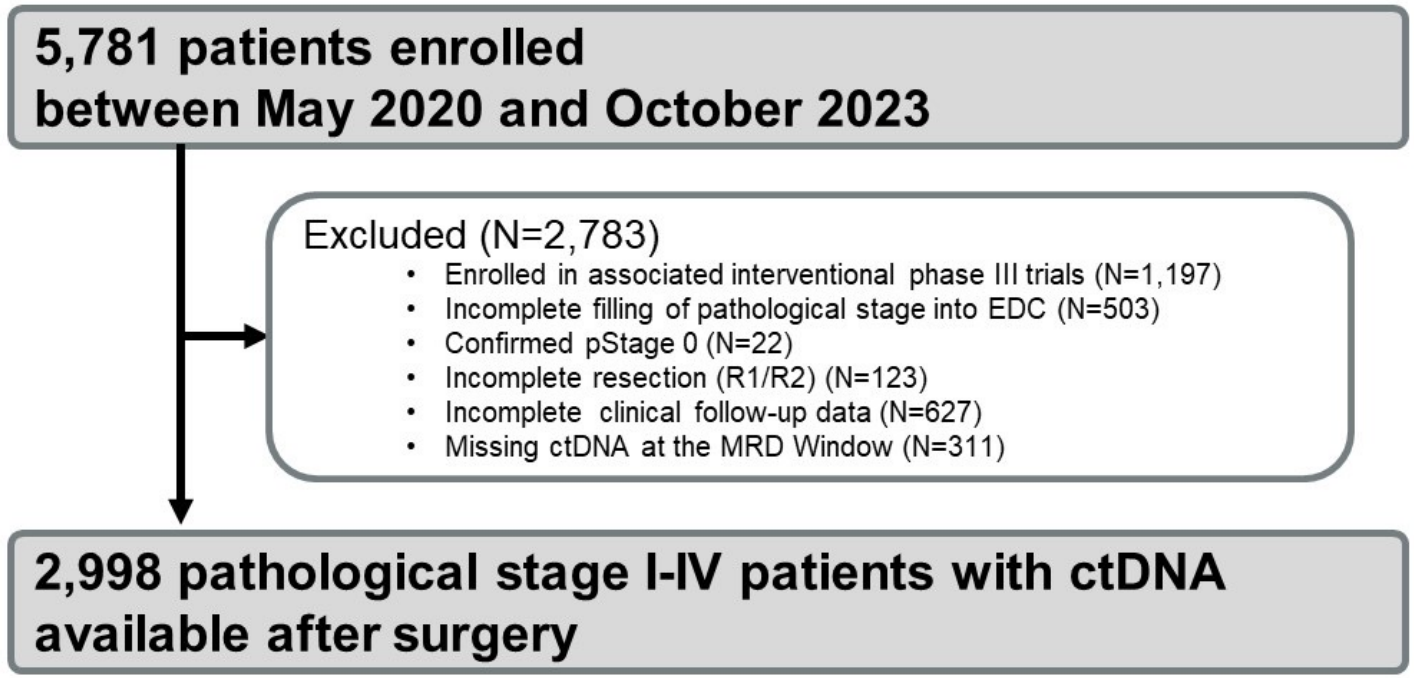
Potential applications:

- Selecting high risk patients for aggressive therapy when post-operative observation is SOC
- Spare patients chemotherapy/treatment if no residual disease (when SOC calls for additional therapy)



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

Clinical validation of tumor informed MRD testing: GALAXY patient characteristics

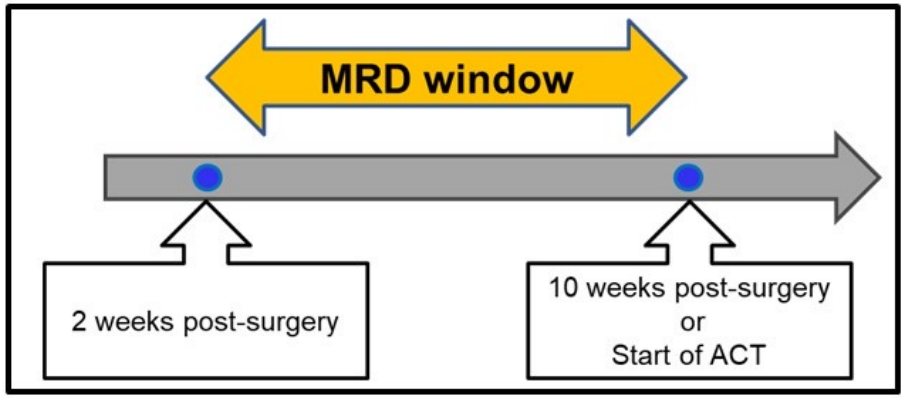


Median Follow-up: 16.14 months (range: 0.23-42.14)

Pathological Stage	
I	415 (14%)
II	901 (30%)
III	1,231 (41%)
IV	451 (15%)
MSI status	
MSS or MSI-Low	2,686 (91%)
MSI-High	280 (9%)
Unknown	32
Clinical or Radiological Recurrence	
Recurrence	530 (18%)
No Recurrence	2,468 (82%)
Total Follow-up (months)	16.1 (0.2 - 42)

Yukami et. al., J Clin Oncol 42, 2024 (suppl 3; abstr 6). Presented at ASCO GI 2024

GALAXY: MRD status after surgery is strongly prognostic

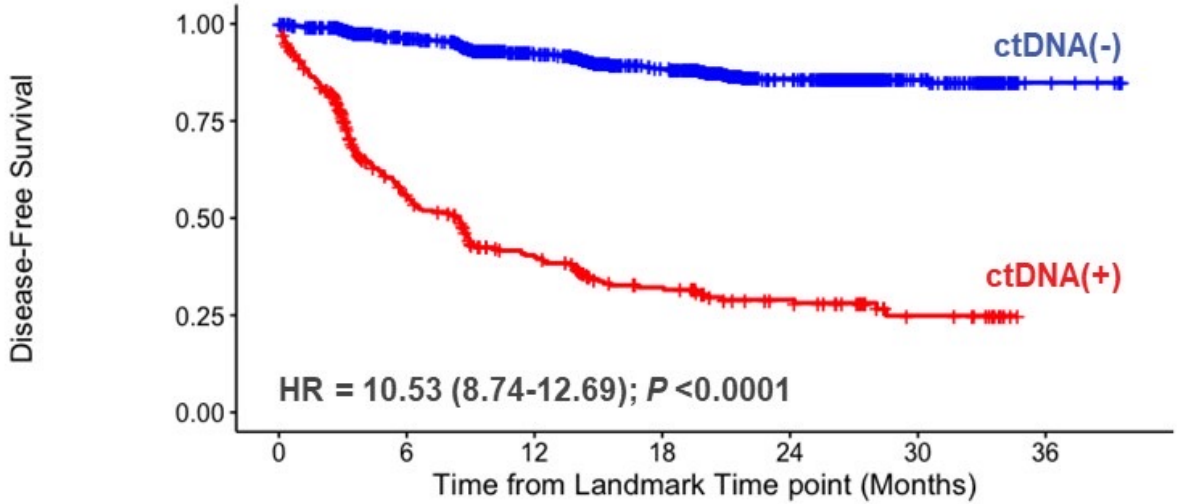


ACT: adjuvant chemotherapy

2,998 stage I-IV patients included in the outcome cohort

Excluded (N=138)
- DFS event prior to the 10 weeks landmark timepoint (n=138)

MRD Window analysis cohort (n=2,860)



Number at risk

ctDNA Negative	2491	2031	1441	1041	495	135	8
ctDNA Positive	369	165	98	59	35	13	0

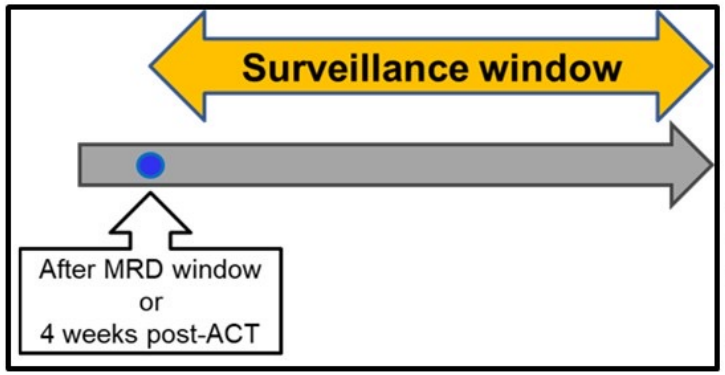
ctDNA status	Negative	Positive
Events %	9.4 (235/2491)	58.8 (217/369)
24M-DFS % (95% CI)*	85.9 (83.9–87.7)	28.9 (23.4–34.8)

**DFS % from landmark time point*

MRD window: 2-10 weeks post surgery, prior to start of any adjuvant therapy - Landmark 10 weeks post-surgery

Yukami et. al., J Clin Oncol 42, 2024 (suppl 3; abstr 6). Presented at ASCO GI 2024

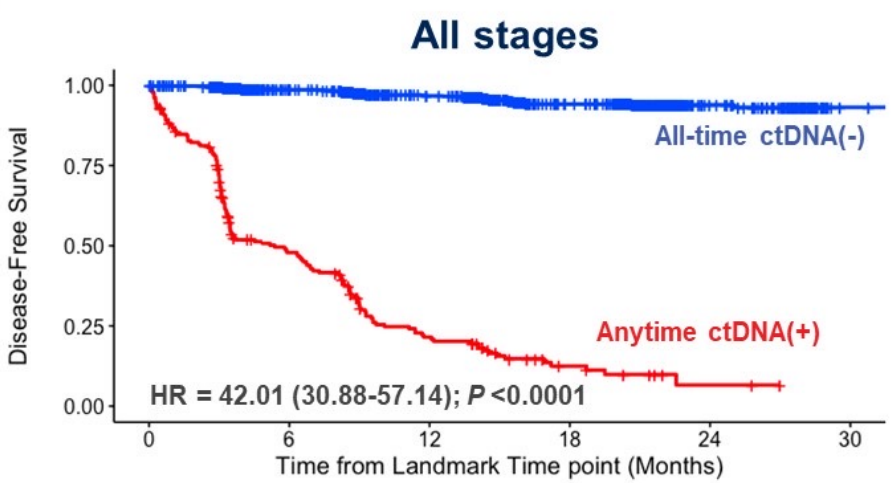
GALAXY: ctDNA-positive in the surveillance window predicts inferior DFS



2,998 stage I-IV patients included in the outcome cohort

Excluded (N=1,212)
- No subsequent timepoints available (n=858)
- DFS event prior to the 8 months landmark timepoint (n=354)

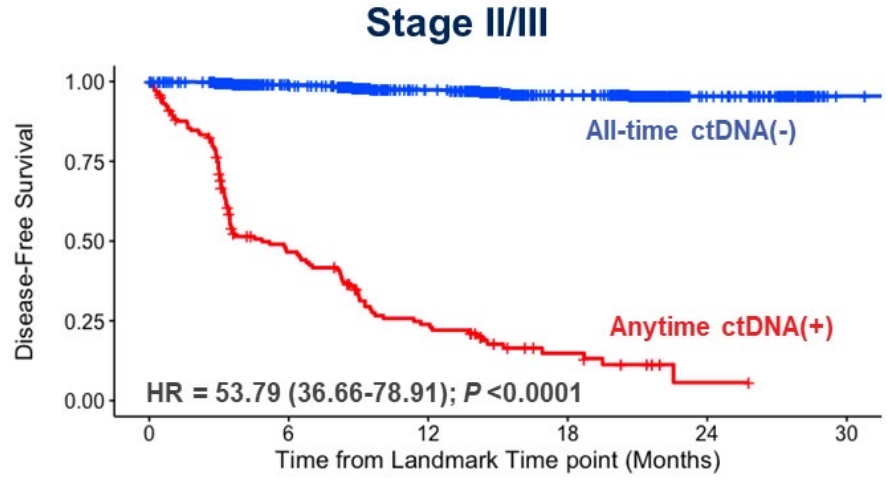
Surveillance Window analysis cohort (n=1,786)



Number at risk

ctDNA Negative	1582	1211	885	432	125	8
ctDNA Positive	204	84	33	10	2	0

ctDNA status	All-time Negative	Anytime Positive
Events %	3.7 (58/1582)	77.5 (158/204)
24M-DFS % (95% CI)*	93.9 (92–95.4)	6.6 (2–14.9)



Number at risk

ctDNA Negative	1326	1022	737	355	97	5
ctDNA Positive	146	57	26	9	1	0

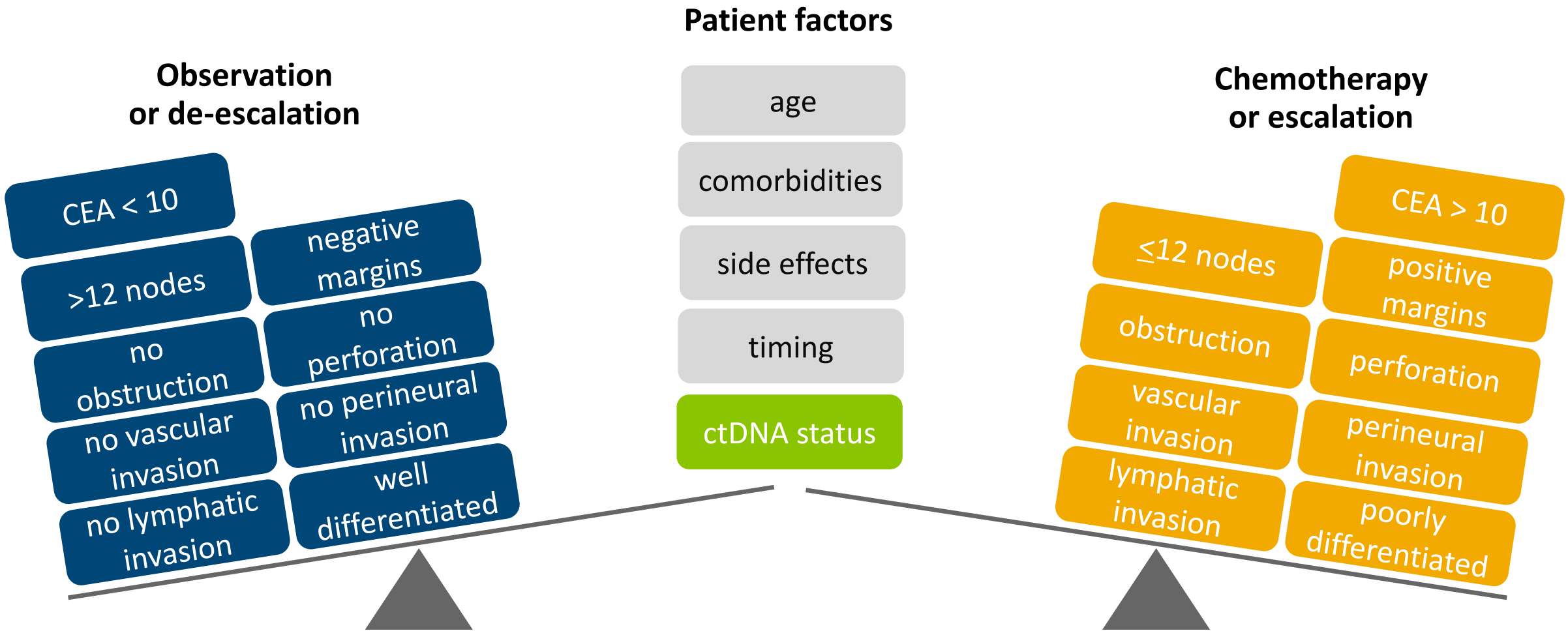
ctDNA status	All-time Negative	Anytime Positive
Events %	2.7 (36/1326)	75.3 (110/146)
24M-DFS % (95% CI)*	95.4 (93.5–96.8)	5.6 (0.8–18.3)

**DFS % from landmark time point*

- *Surveillance window starts from 4 weeks post-ACT or at the end of MRD window if patient had no ACT, until the last follow up or relapse.*
- *Landmark 8 months post-surgery (2 months for ACT initiation + 6 months of ACT duration)*

Yukami et. al., J Clin Oncol 42, 2024 (suppl 3; abstr 6). Presented at ASCO GI 2024

Factors that influence adjuvant chemotherapy



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., Presented at 2022 ASCO Annual Meeting
Tie et al., N Engl J Med 2022 Jun 16: 386(24): 2261-2272.

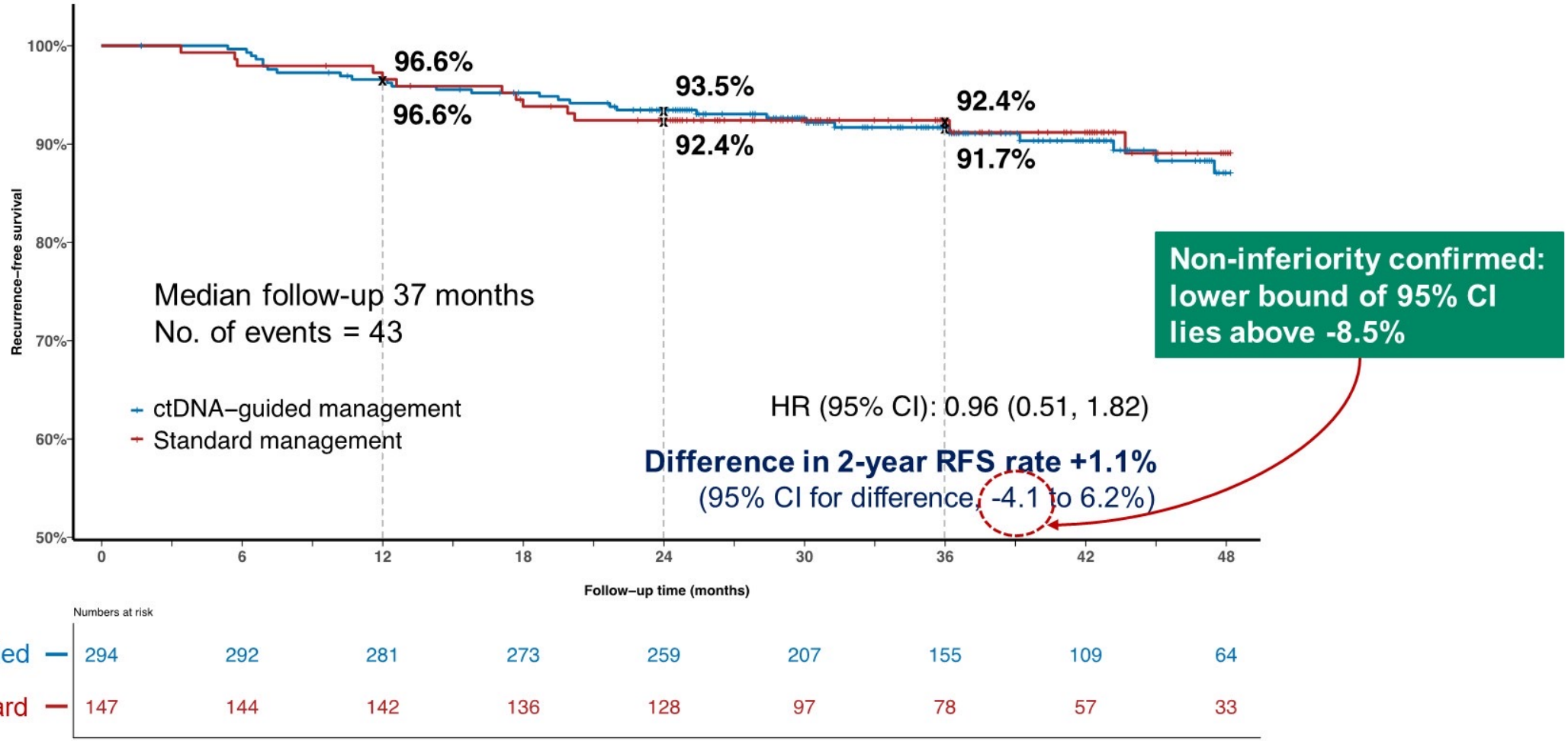
DYNAMIC: Adjuvant chemotherapy given less in the ctDNA-guided management group

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

Tie et al., Presented at 2022 ASCO Annual Meeting

Tie et al., N Engl J Med 2022 Jun 16: 386(24): 2261-2272.

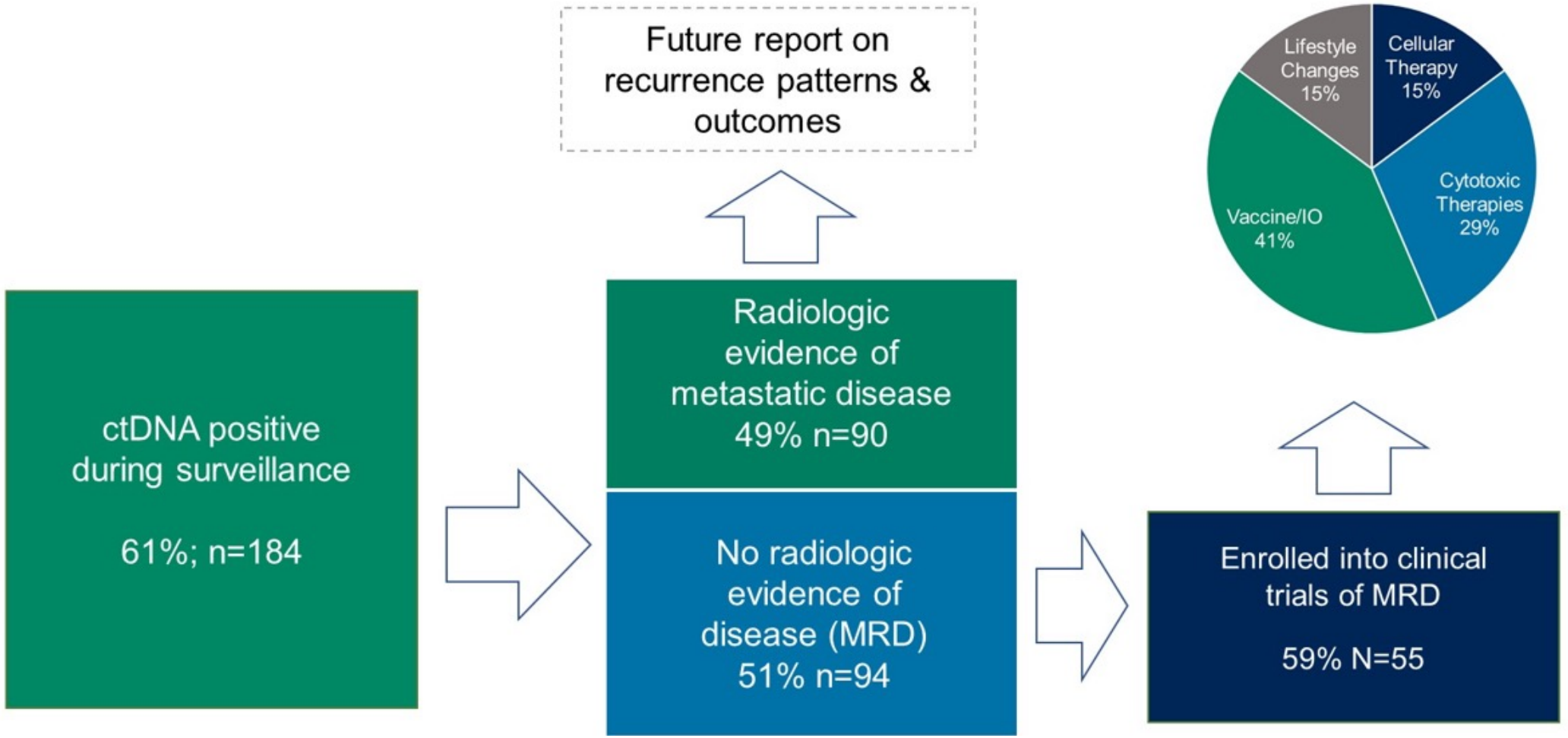
DYNAMIC: RFS identical despite lower use of adjuvant chemotherapy for ctDNA guided management



Tie et al., Presented at 2022 ASCO Annual Meeting

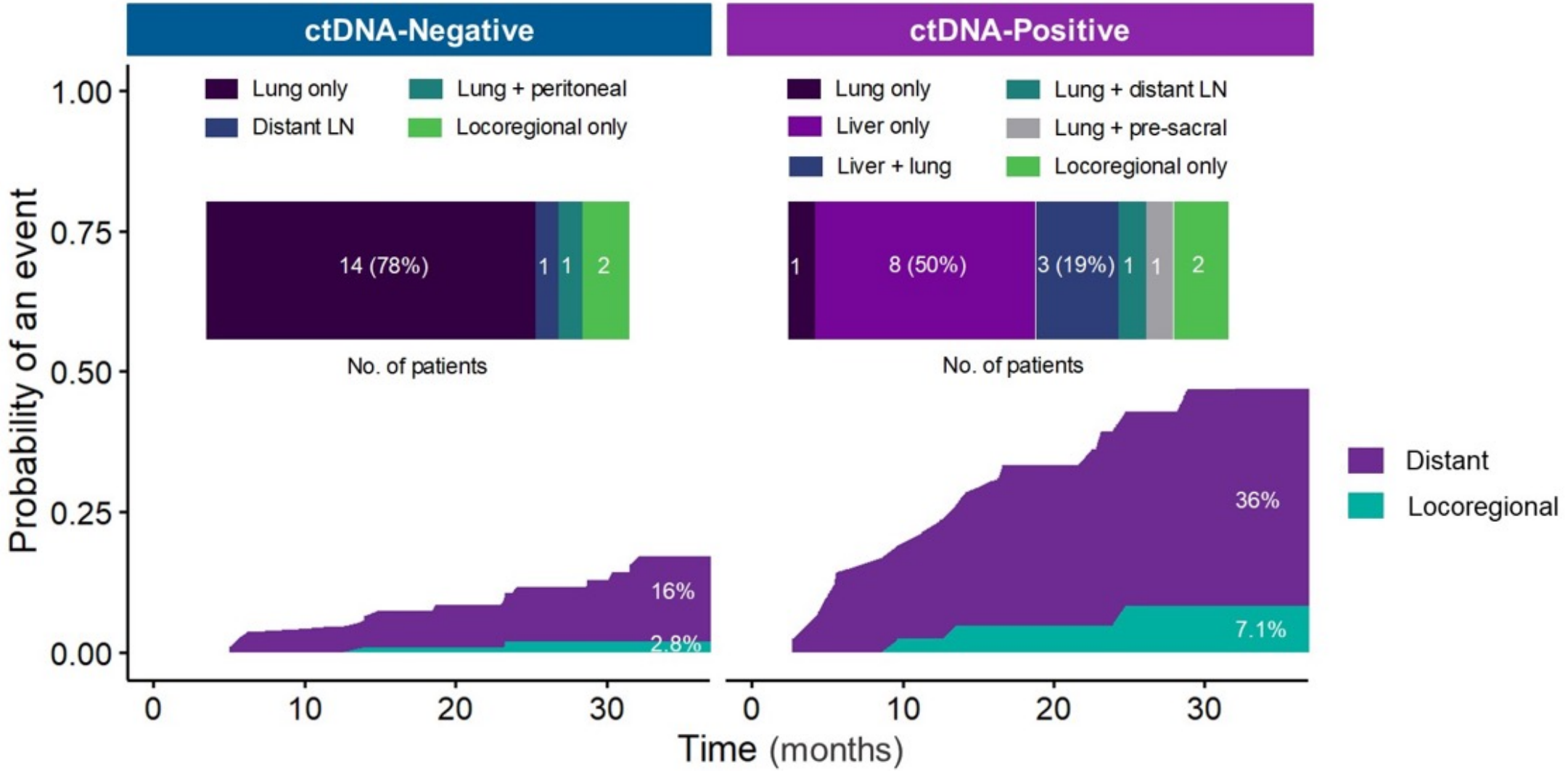
Tie et al., N Engl J Med 2022 Jun 16: 386(24): 2261-2272.

MDACC INTERCEPT: ~Half of all ctDNA+ patients had no radiologic evidence of disease (MRD+)



Dasari et. al., J Clin Oncol 41, 2023 (suppl 16; abstr 3522). Presented at ASCO 2023

DYNAMIC-Rectal: Sites of Relapse by Post-Op ctDNA Status

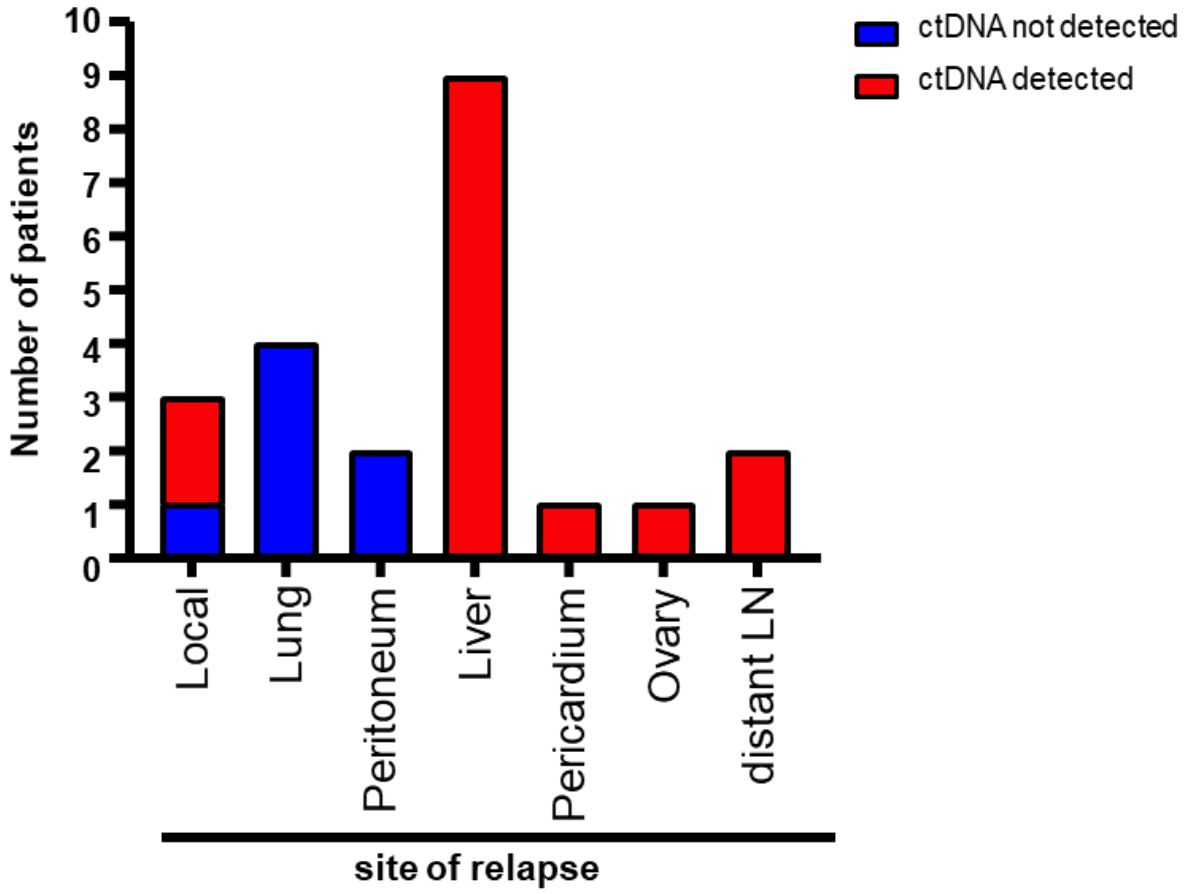


Tie et al., Presented at 2024 ASCO GI Annual Meeting
Tie et al., J Clin Oncol 42, 2024 (suppl 3; abstr 12)

PEGASUS: Site of Relapse by Post-Op ctDNA status

22 relapses: 10 in ctDNA negative and 12 in ctDNA positive patients

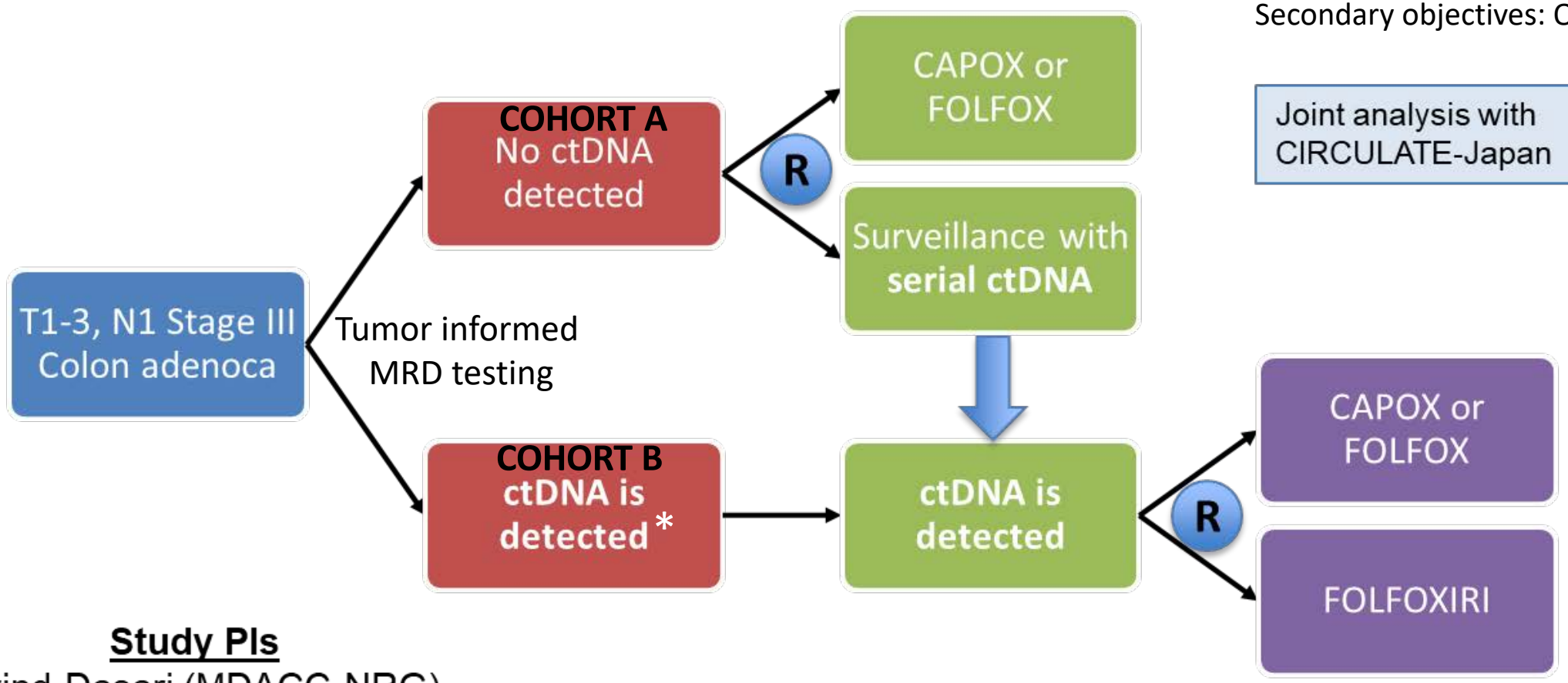
- **PEGASUS** tested a genetic and epigenetic, plasma-based assay (Lunar 1.2; Guardant Health, Inc.)
- **Population**: Radically resected, high-risk stage 2 and stage 3 colon cancer
- **Aim**: Explore feasibility and benefit of treatment escalation in ctDNA+ patients after capecitabine-based chemotherapy (CAPE to CAPOX, CAPOX to FOLFIRI)



Lonardi et al., Presented at 2023 ESMO Congress, LBA28
Lonardi et al., Annals of Oncology (2023) 34 (suppl_2): S1254-S1335.

CIRCULATE-US (NRG-GI008)

Primary objective: DFS (ph3)
Secondary objectives: OS, TTR



Joint analysis with CIRCULATE-Japan

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

* Stage III (T1-3, N1/N1c) or ctDNA+ stage II or IIIC post-R0 resection

Questions?

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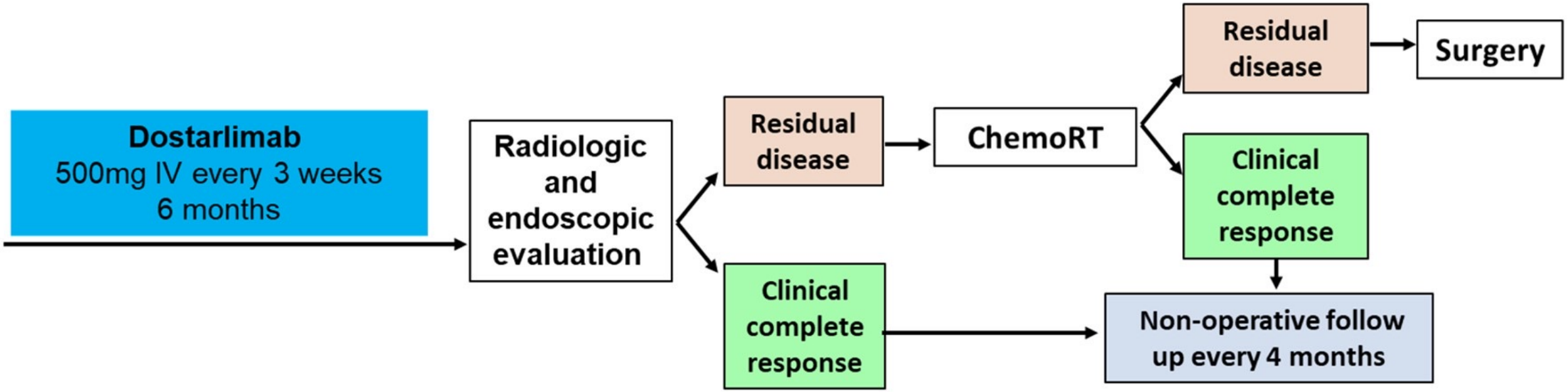
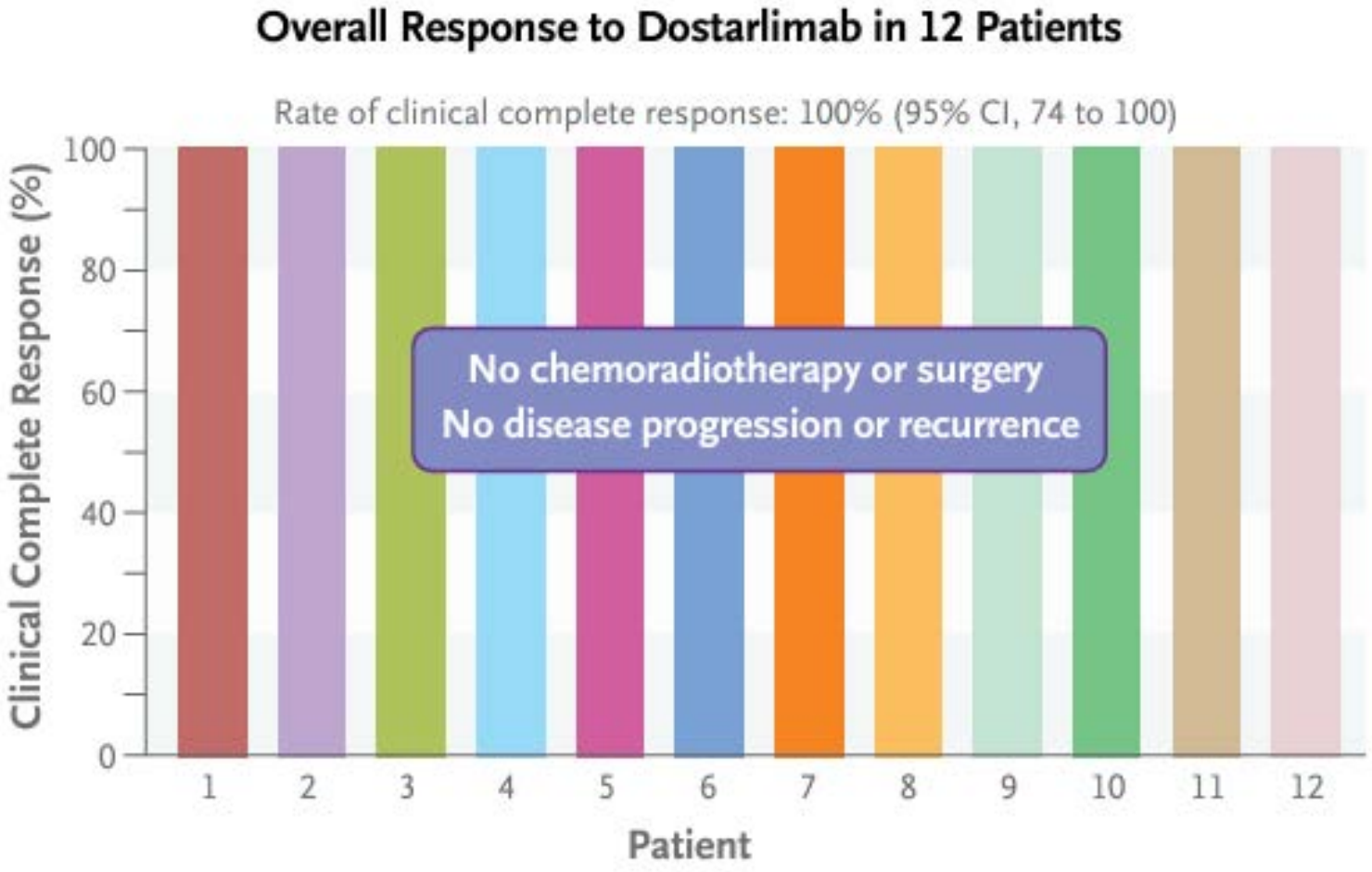
PD-1 blockade in dMMR/ MSI-H locally advanced rectal cancer: Study design



- Patient population: Stage II/III mismatch repair deficient rectal cancer
- Target enrollment: 30 subjects
- Primary objectives: Overall response rate +/- chemoradiation, pathologic complete response (pCR) or clinical complete response (cCR) at 12 months after PD-1 blockade +/- chemoradiation

Cercek et al., Presented at 2022 ASCO Annual meeting
Cercek et al., N Engl J Med 2022;386:2363-2376

PD-1 blockade in dMMR/ MSI-H locally advanced rectal cancer: Results

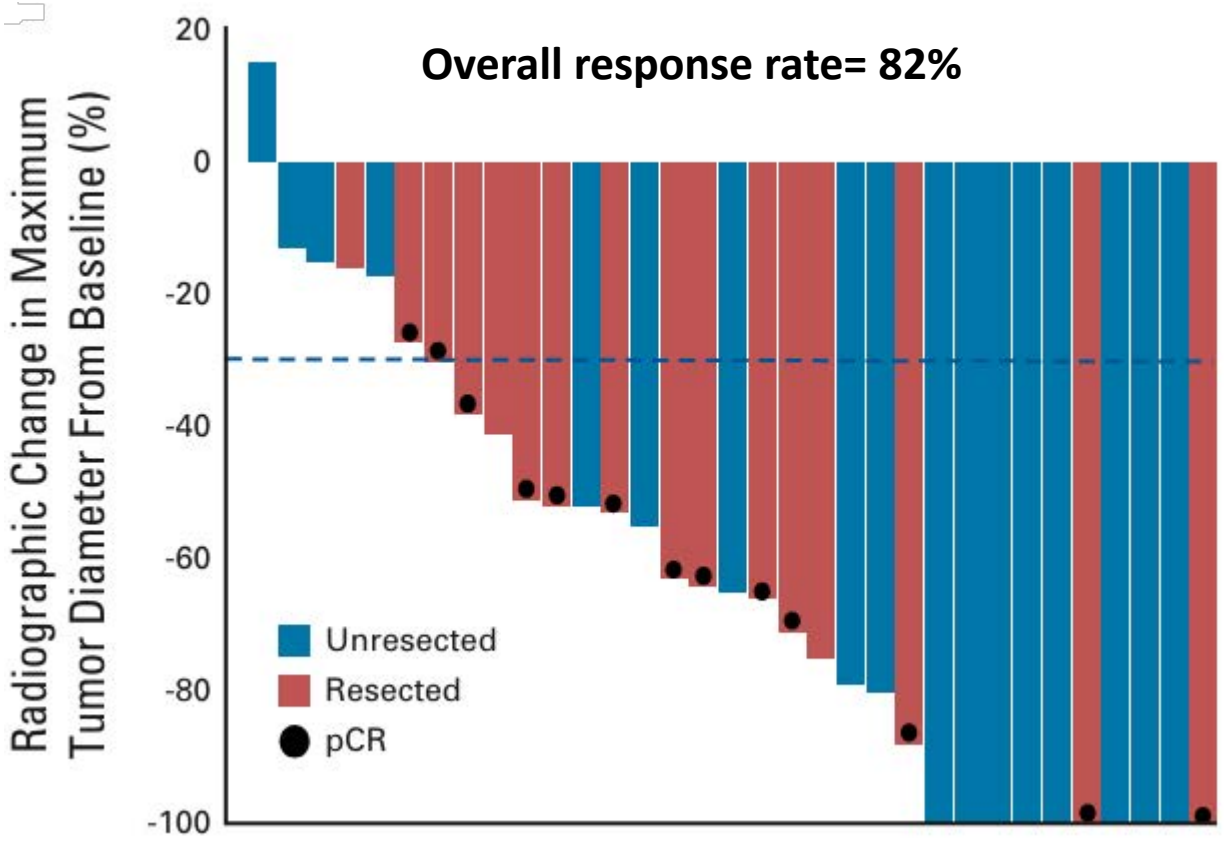


- The first 12 evaluable patients had complete response
- No patient received chemoradiotherapy or underwent surgery
- No patients had disease progression or recurrence
- No adverse events grade 3 or higher occurred

Cercek et al., Presented at 2022 ASCO Annual meeting
Cercek et al., N Engl J Med 2022;386:2363-2376

Neoadjuvant pembrolizumab in non-metastatic MSI-H/dMMR solid tumors

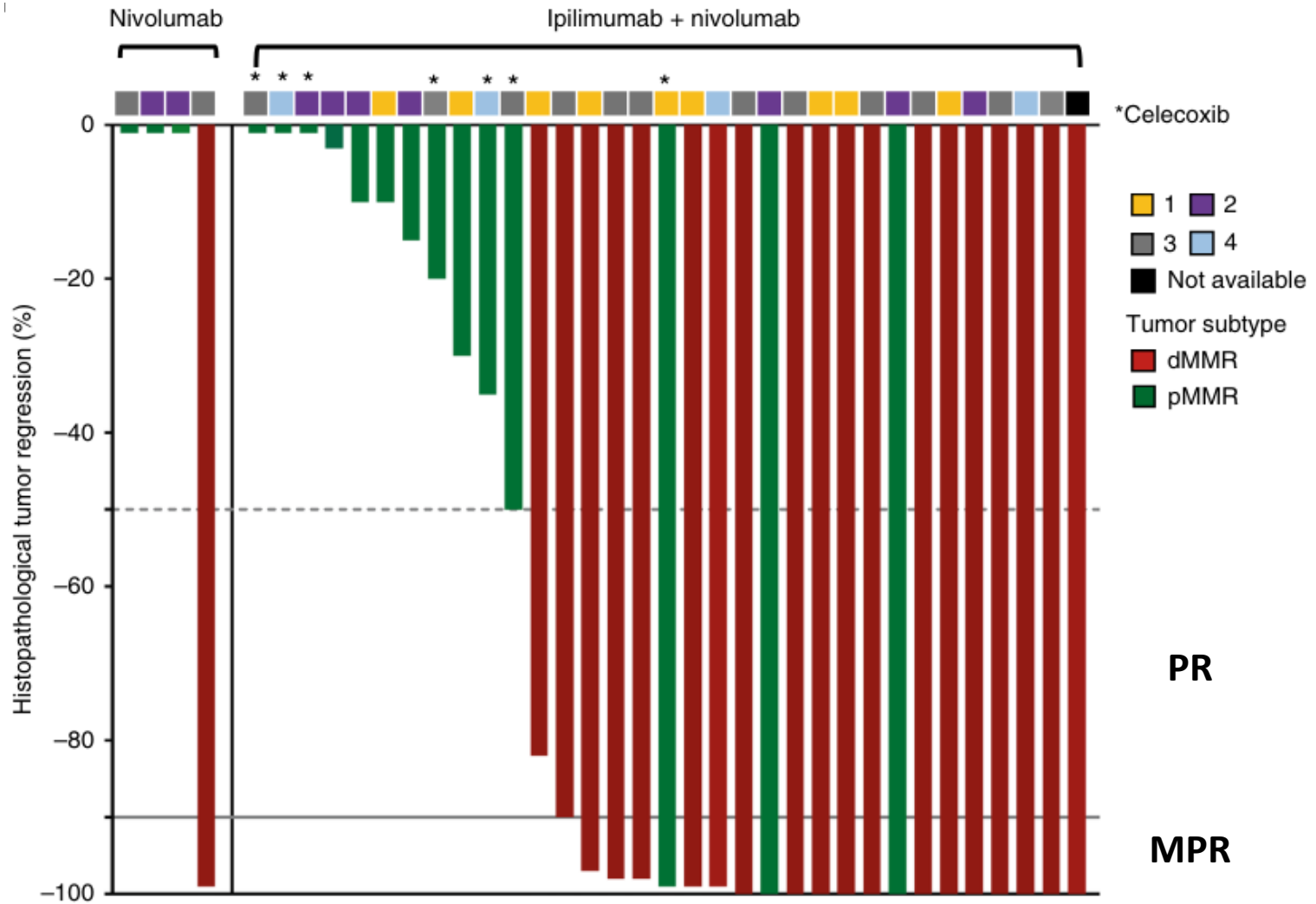
- Phase II, open-label
- Pembrolizumab 200mg IV Q3 weeks x 6 months
- Option for surgical resection or observation
- Primary endpoints: Safety and pathologic complete response
- Patient population:
  - 27 patients with CRC
  - 8 patients with other solid tumors



14 patients with CRC underwent surgery
Pathologic complete response rate= 79%

Ludford et al., J Clin Oncol 2023; 41(12):2181-2191

NICHE-1: Neoadjuvant ipilimumab + nivolumab for resectable/ non-metastatic colon cancer



- Primary objective: Feasibility and safety
- Single dose of ipilimumab and two doses of nivolumab before surgery
- In dMMR tumors: Pathological response in 20/20 tumors, with 19 MPRs (≤10% residual viable tumor) and 12 pathological CRs
- In pMMR tumors: 4/15 (27%; 95% exact CI: 8–55%) pathological responses, with 3 MPRs and 1 partial response

Chalabi et al., Nature Medicine 2020;26:566-576

NICHE-2: Neoadjuvant ipilimumab + nivolumab for locally advanced MMR-deficient colon cancer

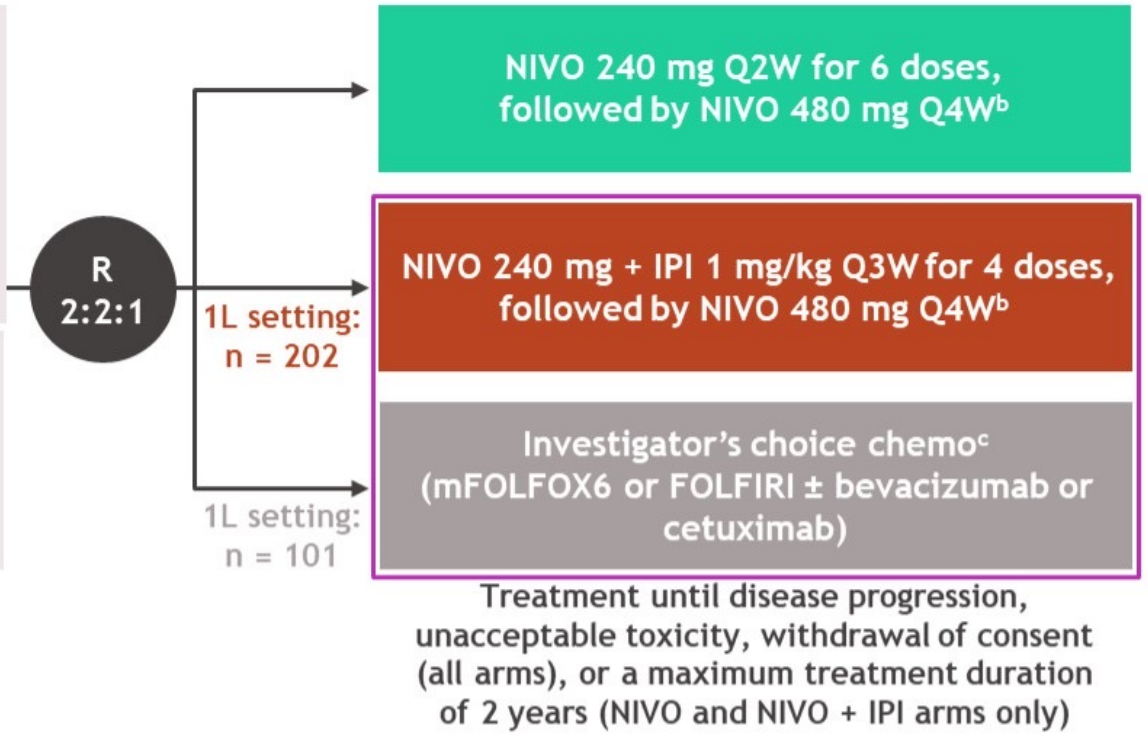
Major pathologic response in 95% of patients; 67% pCR (n=107 patients)

Chalabi et al., Presented at 2022 ESMO Congress
Chalabi et al., Annals of Oncology (2022) 33 (suppl_7): S808-S869.

CheckMate 8HW: Study design

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)



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

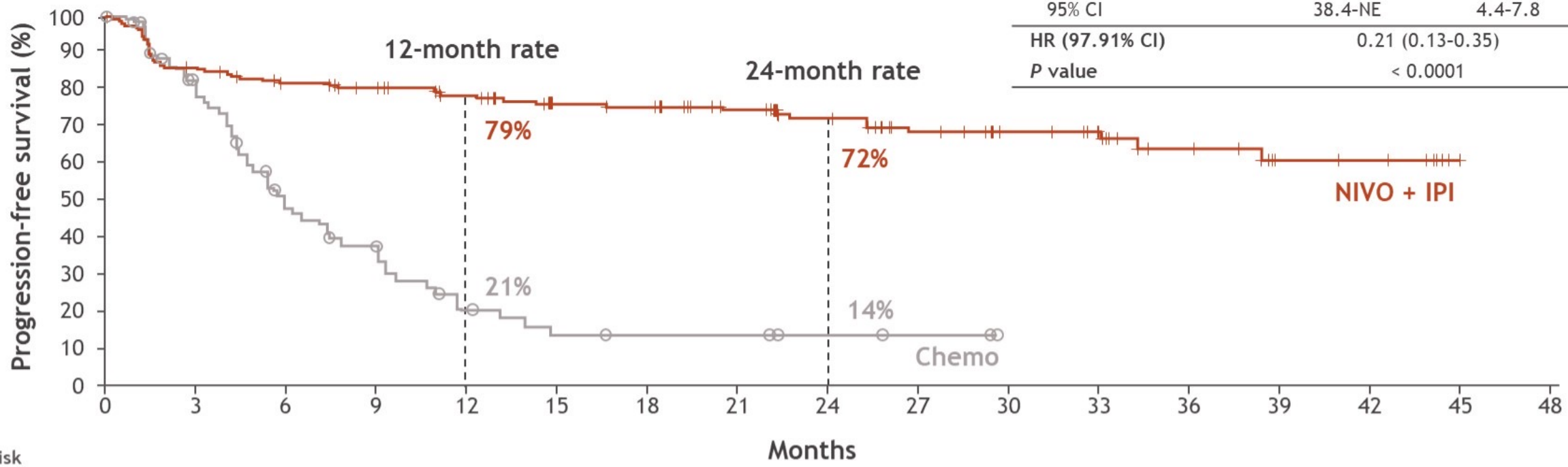
Other select endpoints:
- Safety
- OS; ORR by BICR[e]; PROs

Median follow-up = 24.3 months

Andre et al., Presented at 2024 ASCO Cancers GI Symposium
Andre et al., J Clin Oncol 42, 2024 (suppl 3; abstr LBA768)

CheckMate 8HW: Progression-free survival

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	

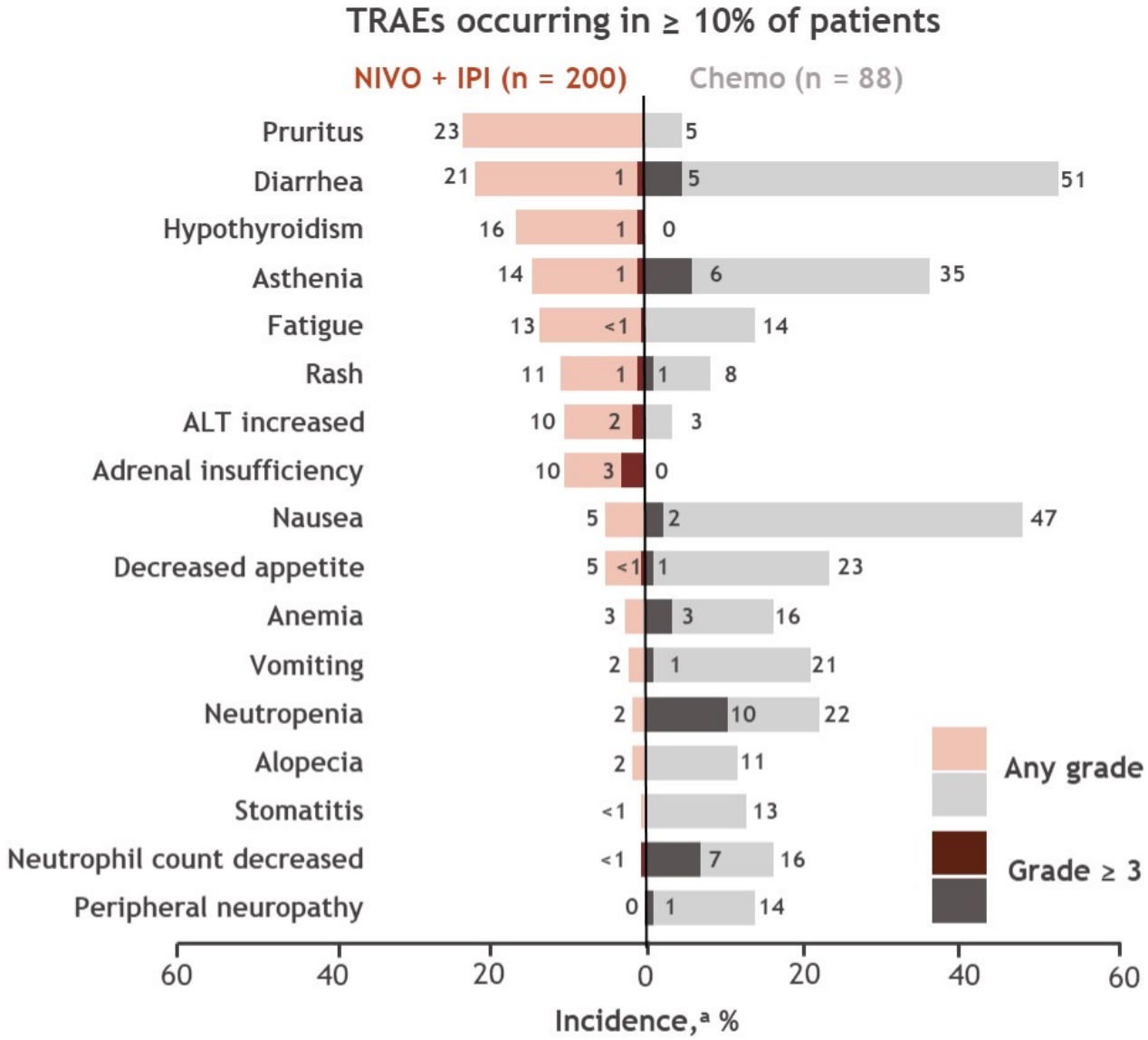


No. at risk

NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

Andre et al., Presented at 2024 ASCO Cancers GI Symposium
Andre et al., J Clin Oncol 42, 2024 (suppl 3; abstr LBA768)

CheckMate 8HW: Treatment-related adverse events



1L all treated patients	NIVO + IPI (n = 200)		Chemo (n = 88)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs,[a] n (%)				
Any TRAEs	160 (80)	46 (23)	83 (94)	42 (48)
Serious TRAEs	38 (19)	32 (16)	17 (19)	14 (16)
TRAEs leading to discontinuation	33 (17)	23 (12)	28 (32)	9 (10)
Treatment-related deaths, n (%)	2 (1)[b]		0 (0)[c]	
IMAEs,[d] n (%)				
Non-endocrine events				
Diarrhea/colitis	13 (7)	9 (5)	1 (1)	0
Hepatitis	11 (6)	6 (3)	0	0
Rash	11 (6)	3 (2)	0	0
Pneumonitis	4 (2)	3 (2)	0	0
Endocrine events				
Hypothyroidism/thyroiditis	34 (17)	3 (2)	1 (1)	0
Adrenal insufficiency	21 (11)	7 (4)	0	0
Hyperthyroidism	18 (9)	0	1 (1)	0
Hypophysitis	10 (5)	5 (3)	0	0

Andre et al., Presented at 2024 ASCO Cancers GI Symposium
Andre et al., J Clin Oncol 42, 2024 (suppl 3; abstr LBA768)

ASCO 2024

- Raghav K et al. **A randomized study evaluating tailoring of advanced/metastatic colorectal cancer (mCRC) therapy using circulating tumor DNA (ctDNA): TACT-D.** ASCO 2024;Abstract LBA3557.
- LaPelusa M et al. **Circulating tumor DNA as a predictive biomarker for pathologic response after treatment with neoadjuvant immunotherapy for localized dMMR/MSI-H colorectal cancer.** ASCO 2024;Abstract 3612.
- Dasari A et al. **Colon adjuvant chemotherapy based on evaluation of residual disease (CIRCULATE-NORTH AMERICA): NRG-GI008.** ASCO 2024;Abstract TPS3641.
- Lenz H et al. **Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) as first-line (1L) treatment for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Expanded efficacy analysis from CheckMate 8HW.** ASCO 2024;Abstract 3503.
- Shiu K et al. **NEOPRISM-CRC: Neoadjuvant pembrolizumab stratified to tumour mutation burden for high risk stage 2 or stage 3 deficient-MMR/MSI-high colorectal cancer.** ASCO 2024;Abstract LBA3504.
- Cercek A et al. **Durable complete responses to PD-1 blockade alone in mismatch repair deficient locally advanced rectal cancer.** ASCO 2024;Abstract LBA3512.

ASCO 2024

- Rocha Lima CM et al. **NRG-GI004/SWOG-S1610: Colorectal cancer metastatic dMMR immuno-therapy (COMMIT) study — A randomized phase III study of atezolizumab (atezo) monotherapy versus mFOLFOX6/bevacizumab/atezo in the first-line treatment of patients with deficient DNA mismatch repair (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC).** ASCO 2024;Abstract TPS3632.
- Pellatt A et al. **A phase II trial of TAS-102 in patients with colorectal cancer with ctDNA-defined minimal residual disease post-adjuvant therapy compared to synthetic control cohort: Results from the MD Anderson INTERCEPT program.** ASCO 2024;Abstract 3623.
- Sharma M et al. **First-in-human study of ABBV-400, a novel c-Met–targeting antibody-drug conjugate, in advanced solid tumors: Results in colorectal cancer.** ASCO 2024;Abstract 3515.
- Perets R et al. **Phase 1b study evaluating the efficacy and safety of ABBV-400, a c-Met–targeting antibody-drug conjugate, in select advanced solid tumor indications.** ASCO 2024;Abstract TPS3162.
- Raghav K et al. **Phase 2 randomized study evaluating safety, efficacy, and optimal dose of ABBV-400 in combination with fluorouracil, folinic acid, and bevacizumab in previously treated patients with metastatic colorectal cancer.** ASCO 2024;Abstract TPS3636.

ASCO 2024

- Zhang H et al. **Phase I trial of hypoxia-responsive CEA CAR-T cell therapy in patients with heavily pretreated solid tumor via intraperitoneal or intravenous transfusion.** ASCO 2024;Abstract 3514.
- Adam R et al. **Chemotherapy and liver transplantation versus chemotherapy alone in patients with definitively unresectable colorectal liver metastases: A prospective multicentric randomized trial (TRANSMET).** ASCO 2024;Abstract 3500.
- Meijerink MR et al. **Surgery versus thermal ablation for small-size colorectal liver metastases (COLLISION): An international, multicenter, phase III randomized controlled trial.** ASCO 2024;Abstract LBA3501.

Agenda

Module 1: Recent Therapeutic Advances in Colorectal Cancer (CRC) — Dr Strickler

Module 2: New Developments in Targeted Therapy for Metastatic CRC — Dr Kopetz

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Cases from General Medical Oncologists
HER2

- **65-year-old woman, HER2-positive mCRC, received T-DXd with stable disease, neutropenia**
- **74-year-old man, RAS wild-type, ERBB2-amplified on NGS done on primary tumor, received FOLFOX/bevacizumab → FOLFIRI/bevacizumab → currently on trastuzumab/pertuzumab with no side effects so far**
- **75-year-old man, HER2-positive mCRC, received trastuzumab/pertuzumab with stable disease, diarrhea/fatigue**
- **64-year-old man, HER2-mutated, RAS wild-type mCRC, received T-DXd with a PR, thrombocytopenia**
- **55-year-old woman, HER2-positive mCRC, received tucatinib/trastuzumab with a PR, diarrhea**
- **73-year-old man, HER2-positive mCRC, received tucatinib/trastuzumab with good cancer control but experienced weight loss of unknown etiology and eventually went to hospice**

Survey of US-based general medical oncologists, May 2024.

Cases from General Medical Oncologists
KRAS

- **50-year-old woman, mCRC with a KRAS G12C mutation, received adagrasib with a PR, fatigue**
- **67-year-old woman, mCRC with a KRAS G12C mutation, received adagrasib/cetuximab with reduction in tumor size, actinic skin changes**
- **54-year-old man, mCRC with a KRAS G12C mutation, received third-line sotorasib with a PR; at treatment onset, high baseline glucose became persistently low and diabetic medications were discontinued**

Survey of US-based general medical oncologists, May 2024.

Questions from General Medical Oncologists

- **Preference for which anti-EGFR with adagrasib?**
- **What line of therapy for KRAS G12C or HER2 therapy?**
- **KRAS incorporation first line? What if having GI bleed or concerns for obstruction/fistula? Do we worry about AEs similar to other TKIs or VEGF inhibitors?**

Survey of US-based general medical oncologists, May 2024.

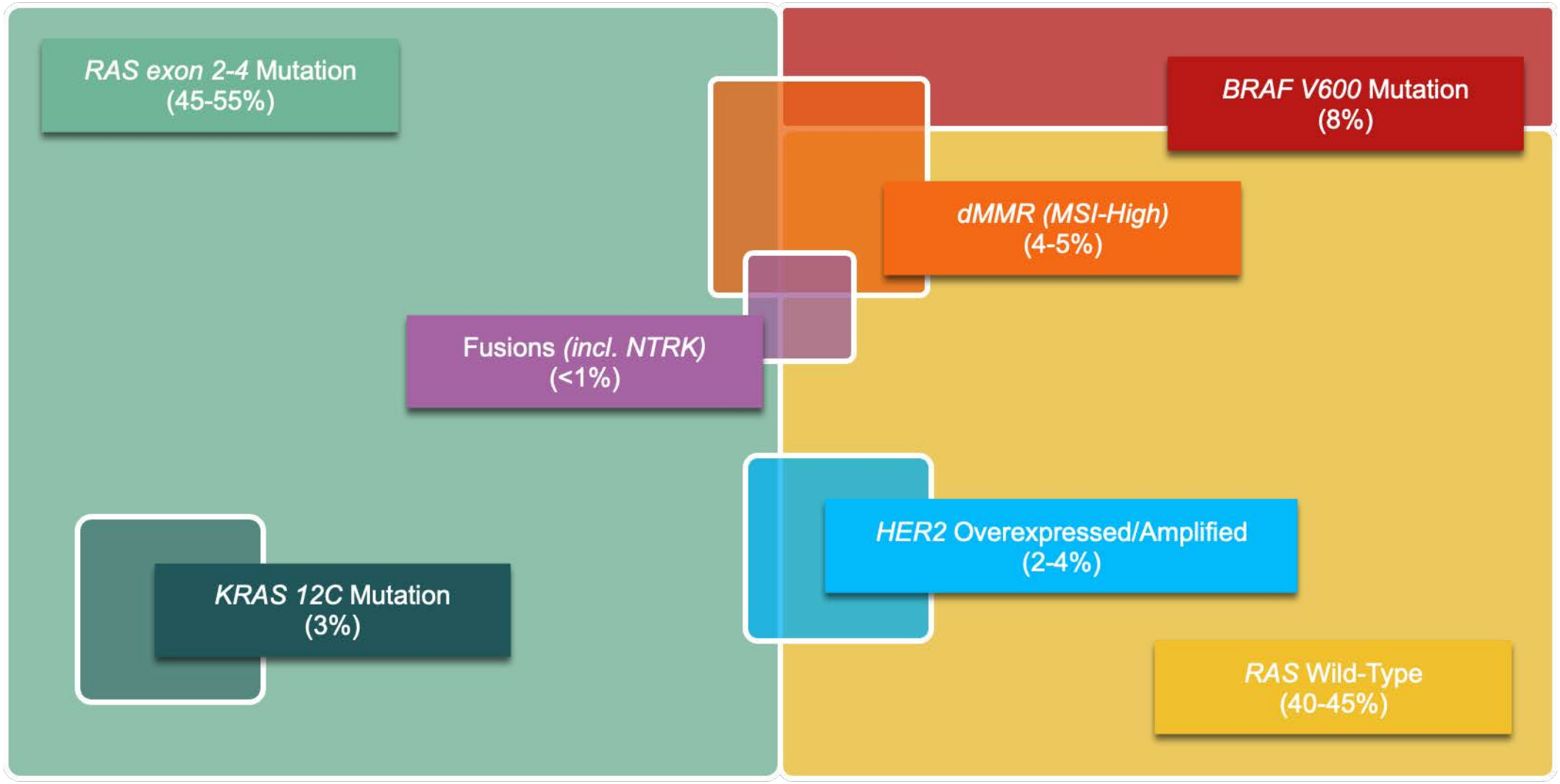
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

New Developments in Targeted Therapy for mCRC

Scott Kopetz, MD, PhD

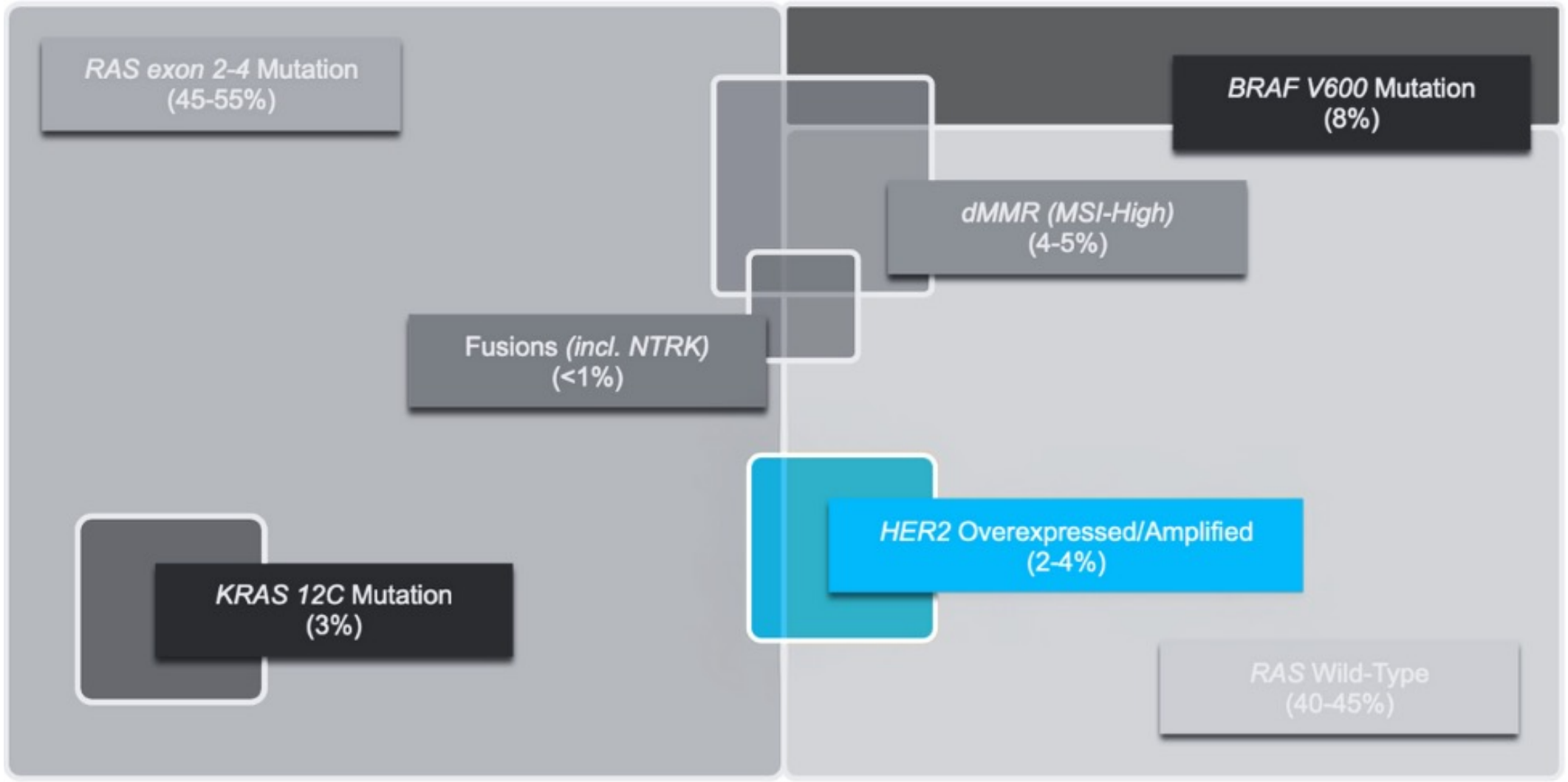
Professor, GI Medical Oncology
Associate VP Translational Integration, VP Research

Distribution of Actionable Alterations in Colorectal Cancer



Slide Courtesy of Kanwal Raghav

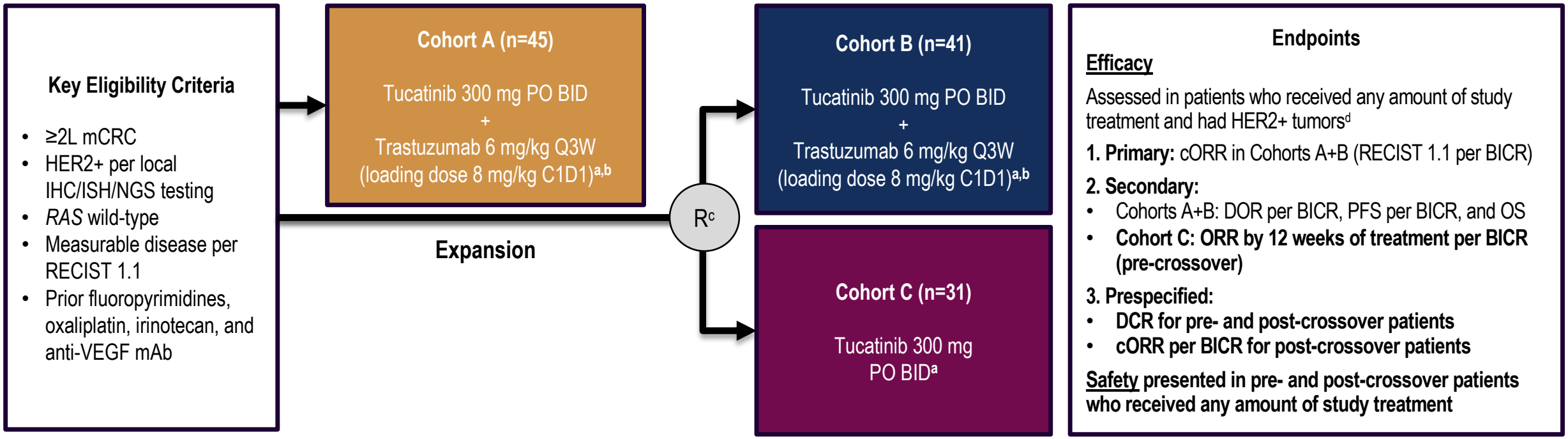
Distribution of Actionable Alterations in Colorectal Cancer



Slide Courtesy of Kanwal Raghav

Tucatinib and Trastuzumab

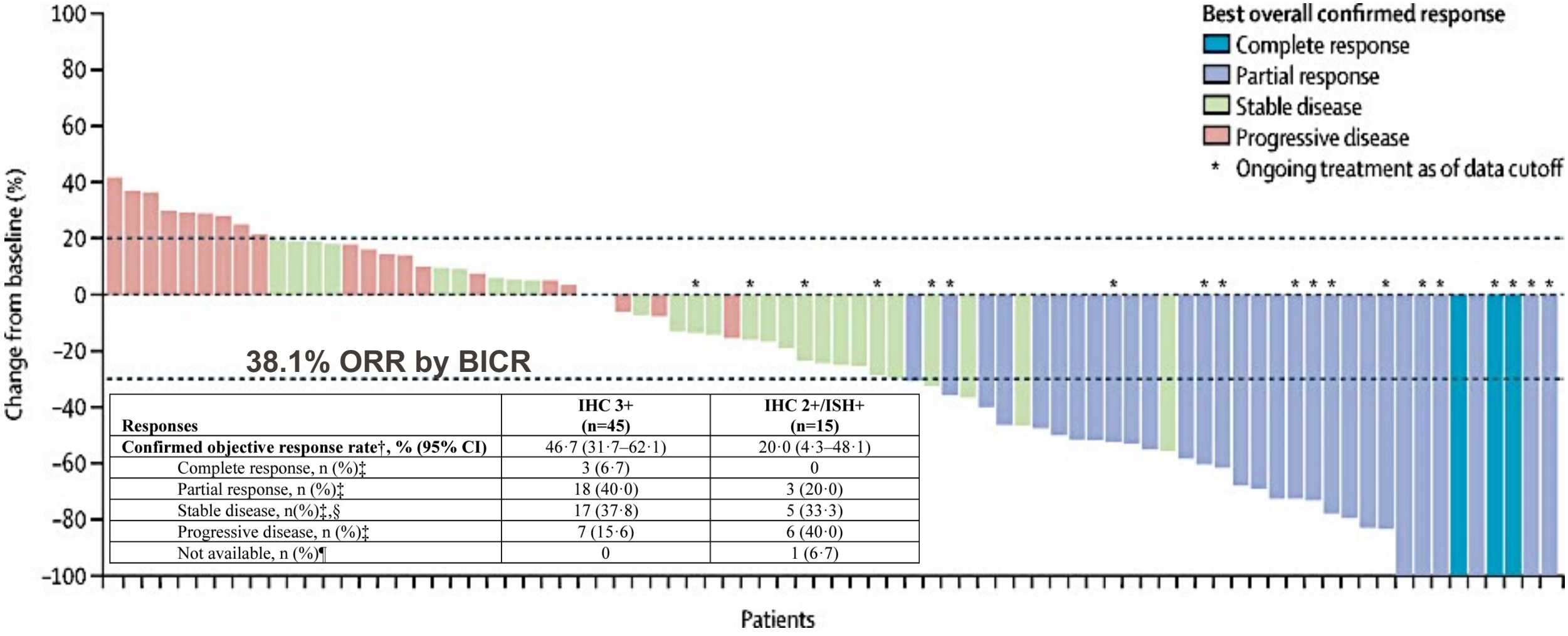
MOUNTAINEER Trial: Study Design



Patients treated with tucatinib monotherapy 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

Strickler Lancet Onc. (2023)

MOUNTAINEER Trial: Results

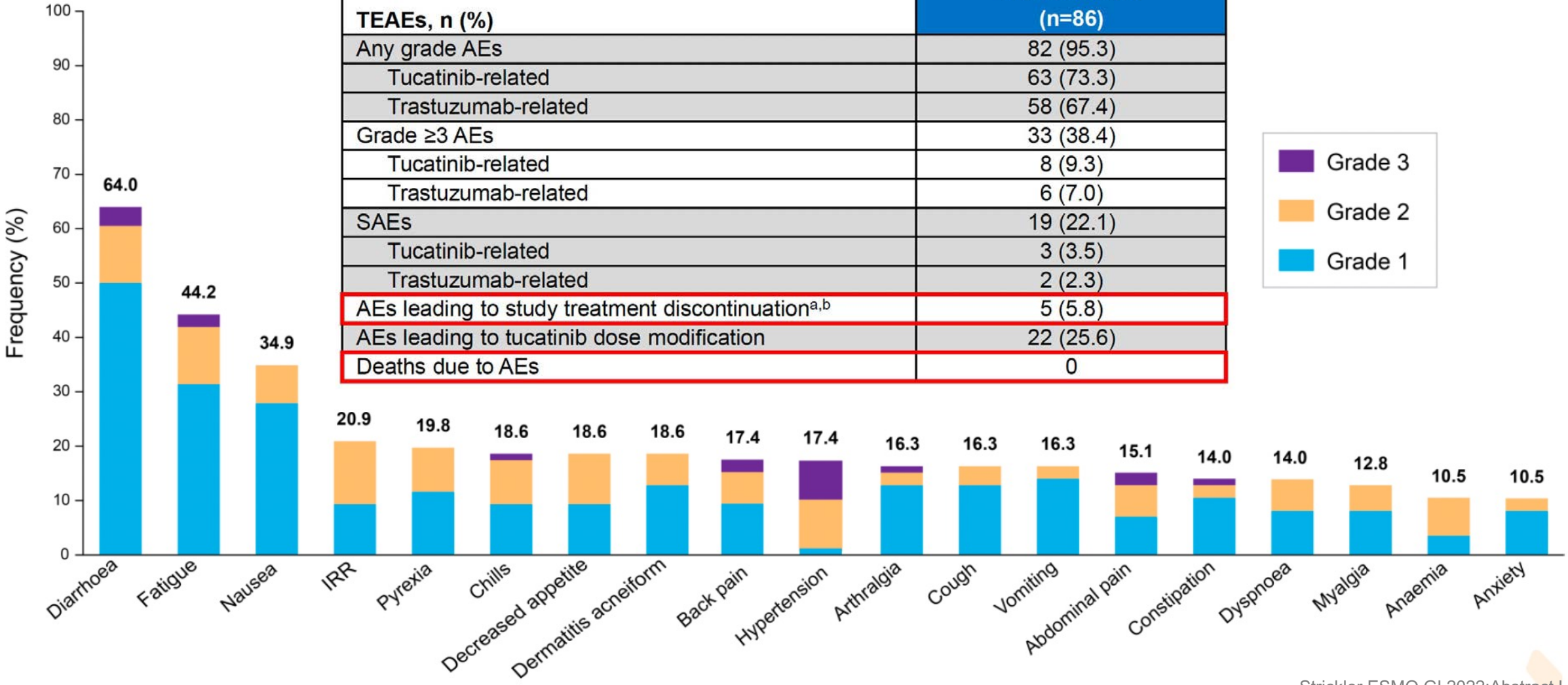


Responses	IHC 3+ (n=45)	IHC 2+/ISH+ (n=15)
Confirmed objective response rate†, % (95% CI)	46·7 (31·7–62·1)	20·0 (4·3–48·1)
Complete response, n (%)‡	3 (6·7)	0
Partial response, n (%)‡	18 (40·0)	3 (20·0)
Stable disease, n(%)‡,§	17 (37·8)	5 (33·3)
Progressive disease, n (%)‡	7 (15·6)	6 (40·0)
Not available, n (%)¶	0	1 (6·7)

Strickler ESMO GI 2022;Abstract LBA-2. Strickler Lancet Onc. (2023)

MOUNTAINEER Trial: Safety

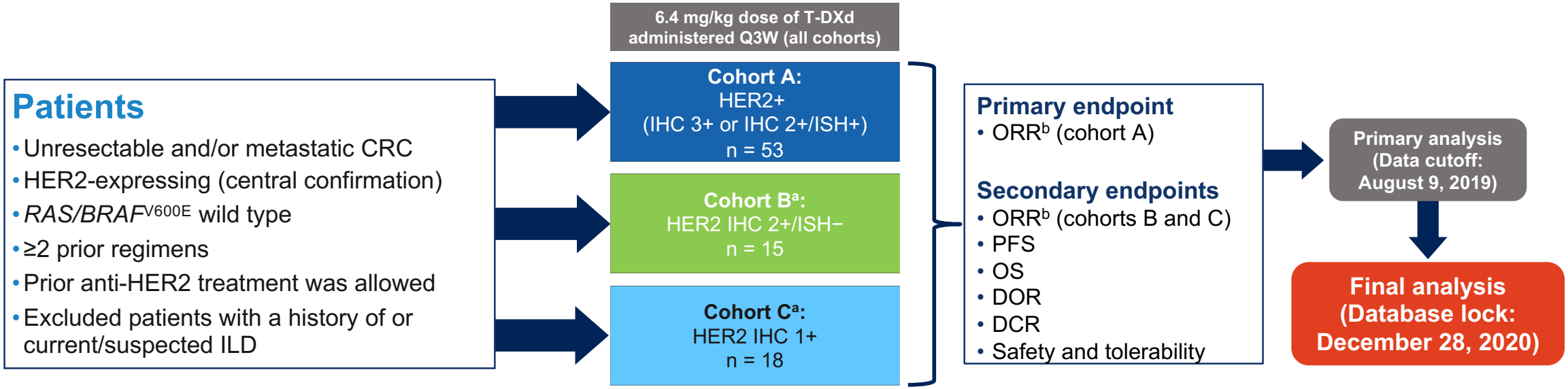
TEAEs, n (%)	Tucatinib + Trastuzumab Cohorts A+B (n=86)
Any grade AEs	82 (95.3)
Tucatinib-related	63 (73.3)
Trastuzumab-related	58 (67.4)
Grade ≥3 AEs	33 (38.4)
Tucatinib-related	8 (9.3)
Trastuzumab-related	6 (7.0)
SAEs	19 (22.1)
Tucatinib-related	3 (3.5)
Trastuzumab-related	2 (2.3)
AEs leading to study treatment discontinuation[a,b]	5 (5.8)
AEs leading to tucatinib dose modification	22 (25.6)
Deaths due to AEs	0



Strickler ESMO GI 2022;Abstract LBA-2.

Trastuzumab Deruxtecan (T-DXd): DESTINY-CRC01

Linker	Payload	DAR
Cleavable	DXd – Topoisomerase I Inhibitor	8



Primary analysis of cohort A[1]

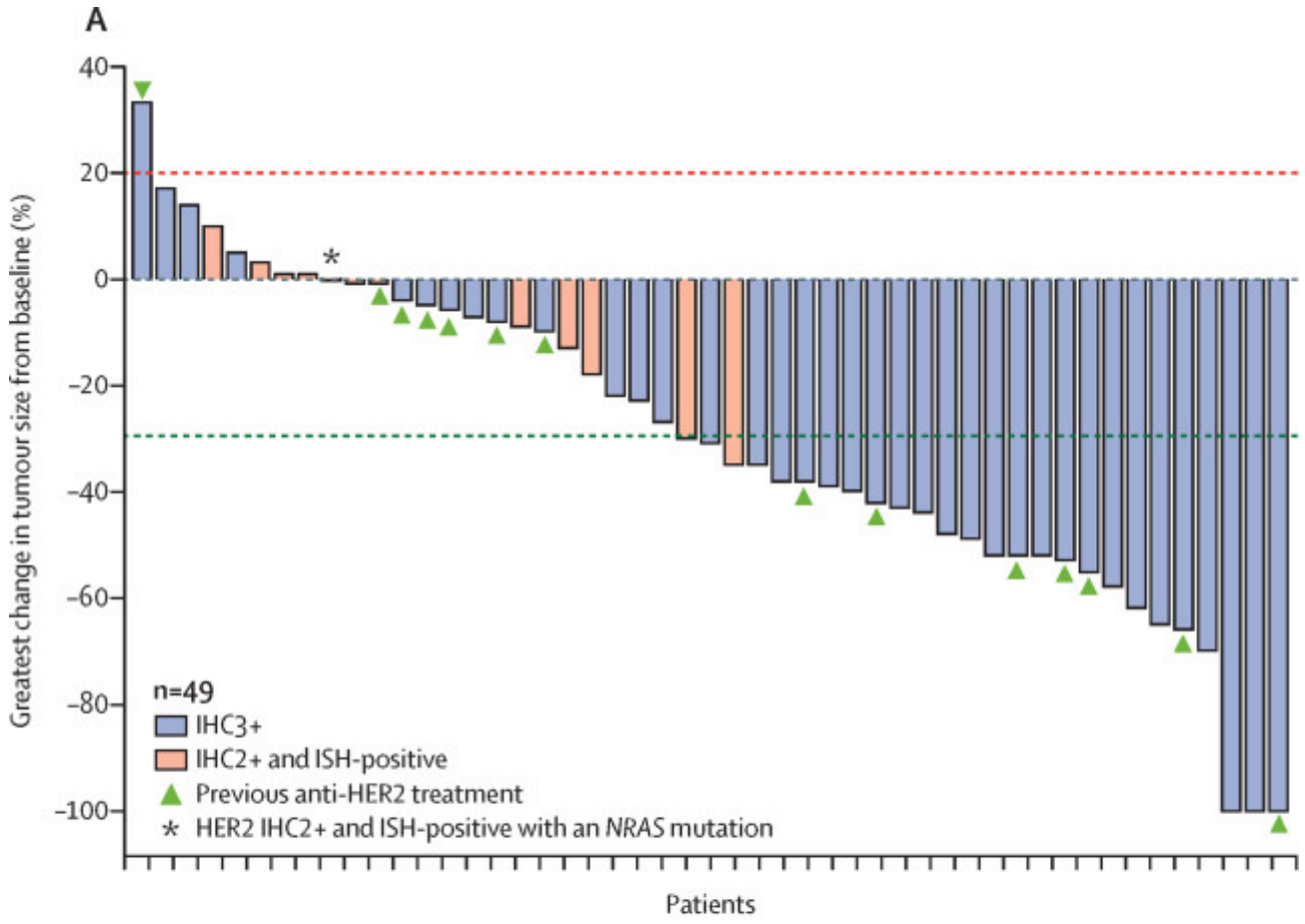
- Results yielded promising antitumor activity and a manageable safety profile
- The median follow-up was 27.1 weeks at data cutoff

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

Yoshino et al. ASCO GI 2022;Abstract 119. Siena et. al. Lancet Onc. 2021

DESTINY-CRC01: DS-8201/T-DXd/Trastuzumab Deruxtecan



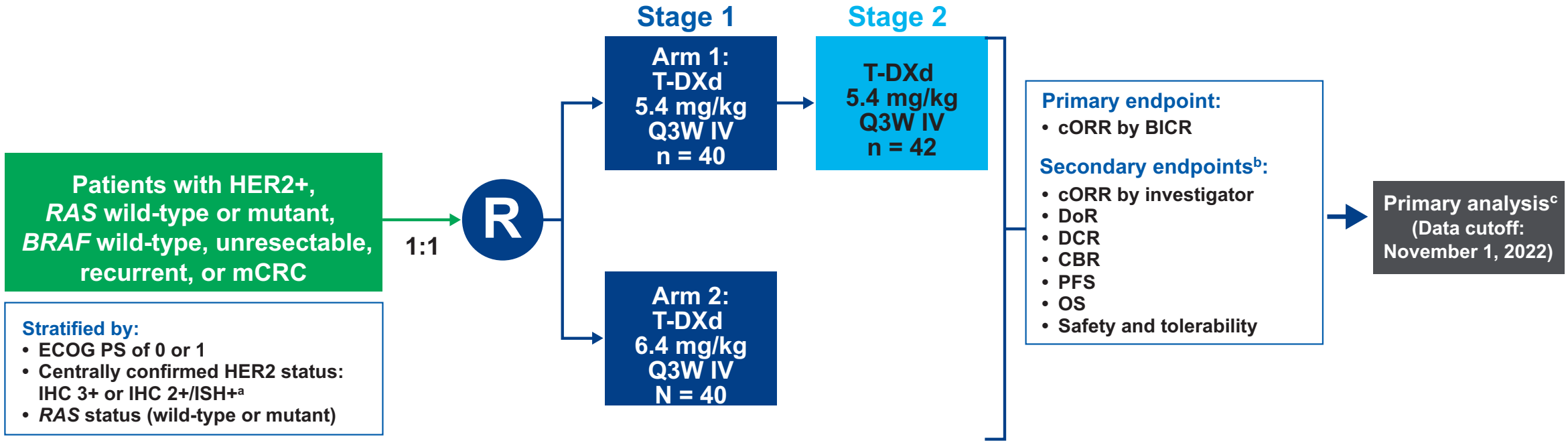
	Cohort A (HER2-positive; n=53)
Confirmed ORR by ICR, % (95% CI)	45·3 (31·6–59·6)
Complete response	1 (2%)
Partial response	23 (43%)
Stable disease	20 (38%)
Progressive disease	5 (9%)
Non-evaluable*	4 (8%)
Confirmed ORR by investigator, % (95% CI)	45·3 (31·6–59·6)
Complete response	0
Partial response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

Yoshino et al. ASCO GI 2022;Abstract 119. Siena et. al. Lancet Onc. 2021

DESTINY-CRC02 Study (T-DXd)

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



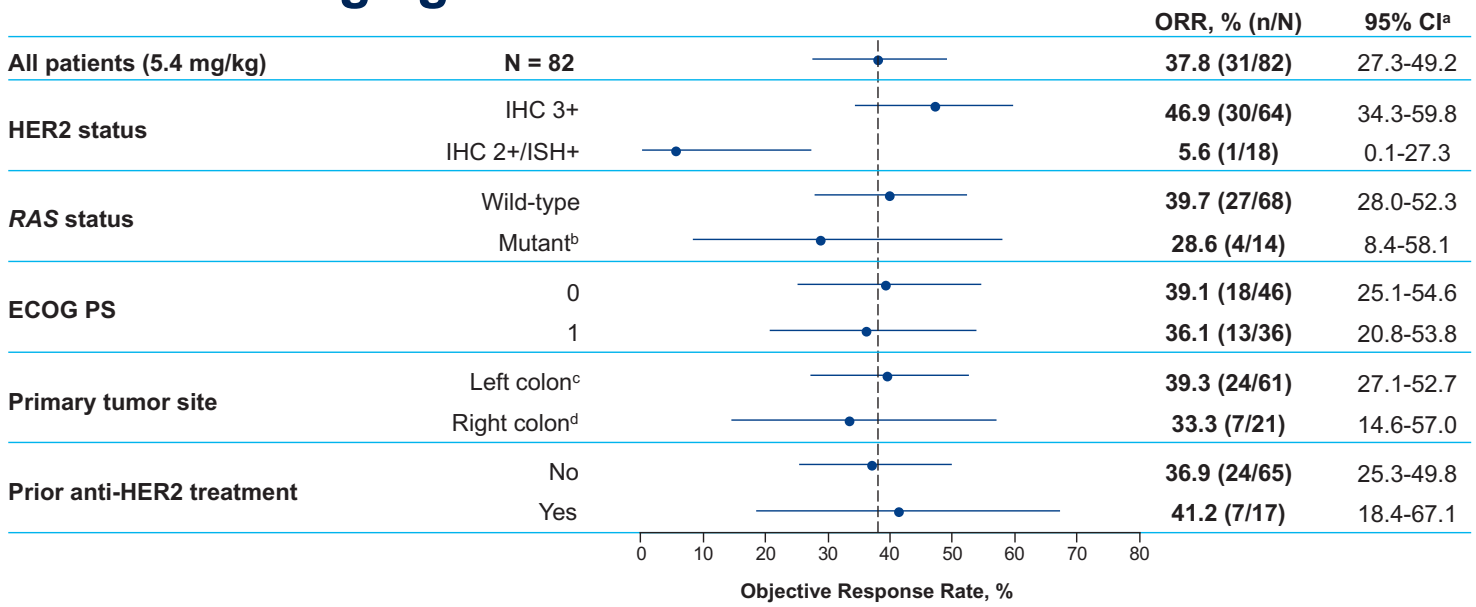
This study was not powered to statistically compare the two arms.

Raghav et. al. ASCO 2023

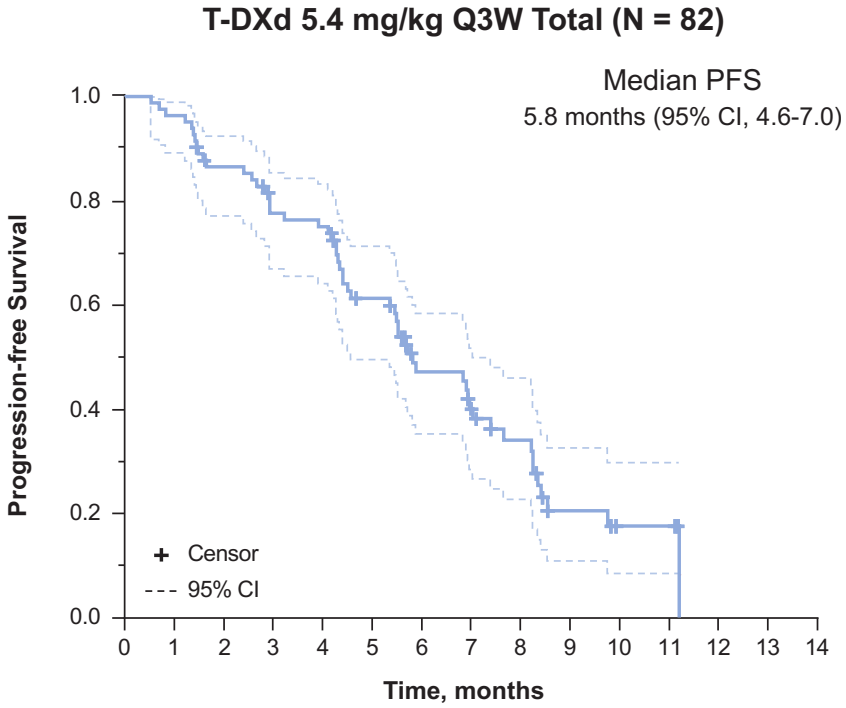
MD Anderson

DESTINY-CRC02 Study (T-DXd)

T-DXd 5.4 mg/kg



ORR by BICR: 37.8%



Median PFS: 5.8m

Raghav et. al. ASCO 2023

DESTINY-CRC02 Study (T-DXd)

n (%)	T-DXd 5.4 mg/kg Q3W Total N = 83[b]		T-DXd 6.4 mg/kg Q3W Stage 1 N = 39	
	Any-grade	Grade ≥3	Any-grade	Grade ≥3
Any TEAEs	82 (98.8)	41 (49.4)	39 (100)	23 (59.0)
Nausea	48 (57.8)	7 (8.4)	22 (56.4)	0
Fatigue[c]	38 (45.8)	8 (9.6)	18 (46.2)	2 (5.1)
Neutropenia[d]	25 (30.1)	14 (16.9)	18 (46.2)	11 (28.2)
Decreased appetite	25 (30.1)	2 (2.4)	6 (15.4)	0
Anemia[e]	22 (26.5)	8 (9.6)	16 (41.0)	9 (23.1)
Thrombocytopenia[f]	21 (25.3)	5 (6.0)	14 (35.9)	5 (12.8)
Alopecia	20 (24.1)	0	11 (28.2)	0
Constipation	20 (24.1)	0	5 (12.8)	0
Diarrhea	19 (22.9)	2 (2.4)	11 (28.2)	0
Vomiting	17 (20.5)	4 (4.8)	3 (7.7)	0
Pneumonitis/ILD	7 (8.4)	0	5 (12.8)	1 (2.6%)

Raghav et. al. ASCO 2023

Questions?

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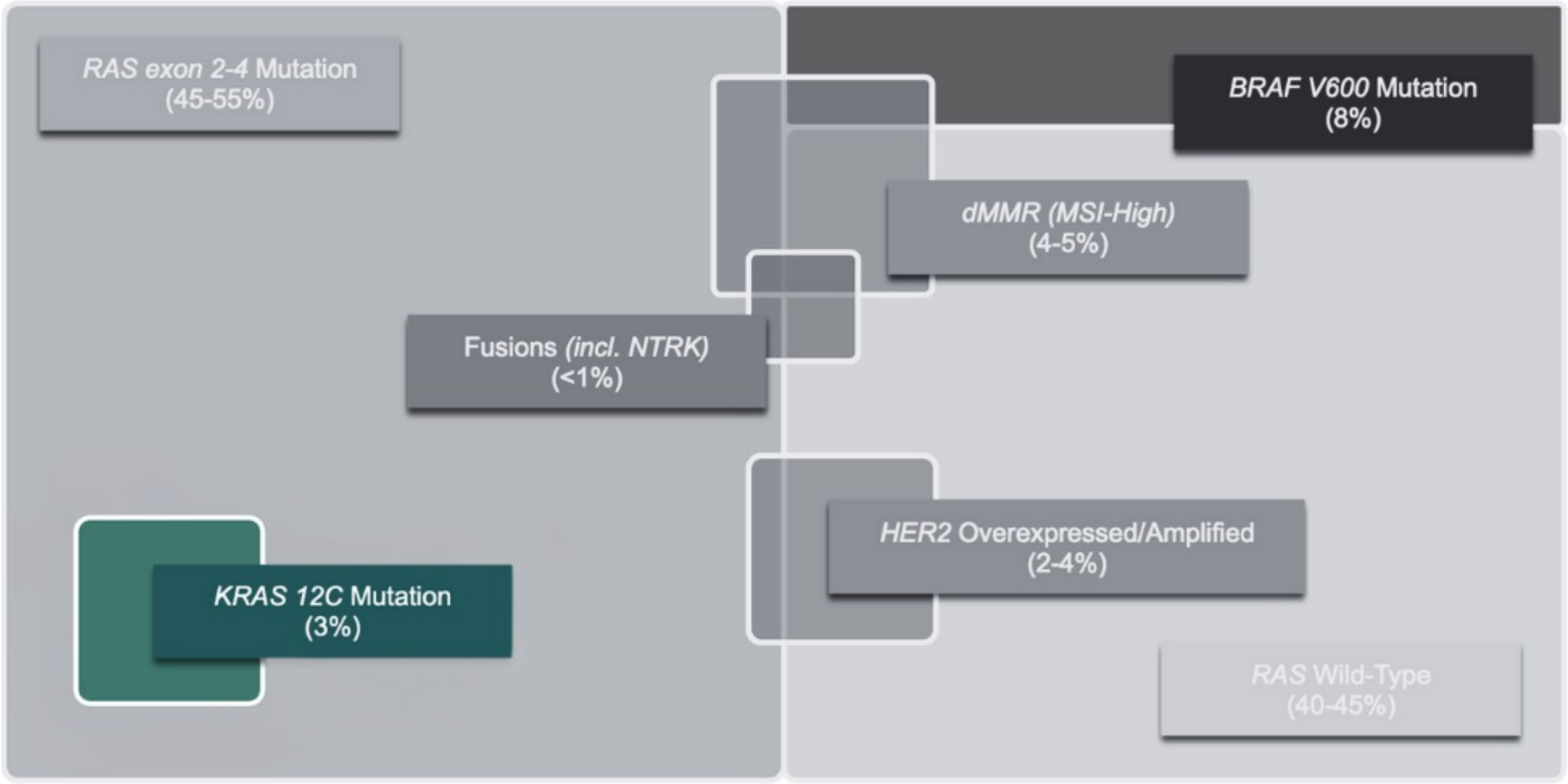
Distribution of Actionable Alterations in Colorectal Cancer

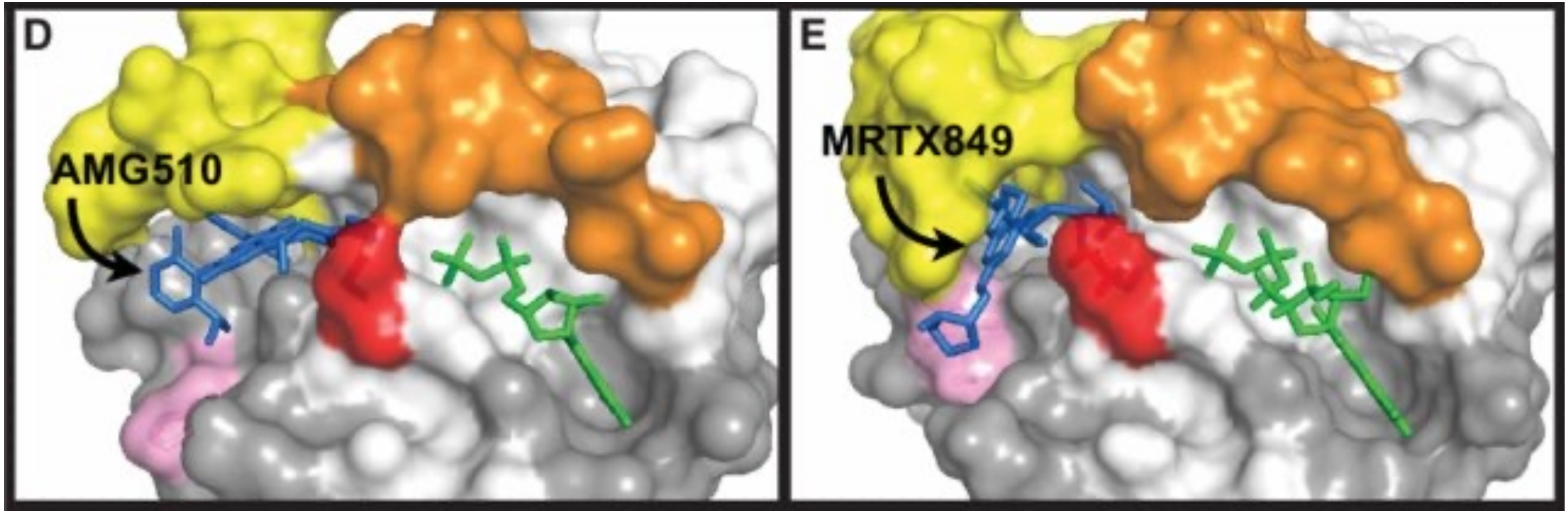


Slide Courtesy of Kanwal Raghav

Switch II inhibitors of $KRAS^{G12C}$ provide new therapeutic options

Sotorasib

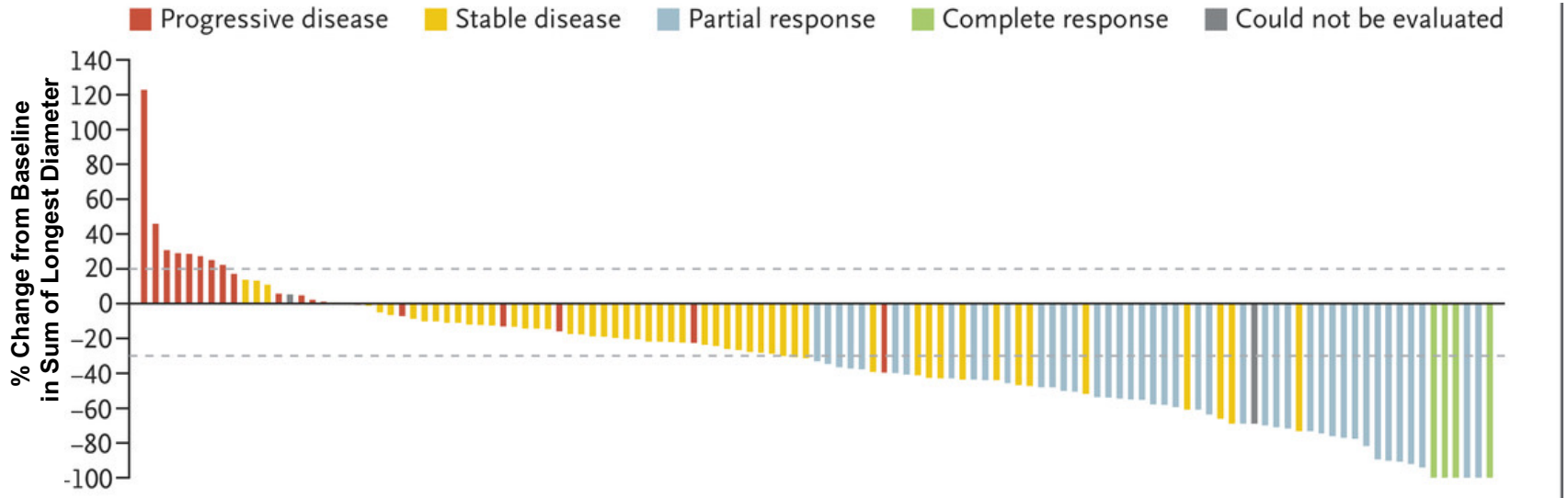
Adagrasib



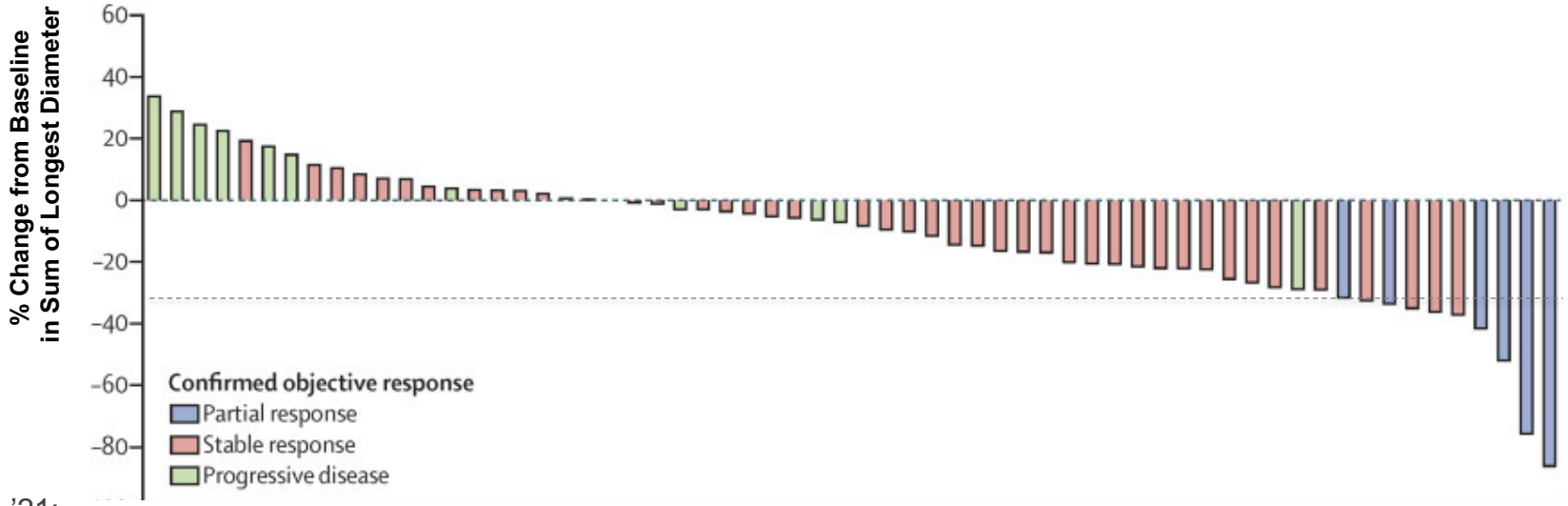
Zuberi et al Biochemical Society Transactions 2020

NSCLC and CRC: Different Responses to G12C Inhibition

NSCLC:
37% response rate

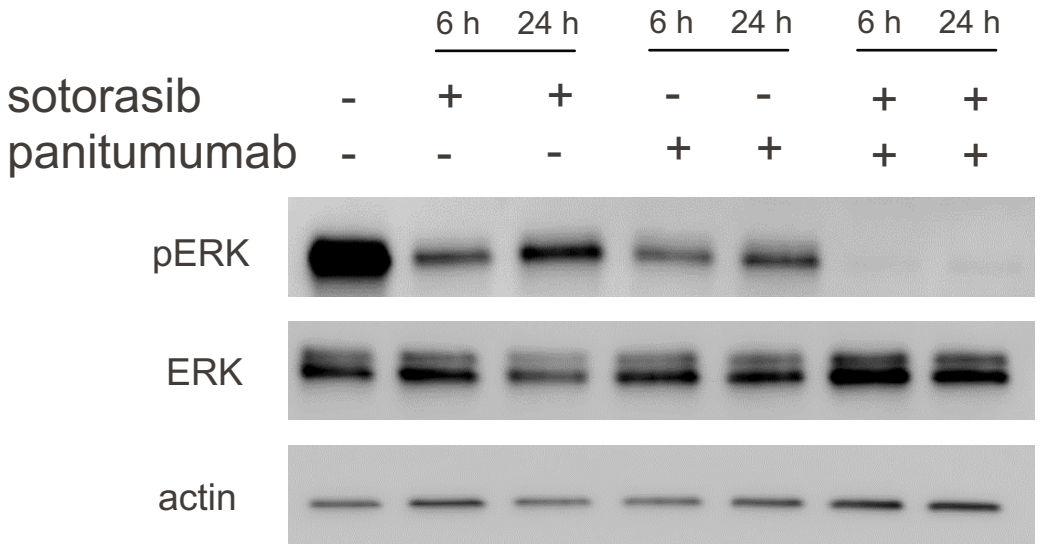


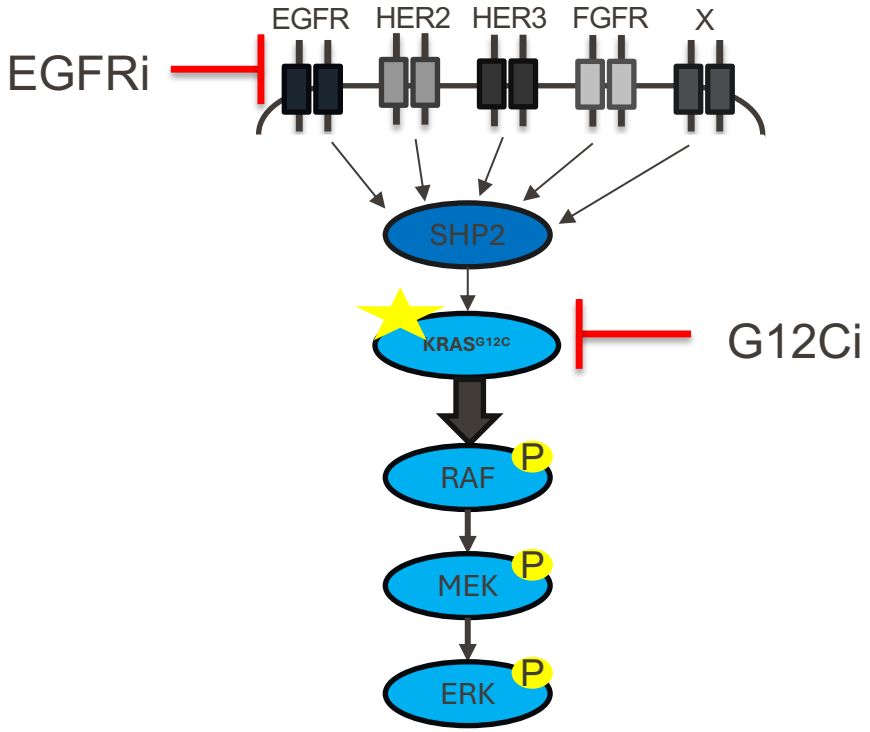
CRC:
9% response rate



Hong et al NEJM ‘20; Skoulidis et al NEJM ’21;
Fakih, Kopetz et al Lancet Oncology ‘22

Adaptive resistance to KRAS^{G12C} inhibition is blocked by EGFRi



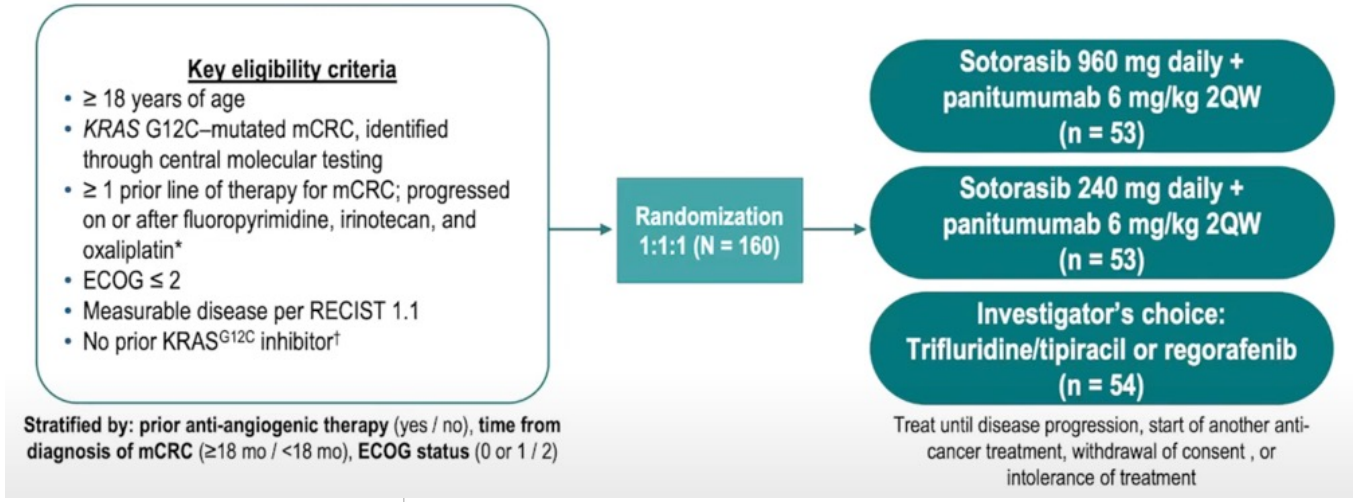


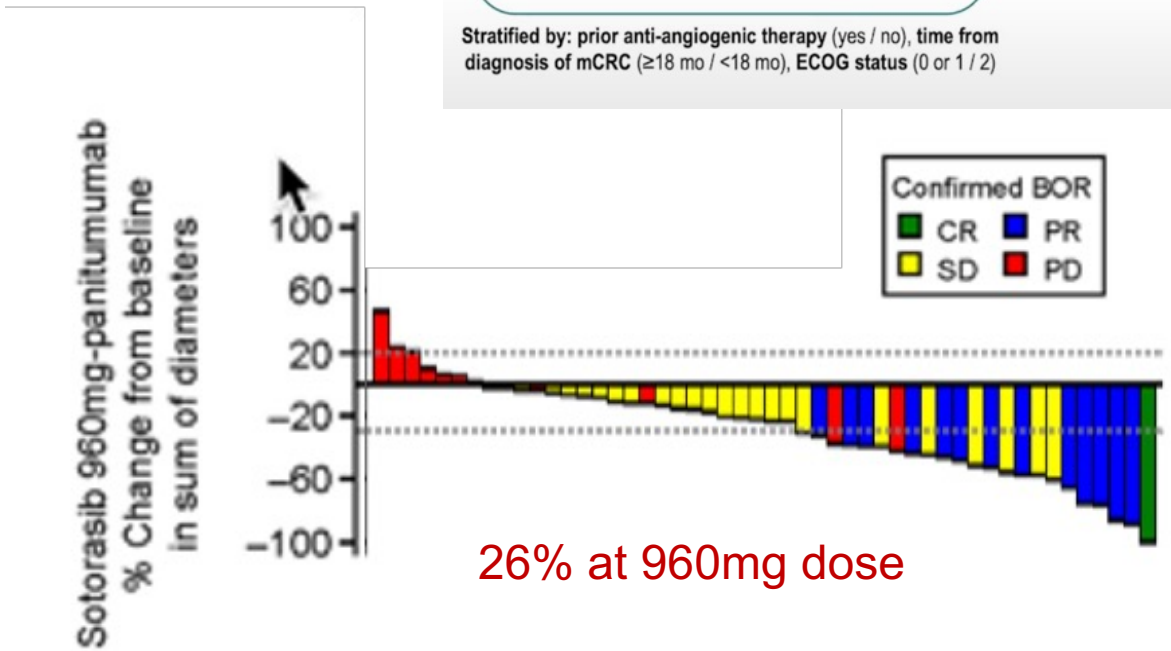
- Inhibition of G12C with sotorasib is associated with only partial pathway inhibition
- However, the pathway can be substantially inhibited with dual G12C and EGFR inhibition

See Amadio et al Cancer Discovery ‘20; Ryan et al CCR ‘20

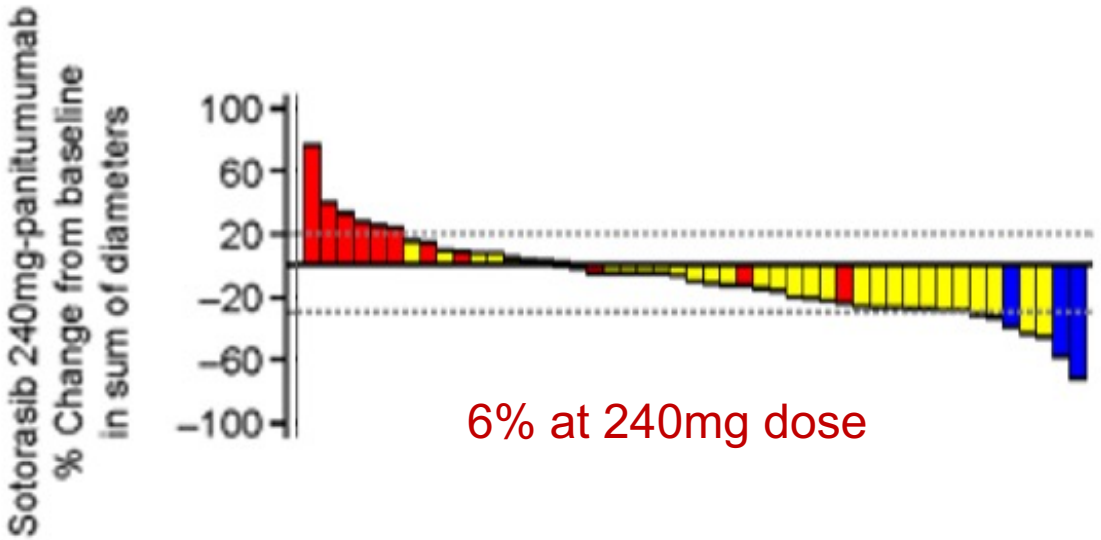
Olu Coker, Kopetz AACR ‘24

Responses to Sotorasib + Panitumumab: CodeBreaK 300





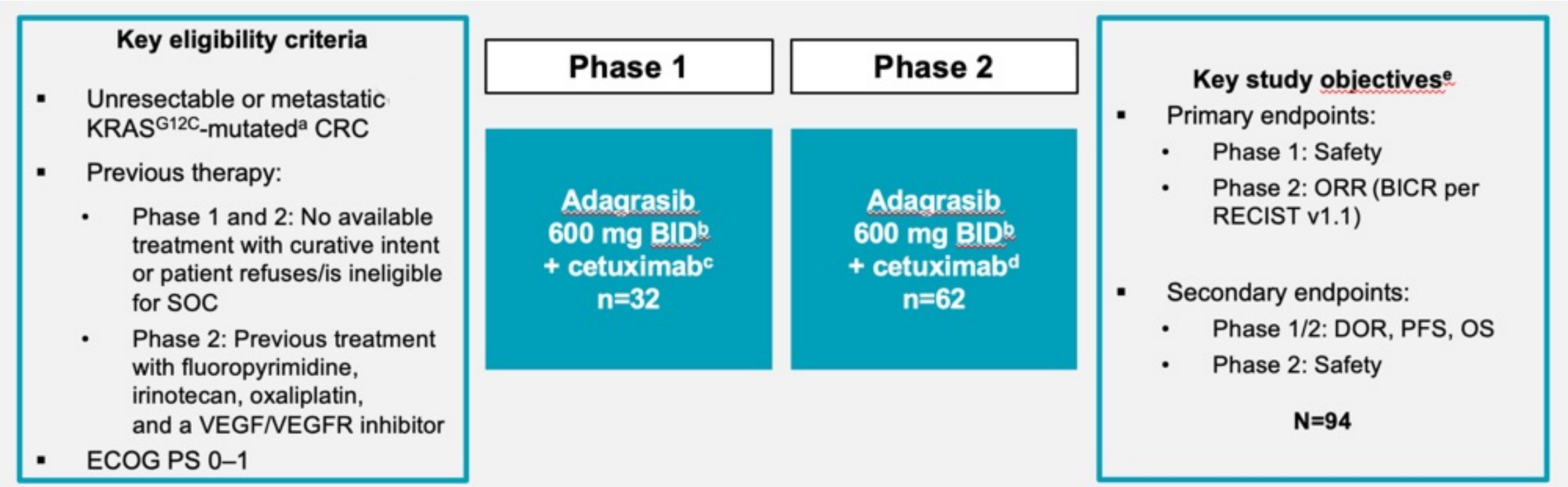
26% at 960mg dose



6% at 240mg dose

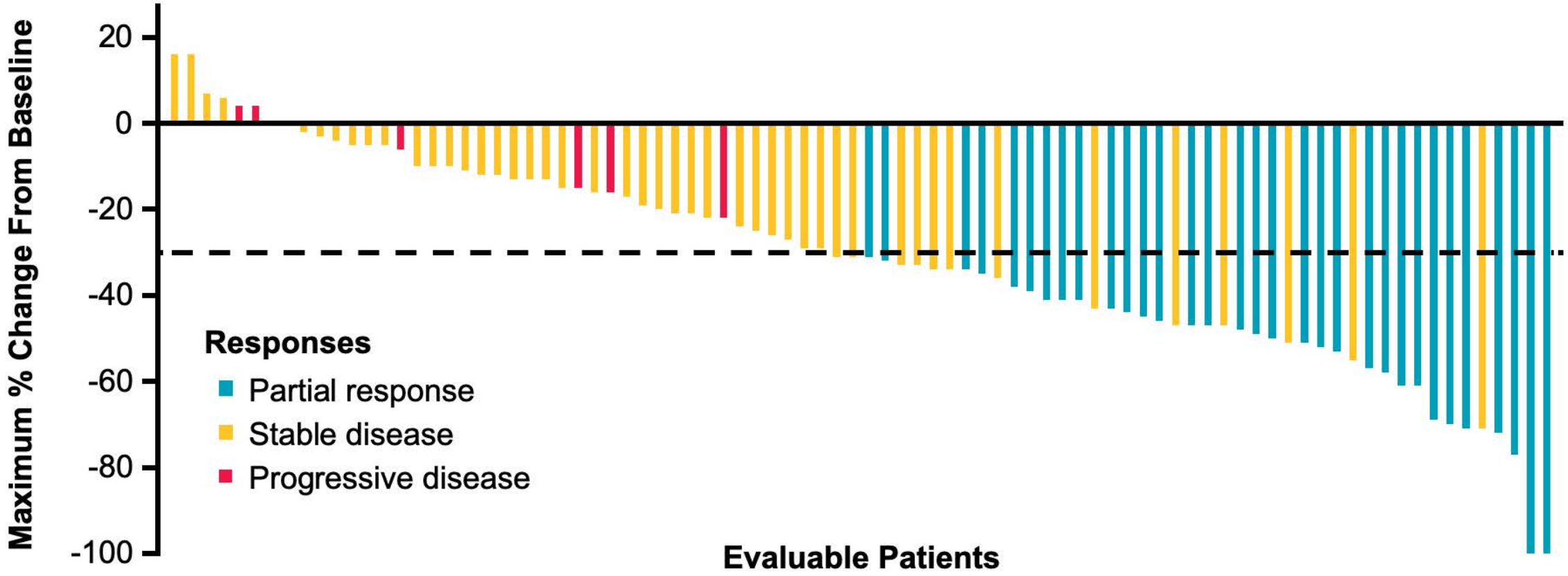
Adapted from Pietrantonio ESMO '23; Fakih et al NEJM 2023

Adagrasib + Cetuximab: Efficacy for KRYSTAL-1 Study



Kopetz et al AACR ’24, Yaeger et al Can Disc ‘24

Best Tumor Change From Baseline



Confirmed objective response rate was 34.0%[a]

Disease control was observed in 80/94 patients (85.1%)

Median PFS was 6.9 months
(95% CI, 5.7–7.4)

[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 et al AACR '24, Yaeger et al Can Disc '24

Conclusions

Treatment options for HER2 amplified cancers include:

- Trastuzumab + tucatinib: For *RAS wild type only*, targets cellular signaling
- Trastuzumab deruxtecan: Any RAS status, ADC w/ topoisomerase payload

Treatment options for KRAS G12C mutated CRC include:

- Sotorasib + panitumumab
- Adagrasib + cetuximab

Durability of the regimens remains a limitation with PFS generally ~6 months

Future therapies targeting other RAS mutations are anticipated

ASCO 2024

- Strickler JH et al. **Final results of a phase 2 study of tucatinib and trastuzumab for HER2-positive mCRC (MOUNTAINEER).** ASCO 2024;Abstract 3509.
- Fakih M et al. **Overall survival (OS) of phase 3 CodeBreaK 300 study of sotorasib plus panitumumab (soto+pani) versus investigator's choice of therapy for KRAS G12C-mutated metastatic colorectal cancer (mCRC).** ASCO 2024;Abstract LBA3510.
- Morris V et al. **SWOG S2107: Randomized phase II trial of encorafenib and cetuximab with or without nivolumab for patients with previously treated, microsatellite stable, BRAFV600E metastatic and/or unresectable colorectal cancer.** ASCO 2024;Abstract TPS3640.

What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Metastatic Breast Cancer

A CME Symposium Held in Conjunction with the 2024 ASCO® Annual Meeting

Monday, June 3, 2024

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Aditya Bardia, MD, MPH
Harold J Burstein, MD, PhD
Professor Giuseppe Curigliano, MD, PhD
Sara A Hurvitz, MD, FACP
Joyce O'Shaughnessy, MD

Moderator

Hope S Rugo, MD

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