Meet The Professor

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

Axel Grothey, MD

Director, GI Cancer Research

West Cancer Center and Research Institute

Medical Director

OneOncology Research Network

Germantown, Tennessee

Commercial Support

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Dr Love — Disclosures

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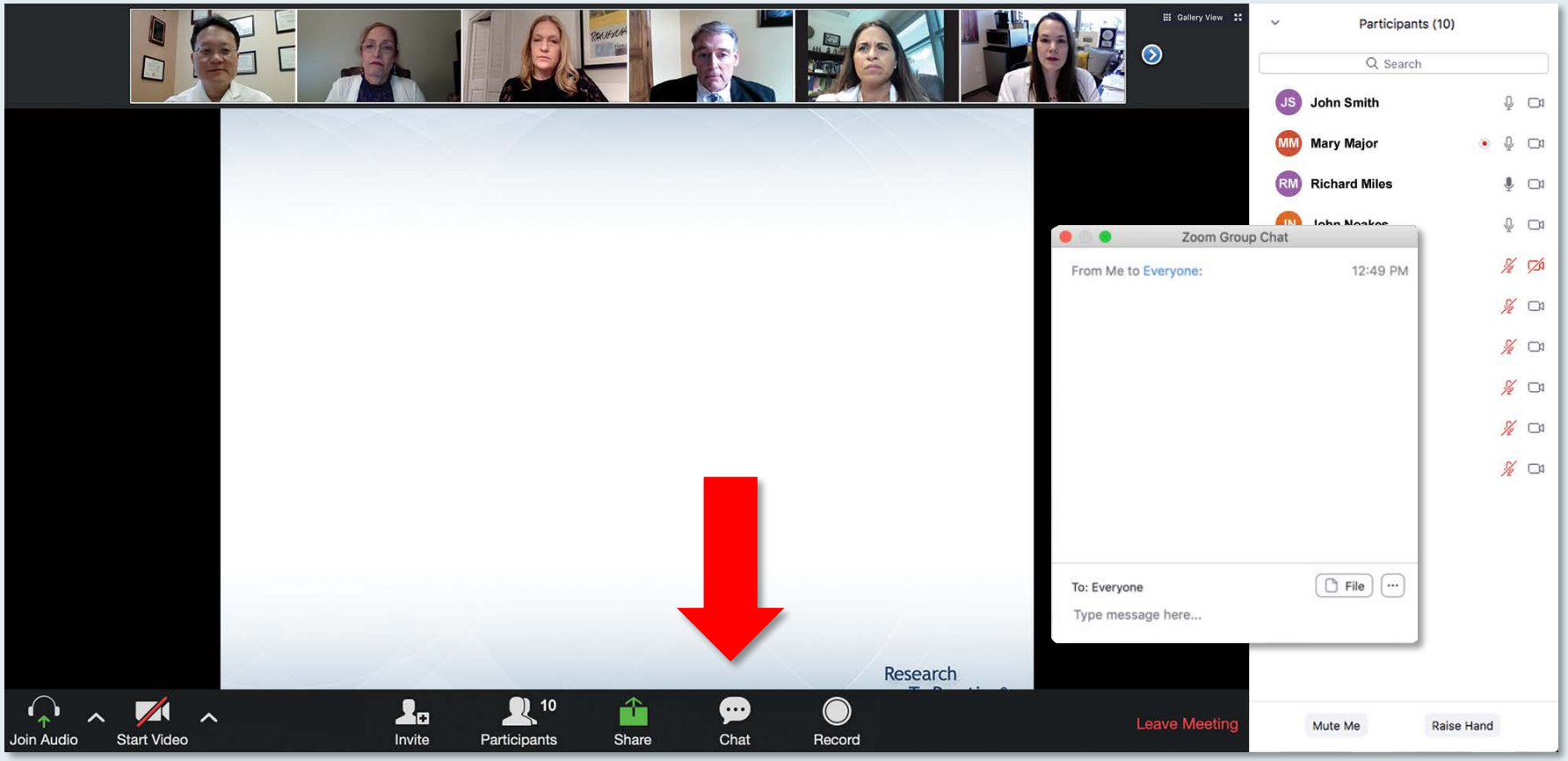
We Encourage Clinicians in Practice to Submit Questions



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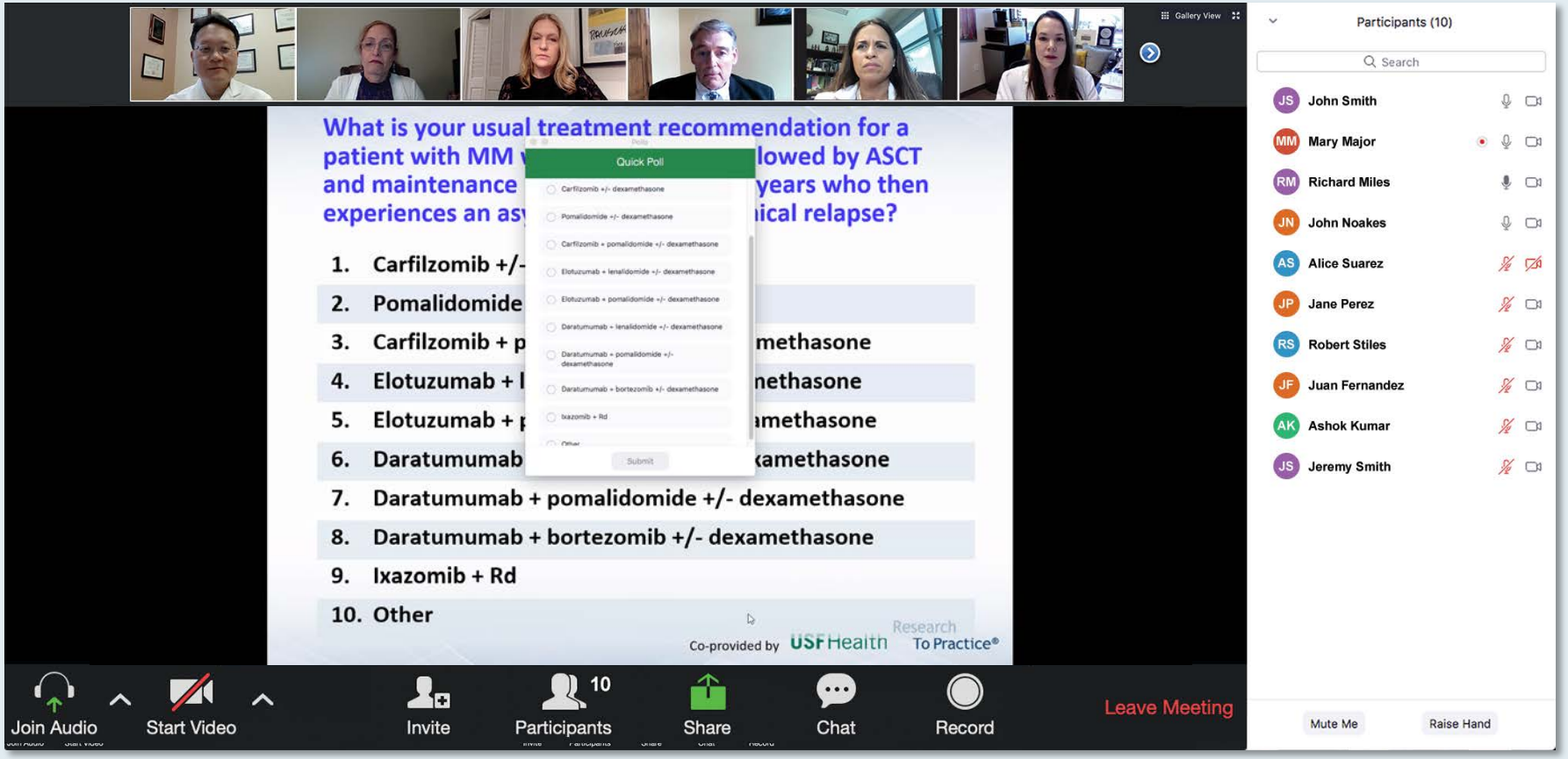

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Optimizing the Selection and Sequencing of Therapy for Patients with Renal Cell Carcinoma

Wednesday, February 17, 2021
12:00 PM – 1:00 PM ET

Faculty

Eric Jonasch, MD

Moderator

Neil Love, MD

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What Clinicians Want to Know: Understanding the Factors Affecting the Optimal Diagnosis and Management of Ovarian Cancer

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Kathleen Moore, MD
David M O'Malley, MD

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RTP RESEARCH TO PRACTICE

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Management of Multiple Myeloma

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A Keith Stewart, MB, ChB

Moderator

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Cancer Conference Update: What Happened at the 2020 San Antonio Breast Cancer Symposium®

Management of Triple-Negative Breast Cancer

Monday, February 22, 2021
5:00 PM – 6:00 PM ET

Faculty

Joyce O'Shaughnessy, MD

Moderator

Neil Love, MD

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Meet The Professor
Management of Lung Cancer

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Recent Advances in Hematologic Oncology: A 4-Part Live Webinar Series Reviewing Key Data and Presentations from the 62nd ASH Annual Meeting

Part 4 — Chronic Lymphocytic Leukemia

Wednesday, February 24, 2021
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Matthew S Davids, MD, MMSc
Kerry Rogers, MD

Moderator

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RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss Emerging Research and Actual Patients with Prostate Cancer (Part 1 of a 3-Part Series)

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Fred Saad, MD
A Oliver Sartor, MD
Matthew R Smith, MD, PhD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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WITH DR NEIL LOVE

Key Recent Data Sets in Gastrointestinal Cancers

DR PHILIP A PHILIP

KARMANOS CANCER INSTITUTE

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esentation: Dr Ma
woman, frail, anemic and with coronary artery
se, diabetes and severe lower-extremity edema
notivated to be treated
2
tal cancer with some bleeding, diarrhea and
se liver mets. MSS RAS WT, HER2-negative
pecitabine: Minor response, well tolerated
rrently on TAS-102, initially at reduced dose but
w full dose: Tolerating it well


Irino/ Cetux +/- vemurafenib: PFS


6 5 0
15 2 0
18 8 3
22 4 0
20 10 2
16 6 0
11 5 1
2 2 0


A woman in her early 70s with Child-Pugh B multifocal HCC
Child-Pugh B multifocal HCC (largest tumor 7 cm)
– AFP = 2,500
Localized interventional radiation treatment for dominant mass
Sorafenib x 5 months → disease progression
– Hand-foot syndrome, dose reduction
Dr Park


CELESTIAL: Overall Survival
CELESTIAL: Overall Survival
Reserved


Coke
Nutrition Facts
Calories 0


S1406: VIC (Vemurafenib, Cetuximab and Irinotecan)
Primary Endpoint: Progression-free survival
HR = 0.42
P=0.0002
RESERVED


credit for your participation.


Comparison of RR and


2019 ASCO
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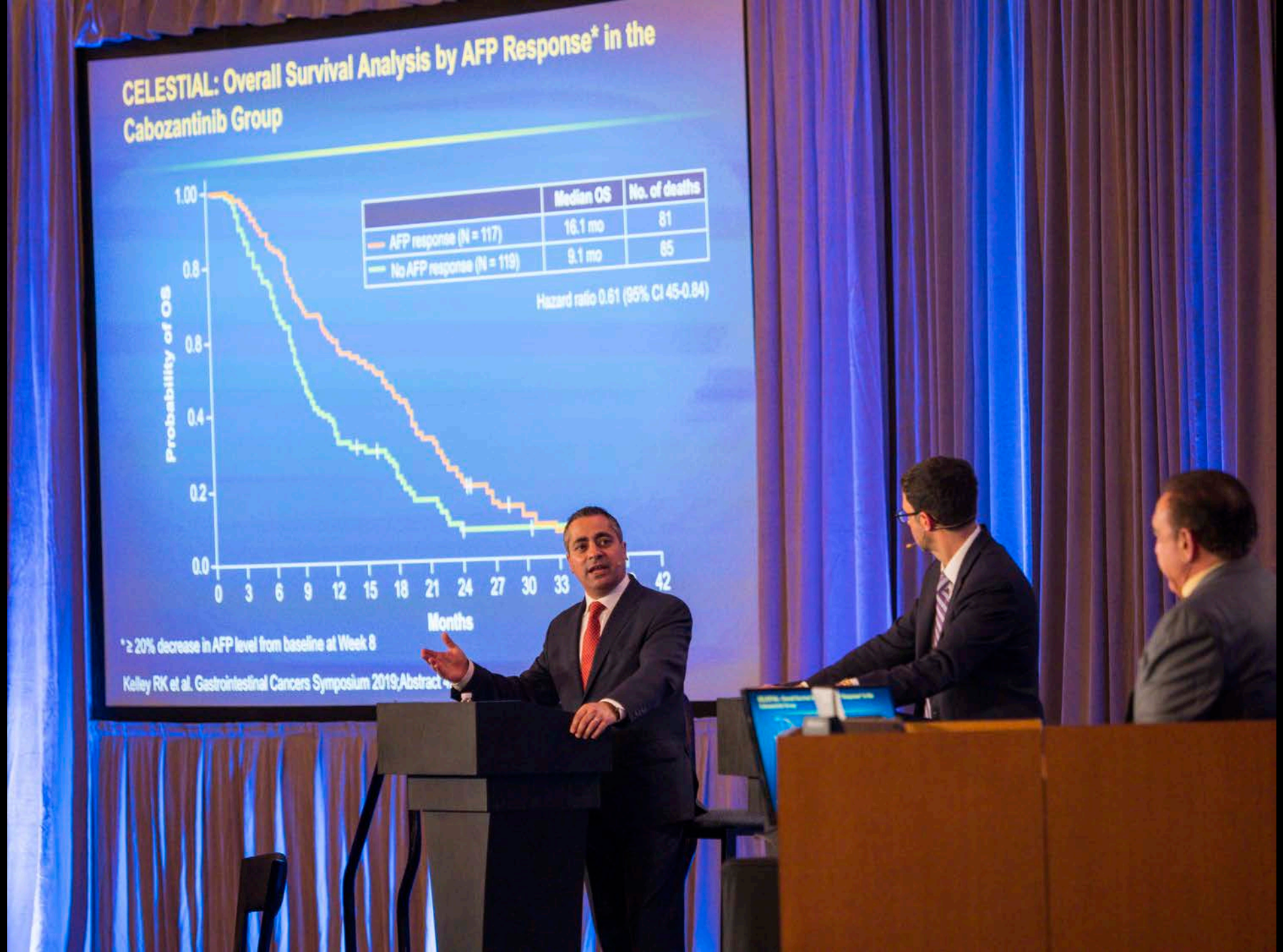
CELESTIAL: Overall Survival Analysis by AFP Response* in the Cabozantinib Group
Median OS
No. of deaths
AFP response (N = 117)
16.1 mo
81
No AFP response (N = 119)
9.1 mo
85
Hazard ratio 0.61 (95% CI 45-0.84)
Probability of OS
1.00
0.8
0.8
0.4
0.2
0.0
0 3 6 9 12 15 18 21 24 27 30 33 42
Months
* ≥ 20% decrease in AFP level from baseline at Week 8
Kelley RK et al. Gastrointestinal Cancers Symposium 2019;Abstract

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Germantown, Tennessee

Meet The Professor Program Participating Faculty

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

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Meet The Professor Program Participating Faculty

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Section Head, Hepatopancreaticobiliary and
Neuroendocrine Cancers
Co-Director, Medical Initiatives
David M Rubenstein Center for Pancreatic Cancer Research
Attending Physician, Member
Memorial Sloan Kettering Cancer Center
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Vice President of Medical Affairs
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Detroit, Michigan

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Medical Oncology and Translational Research
Shorenstein Associate Director
Program Development
Helen Diller Family Comprehensive Cancer Center
University of California, San Francisco
San Francisco, California

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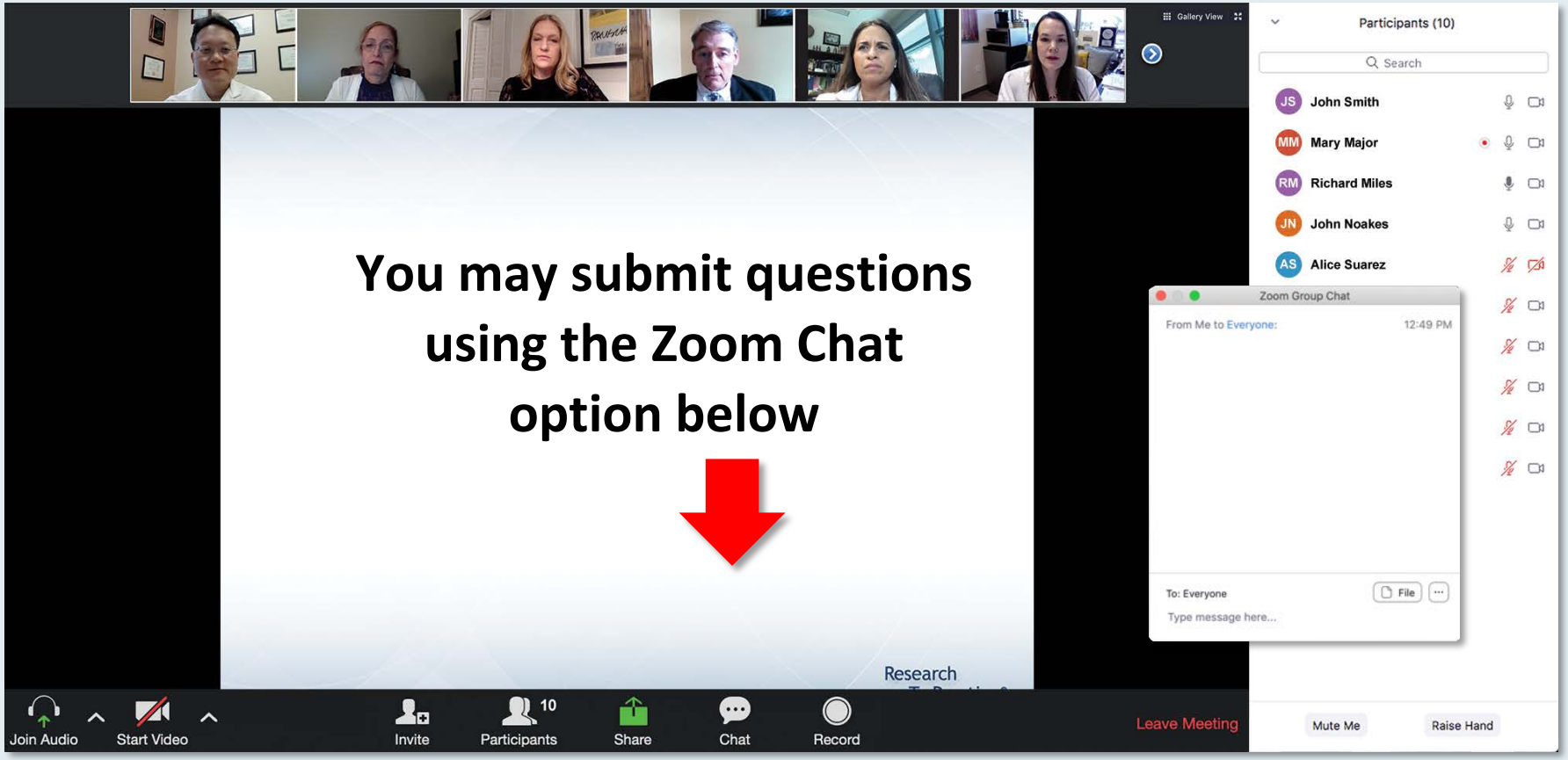

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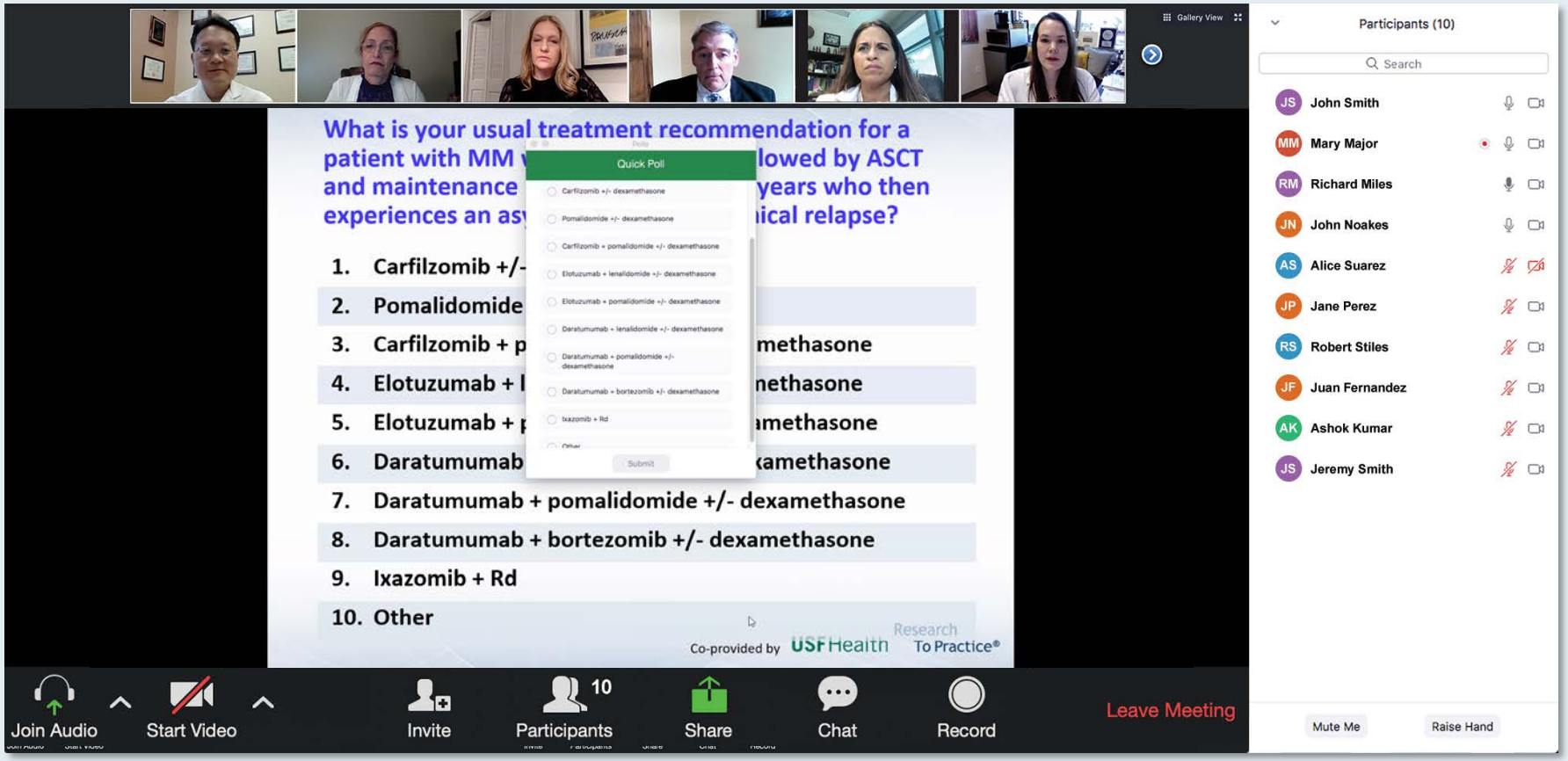

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Liudmila N Schafer, MD
Associate Professor of Medicine
Director of Gastrointestinal Oncology Program
Saint Luke's Cancer Institute
University of Missouri-Kansas City School of Medicine
Kansas City, Missouri

Nasfat Shehadeh, MD
Medical Oncologist
Oncology Specialists of Charlotte
Charlotte, North Carolina

Meet The Professor with Dr Grothey

MODULE 1: Cases and Questions from Drs Schafer and Shehadeh

- Dr Schafer: An 89-year-old woman with MSI-H metastatic colorectal cancer – BRAF V600E mutation
- Dr Schafer: A 64-year-old man with MSS metastatic esophageal adenocarcinoma – HER2 amplification
- Dr Shehadeh: A 70-year-old man with newly diagnosed Child-Pugh A HCC
  - Clinical Investigator Perspective: Dr Philip A Philip
  - Clinical Investigator Perspective: Prof Eric Van Cutsem

MODULE 2: Gastrointestinal Cancers Journal Club with Dr Grothey

MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

MODULE 4: Key Recent Data Sets

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Case Presentation – Dr Schafer: An 89-year-old woman with MSI-H metastatic colorectal cancer – BRAF V600E mutation

Dr Liudmila Schafer

- PMH: Lobular breast cancer in 2007, mastectomy, docetaxel and cyclophosphamide x 4 cycles, completed tamoxifen in 2018
- 11/2019: Stage IIIB adenocarcinoma of the cecum, with bowel perforation, s/p right hemicolectomy, CEA: 1.5
  - MSI-H, BRAF V600E mutation, KRAS and NRAS wildtype
  - Patient declined adjuvant chemotherapy
- 5/2020: Large peritoneal deposits, CEA 2.4 → Pembrolizumab
- 8/2020: Radiological resolution of large peritoneal deposit
- 12/2020: Dyskinesia, anti-striatal antibody
  - Currently stable scans and receiving IVIG

Questions

- Are there data on tardive dyskinesia as a side effect of immune checkpoint inhibitors?
- Would you use encorafenib and cetuximab in the second line versus chemotherapy?

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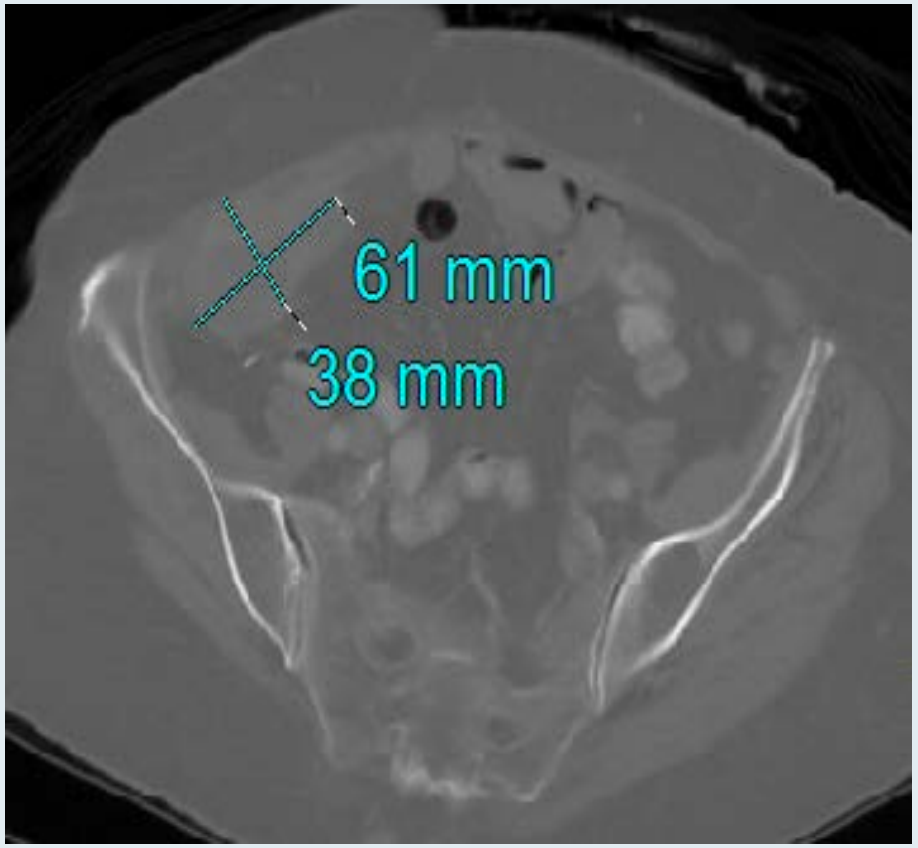
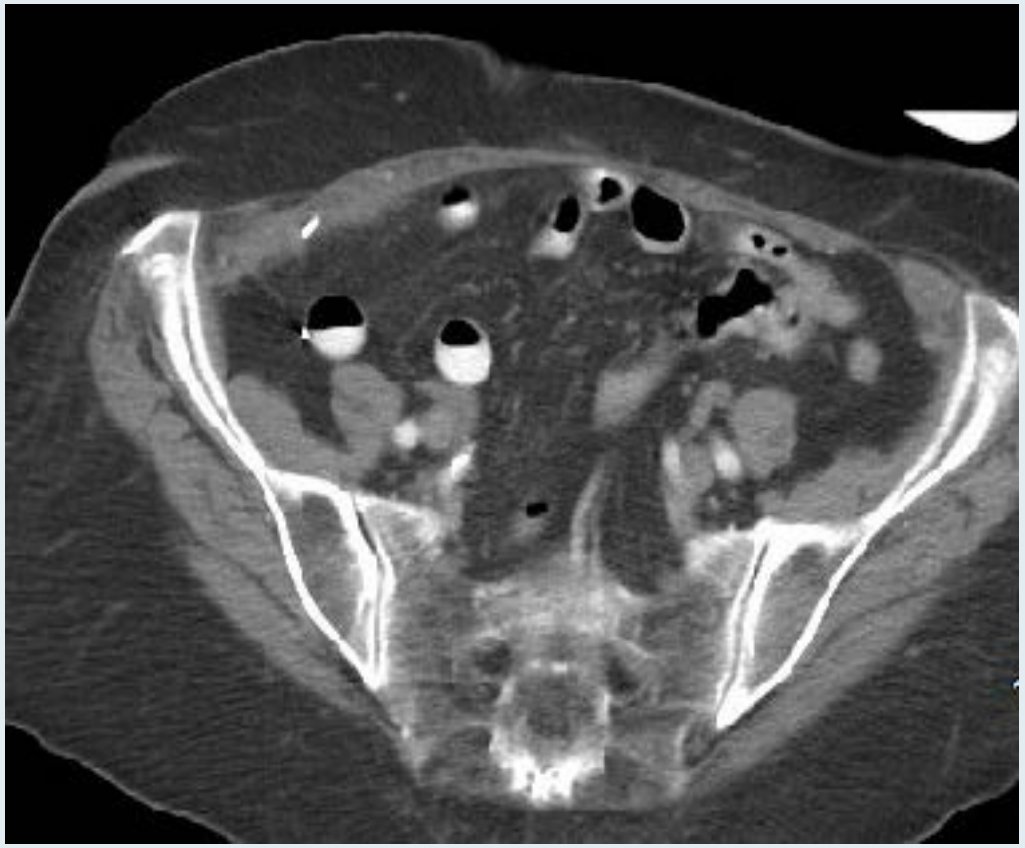
Case Presentation – Dr Schafer: An 89-year-old woman – CT scans before and after pembrolizumab

Dr Liudmila Schafer

5/2020 CT: PD with large peritoneal deposits (6.1 x 3.8 cm)



8/2020 CT after pembrolizumab x 3 months: Near complete radiologic response of peritoneal deposits



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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 + biologic
6. Chemotherapy + immunotherapy
7. 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?

 PROFESSOR DIRK ARNOLD, MD, PHD	Pembrolizumab	 WELLS A MESSERSMITH, MD	Pembrolizumab
 TANIOS BEKAII-SAAB, MD	Pembrolizumab	 EILEEN M O'REILLY, MD	Pembrolizumab
 JOHANNA BENDELL, MD	Pembrolizumab	 PHILIP AGOP PHILIP, MD, PHD, FRCP	Pembrolizumab
 DANIEL CATENACCI, MD	Pembrolizumab	 ALAN P VENOOK, MD	Pembrolizumab
 KRISTEN K CIOMBOR, MD, MSCI	Pembrolizumab	 ZEV WAINBERG, MD, MSC	Pembrolizumab
 AXEL GROTHEY, MD	Pembrolizumab		

RTP RESEARCH TO PRACTICE

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

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?

 PROFESSOR DIRK ARNOLD, MD, PHD	Second line
 TANIOS BEKAII-SAAB, MD	Second line
 JOHANNA BENDELL, MD	Second line
 DANIEL CATENACCI, MD	Second line
 KRISTEN K CIOMBOR, MD, MSCI	Second line
 AXEL GROTHEY, MD	Second line
 WELLS A MESSERSMITH, MD	Third line or beyond
 EILEEN M O'REILLY, MD	Second line
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Second line
 ALAN P VENOOK, MD	Second line
 ZEV WAINBERG, MD, MSC	Second line

RTP RESEARCH TO PRACTICE

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

 PROFESSOR DIRK ARNOLD, MD, PHD	Encorafenib + cetuximab
 TANIOS BEKAII-SAAB, MD	Encorafenib + panitumumab
 JOHANNA BENDELL, MD	Encorafenib + panitumumab
 DANIEL CATENACCI, MD	Encorafenib + cetuximab
 KRISTEN K CIOMBOR, MD, MSCI	Encorafenib + panitumumab
 AXEL GROTHEY, MD	Encorafenib + panitumumab
 WELLS A MESSERSMITH, MD	Encorafenib + panitumumab
 EILEEN M O'REILLY, MD	Encorafenib + cetuximab
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Encorafenib + panitumumab
 ALAN P VENOOK, MD	Encorafenib + panitumumab
 ZEV WAINBERG, MD, MSC	Encorafenib + binimetinib + cetuximab

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Case Presentation – Dr Schafer: A 64-year-old man with MSS metastatic esophageal adenocarcinoma – HER2 amplified

Dr Liudmila Schafer

- 9/2020: Diagnosed with metastatic esophageal adenocarcinoma by EUS, with hepatic, osseous and soft tissue muscular lesions
- HER2-amplified, microsatellite stable (MSS), PD-L1<1%
- FOLFOX/trastuzumab → PD after 4 cycles, with osseus metastases
- 1/2021: Plan trastuzumab deruxtexan

Questions

- What's your opinion about whether this is HER2-resistant disease? Based on the recent approval, would you treat in the second line using paclitaxel/ramucirumab, or trastuzumab deruxtecan?
- What are you using in the third-line setting? Would you consider follow up with ctDNA to assess the response to treatment?

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Regulatory and reimbursement issues aside, in which line of therapy if any would you generally recommend an anti-PD-1/PD-L1 antibody (with or without chemotherapy) for a 65-year-old patient with metastatic HER2-negative, MSS adenocarcinoma of the GEJ with a PD-L1 CPS of 1?

1. First line
2. Second line
3. Third line
4. Beyond third line
5. I would not recommend an anti-PD-1/PD-L1 antibody

Regulatory and reimbursement issues aside, in which line of therapy would you generally recommend an anti-PD-1/PD-L1 antibody (with or without chemotherapy) for a 65-year-old patient with metastatic HER2-negative, MSS adenocarcinoma of the GEJ with a PD-L1 CPS of 1?

 PROFESSOR DIRK ARNOLD, MD, PHD	Third line — nivolumab or pembrolizumab
 TANIOS BEKAII-SAAB, MD	Beyond third line — pembrolizumab
 JOHANNA BENDELL, MD	Third line — pembrolizumab
 DANIEL CATENACCI, MD	Beyond third line — pembrolizumab
 KRISTEN K CIOMBOR, MD, MSCI	Third line — pembrolizumab
 AXEL GROTHEY, MD	Third line — pembrolizumab
 WELLS A MESSERSMITH, MD	Third line — pembrolizumab
 EILEEN M O'REILLY, MD	First line — FOLFOX/nivolumab
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Third line — pembrolizumab
 ALAN P VENOOK, MD	Would not recommend an anti-PD-1/PD L1 antibody
 ZEV WAINBERG, MD, MSC	Third line — pembrolizumab or nivolumab

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Regulatory and reimbursement issues aside, in which line of therapy if any would you generally recommend an anti-PD-1/PD-L1 antibody (with or without chemotherapy) for a 65-year-old patient with metastatic HER2-negative, MSS adenocarcinoma of the GEJ with a PD-L1 CPS of 10?

1. First line
2. Second line
3. Third line
4. Beyond third line
5. I would not recommend an anti-PD-1/PD-L1 antibody

Regulatory and reimbursement issues aside, in which line of therapy would you generally recommend an anti-PD-1/PD-L1 antibody (with or without chemotherapy) for a 65-year-old patient with metastatic HER2-negative, MSS adenocarcinoma of the GEJ with a PD-L1 CPS of 10?

 PROFESSOR DIRK ARNOLD, MD, PHD	First line — pembrolizumab
 TANIOS BEKAII-SAAB, MD	First line — pembrolizumab/FOLFOX
 JOHANNA BENDELL, MD	First line — nivolumab/FOLFOX
 DANIEL CATENACCI, MD	First line — pembrolizumab/FOLFOX
 KRISTEN K CIOMBOR, MD, MSCI	First line — pembrolizumab/FOLFOX
 AXEL GROTHEY, MD	First line — nivolumab/FOLFOX
 WELLS A MESSERSMITH, MD	Second line — pembrolizumab
 EILEEN M O'REILLY, MD	First line — nivolumab/FOLFOX
 PHILIP AGOP PHILIP, MD, PHD, FRCP	First line — nivolumab
 ALAN P VENOOK, MD	First line — nivolumab or pembrolizumab + FOLFOX
 ZEV WAINBERG, MD, MSC	First line — nivolumab + FOLFOX or CAPOX

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Case Presentation – Dr Shehadeh: A 70-year-old man with newly diagnosed Child-Pugh A HCC

Dr Nasfat Shehadeh

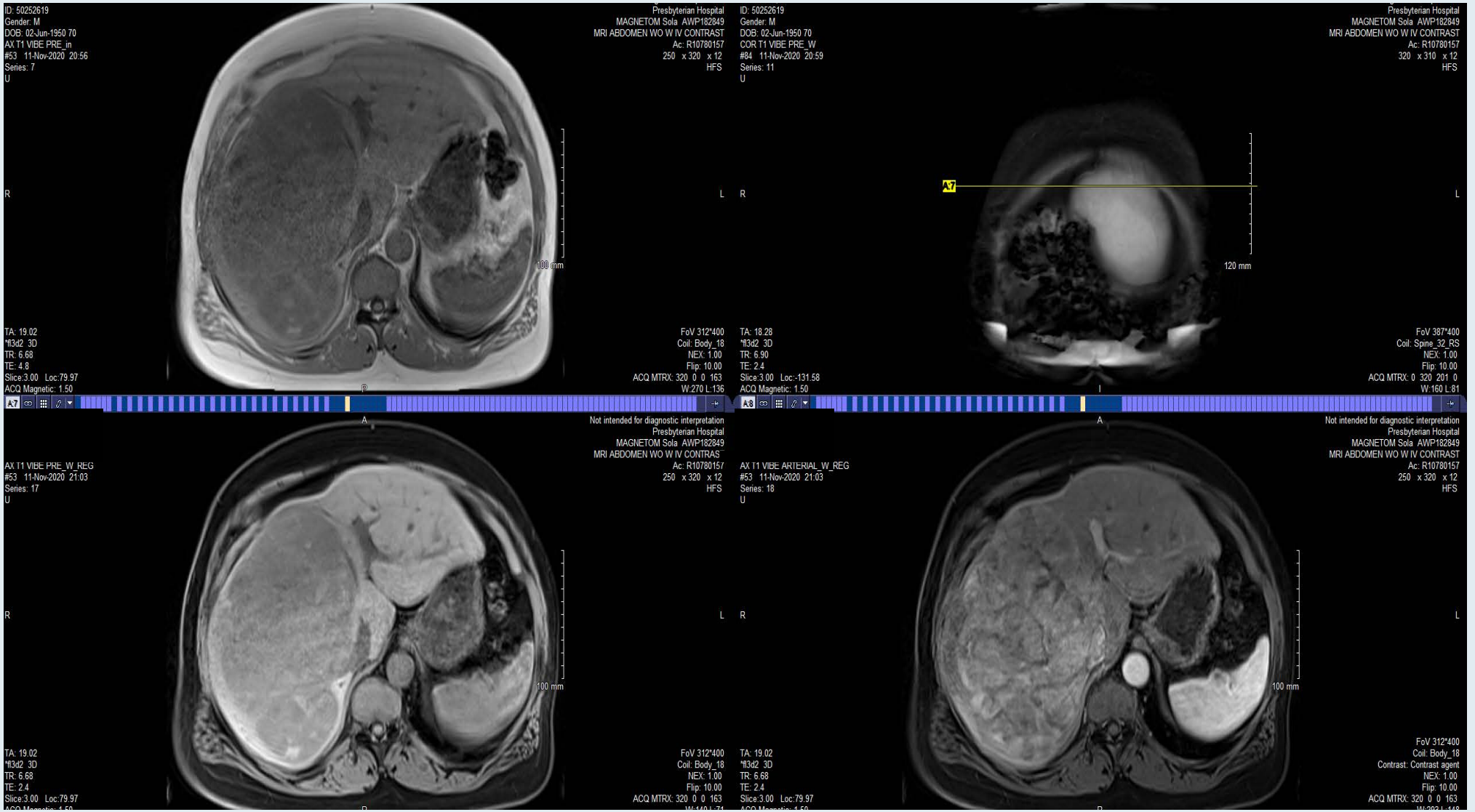
- PMH: Treated hepatitis C, alcohol abuse
- 11/2020: Child-Pugh A HCC (MELD: 7) heavily involving the right lobe (see images), with no extrahepatic disease
  - AFP: 63,000 ng/mL
- Referred for liver-directed therapy (delayed due to social issues)
- 1/2021: Admitted with SOB, wide complex tachycardia, probably alcohol-induced cardiomyopathy
  - Currently stable on medications, EF: 35%, PS 1
- Interventional radiology/radiation oncology plan: yttrium-90 radioembolization

Questions

- How to decide between radioembolization vs chemoembolization for patients like him? Since his right lobe is almost totally occupied by HCC, do you consider multi-stage embolization, and how often?
- What about future TKI and IO in the context of his significant cardiomyopathy?

Case Presentation – Dr Shehadeh: A 70-year-old man
MRI Abdomen (11/11/2020)

Dr Nasfat Shehadeh



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Clinical Investigator Perspective

Philip A Philip, MD, PhD, FRCP
Kathryn Cramer Endowed Chair in Cancer Research
Professor of Oncology and Pharmacology
Leader, GI and Neuroendocrine Oncology
Karmanos Cancer Institute
Wayne State University
Detroit, Michigan

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Clinical Investigator Perspective

Eric Van Cutsem, MD, PhD
Professor of Medicine
Digestive Oncology
University Hospitals Leuven
Leuven, Belgium

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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?

 PROFESSOR DIRK ARNOLD, MD, PHD	Atezolizumab/bevacizumab
 TANIOS BEKAII-SAAB, MD	Atezolizumab/bevacizumab
 JOHANNA BENDELL, MD	Atezolizumab/bevacizumab
 DANIEL CATENACCI, MD	Atezolizumab/bevacizumab
 KRISTEN K CIOMBOR, MD, MSCI	Sorafenib
 AXEL GROTHEY, MD	Atezolizumab/bevacizumab
 WELLS A MESSERSMITH, MD	Atezolizumab/bevacizumab
 EILEEN M O'REILLY, MD	Lenvatinib
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Atezolizumab/bevacizumab
 ALAN P VENOOK, MD	Atezolizumab/bevacizumab
 ZEV WAINBERG, MD, MSC	Lenvatinib

RTP RESEARCH TO PRACTICE

What would be your second-line therapy for a 65-year-old patient with HCC, a Child-Pugh B7 score and PS 1 who received first-line atezolizumab/bevacizumab and experienced disease progression after 14 months (AFP 2,500 ng/mL)?

1. Cabozantinib
2. Lenvatinib
3. Anti-PD-1 antibody
4. Nivolumab/ipilimumab
5. Ramucirumab
6. Regorafenib
7. Sorafenib
8. Other

What would be your most likely second-line systemic therapy for a 65-year-old patient with HCC, a Child-Pugh B7 score and a PS of 1 who received first-line atezolizumab/bevacizumab with minimal toxicity, had stable disease for 14 months and then experienced disease progression (AFP 2,500 ng/mL)?

 PROFESSOR DIRK ARNOLD, MD, PHD	Nivolumab
 TANIOS BEKAII-SAAB, MD	Cabozantinib
 JOHANNA BENDELL, MD	Cabozantinib
 DANIEL CATENACCI, MD	Lenvatinib
 KRISTEN K CIOMBOR, MD, MSCI	Sorafenib
 AXEL GROTHEY, MD	Ramucirumab
 WELLS A MESSERSMITH, MD	Lenvatinib
 EILEEN M O'REILLY, MD	Lenvatinib
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Lenvatinib
 ALAN P VENOOK, MD	Lenvatinib
 ZEV WAINBERG, MD, MSC	Lenvatinib

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Grothey

MODULE 1: Cases and Questions from Drs Schafer and Shehadeh

MODULE 2: Gastrointestinal Cancers Journal Club with Dr Grothey – Part 1

- Landscape of POLE variants in colorectal cancer (CRC): Correlation with MSI and tumor mutation burden
- ReDOS: Regorafenib dose optimization for patients with refractory metastatic CRC
- Evolving role of regorafenib for the treatment of advanced cancers
- MSI in Stage III colon cancer receiving fluoropyrimidine with or without oxaliplatin: ACCENT pooled analysis
- Efficacy of immunotherapy for MSS or mismatch repair-proficient CRC – Fact or fiction?
- EGFR antibodies for resectable metastatic colorectal liver metastasis – More harm than benefit?
- KEYNOTE-177: Pembrolizumab in MSI-H dMMR advanced CRC – A new standard
- CALGB/SWOG-80702: Celecoxib in addition to FOLFOX for Stage III CRC
- DESTINY-CRC01: Trastuzumab deruxtecan for HER2-expressing metastatic CRC

RTP
RESEARCH
TO PRACTICE

Meet The Professor with Dr Grothey

MODULE 1: Cases and Questions from Drs Schafer and Shehadeh

MODULE 2: Gastrointestinal Cancers Journal Club with Dr Grothey – Part 2

- Molecular differences between peritoneal metastases and primary colorectal adenocarcinoma
- BEACON: Encorafenib with cetuximab for previously treated metastatic CRC with a BRAF V600E mutation
- Total neoadjuvant therapy for borderline/locally advanced pancreatic cancer
- Comprehensive molecular analysis of MSS tumors with high mutational burden in GI cancers
- Meta-analysis: Treatment-related adverse events with PD-1 and PD-L1 inhibitors in clinical trials

MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

MODULE 4: Key Recent Data Sets

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RESEARCH
TO PRACTICE

The Landscape of POLE Variants in Colorectal and Endometrial Tumors: Correlation with Microsatellite Instability (MSI) and Tumor Mutation Burden (TMB)

Arora S et al.
ASCO 2020;Abstract e13538.

Articles

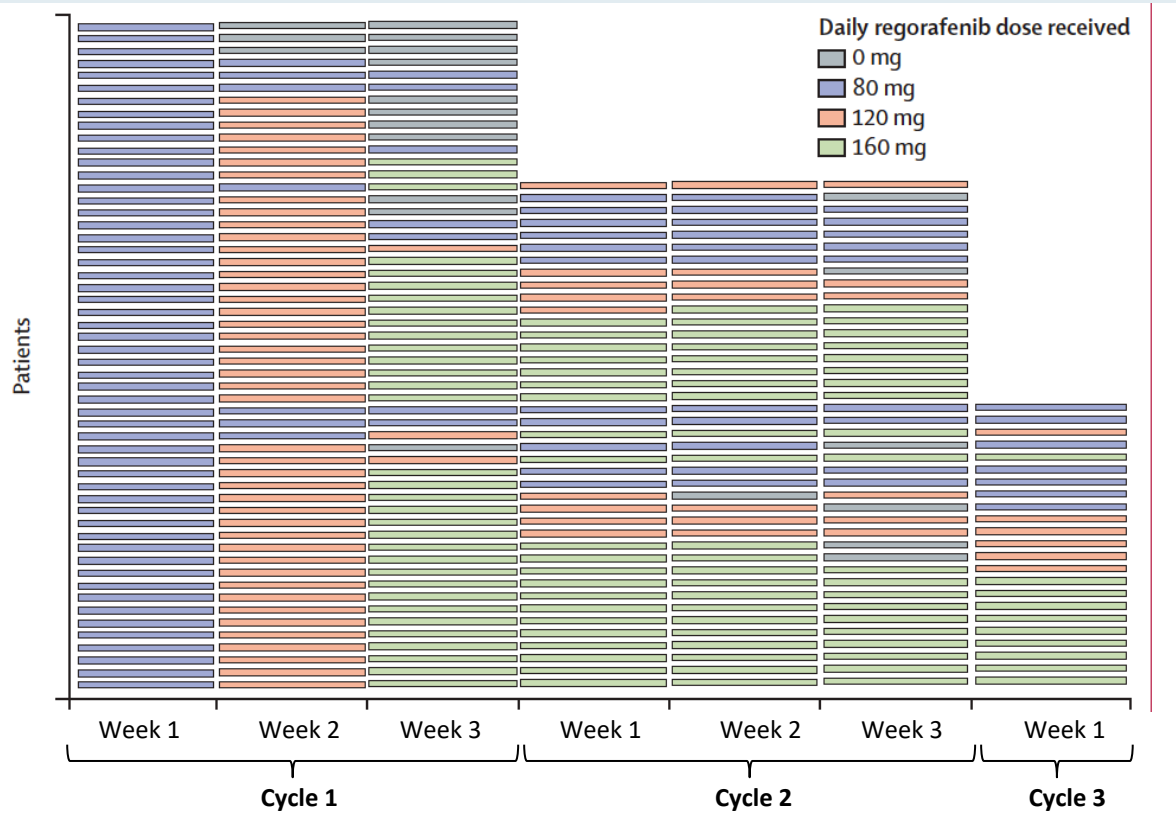
Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study

Tanios S Bekaii-Saab, Fang-Shu Ou, Daniel H Ahn, Patrick M Boland, Kristen K Ciombor, Erica N Heying, Travis J Dockter, Nisha L Jacobs, Boris C Pasche, James M Cleary, Jeffrey P Meyers, Rodwige J Desnoyers, Jeannine S McCune, Katrina Pedersen, Afsaneh Barzi, E Gabriela Chiorean, Jeffrey Sloan, Mario E Lacouture, Heinz-Josef Lenz, Axel Grothey

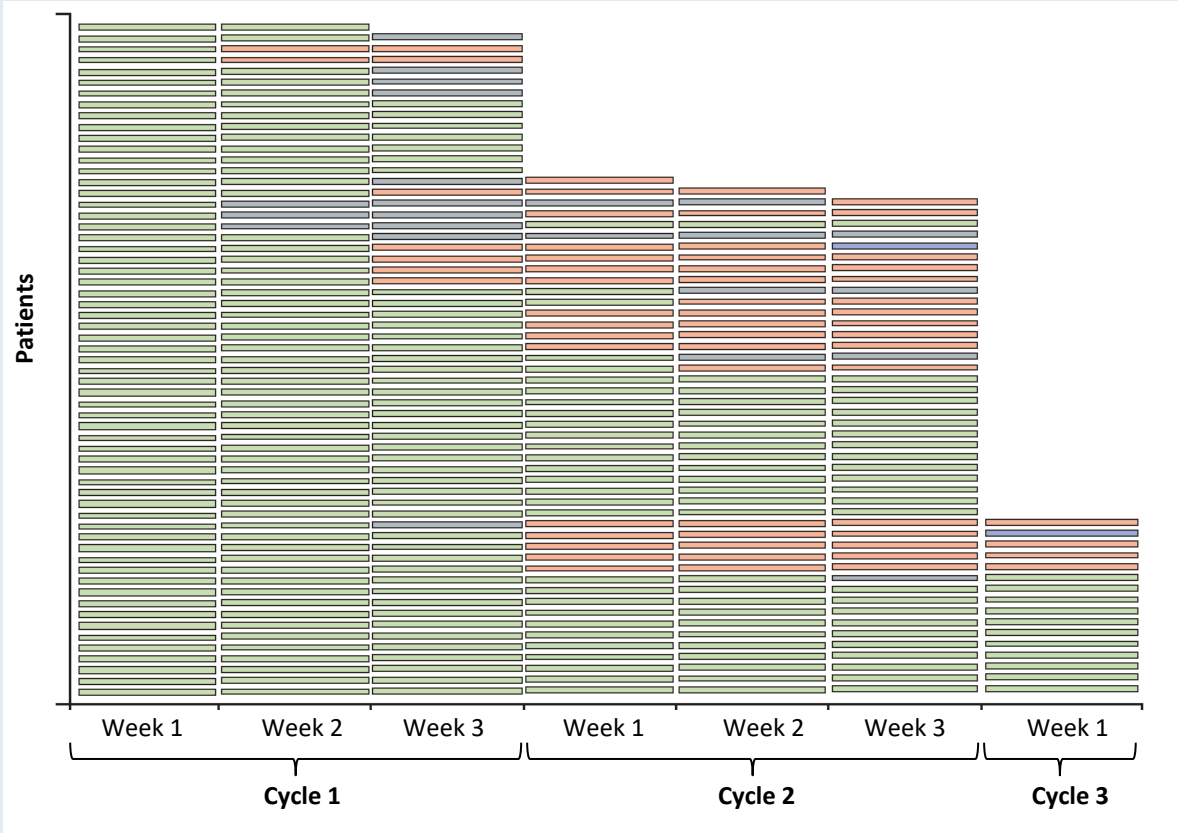
***Lancet Oncol* 2019;20(8):1070-82.**

ReDOS: A Phase II Study of Regorafenib Dose Optimization in mCRC

Dose-escalation group (n = 54)



Standard-dose group (n = 62)



Bekaii-Saab TS et al. *Lancet Oncol* 2019;20(8):1070-82.

RTP RESEARCH TO PRACTICE

Cancer Treatment Reviews 86 (2020) 101993

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Evolving role of regorafenib for the treatment of advanced cancers

Axel Grothey[a,*], Jean-Yves Blay[b], Nick Pavlakis[c], Takayuki Yoshino[d], Jordi Bruix[e]

original reports

Microsatellite Instability in Patients With Stage III Colon Cancer Receiving Fluoropyrimidine With or Without Oxaliplatin: An ACCENT Pooled Analysis of 12 Adjuvant Trials

Romain Cohen, MD, PhD[1,2]; Julien Taieb, MD, PhD[3]; Jack Fiskum[2]; Greg Yothers, PhD[4]; Richard Goldberg, MD[5]; Takayuki Yoshino, MD[6]; Steven Alberts, MD[7]; Carmen Allegra, MD[8]; Aimery de Gramont, MD, PhD[9]; Jean-Francois Seitz, MD[10]; Michael O'Connell, MD[7]; Daniel Haller, MD[11]; Norman Wolmark, MD[12]; Charles Erlichman, MD[7]; Alberto Zaniboni, MD[13]; Sara Lonardi, MD[14]; Rachel Kerr, MD[15]; Axel Grothey, MD[16]; Frank A. Sinicrope, MD[7]; Thierry André, MD[1]; and Qian Shi, PhD[2]

J Clin Oncol 2020;[Online ahead of print].

Comment

EGFR antibodies in resectable metastatic colorectal liver metastasis: more harm than benefit?

Gholami S, Grothey A. *Lancet Oncol* 2020;21(3):324-26.

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*

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Pembrolizumab in MSI-H–dMMR Advanced Colorectal Cancer — A New Standard of Care

Axel Grothey, M.D.

Celecoxib in Addition to Standard Adjuvant Therapy with 5-Fluorouracil, Leucovorin, Oxaliplatin (FOLFOX) in Stage III Colon Cancer: Results from CALGB/SWOG 80702

Meyerhardt JA et al.

ASCO 2020;Abstract 4003.

Conclusions

- The addition of celecoxib to FOLFOX adjuvant therapy in stage III colon cancer did not significantly improve disease-free or overall survival.
- Tumor blocks, blood and questionnaire data were obtained from ~70% of participants to allow for extensive correlatives to learn more about stage III colon cancer biology and behavior.
- Several aspirin studies as adjuvant therapy are ongoing or pending maturation to report.

Meyerhardt JA et al. ASCO 2020;Abstract 4003.

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.

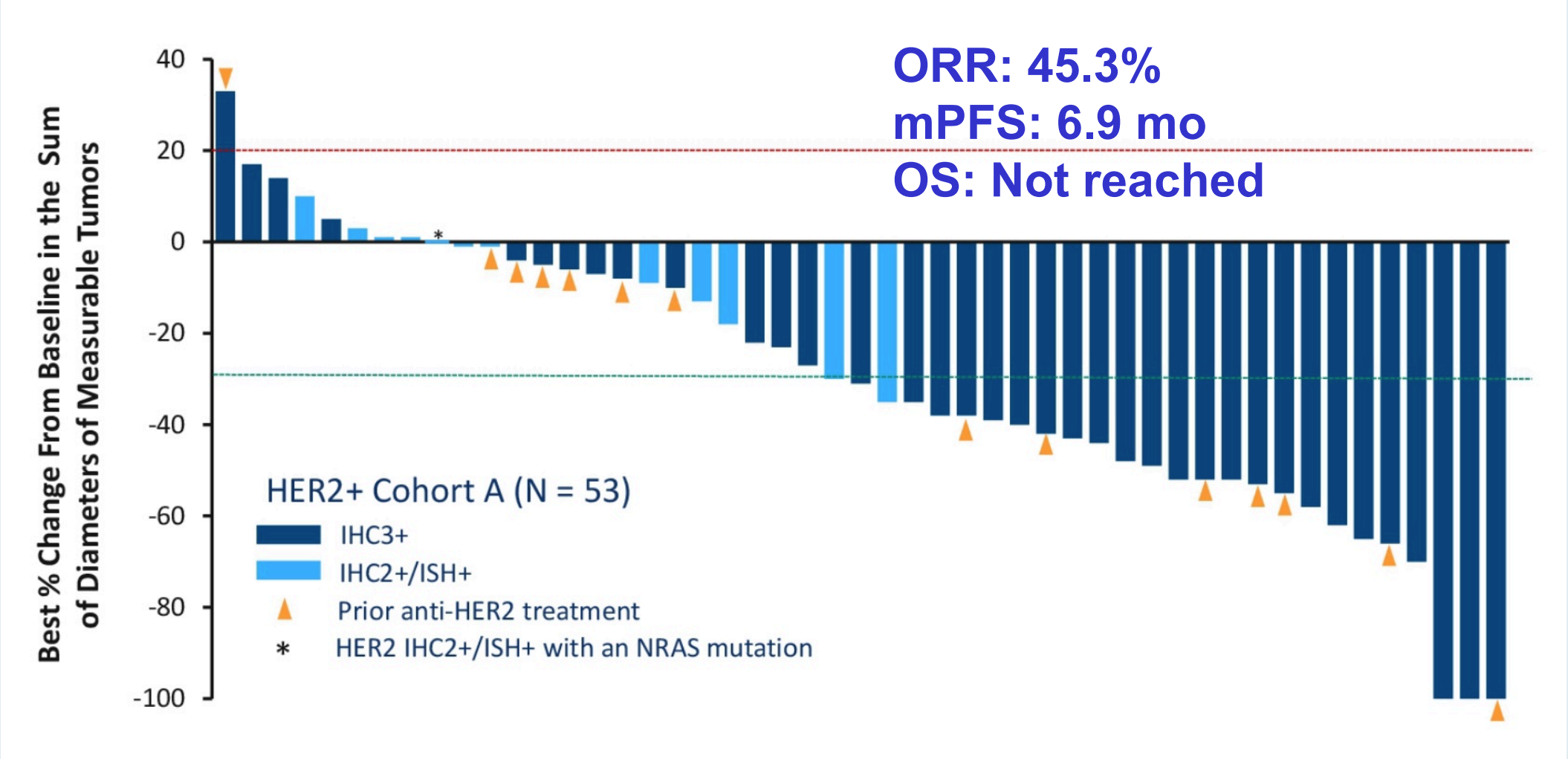
ASCO 2020;Abstract 4000.

DESTINY-CRC01: Response Rates

	HER2+ Cohort A (N = 53)
Confirmed ORR by ICR	**45.3% (n = 24)** (95% CI, 31.6%-59.6%)
CR	1.9% (n = 1)
PR	43.4% (n = 23)
SD	37.7% (n = 20)
PD	9.4% (n = 5)
Not evaluable	7.5% (n = 4)[a]
Disease control rate	83.0% (95% CI, 70.2%-91.9%)
Duration of response, median	Not reached (95% CI, 4.2 months-NE)

Siena S et al. ASCO 2020;Abstract 4000.

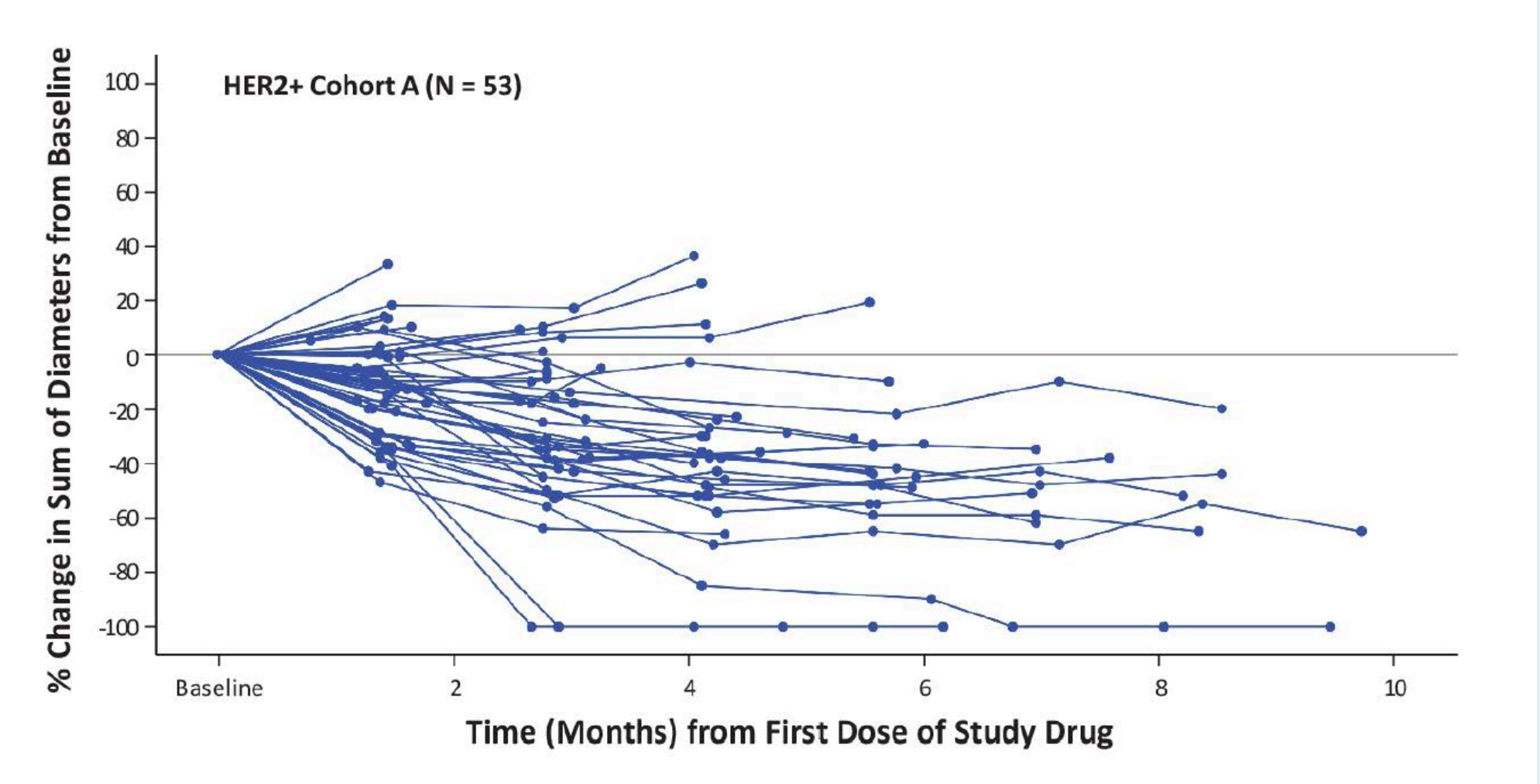
DESTINY-CRC01: Best Change in Tumor Size Over Time



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.

J Surg Oncol. 2020 June ; 121(8): 1320–1328. doi:10.1002/jso.25899.

Comprehensive tumor profiling reveals unique molecular differences between peritoneal metastases and primary colorectal adenocarcinoma

Matthew K. Stein, MD[1], Forrest W. Williard, BS[2], Joanne Xiu, PhD[3], Miriam W. Tsao, MD[4], Michael G. Martin, MD[5], Benjamin W. Deschner, MD[4], Paxton V. Dickson, MD[4], Evan S. Glazer, MD, PhD[4], Danny Yakoub, MD, PhD[4], David Shibata, MD[4], Axel F. Grothey, MD[5], Philip A. Philip, MD, PhD[6], Jimmy J. Hwang, MD[7], Anthony F. Shields, MD, PhD[6], John L. Marshall, MD[8], W. Michael Korn, MD[3], Heinz-Josef Lenz, MD[9], Jeremiah L. Deneve, DO[4]

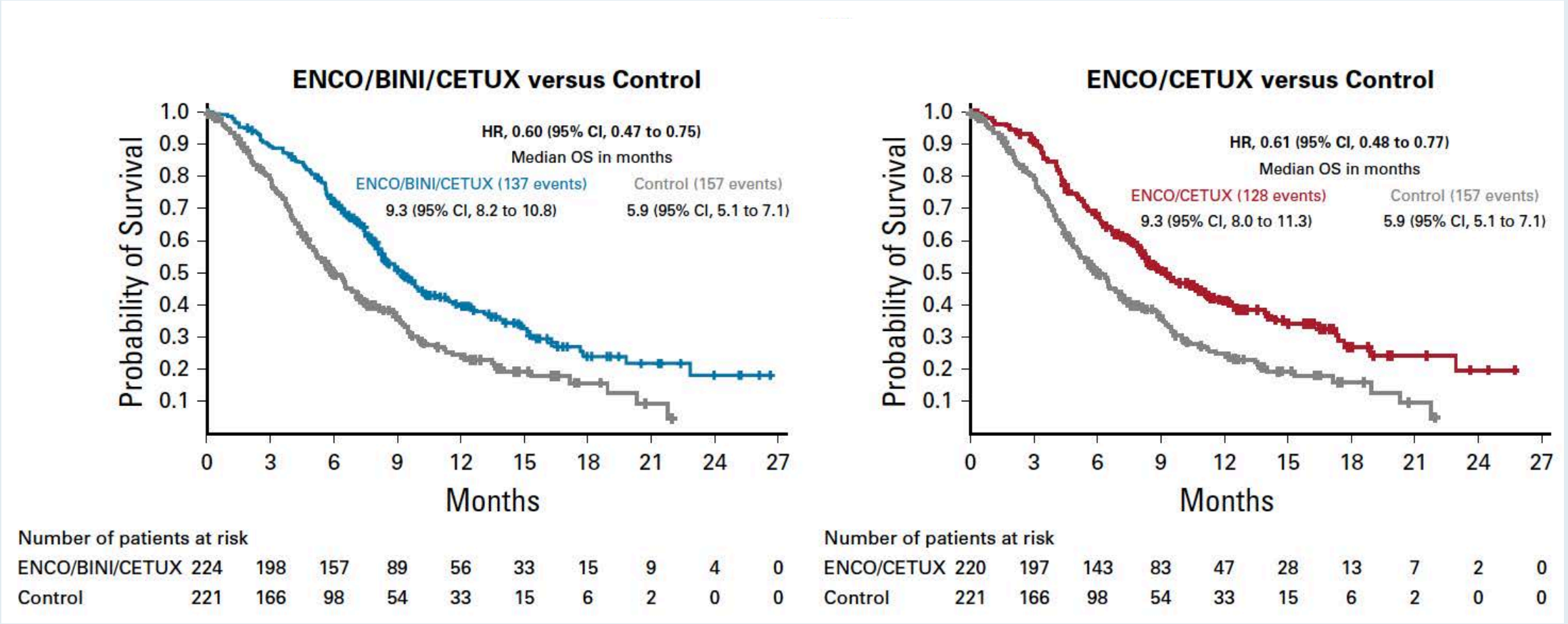
rapid communications

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



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

RTP RESEARCH TO PRACTICE

JAMA Network Open

Original Investigation | Oncology

Total Neoadjuvant Therapy vs Standard Therapy in Locally Advanced Rectal Cancer

A Systematic Review and Meta-analysis

Anup Kasi, MD, MPH; Saqib Abbasi, MD; Shivani Handa, MD; Raed Al-Rajabi, MD; Anwaar Saeed, MD; Joaquina Baranda, MD; Weijing Sun, MD

JAMA Netw Open 2020;3(12):e2030097.

JAMA Network Open

Invited Commentary | Oncology

Personalizing Treatment for Rectal Cancer

Total Neoadjuvant Therapy Is Leading the Way

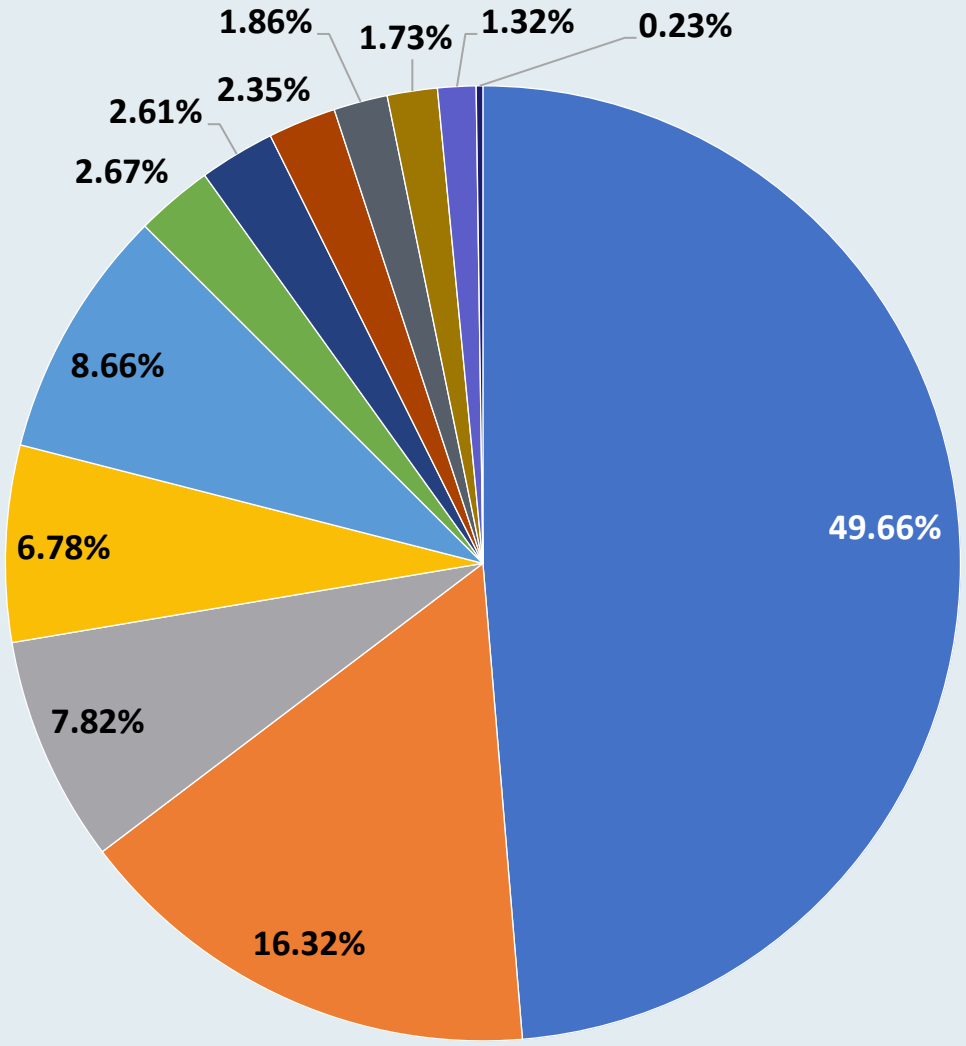
Noam VanderWalde, MD, MS; Axel Grothey, MD

JAMA Netw Open 2020;3(12):e2030508.

Comprehensive Molecular Analysis of Microsatellite-Stable (MSS) Tumors with High Mutational Burden in Gastrointestinal (GI) Cancers

Wang J et al.
ASCO 2020;Abstract 3631.

Cancer Type



- Colorectal Adenocarcinoma
- Pancreatic cancer
- Cholangiocarcinoma
- Gastric Adenocarcinoma
- Esophageal Cancer
- Small Intestinal Malignancies
- Esophagogastric Junction Carcinoma
- Appendiceal Cancer
- Liver Hepatocellular Carcinoma
- Gastrointestinal Stromal Tumors (GIST)
- Anal Carcinoma
- Gastroesophageal, unclear

Wang J et al. ASCO 2020;Abstract 3631.

Research

JAMA Oncology | Original Investigation

Treatment-Related Adverse Events of PD-1 and PD-L1 Inhibitors in Clinical Trials

A Systematic Review and Meta-analysis

Yucai Wang, MD, PhD; Shouhao Zhou, PhD; Fang Yang, MD, PhD; Xinyue Qi, MS; Xin Wang, MD; Xiaoxiang Guan, MD, PhD; Chan Shen, PhD; Narjust Duma, MD; Jesus Vera Aguilera, MC; Ashish Chintakuntlawar, MD; Katharine A. Price, MD; Julian R. Molina, MD, PhD; Lance C. Pagliaro, MD; Thorvardur R. Halfdanarson, MD; Axel Grothey, MD; Svetomir N. Markovic, MD, PhD; Grzegorz S. Nowakowski, MD; Stephen M. Ansell, MD, PhD; Michael L. Wang, MD

JAMA Oncol 2019;5(7):1008-19.

Meet The Professor with Dr Grothey

MODULE 1: Cases and Questions from Drs Schafer and Shehadeh

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MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

MODULE 4: Key Recent Data Sets

RTP
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TO PRACTICE

Selection and Sequencing of Therapy for Patients with Advanced Gastroesophageal Cancers

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TO PRACTICE

Regulatory and reimbursement issues aside, in which line of therapy would you generally recommend an anti-PD-1/PD-L1 antibody (with or without chemotherapy) for a 65-year-old patient with metastatic HER2-negative, microsatellite-stable (MSS) adenocarcinoma of the gastroesophageal junction (GEJ) with a PD-L1 combined positive score (CPS) of 0?

 PROFESSOR DIRK ARNOLD, MD, PHD	Beyond third line — nivolumab or pembrolizumab
 TANIOS BEKAII-SAAB, MD	Would not recommend an anti-PD-1/PD-L1 antibody
 JOHANNA BENDELL, MD	Beyond third line — nivolumab
 DANIEL CATENACCI, MD	Would not recommend an anti-PD-1/PD-L1 antibody
 KRISTEN K CIOMBOR, MD, MSCI	Would not recommend an anti-PD-1/PD-L1 antibody
 AXEL GROTHEY, MD	Would not recommend an anti-PD-1/PD-L1 antibody
 WELLS A MESSERSMITH, MD	Beyond third line — pembrolizumab
 EILEEN M O'REILLY, MD	First line — FOLFOX/nivolumab
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Beyond third line — pembrolizumab
 ALAN P VENOOK, MD	Would not recommend an anti-PD-1/PD-L1 antibody
 ZEV WAINBERG, MD, MSC	Would not recommend an anti-PD-1/PD-L1 antibody

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in which line of therapy would you generally recommend an anti-PD-1/PD-L1 antibody (with or without chemotherapy) for a 65-year-old patient with metastatic HER2-negative, MSS adenocarcinoma of the GEJ with a PD-L1 CPS of 1?

 PROFESSOR DIRK ARNOLD, MD, PHD	Third line — nivolumab or pembrolizumab
 TANIOS BEKAII-SAAB, MD	Beyond third line — pembrolizumab
 JOHANNA BENDELL, MD	Third line — pembrolizumab
 DANIEL CATENACCI, MD	Beyond third line — pembrolizumab
 KRISTEN K CIOMBOR, MD, MSCI	Third line — pembrolizumab
 AXEL GROTHEY, MD	Third line — pembrolizumab
 WELLS A MESSERSMITH, MD	Third line — pembrolizumab
 EILEEN M O'REILLY, MD	First line — FOLFOX/nivolumab
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Third line — pembrolizumab
 ALAN P VENOOK, MD	Would not recommend an anti-PD-1/PD L1 antibody
 ZEV WAINBERG, MD, MSC	Third line — pembrolizumab or nivolumab

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in which line of therapy would you generally recommend an anti-PD-1/PD-L1 antibody (with or without chemotherapy) for a 65-year-old patient with metastatic HER2-negative, MSS adenocarcinoma of the GEJ with a PD-L1 CPS of 5?

 PROFESSOR DIRK ARNOLD, MD, PHD	First line — pembrolizumab
 TANIOS BEKAII-SAAB, MD	First line — nivolumab/FOLFOX
 JOHANNA BENDELL, MD	First line — nivolumab/FOLFOX
 DANIEL CATENACCI, MD	First line — nivolumab/FOLFOX
 KRISTEN K CIOMBOR, MD, MSCI	First line — nivolumab/FOLFOX
 AXEL GROTHEY, MD	First line — nivolumab/FOLFOX
 WELLS A MESSERSMITH, MD	Third line — pembrolizumab
 EILEEN M O'REILLY, MD	First line — nivolumab/FOLFOX
 PHILIP AGOP PHILIP, MD, PHD, FRCP	First line — nivolumab
 ALAN P VENOOK, MD	First line — nivolumab or pembrolizumab + FOLFOX
 ZEV WAINBERG, MD, MSC	First line — nivolumab + FOLFOX or CAPOX

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in which line of therapy would you generally recommend an anti-PD-1/PD-L1 antibody (with or without chemotherapy) for a 65-year-old patient with metastatic HER2-negative, MSS adenocarcinoma of the GEJ with a PD-L1 CPS of 10?

 PROFESSOR DIRK ARNOLD, MD, PHD	First line — pembrolizumab
 TANIOS BEKAII-SAAB, MD	First line — pembrolizumab/FOLFOX
 JOHANNA BENDELL, MD	First line — nivolumab/FOLFOX
 DANIEL CATENACCI, MD	First line — pembrolizumab/FOLFOX
 KRISTEN K CIOMBOR, MD, MSCI	First line — pembrolizumab/FOLFOX
 AXEL GROTHEY, MD	First line — nivolumab/FOLFOX
 WELLS A MESSERSMITH, MD	Second line — pembrolizumab
 EILEEN M O'REILLY, MD	First line — nivolumab/FOLFOX
 PHILIP AGOP PHILIP, MD, PHD, FRCP	First line — nivolumab
 ALAN P VENOOK, MD	First line — nivolumab or pembrolizumab + FOLFOX
 ZEV WAINBERG, MD, MSC	First line — nivolumab + FOLFOX or CAPOX

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in which line of therapy would you generally recommend an anti-PD-1/PD-L1 antibody (with or without chemotherapy) for a 65-year-old patient with metastatic HER2-negative, microsatellite instability (MSI)-high adenocarcinoma of the GEJ?

 PROFESSOR DIRK ARNOLD, MD, PHD	First line — pembrolizumab
 TANIOS BEKAII-SAAB, MD	First line — pembrolizumab
 JOHANNA BENDELL, MD	First line — nivolumab/FOLFOX or possibly pembrolizumab
 DANIEL CATENACCI, MD	First line — nivolumab/FOLFOX, possibly nivolumab monotherapy
 KRISTEN K CIOMBOR, MD, MSCI	Second line — pembrolizumab
 AXEL GROTHEY, MD	First line — pembrolizumab
 WELLS A MESSERSMITH, MD	Second line — pembrolizumab
 EILEEN M O'REILLY, MD	First line — pembrolizumab
 PHILIP AGOP PHILIP, MD, PHD, FRCP	First line — pembrolizumab
 ALAN P VENOOK, MD	First line — nivolumab or pembrolizumab
 ZEV WAINBERG, MD, MSC	First line — pembrolizumab

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in which line of therapy would you generally recommend an anti-PD-1/PD-L1 antibody (with or without chemotherapy) for a 65-year-old patient with metastatic HER2-negative, MSS squamous cell carcinoma of the esophagus with a PD-L1 CPS of 0?

 PROFESSOR DIRK ARNOLD, MD, PHD	Second line — nivolumab
 TANIOS BEKAII-SAAB, MD	First line — pembrolizumab/FOLFOX
 JOHANNA BENDELL, MD	First line — pembrolizumab/FOLFOX
 DANIEL CATENACCI, MD	Would not recommend an anti-PD-1/PD-L1 antibody
 KRISTEN K CIOMBOR, MD, MSCI	Would not recommend an anti-PD-1/PD-L1 antibody
 AXEL GROTHEY, MD	Would not recommend an anti-PD-1/PD-L1 antibody
 WELLS A MESSERSMITH, MD	First line — nivolumab
 EILEEN M O'REILLY, MD	First line — pembrolizumab/FOLFOX
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Second line — pembrolizumab
 ALAN P VENOOK, MD	Second line — nivolumab or pembrolizumab
 ZEV WAINBERG, MD, MSC	First line — pembrolizumab + 5-FU/platinum

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in which line of therapy would you generally recommend an anti-PD-1/PD-L1 antibody (with or without chemotherapy) for a 65-year-old patient with metastatic HER2-negative, MSS squamous cell carcinoma of the esophagus with a PD-L1 CPS of 1?

 PROFESSOR DIRK ARNOLD, MD, PHD	Second line — nivolumab
 TANIOS BEKAII-SAAB, MD	First line — pembrolizumab/FOLFOX
 JOHANNA BENDELL, MD	First line — pembrolizumab/FOLFOX
 DANIEL CATENACCI, MD	Second line — pembrolizumab
 KRISTEN K CIOMBOR, MD, MSCI	Second line — nivolumab
 AXEL GROTHEY, MD	Third line — pembrolizumab
 WELLS A MESSERSMITH, MD	Second line — nivolumab
 EILEEN M O'REILLY, MD	First line — pembrolizumab/FOLFOX
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Second line — pembrolizumab
 ALAN P VENOOK, MD	Second line — nivolumab or pembrolizumab
 ZEV WAINBERG, MD, MSC	First line — pembrolizumab + 5-FU/platinum

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in which line of therapy would you generally recommend an anti-PD-1/PD-L1 antibody (with or without chemotherapy) for a 65-year-old patient with metastatic HER2-negative, MSS squamous cell carcinoma of the esophagus with a PD-L1 CPS of 5?

 PROFESSOR DIRK ARNOLD, MD, PHD	First line — pembrolizumab + platinum-based chemo with taxane or 5-FU
 TANIOS BEKAII-SAAB, MD	First line — pembrolizumab/FOLFOX
 JOHANNA BENDELL, MD	First line — pembrolizumab/FOLFOX
 DANIEL CATENACCI, MD	Second line — pembrolizumab
 KRISTEN K CIOMBOR, MD, MSCI	Second line — nivolumab
 AXEL GROTHEY, MD	Second line — pembrolizumab
 WELLS A MESSERSMITH, MD	Second line — nivolumab
 EILEEN M O'REILLY, MD	First line — pembrolizumab/FOLFOX
 PHILIP AGOP PHILIP, MD, PHD, FRCP	First line — pembrolizumab
 ALAN P VENOOK, MD	Second line — nivolumab or pembrolizumab
 ZEV WAINBERG, MD, MSC	First line — pembrolizumab + 5-FU/platinum

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in which line of therapy would you generally recommend an anti-PD-1/PD-L1 antibody (with or without chemotherapy) for a 65-year-old patient with metastatic HER2-negative, MSS squamous cell carcinoma of the esophagus with a PD-L1 CPS of 10?

 PROFESSOR DIRK ARNOLD, MD, PHD	First line — pembrolizumab + platinum-based chemo with taxane or 5-FU
 TANIOS BEKAII-SAAB, MD	First line — pembrolizumab/FOLFOX
 JOHANNA BENDELL, MD	First line — pembrolizumab/FOLFOX
 DANIEL CATENACCI, MD	First line — pembrolizumab/FOLFOX
 KRISTEN K CIOMBOR, MD, MSCI	Second line — pembrolizumab
 AXEL GROTHEY, MD	First line — pembrolizumab
 WELLS A MESSERSMITH, MD	Second line — pembrolizumab
 EILEEN M O'REILLY, MD	First line — nivolumab/FOLFOX
 PHILIP AGOP PHILIP, MD, PHD, FRCP	First line — pembrolizumab
 ALAN P VENOOK, MD	Second line — nivolumab or pembrolizumab
 ZEV WAINBERG, MD, MSC	First line — pembrolizumab + 5-FU/platinum

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?

 PROFESSOR DIRK ARNOLD, MD, PHD	Ramucirumab/paclitaxel
 TANIOS BEKAII-SAAB, MD	Test for PD-L1 CPS and administer pembrolizumab if ≥10
 JOHANNA BENDELL, MD	Test for PD-L1 CPS and administer pembrolizumab if ≥10
 DANIEL CATENACCI, MD	FOLFIRI/ramucirumab
 KRISTEN K CIOMBOR, MD, MSCI	FOLFIRI/ramucirumab
 AXEL GROTHEY, MD	Test for PD-L1 CPS and administer pembrolizumab if ≥10
 WELLS A MESSERSMITH, MD	Pembrolizumab if PD-L1 CPS ≥10, else ramucirumab/paclitaxel
 EILEEN M O'REILLY, MD	Ramucirumab/paclitaxel
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Ramucirumab/paclitaxel
 ALAN P VENOOK, MD	Ramucirumab/paclitaxel
 ZEV WAINBERG, MD, MSC	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?

 PROFESSOR DIRK ARNOLD, MD, PHD	Ramucirumab/paclitaxel
 TANIOS BEKAII-SAAB, MD	Trastuzumab deruxtecan
 JOHANNA BENDELL, MD	Test for PD-L1 CPS and administer pembrolizumab if ≥10%
 DANIEL CATENACCI, MD	Continue trastuzumab and switch chemotherapy
 KRISTEN K CIOMBOR, MD, MSCI	FOLFIRI/ramucirumab
 AXEL GROTHEY, MD	Trastuzumab deruxtecan
 WELLS A MESSERSMITH, MD	Test for PD-L1 CPS and administer pembrolizumab if ≥10%
 EILEEN M O'REILLY, MD	Trastuzumab deruxtecan
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Trastuzumab deruxtecan
 ALAN P VENOOK, MD	Ramucirumab/paclitaxel
 ZEV WAINBERG, MD, MSC	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?

 PROFESSOR DIRK ARNOLD, MD, PHD	Third line
 TANIOS BEKAII-SAAB, MD	Second line
 JOHANNA BENDELL, MD	Second line
 DANIEL CATENACCI, MD	Third line
 KRISTEN K CIOMBOR, MD, MSCI	Third line
 AXEL GROTHEY, MD	Second line
 WELLS A MESSERSMITH, MD	Third line
 EILEEN M O'REILLY, MD	Second line
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Second line
 ALAN P VENOOK, MD	Second line
 ZEV WAINBERG, MD, MSC	Second line

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what adjuvant systemic therapy would you currently recommend to a patient with HER2-negative, MSS adenocarcinoma of the GEJ (PD-L1 CPS ≥1) who receives neoadjuvant FLOT (docetaxel/oxaliplatin/leucovorin/5-FU) and has residual disease at surgery?

 PROFESSOR DIRK ARNOLD, MD, PHD	Consider chemoradiation therapy
 TANIOS BEKAII-SAAB, MD	Nivolumab
 JOHANNA BENDELL, MD	FLOT
 DANIEL CATENACCI, MD	FLOT for 2 months adjuvantly
 KRISTEN K CIOMBOR, MD, MSCI	FLOT
 AXEL GROTHEY, MD	FLOT
 WELLS A MESSERSMITH, MD	FLOT
 EILEEN M O'REILLY, MD	Anti-PD-1/PD-L1 monotherapy
 PHILIP AGOP PHILIP, MD, PHD, FRCP	FOLFOX
 ALAN P VENOOK, MD	Nivolumab
 ZEV WAINBERG, MD, MSC	FLOT

RTP RESEARCH TO PRACTICE

Evidence-Based Management of Advanced Hepatocellular Carcinoma (HCC)

RTP
RESEARCH
TO PRACTICE

What would be your current preferred first-line systemic treatment for a 65-year-old patient with hepatocellular carcinoma (HCC), a Child-Pugh A score and a performance status (PS) of 0?

 PROFESSOR DIRK ARNOLD, MD, PHD	Atezolizumab/bevacizumab	 WELLS A MESSERSMITH, MD	Atezolizumab/bevacizumab
 TANIOS BEKAII-SAAB, MD	Atezolizumab/bevacizumab	 EILEEN M O'REILLY, MD	Atezolizumab/bevacizumab
 JOHANNA BENDELL, MD	Atezolizumab/bevacizumab	 PHILIP AGOP PHILIP, MD, PHD, FRCP	Atezolizumab/bevacizumab
 DANIEL CATENACCI, MD	Atezolizumab/bevacizumab	 ALAN P VENOOK, MD	Atezolizumab/bevacizumab
 KRISTEN K CIOMBOR, MD, MSCI	Atezolizumab/bevacizumab	 ZEV WAINBERG, MD, MSC	Atezolizumab/bevacizumab
 AXEL GROTHEY, MD	Atezolizumab/bevacizumab		

RTP RESEARCH TO PRACTICE

What would be your current preferred first-line systemic treatment for a 65-year-old patient with HCC, a Child-Pugh A score and Grade 1 esophageal varices being managed with a beta blocker?

 PROFESSOR DIRK ARNOLD, MD, PHD	Atezolizumab/bevacizumab
 TANIOS BEKAII-SAAB, MD	Atezolizumab/bevacizumab
 JOHANNA BENDELL, MD	Atezolizumab/bevacizumab
 DANIEL CATENACCI, MD	Atezolizumab/bevacizumab
 KRISTEN K CIOMBOR, MD, MSCI	Atezolizumab/bevacizumab
 AXEL GROTHEY, MD	Atezolizumab/bevacizumab
 WELLS A MESSERSMITH, MD	Atezolizumab/bevacizumab
 EILEEN M O'REILLY, MD	Lenvatinib
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Lenvatinib
 ALAN P VENOOK, MD	Lenvatinib
 ZEV WAINBERG, MD, MSC	Atezolizumab/bevacizumab

RTP RESEARCH TO PRACTICE

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?

 PROFESSOR DIRK ARNOLD, MD, PHD	Atezolizumab/bevacizumab
 TANIOS BEKAII-SAAB, MD	Atezolizumab/bevacizumab
 JOHANNA BENDELL, MD	Atezolizumab/bevacizumab
 DANIEL CATENACCI, MD	Atezolizumab/bevacizumab
 KRISTEN K CIOMBOR, MD, MSCI	Sorafenib
 AXEL GROTHEY, MD	Atezolizumab/bevacizumab
 WELLS A MESSERSMITH, MD	Atezolizumab/bevacizumab
 EILEEN M O'REILLY, MD	Lenvatinib
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Atezolizumab/bevacizumab
 ALAN P VENOOK, MD	Atezolizumab/bevacizumab
 ZEV WAINBERG, MD, MSC	Lenvatinib

RTP RESEARCH TO PRACTICE

Do you believe that more patients with unresectable HCC limited to the liver who in the past underwent liver-directed therapy such as TACE are now instead receiving initial systemic treatment (eg, atezolizumab/bevacizumab)?

 PROFESSOR DIRK ARNOLD, MD, PHD	Yes
 TANIOS BEKAII-SAAB, MD	Yes
 JOHANNA BENDELL, MD	No
 DANIEL CATENACCI, MD	No
 KRISTEN K CIOMBOR, MD, MSCI	No
 AXEL GROTHEY, MD	Yes
 WELLS A MESSERSMITH, MD	Yes
 EILEEN M O'REILLY, MD	Yes
 PHILIP AGOP PHILIP, MD, PHD, FRCP	No
 ALAN P VENOOK, MD	Yes
 ZEV WAINBERG, MD, MSC	Yes

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)?

 PROFESSOR DIRK ARNOLD, MD, PHD	Cabozantinib
 TANIOS BEKAII-SAAB, MD	Cabozantinib
 JOHANNA BENDELL, MD	Cabozantinib
 DANIEL CATENACCI, MD	Lenvatinib
 KRISTEN K CIOMBOR, MD, MSCI	Sorafenib
 AXEL GROTHEY, MD	Lenvatinib
 WELLS A MESSERSMITH, MD	Lenvatinib
 EILEEN M O'REILLY, MD	Lenvatinib
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Lenvatinib
 ALAN P VENOOK, MD	Lenvatinib
 ZEV WAINBERG, MD, MSC	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)?

 PROFESSOR DIRK ARNOLD, MD, PHD	Nivolumab
 TANIOS BEKAII-SAAB, MD	Atezolizumab/bevacizumab
 JOHANNA BENDELL, MD	Atezolizumab/bevacizumab
 DANIEL CATENACCI, MD	Atezolizumab/bevacizumab
 KRISTEN K CIOMBOR, MD, MSCI	Atezolizumab/bevacizumab
 AXEL GROTHEY, MD	Atezolizumab/bevacizumab
 WELLS A MESSERSMITH, MD	Atezolizumab/bevacizumab
 EILEEN M O'REILLY, MD	Nivolumab/ipilimumab
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Nivolumab/ipilimumab
 ALAN P VENOOK, MD	Atezolizumab/bevacizumab
 ZEV WAINBERG, MD, MSC	Ramucirumab

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 4 months and then experienced disease progression (AFP 2,500 ng/mL)?

 PROFESSOR DIRK ARNOLD, MD, PHD	Nivolumab
 TANIOS BEKAII-SAAB, MD	Atezolizumab/bevacizumab
 JOHANNA BENDELL, MD	Atezolizumab/bevacizumab
 DANIEL CATENACCI, MD	Atezolizumab/bevacizumab
 KRISTEN K CIOMBOR, MD, MSCI	Atezolizumab/bevacizumab
 AXEL GROTHEY, MD	Atezolizumab/bevacizumab
 WELLS A MESSERSMITH, MD	Atezolizumab/bevacizumab
 EILEEN M O'REILLY, MD	Nivolumab/ipilimumab
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Atezolizumab/bevacizumab
 ALAN P VENOOK, MD	Atezolizumab/bevacizumab
 ZEV WAINBERG, MD, MSC	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 B7 score and a PS of 1 who received first-line atezolizumab/bevacizumab with minimal toxicity, had stable disease for 14 months and then experienced disease progression (AFP 2,500 ng/mL)?

 PROFESSOR DIRK ARNOLD, MD, PHD	Nivolumab
 TANIOS BEKAII-SAAB, MD	Cabozantinib
 JOHANNA BENDELL, MD	Cabozantinib
 DANIEL CATENACCI, MD	Lenvatinib
 KRISTEN K CIOMBOR, MD, MSCI	Sorafenib
 AXEL GROTHEY, MD	Ramucirumab
 WELLS A MESSERSMITH, MD	Lenvatinib
 EILEEN M O'REILLY, MD	Lenvatinib
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Lenvatinib
 ALAN P VENOOK, MD	Lenvatinib
 ZEV WAINBERG, MD, MSC	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 B7 score and a PS of 1 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)?

 PROFESSOR DIRK ARNOLD, MD, PHD	Nivolumab
 TANIOS BEKAII-SAAB, MD	Atezolizumab/bevacizumab
 JOHANNA BENDELL, MD	Atezolizumab/bevacizumab
 DANIEL CATENACCI, MD	Atezolizumab/bevacizumab
 KRISTEN K CIOMBOR, MD, MSCI	Nivolumab
 AXEL GROTHEY, MD	Ramucirumab
 WELLS A MESSERSMITH, MD	Atezolizumab/bevacizumab
 EILEEN M O'REILLY, MD	Nivolumab/ipilimumab
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Nivolumab/ipilimumab
 ALAN P VENOOK, MD	Atezolizumab/bevacizumab
 ZEV WAINBERG, MD, MSC	Lenvatinib

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)?

 PROFESSOR DIRK ARNOLD, MD, PHD	Nivolumab
 TANIOS BEKAII-SAAB, MD	Cabozantinib
 JOHANNA BENDELL, MD	Cabozantinib
 DANIEL CATENACCI, MD	Ramucirumab
 KRISTEN K CIOMBOR, MD, MSCI	Ramucirumab
 AXEL GROTHEY, MD	Cabozantinib
 WELLS A MESSERSMITH, MD	Ramucirumab
 EILEEN M O'REILLY, MD	Nivolumab/ipilimumab
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Cabozantinib
 ALAN P VENOOK, MD	Cabozantinib
 ZEV WAINBERG, MD, MSC	Ramucirumab

RTP RESEARCH TO PRACTICE

Optimizing Personalized Treatment for Metastatic Colorectal Cancer (mCRC)

RTP
RESEARCH
TO PRACTICE

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?

 PROFESSOR DIRK ARNOLD, MD, PHD	Second line
 TANIOS BEKAII-SAAB, MD	Second line
 JOHANNA BENDELL, MD	Second line
 DANIEL CATENACCI, MD	Second line
 KRISTEN K CIOMBOR, MD, MSCI	Second line
 AXEL GROTHEY, MD	Second line
 WELLS A MESSERSMITH, MD	Third line or beyond
 EILEEN M O'REILLY, MD	Second line
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Second line
 ALAN P VENOOK, MD	Second line
 ZEV WAINBERG, MD, MSC	Second line

RTP RESEARCH TO PRACTICE

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

 PROFESSOR DIRK ARNOLD, MD, PHD	Encorafenib + cetuximab
 TANIOS BEKAII-SAAB, MD	Encorafenib + panitumumab
 JOHANNA BENDELL, MD	Encorafenib + panitumumab
 DANIEL CATENACCI, MD	Encorafenib + cetuximab
 KRISTEN K CIOMBOR, MD, MSCI	Encorafenib + panitumumab
 AXEL GROTHEY, MD	Encorafenib + panitumumab
 WELLS A MESSERSMITH, MD	Encorafenib + panitumumab
 EILEEN M O'REILLY, MD	Encorafenib + cetuximab
 PHILIP AGOP PHILIP, MD, PHD, FRCP	Encorafenib + panitumumab
 ALAN P VENOOK, MD	Encorafenib + panitumumab
 ZEV WAINBERG, MD, MSC	Encorafenib + binimetinib + cetuximab

RTP RESEARCH TO PRACTICE

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?

 PROFESSOR DIRK ARNOLD, MD, PHD	Pembrolizumab	 WELLS A MESSERSMITH, MD	Pembrolizumab
 TANIOS BEKAII-SAAB, MD	Pembrolizumab	 EILEEN M O'REILLY, MD	Pembrolizumab
 JOHANNA BENDELL, MD	Pembrolizumab	 PHILIP AGOP PHILIP, MD, PHD, FRCP	Pembrolizumab
 DANIEL CATENACCI, MD	Pembrolizumab	 ALAN P VENOOK, MD	Pembrolizumab
 KRISTEN K CIOMBOR, MD, MSCI	Pembrolizumab	 ZEV WAINBERG, MD, MSC	Pembrolizumab
 AXEL GROTHEY, MD	Pembrolizumab		

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Grothey

MODULE 1: Cases and Questions from Drs Schafer and Shehadeh

MODULE 2: Gastrointestinal Cancers Journal Club with Dr Grothey

MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

MODULE 4: Key Recent Data Sets

RTP
RESEARCH
TO PRACTICE

Gastric/Gastroesophageal Cancer

RTP
RESEARCH
TO PRACTICE

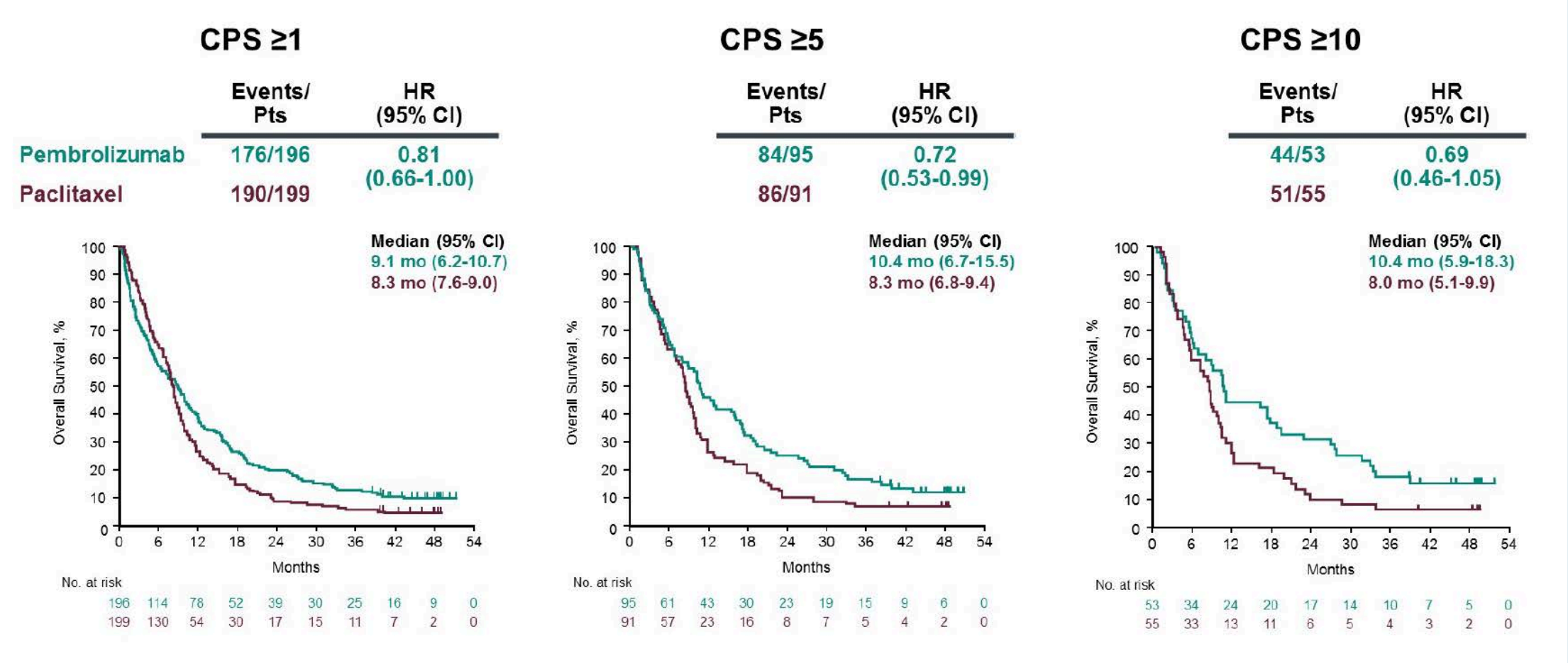
Pembrolizumab in Advanced Gastric or Gastroesophageal Cancer

- Accelerated approval of pembrolizumab monotherapy as third- or later-line therapy was based on the Phase II KEYNOTE-059 study
  - ORR: 11.6% (all patients), 15.5% (PD-L1-positive), 57% (MSI-high)
- Primary analysis of the Phase III KEYNOTE-061 trial of pembrolizumab versus paclitaxel as second-line therapy demonstrated that the primary endpoint of OS in patients with CPS ≥1 was not met
  - Median OS: Pembrolizumab 9.1 mo, paclitaxel 8.3 mo (HR 0.82; $p = 0.042$)
- Phase III KEYNOTE-062 trial evaluates pembrolizumab with or without chemotherapy versus chemotherapy as first-line therapy

Fuchs C et al. *JAMA Oncol* 2018;4(5):e180013; Shitara K et al. *Lancet* 2018;392(10142):123-33; Tabernero J et al. ASCO 2019; Abstract LBA4007; Shitara K et al. ESMO 2019;Abstract LBA44.

KEYNOTE-061: Updated Results with Additional 2 Years of Follow-Up

Overall Survival by CPS Score



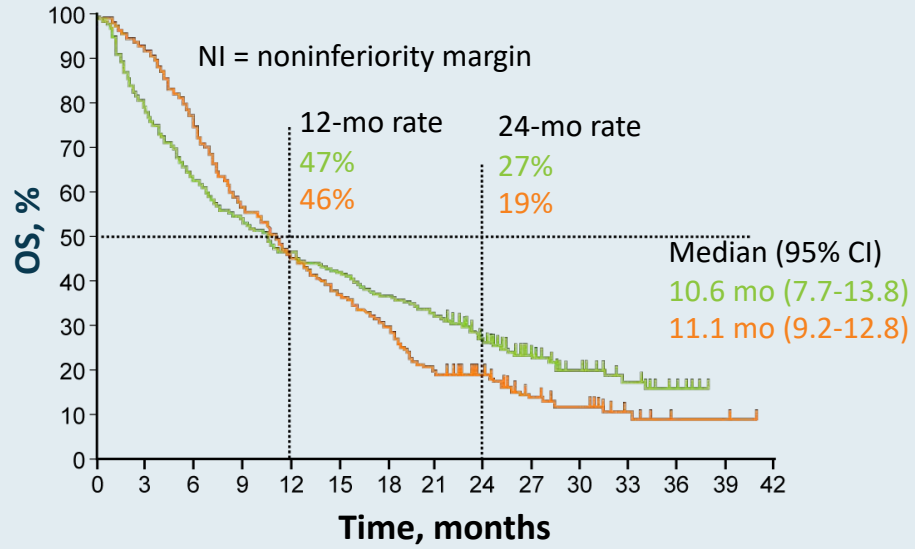
- No significant differences in PFS were observed between groups
- Response rates were numerically higher and more durable with pembrolizumab

Fuchs CS et al. ASCO 2020;Abstract 4503.

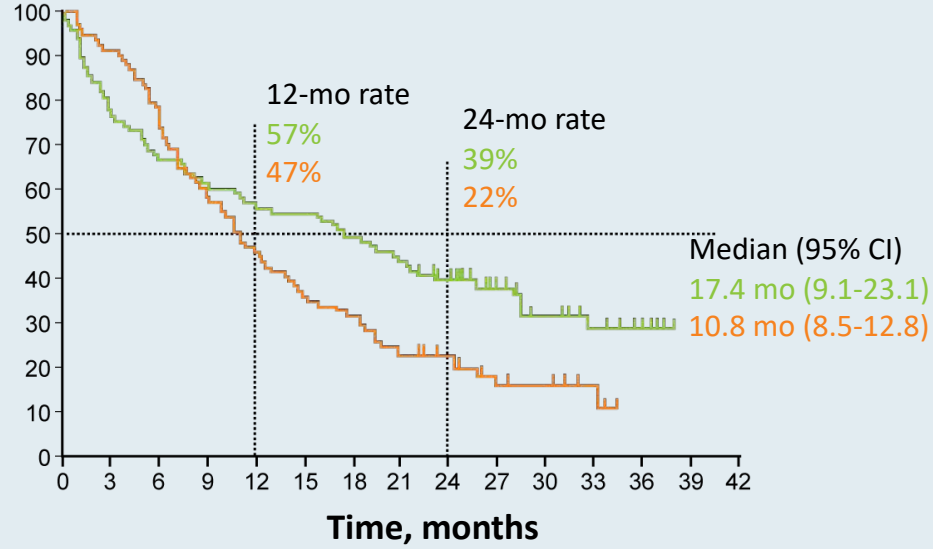
RTP RESEARCH TO PRACTICE

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

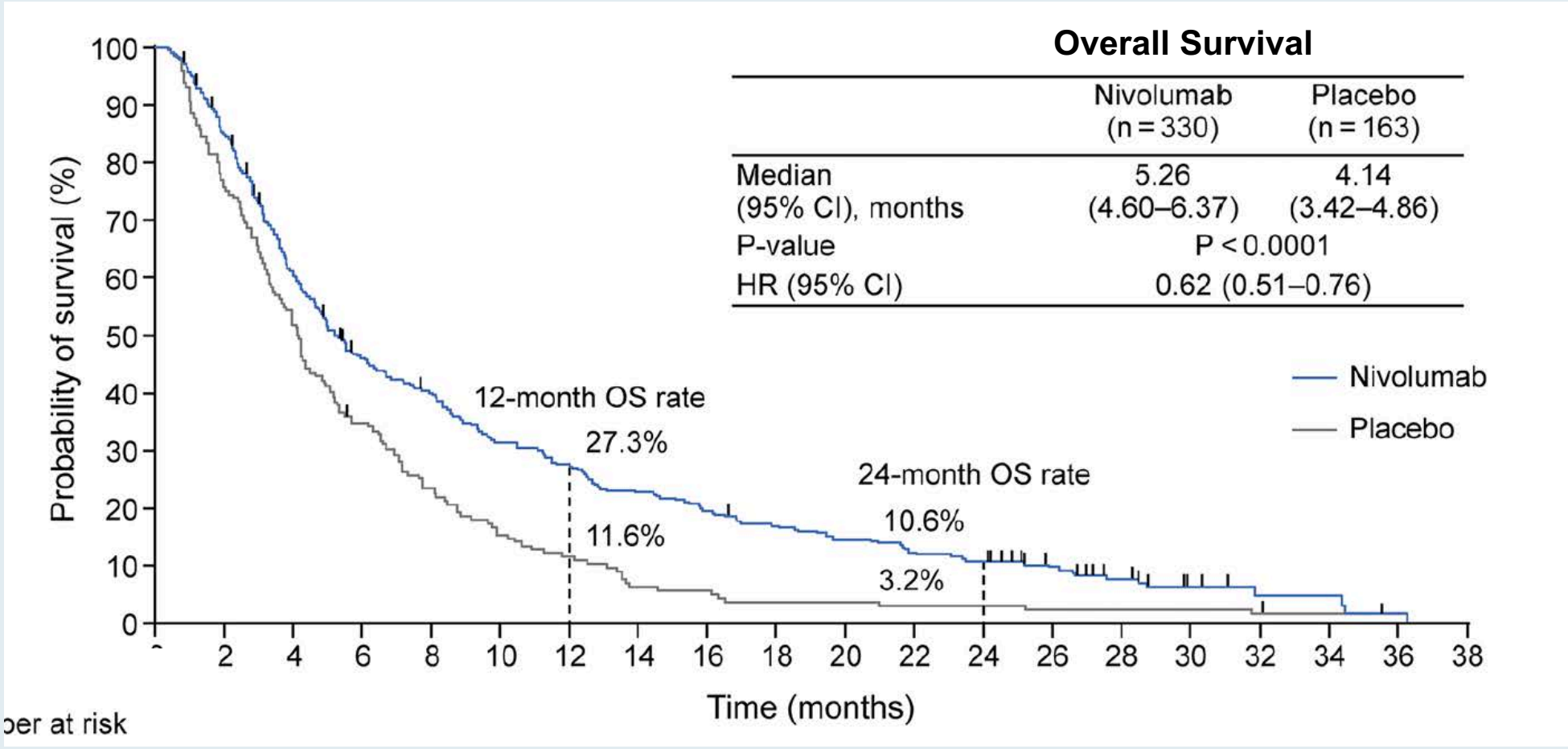
Gastric Cancer (2020) 23:510–519
https://doi.org/10.1007/s10120-019-01034-7

ORIGINAL ARTICLE

A phase 3 study of nivolumab in previously treated advanced gastric or gastroesophageal junction cancer (ATTRACTION-2): 2-year update data

Li-Tzong Chen[1,2] · Taroh Satoh[3] · Min-Hee Ryu[4] · Yee Chao[5] · Ken Kato[6] · Hyun Cheol Chung[7] · Jen-Shi Chen[8] · Kei Muro[9] · Won Ki Kang[10] · Kun-Huei Yeh[11,12] · Takaki Yoshikawa[13,26] · Sang Cheul Oh[14] · Li-Yuan Bai[15] · Takao Tamura[16,27] · Keun-Wook Lee[17] · Yasuo Hamamoto[18] · Jong Gwang Kim[19] · Keisho Chin[20] · Do-Youn Oh[21] · Keiko Minashi[22] · Jae Yong Cho[23] · Masahiro Tsuda[24] · Hiroki Sameshima[25] · Yoon-Koo Kang[4] · Narikazu Boku[6]

ATTRACTION-2: 2-Year Updated Results with Nivolumab in Previously Treated Advanced Gastric or GEJ Cancer



The OS benefit was observed regardless of tumor PD-L1 expression.

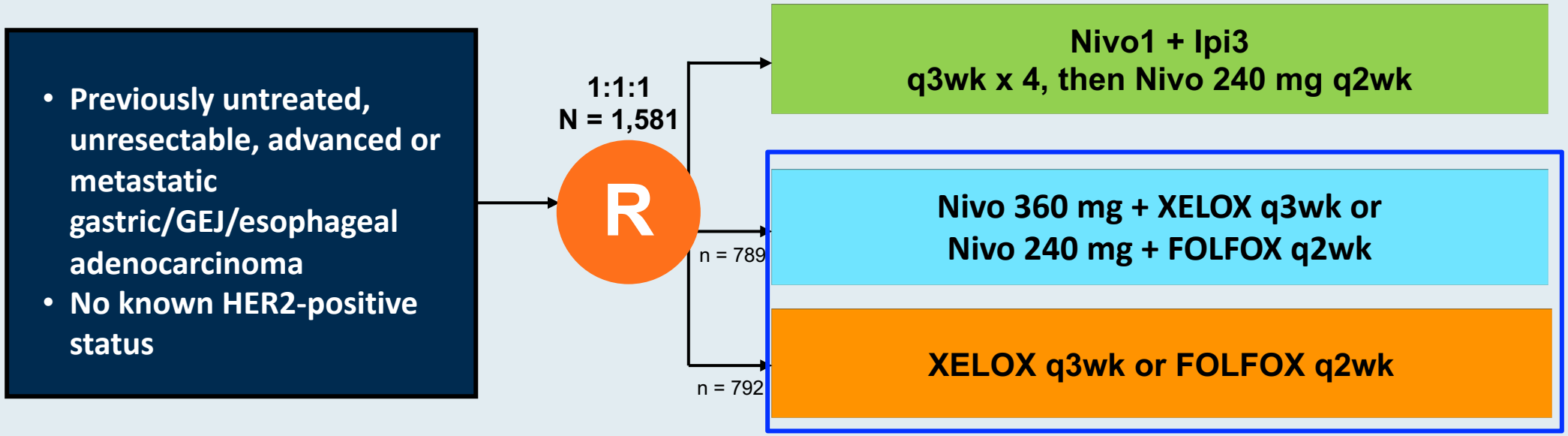
Chen LT et al. *Gastric Cancer* 2020;23(3):510-9.

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.

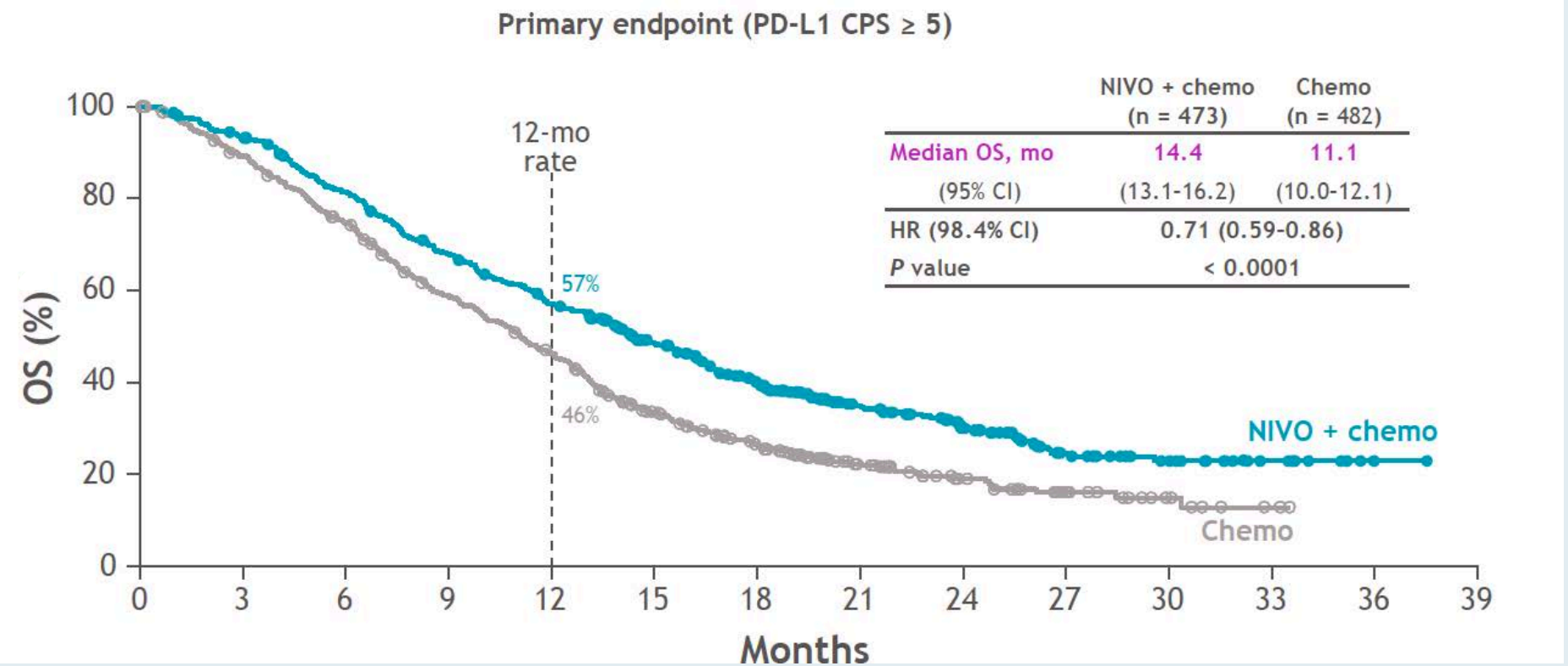
CheckMate 649 Phase III Schema



Co-Primary Endpoints
Progression-free survival (PFS),
Overall survival (OS)

Moehler M et al. ESMO 2020;Abstract LBA6.

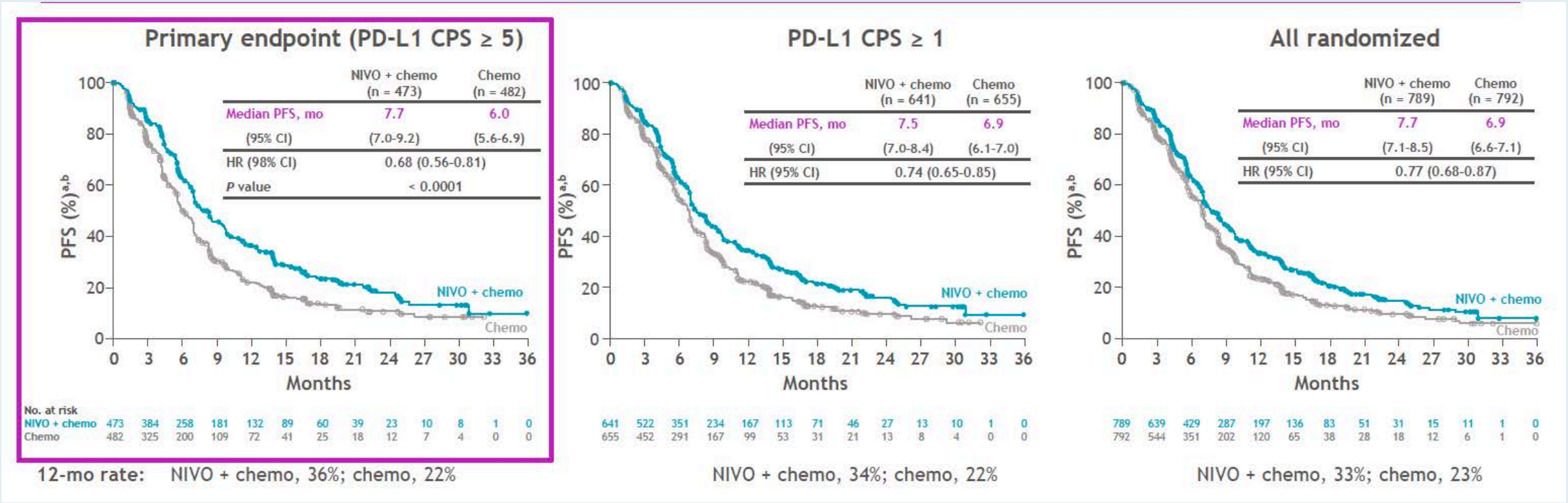
CheckMate 649: Overall Survival



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.

CheckMate 649: Progression-Free Survival



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

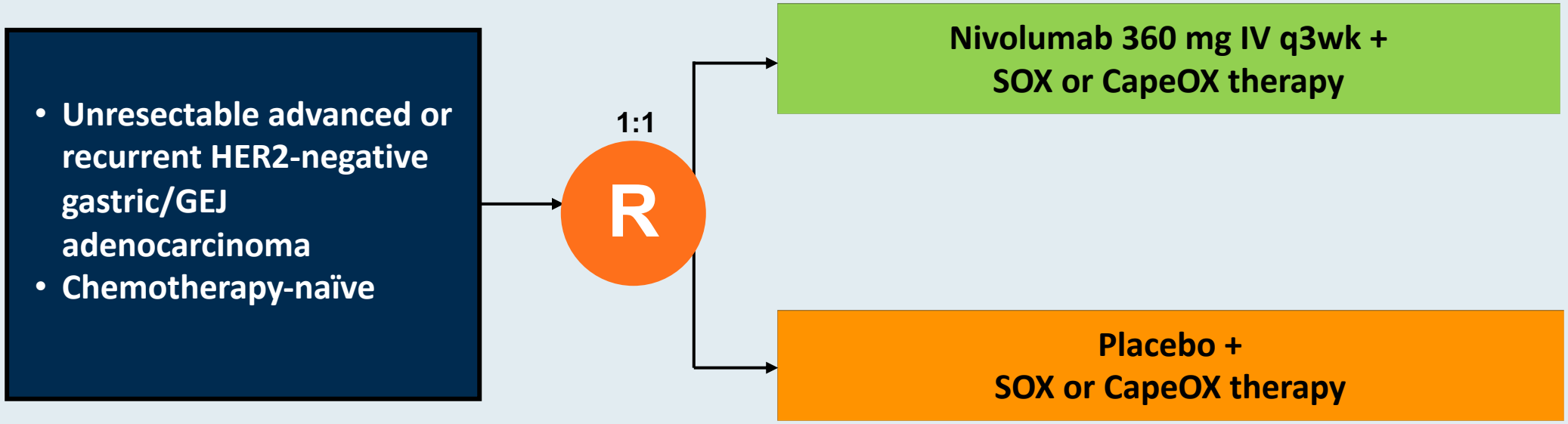
Boku N et al.

ESMO 2020;Abstract LBA7_PR.

ATTRACTION-4: Phase III Schema

- Study conducted at 130 centers in Japan, Taiwan and Korea

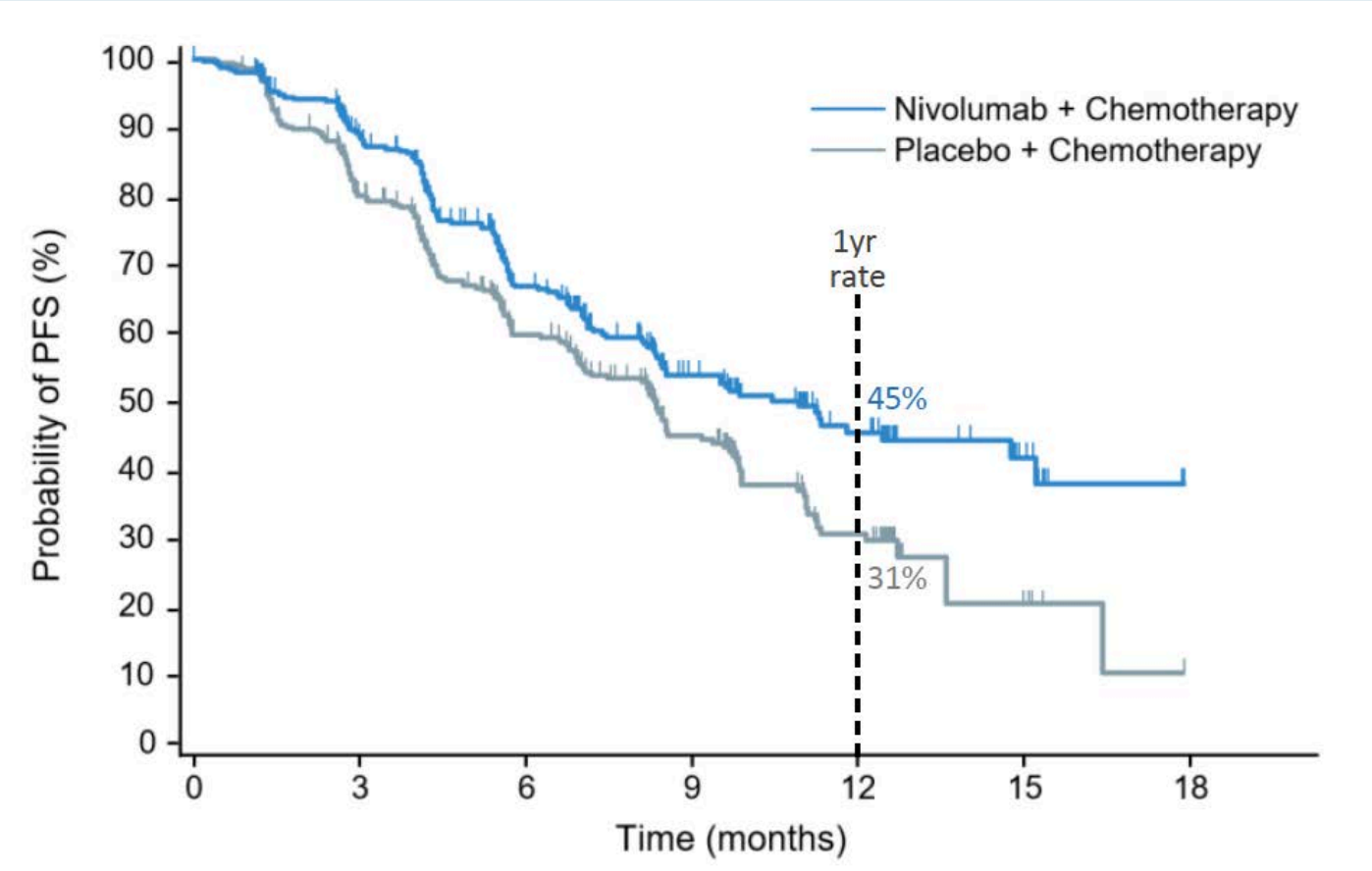
Clinical Trial Identifier: NCT02746796



Co-Primary Endpoints
Progression-free survival (PFS),
Overall survival (OS)

Boku N et al. ESMO 2020;Abstract LBA7_PR.

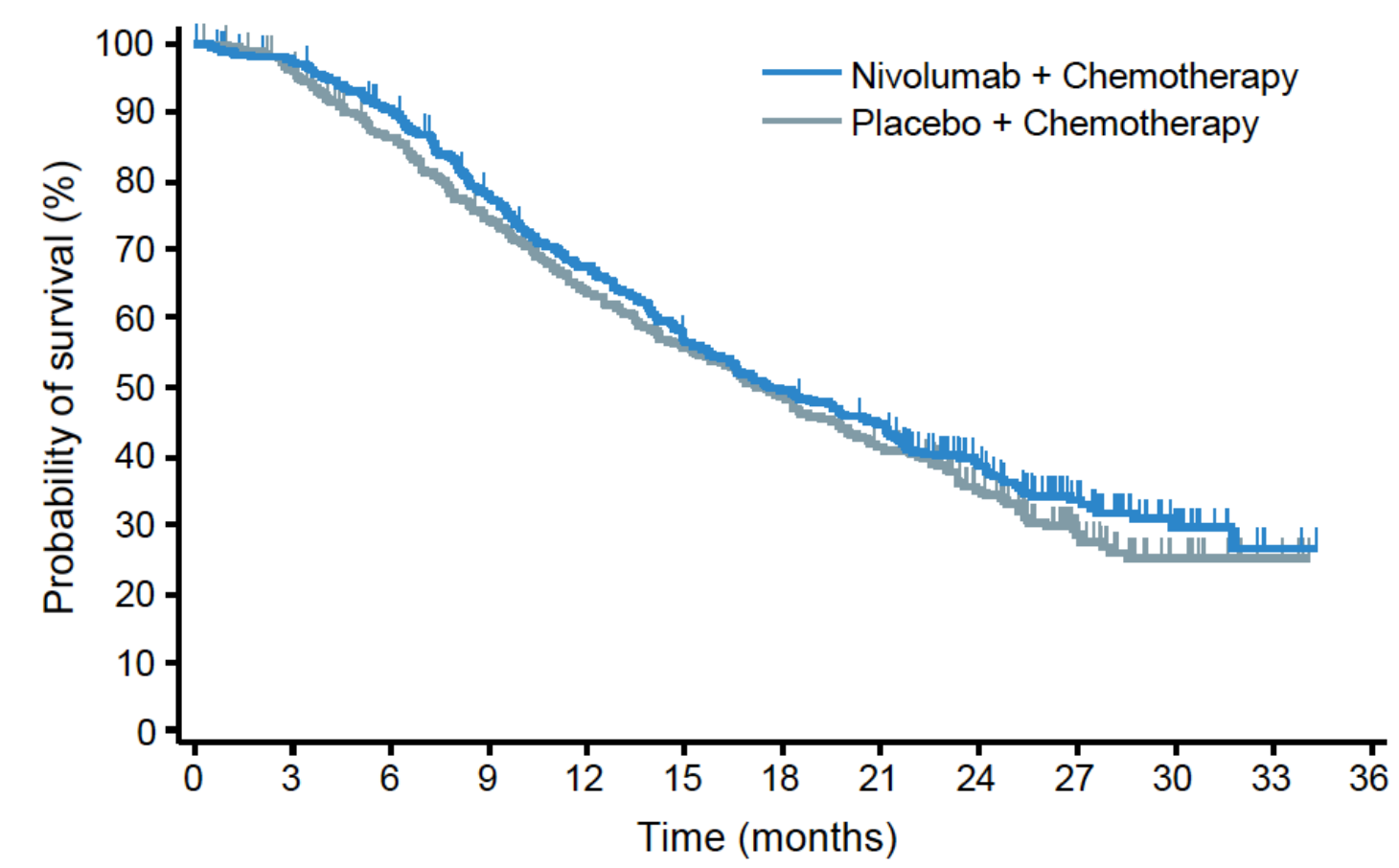
ATTRACTION-4: Interim Analysis of PFS



	Nivo + chemo (n = 362)	Placebo + chemo (n = 362)	HR (*p*-value)
Median PFS	10.45 mo	8.34 mo	0.68 (0.0007)
1-yr PFS rate	45.4%	30.6%	—

Boku N et al. ESMO 2020;Abstract LBA7_PR.

ATTRACTION-4: Final Analysis of OS



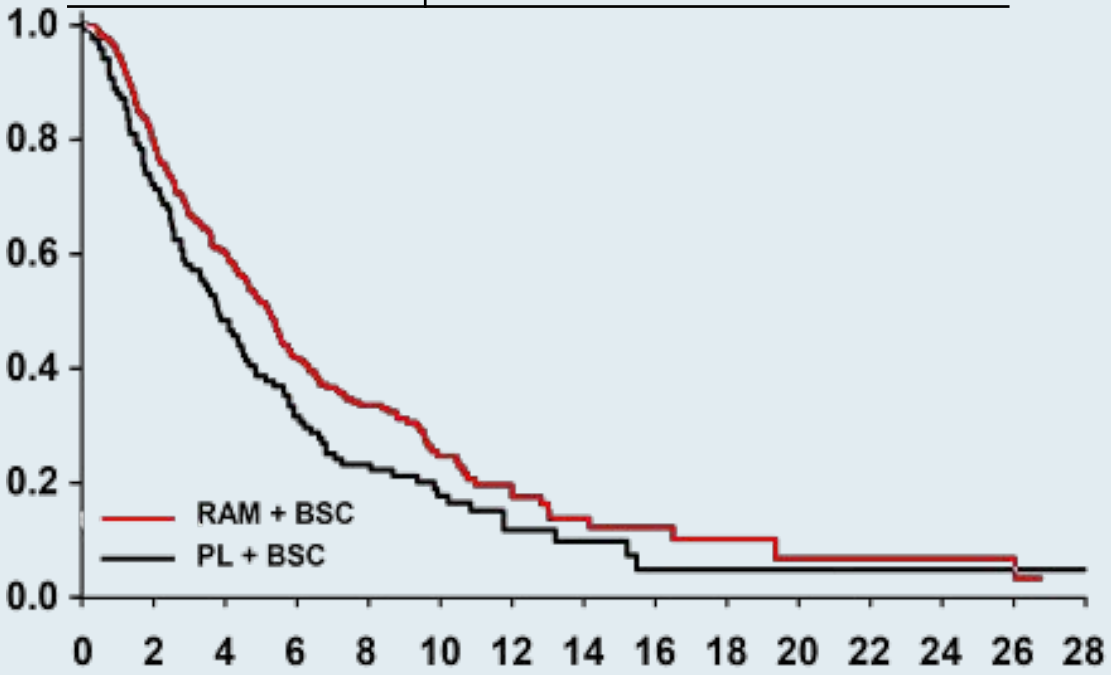
	Nivo + chemo (n = 362)	Placebo + chemo (n = 362)	HR (*p*-value)
Median OS	17.45 mo	17.15 mo	0.90 (0.257)

Boku N et al. ESMO 2020;Abstract LBA7_PR.

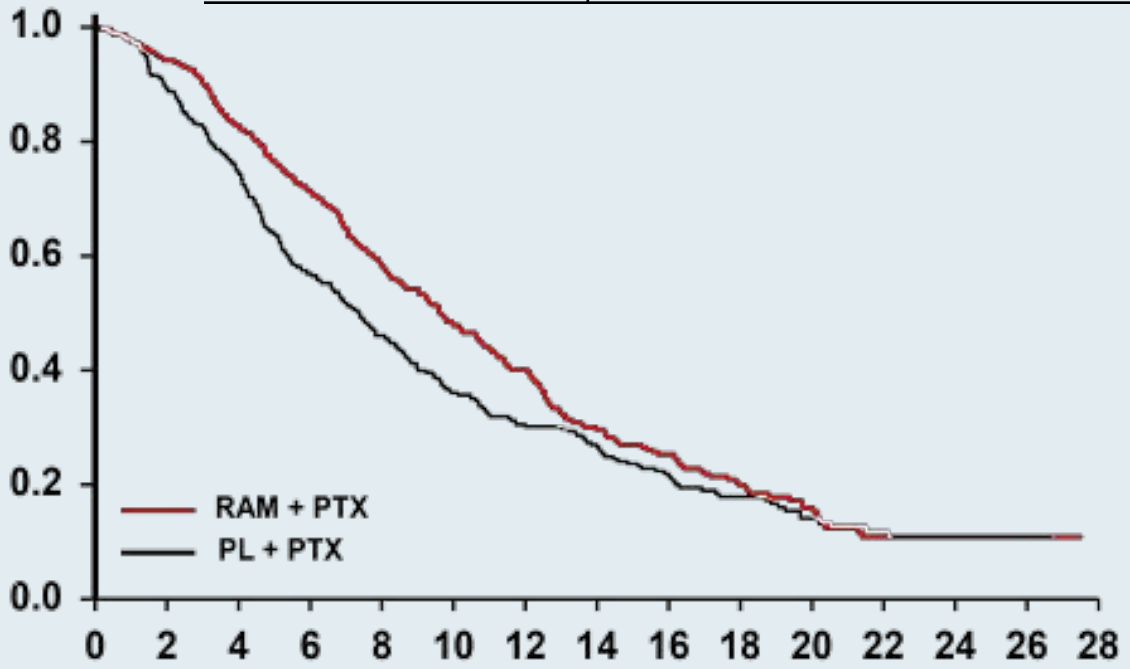
RTP RESEARCH TO PRACTICE

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)**		



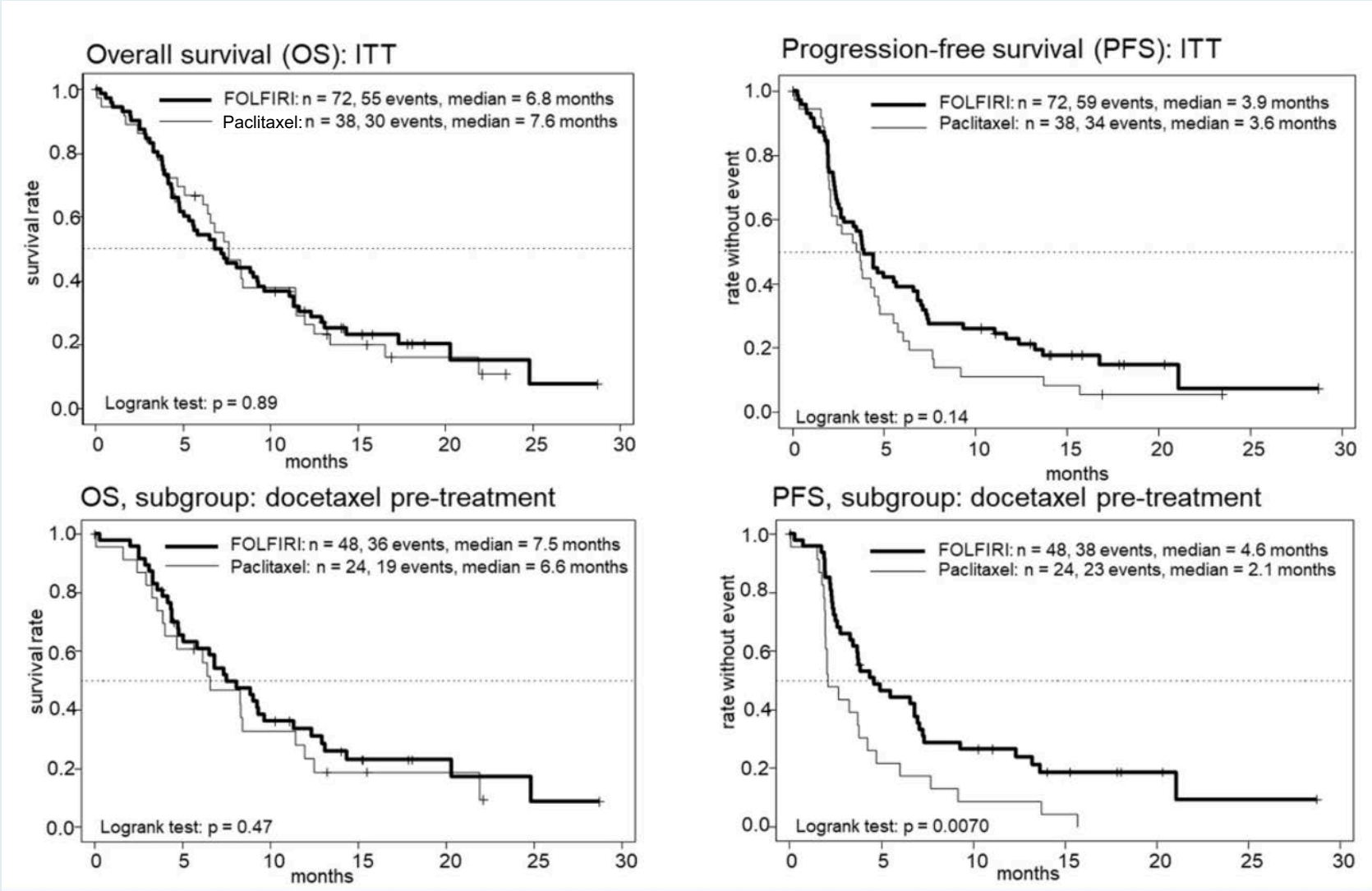
RAINBOW[2] OS	RAM	Placebo	*p*-value
Median (mo)	**9.6**	**7.4**	**0.017**
HR (95% CI)	**0.807 (0.678-0.962)**		



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



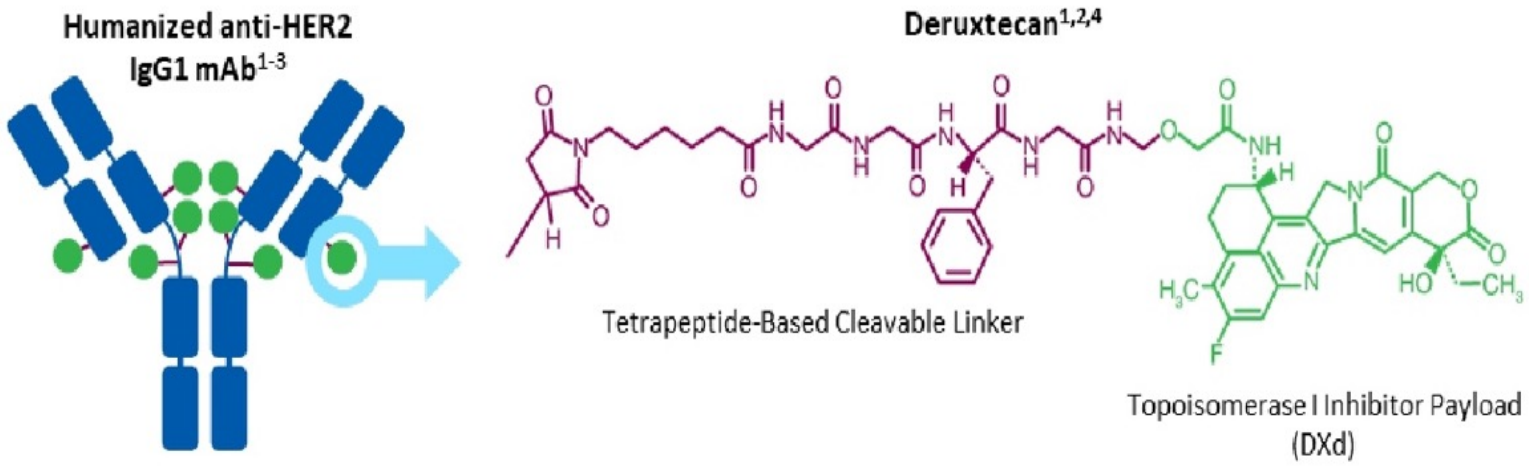
Lorenzen S et al. ASCO 2020;Abstract 4514.

RTP RESEARCH TO PRACTICE

Trastuzumab Deruxtecan Mechanism of Action

T-DXd is an ADC with 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

Courtesy of Crystal Denlinger, MD

FDA Approves fam-Trastuzumab Deruxtecan-nxki for HER2-Positive Gastric Adenocarcinomas

Press Release – January 15, 2020

"On January 15, 2021, the Food and Drug Administration approved fam-trastuzumab deruxtecan-nxki for adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

Efficacy was evaluated in a multicenter, open-label, randomized trial (DESTINY-Gastric01, NCT03329690) in patients with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma who had progressed on at least two prior regimens, including trastuzumab, a fluoropyrimidine- and a platinum-containing chemotherapy."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-fam-trastuzumab-deruxtecan-nxki-her2-positive-gastric-adenocarcinomas

The NEW ENGLAND JOURNAL of MEDICINE

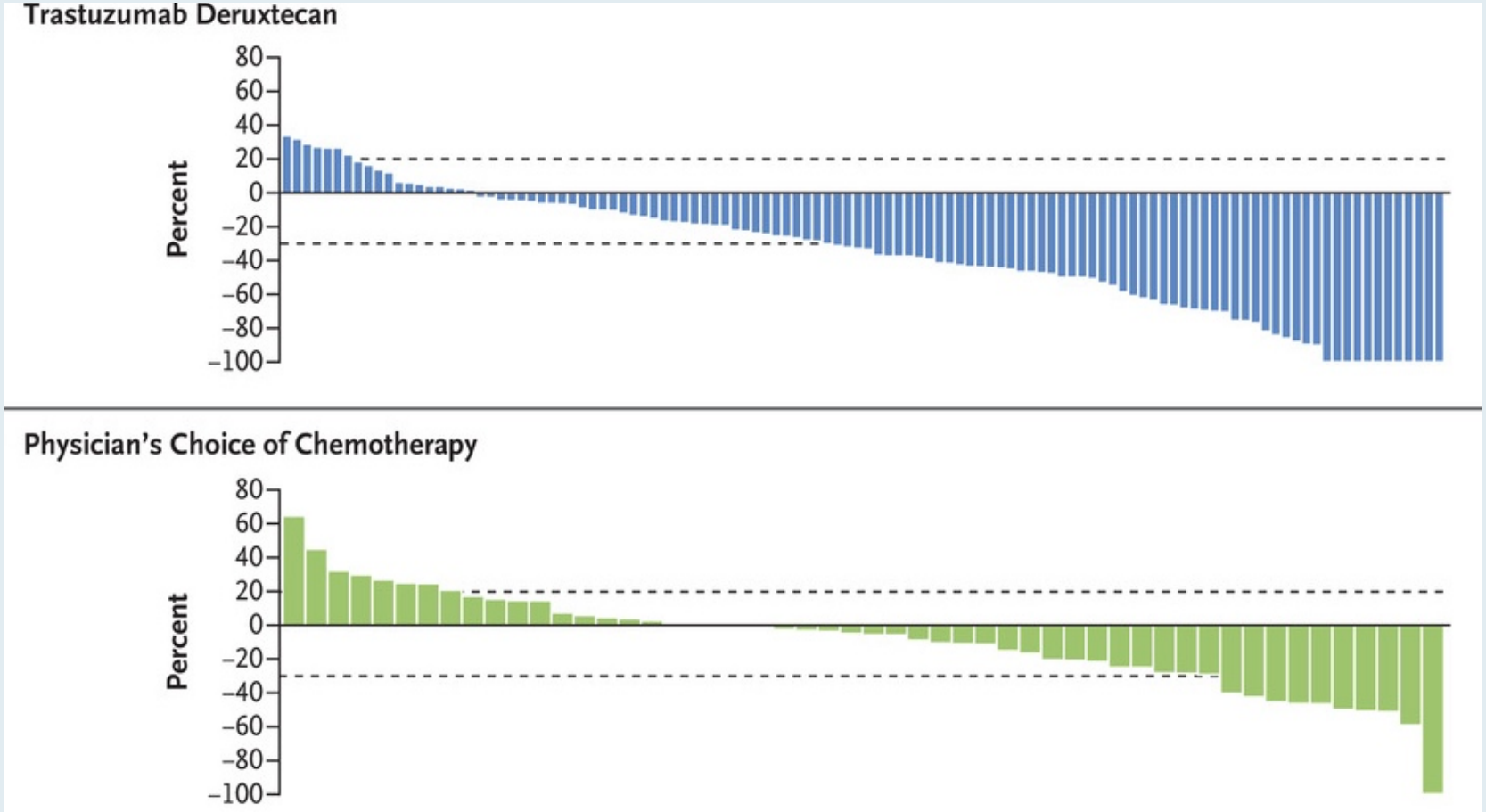
ORIGINAL ARTICLE

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

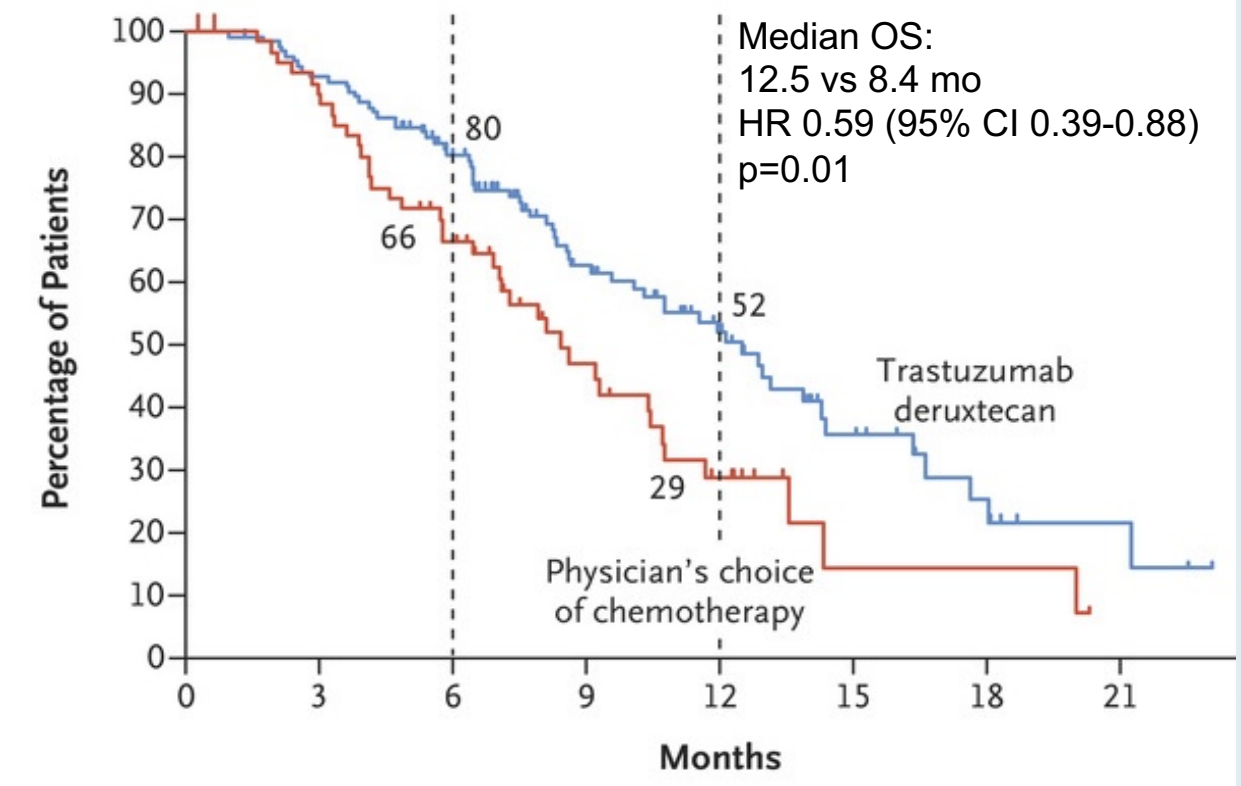


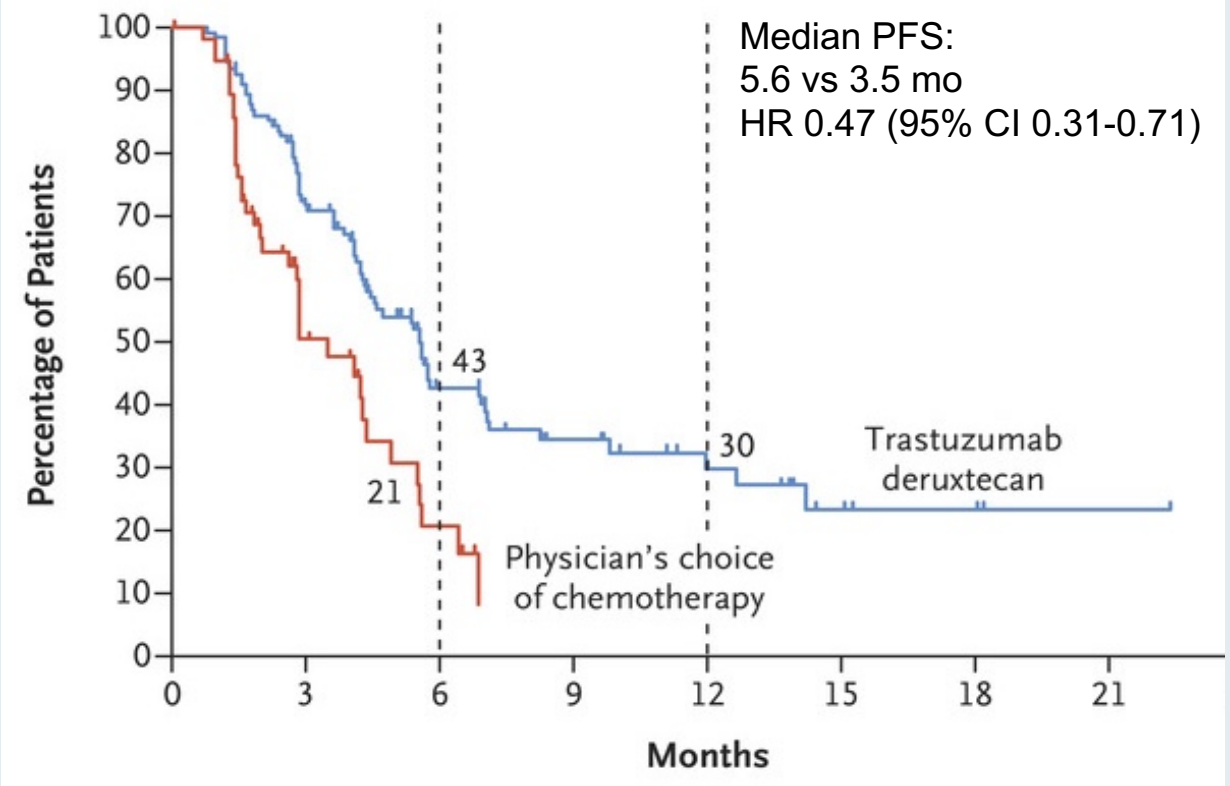
	T-DXd (n = 119)	PC (n = 56)
ORR	**51%**	**14%**
Confirmed ORR	**43%**	**12%**
CR	8%	0%
PR	34%	12%

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

RTP RESEARCH TO PRACTICE

DESTINY-Gastric01: Survival Results





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

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.

Phase II FIGHT Trial Results Validate Importance of FGFR2b Overexpression and Reinforce Potential of Bemarituzumab with Chemotherapy as a Front-Line Targeted Treatment

Press Release – January 15, 2021

"Clinical results [were reported] from the global, randomized, double-blind placebo-controlled Phase 2 FIGHT trial evaluating first-in-class targeted therapy bemarituzumab in advanced gastric or gastroesophageal junction (GEJ) cancer. Trial results were presented in a late-breaking oral presentation today by UCLA Health's Zev Wainberg, MD, at the 2021 ASCO Gastrointestinal Cancers Virtual Annual Symposium (ASCO GI).

The FIGHT trial evaluated bemarituzumab plus chemotherapy (mFOLFOX6) versus placebo plus chemotherapy in patients with fibroblast growth factor receptor 2b-positive (FGFR2b+), non HER2 positive frontline advanced gastric or GEJ cancer. The Phase 2 trial met all three efficacy endpoints and demonstrated statistically significant and clinically meaningful improvements in the primary endpoint of progression-free survival (PFS) and secondary endpoints of overall survival (OS) and overall response rate (ORR)."

https://investor.fiveprime.com/news-releases/news-release-details/phase-2-fight-trial-results-presented-asco-gi-validate

RTP RESEARCH TO PRACTICE

FIGHT The FIGHT Clinical Trial

A double-blind randomized study of bemarituzumab (bema) plus mFOLFOX6 versus placebo plus mFOLFOX6 as first-line treatment for advanced gastric/gastroesophageal junction cancer (FIGHT)

Zev A Wainberg, Peter Enzinger, Yoon-Koo Kang, Kensai Yamaguchi, Shukui Qin, Keun-Wook Lee, Sang Cheul Oh, Jin Li, Haci Mehmet Turk, Alexandra Teixeira, Giovanni Gerardo Cardellino, Rachel Guardeno Sanchez, Siddhartha Mitra, Yingsi Yang, Helen Collins, Daniel V Catenacci

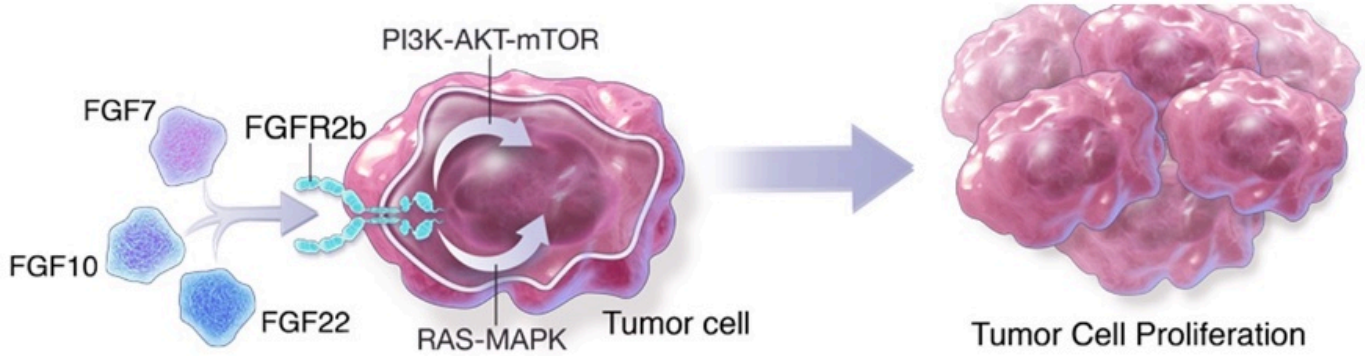
[1]University of California, Los Angeles, USA, [2]Dana Farber Cancer Institute, Boston, USA, [3]Asan Medical Center, Seoul, South Korea, [4]The Cancer Institute Hospital of JFCR, Koto-Ku , Tokyo, Japan, [5]81 Hospital Nanjing University of Chinese Medicine, Nanjing, China, [6]Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, S.Korea, [7]Korea University Guro Hospital, Seoul, South Korea, [8]Shanghai East Hospital, Shanghai, China, [9]Bezmialem Vakif Universitesi Tip Fakultesi Hastanesi, Fatih, Turkey, [10]Hospital Senhora Da Oliveira, Guimaraes, Portugal, [11]Dipartimento di Oncologia, Azienda Ospedaliero Universitaria, Udine, Italy, [12]Institut Catala d Oncologia Girona, Spain, [13]Five Prime Therapeutics, South San Francisco, USA, [14]University of Chicago, Chicago, USA

Late Breaking Abstract (LBA160)

ASCO Gastrointestinal Cancer Symposium 2021

Fibroblast Growth Factor Receptor 2b (FGFR2b) in Cancer

- FGFR2b is a member of the FGFR family (FGFR1-4) and is a splice isoform of FGFR2
- FGFR2b overexpression: 3-61% of gastric cancer depending on tumor stage and assay[1]



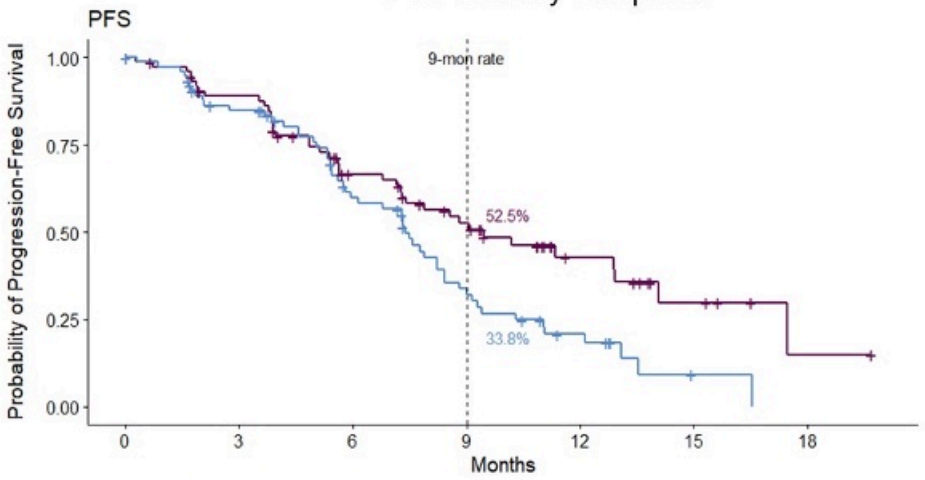
- FGFR tyrosine kinase inhibitors[2] have shown clinical benefit in cancers with FGFR mutations, fusions or translocations

[1]Han et al, Pathobiology 2015, Ahn et al, Modern Pathology 2016, Nagatsuma et al, Gastric Cancer 2015, Tokunga et al, Oncotarget 2016
[2]Abou-Alfa GK et al, Lancet Onc 2020; Loriot Y et al, NEJM 2019

Wainberg ZA et al. Gastrointestinal Cancers Symposium 2021;Abstract LBA160.

Progression-Free Survival and Overall Survival: Intent to Treat

PFS Primary Endpoint

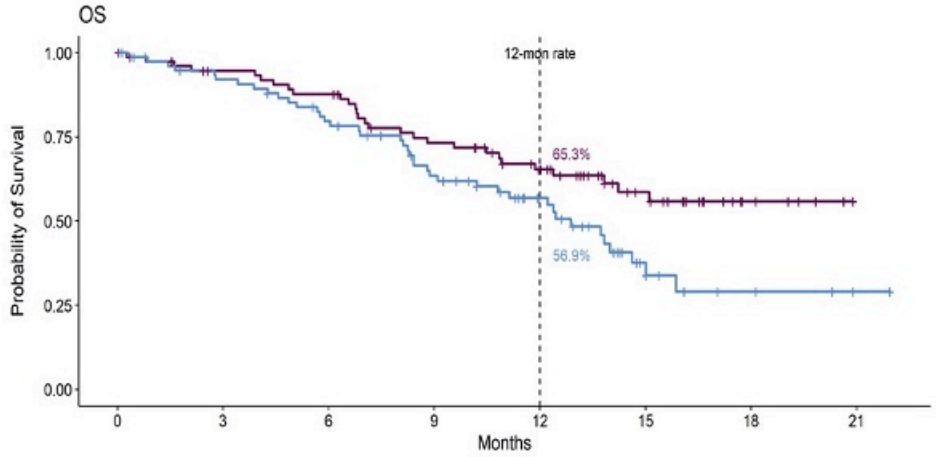


Number at risk

BEMA + mFOLFOX6	77	62	40	28	12	5	1
PLACEBO + mFOLFOX6	78	59	37	19	9	1	0

	Bema N = 77	Placebo N = 78
Median PFS, mo (95% CI)	9.5 (7.3, 12.9)	7.4 (5.8, 8.4)
	P=0.0727	
HR (95% CI)	0.68 (0.44, 1.04)	

OS Key Secondary Endpoint



Number at risk

BEMA + mFOLFOX6	77	68	63	50	38	21	6	0
PLACEBO + mFOLFOX6	78	68	57	42	27	10	4	1

	Bema N = 77	Placebo N = 78
Median OS, mo (95% CI)	NR (13.8, NR)	12.9 (9.1, 15.0)
	P=0.0268	
HR (95% CI)	0.58 (0.35, 0.95)	

Wainberg ZA et al. Gastrointestinal Cancers Symposium 2021;Abstract LBA160.

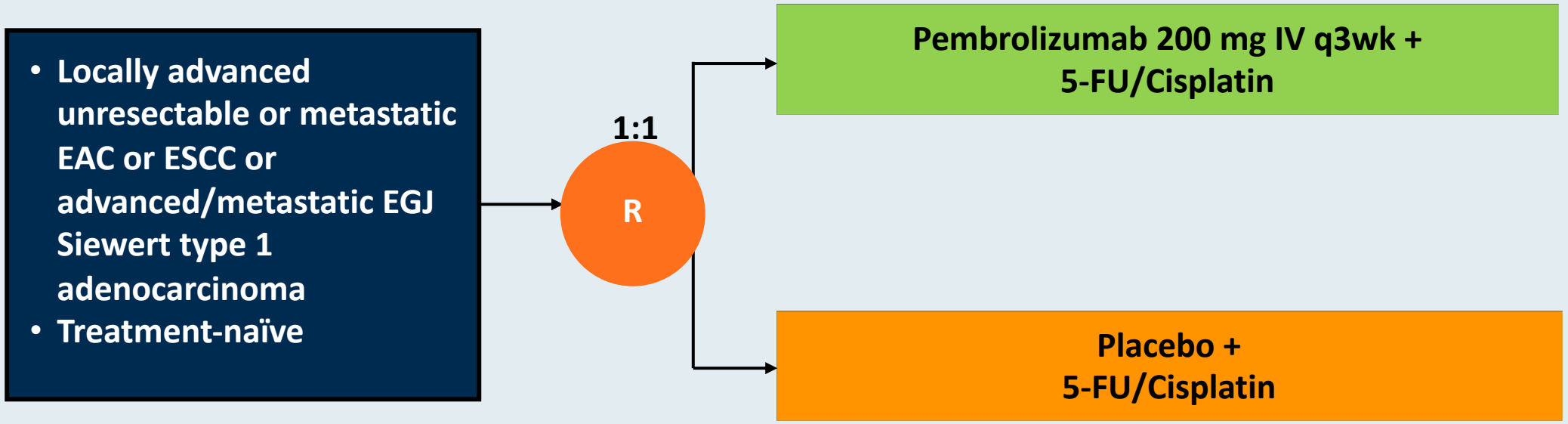
Pembrolizumab plus Chemotherapy versus Chemotherapy as First-line Therapy in Patients with Advanced Esophageal Cancer: The Phase 3 KEYNOTE-590 Study

Kato K et al.
ESMO 2020;Abstract LBA8_PR.

KEYNOTE-590: Phase III Schema

- Study conducted at 130 centers in Japan, Taiwan and Korea

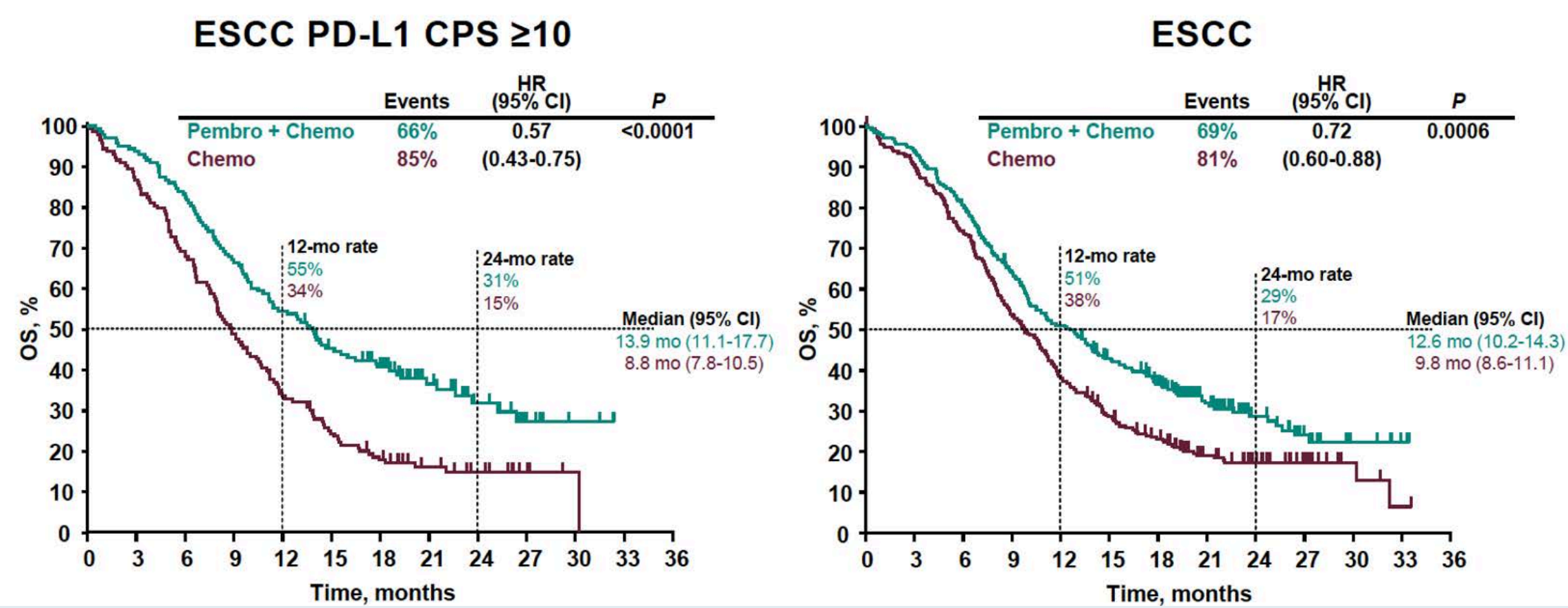
Clinical Trial Identifier: NCT03189719



Co-Primary Endpoints
Progression-free survival (PFS),
Overall survival (OS)

Kato K et al. ESMO 2020;Abstract LBA8_PR.

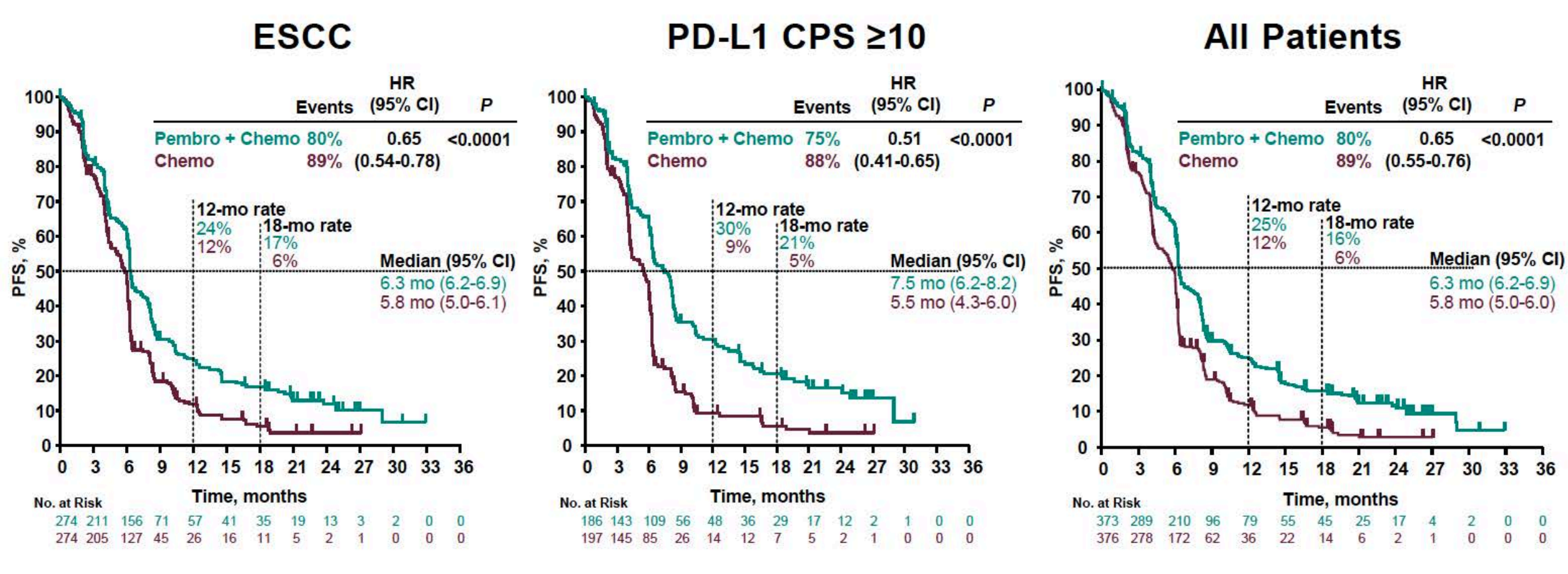
KEYNOTE-590: Overall Survival



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 Approves Nivolumab for Esophageal Squamous Cell Carcinoma

Press Release – June 10, 2020

"On June 10, 2020, the Food and Drug Administration approved nivolumab for patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

Efficacy was investigated in ATTRACTION-3 (NCT02569242), a multicenter, randomized (1:1), active-controlled, open-label trial in 419 patients with unresectable advanced, recurrent, or metastatic ESCC.

The recommended nivolumab dose for ESCC is 240 mg every 2 weeks or 480 mg every 4 weeks."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-nivolumab-esophageal-squamous-cell-carcinoma

RTP RESEARCH TO PRACTICE

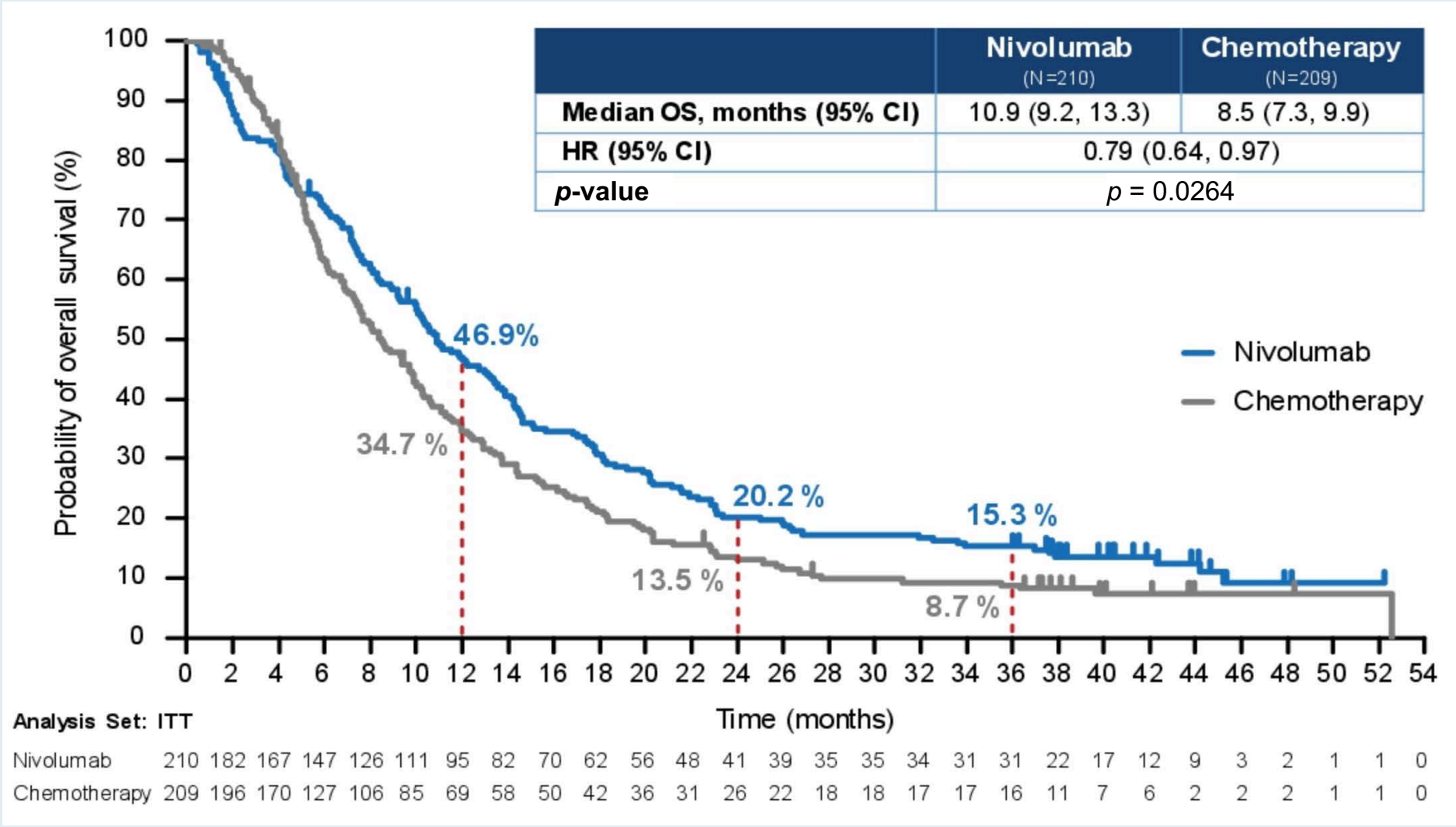
Three-year Follow-up of ATTRACTION-3: A Phase III Study of Nivolumab (Nivo) in Patients with Advanced Esophageal Squamous Cell Carcinoma (ESCC) That Is Refractory or Intolerant to Previous Chemotherapy

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.

Hepatocellular Cancer

ASCO special articles

Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline

John D. Gordan, MD, PhD[1]; Erin B. Kennedy, MHSc[2]; Ghassan K. Abou-Alfa, MD, MBA[3]; Muhammad Shaalan Beg, MD, MS[4]; Steven T. Brower, MD[5]; Terence P. Gade, MD, PhD[6]; Laura Goff, MD[7]; Shilpi Gupta, MD[8]; Jennifer Guy, MD[9]; William P. Harris, MD[10]; Renuka Iyer, MD[11]; Ishmael Jaiyesimi, DO, MS[12]; Minaxi Jhawer, MD[13]; Asha Karippot, MD[14]; Ahmed O. Kaseb, MD[15]; R. Kate Kelley, MD[1]; Jennifer J. Knox, MD, MS[16]; Jeremy Kortmansky, MD[17]; Andrea Leaf, MD[18]; William M. Remak, MT[19]; Rachna T. Shroff, MD, MS[20]; Davendra P.S. Sohal, MD, MPH[21]; Tamar H. Taddei, MD[22]; Neeta K. Venepalli, MD, MBA[23]; Andrea Wilson, MFA[24]; Andrew X. Zhu, MD, PhD[25]; and Michal G. Rose, MD[26]

J Clin Oncol 2020;38:4317-45.

RTP RESEARCH TO PRACTICE

ASCO Guideline: First-Line Therapy Recommendation Summary

Recommendation 1.1. Atezolizumab-bevacizumab (atezo + bev) may be offered as first-line treatment for most patients with advanced HCC, Child-Pugh class A, ECOG PS 0-1, and following management of esophageal varices, when present, according to institutional guidelines (Type: evidence based, benefits outweigh harms; Evidence quality: moderate to high; Strength of recommendation: strong).

Recommendation 1.2. Where there are contraindications to atezolizumab and/or bevacizumab, tyrosine kinase inhibitors (TKIs) sorafenib or lenvatinib may be offered as first-line treatment of patients with advanced HCC, Child-Pugh class A, and ECOG PS 0-1 (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Gordan JD et al. *J Clin Oncol* 2020;38:4317-45.

RTP RESEARCH TO PRACTICE

FDA Approves First-Line Atezolizumab with Bevacizumab for Unresectable or Metastatic HCC

Press Release – May 29, 2020

"On May 29, 2020, the Food and Drug Administration approved atezolizumab in combination with bevacizumab for patients with unresectable or metastatic hepatocellular carcinoma who have not received prior systemic therapy.

Efficacy was investigated in IMbrave150 (NCT03434379), a multicenter, international, open-label, randomized trial in patients with locally advanced unresectable or metastatic hepatocellular carcinoma who had not received prior systemic therapy. A total of 501 patients were randomized (2:1) to receive either atezolizumab 1200 mg as an intravenous infusion (IV) followed by bevacizumab 15 mg/kg IV on the same day, every 3 weeks, or sorafenib orally twice daily."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-plus-bevacizumab-unresectable-hepatocellular-carcinoma

The NEW ENGLAND JOURNAL of MEDICINE

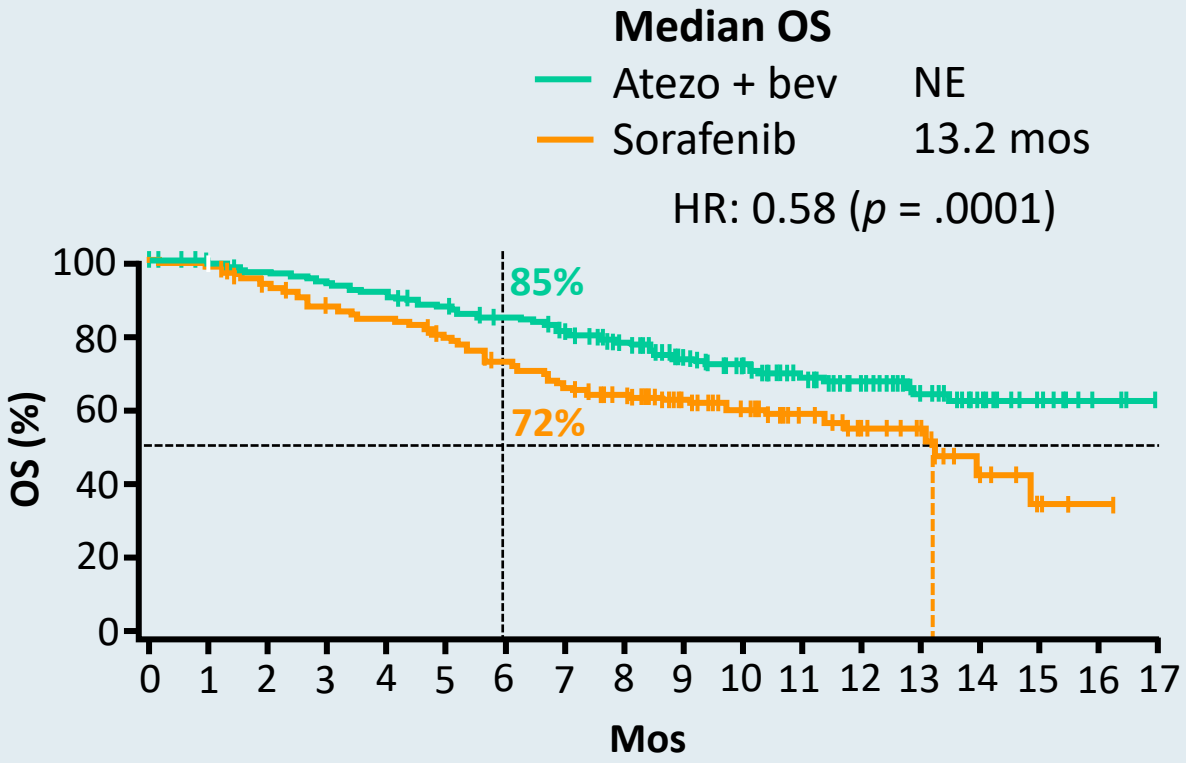
ORIGINAL ARTICLE

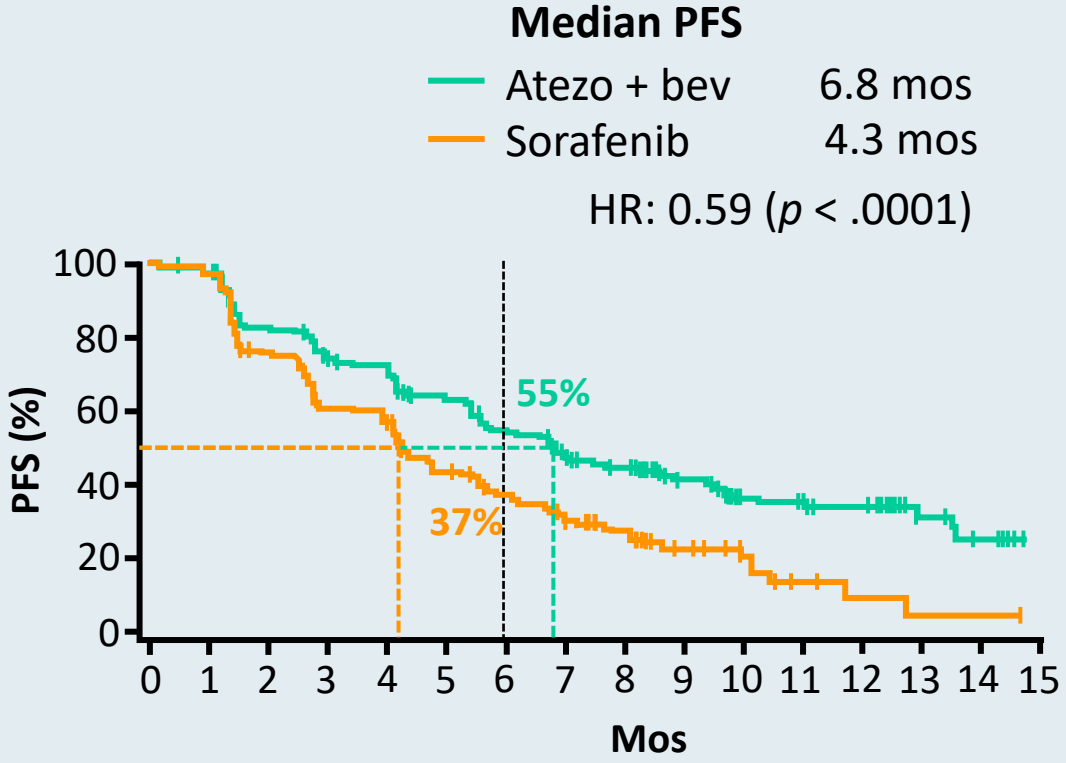
Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma

Richard S. Finn, M.D., Shukui Qin, M.D., Masafumi Ikeda, M.D., Peter R. Galle, M.D., Michel Ducreux, M.D., Tae-You Kim, M.D., Masatoshi Kudo, M.D., Valeriy Breder, M.D., Philippe Merle, M.D., Ahmed O. Kaseb, M.D., Daneng Li, M.D., Wendy Verret, Ph.D., Derek-Zhen Xu, M.D., Sairy Hernandez, Ph.D., Juan Liu, Ph.D., Chen Huang, M.D., Sohail Mulla, Ph.D., Yulei Wang, Ph.D., Ho Yeong Lim, M.D., Andrew X. Zhu, M.D., Ph.D., and Ann-Lii Cheng, M.D., for the IMbrave150 Investigators*

N Engl J Med 2020;382:1894-905

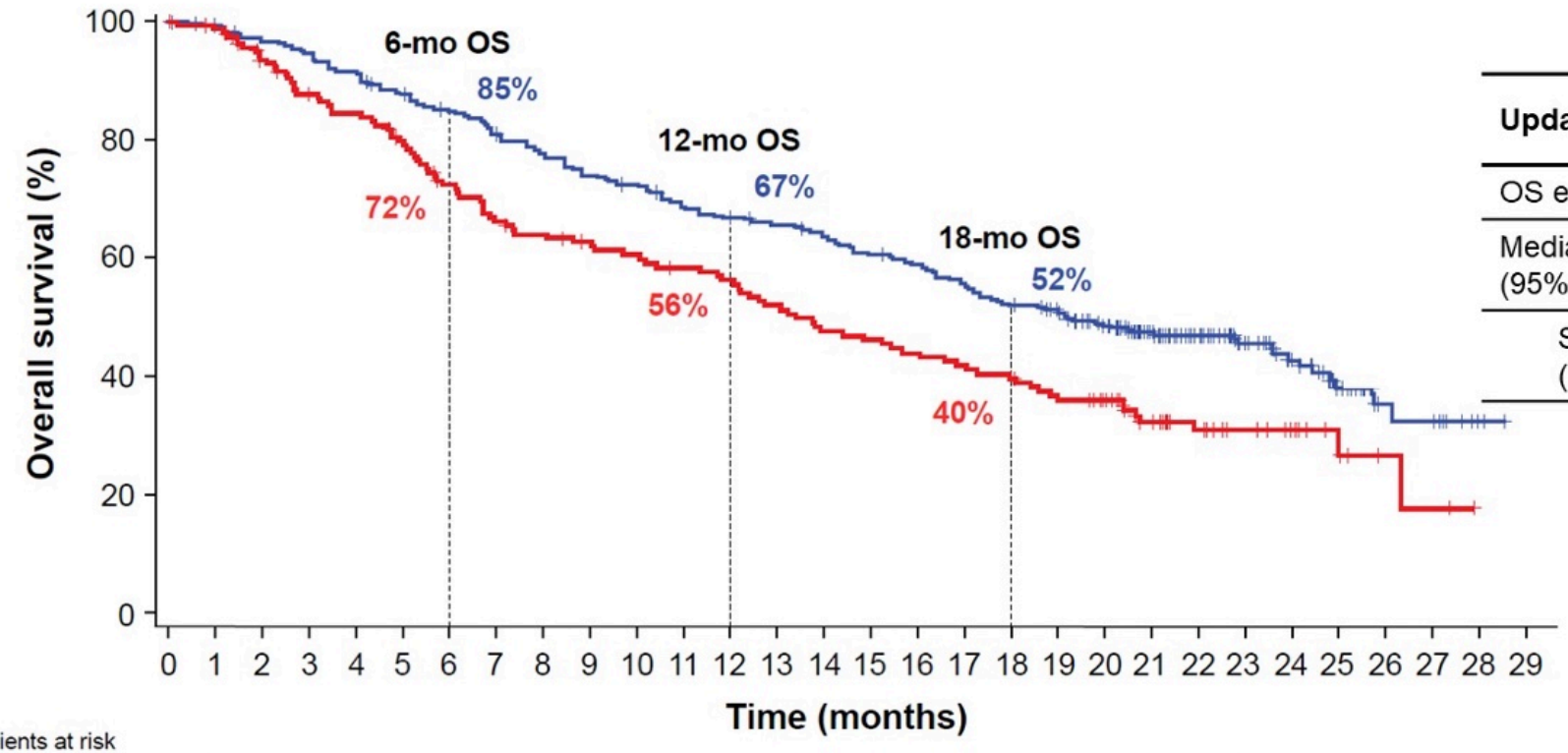
IMbrave150: PFS and OS





Finn RS et al. *N Engl J Med* 2020;382:1894-905.

IMbrave150: Updated Overall Survival



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]	

No. of patients at risk

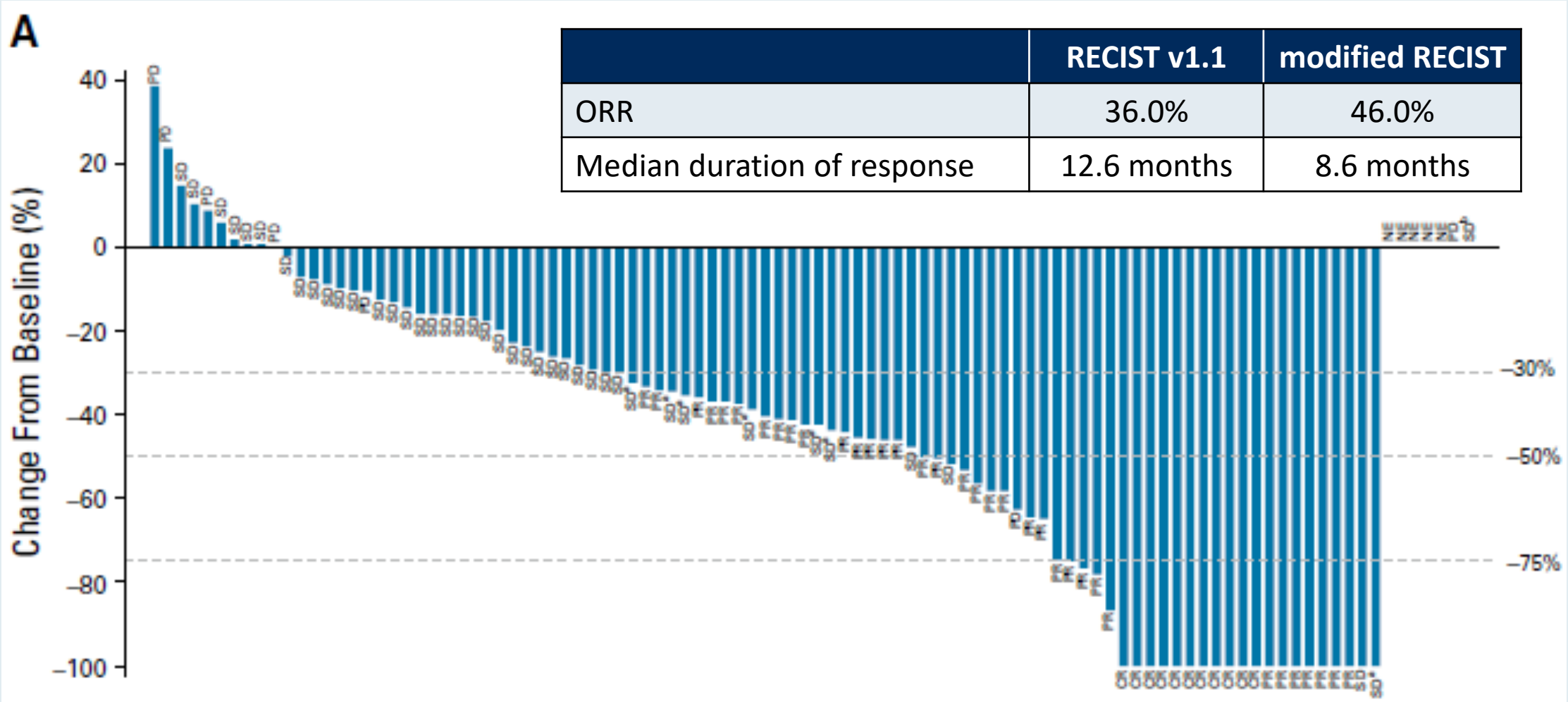
Atezo + Bev	336	329	320	312	302	288	276	263	252	240	233	221	214	209	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.
[a] Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs Rest of World), AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per interactive voice/web response system (IxRS).[b] *P* value for descriptive purposes only.

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

KEYNOTE-524: Phase Ib Study of Lenvatinib with Pembrolizumab for Patients with Unresectable Hepatocellular Carcinoma

	RECIST v1.1	modified RECIST
ORR	36.0%	46.0%
Median duration of response	12.6 months	8.6 months



Finn RS et al. *J Clin Oncol* 2020;38(26):2960-70.

Donafenib versus Sorafenib as First-Line Therapy in Advanced Hepatocellular Carcinoma: An Open-Label, Randomized, Multicentre Phase II/III Trial

Feng Bi et al.
ASCO 2020;Abstract 4506.

Conclusions

- Donafenib demonstrated superiority versus sorafenib in overall survival in patients with HCC (12.1 months *vs* 10.3 months, HR 0.831, 95% CI 0.699–0.988, $p = 0.0363$)
- Donafenib showed improved trends versus sorafenib in PFS, ORR, and DCR, though differences were not significant
- Donafenib exhibited favourable safety and tolerability compared with sorafenib
- Donafenib should be considered an optimal first-line therapy for advanced HCC

Feng Bi et al. ASCO 2020;Abstract 4506.

ASCO Guideline: Second-Line Therapy Recommendation Summary

Recommendation 2.1. Following first-line treatment with atezo + bev, second-line therapy with a TKI (ie, sorafenib, lenvatinib, cabozantinib, or regorafenib) may be recommended (Type: informal consensus, benefits may outweigh harms; Evidence quality: low; Strength of recommendation: weak).
Qualifying statement:

- No data have been published on therapy options after first-line treatment with atezo + bev. It is the opinion of the Expert Panel that a TKI, preferably sorafenib or lenvatinib, may be offered. Cabozantinib or regorafenib are also reasonable options for second-line therapy following atezo + bev.

Recommendation 2.2. Following first-line therapy with sorafenib or lenvatinib, second-line therapy with another TKI (cabozantinib or regorafenib), ramucirumab (AFP $\geq$ 400 ng/mL), or atezo + bev may be recommended for appropriate candidates. Considerations regarding choice of therapy are included in the Clinical Interpretation (Type: informal consensus, benefits may outweigh harms; Evidence quality: low to moderate; Strength of recommendation: weak).
Qualifying statement:

- It is likely that most patients being considered for atezo + bev in the second-line setting did not have access to this combination when they started first-line treatment.

Recommendation 2.3. Following first-line therapy with sorafenib or lenvatinib, pembrolizumab or nivolumab are reasonable options that may be considered for appropriate candidates (Type: informal consensus, benefits may outweigh harms; Evidence quality: low; Strength of recommendation: weak).
Qualifying statement:

- Immune checkpoint inhibitors pembrolizumab or nivolumab may be especially beneficial for patients who have contraindications to or cannot tolerate TKIs.

Gordan JD et al. *J Clin Oncol* 2020;38:4317-45.

RTP RESEARCH TO PRACTICE

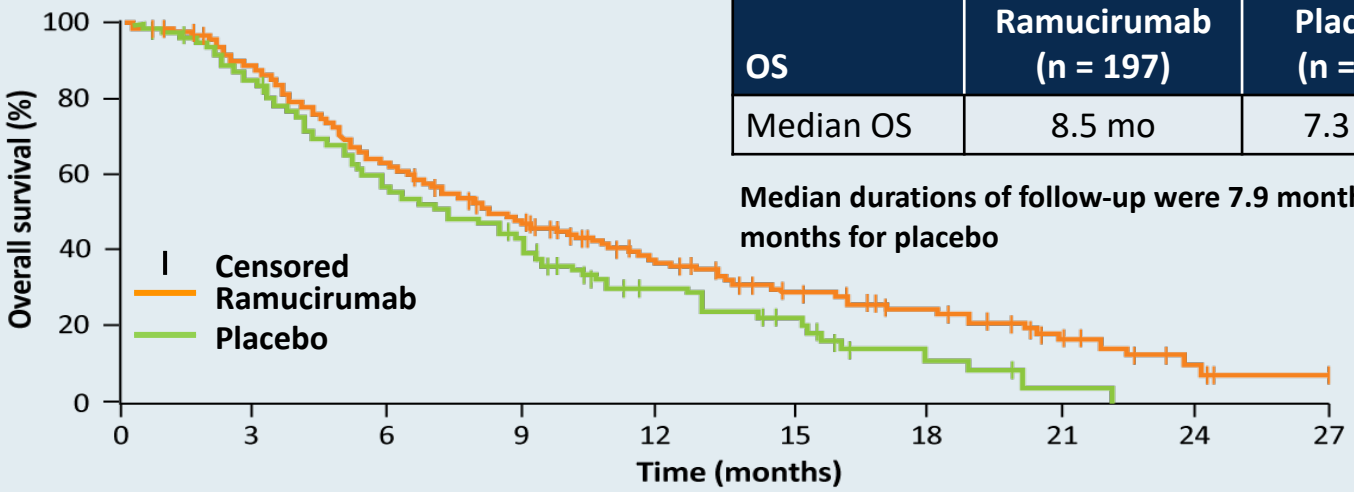
Articles

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**

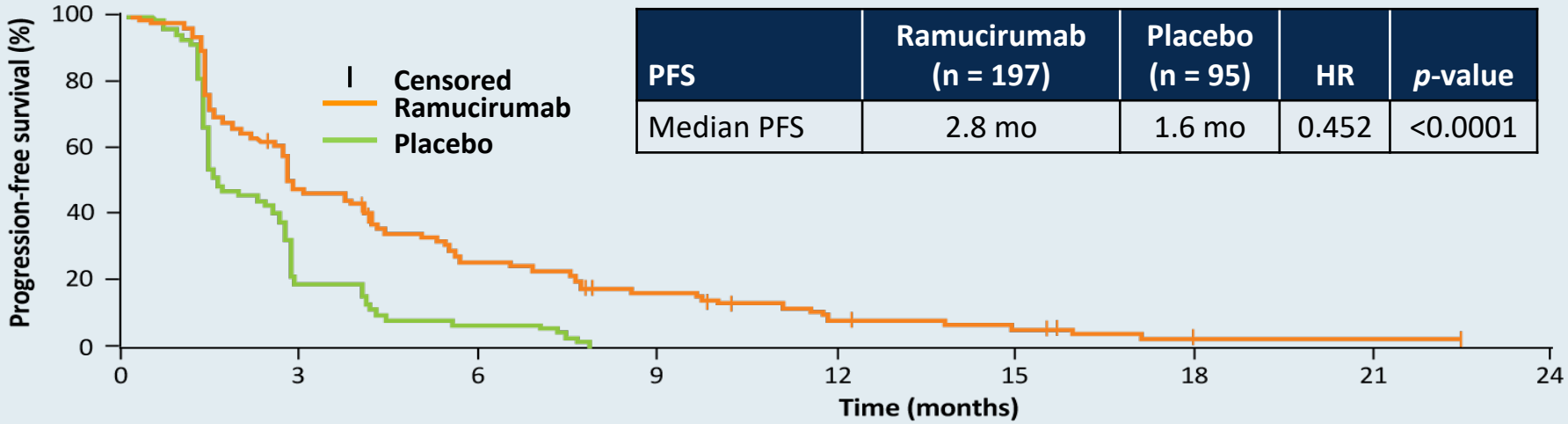
Lancet Oncol 2019;20(2):282-96.

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.

RTP RESEARCH TO PRACTICE

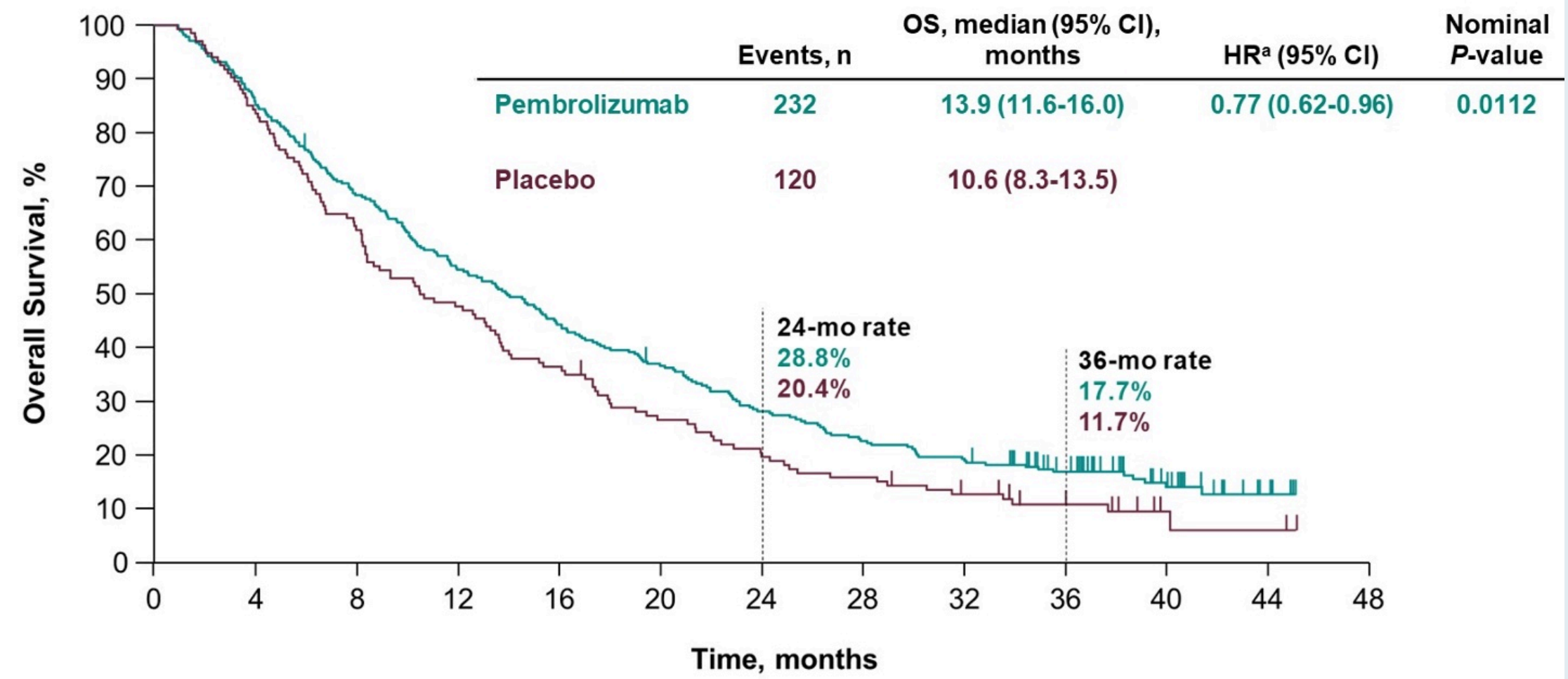
Pembrolizumab versus Placebo in Patients with Advanced Hepatocellular Carcinoma Previously Treated with Sorafenib: Updated Data from the Randomized, Phase 3 KEYNOTE-240 Study

Merle P et al.

Gastrointestinal Cancers Symposium 2021;Abstract 268.

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

Overall Survival

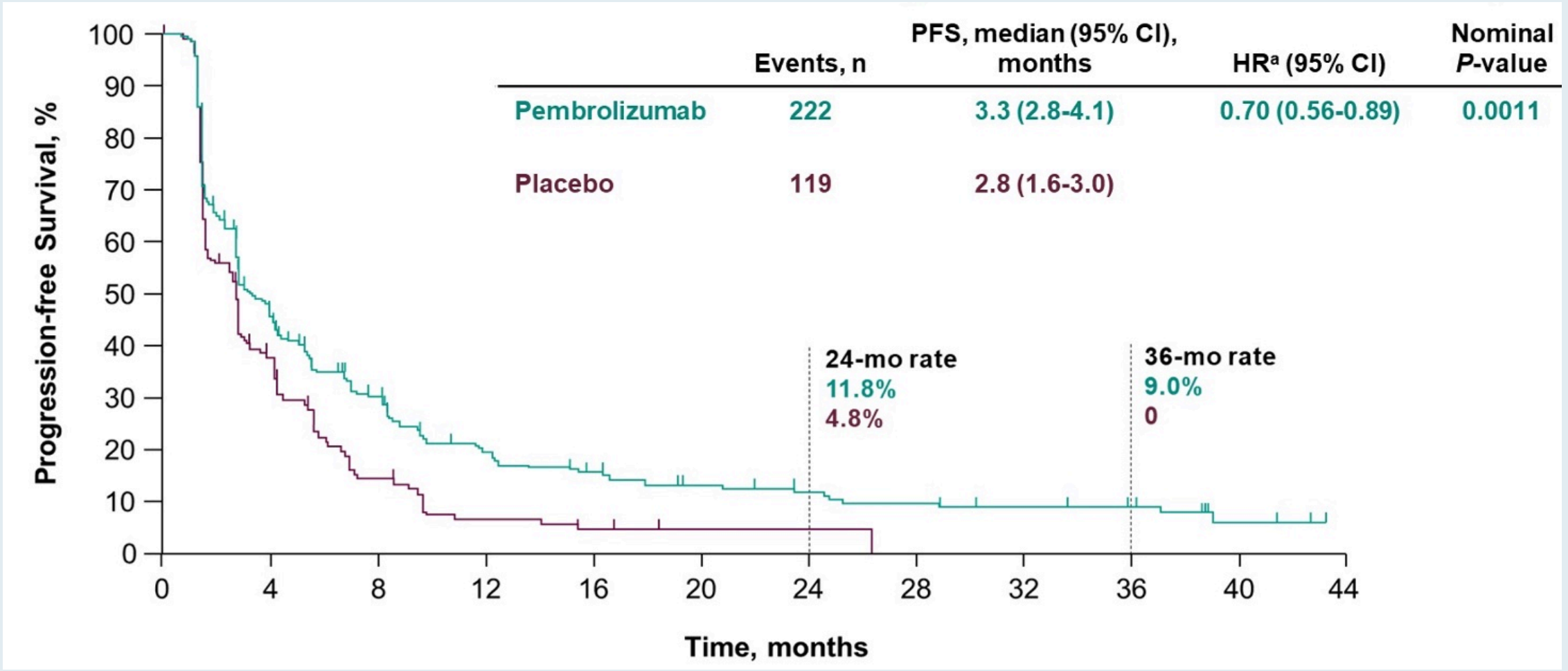


Merle P et al. Gastrointestinal Cancers Symposium 2021;Abstract 268.

RTP RESEARCH TO PRACTICE

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

Progression-Free Survival



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

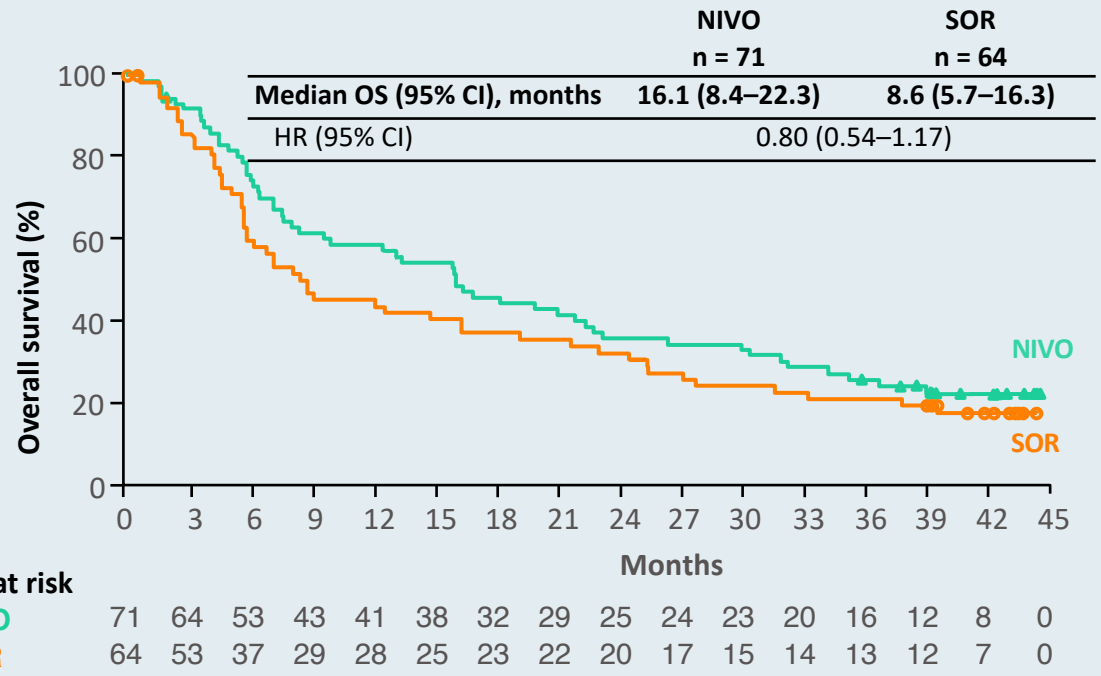
RTP RESEARCH TO PRACTICE

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

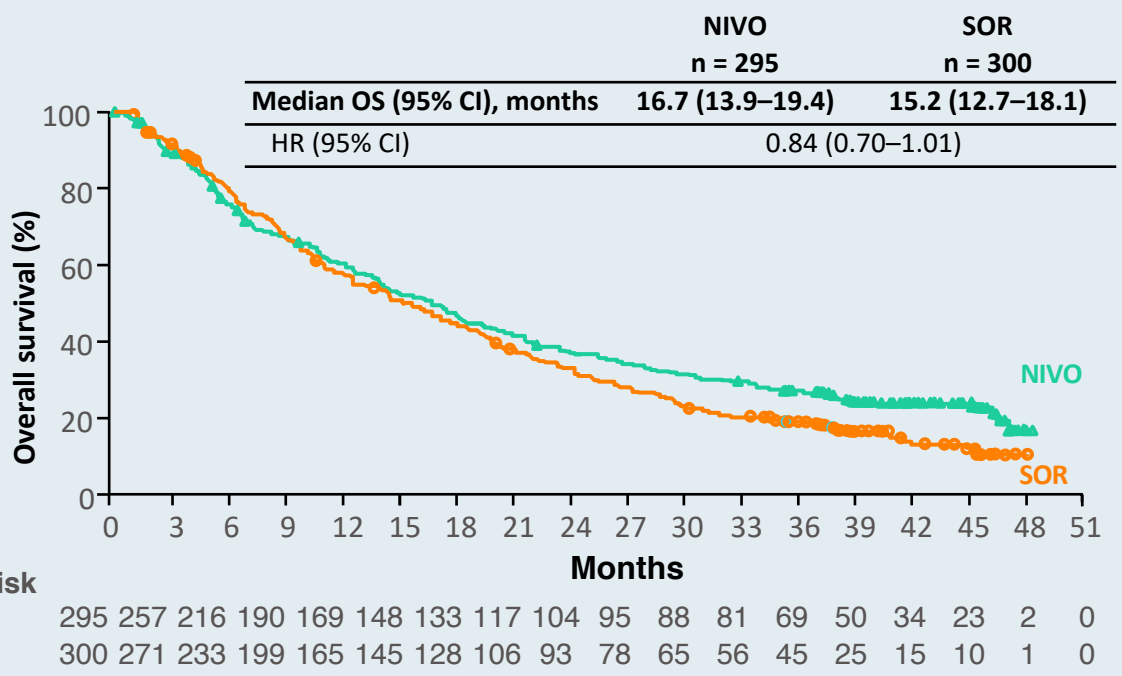
Sangro B et al.
ESMO World GI Congress 2020;Abstract LBA-3.

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

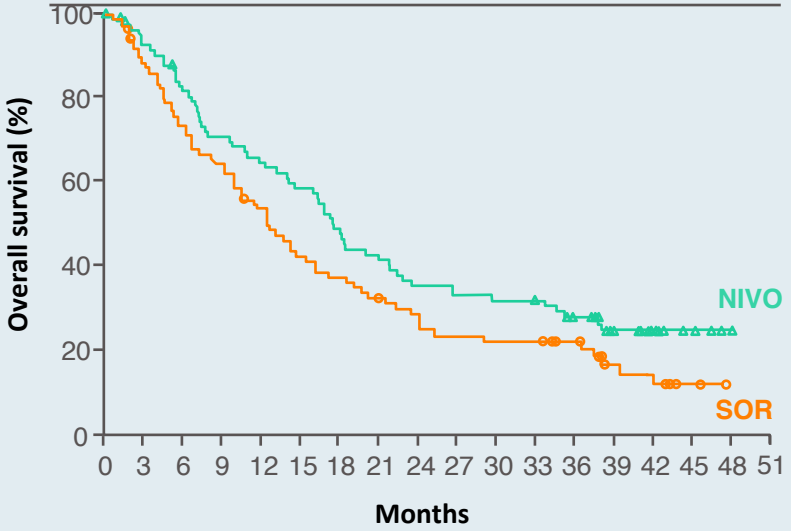
Sangro B et al. ESMO World GI Congress 2020;Abstract LBA-3.

RTP RESEARCH TO PRACTICE

CheckMate 459: Overall Survival by Etiology

HCV

	NIVO n = 87	SOR n = 86
Median OS (95% CI), months	17.5 (13.9–21.9)	12.7 (9.9–16.2)
HR (95% CI)	0.72 (0.51–1.02)	

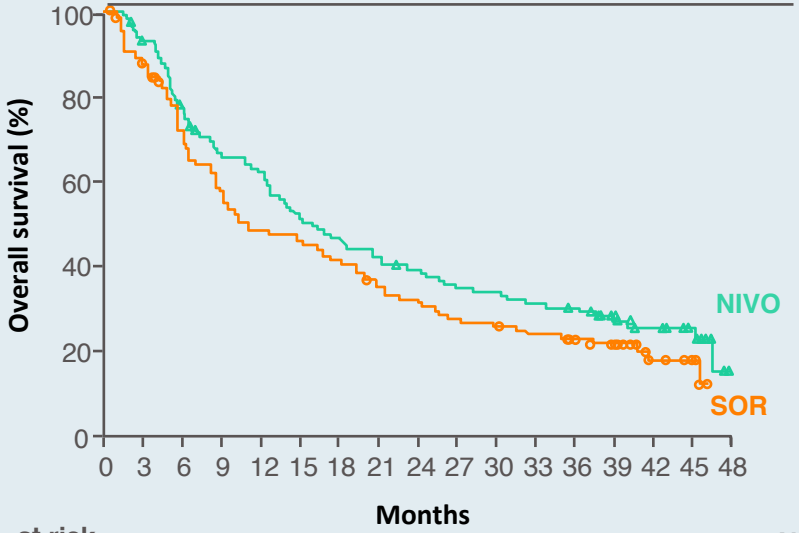


No. at risk

NIVO	87	77	67	58	53	48	40	34	29	27	26	25	20	13	8	4	1	0
SOR	86	74	61	54	43	34	30	25	22	18	17	17	14	7	5	2	0	0

HBV

	NIVO n = 116	SOR n = 117
Median OS (95% CI), months	16.1 (12.5–21.3)	10.4 (8.5–17.3)
HR (95% CI)	0.79 (0.59–1.07)	

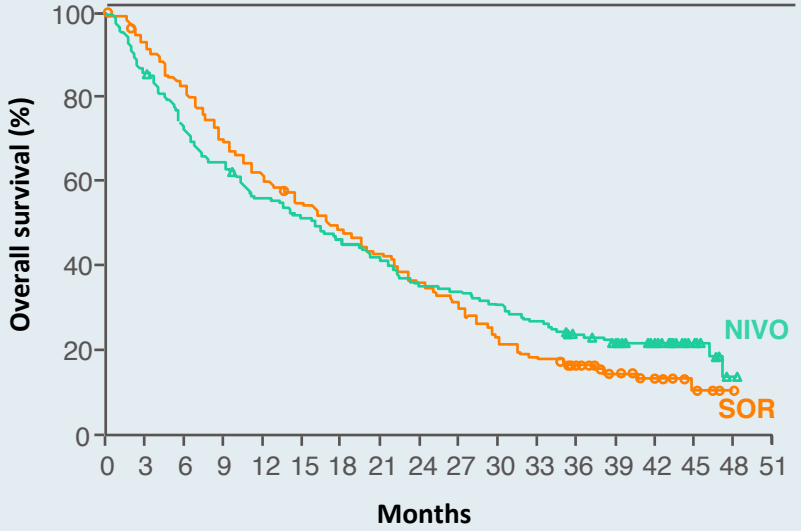


No. at risk

NIVO	116	106	86	72	68	56	51	46	42	37	36	33	31	21	14	9	0	
SOR	117	101	77	63	53	50	45	37	33	29	27	24	21	17	8	4	0	

Uninfected

	NIVO n = 168	SOR n = 168
Median OS (95% CI), months	16.0 (10.8–20.2)	17.4 (13.7–21.3)
HR (95% CI)	0.91 (0.72–1.16)	



No. at risk

NIVO	168	143	120	107	92	85	76	68	59	56	50	44	35	29	20	10	1	0	
SOR	168	154	137	116	101	90	80	70	60	50	37	30	23	13	9	4	1	0	

- In the HCV and HBV groups, median OS was numerically longer with NIVO versus SOR

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

RTP RESEARCH TO PRACTICE

FDA Grants Accelerated Approval to Nivolumab and Ipilimumab Combination for HCC

Press Release – March 10, 2020

"On March 10, 2020, the Food and Drug Administration granted accelerated approval to the combination of nivolumab and ipilimumab for patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

Efficacy of the combination was investigated in Cohort 4 of CHECKMATE-040, (NCT01658878) a multicenter, multiple cohort, open-label trial conducted in patients with HCC who progressed on or were intolerant to sorafenib. A total of 49 patients received nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for four doses, followed by single-agent nivolumab 240 mg every 2 weeks until disease progression or unacceptable toxicity.

The main efficacy outcome measures were overall response rate and duration of response as determined by blinded independent central review (BICR) using RECIST v1.1. ORR was 33% (n=16; 95% CI: 20, 48), with 4 complete responses and 12 partial responses. Response duration ranged from 4.6 to 30.5+ months, with 31% of responses lasting at least 24 months."

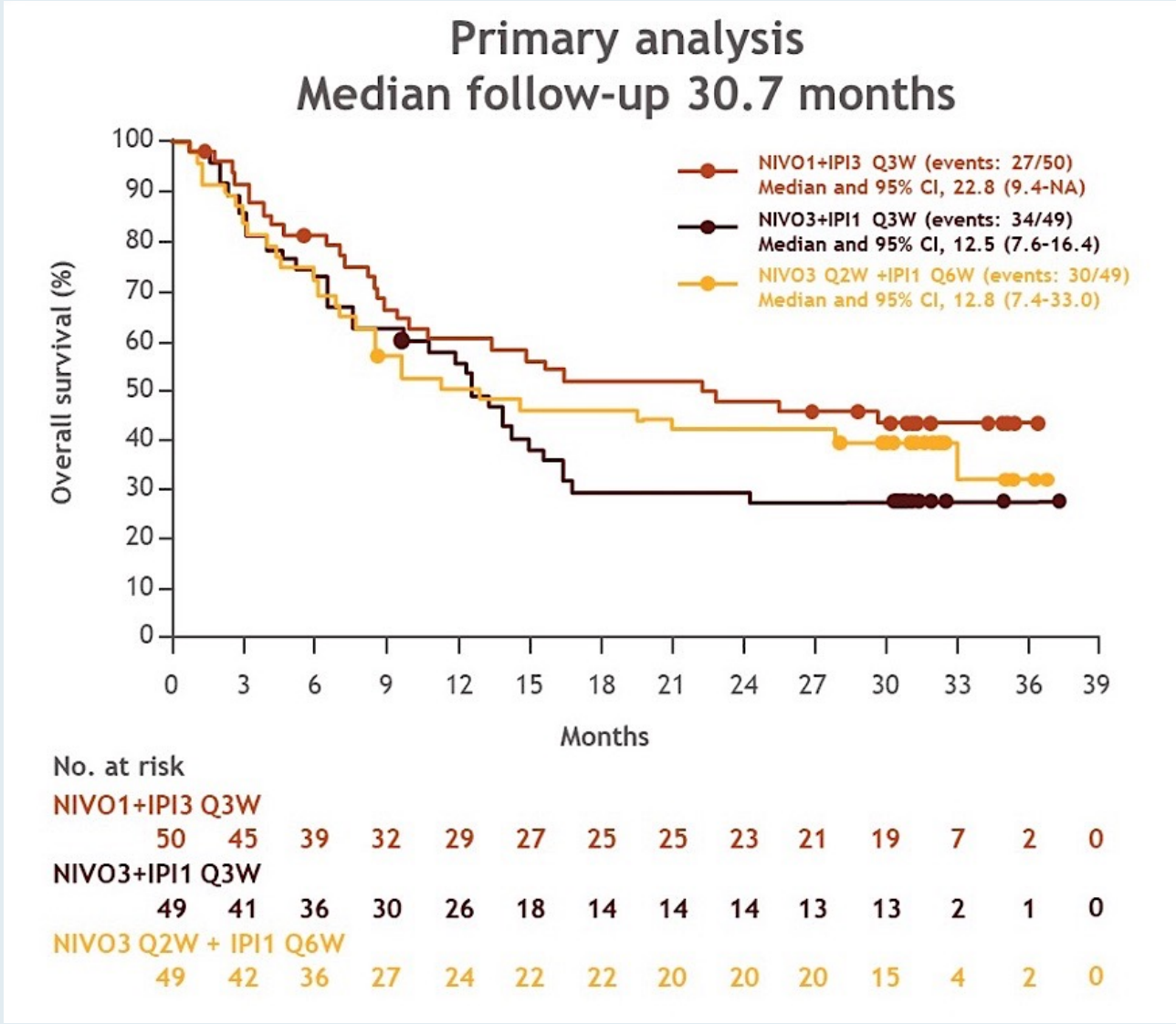
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-and-ipilimumab-combination-hepatocellular-carcinoma

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.

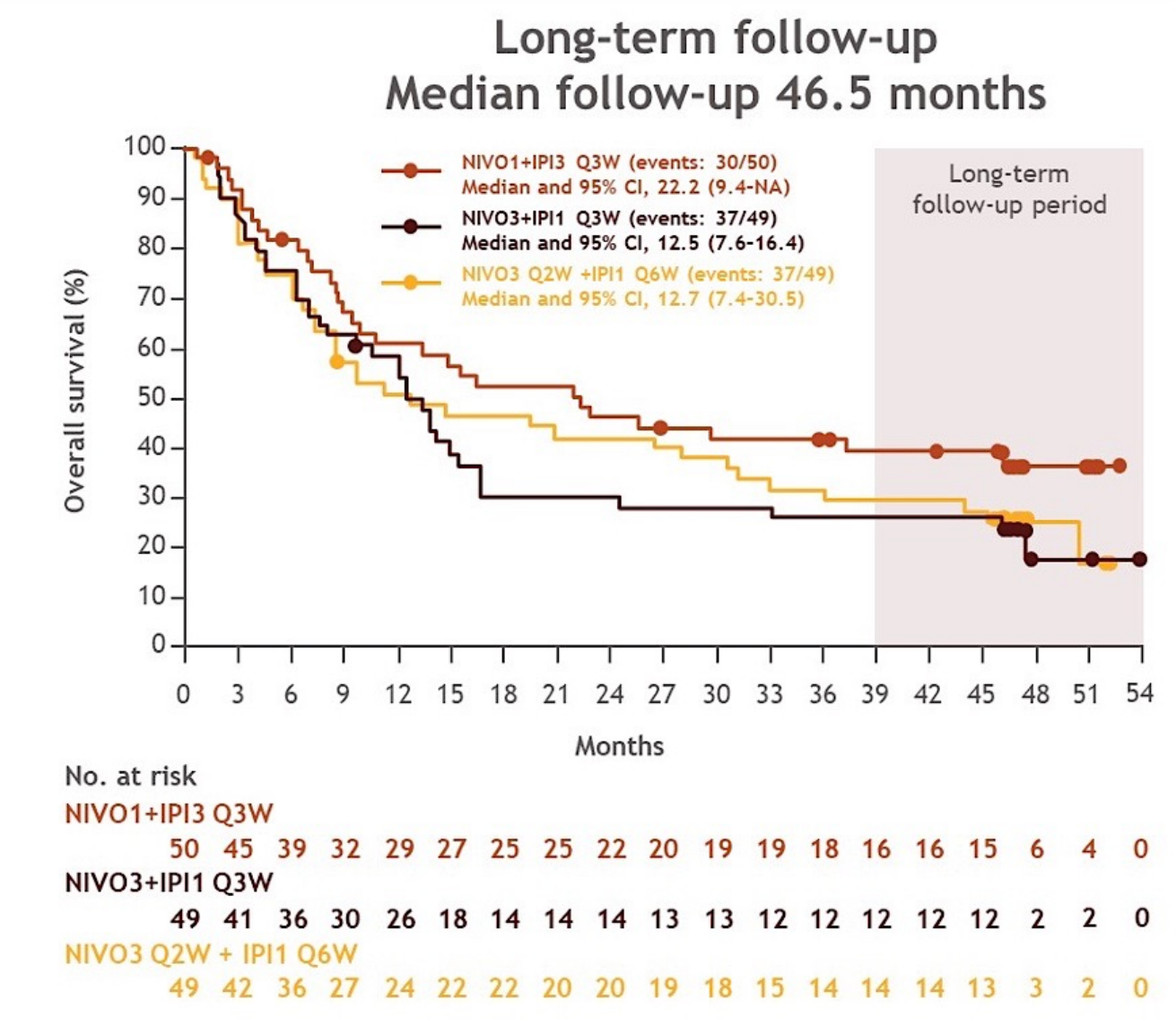
CheckMate 040: Updated Overall Survival with Ipilimumab/Nivolumab



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

RTP RESEARCH TO PRACTICE

CheckMate 040: Updated Overall Survival with Ipilimumab/Nivolumab



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

RTP RESEARCH TO PRACTICE

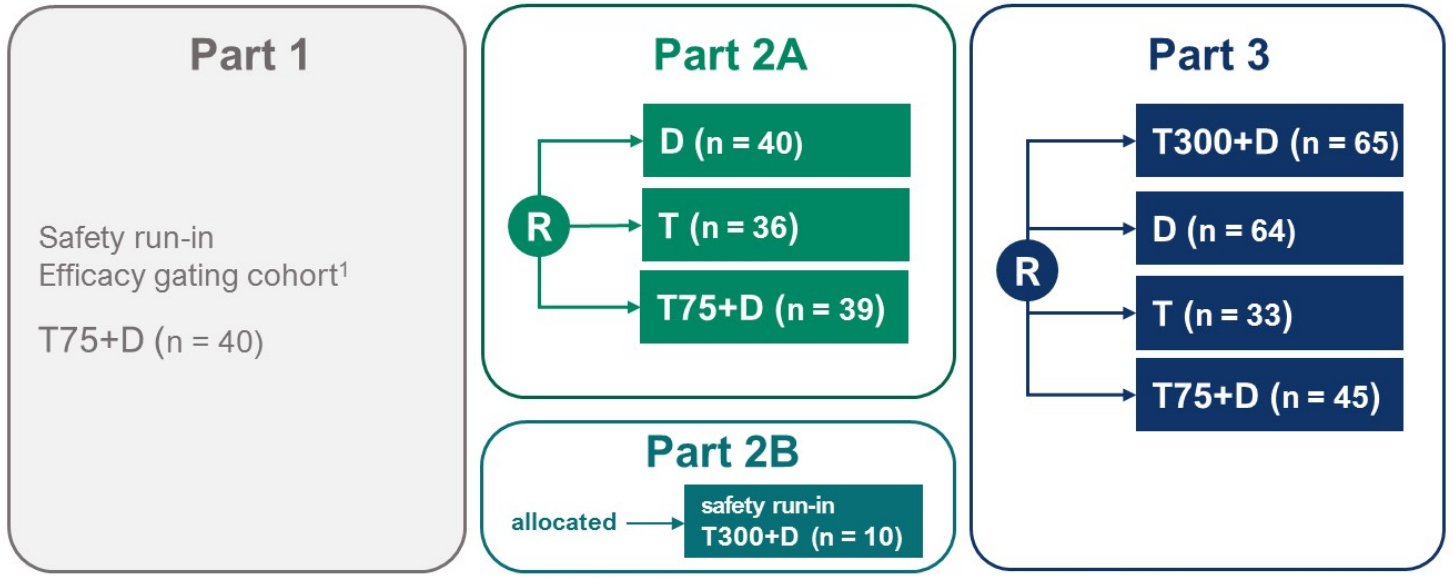
Efficacy, Tolerability, and Biologic Activity of a Novel Regimen of Tremelimumab (T) in Combination with Durvalumab (D) for Patients (pts) with Advanced Hepatocellular Carcinoma (aHCC)

Kelley RK et al.
ASCO 2020;Abstract 4508.

CheckMate 459: Long-Term (Minimum Follow-Up 33.6 Months) Survival 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 O-6.

Study 22: Tremelimumab in Combination with Durvalumab for Advanced HCC



Key Milestones

FSI Part 2A	February 2017
FSI Part 2B	October 2017

Key Milestones

FSI Part 3	February 2018
LSI Part 3	April 2019

Treatments and Regimens

T300+D	tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W
D	durvalumab 1500 mg Q4W
T	tremelimumab monotherapy 750 mg Q4W × 7 doses, Q12W thereafter
T75+D	tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W

Key Eligibility

- Unresectable HCC with fresh or archival tumor biopsy sample available
- Progressed on, intolerant to, or refused prior sorafenib
- Child Pugh A liver function

Objectives and Assessments

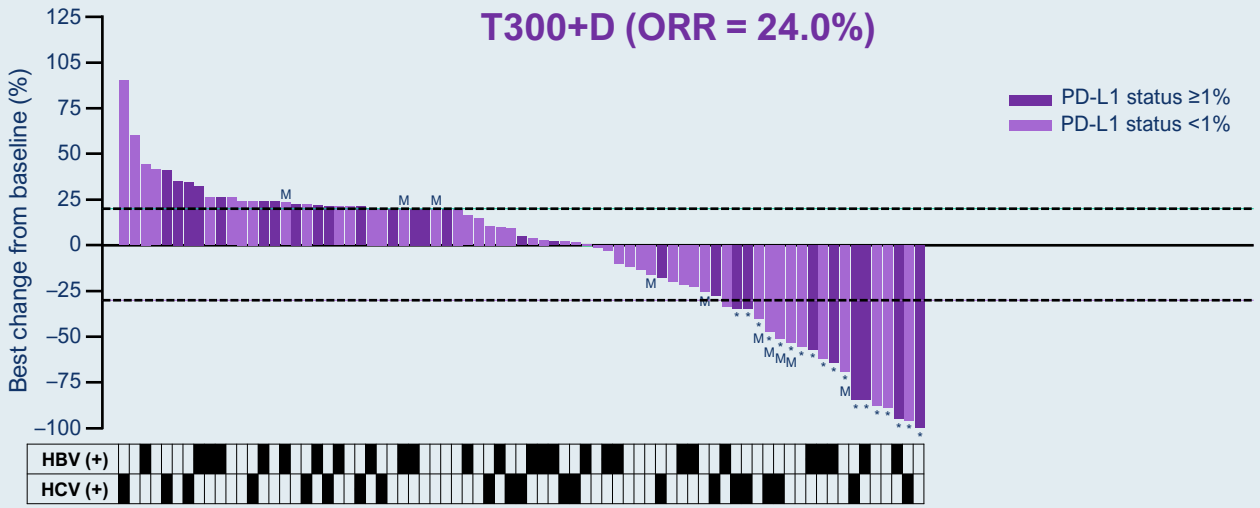
Primary Endpoint: Safety

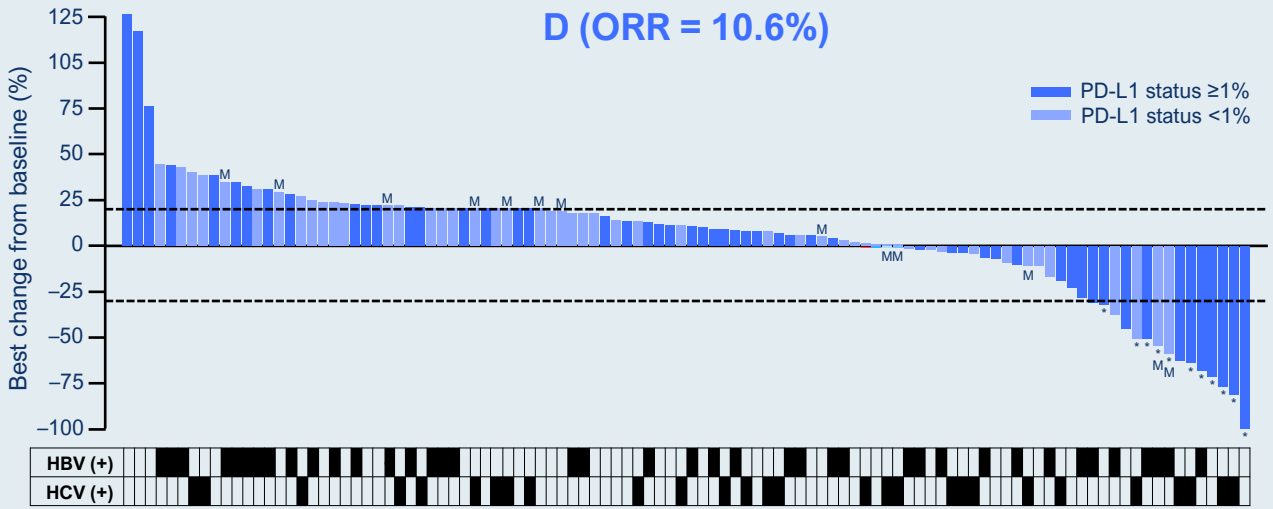
Key Secondary Endpoints
- Overall survival
- Objective response rate
- Duration of response

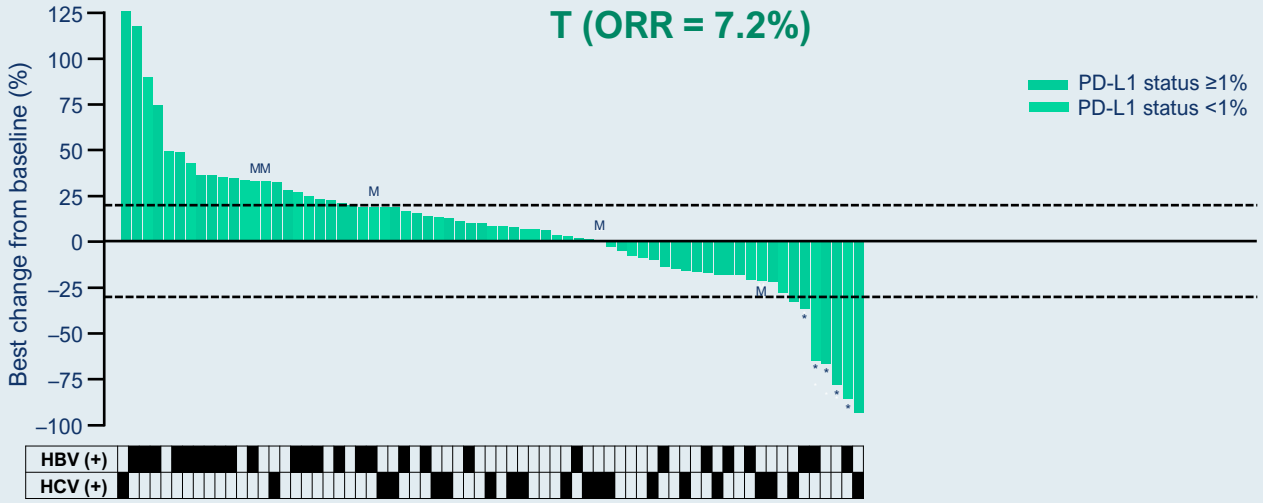
Key Assessments
- Multiphase imaging Q8 weeks
- Circulating immune cells
- PD-L1 status (Ventana SP263)

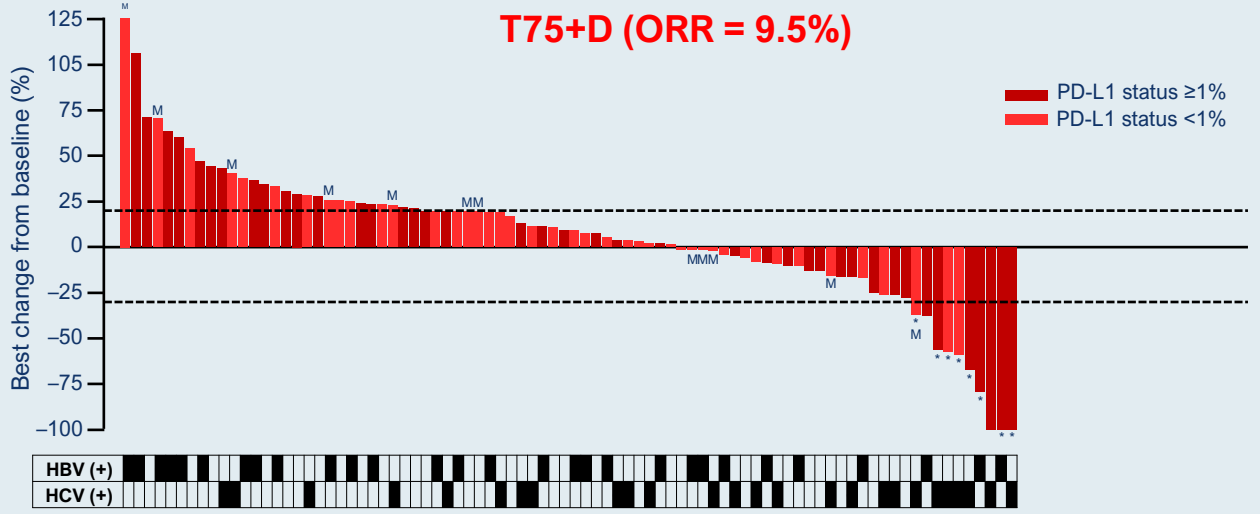
Sangro B et al. ESMO World GI Congress 2020;Abstract O-6; Kelley RK et al. ASCO 2020;Abstract 4508.

Study 22: Responses Observed Regardless of PD-L1 or Viral Status





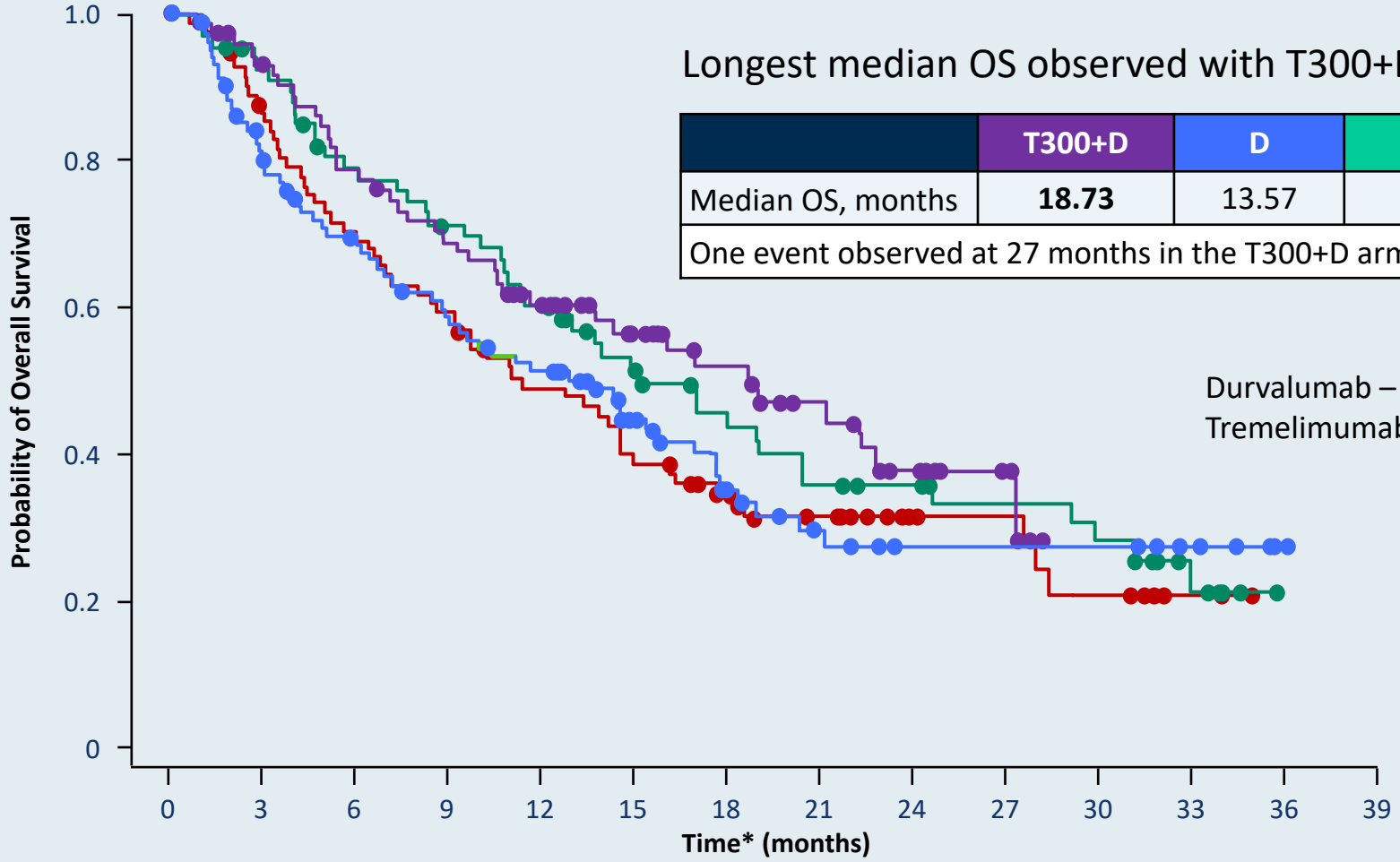




Kelley RK et al. ASCO 2020;Abstract 4508.

RTP RESEARCH TO PRACTICE

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.

FDA Grants Priority Review to Infigratinib for the Treatment of Cholangiocarcinoma

Press Release – December 1, 2020

"The FDA has accepted a New Drug Application for the oral FGFR1-3 selective inhibitor, infigratinib (formerly BGJ398) and granted it Priority Review for the treatment of patients with cholangiocarcinoma…

The NDA for infigratinib will be evaluated through the FDA's Real-Time Oncology Review pilot program and applications for approval will also be submitted in Canada and Australia under the Project Orbis Program.

Results from a phase 2, multicenter, single-arm study (NCT02150967) of infigratinib as third- or later-line treatment of patients with FGFR2 fusion–positive cholangiocarcinoma were most recently presented during the European Society of Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer 2020. The study showed that second-line chemotherapy, the most common second-line treatment approach for the disease, led to similar outcomes as front-line treatment in previously published studies, but clinical meaningful improvements in progression-free survival (PFS) and overall response rates (ORRs) were observed when the drug was administered as third-line treatment or later."

https://www.targetedonc.com/view/fda-grants-priority-review-to-infigratinib-for-the-treatment-of-cholangiocarcinoma

RTP RESEARCH TO PRACTICE

Final results from a phase 2 study of infigratinib (BGJ398), an FGFR-selective tyrosine kinase inhibitor, in patients with previously-treated advanced cholangiocarcinoma containing *FGFR2* fusions/rearrangements

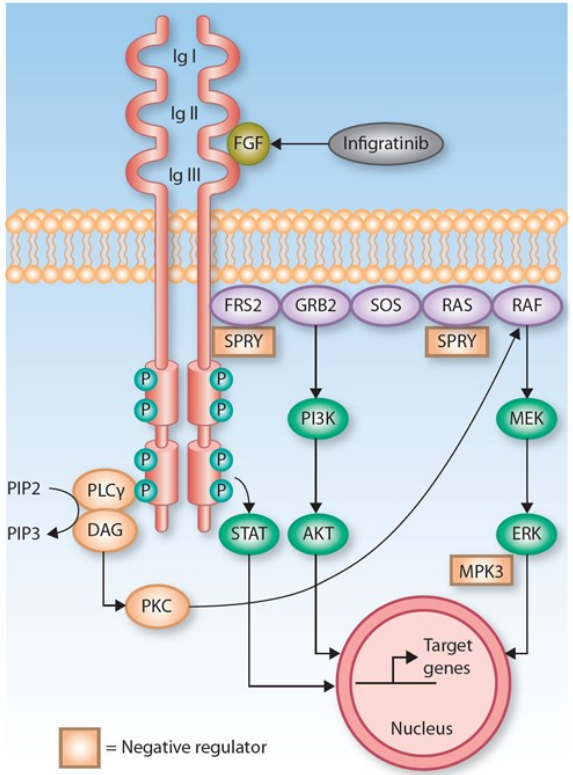
Milind Javle,[1] Sameek Roychowdhury,[2] Robin Kate Kelley,[3] Saeed Sadeghi,[4] Teresa Macarulla,[5] Karl-Heinz Weiss,[6] Dirk-Thomas Waldschmidt,[7] Lipika Goyal,[8] Andrew Zhu,[8] Ivan Borbath,[9] Anthony El-Khoueiry,[10] Mitesh Borad,[11] Wei Peng Yong,[12] Philip A. Philip,[13] Michael Bitzer,[14] Surbpong Tanasanvimon,[15] Ai Li,[16] Amit Pande,[16] Harris S. Soifer,[16] Stacie Peacock Shepherd,[16] Susan Moran,[16] Tanios S Bekaii-Saab,[11] Ghassan K Abou-Alfa[17]

[1]MD Anderson Cancer Center, Houston, TX, USA; [2]Ohio State Comprehensive Cancer Center/James Cancer Hospital, Columbus, OH, USA [3]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [4]David Geffen School of Medicine at UCLA; [5]Hospital Vall d'Hebron, Barcelona, Spain; [6]University Hospital Heidelberg, Heidelberg, Germany; [7]Klinikum der Universitaet zu Köln, Cologne, Germany; [8]Massachusetts General Hospital, Boston, MA, USA; [9]Cliniques Universitaires St Luc, Brussels, Belgium; [10]USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA, USA; [11]Mayo Clinic, Scottsdale, AZ, USA; [12]National University Cancer Institute Singapore, Singapore; [13]Karmanos Cancer Institute, Detroit, MI, USA; [14]University Hospital Tübingen, Tübingen, Germany; [15]Chulalongkorn University, Bangkok, Thailand; [16]QED Therapeutics Inc., San Francisco, CA, USA; [17]Memorial Sloan Kettering Cancer Center, New York, New York, USA

ASCO GI 2021

Gastrointestinal Cancers Symposium 2021;Abstract 265.

Targeting *FGFR* genomic alterations with infigratinib: an FGFR1–3 selective tyrosine kinase inhibitor



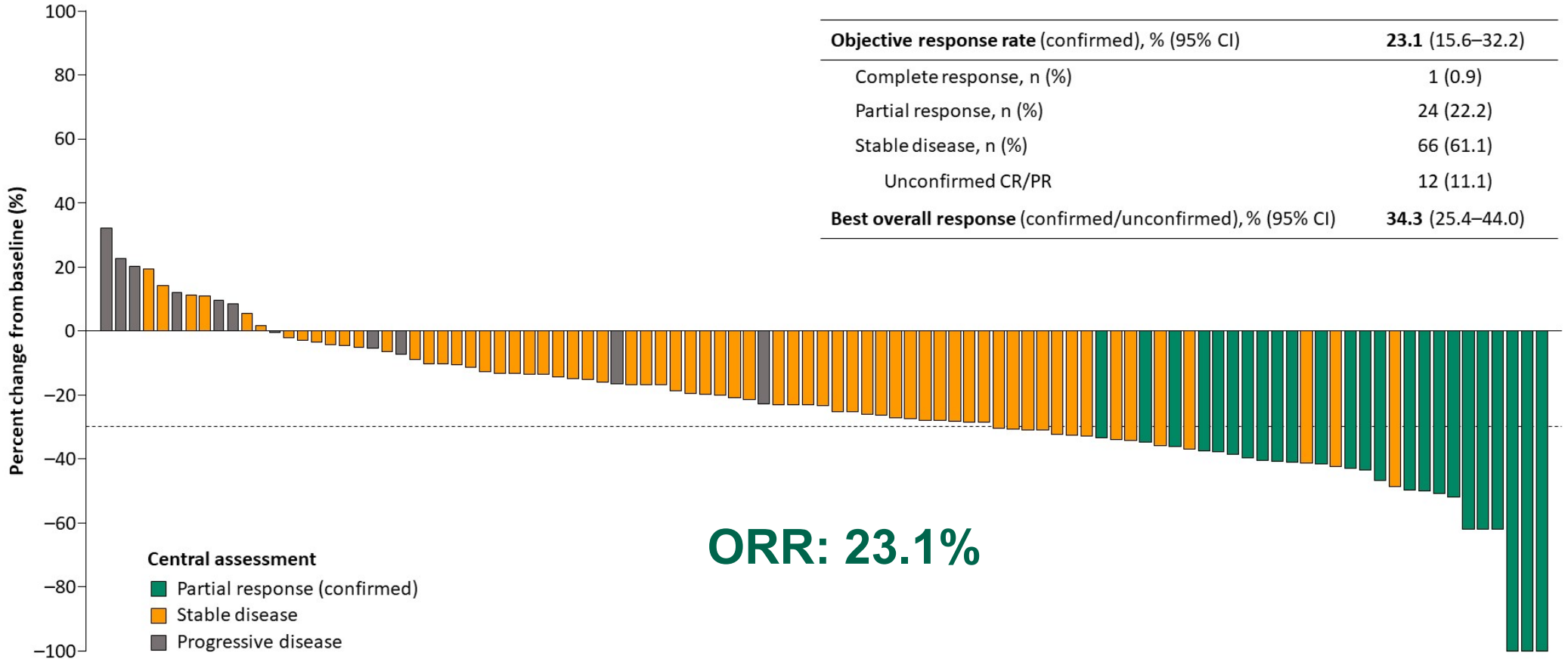
- *FGFR* fusions are found in up to ~14% of intrahepatic CCA cases and predict tumor sensitivity to FGFR inhibitors[1–4]
- Second-line chemotherapy seems to have limited efficacy in patients with CCA and *FGFR2* fusions, similar to that reported in the general CCA population:
  - A retrospective analysis of 37 patients with *FGFR2* fusions who received second-line chemotherapy showed a median PFS of only 4.6 months and an ORR of 5.4%[5]
- Infigratinib (BGJ398), an ATP-competitive FGFR1–3-selective oral tyrosine kinase inhibitor, has shown preliminary clinical activity against tumors with *FGFR* alterations[6]
- In early-phase clinical evaluation, infigratinib showed a manageable safety profile and single-agent activity[3,7]

1. Graham RP, et al. Hum Pathol 2014;45:1630–8; 2. Arai Y, et al. Hepatology 2014;59:1427–34; 3. Javle MM, et al. J Clin Oncol 2016;34(suppl 4S; abstr 335)
4. Lowery MA, et al. Clin Cancer Res 2018;24:4154–61; 5. Javle M, et al. Proc ASCO 2020 (poster #4591); 6. Guagnano V, et al. Cancer Discov 2012;2:1118–33; 7. Nogova L, et al. J Clin Oncol 2017;35:157–65

Javle M et al. Gastrointestinal Cancers Symposium 2021;Abstract 265.

Best percentage change in target-lesion size: ORR confirmed responses by BICR

Objective response rate (confirmed), % (95% CI)	**23.1** (15.6–32.2)
Complete response, n (%)	1 (0.9)
Partial response, n (%)	24 (22.2)
Stable disease, n (%)	66 (61.1)
Unconfirmed CR/PR	12 (11.1)
Best overall response (confirmed/unconfirmed), % (95% CI)	**34.3** (25.4–44.0)



Only patients with measurable disease at baseline and with at least one post-baseline scan are shown in the waterfall plot (n=100)

Javle M et al. Gastrointestinal Cancers Symposium 2021;Abstract 265.

Colorectal Cancer

RTP
RESEARCH
TO PRACTICE

FDA Approves Encorafenib in Combination with Cetuximab for Metastatic Colorectal Cancer with a BRAF V600E Mutation

Press Release – April 8, 2020

"On April 8, 2020, the Food and Drug Administration approved encorafenib in combination with cetuximab for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, detected by an FDA-approved test, after prior therapy.

Efficacy was evaluated in a randomized, active-controlled, open-label, multicenter trial (BEACON CRC; NCT02928224). Eligible patients were required to have BRAF V600E mutation-positive metastatic CRC with disease progression after one or two prior regimens.

The recommended encorafenib dose is 300 mg orally once daily in combination with cetuximab."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-encorafenib-combination-cetuximab-metastatic-colorectal-cancer-braf-v600e-mutation

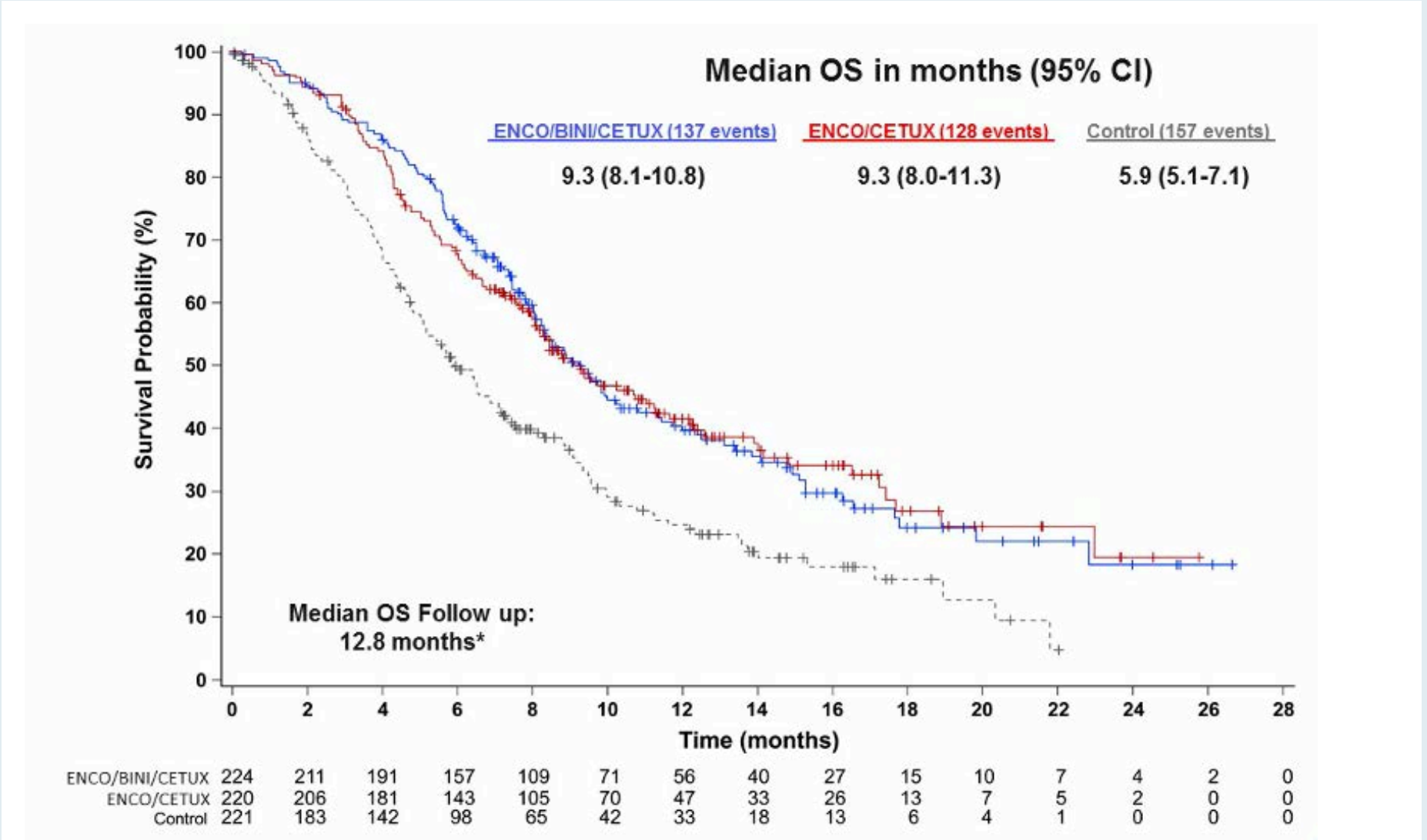
RTP RESEARCH TO PRACTICE

Encorafenib plus Cetuximab with or without Binimetinib for BRAF V600E Metastatic Colorectal Cancer: Updated Survival Results from a Randomized, Three-Arm, Phase III Study versus Choice of Either Irinotecan or FOLFIRI plus Cetuximab (BEACON CRC)

Kopetz S et al.

ASCO 2020;Abstract 4001.

BEACON CRC: Updated Overall Survival Analysis



Kopetz S et al. ASCO 2020;Abstract 4001.

RTP RESEARCH TO PRACTICE

FDA Approves Pembrolizumab for First-Line Treatment of MSI-H/dMMR Colorectal Cancer

Press Release – June 29, 2020

"On June 29, 2020, the Food and Drug Administration approved pembrolizumab for the first-line treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer.

Approval was based on KEYNOTE-177 (NCT02563002), a multicenter, international, open-label, active-controlled, randomized trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR colorectal cancer. Determination of MSI or MMR tumor status was made locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively.

The recommended pembrolizumab dose for MSI-H/dMMR colorectal cancer is 200 mg every 3 weeks or 400 mg every 6 weeks."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-first-line-treatment-msi-hdmmr-colorectal-cancer

RTP RESEARCH TO PRACTICE

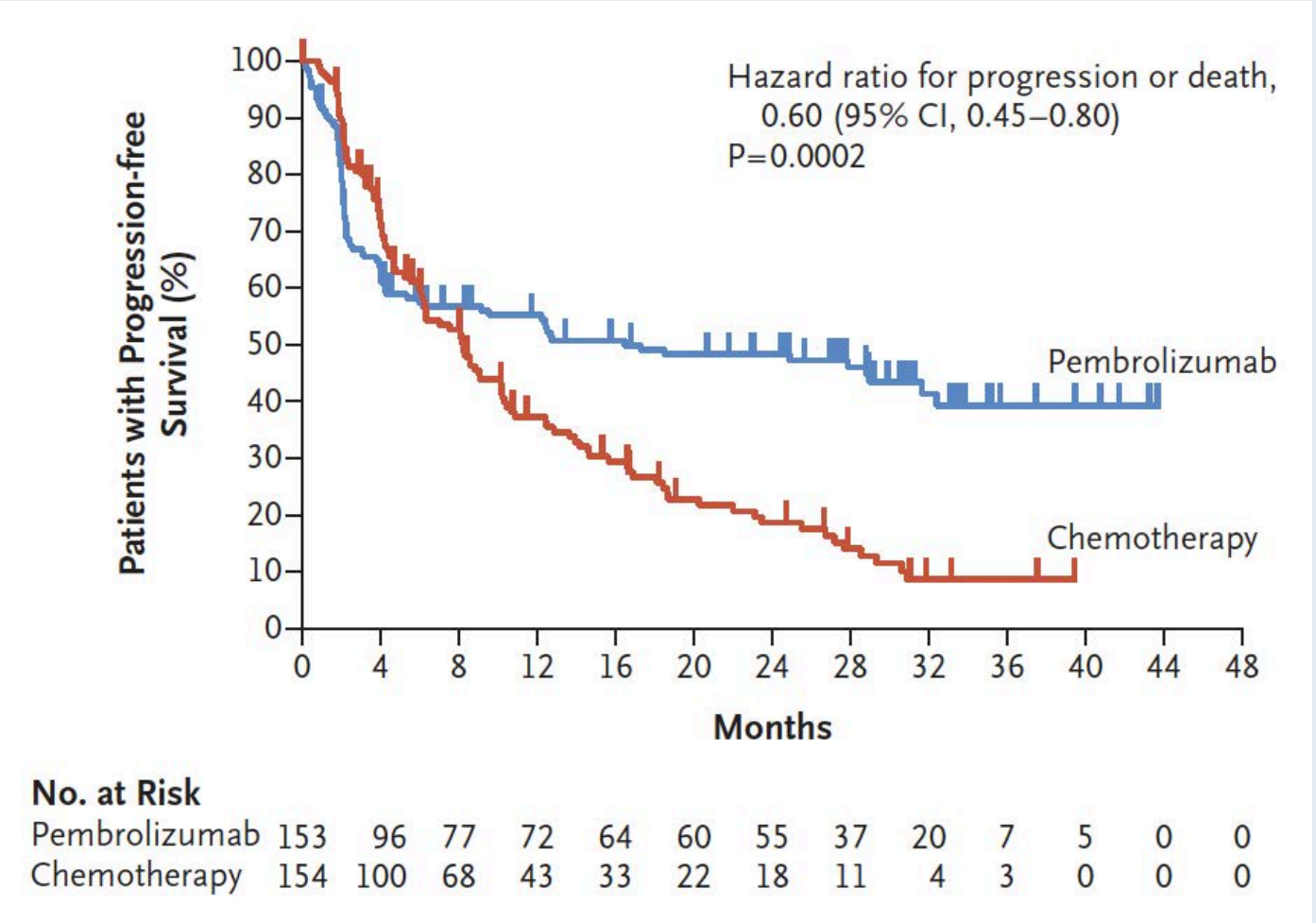
The NEW ENGLAND JOURNAL of MEDICINE

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*

KEYNOTE-177: Primary Survival Endpoints



At the time of data cutoff, data on overall survival were still evolving.

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

KEYNOTE-177: Antitumor Activity

Variable	Pembrolizumab (N = 153)	Chemotherapy (N = 154)
Overall response*		
No. of patients	67	51
% (95% CI)	43.8 (35.8 to 52.0)	33.1 (25.8 to 41.1)
Best response — no. (%)†		
Complete response	17 (11.1)	6 (3.9)
Partial response	50 (32.7)	45 (29.2)
Stable disease	32 (20.9)	65 (42.2)
Progressive disease	45 (29.4)	19 (12.3)
Could not be evaluated or no assessment made‡	9 (5.9)	19 (12.3)
Median time to response (range) — mo	2.2 (1.8 to 18.8)	2.1 (1.7 to 24.9)
Median duration of response (range) — mo§	NR (2.3+ to 41.4+)	10.6 (2.8 to 37.5+)
Response duration of ≥24 months — %§	82.6	35.3

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

RTP RESEARCH TO PRACTICE

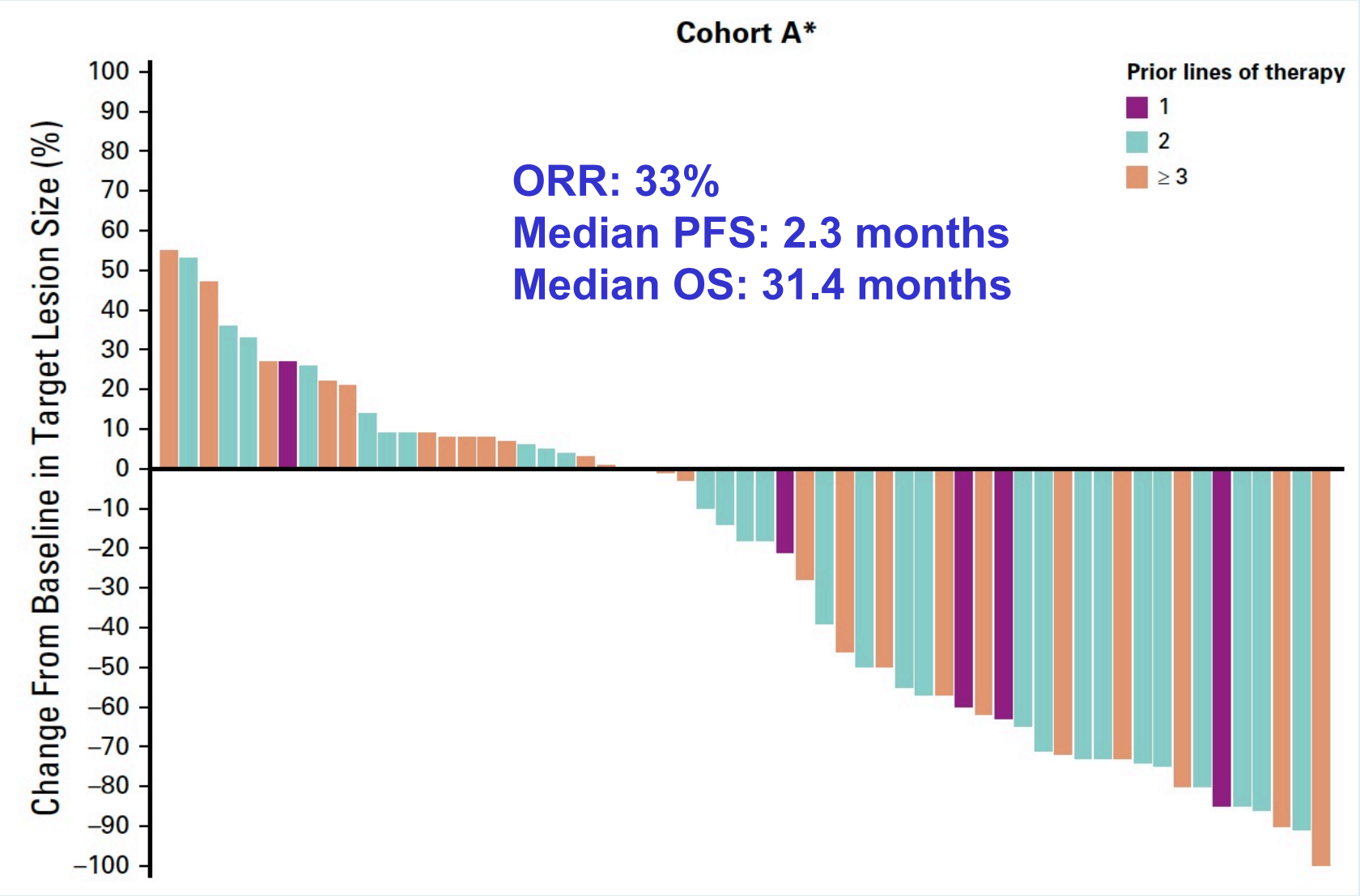
rapid communications

Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability–High/Mismatch Repair–Deficient Metastatic Colorectal Cancer: KEYNOTE-164

Dung T. Le, MD[1]; Tae Won Kim, MD[2]; Eric Van Cutsem, MD, PhD[3]; Ravit Geva, MD[4]; Dirk Jäger, MD[5]; Hiroki Hara, MD[6]; Matthew Burge, MBChB, FRACP[7]; Bert O'Neil, MD[8]; Petr Kavan, MD, PhD[9]; Takayuki Yoshino, MD[10]; Rosine Guimbaud, MD, PhD[11]; Hiroya Taniguchi, MD, PhD[12]; Elena Elez, MD, PhD[13]; Salah-Eddin Al-Batran, MD[14]; Patrick M. Boland, MD[15]; Todd Crocenzi, MD[16]; Chloe E. Atreya, MD, PhD[17]; Yi Cui, PhD[18]; Tong Dai, MD, PhD[19]; Patricia Marinello, PharmD[19]; Luis A. Diaz Jr, MD[20]; and Thierry André, MD[21]

J Clin Oncol 2020;38(1):11-9.

KEYNOTE-164: Pembrolizumab in MSI-H/dMMR Refractory mCRC
Cohort A – ≥2 prior lines of standard therapy



Le DT et al. *J Clin Oncol* 2020;38(1):11-9.

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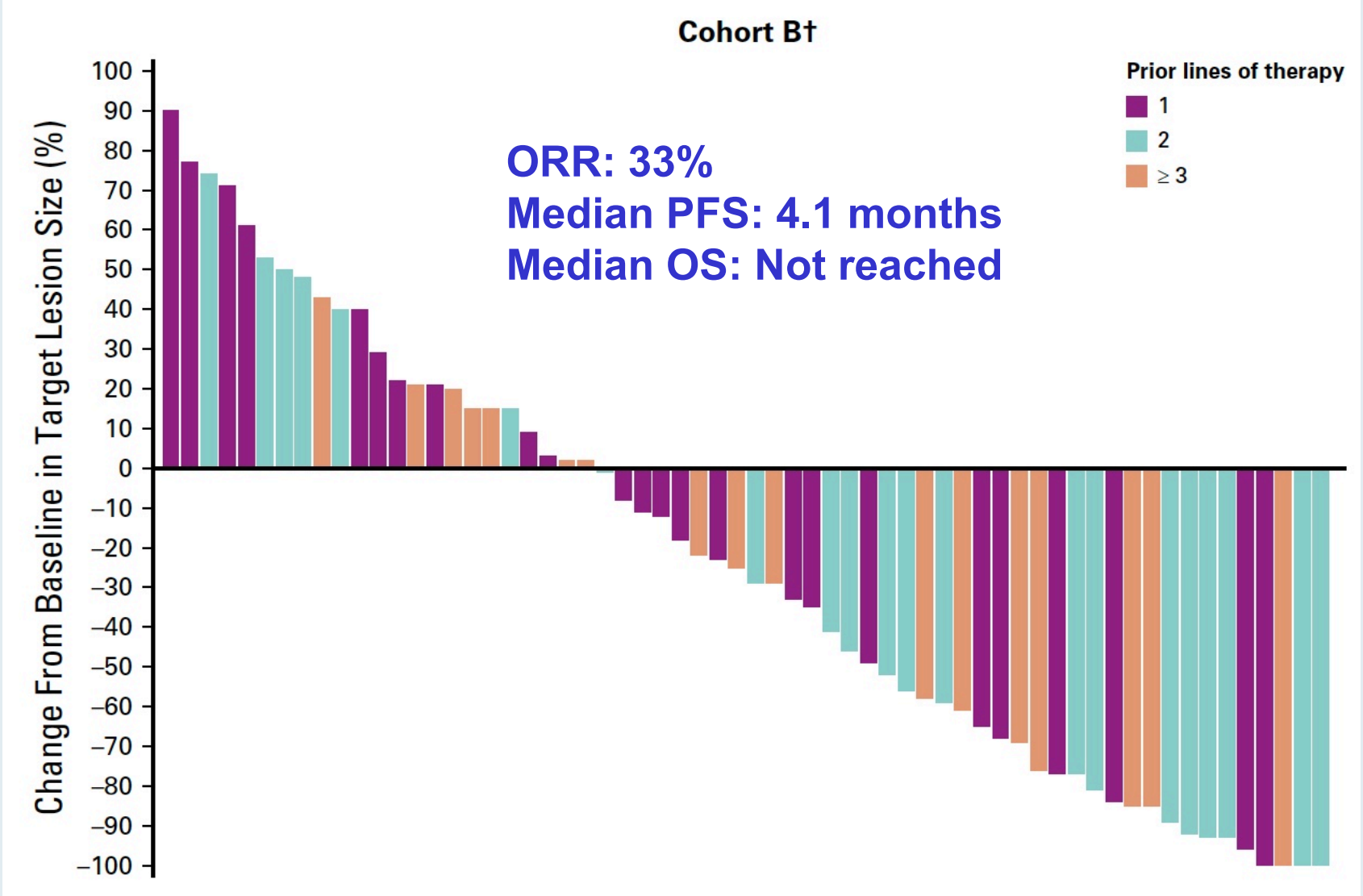
KEYNOTE-164: Pembrolizumab in MSI-H/dMMR Refractory mCRC
Cohort B – ≥1 prior lines of standard therapy



Le DT et al. *J Clin Oncol* 2020;38(1):11-9.

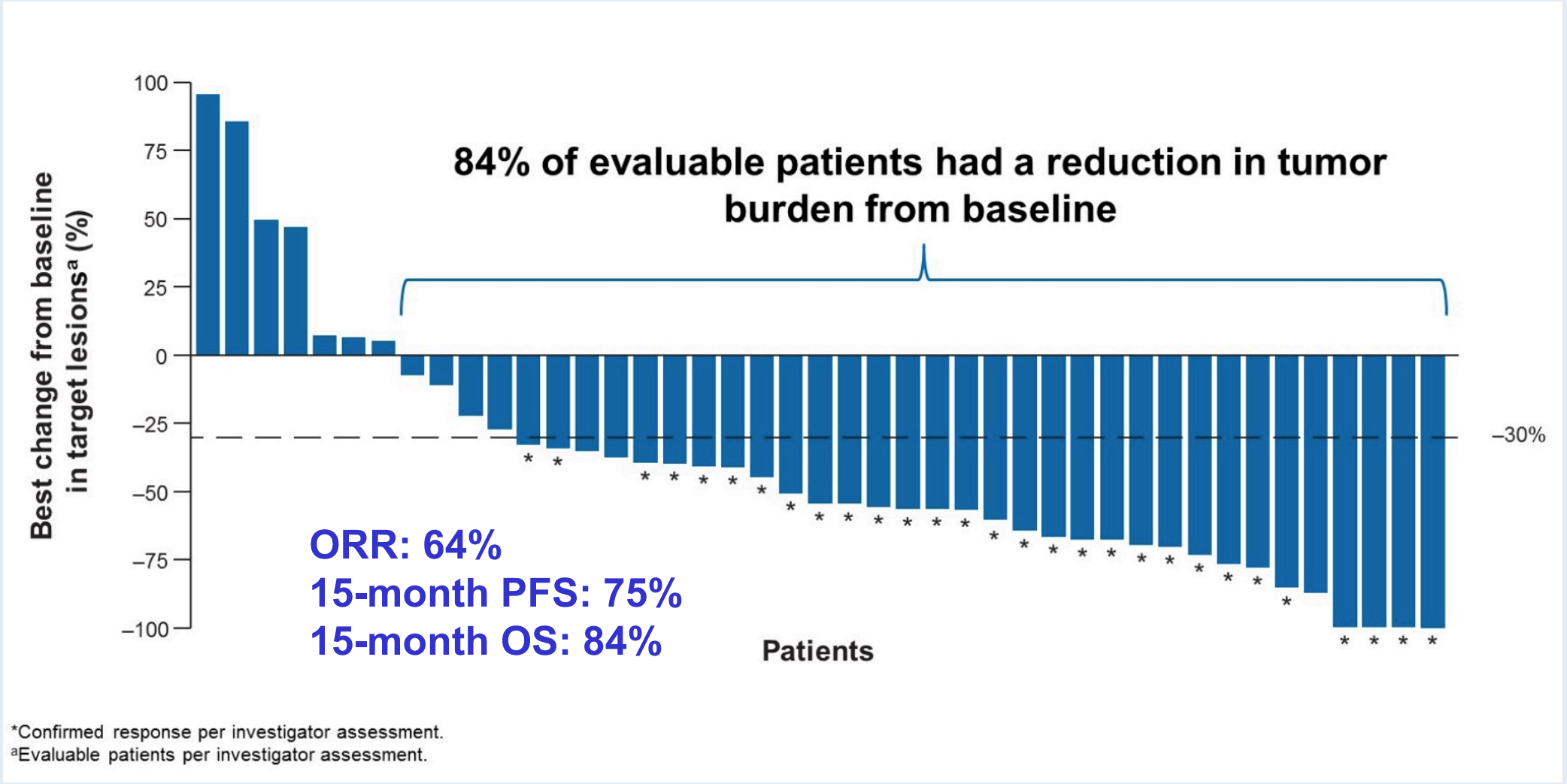
RTP RESEARCH TO PRACTICE

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.

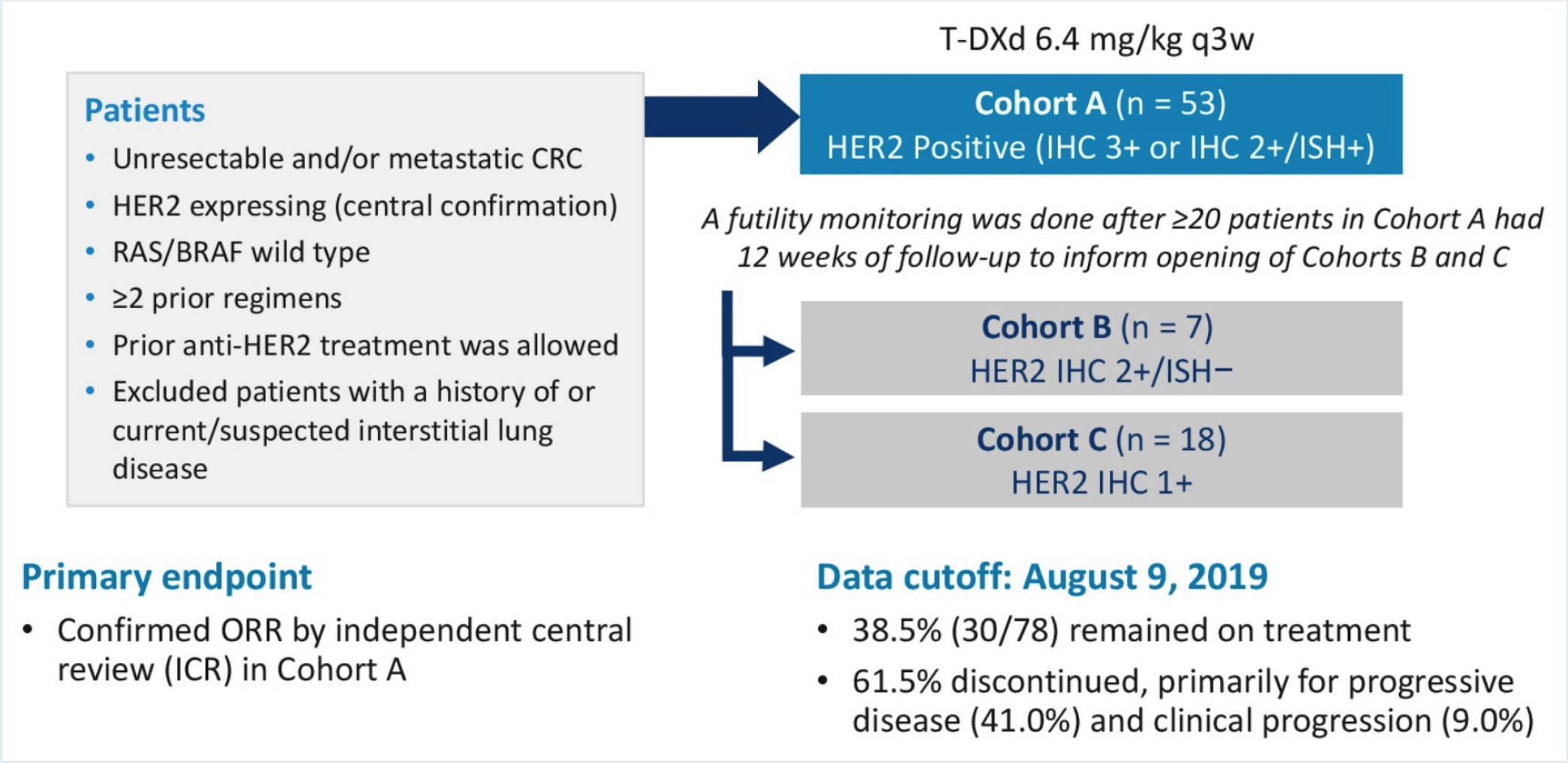
RTP RESEARCH TO PRACTICE

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 Phase II Study Design



Primary endpoint

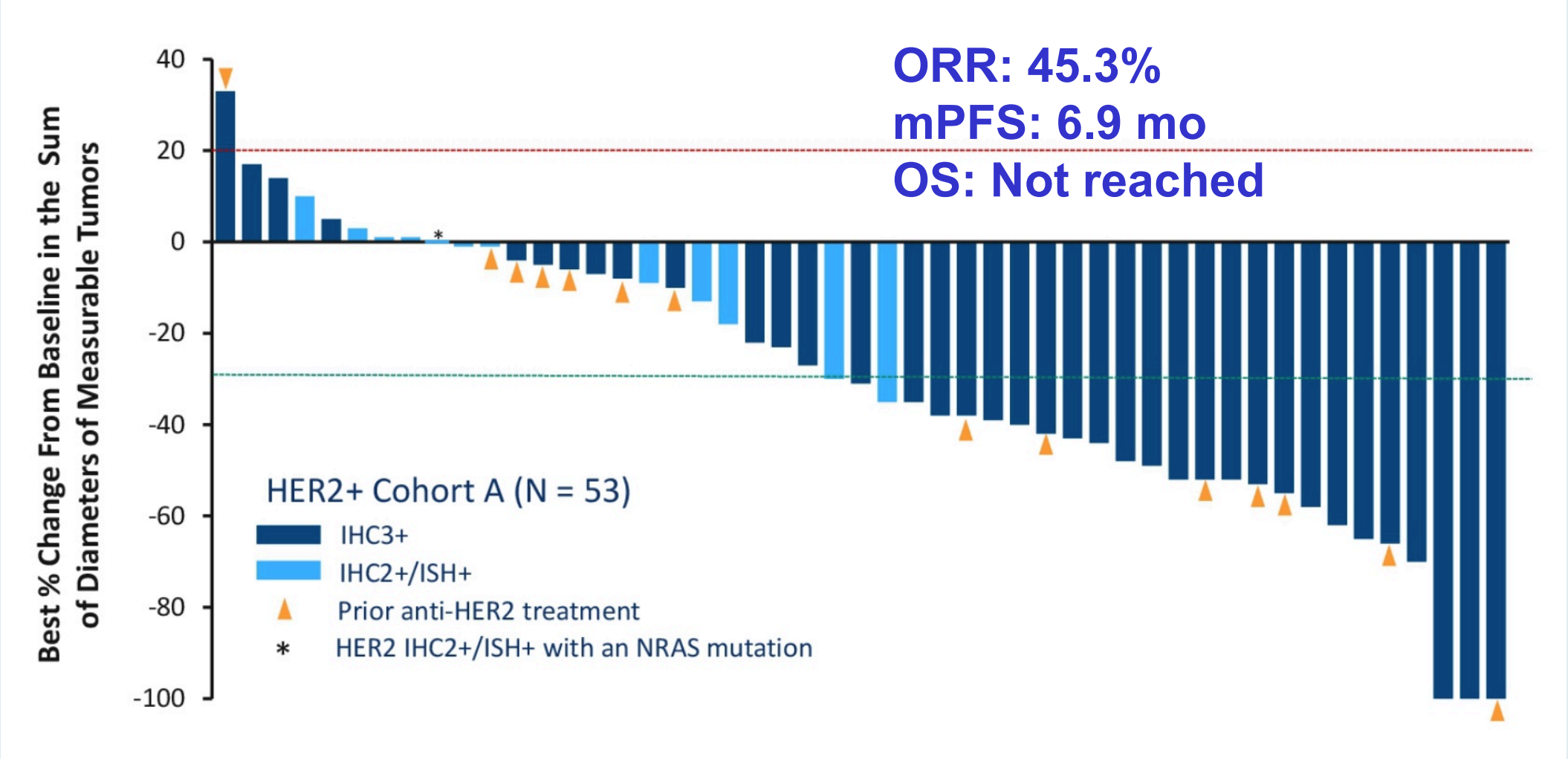
- Confirmed ORR by independent central review (ICR) in Cohort A

Data cutoff: August 9, 2019

- 38.5% (30/78) remained on treatment
- 61.5% discontinued, primarily for progressive disease (41.0%) and clinical progression (9.0%)

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.

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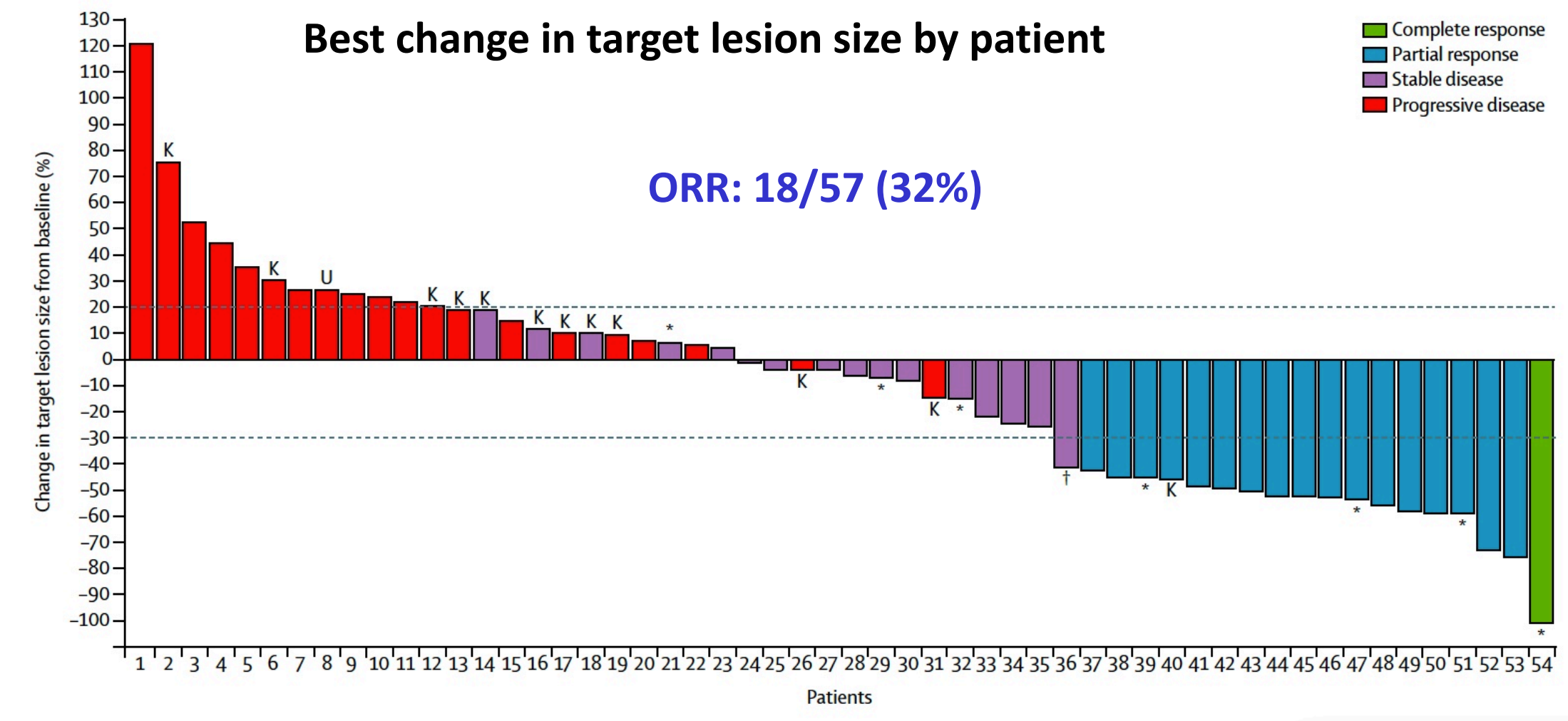
Lancet Oncol 2019;20:518-30

Pertuzumab plus trastuzumab for *HER2*-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study

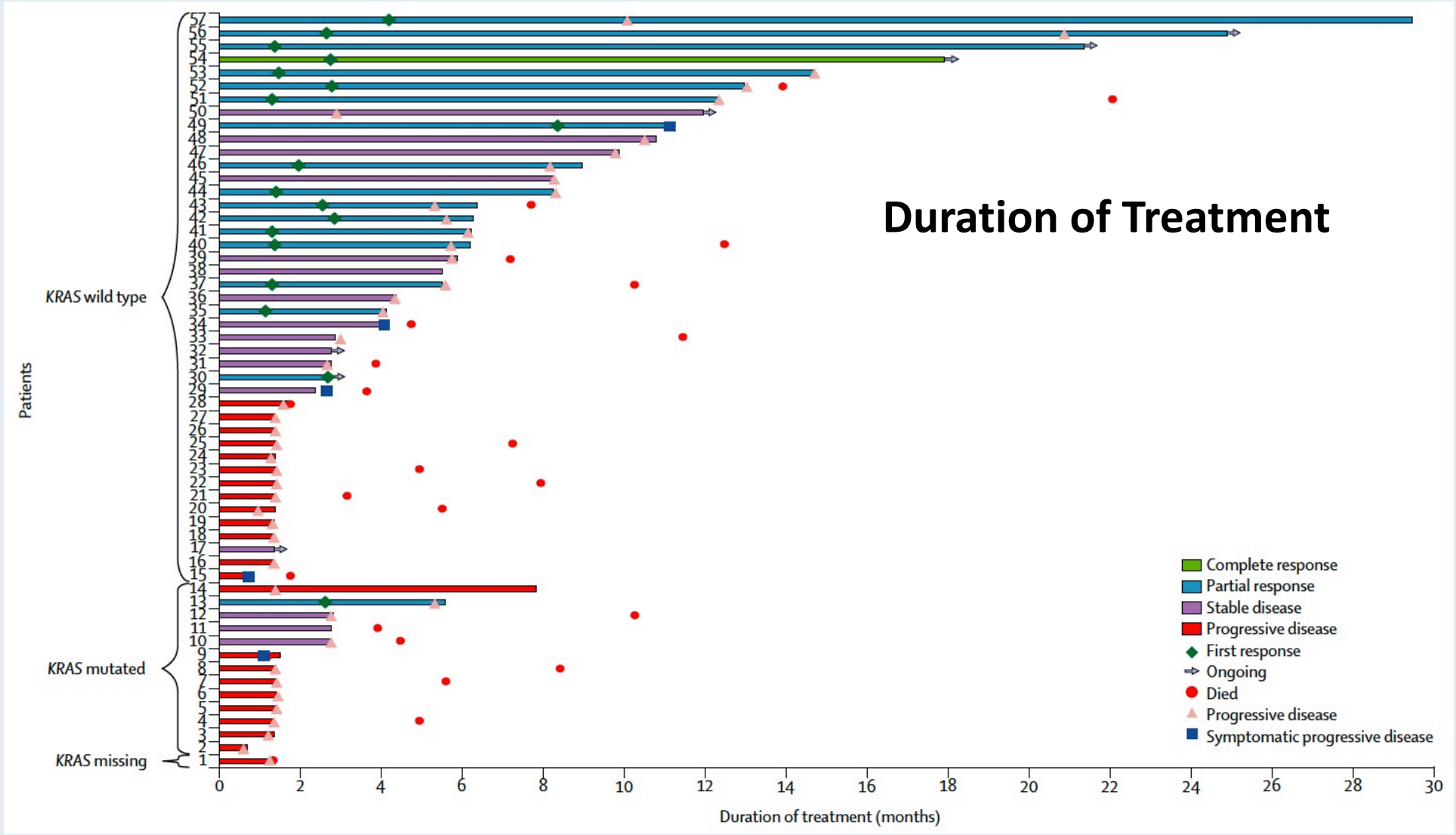
Funda Meric-Bernstam, Herbert Hurwitz*, Kanwal Pratap Singh Raghav, Robert R McWilliams, Marwan Fakih, Ari VanderWalde, Charles Swanton, Razelle Kurzrock, Howard Burris, Christopher Sweeney, Ron Bose, David R Spigel, Mary S Beattie, Steven Blotner, Alyssa Stone, Katja Schulze, Vaikunth Cuchelkar, John Hainsworth*

MyPathway: Pertuzumab with Trastuzumab for HER2-Amplified mCRC



Meric-Bernstam F et al. *Lancet Oncol* 2019;20:518-30.

MyPathway: Pertuzumab with Trastuzumab for HER2-Amplified mCRC



Meric-Bernstam F et al. *Lancet Oncol* 2019;20:518-30.

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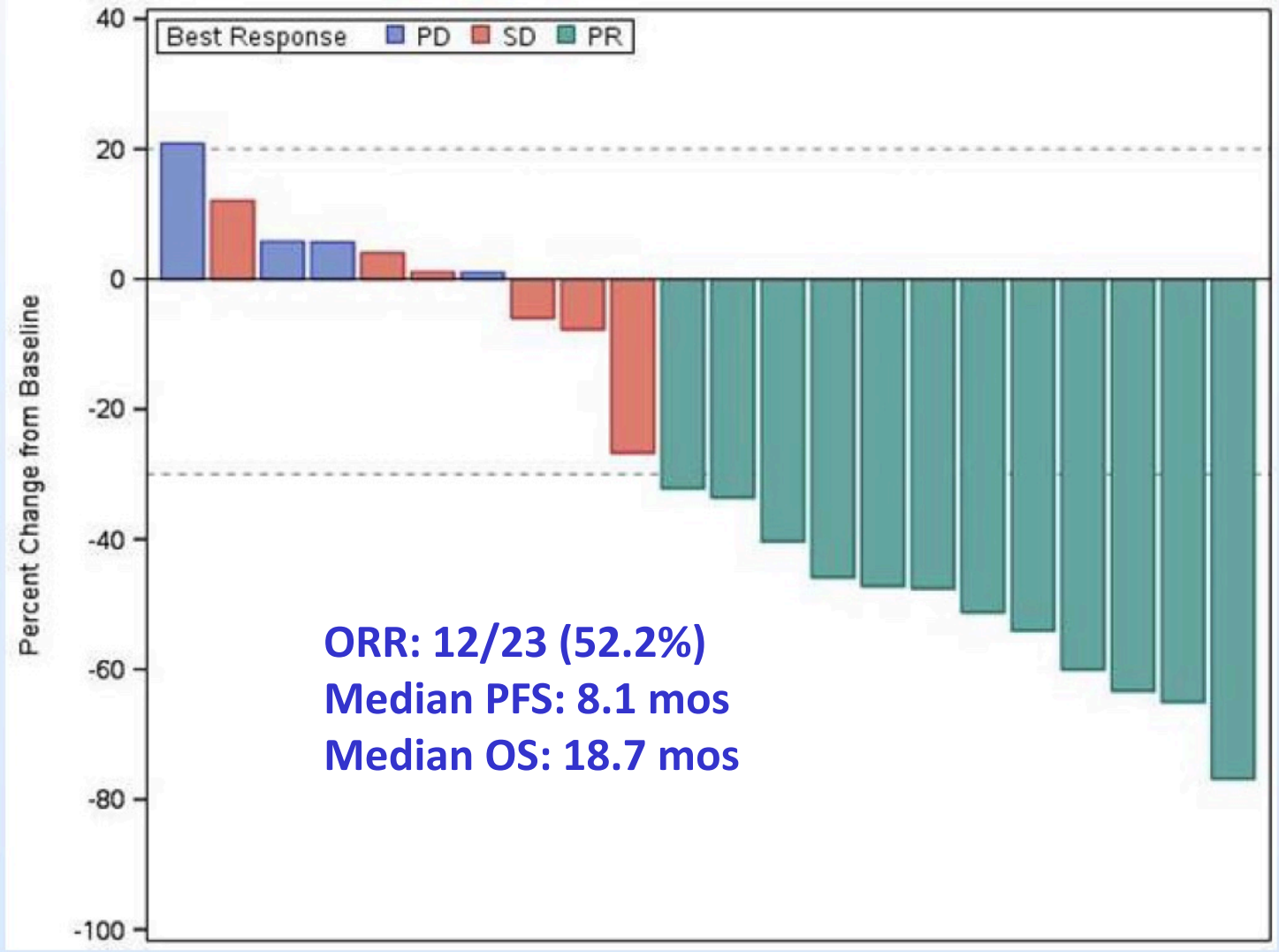
Trastuzumab and Tucatinib for the Treatment of HER2 Amplified Metastatic Colorectal Cancer: Initial Results from the MOUNTAINEER Trial

Strickler JH et al.

ESMO 2019;Abstract 527PD.

MOUNTAINEER: Response and Survival



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

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Renal Cell Carcinoma

Wednesday, February 17, 2021
12:00 PM – 1:00 PM ET

Faculty

Eric Jonasch, MD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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