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

A Multitumor CME/MOC-Accredited Live Webinar Series

Colorectal Cancer

Tuesday, March 5, 2024
5:00 PM – 6:00 PM ET

Faculty

Professor Thierry André, MD
Arvind Dasari, MD, MS

Moderator

Neil Love, MD

RTP Year in Review 2024

Faculty

Professor Thierry André, MD
Professor, Medical Oncology
Head, Department of Medical Oncology
Sorbonne Université
Hôpital Saint-Antoine
Paris, France

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

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

RTP Year in Review 2024

Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Daiichi Sankyo Inc, and Seagen Inc.

Dr Love — Disclosures

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Prof André — Disclosures

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Data and Safety Monitoring Board/Committee	Inspirna
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Nonrelevant Financial Relationship	Foundation ARCAD (Aide et Recherche en Cancérologie Digestive) — Foundation president

Dr Dasari — Disclosures

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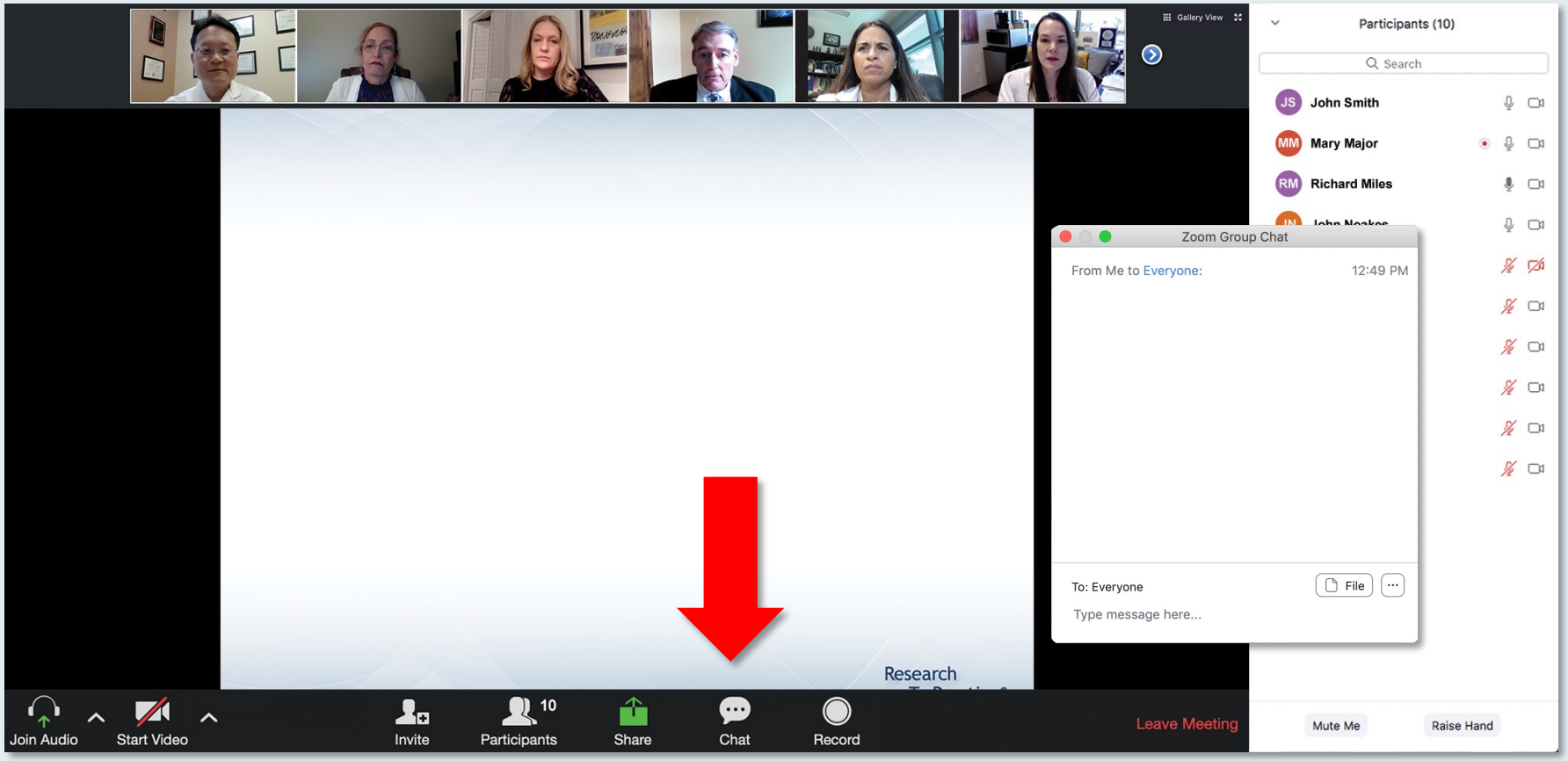
We Encourage Clinicians in Practice to Submit Questions



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

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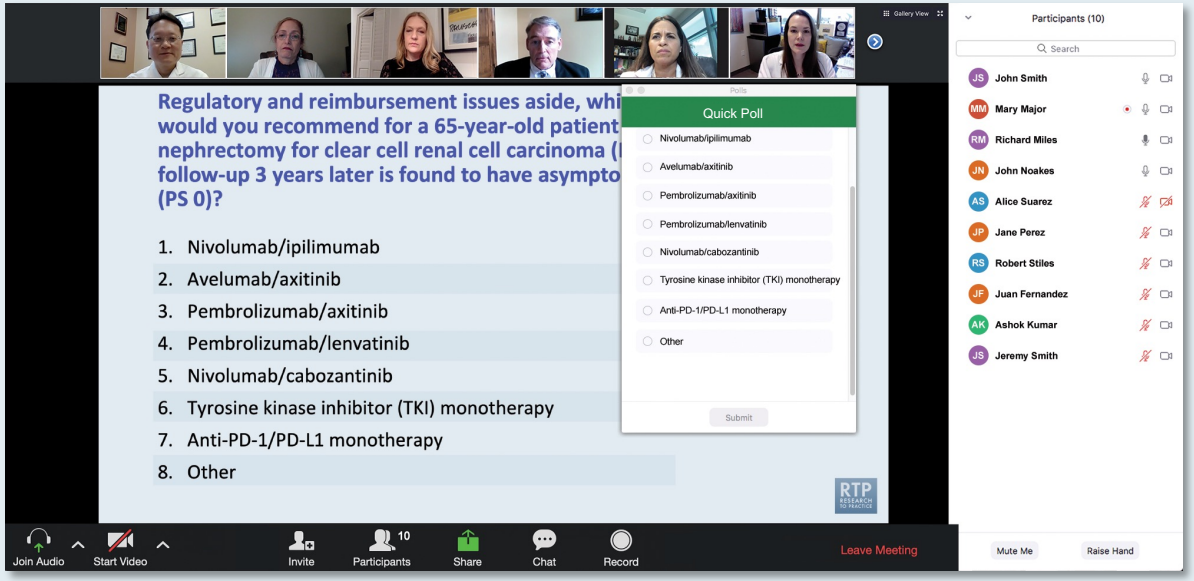

ONCOLOGY TODAY

WITH DR NEIL LOVE

Practical Perspectives: Investigators Discuss Current Management and Actual Cases of Relapsed/Refractory Metastatic Colorectal Cancer

DR KRISTEN CIOMBOR
VANDERBILT-INGRAM CANCER CENTER

DR J RANDOLPH HECHT
UCLA DAVID GEFFEN SCHOOL OF MEDICINE

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Prostate Cancer

Wednesday, March 6, 2024
5:00 PM – 6:00 PM ET

Faculty

Andrew J Armstrong, MD, ScM

Maha Hussain, MD, FACP, FASCO

Moderator

Neil Love, MD

RTP Year in Review 2024

Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Ovarian Cancer

Part 1 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer®

Monday, March 18, 2024

6:30 AM – 8:00 AM PT (9:30 AM – 11:00 AM ET)

Faculty

Joyce F Liu, MD, MPH

Mansoor Raza Mirza, MD

David M O'Malley, MD

Moderator

Kathleen N Moore, MD, MS

RTP RESEARCH TO PRACTICE

Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Endometrial Cancer

Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer®

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Matthew A Powell, MD

Brian M Slomovitz, MD

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Shannon N Westin, MD, MPH, FASCO, FACOG

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MARCH 22-24, 2024

JW Marriott Miami Turnberry

To Learn More or to Register, Visit
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Meet The Professor

Optimizing the Management of Myelofibrosis

Wednesday, April 3, 2024
5:00 PM – 6:00 PM ET

Faculty

Ruben A Mesa, MD

Moderator

Neil Love, MD

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Agenda

INTRODUCTION: Year in Review on the Ground

MODULE 1: Treatment of HER2-Positive Colorectal Cancer (CRC)

MODULE 2: Immune Checkpoint Inhibitors for Microsatellite Instability-High CRC

MODULE 3: Other Key Issues

MODULE 4: Questions and Cases from the Community

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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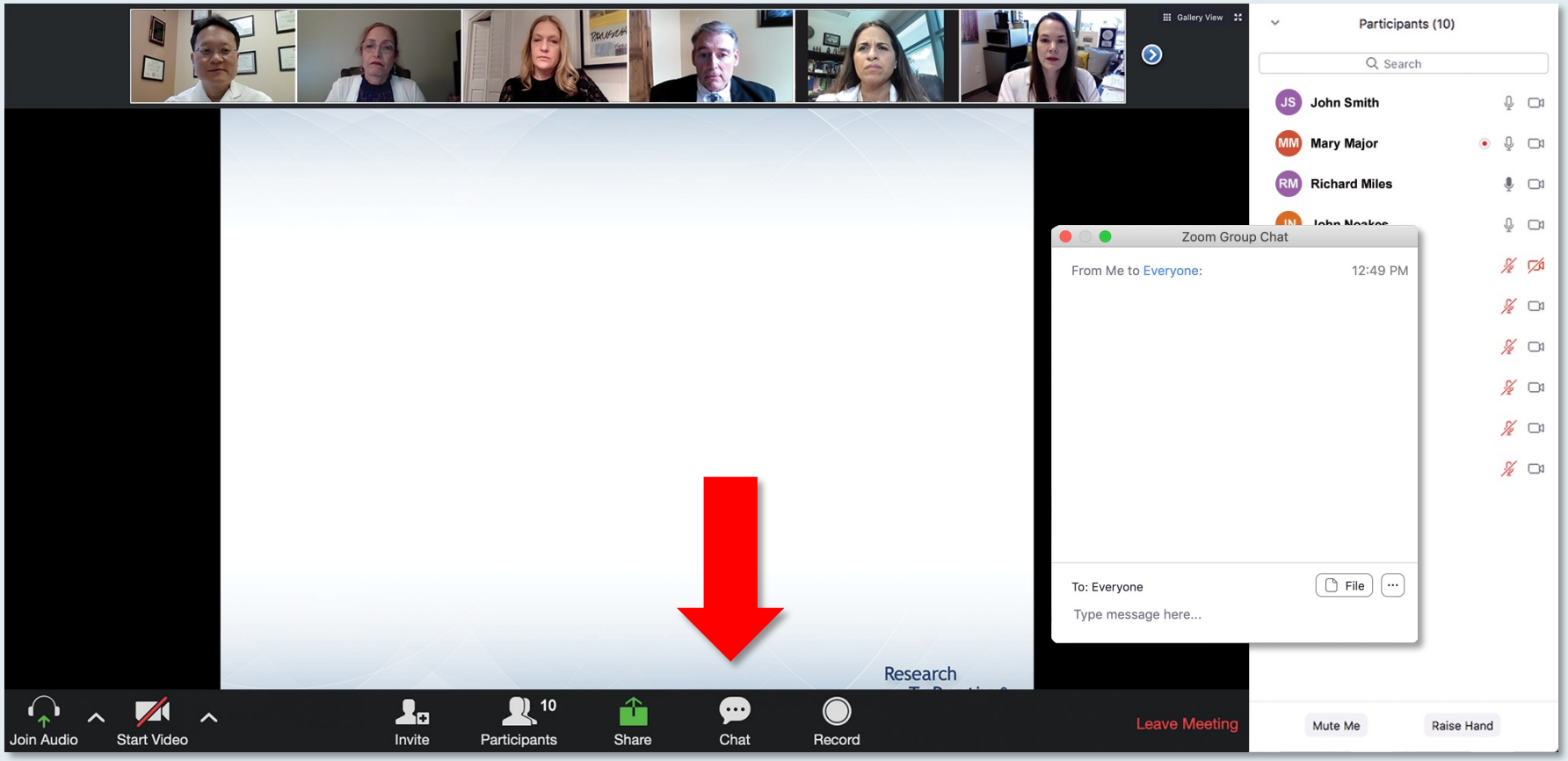

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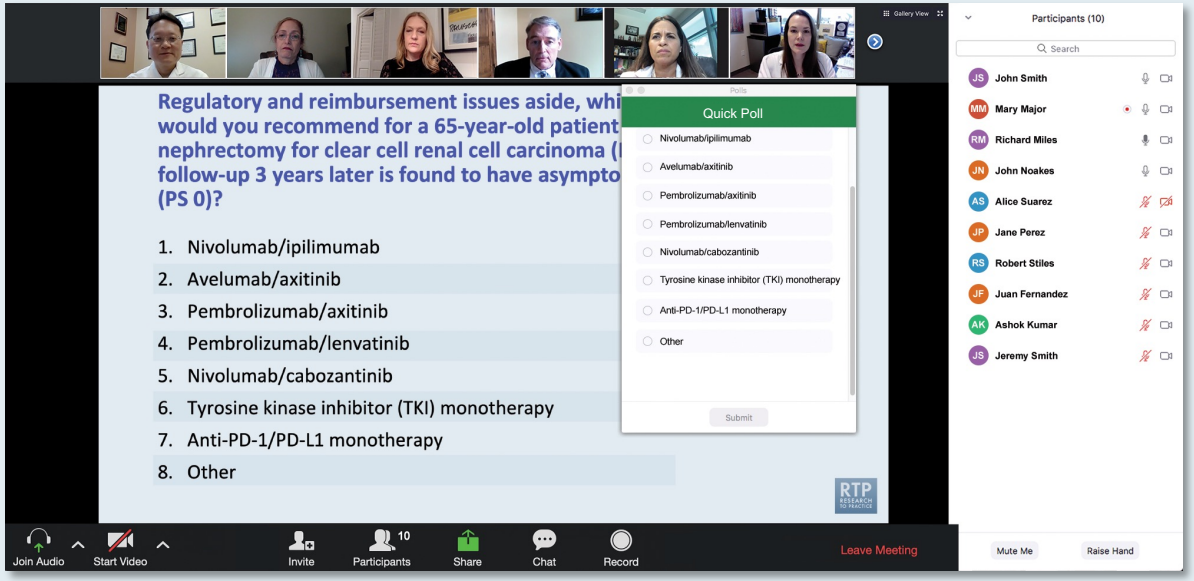

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Third Annual **National General Medical Oncology Summit**

Friday, March 22, 2024

6:30 PM – 7:00 PM

Welcome Reception

7:00 PM – 9:00 PM

Keynote Session: ER-Positive Metastatic Breast Cancer

Erika Hamilton, MD
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

Special Feature: Clinicians with Breast Cancer

Third Annual **National General Medical Oncology Summit**

Saturday, March 23, 2024

7:30 AM – 9:10 AM

Hodgkin and Non-Hodgkin Lymphoma

Ann S LaCasce, MD, MMSc
Matthew Lunning, DO
Kami Maddocks, MD
Andrew D Zelenetz, MD, PhD

9:30 AM – 10:20 AM

Gynecologic Cancers

Bradley J Monk, MD
David M O'Malley, MD

10:20 AM – 11:10 AM

Localized Breast Cancer; SABCS 2023 Review

Virginia Kaklamani, MD, DSc
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD

11:10 AM – 12:00 PM

Metastatic Breast Cancer, Triple-Negative Breast Cancer, HER2-Positive Breast Cancer; SABCS 2023 Review

Erika Hamilton, MD
Virginia Kaklamani, MD, DSc
Hope S Rugo, MD

Third Annual **National General Medical Oncology Summit**

Saturday, March 23, 2024

12:30 PM – 1:20 PM

Prostate Cancer

Emmanuel S Antonarakis, MD
Rana R McKay, MD

1:20 PM – 2:10 PM

Urothelial Bladder Cancer

Matthew D Galsky, MD
Jonathan E Rosenberg, MD

2:10 PM – 3:00 PM

Renal Cell Carcinoma

Eric Jonasch, MD
Brian Rini, MD

3:20 PM – 4:10 PM

Targeted Therapy for Non-Small Cell Lung Cancer

Ibiayi Dagogo-Jack, MD
Helena Yu, MD

4:10 PM – 5:00 PM

Nontargeted Treatments for Lung Cancer

Edward B Garon, MD, MS
Corey J Langer, MD

Third Annual **National General Medical Oncology Summit**

Sunday, March 24, 2024

7:30 AM – 8:20 AM

Multiple Myeloma

Natalie S Callander, MD
Paul G Richardson, MD

8:20 AM – 9:10 AM

Gastroesophageal Cancers

Yelena Y Janjigian, MD
Samuel J Klempner, MD

9:30 AM – 10:20 AM

Hepatobiliary Cancers

Ghassan Abou-Alfa, MD, MBA
Richard S Finn, MD

10:20 AM – 11:10 AM

Colorectal Cancer

Kristen K Ciombor, MD, MSCI
John Strickler, MD

11:10 AM – 12:00 PM

Pancreatic Cancer

Andrew H Ko, MD
Eileen M O'Reilly, MD

Meet The Professor

Optimizing the Management of Myelofibrosis

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Prof André — Disclosures

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Dr Dasari — Disclosures

Advisory Committee	HUTCHMED, Illumina, Personalis, Takeda Pharmaceuticals USA Inc
Contracted Research	Eisai Inc, Enterome, Guardant Health, HUTCHMED, Xencor

Targeted Treatment Approaches for Colorectal Cancer (CRC)

Thierry André
Service d'Oncologie Médicale
Et unité INSERM UMRS 938

Sorbonne Université
Hôpital Saint Antoine

Other Considerations in the Management of CRC

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

Key Data Sets

Professor Thierry André, MD

- Ludford K et al. **Neoadjuvant pembrolizumab** in localized **microsatellite instability high/deficient mismatch repair** solid tumors. *J Clin Oncol* 2023;41(12):2181-90.
- Verschoor YL et al. **Neoadjuvant nivolumab plus relatlimab** (anti-LAG3) in locally advanced **MMR-deficient colon cancers**: The NICHE-3 study. ESMO 2023;Abstract LBA31.
- Shiu KK et al. **Pembrolizumab** versus chemotherapy in microsatellite instability-high **(MSI-H)**/mismatch repair-deficient **(dMMR)** metastatic colorectal cancer **(mCRC)**: **5-year follow-up** of the randomized phase III **KEYNOTE-177** study. ESMO 2023;Abstract LBA32.
- Andre T 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**): First results of the **CheckMate 8HW** study. Gastrointestinal Cancers Symposium 2024;Abstract LBA768.
- Lenz HJ et al. **First-line (1L) nivolumab (NIVO) + ipilimumab (IPI)** in patients (pts) with microsatellite instability-high/mismatch repair deficient (**MSI-H/dMMR**) metastatic colorectal cancer (**mCRC**): 64-month (mo) follow-up from **CheckMate 142**. Gastrointestinal Cancers Symposium 2024;Abstract 97.

Key Data Sets

Professor Thierry André, MD

- Taieb J et al. **Adverse events** associated with **encorafenib plus cetuximab** in patients with **BRAFV600E-mutant metastatic colorectal cancer**: An in-depth analysis of the **BEACON CRC study**. Clin Colorectal Cancer 2023;22(1):59-66.
- Van Cutsem E et al. **ANCHOR CRC**: Results from a single-arm, phase II study of **encorafenib plus binimetinib and cetuximab** in **previously untreated BRAFV600E-mutant** metastatic colorectal cancer. *J Clin Oncol* 2023;41(14):2628-37.
- Strickler JH et al. **Tucatinib plus trastuzumab** for chemotherapy-refractory, **HER2-positive**, RAS wild-type unresectable or metastatic colorectal cancer (**MOUNTAINEER**): A multicentre, open-label, phase 2 study. *Lancet Oncol* 2023;24(5):496-508.
- Strickler JH et al. **HER2 testing** in the **MOUNTAINEER** trial: Analysis of treatment response based on central HER2 assessment using IHC/ISH and NGS. ASCO 2023;Abstract 3528.
- Yoshino T et al. **Final results** of **DESTINY-CRC01** investigating **trastuzumab deruxtecan** in patients with HER2-expressing metastatic colorectal cancer. *Nat Commun* 2023;14(1):3332.

Key Data Sets

Professor Thierry André, MD

- Raghav KPS et al. **Trastuzumab deruxtecan (T-DXd)** in patients (pts) with **HER2-overexpressing/amplified (HER2+)** metastatic colorectal cancer (mCRC): **Primary results** from the multicenter, randomized, phase 2 **DESTINY-CRC02** study. ASCO 2023;Abstract 3501.
- Fakih MG et al. **Sotorasib plus panitumumab** in refractory colorectal cancer with **mutated KRAS G12C**. *N Engl J Med* 2023;389(23):2125-39.
- Yaeger R et al. **Adagrasib with or without cetuximab** in colorectal cancer with **mutated KRAS G12C**. *N Engl J Med* 2023;388(1):44-54.

Key Data Sets

Arvind Dasari, MD, MS

- Jensen LH et al. **Phase III** randomized clinical trial comparing the efficacy of **neoadjuvant chemotherapy and standard treatment** in patients with locally advanced colon cancer: The NeoCol trial. ASCO 2023;Abstract LBA3503.
- Schrag D et al. **Preoperative treatment** of **locally advanced rectal cancer**. *N Engl J Med* 2023;389(4):322-34.
- Dasari A et al. Association of **positive ctDNA-based minimal residual disease assays** during surveillance and **undiagnosed concomitant radiographic recurrences** in colorectal cancer (CRC): Results from the MD Anderson **INTERCEPT program**. ASCO 2023;Abstract 3522.
- Yukami H et al. **Circulating tumor DNA (ctDNA) dynamics** in patients with colorectal cancer (CRC) with molecular residual disease: **Updated analysis from GALAXY study** in the CIRCULATE-JAPAN. Gastrointestinal Cancers Symposium 2024;Abstract 6.
- Kasi PM et al. **Circulating tumor DNA (ctDNA)** for informing **adjuvant chemotherapy** (ACT) in stage II/III colorectal cancer (CRC): Interim analysis of **BESPOKE CRC study**. Gastrointestinal Cancers Symposium 2024;Abstract 9.

Key Data Sets

Arvind Dasari, MD, MS

- Watanabe J et al. **Panitumumab** vs bevacizumab **added to standard first-line chemotherapy** and overall survival among patients with RAS wild-type, **left-sided metastatic colorectal cancer**: A randomized clinical trial. *JAMA* 2023;329(15):1271-82.
- Yamazaki K et al. Efficacy of **panitumumab in patients with left-sided disease**, MSS/MSI-L, and RAS/BRAF WT: A **biomarker study** of the phase III **PARADIGM** trial. ASCO 2023;Abstract 3508.
- Raghav K et al. **Acquired genomic alterations** on **first-line chemotherapy with cetuximab** in advanced colorectal cancer: **Circulating tumor DNA analysis** of the **CALGB/SWOG-80405** trial (Alliance). *J Clin Oncol* 2023;41(3):472-8.
- Ciardiello D et al. **Rechallenge with EGFR inhibitors** in ctDNA RAS/BRAF wild type refractory metastatic colorectal cancer: Individual patients' data **pooled analysis from 4 phase II trials**. ESMO 2023;Abstract 559MO.

Key Data Sets

Arvind Dasari, MD, MS

- Prager GW et al. **Trifluridine-tipiracil and bevacizumab** in refractory **metastatic colorectal cancer**. *N Engl J Med* 2023;388(18):1657-67.
- Taieb J et al. Effect of **trifluridine/tipiracil in combination with bevacizumab on ECOG-PS** in refractory metastatic colorectal cancer: An **analysis of the phase 3 SUNLIGHT** trial. ASCO 2023;Abstract 3594.
- Dasari A et al. **Fruquintinib** versus placebo in patients with **refractory metastatic colorectal cancer (FRESCO-2)**: An international, multicentre, randomised, double-blind, **phase 3 study**. *Lancet* 2023;402(10395):41-53.
- Dasari A et al. **Subgroup analyses** of safety and efficacy **by number and types of prior lines of treatment** in **FRESCO-2**, a global phase III study of **fruquintinib** in patients with refractory metastatic colorectal cancer. ASCO 2023;Abstract 3604.

Agenda

INTRODUCTION: Year in Review on the Ground

MODULE 1: Treatment of HER2-Positive Colorectal Cancer (CRC)

MODULE 2: Immune Checkpoint Inhibitors for Microsatellite Instability-High CRC

MODULE 3: Other Key Issues

MODULE 4: Questions and Cases from the Community

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Key Global Issues in Colorectal Cancer

- **Biomarker-based systemic treatment strategy – what is most important to know practically?**

- **Uncommon (MSI-high, HER2-positive) cases/better outcomes (non-small cell lung cancer)?**
  What is the incidence? What is the optimal approach to testing? Which biomarkers should be tested?

Please provide an impediment or barrier you have encountered in your attempts to deliver high-quality care to your patients with CRC.

- I think that we should stop chasing these mutations since there are no good drugs that exist and they are so rare. We just need new good medications to treat colon cancer. Nothing new has been discovered since oxaliplatin came on the market way over 10 years ago...

Agenda

INTRODUCTION: Year in Review on the Ground

MODULE 1: Treatment of HER2-Positive Metastatic Colorectal Cancer (CRC)

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HER2-Positive Colorectal Cancer

- Strickler JH et al. **Tucatinib plus trastuzumab** for chemotherapy-refractory, **HER2-positive**, RAS wild-type unresectable or metastatic colorectal cancer (**MOUNTAINEER**): A multicentre, open-label, phase 2 study. *Lancet Oncol* 2023;24(5):496-508.
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Frequently Asked Clinical Questions About Colorectal Cancer

- What type of HER2 testing do you order and when?
- Which patients with CRC should undergo HER2 testing?
- At what point do you integrate HER2-targeted agents into the treatment algorithm?

Frequently Asked Clinical Questions About Colorectal Cancer

- What is known about the efficacy and tolerability of the MOUNTAINEER (tucatinib/trastuzumab) regimen?
- How do you manage the GI toxicity associated with the MOUNTAINEER regimen?
- What anti-HER2 strategy would you most likely use for a patient with brain metastases?

Frequently Asked Clinical Questions About Colorectal Cancer

- What is known about the efficacy and tolerability of trastuzumab deruxtecan, including acute GI toxicity?
- What is the incidence of interstitial lung disease associated with trastuzumab deruxtecan? How do you monitor patients?
- If a patient has recovered from ILD, would you re-treat with trastuzumab deruxtecan?

Frequently Asked Clinical Questions About Colorectal Cancer

- At what point, if any, should HER2 testing be repeated?
- How do you sequence anti-HER2 agents?

Tucatinib plus trastuzumab for chemotherapy-refractory, HER2-positive, RAS wild-type unresectable or mCRC (MOUNTAINEER): A multicentre, open-label, phase 2 study (1)

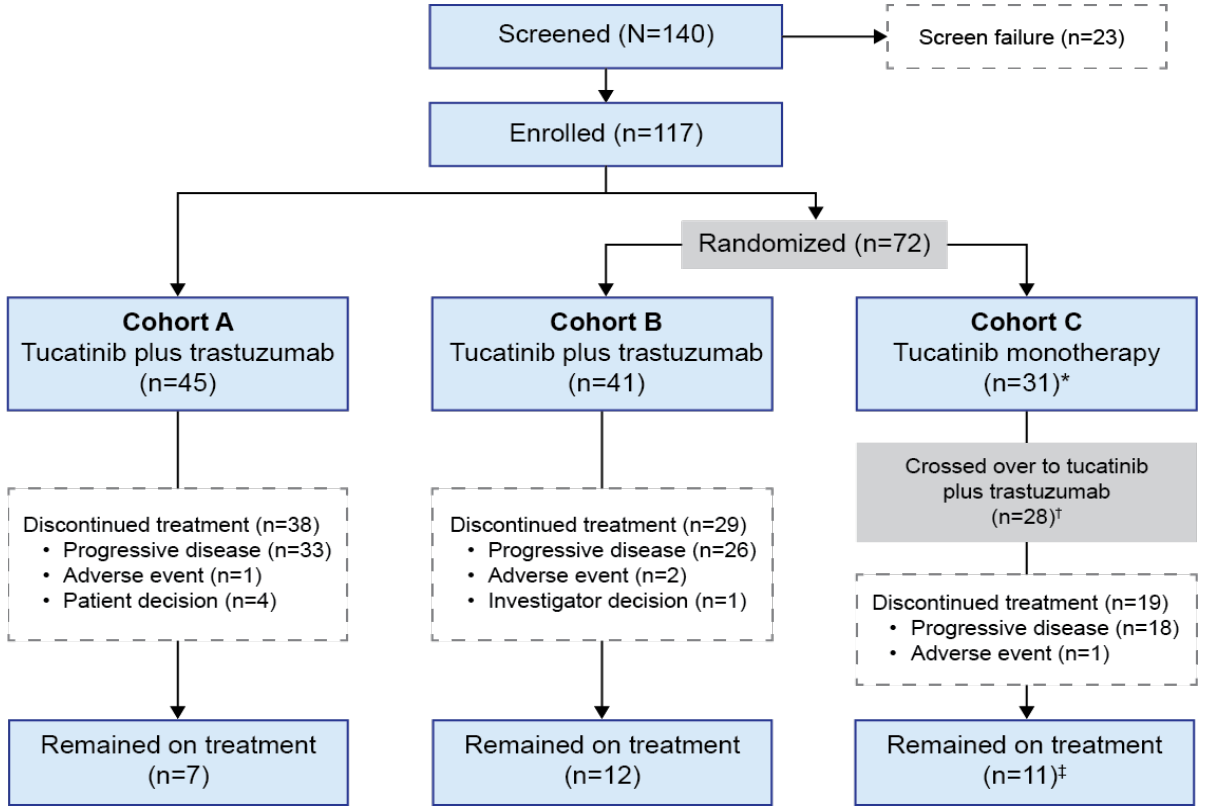
- HER2 status: local determination

Eligible patients: if IHC+++ or IHC++ and FISH+,
or amplification by next-generation sequencing (NGS)

- Inclusion criteria: mCRC HER2 over expressed, *RAS* wild-type, patients previously treated with fluoropyrimidines, oxaliplatin, irinotecan, a VEGF monoclonal antibody, and anti-PD-1 if MSI-H

- 117 patients included

- Previous lines of systemic therapy median :3

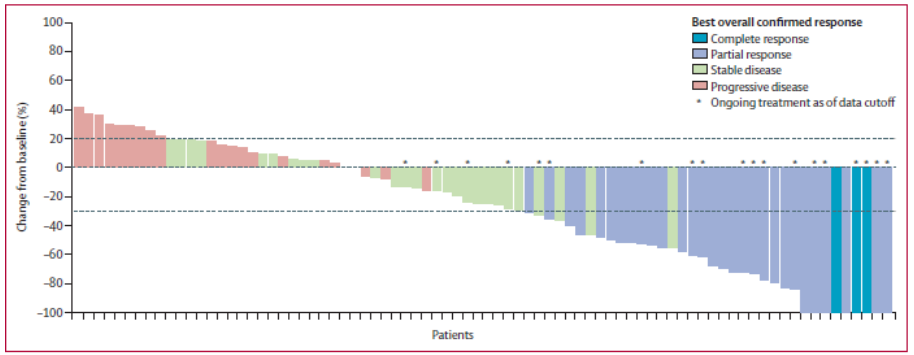


Courtesy of Thierry André, MD

Strickler JH et al. Lancet Oncol 2023;24(5):496-508.

Tucatinib plus trastuzumab for chemotherapy-refractory, HER2-positive, RAS wild-type unresectable or mCRC (MOUNTAINEER): A multicentre, open-label, phase 2 study (2)

Response	Tucatinib + Trastuzumab (N = 84)
Confirmed objective response rate* — % (95% CI)	38·1 (27·7–49·3)
Complete response — no. (%)†	3 (3·6)
Partial response — no. (%)†	29 (34·5)
Stable disease — no. (%)†,‡	28 (33·3)
Progressive disease — no. (%)†	22 (26·2)
Not available — no. (%)§	2 (2·4)
Disease control rate — n (%)	60 (71·4)
Duration of response, months — median (IQR)	12·4 (8·3–25·5)



- In combination arm median PFS per BICR was 8.2 months (IQR 2.1–18.4), and median OS was 24.1 months (IQR 10·5–not achieved).
- The objective response per BICR by week 12 with monotherapy (n = 31) : 3% (95% CI 0.1–17.2).
- The most common treatment-emergent adverse events with tucatinib+trastuzumab were diarrhoea (64% all; 3.5% grade 3-4), fatigue (44%; 2.3% grade 3-4), and nausea (35%; 0 % grade3-4). There were no deaths due to adverse events.

Strickler JH et al. Lancet Oncol 2023;24(5):496-508.

Courtesy of Thierry André, MD

HER2 testing in the MOUNTAINEER trial: Analysis of treatment response based on central HER2 assessment using IHC/ISH and NGS

- Treatment response to Tucatinib + Trastuzumab was predicted by a HER2+ result from any of the three testing platforms (IHC, NGS tissue-based assay or NGS blood ctDNA)
- High level of percent agreement of HER2 status observed across multiple central HER2 testing modalities (all cohorts included; pairwise comparisons)
- Patients in which HER2 amplification was not detected by ctDNA NGS may have HER2 amplification by a tissue-based assay and may benefit from treatment with a HER2-directed therapy
- Confirmed ORR in IHC2+/ISH+ was numerically lower than IHC3+

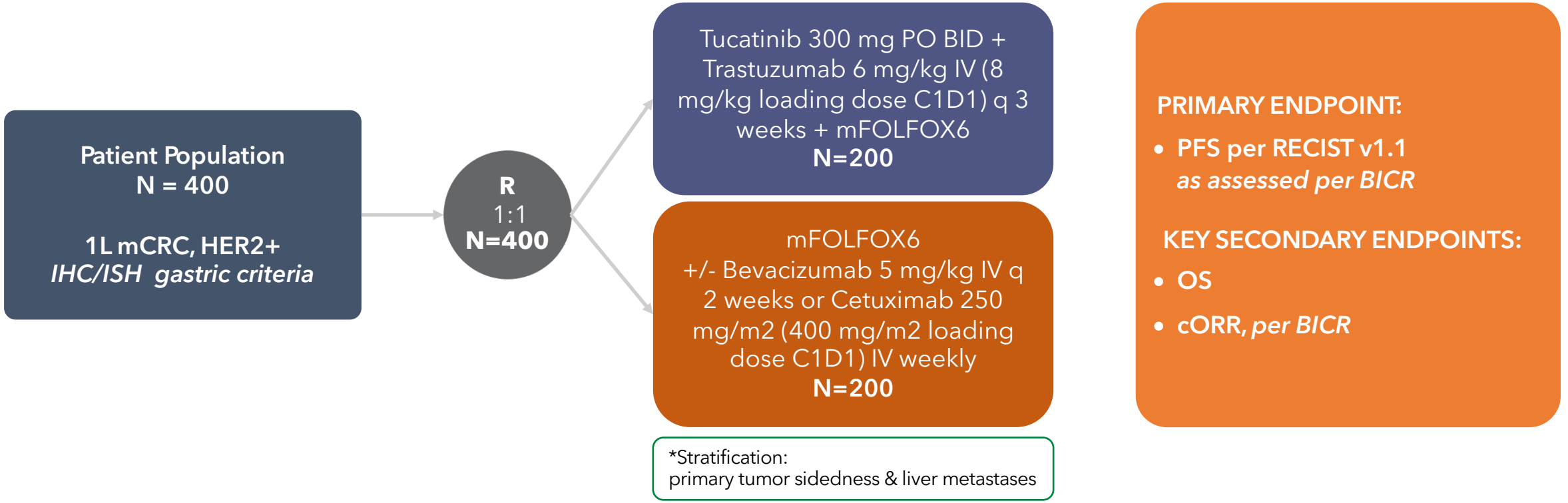
Response	Central IHC + FISH (n=70)		
	Positive (IHC3+) (n=45)	Positive (IHC2+/ISH+) (n=15)	Negative (n=10)
CR	3	0	0
PR	18	3	1
SD[a]	17	5	4
PD	7	6	5
NA	0	1	0
cORR, n (%) (95% CI)	21 (46.7%) (31.7, 62.1)	3 (20.0%) (4.3, 48.1)	1 (10.0%) (0.3, 44.5)
mDOR, months (95% CI)	16.4 (10.6, 25.5)		-
mPFS, months (95% CI)	10.1 (4.2, 15.2)		2.8 (1.2, 6.3)

[a]Includes non-CR/non-PD

Courtesy of Thierry André, MD

Strickler JH et al. ASCO 2023;Abstract 3528.

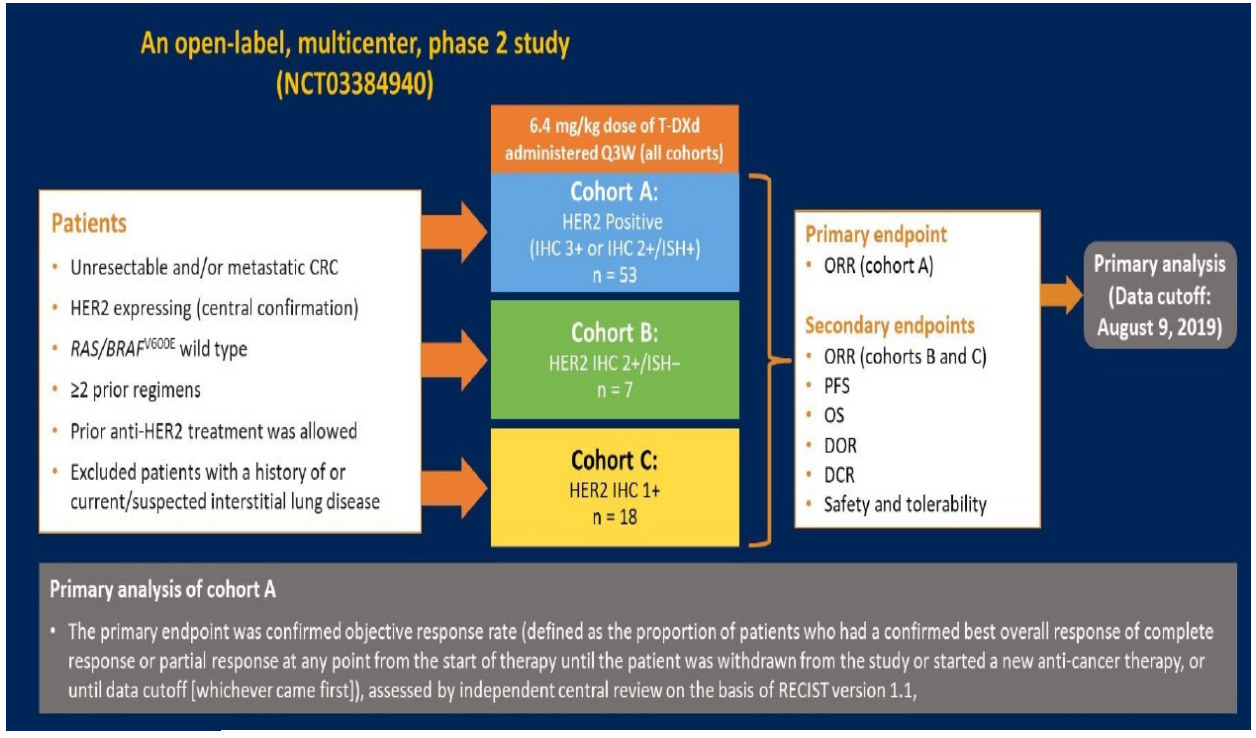
MOUNTAINEER-03 Study design (study ongoing)

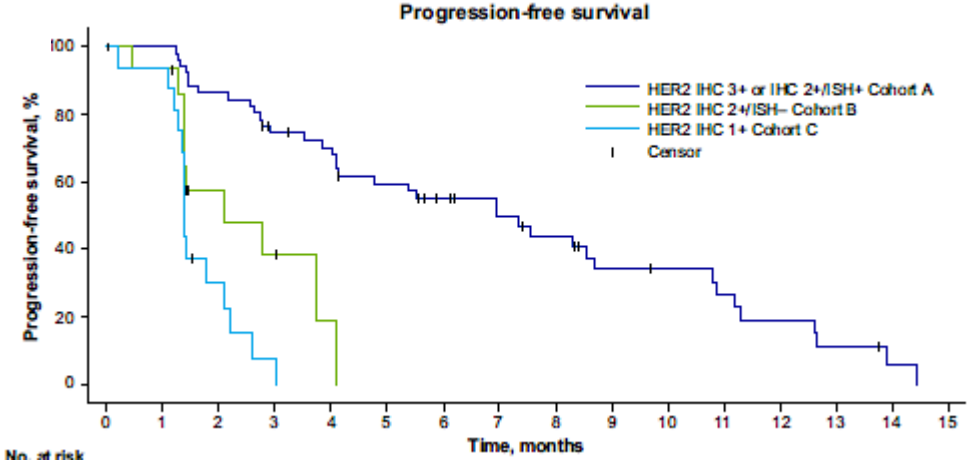


BICR, blinded independent central review; ISH, in situ hybridization; HER2+, HER2 gene amplification; IHC, immunohistochemistry; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; BID, bis in die; C1D1, cycle 1 day 1; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Courtesy of Thierry André, MD

Final results of DESTINY-CRC01 investigating trastuzumab deruxtecan in patients with HER2-expressing mCRC



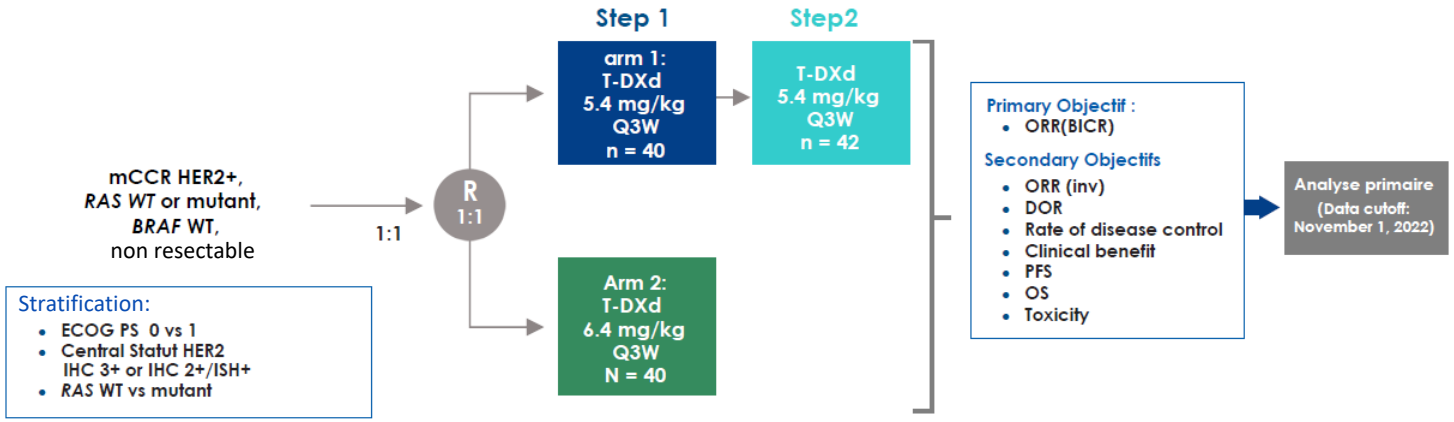


- 86 patients were enrolled (53 in cohort A, 15 in cohort B, and 18 in cohort C)
- ORR of 45.3% in cohort A
- No responses occurred in cohorts B or C
- In cohort A median PFS: 6.9 months and median OS: 15.5 months
- Most common grade ≥3: decreased neutrophil count and anemia
- Interstitial lung disease/pneumonitis: 8 patients (9.3%)
- These findings support the continued exploration of T-DXd in HER2-positive mCRC

Yoshino T et al. Nat Commun 2023;14(1):3332.

Courtesy of Thierry André, MD

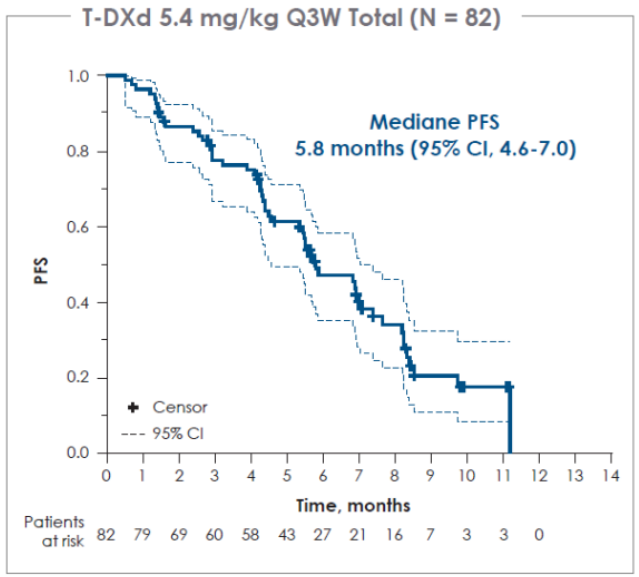
Trastuzumab deruxtecan (T-DXd) in patients with HER2+ mCR: Primary results from the randomized, phase 2 DESTINY-CRC02 study (1)

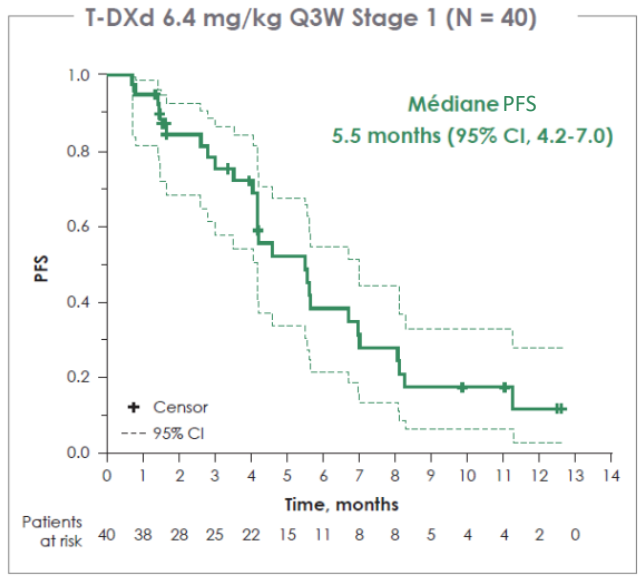


Non comparative.

	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	**18 (45.0)**	**13 (31.0)**	**31 (37.8)**	**11 (25)**
(%) 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)

PFS by BICR



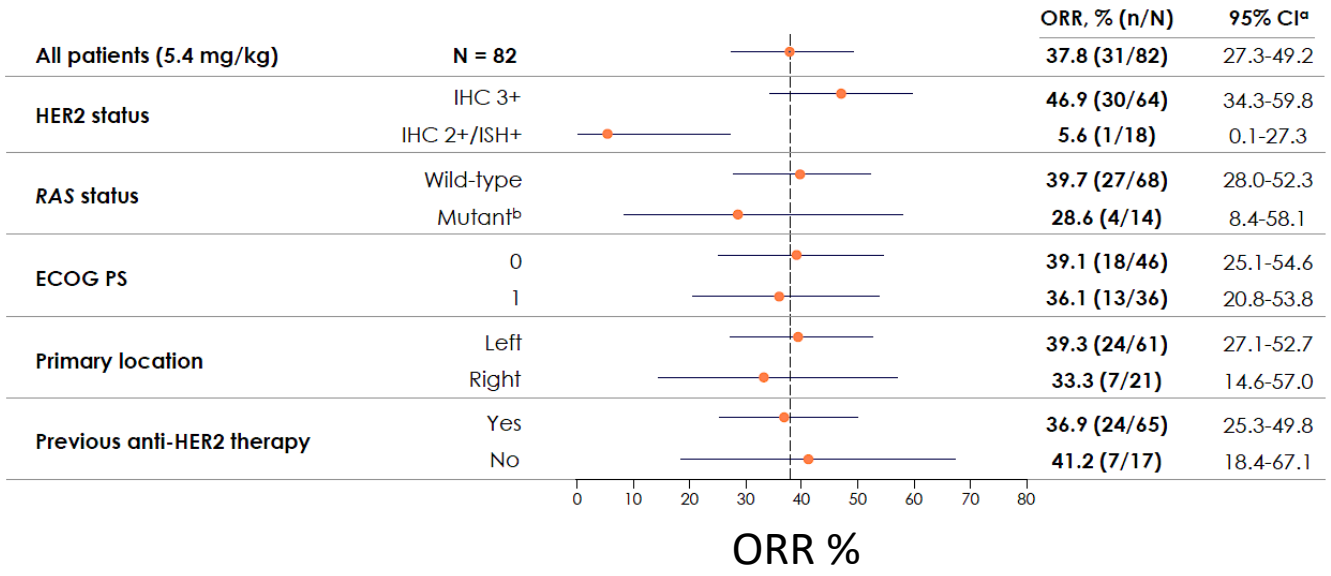


Courtesy of Thierry André, MD

Raghav KPS et al. ASCO 2023;Abstract 3501.

Trastuzumab deruxtecan (T-DXd) in patients with HER2+ mCR: Primary results from the randomized, phase 2 DESTINY-CRC02 study (2)

Response for subgroup with T-DXd 5.4 mg/kg



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)

Conclusion DESTINY-CRC02

- Good anti-tumor efficacy of T-DXd
- Better response rate in IHC3+ patients
- Good efficacy of low dose with less pulmonary toxicity
- Maintained efficacy if already treated with antiHER2 and mutated RAS
- ***5.4 mg/kg/d every 21 days: new standard dose***

Courtesy of Thierry André, MD

Raghav KPS et al. ASCO 2023;Abstract 3501.

Agenda

INTRODUCTION: Year in Review on the Ground

MODULE 1: Treatment of HER2-Positive Metastatic Colorectal Cancer (CRC)

MODULE 2: Immune Checkpoint Inhibitors for Microsatellite Instability-High CRC

MODULE 3: Other Key Issues

MODULE 4: Questions and Cases from the Community

Immunotherapy for Localized and Metastatic Colorectal Cancer

- Ludford K et al. **Neoadjuvant pembrolizumab** in localized **microsatellite instability high/deficient mismatch repair** solid tumors. *J Clin Oncol* 2023;41(12):2181-90.
- Verschoor YL et al. **Neoadjuvant nivolumab plus relatlimab** (anti-LAG3) in locally advanced **MMR-deficient colon cancers**: The NICHE-3 study. ESMO 2023;Abstract LBA31.
- Andre T 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**): First results of the **CheckMate 8HW** study. Gastrointestinal Cancers Symposium 2024;Abstract LBA768.
- Lenz HJ et al. **First-line (1L) nivolumab (NIVO) + ipilimumab (IPI)** in patients (pts) with microsatellite instability-high/mismatch repair deficient (**MSI-H/dMMR**) metastatic colorectal cancer (**mCRC**): 64-month (mo) follow-up from **CheckMate 142**. Gastrointestinal Cancers Symposium 2024;Abstract 97.
- Shiu KK et al. **Pembrolizumab** versus chemotherapy in microsatellite instability-high **(MSI-H)**/mismatch repair-deficient **(dMMR)** metastatic colorectal cancer **(mCRC)**: **5-year follow-up** of the randomized phase III **KEYNOTE-177** study. ESMO 2023;Abstract LBA32.

Frequently Asked Clinical Questions About Colorectal Cancer

- What type of PD-L1/microsatellite instability (MSI) testing do you order and when?
- Which patients should be considered for neoadjuvant or adjuvant immunotherapy?
- What is the optimal first-line treatment for MSI-high metastatic CRC?

Frequently Asked Clinical Questions About Colorectal Cancer

- In what situations should combination anti-CTLA-4 and anti-PD-1/PD-L1 antibodies be used? What about chemotherapy in combination with anti-PD-1/PD-L1?

- For a patient with MSI-high mCRC who is experiencing disease progression on anti-PD-1 therapy alone, would you consider switching to combination immunotherapy?

Frequently Asked Clinical Questions About Colorectal Cancer

- What is known about the efficacy and tolerability of anti-PD-1/PD-L1 in combination with anti-LAG3?
- What are the relative and absolute contraindications to treatment with immunotherapy?
- How to you approach the monitoring and management of immune-related toxicities?

Questions from General Medical Oncologists

- **I have a 57-year-old man with HNPCC and BRAF-mutated CRC. Would you opt for first-line IO or chemo prior to BRAF targeted therapy?**

Tumor types	
Colon adenocarcinoma	19 (54)
Rectal adenocarcinoma	8 (23)
Pancreatic adenocarcinoma	2 (6)
Duodenal adenocarcinoma	2 (6)
Other[a]	4 (11)

Neoadjuvant Pembrolizumab in Localized Microsatellite Instability High/Deficient Mismatch Repair Solid Tumors (1)

- 35 pts: 19 colon, 8 rectum and 8 others various types tumors at MD Anderson

- 17 pts (49%) with surgery (median of 3 pembrolizumab inj before surgery)
  - 15 patients evaluable for pathological response after 3 cycles: 10 are in cPR
  - 2 patients evaluable for pathological response after 1 or 2 cycles: one in cPR
  - Six of 17 surgically resected patients did not demonstrate a pCR
  - 11 patients on 17 with cPR (65%)

- 18 pts (51%)
  - 10 received one year of pembrolizumab without PD
  - 5 received less than 1 year: 3 are in CR radiographic or endoscopic response and 2 were with SD

Courtesy of Thierry André, MD

Ludford K et al. J Clin Oncol 2023;41(12):2181-90.

Neoadjuvant Pembrolizumab in Localized Microsatellite Instability High/Deficient Mismatch Repair Solid Tumors (2)

- During the study course and subsequent follow-up, progression events were seen in 6 patients.
  - 2 patients with pancreatic cancer with PD at 6 and 4 months, respectively
  - 2 colorectal patients with PD at 6 weeks
  - 2 other CRC patients
    with PD at 6 and 9 months following initial response of PR and SD, respectively

Proof of concept for locally un-resectable GI/CRC:

Growing body of evidence role of anti-PD1 antibody therapy in GI cancers dMMR/MSI-H, where deep and major pathologic responses are observed in a substantial majority of patients with localized disease.

But many questions:

How many cycles before surgery?

Watch and Wait approach possible for who? And in this case duration of treatment with pembrolizumab?

Predictive factor of efficacy?

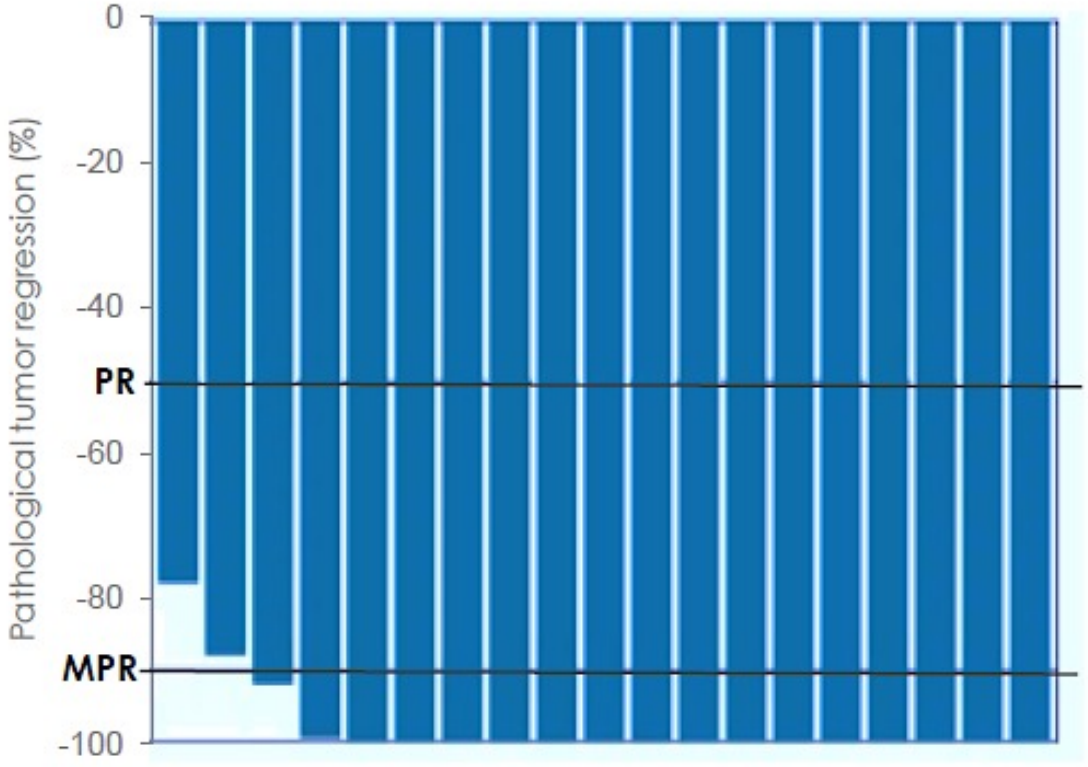
Courtesy of Thierry André, MD

Ludford K et al. J Clin Oncol 2023;41(12):2181-90.

Neoadjuvant nivolumab plus relatlimab (anti-LAG3) in locally advanced MMR-deficient colon cancers: The NICHE-3 study (1)

Nivolumab d1-d15 & relatlimab (anti-LAG3) d1, Surgery 6 weeks after (n=19)

Characteristics	n=19
Age, median (range)	**56 (36-85)**
Sex female	**10 (53%)**
ECOG PS 0 1	 **14 (74%)** **5 (26%)**
Radiologic Stage T (cT) T2 T3 T4	 **1 (5%)** **11 (58%)** **7 (37%)**
Radiologic Stage N (cN) N- N+	 **5 (26%)** **14 (74%)**
Localisation Right Colon Left Colon	 **16 (84%)** **3 (16%)**
Lynch syndrome	**5 (26%)**



Verschoor YL et al. ESMO 2023;Abstract LBA31

Courtesy of Thierry André, MD

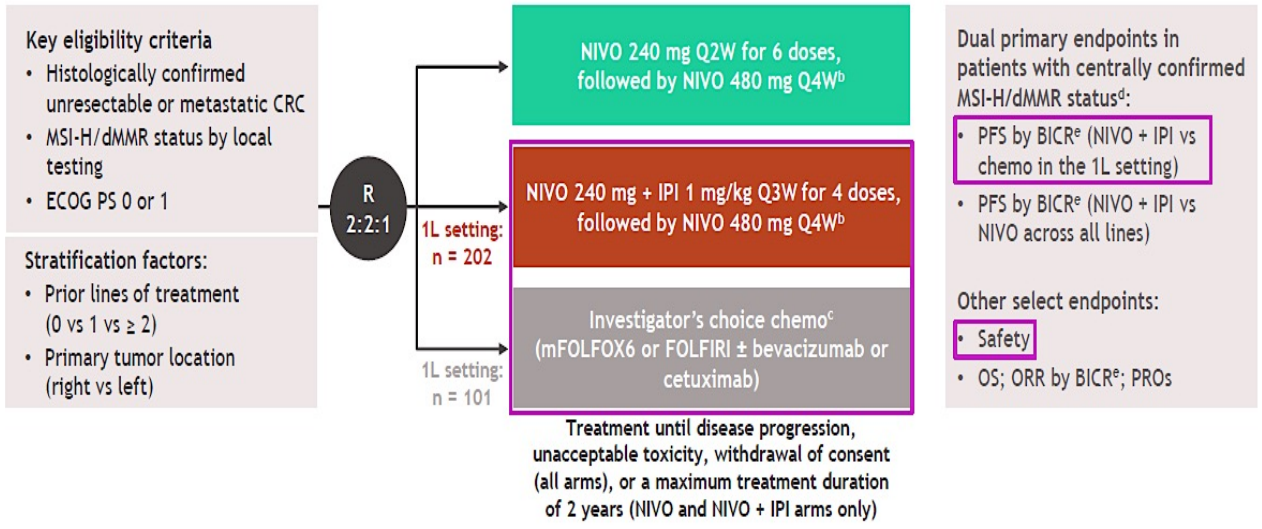
Neoadjuvant nivolumab plus relatlimab (anti-LAG3) in locally advanced MMR-deficient colon cancers: The NICHE-3 study (2)

Pathologic Response Residual Viable Tumor	Niche 1-2 n=107 MSI/dMMR	Niche 3 n=19 MSI/dMMR	Toripalimab n=34 MSI/dMMR	Niche 1 n=22 MSS/pMMR
Yes (≤ 50%)	106 (99%)	19 (100%)	19 (100%)	5 (22.7%)
Complete (0%)	**72 (67%)**	**15 (79%)**	**26 (76%)**	**2 (9%)**
Major but not complete (≤ 10%)	36 (38%)	2 (10%)	6 (16%)	2 (9%)
Partial (10%-50%)	4 (4%)	2 (11%)	0	1 (4.5%)
No or minor (> 50%) or NE	1 (1%)	0	2 (8%)	17 (77%)

Verschoor YL et al., ESMO 2023;Abstract LBA31; Chalabi, Nature Med 2020; Chalabi M et al., ESMO 2022 abstr. LBA7; Hu, Lancet Gastro & Hep 2021

Courtesy of Thierry André, MD

Nivolumab plus ipilimumab vs chemotherapy as first-line treatment for MSI-H/dMMR mCRC: First results of the CheckMate 8HW study (1)



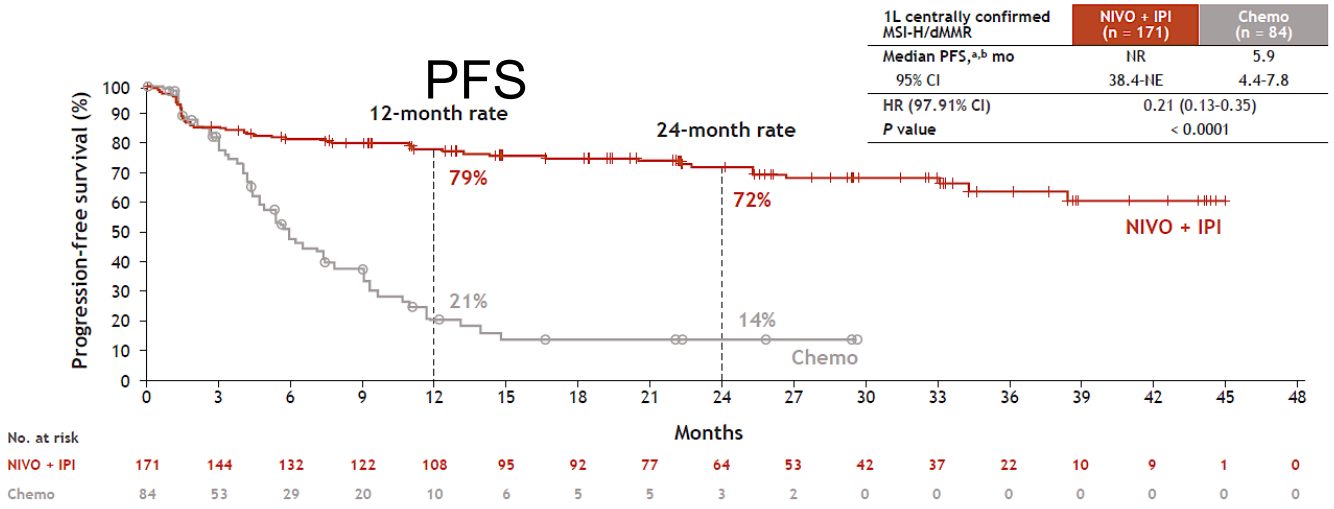
At data cutoff (October 12, 2023), the median follow-up[f] was 24.3 months

Characteristic (1L all randomized patients)	Category	NIVO + IPI (n = 202)	Chemo (n = 101)
Age	Median (range), years	62 (21–86)	65 (26–87)
	< 65 years	58	46
Sex	Male	47	45
Region	US/Canada/Europe	66	70
	Asia	9	11
	Rest of world	25	19
ECOG PS	0	55	51
Disease stage at initial diagnosis	Stage IV	42	49
Tumor sidedness	Right	68	67
Sites of metastases[a,b]	Liver	38	42
	Lung	22	25
	Peritoneum	42	43
Centrally confirmed MSI-H/dMMR status	Yes	85	83
	No	15	17
Tumor cell PD-L1[c,d]	< 1%	72	79
	≥ 1%	21	12
***BRAF, KRAS, NRAS* mutation status[d,e]**	*BRAF/KRAS/NRAS* all wild-type	23	23
	BRAF mutant	26	24
	KRAS or *NRAS* mutant	21	21
	Unknown	27	31
Clinical history of Lynch syndrome[d,f]	Yes	11	17
	No	67	49
	Reported as unknown	22	30

Courtesy of Thierry André, MD

Andre T et al. Gastrointestinal Cancers Symposium 2024;Abstract LBA768.

Nivolumab plus ipilimumab vs chemotherapy as first-line treatment for MSI-H/dMMR mCRC: First results of the CheckMate 8HW study (2)

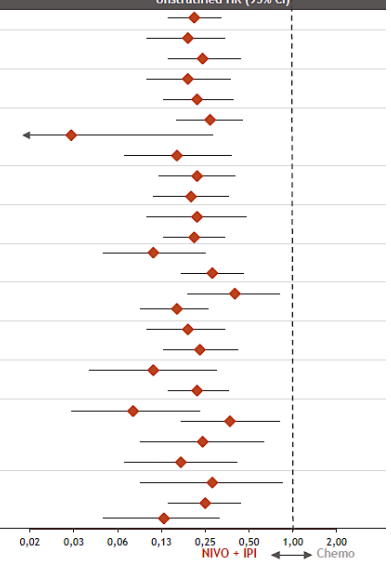


1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.4-7.8
HR (97.91% CI)	0.21 (0.13-0.35)	
P value	< 0.0001	

- PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity analyses, including PFS by BICR in 1L all randomized patients (HR 0.32; 95% CI, 0.23-0.46)

Category (1L centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] mo NIVO + IPI	Median PFS,[a] mo Chemo	Unstratified HR
Overall (N = 255)		NR	5.9	0.21
Age, years	< 65 (n = 138)	NR	5.7	0.19
	≥ 65 (n = 117)	NR	5.9	0.24
Sex	Male (n = 117)	NR	5.9	0.19
	Female (n = 138)	NR	6.2	0.22
Region	US/Canada/Europe (n = 167)	NR	5.7	0.27
	Asia (n = 28)	NR	7.4	0.03
	Rest of world (n = 60)	NR	6.2	0.16
ECOG PS	0 (n = 142)	NR	9.0	0.22
	≥ 1 (n = 113)	NR	4.2	0.20
Tumor sidedness	Left (n = 70)	NR	4.4	0.22
	Right (n = 185)	NR	7.1	0.21
Liver metastases[a]	Yes (n = 87)	NR	5.9	0.11
	No (n = 166)	NR	5.4	0.28
Lung metastases[a]	Yes (n = 53)	13.2	4.9	0.40
	No (n = 200)	NR	6.2	0.16
Peritoneal metastases[a]	Yes (n = 115)	NR	4.4	0.19
	No (n = 138)	NR	7.4	0.23
Tumor cell PD-L1 expression	≥ 1% (n = 55)	NR	3.4	0.11
	< 1% (n = 191)	NR	6.5	0.22
BRAF/*KRAS*/*NRAS* mutation status	*BRAF*/*KRAS*/*NRAS* all wild type (n = 58)	34.3	5.4	0.08
	BRAF mutant (n = 72)	NR	9.2	0.37
	KRAS or *NRAS* mutant (n = 45)	NR	5.7	0.24
	Unknown (n = 74)	NR	4.9	0.17
Lynch syndrome	Yes (n = 31)	NR	7.4	0.28
	No (n = 152)	NR	6.2	0.25
	Unknown (n = 66)	NR	5.5	0.13

[a]Per BICR.



1L all treated patients	NIVO + IPI (n = 200) Any grade	NIVO + IPI (n = 200) Grade 3/4	Chemo (n = 88) Any grade	Chemo (n = 88) 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 T et al. Gastrointestinal Cancers Symposium 2024;Abst LBA768.

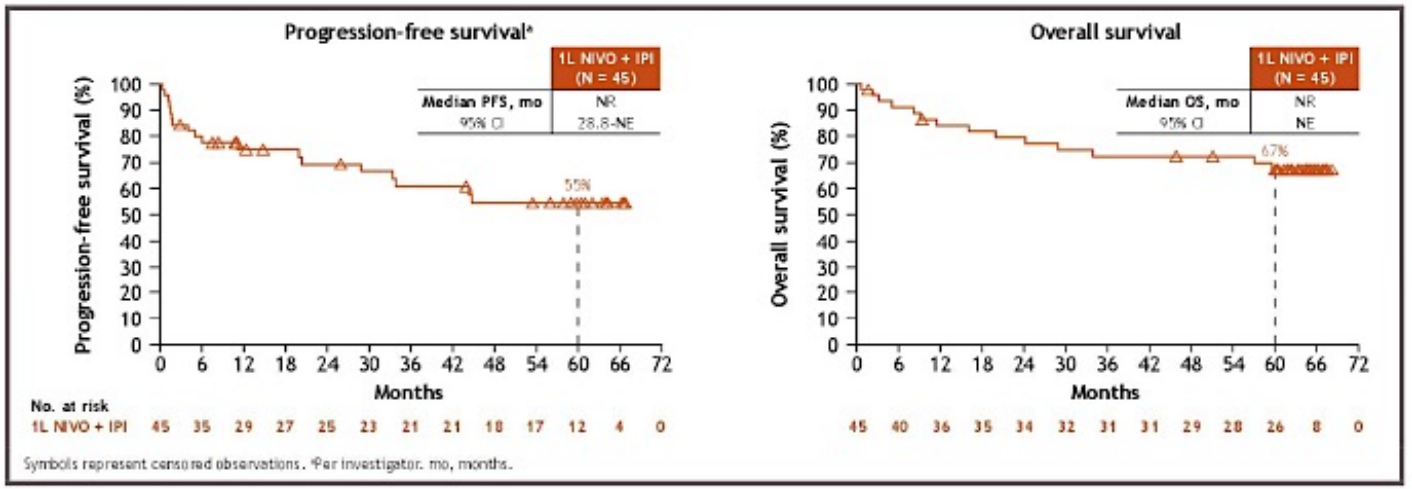
Courtesy of Thierry André, MD

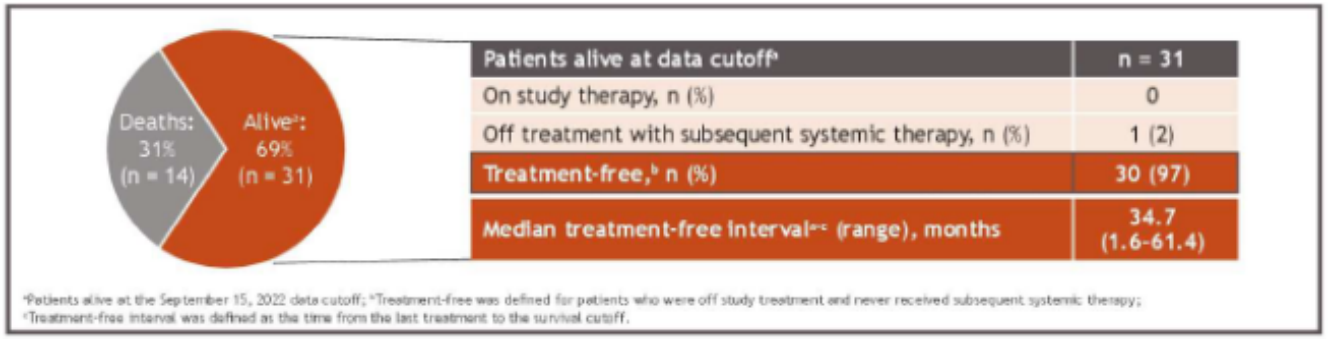
First-line (1L) nivolumab (NIVO) + ipilimumab (IPI) in patients (pts) with microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): 64-month (mo) follow-up from CheckMate 142

NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W until disease progression or unacceptable toxicity.

Efficacy	1L NIVO + IPI (N = 45)
ORR[a,b] (95% CI), %	71 (56–84)
DCR[a,c] (95% CI), %	84 (71–94)
mPFS[a] (95% CI), mo	NR (28.8–NE)
60-mo PFS rate (95% CI), %	55 (38–69)
mOS (95% CI), mo	NR (NE)
60-mo OS rate (95% CI), %	67 (51–79)
Safety, n (%)	
Any-grade/grade 3 or 4 TRAEs	36 (80)/9 (20)
Any-grade TRAEs leading to discontinuation	7 (16)

[a]Per INV; [b]Pts with CR or PR divided by the number of treated pts; [c]Pts with CR, PR, or SD (for ≥ 12 weeks) divided by the number of treated pts. NE, not estimable; NR, not reached; TRAE, treatment-related adverse event.

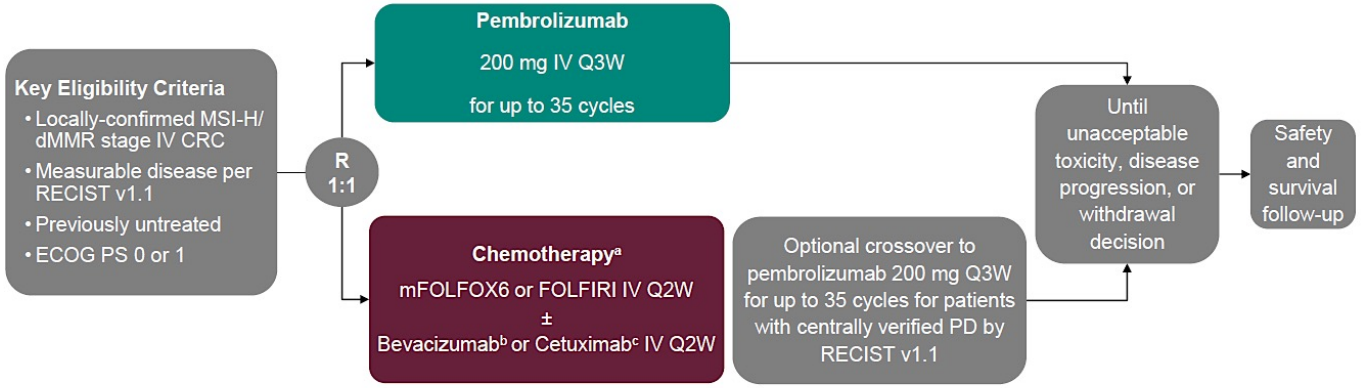




Courtesy of Thierry André, MD

Lenz HJ et al. Gastrointestinal Cancers Symposium 2024;Abstract 97.

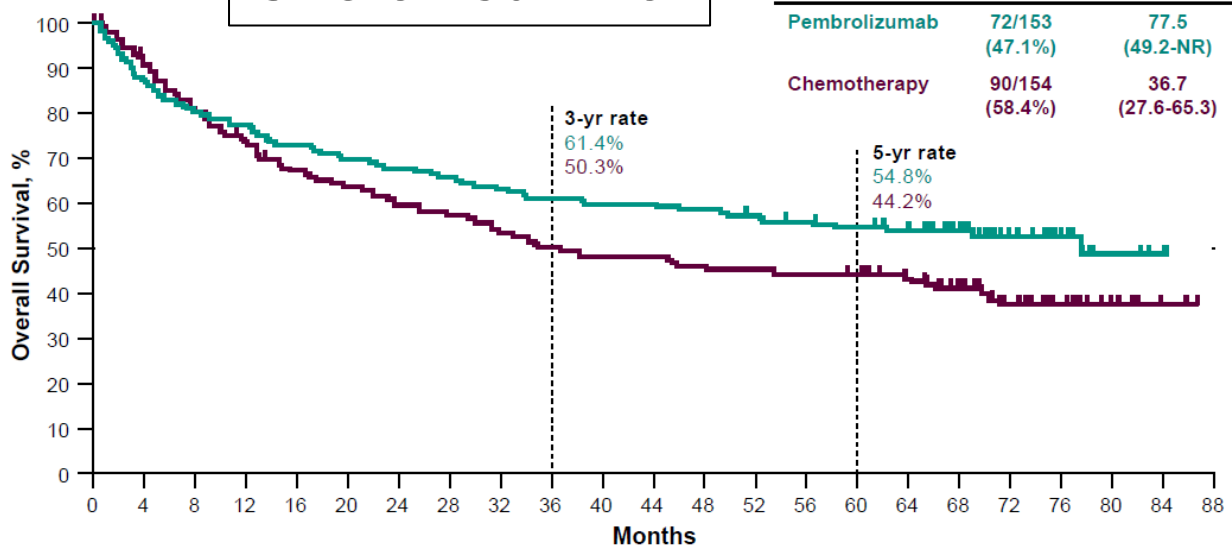
Pembrolizumab Versus Chemotherapy in MSI-H/dMMR mCRC : 5-Year Follow-Up of the Randomized Phase 3 KEYNOTE-177 Study (1)



- **Dual primary end points:** PFS per RECIST v1.1 by BICR; OS
- **Secondary end point:** Safety
- **Exploratory end point:** DOR per RECIST v1.1 by BICR

- **Median time from randomization to data cutoff:** 73.3 months (6.1 years; range, 64.9-89.2 months)

Overall survival



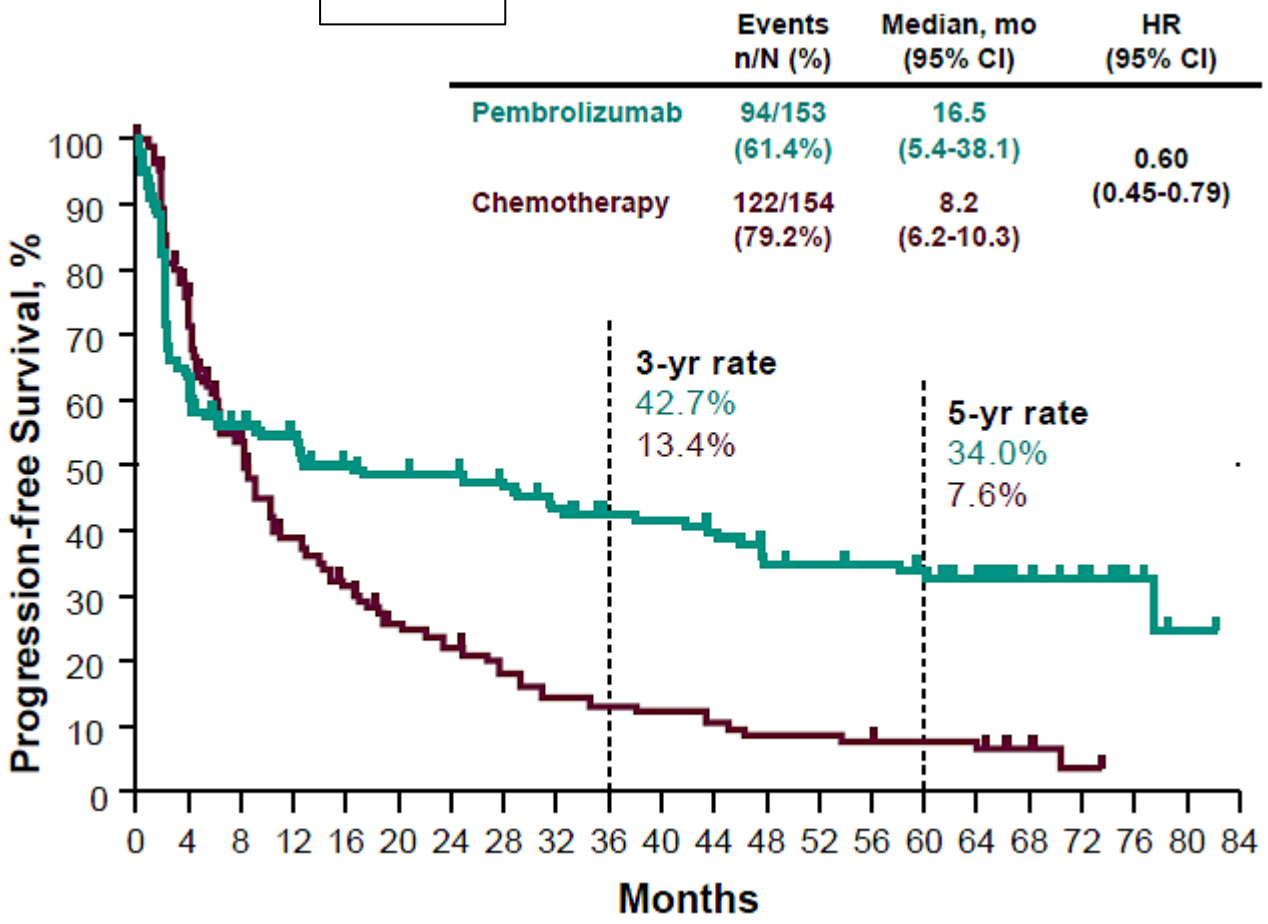
	Events n/N (%)	Median, mo (95% CI)	HR (95% CI)
Pembrolizumab	72/153 (47.1%)	77.5 (49.2-NR)	0.73 (0.53-0.99)
Chemotherapy	90/154 (58.4%)	36.7 (27.6-65.3)	

Courtesy of Thierry André, MD

Shiu KK et al. ESMO 2023;Abstract LBA32.

Pembrolizumab Versus Chemotherapy in MSI-H/dMMR mCRC : 5-Year Follow-Up of the Randomized Phase 3 KEYNOTE-177 Study (2)

PFS



Courtesy of Thierry André, MD

Adverse Events

n (%)	Pembrolizumab N = 153	Chemotherapy N = 143
Any AE	**149 (97.4)**	**142 (99.3)**
Treatment-related AE	**122 (79.7)**	**141 (98.6)**
Grade 3-5	33 (21.6)	96 (67.1)
Led to treatment discontinuation	15 (9.8)	10 (7.0)
Led to death	0	1 (0.7)
Immune-mediated AEs and Infusion Reactions		
All	51 (33.3)	23 (16.1)
Grade 3-5	16 (10.5)	3 (2.1)

Shiu KK et al. ESMO 2023;Abstract LBA32.

Agenda

INTRODUCTION: Year in Review on the Ground

MODULE 1: Treatment of HER2-Positive Metastatic Colorectal Cancer (CRC)

MODULE 2: Immune Checkpoint Inhibitors for Microsatellite Instability-High CRC

MODULE 3: Other Key Issues

- **ctDNA: BESPOKE CRC — Signatera™; KRAS G12C inhibitors; EGFR antibodies; BRAF/MEK dual inhibition; TAS-102, fruquintinib**

MODULE 4: Questions and Cases from the Community

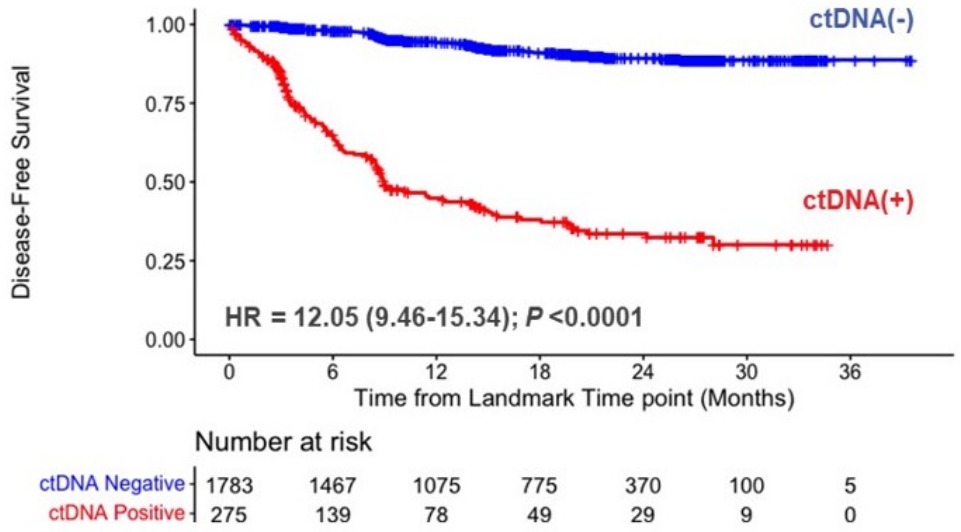
Clinical Utility of Circulating Tumor DNA (ctDNA)

- Dasari A et al. Association of **positive ctDNA-based minimal residual disease assays** during surveillance and **undiagnosed concomitant radiographic recurrences** in colorectal cancer (CRC): Results from the MD Anderson **INTERCEPT program**. ASCO 2023;Abstract 3522.
- Yukami H et al. **Circulating tumor DNA (ctDNA) dynamics** in patients with colorectal cancer (CRC) with molecular residual disease: **Updated analysis from GALAXY study** in the CIRCULATE-JAPAN. Gastrointestinal Cancers Symposium 2024;Abstract 6.
- Kasi PM et al. **Circulating tumor DNA (ctDNA)** for informing **adjuvant chemotherapy** (ACT) in stage II/III colorectal cancer (CRC): Interim analysis of **BESPOKE CRC study**. Gastrointestinal Cancers Symposium 2024;Abstract 9.

Questions from General Medical Oncologists

- Recently I saw a patient for a second opinion where she has stage IIa colon cancer that was being monitored with ctDNA, which was negative for almost 9 months and suddenly her ctDNA was positive and a month later she had CT scans that showed metastatic disease. The patient's CEA was always normal and is normal even after metastatic disease.
- Now she is getting treated for her stage IV colon cancer, would you monitor her with ctDNA as we have done with CEA in the past? Based on clinical trial data, given her ctDNA was initially negative with stage IIa cancer and she does not have any high-risk features, she would have been monitored. Are there any other markers available in CEA-negative colon cancer patients? ctDNA is a step in the right direction but is not applicable to all patients

CIRCULATE-JAPAN ctDNA Dynamics in CRC Patients: Updated Results

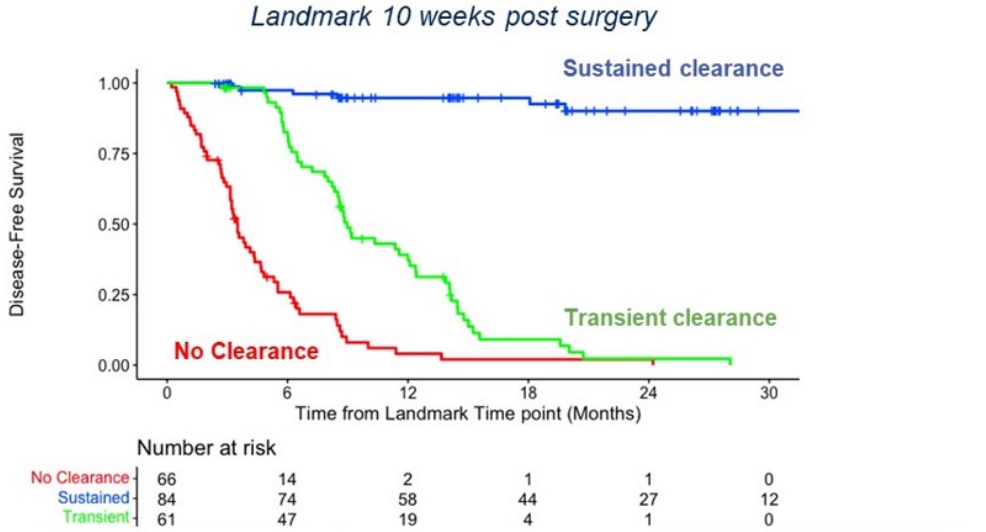


Dynamics	ctDNA Negative	ctDNA Positive
Events %	7.8 (126/1783)	56.5 (143/275)
24M-DFS % (95% CI)*	89.3 (87.2–91.1)	33.5 (26.5–40.7)

*DFS % from landmark time point

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

ctDNA-positive after surgery associated with worse DFS



ctDNA Clearance	Sustained Clearance	Transient Clearance	No Clearance
Events %	7.1 (6/84)	85.2 (52/61)	89.4 (59/66)
Median DFS months (95% CI)	NR	9 (8.5–12.4)	3.5 (3.2–4.7)
24M-DFS % (95% CI)*	90.1 (78.6–95.6)	2.3 (0.02–10.3)	2 (0.02–9.2)
HR	**Reference**	**25.13**	**87.08**
95% CI	Not applicable	10.57–59.73	36.14–209.84
P	Not applicable	<0.0001	<0.0001

*DFS % from landmark time point

Sustained clearance associated with superior DFS

Courtesy of Arvind Dasari, MD, MS

Yukami et al, ASCO GI 2024

BESPOKE: Results

ctDNA-positivity at MRD time point is predictive of inferior DFS

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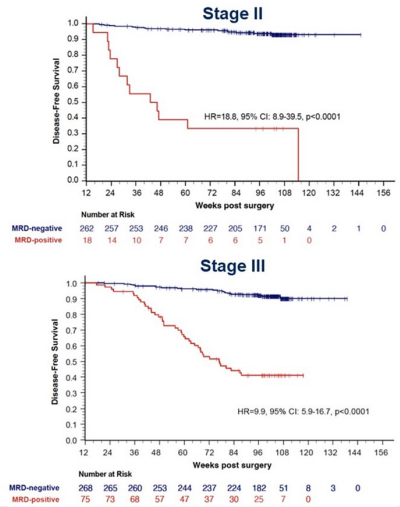
MRD-positivity rate by stage II-III

Stage	Total, N	MRD-negative, n (%)	MRD-positive, n (%)	95% CI for positivity rate
II	280	262 (93.57)	18 (6.43)	4.10-9.93
III	343	268 (78.13)	75 (21.87)	17.82-26.54
Total	623	530	93	

Benchmark for proportion (%) of patients who are MRD-positive with stage II and III colorectal cancer.



Benefit from ACT observed in MRD-positive but not MRD-negative patients

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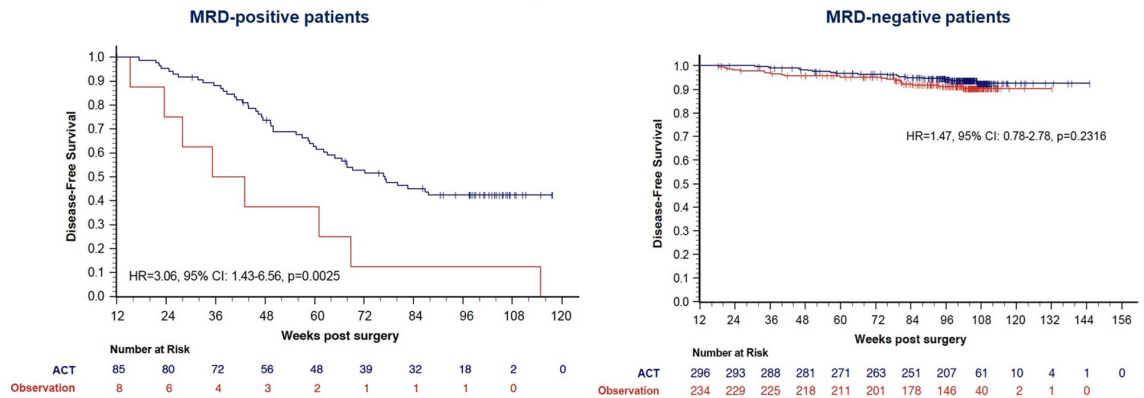
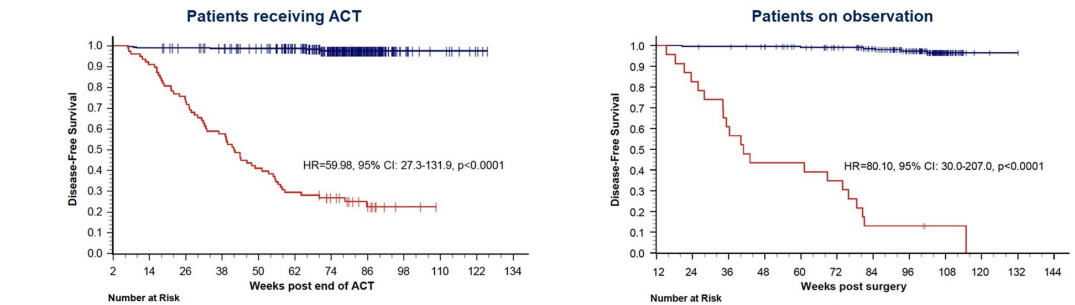


Adjuvant strategy	ACT	Observation
Numbers of events (%)	47/85 (55.29)	8/8 (100)
2-year DFS post surgery, % (95% CI)	42.44 (31.55-52.91)	12.50 (0.66-42.27)
Median DFS post surgery, months (95%)	17.78 (14.37-not reached)	7.52 (3.52-15.88)

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

ctDNA-positivity during surveillance is predictive of inferior DFS regardless of adjuvant therapy (ACT or observation)

7



ctDNA status (surveillance)	ctDNA-negative	ctDNA-positive
Numbers of events (%)	7/329 (2.13)	59/78 (75.64)
2-year DFS post end of ACT, % (95% CI)	97.58 (94.96-98.84)	22.56 (13.49-33.08)
Median DFS post end of ACT, months (95%)	Not reached	9.70 (7.43-12.32)

ctDNA status (surveillance)	ctDNA-negative	ctDNA-positive
Numbers of events (%)	6/225 (2.67)	21/23 (91.30)
2-year DFS post surgery, % (95% CI)	96.60 (92.44-98.49)	13.04* (3.27-29.72)
Median DFS post surgery, months (95%)	Not reached	9.44 (7.86-17.03)

*Most recurrences occurred within the 1st year.

Sustained ctDNA clearance is associated with superior DFS when compared to transient or no clearance

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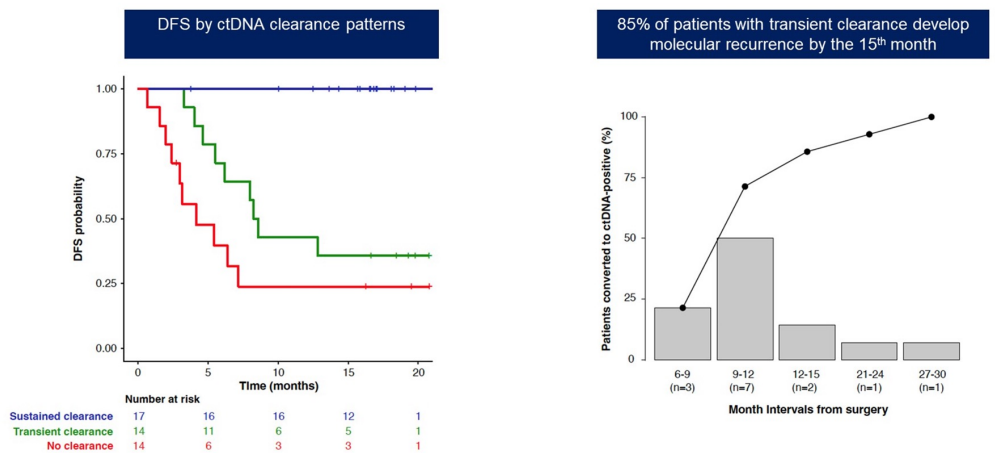


Courtesy of Arvind Dasari, MD, MS

Kasi et al, ASCO GI 2024

CIRCULATE-JAPAN & BESPOKE: Conclusions & Takeaways

- Confirms the known prognostic effects of ctDNA positivity in post-operative and surveillance settings
- Sustained ctDNA clearance post-adjuvant therapy is significantly associated with > 90% DFS
- Transient ctDNA clearance on adjuvant therapy correlated with improved median DFS compared to non-cleared patients but prognosis remains poor
- Patients value and would like to use ctDNA testing

Takeaway:
ctDNA is a very strong prognostic marker but need to await results of interventional trials to establish clinical utility

NCCN Guidelines (v1.2024): *Circulating tumor (ctDNA) is emerging as a prognostic marker; however, there is currently insufficient evidence to recommend routine use of ctDNA assays outside of a clinical trial. Participation in clinical trials is encouraged.*

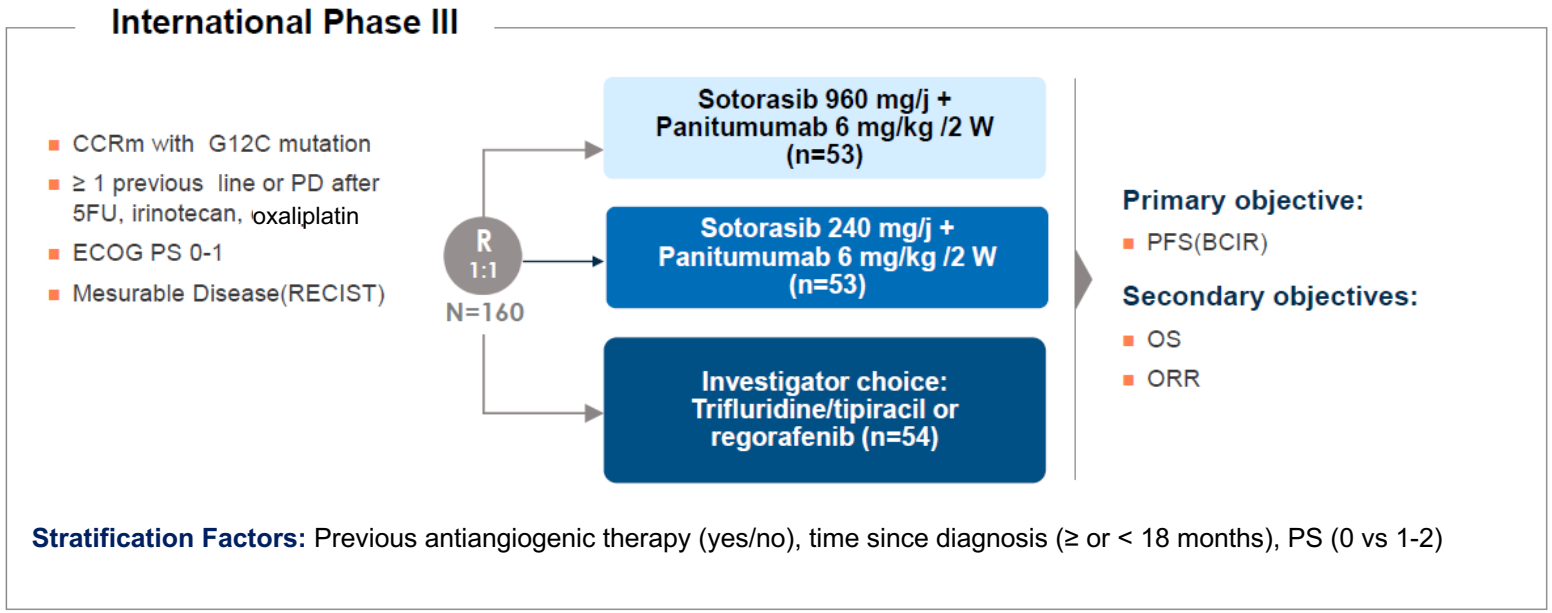
Courtesy of Arvind Dasari, MD, MS

KRAS-Mutant Metastatic Colorectal Cancer

- Fakih MG et al. **Sotorasib plus panitumumab** in refractory colorectal cancer with **mutated KRAS G12C**. *N Engl J Med* 2023;389(23):2125-39.
- Yaeger R et al. **Adagrasib with or without cetuximab** in colorectal cancer with **mutated KRAS G12C**. *N Engl J Med* 2023;388(1):44-54.

Sotorasib plus panitumumab in refractory colorectal cancer with mutated KRAS G12C (1)

- KRAS G12C mutations: 3% of CCRm
- Sotorasib: Inhibitor of KRAS G12C

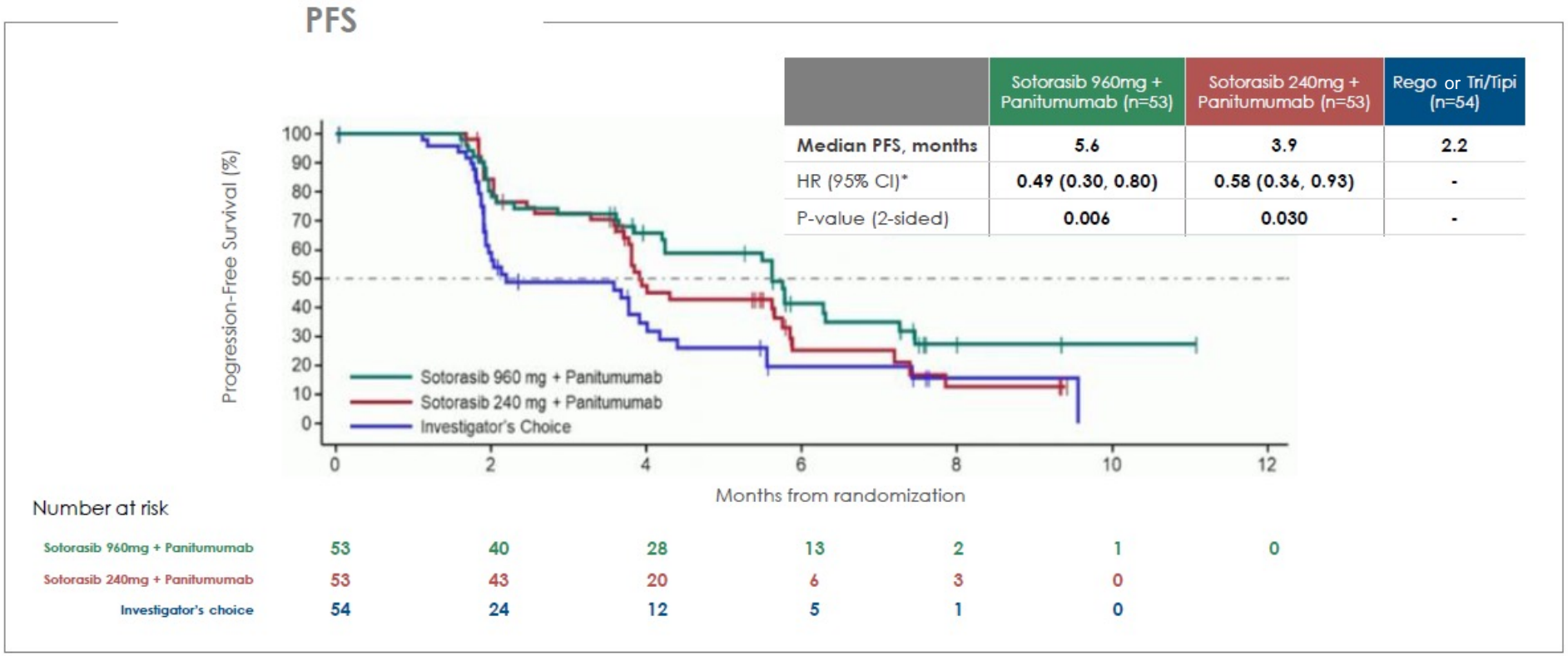


ORR	Sotorasib 960mg + Panitumumab (n=53)	Sotorasib 240mg + Panitumumab (n=53)	Investigator's choice (n=54)
ORR, % (95% CI)*†	**26 (15.3-40.3)**	**6 (1.2-15.7)**	**0 (0-6.6)**
CR, n (%)	**1 (2)**	**0**	**0**
PR, n(%)	**13 (25)**	**3 (6)**	**0**
SD, n (%)	**24 (45)**	**33 (62)**	**25 (46)**
PD, n(%)	**12 (23)**	**13 (25)**	**17 (31)**
Non evaluable/ non doden(%)	**3 (6)**	**2 (4)**	**11 (20)**
Tumoral control % (95% CI)*	**72 (57.7-83.2)**	**68 (53.7-80.1)**	**46 (32.6-60.4)**

Fakih MG et al. N Engl J Med 2023;389(23):2125-39.

Courtesy of Thierry André, MD

Sotorasib plus panitumumab in refractory colorectal cancer with mutated KRAS G12C (2)



- TRAE of grade 3 or higher: 35.8%, 30.2%, and 43.1% of patients, respectively.
- Skin-related toxic effects and hypomagnesemia = most common AE observed with sotorasib–pani.

Courtesy of Thierry André, MD

Fakih MG et al. N Engl J Med 2023;389(23):2125-39.

Adagrasib ± cetuximab in mCRC with mutated KRAS G12C

- Phase 1–2, open-label, nonrandomized clinical trial
- Heavily pretreated patients with mCRC cancer with mutant KRAS G12C
- Treatment:
  - Adagrasib monotherapy (600 mg orally twice daily)
  - Adagrasib (at the same dose) in combination with cetuximab*
- The primary end points were objective response (complete or partial response) and safety

ORR	Adagrasib monotherapy (n=43)	Adagrasib + cetuximab (n=28)
ORR, % (95% CI) by BICR	**23% (12-39)**	**46% (28-66)**
CR, n (%)	**0%**	**0%**
PR, n(%)	**19%**	**46%**
SD, n (%)	**67%**	**54%**
PD, n(%)	**14%**	**0%**
Non evaluable/ non doden(%)	**0%**	**0%**
Median duration of response (months)	**4.3**	**7.6**
Median PFS (months) (95% CI)	**5.6 (4.1-8.3)**	**6.9 (5.5-8.1)**
Median OS (months) (95% CI)	**19.8 (12.5-23)**	**13.4 (9.5-20.1)**

- The percentage of grade 3 or 4 treatment-related adverse events was 34% in the monotherapy group and 16% in the combination-therapy group
- No grade 5 adverse events were observed

*IV cetuximab once a week (initial dose of 400 mg/m^2, followed by a dose of 250 mg mg/m^2) or every 2 weeks (with a dose of 500 mg per square meter).

Yaeger R et al. N Engl J Med 2023;388(1):44-54.

Courtesy of Thierry André, MD

Antitumor Activity of EGFR Antibodies; Effectiveness of Rechallenge

- Watanabe J et al. **Panitumumab** vs bevacizumab **added to standard first-line chemotherapy** and overall survival among patients with RAS wild-type, **left-sided metastatic colorectal cancer**: A randomized clinical trial. *JAMA* 2023;329(15):1271-82.
- Yamazaki K et al. Efficacy of **panitumumab in patients with left-sided disease**, MSS/MSI-L, and RAS/BRAF WT: A **biomarker study** of the phase III **PARADIGM** trial. ASCO 2023;Abstract 3508.
- Raghav K et al. **Acquired genomic alterations** on **first-line chemotherapy with cetuximab** in advanced colorectal cancer: **Circulating tumor DNA analysis** of the **CALGB/SWOG-80405** trial (Alliance). *J Clin Oncol* 2023;41(3):472-8.
- Ciardiello D et al. **Rechallenge with EGFR inhibitors** in ctDNA RAS/BRAF wild type refractory metastatic colorectal cancer: Individual patients' data **pooled analysis from 4 phase II trials**. ESMO 2023;Abstract 559MO.

BRAF-Mutant Metastatic Colorectal Cancer

- Taieb J et al. **Adverse events** associated with **encorafenib plus cetuximab** in patients with **BRAFV600E-mutant metastatic colorectal cancer**: An in-depth analysis of the **BEACON CRC study**. *Clin Colorectal Cancer* 2023;22(1):59-66.
- Van Cutsem E et al. **ANCHOR CRC**: Results from a single-arm, phase II study of **encorafenib plus binimetinib and cetuximab** in **previously untreated BRAFV600E-mutant** metastatic colorectal cancer. *J Clin Oncol* 2023;41(14):2628-37.

TAS-102 in Combination with Bevacizumab

- Prager GW et al. **Trifluridine-tipiracil and bevacizumab** in refractory **metastatic colorectal cancer**. *N Engl J Med* 2023;388(18):1657-67.
- Taieb J et al. Effect of **trifluridine/tipiracil in combination with bevacizumab on ECOG-PS** in refractory metastatic colorectal cancer: An **analysis of the phase 3 SUNLIGHT** trial. ASCO 2023;Abstract 3594.

Fruquintinib

- Dasari A et al. **Fruquintinib** versus placebo in patients with **refractory metastatic colorectal cancer (FRESCO-2)**: An international, multicentre, randomised, double-blind, **phase 3 study**. *Lancet* 2023;402(10395):41-53.
- Dasari A et al. **Subgroup analyses** of safety and efficacy **by number and types of prior lines of treatment** in **FRESCO-2**, a global phase III study of **fruquintinib** in patients with refractory metastatic colorectal cancer. ASCO 2023;Abstract 3604.

Agenda

INTRODUCTION: Year in Review on the Ground

MODULE 1: Treatment of HER2-Positive Metastatic Colorectal Cancer (CRC)

MODULE 2: Immune Checkpoint Inhibitors for Microsatellite Instability-High CRC

MODULE 3: Other Key Stories

MODULE 4: Questions and Cases from the Community

Questions from General Medical Oncologists About HER2

- Should HER2 therapy be added up front, ie with first-line chemo?
- Any situations where you would use trastuzumab deruxtecan before tucatinib and trastuzumab? Which drug should be used if the patient is HER2-positive but also has a KRAS mutation?
- Which assay is best to utilize in CRC for HER2?
- If patient is HER2-negative at diagnosis, should HER2 test be repeated when cancer is in progression after the first-line chemotherapy?
- What emerging data related to HER2-targeting therapies in the front line should general oncologists be aware of?
- What do you do if your CRC patient with HER2 amplification lost HER2 expression?
- Which line of therapy, and are responses possible after a selected HER2 therapy progression with another HER2 therapy, or is better to select a non-HER2 therapy prior to its reintroduction?
- Can trastuzumab deruxtecan be used?
- Are there data using trastuzumab deruxtecan in HER2-positive colon cancer?

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Questions from General Medical Oncologists About HER2

- Any data to suggest use of HER2 antibody as first-line therapy?
- What is the best regimen for HER2 treatment and should it be used in second line or later? Also do we target HER2 if patient also has a KRAS mutation?
- Would you reserve T-DXd for after progression on chemotherapy plus trastuzumab like breast cancer? Or would you directly use T-DXd in a metastatic setting?
- What is latest and is it front line? How to check HER2?
- Sequencing anti-HER2 in early stage and metastatic settings
- Line of therapy and use of trastuzumab deruxtecan on progression on trastuzumab
- Can two different HER2 inhibitors be used in sequence for HER2-positive metastatic CRC?
- At the time of progression on chemo + anti-HER2 treatment, should you continue anti-HER2 treatment, which is sometimes done in GEJ cancers?
- The MOUNTAINEER-03 study result is eagerly awaited but do not know if simply adding all the treatment together in early-line setting will be the answer. Also curious to see more data for anti-HER2 treatment in KRAS-mutated patients other than the DESTINY-CRC03 data
- What is the proper treatment sequence when HER2 mutation is identified in addition to KRAS and/or BRAF mutation?

Questions from General Medical Oncologists About MSI-High CRC

- When should one choose chemo over immunotherapy in these pts?
- Selection of patients for combined or dual-agent immunotherapy versus single-agent immunotherapy in this situation. Is it just response rates?
- What is the best ICI in MSI-H CRC?
- When do you use the combination of PD-1 and CTLA inhibitor? Do you check ctDNA to assess response?
- Is front-line single-agent IO always sufficient for these patients? When would dual ICI be considered over single-agent?
- In patients with MSI-H and NTRK fusion how do you sequence treatment?
- Immune therapy only for MRD+ or immune combinations, and which combinations are recommended?
- Do we need Ipi or is IO alone ok?
- What is the best combo using PD-L1 inhibitors?
- When would you choose CTLA-4/PD-L1 inhibitor vs just PD-L1 inhibitor? Young patient, large disease burden?

Questions from General Medical Oncologists About ctDNA

- Can we reliably use ctDNA for clinical decisions?
- I am wondering if we can use MRD data to decide on adjuvant therapy
- What is the best test or biomarker to identify peritoneal metastasis since ctDNA testing does not appear to be effective?
- In a patient with stage III colon cancer and standard risk who would like to avoid chemotherapy, is there a role for ctDNA testing to inform decision-making?
- Do you recommend ctDNA testing in every stage 2 and 3 disease? Do you wait until radiological progression to begin adjuvant therapy among those who have positive ctDNA in low-risk stage 2?
- How does long term data look? Is it going to replace imaging?
- In stage II colorectal cancer s/p resection with negative margin and negative ctDNA after surgery, what is the standard of care for following up with ctDNA as surveillance?
- Treatment change if ctDNA levels go up
- Can treatment of CRC be adapted to presence or absence of minimal residual disease (MRD) based on ctDNA assays? Does the data on survival from randomized phase 3 studies that suggest treatment duration and type be adapted to MRD results after initial treatment?

Questions from General Medical Oncologists About KRAS G12C

- Does tumor evolve over time and become less KRAS G12C mutant?
- Do KRAS G12C inhibitors need to be combined with EGFR inhibitor therapy such as cetuximab or panitumumab for them to work in colon cancer?
- What is the role of KRAS targeting in CRC?
- Is adagrasib + panitumumab regimen used as the first line?
- Which of the KRAS inhibitors has the greatest data in this setting?
- What is the treatment of choice at this time and in what line of therapy do you use it?
- Present options not very effective, therefore what are the new options being studied?
- I think that we should stop chasing these mutations since there are no good drugs that exist and they are so rare. We just need new good medications to treat colon cancer. Nothing new has been discovered since oxaliplatin came on the market way over 10 years ago...
- How best to sequence lines of therapy in KRAS mutated CRC
- Adagrasib seems to be the winner in lung cancer. How about in colon cancer? Any role for sotorasib alone or in combo with chemo or bev?
- Should we target this in second line or later, and which inhibitor is more effective?

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

A Multitumor CME/MOC-Accredited Live Webinar Series

Prostate Cancer

Wednesday, March 6, 2024
5:00 PM – 6:00 PM ET

Faculty

Andrew J Armstrong, MD, ScM

Maha Hussain, MD, FACP, FASCO

Moderator

Neil Love, MD

RTP Year in Review 2024

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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