Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Advanced Gastrointestinal Cancers

Johanna Bendell, MD

Chief Development Officer

Director, Drug Development Unit Nashville

Sarah Cannon Research Institute

Tennessee Oncology

Nashville, Tennessee

Commercial Support

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Dr Love — Disclosures

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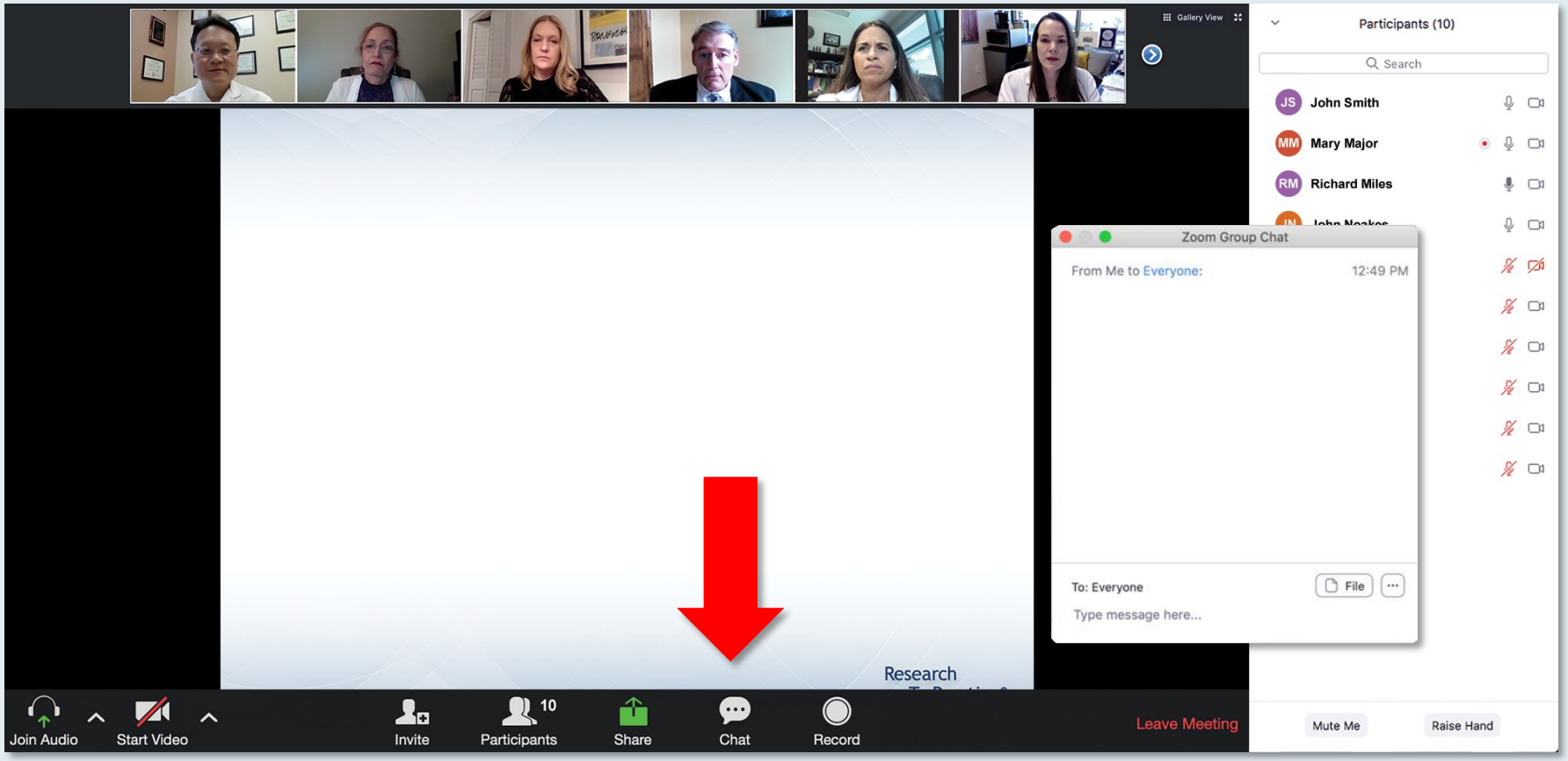
We Encourage Clinicians in Practice to Submit Questions



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

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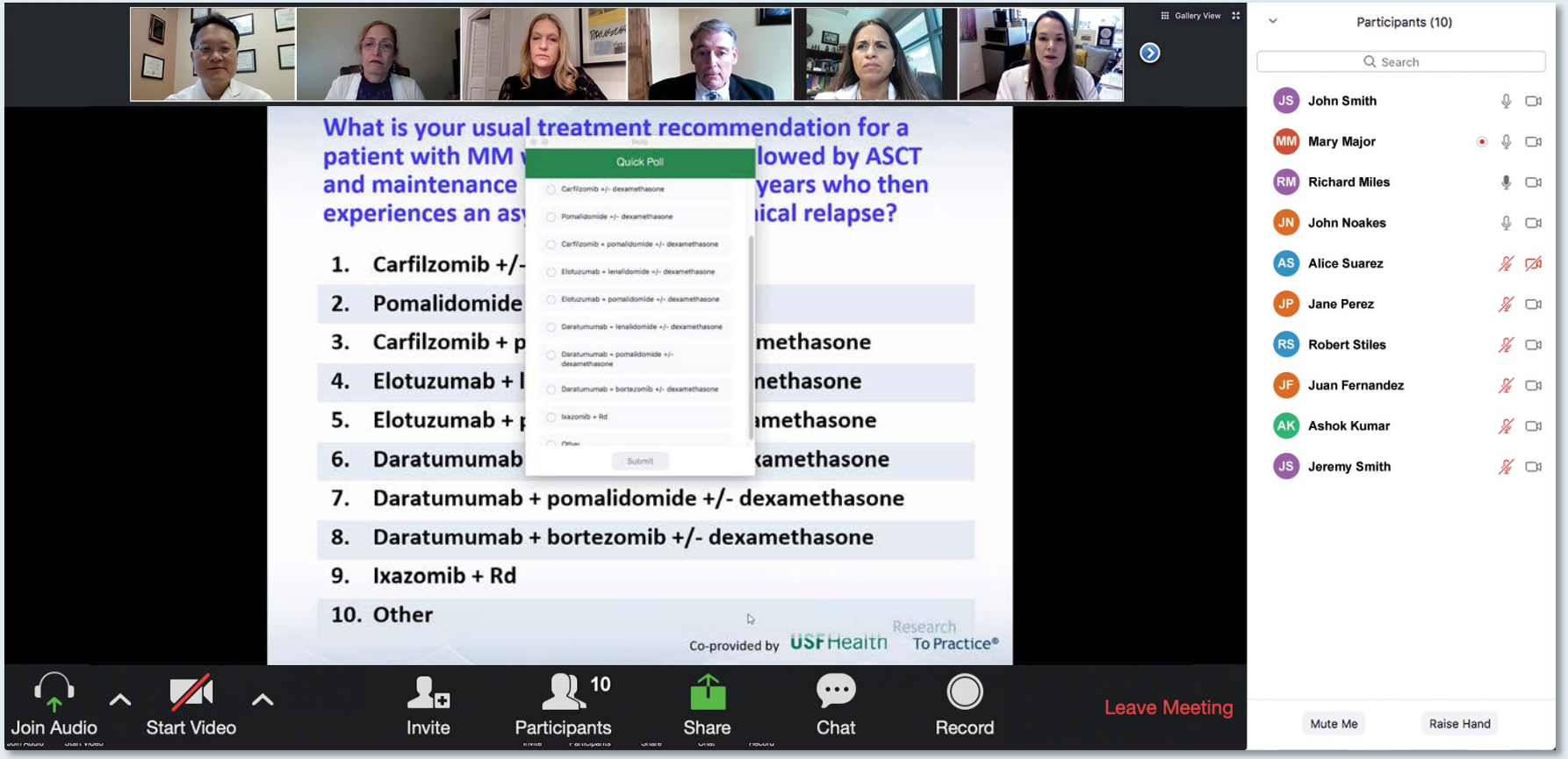
Familiarizing Yourself with the Zoom Interface

How to answer poll questions



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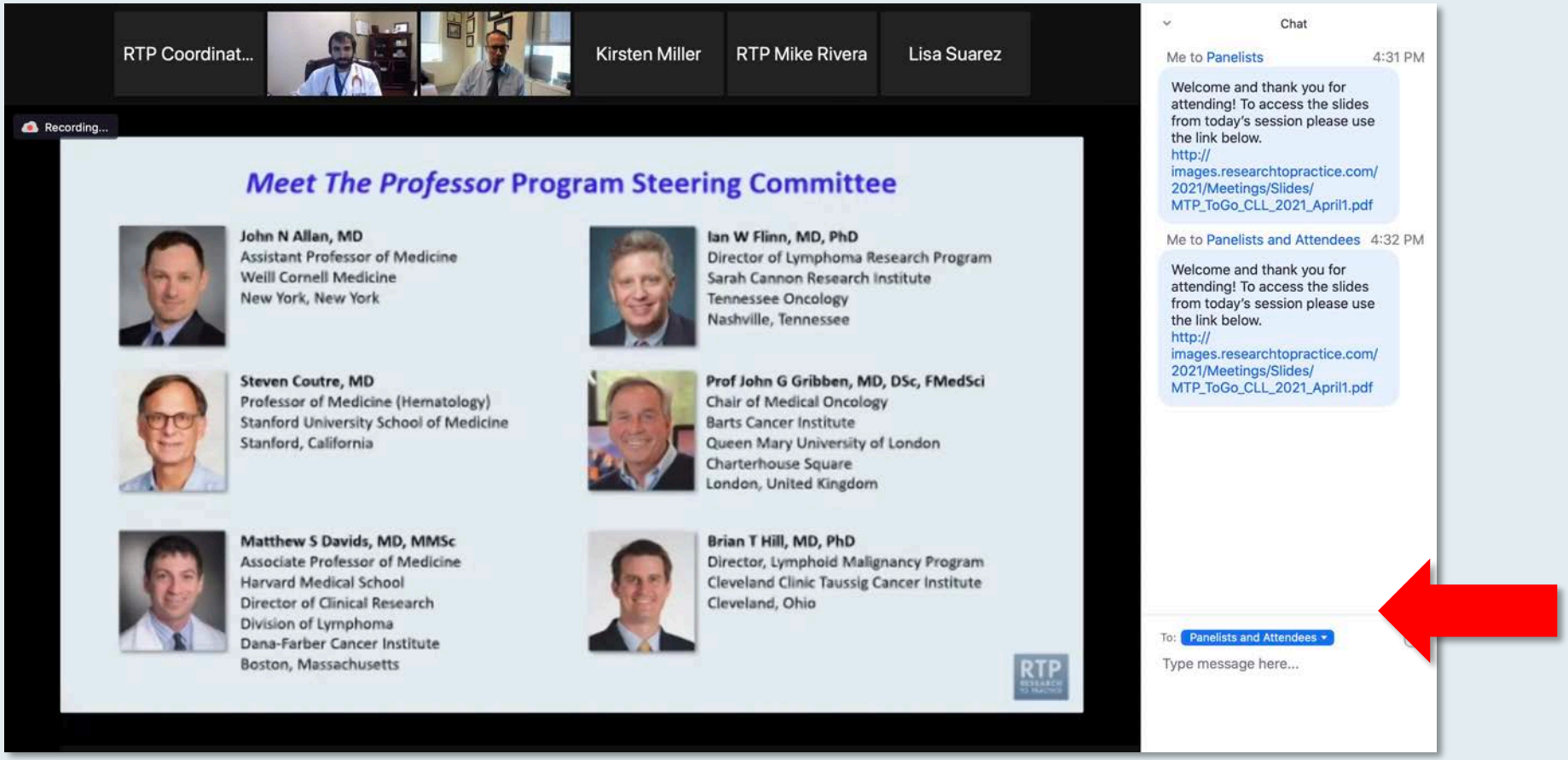
Familiarizing Yourself with the Zoom Interface

Expand chat submission box



Drag the white line above the submission box up to create more space for your message.

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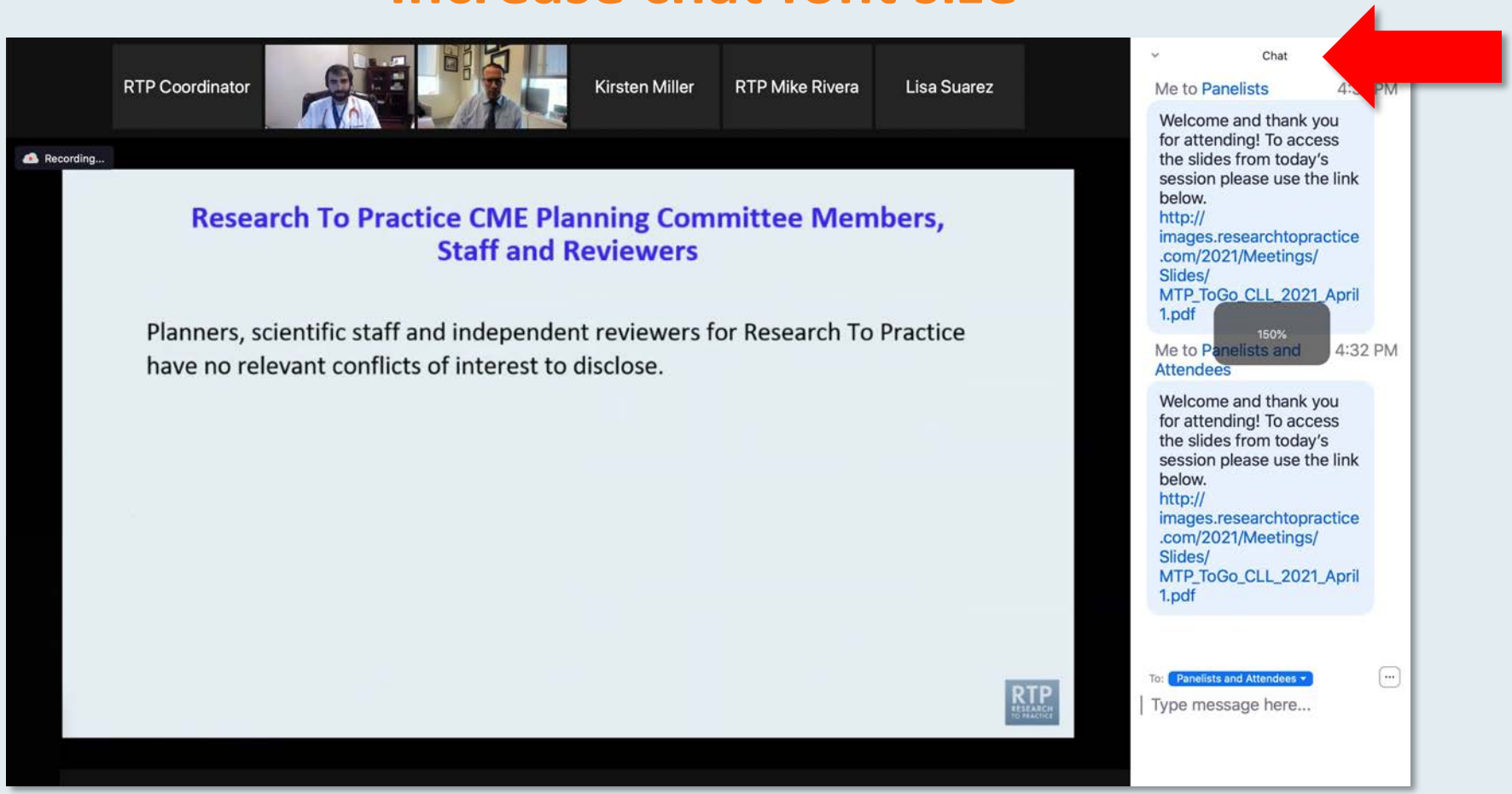
Increase chat font size



Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

Ask the Expert: Clinical Investigators Provide Perspectives on the Management of Renal Cell Carcinoma

In Partnership with Project Echo® and Florida Cancer Specialists

Tuesday, May 4, 2021
5:00 PM – 6:00 PM ET

Faculty

Chung-Han Lee, MD, PhD

Moderator

Neil Love, MD

Meet The Professor

Management of Chronic Lymphocytic Leukemia

Wednesday, May 5, 2021
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Jeremy Abramson, MD

Moderator

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Immunotherapy and Novel Agents in Gynecologic Cancers

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Moderator

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Current Concepts and Recent Advances in Oncology

A Daylong Clinical Summit Hosted in Partnership with Medical Oncology Association of Southern California (MOASC)

Saturday, May 15, 2021
10:30 AM – 6:30 PM ET

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10:30 AM — Breast Cancer
Ruth O'Regan, Tiffany A Traina

11:30 AM — Multiple Myeloma
Kenneth Anderson, Noopur Raje

12:50 PM — Chronic Lymphocytic Leukemia and Lymphomas
Craig Moskowitz, Jeff Sharman

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Meet The Professor
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Irene M Ghobrial, Sagar Lonial

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Virginia Kaklamani, Nancy U Lin

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Key Recent Data Sets in Gastrointestinal Cancers

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KARMANOS CANCER INSTITUTE

WAYNE STATE UNIVERSITY

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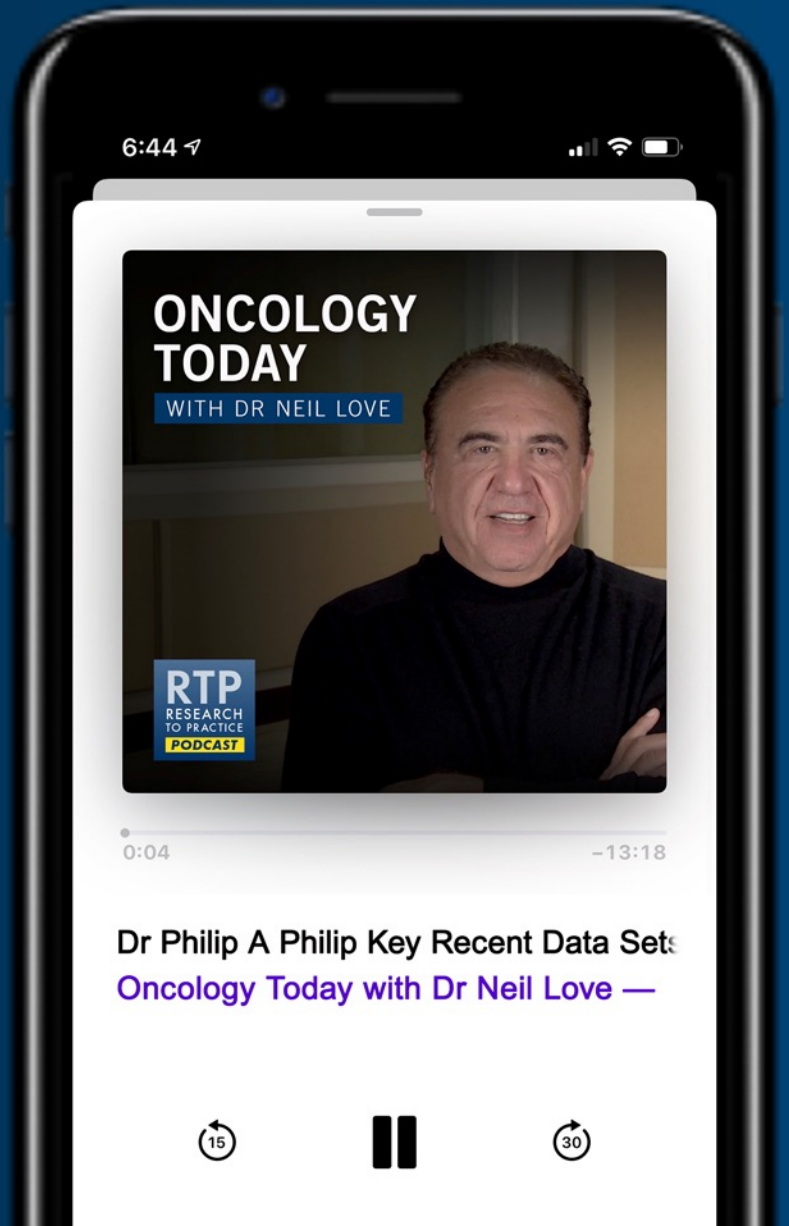

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Tennessee Oncology

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Meet The Professor Program Participating Faculty

Dirk Arnold, MD, PhD
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Asklepios Klinik Altona
Hamburg, Germany

Johanna Bendell, MD
Chief Development Officer
Director, Drug Development Unit Nashville
Sarah Cannon Research Institute
Tennessee Oncology
Nashville, Tennessee

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Mayo Clinic Cancer Center (AZ, FL and MN)
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Director, Interdisciplinary Gastrointestinal Oncology Program
Assistant Director, Translational Research
Comprehensive Cancer Center
The University of Chicago Medical Center and Biological Sciences
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Meet The Professor Program Participating Faculty

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Associate Director for Translational Research
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Axel Grothey, MD
Director, GI Cancer Research
West Cancer Center and Research Institute
Medical Director
OneOncology Research Network
Germantown, Tennessee

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Co-Director, Medical Initiatives
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Memorial Sloan Kettering Cancer Center
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Meet The Professor Program Participating Faculty

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Leader, GI and Neuroendocrine Oncology
Vice President of Medical Affairs
Karmanos Cancer Institute
Wayne State University
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Co-Director, UCLA GI Oncology Program
Jonsson Comprehensive Cancer Center
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Alan P Venook, MD
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Medical Oncology and Translational Research
Shorenstein Associate Director
Program Development
Helen Diller Family Comprehensive Cancer Center
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San Francisco, California

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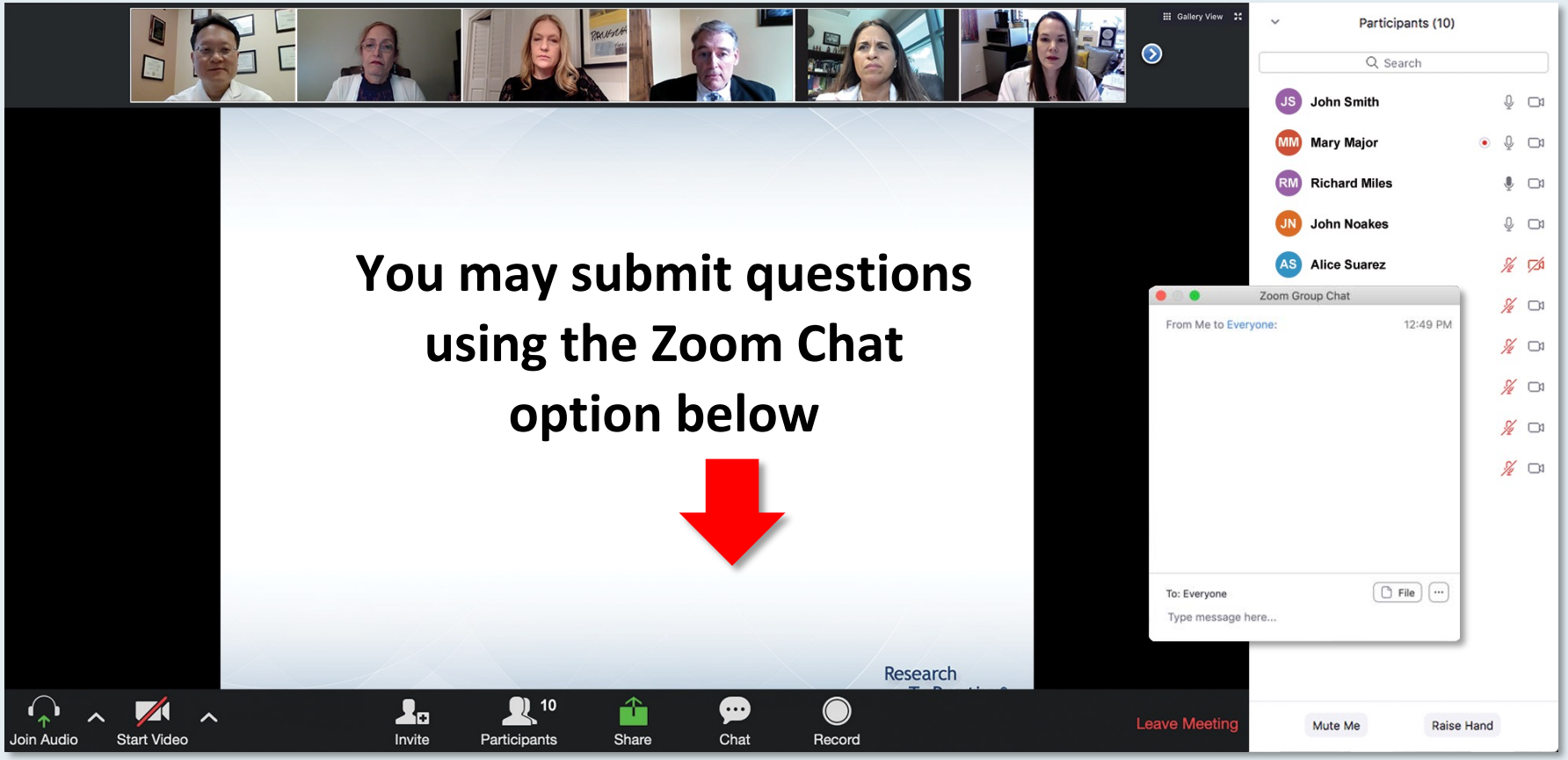

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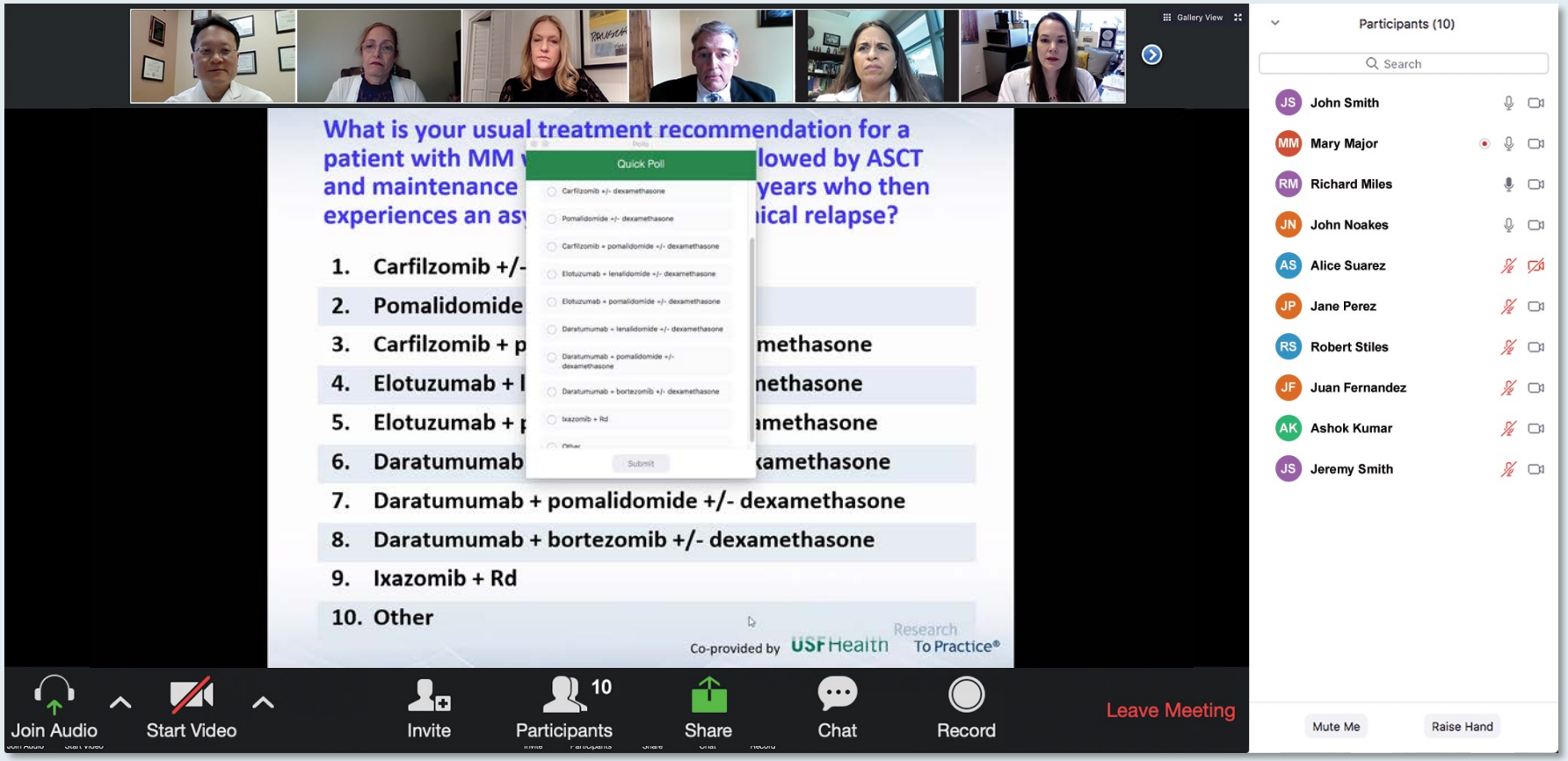

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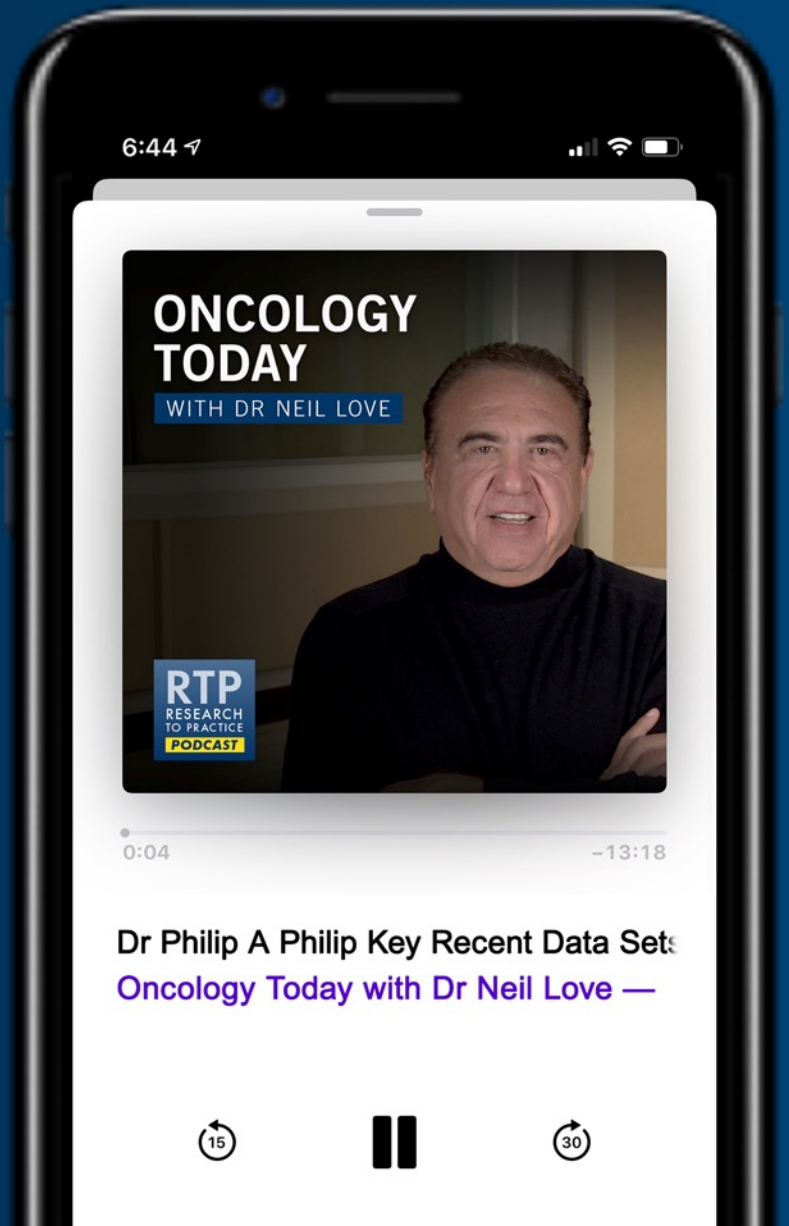

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Nashville, Tennessee

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Lynn Cancer Institute
Boca Raton, Florida

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Saint Luke's Cancer Institute
University of Missouri-Kansas City School of Medicine
Kansas City, Missouri

Rahul Gosain, MD
Division of Hematology and Oncology
Guthrie Corning Cancer Center
Corning, New York

John Yang, MD
Chief of Hematology/Oncology
Steward/St Anne's Hospital
Westwood, Massachusetts

Meet The Professor with Dr Bendell

MODULE 1: Cases from Drs Schafer and Yang

- Dr Yang: A 66-year-old woman with MSI-high colorectal cancer with a BRAF V600E mutation
- Dr Schafer: A 66-year-old man with MMR-proficient metastatic colorectal cancer – MSH3 germline mutation VUS

MODULE 2: Beyond the Guidelines; Key Data – Colorectal Cancer

MODULE 3: Case from Dr Gosain

- A 56-year-old man with MSS, HER2-positive GEJ cancer – PD-L1-negative

MODULE 4: Beyond the Guidelines; Key Data – Gastroesophageal Cancers

MODULE 5: Cases from Dr Brenner

- A 58-year-old man with advanced Child-Pugh B8 hepatocellular carcinoma (HCC)
- An 83-year-old man with advanced HCC and disease progression on bevacizumab/atezolizumab

MODULE 6: Beyond the Guidelines; Key Data – Hepatocellular Carcinoma

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Case Presentation – Dr Yang: A 66-year-old woman with MSI-high colorectal cancer (CRC) with a BRAF V600E mutation (Part 1)

Dr John Yang

- Diagnosed with Stage III MSI-high BRAF V600E-mutated colon cancer with 2/20 positive lymph nodes and a positive mesenteric nodule
- Resection
- Adjuvant FOLFOX
  - By cycle 8, worsening pelvic and abdominal pain, CEA has risen from 2 to 18. CT: Widespread liver/pelvic metastases

Questions

- How long would you treat with immunotherapy? What would you do upon disease progression?
- How do you respond to patients who ask, “Will I potentially be cured?”

Case Presentation – Dr Yang: A 66-year-old woman with MSI-high colorectal cancer (CRC) with a BRAF V600E mutation (Part 2)

Dr John Yang

- Diagnosed with Stage III MSI-high BRAF V600E-mutated colon cancer with 2/20 positive lymph nodes and a positive mesenteric nodule
- Resection
- Adjuvant FOLFOX
  - By cycle 8, worsening pelvic and abdominal pain, CEA has risen from 2 to 18. CT: Widespread liver/pelvic metastases
- ***Pembrolizumab x 15 cycles; CT scans showed marked improvement in liver metastases, but there is still a significant tumor burden in the liver. CEA remains normal.***

Questions

- How long would you treat with immunotherapy? What would you do upon disease progression?
- How do you respond to patients who ask, “Will I potentially be cured?”
- ***How would you sequence therapies for this patient with a BRAF V600E mutation?***

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Case Presentation – Dr Schafer: A 66-year-old man with MMR-proficient metastatic CRC – MSH3 germline mutation VUS

Dr Liudmila Schafer

- 3/2020: Stage IIIC MSS adenocarcinoma of the sigmoid colon s/p sigmoidectomy
  - KRAS wildtype, NRAS wildtype, BRAF wildtype, VUS MSH3 germline mutation, FLT3 mutation
  - Single liver lesion postoperatively
  - ctDNA: 31.9 MTM/mL increasing to 82.55 MTM/mL after several weeks
- FOLFOX/panitumumab x 6 months, with resolution of liver lesion after 3 months, CEA: 2.0
  - ctDNA: 0 MTM/mL
- 11/2020: CEA 7.0, no radiologic evidence of disease

Questions

- With a rising CEA and no radiologic evidence of disease, what would you recommend?
- Is there a role of MSH3, variant of unknown significance, as a predictive biomarker for the use of immune checkpoint inhibitors up front?

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MODULE 1: Cases from Drs Schafer and Yang

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What is your usual first-line treatment recommendation for a clinically stable 60-year-old patient with left-sided, MSS, pan-RAS wild-type, BRAF wild-type metastatic colorectal cancer (mCRC)?

1. Chemotherapy
2. Chemotherapy + anti-VEGF antibody
3. Chemotherapy + anti-EGFR antibody
4. Chemotherapy + immunotherapy
5. Other

What is your usual first-line treatment recommendation for a clinically stable 60-year-old patient with left-sided, MSS, pan-RAS wild-type, BRAF wild-type metastatic colorectal cancer (mCRC)?

 Prof Arnold	FOLFOX + cetuximab	 Dr Grothey	FOLFOX/CAPOX + panitumumab
 Dr Bekaii-Saab	FOLFOXIRI + bevacizumab	 Dr O'Reilly	FOLFOX/CAPOX + bevacizumab
 Dr Bendell	FOLFOXIRI + bevacizumab	 Dr Venook	FOLFOXIRI + bevacizumab
 Dr Ciombor	FOLFOX/CAPOX + bevacizumab	 Dr Wainberg	FOLFOX/CAPOX + bevacizumab

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What is your usual first-line treatment recommendation for a clinically stable 60-year-old patient with left-sided, pan-RAS wild-type, BRAF wild-type, MSI-high mCRC?

1. Pembrolizumab
2. Nivolumab
3. Nivolumab/ipilimumab
4. Chemotherapy
5. Chemotherapy + anti-VEGF antibody
6. Chemotherapy + anti-EGFR antibody
7. Chemotherapy + immunotherapy
8. Other

What is your usual first-line treatment recommendation for a clinically stable 60-year-old patient with left-sided, pan-RAS wild-type, BRAF wild-type, MSI-high mCRC?

 Prof Arnold	Pembrolizumab	 Dr Grothey	Pembrolizumab
 Dr Bekaii-Saab	Pembrolizumab	 Dr O'Reilly	Pembrolizumab
 Dr Bendell	Pembrolizumab	 Dr Venook	Pembrolizumab
 Dr Ciombor	Pembrolizumab	 Dr Wainberg	Pembrolizumab

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Regulatory and reimbursement issues aside, for a patient with pan-RAS wild-type mCRC with a BRAF V600E mutation, in what line of therapy would you generally administer BRAF-targeted therapy?

 Prof Arnold	Second line	 Dr Grothey	Second line
 Dr Bekaii-Saab	Second line	 Dr O'Reilly	Second line
 Dr Bendell	Second line	 Dr Venook	Second line
 Dr Ciombor	Second line	 Dr Wainberg	Second line

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For a patient with mCRC with a BRAF V600E mutation to whom you would administer BRAF-targeted therapy, what would be your preferred treatment?

1. Irinotecan + vemurafenib + EGFR antibody
2. Dabrafenib + trametinib + EGFR antibody
3. Encorafenib + binimetinib + EGFR antibody
4. Encorafenib + EGFR antibody
5. Other

For a patient with mCRC with a BRAF V600E mutation to whom you would administer BRAF-targeted therapy, what would be your preferred treatment?

 Prof Arnold	Encorafenib + EGFR antibody	 Dr Grothey	Encorafenib + EGFR antibody
 Dr Bekaii-Saab	Encorafenib + EGFR antibody	 Dr O'Reilly	Encorafenib + EGFR antibody
 Dr Bendell	Encorafenib + EGFR antibody	 Dr Venook	Encorafenib + EGFR antibody
 Dr Ciombor	Encorafenib + EGFR antibody	 Dr Wainberg	Encorafenib + binimetinib + EGFR antibody

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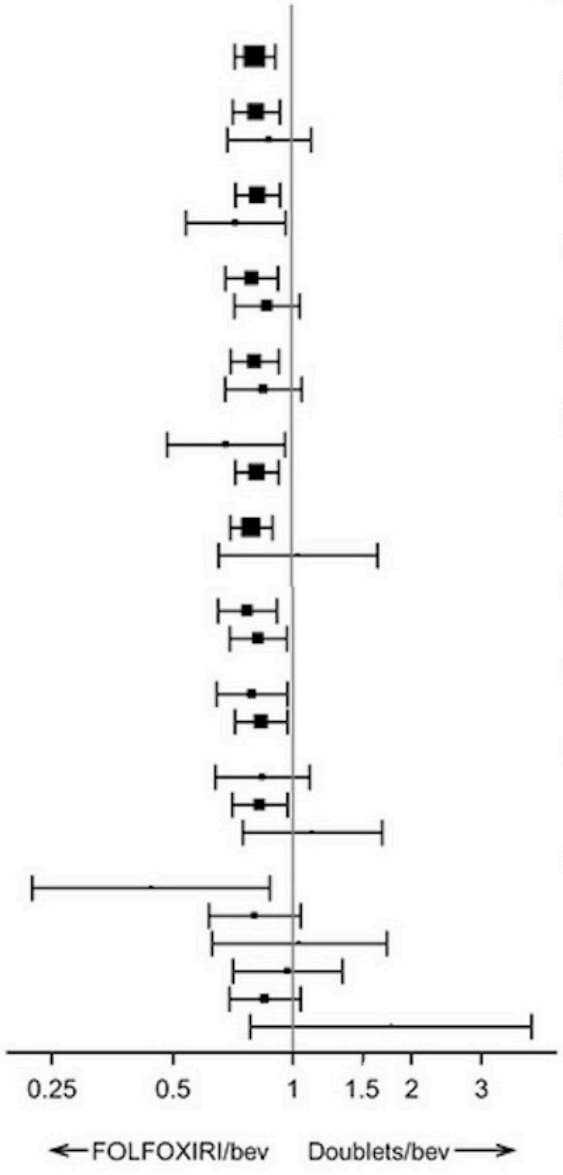
FOLFOXIRI/Bevacizumab (Bev) versus Doublets/Bev as Initial Therapy of Unresectable Metastatic Colorectal Cancer (mCRC): A Meta-Analysis of Individual Patient Data (IPD) from Five Randomized Trials

Cremolini C et al.

ASCO 2020;Abstract 4015.

Subgroup Analyses for Overall Survival

Subgroup	Doublets/bev Events/N (%)		FOLFOXIRI/bev Events/N (%)		HR (95% CI)	P Value
Intention to treat population	591/851	(69.4)	527/846	(62.3)	0.81 (0.72, 0.91)	
ECOG PS						0.855
0	441/656	(67.2)	398/667	(59.7)	0.82 (0.71, 0.94)	
0-1	149/192	(77.6)	126/175	(72.0)	0.88 (0.69, 1.12)	
Age						0.492
<70 years	493/722	(68.3)	436/707	(61.7)	0.82 (0.72, 0.94)	
>70 years	98/129	(76.0)	91/139	(65.5)	0.72 (0.54, 0.97)	
Gender						0.533
Male	376/518	(72.6)	307/489	(62.8)	0.80 (0.68, 0.93)	
Female	215/333	(64.6)	220/357	(61.6)	0.87 (0.72, 1.05)	
Liver only						0.665
No	441/596	(74.0)	358/543	(65.9)	0.81 (0.70, 0.93)	
Yes	150/254	(59.1)	168/300	(56.0)	0.85 (0.68, 1.06)	
Time to metastases						0.408
Metachronous	83/130	(63.8)	57/130	(43.8)	0.69 (0.49, 0.96)	
Synchronous	508/720	(70.6)	470/716	(65.6)	0.82 (0.72, 0.93)	
Previous adjuvant						0.296
No	552/790	(69.9)	492/782	(62.9)	0.79 (0.70, 0.90)	
Yes	39/61	(63.9)	35/63	(55.6)	1.04 (0.66, 1.65)	
Primary resection						0.623
No	284/386	(73.6)	267/400	(66.8)	0.77 (0.65, 0.91)	
Yes	307/465	(66.0)	260/445	(58.4)	0.82 (0.69, 0.97)	
Tumor site						0.656
Right	185/255	(72.5)	193/295	(65.4)	0.79 (0.64, 0.97)	
Left / rectum	367/535	(68.6)	317/496	(63.9)	0.83 (0.72, 0.97)	
RAS						0.337
RAS-BRAF wt	107/172	(62.2)	99/177	(55.9)	0.84 (0.64, 1.10)	
RAS mut	316/430	(73.5)	289/422	(68.5)	0.83 (0.70, 0.97)	
BRAF mut	43/54	(79.6)	53/61	(86.9)	1.12 (0.75, 1.68)	
Site–RAS/BRAF						0.320
Right-RAS/BRAF wt	21/31	(67.7)	21/44	(47.7)	0.44 (0.22, 0.88)	
Right-RAS mut	110/149	(73.8)	113/168	(67.3)	0.80 (0.62, 1.05)	
Right-BRAF mut	33/40	(82.5)	34/39	(87.2)	1.04 (0.63, 1.72)	
Left-RAS/BRAF wt	79/134	(59.0)	78/132	(59.1)	0.97 (0.71, 1.33)	
Left-RAS mut	199/273	(72.9)	173/250	(69.2)	0.85 (0.69, 1.05)	
Left-BRAF mut	9/13	(69.2)	19/22	(86.4)	1.77 (0.78, 4.01)	



Cremolini C et al. ASCO 2020;Abstract 4015.

Oncologist 2021;26(4):302-9.

The Oncologist®

Gastrointestinal Cancer

FOLFOXIRI-Bevacizumab or FOLFOX-Panitumumab in Patients with Left-Sided *RAS/BRAF* Wild-Type Metastatic Colorectal Cancer: A Propensity Score-Based Analysis

Filippo Pietrantonio,[a,b,†] Giovanni Fucà,[a,†] Daniele Rossini,[c,d] Hans-Joachim Schmoll,[e] Johanna C. Bendell,[f] Federica Morano,[a] Carlotta Antoniotti,[c,d] Salvatore Corallo,[a] Beatrice Borelli,[c,d] Alessandra Raimondi,[a] Federica Marmorino,[c,d] Monica Niger,[a] Alessandra Boccaccino,[c,d] Gianluca Masi,[c,d] Sara Lonardi,[g] Luca Boni,[h] Filippo de Braud,[a,b] Maria Di Bartolomeo,[a] Alfredo Falcone,[c,d] Chiara Cremolini[c,d]

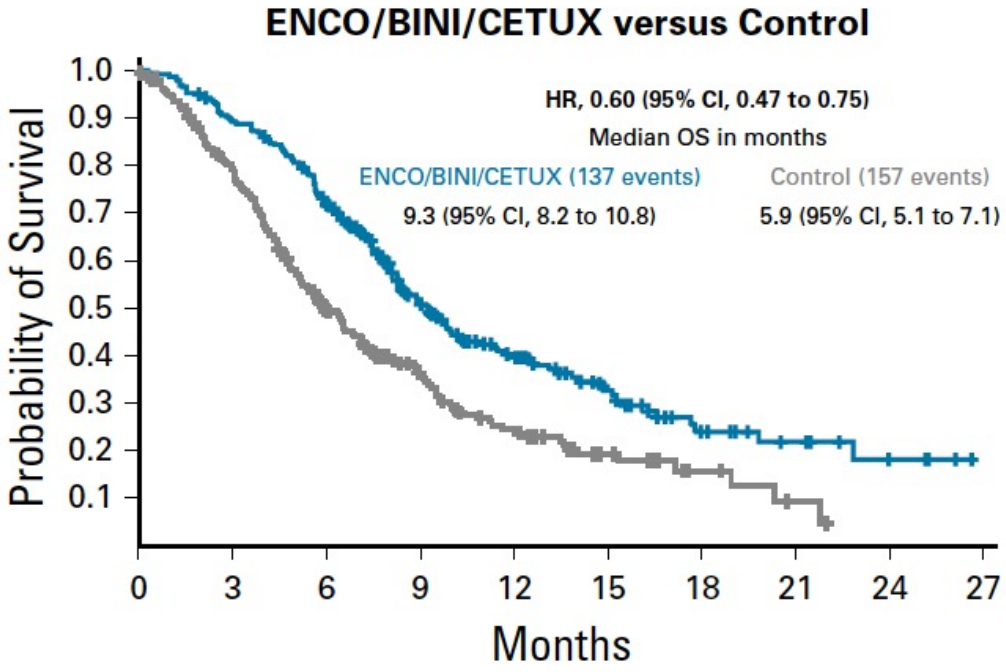
rapid communications

Encorafenib Plus Cetuximab as a New Standard of Care for Previously Treated *BRAF* V600E–Mutant Metastatic Colorectal Cancer: Updated Survival Results and Subgroup Analyses from the BEACON Study

Josep Tabernero, MD, PhD[1]; Axel Grothey, MD[2]; Eric Van Cutsem, MD, PhD[3]; Rona Yaeger, MD[4]; Harpreet Wasan, MD[5]; Takayuki Yoshino, MD, PhD[6]; Jayesh Desai, MBBS[7]; Fortunato Ciardiello, MD, PhD[8]; Fotios Loupakis, MD, PhD[9]; Yong Sang Hong, MD, PhD[10]; Neeltje Steeghs, MD, PhD[11]; Tormod Kyrre Guren, MD, PhD[12]; Hendrik-Tobias Arkenau, MD, PhD[13]; Pilar Garcia-Alfonso, MD[14]; Elena Elez, MD, PhD[1]; Ashwin Gollerkeri, MD[15]; Kati Maharry, PhD[15]; Janna Christy-Bittel, MSN[15]; and Scott Kopetz, MD, PhD[16]

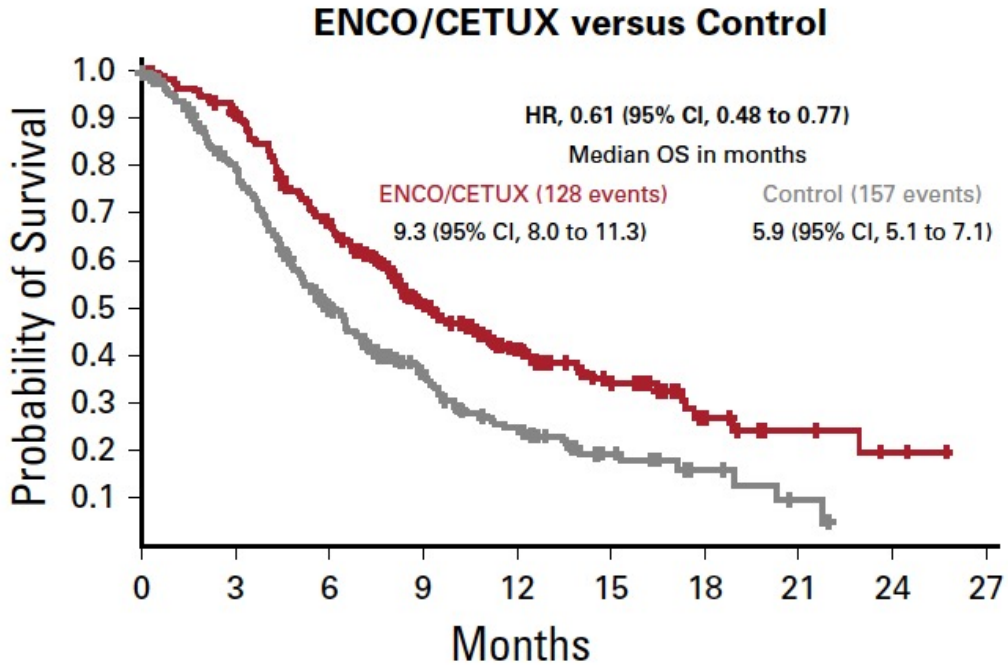
J Clin Oncol 2021;39(4):273-84.

BEACON: Overall Survival Results



Number of patients at risk

ENCO/BINI/CETUX	224	198	157	89	56	33	15	9	4	0
Control	221	166	98	54	33	15	6	2	0	0



Number of patients at risk

ENCO/CETUX	220	197	143	83	47	28	13	7	2	0
Control	221	166	98	54	33	15	6	2	0	0

Tabanero J et al. *J Clin Oncol* 2021;39(4):273-84.

RTP RESEARCH TO PRACTICE

FDA Approves New Dosing Regimen for Cetuximab

Press Release – April 6, 2021

"On April 6, 2021, the Food and Drug Administration approved a new dosage regimen of 500 mg/m^2 as a 120-minute intravenous infusion every two weeks (Q2W) for cetuximab for patients with K-Ras wild-type, EGFR-expressing colorectal cancer (mCRC) or squamous cell carcinoma of the head and neck (SCCHN).

The approval was based on population pharmacokinetic (PK) modeling analyses that compared the predicted exposures of cetuximab 500 mg Q2W to observed cetuximab exposures in patients who received cetuximab 250 mg weekly. The application was also supported by pooled analyses of overall response rates, progression-free survival, and overall survival (OS) from published literature in patients with CRC and SCCHN, and OS analyses using real-world data in patients with mCRC who received either the weekly cetuximab or Q2W regimens. In these exploratory analyses, the observed efficacy results were consistent across dosage regimens and supported the results of the population PK modeling analyses.

The most common adverse reactions (incidence ≥25%) to cetuximab are cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-new-dosing-regimen-cetuximab

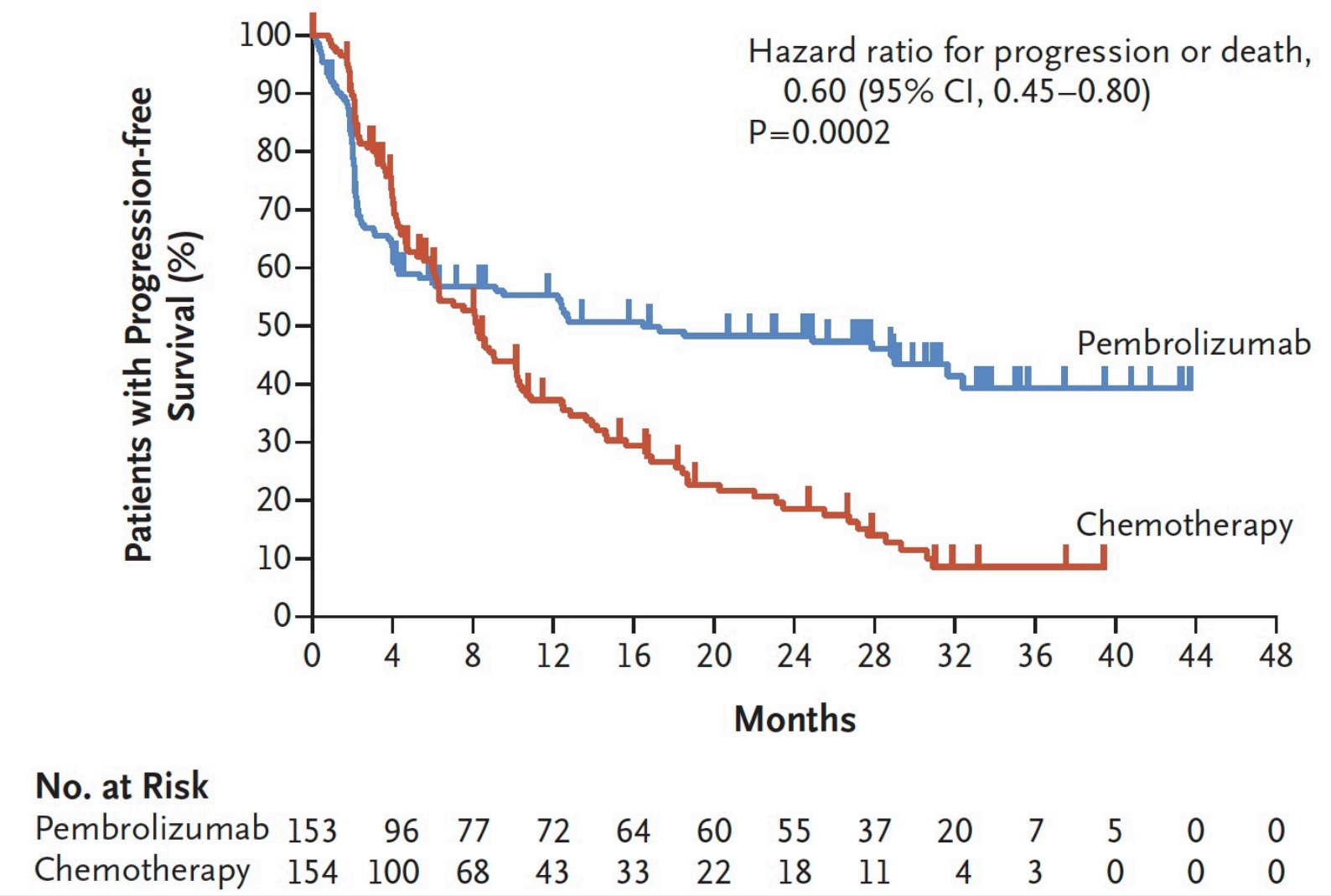
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 3, 2020 VOL. 383 NO. 23

Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

T. André, K.-K. Shiu, T.W. Kim, B.V. Jensen, L.H. Jensen, C. Punt, D. Smith, R. Garcia-Carbonero, M. Benavides, P. Gibbs, C. de la Fouchardiere, F. Rivera, E. Elez, J. Bendell, D.T. Le, T. Yoshino, E. Van Cutsem, P. Yang, M.Z.H. Farooqui, P. Marinello, and L.A. Diaz, Jr., for the KEYNOTE-177 Investigators*

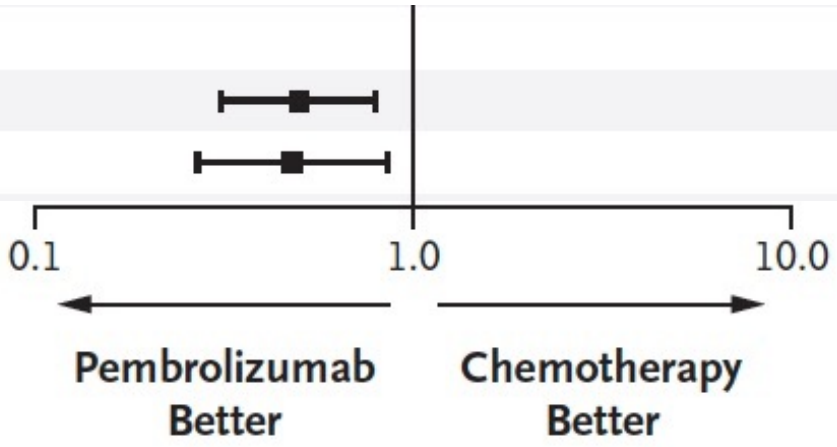
Progression-Free Survival for Patients with MSI-H/dMMR Metastatic Colorectal Cancer



André T et al. *N Engl J Med* 2020;383(23):2207-18.

Progression-Free Survival in Key Subgroups of Patients with MSI-H/dMMR Metastatic Colorectal Cancer

Subgroup	No. of Events/No. of Patients	Hazard Ratio (95% CI)
BRAF		
BRAF wild type	78/131	0.50 (0.31–0.80)
BRAF^{V600E}	51/77	0.48 (0.27–0.86)



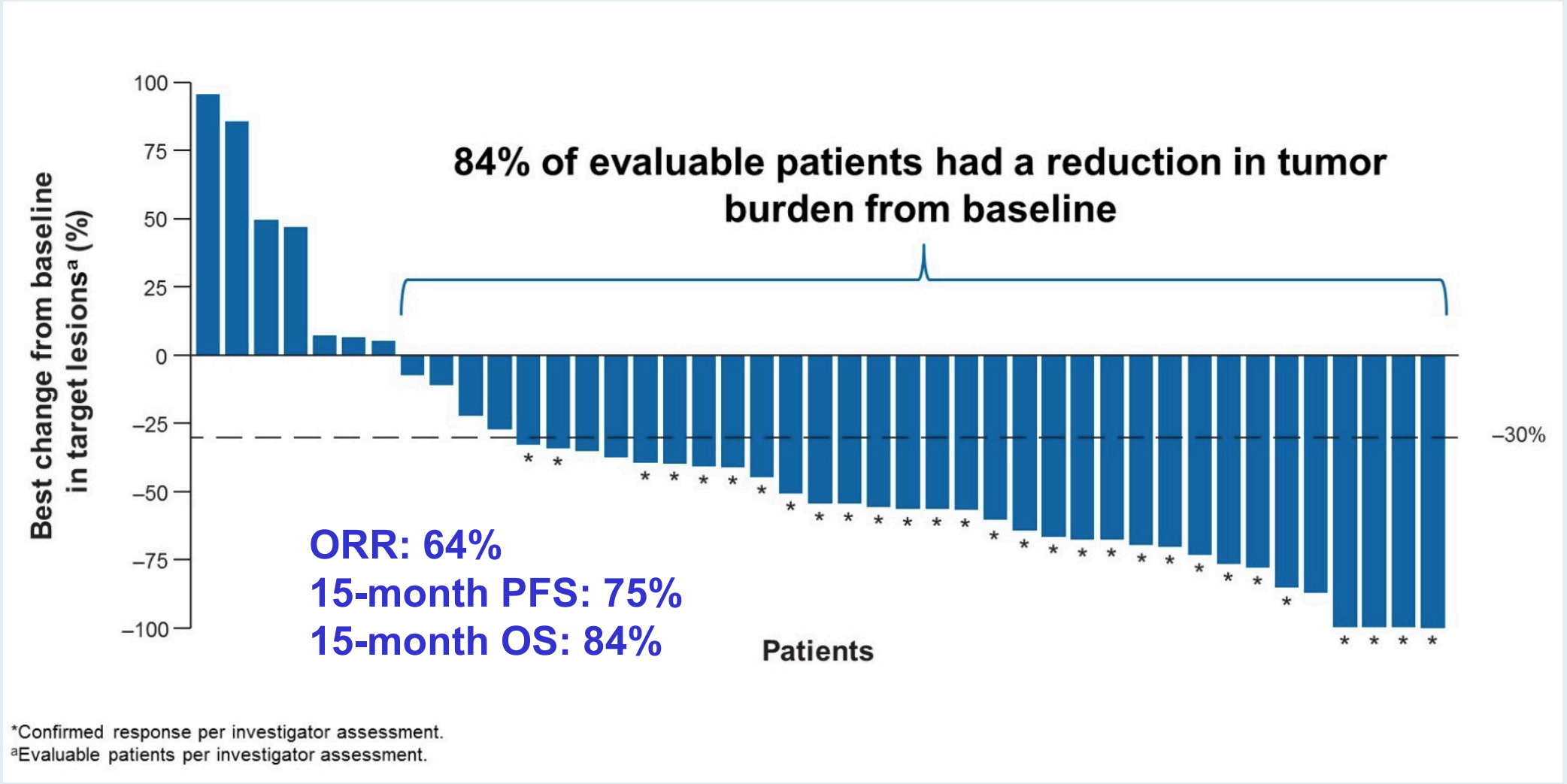
André T et al. *N Engl J Med* 2020;383(23):2207-18.

Nivolumab plus Low-Dose Ipilimumab as First-Line Therapy in Microsatellite Instability-High/DNA Mismatch Repair Deficient mCRC: Clinical Update

Lenz H-J et al.

Gastrointestinal Cancers Symposium 2020;Abstract 11.

CheckMate 142: Nivolumab/Ipilimumab as First-Line Therapy in MSI-H/dMMR mCRC



*Confirmed response per investigator assessment.
[a]Evaluable patients per investigator assessment.

Lenz H-J et al. Gastrointestinal Cancers Symposium 2020;Abstract 11.

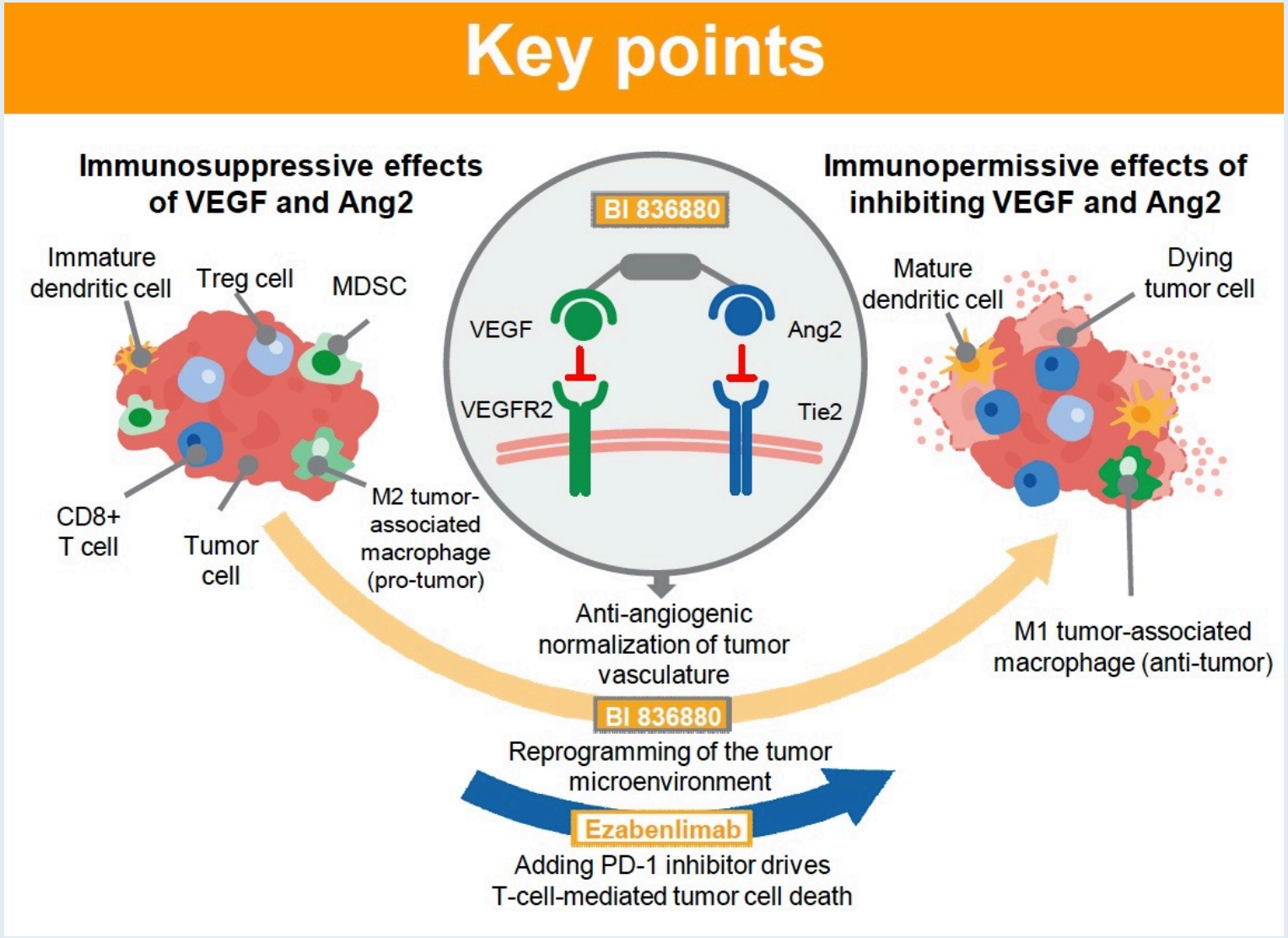
RTP RESEARCH TO PRACTICE

Platform Trial of BI 754091, an Anti-PD-1 Antibody, in Patients with Previously Treated Advanced Solid Tumors: Combination with BI 836880, a VEGF/Ang2-blocking Nanobody

Hussein et al.

Gastrointestinal Cancers Symposium 2021;Abstract TPS152.

Immunopermissive Mechanism of Action of Dual VEGF/Ang2 Inhibition



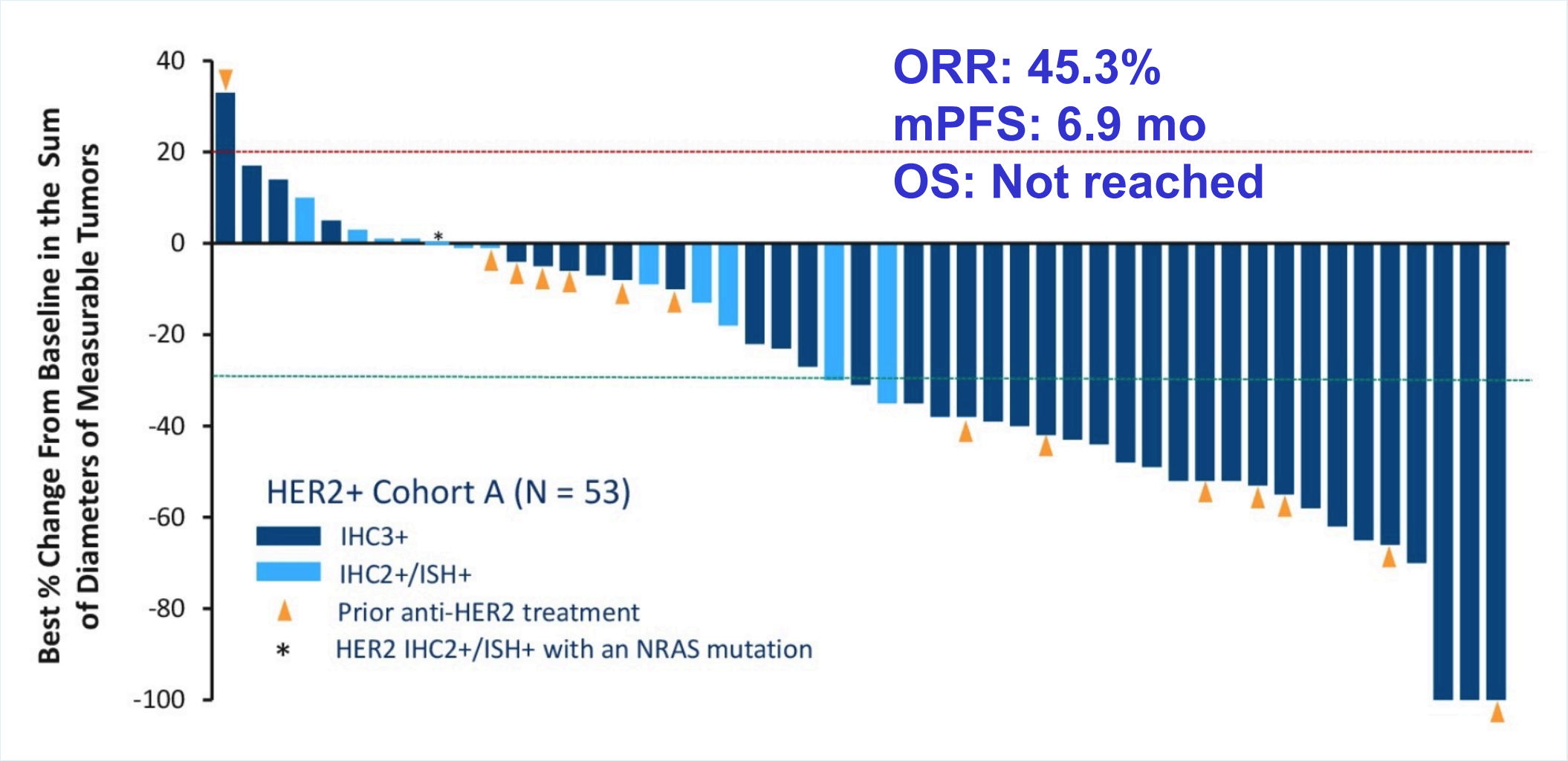
Hussein et al. Gastrointestinal Cancers Symposium 2021;Abstract TPS152.

A Phase II, Multicenter, Open-Label Study of Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients (pts) with HER2-Expressing Metastatic Colorectal Cancer (mCRC): DESTINY-CRC01

Siena S et al.

ASCO 2020;Abstract 4000.

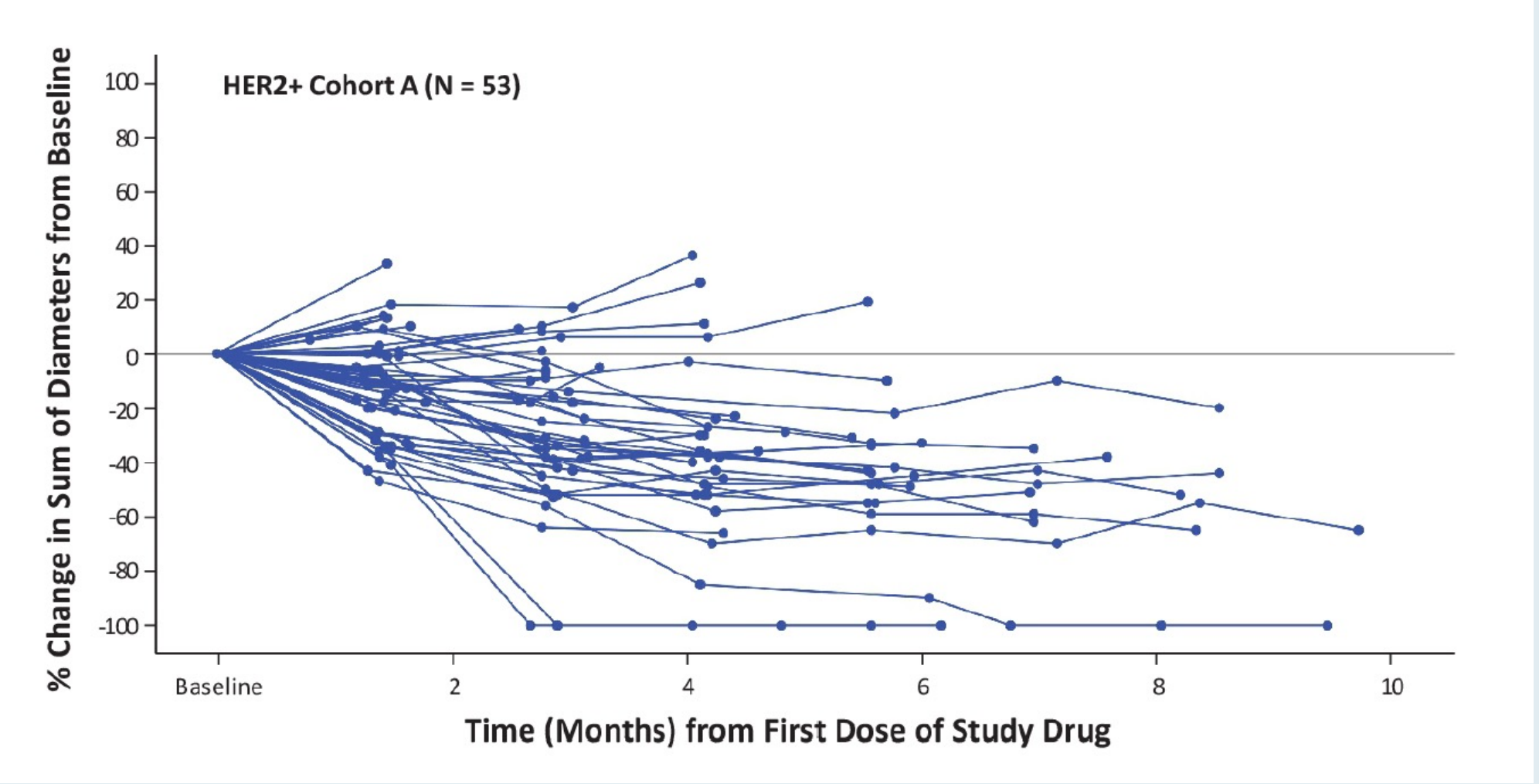
DESTINY-CRC01: Best Change in Tumor Size Over Time



Siena S et al. ASCO 2020;Abstract 4000.

RTP RESEARCH TO PRACTICE

DESTINY-CRC01: Tumor Shrinkage Over Time



Siena S et al. ASCO 2020;Abstract 4000.

DESTINY-CRC01: AEs of Special Interest

	All Patients (N = 78)					
Preferred Term, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
Interstitial Lung Disease	0	2 (2.6)	1 (1.3)	0	2 (2.6)	5 (6.4)

Among the 5 total events:

- Median time to investigator-reported onset was 80 days (range, 22-132)
- 5 of 5 patients with grade ≥ 2 ILD received corticosteroids
- 2 patients recovered, 1 did not recover (later died due to disease progression), and 2 died
- In the 2 fatal cases, onset was from 40-126 days, both received steroids as part of treatment, and death occurred 6-18 days after diagnosis

Protocol recommendations: Monitor for symptoms. Hold T-DXd and start steroids as soon as ILD is suspected

Siena S et al. ASCO 2020;Abstract 4000.

A Phase I Dose Escalation Study of PRS-343, a HER2/4-1BB Bispecific Molecule, in Patients with HER2-Positive Malignancies

Ku G et al.

ESMO 2020;Abstract 525O.

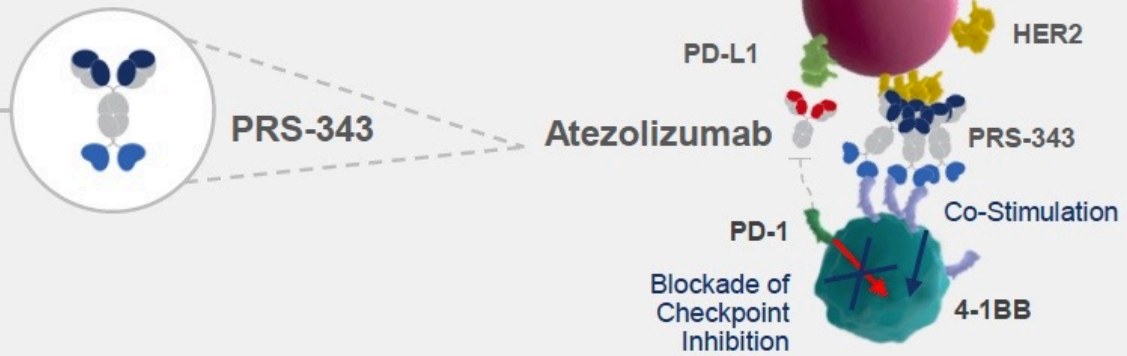
PRS-343, a HER2 4-1BB Bispecific, Drives 4-1BB Agonism in the Tumor Microenvironment in HER2 Positive Solid Tumors

HER2-targeting moiety of the drug localizes to the tumor microenvironment and facilitates 4-1BB cross-linking

4-1BB cross-linking ameliorates T-cell exhaustion and is critical for T-cell expansion

HER2 targeting Antibody

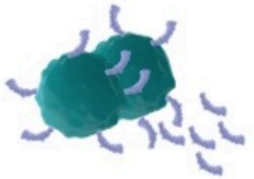
4-1BB targeting Anticalin® Proteins



CLINICALLY-RELEVANT BIOMARKERS

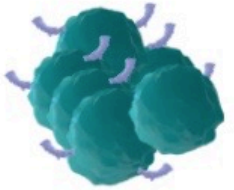
4-1BB Pathway Activation

Soluble 4-1BB



T-cell Proliferation

$CD8^+$ and $CD8^+/Ki67^+$



Ku G et al. ESMO 2020;Abstract 525O.

Phase I Dose-Escalation Study of MCLA-158, a First-in-Class Bispecific Antibody Targeting EGFR and LGR5, in Metastatic Colorectal Cancer (CRC)

Argiles G et al.

Gastrointestinal Cancers Symposium 2021;Abstract 62.

MCLA-158

- MCLA-158 is an ADCC enhanced human IgG1 Biclonics® bispecific antibody (bAb) targeting EGFR and LGR5.
- MCLA-158 was selected from functional screening of patient-derived organoids (PDO) generated from diagnostic/resection tissue of colorectal (CRC) patients.
- MCLA-158 exposure leads to EGFR signaling blockade and receptor degradation in LGR5+ cancer cells.
- MCLA-158 exhibits potent growth inhibition of *RASmut* and RAS*wt* CRC PDOs.
- Minimal growth inhibition is observed in non-tumoral PDOs treated with MCLA-158.
- In preclinical *in vivo* models MCLA-158 blocked metastasis initiation.

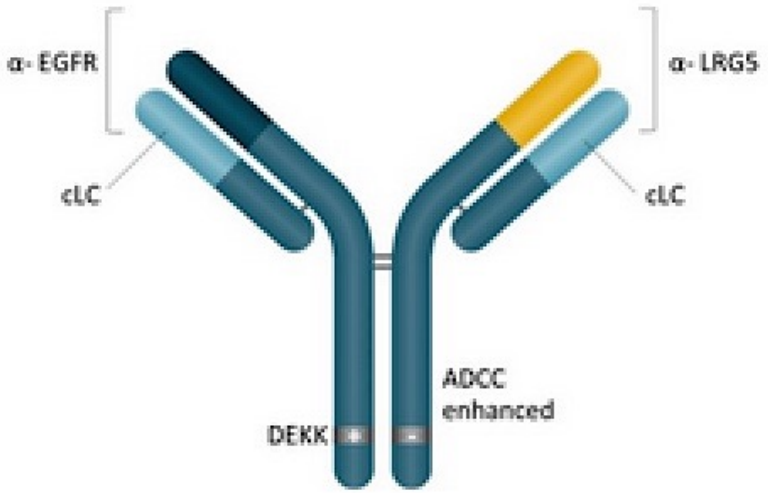


Figure 1 | MCLA-158 structure. A full-length, common light chain (cLC), CH3-engineered (DEKK), ADCC enhanced (GLYMAXX) bispecific antibody targeting EGFR and LGR5

Argiles G et al. Gastrointestinal Cancers Symposium 2021;Abstract 62.

Meet The Professor with Dr Bendell

MODULE 1: Cases from Drs Schafer and Yang

- Dr Yang: A 66-year-old woman with MSI-high colorectal cancer with a BRAF V600E mutation
- Dr Schafer: A 66-year-old man with MMR-proficient metastatic colorectal cancer – MSH3 germline mutation VUS

MODULE 2: Beyond the Guidelines; Key Data – Colorectal Cancer

MODULE 3: Case from Dr Gosain

- A 56-year-old man with MSS, HER2-positive GEJ cancer – PD-L1-negative

MODULE 4: Beyond the Guidelines; Key Data – Gastroesophageal Cancers

MODULE 5: Cases from Dr Brenner

- A 58-year-old man with advanced Child-Pugh B8 hepatocellular carcinoma (HCC)
- An 83-year-old man with advanced HCC and disease progression on bevacizumab/atezolizumab

MODULE 6: Beyond the Guidelines; Key Data – Hepatocellular Carcinoma

RTP
RESEARCH
TO PRACTICE

Case Presentation – Dr Gosain: A 56-year-old man with MSS, HER2-positive gastroesophageal junction cancer – PD-L1-negative

Dr Rahul Gosain

- Worsening dysphagia, weight loss → EGD c/w poorly differentiated adenocarcinoma
  - MSS, HER2-positive, PD-L1-negative
  - PET/CT: Gastro-hepatic adenopathy; no other distant disease
- Peri-operative carboplatin/paclitaxel + RT
  - Repeat EGD c/w residual disease
- Patient declined surgery
- Palliative FOLFOX/trastuzumab

Questions

- For a patient like this with residual disease, would you consider adjuvant immunotherapy, despite PD-L1 being negative?
- Is there any data for trastuzumab or trastuzumab deruxtecan in the neoadjuvant or adjuvant setting?

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Bendell

MODULE 1: Cases from Drs Schafer and Yang

- Dr Yang: A 66-year-old woman with MSI-high colorectal cancer with a BRAF V600E mutation
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MODULE 6: Beyond the Guidelines; Key Data – Hepatocellular Carcinoma

RTP
RESEARCH
TO PRACTICE

Regulatory and reimbursement issues aside, what would you currently recommend as second-line therapy for a patient with metastatic HER2-negative, MSS adenocarcinoma of the GEJ who has experienced disease progression on first-line FOLFOX?

 Prof Arnold	Ramucirumab/ paclitaxel	 Dr Grothey	Test for PD-L1 CPS and administer pembrolizumab if ≥10
 Dr Bekaii-Saab	Test for PD-L1 CPS and administer pembrolizumab if ≥10	 Dr O'Reilly	Ramucirumab/ paclitaxel
 Dr Bendell	Test for PD-L1 CPS and administer pembrolizumab if ≥10	 Dr Venook	Ramucirumab/ paclitaxel
 Dr Ciombor	FOLFIRI/ramucirumab	 Dr Wainberg	Ramucirumab/ paclitaxel

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what would you currently recommend as second-line therapy for a patient with metastatic HER2-positive, MSS adenocarcinoma of the GEJ who has experienced disease progression on first-line FOLFOX/trastuzumab?

 Prof Arnold	Ramucirumab/ paclitaxel	 Dr Grothey	Trastuzumab deruxtecan
 Dr Bekaii-Saab	Trastuzumab deruxtecan	 Dr O'Reilly	Trastuzumab deruxtecan
 Dr Bendell	Test for PD-L1 CPS and administer pembrolizumab if ≥10%	 Dr Venook	Ramucirumab/ paclitaxel
 Dr Ciombor	FOLFIRI/ramucirumab	 Dr Wainberg	Trastuzumab deruxtecan

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in which line of therapy would you generally recommend trastuzumab deruxtecan for a 65-year-old patient with metastatic HER2-positive, MSS adenocarcinoma of the GEJ?

 Prof Arnold	Third line	 Dr Grothey	Second line
 Dr Bekaii-Saab	Second line	 Dr O'Reilly	Second line
 Dr Bendell	Second line	 Dr Venook	Second line
 Dr Ciombor	Third line	 Dr Wainberg	Second line

RTP RESEARCH TO PRACTICE

Checkpoint Inhibitor Approvals in Gastric, GEJ and Esophageal Cancers

Regimen	Location	Histology	Setting	PD-L1
Pembrolizumab 9/22/2017	Gastric, GEJ	Adenocarcinoma	• Recurrent locally advanced or metastatic • Progression on or after ≥2 prior lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy	CPS ≥1
Pembrolizumab 7/30/2019	Esophageal, GEJ	Squamous	• Recurrent locally advanced or metastatic • Not amenable to surgical resection or definitive chemoradiation • After ≥1 prior lines of systemic therapy	CPS ≥10
Nivolumab 6/10/2020	Esophageal	Squamous	• Unresectable advanced, recurrent or metastatic • After prior fluoropyrimidine- and platinum-based chemotherapy	Not required
Pembrolizumab + cisplatin/5-FU 3/22/2021	Esophageal, GEJ	Adenocarcinoma and squamous	• Recurrent locally advanced or metastatic • Not amenable to surgical resection or definitive chemoradiation	Not required
Nivolumab + mFOLFOX6 or CAPOX 4/16/2021	Gastric, GEJ, esophageal	Adenocarcinoma	• Advanced or metastatic gastric, GEJ or esophageal adenocarcinoma	Not required

RTP RESEARCH TO PRACTICE

Selected Adjuvant and Neoadjuvant Studies of Immunotherapy in Gastric Cancers

Study/IO agents	Phase	Protocol summary
CheckMate 577 Nivolumab	3	Adjuvant immunotherapy in patients with resected (R0) stage II or III esophageal or gastroesophageal junction cancer who had received neoadjuvant chemoradiotherapy and had residual pathological disease
KEYNOTE-585 Pembrolizumab	3	Pembrolizumab (MK-3475) Plus Chemotherapy (XP or FP) Versus Placebo Plus Chemotherapy (XP or FP) as Neoadjuvant/Adjuvant Treatment for Gastric and Gastroesophageal Junction (GEJ) Adenocarcinoma
ONO-4538-38 Nivolumab	3	Adjuvant chemotherapy with Nivolumab in combination with S-1 therapy or capecitabine + oxaliplatin, in comparison with placebo in combination with S-1 therapy or CapeOX therapy, in Stage III gastric cancer (including esophagogastric junction cancer) after D2 or more extensive lymph node dissection.
VESTIGE Nivolumab, ipilimumab	2	Adjuvant Immunotherapy in Patients With Resected Esophageal, Gastroesophageal Junction and Gastric Cancer Following Preoperative Chemotherapy With High Risk for Recurrence (N+ and/or R1)
NCT04745988 Pembrolizumab	2	Lenvatinib With Pembrolizumab in the Neoadjuvant / Adjuvant Treatment for Patients With Gastric Cancer
RESONANCE-III Nivolumab	2	Nivolumab, S-1 Combined With Oxaliplatin (Nivo+SOX) Versus Nivolumab (Nivo) as Neoadjuvant Therapy in Patients With Locally Advanced Gastric Adenocarcinoma

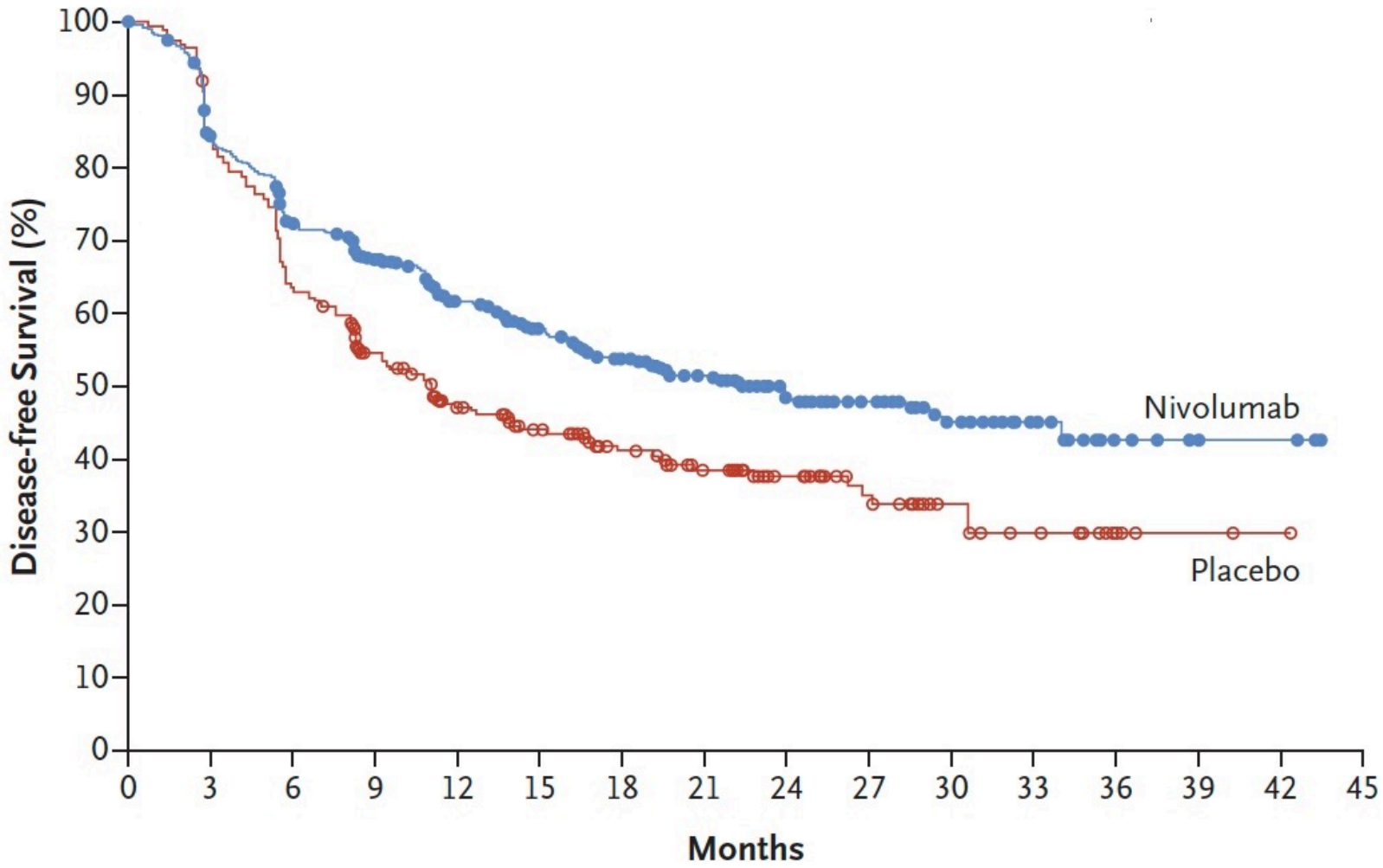
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 1, 2021 VOL. 384 NO. 13

Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

R.J. Kelly, J.A. Ajani, J. Kuzdzal, T. Zander, E. Van Cutsem, G. Piessen, G. Mendez, J. Feliciano, S. Motoyama, A. Lièvre, H. Uronis, E. Elimova, C. Grootscholten, K. Geboes, S. Zafar, S. Snow, A.H. Ko, K. Feeney, M. Schenker, P. Kocon, J. Zhang, L. Zhu, M. Lei, P. Singh, K. Kondo, J.M. Cleary, and M. Moehler, for the CheckMate 577 Investigators*

Disease-Free Survival in the Overall Population



	No. of Patients	Median Disease-free Survival
		mo (95% CI)
Nivolumab	532	22.4 (16.6–34.0)
Placebo	262	11.0 (8.3–14.3)

Hazard ratio for disease recurrence or death, 0.69 (96.4% CI, 0.56–0.86)
P<0.001

Kelly RJ et al. *N Engl J Med* 2021;384(13):1191-203.

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

Analyses of PD-L1 and Inflammatory Gene Expression Association with Efficacy of Nivolumab ± Ipilimumab in Gastric Cancer/Gastroesophageal Junction Cancer

Ming Lei[1], Nathan O. Siemers[1], Dimple Pandya[1], Han Chang[1], Teresa Sanchez[1], Christopher Harbison[1], Peter M. Szabo[1], Yelena Janjigian[2], Patrick A. Ott[3], Padmanee Sharma[4], Johanna Bendell[5], Thomas R. Jeffry Evans[6], Filippo de Braud[7,8], Ian Chau[9], and Zachary Boyd[1]

***Clin Cancer Res* 2021;[Online ahead of print].**

Cancers (Basel) 2020;12(10):2985.

cancers

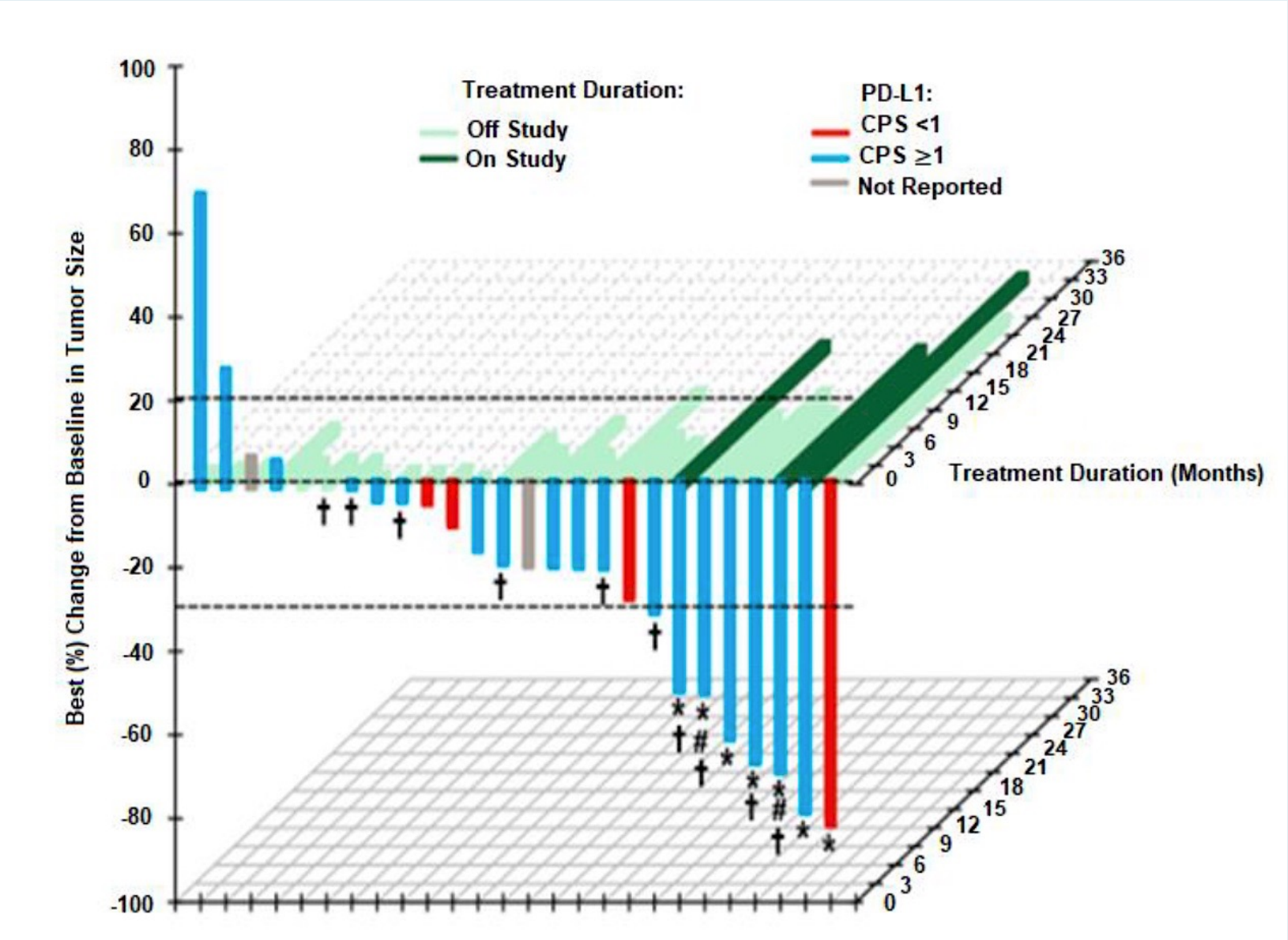
MDPI

Article

Ramucirumab in Combination with Pembrolizumab in Treatment-Naïve Advanced Gastric or GEJ Adenocarcinoma: Safety and Antitumor Activity from the Phase 1a/b JVDF Trial

Ian Chau [1,*], Nicolas Penel [2], Andres O. Soriano [3], Hendrik-Tobias Arkenau [4], Jennifer Cultrera [5], Rafael Santana-Davila [6], Emiliano Calvo [7], Christophe Le Tourneau [8], Lars Zender [9], Johanna C. Bendell [10], Gu Mi [11], Ling Gao [11], Samuel Clark McNeely [11], Joana M. Oliveira [12], David Ferry [12], Roy S. Herbst [13] and Charles S. Fuchs [13,14]

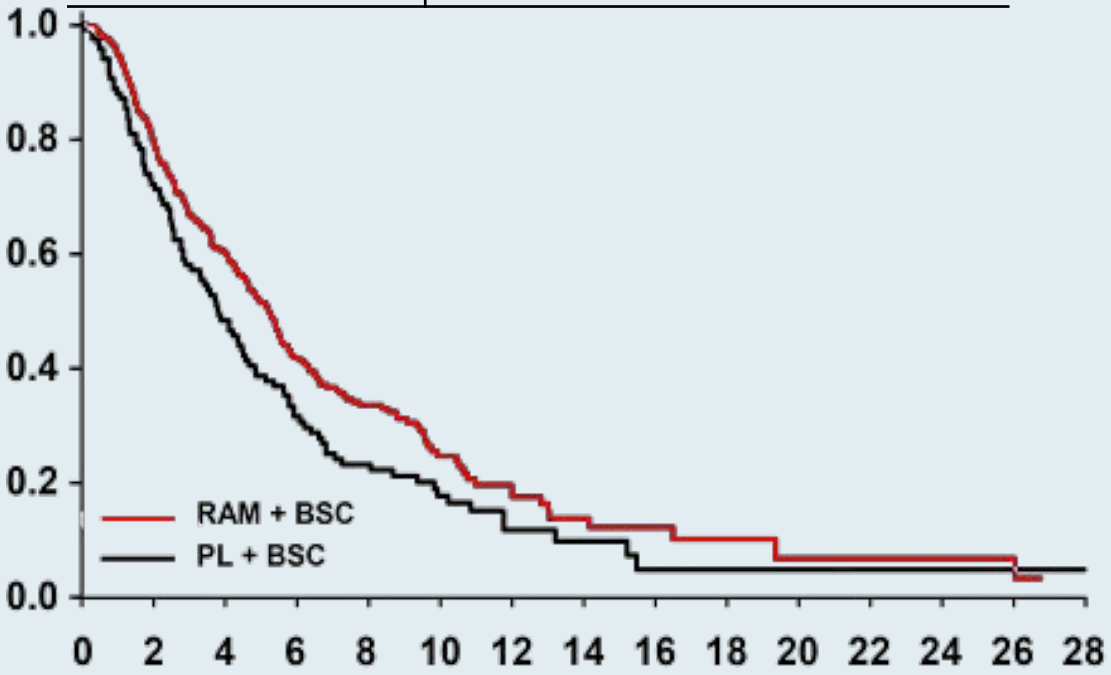
Best Percentage Change of Targeted Lesions from Baseline versus Treatment Duration



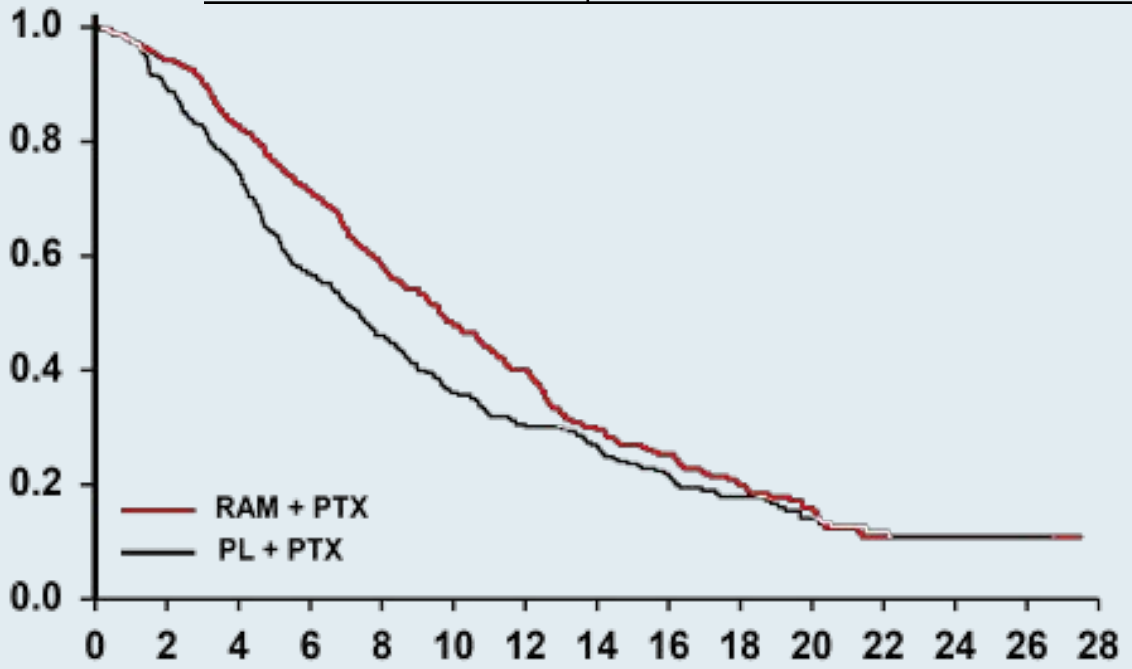
Chau I et al. *Cancers (Basel)* 2020;12(10):2985.

Overall Survival Results from 2 Phase III Trials of Ramucirumab as Second-Line Treatment for Advanced Gastric or GEJ Adenocarcinoma REGARD and RAINBOW

REGARD[1] OS	RAM	Placebo	*p*-value
Median (mo)	**5.2**	**3.8**	**0.047**
HR (95% CI)	**0.776 (0.603-0.998)**		



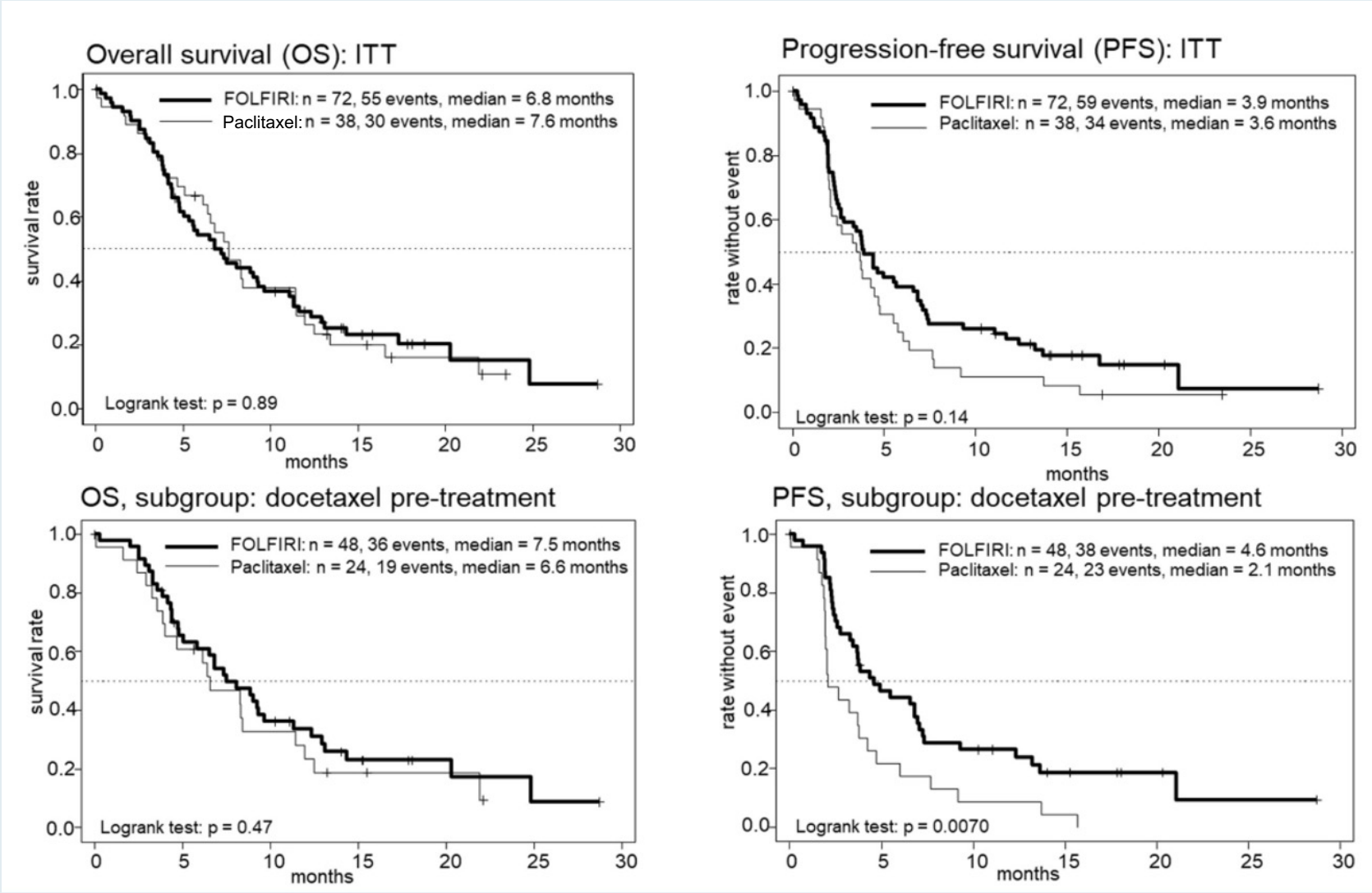
RAINBOW[2] OS	RAM	Placebo	*p*-value
Median (mo)	**9.6**	**7.4**	**0.017**
HR (95% CI)	**0.807 (0.678-0.962)**		



Abbreviations: BSC = best supportive care; PL = placebo; PTX = paclitaxel; RAM = ramucirumab

Muro K et al. Gastrointestinal Cancers Symposium 2017;Abstract 03 (Plots); [1] Fuchs CS et al. *Lancet* 2014;383(9911):31-9; [2] Wilke H et al. *Lancet Oncol* 2014;15(11):1224-35.

Phase II RAMIRIS Trial of Second-Line Ramucirumab plus FOLFIRI – Patients with Advanced or Metastatic Gastroesophageal Adenocarcinoma with or without Prior Docetaxel



Lorenzen S et al. ASCO 2020;Abstract 4514.

The NEW ENGLAND JOURNAL of MEDICINE

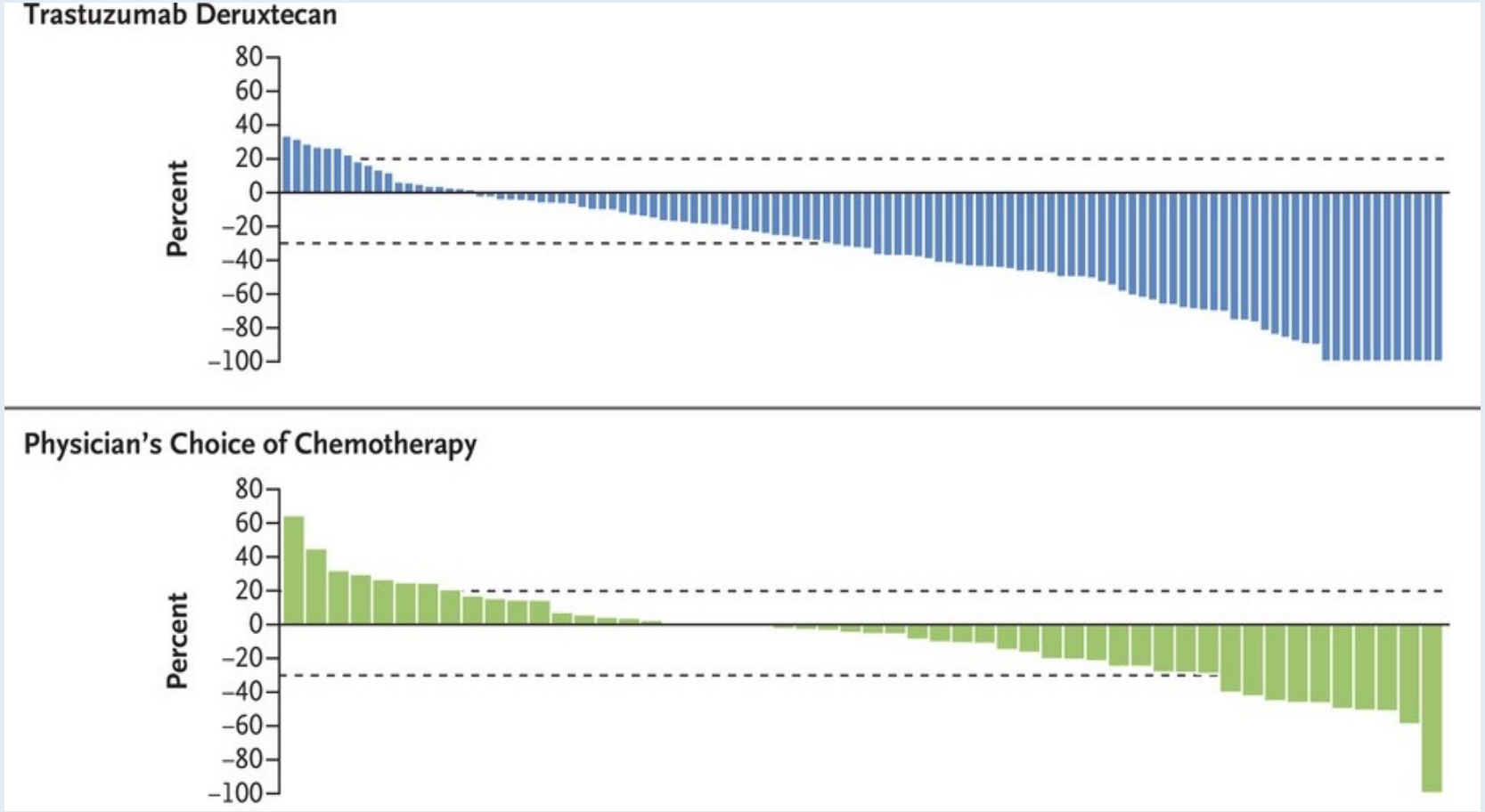
ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer

K. Shitara, Y.-J. Bang, S. Iwasa, N. Sugimoto, M.-H. Ryu, D. Sakai, H.-C. Chung, H. Kawakami, H. Yabusaki, J. Lee, K. Saito, Y. Kawaguchi, T. Kamio, A. Kojima, M. Sugihara, and K. Yamaguchi, for the DESTINY-Gastric01 Investigators*

***N Engl J Med* 2020;382(25):2419-30.**

DESTINY-Gastric01:Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer



	T-DXd (n = 119)	PC (n = 56)
ORR	**51%**	**14%**
Confirmed ORR	**43%**	**12%**
CR	8%	0%
PR	34%	12%

Shitara K et al. *N Engl J Med* 2020;382(25):2419-30.

RTP RESEARCH TO PRACTICE

DESTINY-Gastric01: Select Adverse Events

Adverse event	Trastuzumab deruxtecan (n = 125)			Physician's choice of chemo (n = 62)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Neutrophil count decreased	63%	38%	13%	35%	16%	8%
Anemia	58%	38%	0	31%	21%	2%
Platelet count decreased	39%	10%	2%	6%	2%	2%
White cell count decreased	38%	21%	0	35%	8%	3%
Fatigue	22%	7%	0	24%	3%	0
Lymphocyte count decreased	22%	6%	5%	3%	0	2%

- A total of 12 patients (10%) in the trastuzumab deruxtecan group had drug-related interstitial lung disease or pneumonitis compared to 0 patients in the physician's choice group
- 1 drug-related death (pneumonia) occurred in the trastuzumab deruxtecan group

Shitara K et al. *N Engl J Med* 2020;382(25):2419-30.

Meet The Professor with Dr Bendell

MODULE 1: Cases from Drs Schafer and Yang

- Dr Yang: A 66-year-old woman with MSI-high colorectal cancer with a BRAF V600E mutation
- Dr Schafer: A 66-year-old man with MMR-proficient metastatic colorectal cancer – MSH3 germline mutation VUS

MODULE 2: Beyond the Guidelines; Key Data – Colorectal Cancer

MODULE 3: Case from Dr Gosain

- A 56-year-old man with MSS, HER2-positive GEJ cancer – PD-L1-negative

MODULE 4: Beyond the Guidelines; Key Data – Gastroesophageal Cancers

MODULE 5: Cases from Dr Brenner

- A 58-year-old man with advanced Child-Pugh B8 hepatocellular carcinoma (HCC)
- An 83-year-old man with advanced HCC and disease progression on bevacizumab/atezolizumab

MODULE 6: Beyond the Guidelines; Key Data – Hepatocellular Carcinoma

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Case Presentation – Dr Brenner: A 58-year-old man with advanced Child-Pugh B8 HCC

Dr Warren Brenner

- Presents with “horrific” pruritus, bilirubin 10, fatigue
- 9/2020: HCC with extensive liver disease
  - Child-Pugh B8, thought to be on the basis of steatohepatitis
- Nivolumab

Questions

- What options are available for the treatment of patients with HCC who have Child-Pugh B disease and still have good functional status?
- What is the role of treatment if bilirubin is elevated from disease involvement rather than due to liver disease?
- Should we consider lenvatinib based on its higher response rates?

Case Presentation – Dr Brenner: An 83-year-old man with advanced HCC and disease progression on bevacizumab/atezolizumab

Dr Warren Brenner

- 7/2015: T1 hepatoma arising in a cirrhotic liver s/p preoperative yttrium embolization → Surgical resection (T1 tumor with clear margins) → Observation
- 4/2018: Recurrent right hepatic metastasis → Microwave ablation
- 1/2020: Recurrent right hepatic metastasis → Yttrium 90
- 7/2020: PD, with tumor extending into the right atrium
- Atezolizumab/bevacizumab, with PD after 6 months

Questions

- What is the safety of using bevacizumab in patients who have major vascular involvement?
- How do we choose amongst the second-line treatment options? Are there any biomarkers outside of alpha-fetoprotein that can help us decide which agent may be better in the second line in patients who have received atezolizumab and bevacizumab?
- In patients who have resected hepatoma with negative margins, is there any role for adjuvant-type therapy to lower risk of disease recurrence? In patients who may have a borderline-resectable tumor, is there any role to giving preoperative neoadjuvant-type therapy? And if so, what agents would you recommend?

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Bendell

MODULE 1: Cases from Drs Schafer and Yang

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- An 83-year-old man with advanced HCC and disease progression on bevacizumab/atezolizumab

MODULE 6: Beyond the Guidelines; Key Data – Hepatocellular Carcinoma

What would be your current preferred first-line systemic treatment for a 65-year-old patient with HCC, a Child-Pugh B7 score and PS 1?

1. Sorafenib
2. Lenvatinib
3. Atezolizumab/bevacizumab
4. Chemotherapy
5. Other

What would be your current preferred first-line systemic treatment for a 65-year-old patient with HCC, a Child-Pugh B7 score and a PS of 1?

 Prof Arnold	Atezolizumab/ bevacizumab	 Dr Grothey	Atezolizumab/ bevacizumab
 Dr Bekaii-Saab	Atezolizumab/ bevacizumab	 Dr O'Reilly	Lenvatinib
 Dr Bendell	Atezolizumab/ bevacizumab	 Dr Venook	Atezolizumab/ bevacizumab
 Dr Ciombor	Sorafenib	 Dr Wainberg	Lenvatinib

RTP RESEARCH TO PRACTICE

What would be your most likely second-line systemic therapy for a 65-year-old patient with HCC, a Child-Pugh A score and a PS of 0 who received first-line atezolizumab/bevacizumab with minimal toxicity, had stable disease for 14 months and then experienced disease progression (alpha-fetoprotein, AFP, 2,500 ng/mL)?

 Prof Arnold	Cabozantinib	 Dr Grothey	Lenvatinib
 Dr Bekaii-Saab	Cabozantinib	 Dr O'Reilly	Lenvatinib
 Dr Bendell	Cabozantinib	 Dr Venook	Lenvatinib
 Dr Ciombor	Sorafenib	 Dr Wainberg	Ramucirumab

RTP RESEARCH TO PRACTICE

What would be your most likely second-line systemic therapy for a 65-year-old patient with HCC, a Child-Pugh A score and a PS of 0 who received first-line standard-dose sorafenib with minimal toxicity, had stable disease for 14 months and then experienced disease progression (AFP 2,500 ng/mL)?

 Prof Arnold	Nivolumab	 Dr Grothey	Atezolizumab/ bevacizumab
 Dr Bekaii-Saab	Atezolizumab/ bevacizumab	 Dr O'Reilly	Nivolumab/ ipilimumab
 Dr Bendell	Atezolizumab/ bevacizumab	 Dr Venook	Atezolizumab/ bevacizumab
 Dr Ciombor	Atezolizumab/ bevacizumab	 Dr Wainberg	Ramucirumab

RTP RESEARCH TO PRACTICE

What would be your most likely third-line systemic therapy recommendation for an otherwise healthy 65-year-old patient with HCC who experienced disease progression on first-line atezolizumab/bevacizumab and second-line lenvatinib (AFP 2,500 ng/mL)?

 Prof Arnold	Ramucirumab	 Dr Grothey	Cabozantinib
 Dr Bekaii-Saab	Cabozantinib	 Dr O'Reilly	Nivolumab/ ipilimumab
 Dr Bendell	Cabozantinib	 Dr Venook	Cabozantinib
 Dr Ciombor	Ramucirumab	 Dr Wainberg	Ramucirumab

RTP RESEARCH TO PRACTICE

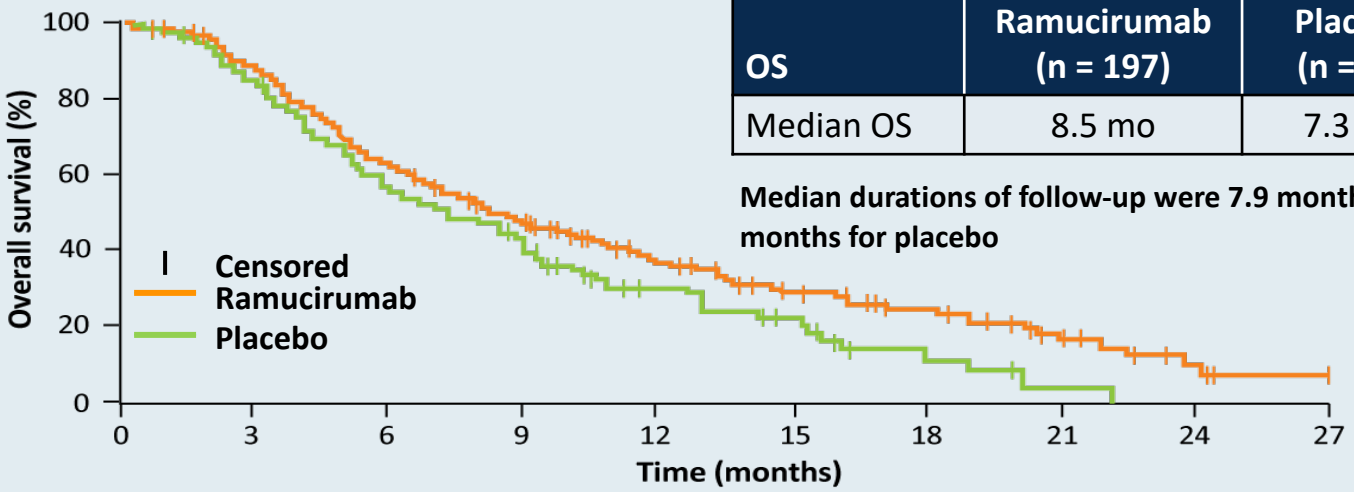
Articles

Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial

*Andrew X Zhu, Yoon-Koo Kang, Chia-Jui Yen, Richard S Finn, Peter R Galle, Josep M Llovet, Eric Assenat, Giovanni Brandi, Marc Pracht, Ho Yeong Lim, Kun-Ming Rau, Kenta Motomura, Izumi Ohno, Philippe Merle, Bruno Daniele, Dong Bok Shin, Guido Gerken, Christophe Borg, Jean-Baptiste Hiriart, Takuji Okusaka, Manabu Morimoto, Yanzhi Hsu, Paolo B Abada, Masatoshi Kudo, for the REACH-2 study investigators**

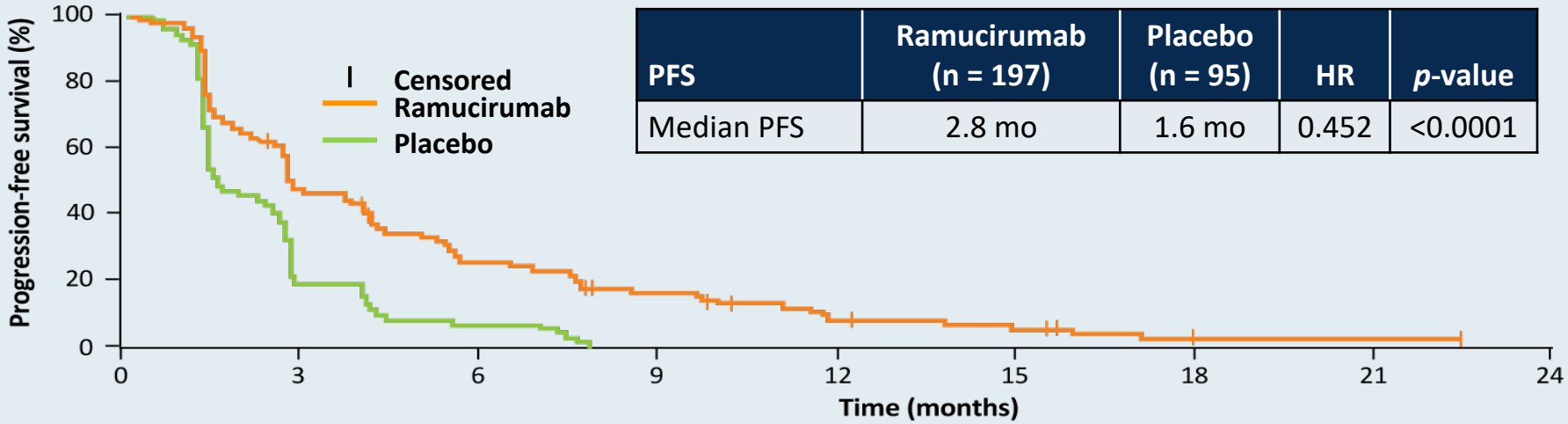
Lancet Oncol 2019;20(2):282-96.

REACH-2: A Phase III Trial of Ramucirumab After Sorafenib for Patients with Advanced HCC and Increased AFP



OS	Ramucirumab (n = 197)	Placebo (n = 95)	HR	*p*-value
Median OS	8.5 mo	7.3 mo	0.710	0.0199

Median durations of follow-up were 7.9 months for ramucirumab, 6.6 months for placebo



PFS	Ramucirumab (n = 197)	Placebo (n = 95)	HR	*p*-value
Median PFS	2.8 mo	1.6 mo	0.452	<0.0001

Grade ≥3 AEs associated with ramucirumab included hypertension and hyponatremia.

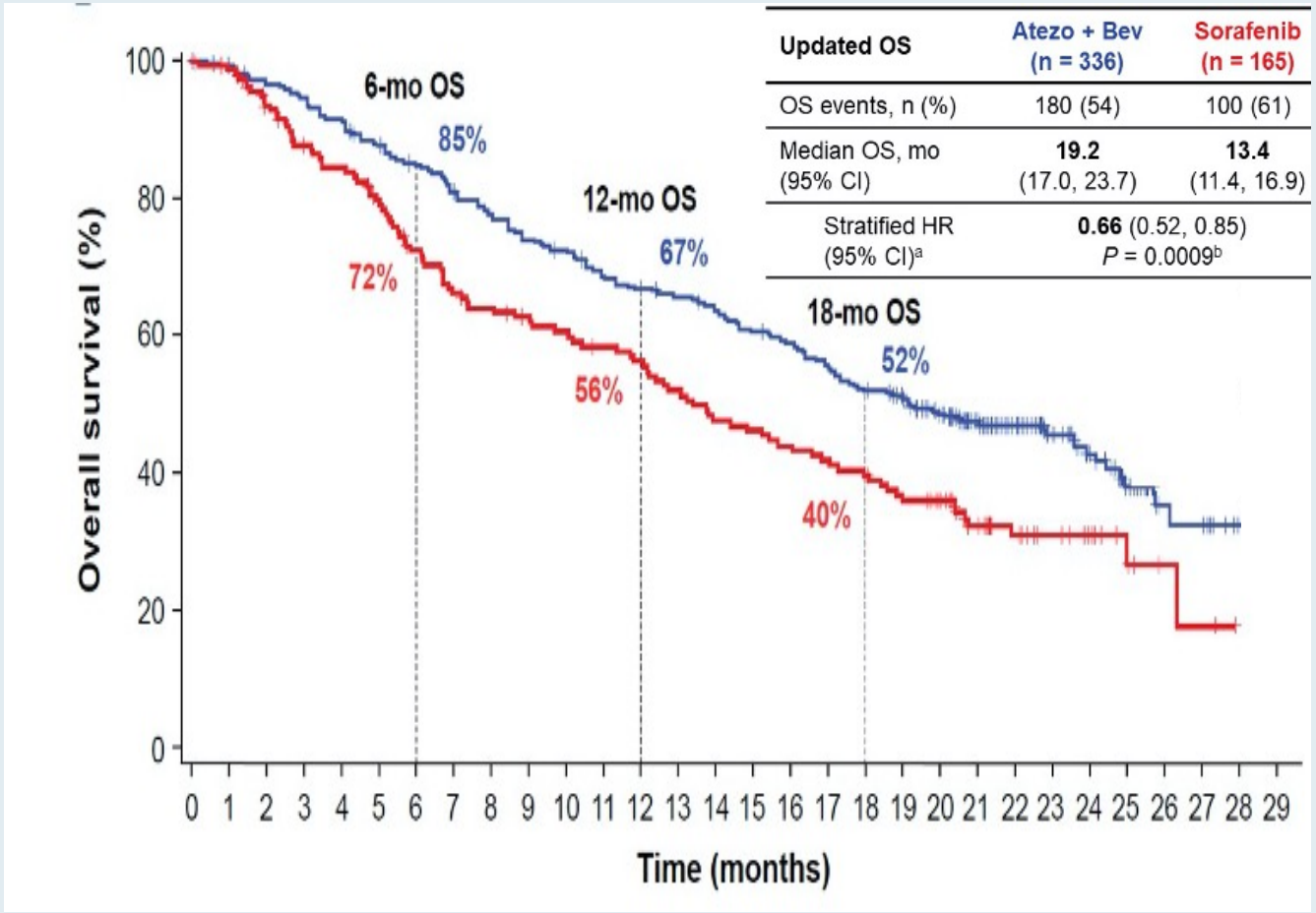
Zhu AX et al. ASCO 2018;Abstract 4003; *Lancet Oncol* 2019;20(2):282-96.

IMbrave150: Updated Overall Survival (OS) Data from a Global, Randomized, Open-Label Phase III Study of Atezolizumab (atezo) + Bevacizumab (bev) versus Sorafenib (sor) in Patients (pts) with Unresectable Hepatocellular Carcinoma (HCC)

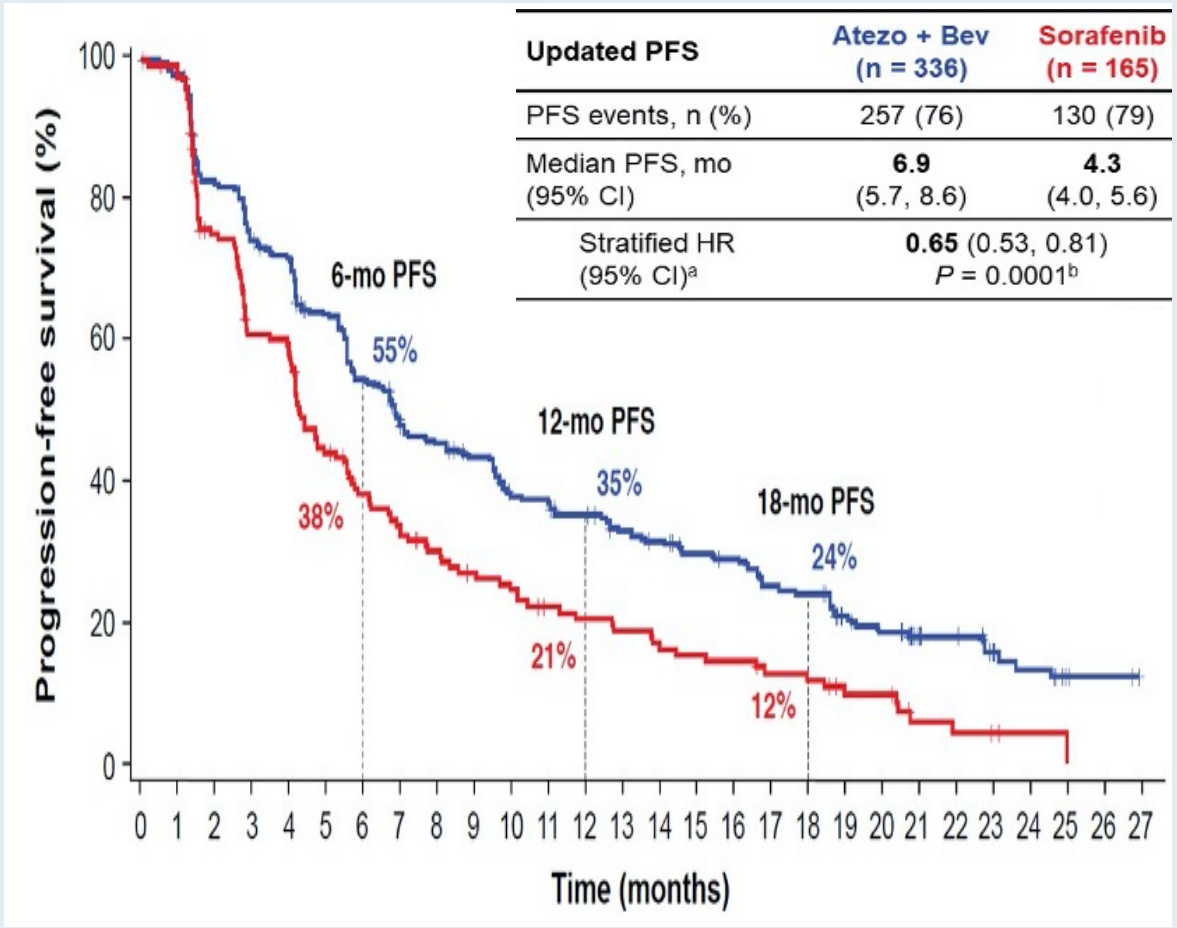
Finn RS et al.

Gastrointestinal Cancers Symposium 2021;Abstract 267.

IMbrave150: Updated OS and PFS (Median Follow-Up = 15.6 Months)



Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	



Updated PFS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
PFS events, n (%)	257 (76)	130 (79)
Median PFS, mo (95% CI)	**6.9** (5.7, 8.6)	**4.3** (4.0, 5.6)
Stratified HR (95% CI)[a]	**0.65** (0.53, 0.81) *P* = 0.0001[b]	

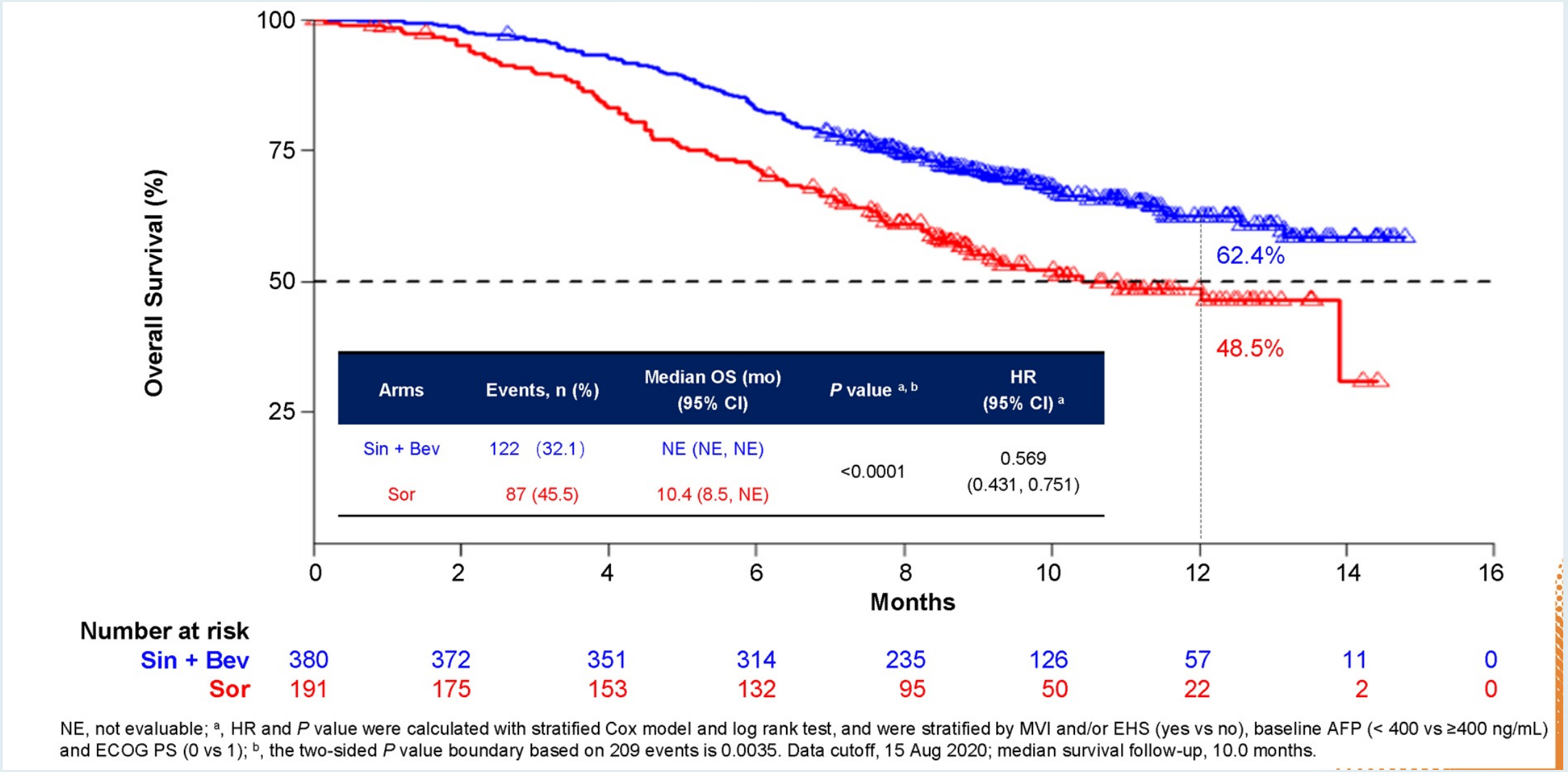
Finn RS et al. Gastrointestinal Cancers Symposium 2021;Abstract 267.

RTP RESEARCH TO PRACTICE

Sintilimab plus Bevacizumab Biosimilar vs Sorafenib as First-Line Treatment for Advanced Hepatocellular Carcinoma (ORIENT-32)

Ren Z et al. ESMO Asia 2020;Abstract LBA2.

ORIENT-32 Coprimary Endpoint: Overall Survival



Arms	Events, n (%)	Median OS (mo) (95% CI)	*P* value [a, b]	HR (95% CI) [a]
Sin + Bev	122 (32.1)	NE (NE, NE)	<0.0001	0.569 (0.431, 0.751)
Sor	87 (45.5)	10.4 (8.5, NE)		

Number at risk

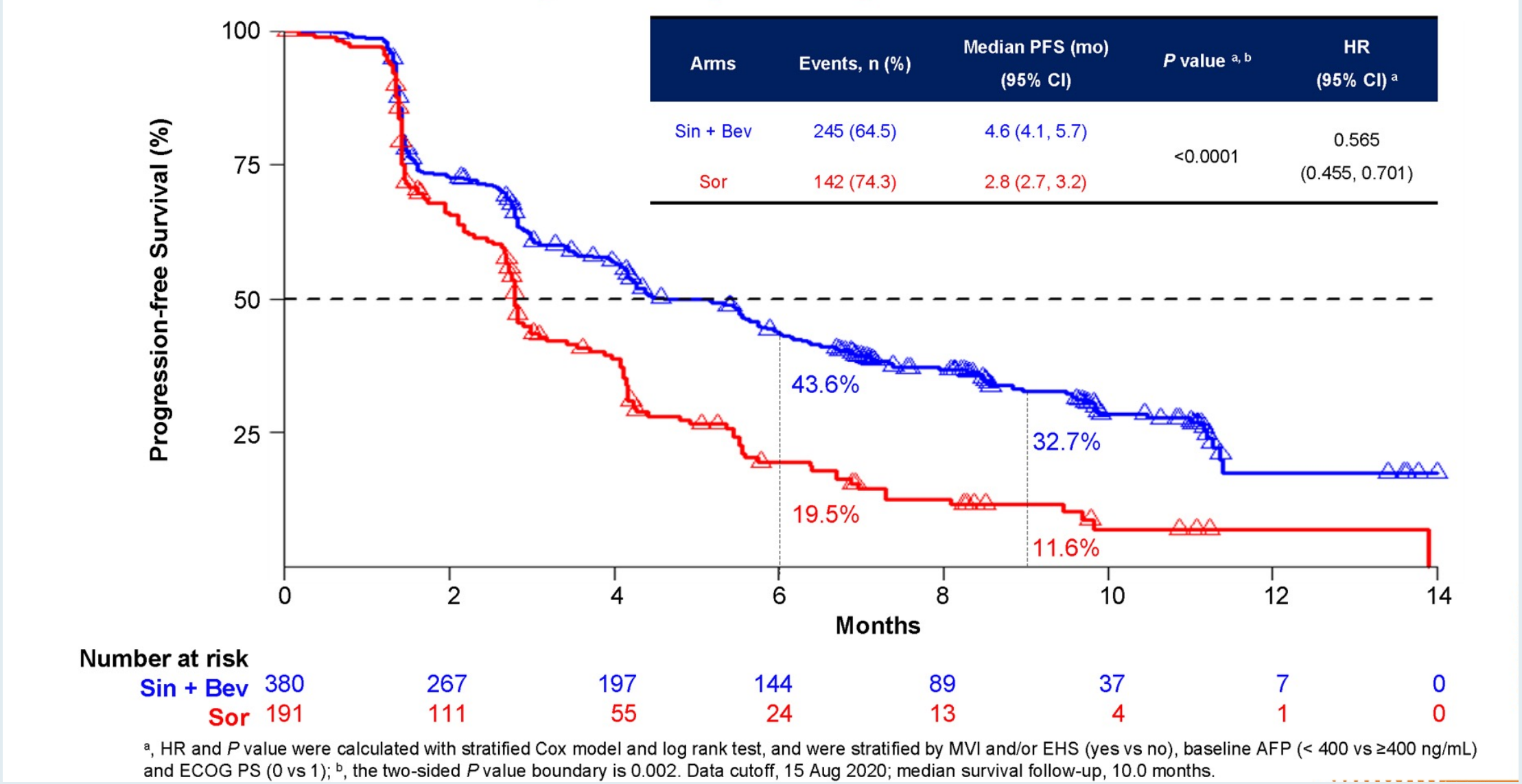
Sin + Bev	380	372	351	314	235	126	57	11	0
Sor	191	175	153	132	95	50	22	2	0

NE, not evaluable; [a], HR and *P* value were calculated with stratified Cox model and log rank test, and were stratified by MVI and/or EHS (yes vs no), baseline AFP (< 400 vs ≥400 ng/mL) and ECOG PS (0 vs 1); [b], the two-sided *P* value boundary based on 209 events is 0.0035. Data cutoff, 15 Aug 2020; median survival follow-up, 10.0 months.

The superior OS benefit with sintilimab plus bev biosimilar was generally consistent across all subgroups

Ren Z et al. ESMO Asia 2020;Abstract LBA2.

ORIENT-32 Coprimary Endpoint: Progression-Free Survival



Arms	Events, n (%)	Median PFS (mo) (95% CI)	*P* value [a, b]	HR (95% CI) [a]
Sin + Bev	245 (64.5)	4.6 (4.1, 5.7)	<0.0001	0.565 (0.455, 0.701)
Sor	142 (74.3)	2.8 (2.7, 3.2)		

Number at risk								
Sin + Bev	380	267	197	144	89	37	7	0
Sor	191	111	55	24	13	4	1	0

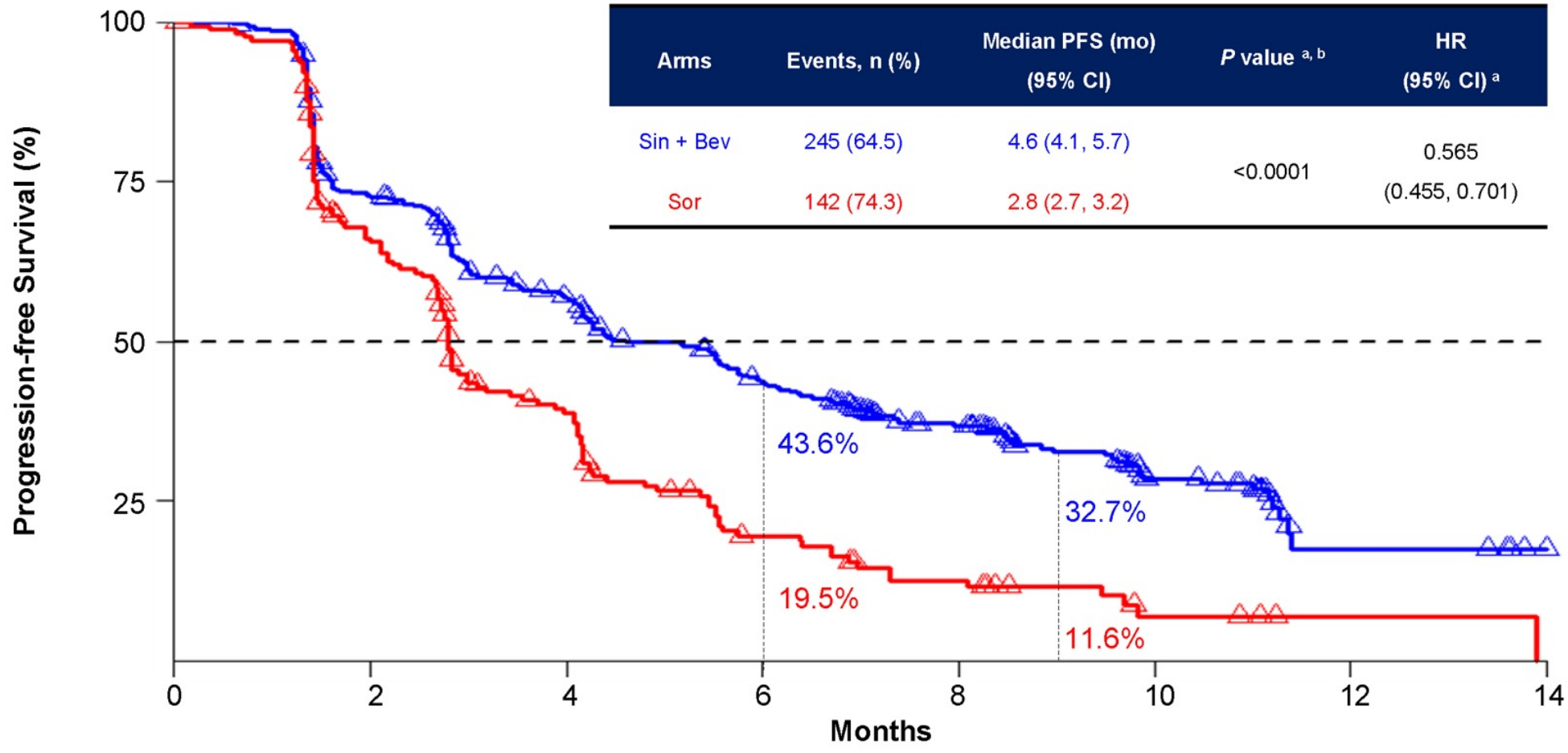
[a], HR and *P* value were calculated with stratified Cox model and log rank test, and were stratified by MVI and/or EHS (yes vs no), baseline AFP (< 400 vs ≥400 ng/mL) and ECOG PS (0 vs 1); [b], the two-sided *P* value boundary is 0.002. Data cutoff, 15 Aug 2020; median survival follow-up, 10.0 months.

The superior PFS benefit with sintilimab plus bev biosimilar was generally consistent across all subgroups

Ren Z et al. ESMO Asia 2020;Abstract LBA2.

RTP RESEARCH TO PRACTICE

ORIENT-32 Coprimary Endpoint: Progression-Free Survival



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Sin + Bev	245 (64.5)	4.6 (4.1, 5.7)	<0.0001	0.565 (0.455, 0.701)
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[a], HR and *P* value were calculated with stratified Cox model and log rank test, and were stratified by MVI and/or EHS (yes vs no), baseline AFP (< 400 vs ≥400 ng/mL) and ECOG PS (0 vs 1); [b], the two-sided *P* value boundary is 0.002. Data cutoff, 15 Aug 2020; median survival follow-up, 10.0 months.

The superior PFS benefit with sintilimab plus bev biosimilar was generally consistent across all subgroups

Ren Z et al. ESMO Asia 2020;Abstract LBA2.

APPENDIX

Additional Relevant Data Sets

Colorectal Cancer

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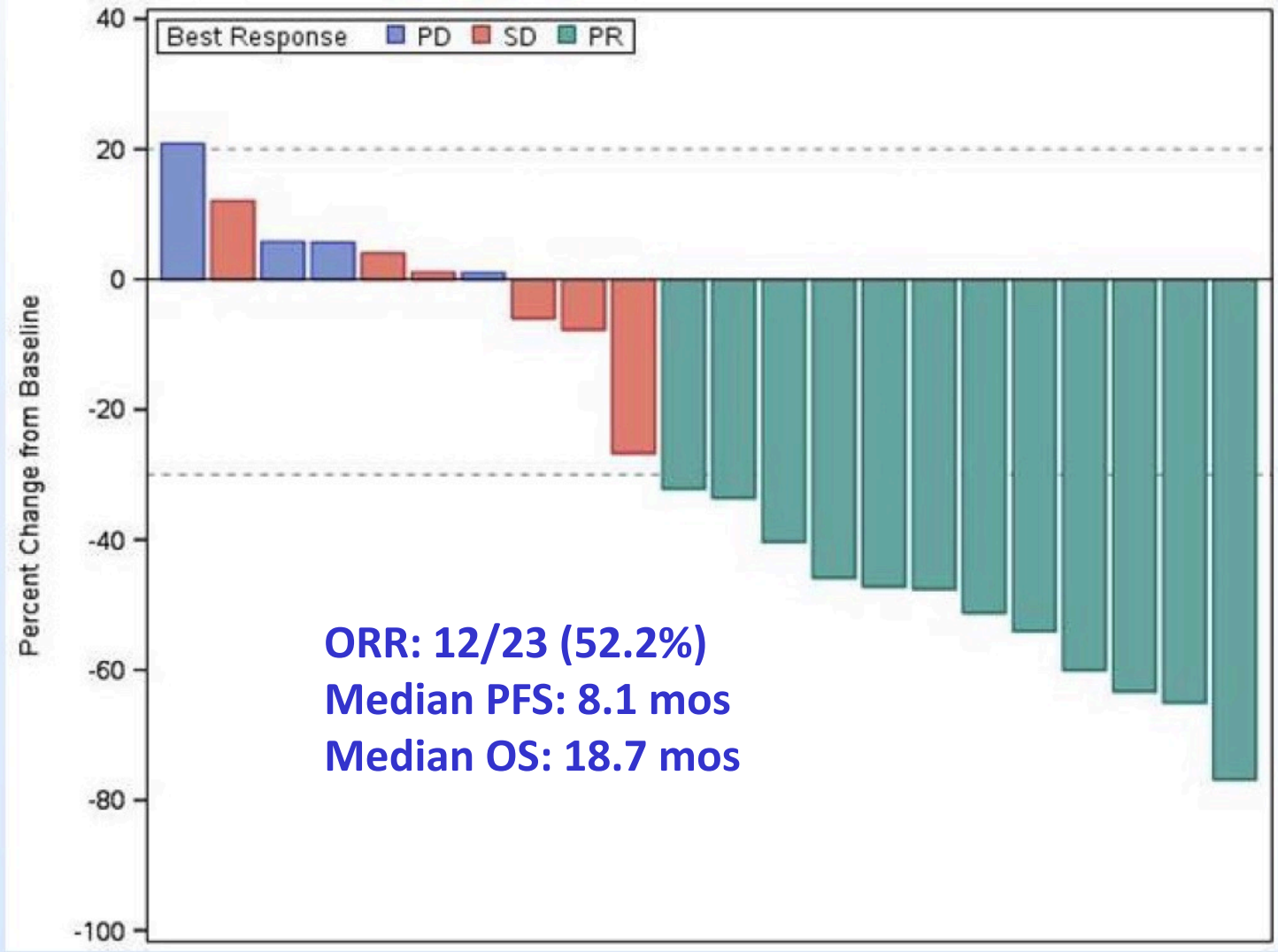
Trastuzumab and Tucatinib for the Treatment of HER2 Amplified Metastatic Colorectal Cancer: Initial Results from the MOUNTAINEER Trial

Strickler JH et al.

ESMO 2019;Abstract 527PD.

MOUNTAINEER: Response and Survival



Strickler JH et al. ESMO 2019;Abstract 527PD.

Gastric/Gastroesophageal Cancer

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RESEARCH
TO PRACTICE

FDA Approves Nivolumab with Chemotherapy for Front-Line Advanced Gastric Cancer

Press Release – April 16, 2021

"The FDA approved nivolumab in combination with certain types of chemotherapy for the frontline treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma, making it the first approved immunotherapy for this patient population.

The agency based the approval on data from the randomized, multicenter, open-label phase 3 CheckMate-649 trial, designed to evaluate nivolumab – a monoclonal antibody that inhibits tumor growth by enhancing T-cell function – plus chemotherapy in 1,581 patients with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma. Of the 789 patients treated in the nivolumab arm, median overall survival was 13.8 months, compared with 11.6 months for patients who received chemotherapy alone."

https://www.cancernetwork.com/view/fda-approves-nivolumab-plus-chemo-for-frontline-advanced-gastric-cancer

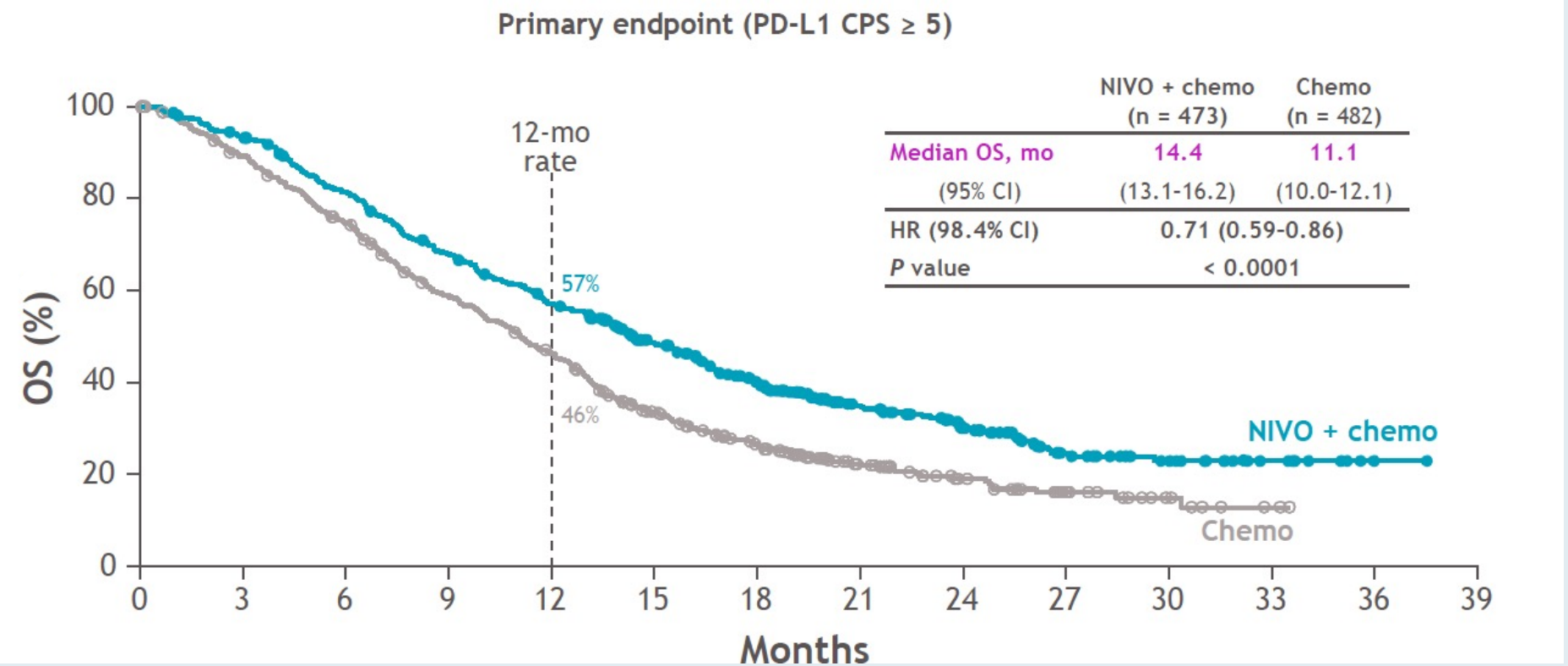
RTP RESEARCH TO PRACTICE

Nivolumab (Nivo) plus Chemotherapy (Chemo) versus Chemo as First-Line (1L) Treatment for Advanced Gastric Cancer/Gastroesophageal Junction Cancer (GC/GEJC)/Esophageal Adenocarcinoma (EAC): First Results of the CheckMate 649 Study

Moehler M et al.

ESMO 2020;Abstract LBA6.

CheckMate 649: Overall Survival



Median OS	Nivo + Chemo (n = 641)	Chemo (n = 655)	HR (*p*-value)
PD-L1 CPS ≥ 1	14.0 mo	11.3 mo	0.77 (0.0001)
All treated patients	13.8 mo	11.6 mo	0.80 (0.0002)

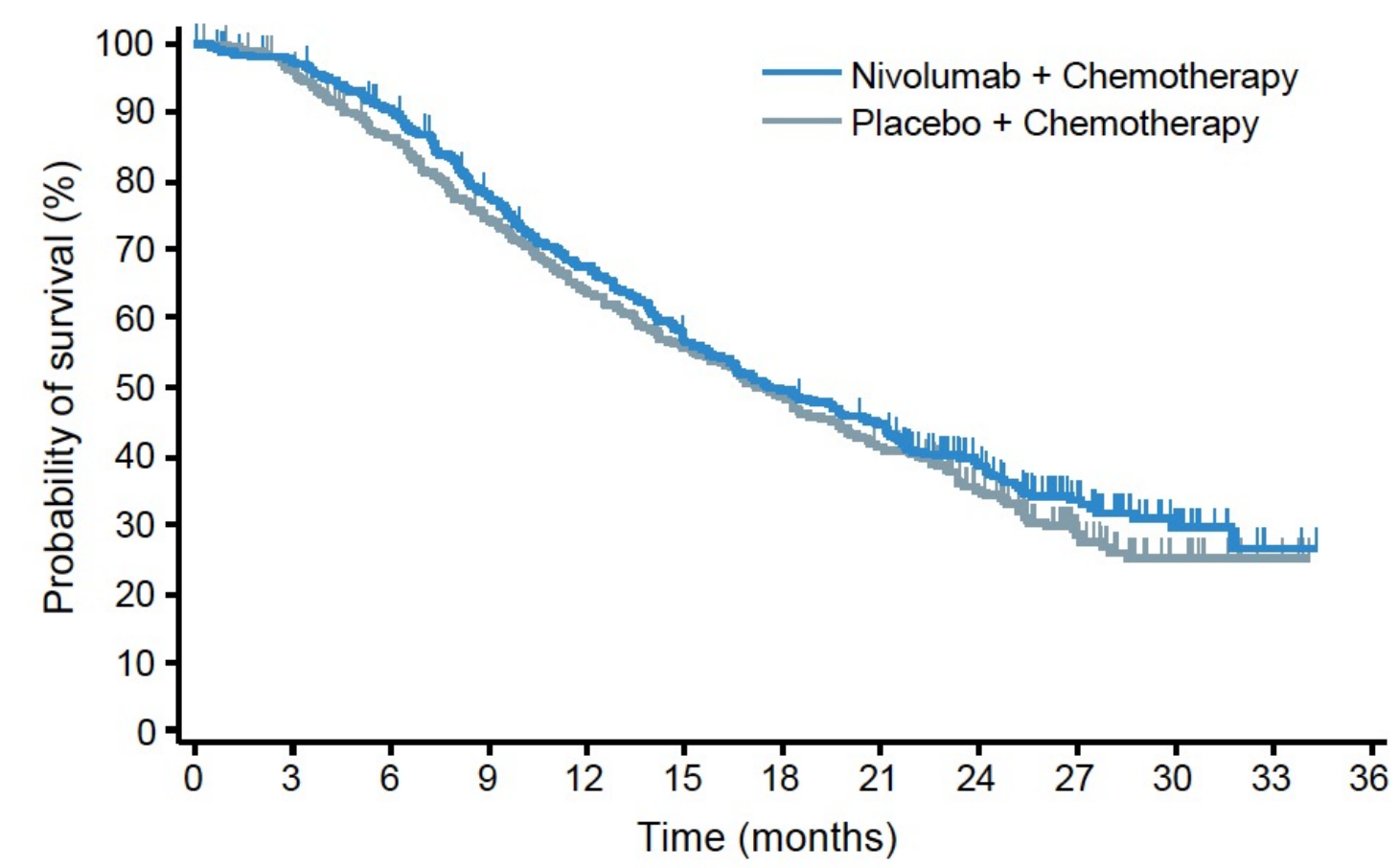
Moehler M et al. ESMO 2020;Abstract LBA6.

Nivolumab plus Chemotherapy versus Chemotherapy Alone in Patients with Previously Untreated Advanced or Recurrent Gastric/Gastroesophageal Junction (G/GEJ) Cancer: ATTRACTION-4 (ONO-4538-37) Study

Boku N et al.

ESMO 2020;Abstract LBA7_PR.

ATTRACTION-4: Final Analysis of OS



	Nivo + chemo (n = 362)	Placebo + chemo (n = 362)	HR (*p*-value)
Median OS	17.45 mo	17.15 mo	0.90 (0.257)

Boku N et al. ESMO 2020;Abstract LBA7_PR.

RTP RESEARCH TO PRACTICE

Original Investigation

September 3, 2020

Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer

The KEYNOTE-062 Phase 3 Randomized Clinical Trial

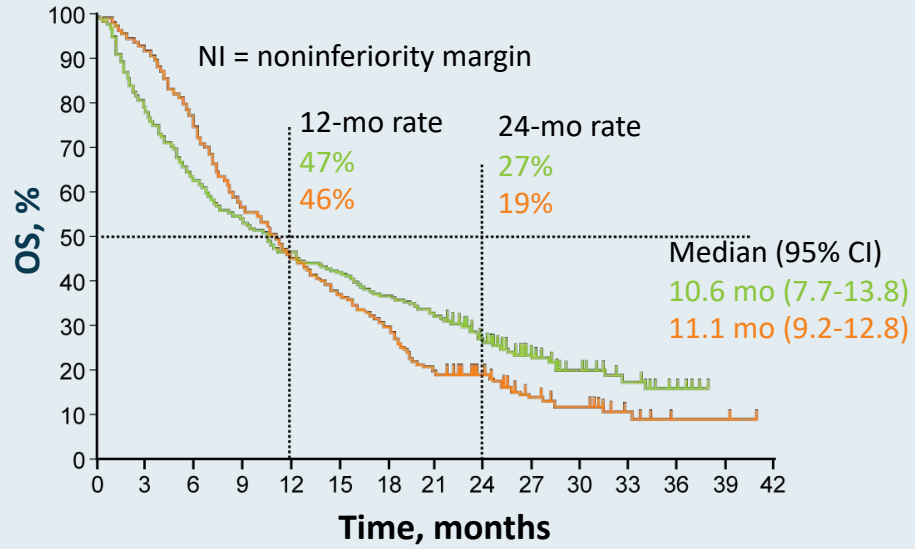
Kohei Shitara, MD[1]; Eric Van Cutsem, MD[2]; Yung-Jue Bang, MD[3]; et al

» Author Affiliations

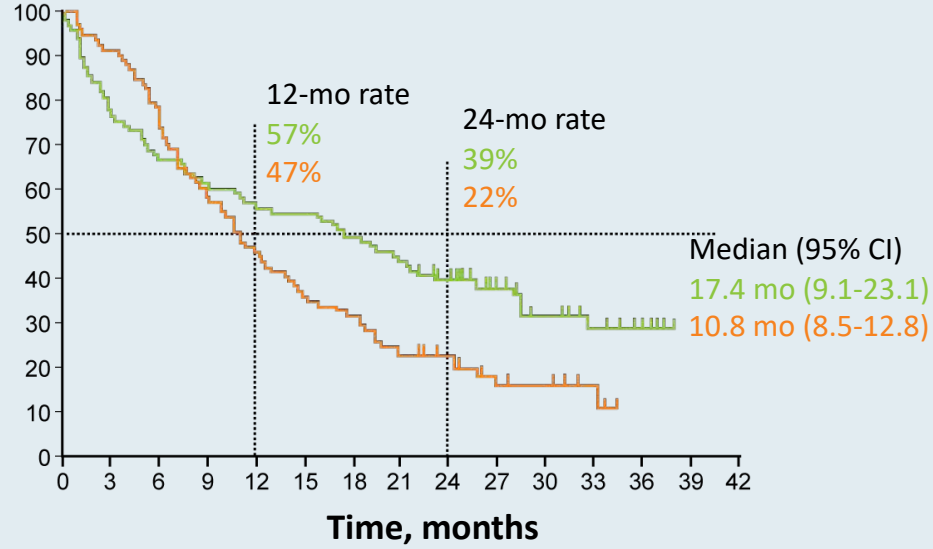
JAMA Oncol. 2020;6(10):1571-1580. doi:10.1001/jamaoncol.2020.3370

KEYNOTE-062: Overall Survival by PD-L1 CPS Score

OS: CPS ≥1	Events	HR	NI
Pembro alone	79%	0.91	1.2
Chemo	86%		



OS: CPS ≥10	Events	HR
Pembro alone	66%	0.69
Chemo	83%	



- Pembrolizumab was noninferior to chemotherapy for OS in patients with CPS ≥1, and a clinically meaningful improvement in OS was reported with pembro vs chemo for patients with CPS ≥10.
- Pembrolizumab + chemotherapy did not show superior OS for patients with CPS ≥1 or CPS ≥10, and the combination did not show superior PFS for patients with CPS ≥1.

Shitara K et al. *JAMA Oncol* 2020;6(10):1571-80.

RTP RESEARCH TO PRACTICE

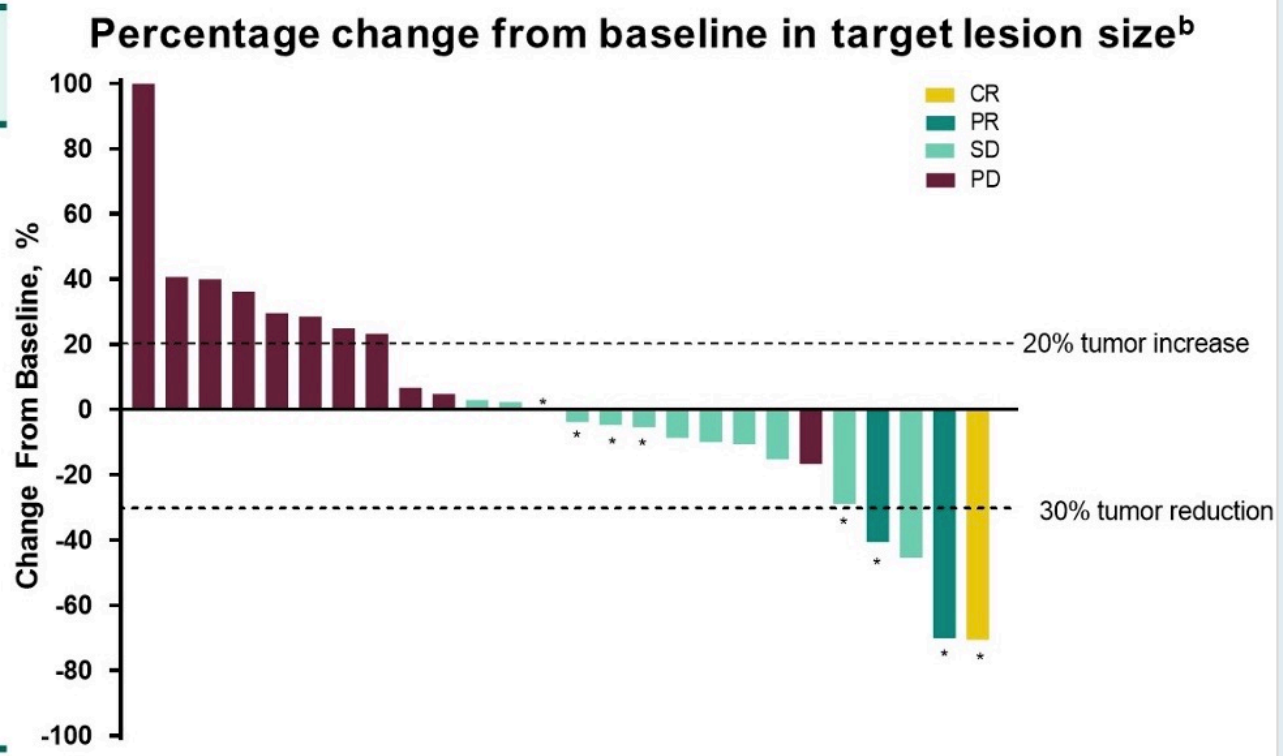
LEAP-005: A Phase II Multicohort Study of Lenvatinib plus Pembrolizumab in Patients with Previously Treated Selected Solid Tumors: Results from the Gastric Cancer Cohort

Chung HC et al.

Gastrointestinal Cancers Symposium 2021;Abstract 230.

LEAP-005: Antitumor Activity

	N = 31
ORR, % (95% CI)	10 (2–26)
DCR,[a] % (95% CI)	48 (30–67)
Best overall response, n (%)[b]	
CR	1 (3)
PR	2 (6)
SD	12 (39)
PD	11 (35)
No assessment[c]	5 (16)
DOR, median (range), mo	NR (2.1+ to 2.3+)



CI, confidence interval; CR, complete response; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Defined as best overall response of CR, PR or SD. [b]Both patients with PR had PD-L1 CPS ≥1; patient with CR had PD-L1 CPS <1. [c]Patient had no post-baseline imaging.
*Patient with treatment ongoing.
Data cutoff date: April 10, 2020.

Chung HC et al. Gastrointestinal Cancers Symposium 2021;Abstract 230.

FDA Approves Pembrolizumab in Combination with Chemotherapy for Esophageal or GEJ Carcinoma

Press Release – March 22, 2021

"On March 22, 2021, the Food and Drug Administration approved pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy for patients with metastatic or locally advanced esophageal or gastroesophageal (GEJ) (tumors with epicenter 1 to 5 centimeters above the gastroesophageal junction) carcinoma who are not candidates for surgical resection or definitive chemoradiation.

Efficacy was evaluated in KEYNOTE-590 (NCT03189719), a multicenter, randomized, placebo-controlled trial that enrolled 749 patients with metastatic or locally advanced esophageal or gastroesophageal junction carcinoma who were not candidates for surgical resection or definitive chemoradiation.

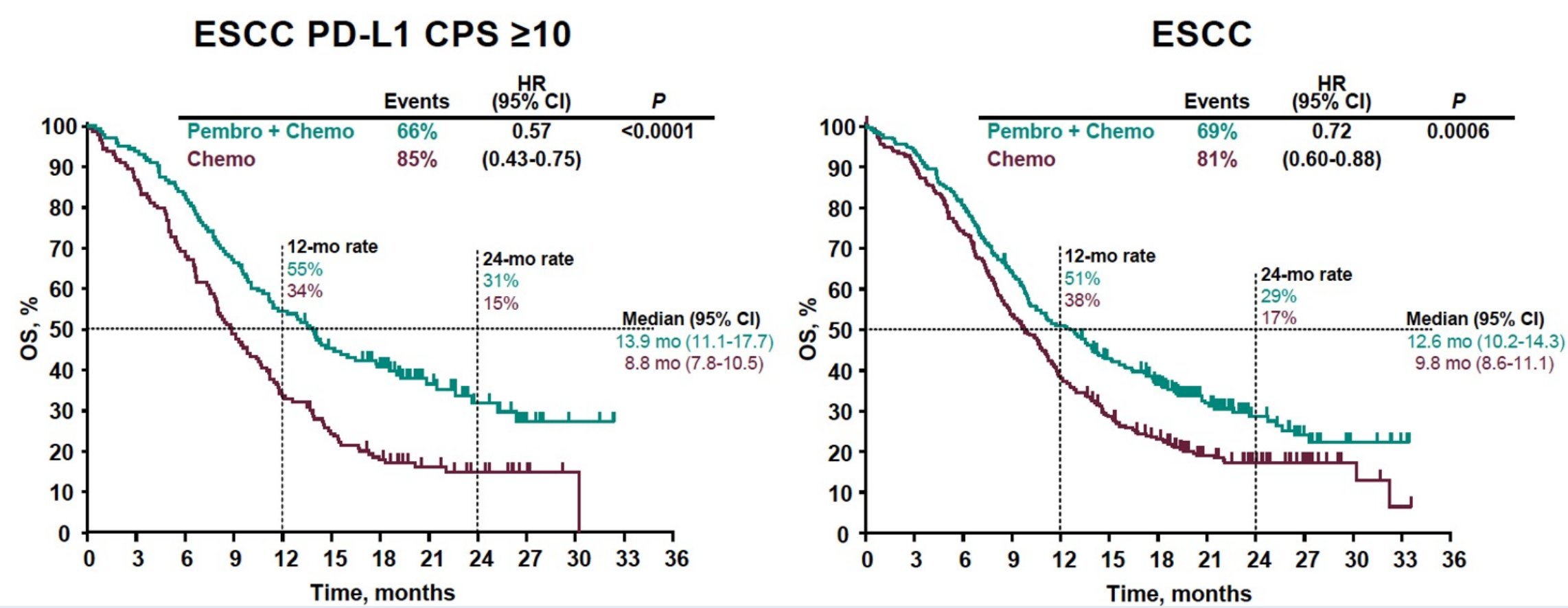
The recommended pembrolizumab dose for esophageal cancer is 200 mg every 3 weeks or 400 mg every 6 weeks."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-esophageal-or-gej-carcinoma?utm_medium=email&utm_source=govdelivery

Pembrolizumab plus Chemotherapy versus Chemotherapy as First-line Therapy in Patients with Advanced Esophageal Cancer: The Phase 3 KEYNOTE-590 Study

Kato K et al.
ESMO 2020;Abstract LBA8_PR.

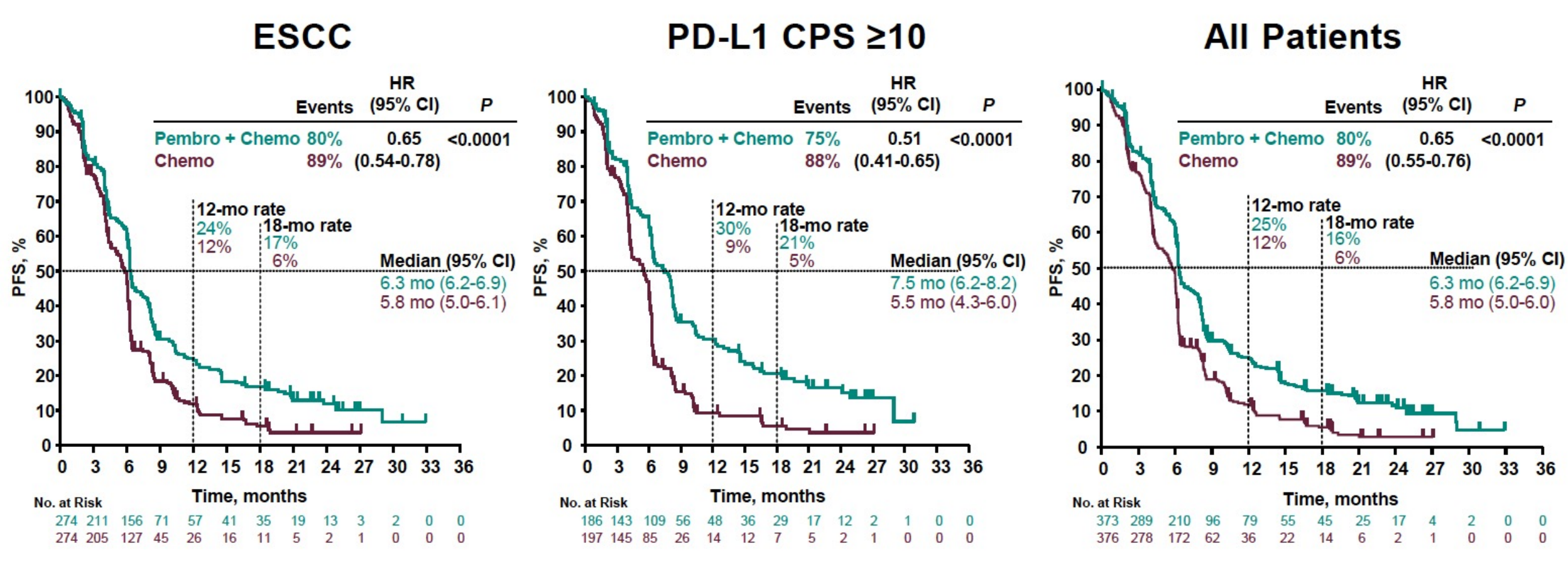
KEYNOTE-590: Overall Survival



Median OS	Pembro + Chemo	Chemo	HR (*p*-value)
All patients	12.4 mo	9.8 mo	0.73 (<0.0001)
PD-L1 CPS ≥ 10	13.5 mo	9.4 mo	0.62 (<0.0001)

Kato K et al. ESMO 2020;Abstract LBA8_PR.

KEYNOTE-590: Progression-Free Survival



Kato K et al. ESMO 2020;Abstract LBA8_PR.

RTP RESEARCH TO PRACTICE

FDA's ODAC Votes Against Continuation of Pembrolizumab Third-Line Indication in Gastric/GEJ Cancer

Press Release – April 29, 2021

"The FDA's Oncologic Drugs Advisory Committee (ODAC) has voted 6 to 2 against the continued approval of pembrolizumab (Keytruda) as indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (combined positive score [CPS] ≥1) who experienced disease progression on or after 2 or more prior lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2-targeted therapy.

Initial approval was granted in September 2017 based on findings from the phase 2 KEYNOTE-059 trial (NCT02335411), which showed responses in patients with gastric/GEJ adenocarcinoma treated with pembrolizumab in the third-line setting or beyond.

The objective response rate was 13.3% (95% CI, 8.2%-20.0%) among patients with microsatellite stable disease or undetermined status. The median duration of response ranged from 2.8+ to 19.4+ months."

https://www.targetedonc.com/view/fda-s-odac-votes-against-continuation-of-pembrolizumab-third-line-indication-in-gastric-gej-cancer

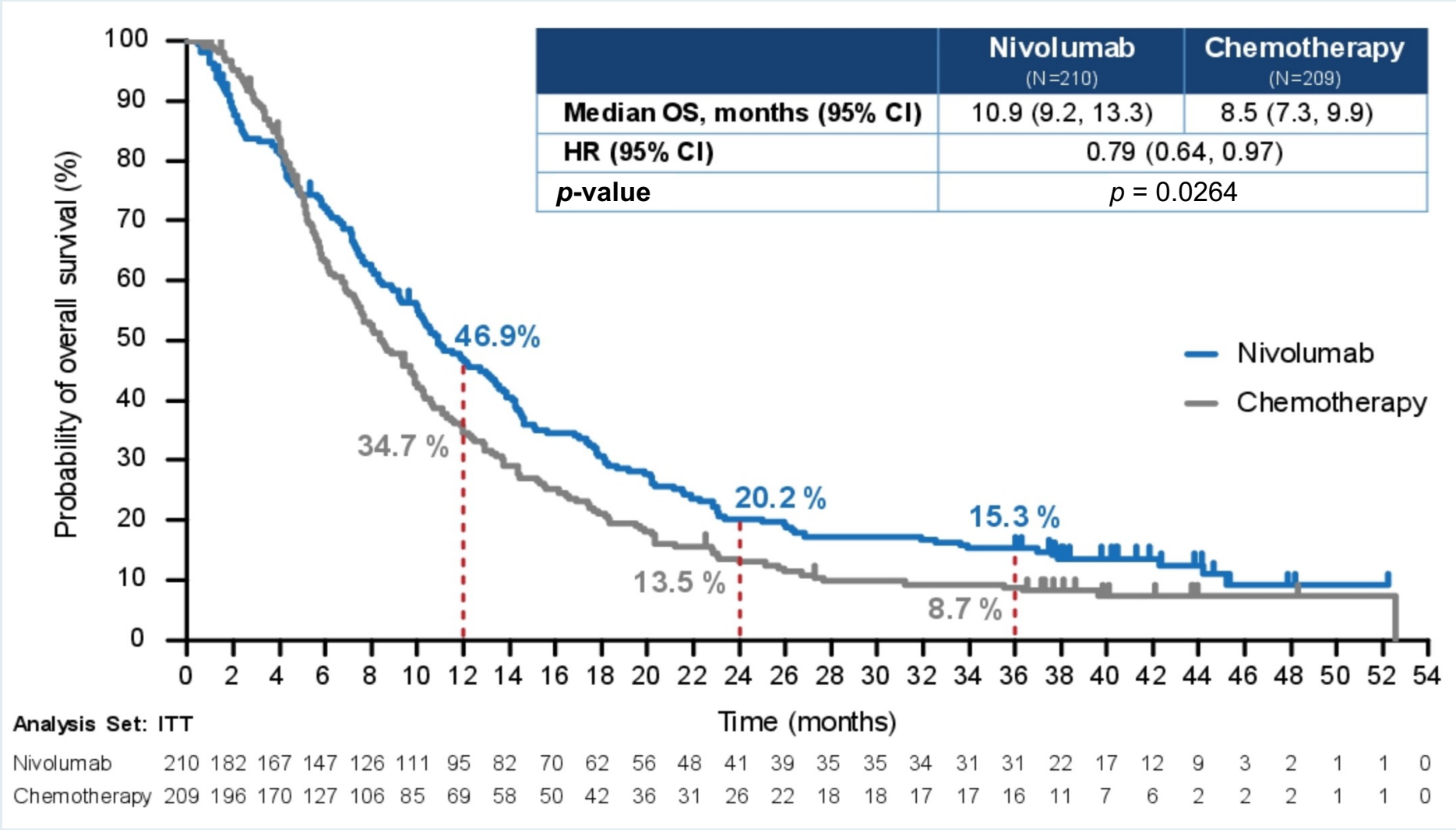
Three-year Follow-up of ATTRACTION-3: A Phase III Study of Nivolumab (Nivo) in Patients with Advanced Esophageal Squamous Cell Carcinoma (ESCC) That Is Refractory or Intolerant to Previous Chemotherapy

Chin K et al.

Gastrointestinal Cancers Symposium 2021;Abstract 204.

ATTRACTION-3: Three-Year Overall Survival Update

	Nivolumab (N=210)	Chemotherapy (N=209)
Median OS, months (95% CI)	10.9 (9.2, 13.3)	8.5 (7.3, 9.9)
HR (95% CI)	0.79 (0.64, 0.97)	
***p*-value**	*p* = 0.0264	



Chin K et al. Gastrointestinal Cancers Symposium 2021;Abstract 204.

RTP RESEARCH TO PRACTICE

Hepatocellular Cancer

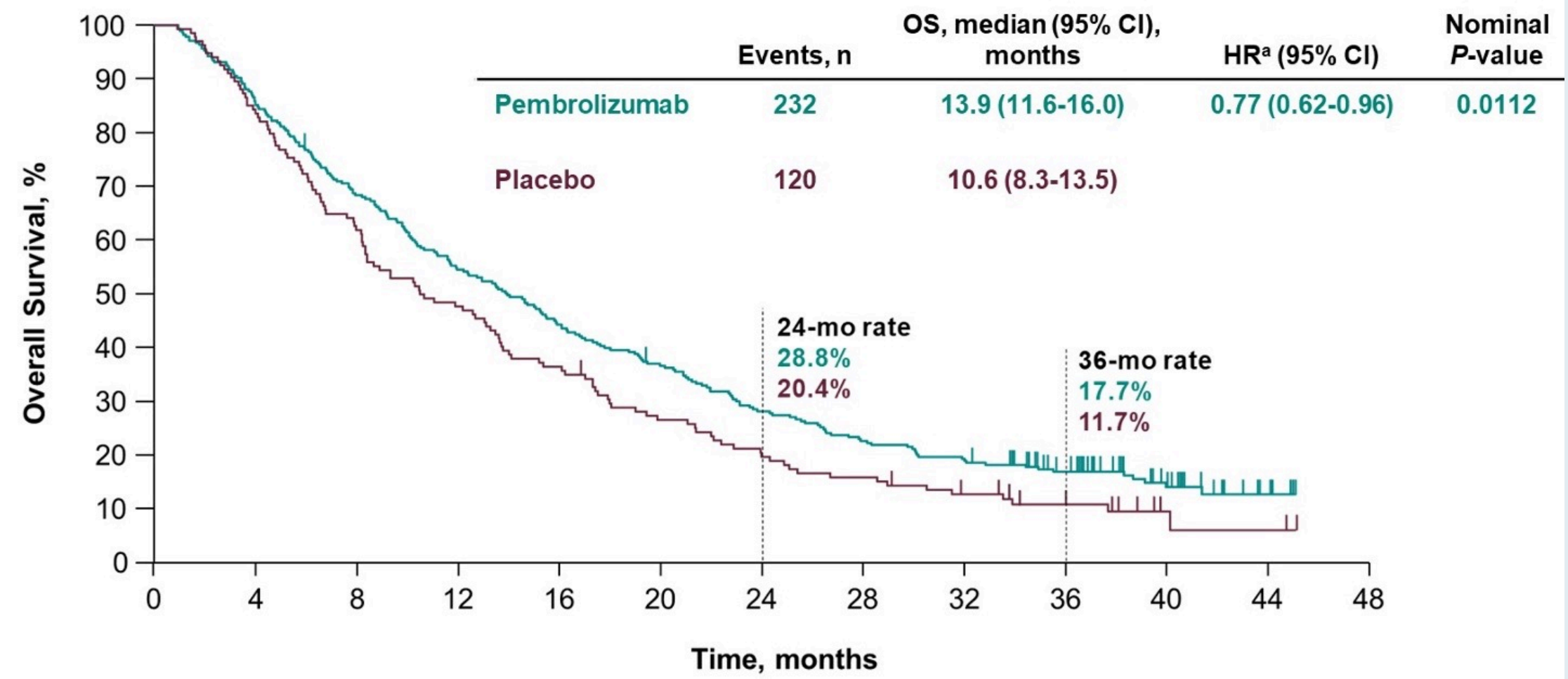
Pembrolizumab versus Placebo in Patients with Advanced Hepatocellular Carcinoma Previously Treated with Sorafenib: Updated Data from the Randomized, Phase 3 KEYNOTE-240 Study

Merle P et al.

Gastrointestinal Cancers Symposium 2021;Abstract 268.

KEYNOTE-240: Updated OS
Hazard Ratios Maintained with Longer Follow-Up

Overall Survival



Merle P et al. Gastrointestinal Cancers Symposium 2021;Abstract 268.

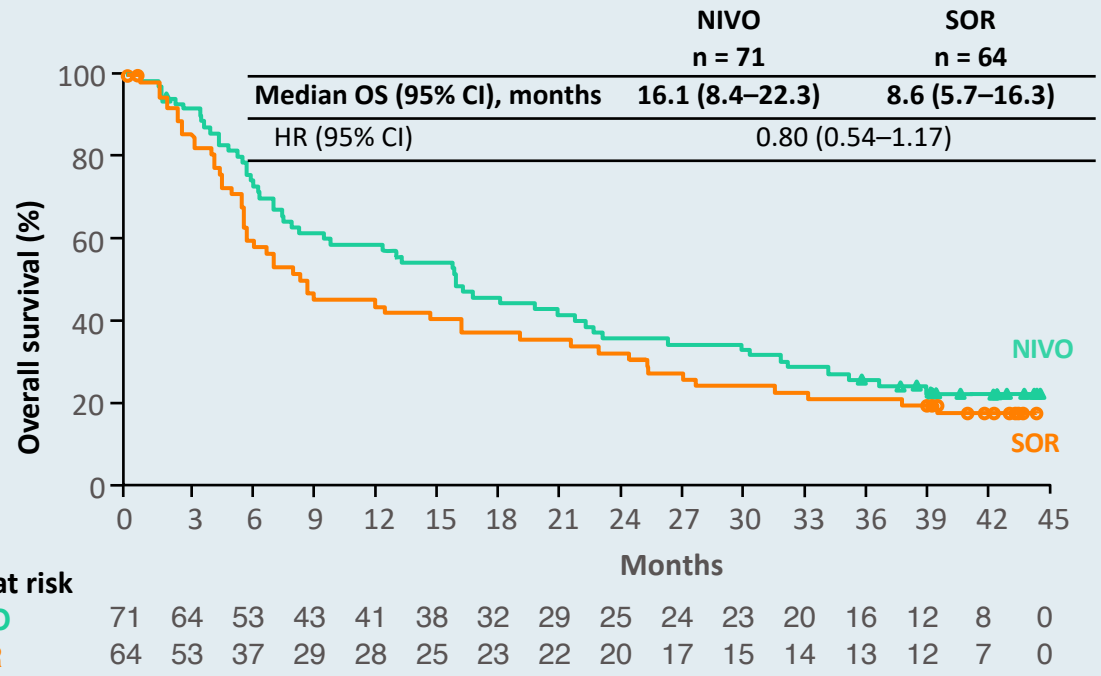
RTP RESEARCH TO PRACTICE

CheckMate 459: Long-Term Efficacy Outcomes with Nivolumab versus Sorafenib as First-line Treatment in Patients with Advanced Hepatocellular Carcinoma

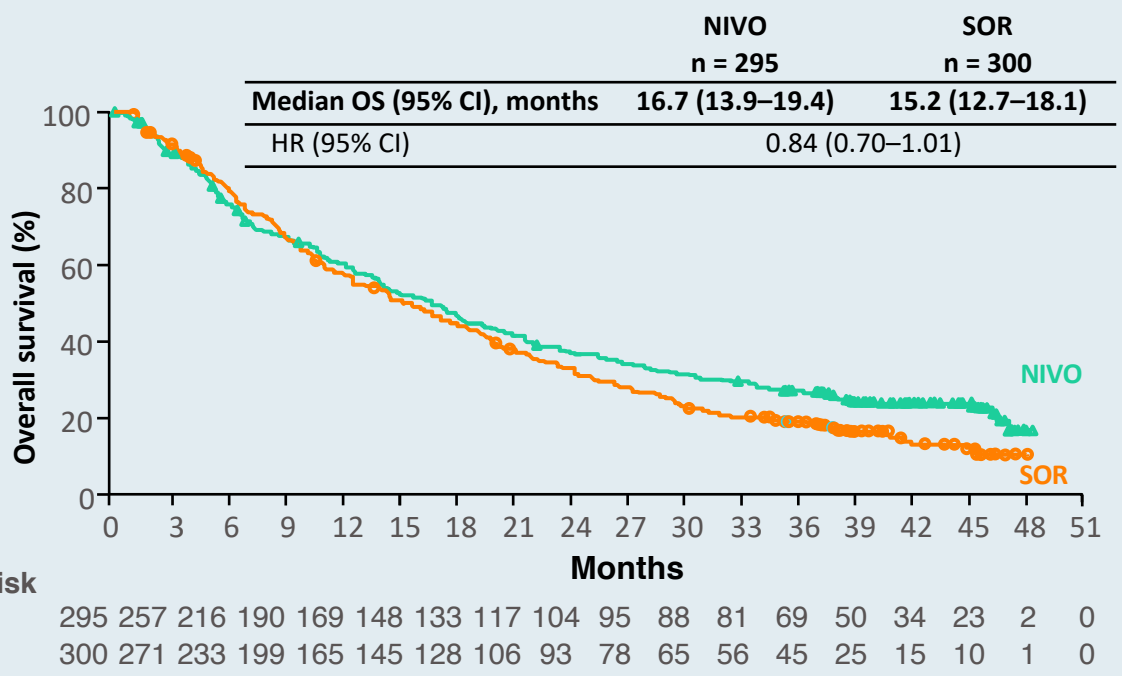
Sangro B et al.
ESMO World GI Congress 2020;Abstract LBA-3.

CheckMate 459: Overall Survival by PD-L1 Expression with First-Line Sorafenib in Advanced HCC

Tumor cell PD-L1 expression ≥ 1%



Tumor cell PD-L1 expression < 1%



- OS in the PD-L1 ≥ 1% group was longer in the NIVO arm compared to the SOR arm

Sangro B et al. ESMO World GI Congress 2020;Abstract LBA-3.

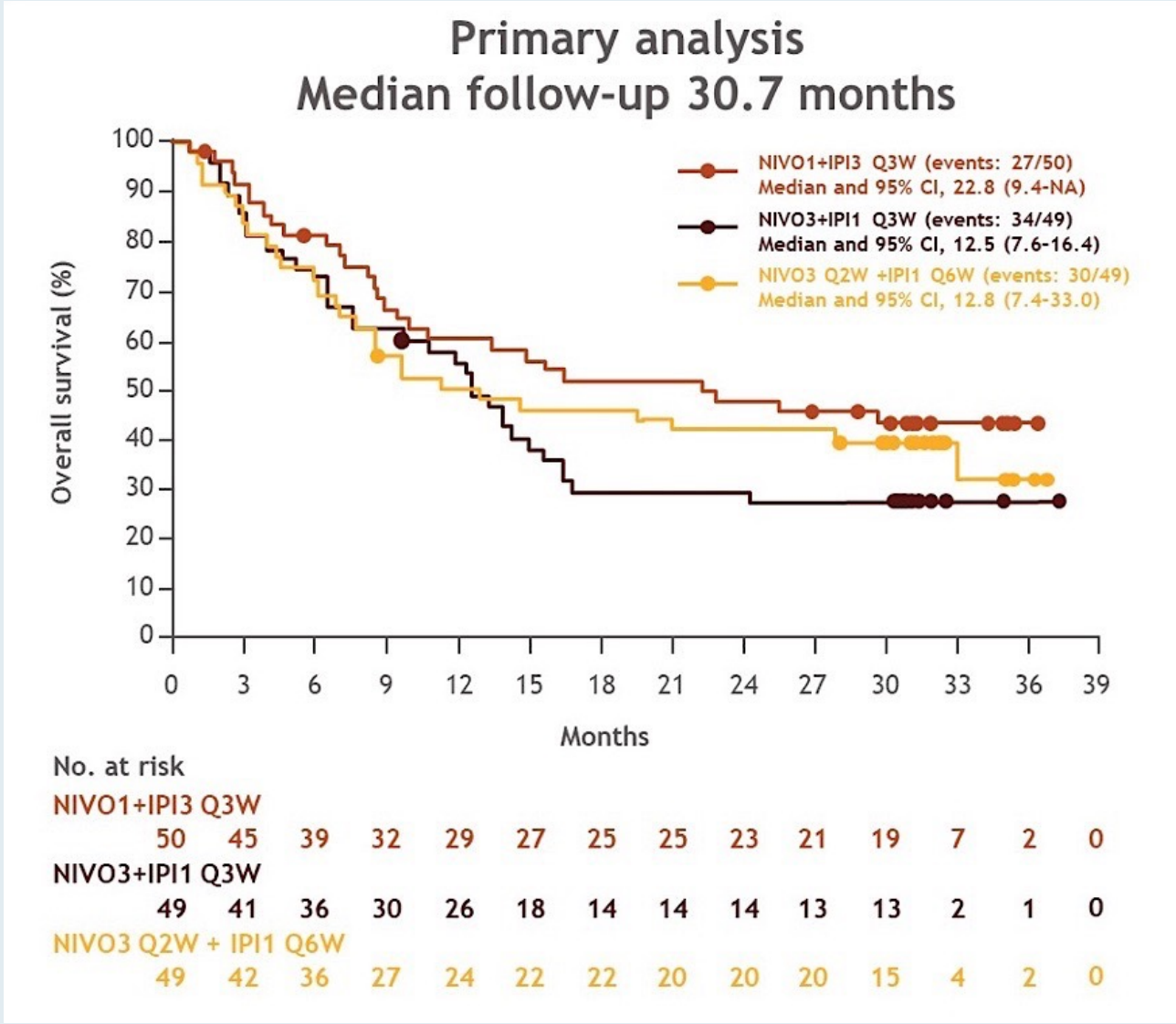
RTP RESEARCH TO PRACTICE

Nivolumab (NIVO) plus Ipilimumab (IPI) Combination Therapy in Patients (Pts) with Advanced Hepatocellular Carcinoma (aHCC): Long-Term Results from CheckMate 040

El-Khoueiry AB et al.

Gastrointestinal Cancers Symposium 2021;Abstract 269.

CheckMate 040: Updated Overall Survival with Ipilimumab/Nivolumab



El-Khoueiry AB et al. Gastrointestinal Cancers Symposium 2021;Abstract 269.

RTP RESEARCH TO PRACTICE

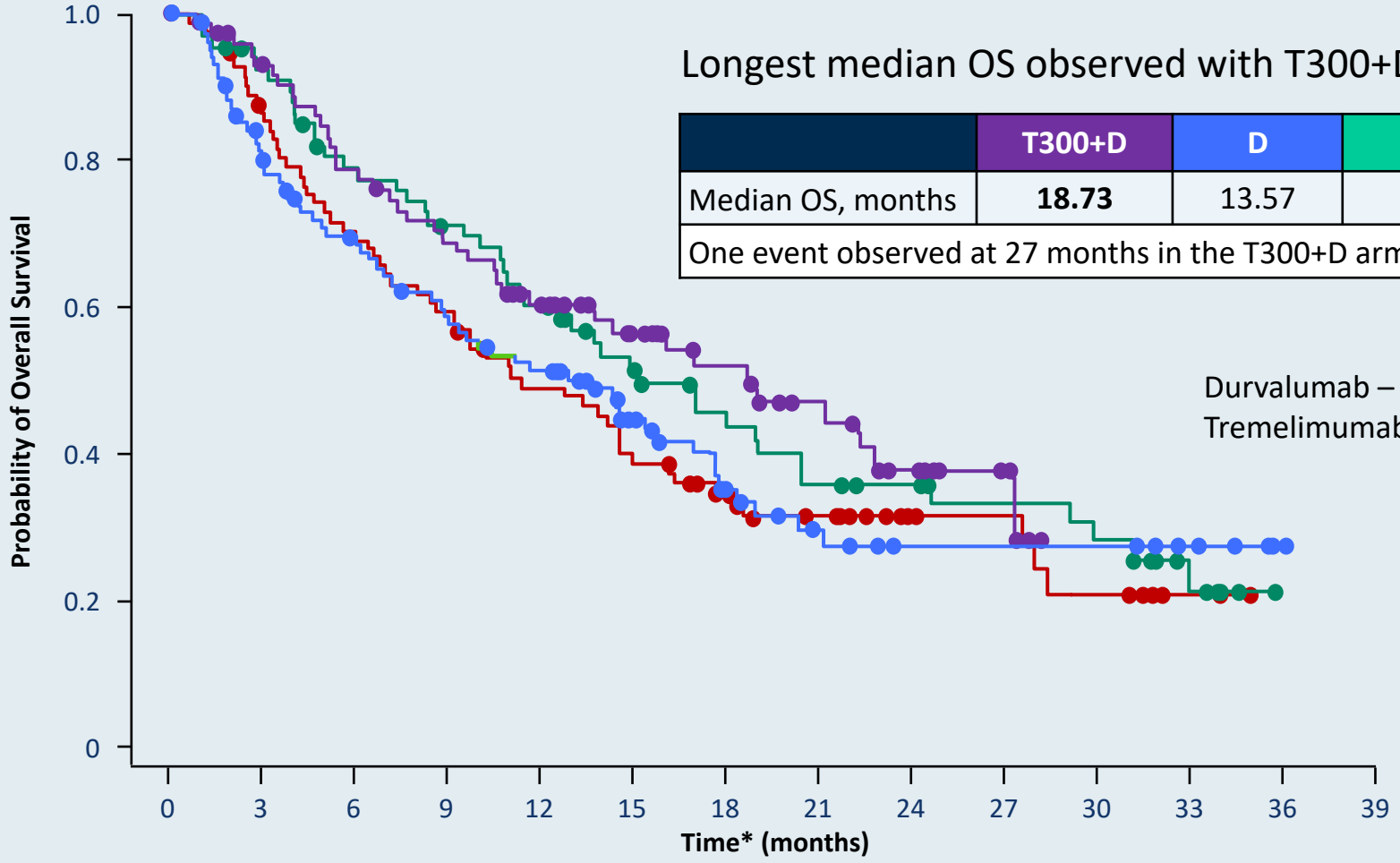
Efficacy, Tolerability, and Biologic Activity of a Novel Regimen of Tremelimumab (T) in Combination with Durvalumab (D) for Patients (pts) with Advanced Hepatocellular Carcinoma (aHCC)

Kelley RK et al.
ASCO 2020;Abstract 4508.

The Novel Regimen of Tremelimumab in Combination with Durvalumab Provides a Favorable Safety Profile and Clinical Activity for Patients with Advanced Hepatocellular Carcinoma

Sangro B et al.
ESMO World GI Congress 2020;Abstract O-6.

Study 22: Overall Survival



Longest median OS observed with T300+D

	T300+D	D	T	T75+D
Median OS, months	**18.73**	13.57	15.11	11.30
One event observed at 27 months in the T300+D arm				

Durvalumab – anti-PD1
Tremelimumab - anti-CTLA4

Number of patients at risk														
T300+D	75	67	56	48	39	30	22	16	10	5	0	0	0	0
D	104	78	65	54	46	31	20	14	8	8	8	5	1	0
T	69	62	51	45	38	29	23	18	16	13	11	5	0	0
T75+D	84	69	56	48	38	30	23	17	10	9	6	2	0	0

Sangro B et al. ESMO World GI Congress 2020;Abstract O-6; Kelley RK et al. ASCO 2020;Abstract 4508.

ODAC Opposes Ongoing FDA Approval of Nivolumab for HCC in Patients Pretreated With Sorafenib

Press Release – April 29, 2021

"The FDA's Oncologic Drug Advisory Committee voted 5 to 4 against the continued accelerated approval of nivolumab for the treatment of patients with hepatocellular carcinoma who were previously treated with sorafenib.

In September of 2017, the FDA granted accelerated approval to nivolumab as a monotherapy for the treatment of HCC in patients who have been previously treated with sorafenib. Approval was based on a 154-patient subgroup of CHECKMATE-040 (NCT01658878) study, which evaluated nivolumab as a monotherapy for patients who HCC and Child-Pugh A cirrhosis who progressed on or were intolerant to sorafenib. The overall response rate to the age was 14.3%, which included 3 complete responses and 19 partial responses. Duration of response (DOR) ranged from 3.2 months to 38.2 months and longer. Of those who responded, 91% had a response lasting 6 months or longer and 55% had a response lasting 12 months or longer."

https://www.targetedonc.com/view/odac-opposes-ongoing-fda-approval-of-nivolumab-for-hcc-in-patients-pretreated-with-sorafenib

Late-Breaking Clinical Trial Data for TheraSphere™ Y-90 Glass Microspheres Demonstrates Improved Survival in Primary Liver Cancer

Press Release – March 25, 2021

"Boston Scientific Corporation announced positive data from the TARGET study of the TheraSphere™ Y-90 Glass Microspheres (TheraSphere) – a type of radioembolization comprised of millions of microscopic glass beads containing radioactive yttrium (Y-90) – during a late-breaking clinical trial presentation at the annual scientific meeting for the Society of Interventional Radiology (SIR).

The global, retrospective TARGET study evaluated the safety and efficacy of TheraSphere therapy in patients with hepatocellular carcinoma (HCC) – the most common type of primary liver cancer – using a dosing method known as multicompartment dosimetry, which maximizes the dose of Y-90 reaching the tumor while minimizing the radiation dose that reaches normal liver tissue. In the study, imaging software was used retroactively to calculate the dose delivered within each patient's liver tissue. Data confirmed treatment was safe and well tolerated, with only 4.8% of patients experiencing adverse events, defined in the primary endpoint as ≥ Grade 3 hyperbilirubinemia. Hyperbilirubinemia, commonly referred to as jaundice, is the build-up of bilirubin in the blood and can indicate abnormal liver function. The TARGET study findings create the opportunity for future TheraSphere treatment optimization and Y-90 dose escalation without compromising safety."

https://news.bostonscientific.com/2021-03-25-Late-Breaking-Clinical-Trial-Data-for-TheraSphere-TM-Y-90-Glass-Microspheres-Demonstrates-Improved-Survival-in-Primary-Liver-Cancer

RTP RESEARCH TO PRACTICE

TheraSphere SIRT Received FDA Approval for Treatment of Unresectable HCC

Press Release – March 18, 2021

"FDA approval has been granted to the TheraSphere Y-90 Glass Microspheres for the treatment of unresectable hepatocellular carcinoma (HCC).

The decision by the FDA was based on results of the LEGACY study, which looked at efficacy and safety of this therapy in both early and advanced HCC. Data presented at the European Society for Medical Oncology 2020 Virtual Congress showed that the study met both primary end points of objective response rate (72.2% at 4 weeks) and duration of response (76.1% at 6 months) in the 162-patient cohort. Of the patients not achieving a response, all were considered not evaluable due to transplant or resection (n = 20), lack of confirmatory imaging (n = 20), or other reasons (n = 5).

The data also indicated that treatment with TheraSphere was suitable as either adjuvant therapy or as monotherapy. The median overall survival (OS) in the intent-to-treat population was 57.9 months and the rate of OS at 3 years was 86.6%. Liver function as determined by levels of albumin and bilirubin were maintained for 92.9% and 85.3% of patients, respectively."

https://www.cancernetwork.com/view/therasphere-sirt-received-fda-approval-for-treatment-of-unresectable-hcc

Ask the Expert: Clinical Investigators Provide Perspectives on the Management of Renal Cell Carcinoma

In Partnership with Project Echo® and Florida Cancer Specialists

Tuesday, May 4, 2021
5:00 PM – 6:00 PM ET

Faculty

Chung-Han Lee, MD, PhD

Moderator

Neil Love, MD

Thank you for joining us!

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

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