What I Tell My Patients: Integrating New Research Information into Current Clinical Care

A Complimentary NCPD Hybrid Symposium Series Held During the 49th Annual ONS Congress

Gastroesophageal and Colorectal Cancers

Saturday, April 27, 2024
6:00 PM – 8:00 PM

Faculty

Deanna A Griffie, MSN, AGNP-C
Caroline Kuhlman, MSN, APRN-BC
Manish A Shah, MD
John Strickler, MD

Moderator

Neil Love, MD

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Faculty

Deanna A Griffie, MSN, AGNP-C
Nurse Practitioner
GI Medical Oncology
Duke Cancer Institute
Durham, North Carolina

Caroline Kuhlman, MSN, APRN-BC
Nurse Practitioner
Tucker Gosnell Center for Gastrointestinal Cancers
Massachusetts General Hospital
Boston, Massachusetts

Manish A Shah, MD
Chief, Solid Tumor Oncology Service
Director, Gastrointestinal Oncology Program
Co-Director, Center for Advanced Digestive Care
Bartlett Family Professor
of Gastrointestinal Oncology
Weill Cornell Medicine/NewYork-Presbyterian Hospital
New York, New York

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

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Ms Griffie — Disclosures

No relevant conflicts of interest to disclose

Ms Kuhlman — Disclosures

No relevant conflicts of interest to disclose

Dr Shah — Disclosures

Contracted Research	Bristol Myers Squibb, Merck, Oncolys BioPharma

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Dr Strickler — Disclosures

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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
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Commercial Support

This activity is supported by educational grants from Astellas, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, and Taiho Oncology Inc.

Research To Practice NCPD Planning Committee Members, Staff and Reviewers

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

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

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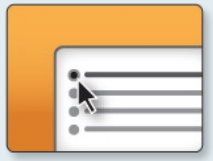
Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

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

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

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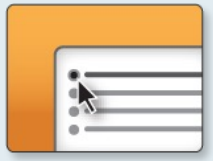
Clinicians Attending via Zoom

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



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

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

Get NCPD Credit: An NCPD credit link will be provided in the chat room at the conclusion of the program.

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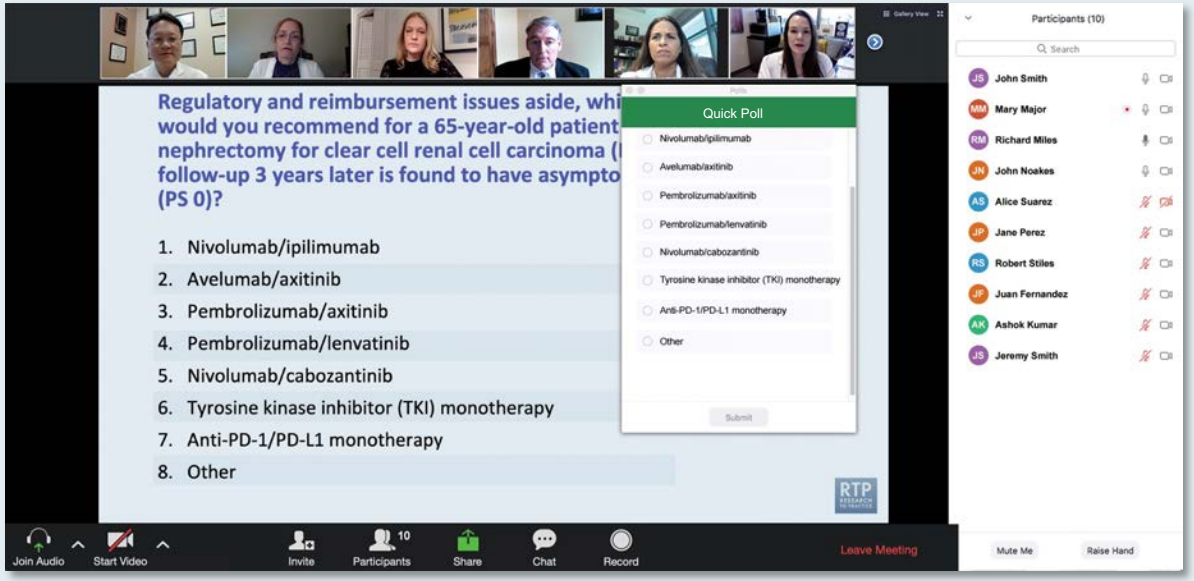
Clinicians, Please Complete the Pre- and Postmeeting Surveys



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About the Enduring Program

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

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“What I Tell My Patients”
Sixteenth Annual RTP-ONS NCPD Symposium Series

Wednesday April 24	**Hormone Receptor–Positive Breast Cancer** 6:00 PM – 8:00 PM ET
Thursday April 25	**Endometrial Cancer** 6:00 AM – 7:30 AM ET
	Antibody–Drug Conjugates 12:15 PM – 1:45 PM ET
	Chronic Lymphocytic Leukemia and Bispecific Antibodies in Lymphoma 6:00 PM – 8:00 PM ET
Friday April 26	**Head and Neck Cancer** 6:00 AM – 7:30 AM ET
	Non–Small Cell Lung Cancer with an EGFR Mutation 12:15 PM – 1:45 PM ET
	Ovarian Cancer 6:00 PM – 7:30 PM ET
Saturday April 27	**Hepatobiliary Cancers** 6:00 AM – 7:30 AM ET
	Myelofibrosis 12:15 PM – 1:45 PM ET
	Gastroesophageal and Colorectal Cancers 6:00 PM – 8:00 PM ET
Wednesday, May 1	**LIVE WEBINAR — Prostate Cancer** 7:00 PM – 8:00 PM ET

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Consulting Nurse Faculty

Jacqueline Broadway-Duren, PhD, DNP, APRN, FNP-BC
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Kathleen D Burns, RN, MSN, AGACNP-BC, OCN
City of Hope Comprehensive Cancer Center
Duarte, California

Sonia Glennie, ARNP, MSN, OCN
Swedish Cancer Institute Center for Blood Disorders
Seattle, Washington

Amy Goodrich, CRNP
The Sidney Kimmel Comprehensive Cancer Center
Baltimore, Maryland

Jessica Mitchell, APRN, CNP, MPH
Mayo Clinic College of Medicine and Science
Rochester, Minnesota

Tiffany A Richards, PhD, ANP-BC, AOCNP
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Kimberly A Spickes, MNSc, RN, APRN, OCN, ACNP-BC
University of Arkansas for Medical Sciences
Little Rock, Arkansas

Ronald Stein, JD, MSN, NP-C, AOCNP
USC Norris Comprehensive Cancer Center
Los Angeles, California

https://www.ResearchToPractice.com/ONS2024Clips

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Agenda

Introduction

Part 1: Gastroesophageal Cancer

Part 2: Colorectal Cancer

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Introduction

Part 1: Gastroesophageal Cancer

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Consulting Nursing Faculty Comments

Assessing the patient with newly diagnosed cancer

Kathleen D Burns, RN, MSN, AGACNP-BC, OCN

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Agenda

Introduction

Part 1: Gastroesophageal Cancer

- **Module 1: Immune Checkpoint Inhibitors in the Management of Nonmetastatic Gastroesophageal Cancers**
- **Module 2: First-Line Therapy for Metastatic Gastroesophageal Cancers**
- **Module 3: Current and Future Role of Targeted Therapy in the Management of Gastroesophageal Cancers**

Part 2: Colorectal Cancer

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Part 1: Gastroesophageal Cancer

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Part 2: Colorectal Cancer

The Current Role of Anti-PD-1/PD-L1 Antibodies in the Management of Nonmetastatic Gastroesophageal Cancers

Dr Shah
New York, New York

Dr Strickler
Durham, North Carolina

- **Long-term outcomes achieved with historical treatment approaches for patients with localized/locally advanced gastroesophageal tumors**
- **Key efficacy and safety findings with adjuvant nivolumab for patients with resected esophageal or gastroesophageal junction (GEJ) cancer**
- **Appropriate selection of candidates for treatment with adjuvant nivolumab**

Adjuvant Nivolumab

Mechanism of action

- **Anti-PD-1 antibody**

Indication

- **For the adjuvant treatment of completely resected esophageal or GEJ cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiation therapy**

Recommended dose

- **240 mg IV infusion every 2 weeks or 480 mg IV infusion every 4 weeks for total treatment duration of 1 year**

Nivolumab package insert, 3/2024.

2021 ASCO ANNUAL MEETING

Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiotherapy: expanded efficacy and safety analyses from CheckMate 577

Ronan J. Kelly,[1] Jaffer A. Ajani,[2] Jaroslaw Kuzdzal,[3] Thomas Zander,[4] Eric Van Cutsem,[5] Guillaume Piessen,[6] Guillermo Mendez,[7] Josephine Feliciano,[8] Satoru Motoyama,[9] Astrid Lièvre,[10] Hope Uronis,[11] Elena Elimova,[12] Cecile Grootscholten,[13] Karen Geboes,[14] Jenny Zhang,[15] Samira Soleymani,[15] Ming Lei,[15] Prianka Singh,[15] James M. Cleary,[16] Markus Moehler[17]

[1]The Charles A. Sammons Cancer Center at Baylor University Medical Center, Dallas, TX; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Jagiellonian University, John Paul II Hospital, Cracow, Poland; [4]University Hospital of Cologne, Cologne, Germany; [5]University Hospitals Gasthuisberg, Leuven and KULeuven, Leuven, Belgium; [6]University of Lille, Claude Huriez University Hospital, Lille, France; [7]Fundacion Favaloro, Buenos Aires, Argentina; [8]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [9]Akita University Hospital, Akita, Japan; [10]CHU Pontchaillou, Rennes 1 University, Rennes, France; [11]Duke Cancer Institute, Durham, NC; [12]Princess Margaret Cancer Centre, Toronto, ON, Canada; [13]Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; [14]UZ Gent, Gent, Belgium; [15]Bristol Myers Squibb, Princeton, NJ; [16]Dana Farber Cancer Institute, Boston, MA; [17]Johannes-Gutenberg University Clinic, Mainz, Germany

Abstract number 4003

The Potential Role of Immune Checkpoint Inhibitors as Neoadjuvant Therapy for Patients with Gastric/GEJ Cancer

Dr Shah
New York, New York

Dr Strickler
Durham, North Carolina

- **Early data with immune checkpoint inhibitors as neoadjuvant therapy for resectable microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) gastric/GEJ adenocarcinoma**
- **Improvement in pathologic complete response rate with the addition of durvalumab to neoadjuvant FLOT (fluorouracil/leucovorin/oxaliplatin/docetaxel) for patients with resectable gastric/GEJ cancer in the Phase III MATTERHORN trial**
- **Ongoing evaluation of perioperative durvalumab in the MATTERHORN study and potential clinical role of this strategy**

Durvalumab

Mechanism of action

- **Anti-PD-L1 antibody**

Indication for gastric/GEJ cancer

- **Investigational**

Pivotal clinical trial

- **Phase III MATTERHORN trial of neoadjuvant-adjuvant durvalumab and FLOT chemotherapy for resectable gastric and GEJ cancer**

Al-Batran S-E et al. ESMO 2023;Abstract 129O.

MADRID 2023 ESMO congress

Abstract 129O

Pathological complete response to durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) in resectable gastric and gastro-oesophageal junction cancer: interim results of the global, Phase 3 MATTERHORN study

Salah-Eddin Al-Batran, MD

20 October 2023

Yelena Y. Janjigian[1], Salah-Eddin Al-Batran[2], Zev A. Wainberg[3], Eric Van Cutsem[4], Daniela Molena[5], Kei Muro[6], Woo Jin Hyung[7], Lucjan Wyrwicz[8], Do-Youn Oh[9], Takeshi Omori[10], Markus Moehler[11], Marcelo Garrido[12], Sulene C.S. Oliveira[13], Moishe Liberman[14], Victor C. Oliden[15], Mehmet Bilici[16], John F. Kurland[17], Ioannis Xynos[18], Helen Mann[18], Josep Tabernero[19]

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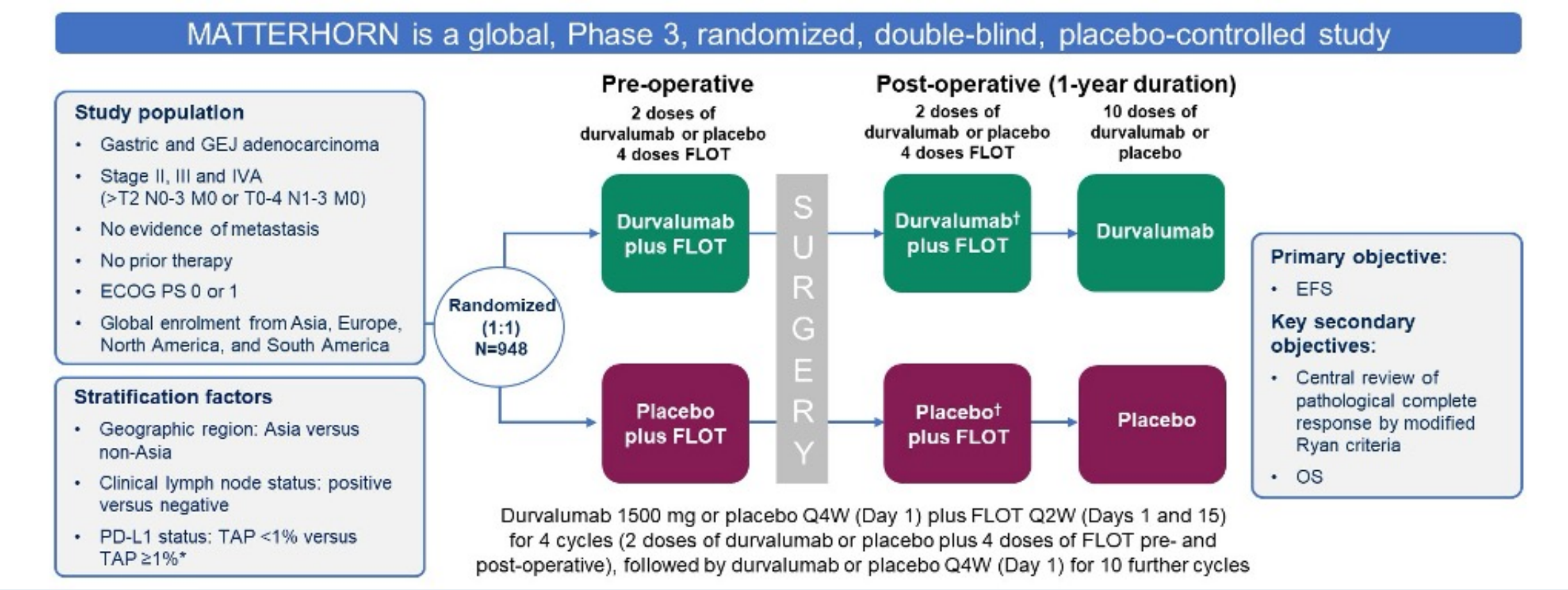
MATTERHORN Trial Design



Al-Batran S-E et al. ESMO 2023;Abstract 129O.

Caroline Kuhlman, MSN, APRN-BC

What I tell my patients about (neo)adjuvant systemic therapy for localized/locally advanced gastroesophageal cancer

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 23, 2022 VOL. 386 NO. 25

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

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

Agenda

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Part 2: Colorectal Cancer

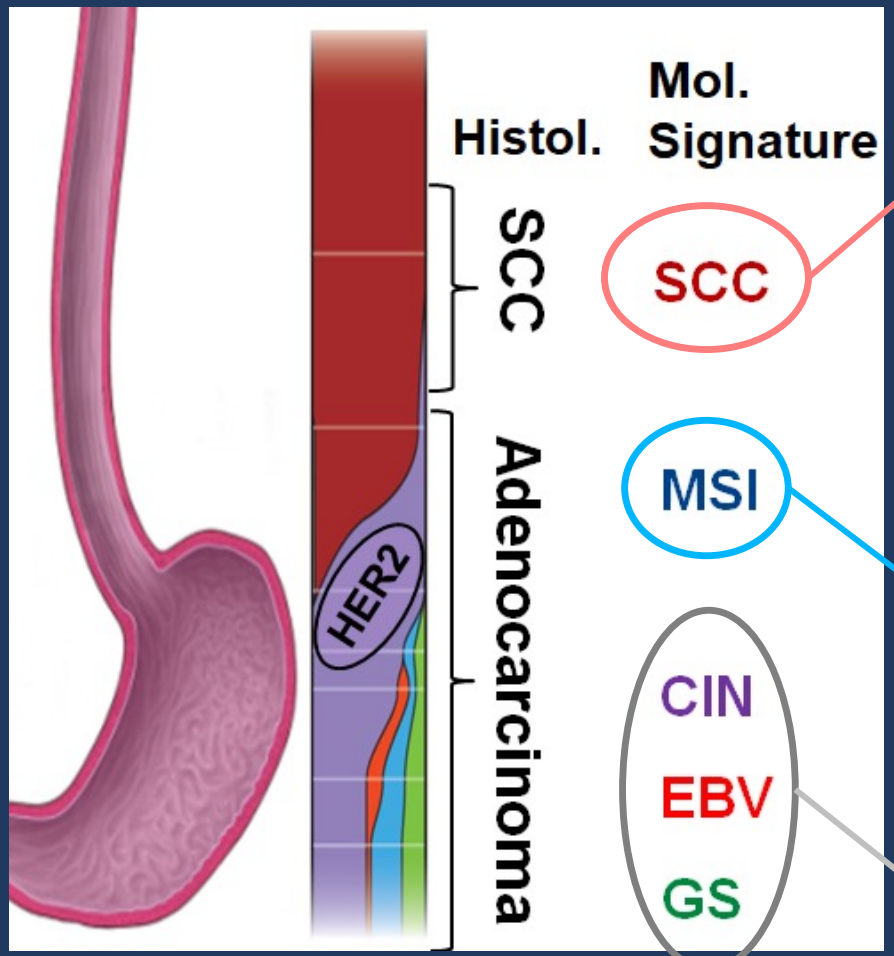
First-Line Therapy for Metastatic Gastroesophageal Cancers

Dr Shah
New York, New York

Dr Strickler
Durham, North Carolina

- **Biological similarities and differences between gastric, GEJ and esophageal cancers; effect of tumor location and histology on management approach**
- **Influence of PD-L1 status on the selection of first-line treatment; appropriate timing of and optimal approaches to PD-L1 assessment**
- **Published data sets demonstrating the efficacy of first-line nivolumab- and pembrolizumab-containing regimens for advanced gastric, GEJ and esophageal cancer**
- **Evidence-based selection of chemotherapy alone versus combined chemoimmunotherapy versus dual immune checkpoint inhibition for patients with newly diagnosed gastroesophageal tumors**

2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal cancer (NCCN Category 1 or 2A)



Any PD-L1 status
Nivo + oxaliplatin/FP
Nivo + IPI

PD-L1 CPS ≥ 10
Pembro + oxaliplatin/FP

Pembro +/- chemo
Nivo + FOLFOX
Nivo + IPI
Dostarlimab

PD-L1 CPS ≥ 5-10 (CPS ≥ 1 ?)
Nivo or pembro + platin/FP

CPS, Combined positive score; FP, fluoropyrimidine; nivo, nivolumab; pembro, pembrolizumab; ICI, immune checkpoint inhibition; IPI, ipilimumab

Courtesy of Harry Y Yoon, MD, MHS

Select Phase III Trials Evaluating Nivolumab or Nivolumab/Ipilimumab as First-Line Treatment of Gastroesophageal Cancers

Trial name	Histology	Study arms	Key endpoints
CheckMate 649	GEJ adenocarcinoma; HER2-negative	**Nivo + FP** vs FP	CPS ≥5 OS HR: 0.70 All patients OS HR: 0.79
		Nivo 1 mg/kg + Ipi 3 mg/kg vs FP	CPS ≥5 OS HR: 0.89 All patients OS HR: 0.91
CheckMate 648	Esophageal SCC	**Nivo 3 mg/kg + Ipi 1mg/kg** vs FP	PD-L1 ≥1% OS HR: 0.62 All patients OS HR: 0.77
		Nivo + FP vs FP	PD-L1 ≥1% OS HR: 0.59 All patients OS HR: 0.78
ATTRACTION-4	Gastric or GEJ cancer	**Nivo + FP** vs FP	All patients OS HR: 0.9

GEJ = gastroesophageal junction; FP = fluoropyrimidine + platinum agent; CPS = combined positive score for PD-L1; OS = overall survival; HR = hazard ratio; SCC = squamous cell carcinoma

Adapted from Karim F et al. *Cancers (Basel)* 2023;15(16):4099; Janjigian YY et al. *J Clin Oncol* 2024; February 21 [Online ahead of print].; Kato K et al. Gastrointestinal Cancers Symposium 2023;Abstract 290. Shitara K et al. *Nature* 2022;603:942-8. Kang Y-K et al; *Lancet Oncol* 2022;23(2):234-47.

Select Phase III Trials Evaluating Pembrolizumab as First-Line Treatment of Gastroesophageal Cancers

Trial name	Histology	Study arms	Key endpoints	
KEYNOTE-590	Esophageal or GEJ SCC	**Pembro + FP** vs Placebo + FP	All patients	OS HR: 0.72 PD-L1 CPS ≥10 OS HR: 0.64
			Esophageal SCC	OS HR: 0.71 PD-L1 CPS ≥10 OS HR: 0.60
KEYNOTE-062	Gastric or GEJ adenocarcinoma	**Pembro alone** vs Placebo + FP	CPS ≥1 OS HR: 0.91 CPS ≥10 OS HR: 0.69	
		Pembro + FP vs Placebo + FP	CPS ≥1 OS HR: 0.85 CPS ≥10 OS HR: 0.85	
KEYNOTE-859	Gastric or GEJ adenocarcinoma	**Pembro + FP** vs Placebo + FP	CPS ≥1 OS HR: 0.74 CPS ≥10 OS HR: 0.65	

GEJ = gastroesophageal junction; SCC = squamous cell carcinoma; FP = fluoropyrimidine + platinum agent; OS = overall survival; HR = hazard ratio; CPS = combined positive score

Adapted from Karim F et al. *Cancers (Basel)* 2023;15(16):4099; Shah MA Gastrointestinal Cancers Symposium 2024;Abstract 250; Rha SY et al. *Lancet Oncol* 2023;24(11):1181-95. Shitara K et al. *JAMA Oncol* 2020;6(10):1571-80.

Deanna A Griffie, MSN, AGNP-C

What I tell my patients who are about to start first-line chemoimmunotherapy for metastatic gastroesophageal cancer

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Introduction

Part 1: Gastroesophageal Cancer

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Part 2: Colorectal Cancer

The Potential Role of Therapy Targeting Claudin 18.2 (CLDN18.2) for Gastroesophageal Cancers

Dr Shah
New York, New York

Dr Strickler
Durham, North Carolina

- **Biological rationale for targeting CLDN18.2 in gastric/GEJ cancers; mechanism of antitumor activity of zolbetuximab**
- **Published efficacy and safety findings with zolbetuximab in combination with chemotherapy as first-line therapy for patients with advanced CLDN18.2-positive gastric/GEJ cancer**
- **Potential clinical role of up-front zolbetuximab/chemotherapy and implications for biomarker assessment**
- **Incidence, severity and timing of nausea and vomiting observed with zolbetuximab for patients with and without prior gastrectomy**
- **Role of antiemetics and other supportive care measures for patients receiving zolbetuximab**
- **Spectrum, frequency and management of other toxicities reported with zolbetuximab**

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Zolbetuximab

Mechanism of action

- **Anti-CLDN18.2 antibody**

Indication

- **Investigational**

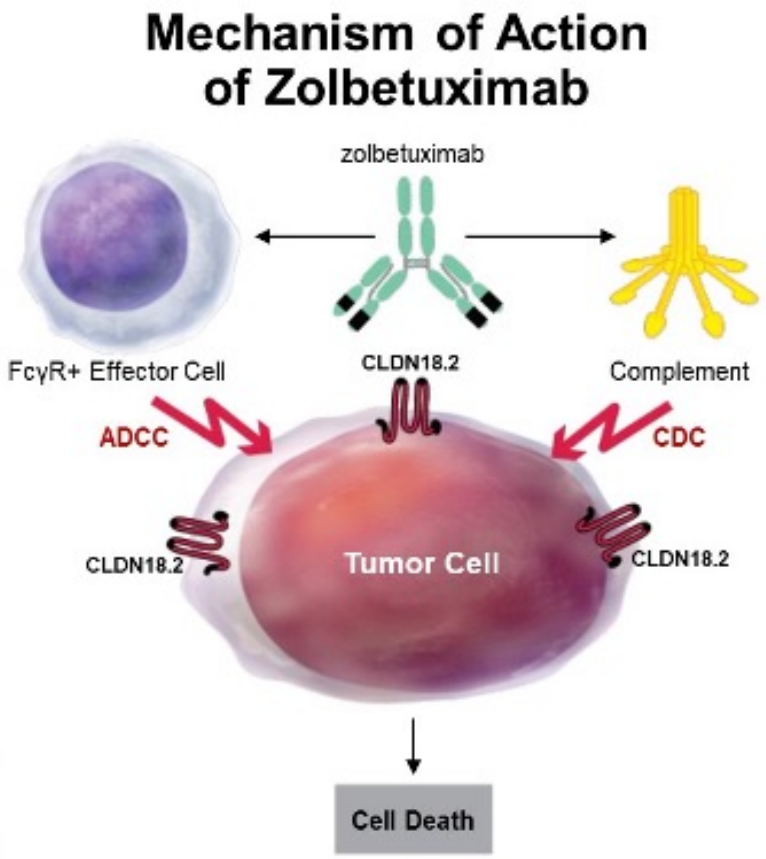
Pivotal clinical data

- **Phase III SPOTLIGHT[1] and GLOW[2] trials evaluating zolbetuximab in combination with either FOLFOX or CAPOX as first-line treatment for patients with HER2-negative locally advanced unresectable or metastatic gastric or GEJ cancers**

1. Shitara K et al. *Lancet* 2023;401:1655-68.
2. Shah MA et al. *Nat Med* 2023;29(8):2133-41.

Mechanism of Action of Zolbetuximab

- CLDN18.2 is a tight junction protein normally expressed in gastric mucosa cells and retained in G/GEJ adenocarcinoma[1–8]
- CLDN18.2 may become exposed on the surface of G/GEJ adenocarcinoma cells, making it a promising target[2–8]
- Zolbetuximab is a first-in-class chimeric IgG1 monoclonal antibody that targets CLDN18.2 and induces ADCC/CDC[4–8]
- In the phase 2b FAST study, EOX ± zolbetuximab prolonged survival in a subgroup of patients with higher expression of CLDN18.2 in tumor cells[8]
  - mPFS: 9.0 vs 5.7 months with zolbetuximab + EOX vs EOX alone
  - mOS: 16.5 vs 8.9 months with zolbetuximab + EOX vs EOX alone



Shitara K et al. Gastrointestinal Cancers Symposium 2023;Abstract LBA292.

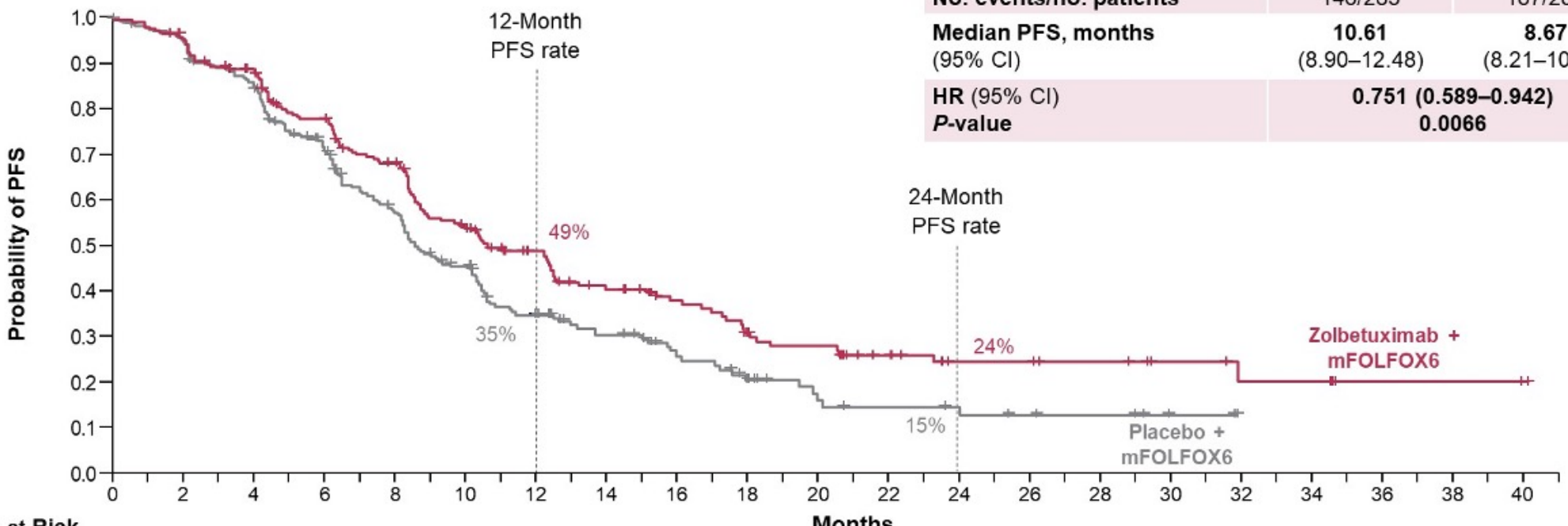
Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial

Kohei Shitara, Florian Lordick, Yung-Jue Bang, Peter Enzinger, David Ilson, Manish A Shah, Eric Van Cutsem, Rui-Hua Xu, Giuseppe Aprile, Jianming Xu, Joseph Chao, Roberto Pazo-Cid, Yoon-Koo Kang, Jianning Yang, Diarmuid Moran, Pranob Bhattacharya, Ahsan Arozullah, Jung Wook Park, Mok Oh, Jaffer A Ajani

***Lancet* 2023;401:1655-68.**

SPOTLIGHT: Progression-Free Survival (Primary Endpoint)

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	146/283	167/282
Median PFS, months (95% CI)	**10.61** (8.90–12.48)	**8.67** (8.21–10.28)
HR (95% CI)	**0.751 (0.589–0.942)**	
***P*-value**	**0.0066**	



No. at Risk

Zolbetuximab + mFOLFOX6	283	263	254	232	226	190	187	148	143	108	102	84	78	59	56	53	43	40	33	28	28	21	19	17	12	12	12	10	10	9	7	7	5	5	5	2	2	2	2	2	1	0
Placebo + mFOLFOX6	282	273	260	237	226	183	168	136	122	91	83	60	56	43	40	38	26	25	19	14	12	9	9	9	8	7	6	5	5	4	2	2	0	0	0	0	0	0	0	0	0	0

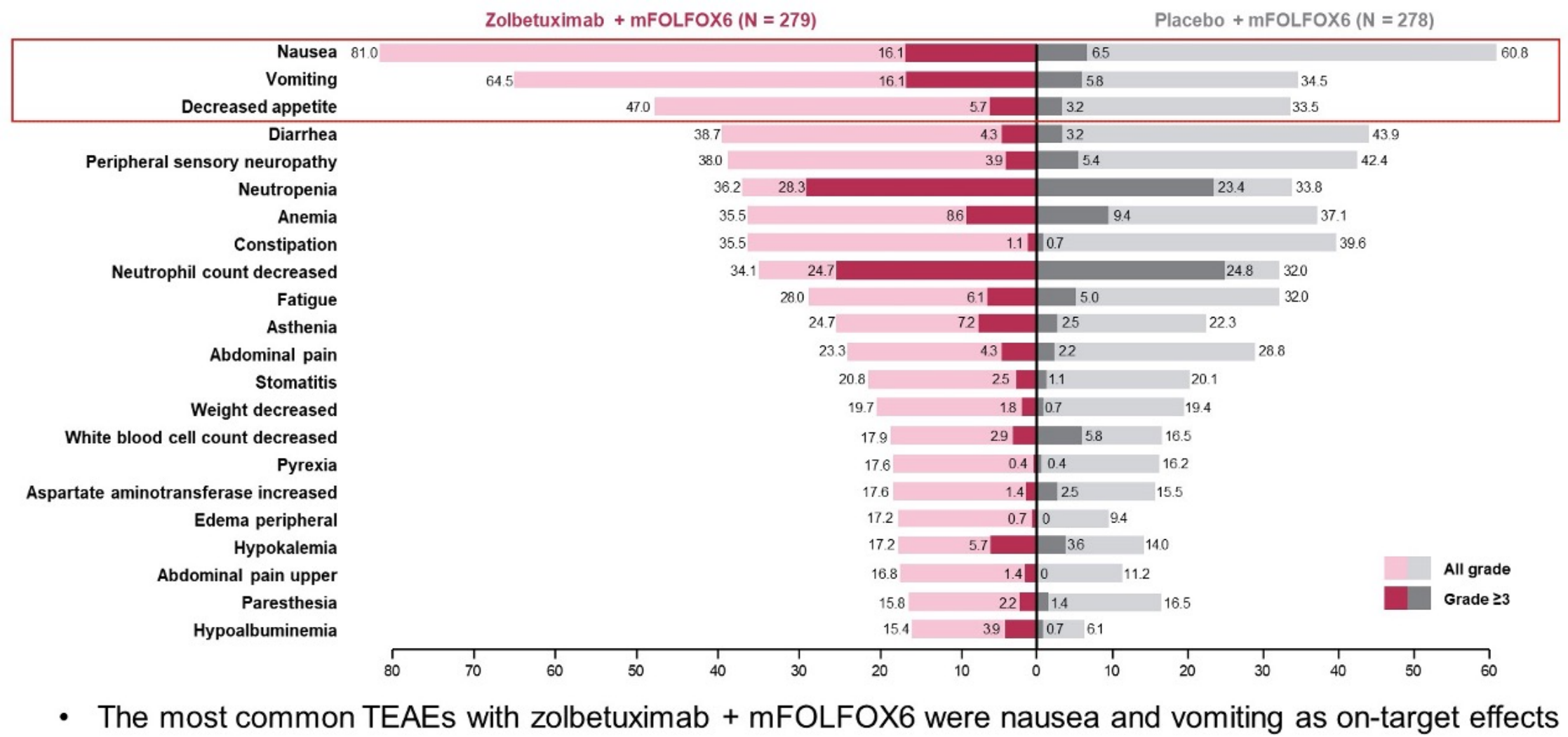
- PFS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

Data cutoff: September 9, 2022; Median follow-up = 12.94 months (zolbetuximab + mFOLFOX6) vs 12.65 months (placebo + mFOLFOX6).

[a]Per RECIST version 1.1.

Shitara K et al. Gastrointestinal Cancers Symposium 2023;Abstract LBA292. Shitara K et al. *Lancet* 2023;401:1655-68.

SPOTLIGHT: TEAEs Occurring in ≥15% of Patients



- The most common TEAEs with zolbetuximab + mFOLFOX6 were nausea and vomiting as on-target effects

TEAEs = treatment-emergent adverse events

Shitara K et al. Gastrointestinal Cancers Symposium 2023;Abstract LBA292. Shitara K et al. *Lancet* 2023;401:1655-68.

nature medicine

2023;29(8):2133-41.

Article

https://doi.org/10.1038/s41591-023-02465-7

Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial

Received: 5 May 2023

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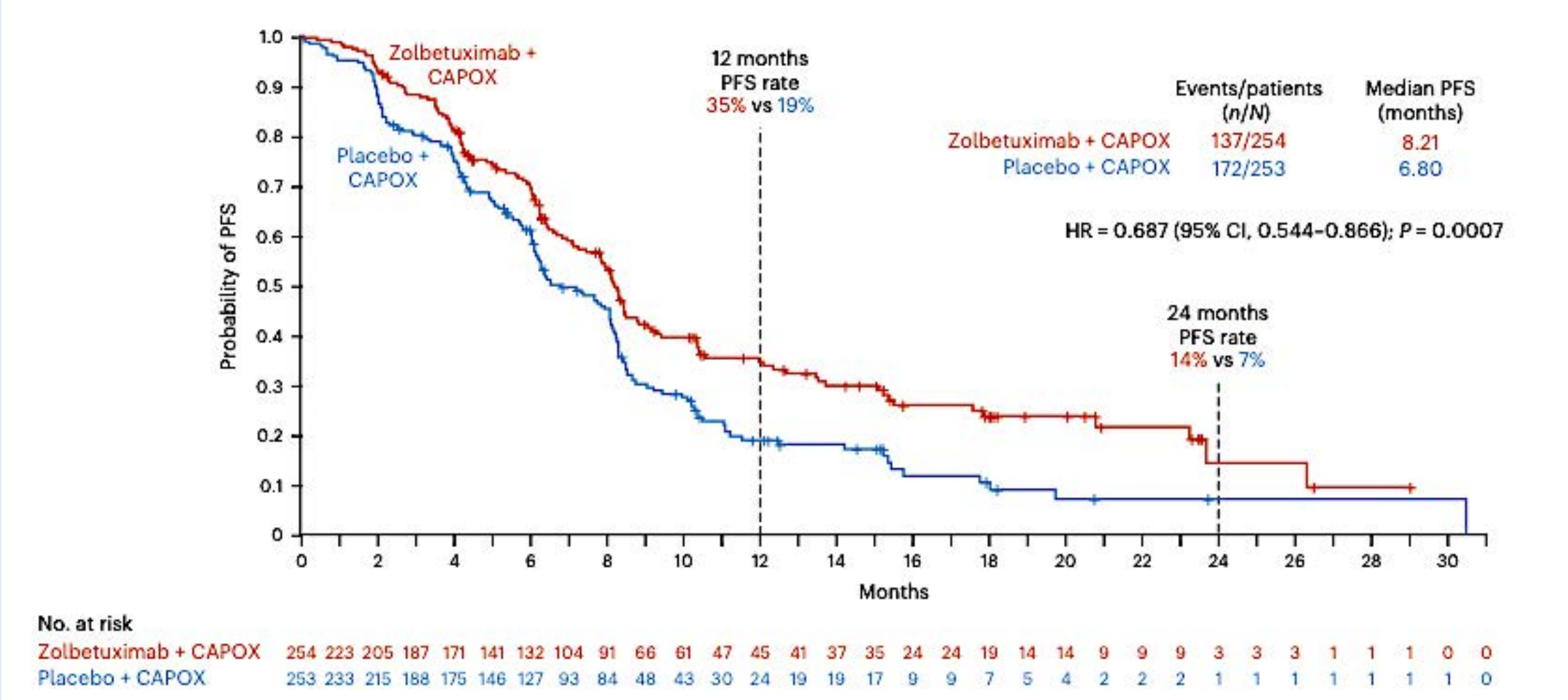
Manish A. Shah[1], Kohei Shitara[2], Jaffer A. Ajani[3], Yung-Jue Bang[4], Peter Enzinger[5], David Ilson[6], Florian Lordick[7], Eric Van Cutsem[8], Javier Gallego Plazas[9], Jing Huang[10], Lin Shen[11], Sang Cheul Oh[12], Patrapim Sunpaweravong[13], Hwoei Fen Soo Hoo[14], Haci Mehmet Turk[15], Mok Oh[16], Jung Wook Park[16], Diarmuid Moran[16], Pranob Bhattacharya[16], Ahsan Arozullah[16] & Rui-Hua Xu[17]

GLOW: Progression-Free Survival (PFS) by Independent Review Committee (Primary Endpoint)



Shah MA et al. *Nat Med* 2023;29(8):2133-41.

Caroline Kuhlman, MSN, APRN-BC

What I tell my patients with gastric/GEJ cancers who are about to begin therapy with zolbetuximab

RTP
RESEARCH
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Targeted Therapies for HER2-Positive Gastroesophageal Cancers

Dr Shah
New York, New York

Dr Strickler
Durham, North Carolina

- **Principal outcomes supporting the addition of pembrolizumab to chemotherapy/trastuzumab for previously untreated HER2-positive advanced gastric/GEJ adenocarcinoma; effect of PD-L1 status on eligibility for this approach**
- **Published data with trastuzumab deruxtecan (T-DXd) for patients with progressive HER2-positive gastric/GEJ cancer**
- **Spectrum, frequency and management of toxicities associated with T-DXd**

FDA Amends Gastric Cancer Indication for Pembrolizumab

Press Release – November 7, 2023

"… the Food and Drug Administration revised the existing indication of pembrolizumab with trastuzumab, fluoropyrimidine, and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma. **This updated indication, which remains approved under accelerated approval regulations, restricts its use to patients whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.**

The FDA also approved ... PD-L1 IHC 22C3 pharmDx as a companion diagnostic device to select patients with gastric or GEJ adenocarcinoma whose tumors express PD-L1 (CPS ≥1).

Efficacy was evaluated in KEYNOTE-811 (NCT03615326), a multicenter, randomized, double-blind, placebo-controlled trial in patients with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma who have not previously received systemic therapy for metastatic disease. ... In a recent, prespecified interim analysis of the fully enrolled trial (N = 698), in a subgroup analysis conducted in patients with PD-L1 CPS <1 (N = 104), the hazard ratio (HR) for OS and PFS were 1.41 (95% CI 0.90, 2.20) and 1.03 (95% CI 0.65, 1.64), respectively."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-amends-pembrolizumabs-gastric-cancer-indication

RTP RESEARCH TO PRACTICE

Trastuzumab Deruxtecan: Gastric and Gastroesophageal Cancers

Mechanism of action

- **Antibody-drug conjugate directed against HER2**

Indication

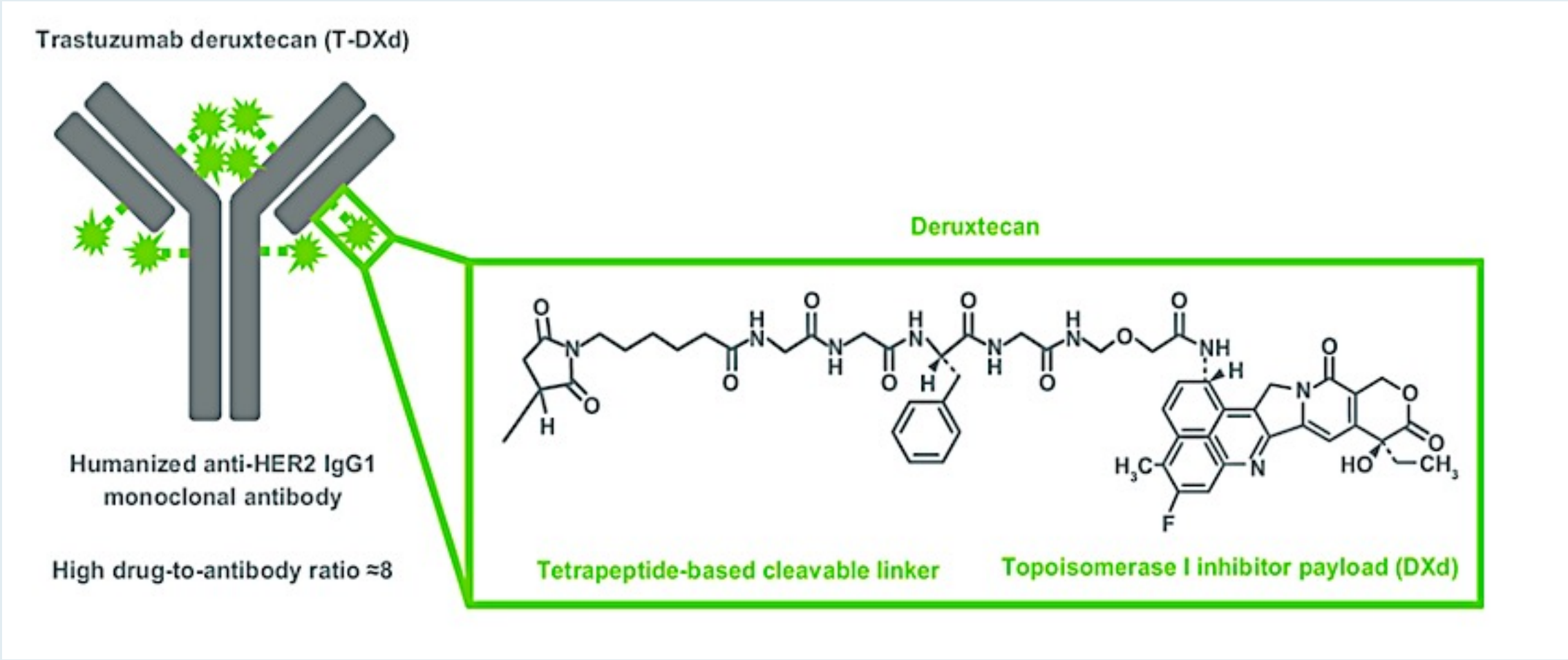
- **For patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH-positive) gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen**

Recommended dosing

- **6.4 mg/kg given IV every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity**

Trastuzumab deruxtecan prescribing information, 4/2024.

Trastuzumab Deruxtecan



Courtesy of Markus Moehler, MD.

Lancet Oncol 2023;24:744-56.

Articles

Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal junction cancer with disease progression on or after a trastuzumab-containing regimen (DESTINY-Gastric02): primary and updated analyses from a single-arm, phase 2 study

Eric Van Cutsem, Maria di Bartolomeo, Elizabeth Smyth, Ian Chau, Haeseong Park, Salvatore Siena, Sara Lonardi, Zev A Wainberg, Jaffer Ajani, Joseph Chao, Yelena Janjigian, Amy Qin, Jasmeet Singh, Ferdous Barlaskar, Yoshinori Kawaguchi, Geoffrey Ku

DESTINY-Gastric02: Overall Safety Summary and ILD/Pneumonitis

% (n)	Patients (N = 79)
Any TEAE	100 (79)
Drug-related	94.9 (75)
TEAE grade ≥3	55.7 (44)
Drug-related	30.4 (24)
Serious TEAE	41.8 (33)
Drug-related	12.7 (10)
TEAE associated with study drug discontinuation	19.0 (15)
Drug-related	12.7 (10)
TEAE associated with dose reduction	21.5 (17)
Drug-related	17.7 (14)
TEAE associated with an outcome of death	13.9 (11)
Drug-related	2.5 (2)
Adjudicated drug-related ILD/pneumonitis	10.1 (8)[a]
Adjudicated drug-related ILD/pneumonitis grade 5	2.5 (2)

- Median treatment duration was 4.3 months (range, 0.7-22.1 months)
- The most common TEAEs were nausea (67.1%), vomiting (44.3%), and fatigue (41.8%)
- Grade 1 adjudicated drug-related ILD/pneumonitis occurred in 2 patients (2.5%), grade 2 in 4 patients (5.1%), and grade 5 in 2 patients (2.5%)
- Median time to onset of adjudicated drug-related ILD/pneumonitis was 80.5 days (range, 42-344 days), with a median duration of 36.0 days (range, 15-142 days)
- Of the 2 fatal ILD/pneumonitis cases, 1 occurred 171 days after drug initiation and the second after 353 days

ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.
Cutoff date: November 8, 2021.
[a]Of the 6 grade 1/2 ILD/pneumonitis cases, 3 patients had recovered or were recovering at the time of data cutoff, 1 had recovered with sequelae, 1 had not recovered, and 1 had an outcome that was unknown.

Ku G et al. ESMO 2022;Abstract 1205MO; Van Cutsem E et al. *Lancet Oncol* 2023;24:744-56.

The Integration of Therapies Targeting HER2 into the Management of mCRC

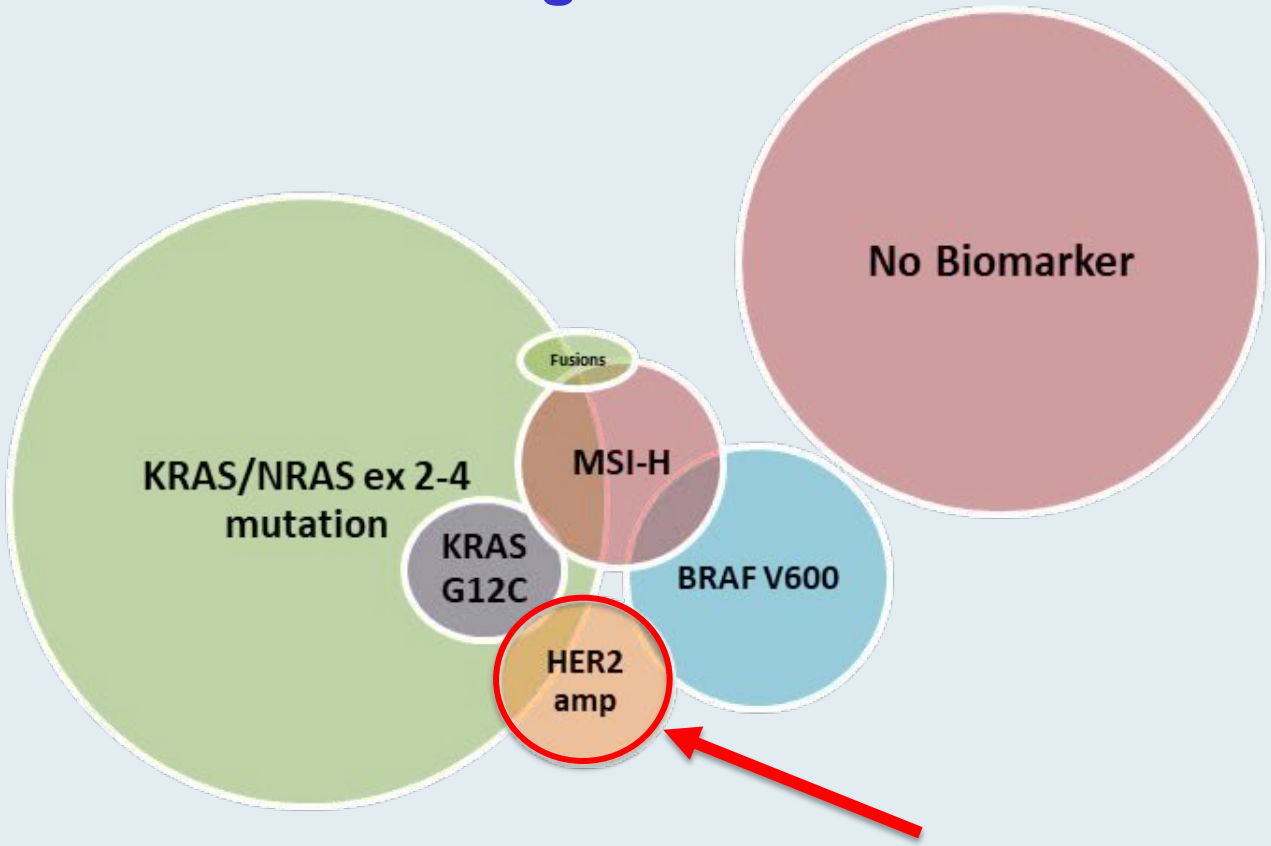
Dr Shah
New York, New York

Dr Strickler
Durham, North Carolina

- **Incidence of HER2 amplification/overexpression in patients with mCRC; recommended timing of and appropriate platforms for HER2 testing**
- **Pivotal data with tucatinib/trastuzumab for previously treated HER2-positive mCRC**
- **FDA approval and current clinical role of tucatinib/trastuzumab**
- **Available efficacy and safety findings with T-DXd in HER2-expressing mCRC**
- **Current and future nonresearch role of T-DXd**

HER2 as an Emerging Precision Cancer Medicine Target in Metastatic CRC

Actionable targets in metastatic CRC



- Usually <u>left sided</u>
- <u>Not</u> mutually exclusive with *RAS* or *BRAF* mutations
- Associated with lung and brain metastases
- May predict resistance to EGFR antibodies

Courtesy of John H Strickler, MD

Tucatinib: Colorectal Cancer

Mechanism of action

- **HER2 tyrosine kinase inhibitor**

Indication

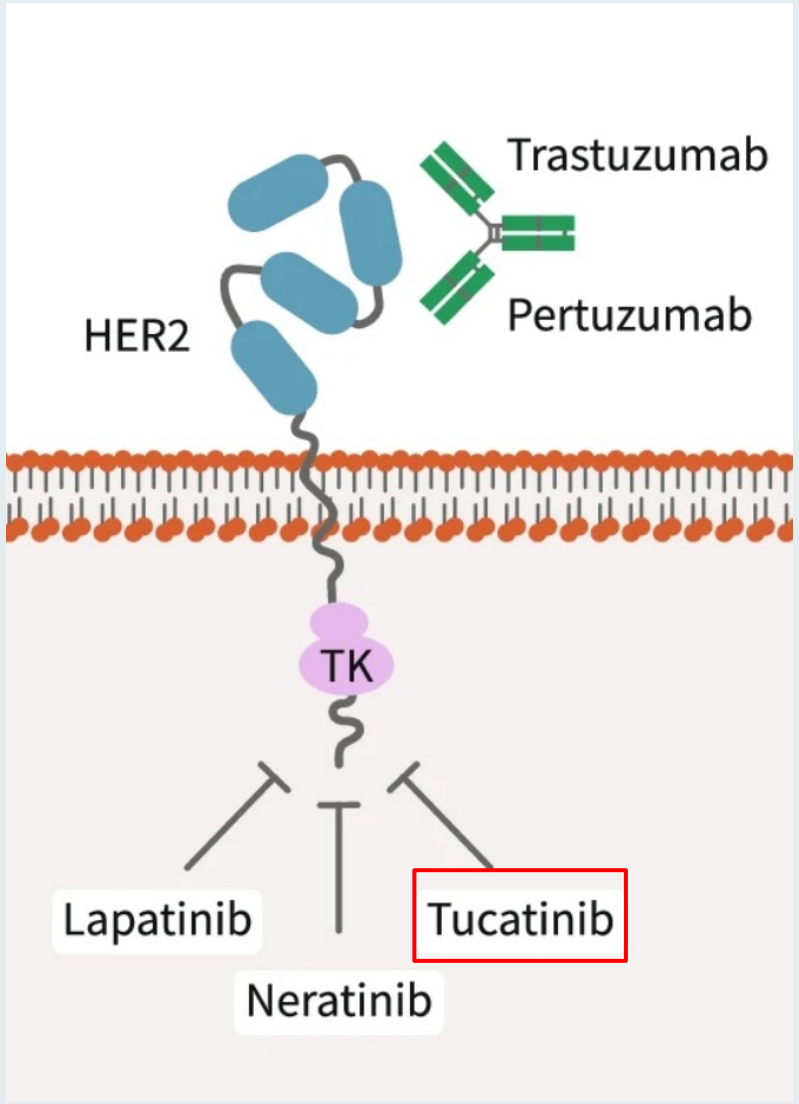
- **In combination with trastuzumab for patients with RAS wild-type HER2-positive unresectable or metastatic colorectal cancer that has progressed after fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy**

Tucatinib recommended dose

- **300 mg orally twice daily with or without food**

Tucatinib prescribing information, 1/2023.

Tucatinib Mechanism of Action



Wynn CS et al. *Cancer Metastasis Rev* 2022;41(1):193-209.

RTP RESEARCH TO PRACTICE

Trastuzumab Deruxtecan: HER2-Positive Solid Tumors

Mechanism of action

- **Antibody-drug conjugate directed against HER2**

Indication

- **For patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options**

Recommended dosing

- **5.4 mg/kg IV infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity**

Trastuzumab deruxtecan prescribing information, 4/2024.

FDA Grants Accelerated Approval to Trastuzumab-Deruxtecan for Unresectable or Metastatic HER2-Positive Solid Tumors

Press Release – April 5, 2024

"…the Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

Efficacy was evaluated in 192 adult patients with previously treated unresectable or metastatic HER2-positive (IHC 3+) solid tumors who were enrolled in one of three multicenter trials: DESTINY-PanTumor02 (NCT04482309), DESTINY-Lung01 (NCT03505710), and DESTINY-CRC02 (NCT04744831).

"The major efficacy outcome measure in all three trials was confirmed objective response rate (ORR), and an additional efficacy outcome was duration of response (DOR). All outcomes were assessed by independent central review (ICR) based on RECIST v1.1. In DESTINY-PanTumor02, ORR was 51.4% (95% CI: 41.7, 61.0) and median DOR was 19.4 months (range 1.3, 27.9+). In DESTINY-Lung01, ORR was 52.9% (95% CI: 27.8, 77.0) and median DOR was 6.9 months (range 4.0, 11.7+). In DESTINY-CRC02, ORR was 46.9% (95% CI: 34.3, 59.8), and DOR was 5.5 months (range 1.3+, 9.7+)."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2

RTP RESEARCH TO PRACTICE

2023 ASCO ANNUAL MEETING

Abstract 3501

T-DXd in Patients With HER2-Overexpressing/Amplified (HER2+) Metastatic Colorectal Cancer (mCRC): Primary Results From the Multicenter, Randomized, Phase 2 DESTINY-CRC02 Study

Kanwal Raghav

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

June 4, 2023

Additional authors: Salvatore Siena, Atsuo Takashima, Takeshi Kato, Marc Van Den Eynde, Maria Di Bartolomeo, Yoshito Komatsu, Hisato Kawakami, Marc Peeters, Thierry Andre, Sara Lonardi, Kensei Yamaguchi, Jeanne Tie, Christina Gravalos Castro, John Strickler, Daniel Barrios, Qi Yan, Takahiro Kamio, Kojiro Kobayashi, Takayuki Yoshino

Deanna A Griffie, MSN, AGNP-C

What I tell my patients about to begin therapy with trastuzumab deruxtecan

JAMA Network | Open

Original Investigation | Global Health

Patterns in Cancer Incidence Among People Younger Than 50 Years in the US, 2010 to 2019

Benjamin Koh; Darren Jun Hao Tan; Cheng Han Ng, MBBS; Clarissa Elysia Fu; Wen Hui Lim; Rebecca Wenling Zeng; Jie Ning Yong; Jia Hong Koh, MBBS; Nicholas Syn, MBBS; Wang Meng, MBBS; Karn Wijarnpreecha, MD; Ken Liu, PhD; Choon Seng Chong, MBBS; Mark Muthiah, MBBS; Hung N. Luu, PhD; Arndt Vogel, MD; Siddharth Singh, MD; Khay Guan Yeoh, MBBS; Rohit Loomba, MD; Daniel Q. Huang, MBBS, MMED

Consulting Nursing Faculty Comments

Support avenues for younger patients with cancer

Jessica Mitchell, APRN, CNP, MPH

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Agenda

Introduction

Part 1: Gastroesophageal Cancer

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- **Module 4: Adjuvant Therapy in the Management of Localized CRC**
- **Module 5: Immunotherapy in the Management of Metastatic CRC (mCRC)**
- **Module 6: Management Approaches for Patients with Relapsed/Refractory (R/R) mCRC**
- **Module 7: Use of Novel Targeted Therapy in the Management of mCRC**

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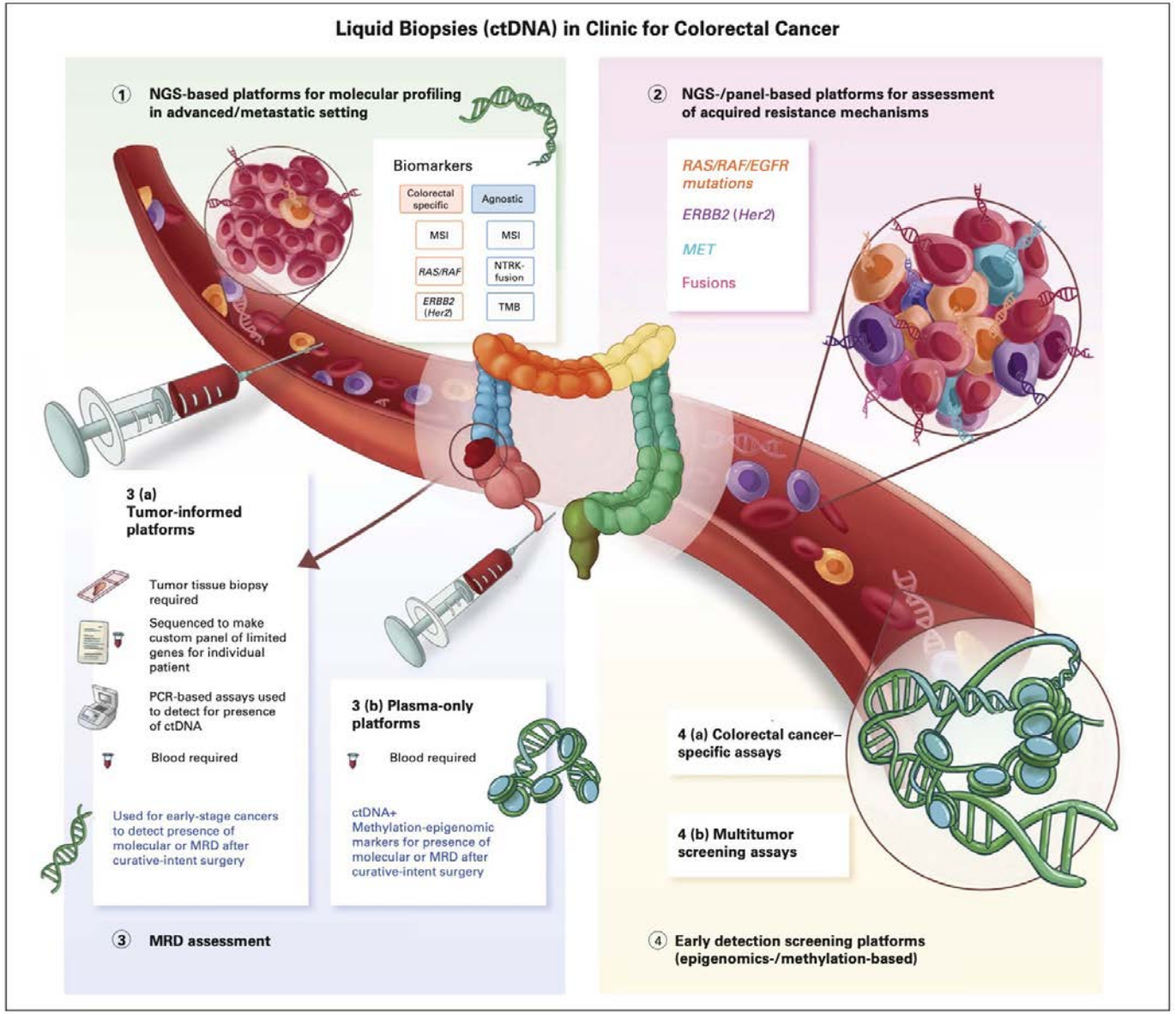
Use of Adjuvant Therapy in the Management of Localized CRC

Dr Shah
New York, New York

Dr Strickler
Durham, North Carolina

- **Factors guiding the use of adjuvant chemotherapy for patients with Stage II and Stage III CRC**
- **Rationale for the assessment of molecular residual disease (MRD) using circulating tumor DNA (ctDNA) to help inform treatment decision-making for patients with localized CRC**
- **Published research data with ctDNA testing to identify patients at increased risk for recurrence who are likely to benefit from adjuvant chemotherapy**
- **Active studies examining the clinical utility of ctDNA-based MRD testing for guiding treatment decisions and monitoring recurrence in CRC; current and future clinical role**

Rationale for ctDNA-Based MRD Monitoring in Localized CRC



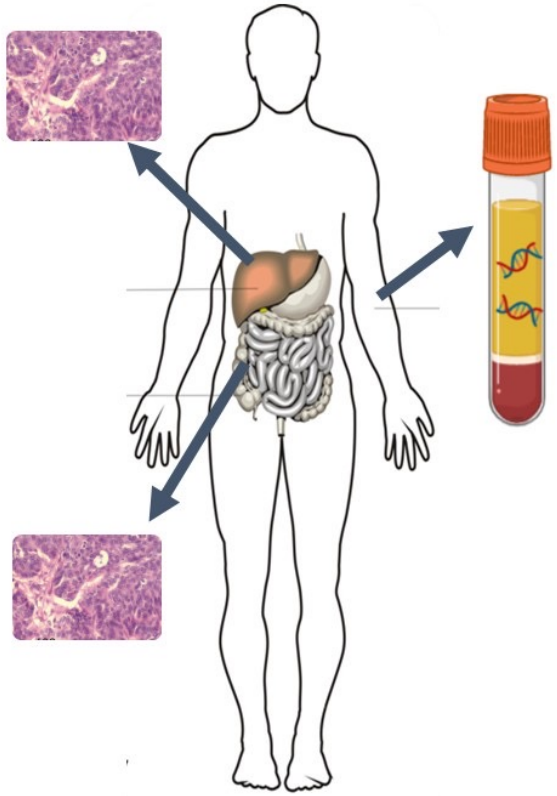
Malla M et al. *J Clin Oncol* 2022;40(24):2846-57.

Courtesy of Christopher Lieu, MD

Tumor Tissue vs. Blood NGS Testing

Tumor Tissue Assay

- **Delayed** results
- Invasive, biopsy risk, serial biopsy more difficult
- Represent one small tumor region
- Uses existing tissue processing approaches
- No assessment of tumor load
- Larger panel
- Limitations: Accessibility, quality, and quantity



ctDNA Assay

- **Quick** results
- Less invasive, easy serial testing
- More representative of whole tumor or all metastatic sites
- Requires special processing or use cell stabilizing tubes
- Quantitative analysis correlates with tumor load
- Reduced logistics
- Smaller biomarker panel

*Excellent concordance previously demonstrated

Acknowledgement: Jeanne Tie, ASCO 2022; Bardelli et al: Cell Press, 2022

Courtesy of Cathy Eng, MD, FACP, FASCO

Caroline Kuhlman, MSN, APRN-BC

What I tell my patients being considered for adjuvant chemotherapy after surgery for localized CRC about the role of ctDNA

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- **Module 7: Use of Novel Targeted Therapy in the Management of mCRC**

The Current Role of Immune Checkpoint Inhibitors (ICIs) in the Treatment of Metastatic CRC (mCRC)

Dr Shah
New York, New York

Dr Strickler
Durham, North Carolina

- **Incidence of MSI-H/dMMR mCRC; rationale for the activity of ICIs in MSI-H/dMMR tumors**
- **Long-term outcomes with front-line pembrolizumab for MSI-H/dMMR mCRC**
- **Recently presented findings indicating improved progression-free survival with first-line nivolumab/ipilimumab compared to chemotherapy for patients with MSI-H/dMMR mCRC; potential role of this strategy**
- **Rational incorporation of pembrolizumab, nivolumab and nivolumab/ipilimumab into treatment for patients with progressive MSI-H/dMMR mCRC**

Tolerability and Other Practical Considerations with ICIs

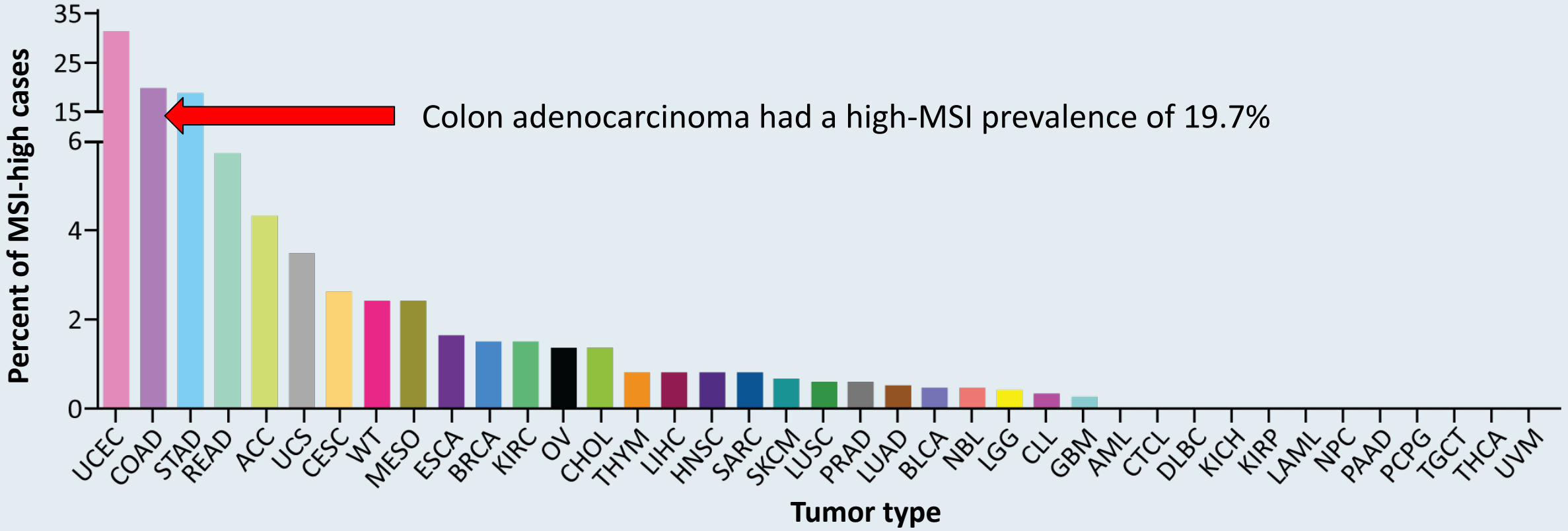
Dr Shah
New York, New York

Dr Strickler
Durham, North Carolina

- **Pathophysiology, spectrum, frequency, severity and timing of immune-mediated and other adverse events (AEs) observed with anti-PD-1/PD-L1 antibodies**
- **Effect on the tolerability of anti-PD-1/PD-L1 antibodies when administered in combination with other systemic therapies such as chemotherapy and anti-CTLA-4 antibodies**
- **Optimal approaches to monitoring and management for immune-related and other AEs with ICIs; differences in approach, if any, for patients with localized versus metastatic disease**
- **Optimal duration of immune checkpoint inhibition**

High MSI Across 39 Cancer Types

Whole-exome data from 11,139 tumor-normal pairs from The Cancer Genome Atlas and Therapeutically Applicable Research to Generate Effective Treatments projects



COAD = colon adenocarcinoma

Bonneville R et al. *JCO Precis Oncol* 2017;1:1-15; Green AK et al. *ASCO Educational Book* 2020.

RTP RESEARCH TO PRACTICE

Pembrolizumab Versus Chemotherapy in Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: 5-Year Follow-Up of the Randomized Phase 3 KEYNOTE-177 Study

Kai-Keen Shiu,[1] Thierry Andre,[2] Tae Won Kim,[3] Benny Vittrup Jensen,[4] Lars Henrik Jensen,[5] Cornelis J. A. Punt,[6,7] Denis Smith,[8] Rocio Garcia-Carbonero,[9] Julia Alcaide García,[10] Peter Gibbs,[11] Christelle de la Fouchardiere,[12] Fernando Rivera,[13] Elena Elez,[14] Dung T. Le,[15] Takayuki Yoshino,[16] Yi Zuo,[17] David Fogelman,[18] David Adelberg,[18] Luis A. Diaz, Jr.[19]

[1]University College Hospital, NHS Foundation Trust, London, UK; [2]Sorbonne University, Saint-Antoine Hospital, AP-HP, INSERM 938, SIRIC CURAMUS, Paris, France; [3]Asan Medical Center, University of Ulsan, Seoul, South Korea; [4]Herlev and Gentofte Hospital, Herlev, Denmark; [5]University Hospital of Southern Denmark, Vejle, Denmark; [6]Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands; [7]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands; [8]Bordeaux University Hospital, Bordeaux, France; [9]Hospital Universitario 12 de Octubre, Imas12, UCM, Madrid, Spain; [10]Hospitales Universitarios Regional y Virgen de la Victoria IBIMA, Málaga, Spain; [11]Western Health, St. Albans, VIC, Australia; [12]Centre Léon Bérard, Lyon, France; [13]Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain; [14]Vall d'Hebron Barcelona Hospital Campus, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [15]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA; [16]National Cancer Center Hospital East, Kashiwa, Japan; [17]MSD China, Beijing, China; [18]Merck & Co., Inc., Rahway, NJ, USA; [19]Memorial Sloan Kettering Cancer Center, New York, NY, USA.

Shiu K et al. ESMO 2023;Abstract LBA32.

ASCO Gastrointestinal Cancers Symposium

Nivolumab plus ipilimumab vs chemotherapy as first-line treatment for microsatellite instability-high/ mismatch repair-deficient metastatic colorectal cancer: first results of the CheckMate 8HW study

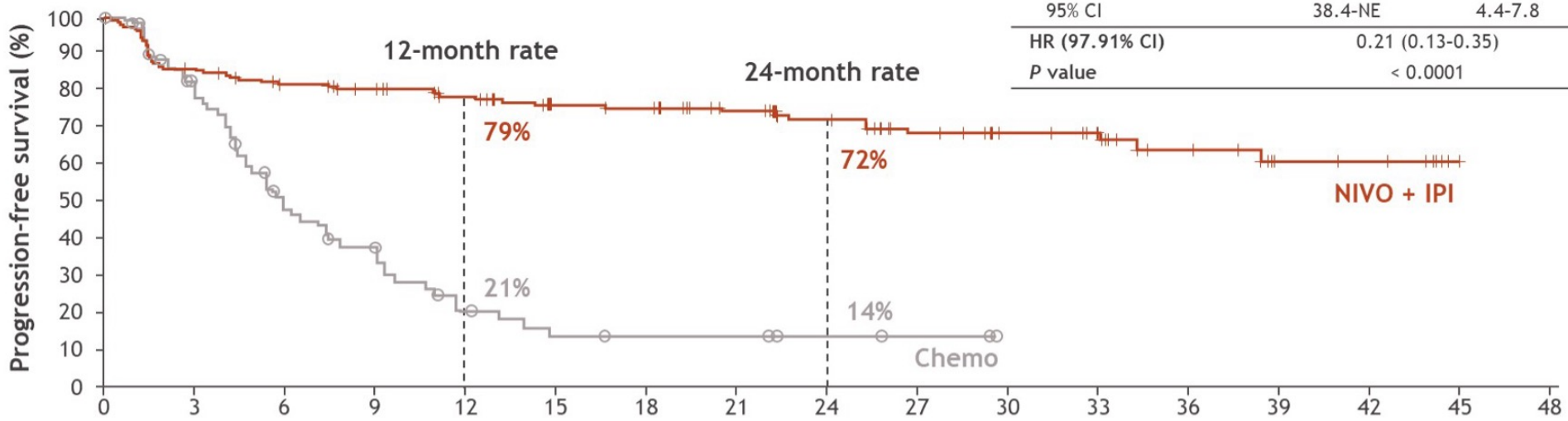
Thierry Andre,[1] Elena Elez,[2] Eric Van Cutsem,[3] Lars Henrik Jensen,[4] Jaafar Bennouna,[5] Guillermo Ariel Mendez,[6] Michael Schenker,[7] Christelle de la Fouchardiere,[8] Maria Luisa Limon,[9] Takayuki Yoshino,[10] Jin Li,[11] Heinz-Josef Lenz,[12] Jose Manzano Mozo,[13] Giampaolo Tortora,[14] Rocio Garcia-Carbonero,[15] Elvis Cela,[16] Yingsi Yang,[16] Ming Lei,[16] Lixian Jin,[16] Sara Lonardi[17]

[1]Sorbonne Université and Hôpital Saint Antoine, Assistance Publique Hôpitaux de Paris, Paris, France; [2]Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; [3]University Hospitals Gasthuisberg and University of Leuven (KU Leuven), Leuven, Belgium; [4]University Hospital of Southern Denmark, Vejle Hospital, Vejle, Denmark; [5]Centre Hospitalier Universitaire de Nantes, Nantes, France; [6]Hospital Universitario Fundacion Favaloro, Buenos Aires, Argentina; [7]Centrul de Oncologie Sf Nectarie, Craiova, Romania; [8]Centre Léon Bérard, Lyon Cedex, France; [9]Hospital Universitario Virgen del Rocío, Sevilla, Spain; [10]National Cancer Center Hospital East, Chiba, Japan; [11]Shanghai East Hospital, Shanghai, China; [12]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; [13]Institut Català d'Oncologia, Badalona, Spain; [14]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [15]Hospital Universitario 12 de Octubre Imas12, UCM, Madrid, Spain; [16]Bristol Myers Squibb, Princeton, NJ; [17]Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy

Abstract number 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

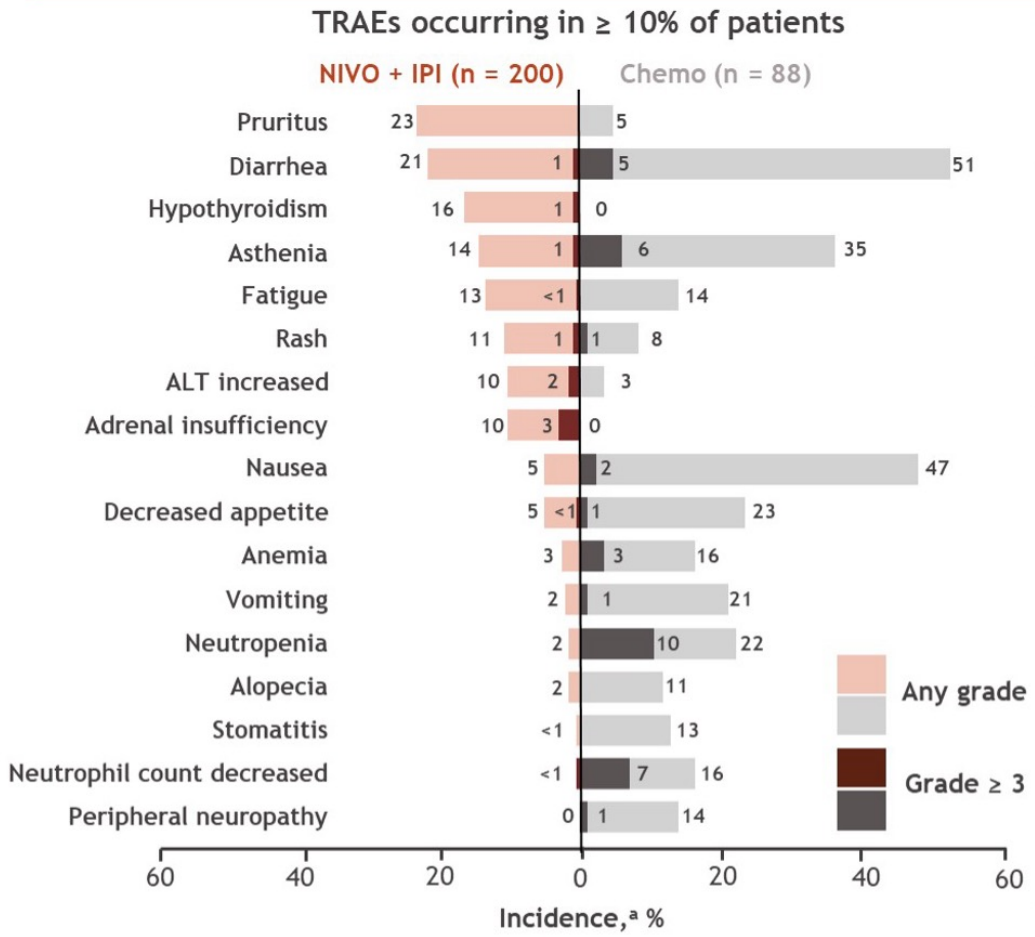
NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

- 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)

[a]Per BICR. [b]Median follow-up, 24.3 months.

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

CheckMate 8HW: Treatment-Related Adverse Events (TRAEs)



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

[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Includes 1 event each of myocarditis and pneumonitis. [c]One death (acute myocarditis) was related to crossover treatment. [d]Includes events reported within 100 days of last dose of study therapy reported in ≥ 2% of patients.

1L = first line; IMAEs = immune-mediated adverse events

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

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Symptoms of Immunotherapy Toxicity

Hypophysitis
(fatigue)

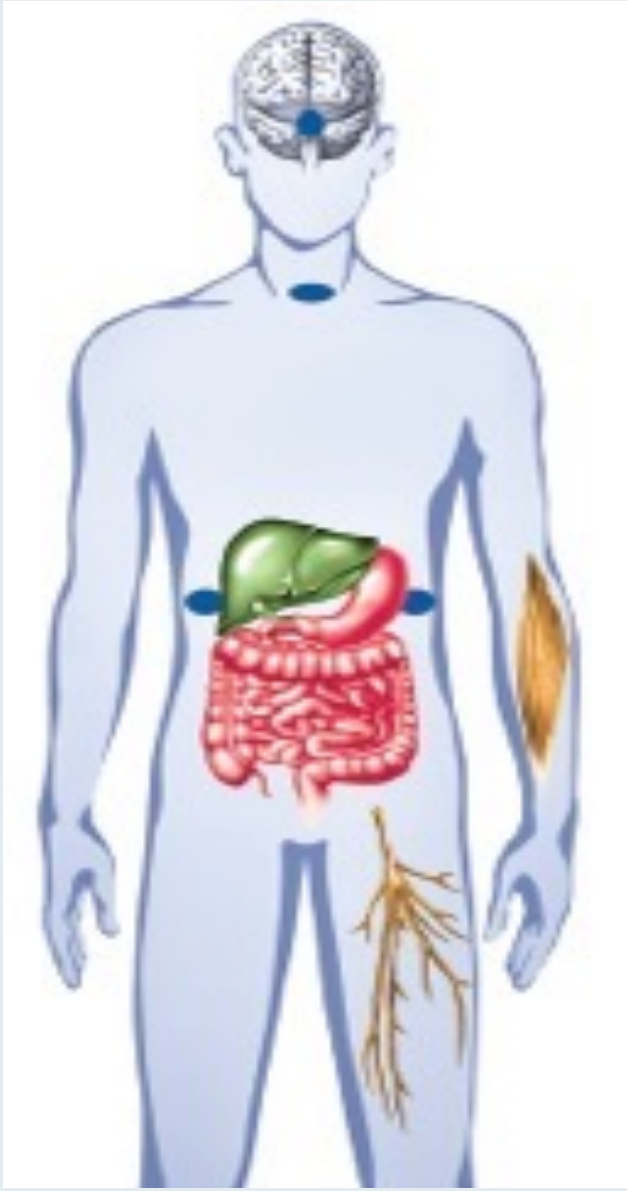
Thyroiditis
(over/underactive thyroid)

Adrenal Insufficiency
(fatigue)

Diabetes Mellitus
(type I, II, fatigue, DKA)

Colitis
(diarrhea, abd pain)

Dermatitis
(rash, itch, blistering)



Pneumonitis
(dyspnea, cough)

Myocarditis
(chest pain, dyspnea)

Hepatitis
(abn LFTs, jaundice)

Pancreatitis
(abd pain)

Neurotoxicities
(MG, encephalitis)

Arthritis
(joint pain)

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Deanna A Griffie, MSN, AGNP-C

What I tell my patients with metastatic CRC who are about to begin therapy with an immune checkpoint inhibitor

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- **Module 7: Use of Novel Targeted Therapy in the Management of mCRC**

The Role of TAS-102/Bevacizumab in the Management of Relapsed/Refractory (R/R) mCRC

Dr Shah
New York, New York

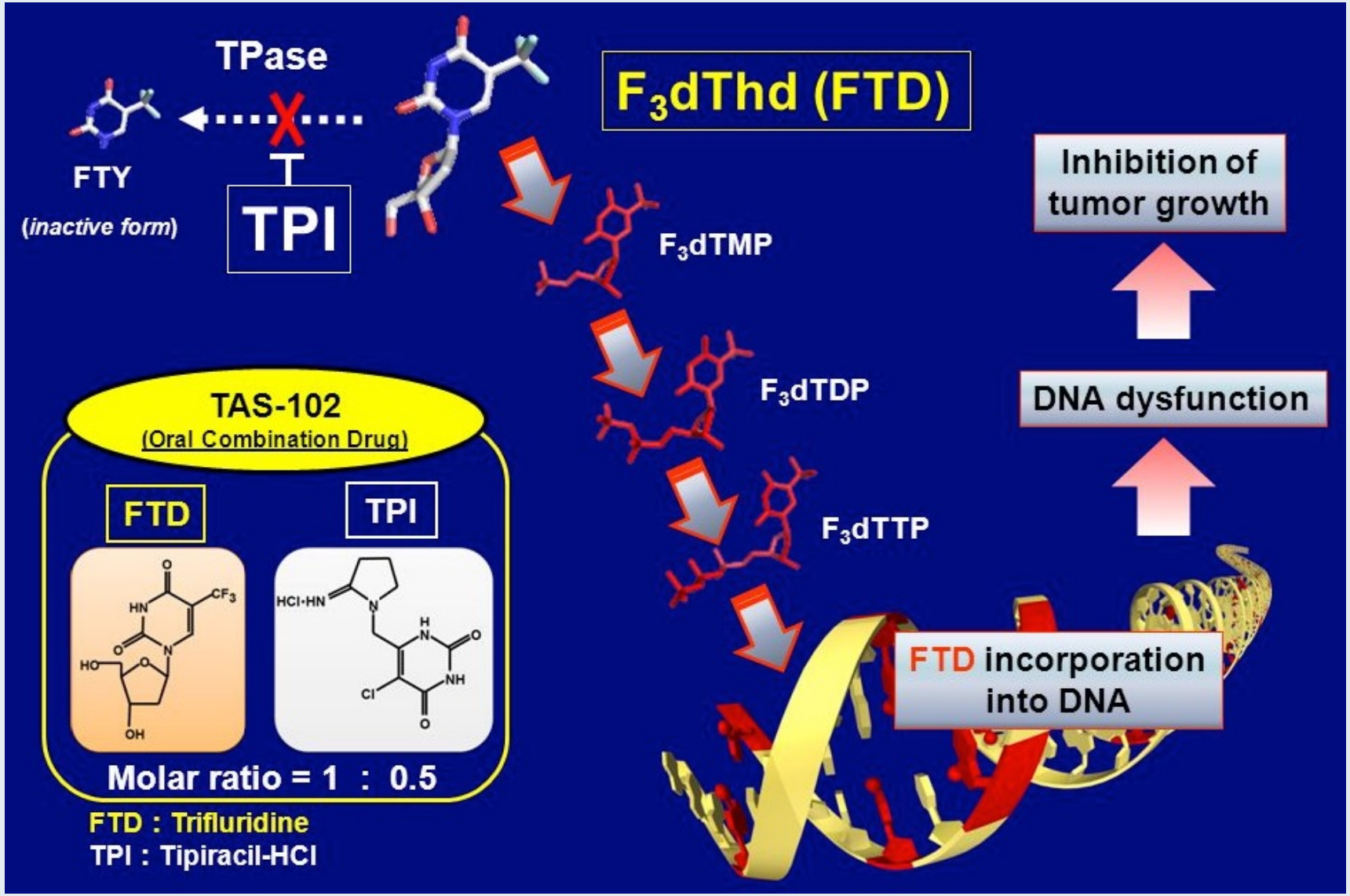
Dr Strickler
Durham, North Carolina

- **Long-term findings with TAS-102 monotherapy for patients with multiregimen-relapsed mCRC**
- **Published efficacy and safety data with TAS-102 in combination with bevacizumab for patients with R/R mCRC**
- **Recent FDA approval of TAS-102/bevacizumab and current clinical role**
- **Factors influencing the sequencing of TAS-102 with or without bevacizumab vis-à-vis other available therapies for progressive mCRC, such as regorafenib, EGFR antibodies and fruquintinib**
- **Spectrum and frequency of toxicities reported with TAS-102 with or without bevacizumab; recommended monitoring and management protocols**

Select Later-Line Options for Metastatic Colorectal Cancer

Agent	Indications
Regorafenib	mCRC previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, anti-VEGF therapy and, if RAS wild-type, anti-EGFR therapy
TAS-102	As a single agent or in combination with bevacizumab for mCRC previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, anti-VEGF therapy and, if RAS wild-type, anti-EGFR therapy
Fruquintinib	mCRC previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, anti-VEGF therapy and, if RAS wild-type and medically appropriate, anti-EGFR therapy

TAS-102: Mechanism of Action



Yoshino T et al. ESMO 2014;Abstract O-0022.

Trifluridine and Tipiracil (TAS-102)

Mechanism of action

- **Combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor**

Indication

- **As a single agent or in combination with bevacizumab for patients with mCRC who have previously received fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy and, if RAS wild type, an anti-EGFR therapy**

Recommended dose

- **35 mg/m^2 (maximum 80 mg based on trifluridine) orally twice daily with food on days 1 through 5 and days 8 through 12 of each 28-day cycle until disease progression or unacceptable toxicity**

TAS-102 (trifluridine and tipiracil) package insert, 8/2023.

FDA Approves Trifluridine and Tipiracil with Bevacizumab for Previously Treated Metastatic Colorectal Cancer

Press Release – August 2, 2023

"On August 2, 2023, the Food and Drug Administration approved trifluridine and tipiracil with bevacizumab, for metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. FDA had previously approved single-agent trifluridine and tipiracil for this indication in September 2015.

Safety and efficacy were evaluated in SUNLIGHT (NCT04737187), a randomized, open-label, multicenter, global trial of trifluridine and tipiracil with bevacizumab compared to single-agent trifluridine and tipiracil in 492 patients with mCRC who received a maximum of two prior chemotherapy regimens and demonstrated progressive disease or intolerance to the last regimen.

The recommended trifluridine and tipiracil dose is 35 mg/m^2 orally twice daily with food on days 1 through 5 and days 8 through 12 of each 28-day cycle"

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-trifluridine-and-tipiracil-bevacizumab-previously-treated-metastatic-colorectal-cancer

TAS-102/Bevacizumab: Common Side Effects

The most common side effects of TAS-102 when used alone include

- Low blood counts
- Tiredness and weakness
- Nausea
- Decreased appetite
- Diarrhea
- Vomiting
- Abdominal pain
- Fever

The most common side effects of TAS-102 when used in combination with bevacizumab include

- Low blood counts
- Tiredness and weakness
- Nausea
- Certain abnormal liver function blood tests
- Decreased sodium in blood
- Diarrhea
- Abdominal pain
- Decreased appetite

TAS-102 (trifluridine and tipiracil) patient information, 8/2023

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Caroline Kuhlman, MSN, APRN-BC

What I tell my patients with mCRC who are about to begin therapy with TAS-102/bevacizumab

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Agenda

Introduction

Part 1: Gastroesophageal Cancer

Part 2: Colorectal Cancer (CRC)

- **Module 4: Adjuvant Therapy in the Management of Localized CRC**
- **Module 5: Immunotherapy in the Management of Metastatic CRC (mCRC)**
- **Module 6: Management Approaches for Patients with Relapsed/Refractory (R/R) mCRC**
- **Module 7: Use of Novel Targeted Therapy in the Management of mCRC**

The Potential Role of KRAS-Targeted Therapy in the Management of mCRC

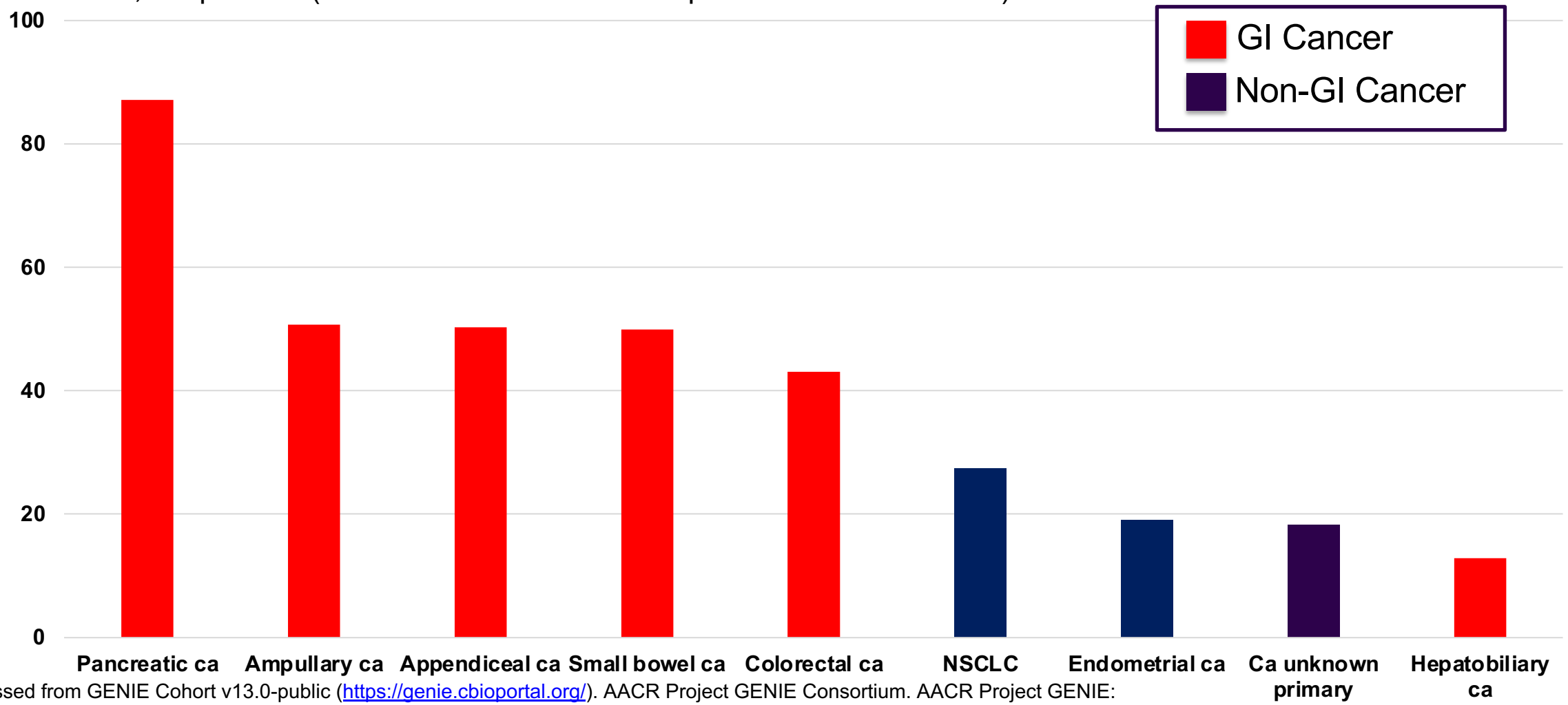
Dr Shah
New York, New York

Dr Strickler
Durham, North Carolina

- **Incidence of KRAS G12C mutations in mCRC; mechanism of action of sotorasib and adagrasib**
- **Available efficacy and safety data with sotorasib and adagrasib monotherapy for patients with mCRC and KRAS G12C mutations**
- **Rationale for combining KRAS-targeted agents with anti-EGFR therapy for mCRC**
- **Recently presented findings with sotorasib and panitumumab for patients with chemorefractory mCRC with a KRAS G12C mutation; potential clinical role of this strategy**

KRAS: An Important Target for GI Cancers

N= 148,268 patients (tumors with *KRAS* mutation prevalence > 10% listed)



Accessed from GENIE Cohort v13.0-public (https://genie.cbioportal.org/). AACR Project GENIE Consortium. AACR Project GENIE: powering precision medicine through an international consortium. Cancer Discov 2017; 7: 818-31.

Courtesy of John H Strickler, MD

Adagrasib and Sotorasib: Colorectal Cancer

Mechanism of action

- **RAS GTPase inhibitors**

Indication

- **Investigational for CRC**

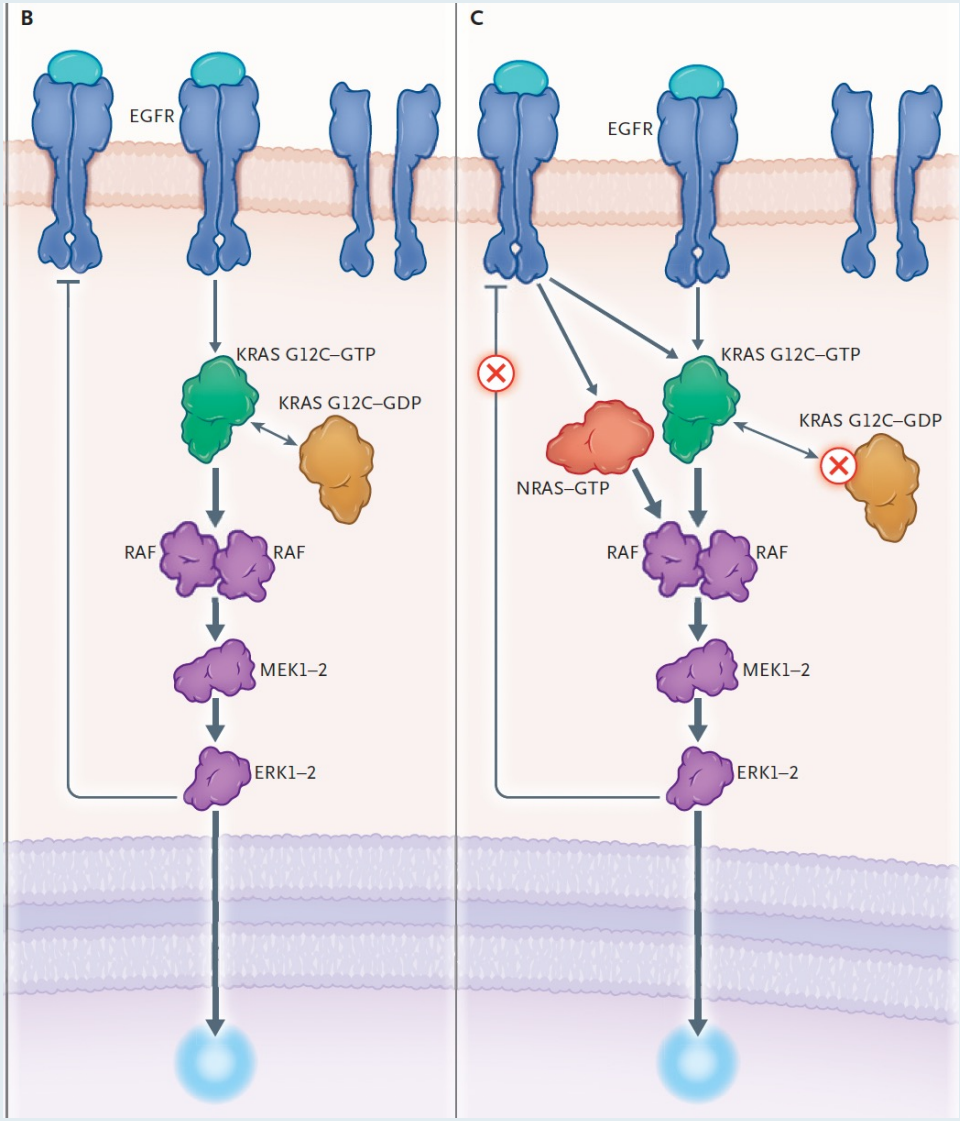
Pivotal clinical data

- **Phase I/II KRYSTAL-1 study of adagrasib with or without cetuximab for patients with previously treated KRAS G12C-mutated metastatic CRC**
- **Phase II CodeBreaK 100 study of sotorasib for advanced solid tumors harboring a KRAS G12C mutation**
- **Phase III CodeBreaK 300 trial of sotorasib and panitumumab for chemorefractory metastatic CRC with a KRAS G12C mutation**

Yaeger R et al. *N Engl J Med* 2023;388:44-54; Yaeger R et al. *Cancer Discov* 2024;April 8:OF1-OF12.
Fakih MG et al. *Lancet Oncol* 2022;23:115-24; Fakih MG et al. *N Engl J Med* 2023;389(23):2125-39.

Rationale for KRAS-Targeted and Anti-EGFR Combination Therapy in mCRC

Panel B shows signaling in receptor tyrosine kinase (RTK)–rich tissue, such as that of the colorectum, where negative feedback loops resulting from activated extracellular signal-related kinase (ERK) largely suppress signaling from RTKs such as EGFR.



Arrow thickness indicates the relative strength of signal.

Panel C shows the effects of KRAS G12C mutation selective inhibition wherein ERK inhibition by drug releases the negative feedback loops, leading to activation of RTK and downstream signaling and ultimately resulting in a rebound in ERK signaling.

The high level of RTKs seen with colorectal cancer effectively raises the threshold needed to sufficiently inhibit the ERK pathway to elicit tumor regression.

The EGFR inhibitor in this combination treatment serves to inhibit the feedback reactivation.

Yaeger R. *N Engl J Med* 2023;389(23):2197-99.

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Deanna A Griffie, MSN, AGNP-C

What I tell my patients with mCRC and a KRAS G12C mutation who are about to begin therapy with a KRAS inhibitor

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Consulting Nursing Faculty Comments

Isn’t oncology depressing?

Tiffany A Richards, PhD, ANP-BC, AOCNP

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Consulting Nursing Faculty Comments

Advice to someone entering the oncology nursing field

Tiffany A Richards, PhD, ANP-BC, AOCNP

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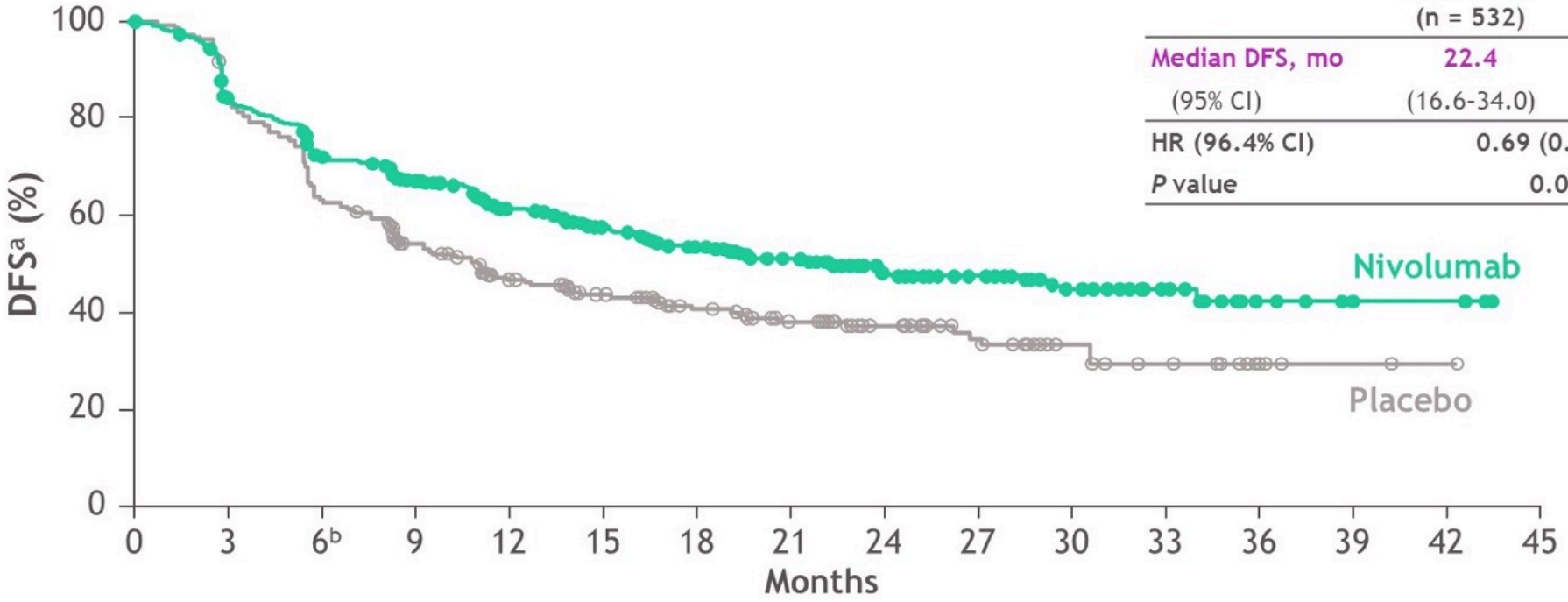
Appendix

CheckMate 577 Trial: Disease-Free Survival (DFS)



	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6-34.0)	(8.3-14.3)
HR (96.4% CI)	0.69 (0.56-0.86)	
P value	0.0003[c]	

No. at risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

Kelly RJ et al. ASCO 2021;Abstract 4003.

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CheckMate 577: Treatment-Related Adverse Events (TRAEs) with Immunologic Etiology

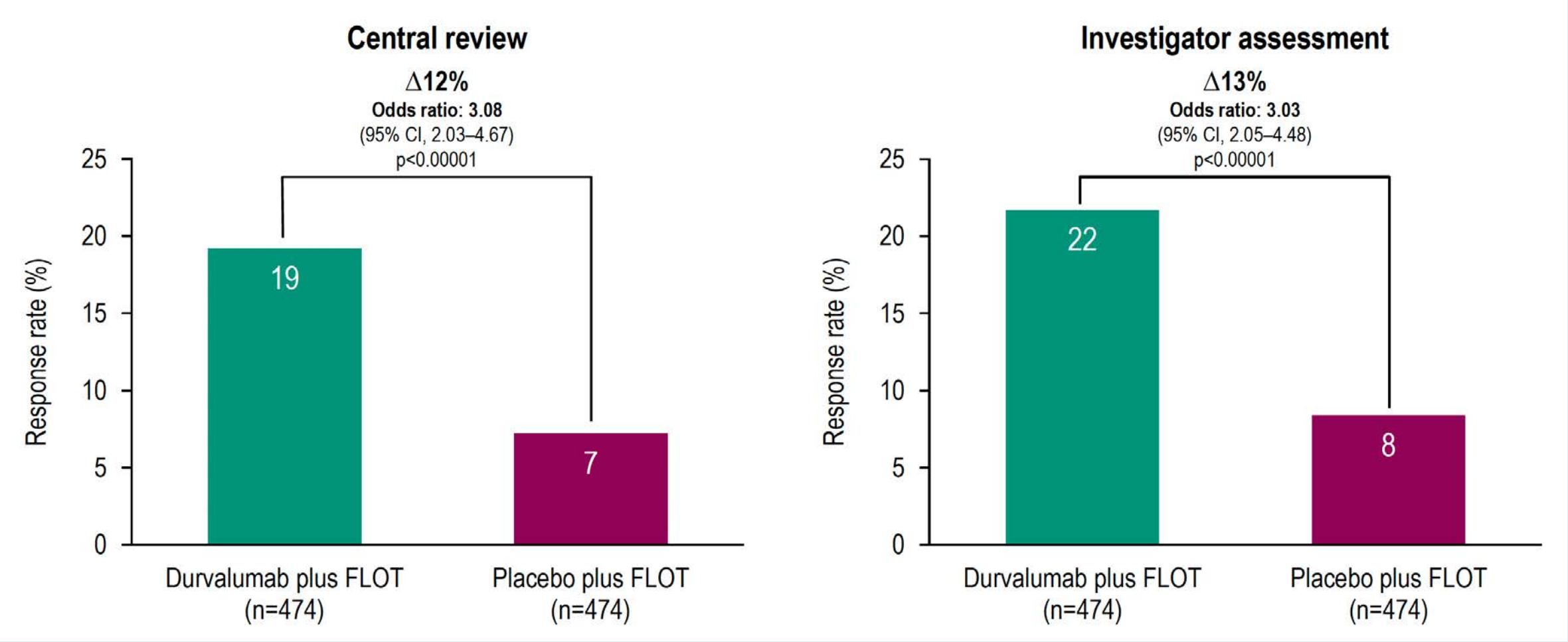
Select TRAEs,[a,b] n (%)	Nivolumab (n = 532)[c]	
	Any grade	Grade 3-4
Endocrine	93 (17)	5 (<1)
Gastrointestinal	91 (17)	4 (<1)
Hepatic	49 (9)	6 (1)
Pulmonary	23 (4)	6 (1)
Renal	7 (1)	1 (<1)
Skin	130 (24)	7 (1)

- The majority of select TRAEs were grade 1 or 2
- Grade 3-4 select TRAEs occurred in ≤ 1% of patients in the nivolumab arm and there were no grade 5 select TRAEs

[a]Select TRAEs are those with potential immunologic etiology that require frequent monitoring/intervention; [b]Events reported between first dose and 30 days after last dose of study drug; [c]Patients who received ≥ 1 dose of study treatment.
Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203.

Kelly RJ et al. ASCO 2021;Abstract 4003.

MATTERHORN Interim Analysis: Pathologic Complete Response



Al-Batran S-E et al. ESMO 2023;Abstract 129O.

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MATTERHORN Interim Analysis: Safety and Tolerability

	Durvalumab + FLOT (n=475)*	Placebo + FLOT (n=469)
Any-grade all-causality adverse events, n (%)	470 (99)	463 (99)
Max Grade 3 / 4	326 (69)	317 (68)
Serious adverse events	210 (44)	196 (42)
Leading to death	24 (5)	19 (4)
Leading to surgery delay	15 (3)	8 (2)
Leading to discontinuation of durvalumab or placebo	34 (7)	29 (6)
Leading to discontinuation of FLOT	110 (23)	94 (20)
Any adverse event possibly related to any study treatment, n (%)	452 (95)	441 (94)
Max Grade 3/4 treatment-related adverse events	275 (58)	264 (56)
Serious treatment-related adverse events	96 (20)	75 (16)
Treatment-related adverse events leading to death	5 (1)	2 (0)
Max Grade 3 / 4 most common (≥5%†) adverse events possibly related to any study treatment, n (%)		
Neutropenia	93 (20)	96 (21)
Neutrophil count decreased	90 (19)	102 (22)
Diarrhoea	25 (5)	20 (4)
White blood cell count decreased	25 (5)	27 (6)

Al-Batran S-E et al. ESMO 2023;Abstract 129O.

ASCO Gastrointestinal Cancers Symposium

Abstract LBA246

Pathological complete response to 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) with or without durvalumab in resectable gastric and gastroesophageal junction cancer: subgroup analysis by region from the Phase 3, randomized, double-blind MATTERHORN study

Yelena Y. Janjigian, MD

Yelena Y. Janjigian[1], Salah-Eddin Al-Batran[2], Zev A. Wainberg[3], Eric Van Cutsem[4], Daniela Molena[5], Kei Muro[6], Woo Jin Hyung[7], Lucjan Wyrwicz[8], Do-Youn Oh[9], Takeshi Omori[10], Markus Moehler[11], Marcelo Garrido[12], Sulene C.S. Oliveira[13], Moishe Liberman[14], Victor Castro Oliden[15], Mehmet Bilici[16], John F. Kurland[17], Ioannis Xynos[18], Helen Mann[18], Josep Tabernero[19]

[1]Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Institute of Clinical Cancer Research, Krankenhaus Nordwest, University Cancer Center, Frankfurt, Germany; [3]Department of Gastrointestinal Medical Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [4]Department of Gastroenterology/Digestive Oncology, University Hospitals Leuven and KU Leuven, Leuven, Belgium; [5]Division of Thoracic Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [7]Department of Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea; [8]Department of Oncology and Radiotherapy, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [9]Division of Medical Oncology, Department of Internal Medicine, Seoul National University Hospital; Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [10]Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan; [11]Research Center for Immunotherapy (FZI), Johannes Gutenberg-University Clinic, Mainz, Germany; [12]Hemato-Oncology Department, SAGA Clinical Trial Centre and Universidad Mayor, Santiago, Chile; [13]Clinical Oncology, The Clinical Research Center, Northern Riograndense League Against Cancer, Natal, Rio Grande do Norte, Brazil; [14]Division of Thoracic Surgery, Department of Surgery, Centre Hospitalier de l'Université de Montréal, Centre de Recherche du CHUM, Montréal, QC, Canada; [15]National Institute of Neoplastic Diseases (INEN), Lima, Peru; [16]Department of Medical Oncology, Atatürk University Faculty of Medicine, Erzurum, Turkey; [17]Oncology R&D, Late-Stage Development, AstraZeneca, Gaithersburg, MD, USA; [18]Oncology R&D, Late-Stage Development, AstraZeneca, Cambridge, UK; [19]Medical Oncology Department, Vall d'Hebron Hospital Campus & Institute of Oncology (VHIO), IOB-Quiron, UVic-UCC, Barcelona, Spain

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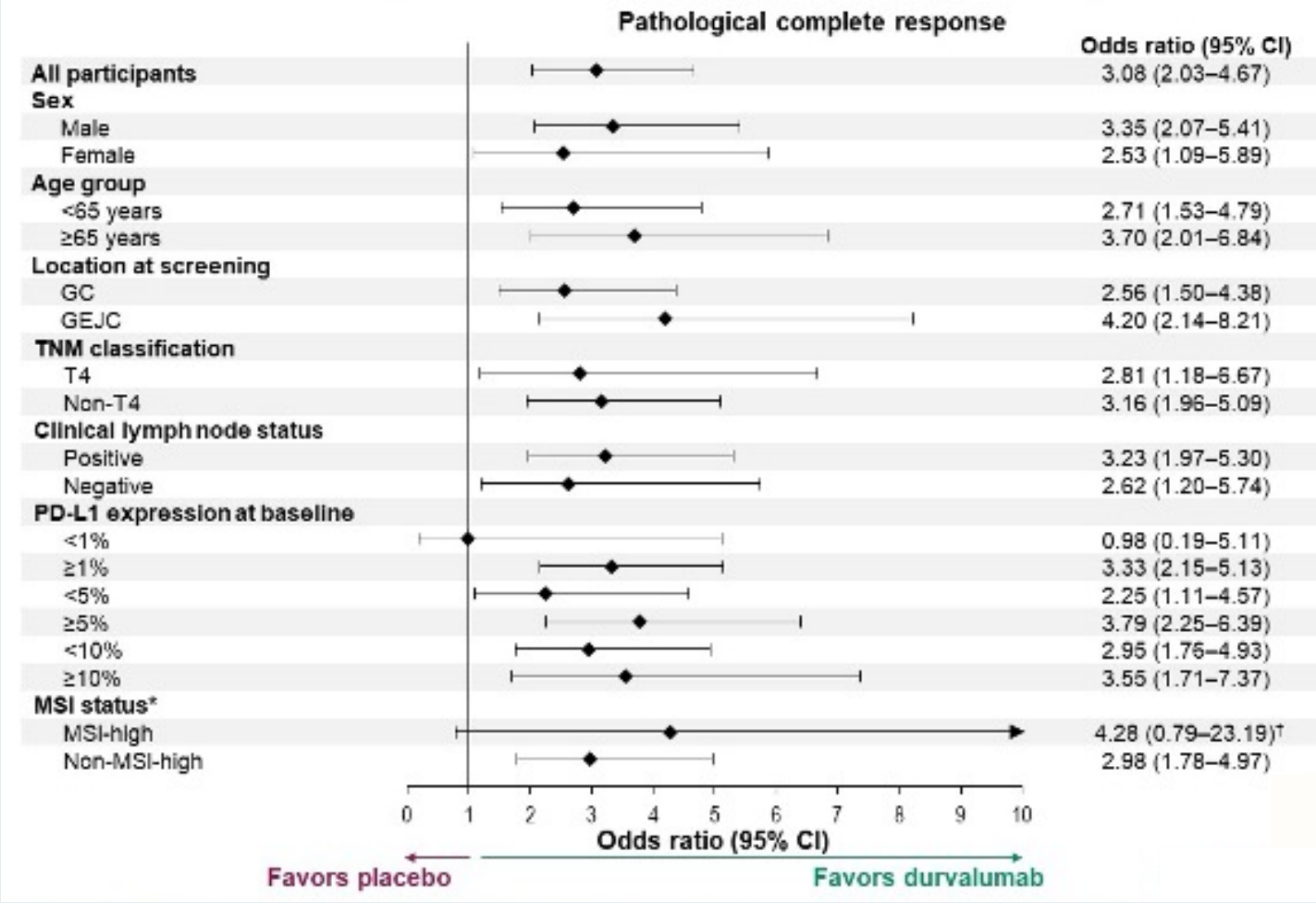
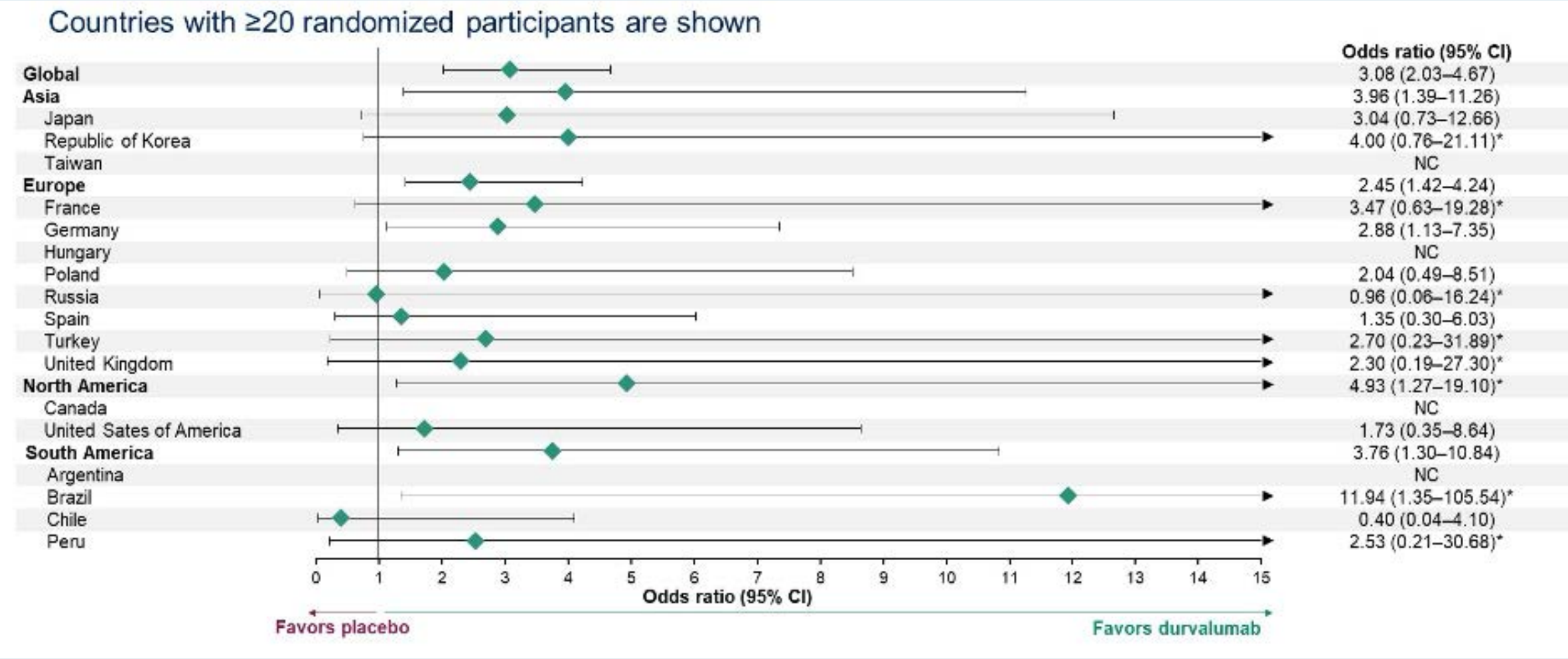
MATTERHORN Expanded Analysis: Pathologic Complete Response by Subgroup



Janjigian YY et al. Gastrointestinal Cancers Symposium 2024;Abstract LBA246.

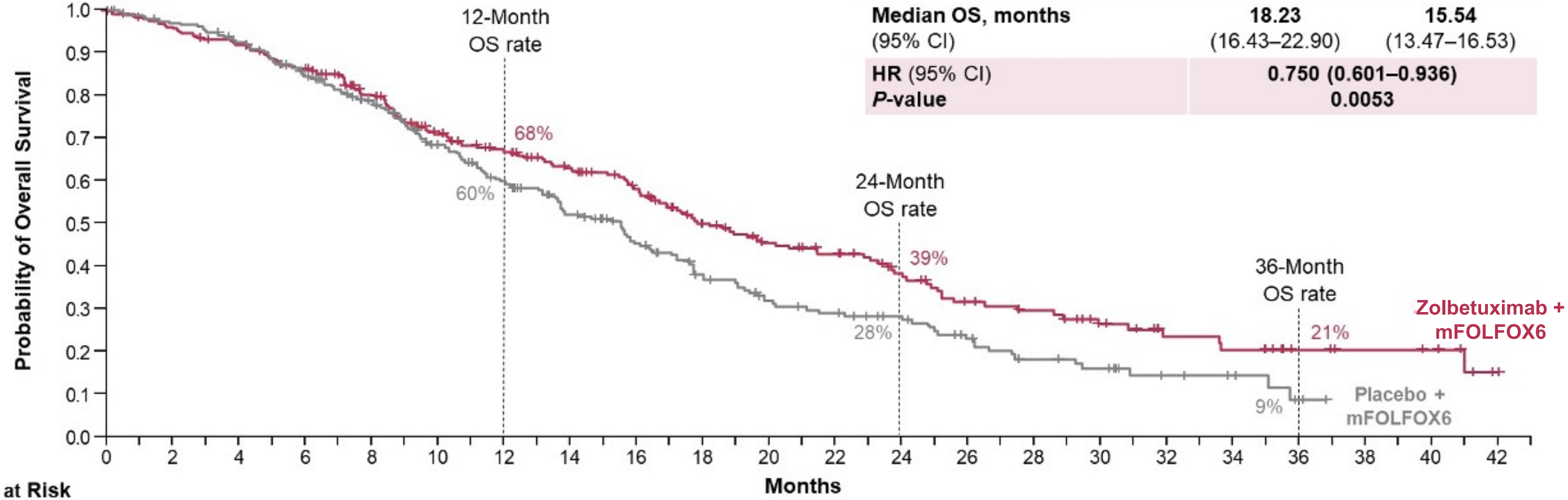
MATTERHORN Expanded Analysis: Pathologic Complete Response by Region



Janjigian YY et al. Gastrointestinal Cancers Symposium 2024;Abstract LBA246.

SPOTLIGHT: Overall Survival (Key Secondary Endpoint)

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	149/283	177/282
Median OS, months (95% CI)	**18.23** (16.43–22.90)	**15.54** (13.47–16.53)
HR (95% CI)	**0.750 (0.601–0.936)**	
***P*-value**	**0.0053**	



No. at Risk

Zolbetuximab + mFOLFOX6	283	270	264	255	251	241	233	217	196	178	164	152	146	135	125	117	107	93	83	75	70	67	62	58	49	42	34	32	30	27	23	20	15	15	13	13	9	8	7	7	6	4	1	0
Placebo + mFOLFOX6	282	277	271	266	253	242	224	210	197	183	164	152	139	129	108	101	85	77	64	60	49	42	40	36	34	30	25	21	18	17	15	9	8	7	6	5	2	0	0	0	0	0	0	0

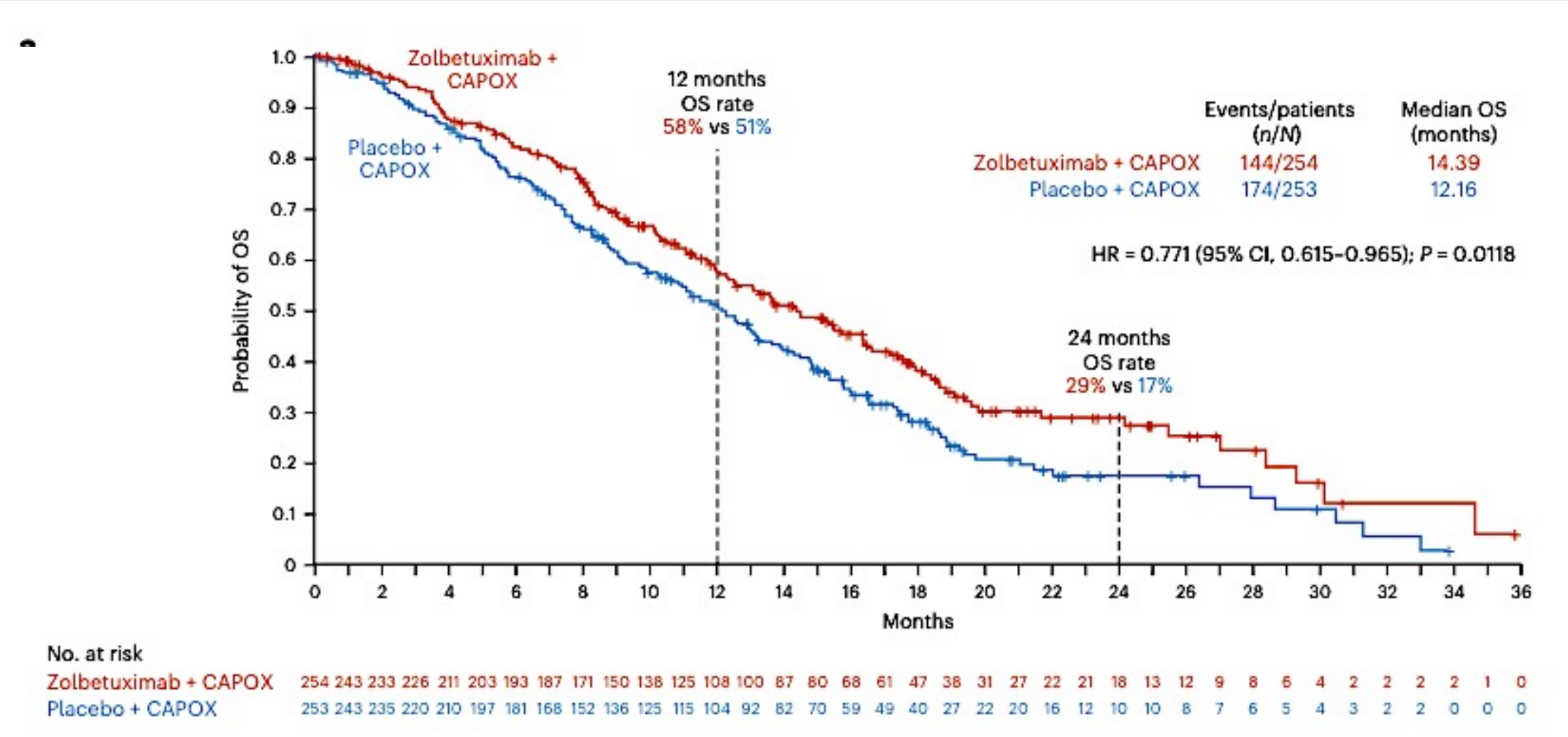
- OS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

Data cutoff: September 9, 2022; Median follow-up = 22.14 months (zolbetuximab + mFOLFOX6) vs 20.93 months (placebo + mFOLFOX6).

Shitara K et al. Gastrointestinal Cancers Symposium 2023;Abstract LBA292. Shitara K et al. *Lancet* 2023;401:1655-68.

RTP RESEARCH TO PRACTICE

GLOW: Overall Survival (Key Secondary Endpoint)



Shah MA et al. *Nat Med* 2023;29(8):2133-41.

Lancet 2023;402;2197-208.

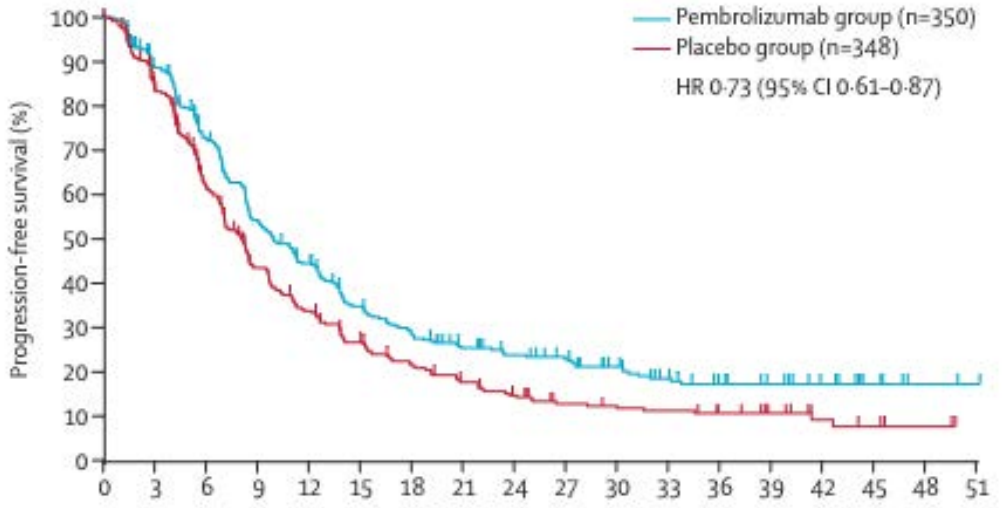
Articles

Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial

*Yelena Y Janjigian, Akihito Kawazoe, Yuxian Bai, Jianming Xu, Sara Lonardi, Jean Phillipe Metges, Patricio Yanez, Lucjan S Wyrwicz, Lin Shen, Yuriy Ostapenko, Mehmet Bilici, Hyun Cheol Chung, Kohei Shitara, Shu-Kui Qin, Eric Van Cutsem, Josep Tabernero, Kan Li, Chie-Schin Shih, Pooja Bhagia, Sun Young Rha, on behalf of the KEYNOTE-811 Investigators**

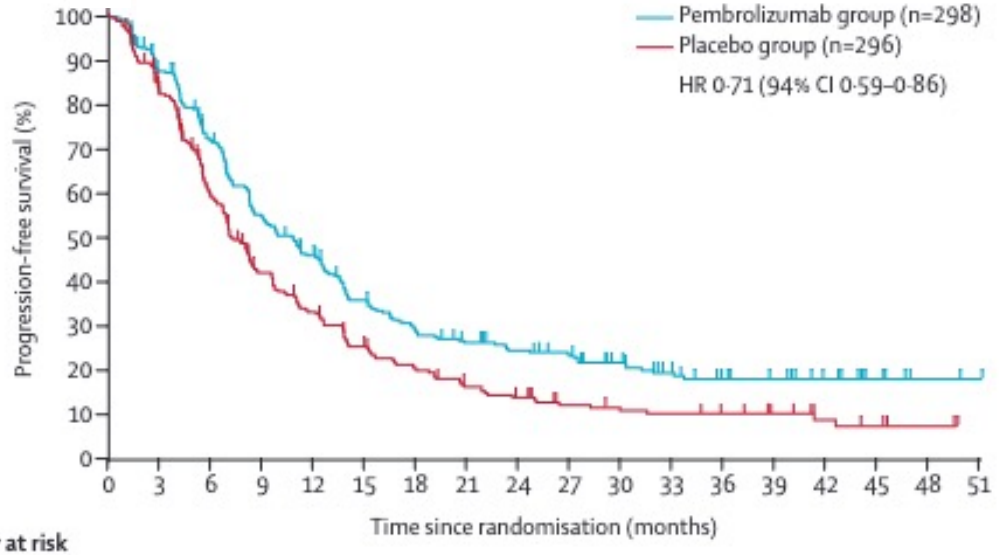
KEYNOTE-811: PFS at Interim Analysis

All Patients



Number at risk (number censored)																		
Pembrolizumab group	350	296	234	173	139	102	84	67	59	53	41	31	24	20	14	6	2	1
	(0)	(16)	(25)	(28)	(31)	(39)	(40)	(47)	(51)	(55)	(63)	(68)	(73)	(77)	(83)	(91)	(85)	(96)
Placebo group	348	274	184	121	93	71	55	43	34	25	23	21	17	11	6	4	2	0
	(0)	(22)	(43)	(52)	(53)	(56)	(59)	(61)	(63)	(68)	(69)	(69)	(72)	(78)	(82)	(83)	(85)	(87)

PD-L1 CPS ≥1

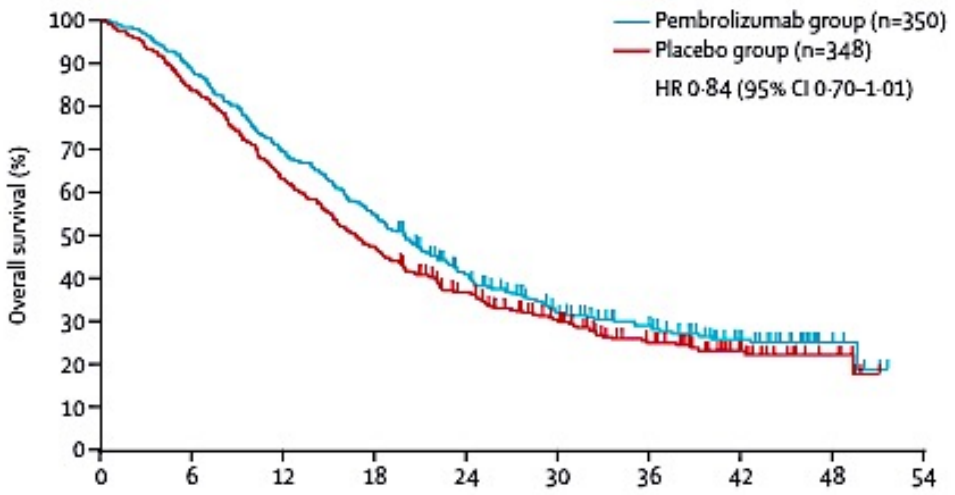


Number at risk (number censored)																		
Pembrolizumab group	298	250	200	151	123	91	74	63	56	51	39	30	23	20	14	6	2	1
	(0)	(13)	(19)	(21)	(24)	(30)	(31)	(34)	(37)	(40)	(48)	(53)	(58)	(61)	(67)	(75)	(79)	(80)
Placebo group	296	231	152	100	78	58	45	34	28	20	18	16	14	10	6	4	2	0
	(0)	(19)	(36)	(43)	(44)	(46)	(48)	(50)	(51)	(56)	(57)	(57)	(59)	(63)	(66)	(67)	(69)	(71)

Janjigian YY et al. *Lancet* 2023;402;2197-208.

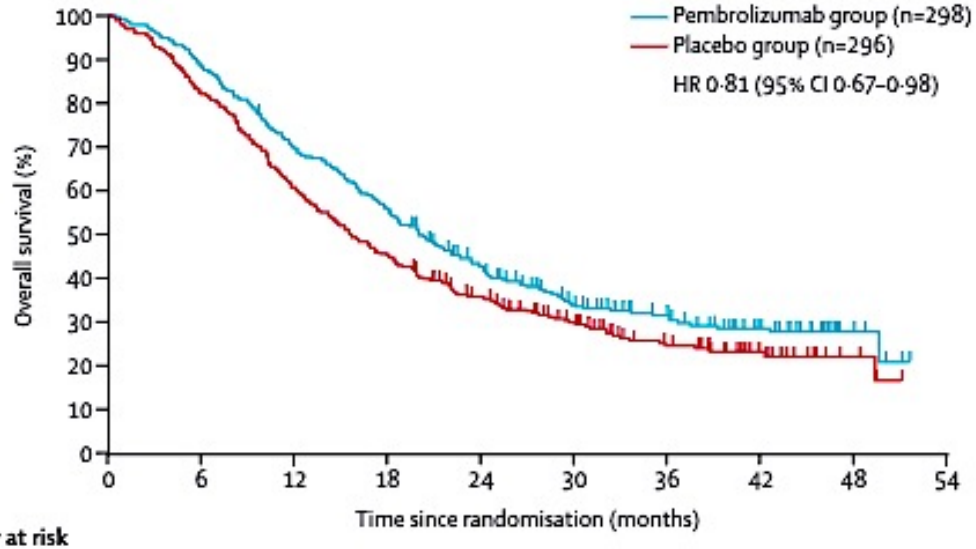
KEYNOTE-811: Overall Survival at Interim Analysis

All Patients



Number at risk (number censored)										
Pembrolizumab group	350	311	243	192	126	84	61	37	7	0
	(0)	(0)	(0)	(0)	(19)	(36)	(52)	(70)	(99)	(105)
Placebo group	348	292	220	165	116	83	51	25	8	0
	(0)	(0)	(0)	(0)	(13)	(27)	(46)	(69)	(85)	(92)

PD-L1 CPS ≥1



Number at risk (number censored)										
Pembrolizumab group	298	265	207	166	115	78	58	37	7	0
	(0)	(0)	(0)	(0)	(13)	(28)	(43)	(59)	(88)	(94)
Placebo group	296	244	180	135	96	67	41	21	5	0
	(0)	(0)	(0)	(0)	(11)	(25)	(41)	(59)	(74)	(78)

Janjigian YY et al. *Lancet* 2023;402;2197-208.

RTP RESEARCH TO PRACTICE

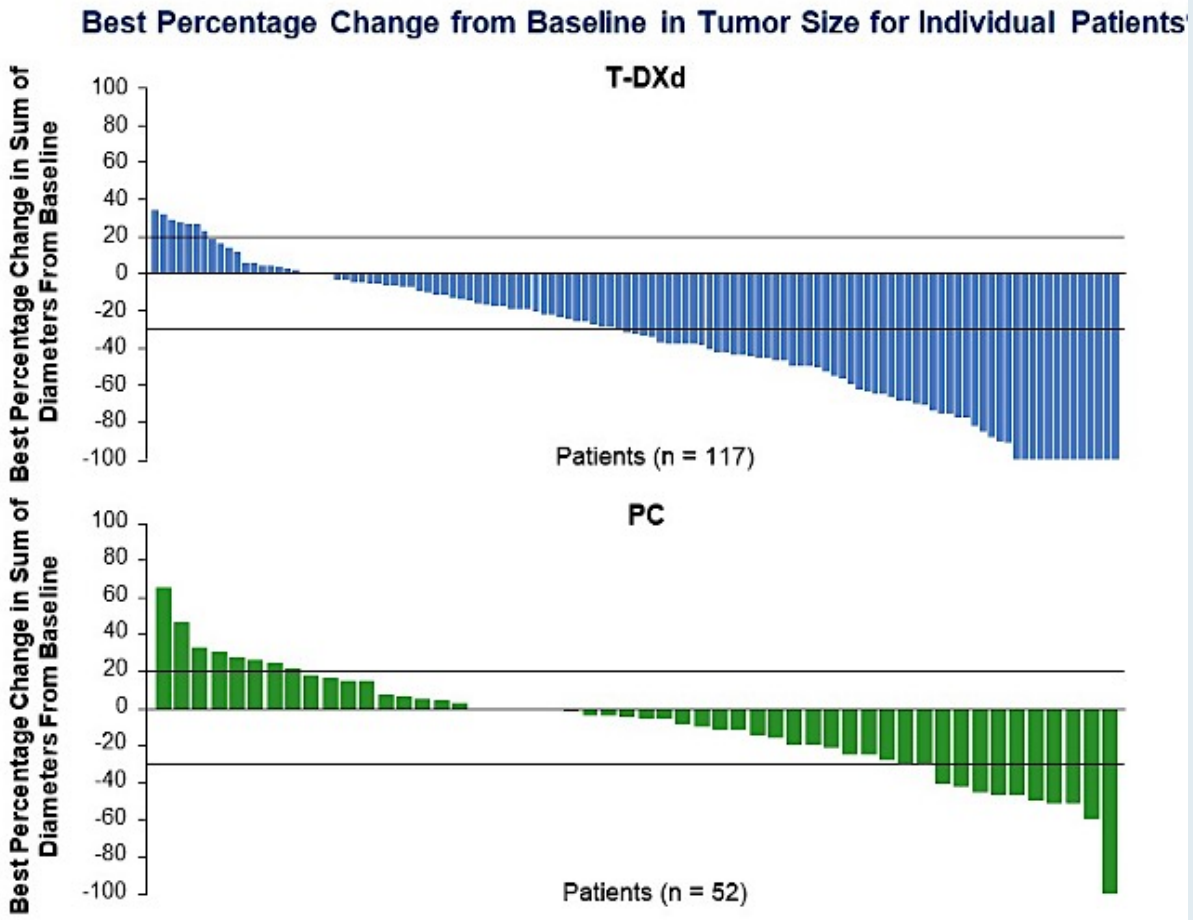
Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients with HER2-Positive Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma: Final Overall Survival (OS) Results from a Randomized, Multicenter, Open-Label, Phase 2 Study (DESTINY-Gastric01)

Yamaguchi K et al.

Gastrointestinal Cancers Symposium 2022;Abstract 242.

DESTINY-Gastric01: Antitumor Activity of Trastuzumab Deruxtecan

	T-DXd n = 119	PC Overall n = 56
ORR (CR + PR) by ICR, n (%)[a]	**61 (51.3) 95% CI, 41.9-60.5**	**8 (14.3) 95% CI, 6.4-26.2**
	P < 0.0001[b]	
CR	11 (9.2)	0
PR	50 (42.0)	8 (14.3)
SD	42 (35.3)	27 (48.2)
PD	14 (11.8)	17 (30.4)
Not evaluable	2 (1.7)	4 (7.1)
Confirmed ORR (CR + PR) by ICR, n (%)[a]	50 (42.0) 95% CI, 33.0-51.4	7 (12.5) 95% CI, 5.2-24.1
CR	10 (8.4)	0
PR	40[c] (33.6)	7 (12.5)
SD	52 (43.7)	28 (50.0)
PD	14 (11.8)	17 (30.4)
Not evaluable	3 (2.5)	4 (7.1)
Confirmed DCR (CR + PR + SD), n (%)[a]	102 (85.7) 95% CI, 78.1-91.5	35 (62.5) 95% CI, 48.5-75.1
Confirmed DOR, median, months	12.5 95% CI, 5.6-NE	3.9 95% CI, 3.0-4.9
TTR, median, months	1.5 95% CI, 1.4-1.7	1.6 95% CI, 1.3-1.7

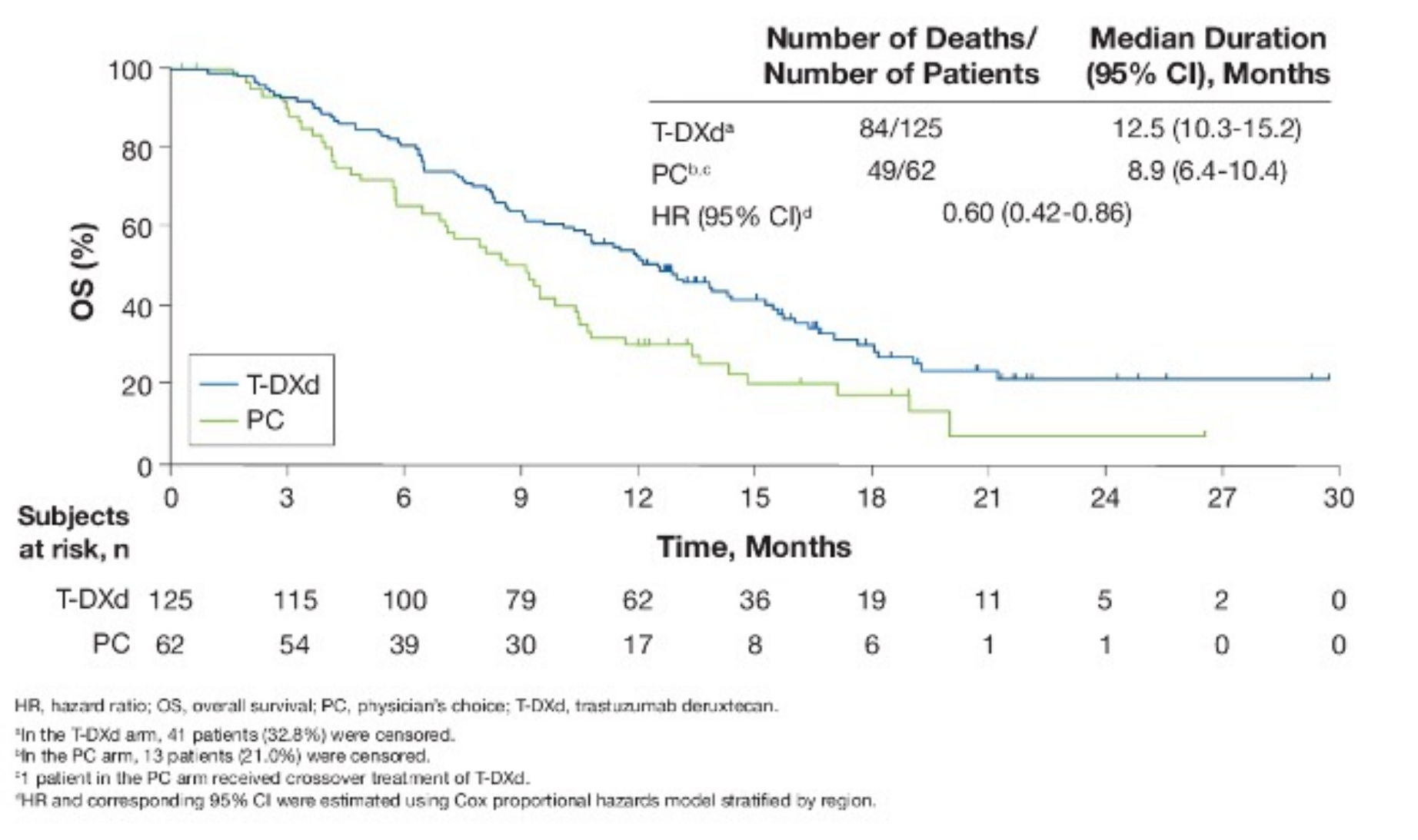


PC = physician's choice

Yamaguchi K et al. Gastrointestinal Cancers Symposium 2022;Abstract 242.

RTP RESEARCH TO PRACTICE

DESTINY-Gastric01: Final OS Analysis



HR, hazard ratio; OS, overall survival; PC, physician's choice; T-DXd, trastuzumab deruxtecan.

[a]In the T-DXd arm, 41 patients (32.8%) were censored.
[b]In the PC arm, 13 patients (21.0%) were censored.
[c]1 patient in the PC arm received crossover treatment of T-DXd.
[d]HR and corresponding 95% CI were estimated using Cox proportional hazards model stratified by region.

Yamaguchi K et al. Gastrointestinal Cancers Symposium 2022;Abstract 242.

DESTINY-Gastric01: TEAEs in ≥20% of Patients Who Received Trastuzumab Deruxtecan (T-DXd)

Preferred Term, %	T-DXd n = 125			PC Overall n = 62		
	Grade			Grade		
	Any	3	4	Any	3	4
Neutrophil count decreased[b]	64.8	38.4	12.8	35.5	16.1	8.1
Nausea	63.2	5.6	0	46.8	1.6	0
Decreased appetite	60.8	16.8	0	45.2	12.9	0
Anemia[c]	57.6	38.4	0	30.6	21.0	1.6
Platelet count decreased[d]	40.0	9.6	1.6	6.5	1.6	1.6
White blood cell count decreased[e]	38.4	20.8	0	35.5	8.1	3.2
Malaise	34.4	0.8	0	16.1	0	0
Diarrhea	32.8	2.4	0	32.3	1.6	0
Vomiting	26.4	0	0	8.1	0	0
Pyrexia	24.8	0	0	16.1	0	0
Constipation	24.8	0	0	24.2	0	0
Lymphocyte count decreased[f]	23.2	7.2	4.8	3.2	0	1.6
Alopecia	22.4	0	0	14.5	0	0
Fatigue	21.6	7.2	0	24.2	3.2	0

PC, physician's choice; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
No additional TEAEs were observed in ≥20% of patients receiving PC.

[a]There were no grade 5 events.
[b]Includes preferred terms "neutrophil count decreased" and "neutropenia."
[c]Includes preferred terms "hemoglobin decreased," "red blood cell count decreased," "anemia," and "hematocrit decreased."
[d]Includes preferred terms "platelet count decreased" and "thrombocytopenia."
[e]Includes preferred terms "leukopenia" and "white blood cell count decreased."
[f]Includes preferred terms "lymphocyte count decreased" and "lymphopenia."

- 16 patients (12.8%) had T-DXd-related interstitial lung disease (ILD)/pneumonitis, as determined by an independent adjudication committee. No Grade 5 T-DXd-related ILD/pneumonitis events were reported.

Yamaguchi K et al. Gastrointestinal Cancers Symposium 2022;Abstract 242.

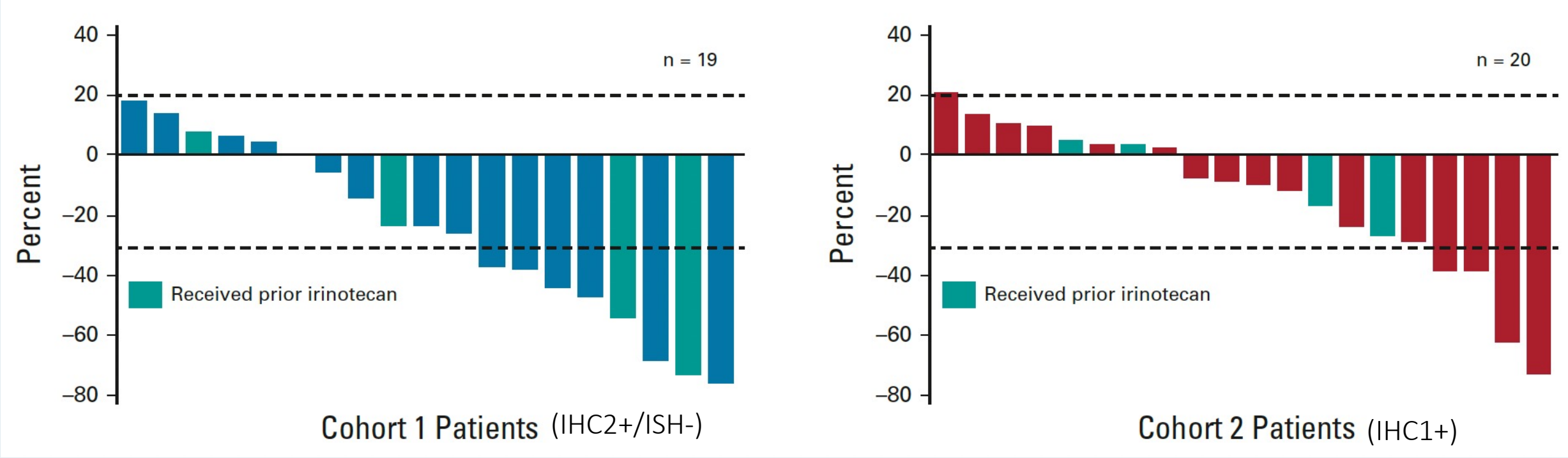
original reports

Trastuzumab Deruxtecan in Anti–Human Epidermal Growth Factor Receptor 2 Treatment–Naive Patients With Human Epidermal Growth Factor Receptor 2–Low Gastric or Gastroesophageal Junction Adenocarcinoma: Exploratory Cohort Results in a Phase II Trial

Kensei Yamaguchi, MD[1]; Yung-Jue Bang, MD, PhD[2]; Satoru Iwasa, MD[3]; Naotoshi Sugimoto, MD[4]; Min-Hee Ryu, MD, PhD[5]; Daisuke Sakai, MD[6]; Hyun Cheol Chung, MD, PhD[7]; Hisato Kawakami, MD, PhD[8]; Hiroshi Yabusaki, MD[9]; Jeeyun Lee, MD[10]; Tatsu Shimoyama, MD[11]; Keun-Wook Lee, MD, PhD[12]; Kaku Saito, MSc, MBA[13]; Yoshinori Kawaguchi, MSc, MBA[13]; Takahiro Kamio, MD[13]; Akihito Kojima, MSc[14]; Masahiro Sugihara, PhD[14]; and Kohei Shitara, MD[15]

J Clin Oncol 2023 February 1;41(4):816-25.

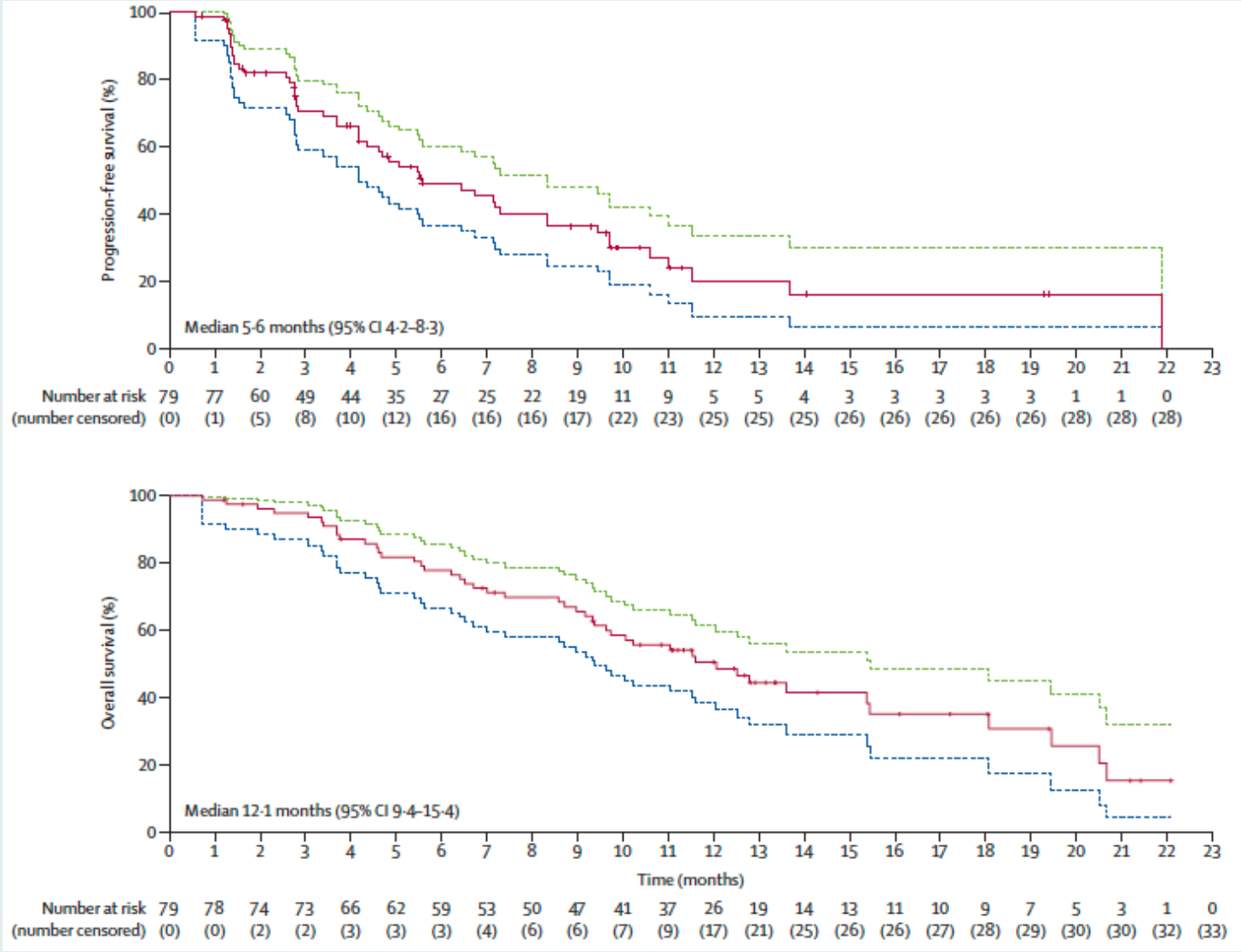
DESTINY-Gastric01: Antitumor Activity of Trastuzumab Deruxtecan in Patients with Untreated HER2-Low Gastric or Gastroesophageal Cancer



Yamaguchi K et al. *J Clin Oncol* 2023 February 1;41(4):816-25.

RTP RESEARCH TO PRACTICE

DESTINY-Gastric02: PFS and OS with Trastuzumab Deruxtecan



Van Cutsem E et al. *Lancet Oncol* 2023;24:744-56.

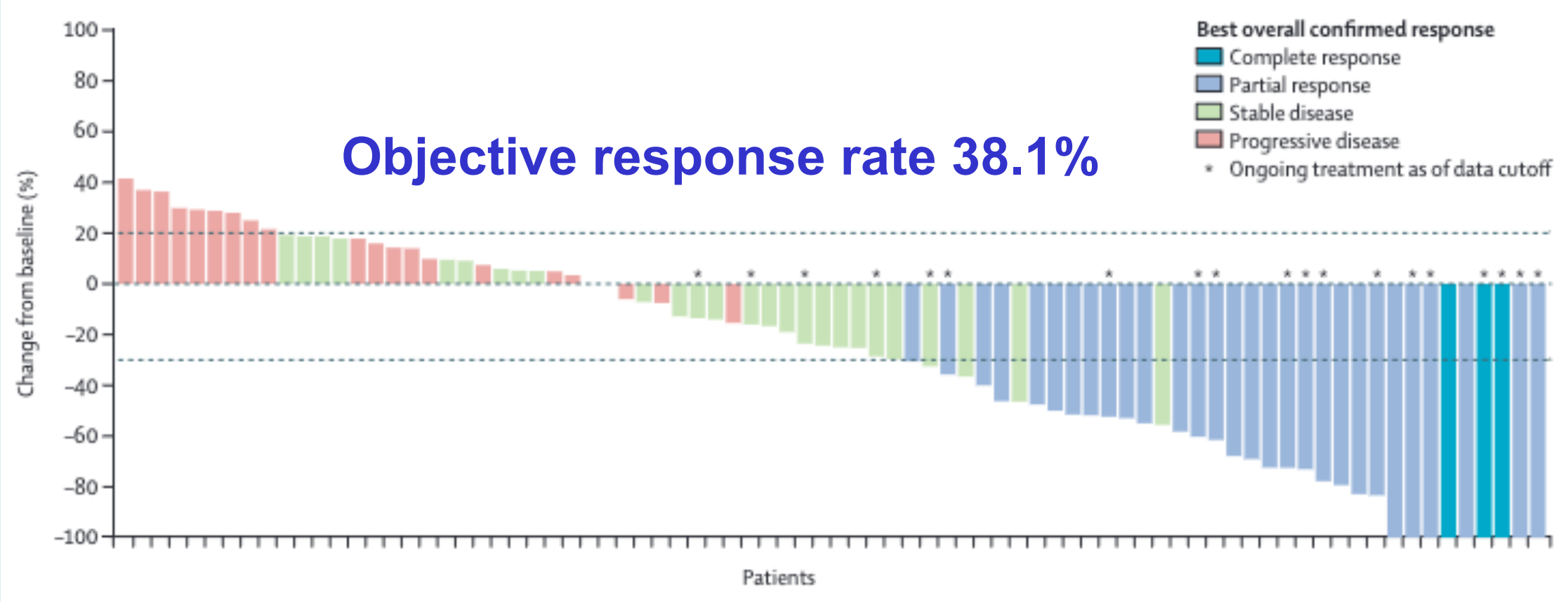
Lancet Oncol 2023;24(5):496-508.

Articles

Tucatinib plus trastuzumab for chemotherapy-refractory, HER2-positive, *RAS* wild-type unresectable or metastatic colorectal cancer (MOUNTAINEER): a multicentre, open-label, phase 2 study

*John H Strickler, Andrea Cercek, Salvatore Siena, Thierry André, Kimmie Ng, Eric Van Cutsem, Christina Wu, Andrew S Paulson, Joleen M Hubbard, Andrew L Coveler, Christos Fountzilas, Adel Kardosh, Pashtoon M Kasi, Heinz-Josef Lenz, Kristen K Ciombor, Elena Elez, David L Bajor, Chiara Cremolini, Federico Sanchez, Michael Stecher, Wentao Feng, Tanios S Bekaii-Saab, on behalf of the MOUNTAINEER investigators**

MOUNTAINEER: Efficacy of Tucatinib and Trastuzumab



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

DESTINY-CRC02: Efficacy Results

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

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

Raghav K et al. ASCO 2023;Abstract 3501.

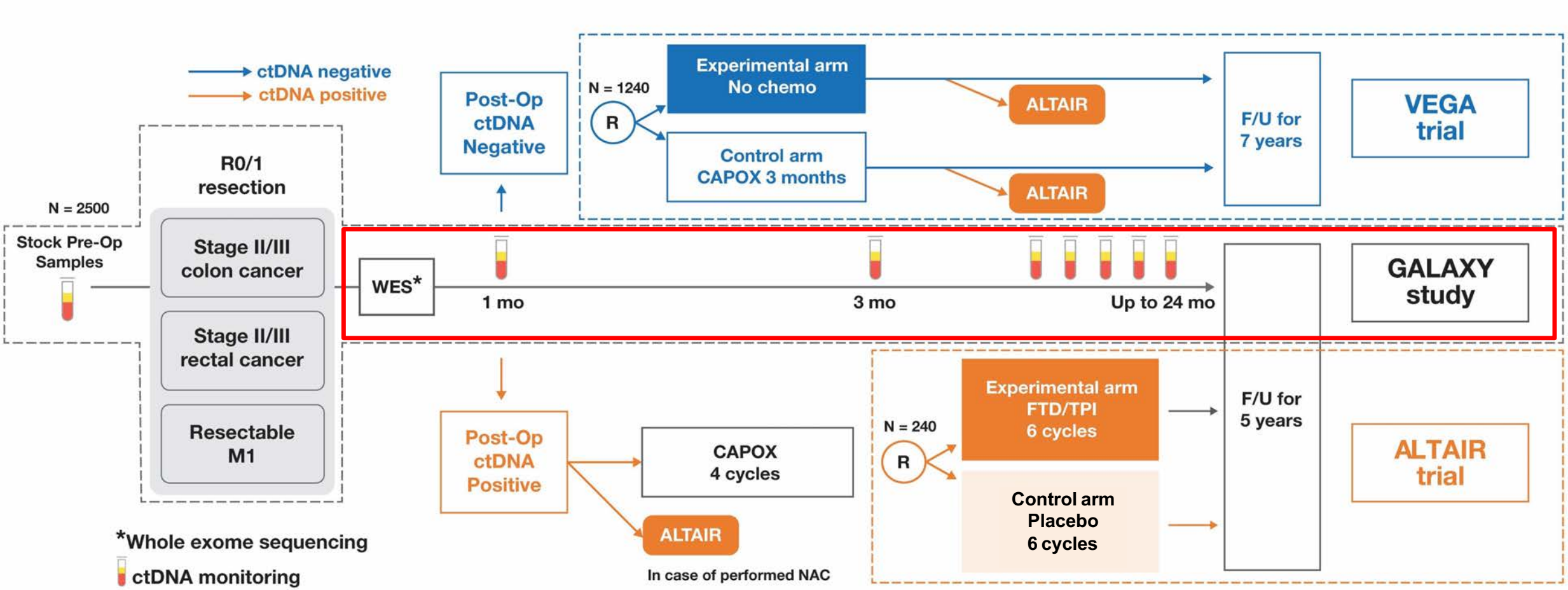
DESTINY-CRC02: Adjudicated Drug-Related ILD/Pneumonitis by Independent Adjudication Committee

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

ILD, interstitial lung disease; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.
[a]1 patient randomized to receive T-DXd 6.4 mg/kg was mistakenly given T-DXd 5.4 mg/kg and counted in the 5.4 mg/kg arm safety analysis set. [b]There was 1 adjudicated, drug-related, grade 5 ILD/pneumonitis event, which was reported as respiratory failure, which was considered unrelated to study drug by investigator.

Van Cutsem E et al. *Lancet Oncol* 2023;24:744–56.

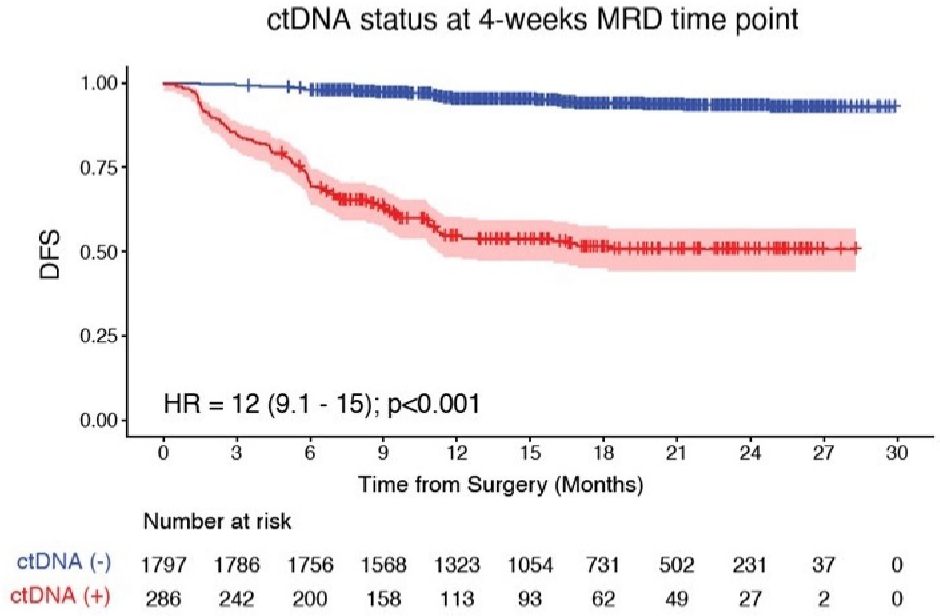
CIRCULATE-Japan Overview

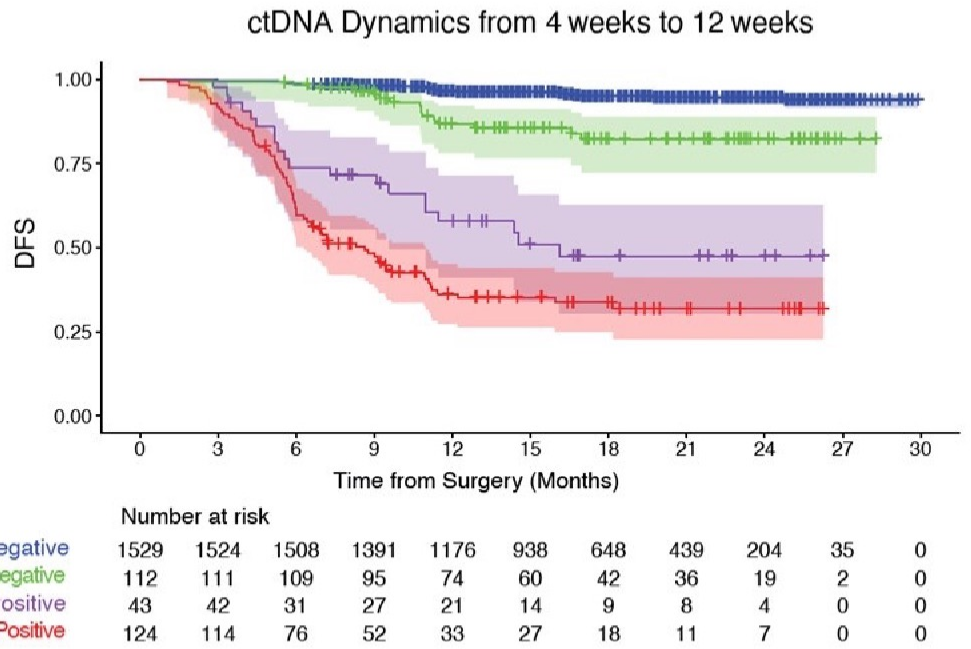


Oki E et al. 2023 ASCO Annual Meeting. Abstract 3521.

Courtesy of Christopher Lieu, MD

ctDNA dynamics between weeks 4 and 12 post surgery is prognostic of DFS





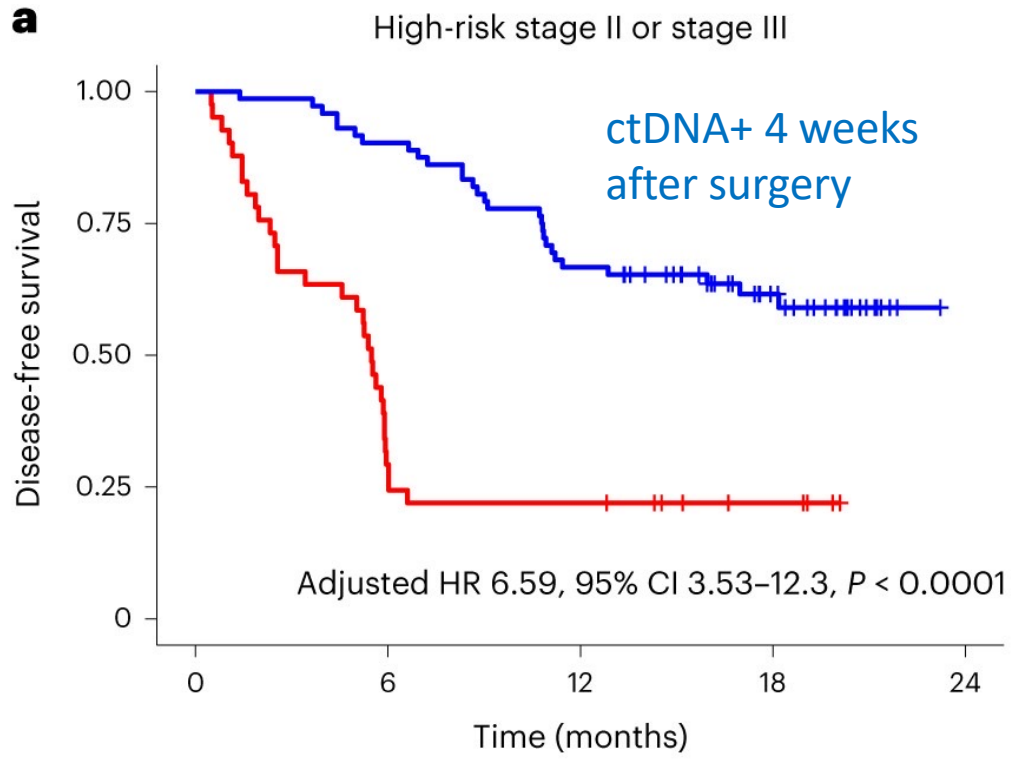
Dynamics	ctDNA Negative	ctDNA Positive
Events (n)	96/1797 (5.3%)	130/286 (45.5%)
18M - DFS	93.9 (92.5 - 95)	51.6 (45.2 - 57.6)
HR	Reference	12
95% CI	Not applicable	9.1 - 15
P	Not applicable	<0.001

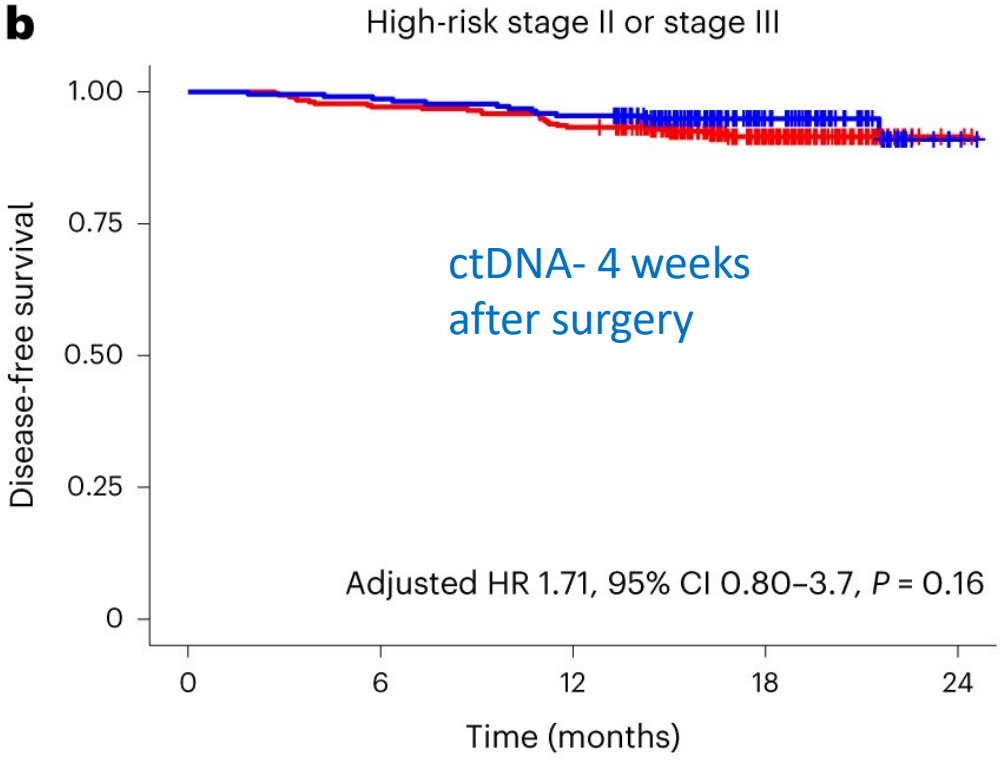
Dynamics	Persistently Negative	Converted Negative	Converted Positive	Persistently Positive
Events (n)	69/1529 (4.5%)	16/112 (14.3%)	20/43 (46.5%)	78/124 (62.9%)
18M - DFS	94.9 (93.5 - 96)	82.2 (72.3 - 88.9)	47.4 (30.4 - 62.7)	33.8 (25 - 42.8)
HR	Reference	3.5	14.5	25.4
95% CI	Not applicable	1.9 - 5.8	8.8 - 23.8	18.3 - 35.3
P	Not applicable	<0.001	<0.001	<0.001

Oki E et al. 2023 ASCO Annual Meeting. Abstract 3521.

Courtesy of Christopher Lieu, MD

ctDNA Testing Predicts Response to Adjuvant Therapy





Number at risk

Observation	41	12	9	4	0
ACT	72	65	48	26	0

Treatment	Number of events	6M-DFS (95% CI)	12M-DFS (95% CI)	18M-DFS (95% CI)
Observation	32 out of 41	29.3% (16.4–43.4)	22.0% (10.9–35.5)	22.0% (10.9–35.5)
ACT	28 out of 72	90.3% (80.7–95.2)	66.7% (54.5–76.3)	61.6% (49.0–71.9)

Number at risk

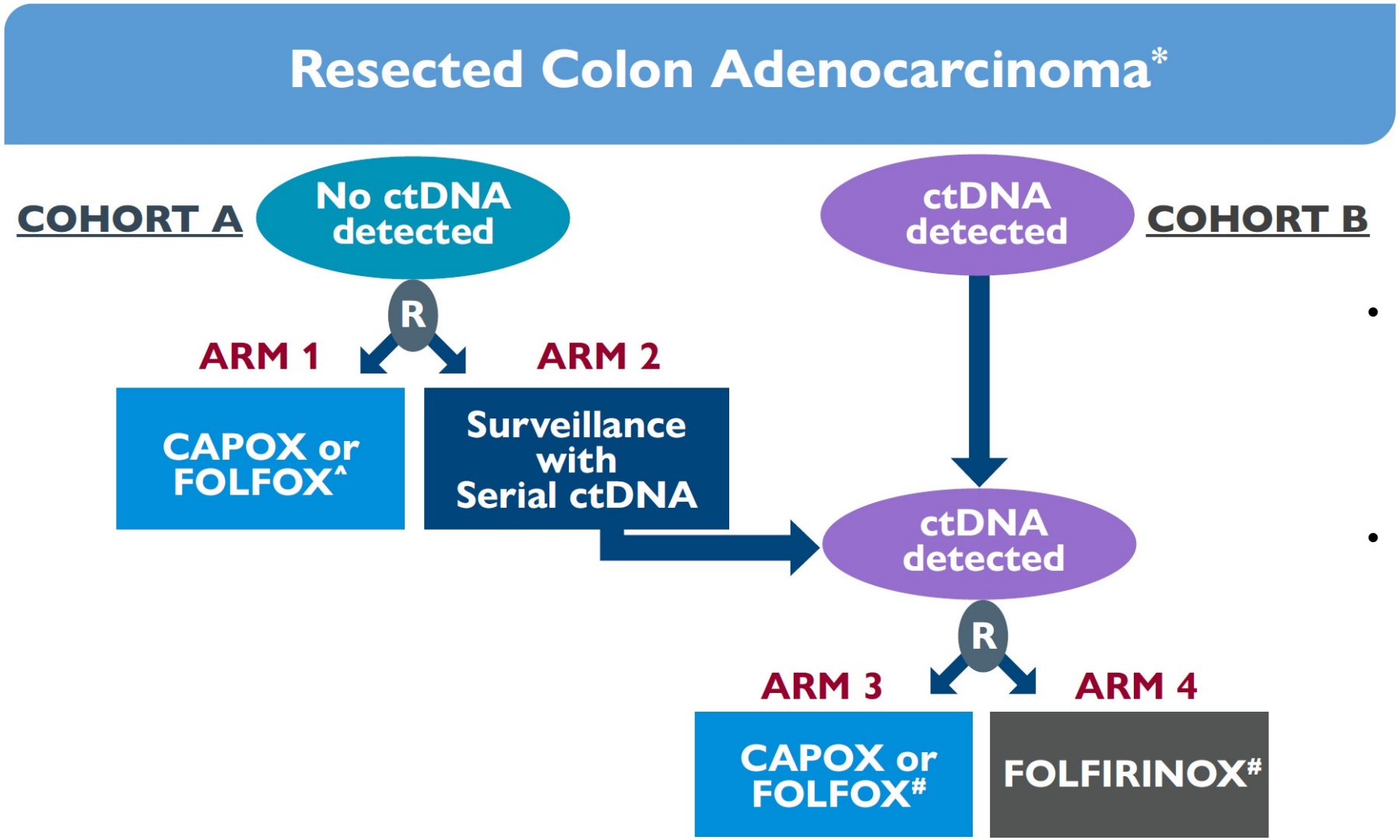
Observation	312	303	291	131	2
ACT	219	216	209	87	2

Treatment	Number of events	6M-DFS (95% CI)	12M-DFS (95% CI)	18M-DFS (95% CI)
Observation	25 out of 312	97.1% (94.5–98.5)	93.3% (89.9–95.6)	91.5% (87.6–94.2)
ACT	12 out of 219	98.6% (95.8–99.6)	95.4% (91.7–97.5)	94.9% (91.0–97.2)

Kotani D et al. *Nat Med.* 2023;29(1):127-134.

Courtesy of Christopher Lieu, MD

CIRCULATE North America: Stage III Colon Cancer Study
Amended Schema



- Study population amended to include <u>all</u> patients with Stage IIB, IIC, and Stage III colon adenocarcinoma
- One dose of chemotherapy allowed while awaiting Step 2 randomization

PIs: Dasari and Lieu (NRG-GI008 – NCT0517416)

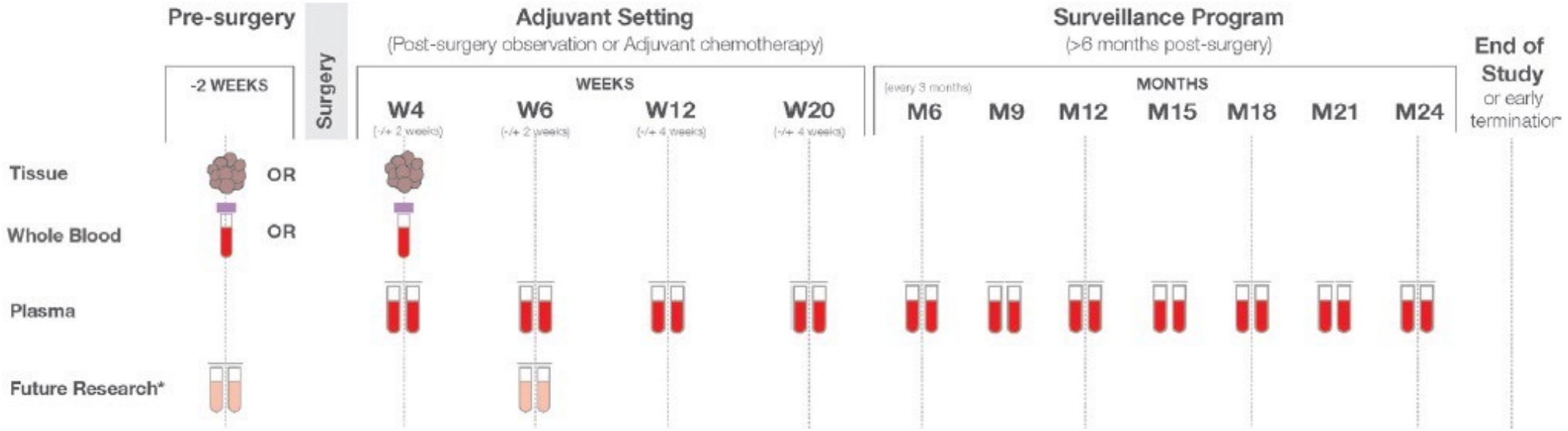
Courtesy of Christopher Lieu, MD

NRG ONCOLOGY™

BESPOKE CRC: A Prospective, Case-Controlled Observational Study

Estimated enrollment (N = 2,000)

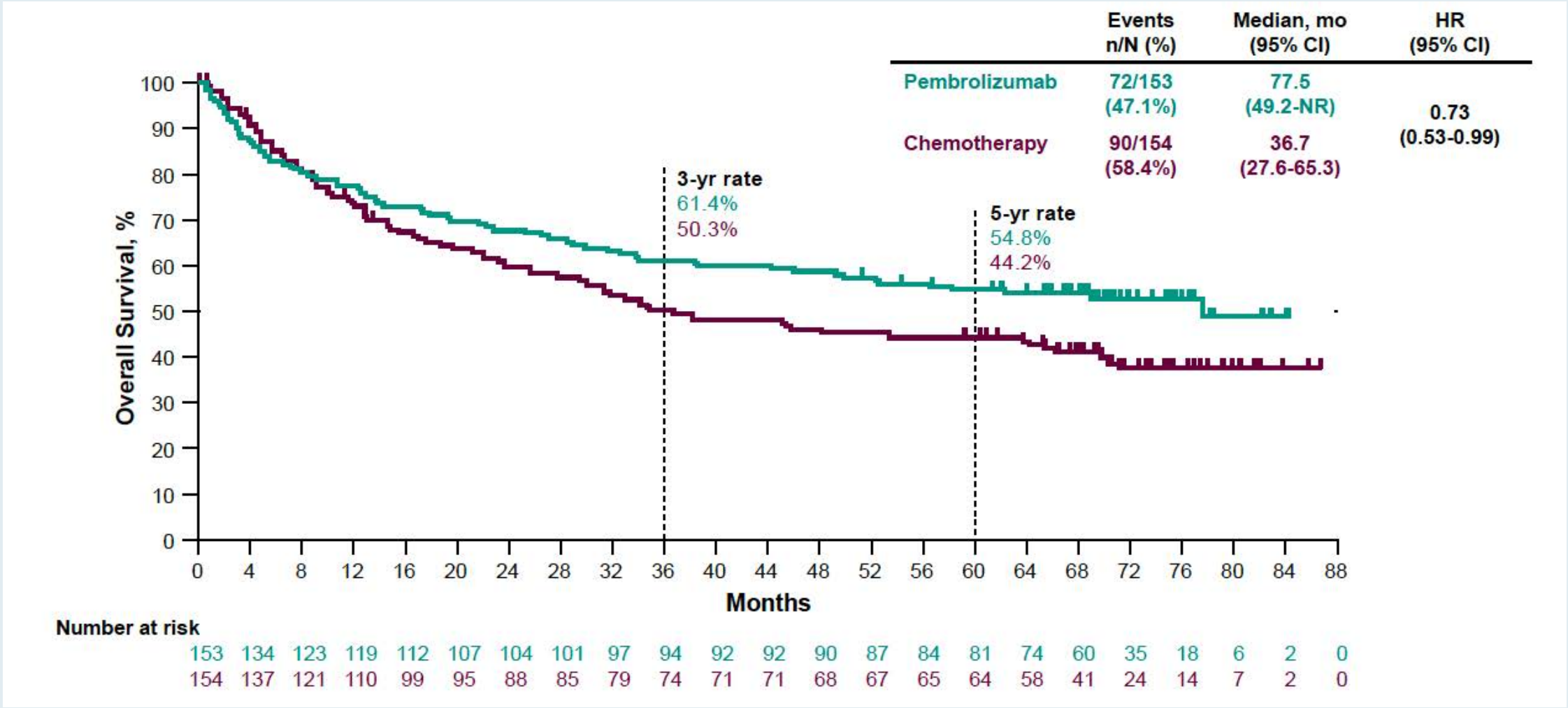
- Stage I-IV CRC or Stage IV CRC with oligometastatic disease eligible for post-operative systemic therapy



NCT04264702 Kasi PM et al. *BMJ Open* 2021;11:e047831.

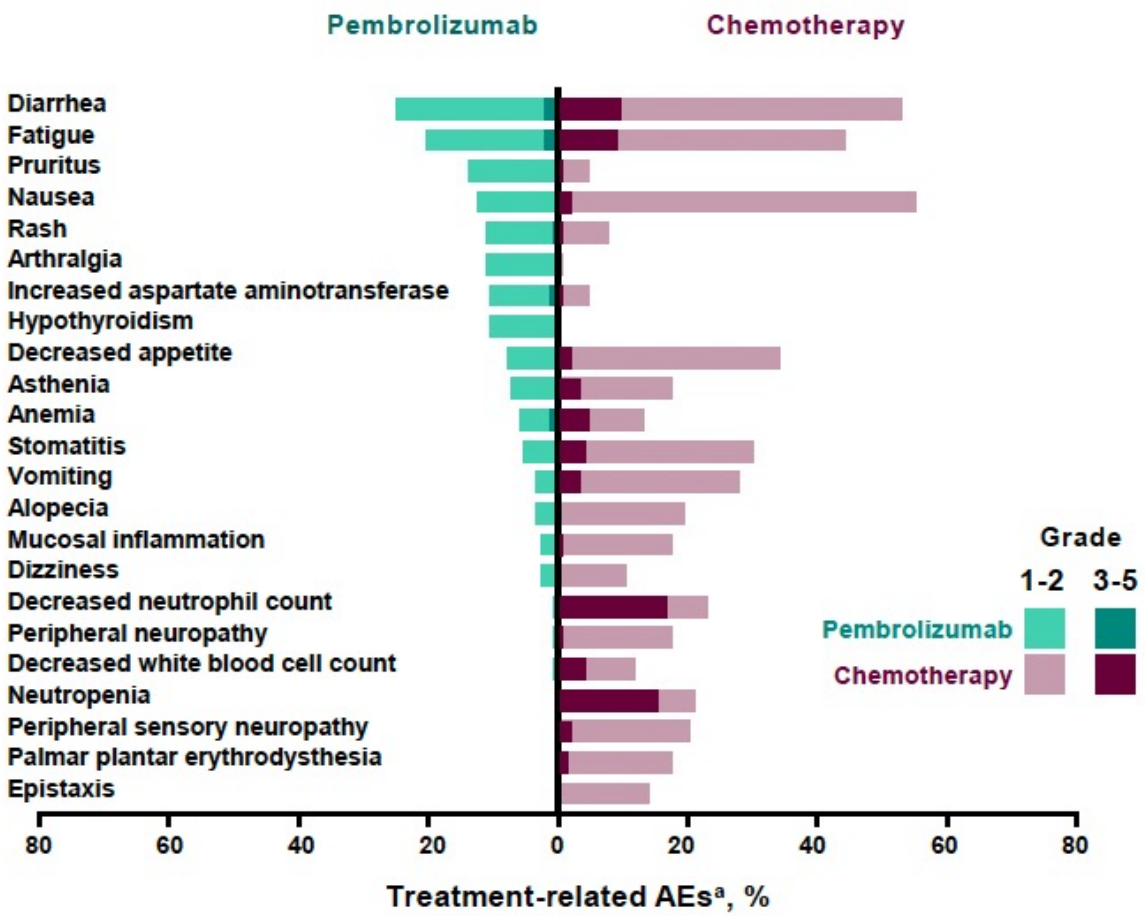
Courtesy of Christopher Lieu, MD

KEYNOTE-177 Follow-Up: Overall Survival



Shiu K-K et al. ESMO 2023;Abstract LBA32.

KEYNOTE-177 Follow-Up: Safety



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)
Led to death	0	0

Shiu K-K et al. ESMO 2023;Abstract LBA32.

J Clin Oncol 2021;39:4073-126.

ASCO special articles

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

Bryan J. Schneider, MD[1]; Jarushka Naidoo, MD[2,3]; Bianca D. Santomasso, MD, PhD[4]; Christina Lacchetti, MHSc[5]; Sherry Adkins, MS[6]; Milan Anadkat, MD[7]; Michael B. Atkins, MD[8]; Kelly J. Brassil, PhD[6]; Jeffrey M. Caterino, MD, MPH[9]; Ian Chau, MD[10]; Marianne J. Davies, DNP[11]; Marc S. Ernstoff, MD[12]; Leslie Fecher, MD[1]; Monalisa Ghosh, MD[13]; Ishmael Jaiyesimi, DO, MS[14]; Jennifer S. Mammen, MD, PhD[15]; Aung Naing, MD[6], Loretta J. Nastoupil, MD[6]; Tanyanika Phillips, MD[16]; Laura D. Porter, MD[17]; Cristina A. Reichner, MD[18]; Carole Seigel, MBA[19], Jung-Min Song, MSN, RN, CNS[20]; Alexander Spira, MD, PhD[21]; Maria Suarez-Almazor, MD[6]; Umang Swami, MD[22]; John A. Thompson, MD[23]; Praveen Vikas, MD[24]; Yinghong Wang, MD[6]; Jeffrey S. Weber, MD, PhD[25]; Pauline Funchain, MD[20]; and Kathryn Bollin, MD[26]

RTP RESEARCH TO PRACTICE

Signs and Symptoms of Immune Checkpoint Inhibitor-Related Toxicities

CONDITIONS	SIGNS AND SYMPTOMS (MAY INCLUDE ONE OR MORE)
CARDIO: Myocarditis	Chest pain, shortness of breath, fatigue, palpitations (arrhythmia: heart block or ventricular ectopic beats), syncope, generalized weakness. This adverse event may occur in conjunction with myositis and/or myasthenia gravis; these entities must be ruled out.
DERM: Bullous dermatitis	Inflammation of the skin and the presence of bullae, which are filled with fluid. The most common immune-related bullous dermatitis is bullous pemphigoid. May be intense or widespread; intermittent; skin changes from scratching (eg, edema, excoriations, lichenification, oozing/crusts); limiting instrumental activities of daily living (iADLs).
DERM: Maculopapular rash (morbilliform rash)	Macules (flat) and papules (elevated)
DERM: Pruritus	Itching sensation, with or without rash
DERM: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10%–30%, and >30% body surface area (BSA), respectively
DERM: Lichen planus	Violaceous (dark red/purple) papules and plaques without scale over the trunk and extremities, significant pruritus. Erosions and striae (white lines intersecting) in the oral and vulvar mucosa.
DERM: Psoriasis and psoriasiform disease	Thick red scaly plaques, accentuated on extensor surfaces, scalp, umbilicus, postauricular surfaces
DERM: Oral mucosa inflammation	Irritated gums and/or oropharynx, red/white lesions and/or ulcers, lichen planus, mucositis
DERM: Dry mouth (Sicca syndrome)	Dry mouth, oral sensitivity, dysarthria, dysphagia, dysgeusia, dental caries/erosion with prolonged salivary hypofunction, dry eye, lack of lubrication
DERM: Oral dysesthesia	Pain most often described as "burning" in the absence of, or disproportionate to, skin changes, oral sensitivity, dysgeusia, phantogeusia, or other altered sensation with normal clinical findings
ENDO: Hyperglycemia-related diabetic ketoacidosis (DKA)	Excessive thirst, frequent urination, general weakness, vomiting, confusion, abdominal pain, dry skin, dry mouth, increased heart rate, and fruity odor on the breath
ENDO: Overt hypothyroidism	Fatigue, lethargy, sensation of being cold, possible constipation
ENDO: Thyrotoxicosis due to thyroiditis	Most patients with thyrotoxicosis due to thyroiditis have minimal, if any symptoms. If symptoms do arise, may include uncommonly, tachycardia, tremor, anxiety, enlarged and tender thyroid gland (rarely).
ENDO: Hypophysitis	Acute onset headache, photophobia, nausea/emesis, fatigue, muscle weakness, may have low blood pressure
ENDO: Primary adrenal insufficiency	High ACTH with low morning cortisol, abnormal cosyntropin stimulation test. This is a rare diagnosis not usually associated with checkpoint immunotherapy.

National Comprehensive Cancer Network (NCCN®). **NCCN clinical practice guidelines in oncology. Immunotherapy-related toxicities — Version 1.2024.**

RTP RESEARCH TO PRACTICE

Signs and Symptoms of Immune Checkpoint Inhibitor-Related Toxicities (Continued)

CONDITIONS	SIGNS AND SYMPTOMS (MAY INCLUDE ONE OR MORE)
ENDO: Central hypothyroidism	Symptoms of overt hypothyroidism (fatigue, lethargy, sensation of being cold, possible constipation) plus symptoms of central adrenal insufficiency (nausea/emesis, not feeling well, generalized malaise).
GI: Colitis	Watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, nocturnal bowel movements. Blood in the stool and/or fever should prompt a more thorough workup for infection and for other causes of gastrointestinal (GI) bleeding, including peptic ulcer disease (PUD) and malignant bleeding.
GI: Transaminitis	Elevated alanine transaminase (ALT) and aspartate transaminase (AST)
GI: Cholestasis	Elevated alkaline phosphatase (predominant) with or without bilirubin/AST/ALT elevation.
GI: Pancreatitis	Acute pancreatitis: epigastric pain, nausea, possible vomiting Chronic pancreatitis: chronic abdominal pain, deficiency in pancreatic enzyme production with possible malabsorption
MUSCULO: Inflammatory arthritis	Joint pain, joint swelling; inflammatory symptoms: stiffness after inactivity, improvement with activity
MUSCULO: Myositis	Myositis is characterized by inflammation and/or weakness involving the skeletal muscles. This adverse event may occur in conjunction with myocarditis and/or myasthenia gravis; these entities must be ruled out. Common presenting symptoms may include muscle weakness, elevated creatinine kinase (CK), elevated transaminases, and myalgias.
MUSCULO: Polymyalgia rheumatica (PMR)	PMR symptoms: fatigue and/or muscle and joint pain typically in shoulders and hips
MUSCULO: Giant cell arteritis (GCA)	Visual symptoms, headache, scalp tenderness, jaw claudication
NEURO: Aseptic meningitis	Headache, photophobia, and neck stiffness, often afebrile but may be febrile. There may be nausea/vomiting. Mental status should be normal (distinguishes from encephalitis).
NEURO: Encephalitis	Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality
NEURO: Guillain-Barré syndrome (GBS)	Progressive, most often symmetrical, ascending muscle weakness with absent or reduced deep tendon reflexes. May involve extremities, facial, respiratory, and bulbar and oculomotor nerves. May have dysregulation of autonomic nerves. Often starts with pain in lower back and thighs.
NEURO: Myasthenia gravis	Progressive or fluctuating muscle weakness, generally proximal to distal. May have bulbar involvement (ie, ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, facial muscle weakness) and/or respiratory muscle weakness. May occur with myositis and myocarditis, which must be ruled out. Respiratory symptoms may require evaluation to rule out pneumonitis. Miller Fisher variant of GBS has overlapping symptoms (ophthalmoplegia and ascending weakness).

National Comprehensive Cancer Network (NCCN®). **NCCN clinical practice guidelines in oncology. Immunotherapy-related toxicities — Version 1.2024.**

RTP RESEARCH TO PRACTICE

Signs and Symptoms of Immune Checkpoint Inhibitor-Related Toxicities (Continued)

CONDITIONS	SIGNS AND SYMPTOMS (MAY INCLUDE ONE OR MORE)
NEURO: Peripheral neuropathy	Asymmetric or symmetric sensory-motor deficit. Sensory deficit may be painful or painless paresthesias or potentially life-threatening autonomic (eg, myenteric plexus) dysfunction. Hypo- or areflexia. Isolated sensory deficit or sensory plus lower motor neuron deficit. GI tract paresis due to myenteric neuritis is a rare toxicity associated with immune checkpoint inhibitor (ICI) therapy. The presentation may be fulminant with profound ileus.
NEURO: ADEM (acute demyelinating encephalomyelitis)	Headache, confusion, seizures, depressed level of consciousness, speech abnormality, focal weakness, sensory change (numbness or tingling), ataxia/loss of balance, or vision loss.
NEURO: Optic neuritis	Vision loss, eye pain, decreased visual acuity, visual field loss, dyschromatopsia, relative afferent pupillary defect, optic disc edema
NEURO: Transverse myelitis	Acute or subacute weakness or sensory changes bilaterally, often with bowel/bladder changes and spinal level to pinprick, hyperreflexia, positive Babinski.
OCULAR: Vision changes	Blurred/distorted vision, new floaters, itchy eyes, blind spots, change in color vision, photophobia, tenderness/pain, eyelid swelling, and proptosis. Episcleritis can be associated with red discoloration of the eye. Uveitis can be associated with eye redness.
PULM: Pneumonitis	Dry cough, shortness of breath, fever, chest pain
RENAL: Acute kidney injury (AKI)	Elevation of creatinine/blood urea nitrogen (BUN), inability to maintain acid/base or electrolyte balance, and urine output change (usually decreased)

National Comprehensive Cancer Network (NCCN®). **NCCN clinical practice guidelines in oncology. Immunotherapy-related toxicities — Version 1.2024.**

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

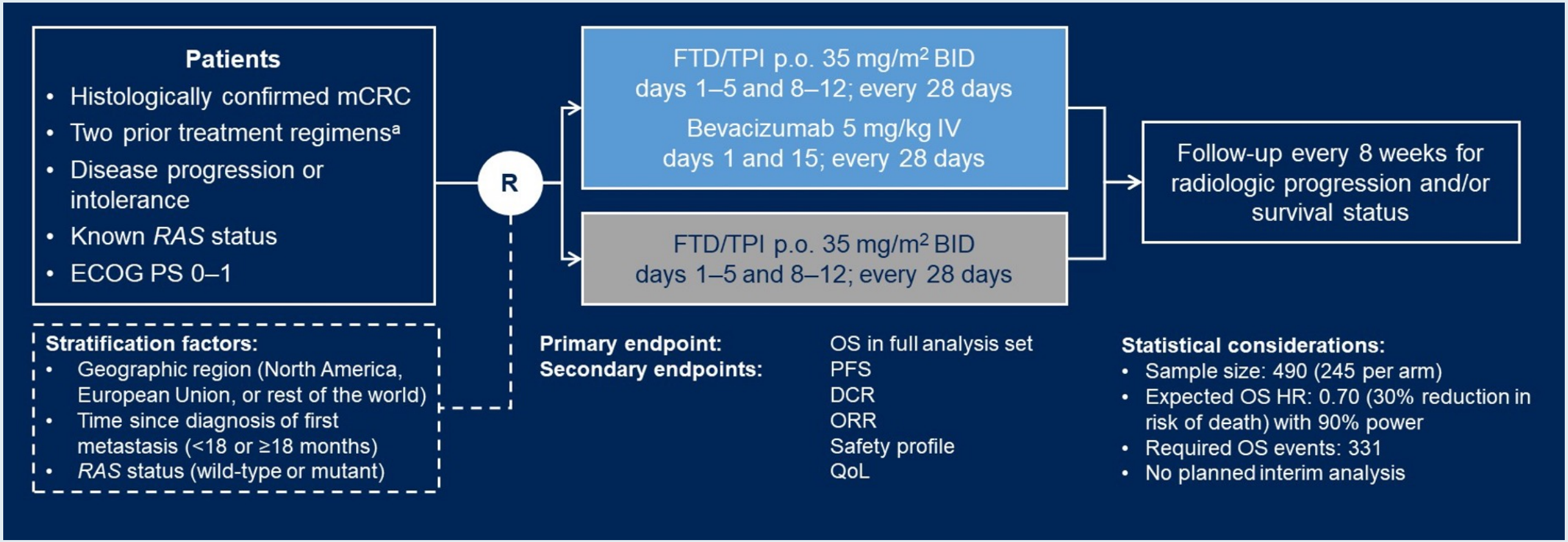
ORIGINAL ARTICLE

Trifluridine–Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer

Gerald W. Prager, M.D., Julien Taieb, M.D., Ph.D., Marwan Fakih, M.D., Fortunato Ciardiello, M.D., Ph.D., Eric Van Cutsem, M.D., Ph.D., Elena Elez, M.D., Ph.D., Felipe M. Cruz, M.D., Ph.D., Lucjan Wyrwicz, M.D., Ph.D., Daniil Stroyakovskiy, M.D., Ph.D., Zsuzsanna Pápai, M.D., Pierre-Guillaume Poureau, M.D., Gabor Liposits, M.D., Chiara Cremolini, M.D., Ph.D., Igor Bondarenko, M.D., Ph.D., Dominik P. Modest, M.D., Karim A. Benhadji, M.D., Nadia Amellal, M.D., Catherine Leger, M.Sc., Loïck Vidot, M.Sc., and Josep Tabernero, M.D., Ph.D., for the SUNLIGHT Investigators*

N Engl J Med 2023;388(18):1657-67.

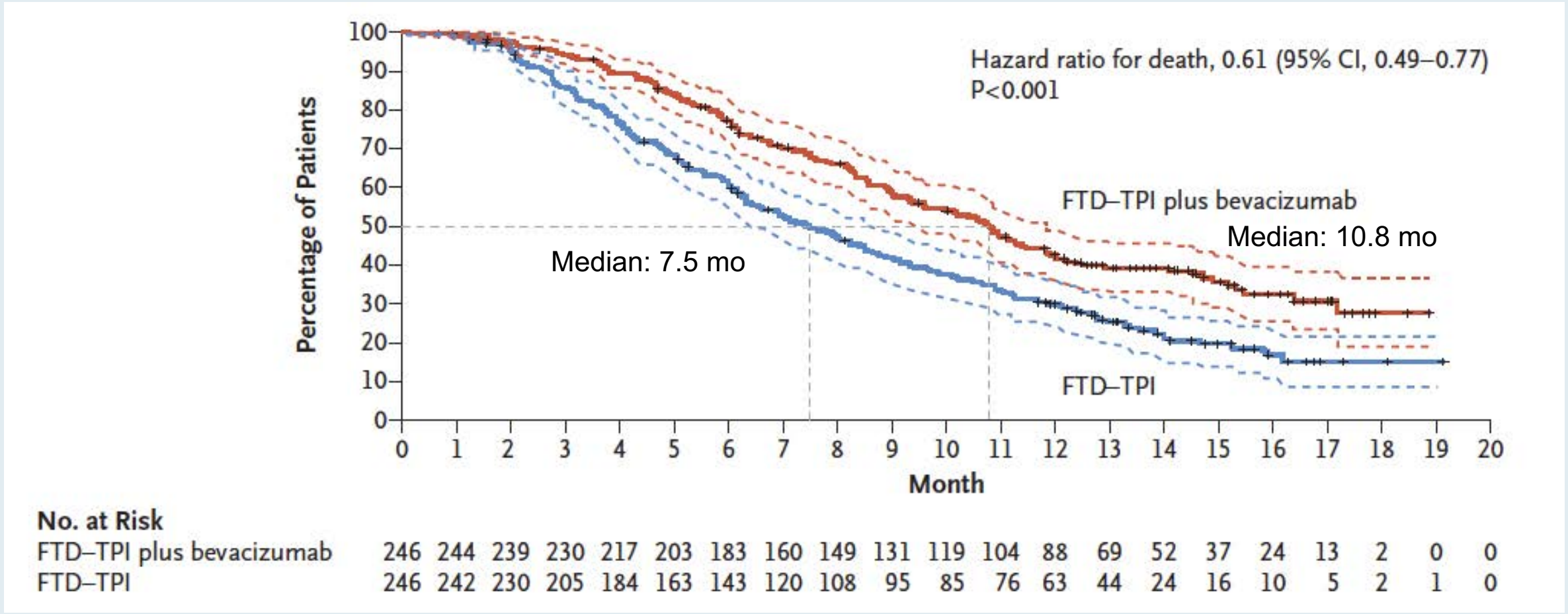
SUNLIGHT Phase III Study Design



FTD/TPI = trifluridine/tipiracil

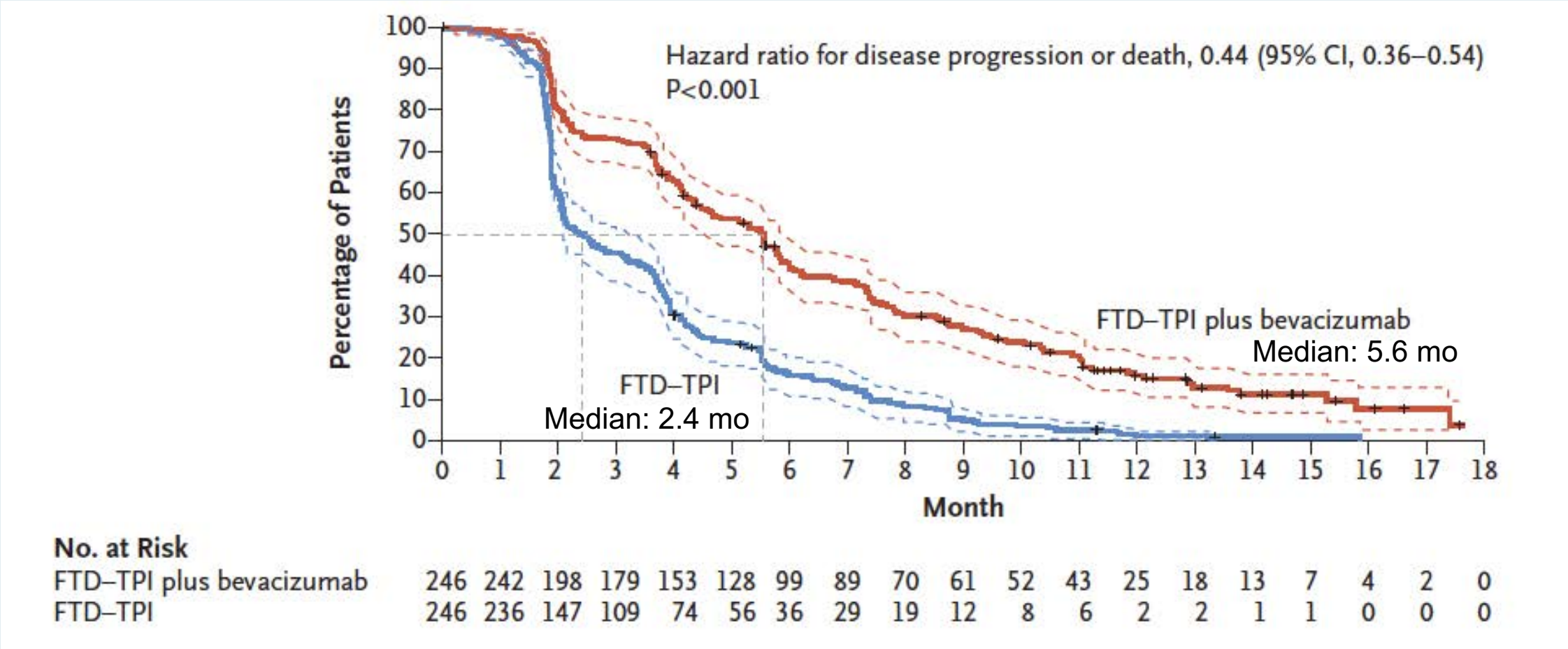
Tabernero J et al. Gastrointestinal Cancers Symposium 2023;Abstract 4.

SUNLIGHT Primary Endpoint: Overall Survival



Prager GW et al. *N Engl J Med* 2023;388(18):1657-67.

SUNLIGHT: Progression-Free Survival



Prager GW et al. *N Engl J Med* 2023;388(18):1657-67.

SUNLIGHT: Adverse Events

Event	FTD–TPI plus Bevacizumab (N = 246)		FTD–TPI (N = 246)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Neutropenia	153 (62.2)	106 (43.1)	126 (51.2)	79 (32.1)
Nausea	91 (37.0)	4 (1.6)	67 (27.2)	4 (1.6)
Anemia	71 (28.9)	15 (6.1)	78 (31.7)	27 (11.0)
Asthenia	60 (24.4)	10 (4.1)	55 (22.4)	10 (4.1)
Fatigue	53 (21.5)	3 (1.2)	40 (16.3)	9 (3.7)
Diarrhea	51 (20.7)	2 (0.8)	46 (18.7)	6 (2.4)
Decreased appetite	50 (20.3)	2 (0.8)	38 (15.4)	3 (1.2)
Vomiting	46 (18.7)	2 (0.8)	36 (14.6)	4 (1.6)
Thrombocytopenia	42 (17.1)	7 (2.8)	28 (11.4)	3 (1.2)
Neutrophil count decreased	34 (13.8)	22 (8.9)	17 (6.9)	13 (5.3)
Abdominal pain	29 (11.8)	5 (2.0)	27 (11.0)	4 (1.6)
Constipation	27 (11.0)	0	28 (11.4)	2 (0.8)
Stomatitis	27 (11.0)	1 (0.4)	9 (3.7)	0
Hypertension	25 (10.2)	14 (5.7)	5 (2.0)	3 (1.2)

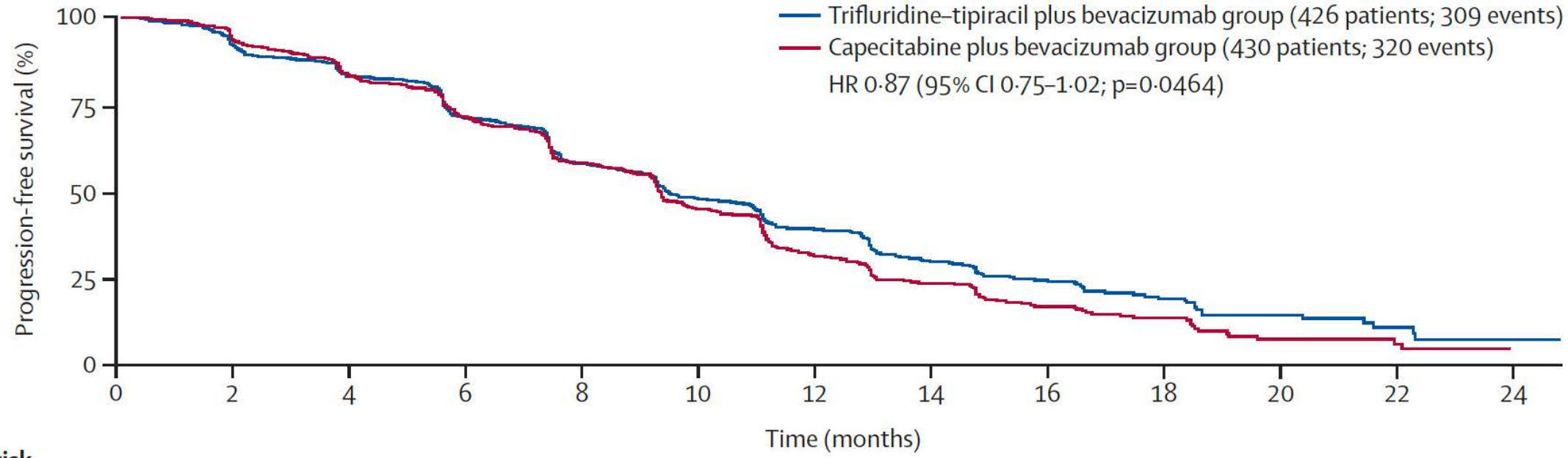
Prager GW et al. *N Engl J Med* 2023;388(18):1657-67.

Lancet Gastroenterol Hepatol 2023;8(2):133-44.

Trifluridine–tipiracil plus bevacizumab versus capecitabine plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer ineligible for intensive therapy (SOLSTICE): a randomised, open-label phase 3 study

Thierry André, Alfredo Falcone, Yaroslav Shparyk, Fedor Moiseenko, Eduardo Polo-Marques, Tibor Csöszi, Arinilda Campos-Bragagnoli, Gabor Liposits, Ewa Chmielowska, Paul Aubel, Lourdes Martín, Ronan Fougeray, Nadia Amellal, Mark P Saunders

SOLSTICE Primary Endpoint: Investigator-Assessed PFS (Intent-to-Treat Population)



Number at risk (number censored)													
Trifluridine–tipiracil plus bevacizumab group	426 (0)	382 (8)	345 (10)	294 (11)	237 (14)	178 (32)	126 (53)	93 (56)	58 (75)	33 (90)	18 (98)	8 (105)	1 (110)
Capecitabine plus bevacizumab group	430 (0)	385 (16)	339 (21)	286 (25)	232 (27)	158 (50)	96 (67)	69 (70)	41 (80)	23 (91)	9 (98)	4 (100)	0 (103)

André T et al. *Lancet Gastroenterol Hepatol* 2023;8(2):133-44.

RTP RESEARCH TO PRACTICE

SOLSTICE: Treatment-Emergent Adverse Events

	Trifluridine–tipiracil plus bevacizumab group (n=423)			Capecitabine plus bevacizumab group (n=427)		
	Grade 3	Grade 4	Any grade*	Grade 3	Grade 4	Any grade*
Any treatment-emergent adverse event	234 (55%)	102 (24%)	418 (99%)	218 (51%)	24 (6%)	412 (96%)
Any treatment-emergent adverse-event leading to death	..	..	30 (7%)	..	..	39 (9%)
Any treatment-related adverse event	230 (54%)	94 (22%)	396 (94%)	171 (40%)	17 (4%)	375 (88%)
Treatment-emergent haematological events						
Neutropenia†	151 (36%)	69 (16%)	278 (66%)	3 (1%)	2 (<1%)	37 (9%)
Anaemia	58 (14%)	2 (<1%)	188 (44%)	16 (4%)	0	58 (14%)
Neutrophil count decreased	59 (14%)	19 (4%)	91 (22%)	2 (<1%)	2 (<1%)	11 (3%)
Thrombocytopenia	14 (3%)	2 (<1%)	81 (19%)	0	0	26 (6%)
Leukopenia	21 (5%)	2 (<1%)	71 (17%)	1 (<1%)	0	13 (3%)

	Trifluridine–tipiracil plus bevacizumab group (n=423)			Capecitabine plus bevacizumab group (n=427)		
	Grade 3	Grade 4	Any grade*	Grade 3	Grade 4	Any grade*
Treatment-emergent non-haematological events						
Diarrhoea	30 (7%)	0	154 (36%)	20 (5%)	0	145 (34%)
Nausea	7 (2%)	0	148 (35%)	4 (1%)	0	102 (24%)
Fatigue	25 (6%)	0	101 (24%)	17 (4%)	0	107 (25%)
Decreased appetite	6 (1%)	1 (<1%)	95 (22%)	7 (2%)	0	77 (18%)
Asthenia	25 (6%)	1 (<1%)	95 (22%)	20 (5%)	0	76 (18%)
Vomiting	7 (2%)	0	68 (16%)	5 (1%)	0	44 (10%)
Hypertension	36 (9%)	0	56 (13%)	48 (11%)	0	74 (17%)
Stomatitis	6 (1%)	0	55 (13%)	3 (1%)	0	51 (12%)
Constipation	2 (<1%)	0	51 (12%)	2 (<1%)	0	46 (11%)
Abdominal pain	7 (2%)	0	50 (12%)	8 (2%)	0	63 (15%)
Weight loss	2 (<1%)	0	47 (11%)	1 (<1%)	0	40 (9%)
Blood bilirubin increased	4 (1%)	0	22 (5%)	7 (2%)	0	47 (11%)
Hand–foot syndrome	0	0	5 (1%)	62 (15%)	0	225 (53%)

André T et al. *Lancet Gastroenterol Hepatol* 2023;8(2):133-44.

RTP RESEARCH TO PRACTICE

Sotorasib and Adagrasib Have Single-Agent Activity in *KRAS*^{G12C}-mutant Metastatic CRC

	Adagrasib (N=43)*	Sotorasib (N=62)
Objective response % (95% CI) per BICR	23% (12-39)	10% (4-20)
Median duration of response months (95%CI)	4.3 mo (2.3-8.3)	4.2 mo (2.9-8.5)
Median progression-free survival months (95%CI)	5.6 mo (4.1-8.3)	4.0 mo (2.8-4.2)
Median overall survival months (95%CI)	19.8 mo (12.5-23.0)	10.6 mo (7.7-15.6)
AE leading to dose reduction, n (%)	17 (39%)	11 (18%)**
AE leading to discontinuation, n (%)	0 (0%)	1 (2%)

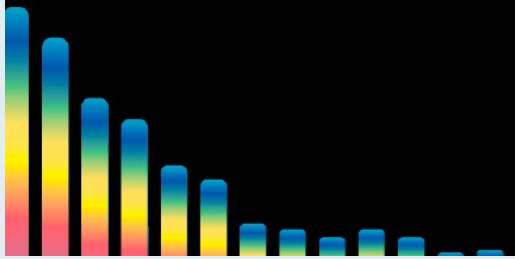
Yaeger et al., N Engl J Med 2023; 388:44-54.
Fakih et al., Lancet Oncol 2022; 23: 115–24,

Courtesy of John H Strickler, MD

RESEARCH ARTICLE

Efficacy and Safety of Adagrasib plus Cetuximab in Patients with *KRAS*^{G12C}-Mutated Metastatic Colorectal Cancer

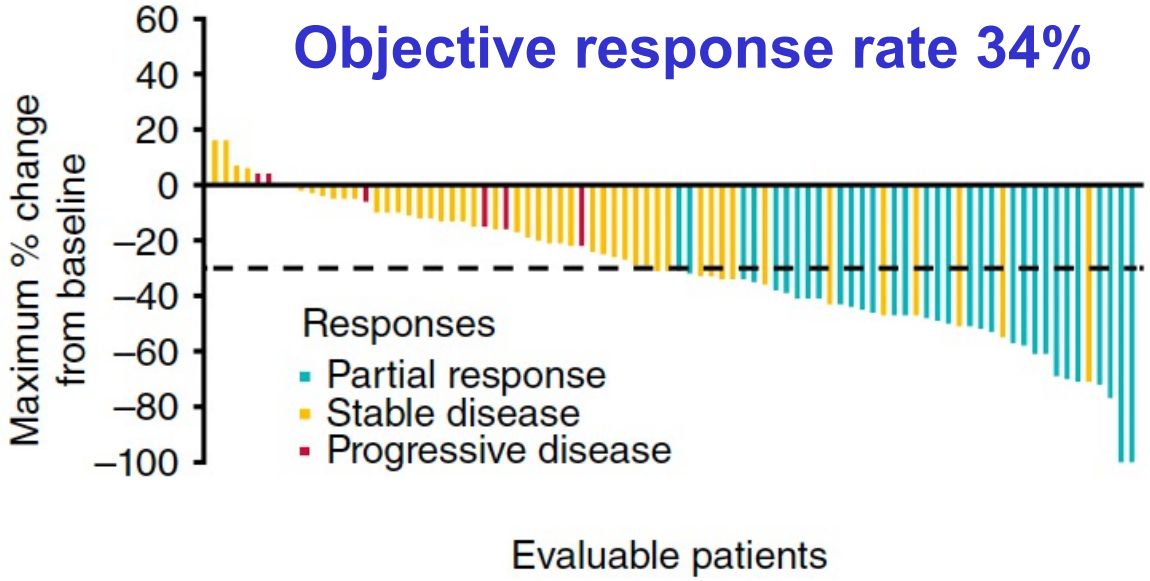
Rona Yaeger[1], Nataliya V. Uboha[2], Meredith S. Pelster[3], Tanios S. Bekaii-Saab[4], Minal Barve[5], Joel Saltzman[6], Joshua K. Sabari[7], Julio A. Peguero[8], Andrew Scott Paulson[9], Pasi A. Jänne[10], Marcia Cruz-Correa[11], Kenna Anderes[12], Karen Velastegui[12], Xiaohong Yan[12], Hirak Der-Torossian[12], Samuel J. Klempner[13], and Scott E. Kopetz[14]

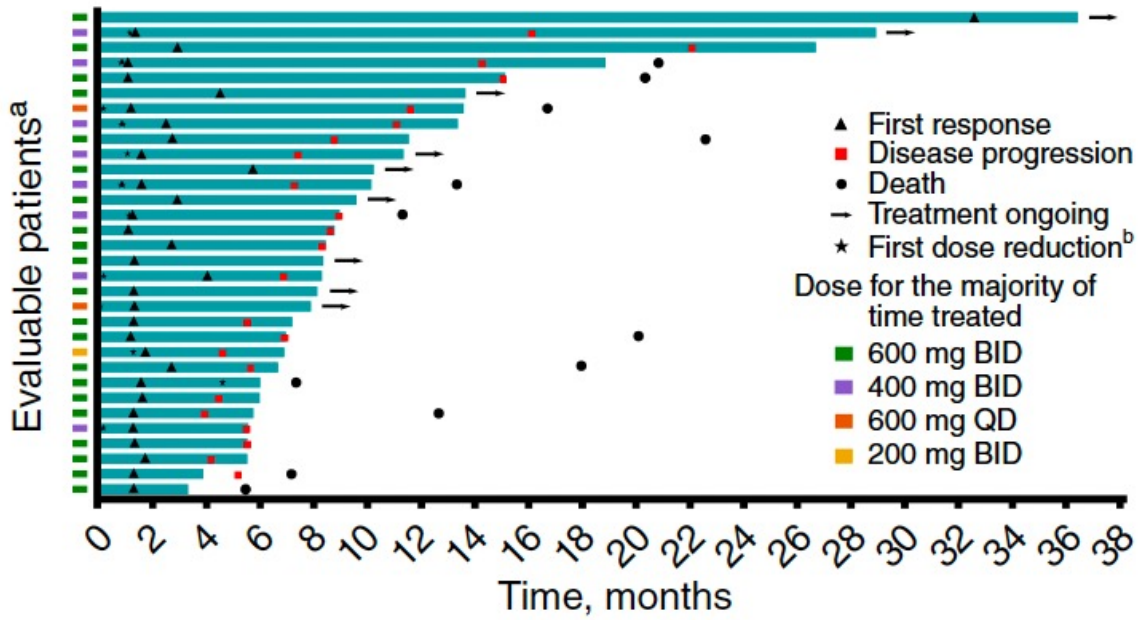


Cancer Discov 2024;14:1-12.

RTP RESEARCH TO PRACTICE

KRYSTAL-1 Trial: Efficacy of Adagrasib with Cetuximab for Metastatic CRC with KRAS G12C Mutation





Yaeger R et al. *Cancer Discov* 2024;14:1-12.

KRYSTAL-1: TRAEs with Adagrasib and Cetuximab for Metastatic CRC with KRAS G12C Mutation

	Adagrasib + cetuximab CRC cohort ($N = 94$)				
TRAEs, *n* (%)	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Any TRAEs	94 (100)	8 (8.5)	60 (63.8)	22 (23.4)	4 (4.3)
Most frequent TRAEs, *n* (%)[a]					
Nausea	57 (60.6)	35 (37.2)	20 (21.3)	2 (2.1)	0
Vomiting	48 (51.1)	30 (31.9)	18 (19.1)	0	0
Diarrhea	46 (48.9)	31 (33.0)	14 (14.9)	1 (1.1)	0
Dermatitis acneiform	45 (47.9)	28 (29.8)	15 (16.0)	2 (2.1)	0
Fatigue	40 (42.6)	23 (24.5)	16 (17.0)	1 (1.1)	0
Dry skin	32 (34.0)	24 (25.5)	8 (8.5)	0	0
Hypomagnesemia	27 (28.7)	17 (18.1)	7 (7.4)	2 (2.1)	1 (1.1)[b]
Headache	25 (26.6)	14 (14.9)	8 (8.5)	3 (3.2)	0
Rash	21 (22.3)	11 (11.7)	8 (8.5)	2 (2.1)	0
TRAEs leading to dose reduction, *n* (%)					
Adagrasib	28 (29.8)	–	–	–	–
Cetuximab	6 (6.4)	–	–	–	–
TRAEs leading to dose interruption, *n* (%)					
Adagrasib	34 (36.2)	–	–	–	–
Cetuximab	33 (35.1)	–	–	–	–
TRAEs leading to discontinuation, *n* (%)					
Adagrasib	0	–	–	–	–
Cetuximab	8 (8.5)	–	7 (7.4)[c]	–	1 (1.1)[d]

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

Abbreviation: ALT, alanine aminotransferase; CRC, colorectal cancer; TRAE, treatment-related adverse event.

[a]Occurring in ≥20% of patients.

[b]Other grade 4 TRAEs were cetuximab-related infusion-related reaction, neutrophil count decrease, and hyperkalemia ($n = 1$ each). There were no grade 5 TRAEs.

[c]TRAEs (grade 1–2) that resulted in discontinuation of cetuximab were: cetuximab-related infusion-related reaction ($n = 3$); malaise ($n = 1$); ALT increase ($n = 1$); dermatitis acneiform ($n = 1$); and flushing ($n = 1$). Of these, 5 patients continued with adagrasib as a single agent.

[d]Cetuximab-related infusion-related reaction, this patient continued with adagrasib as a single agent.

Yaeger R et al. *Cancer Discov* 2024;14:1-12.

RTP RESEARCH TO PRACTICE

FDA Accepts for Priority Review a Supplemental NDA for Adagrasib in Combination with Cetuximab for Previously Treated KRAS G12C-Mutated Locally Advanced or Metastatic CRC

Press Release – February 20, 2024

"…the US Food and Drug Administration (FDA) has accepted for priority review the supplemental new drug application for adagrasib in combination with cetuximab for the treatment of patients with previously treated $KRAS^{G12C}$-mutated locally advanced or metastatic colorectal cancer (CRC). The FDA assigned a Prescription Drug User Fee Act (PDUFA) goal date of June 21, 2024.

The submission is based on the results of KRYSTAL-1 study, a multicohort trial which evaluated adagrasib alone or in combination with other anticancer therapies in patients with advanced solid tumors harboring a $KRAS^{G12C}$ mutation. The primary endpoint for the registrational cohort was objective response rate. The secondary endpoints for the pooled cohorts included duration of response, progression-free survival, overall survival and safety."

https://news.bms.com/news/corporate-financial/2024/U.S.-Food-and-Drug-Administration-FDA-Accepts-Supplemental-New-Drug-Application-for-KRAZATI-adagrasib-in-Combination-with-Cetuximab-as-a-Targeted-Treatment-Option-for-Patients-with-Previously-Treated-KRAS-G12C-Mutated-Locally-Advanced-or/default.aspx

RTP RESEARCH TO PRACTICE

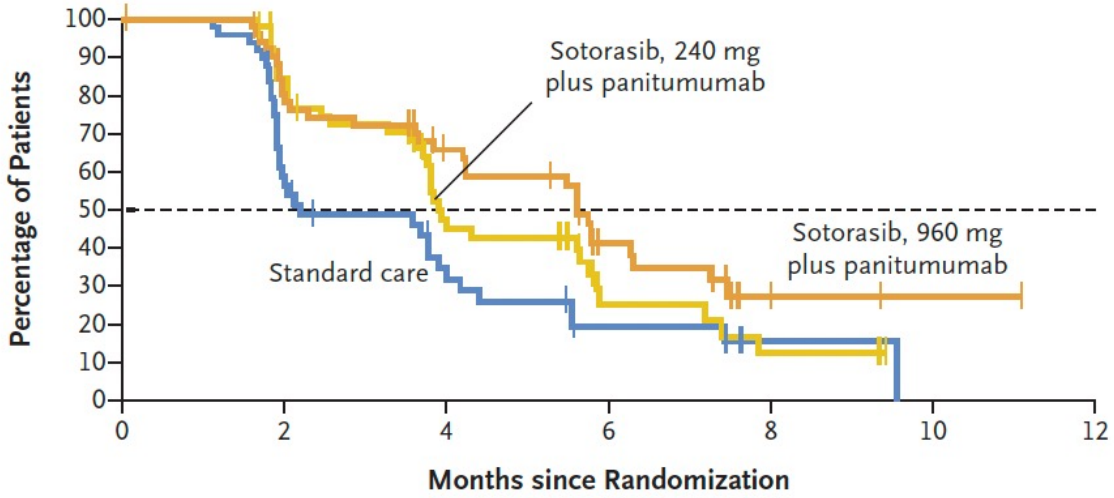
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 7, 2023 VOL. 389 NO. 23

Sotorasib plus Panitumumab in Refractory Colorectal Cancer with Mutated *KRAS* G12C

M.G. Fakih, L. Salvatore, T. Esaki, D.P. Modest, D.P. Lopez-Bravo, J. Taieb, M.V. Karamouzis, E. Ruiz-Garcia, T.-W. Kim, Y. Kuboki, F. Meriggi, D. Cunningham, K.-H. Yeh, E. Chan, J. Chao, Y. Saportas, Q. Tran, C. Cremolini, and F. Pietrantonio

CodeBreaK 300 Trial: Progression-Free Survival with Sotarasib and Panitumumab for Refractory CRC with KRAS G12C Mutation



No. at Risk							
Sotorasib, 960 mg plus panitumumab	53	40	28	13	2	1	0
Sotorasib, 240 mg plus panitumumab	53	43	20	6	3	0	
Standard care	54	24	12	5	1	0	

	Median Progression-free Survival	Hazard Ratio for Disease Progression or Death (95% CI)	Two-Sided P Value
	mo		
Sotorasib, 960 mg plus Panitumumab	5.62	0.49 (0.30–0.80)	0.006
Sotorasib, 240 mg plus Panitumumab	3.91	0.58 (0.36–0.93)	0.03
Standard Care	2.20		

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

RTP RESEARCH TO PRACTICE

CodeBreaK 300: Treatment-Related Adverse Events with Sotorasib and Panitumumab for Refractory CRC with KRAS G12C Mutation

Adverse Event	960-mg Sotorasib–Panitumumab (N=53)	240-mg Sotorasib–Panitumumab (N=53)	Standard Care (N=51)
		number of patients (percent)	
Any adverse event	50 (94.3)	51 (96.2)	42 (82.4)
Grade ≥3 event	19 (35.8)	16 (30.2)	22 (43.1)
Grade ≥4 event	2 (3.8)	0	2 (3.9)
Serious adverse event	3 (5.7)	0	4 (7.8)
Adverse event that resulted in death	0	0	0
Sotorasib-related adverse event	32 (60.4)	34 (64.2)	—
Panitumumab-related adverse event	49 (92.5)	50 (94.3)	—

- Skin-related toxic effects and hypomagnesemia were the most common adverse events observed with sotorasib/panitumumab.

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

What I Tell My Patients: Integrating New Research Information into Current Clinical Care

A Complimentary NCPD Hybrid Symposium Series Held During the 49th Annual ONS Congress

Gastroesophageal and Colorectal Cancers

Saturday, April 27, 2024
6:00 PM – 8:00 PM

Faculty

Deanna A Griffie, MSN, AGNP-C
Caroline Kuhlman, MSN, APRN-BC
Manish A Shah, MD
John Strickler, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

What I Tell My Patients: Integrating New Research Information into Current Clinical Care

A Complimentary NCPD Webinar in Partnership with the Oncology Nursing Society

Prostate Cancer

Wednesday, May 1, 2024
7:00 PM – 8:00 PM ET

Faculty

Andrew J Armstrong, MD, ScM
Brenda Martone, MSN, NP-BC, AOCNP

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us! Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open up to 5 minutes after the meeting ends.

To Claim NCPD Credit

In-person attendees: Please refer to the program syllabus for the NCPD credit link or QR code.

Virtual attendees: The NCPD credit link is posted in the chat room.

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