Meet The Professor
Optimizing the Management of Gastroesophageal Cancers

Samuel J Klempner, MD
Associate Professor
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

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Commercial Support

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

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, the parent company of GHI, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Servier Pharmaceuticals LLC, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc and Zymeworks Inc.

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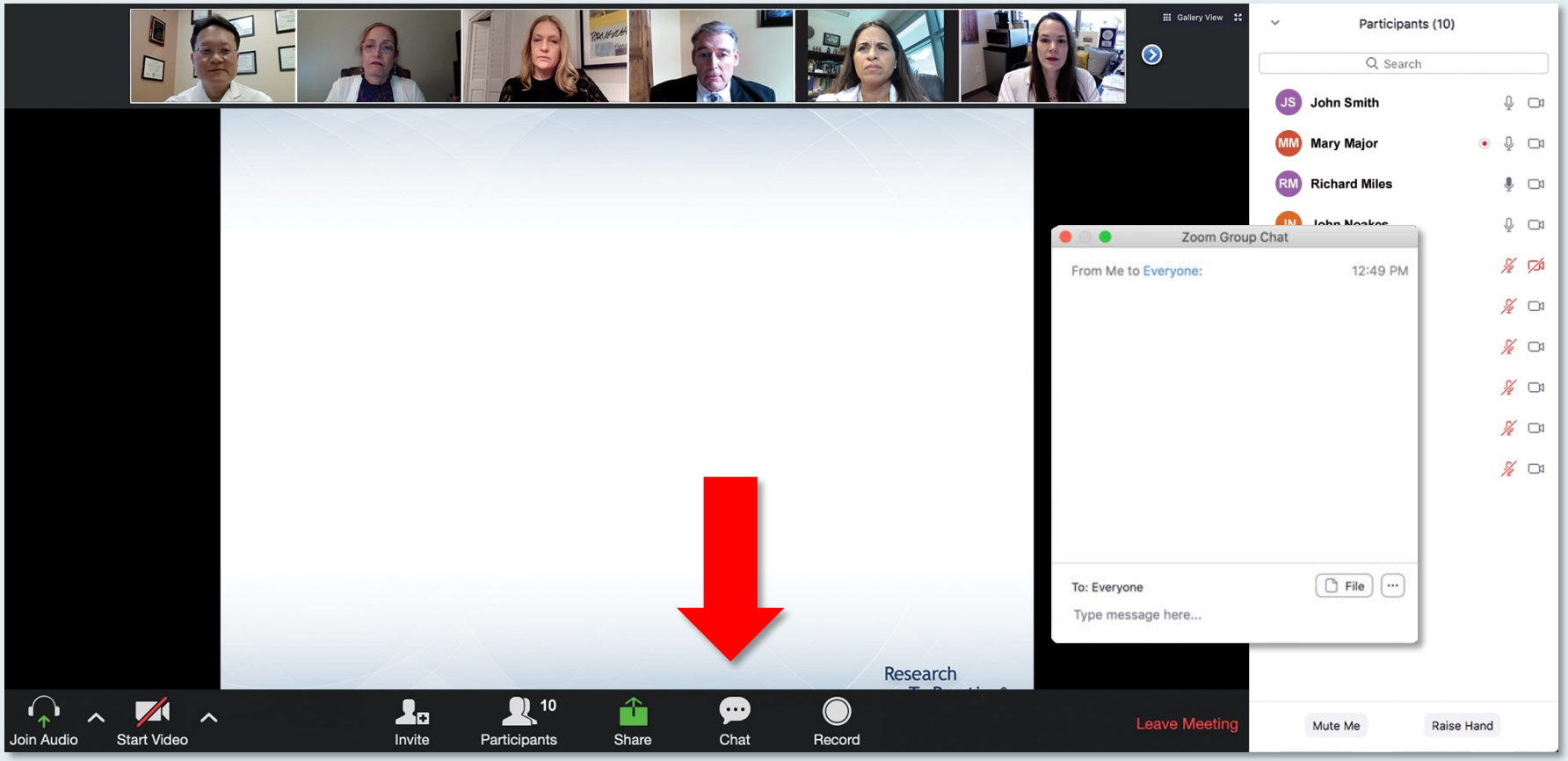
Dr Klempner — Disclosures

No relevant conflicts of interest to disclose.

We Encourage Clinicians in Practice to Submit Questions



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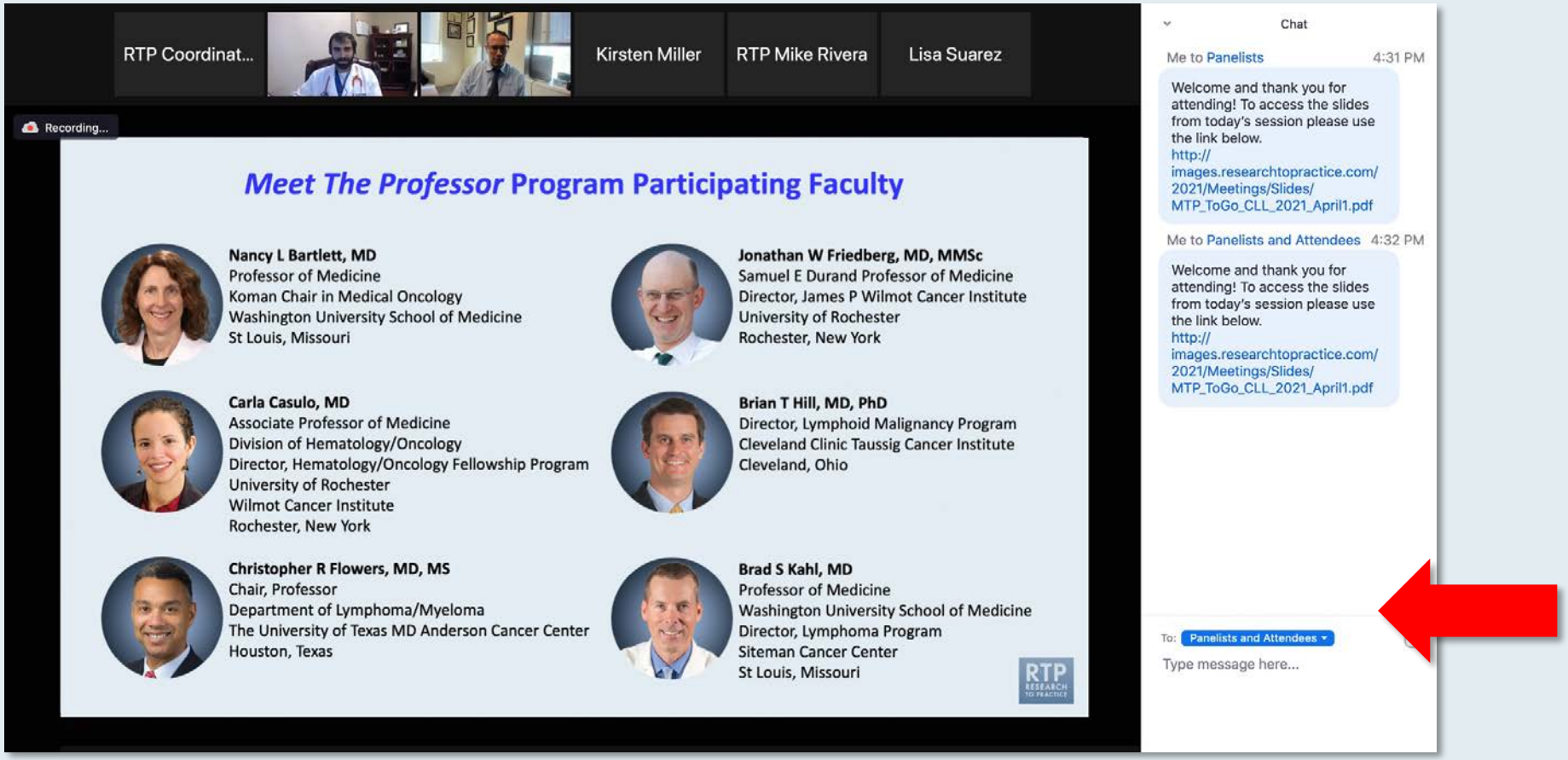

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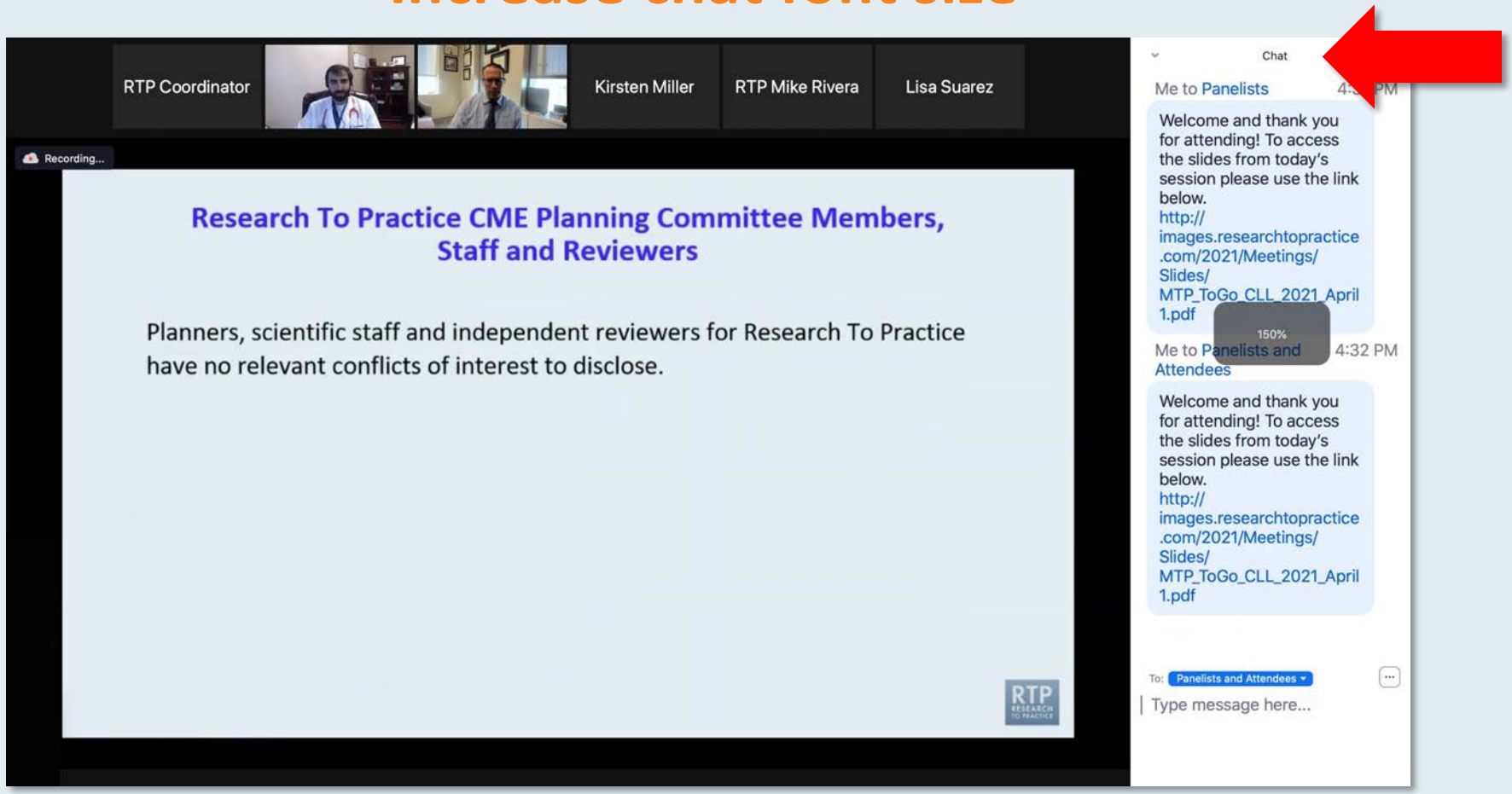

Press Command (for Mac) or Control (for PC) and the + symbol.
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WITH DR NEIL LOVE

Gastroesophageal Cancers

DR SAMUEL KLEMPNER

MASSACHUSETTS GENERAL HOSPITAL

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Management of Acute Myeloid Leukemia and Myelodysplastic Syndromes – A Review of the 2022 ASCO Annual Meeting and EHA Congress

Wednesday, July 13, 2022
5:00 PM – 6:00 PM ET

Faculty

Richard M Stone, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Chronic Myeloid Leukemia

Tuesday, July 19, 2022
5:00 PM – 6:00 PM ET

Faculty

Daniel J DeAngelo, MD, PhD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Hepatobiliary Cancers

Thursday, July 28, 2022
5:00 PM – 6:00 PM ET

Faculty

Robin K Kelley, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Ovarian Cancer

Wednesday, August 3, 2022
5:00 PM – 6:00 PM ET

Faculty

Prof Jonathan A Ledermann

Moderator

Neil Love, MD

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Recent Advances in Medical Oncology:
A daylong CME hybrid (live/online) event

Saturday, August 6, 2022

9:00 AM – 4:30 PM PT (12:00 PM – 7:30 PM ET)

Bellagio Las Vegas | Las Vegas, Nevada

Faculty

Neeraj Agarwal, MD
Harold J Burstein, MD, PhD
Ibiayi Dagogo-Jack, MD
Rafael Fonseca, MD
Brad S Kahl, MD
Rutika Mehta, MD, MPH
Craig Moskowitz, MD
Joyce O'Shaughnessy, MD
Krina Patel, MD, MSc
Philip A Philip, MD, PhD, FRCP
Suresh S Ramalingam, MD
Sandy Srinivas, MD

Moderator

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Meet The Professor

Optimizing the Management of Gastroesophageal Cancers

Tuesday, August 9, 2022
5:00 PM – 6:00 PM ET

Faculty

John Strickler, 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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Meet The Professor
Optimizing the Management of Gastroesophageal Cancers

Samuel J Klempner, MD
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Boston, Massachusetts

Meet The Professor Program Participating Faculty

Peter C Enzinger, MD
Director, Center for Esophageal and Gastric Cancer
Dana-Farber/Brigham and Women's Cancer Center
Institute Physician, Dana-Farber Cancer Institute
Associate Professor, Harvard Medical School
Boston, Massachusetts

Yelena Y Janjigian, MD
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Chief of Gastrointestinal Oncology Service
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Harvard Medical School
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Chief, Solid Tumor Oncology Service
Director, Gastrointestinal Oncology Program
Co-Director, Center for Advanced Digestive Care
Bartlett Family Professor of Gastrointestinal Oncology
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Eric Van Cutsem, MD, PhD
Professor of Medicine
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Harry H Yoon, MD, MHS
Associate Professor of Oncology
Chair, Gastroesophageal Cancer
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Mayo Clinic Comprehensive
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MODERATOR
Neil Love, MD
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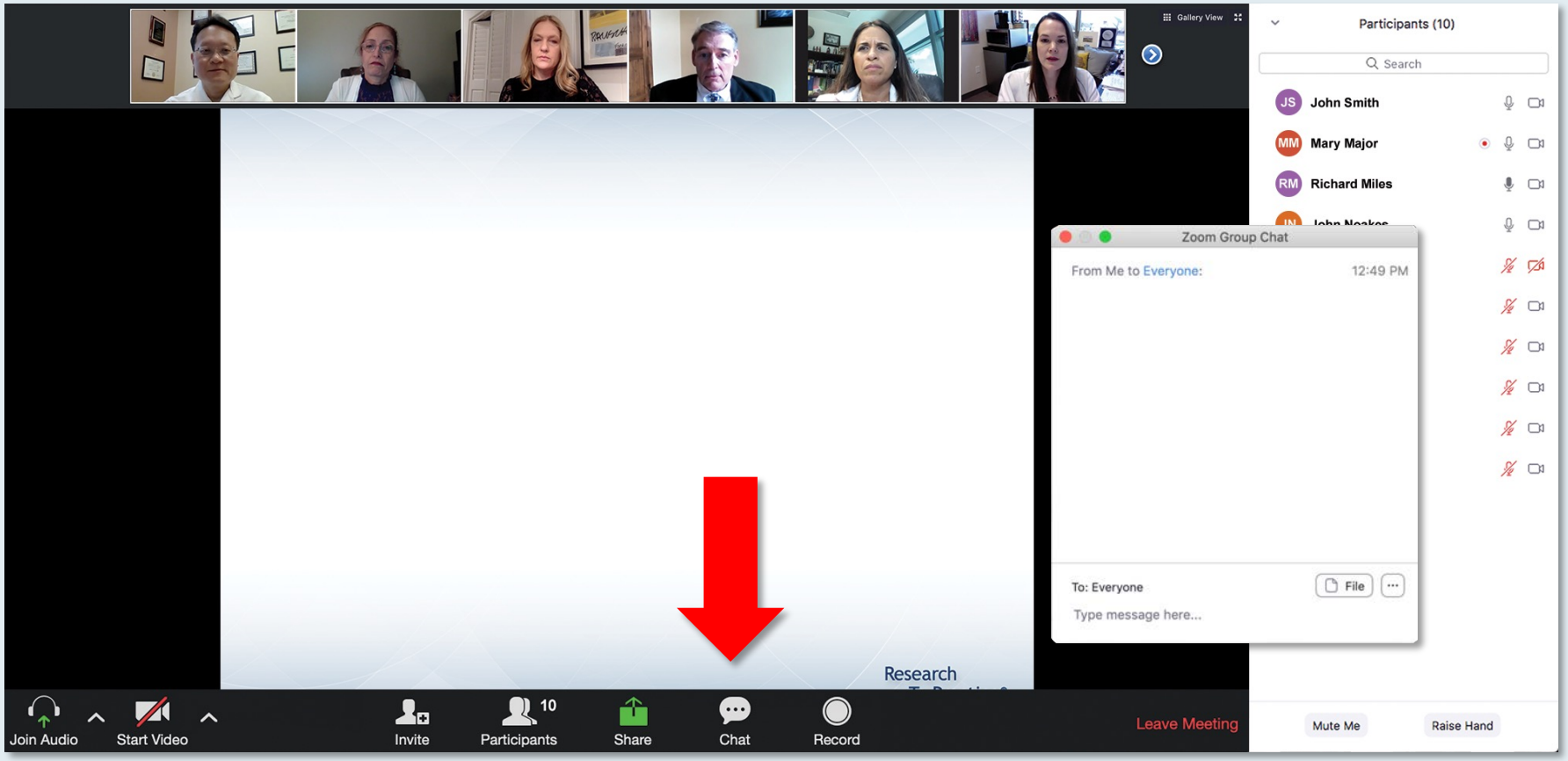

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Research To Practice CME Planning Committee Members, Staff and Reviewers

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

Dr Klempner — Disclosures

No relevant conflicts of interest to disclose.

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Novant Health Cancer Institute
Charlotte, North Carolina

Matthew R Strickland, MD
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Boston, Massachusetts

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Meet The Professor with Dr Klempner: Management of Upper GI Cancers

MODULE 1: HER2-Positive Disease

MODULE 2: MSI-High Disease

MODULE 3: HER2-Negative, Microsatellite-Stable (MSS) Disease

MODULE 4: Appendix of Key Publications

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Meet The Professor with Dr Klempner: Management of Upper GI Cancers

MODULE 1: HER2-Positive Disease

- Dr Gupta: A 76-year-old man with gastric adenocarcinoma and oligometastatic disease to the liver (PD-L1 10%, HER2-positive)
- Dr Bank: A 73-year-old man with locally advanced HER2-positive gastroesophageal junction adenocarcinoma s/p chemoradiation and surgery but develops progressive disease on adjuvant nivolumab; now on CAPOX, trastuzumab (PD-L1 10%, MSS)

MODULE 2: MSI-High Disease

MODULE 3: HER2-Negative, MSS Disease

MODULE 4: Appendix of Key Publications

RTP RESEARCH TO PRACTICE

Case Presentation: A 76-year-old man with gastric adenocarcinoma and oligometastatic disease to the liver (PD-L1 10%, HER2-positive)

Dr Ranju Gupta (Bethlehem, Pennsylvania)

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Case Presentation: A 73-year-old man with locally advanced HER2-positive gastroesophageal junction adenocarcinoma s/p chemoradiation and surgery but develops progressive disease on adjuvant nivolumab; now on CAPOX, trastuzumab (PD-L1 10%, MSS)

Dr Bruce Bank (Rolling Meadows, Illinois)

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what would be your preferred first-line treatment for a patient with newly diagnosed metastatic HER2-positive, MSS gastric adenocarcinoma with a PD-L1 CPS of 0?

 Dr Enzinger	FOLFOX/trastuzumab	 Dr Shah	Trastuzumab/FOLFOX/ pembro
 Dr Janjigian	Trastuzumab/CAPOX/ pembro	 Dr Strickler	FOLFOX/trastuzumab
 Dr Klempner	Trastuzumab/chemo*/ pembro	 Dr Yoon	Trastuzumab/FOLFOX/ pembro

* FOLFOX or CAPOX

Regulatory and reimbursement issues aside, what would be your preferred first-line treatment for a patient with newly diagnosed metastatic HER2-positive, MSS gastric adenocarcinoma with a PD-L1 CPS ≥1?

 Dr Enzinger	Trastuzumab/FOLFOX/ pembro	 Dr Shah	Trastuzumab/FOLFOX/ pembro
 Dr Janjigian	Trastuzumab/CAPOX/ pembro	 Dr Strickler	FOLFOX/trastuzumab
 Dr Klempner	Trastuzumab/CAPOX/ pembro	 Dr Yoon	Trastuzumab/FOLFOX/ pembro

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Regulatory and reimbursement issues aside, what would you currently recommend as second-line therapy for a patient with metastatic HER2-positive, MSS gastric adenocarcinoma (PD-L1 CPS ≥1) with disease progression on FOLFOX/trastuzumab?

 Dr Enzinger	Trastuzumab deruxtecan if HER2+ on rebiopsy	 Dr Shah	Ramucirumab/ paclitaxel
 Dr Janjigian	CAPOX + pembrolizumab	 Dr Strickler	Trastuzumab deruxtecan
 Dr Klempner	Ramucirumab/ paclitaxel	 Dr Yoon	Ramucirumab/ paclitaxel

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Regulatory and reimbursement issues aside, what would you currently recommend as second-line therapy for a patient with metastatic HER2-positive, MSS gastric adenocarcinoma (PD-L1 CPS ≥1) with disease progression on FOLFOX/trastuzumab/pembrolizumab?

 Dr Enzinger	Trastuzumab deruxtecan if HER2+ on rebiopsy	 Dr Shah	Ramucirumab/ paclitaxel
 Dr Janjigian	Trastuzumab deruxtecan	 Dr Strickler	Trastuzumab deruxtecan
 Dr Klempner	Ramucirumab/ paclitaxel	 Dr Yoon	Ramucirumab/ paclitaxel

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What have you observed in terms of the tolerability of trastuzumab deruxtecan?

 Dr Enzinger	Nausea often, ILD sometimes	 Dr Shah	Toxic
 Dr Janjigian	Fine	 Dr Strickler	No significant toxicity
 Dr Klempner	Similar to chemo, cytopenias and GI symptoms	 Dr Yoon	Significant fatigue

ILD = interstitial lung disease

At what grade of ILD would you permanently discontinue therapy with trastuzumab deruxtecan for a patient with HER2-positive gastric/GEJ adenocarcinoma?

 Dr Enzinger	Grade 3	 Dr Shah	Grade 2
 Dr Janjigian	Grade 2	 Dr Strickler	Grade 2
 Dr Klempner	Grade 2	 Dr Yoon	Grade 2

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Have you or would you offer trastuzumab deruxtecan to a patient with HER2-low gastric/GEJ adenocarcinoma outside of a clinical trial?

 Dr Enzinger	I have not but would for the right patient	 Dr Shah	I have not but would for the right patient
 Dr Janjigian	I have	 Dr Strickler	I have not and would not
 Dr Klempner	I have not and would not	 Dr Yoon	I have not and would not

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WORLD CONGRESS ON Gastrointestinal Cancer

SO-7

Co-occurring HER2 and PD-L1 expression in patients with HER2-positive trastuzumab-refractory gastric cancer (GC)/gastroesophageal junction adenocarcinoma (GEJA): biomarker analysis from the trastuzumab deruxtecan (T-DXd) DESTINY-Gastric03 trial

Yelena Y. Janjigian, MD[1]; Sun Young Rha, MD, PhD[2]; Do-Youn Oh, MD, PhD[3]; Marc Díez García, MD[4]; Hanneke van Laarhoven, MD, PhD[5]; Yee Chao, MD, PhD[6]; Maria Di Bartolomeo, MD[7]; Nadia Haj Mohammad, MD, PhD[8]; Wenyan Zhong, PhD[9]; Elizabeth Croydon, MD[10]; Fabiola Cecchi, PhD, PharmD[9]; Jeeyun Lee, MD[11]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Yonsei Cancer Center, Yonsei University College of Medicine, Seodaemun-gu, Seoul, Korea; [3]Seoul National University Hospital, Seoul National University College of Medicine, Jongno-gu, Seoul, Korea; [4]Vall d'Hebron University Hospital-VHIO, Barcelona, Spain; [5]Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; [6]Taipei Veterans General Hospital, National Yang Ming Chiao Tung University, Taipei, Taiwan; [7]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [8]University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands; [9]AstraZeneca Pharmaceuticals LP, Gaithersburg, MD, USA; [10]AstraZeneca Pharmaceuticals LP, Cambridge, UK; [11]Samsung Medical Center, Sungkyunkwan University School of Medicine, Gangnam-gu, Seoul, Korea

ESMO World Congress on Gastrointestinal Cancer 2022, June 29-July 2, 2022, Barcelona, Spain

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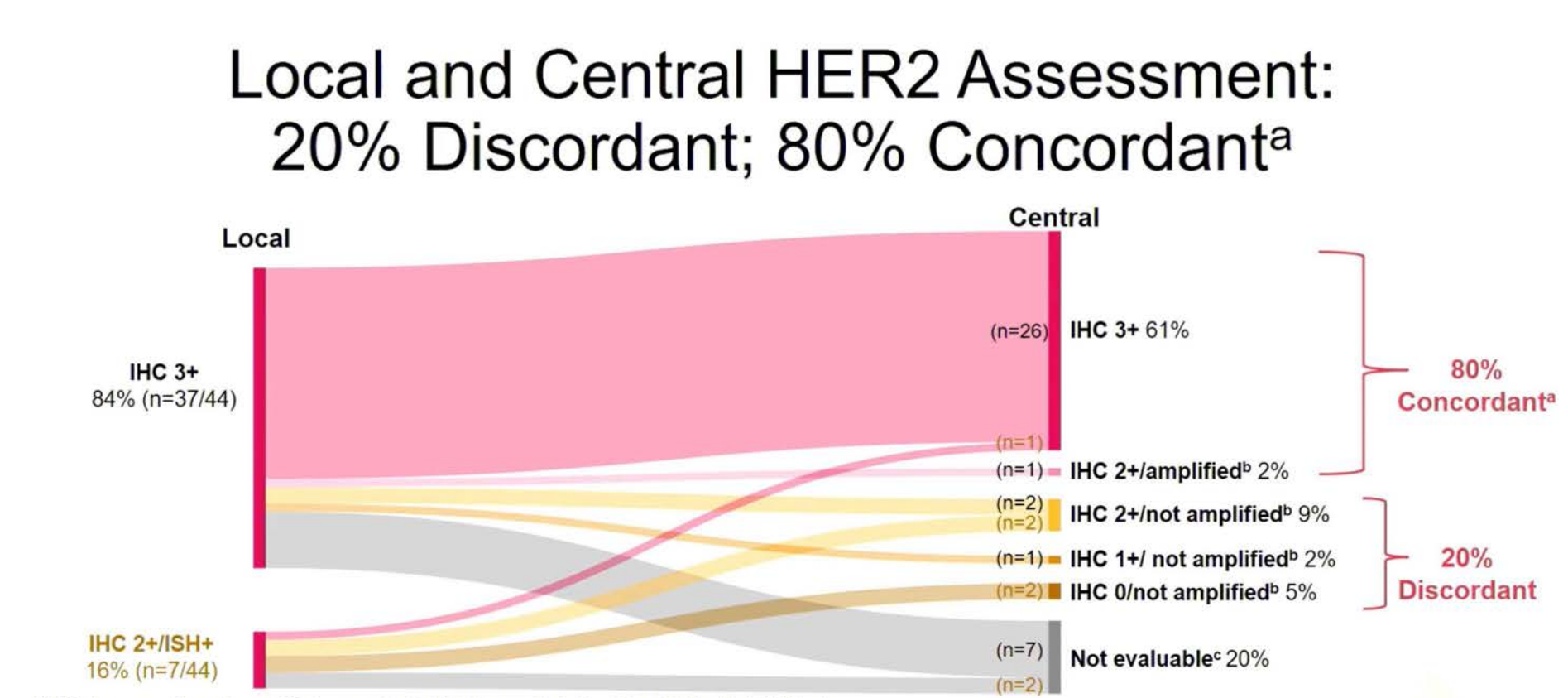
Discordant HER2 Assessment



HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.

[a] Concordance rate was defined as the percentage of samples classified as HER2 positive by both local and central assessment.

[b] HER2 amplification using FoundationOne® (F1CDx).

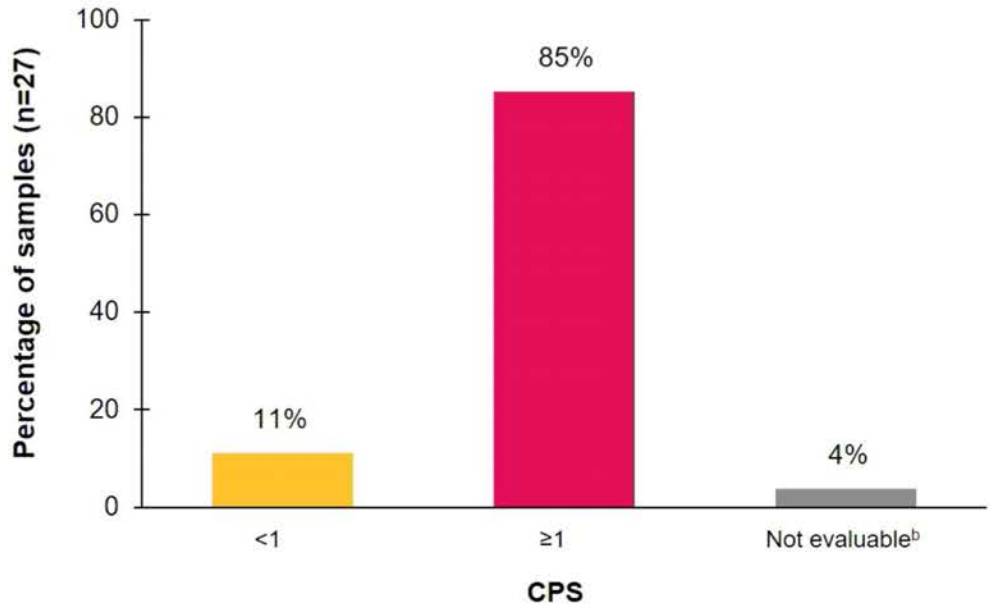
[c] Samples with missing IHC/amplification data due to an insufficient number of tumor cells (<100) on the tissue section for HER2 IHC assessment or insufficient tumor content collected for next-generation sequencing.

Janjigian YY, et al. Co-occurring HER2 and PD-L1 expression in patients with HER2-positive trastuzumab-refractory gastric cancer (GC)/gastroesophageal junction adenocarcinoma (GEJA): biomarker analysis from the trastuzumab deruxtecan (T-DXd) DESTINY-Gastric03 trial. Presented at ESMO World Congress on Gastrointestinal Cancer; June 29-July 2, 2022; Barcelona, Spain. Abstract SO-7.

Janjigian YY et al. ESMO World Congress on Gastrointestinal Cancers;Abstract SO-7.

PD-L1 Expression and HER2 Coexpression

PD-L1 Expression by Central Assessment[a]: 85% PD-L1 Positive



CPS	% (n/N)
CPS <1	11 (3/27)
CPS ≥1	85 (23/27)
CPS ≥1 to <5	37 (10/27)
CPS ≥5	48 (13/27)
Not evaluable[b]	4 (1/27)

CPS, combined positive score; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD-L1, programmed death ligand 1.

[a] PD-L1 expression was centrally assessed using a verified IHC assay (PD-L1 IHC 22C3 pharmDx; Agilent Technologies).

[b] There was an insufficient number of viable tumor cells (<100) present for PD-L1 testing.

Janjigian YY, et al. Co-occurring HER2 and PD-L1 expression in patients with HER2-positive trastuzumab-refractory gastric cancer (GC)/gastroesophageal junction adenocarcinoma (GEJA): biomarker analysis from the trastuzumab deruxtecan (T-DXd) DESTINY-Gastric03 trial. Presented at ESMO World Congress on Gastrointestinal Cancer; June 29-July 2, 2022; Barcelona, Spain. Abstract SO-7.

Janjigian YY et al. ESMO World Congress on Gastrointestinal Cancers;Abstract SO-7.

Support for Dual Anti-HER2 and Anti-PD-L1 Therapy

Conclusions

- In a subset of patients with GC/GEJA in the ongoing DESTINY-Gastric03 trial, 20% discordance was observed between local and central HER2 testing, consistent with previously reported data in GC[1]
  - Discordance may be attributed to tissue heterogeneity
- Substantial overlap (85%) was observed between HER2 and PD-L1 positivity in this GC/GEJA population, consistent with earlier studies[2]
- These data support dual anti-HER2 and anti–PD-L1 therapy in HER2-positive GC/GEJA

GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death ligand 1.

1. Huemer F, et al. *J Clin Med*. 2020;9(4):935. 2. Janjigian YY, et al. *Nature*. 2021;600:727-730.

Janjigian YY, et al. Co-occurring HER2 and PD-L1 expression in patients with HER2-positive trastuzumab-refractory gastric cancer (GC)/gastroesophageal junction adenocarcinoma (GEJA): biomarker analysis from the trastuzumab deruxtecan (T-DXd) DESTINY-Gastric03 trial. Presented at ESMO World Congress on Gastrointestinal Cancer; June 29-July 2, 2022; Barcelona, Spain. Abstract SO-7.

Janjigian YY et al. ESMO World Congress on Gastrointestinal Cancers;Abstract SO-7.

Diseases 2022;10(2):23.

diseases

MDPI

Review

Therapeutic Advances and Challenges in the Management of HER2-Positive Gastroesophageal Cancers

Jeremy Chuang [1], Samuel Klempner [2], Kevin Waters [3], Katelyn Atkins [4], Joseph Chao [1], May Cho [5], Andrew Hendifar [6], Alexandra Gangi [7], Miguel Burch [8], Pareen Mehta [9] and Jun Gong [10,*]

ERBB2 Copy Number (CN) as a Quantitative Biomarker for Real-World (RW) Outcomes to Anti-HER2 Therapy in Advanced Gastroesophageal Adenocarcinoma (Adv GEA)

Klempner SJ et al.

ASCO 2021;Abstract 4045.

JCO Precis Oncol 2022;6:e2100330.

PRECISION MEDICINE

original reports

ERBB2 Copy Number as a Quantitative Biomarker for Real-World Outcomes to Anti–Human Epidermal Growth Factor Receptor 2 Therapy in Advanced Gastroesophageal Adenocarcinoma

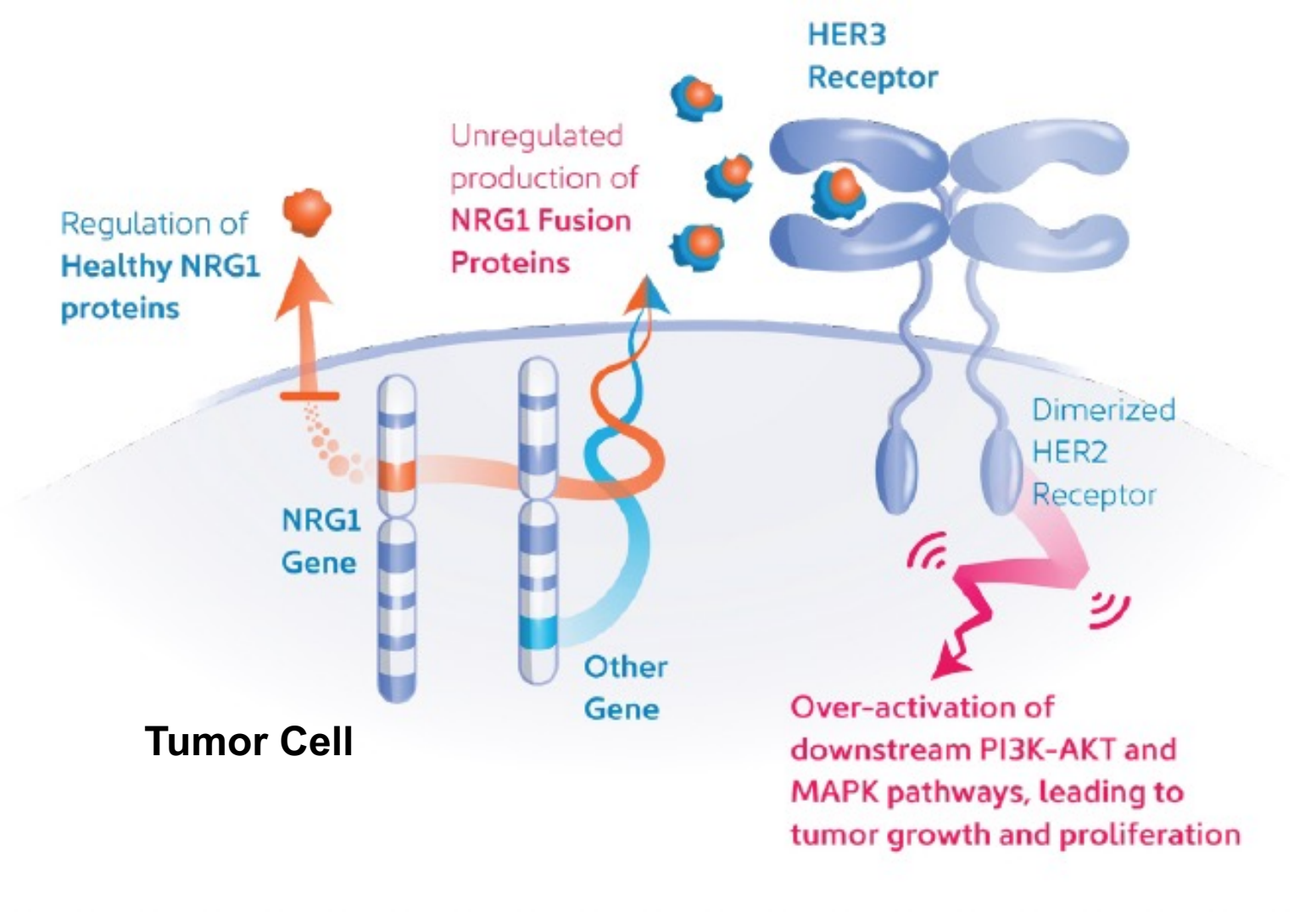
Liangliang Zhang, PhD[1]; Omar Hamdani, PhD[1]; Ole Gjoerup, PhD[1]; Cheryl Cho-Phan, MD[2]; Jeremy Snider, PhD[2]; Emily Castellanos, MD, MPH[2]; Halla Nimeiri, MD[1]; Garrett Frampton, PhD[1]; Jeffrey M. Venstrom, MD[1]; Geoffrey Oxnard, MD[1]; Samuel J. Klempner, MD[3]; and Alexa B. Schrock, PhD[1]

CRESTONE: Clinical Study of Response to Seribantumab in Tumors with Neuregulin-1 (NRG1) Fusions—A Phase II Study of the Anti-HER3 mAb for Advanced or Metastatic Solid Tumors (NCT04383210)

Bendell JC et al.

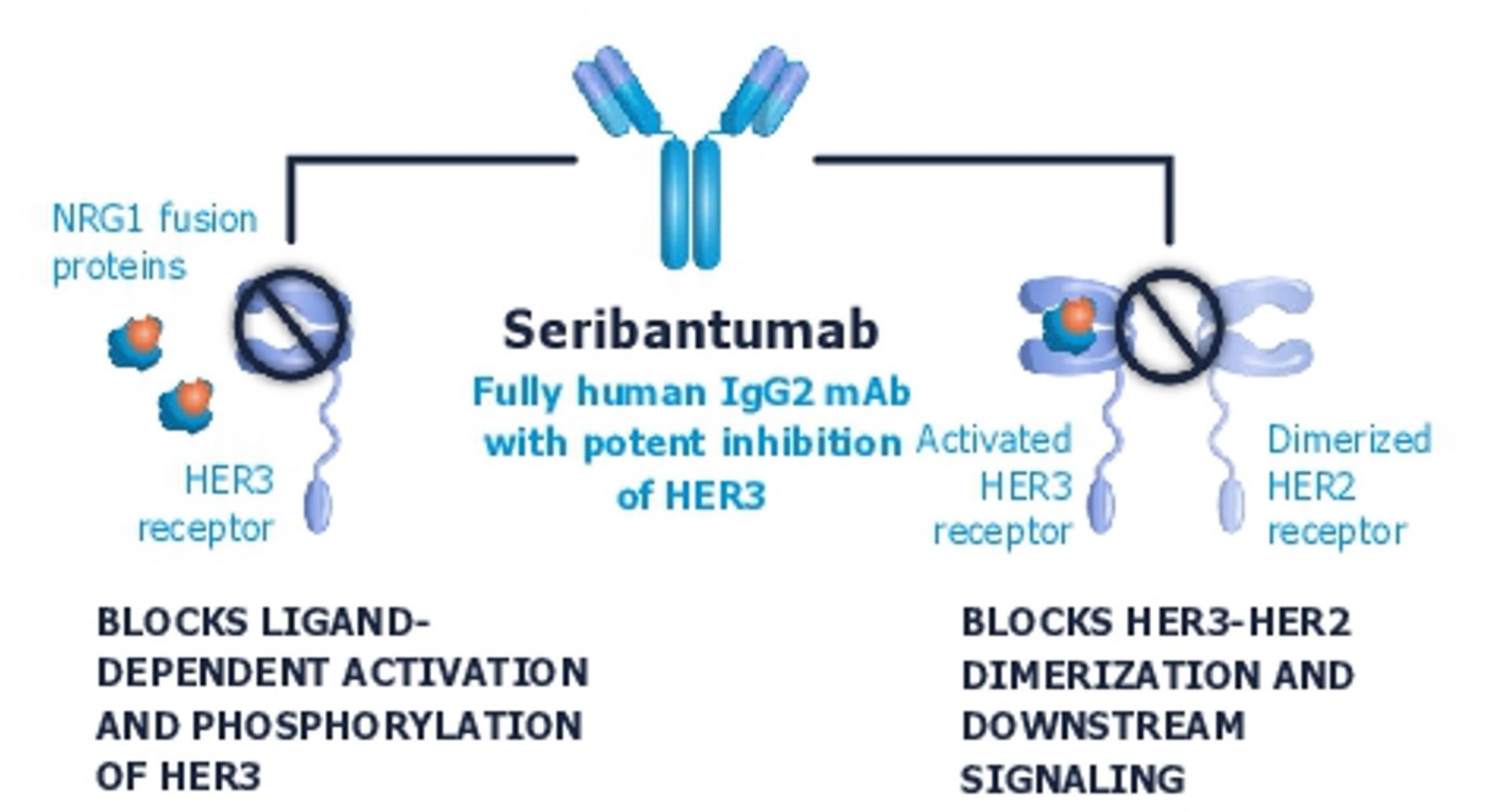
Gastrointestinal Cancers Symposium 2021;Abstract TPS449.

NRG1 Fusion Activation of HER3 and Downstream Pathways



Bendell JC et al. Gastrointestinal Cancers Symposium 2021;Abstract TPS449.

Seribantumab Inhibition of HER3 and Downstream Pathways



Bendell JC et al. Gastrointestinal Cancers Symposium 2021;Abstract TPS449.

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MODULE 1: HER2-Positive Disease

MODULE 2: MSI-High Disease

MODULE 3: HER2-Negative, MSS Disease

MODULE 4: Appendix of Key Publications

RTP RESEARCH TO PRACTICE

A patient with HER2-negative, microsatellite instability (MSI)-high gastric adenocarcinoma receives preoperative FLOT, undergoes resection and has significant residual disease at surgery. Regulatory and reimbursement issues aside, what would you generally recommend?

 Dr Enzinger	Switch to FOLFOX + nivolumab postoperatively	 Dr Shah	No treatment
 Dr Janjigian	Switch to nivo or pembro monotherapy postoperatively	 Dr Strickler	Switch to nivo or pembro monotherapy postoperatively
 Dr Klempner	Switch to nivo or pembro monotherapy postoperatively	 Dr Yoon	Switch to pembro monotherapy postoperatively

Nivo = nivolumab; pembro = pembrolizumab

Outside of a clinical trial, would you attempt to access an anti-PD-1/PD-L1 antibody as part of neoadjuvant therapy for a patient with MSI-high gastroesophageal cancer?

 Dr Enzinger	No	 Dr Shah	Yes
 Dr Janjigian	Yes	 Dr Strickler	Yes
 Dr Klempner	Yes	 Dr Yoon	Yes

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Regulatory and reimbursement issues aside, which first-line therapy would you most likely recommend for a 65-year-old patient presenting with metastatic HER2-negative, MSI-high gastric adenocarcinoma?

 Dr Enzinger	Pembrolizumab	 Dr Shah	FOLFOX + nivolumab
 Dr Janjigian	FOLFOX + nivolumab	 Dr Strickler	FOLFOX + nivolumab
 Dr Klempner	Pembrolizumab	 Dr Yoon	FOLFOX + nivolumab

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Curr Treat Options Oncol 2021;22(11):100.
DOI 10.1007/s11864-021-00893-6

Upper Gastrointestinal Cancers (JD Berlin, Section Editor)

Immunotherapy in Gastroesophageal Cancers: Current Evidence and Ongoing Trials

Jasmine Huynh, MD[1]
Kanishka Patel, MD[1]
Jun Gong, MD[2]
May Cho, MD[3]
Midhun Malla, MD[4]
Aparna Parikh, MD[5]
Samuel Klempner, MD[5,*]

Cancer Discov 2021;11(9):2168-85.

RESEARCH ARTICLE

Determinants of Response and Intrinsic Resistance to PD-1 Blockade in Microsatellite Instability–High Gastric Cancer

Minsuk Kwon[1], Minae An[2], Samuel J. Klempner[3], Hyuk Lee[4], Kyoung-Mee Kim[5], Jason K. Sa[6], Hee Jin Cho[7], Jung Yong Hong[1], Taehyang Lee[1], Yang Won Min[4], Tae Jun Kim[4], Byung-Hoon Min[4], Woong-Yang Park[8], Won Ki Kang[1], Kyu-Tae Kim[9], Seung Tae Kim[1], and Jeeyun Lee[1,10]

Cancer Discov 2021;11(9):2126-28.

VIEWS

IN THE SPOTLIGHT

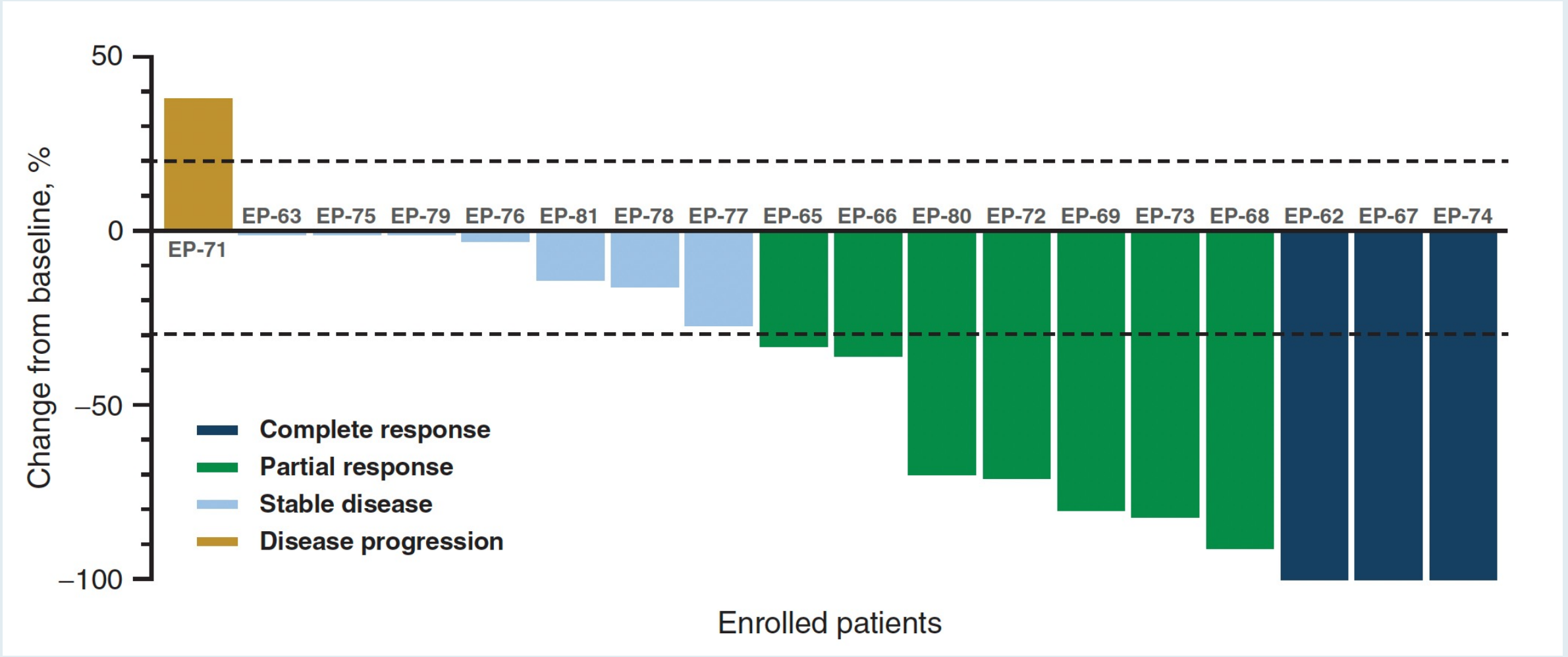
Dissecting Response and Resistance to Anti–PD-1 Therapy in Microsatellite-Unstable Gastric Cancer

Elisa Fontana[1] and Elizabeth C. Smyth[2]

JC JOURNAL CLUB

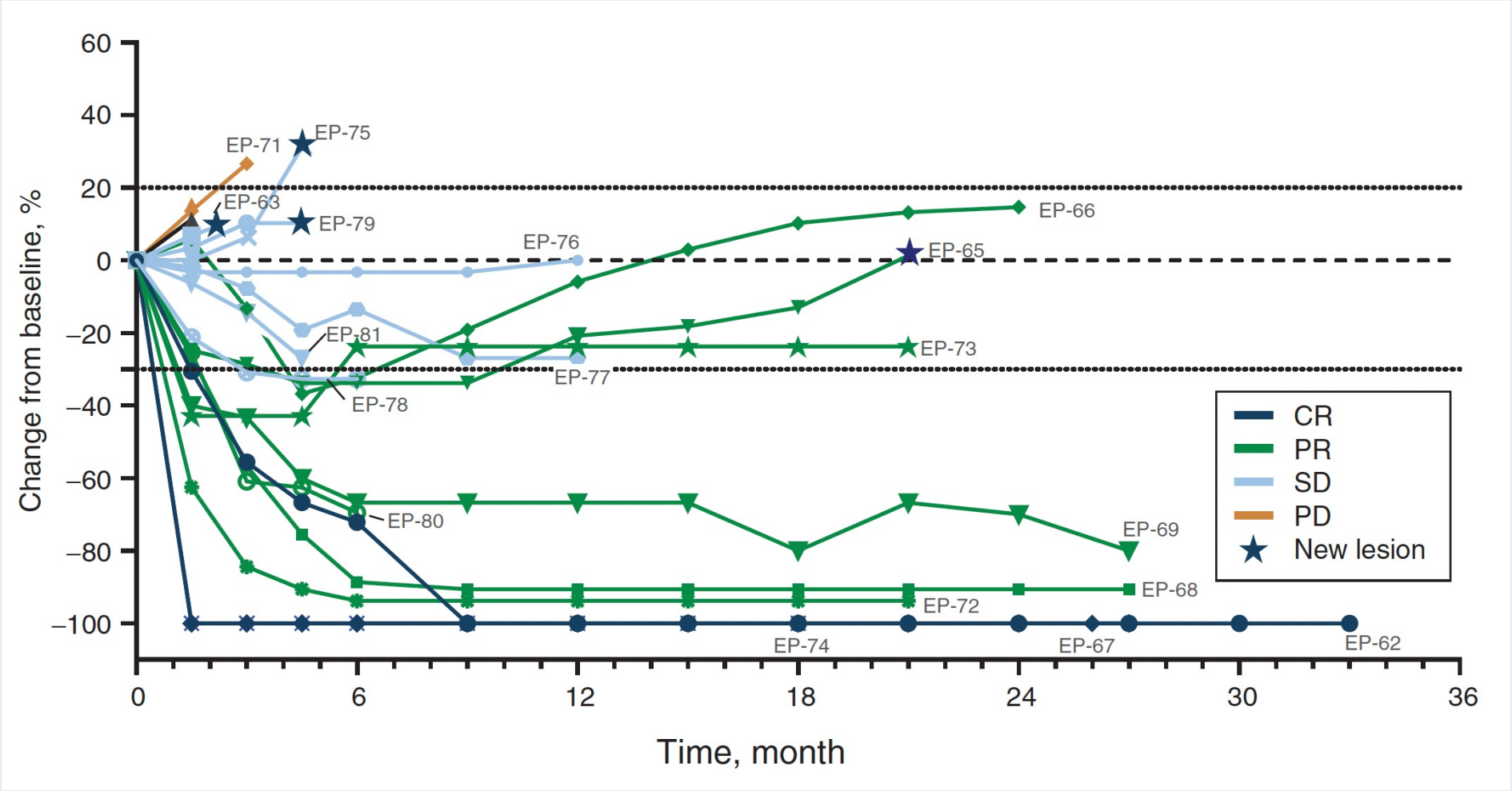
RTP RESEARCH TO PRACTICE

Waterfall Plot of Response to Pembrolizumab in Patients with MSI-High Gastric Cancer



Kwon M et al. *Cancer Discov* 2021;11(9):2168-85.

Spider Plot of the Change in Sum of Target Tumor Measurement from Baseline to Last Assessment



Kwon M et al. *Cancer Discov* 2021;11(9):2168-85.

Clinical Utility of Microsatellite Instability (MSI-H) Identified on Liquid Biopsy in Advanced Gastrointestinal Cancers

Kasi PM et al.

Gastrointestinal Cancers Symposium 2022;Abstract 56.

Open access *J Immunother Cancer* 2022;10(2):e004001. Original research

Journal for ImmunoTherapy of Cancer

Ascites and resistance to immune checkpoint inhibition in dMMR/MSI-H metastatic colorectal and gastric cancers

Giovanni Fucà ,[1] Romain Cohen ,[2] Sara Lonardi ,[3] Kohei Shitara,[4] Maria Elena Elez,[5] Marwan Fakih,[6] Joseph Chao ,[6] Samuel J Klempner,[7,8] Matthew Emmett,[7,8] Priya Jayachandran,[9] Francesca Bergamo,[10] Marc Díez García,[5] Giacomo Mazzoli,[1] Leonardo Provenzano,[1] Raphael Colle,[2] Magali Svrcek,[11] Margherita Ambrosini,[1] Giovanni Randon,[1] Aakash Tushar Shah,[12] Massimiliano Salati,[13] Elisabetta Fenocchio,[14] Lisa Salvatore,[15] Keigo Chida,[4] Akihito Kawazoe,[4] Veronica Conca,[16,17] Giuseppe Curigliano,[18,19] Francesca Corti,[1] Chiara Cremolini,[16,17] Michael Overman,[20] Thierry Andre ,[2] Filippo Pietrantonio [1]

VIEWS

Cancer Discov 2022;12(3):602-3.

IN THE SPOTLIGHT

Are You a TMBeliever? Mutations and Atezolizumab Response in Solid Tumors

Steven B. Maron[1] and Samuel J. Klempner[2]

RESEARCH ARTICLE

Cancer Discov 2022;12(3):654-69.

Atezolizumab Treatment of Tumors with High Tumor Mutational Burden from MyPathway, a Multicenter, Open-Label, Phase IIa Multiple Basket Study

Claire F. Friedman[1,2], John D. Hainsworth[3,4], Razelle Kurzrock[5], David R. Spigel[3,4], Howard A. Burris III[3,4], Christopher J. Sweeney[6], Funda Meric-Bernstam[7], Yong Wang[8], Jonathan Levy[8], Jessica Grindheim[8], David S. Shames[8], Katja Schulze[8], Arisha Patel[8], and Charles Swanton[9,10]

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

N Engl J Med 2022;386:2363-76.

The NEW ENGLAND JOURNAL of MEDICINE

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

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

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

Abstract LBA5.

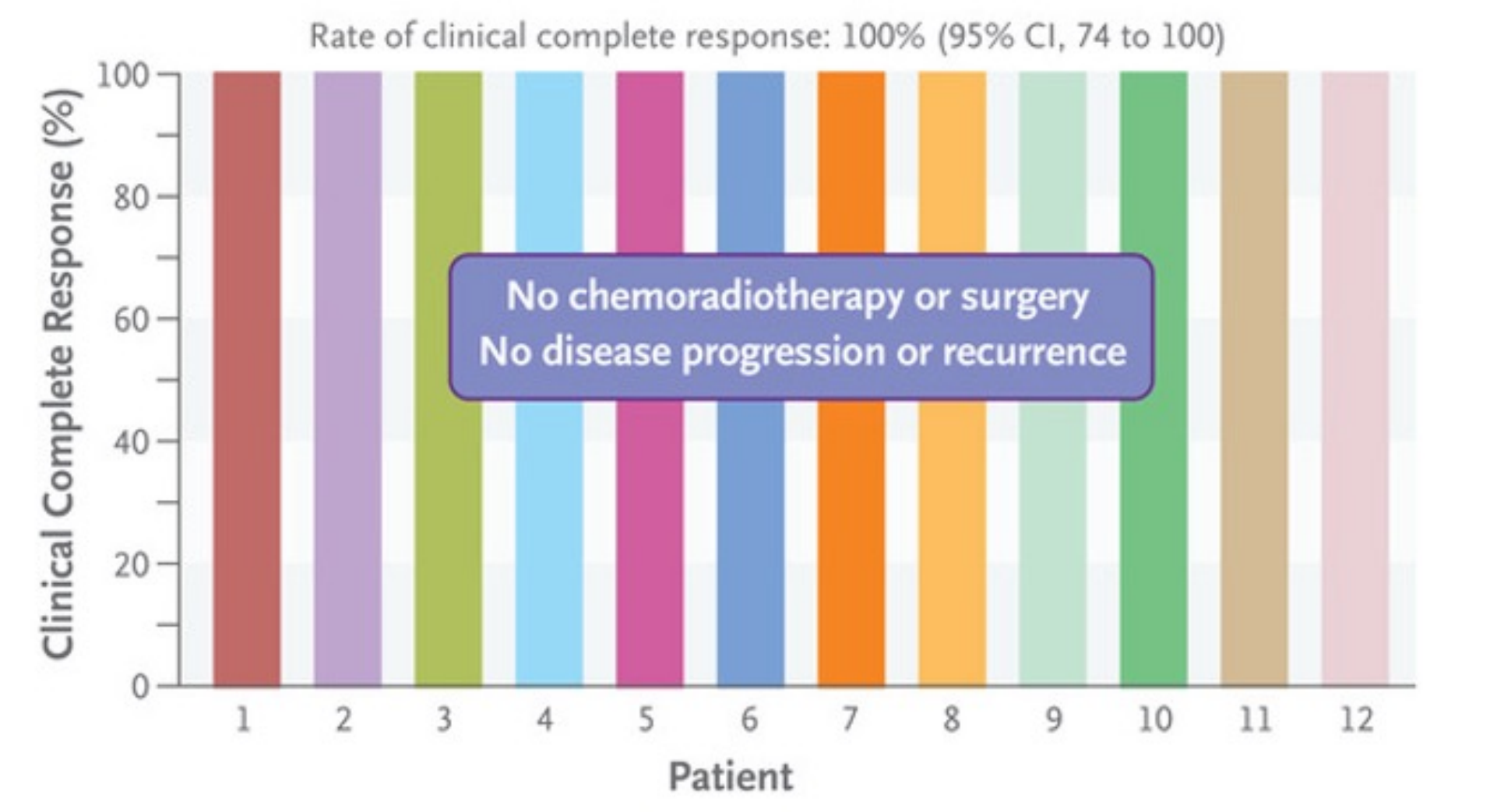
2022 ASCO ANNUAL MEETING

Late breaking abstract

PD-1 blockade as curative-intent therapy in mismatch repair deficient locally advanced rectal cancer

Andrea Cercek, MD
Head, Colorectal Cancer Section
Co-Director Center for Young Onset Colorectal and Gastrointestinal Cancers
Memorial Sloan Kettering Cancer Center

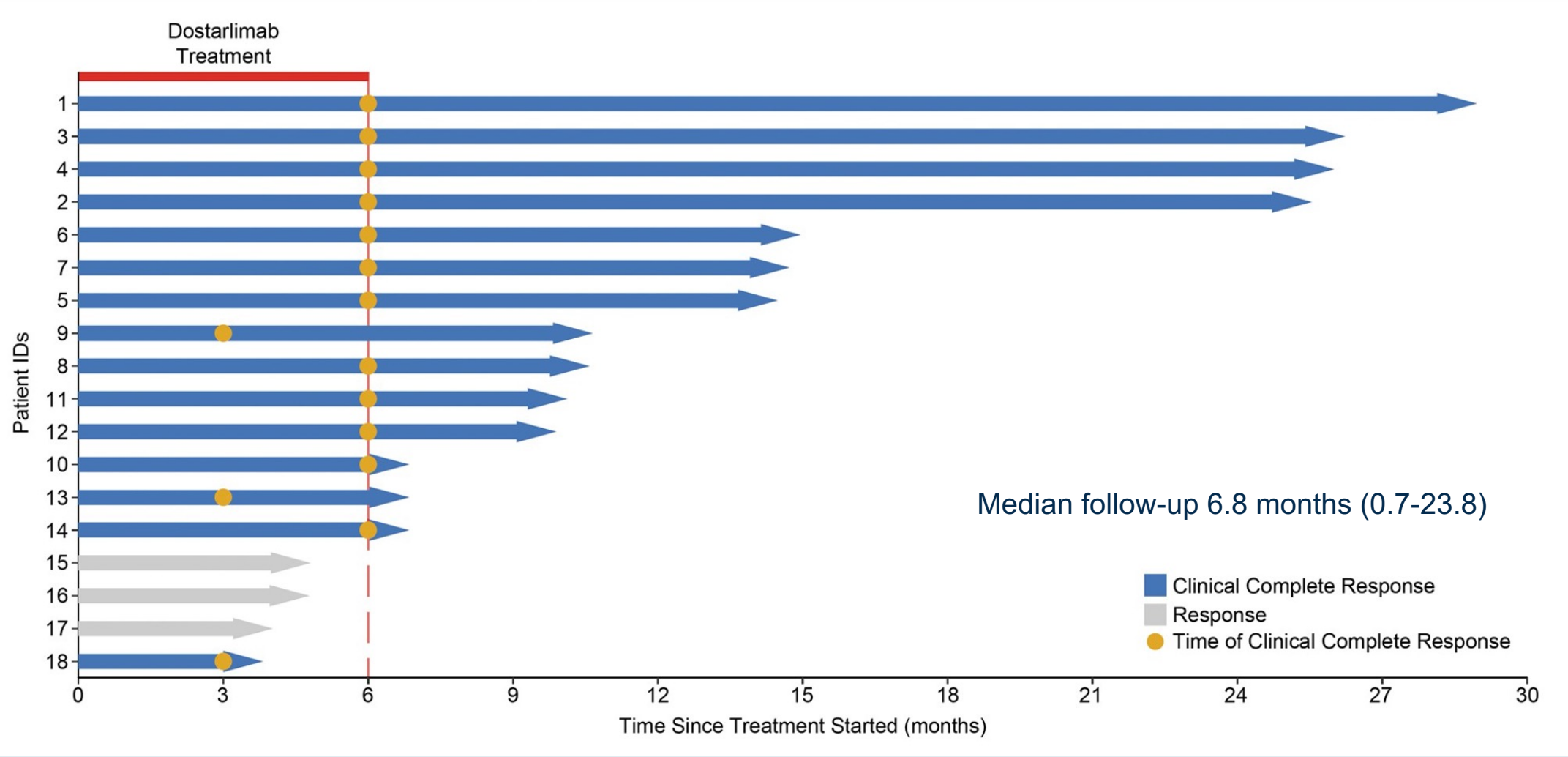
Rate of Clinical Response



CI = confidence interval

Cercek A et al. *N Engl J Med* 2022;386(25):2363-76. Cercek A et al. ASCO 2022;Abstract LBA5.

Duration of Response



Cercek A et al. *N Engl J Med* 2022;386(25):2363-76. Cercek A et al. ASCO 2022;Abstract LBA5.

RTP RESEARCH TO PRACTICE

2022 ASCO® ANNUAL MEETING

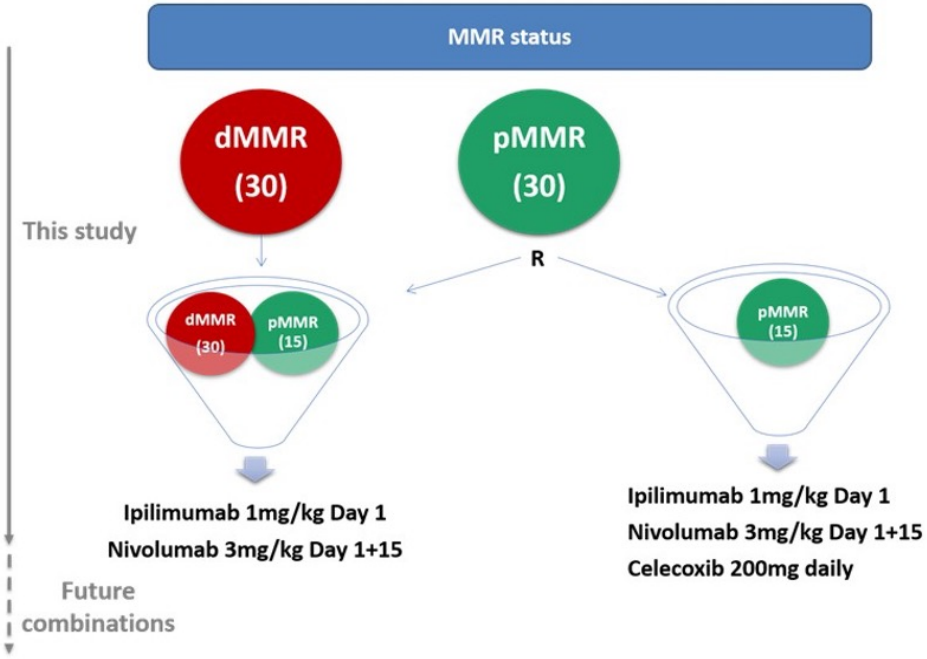
Abstract 3511

Neoadjuvant nivolumab, ipilimumab, and celecoxib in MMR-proficient and MMR-deficient colon cancers: Final clinical analysis of the NICHE study.

Y.L. Verschoor, J. van den Berg, G. Beets, K. Sikorska, A. Aalbers, A. van Lent, C. Grootscholten, I. Huibregtse, H. Marsman, S. Oosterling, M. van de Belt, M. Kok, T. Schumacher, M.E. van Leerdam, J.B.A.G. Haanen, E.E. Voest, M. Chalabi

NICHE Study Design

- Open-label, exploratory study with an adaptive design
- **Study population:** non-metastatic, resectable and previously untreated adenocarcinoma of the colon
- **Original cohorts:** 30 patients with dMMR and 30 with pMMR tumors
- **Treatment** in all patients: nivolumab 3 mg/kg on D1+15 *plus* ipilimumab 1 mg/kg on D1
  - **pMMR cohort:** randomized to additionally receive celecoxib
  - **Surgery within 6 weeks** of registration
- Tumor and normal tissue at baseline and resection, plasma + PBMCs baseline during treatment and follow-up



dMMR = metastatic mismatch repair-deficient; pMMR = metastatic mismatch repair-proficient; PBMCs = peripheral blood mononuclear cells

Verschoor YL et al. ASCO 2022;Abstract 3511.

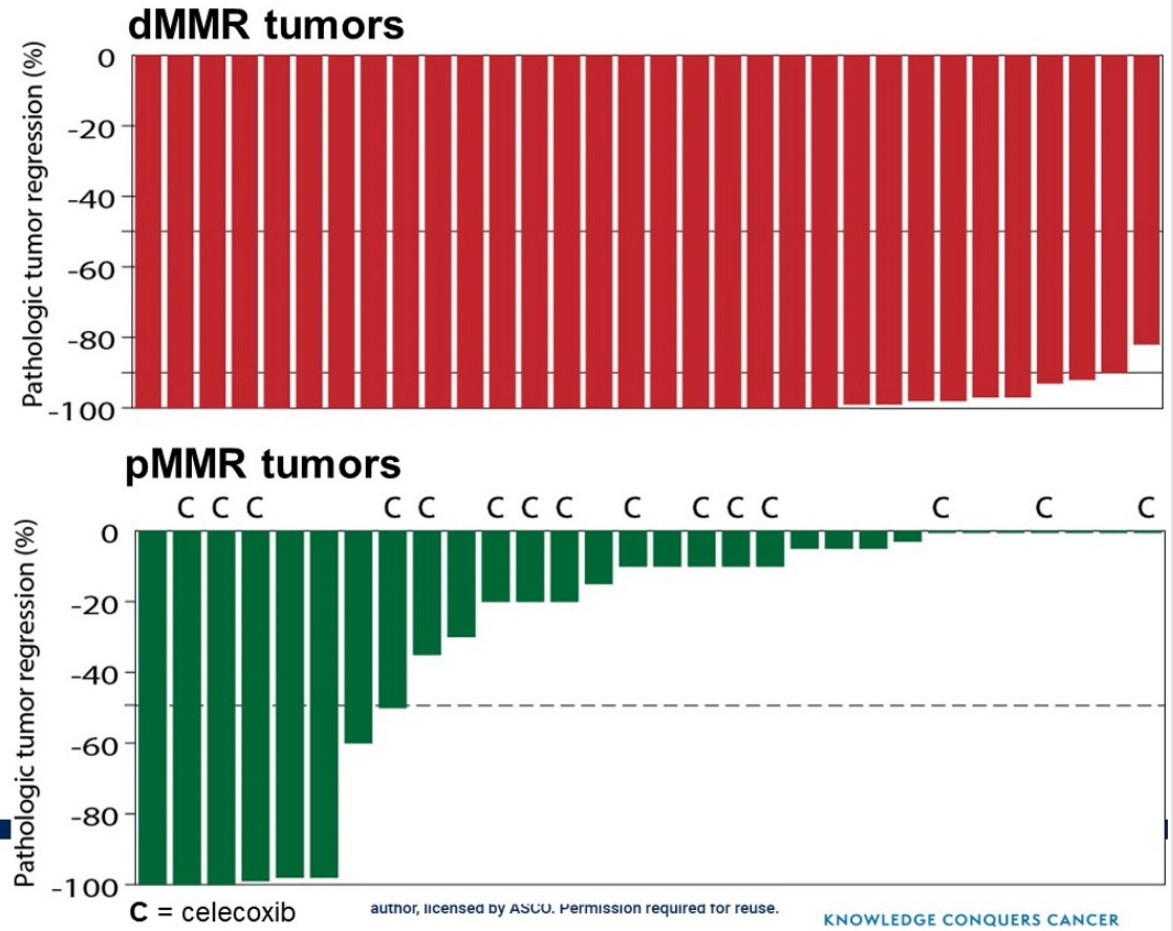
NICHE: Responses in 29% of pMMR and 100% of dMMR Tumors

Pathologic response	dMMR *n*= 32	pMMR *n*= 31
Major (≤10% VTR)	31 (97%)	7 (23%) *
Complete	22 (69%)	4 (13%) *
Partial (≤50% VTR)	1 (3%)	2 (6%)
Nonresponse (>50% VTR)	0 (0%)	22 (71%)

- **dMMR: 32/32 (100%) responders**
  - Lynch: 13/13 MPR, 12 pCR
  - Non-Lynch: 18/19 MPR, 10 pCR; 1 PR
- **pMMR: 9/31 (29%) responders**

*1 patient has not undergone surgery, now 1 year after treatment completion and no longer evidence of intraluminal or radiological disease, incl neg biopsies

VTR= viable tumor rest; MPR = major pathologic response; pCR = pathologic complete response; PR= partial response



2022 ASCO ANNUAL MEETING #ASCO22

KNOWLEDGE CONQUERS CANCER

Verschoor YL et al. ASCO 2022;Abstract 3511.

RTP RESEARCH TO PRACTICE

ASCO Gastrointestinal Cancers Symposium

GERCOR

Neo-adjuvant nivolumab plus ipilimumab and adjuvant nivolumab in patients (pts) with localized MSI/dMMR gastric or oeso-gastric junction (G-OGJ) adenocarcinoma NEONIPIGA phase II GERCOR study

T André,[1] D Tougeron, G Piessen, C de la Fouchardière, C Louvet, A Adenis, M Jary, C Tournigand, T Aparicio, J Desrame, A Lièvre, ML Garcia-Larnicol, T Pudlarz, J Henriques, R Cohen, J Lefèvre, M Svrcek

[1]Sorbonne University, Saint-Antoine Hospital, Department of Medical Oncology, Paris, France

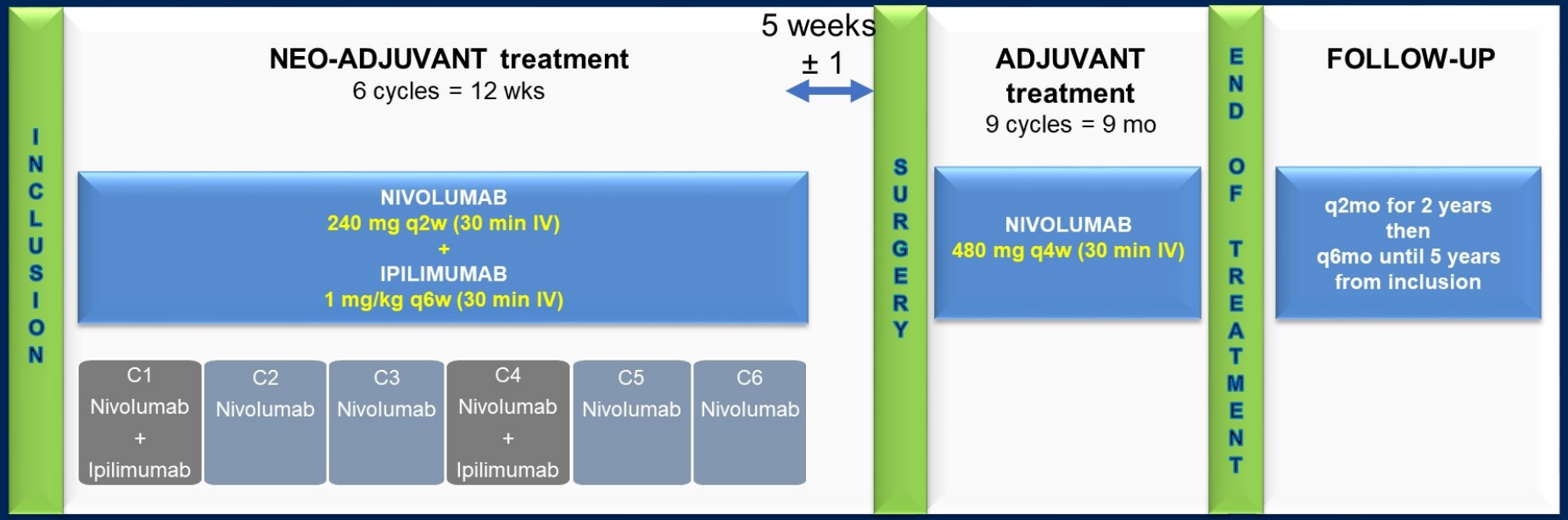
Gastrointestinal Cancers Symposium 2022;Abstract 244.

RTP RESEARCH TO PRACTICE

NEONIPIGA Design

NEONIPIGA: Study design/methods

- Phase II study evaluating efficacy of neo-adjuvant nivolumab and ipilimumab followed by adjuvant nivolumab in pts with resectable OGA MSI/dMMR, T2-T4 NxM0
- The primary objective was pathological complete response rate (pCRR).



ClinicalTrials.gov: NCT04006262

OGA = oeso-gastric adenocarcinoma

Andre T et al. Gastrointestinal Cancers Symposium 2022;Abstract 244.

NEONIPIGA Conclusions

Conclusions

- The primary objective with **59% pathological complete Response Rate was met (17/29 pts evaluable for** pCRR**)**
- Neo-adjuvant nivolumab & ipilimumab is feasible in pts with MSI/dMMR resectable OGJ/gastric adenocarcinoma
- No new safety concerns: with 25% of grade 3-4 TRAE (max/pts)
- Surgical complications are as expected with this type of surgeries
- 94% of pts included are free of events with 12 months follow-up
- Neonipiga raises the question whether the surgery can be delayed or avoided for some pts with localized MSI/dMMR G-OGJ adenocarcinoma if immune-check point inhibitors are effective.

Andre T et al. Gastrointestinal Cancers Symposium 2022;Abstract 244.

Meet The Professor with Dr Klempner: Management of Upper GI Cancers

MODULE 1: HER2-Positive Disease

MODULE 2: MSI-High Disease

MODULE 3: HER2-Negative, MSS Disease

- Dr Brenner: A 69-year-old woman with metastatic gastroesophageal junction (GEJ) adenocarcinoma to liver (MSS, PD-L1 2%, HER2-negative)
- Dr Brenner: A 59-year-old man with GEJ adenocarcinoma s/p neoadjuvant FLOT, found to have 8/18 positive nodes at surgery, s/p FLOT, currently no evidence of disease (PD-L1 <1%)
- Dr Dallas: A 53-year-old man with esophageal adenocarcinoma with FDG avid mediastinal node, s/p chemoradiation and definitive radiation to mediastinal node (MSS, PD-L1 0%, HER2-negative)
- Dr Strickland: A 55-year-old man with past history of Barrett's esophagus with T1bNXM0 adenocarcinoma with signet cell features, s/p endoscopic resection who declines esophagectomy
- Dr Gupta: A 61-year-old man with a 70-lb weight loss and locally advanced high-grade neuroendocrine carcinoma of distal esophagus
- Dr Patel: A 60-year-old frail man with GEJ adenocarcinoma s/p chemoradiation, declined surgery, now with metastatic disease and partial response with FOLFOX/nivolumab (PD-L1 2%, HER2 1+)

MODULE 4: Appendix of Key Publications

RTP RESEARCH TO PRACTICE

Case Presentation: A 69-year-old woman with metastatic gastroesophageal junction (GEJ) adenocarcinoma to liver (MSS, PD-L1 2%, HER2-negative)

Dr Warren Brenner (Boca Raton, Florida)

RTP
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TO PRACTICE

Case Presentation: A 59-year-old man with GEJ adenocarcinoma s/p neoadjuvant FLOT, found to have 8/18 positive nodes at surgery, s/p FLOT, currently no evidence of disease (PD-L1 <1%)

Dr Warren Brenner (Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

Surgical and pathological outcome, and pathological regression, in patients receiving perioperative atezolizumab in combination with FLOT chemotherapy versus FLOT alone for resectable esophagogastric adenocarcinoma: Interim results from DANTE, a randomized, multicenter, phase IIb trial of the FLOT-AIO German Gastric Cancer Group and Swiss SAKK.

Presented by Dr. S-E Al-Batran, Oral Abstract Session

2022 ASCO ANNUAL MEETING

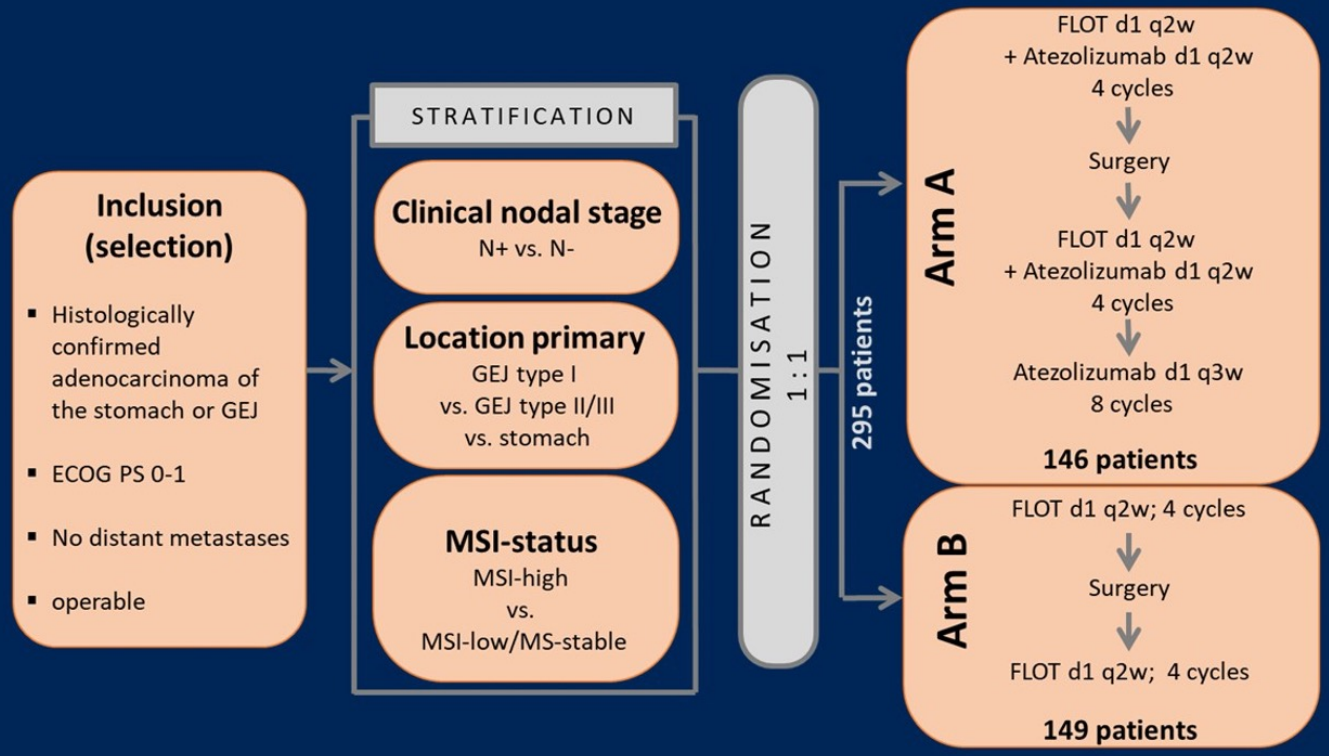
#ASCO22

PRESENTED BY:
Katrina Pedersen, MD, MS

Al-Batran SE et al. ASCO 2022;Abstract 4003. | Discussant, Katrina Pedersen, MD, MS

Study Flow Chart

DANTE is an investigator-initiated phase-II trial with the potential to transition into a phase-III trial



Al-Batran SE et al. ASCO 2022;Abstract 4003. | Discussant, Katrina Pedersen, MD, MS

Histopathology (pTNM)

	FLOT + Atezolizumab (N=146)		FLOT (N=149)	
pT0-stage	34	23%	22	15%
pN0-stage	100	69%	81	54%
pT0/N0	34	23%	21	14%
pT-stage				
≤T1	62	43%	55	37%
T2	27	19%	16	11%
T3	47	32%	61	41%
T4	4	3%	10	7%
pT0-T2	89	61%	71	48%
pT3-T4	51	35%	71	48%
pM1-stage	2	1%	4	3%

Al-Batran SE et al. ASCO 2022;Abstract 4003. | Discussant, Katrina Pedersen, MD, MS

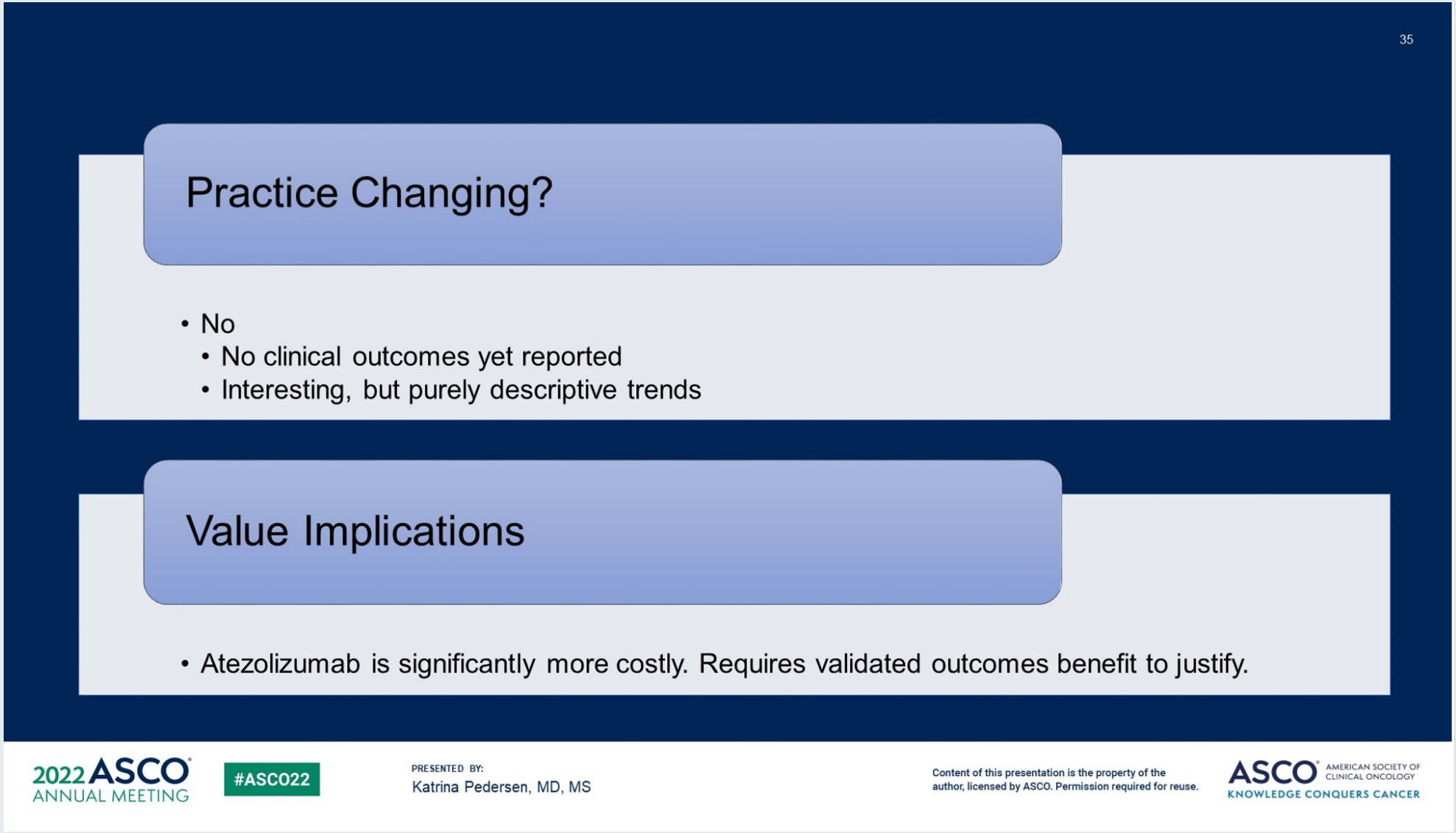
Pathological response (local vs. central assessment)

Pathological Regression **FLOT + Atezolizumab (arm A) vs. FLOT (arm B)**	Local assessment				Central assessment[1]			
	TRG1a[2]		TRG1a/b[3]		TRG1a[2]		TRG1a/b[3]	
	A	B	A	B	A	B	A	B
All patients (N= 295; 146|149)	35 (24%)	23 (15%)	71 (49%)	58 (39%)	37 (25%)	36 (24%)	72 (49%)	66 (44%)
PD-L1 CPS ≥1 (N=170; 82|88)	20 (24%)	13 (15%)	42 (51%)	40 (46%)	21 (26%)	20 (23%)	43 (52%)	41 (47%)
PD-L1 CPS ≥5 (N=81; 40|41)	11 (28%)	8 (20%)	22 (55%)	18 (44%)	13 (33%)	9 (22%)	21 (53%)	19 (46%)
PD-L1 CPS ≥10 (N=53; 27|26)	9 (33%)	3 (12%)	18 (67%)	10 (39%)	11 (41%)	5 (19%)	19 (70%)	13 (50%)
MSI high (N=23; 8|15)	5 (63%)	4 (27%)	6 (75%)	7 (47%)	5 (63%)	4 (27%)	6 (75%)	7 (47%)

[1]central assessment by one pathologist based on a representative tumor sample
[2]pathological complete regression acc. to Becker
[3]pathological subtotal regression acc. to Becker

Al-Batran SE et al. ASCO 2022;Abstract 4003. | Discussant, Katrina Pedersen, MD, MS

Discussant Conclusions



Katrina Pedersen, MD, MS, Discussant

RTP RESEARCH TO PRACTICE

Case Presentation: A 53-year-old man with esophageal adenocarcinoma with FDG avid mediastinal node, s/p chemoradiation and definitive radiation to mediastinal node (MSS, PD-L1 0%, HER2-negative)

Dr Jennifer Dallas (Charlotte, North Carolina)

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Case Presentation: A 55-year-old man with past history of Barrett's esophagus with T1bNXM0 adenocarcinoma with signet cell features, s/p endoscopic resection who declines esophagectomy

Dr Matthew Strickland (Boston, Massachusetts)

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RESEARCH
TO PRACTICE

Case Presentation: A 61-year-old man with a 70-lb weight loss and locally advanced high-grade neuroendocrine carcinoma of distal esophagus

Dr Ranju Gupta (Bethlehem, Pennsylvania)

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 60-year-old frail man with GEJ adenocarcinoma s/p chemoradiation, declined surgery, now with metastatic disease and partial response with FOLFOX/nivolumab (PD-L1 2%, HER2 1+)

Dr Minesh Dinubhai Patel (Peachtree City, Georgia)

A patient with HER2-negative, MSS gastric adenocarcinoma receives preoperative FLOT, undergoes resection and has significant residual disease at surgery (PD-L1 CPS = 0). Regulatory and reimbursement issues aside, what would you generally recommend?

 Dr Enzinger	Continue FLOT postoperatively	 Dr Shah	Continue FLOT postoperatively
 Dr Janjigian	Continue FLOT postoperatively	 Dr Strickler	Continue FLOT postoperatively
 Dr Klempner	Continue FLOT postoperatively	 Dr Yoon	Continue FLOT postoperatively

FLOT = fluorouracil/leucovorin/oxaliplatin/docetaxel

RTP RESEARCH TO PRACTICE

A patient with HER2-negative, MSS gastric adenocarcinoma receives preoperative FLOT, undergoes resection and has significant residual disease at surgery (PD-L1 CPS = 10). Regulatory and reimbursement issues aside, what would you generally recommend?

 Dr Enzinger	Switch to FOLFOX + nivolumab postoperatively	 Dr Shah	Continue FLOT postoperatively
 Dr Janjigian	Continue FLOT postoperatively + PD-1/PD-L1 antibody	 Dr Strickler	Continue FLOT postoperatively
 Dr Klempner	Continue FLOT postoperatively	 Dr Yoon	Continue FLOT postoperatively

RTP RESEARCH TO PRACTICE

Which assay do you generally use to evaluate PD-L1 status in your patients with advanced gastroesophageal cancer?

 Dr Enzinger	Pathologist's choice	 Dr Shah	Ventana PD-L1 (SP263)
 Dr Janjigian	Cell Signaling Technology assay	 Dr Strickler	PD-L1 IHC 22C3 pharmDx
 Dr Klempner	PD-L1 IHC 22C3 pharmDx	 Dr Yoon	PD-L1 IHC 22C3 pharmDx

IHC = immunohistochemistry

Regulatory and reimbursement issues aside, which first-line therapy would you most likely recommend for a 65-year-old patient presenting with metastatic HER2-negative, MSS gastric adenocarcinoma with a PD-L1 CPS of 0?

 Dr Enzinger	FOLFOX	 Dr Shah	FOLFOX
 Dr Janjigian	FOLFOX + nivolumab	 Dr Strickler	FOLFOX
 Dr Klempner	FOLFOX	 Dr Yoon	FOLFOX

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, which first-line therapy would you most likely recommend for a 65-year-old patient presenting with metastatic HER2-negative, MSS gastric adenocarcinoma with a PD-L1 CPS of 5?

 Dr Enzinger	FOLFOX + nivolumab	 Dr Shah	FOLFOX + nivolumab
 Dr Janjigian	FOLFOX + nivolumab	 Dr Strickler	FOLFOX + nivolumab
 Dr Klempner	FOLFOX + nivolumab	 Dr Yoon	FOLFOX or FOLFOX + pembro

RTP RESEARCH TO PRACTICE

Oncologist 2021;26(10):e1704-29.

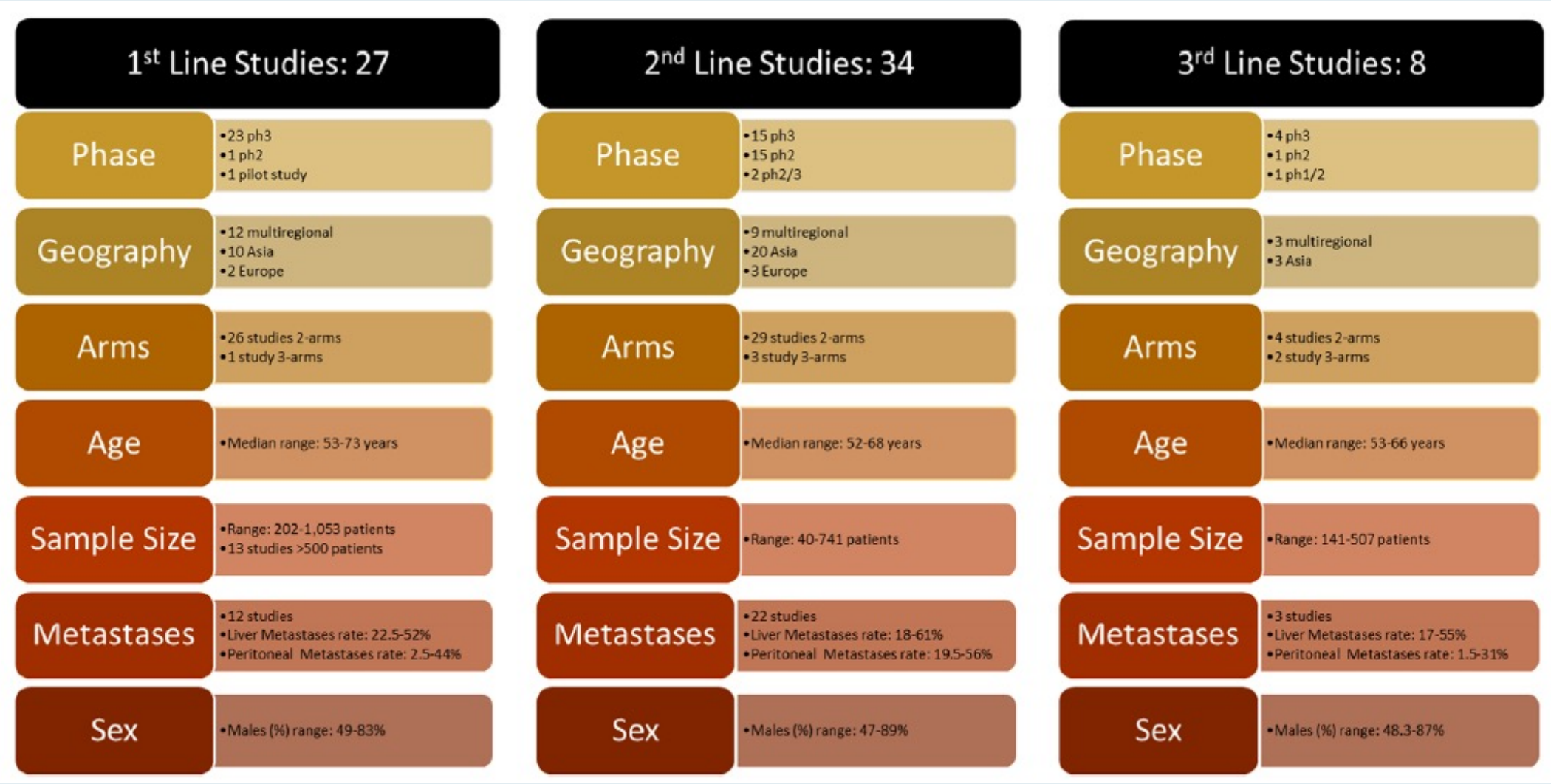
The Oncologist®

Gastrointestinal Cancer

Toward a Treatment Sequencing Strategy: A Systematic Review of Treatment Regimens in Advanced Gastric Cancer/ Gastroesophageal Junction Adenocarcinoma

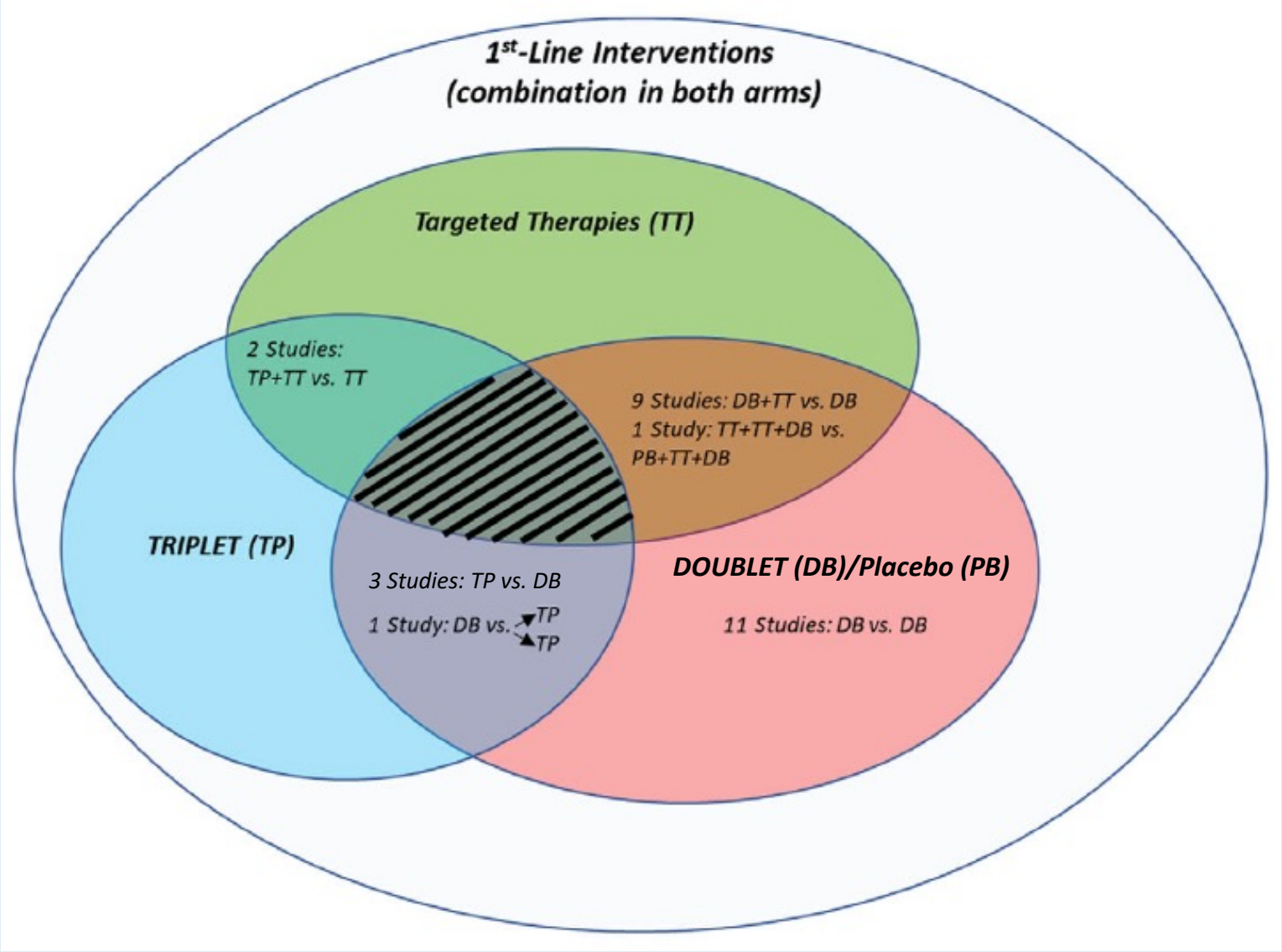
Daniel V. Catenacci,[a,†] Joseph Chao,[b,†] Kei Muro,[c] Salah Eddin Al-Batran,[d] Samuel J. Klempner,[e] Zev A. Wainberg,[f] Manish A. Shah,[g] Sun Young Rha,[h] Atsushi Ohtsu,[i] Astra M. Liepa,[j] Holly Knoderer,[j] Anindya Chatterjee,[j] Eric Van Cutsem[k]

Systematic Review of Treatment Regimens in Advanced Gastric Cancer/GEJ Adenocarcinoma: Overview of Studies Included



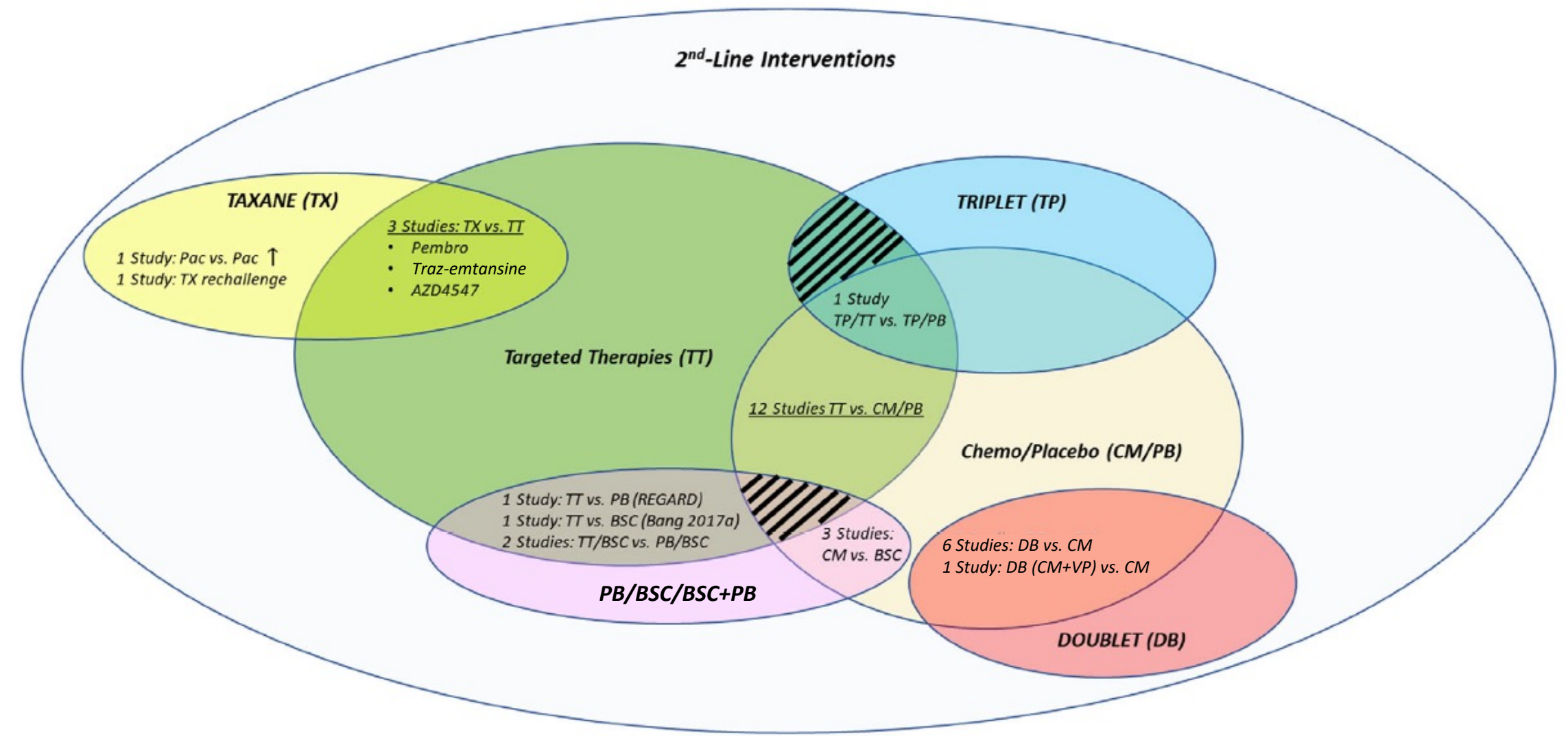
Catenacci DV et al. *Oncologist* 2021;26(10):e1704-29.

Systematic Review of Treatment Regimens in Advanced Gastric Cancer/GEJ Adenocarcinoma: First-Line Interventions



Catenacci DV et al. *Oncologist* 2021;26(10):e1704-29.

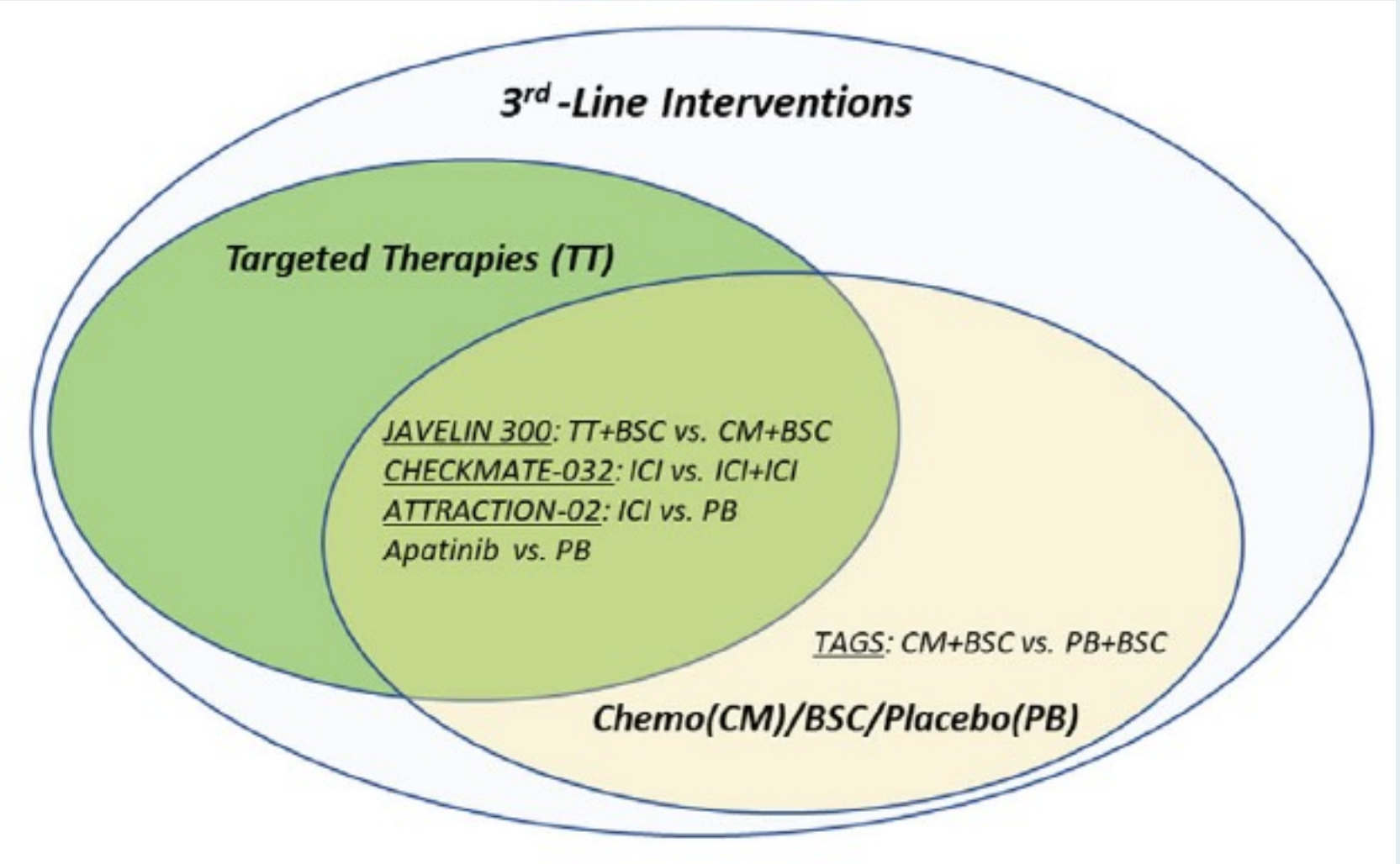
Systematic Review of Treatment Regimens in Advanced Gastric Cancer/GEJ Adenocarcinoma: Second-Line Interventions



Pac = paclitaxel; Pembro = pembrolizumab; BSC = best supportive care; VP = valproic acid

Catenacci DV et al. *Oncologist* 2021;26(10):e1704-29.

Systematic Review of Treatment Regimens in Advanced Gastric Cancer/GEJ Adenocarcinoma: Third-Line Interventions



BSC = best supportive care; ICI = immune checkpoint inhibitor

Catenacci DV et al. *Oncologist* 2021;26(10):e1704-29.

JAMA Network Open

View Article

JAMA Netw Open 2021;4(12):e2138432.

Published online 2021 Dec 10. doi: 10.1001/jamanetworkopen.2021.38432: 10.1001/jamanetworkopen.2021.38432

PMCID: PMC8665367

PMID: 34889947

A Comparison of Clinicopathologic Outcomes Across Neoadjuvant and Adjuvant Treatment Modalities in Resectable Gastric Cancer

Eric Anderson, MD, [1] Alexis LeVee, MD, [2] Sungjin Kim, MS, [3] Katelyn Atkins, MD, PhD, [1] Michelle Guan, BS, [2] Veronica Placencio-Hickok, PhD, [2] Natalie Moshayedi, BS, [2] Andrew Hendifar, MD, [2] Arsen Osipov, MD, [2] Alexandra Gangi, MD, [4] Miguel Burch, MD, [4] Kevin Waters, MD, PhD, [5] May Cho, MD, [6] Samuel Klempner, MD, [7] Joseph Chao, MD, [8] Mitchell Kamrava, MD, [1] and Jun Gong, MD [2]

Adv Radiat Oncol 2021;7(1):100807.

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in radiation oncology

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Scientific Article

A Phase 2 Trial Combining Pembrolizumab and Palliative Radiation Therapy in Gastroesophageal Cancer to Augment Abscopal Immune Responses

Joseph Chao, MD,[a,*] Ting-Fang He, PhD,[b] Massimo D'Apuzzo, MD, PhD,[c] Yi-Jen Chen, MD, PhD,[d] Paul Frankel, PhD,[e] Michael Tajon, PhD,[a] Helen Chen, MD,[d] Shawn Solomon, BS,[b] Samuel J. Klempner, MD,[f,g] Marwan Fakih, MD,[a] and Peter Lee, MD[b]

Oncologist 2021;26(9):e1538-47.

The Oncologist®

Gastrointestinal Cancer

Early Weight Loss as a Prognostic Factor in Patients with Advanced Gastric Cancer: Analyses from REGARD, RAINBOW, and RAINFALL Phase III Studies

Wasat Mansoor,[a] Eric J. Roeland,[b] Aafia Chaudhry,[c] Astra M. Liepa,[c] Ran Wei,[c] Holly Knoderer,[c] Paolo Abada,[c] Anindya Chatterjee,[c] Samuel J. Klempner[b]

JCO Precis Oncol 2022;6(1):e2200015.

TARGETED DRUG THERAPY

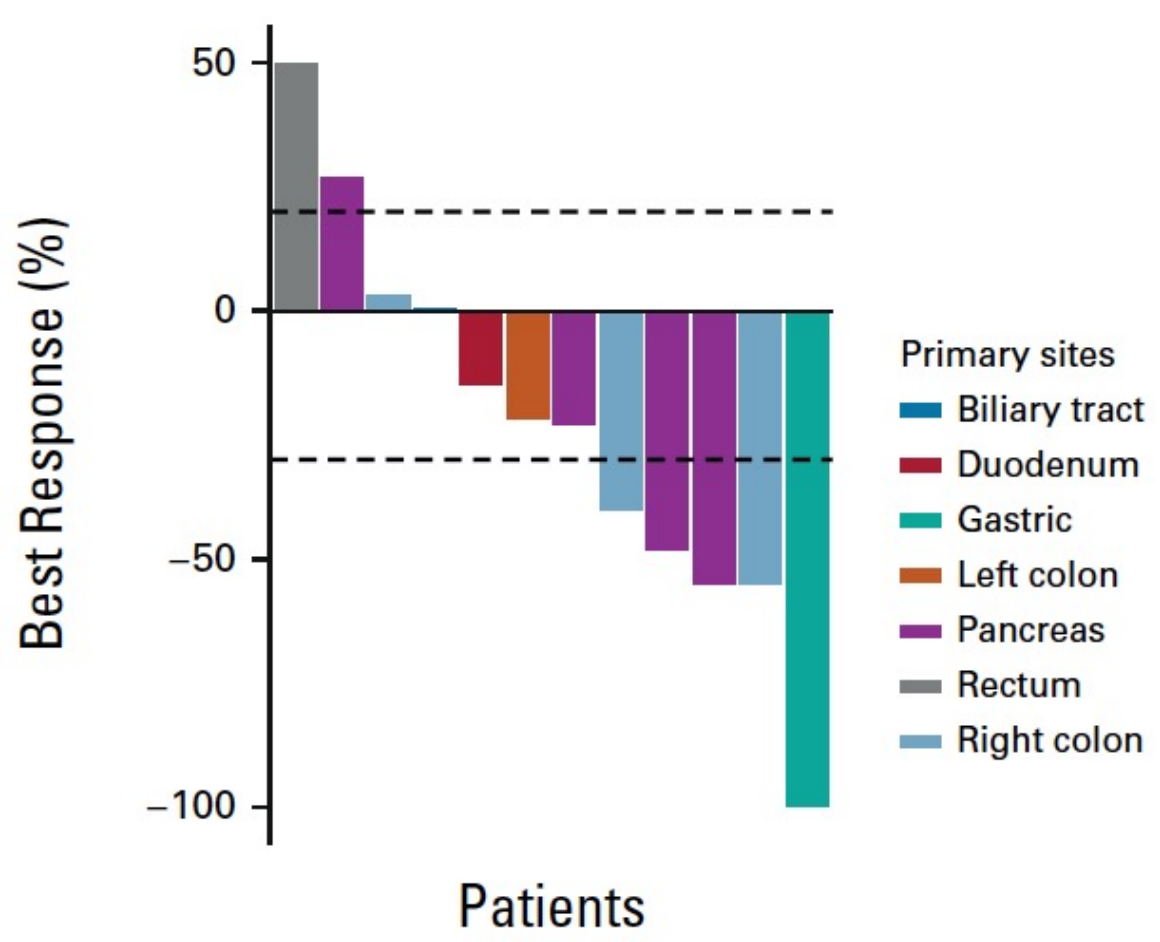
original reports

ALK Inhibitors in Patients With ALK Fusion–Positive GI Cancers: An International Data Set and a Molecular Case Series

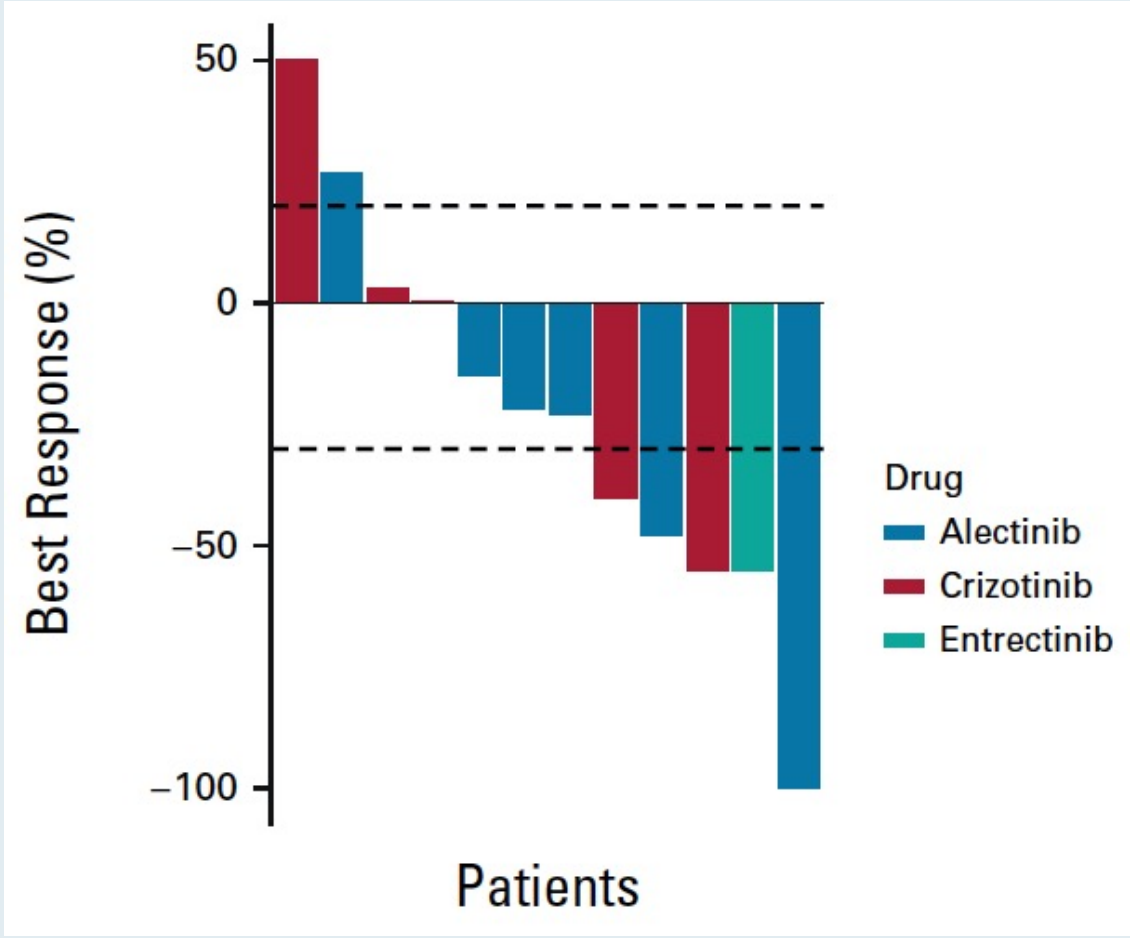
Margherita Ambrosini, MD[1]; Marzia Del Re, MSc[2]; Paolo Manca, MD[1]; Andrew Hendifar, MD[3]; Alexander Drilon, MD[4]; Guilherme Harada, MD[4]; Anne Hansen Ree, MD[5,6]; Samuel Klempner, MD[7]; Gunhild Mari Mælandsmo, MD[8]; Kjersti Flatmark, MD[9]; Hege G. Russnes, MD[10,11]; James M. Cleary, MD[12]; Harshabad Singh, MD[12]; Elisa Sottotetti, MSc[1]; Antonia Martinetti, MSc[1]; Giovanni Randon, MD[1]; Andrea Sartore-Bianchi, MD[13]; Iolanda Capone, MSc[14]; Massimo Milione, MD[14]; Maria Di Bartolomeo, MD[1]; and Filippo Pietrantonio, MD[1]

Response to ALK Inhibitors in Patients with ALK Fusion-Positive GI Cancers

Individual best responses according to the primary site of origin

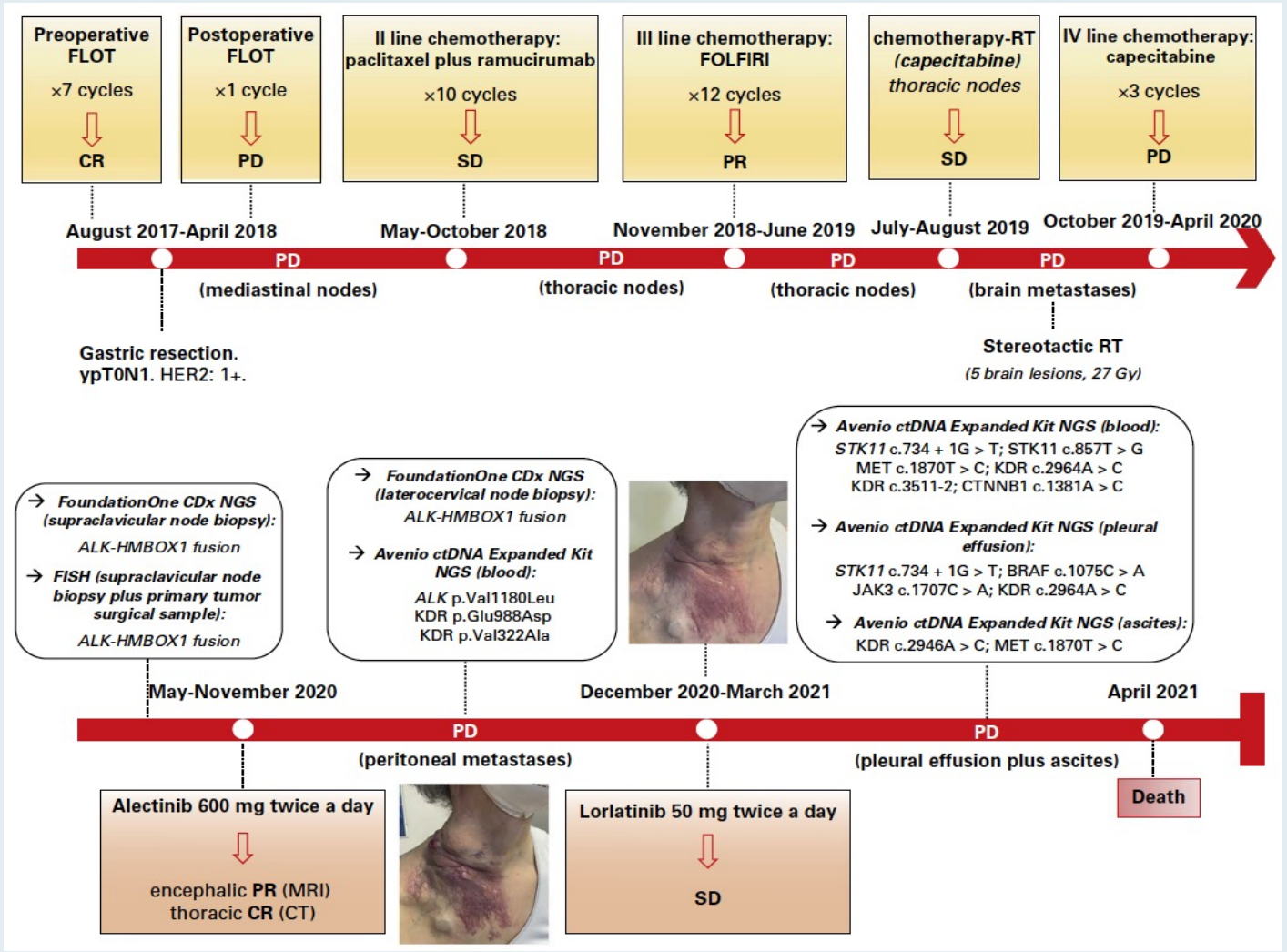


Individual best responses by type of ALK inhibitor received



Ambrosini M et al. *JCO Precis Oncol* 2022;6(1):e2200015.

Molecular Case Report of ALK Rearranged Gastric Cancer on Alectinib-Lorlatinib Sequential Strategy



CR = complete response; PD = disease progression; SD = disease stabilization; PR = partial response; RT = radiotherapy; NGS = next-generation sequencing; FISH = flourescent in situ hybridization; ctDNA = circulating tumor DNA; MRI = magnetic resonance imaging; CT = computed tomography.

Ambrosini M et al. *JCO Precis Oncol* 2022;6(1):e2200015.

Meet The Professor with Dr Klempner: Management of Upper GI Cancers

MODULE 1: HER2-Positive Disease

MODULE 2: MSI-High Disease

MODULE 3: HER2-Negative, MSS Disease

MODULE 4: Appendix of Key Publications

RTP RESEARCH TO PRACTICE

HER2-Negative Gastroesophageal Cancers

Checkpoint Inhibitor Approvals for HER2-Negative Gastric, GEJ and Esophageal Cancers

Regimen/FDA approval date/Pivotal trial	Location	Histology	Setting	PD-L1
Nivolumab 5/20/21 (CM-577)	Esophageal, GEJ	Adenocarcinoma and squamous	• Completed resected, with residual pathologic disease after neoadjuvant chemoradiation	Not required
Pembrolizumab + cisplatin/5-FU 3/22/2021 (KN-590)	Esophageal, GEJ	Adenocarcinoma and squamous	• Recurrent locally advanced or metastatic • Not amenable to surgical resection or definitive chemoradiation	Not required
Nivolumab + mFOLFOX6 or CAPOX 4/16/2021 (CM-649)	Gastric, GEJ, esophageal	Adenocarcinoma	• Advanced or metastatic gastric, GEJ or esophageal adenocarcinoma	Not required
Pembrolizumab 7/30/2019 (KN-181)	Esophageal, GEJ	Squamous	• Recurrent locally advanced or metastatic • Not amenable to surgical resection or definitive chemoradiation • After ≥1 prior lines of systemic therapy	CPS ≥10
Nivolumab 6/10/2020 (ATTRACTION-3)	Esophageal	Squamous	• Unresectable advanced, recurrent or metastatic • After prior fluoropyrimidine- and platinum-based • chemotherapy	Not required

Kelly RJ et al. *New Engl J Med* 2021;384(13):1191-203. Sun J et al. *Lancet* 2021;398(10302):759-71. Janjigian YY et al. *Lancet* 2021;398(10294):27-40. Kojima T et al. *J Clin Oncol* 2020;38(35):4138-48. Kato K et al. *Lancet Oncol* 2019;20(11):1506-17.

Article

Nature 2022;[Online ahead of print].

Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer

https://doi.org/10.1038/s41586-022-04508-4

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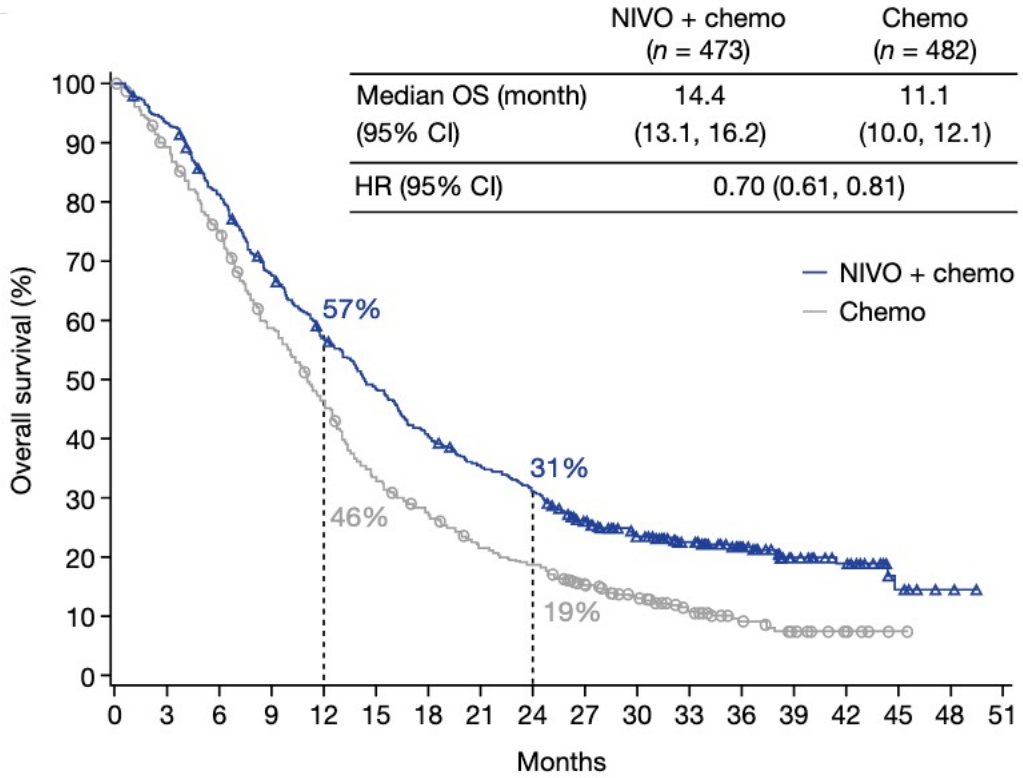
Open access

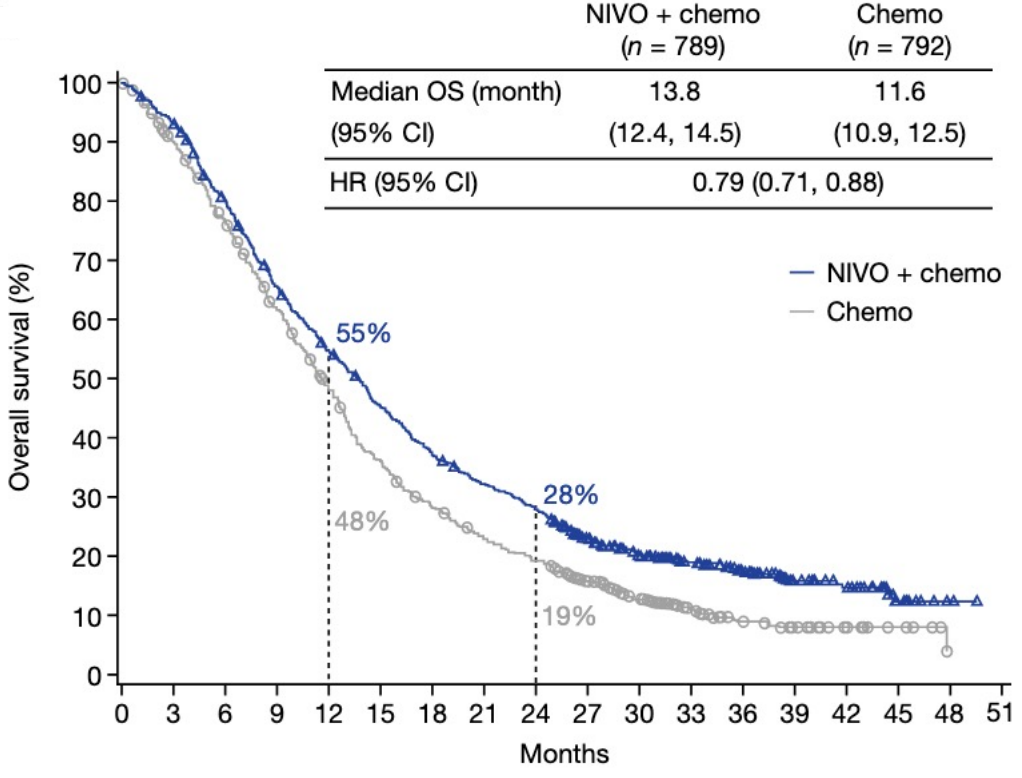
Kohei Shitara[1], Jaffer A. Ajani[2], Markus Moehler[3], Marcelo Garrido[4], Carlos Gallardo[5], Lin Shen[6], Kensei Yamaguchi[7], Lucjan Wyrwicz[8], Tomasz Skoczylas[9], Arinilda Campos Bragagnoli[10], Tianshu Liu[11], Mustapha Tehfe[12], Elena Elimova[13], Ricardo Bruges[14], Thomas Zander[15], Sergio de Azevedo[16], Ruben Kowalyszyn[17], Roberto Pazo-Cid[18], Michael Schenker[19], James M. Cleary[20], Patricio Yanez[21], Kynan Feeney[22], Michalis V. Karamouzis[23], Valerie Poulart[24], Ming Lei[24], Hong Xiao[24], Kaoru Kondo[24], Mingshun Li[24] & Yelena Y. Janjigian[25]✉

CheckMate 649: Overall Survival

PD-L1 CPS ≥5



All randomly assigned patients



CPS = combined positive score

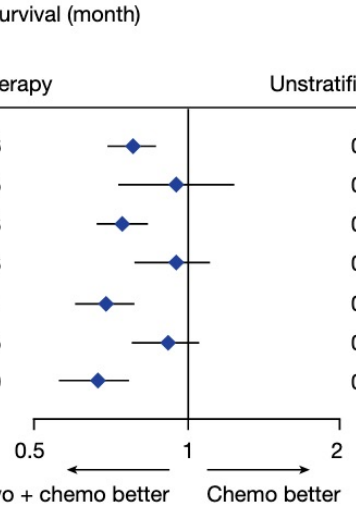
Shitara K et al. *Nature* 2022;[Online ahead of print].

RTP RESEARCH TO PRACTICE

CheckMate 649: Efficacy Subgroup Analysis by PD-L1 CPS Excluding Patients with MSI-High Tumors

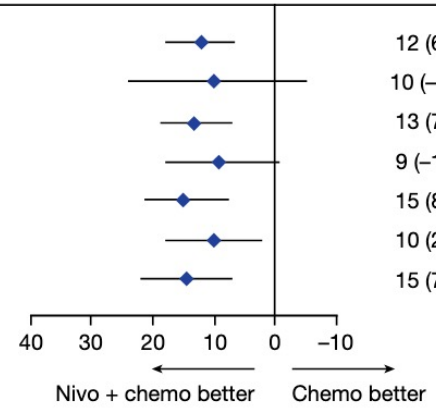
Median overall survival (month)

Population	Nivolumab plus chemotherapy	Chemotherapy	Unstratified HR for death (95% CI)
Overall (*n* = 1,581)	13.8	11.6	0.78 (0.70, 0.87)
PD-L1 CPS <1 (*n* = 265)	13.1	12.5	0.95 (0.73, 1.24)
PD-L1 CPS ≥1 (*n* = 1,297)	13.8	11.3	0.74 (0.66, 0.84)
PD-L1 CPS <5 (*n* = 607)	12.4	12.3	0.94 (0.79, 1.11)
PD-L1 CPS ≥5 (*n* = 955)	14.4	11.1	0.69 (0.60, 0.79)
PD-L1 CPS <10 (*n* = 795)	12.4	12.5	0.91 (0.78, 1.06)
PD-L1 CPS ≥10 (*n* = 767)	15.0	10.9	0.66 (0.56, 0.77)



Objective response rate (%)

Population	Nivolumab plus chemotherapy	Chemotherapy	Unweighted ORR difference (%) (95% CI)
Overall (*n* = 1,210)	58	46	12 (6, 18)
PD-L1 CPS <1 (*n* = 179)	51	41	10 (–5, 24)
PD-L1 CPS ≥1 (*n* = 1,017)	59	46	13 (7, 19)
PD-L1 CPS <5 (*n* = 428)	55	46	9 (–1, 18)
PD-L1 CPS ≥5 (*n* = 768)	60	45	15 (8, 22)
PD-L1 CPS <10 (*n* = 579)	58	47	10 (2, 18)
PD-L1 CPS ≥10 (*n* = 617)	59	44	15 (7, 22)



Shitara K et al. *Nature* 2022;[Online ahead of print].

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

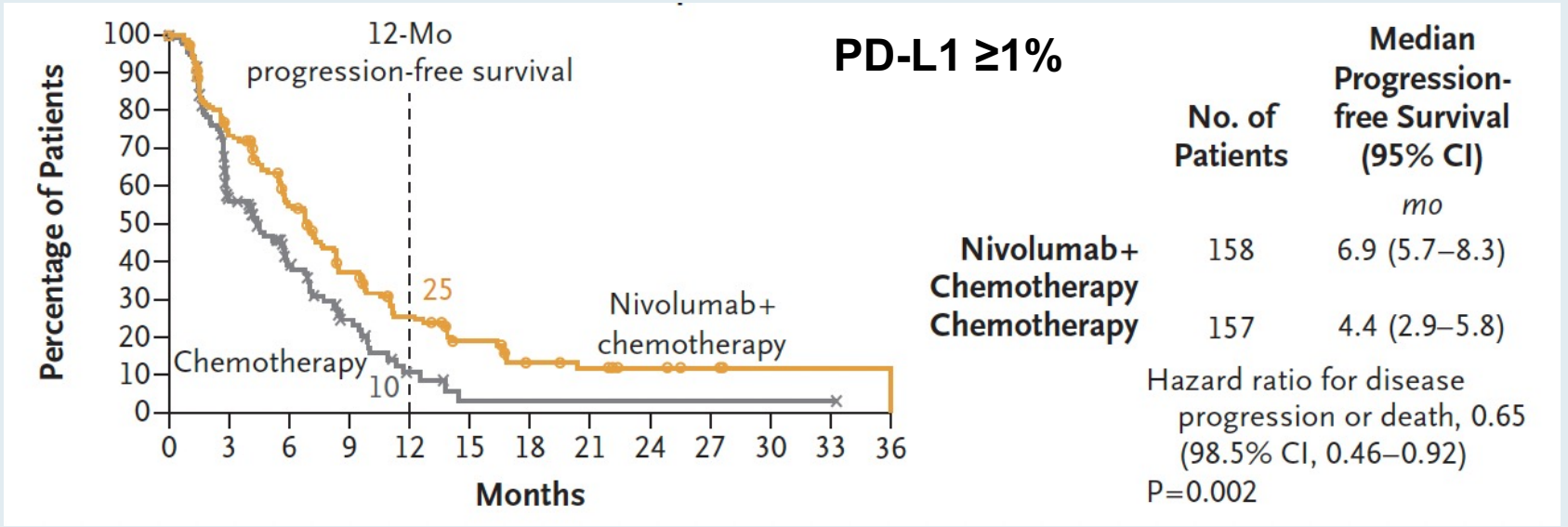
ORIGINAL ARTICLE

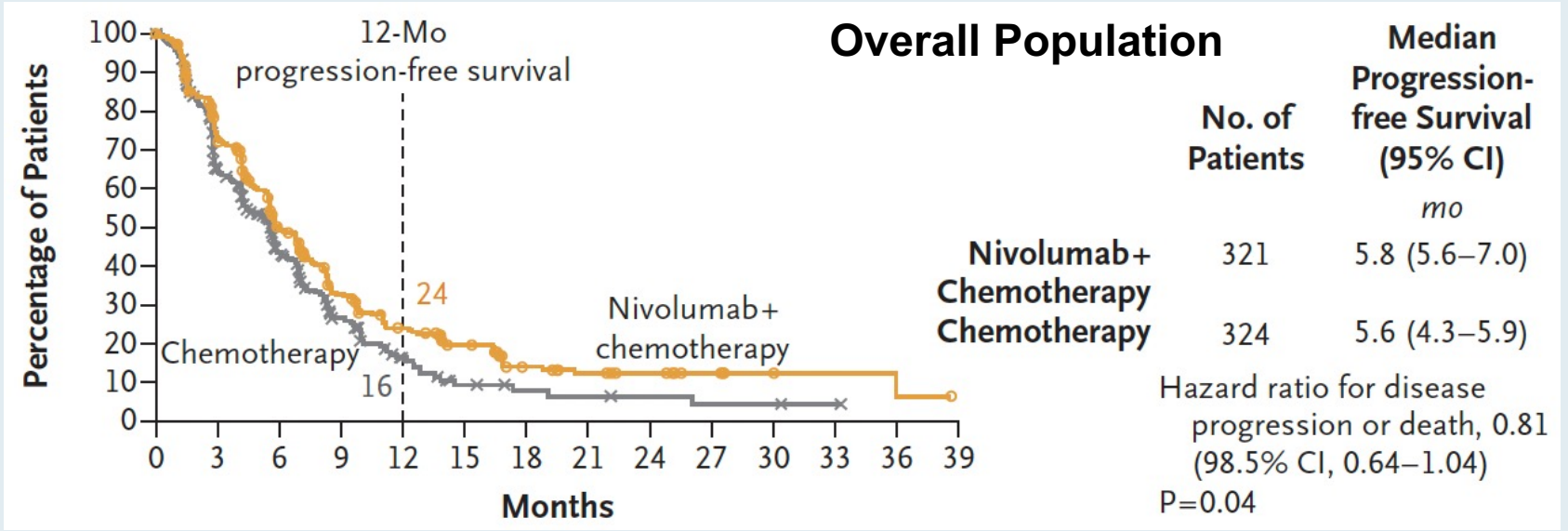
Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma

Y. Doki, J.A. Ajani, K. Kato, J. Xu, L. Wyrwicz, S. Motoyama, T. Ogata, H. Kawakami, C.-H. Hsu, A. Adenis, F. El Hajbi, M. Di Bartolomeo, M.I. Braghiroli, E. Holtved, S.A. Ostoich, H.R. Kim, M. Ueno, W. Mansoor, W.-C. Yang, T. Liu, J. Bridgewater, T. Makino, I. Xynos, X. Liu, M. Lei, K. Kondo, A. Patel, J. Gricar, I. Chau, and Y. Kitagawa, for the CheckMate 648 Trial Investigators*

New Engl J Med 2022;386(5):449-62.

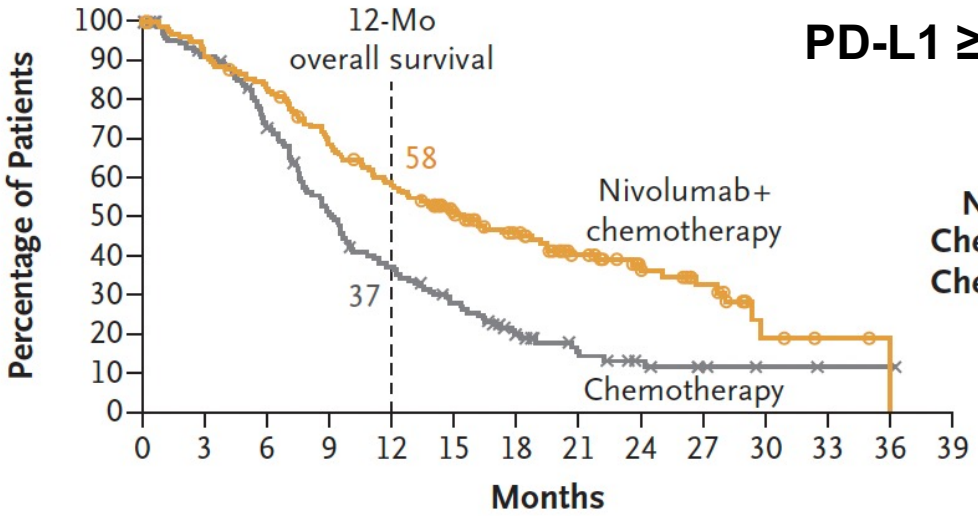
CheckMate 648: Progression-Free Survival for PD-L1 ≥1% and in the Overall Population – Nivolumab + Chemotherapy





Doki Y et al. *N Engl J Med* 2022;386(5):449-62.

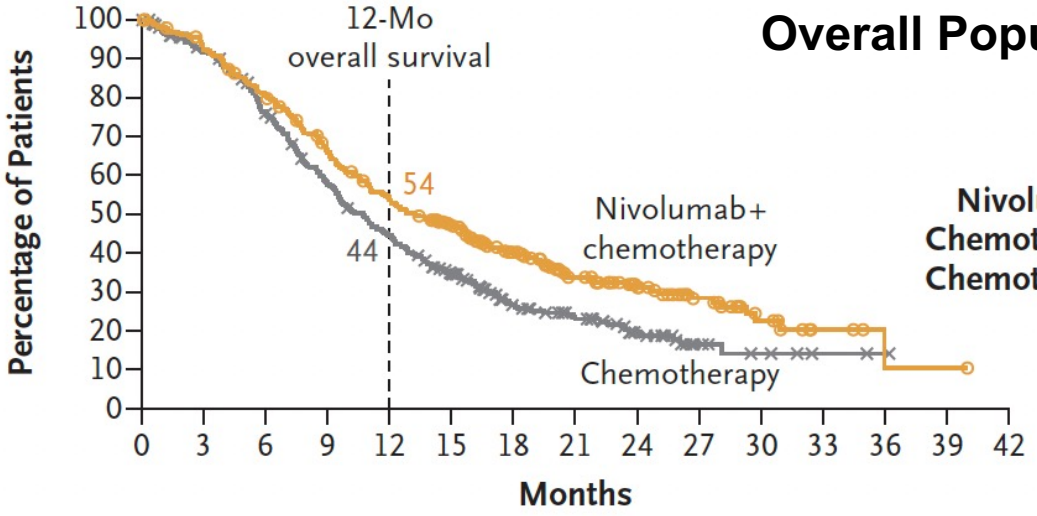
CheckMate 648: Overall Survival for PD-L1 ≥1% and in the Overall Population – Nivolumab + Chemotherapy



PD-L1 ≥1%

	No. of Patients	Median Overall Survival (95% CI)
		mo
Nivolumab+ Chemotherapy	158	15.4 (11.9–19.5)
Chemotherapy	157	9.1 (7.7–10.0)

Hazard ratio for death, 0.54
(99.5% CI, 0.37–0.80)
P<0.001



Overall Population

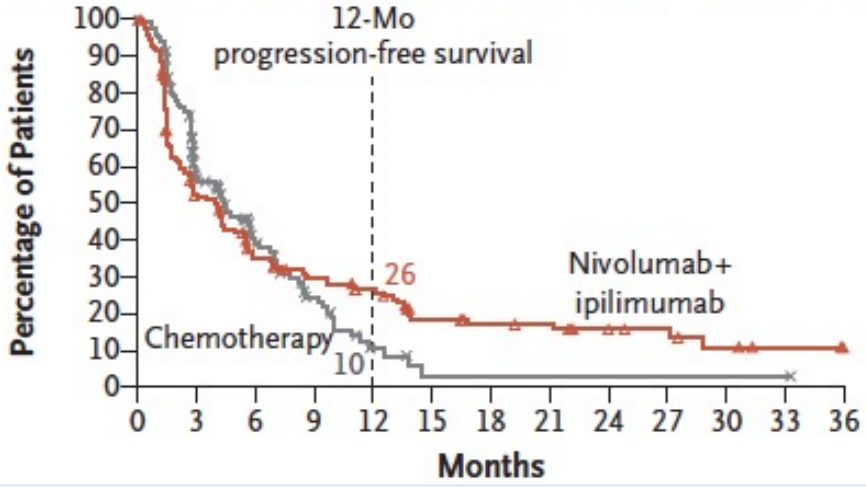
	No. of Patients	Median Overall Survival (95% CI)
		mo
Nivolumab+ Chemotherapy	321	13.2 (11.1–15.7)
Chemotherapy	324	10.7 (9.4–11.9)

Hazard ratio for death, 0.74
(99.1% CI, 0.58–0.96)
P=0.002

Doki Y et al. *N Engl J Med* 2022;386(5):449-62.

CheckMate 648: Progression-Free Survival for PD-L1 ≥1% and in the Overall Population – Nivolumab + Ipilimumab

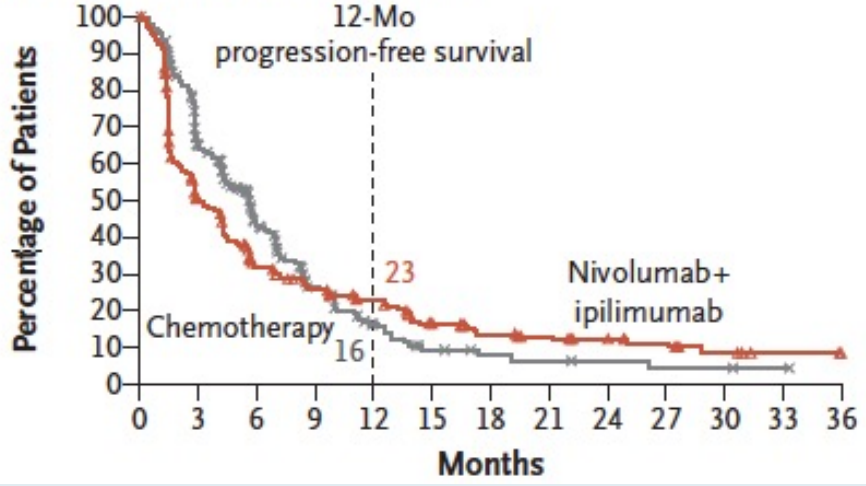
Progression-free Survival in Patients with Tumor-Cell PD-L1 Expression of ≥1%



	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Nivolumab+ Ipilimumab	158	4.0 (2.4–4.9)
Chemotherapy	157	4.4 (2.9–5.8)

Hazard ratio for disease progression or death, 1.02 (98.5% CI, 0.73–1.43)
P=0.90

Progression-free Survival in the Overall Population

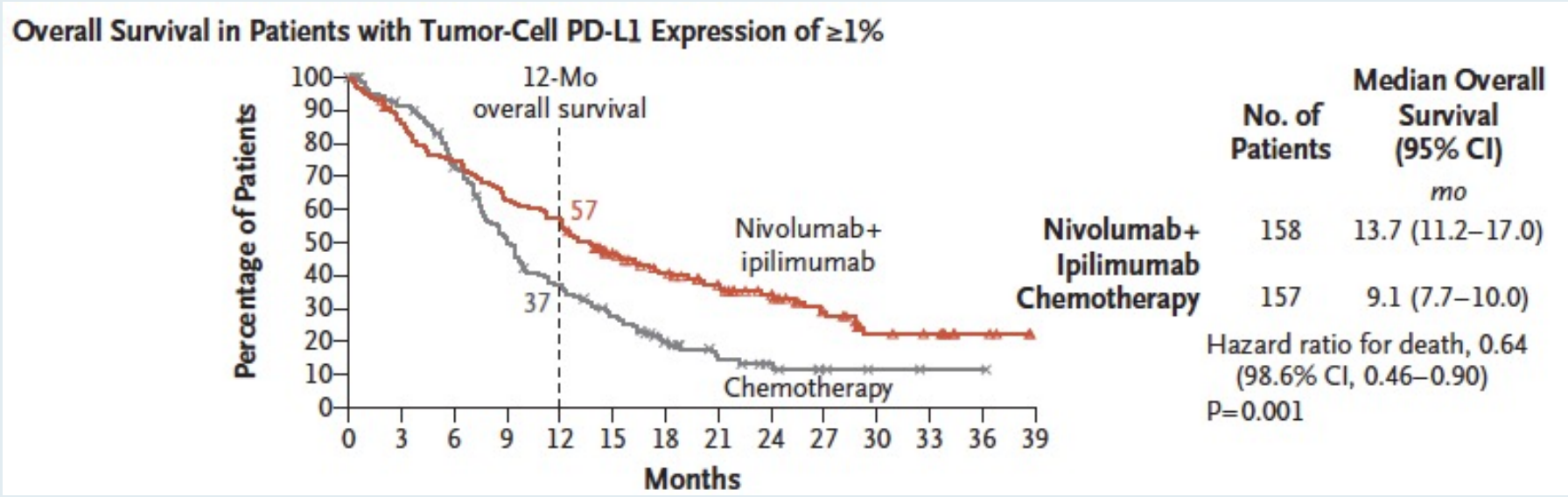


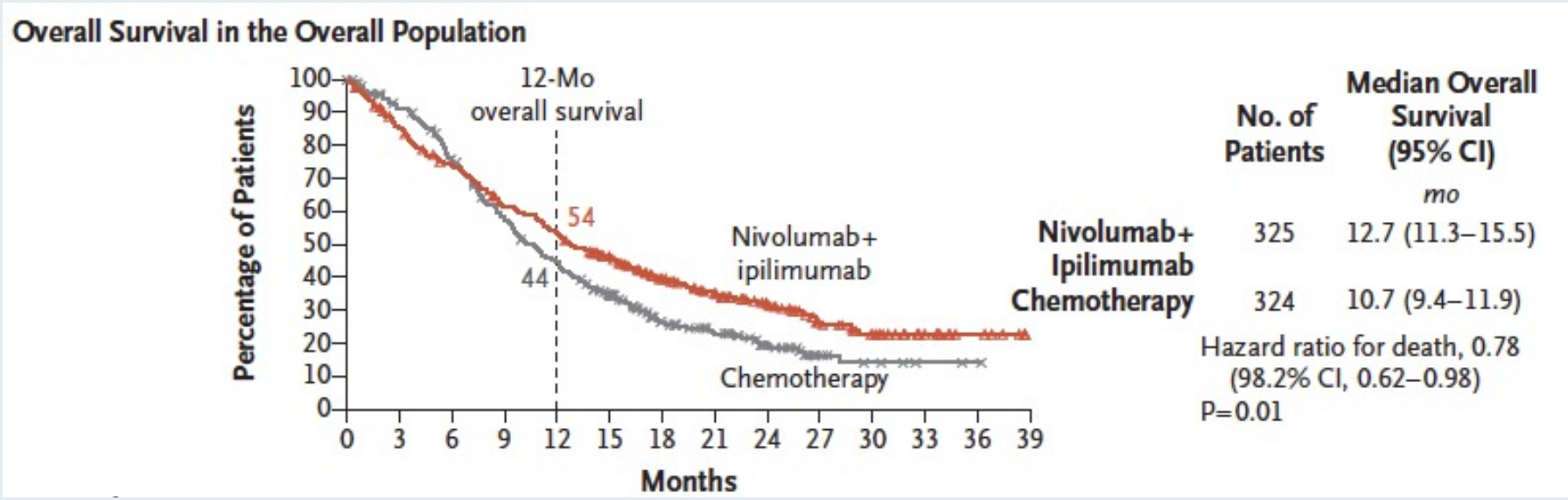
	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Nivolumab+ Ipilimumab	325	2.9 (2.7–4.2)
Chemotherapy	324	5.6 (4.3–5.9)

Hazard ratio for disease progression or death, 1.26 (95% CI, 1.04–1.52)
P value not tested

Doki Y et al. *New Engl J Med* 2022;386(5):449-62.

CheckMate 648: Overall Survival for PD-L1 ≥1% and in the Overall Population – Nivolumab + Ipilimumab





Doki Y et al. *New Engl J Med* 2022;386(5):449-62.

CheckMate 648: Antitumor Activity (BICR)

Endpoint	PD-L1 ≥1%			Overall population		
	Nivo/chemo (n = 158)	Nivo/ipi (n = 158)	Chemotherapy (n = 157)	Nivo/chemo (n = 321)	Nivo/ipi (n = 325)	Chemotherapy (n = 324)
ORR	53%	35%	20%	47%	28%	27%
Best overall response						
CR	16%	18%	5%	13%	11%	6%
PR	37%	18%	15%	34%	17%	21%
SD	25%	27%	46%	32%	32%	46%
PD	14%	30%	15%	13%	32%	12%
Median DoR	8.4 mo	11.8 mo	5.7 mo	8.2 mo	11.1 mo	7.1 mo
Pts with ongoing response	13%	25%	3%	17%	22%	6%

BICR = blinded independent central review

Doki Y et al. *N Engl J Med* 2022;386(5):449-62.

CheckMate 648: Select Treatment-Related Adverse Events

Endpoint	Nivolumab/chemotherapy (N = 310)		Nivolumab/ipilimumab (N = 322)		Chemotherapy (N = 304)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Serious AEs	53%	35%	20%	47%	28%	27%
AEs leading to discontinuation	16%	18%	5%	13%	11%	6%
Nausea	59%	4%	8%	<1%	52%	3%
Stomatitis	32%	6%	4%	0	23%	2%
Anemia	30%	10%	4%	1%	22%	6%
Decreased neutrophils	21%	8%	1%	0	17%	8%
Decreased white cells	14%	4%	1%	0	9%	2%

Doki Y et al. *N Engl J Med* 2022;386(5):449-62.

Checkmate-649 versus Checkmate-648

CM-649 - Gastric cancer

NIVO (1 mg/kg) + IPI (3 mg/kg) Q3W × 4 then NIVO 240 mg Q2W[e]

Different schedules!

CM-648 - Esophageal cancer

NIVO (3 mg/kg) Q2W + IPI (1 mg/kg) Q6W

CM-649: Treatment-related Adverse Events

All treated,[a] n (%)	NIVO + chemo (n = 782)[b]		Chemo (n = 767)[b]		NIVO + IPI (n = 403)[c]		Chemo (n = 389)[c]	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAEs[d]	739 (95)	471 (60)	682 (89)	344 (45)	323 (80)	155 (38)	356 (92)	180 (46)
Serious TRAEs[d]	175 (22)	133 (17)	94 (12)	77 (10)	122 (30)	93 (23)	54 (14)	45 (12)
TRAEs leading to discontinuation[d,e]	300 (38)	141 (18)	188 (25)	70 (9)	88 (22)	68 (17)	101 (26)	37 (10)
Treatment-related deaths[f]	16 (2)[g]		4 (< 1)[h]		10 (2)[i]		3 (< 1)[j]	

Lordick F. ESMO 2021;Discussant.

Nivolumab (NIVO) plus Chemotherapy (Chemo) or Ipilimumab (IPI) vs Chemo as First-Line Treatment for Advanced Esophageal Squamous Cell Carcinoma (ESCC): Expanded Efficacy and Safety Analyses from CheckMate 648

Chau I et al.

ESMO World Congress on Gastrointestinal Cancer 2022;Abstract O-3.

2021 ASCO ANNUAL MEETING

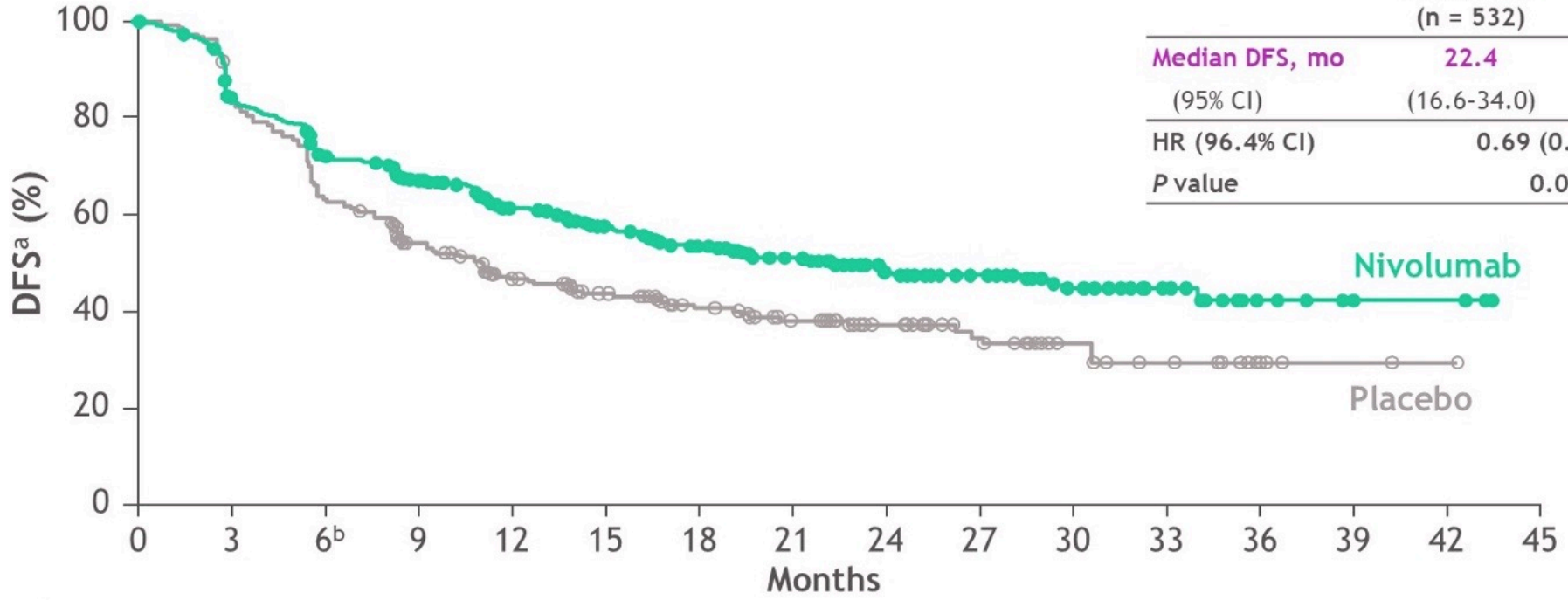
Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiotherapy: expanded efficacy and safety analyses from CheckMate 577

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

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

Abstract number 4003

CheckMate 577: Disease-Free Survival (DFS)



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

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

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

Kelly RJ et al. ASCO 2021;Abstract 4003.

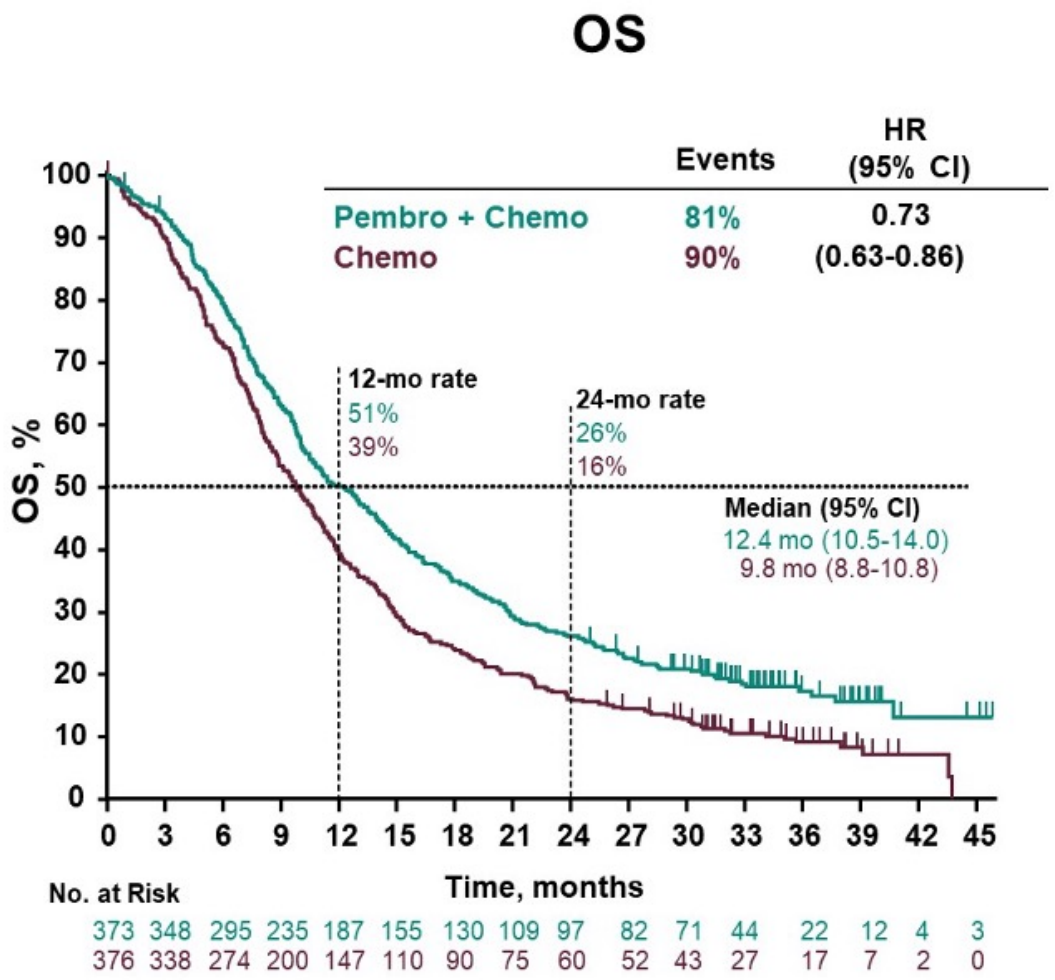
First-line Pembrolizumab Plus Chemotherapy Versus Chemotherapy in Advanced Esophageal Cancer: Longer-term Efficacy, Safety, and Quality-of-life Results From the Phase 3 KEYNOTE-590 Study

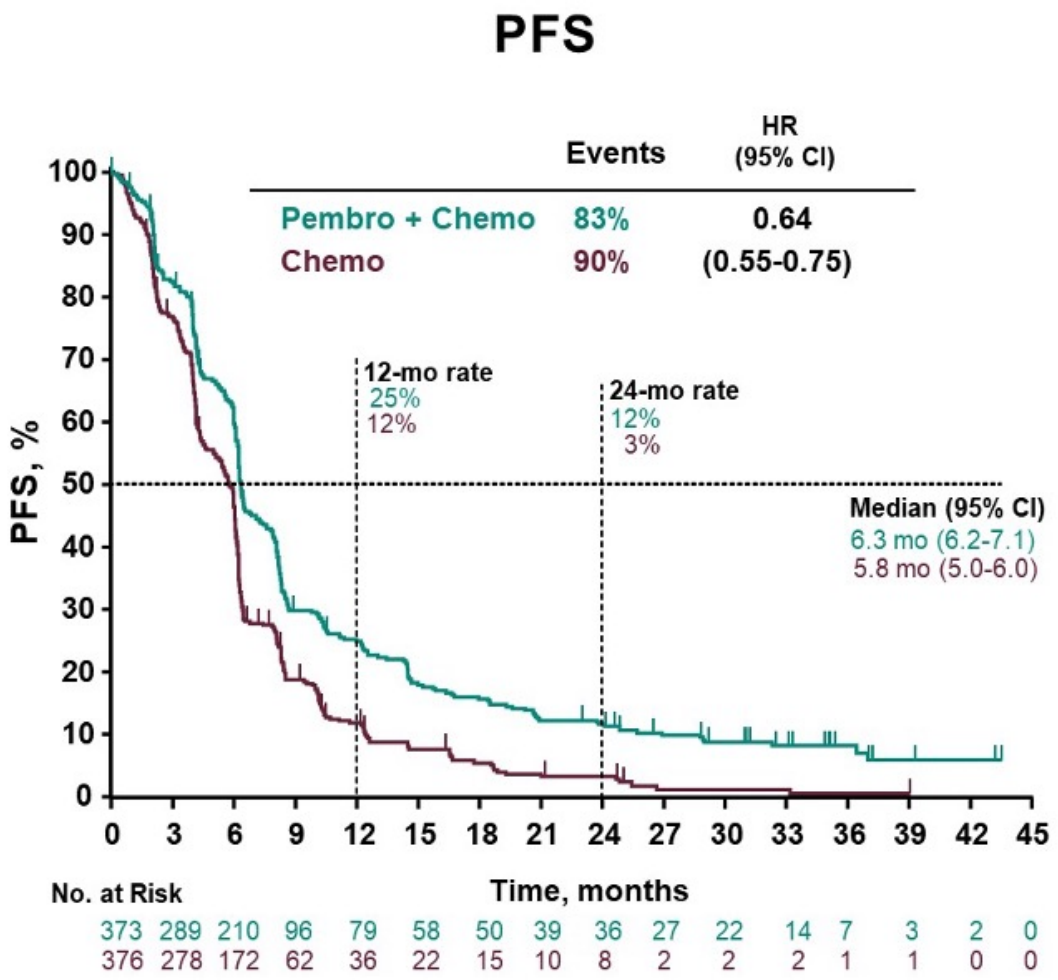
Jean-Philippe Metges,[1] Ken Kato,[2] Jong-Mu Sun,[3] Manish A. Shah,[4] Peter Enzinger,[5] Antoine Adenis,[6] Toshihiko Doi,[7] Takashi Kojima,[7] Zhigang Li,[8] Sung-Bae Kim,[9] Byoung Chul Cho,[10] Wasat Mansoor,[11] Shau-Hsuan Li,[12] Patrapim Sunpaweravong,[13] Maria Alsina Maqueda,[14] Gary L. Buchschacher, Jr,[15] Wu Jimin,[16] Sukrut Shah,[16] Pooja Bhagia,[16] Lin Shen[17]

[1]CHU Brest – Institut de Cancerologie et d'Hematologie ARPEGO Network, Brest, France; [2]National Cancer Center Hospital, Tokyo, Japan; [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [4]Weill Cornell Medical College, New York, NY, USA; [5]Dana Farber Cancer Institute, Boston, MA, USA; [6]IRCM, Inserm, Université Montpellier, ICM, Montpellier, France; [7]National Cancer Center Hospital East, Kashiwa, Japan; [8]Shanghai Chest Hospital Esophageal Disease Center, Shanghai, China; [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [10]Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea; [11]Christie Hospital NHS Trust, Manchester, United Kingdom; [12]Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan; [13]Prince of Songkla University Hospital, Songkhla, Thailand; [14]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [15]Kaiser Permanente Southern California, Los Angeles Medical Center, Los Angeles, CA, USA; [16]Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; [17]Peking University Cancer Hospital & Institute; Beijing, China

Gastrointestinal Cancers Symposium 2022;Abstract 241.

KEYNOTE-590: Survival Analyses (All Patients)



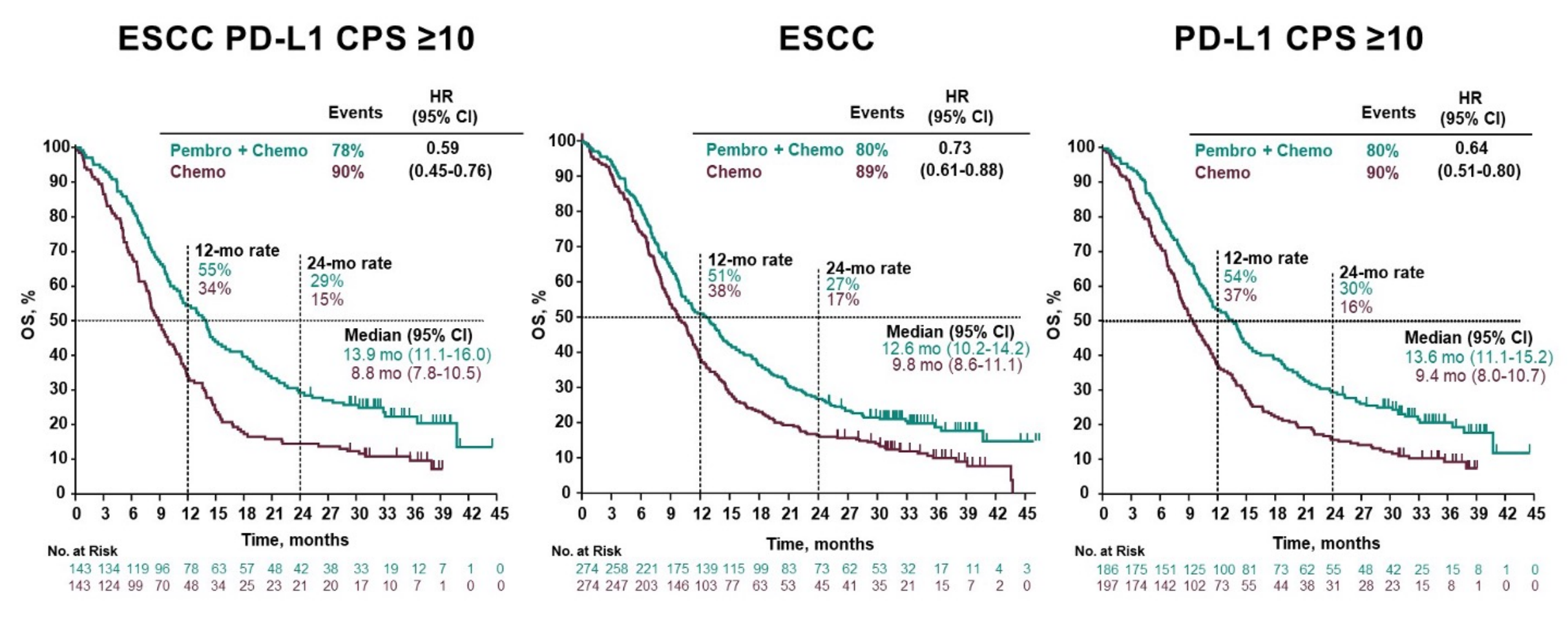


OS = overall survival; PFS = progression-free survival

Metges JP et al. Gastrointestinal Cancers Symposium 2022;Abstract 241.

RTP RESEARCH TO PRACTICE

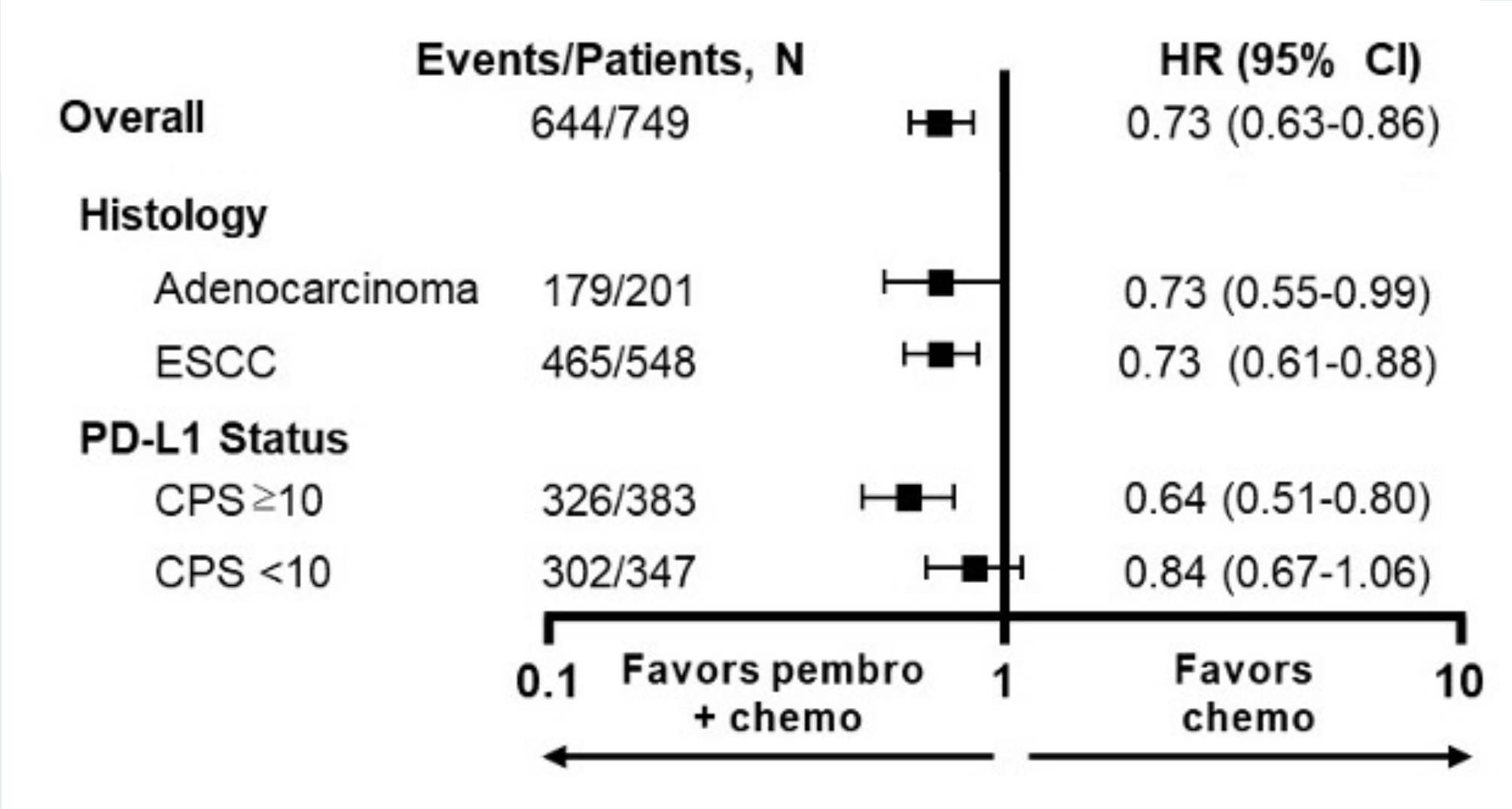
KEYNOTE-590: Overall Survival (OS) in Prespecified Subgroups



ESCC = esophageal squamous cell carcinoma

Metges JP et al. Gastrointestinal Cancers Symposium 2022;Abstract 241.

KEYNOTE-590: Overall Survival in Select Subgroups



Metges JP et al. Gastrointestinal Cancers Symposium 2022;Abstract 241.

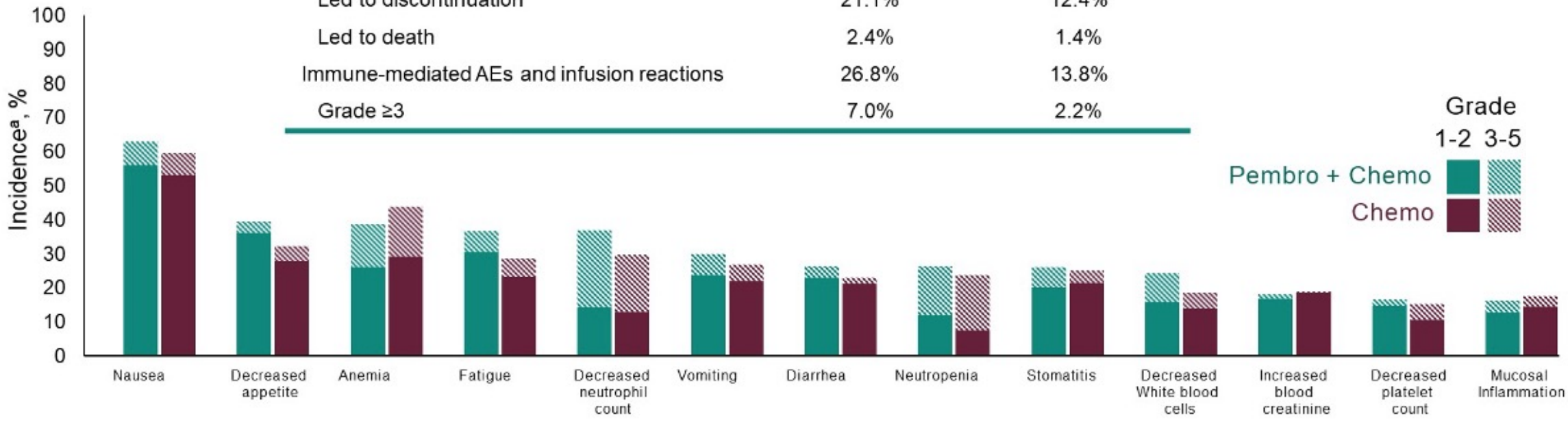
KEYNOTE-590: Antitumor Response

Best response, n (%)	Pembro + Chemo N = 373	Chemo N = 376
ORR, n (%)	**168 (45.0)**	**110 (29.3)**
Complete response	25 (6.7)	9 (2.4)
Partial response	143 (38.3)	101 (26.9)
Stable disease	126 (33.8)	174 (46.3)
Disease control rate	294 (78.8)	284 (75.5)
Progressive disease	43 (11.5)	59 (15.7)
Not evaluable/no assessment	36 (9.6)	33 (8.7)
Median DOR (range), mo	8.3 (1.2+ to 41.7+)	6.0 (1.5+ to 34.9+)
≥ 24 months response duration, %	**20.4**	**6.2**

Metges JP et al. Gastrointestinal Cancers Symposium 2022;Abstract 241.

KEYNOTE-590: Adverse Events Summary

Events, n (%)	Pembro + Chemo N = 373	Chemo N = 376
Any	100%	99.5%
Treatment-related	98.4%	97.3%
Grade ≥3	71.9%	67.6%
Led to discontinuation	21.1%	12.4%
Led to death	2.4%	1.4%
Immune-mediated AEs and infusion reactions	26.8%	13.8%
Grade ≥3	7.0%	2.2%



Metges JP et al. Gastrointestinal Cancers Symposium 2022;Abstract 241.

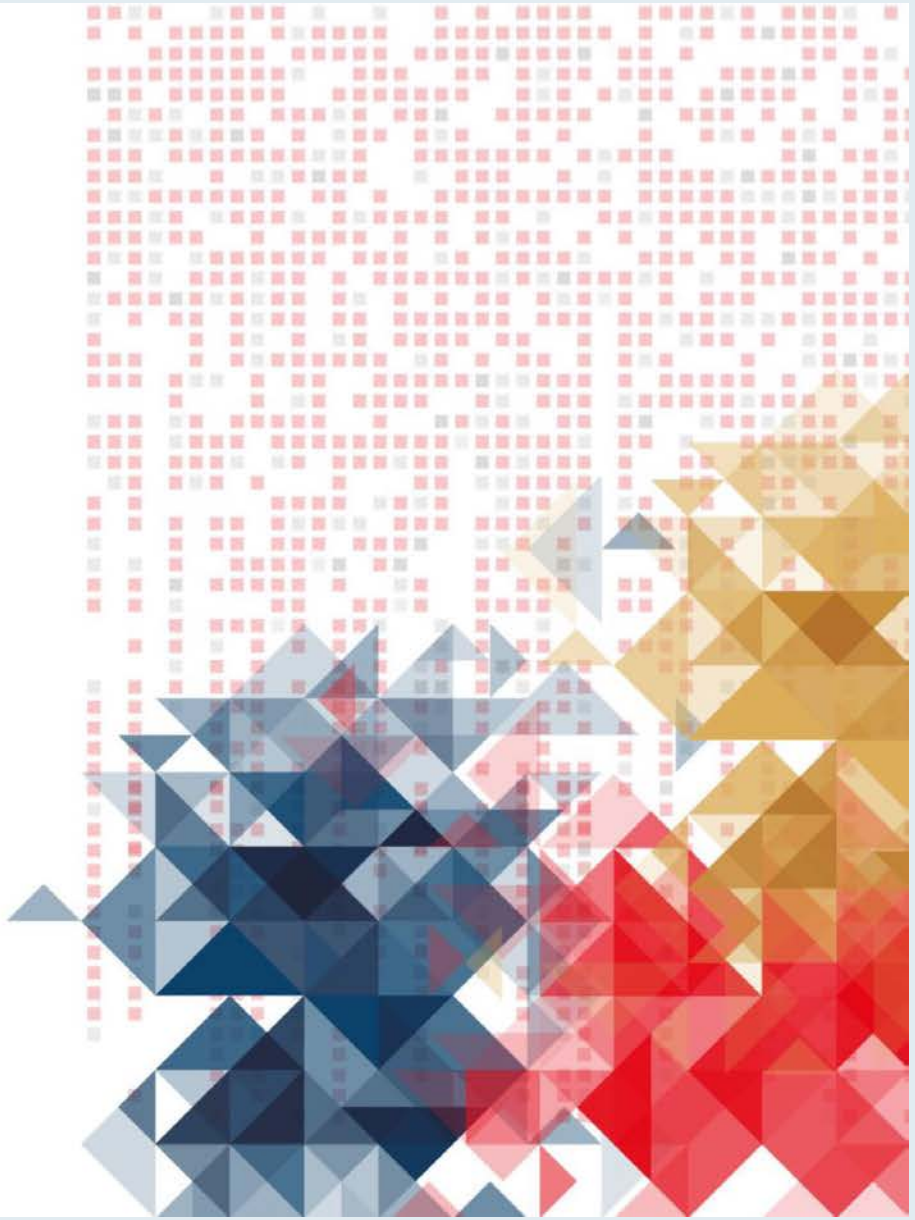
RTP RESEARCH TO PRACTICE

2021 ESMO congress

Sintilimab plus chemotherapy (chemo) versus chemo as the first-line treatment for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma (ORIENT-16)

Jianming Xu*, Haiping Jiang, Yueyin Pan, Kangsheng Gu, Sundong Cang, Lei Han, Yongqian Shu, Jiayi Li, Junhui Zhao, Hongming Pan, Suxia Luo, Yanru Qin, Qunyi Guo, Yuxian Bai, Yang Ling, Yingmei Guo, Ziran Li, Ying Liu, Yan Wang, Hui Zhou

*, presenting author, MD, The Fifth Medical Center, Chinese PLA General Hospital



Abstract LBA53

RTP RESEARCH TO PRACTICE

ORIENT-16: Phase III Trial Design

Sintilimab is a recombinant fully humanized anti-PD-1 monoclonal antibody.

Previous study has shown encouraging anti-tumor activities of Sintilimab plus chemotherapy in 1L G/GEJ cancer.

ORIENT-16[a] is a randomized, double-blind, phase 3 study

Key eligibility criteria
- Previously untreated, unresectable advanced, recurrent or metastatic G/GEJ adenocarcinoma
- ECOG PS 0 or 1
- No known Her2 positive

R 1:1

N=327 → **Sintilimab + XELOX[a] Q3W × 6 cycles, then Sintilimab + Capecitabine[a] Q3W[b]**

N=323 → **Placebo + XELOX[a] Q3W × 6 cycles, then Placebo + Capecitabine[a] Q3W[b]**

Primary endpoints:
- OS in the patients with CPS ≥5
- OS in all randomized patients

Secondary endpoints:
- PFS, ORR, DCR, and DoR
- Safety profile

Stratification factors
- ECOG PS (0 or 1)
- Liver metastasis (yes or no)
- PD-L1 (CPS <10 or ≥10)

- Data cut-off date for interim analysis was June 20, 2021
- Median follow-up: 18.8 months

Statistical considerations
- Type I error is strictly controlled using fixed sequence test. OS in CPS≥5 and all randomized are tested hierarchically
- One interim analysis is planned, and O'Brien-Fleming is used for the alpha boundary (alpha=0.0148).

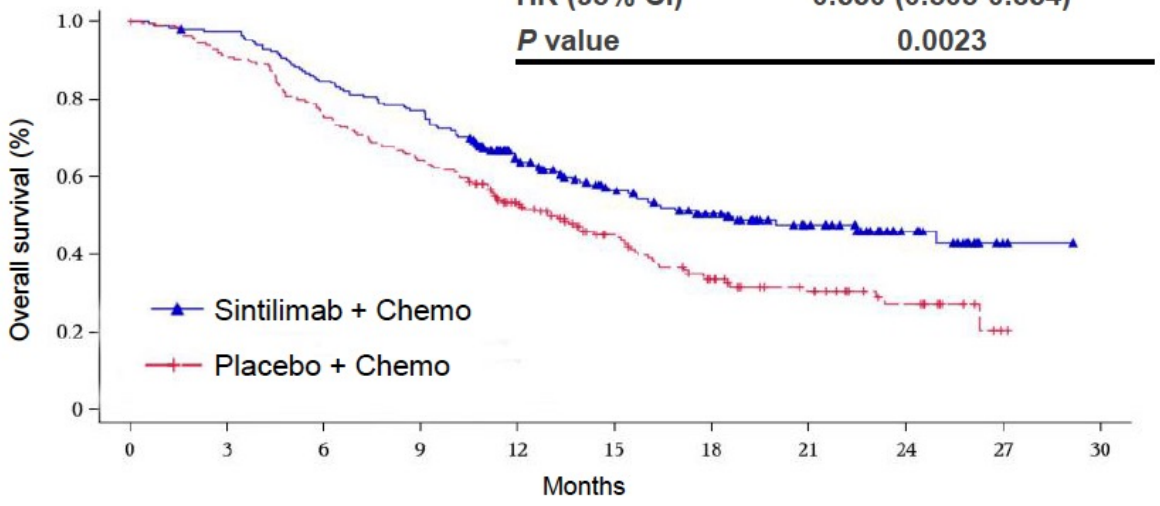
[a] ClinicalTrial.gov number, NCT03745170; [b] Sintilimab 3 mg/kg for body weight <60 kg, 200 mg for ≥60 kg; Oxaliplatin 130 mg/m^2 IV; Capecitabine 1000 mg/m^2 PO Bid d1-14;
[c] Until progressive disease, intolerable toxicity, withdrawal of consent. Treatment is given for a maximum of 2 years.

Xu J et al. ESMO 2021;Abstract LBA53.

ORIENT-16: Overall Survival (OS) with Sintilimab and Chemotherapy for Advanced Gastric or GEJ Adenocarcinoma

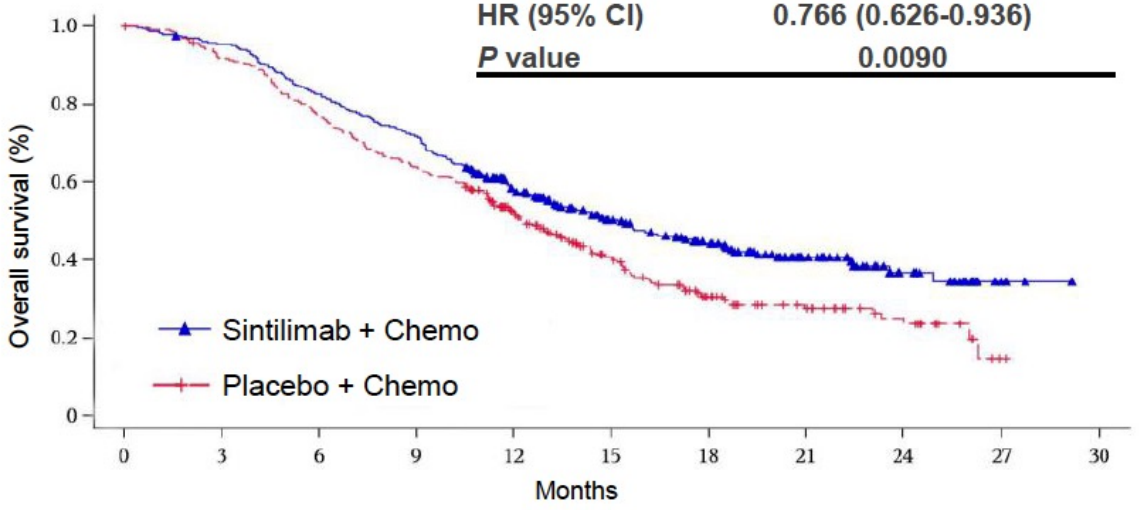
PD-L1 CPS ≥5

	Sin + Chemo (N=197)	Chemo (N=200)
Median OS, mo (95% CI)	18.4 (14.6-NC)	12.9 (11.1-.15.4)
HR (95% CI)	0.660 (0.505-0.864)	
P value	0.0023	



All patients

	Sin + Chemo (N=327)	Chemo (N=323)
Median OS, mo (95% CI)	15.2 (12.9-18.4)	12.3 (11.3-.13.8)
HR (95% CI)	0.766 (0.626-0.936)	
P value	0.0090	



Xu J et al. ESMO 2021;Abstract LBA53.

2021 ESMO congress

Sintilimab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced or metastatic esophageal squamous cell cancer: First Results of the Phase 3 ORIENT-15 study

Lin Shen[1], Zhihao Lu[2], Junye Wang[3], Yongqian Shu[4], Li Kong[5], Lei Yang[6], Buhai Wang[7], Zhiwu Wang[8], Yinghua Ji[9], Guochun Cao[10], Hu Liu[11], Tongjian Cui[12], Na Li[13], Wensheng Qiu[14], Zhuo Ma[15], Yuling Chen[15], Haoyu Li[15], Xing Sun[15], Yan Wang[15], Hui Zhou[15]

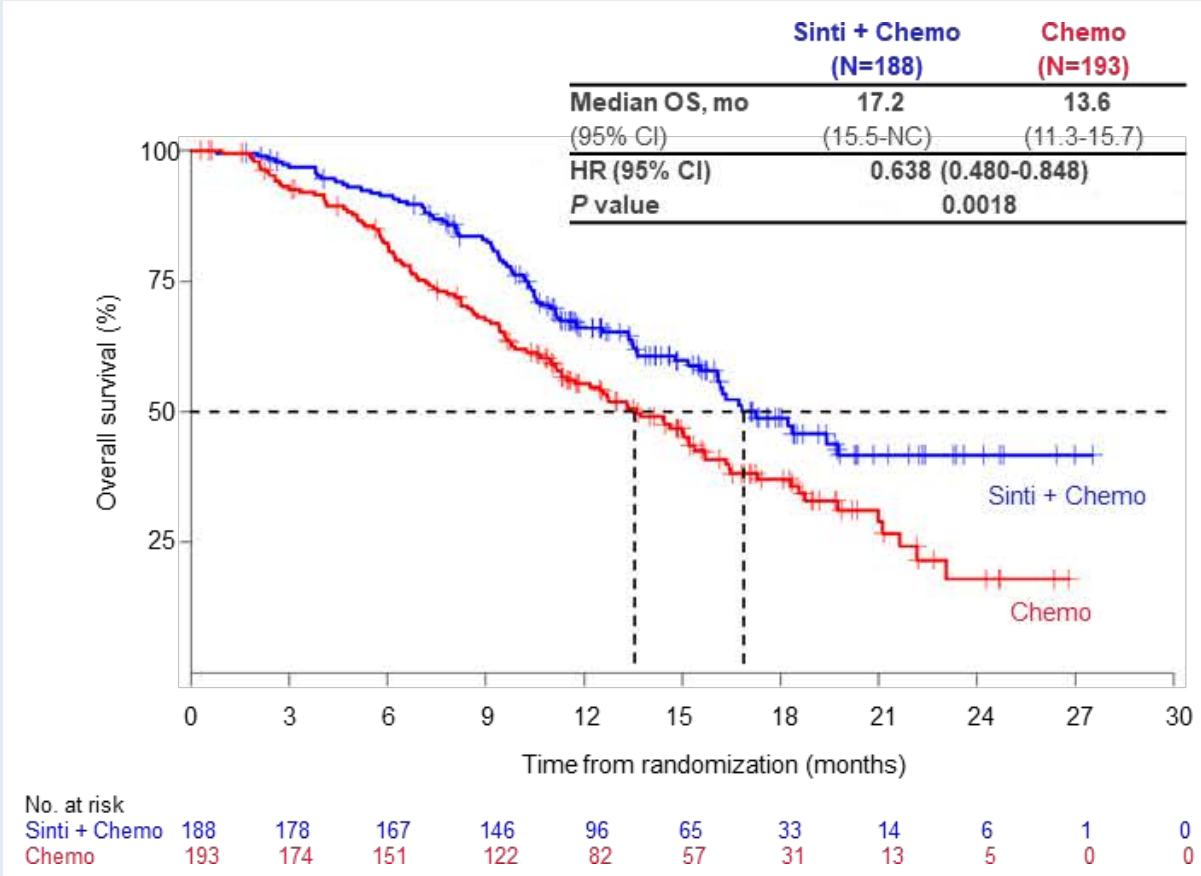
[1]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital and Institute, Beijing, China, [2]Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China, [3]Department of Oncology, The Affiliated Hospital of Jining Medical College, Jining, China, [4]Department of Medical Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China, [5]Special Needs Ward, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, [6]Department of Medical Oncology, Nantong Cancer Hospital, Nantong, China, [7]Department of Medical Oncology, Northern Jiangsu People's Hospital, Affiliated Hospital to Yangzhou University, Yangzhou, China, [8]Department of Radiotherapy and Chemotherapy, Tangshan People Hospital, Tangshan, China, [9]Department of Medical Oncology, The First Affiliated Hospital of Xinxiang Medical University, Xinxiang, China, [10]Department of Oncology, Jiangsu Cancer Hospital, Nanjing Medical University, Nanjing, China, [11]Department of Medical Oncology, Anhui provincial Cancer Hospital, University of Science and Technology of China, Hefei, China, [12]Department of Oncology, Fujian Provincial Hospital, Fuzhou, China, [13]Department of Medical Oncology, Suining Central Hospital, Suining, China, [14]Department of Medical Oncology, The Affiliated Hospital of Qingdao University, Qingdao, China, [15]Medical Oncology, Innovent Biologics, Inc., Suzhou, China, [16]Biostatistics, Innovent Biologics, Inc., Suzhou, China

ESMO 2021;Abstract LBA52.

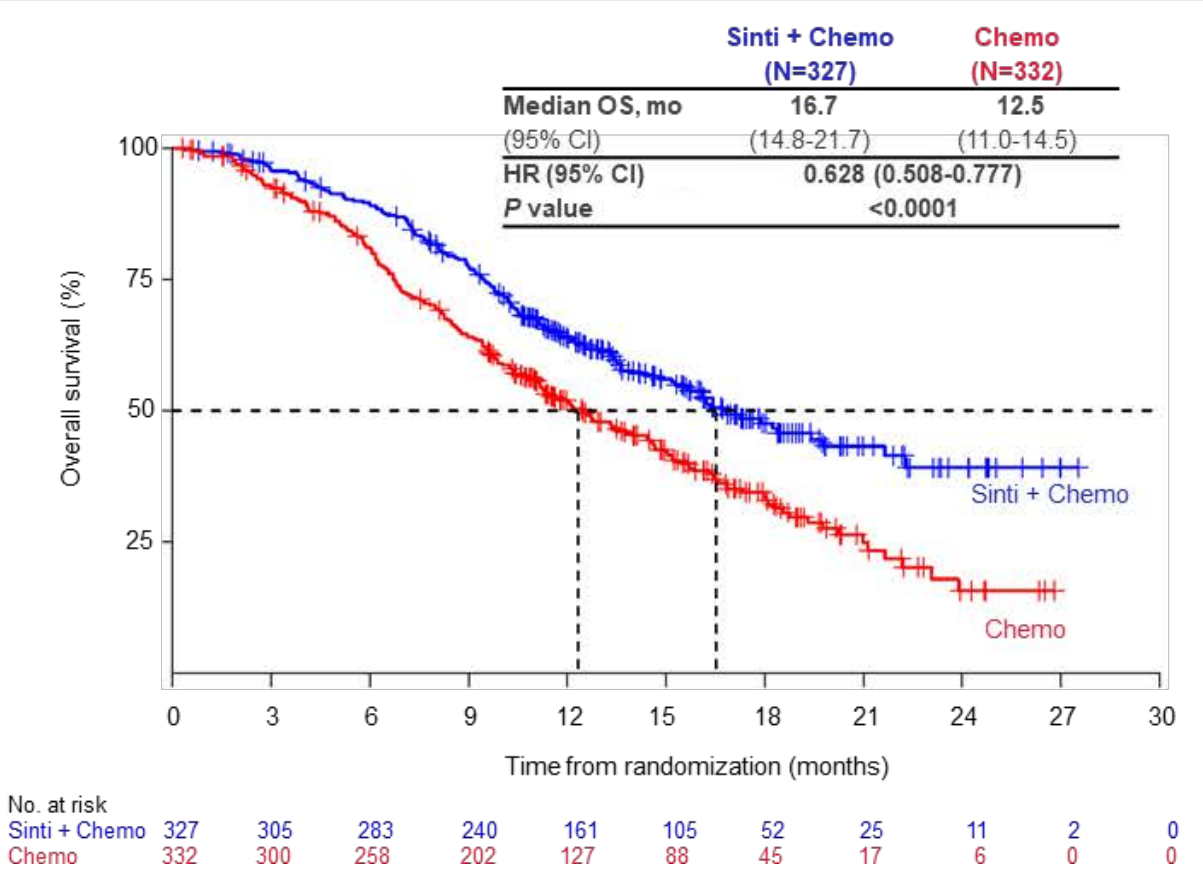
RTP RESEARCH TO PRACTICE

ORIENT-15: Overall Survival with Sintilimab and Chemotherapy for Advanced or Metastatic Esophageal Squamous Cell Carcinoma

PD-L1 CPS ≥10



All patients



Shen L et al. ESMO 2021;Abstract LBA52.

RTP RESEARCH TO PRACTICE

Cancer Cell 2022;40(3):277-88.e3

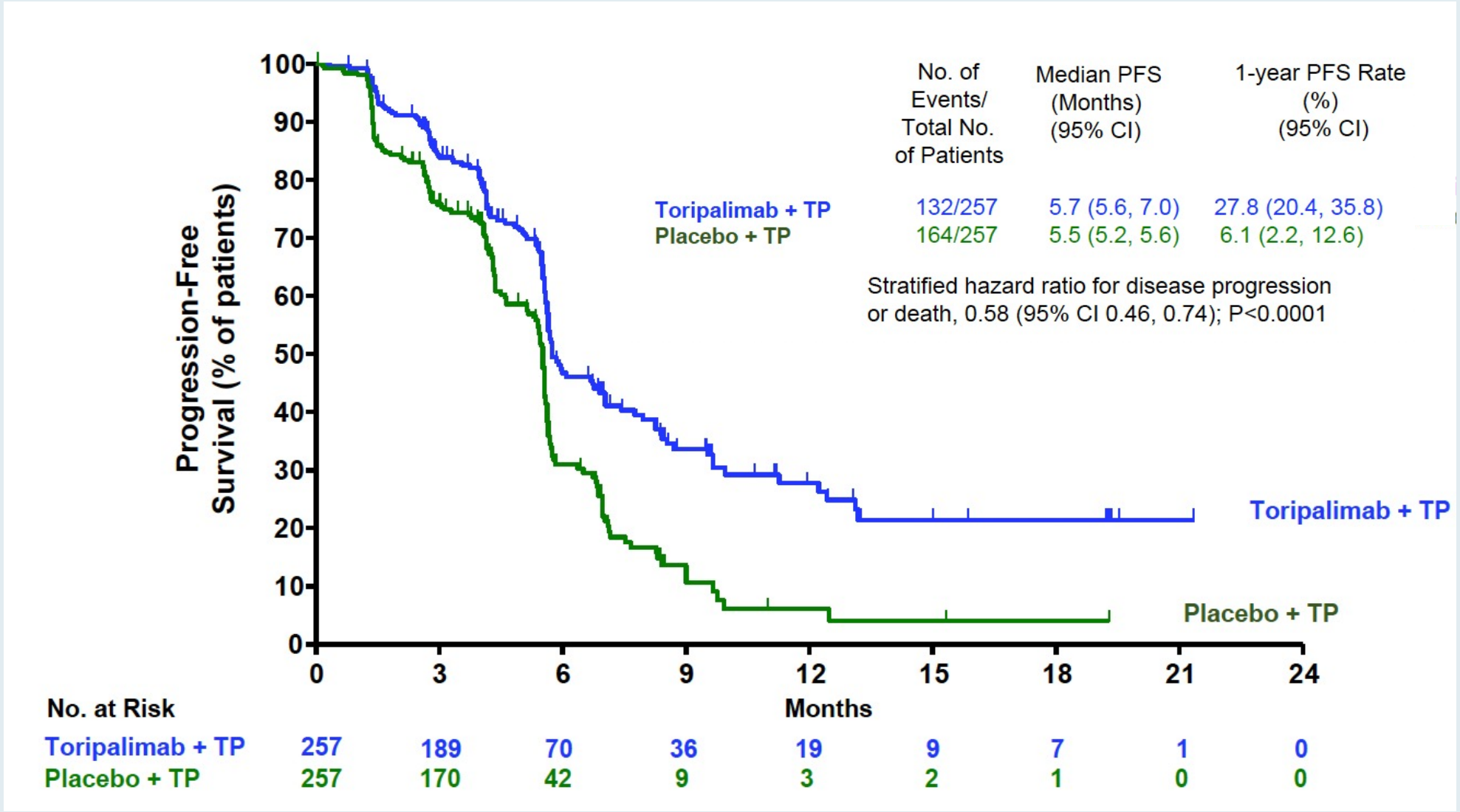
CellPress

Article

Toripalimab plus chemotherapy in treatment-naïve, advanced esophageal squamous cell carcinoma (JUPITER-06): A multi-center phase 3 trial

Zi-Xian Wang,[1,2,76] Chengxu Cui,[3,76] Jun Yao,[4,76] Yanqiao Zhang,[5,76] Mengxia Li,[6] Jifeng Feng,[7] Shujun Yang,[8] Yun Fan,[9] Jianhua Shi,[10] Xizhi Zhang,[11] Lin Shen,[12] Yongqian Shu,[13] Cailian Wang,[14] Tianyang Dai,[15] Teng Mao,[16] Long Chen,[17] Zengqing Guo,[18] Bo Liu,[19] Hongming Pan,[20] Shundong Cang,[21] Yi Jiang,[22] Junye Wang,[23] Min Ye,[24] Zhendong Chen,[25] Da Jiang,[26] Qin Lin,[27] Wei Ren,[28] Junsheng Wang,[29] Lin Wu,[30] Yong Xu,[31] Zhanhui Miao,[32] Meili Sun,[33] Conghua Xie,[34] et al

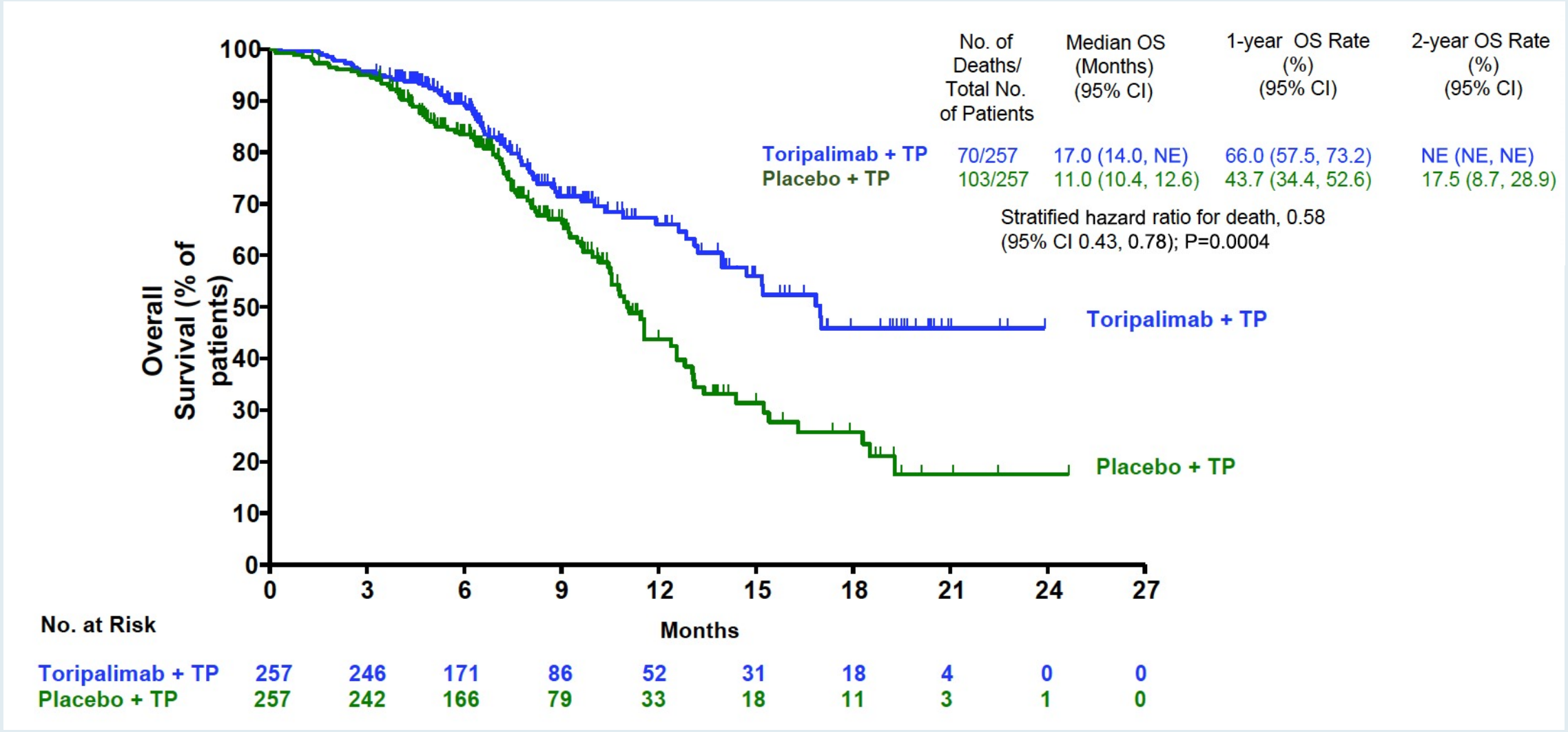
JUPITER-06: Progression-Free Survival (BICR, ITT Population)



Wang ZX et al. *Cancer Cell* 2022;40(3):277-88.e3

RTP RESEARCH TO PRACTICE

JUPITER-06: Overall Survival (ITT Population)



Wang ZX et al. *Cancer Cell* 2022;40(3):277-88.e3

RTP RESEARCH TO PRACTICE

JUPITER-06: Tumor Response

Variable	Toripalimab + TP (n = 257)	Placebo + TP (n = 257)
Best overall response, no. (%)		
Complete response	30 (11.7)	18 (7.0)
Partial response	148 (57.6)	116 (45.1)
Stable disease	51 (19.8)	77 (30.0)
Progressive disease	18 (7.0)	35 (13.6)
Non-CR/non-PD[a]	1 (0.4)	2 (0.8)
Not evaluable[b]	9 (3.5)	9 (3.5)
Objective response rate (ORR)		
ORR % (95% CI)	69.3 (63.2–74.8)	52.1 (45.8–58.4)
Difference in ORR % (95% CI)	17.2 (9.0–25.4)	
p value[c]	<0.0001	
Disease control rate (DCR)		
DCR % (95% CI)	89.1 (84.6–92.6)	82.1 (76.9–86.6)
Difference in DCR % (95% CI)	7.1 (1.1–13.1)	
p value[c]	0.0206	

Wang ZX et al. *Cancer Cell* 2022;40(3):277-88.e3

JUPITER-06: Select Treatment-Emergent Adverse Events (TEAEs)

	Toripalimab + TP (n = 257) no. (%)		Placebo + TP (n = 257) no. (%)	
Adverse event, no. of patients (%)	All grades	grade ≥3	all grades	grade ≥3
Any TEAE	255 (99.2)	188 (73.2)	255 (99.2)	180 (70.0)
Anemia	201 (78.2)	28 (10.9)	207 (80.5)	38 (14.8)
Leukopenia	174 (67.7)	52 (20.2)	138 (53.7)	34 (13.2)
Neutropenia	173 (67.3)	109 (42.4)	139 (54.1)	85 (33.1)
Nausea	111 (43.2)	0 (0)	118 (45.9)	5 (1.9)
Fatigue	110 (42.8)	11 (4.3)	101 (39.3)	5 (1.9)
Neuropathy peripheral	104 (40.5)	3 (1.2)	111 (43.2)	10 (3.9)
Vomiting	103 (40.1)	5 (1.9)	94 (36.6)	5 (1.9)
Decreased appetite	101 (39.3)	3 (1.2)	118 (45.9)	5 (1.9)

Wang ZX et al. *Cancer Cell* 2022;40(3):277-88.e3

Research

JAMA 2021;326(10):916-25.

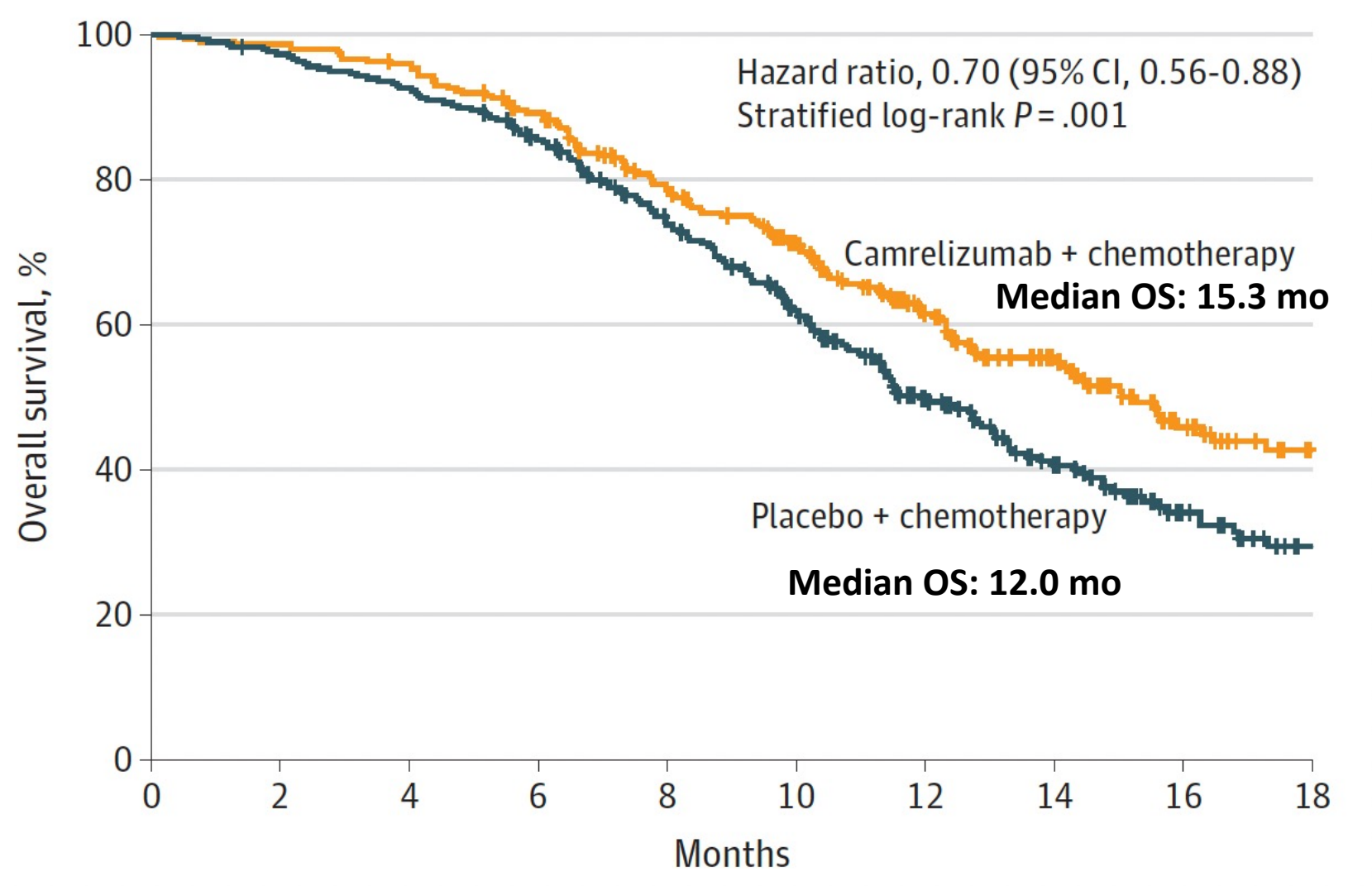
JAMA | Original Investigation

Effect of Camrelizumab vs Placebo Added to Chemotherapy on Survival and Progression-Free Survival in Patients With Advanced or Metastatic Esophageal Squamous Cell Carcinoma

The ESCORT-1st Randomized Clinical Trial

Huiyan Luo, MD, PhD; Jin Lu, BS; Yuxian Bai, MD; Teng Mao, MM; Jun Wang, MD; Qingxia Fan, BS; Yiping Zhang, MB; Kuaile Zhao, MD; Zhendong Chen, MB; Shegan Gao, MD; Jiancheng Li, MD; Zhichao Fu, MD; Kangsheng Gu, MD; Zhihua Liu, MD; Lin Wu, MD; Xiaodong Zhang, MD; Jifeng Feng, PhD; Zuoxing Niu, MM; Yi Ba, MD; Helong Zhang, MD; Ying Liu, MD; Li Zhang, MB; Xuhong Min, BS; Jing Huang, MD; Ying Cheng, MD; Dong Wang, MD; Yu Shen, PhD; Qing Yang, MD; Jianjun Zou, MD; Rui-Hua Xu, MD, PhD; for the ESCORT-1st Investigators

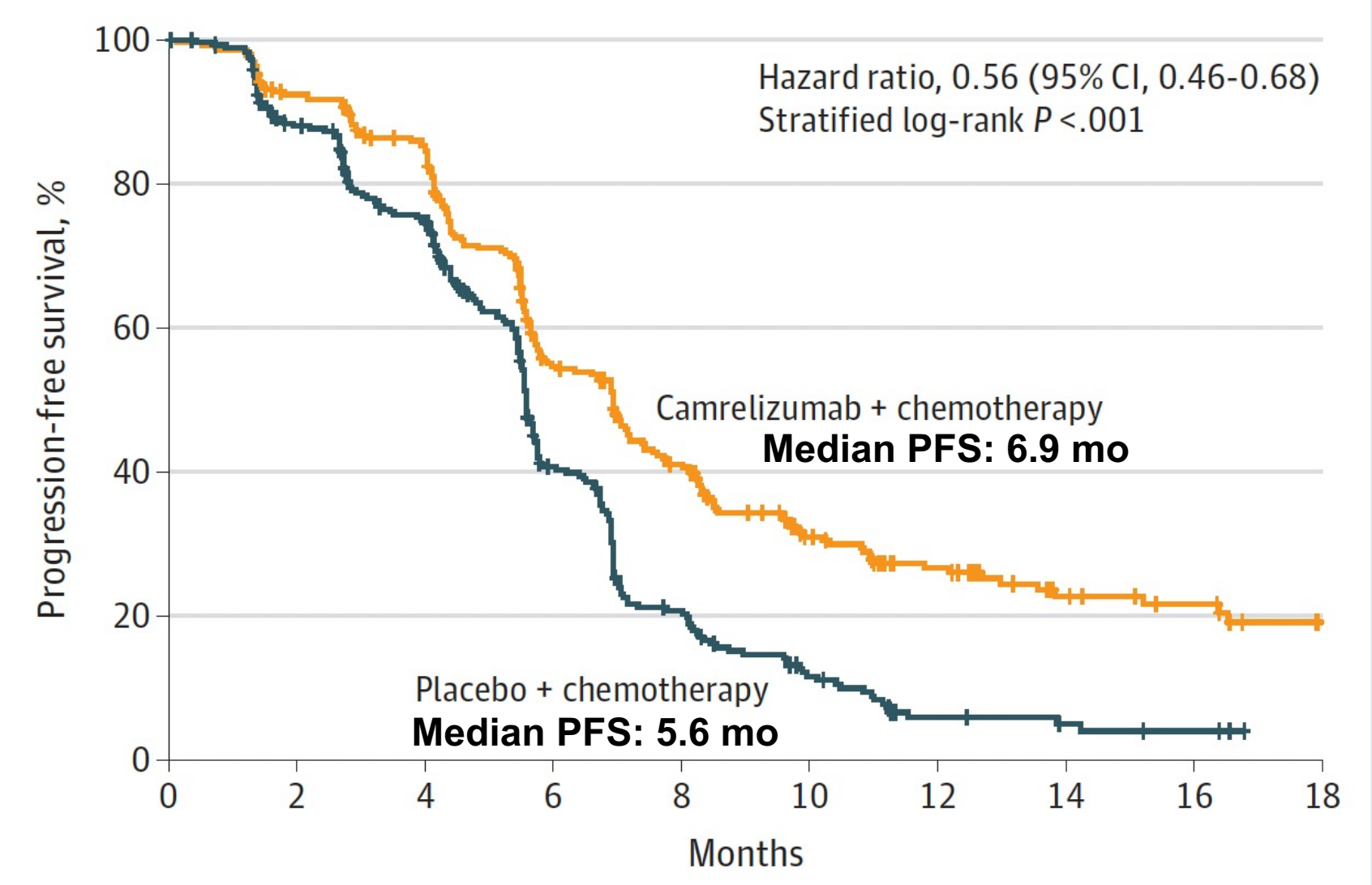
ESCORT-1st: Overall Survival (Coprimary Endpoint)



Luo H et al. *JAMA* 2021;326(10):916-25.

RTP RESEARCH TO PRACTICE

ESCORT-1st: Progression-Free Survival (Coprimary Endpoint)



Luo H et al. *JAMA* 2021;326(10):916-25.

RTP RESEARCH TO PRACTICE

ESCORT-1st: Select Adverse Events

	No. (%) of patients			
	Camrelizumab + chemotherapy (n = 298)		Placebo + chemotherapy (n = 297)	
	Any grade[a]	≥Grade 3	Any grade	≥Grade 3
Treatment-related adverse events[b]	296 (99.3)[c]	189 (63.4)	288 (97.0)	201 (67.7)
Reactive cutaneous capillary endothelial proliferation	238 (79.9)	3 (1.0)	32 (10.8)	0
Anemia	229 (76.8)	52 (17.4)	217 (73.1)	40 (13.5)
White blood cell count decreased	202 (67.8)	72 (24.2)	194 (65.3)	79 (26.6)
Neutrophil count decreased	201 (67.4)	119 (39.9)	186 (62.6)	129 (43.4)
Nausea	150 (50.3)	4 (1.3)	154 (51.9)	5 (1.7)
Asthenia	141 (47.3)	6 (2.0)	129 (43.4)	8 (2.7)
Alopecia	135 (45.3)	1 (0.3)	147 (49.5)	0
Decreased appetite	129 (43.3)	2 (0.7)	134 (45.1)	5 (1.7)
Vomiting	117 (39.3)	10 (3.4)	106 (35.7)	6 (2.0)
Platelet count decreased	77 (25.8)	8 (2.7)	73 (24.6)	6 (2.0)

Luo H et al. *JAMA* 2021;326(10):916-25.

ESCORT-1st: Immune-Related Adverse Events

	No. (%) of patients			
	Camrelizumab + chemotherapy (n = 298)		Placebo + chemotherapy (n = 297)	
	Any grade[a]	≥Grade 3	Any grade	≥Grade 3
Immune-related adverse events[d]	252 (84.6)		98 (33.0)	
Reactive capillary endothelial proliferation	238 (79.9)		32 (10.8)	
Hypothyroidism	34 (11.4)		13 (4.4)	
Pruritus	20 (6.7)		7 (2.4)	
Hyperthyroidism	16 (5.4)		3 (1.0)	
Rash	16 (5.4)		6 (2.0)	
Pneumonitis	15 (5.0)		9 (3.0)	
Blood thyroid stimulating hormone decreased	10 (3.4)		1 (0.3)	

Luo H et al. *JAMA* 2021;326(10):916-25.

Lancet 2014;383(9911):31-9.

Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial

*Charles S Fuchs, Jiri Tomasek, Cho Jae Yong, Filip Dumitru, Rodolfo Passalacqua, Chanchal Goswami, Howard Safran, Lucas Vieira dos Santos, Giuseppe Aprile, David R Ferry, Bohuslav Melichar, Mustapha Tehfe, Eldar Topuzov, John Raymond Zalcberg, Ian Chau, William Campbell, Choondal Sivanandan, Joanna Pikiel, Minori Koshiji, Yanzhi Hsu, Astra M Liepa, Ling Gao, Jonathan D Schwartz, Josep Tabernero, for the REGARD Trial Investigators**

Lancet Oncol 2014;15(11):1224-35.

Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial

*Hansjochen Wilke, Kei Muro, Eric Van Cutsem, Sang-Cheul Oh, György Bodoky, Yasuhiro Shimada, Shuichi Hironaka, Naotoshi Sugimoto, Oleg Lipatov, Tae-You Kim, David Cunningham, Philippe Rougier, Yoshito Komatsu, Jaffer Ajani, Michael Emig, Roberto Carlesi, David Ferry†, Kumari Chandrawansa, Jonathan D Schwartz, Atsushi Ohtsu, for the RAINBOW Study Group**

Pivotal Phase III Studies of Ramucirumab for Advanced Gastric or GEJ Adenocarcinoma

Study	N	Setting	Treatment	Median OS	Hazard ratio (*p*-value)
REGARD	355	PD after first-line therapy	Ramucirumab Placebo	5.2 mo 3.8 mo	HR: 0.776 (*p* = 0.047)
RAINBOW	665	PD after first-line therapy	Ramucirumab/paclitaxel Placebo/paclitaxel	9.6 mo 7.4 mo	HR: 0.807 (*p* = 0.017)

Fuchs CS et al. *Lancet* 2014;383(9911):31-9. Wilke H et al. *Lancet Oncol* 2014;15(11):1224-35.

European Journal of Cancer 165 (2022) 48–57

Available online at www.sciencedirect.com

ScienceDirect

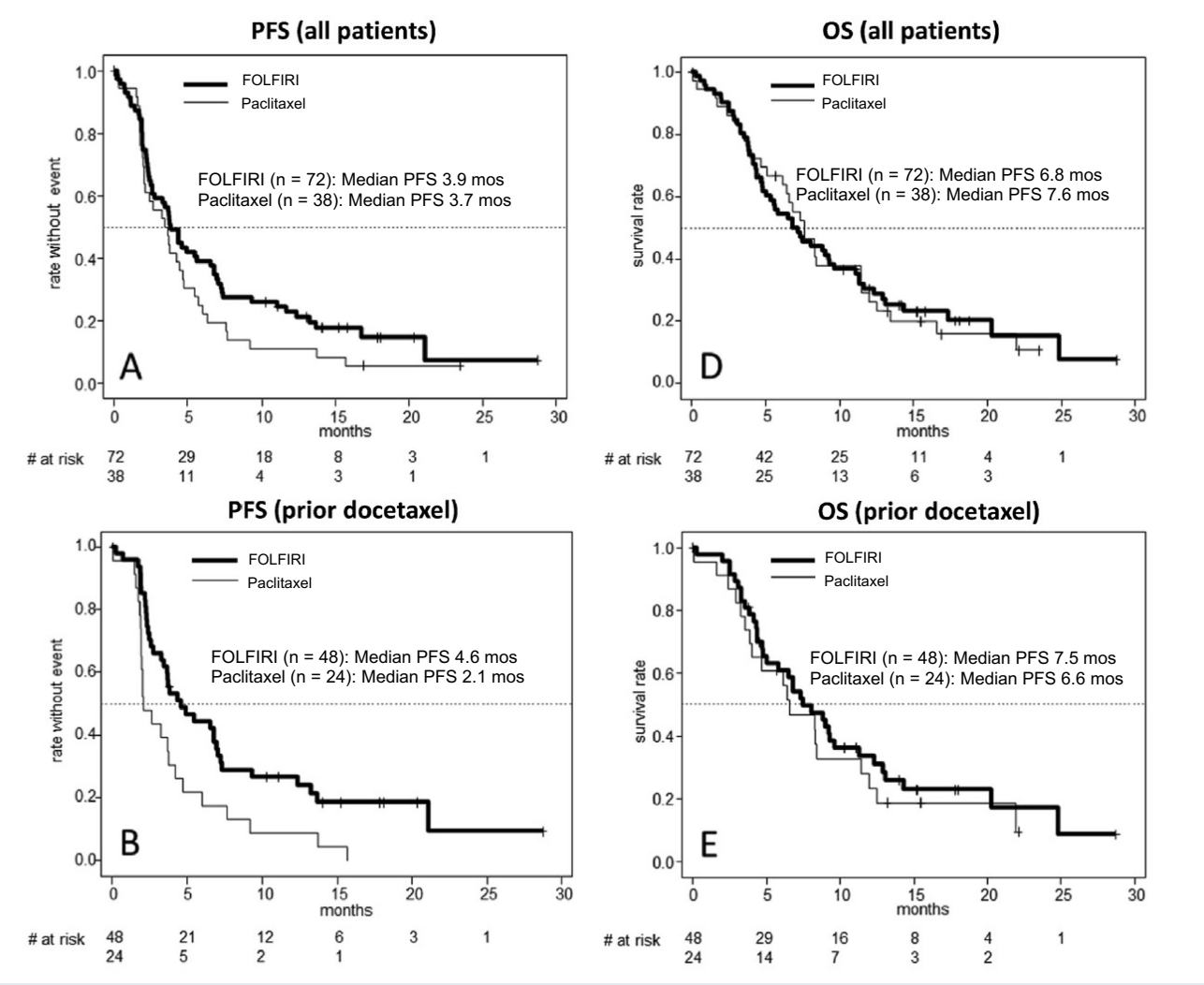
journal homepage: www.ejcancer.com

Original Research

FOLFIRI plus ramucirumab versus paclitaxel plus ramucirumab as second-line therapy for patients with advanced or metastatic gastroesophageal adenocarcinoma with or without prior docetaxel – results from the phase II RAMIRIS Study of the German Gastric Cancer Study Group at AIO

Sylvie Lorenzen [a,*], Peter Thuss-Patience [b], Claudia Pauligk [c], Eray Gökkurt [d], Thomas Ettrich [e], Florian Lordick [f], Michael Stahl [g], Peter Reichardt [h], Martin Sökler [i], Daniel Pink [j,k], Stefan Probst [l], Axel Hinke [m], Thorsten O. Goetze [c,n,1], Salah E. Al-Batran [c,n,1]

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



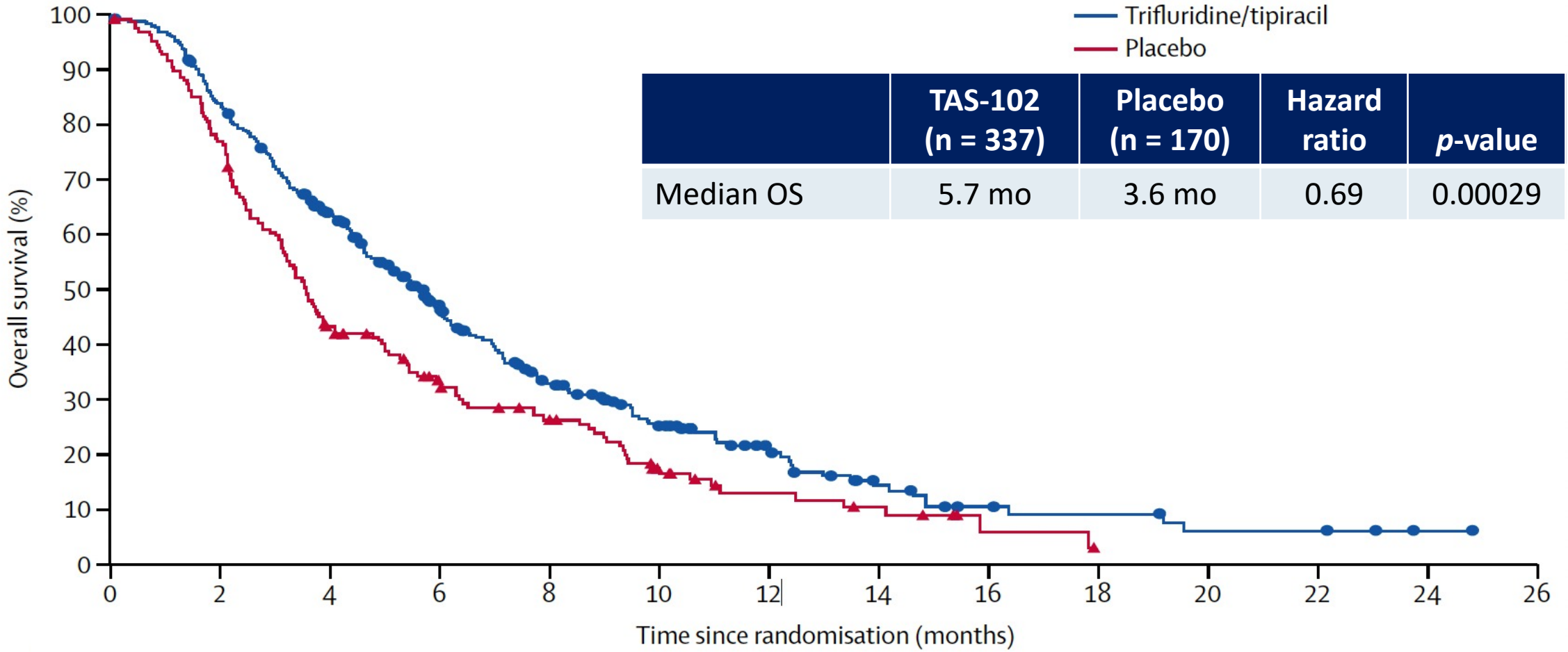
Lorenzen S et al. *Eur J Cancer* 2022;165:48-57.

Lancet Oncol 2018;19(11):1437-48.

Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial

Kohei Shitara, Toshihiko Doi, Mikhail Dvorkin, Wasat Mansoor, Hendrik-Tobias Arkenau, Aliaksandr Prokharau, Maria Alsina, Michele Ghidini, Catia Faustino, Vera Gorbunova, Edvard Zhavrid, Kazuhiro Nishikawa, Ayumu Hosokawa, Şuayib Yalçın, Kazumasa Fujitani, Giordano D Beretta, Eric Van Cutsem, Robert E Winkler, Lukas Makris, David H Ilson, Josep Tabernero

TAGS: Overall Survival (Intent-to-Treat Population)



	TAS-102 (n = 337)	Placebo (n = 170)	Hazard ratio	*p*-value
Median OS	5.7 mo	3.6 mo	0.69	0.00029

Shitara K et al. *Lancet Oncol* 2018;19(11):1437-48.

Phase III RATIONALE 306 Trial of First-Line Tislelizumab with Chemotherapy for Advanced Esophageal Cancer Meets Its Primary Overall Survival Endpoint

Press Release – April 27, 2022

"[Positive topline results were announced] from an interim analysis of the Phase III RATIONALE 306 study, which showed anti-PD-1 immune checkpoint inhibitor tislelizumab plus chemotherapy significantly improved overall survival (OS) compared to chemotherapy in patients with previously untreated unresectable, locally advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC), regardless of PD-L1 expression. These data will be submitted to regulatory authorities, and will be presented at an upcoming medical meeting.

RATIONALE 306 (NCT03783442) is a multi-regional Phase III, randomized, placebo-controlled, double-blind study of tislelizumab in combination with chemotherapy versus chemotherapy alone in patients with unresectable, locally advanced recurrent or metastatic ESCC. Approximately 649 study participants were randomized 1:1 to receive either tislelizumab plus chemotherapy or chemotherapy alone. The primary endpoint is OS. Secondary endpoints include progression-free survival, objective response rate, duration of response, health-related quality of life measures and safety."

https://www.novartis.com/news/media-releases/novartis-tislelizumab-plus-chemotherapy-significantly-improved-overall-survival-first-line-treatment-advanced-esophageal-cancer-phase-iii-study

RATIONALE-306: Randomized, Global, Phase 3 Study of Tislelizumab plus Chemotherapy versus Chemotherapy as First-Line Treatment for Locally Advanced Unresectable or Metastatic Esophageal Squamous Cell Carcinoma (ESCC)

Yoon H et al.

ESMO World Congress on Gastrointestinal Cancer 2022;Abstract LBA-1.

Regulatory and reimbursement issues aside, which first-line therapy would you most likely recommend for a 65-year-old patient presenting with metastatic HER2-negative, MSS squamous cell carcinoma of the esophagus with a PD-L1 CPS of 0?

 Dr Enzinger	FOLFOX	 Dr Shah	FOLFOX
 Dr Janjigian	FOLFOX + nivolumab	 Dr Strickler	FOLFOX
 Dr Klempner	FOLFOX	 Dr Yoon	FOLFOX

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, which first-line therapy would you most likely recommend for a 65-year-old patient presenting with metastatic HER2-negative, MSS squamous cell carcinoma of the esophagus with a PD-L1 CPS of 1?

 Dr Enzinger	FOLFOX	 Dr Shah	FOLFOX
 Dr Janjigian	FOLFOX + nivolumab	 Dr Strickler	FOLFOX
 Dr Klempner	FOLFOX + nivolumab	 Dr Yoon	FOLFOX

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, which first-line therapy would you most likely recommend for a 65-year-old patient presenting with metastatic HER2-negative, MSS squamous cell carcinoma of the esophagus with a PD-L1 CPS of 5?

 Dr Enzinger	FOLFOX + nivolumab	 Dr Shah	FOLFOX
 Dr Janjigian	FOLFOX + nivolumab	 Dr Strickler	FOLFOX + pembrolizumab
 Dr Klempner	FOLFOX + nivolumab	 Dr Yoon	FOLFOX

Regulatory and reimbursement issues aside, which first-line therapy would you most likely recommend for a 65-year-old patient presenting with metastatic HER2-negative, MSS squamous cell carcinoma of the esophagus with a PD-L1 CPS of 10?

 Dr Enzinger	FOLFOX + nivolumab	 Dr Shah	FOLFOX + pembrolizumab
 Dr Janjigian	FOLFOX + nivolumab	 Dr Strickler	FOLFOX + pembrolizumab
 Dr Klempner	FOLFOX + nivolumab	 Dr Yoon	FOLFOX + nivolumab

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, which first-line therapy would you most likely recommend for a 65-year-old patient presenting with metastatic HER2-negative, MSI-high squamous cell carcinoma of the esophagus?

 Dr Enzinger	Pembrolizumab	 Dr Shah	FOLFOX + pembrolizumab
 Dr Janjigian	FOLFOX + nivolumab	 Dr Strickler	FOLFOX + pembrolizumab
 Dr Klempner	Pembrolizumab	 Dr Yoon	FOLFOX + nivolumab

RTP RESEARCH TO PRACTICE

HER2-Positive Gastroesophageal Cancers

Recent FDA Approvals in HER2-Positive Gastric, GEJ and Esophageal Cancer

Regimen/FDA approval date/Pivotal trial	Location	Histology	Setting	PD-L1
Pembrolizumab + trastuzumab + chemotherapy 5/5/2021 (KN-811)	Gastric, GEJ	Adenocarcinoma	• First-line treatment for locally advanced, unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma	Not required
Trastuzumab deruxtecan 1/15/2021 (DESTINY-Gastric01)	Gastric, GEJ	Adenocarcinoma	• Patients who have received a prior trastuzumab-based regimen	Not required

Janjigian YY et al. *Nature* 2021; 600: 727–730. www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fam-trastuzumab-deruxtecan-nxki-her2-positive-gastric-adenocarcinomas

Nature 2021;600(7890):727-30.

Article

The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer

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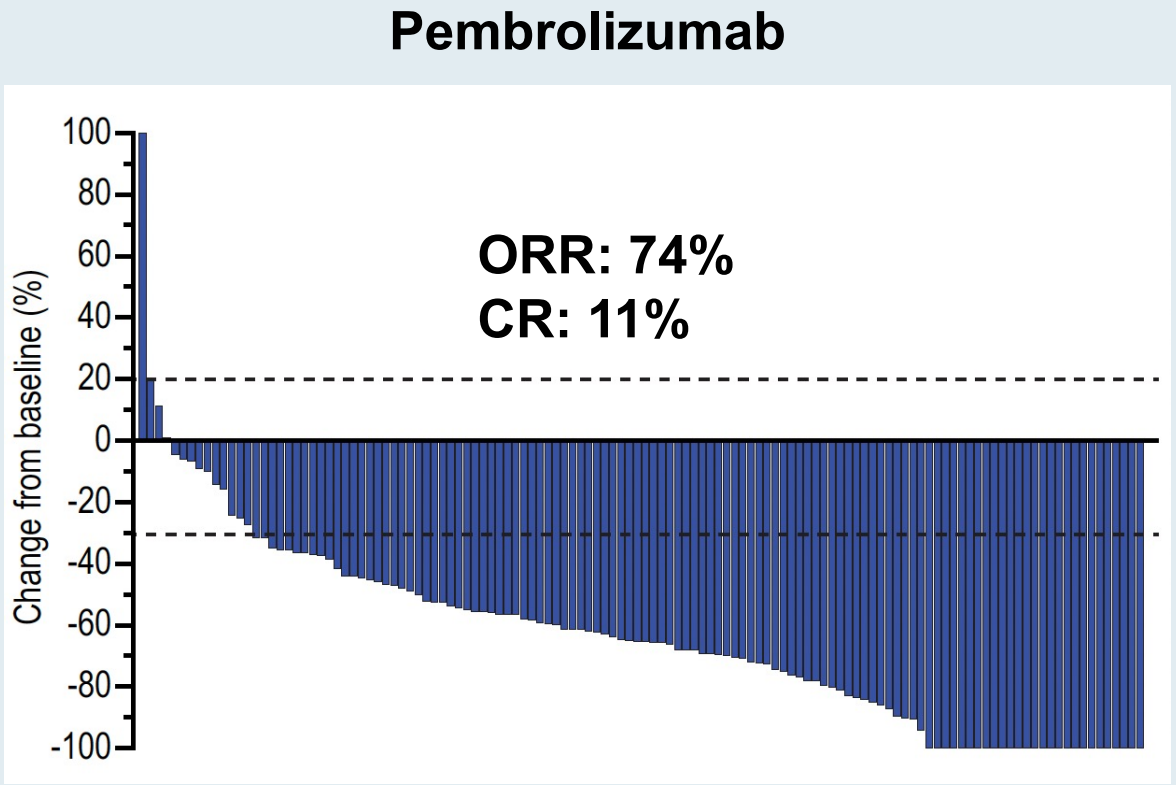
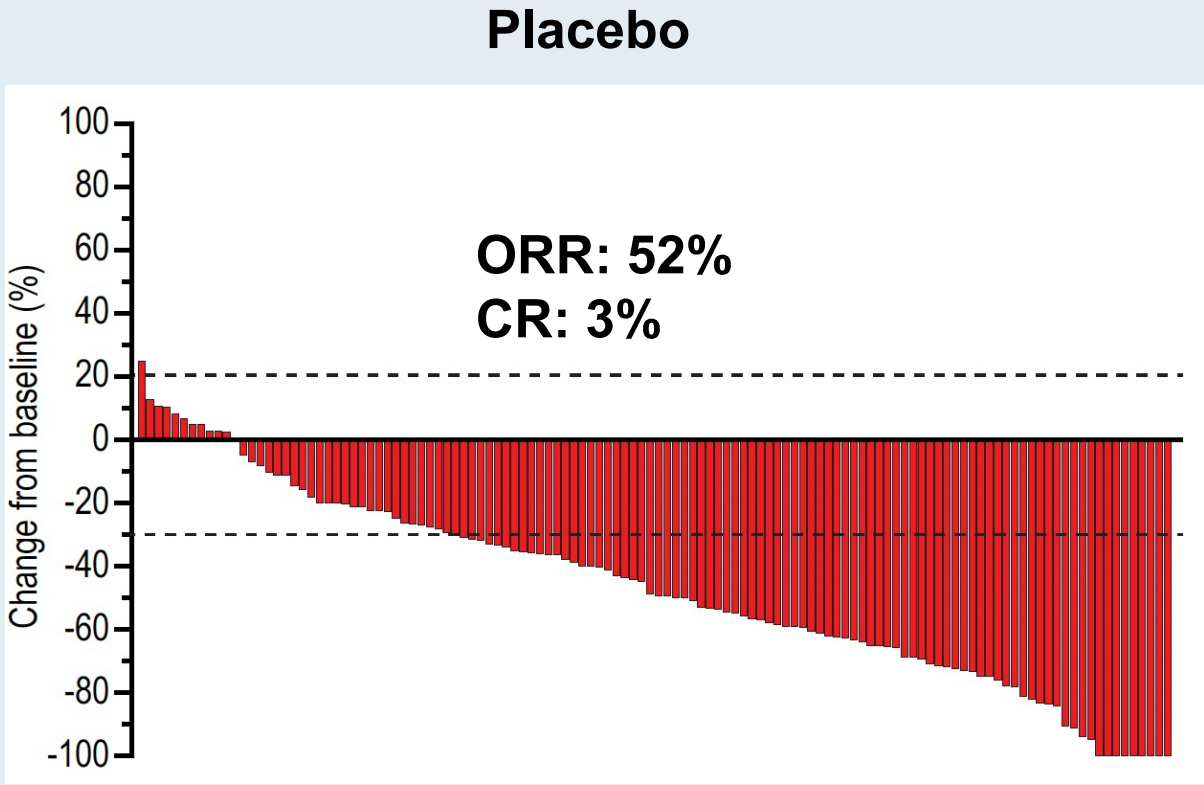
KEYNOTE-811: Overall Response Rate (ORR)





Janjigian YY et al. *Nature* 2021;600(7890):727-30.

RTP RESEARCH TO PRACTICE

KEYNOTE-811: Summary of Adverse Events

Number of events (%)	Any cause		Immune-mediated events and infusion reactions[a]	
	Pembrolizumab group (*n* = 217)	Placebo group (*n* = 216)	Pembrolizumab group (*n* = 217)	Placebo group (*n* = 216)
Any grade	211 (97.2)	212 (98.1)	73 (33.6)	45 (20.8)
Grade 3–5	124 (57.1)	124 (57.4)	21 (9.7)	7 (3.2)
Serious	68 (31.3)	83 (38.4)	19 (8.8)	7 (3.2)
Led to death	7 (3.2)	10 (4.6)	3 (1.4)	1 (0.5)
Led to discontinuation of any drug	53 (24.4)	56 (25.9)	12 (5.5)	5 (2.3)
Pembrolizumab or placebo	12 (5.5)	15 (6.9)	7 (3.2)	2 (0.9)
Trastuzumab	12 (5.5)	16 (7.4)	7 (3.2)	2 (0.9)
Any chemotherapy	50 (23.0)	52 (24.1)	12 (5.5)	5 (2.3)
All drugs	8 (3.7)	12 (5.6)	6 (2.8)	2 (0.9)

The treatment regimen included trastuzumab and chemotherapy in both groups.

[a]Events with a possible immune-mediated cause and infusion reactions were considered regardless of attribution to study treatment or immune relatedness by the investigator and are based on a list of terms provided by the sponsor.

Janjigian YY et al. *Nature* 2021;600(7890):727-30.

Poster 242

ASCO Gastrointestinal Cancers Symposium 2022

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

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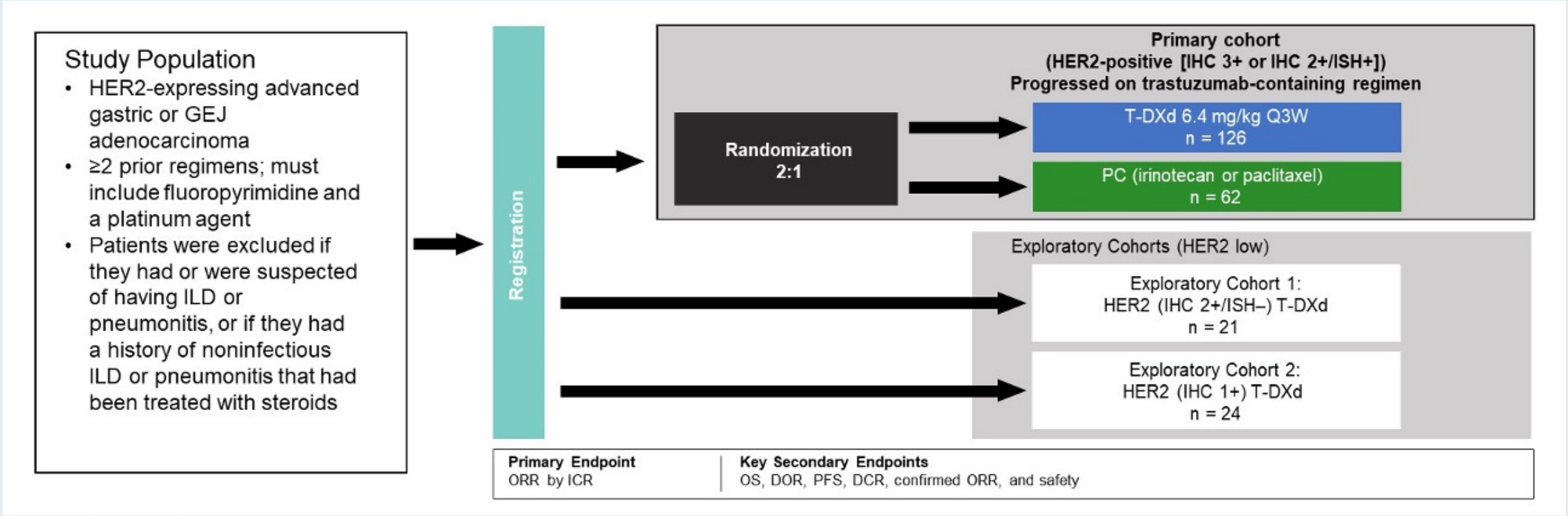
The Cancer Institute Hospital of JFCR, Tokyo, Japan

ON BEHALF OF THE DESTINY-GASTRIC01 INVESTIGATORS

Additional authors: Yung-Jue Bang, Satoru Iwasa, Naotoshi Sugimoto, Min-Hee Ryu, Daisuke Sakai, Hyun Cheol Chung, Hisato Kawakami, Hiroshi Yabusaki, Jeeyun Lee, Kaku Saito, Yoshinori Kawaguchi, Takahiro Kamio, Akihito Kojima, Masahiro Sugihara, Kohei Shitara

PRESENTED BY: Kensei Yamaguchi, MD

DESTINY-Gastric01 Randomized, Phase II Study Design

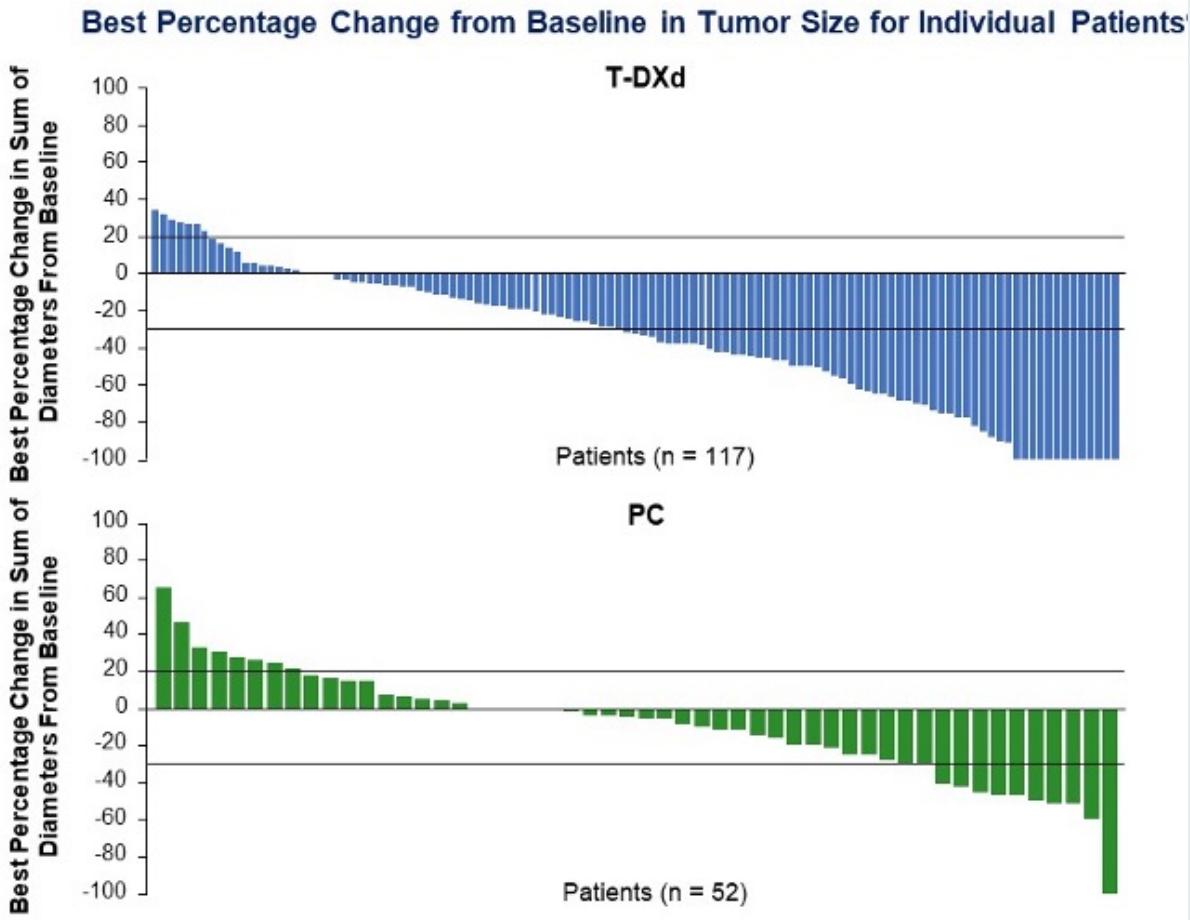


PC = physician's choice

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

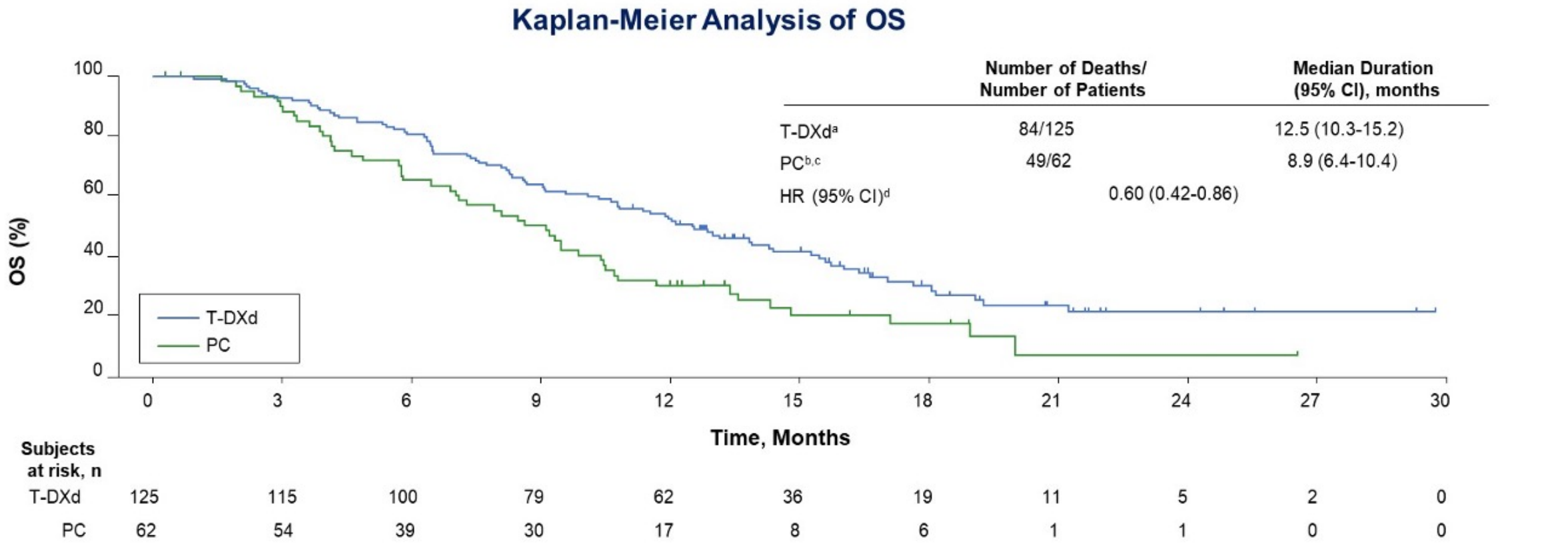
DESTINY-Gastric01: Antitumor Activity

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



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

DESTINY-Gastric01: Final Overall Survival (OS)



As in the primary analysis (101 OS events; 54.0% maturity), in this updated analysis (133 OS events; 71.1% maturity), T-DXd showed superior antitumor activity compared to PC

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

DESTINY-Gastric01: Select Adverse Events

Adverse event	T-DXd (n = 125)		PC overall (n = 62)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutrophil count decrease	65%	51%	36%	24%
Nausea	63%	6%	47%	2%
Decreased appetite	61%	17%	45%	13%
Anemia	58%	38%	31%	23%
Platelet count decrease	40%	11%	7%	3%
WBC count decrease	38%	21%	36%	11%
Lymphocyte count decrease	23%	12%	3%	2%

16 patients (13%) had T-DXd-related interstitial lung disease/pneumonitis

- 13/16 were Grade 1 or 2
- Median time to first onset: 102.5 days

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

DESTINY-Gastric01: Exploratory Biomarker Analysis of OS in HER2-Positive or HER2-Low Advanced Gastric or GEJ Cancer

Exploratory biomarker in primary HER2-positive cohort	Median OS
Plasma HER2 amplification	
Not amplified	12.1 mo
Amplified	13.0 mo
Plasma HER2 copy number*	
Above 6.0	21.2 mo
Below 6.0	12.0 mo
Exploratory biomarker in exploratory HER2-low cohort	
Plasma HER2 extracellular domain†	
Above 11.6 ng/mL	10.1 mo
Below 11.6 ng/mL	4.3 mo

*An exploratory cutoff (copy number = 6.0) value was determined, which minimized *p*-value, estimated by log-rank test. Below 6.0 includes patients without amplification; † An exploratory cutoff value of 11.6 ng/mL in exploratory cohorts was determined, which minimized *p*-value, estimated by log-rank test.

Shitari K et al. ESMO World Congress on Gastrointestinal Cancer 2021;Abstract O-14.

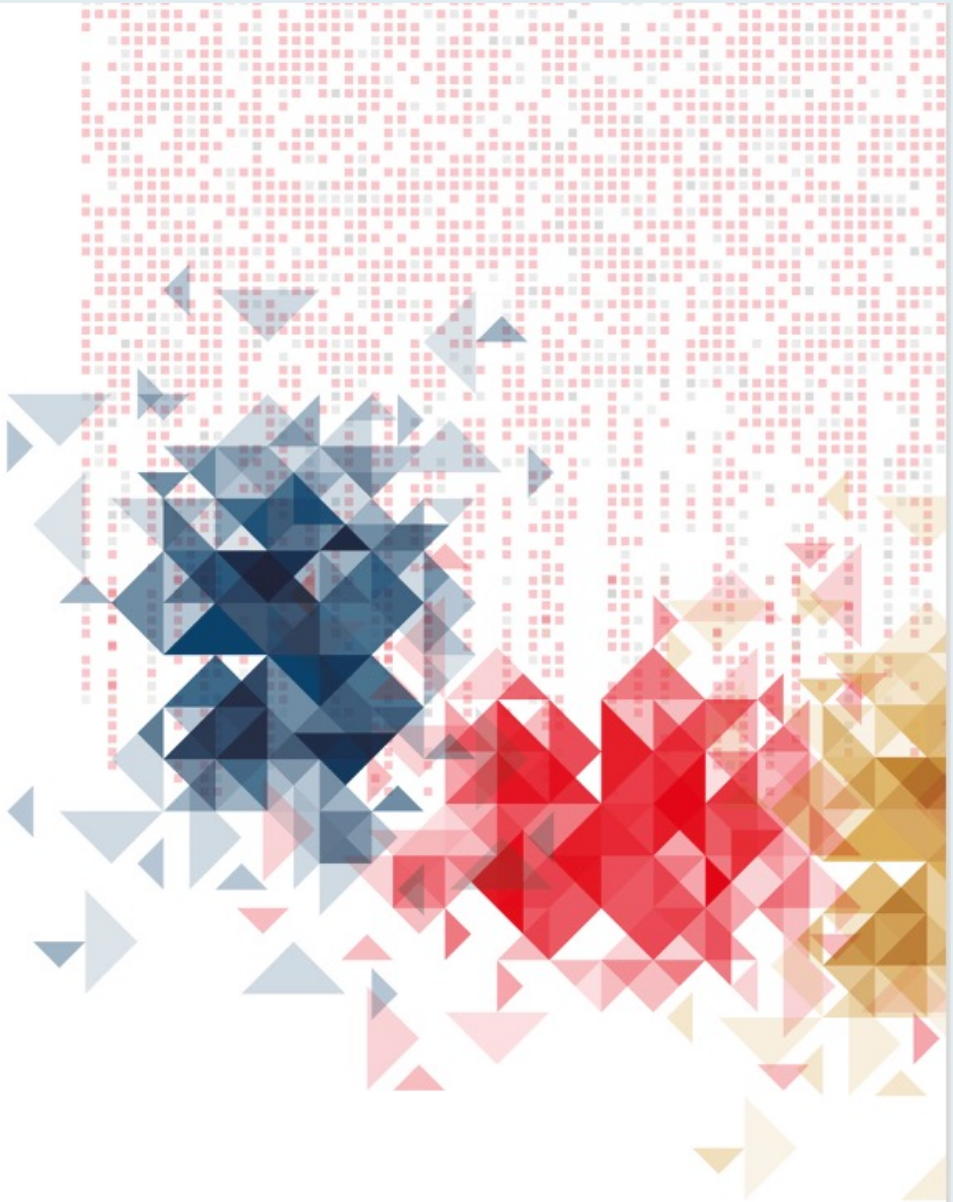
2021 ESMO congress

Primary Analysis of a Phase 2 Single-Arm Trial of Trastuzumab Deruxtecan (T-DXd) in Western Patients With HER2-Positive (HER2+) Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Cancer Who Progressed on or After a Trastuzumab-containing Regimen

Eric Van Cutsem, MD[a], Maria di Bartolomeo, Elizabeth Smyth, Ian Chau, Haeseong Park, Salvatore Siena, Sara Lonardi, Zev A. Wainberg, Jaffer Ajani, Joseph Chao, Jabed Seraj, Yoshinori Kawaguchi, Amy Qin, Jasmeet Singh, Gerold Meinhardt, Geoffrey Ku

On behalf of the DESTINY-Gastric02 investigators

[a]University Hospital Gasthuisberg, Leuven and KU Leuven, Leuven, Belgium



Abstract LBA55

RTP RESEARCH TO PRACTICE

DESTINY-Gastric02 Phase II Study Design

Key eligibility criteria

- Pathologically documented, unresectable or metastatic gastric or GEJ cancer
- Centrally confirmed HER2 positive disease (defined as IHC 3+ or IHC 2+/ISH+) on biopsy after progression on first-line trastuzumab-containing regimen
- ECOG PS 0 or 1

T-DXd
6.4 mg/kg Q3W
N = 79[a]

Primary endpoint

- Confirmed ORR by ICR

Secondary endpoints[b]

- PFS by ICR
- OS
- DOR by ICR
- Safety and tolerability

- DESTINY-Gastric02 is the first study focused only on second-line T-DXd monotherapy in Western patients with HER2+ gastric/GEJ cancer who have progressed on a trastuzumab-containing regimen
  - It is the follow-on study to DESTINY-Gastric01, which evaluated T-DXd third-line or later in Asian patients[1]
- Patients were enrolled in Europe (Belgium, Great Britain, Italy, Spain) and the United States (data cutoff: April 9, 2021)

Van Cutsem E et al. ESMO 2021;Abstract LBA55.

Efficacy Endpoints

	Patients (N = 79)
Confirmed ORR[a], n (%)	**30 (38)** (95% CI, 27.3-49.6)
Confirmed best overall response, n (%)	
CR	**3 (3.8)**
PR	**27 (34.2)**
SD	**34 (43.0)**
PD	**13 (16.5)**
Not evaluable	**2 (2.5)**
Median DOR,[b] months	8.1 (95% CI, 4.1-NE)
Confirmed DCR[c], n (%)	64 (81.0) (95% CI, 70.6-89.0)
Median TTR, months	1.4 (95% CI, 1.4-2.6)
Median PFS,[d] months	5.5 (95% CI, 4.2-7.3)
Median follow up, months	5.7 (range, 0.7-15.2)

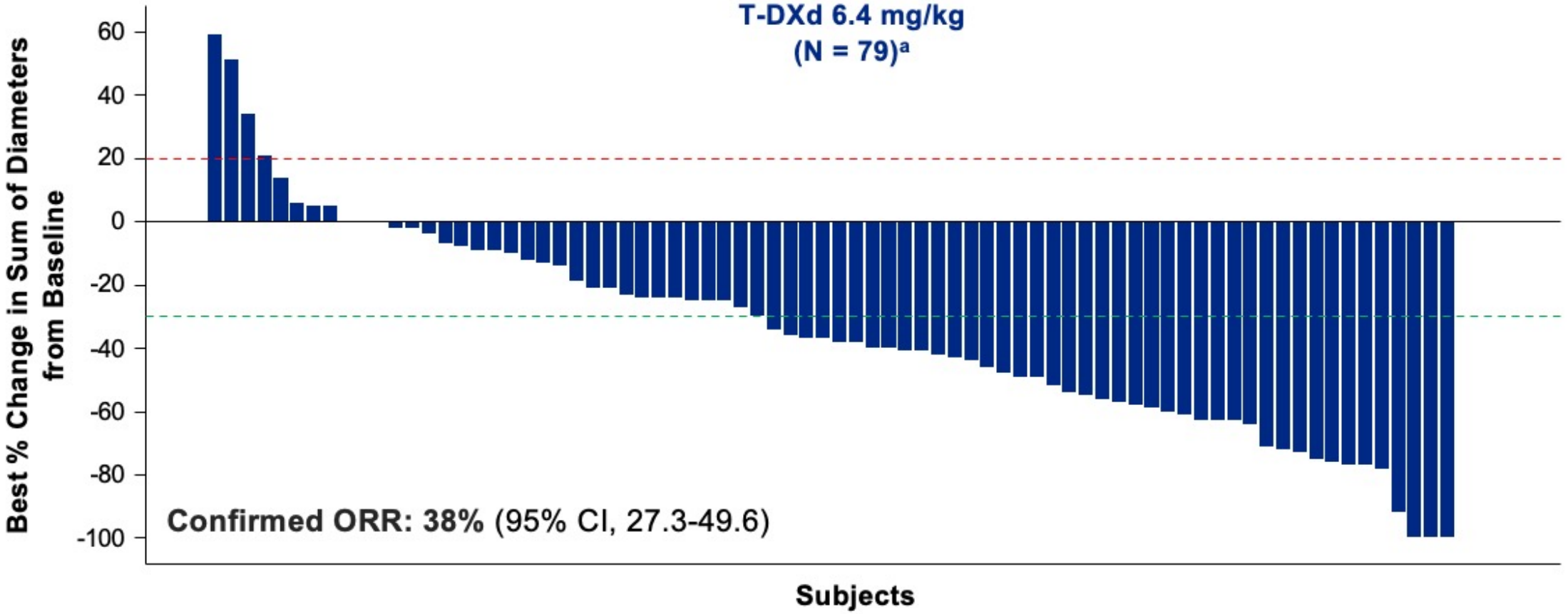
Cutoff date: April 9, 2021.
[a]Primary endpoint. [b]Secondary endpoint analysis based on responders (n=30); 21 patients were censored (reasons: initiating new anticancer therapy, adequate tumor assessment no longer available, and ongoing without occurrence of progressive disease or death). [c]Exploratory endpoint. [d]Secondary endpoint analysis in the full analysis set based on 42 events (36 PD, 6 deaths).
BOR, best overall response; CR, complete response; DCR, disease control rate; mo, months; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response.

2021 ESMO congress

Van Cutsem E et al. ESMO 2021;Abstract LBA55.

RTP RESEARCH TO PRACTICE

DESTINY-Gastric02: Best Percent Change in Tumor Size from Baseline



Van Cutsem E et al. ESMO 2021;Abstract LBA55.

DESTINY-Gastric02: Safety Summary

n (%)	Patients (N = 79)
Any drug-related TEAE	74 (93.7)
Drug-related TEAE Grade ≥3	21 (26.6)
Serious drug-related TEAE	8 (10.1)
Drug-related TEAE associated with discontinuation	7 (8.9)
Drug-related TEAE associated with dose reduction	15 (19.0)
Drug-related TEAE associated with an outcome of death	1 (1.3)

- Median treatment duration was 4.3 months (range, 0.7-15.9 months)
- The most common drug-related TEAEs associated with treatment discontinuation were investigator-reported pneumonitis (3.8%) and ILD (2.5%)
- The most common drug-related TEAEs associated with dose reduction were nausea (7.6%) and decreased neutrophil count (5.1%)

Van Cutsem E et al. ESMO 2021;Abstract LBA55.

DESTINY-Gastric02: Treatment-Emergent Adverse Events (TEAEs)

n (%)	Patients (N = 79)	
	Any Grade	Grade ≥3
Patients with ≥1 drug-related TEAEs	74 (93.7)	21 (26.6)
Drug-related TEAEs with ≥15% incidence in all patients		
Nausea	46 (58.2)	3 (3.8)
Fatigue	29 (36.7)	3 (3.8)
Vomiting	26 (32.9)	1 (1.3)
Diarrhea	22 (27.8)	1 (1.3)
Decreased appetite	18 (22.8)	1 (1.3)
Alopecia	17 (21.5)	0
Anemia	15 (19.0)	6 (7.6)
Decreased platelet count	13 (16.5)	1 (1.3)
Decreased neutrophil count	12 (15.2)	6 (7.6)

Van Cutsem E et al. ESMO 2021;Abstract LBA55.

DESTINY-Gastric02: Adjudicated Drug-Related Interstitial Lung Disease (ILD)/Pneumonitis

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
n (%)	2 (2.5)	3 (3.8)	0	0	1 (1.3)	6 (7.6)

- Median time to onset of adjudicated drug-related ILD/pneumonitis was 80.5 days (range, 53-85 days), with a median duration of 38.0 days (range, 15-142 days)
- 83% of adjudicated drug-related ILD/pneumonitis cases were low grade (Grade 1-2)

Van Cutsem E et al. ESMO 2021;Abstract LBA55.

Conclusions

- DESTINY-Gastric02 is the first study focused only on 2L T-DXd monotherapy in Western HER2+ patients with gastric/GEJ cancer who progressed on a trastuzumab-containing regimen
- Efficacy results demonstrate clinically meaningful and durable responses
- Safety profile was generally consistent with the established safety profile of T-DXd
- DESTINY-Gastric02 provides clinical evidence for T-DXd as a valuable 2L HER2-targeted treatment option and supports the ongoing randomized phase 3 trial, DESTINY-Gastric04 (NCT04704934)

Van Cutsem E et al. ESMO 2021;Abstract LBA55.

Novel Targeted Agents

FDA Grants Bemarituzumab Breakthrough Therapy Designation as First-Line Treatment for Gastric and Gastroesophageal Cancers that Overexpress FGFR2b

Press Release – April 19, 2021

"The US Food and Drug Administration (FDA) granted Breakthrough Therapy Designation for investigational bemarituzumab as first-line treatment for patients with fibroblast growth factor receptor 2b (FGFR2b) overexpressing and human epidermal growth factor receptor 2 (HER2)-negative metastatic and locally advanced gastric and gastroesophageal (GEJ) adenocarcinoma in combination with modified FOLFOX6 (fluoropyrimidine, leucovorin, and oxaliplatin), based on an FDA-approved companion diagnostic assay showing at least 10% of tumor cells overexpressing FGFR2b."

This designation is supported by results from the Phase 2 FIGHT trial.

https://www.amgen.com/newsroom/press-releases/2021/04/amgens-investigational-targeted-treatment-bemarituzumab-granted-breakthrough-therapy-designation

RTP RESEARCH TO PRACTICE

2021 ASCO ANNUAL MEETING

Abstract 4010

FIGHT: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2 STUDY OF BEMARITUZUMAB (BEMA) COMBINED WITH MODIFIED FOLFOX6 IN 1L FGFR2B+ ADVANCED GASTRIC/GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA (GC) (NCT03694522)

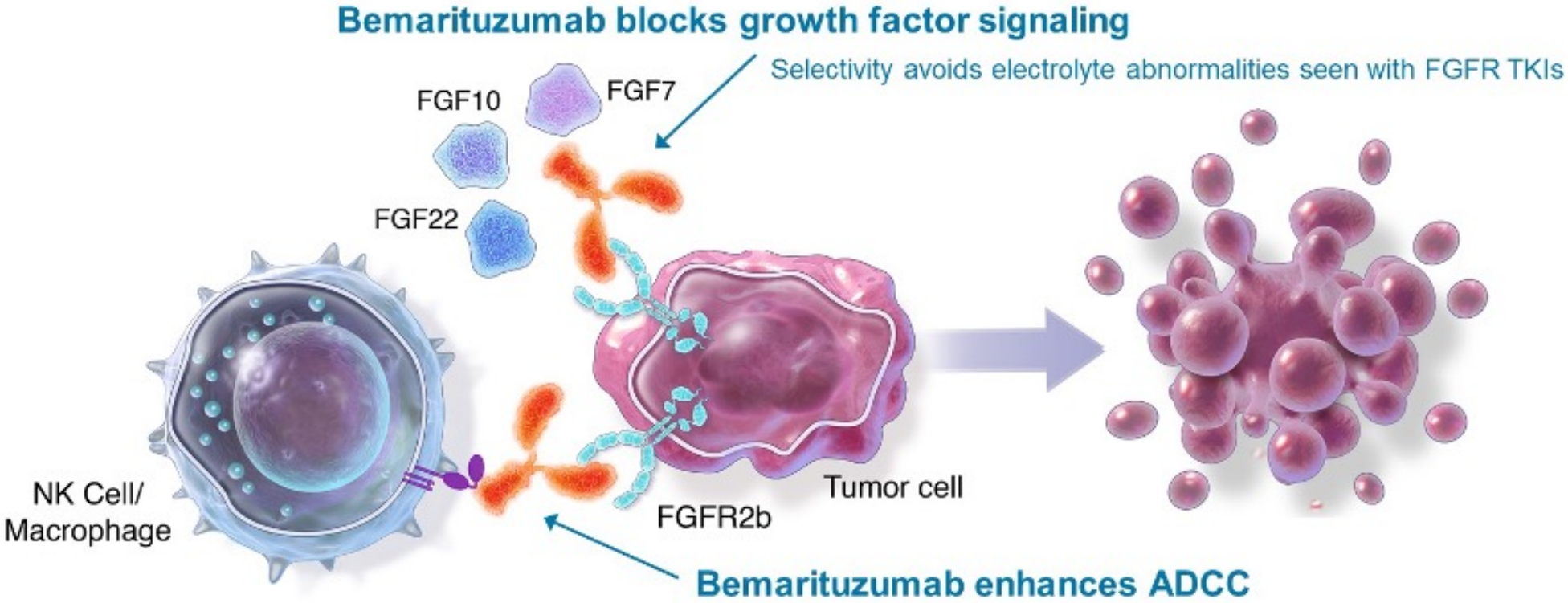
Presenter: Daniel Catenacci, MD
University of Chicago

Authors: Catenacci DV[1], Kang YK[2], Saeed A[3], Yamaguchi K[4], Qin S[5], Lee KW[6], Kim IH[7], Oh SC[8], Li J[9], Turk HM[10], Teixeira AC[11], Borg C[12], Hitre E[13], Udrea AA[14], Cardellino GG[15], Guardeño Sanchez R[16], Mitra S[17], Yang Y[17], Enzinger PC[18], Wainberg ZA[19]

[1]University of Chicago, Chicago, USA; [2]Asan Medical Center, Seoul, South Korea; [3]Kansas University Cancer Center, Westwood, KS, USA; [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 Bundang Hospital, Seoul National University College of Medicine, Seongnam, Gyeonggi-do, South Korea; [7]The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea; [8]Korea University Guro Hospital, Seoul, South Korea; [9]Shanghai East Hospital, Shanghai, China; [10]Department of Medical Oncology, Bezmialem Vakif University, School of Medicine, Istanbul, Turkey; [11]Hospital Senhora Da Oliveira, Guimarães, Portugal; [12]Centre Hospitalier Régional Universitaire de Besançon, Besançon France; [13]National Institute of Oncology, Budapest, Hungary; [14]SC Medisprof SRL, Cluj-Napoca, Romania; [15]Department of Oncology, Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy; [16]Institut Català d'Oncologia, Girona, Spain; [17]FivePrime Therapeutics, Inc., South San Francisco, USA; [18]Dana Farber Cancer Institute, Boston, USA; [19]University of California, Los Angeles, USA

RTP RESEARCH TO PRACTICE

Bemarituzumab Mechanism of Action



18% overall response rate in late-line FGFR2b+ gastroesophageal cancer[1]

ADCC, antibody-dependent cell-mediated cytotoxicity; FGF, fibroblast growth factor; IgG1, immunoglobulin G1; NK, natural killer; TKIs, tyrosine kinase inhibitors.

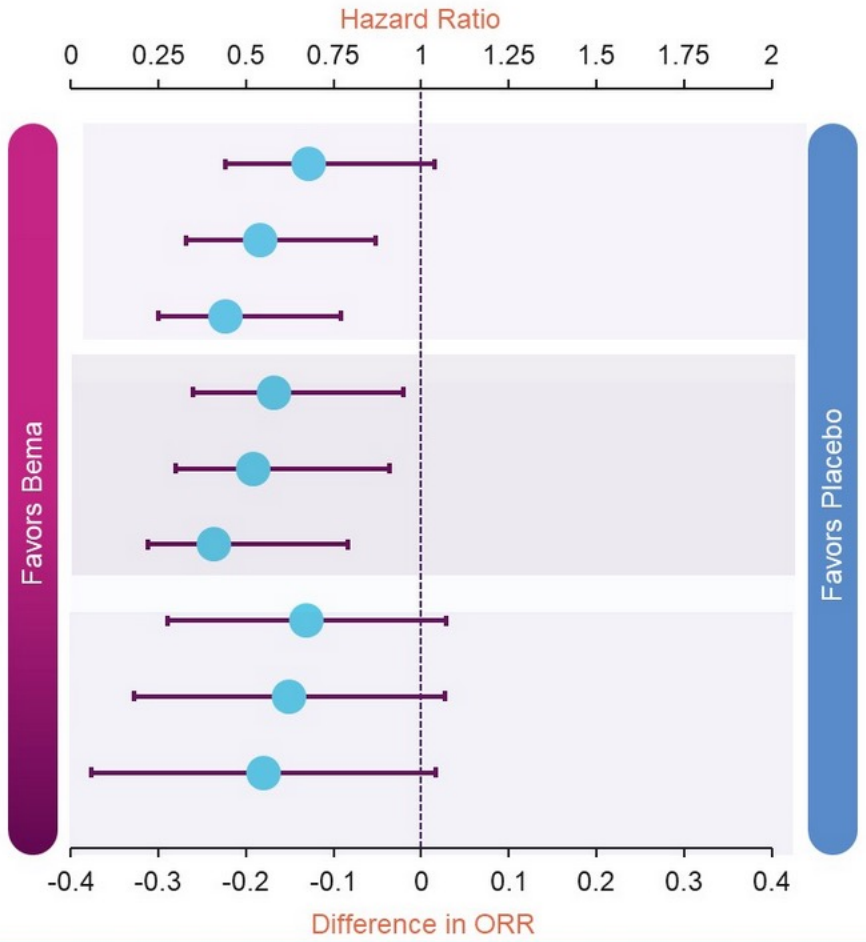
1. Catenacci D, et al. *J Clin Oncol*. 2020.

Catenacci DV et al. ASCO 2021;Abstract 4010.

FIGHT: Efficacy of First-Line Bemarituzumab with Modified FOLFOX6 for Gastric/GEJ Adenocarcinoma

Endpoint	Subgroup	Median PFS/OS (months) Response rate	HR (95% CI) Difference in ORR (95% CI)
PFS	Overall*	Bema: 9.5 Placebo: 7.4	0.68 (0.44, 1.04)
	IHC 2+ or 3+ ≥5%†	Bema: 10.2 Placebo: 7.3	0.54 (0.33, 0.87)
	IHC 2+ or 3+ ≥10%‡	Bema: 14.1 Placebo: 7.3	0.44 (0.25, 0.77)
OS	Overall	Bema: NR Placebo: 12.9	0.58 (0.35, 0.95)
	IHC 2+ or 3+ ≥5%	Bema: NR Placebo: 12.5	0.52 (0.30, 0.91)
	IHC 2+ or 3+ ≥10%	Bema: NR Placebo: 11.1	0.41 (0.22, 0.79)
ORR	Overall	Bema: 36 (46.8%) Placebo: 26 (33.3%)	-13.1%§ (-29.0%, 2.8%)
	IHC 2+ or 3+ ≥5%	Bema: 30 (51.7%) Placebo: 22 (36.7%)	-15.1%§ (-32.8%, 2.7%)
	IHC 2+ or 3+ ≥10%	Bema: 24 (54.5%) Placebo: 19 (36.5%)	-18.0%§ (-37.7%, 1.7%)

*N = 155; †N = 118; ‡N = 96; §difference in ORR is calculated by (placebo ORR – Bema ORR).
NR, not reached.



- Median OS was reached in the overall population with longer follow-up – 5.7-mo improvement

Catenacci DV et al. ASCO 2021;Abstract 4010.

RTP RESEARCH TO PRACTICE

FIGHT: Selected Treatment-Related Adverse Event Summary

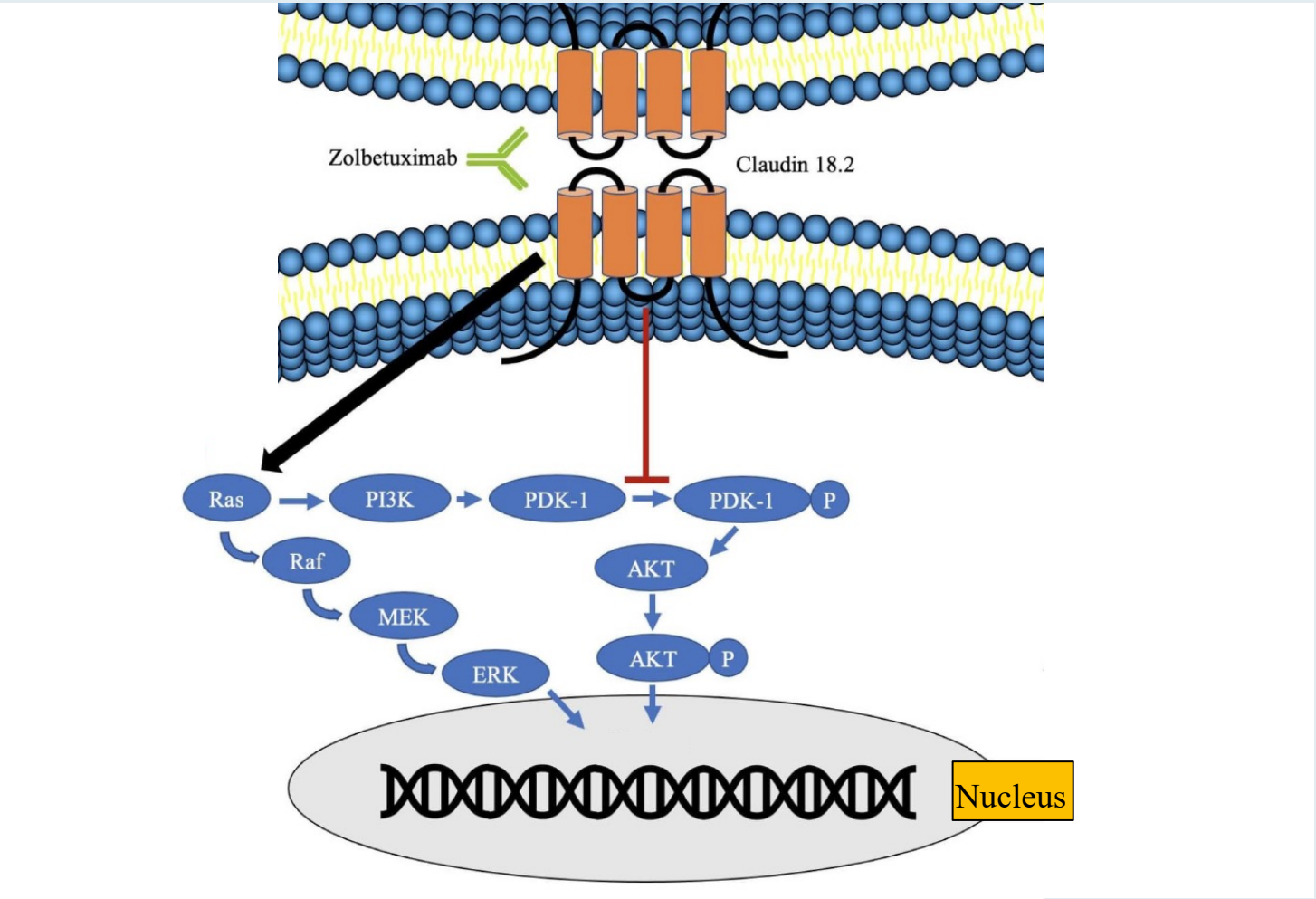
Selected AE (Preferred term)	Any Grade		Grade ≥3	
	Bema (N = 76)	Placebo (N = 77)	Bema (N = 76)	Placebo (N = 77)
Total Events	**76 (100.0%)**	**76 (98.7%)**	**63 (82.9%)**	**57 (74.0%)**
Nausea	36 (47.4%)	41 (53.2%)	0	3 (3.9%)
Vomiting	22 (28.9%)	24 (31.2%)	2 (2.6%)	2 (2.6%)
Diarrhea	31 (40.8%)	24 (31.2%)	2 (2.6%)	1 (1.3%)
Stomatitis	24 (31.6%)	10 (13.0%)	7 (9.2%)	1 (1.3%)
Peripheral sensory neuropathy	15 (19.7%)	15 (19.5%)	4 (5.3%)	3 (3.9%)
Neutrophil count decreased	31 (40.8%)	33 (42.9%)	23 (30.3%)	27 (35.1%)
Platelet count decreased	14 (18.4%)	21 (27.3%)	1 (1.3%)	0
Aspartate aminotransferase increased	23 (30.3%)	15 (19.5%)	4 (5.3%)	2 (2.6%)
Alanine aminotransferase increased	22 (28.9%)	11 (14.3%)	2 (2.6%)	1 (1.3%)
Dry eye	20 (26.3%)	5 (6.5%)	2 (2.6%)	0

AE, adverse event.

Catenacci DV et al. ASCO 2021;Abstract 4010.

RTP RESEARCH TO PRACTICE

Zolbetuximab Mechanism of Action



Adapted from Siddiqui A, Almhanna K. *Cancers* 2021;13(17):4322.

Ann Oncol 2021;32(5):609-19.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

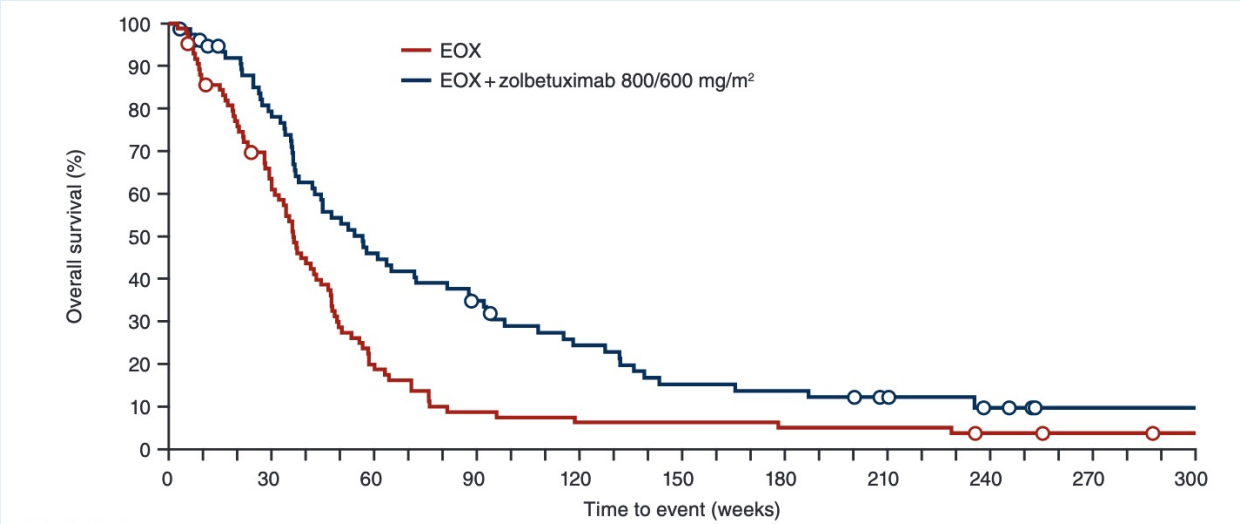
FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma

U. Sahin[1,2,3], Ö. Türeci[3,4], G. Manikhas[5], F. Lordick[6], A. Rusyn[7], I. Vynnychenko[8], A. Dudov[9], I. Bazin[10], I. Bondarenko[11], B. Melichar[12], K. Dhaene[13], K. Wiechen[14], C. Huber[1,3,4], D. Maurus[15], A. Arozullah[16], J. W. Park[16], M. Schuler[17†] & S.-E. Al-Batran[18*†]

RTP RESEARCH TO PRACTICE

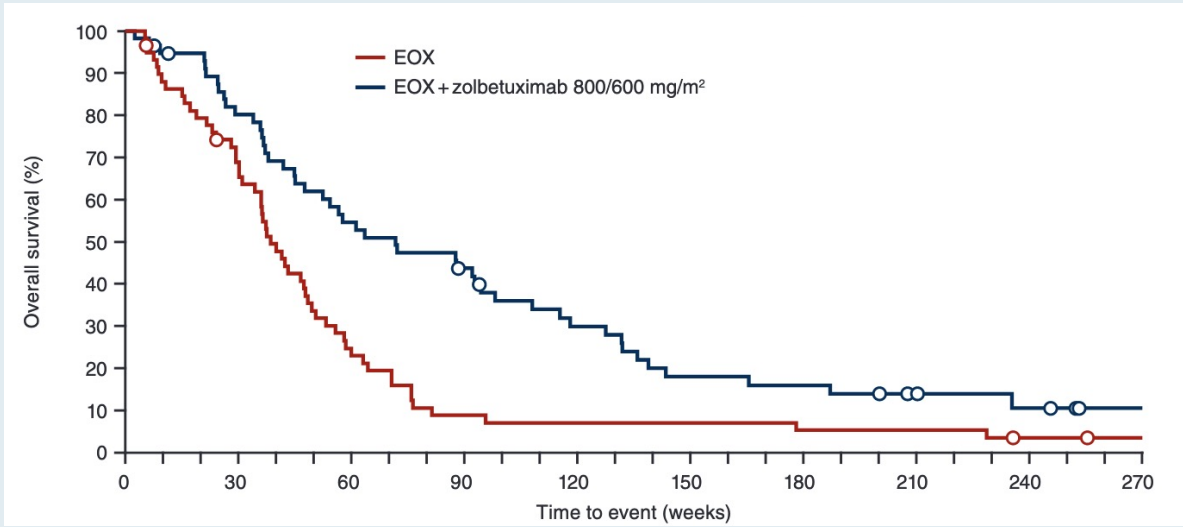
FAST: Overall Survival with Zolbetuximab in Combination with Chemotherapy for Advanced CLDN18.2-Positive Gastric and Gastroesophageal Adenocarcinoma

Overall population



Median OS
EOX (n = 84): 8.3 months
EOX + zolbetuximab (n = 77): 13.0 months
HR (*p*-value): 0.55 (<0.0005)

Patients with ≥70% CLDN18.2-positive tumor cells



Median OS
EOX (n = 59): 8.9 months
EOX + zolbetuximab (n = 57): 16.5 months
HR (*p*-value): 0.50 (<0.0005)

EOX = epirubicin/oxaliplatin/capecitabine

Sahin U et al. *Ann Oncol* 2021;32(5):609-19.

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FAST: Select Treatment-Emergent Adverse Events

Adverse event	EOX (n = 84)		EOX + zolbetuximab (n = 77)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Nausea	76.2%	4.8%	81.8%	6.5%
Vomiting	54.8%	3.6%	67.5%	10.4%
Anemia	35.7%	7.1%	45.5%	11.7%
Neutropenia	34.5%	21.4%	44.2%	32.5%
Weight loss	31.0%	3.6%	32.5%	11.7%
Fatigue	20.2%	3.6%	31.2%	6.5%
Leukopenia	16.7%	6.0%	15.6%	7.8%

Sahin U et al. *Ann Oncol* 2021;32(5):609-19.

Ongoing Phase III Trials of Zolbetuximab in Combination with Chemotherapy as First-Line Therapy for Gastric or GEJ Adenocarcinoma

Trial identifier	N	Setting	Study arms
GLOW (NCT03653507)	507	• Locally advanced unresectable or metastatic • CLDN18.2-positive • HER2-negative	• Zolbetuximab + CAPOX • Placebo + CAPOX
SPOTLIGHT (NCT03504397)	550	• Locally advanced unresectable or metastatic • CLDN18.2-positive • HER2-negative	• Zolbetuximab + mFOLFOX6 • Placebo + mFOLFOX6

www.clinicaltrials.gov. Accessed March 2022.

ILUSTRO: Phase II Study of Zolbetuximab Alone or in Combination with Chemotherapy, Immunotherapy or Both for Metastatic or Locally Advanced Unresectable Gastric or GEJ Adenocarcinoma

Trial Identifier: NCT03505320 (Open)

Histologically confirmed gastric or GEJ adenocarcinoma
Locally advanced, unresectable or metastatic disease

Positivity for CLDN18.2 expression

- **Cohort 1A**
  Zolbetuximab
- **Cohort 2**
  Zolbetuximab + mFOLFOX6
- **Cohort 3A**
  Zolbetuximab + pembrolizumab
- **Cohort 4A/4B**
  Zolbetuximab + mFOLFOX6
  +/- nivolumab

Primary endpoint: Objective response rate with zolbetuximab monotherapy
Secondary endpoints include PFS, pharmacokinetics, safety and tolerability

www.clinicaltrials.gov. Accessed March 2022.

Management of Acute Myeloid Leukemia and Myelodysplastic Syndromes – A Review of the 2022 ASCO Annual Meeting and EHA Congress

Wednesday, July 13, 2022
5:00 PM – 6:00 PM ET

Faculty

Richard M Stone, 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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