Meet The Professor
Optimizing the Management of Gastroesophageal Cancers

Yelena Y Janjigian, MD
Associate Professor
Chief of Gastrointestinal Oncology Service
Department of Medicine
Memorial Sloan Kettering Cancer Center
New York, New York

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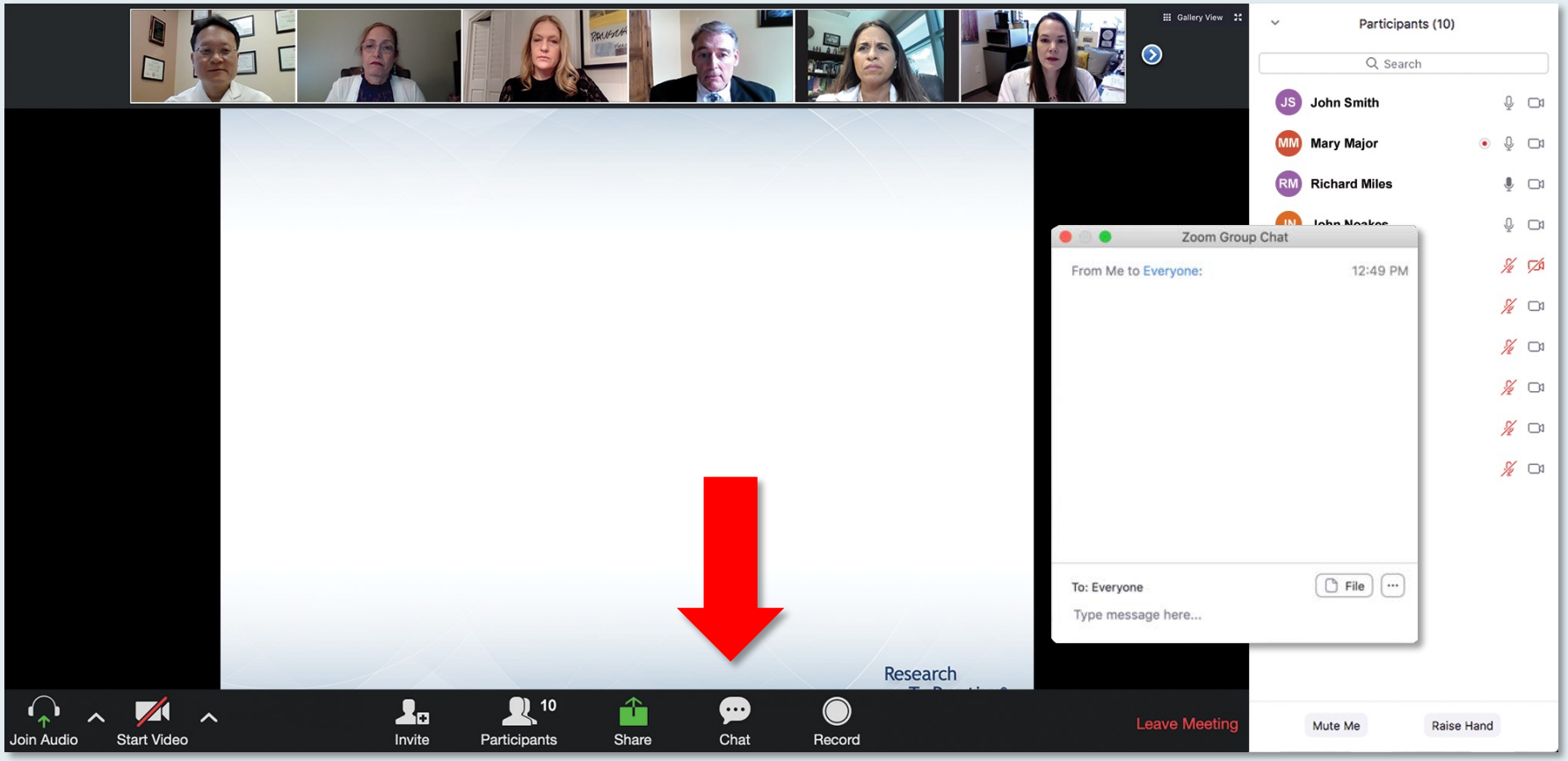
Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Janjigian — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Basilea Pharmaceutica Ltd, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Daiichi Sankyo Inc, Imugene, Lilly, Merck, Merck Serono, MJH Life Sciences, Pfizer Inc, Rgenix, Seagen Inc, Zymeworks Inc
Contracted Research	Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Cycle for Survival, Fred's Team, Genentech, a member of the Roche Group, Lilly, Merck, National Cancer Institute, Rgenix, US Department of Defense
Stock Options	Rgenix

We Encourage Clinicians in Practice to Submit Questions



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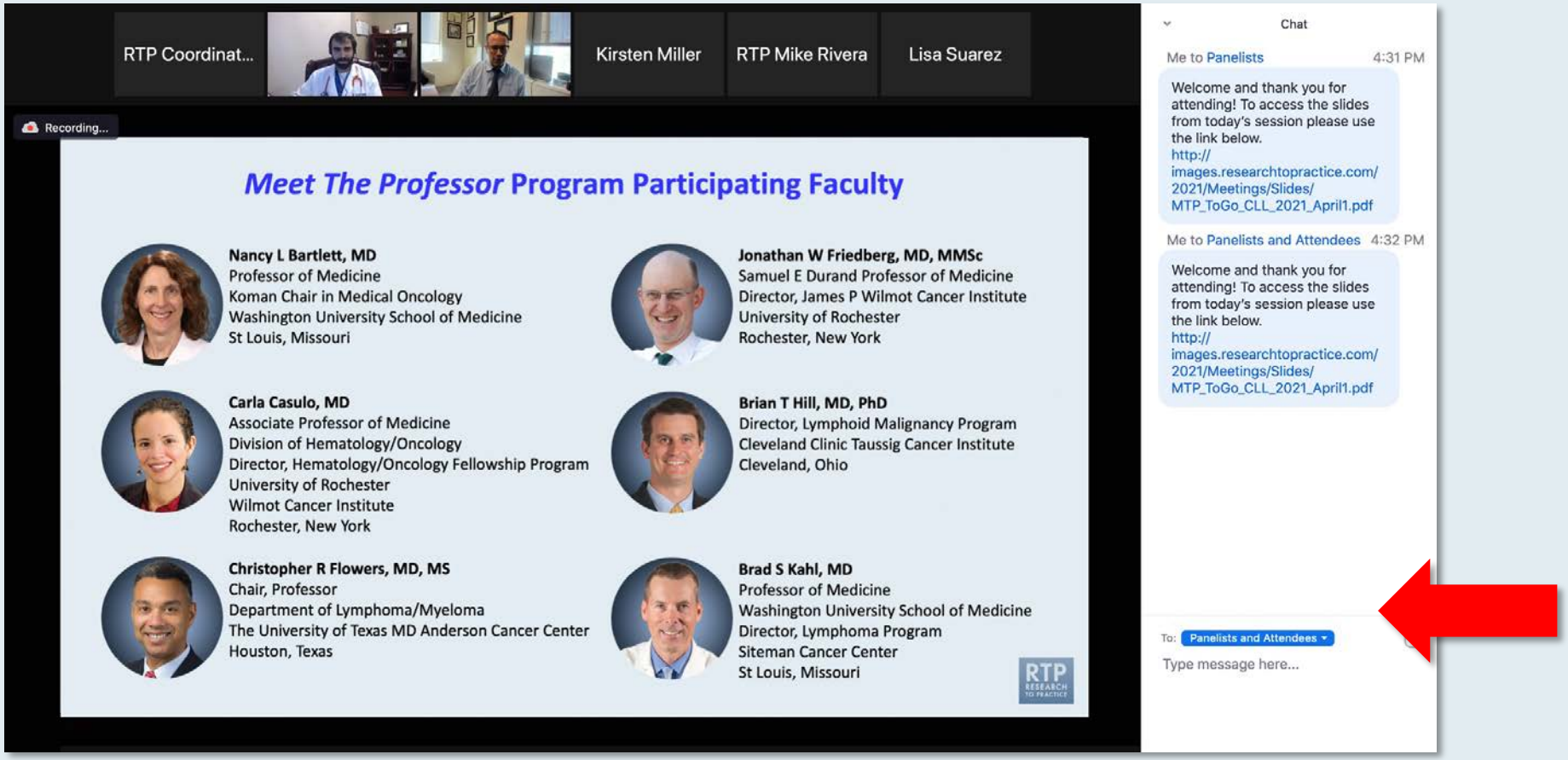

Drag the white line above the submission box up to create more space for your message.

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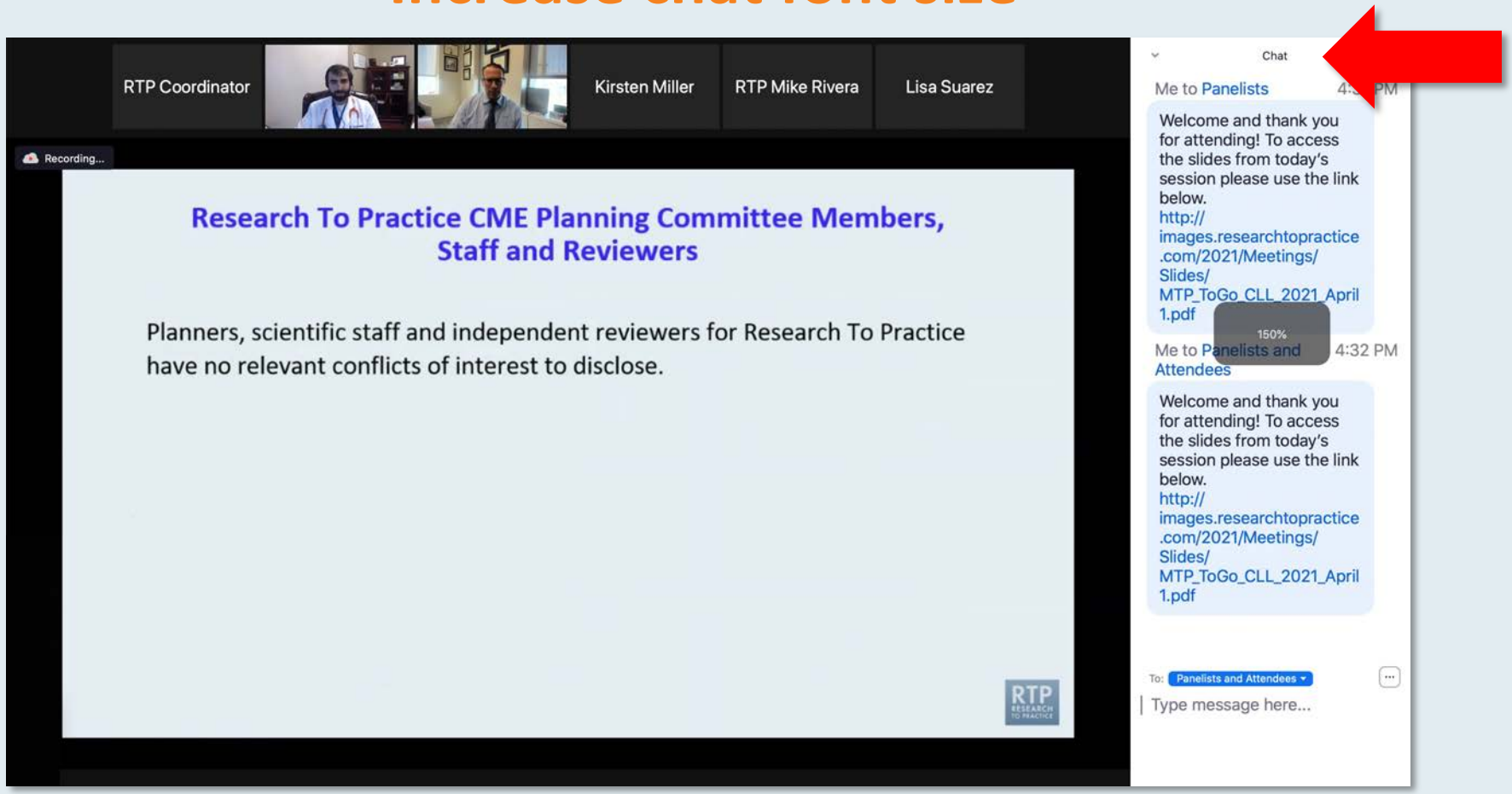

Press Command (for Mac) or Control (for PC) and the + symbol.
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WITH DR NEIL LOVE

Gastroesophageal Cancers

DR SAMUEL KLEMPNER

INSTITUTION MASSACHUSETTS GENERAL HOSPITAL

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Spotify

Listen on Google Podcasts

Cases from the Community: Urologic Oncology Investigators Provide Perspectives on the Optimal Management of Prostate Cancer

Friday, May 13, 2022

8:00 AM – 10:00 AM CT (9:00 AM – 11:00 AM ET)

Faculty

Raoul S Concepcion, MD
Fred Saad, MD
Matthew R Smith, MD, PhD

Moderator

Emmanuel S Antonarakis, MD

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Cases from the Community: Urologic Oncology Investigators Provide Perspectives on the Optimal Management of Urothelial Bladder Cancer

Friday, May 13, 2022

6:00 PM – 8:00 PM CT (7:00 PM – 9:00 PM ET)

Faculty

Matthew D Galsky, MD
Ashish M Kamat, MD, MBBS
Stephen B Williams, MD, MS

Moderator

Sumanta Kumar Pal, MD

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TO PRACTICE

Meet The Professor

Non-Small Cell Lung Cancer with an Actionable Target Beyond EGFR

Tuesday, May 17, 2022
5:00 PM – 6:00 PM ET

Faculty

Justin F Gainor, MD

Special Topics

- **ALK+ NSCLC: First-line treatment, resistance mutations**

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TO PRACTICE

What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

Gastroesophageal Cancers

Wednesday, May 18, 2022
5:00 PM – 6:00 PM ET

Faculty

Kristen K Ciombor, MD, MSCI
Jessica Mitchell, APRN, CNP, MPH

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

Hodgkin and Non-Hodgkin Lymphomas

Date to be announced

Faculty

To be announced

Moderator

Neil Love, MD

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TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Renal Cell Carcinoma

Thursday, May 19, 2022

5:00 PM – 6:00 PM ET

Faculty

Thomas E Hutson, DO, PharmD
Brian I Rini, MD

Moderator

Sumanta Kumar Pal, MD

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TO PRACTICE

Meet The Professor

Current and Future Management of Chronic Lymphocytic Leukemia

Tuesday, May 24, 2022
5:00 PM – 6:00 PM ET

Faculty

Susan O'Brien, MD

Moderator

Neil Love, MD

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Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2022 ASCO Annual Meeting

Acute Myeloid Leukemia and Myelodysplastic Syndromes

Friday, June 3, 2022
11:45 AM – 12:45 PM CT (10:45 AM – 11:45 AM ET)

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Courtney D DiNardo, MD, MSCE
Michael R Savona, MD
Eunice S Wang, MD

Lung Cancer

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Faculty
Justin F Gainor, MD
Corey J Langer, MD
Luis Paz-Ares, MD, PhD
Heather Wakelee, MD
Jared Weiss, MD
Helena Yu, MD

Prostate Cancer

Saturday, June 4, 2022
6:45 AM – 7:45 AM PT (5:45 AM – 6:45 AM ET)

Faculty
Andrew J Armstrong, MD, ScM
Johann de Bono, MBChB, MSc, PhD
Alicia K Morgans, MD, MPH

Gastrointestinal Cancers

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Tanios Bekaii-Saab, MD
Kristen K Ciombor, MD, MSCI
Eric Van Cutsem, MD, PhD
Eileen M O'Reilly, MD
Philip A Philip, MD, PhD, FRCP
John Strickler, MD

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Joyce F Liu, MD, MPH
Kathleen N Moore, MD, MS

Breast Cancer

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

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

John Strickler, MD
Associate Professor
Duke University
Durham, North Carolina

Harry H Yoon, MD, MHS
Associate Professor of Oncology
Chair, Gastroesophageal Cancer Disease Group
Mayo Clinic Comprehensive Cancer Center
Rochester, Minnesota

MODERATOR
Neil Love, MD
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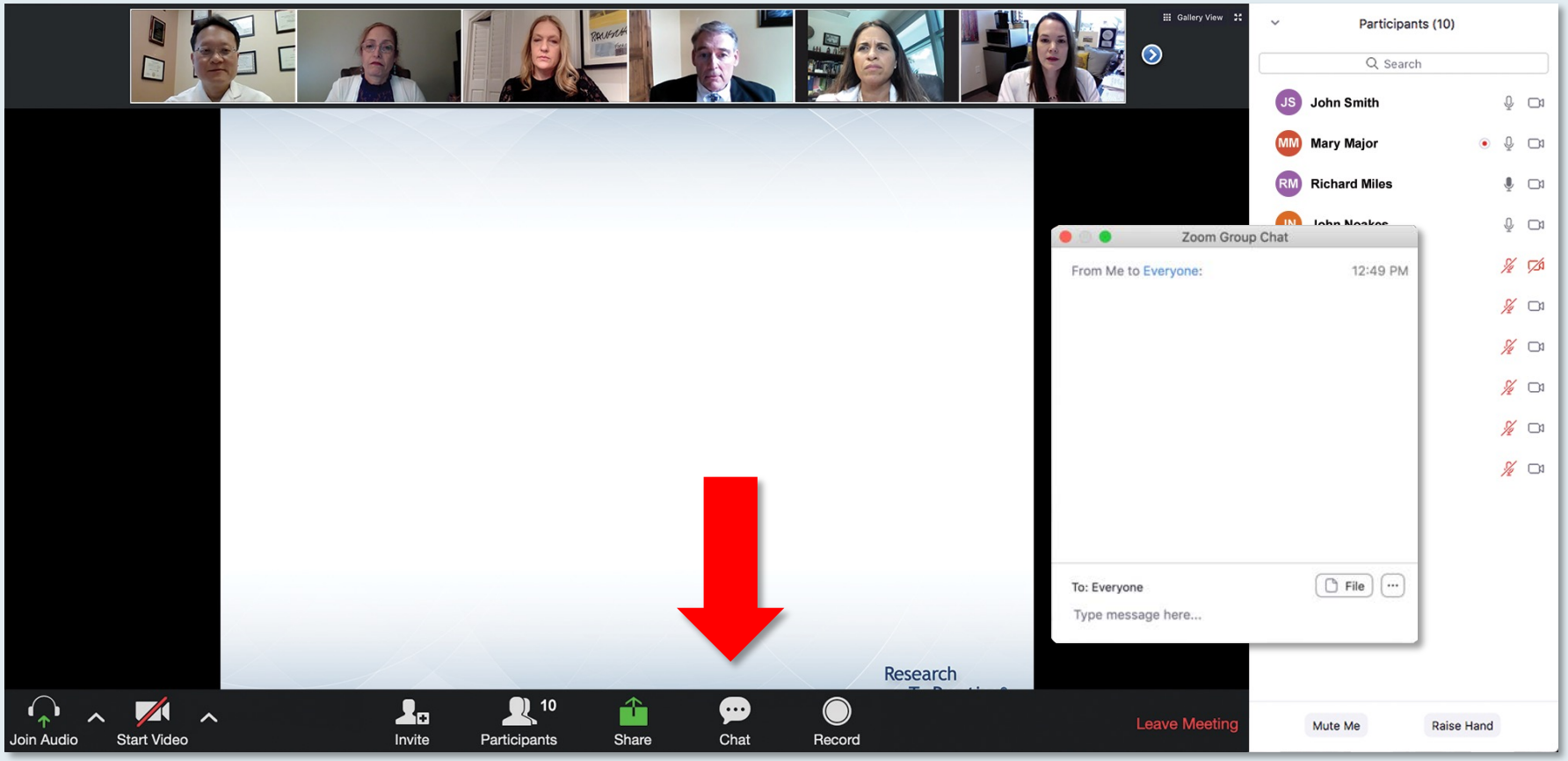

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Special Topics

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A 2-Part Complimentary NCPD Webinar Series

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Dr Janjigian — Disclosures

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Contracted Research	Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Cycle for Survival, Fred's Team, Genentech, a member of the Roche Group, Lilly, Merck, National Cancer Institute, Rgenix, US Department of Defense
Stock Options	Rgenix

Kapisthalam (KS) Kumar, MD
Florida Cancer Specialists
Trinity, Florida

Neil Morganstein, MD
Atlantic Health System
Summit, New Jersey

Gurveen Kaur, MD
WVU Medicine
Wheeling Hospital
Wheeling, West Virginia

G Richard Polkinghorn, MD
MaineGeneral Medical Center
Augusta, Maine

Raymond Lobins, DO
Lake County University Hospitals
Mentor, Ohio

Erik J Rupard, MD
Drexel University College of Medicine
West Reading, Pennsylvania

Paul Markowski, MD
Atlantic Health System
Summit, New Jersey

Liudmila N Schafer, MD
University of Missouri-Kansas City School of Medicine
Kansas City, Missouri

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Meet The Professor with Dr Janjigian

Meet The Professor with Dr Janjigian

Introduction

MODULE 1: HER2-Negative Gastroesophageal Cancers

MODULE 2: HER2-Positive Gastroesophageal Cancers

MODULE 3: Journal Club with Dr Janjigian

MODULE 4: Appendix of Key Publications

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Yelena Y. Janjigian MD @YJanjigianMD · Apr 27

I am riding @Cycle4Survival on May 13 2022 @MSKCancerCenter to raise funds for analysis of microbiome/tumor/blood samples from esophagus & stomach cancer pts who developed cancer at a young age. Please support our team #STGI! secure2.convio.net/mskcc/site/TR/...

Meet The Professor with Dr Janjigian

Introduction

MODULE 1: HER2-Negative Gastroesophageal Cancers

- Dr Kumar: A 60-year-old man with HER2-negative metastatic squamous cell carcinoma of the esophagus – PD-L1 70%
- Dr Kaur: A 57-year-old man with a history of GERD diagnosed with localized esophageal adenocarcinoma
- Dr Polkinghorn: A 50-year-old man with localized gastroesophageal-junction adenocarcinoma
- Dr Lobins: An 83-year-old man with localized HER2-negative esophageal adenocarcinoma
- Dr Rupard: A 63-year-old man with metastatic recurrence 1 year after R0 resection for localized squamous cell carcinoma of the esophagus
- Dr Schafer: A 75-year-old man with HER2-negative metastatic gastroesophageal adenocarcinoma – microsatellite stable (MSS), EGFR amplification
- Dr Morganstein: An 81-year-old man with HER2-negative metastatic gastric cancer – MSS, PD-L1 CPS 5

MODULE 2: HER2-Positive Gastroesophageal Cancers

MODULE 3: Journal Club with Dr Janjigian

MODULE 4: Appendix of Key Publications

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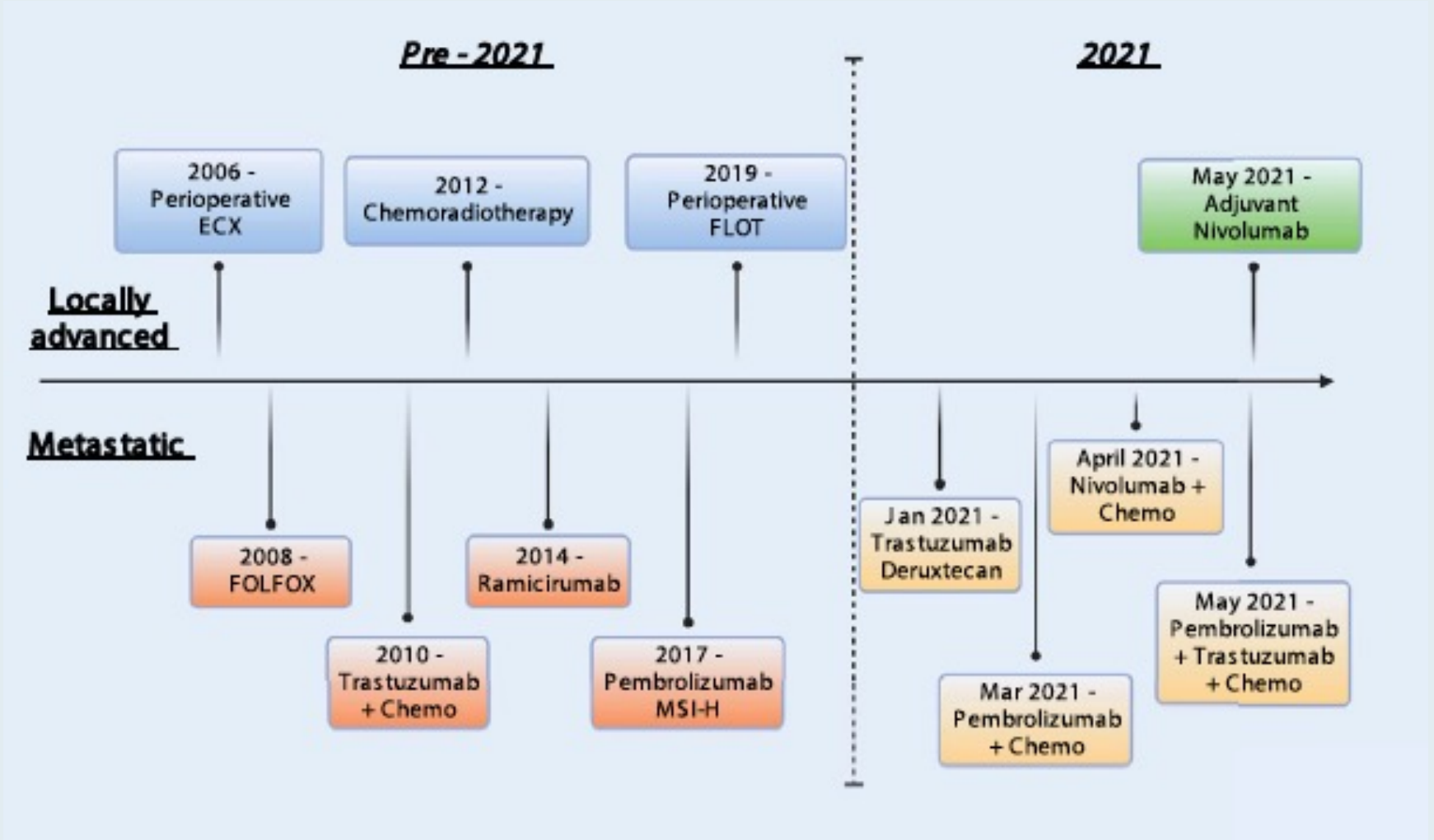
***Cancer* 2022;[Online ahead of print].**

Commentary

Top advances in esophageal/gastroesophageal junction cancers in 2021

Darren Cowzer, MB, BCh ; and Yelena Y. Janjigian, MD

Timeline of US FDA Approvals and Interventions for Esophagogastric Cancer



Cowzer D, Janjigian YY. Cancer. 2022 Feb 18 [online ahead of print].

Fam-Trastuzumab Deruxtecan-nxki approved in the US for patients with HER2-positive metastatic breast cancer treated with a prior anti-HER2-based regimen

Press Release – May 4, 2022

"The Food and Drug Administration approved fam-trastuzumab deruxtecan-nxki for adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy.

In December 2019, fam-trastuzumab deruxtecan-nxki received accelerated approval for adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. The following trial was the confirmatory trial for the accelerated approval.

Efficacy was based on DESTINY-Breast03 (NCT03529110), a multicenter, open-label, randomized trial that enrolled 524 patients with HER2-positive, unresectable, and/or metastatic breast cancer who received prior trastuzumab and taxane therapy for metastatic disease or developed disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy. Patients were randomized 1:1 to receive either trastuzumab deruxtecan or ado-trastuzumab emtansine by intravenous infusion every 3 weeks until unacceptable toxicity or disease progression. Randomization was stratified by hormone receptor status, prior treatment with pertuzumab, and history of visceral disease."

www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-fam-trastuzumab-deruxtecan-nxki-breast-cancer

Trastuzumab Deruxtecan (T-DXd) versus Trastuzumab Emtansine (T-DM1) in Patients (pts) with HER2-Positive (HER2+) Unresectable and/or Metastatic Breast Cancer (mBC): Safety Follow-Up of the Randomized, Phase 3 Study DESTINY-Breast03

Hamilton EP et al.

ASCO 2022;Abstract 1000.

Oral Breast Cancer – Metastatic Session
June 4, 2022, 2:15 PM

Trastuzumab Deruxtecan Significantly Improved Both Progression-Free and Overall Survival in the DESTINY-Breast04 Trial for Patients with HER2-Low Metastatic Breast Cancer

Press Release – February 22, 2022

Positive high-level results from the pivotal DESTINY-Breast04 Phase III trial showed trastuzumab deruxtecan demonstrated a statistically significant and clinically meaningful improvement in both progression-free survival (PFS) and overall survival (OS) in patients with HER2-low unresectable and/or metastatic breast cancer regardless of hormone receptor (HR) status versus physician's choice of chemotherapy.

All patients in the trial received a HER2 test, and the results were centrally confirmed. HER2-low status was defined as an immunohistochemistry (IHC) score of 1+ or IHC 2+ with a negative in-situ hybridisation (ISH) score.

DESTINY-Breast04 met its primary endpoint, where trastuzumab deruxtecan demonstrated superior PFS in previously treated patients with HR-positive HER2-low metastatic breast cancer compared to the standard-of-care chemotherapy. The trial met the key secondary endpoint of PFS in patients with HER2-low metastatic breast cancer regardless of HR status (HR-positive or HR-negative). The trial also met the key secondary endpoints of OS in patients with HR-positive disease and in patients regardless of HR status at interim analysis."

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www.astrazeneca.com/media-centre/press-releases/2022/enhertu-improves-pfs-and-os-in-her2-low-bc.html

Trastuzumab Deruxtecan (T-DXd) versus Treatment of Physician's Choice (TPC) in Patients (pts) with HER2-Low Unresectable and/or Metastatic Breast Cancer (mBC): Results of DESTINY-Breast04, a Randomized, Phase 3 Study

Modi S et al.

ASCO 2022;Abstract LBA3.

Plenary Session
June 5, 2022, 3:17 PM

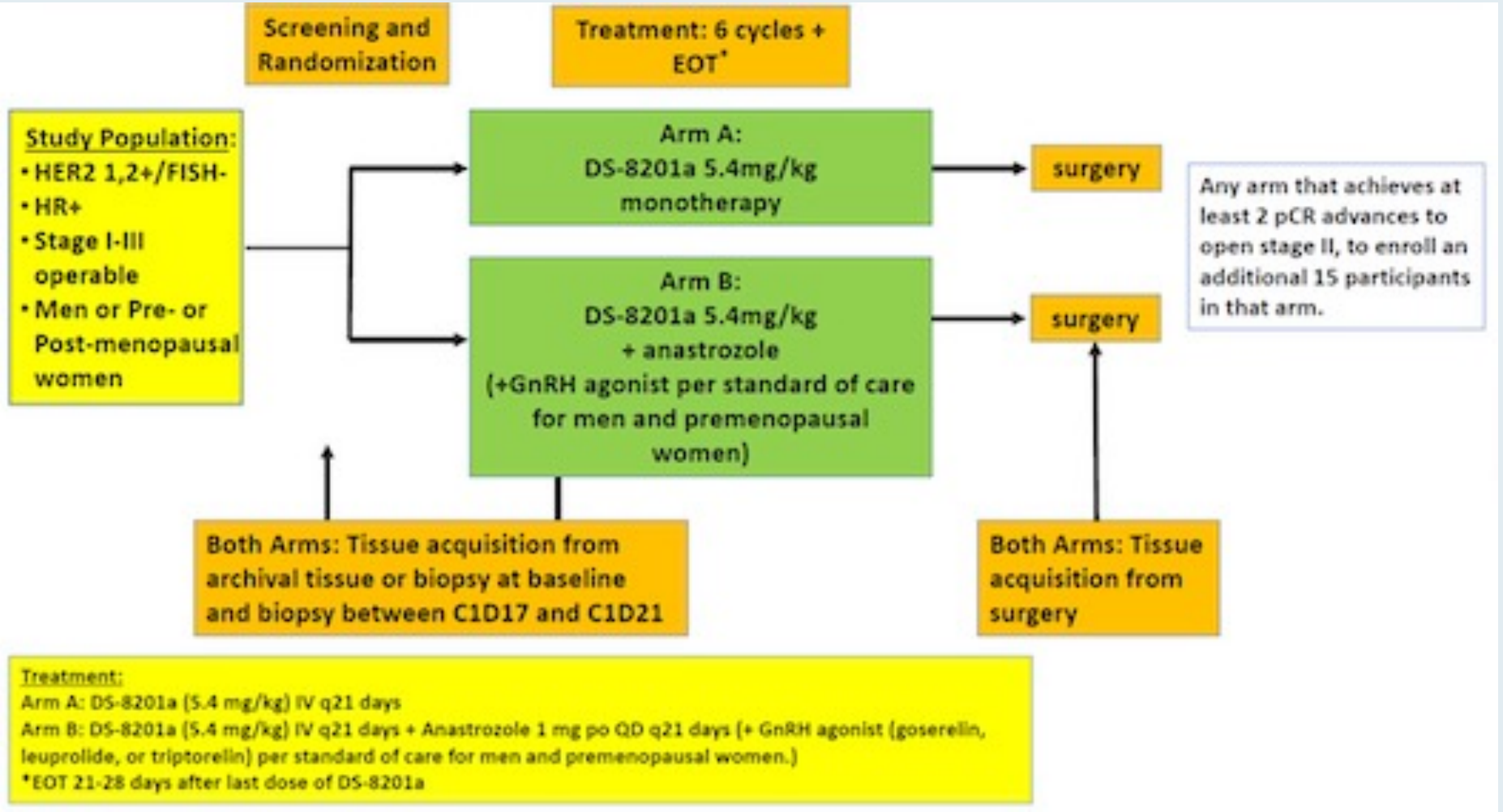
TRIO-US B-12 TALENT: Phase II Neoadjuvant Trial Evaluating Trastuzumab Deruxtecan with or without Anastrozole for HER2-Low, HR+ Early-Stage Breast Cancer

Hurvitz SA et al.

ASCO 2022;Abstract TPS623

Breast Cancer Poster Session – Local/Regional/Adjuvant
June 6, 2022, 9:00 AM

TRIO-US B-12 TALENT Phase II Study Design



Hurvitz SA et al. ASCO 2021;Abstract TPS603.

Cancer Cell 2021;39(6):738-42.

CellPress

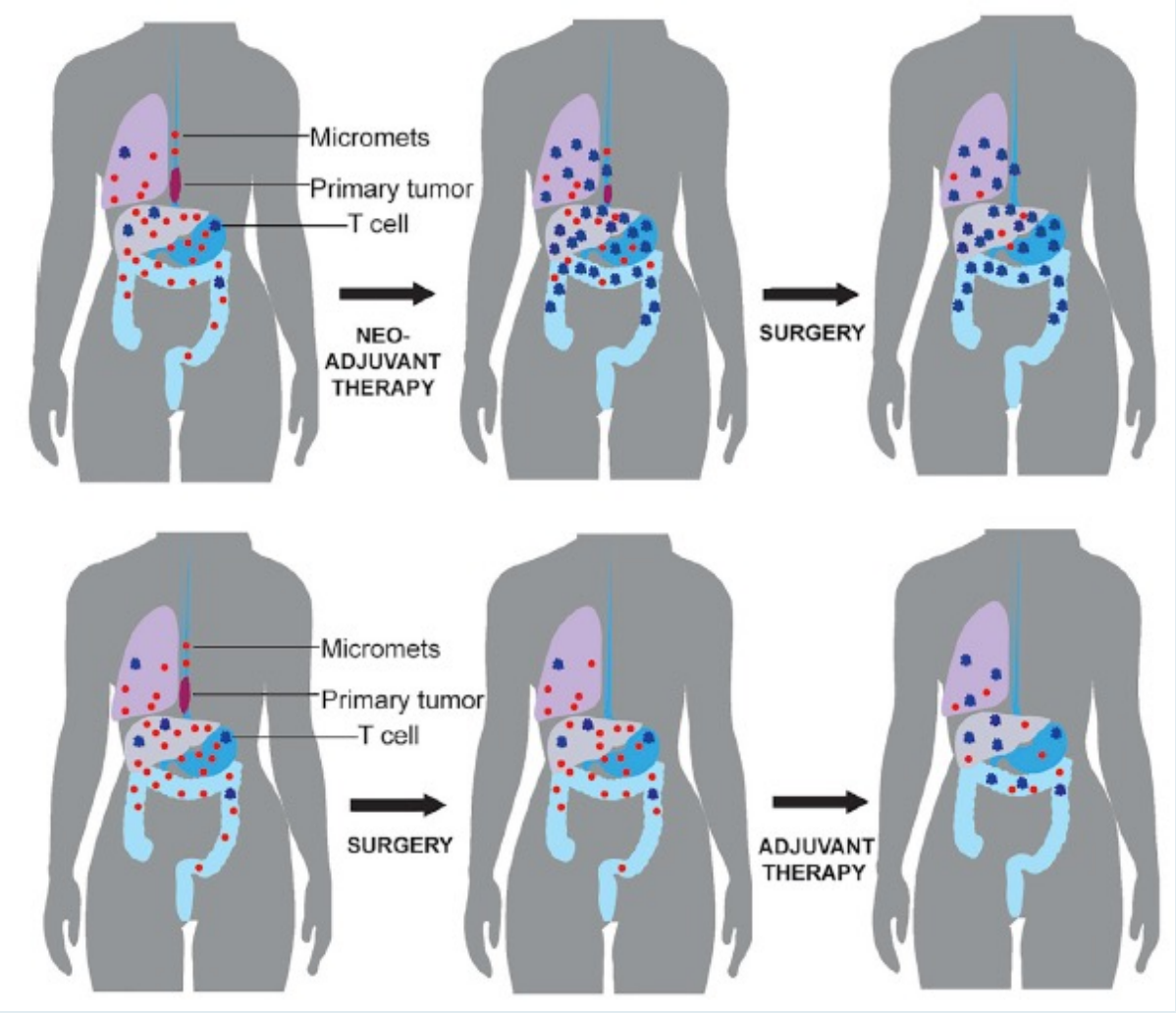
Cancer Cell

Commentary

Eradicating micrometastases with immune checkpoint blockade: Strike while the iron is hot

Yelena Y. Janjigian,[1,*] Jedd D. Wolchok,[2,3] and Charlotte E. Ariyan[4]

T-Cell Response and Expansion in Patients with Locally Advanced Resectable Esophageal Cancer Who Received Neoadjuvant or Adjuvant Immune Checkpoint Blockade



Janjigian YY et al. Cancer Cell 2021;39(6):738-742.

Prior to initiating chemotherapy for a patient with gastroesophageal adenocarcinoma, I always evaluate MSI (microsatellite instability) status.

1. Agree
2. Disagree
3. In between
4. I haven't thought much about it

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?

1. Chemotherapy
2. Pembrolizumab + chemotherapy
3. Nivolumab + chemotherapy
4. Nivolumab + ipilimumab
5. Pembrolizumab
6. Nivolumab
7. Other

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

RTP RESEARCH TO PRACTICE

Case Presentation: A 60-year-old man with HER2-negative metastatic squamous cell carcinoma of the esophagus – PD-L1 70%

Dr KS Kumar (Trinity, Florida)

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 57-year-old man with a history of GERD diagnosed with localized esophageal adenocarcinoma

Dr Gurveen Kaur (Wheeling, West Virginia)

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 50-year-old man with localized gastroesophageal-junction adenocarcinoma

Dr Richard Polkinghorn (Augusta, Maine)

Case Presentation: An 83-year-old man with localized HER2-negative esophageal adenocarcinoma

Dr Raymond Lobins (Mentor, Ohio)

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 63-year-old man with metastatic recurrence 1 year after R0 resection for localized squamous cell carcinoma of the esophagus

Dr Erik J Rupard (West Reading, Pennsylvania)

RTP
RESEARCH
TO PRACTICE

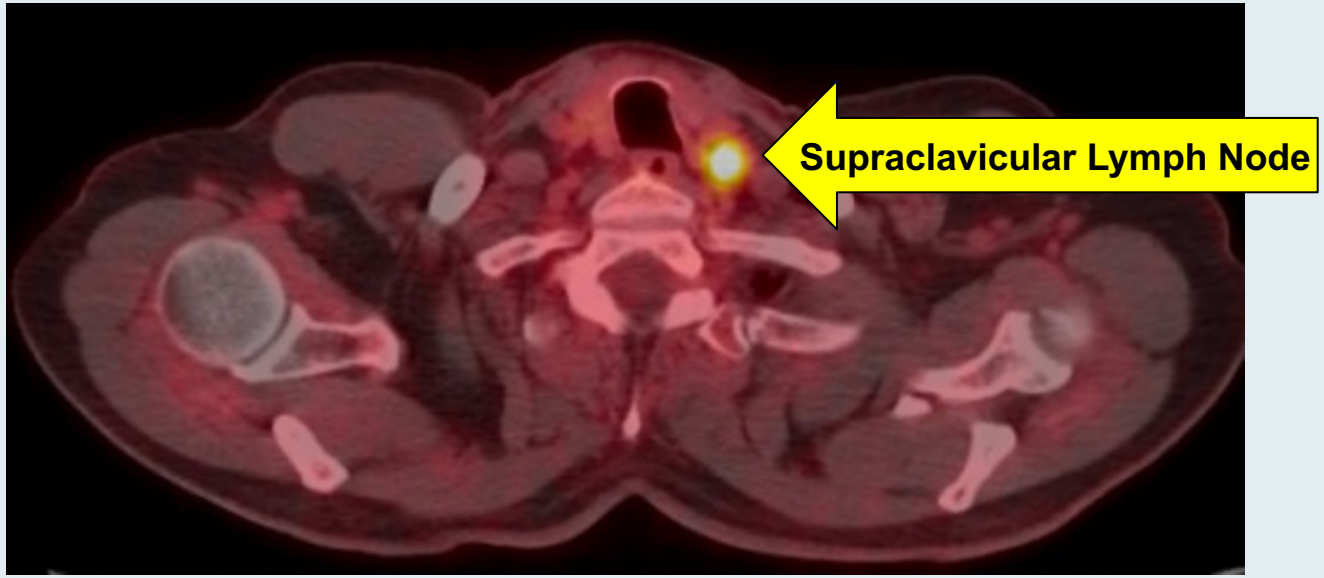
Case Presentation: A 75-year-old man with HER2-negative metastatic GEJ adenocarcinoma – MSS

Dr Liudmila Schafer (Kansas City, Missouri)

RTP
RESEARCH
TO PRACTICE

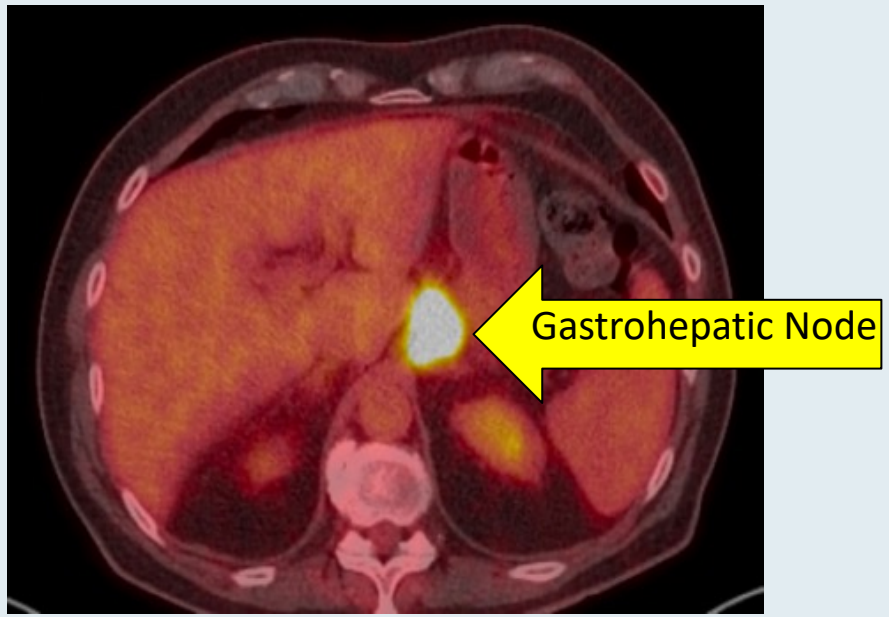
Case Presentation: A 75-year-old man with HER2-negative metastatic GEJ adenocarcinoma – MSS (continued)

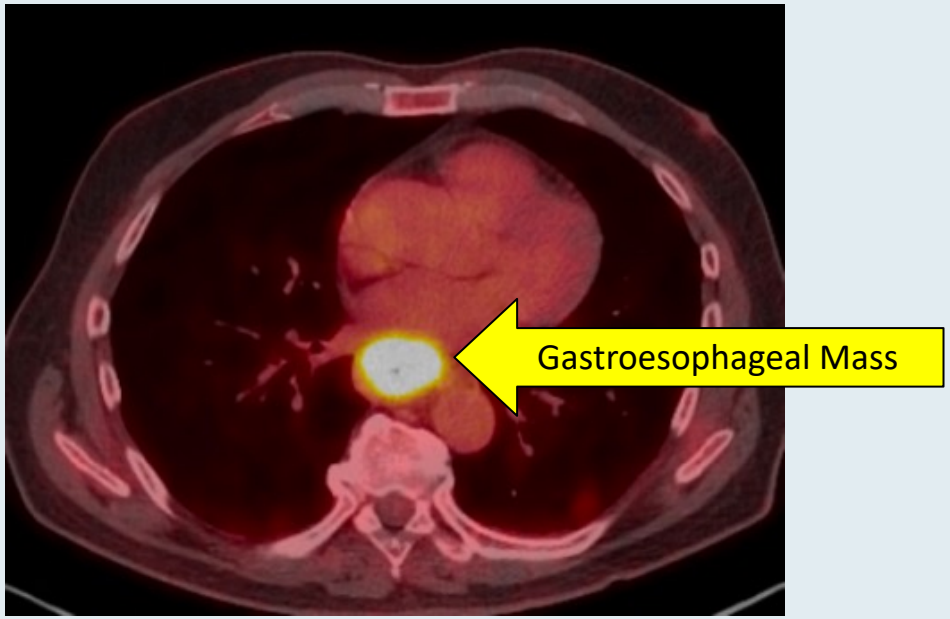
Dr Liudmila Schafer
(Kansas City, Missouri)



Case Presentation: A 75-year-old man with HER2-negative metastatic GEJ adenocarcinoma – MSS (continued)

Dr Liudmila Schafer
(Kansas City, Missouri)





Case Presentation: An 81-year-old man with HER2-negative metastatic GEJ adenocarcinoma – MSS, PD-L1 CPS 5 – received FOLFOX

Dr Neil Morganstein (Summit, New Jersey)

RTP
RESEARCH
TO PRACTICE

Checkpoint Inhibitor Approvals in 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):1191-1203. Sun J et al. *Lancet*. 2021; 398(10302):759-771. Janjigian YY et al. *Lancet* 2021;398(10294):27-40. Kojima T et al. *J Clin Oncol*. 2020;38(35):4138-4148. Kato K et al. *Lancet Oncol*. 2019; 20(11):1506-1517.

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

The NEW ENGLAND JOURNAL of MEDICINE

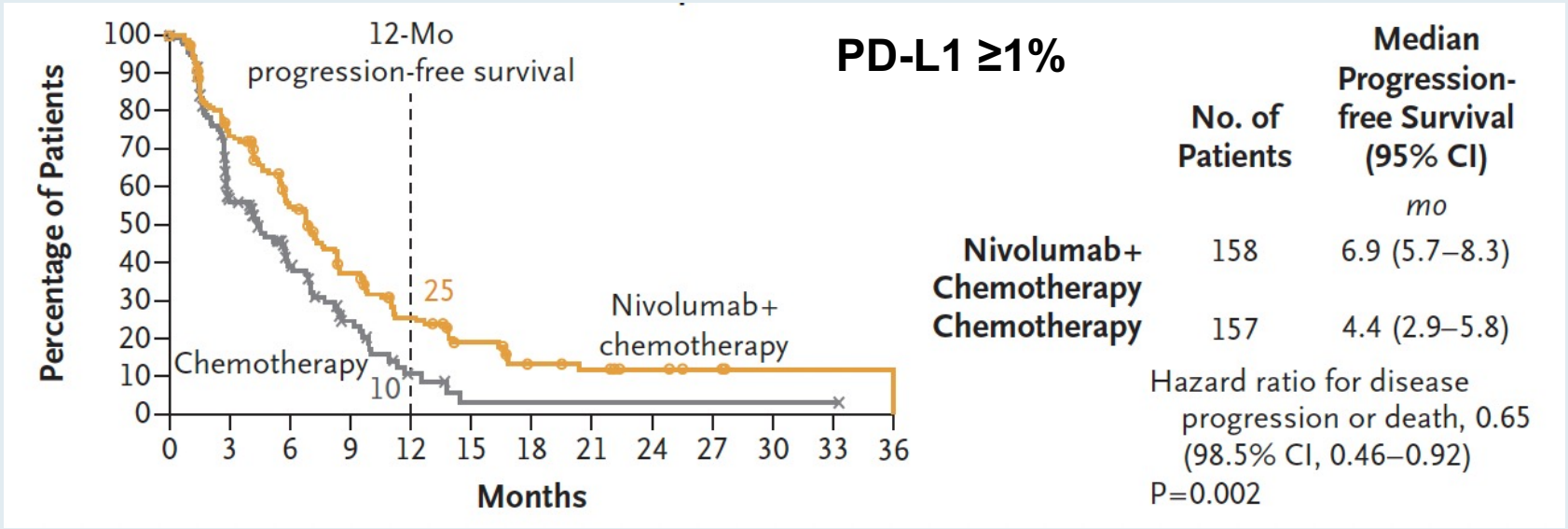
ORIGINAL ARTICLE

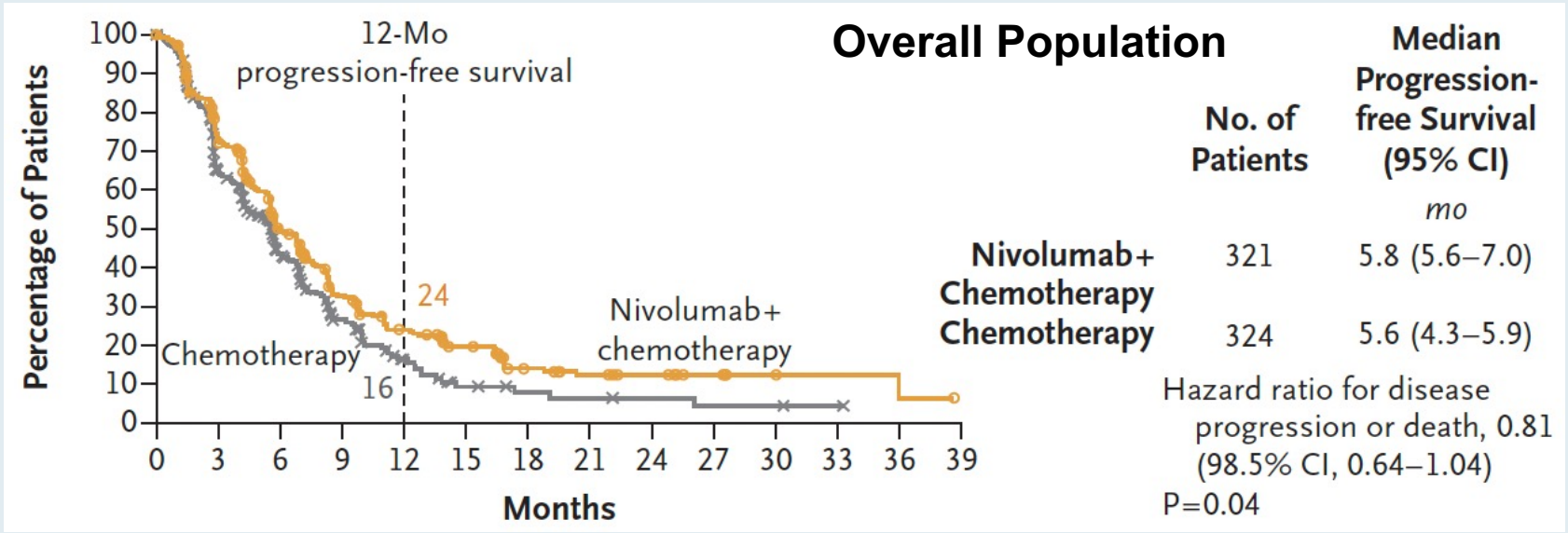
Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma

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;449-62.

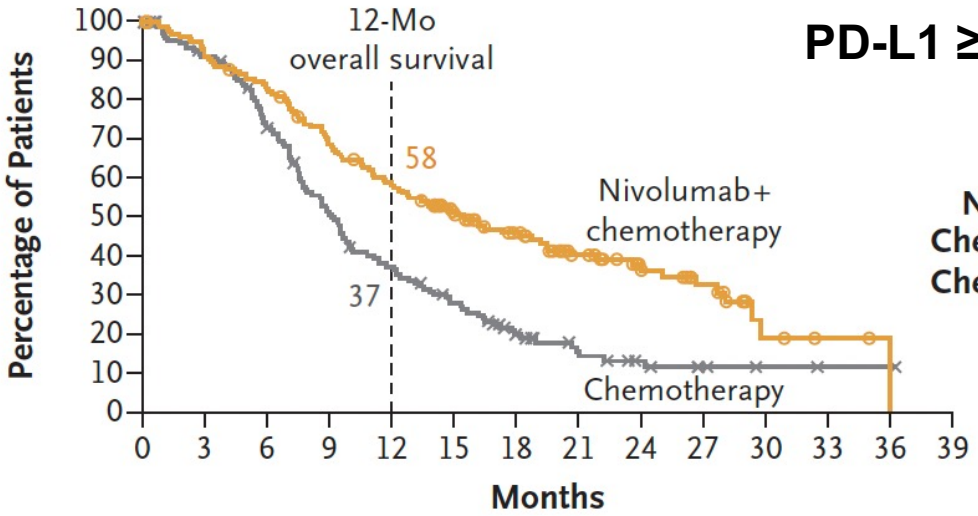
CheckMate 648: Progression-Free Survival for PD-L1 ≥1% and in the Overall Population – Nivolumab + Chemotherapy





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

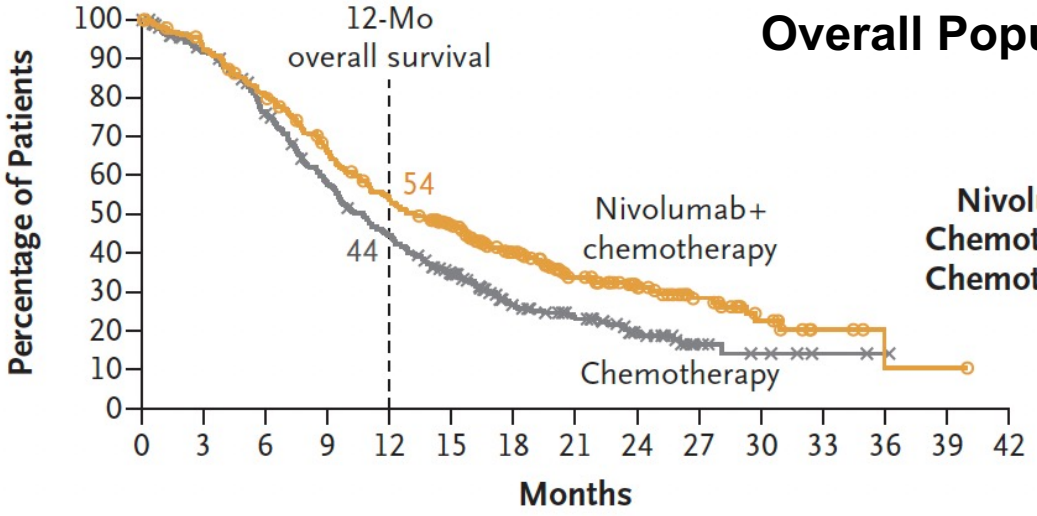
CheckMate 648: Overall Survival for PD-L1 ≥1% and in the Overall Population – Nivolumab + Chemotherapy



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

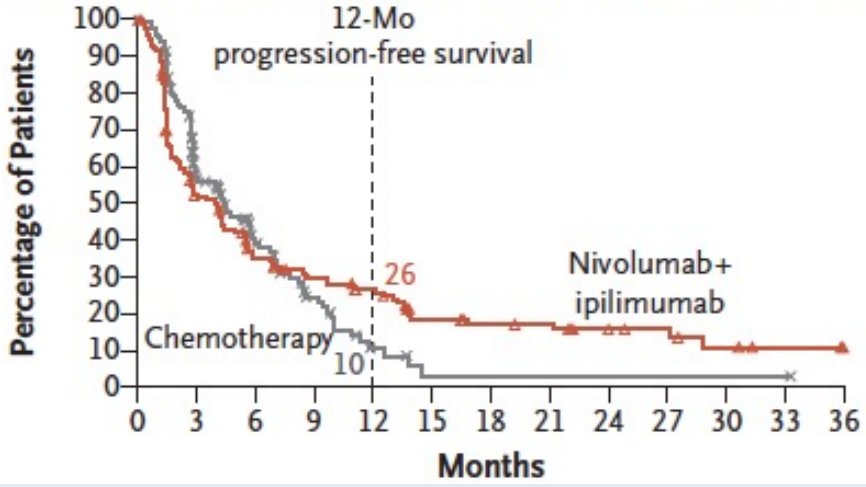
	No. of Patients	Median Overall Survival (95% CI)
		mo
Nivolumab+ Chemotherapy	321	13.2 (11.1–15.7)
Chemotherapy	324	10.7 (9.4–11.9)

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

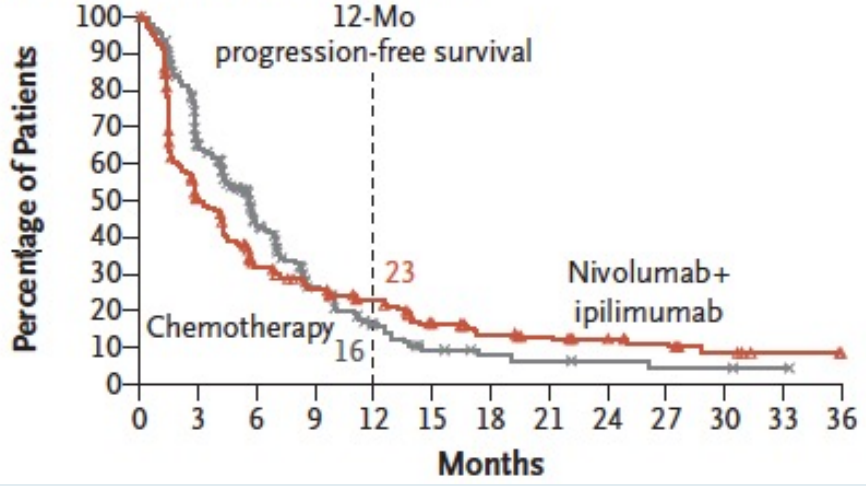
Progression-free Survival in Patients with Tumor-Cell PD-L1 Expression of ≥1%



	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



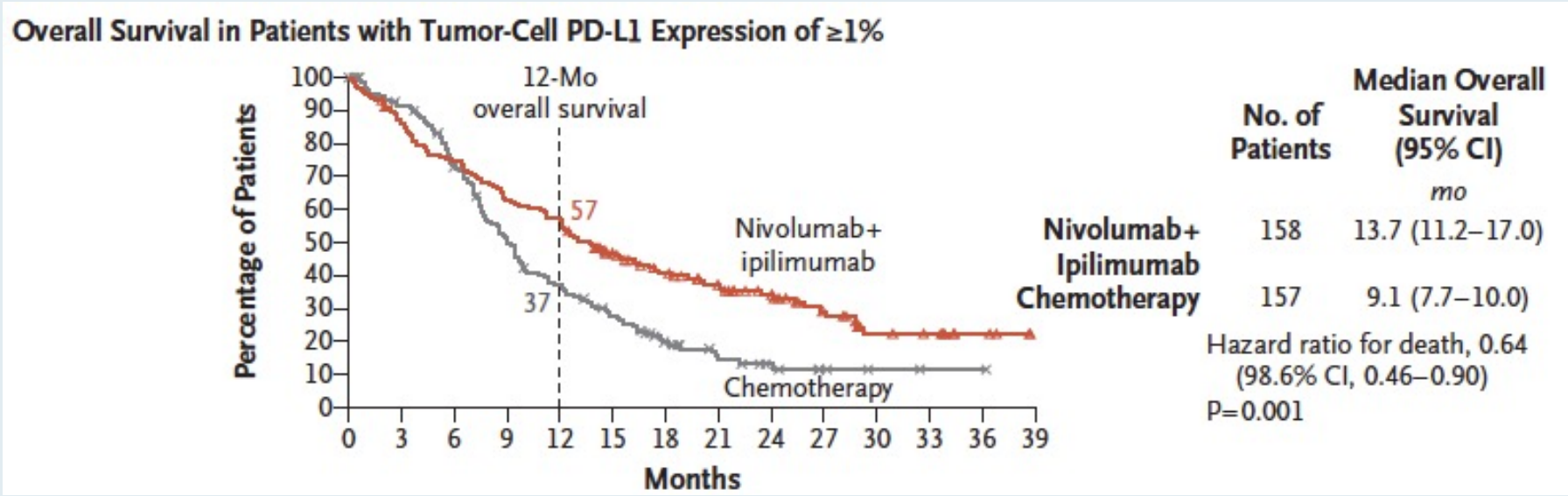
	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Nivolumab+ Ipilimumab	325	2.9 (2.7–4.2)
Chemotherapy	324	5.6 (4.3–5.9)

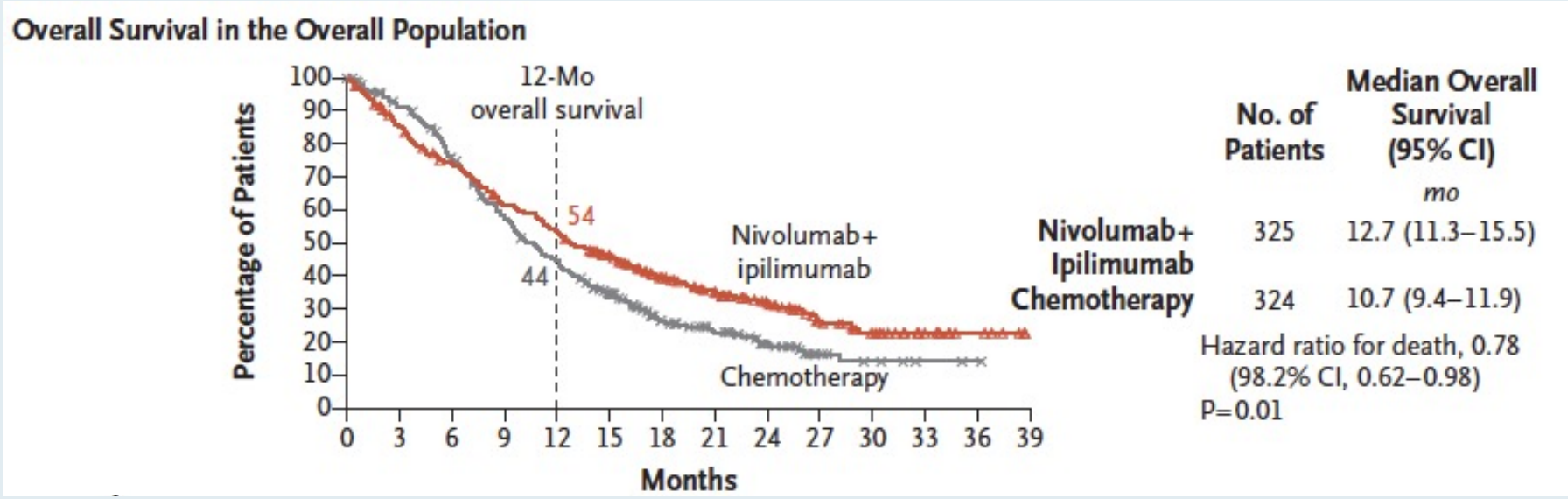
Hazard ratio for disease progression or death, 1.26 (95% CI, 1.04–1.52)
P value not tested

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

RTP RESEARCH TO PRACTICE

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;449-62.

2021 ESMO congress

LBA7

Nivolumab (NIVO) plus chemotherapy (Chemo) or ipilimumab (IPI) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): CheckMate 649 study

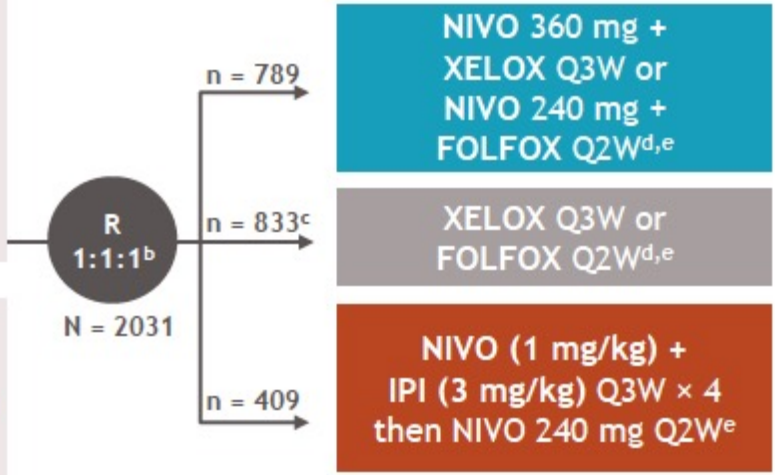
Y.Y. Janjigian[1], J.A. Ajani[2], M. Moehler[3], M. Garrido[4], C. Gallardo[5], L. Shen[6], K. Yamaguchi[7], L. Wyrwicz[8], T. Skoczylas[9], A. Bragagnoli[10], T. Liu[11], M. Tehfe[12], E. Elimova[13], M. Li[14], V. Poulart[15], M. Lei[16], K. Kondo[17], K. Shitara[18]

CheckMate 649 Study Design

- CheckMate 649 is a randomized, open-label, global phase 3 study (NCT02872116)[1]

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/ esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0-1

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[a])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



Dual primary endpoints

NIVO + chemo vs chemo
- OS and PFS per BICR (PD-L1 CPS ≥ 5)

Hierarchically tested secondary efficacy endpoints

NIVO + chemo vs chemo
- OS (PD-L1 CPS ≥ 1, all randomized)

NIVO + IPI vs chemo
- OS (PD-L1 CPS ≥ 5, all randomized)

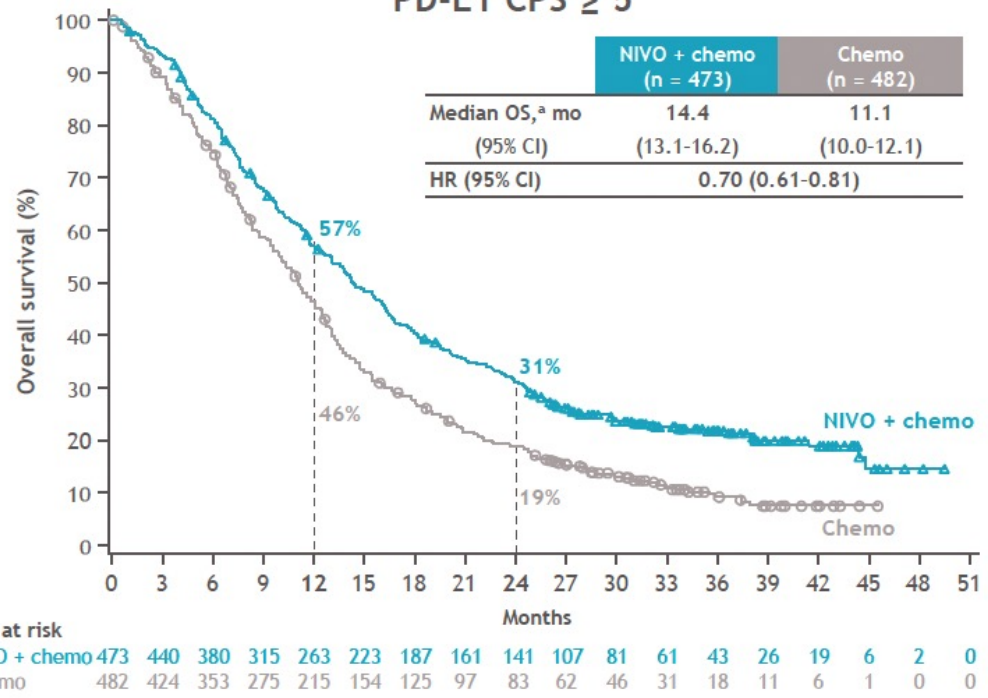
- At data cutoff (May 27, 2021), the minimum follow-up[f] was 24.0 months in the NIVO + chemo arm and 35.7 months in the NIVO + IPI arm

[a]< 1% includes indeterminate tumor cell PD-L1 expression; [b]After NIVO + chemo arm was added and before new patient enrollment in the NIVO + IPI arm was stopped early (5 June 2018) based on DMC recommendation; patients already enrolled in the NIVO + IPI arm were allowed to remain on study; [c]Includes patients concurrently randomized to chemo vs NIVO + IPI (October 2016-June 2018), and to NIVO + chemo (Apr 2017-Apr 2019); [d]XELOX: oxaliplatin 130 mg/m² IV (day 1) and capecitabine 1000 mg/m² orally twice daily (days 1-14); FOLFOX: oxaliplatin 85 mg/m², leucovorin 400 mg/m², and FU 400 mg/m² IV (day 1) and FU 1200 mg/m² IV daily (days 1-2); [e]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo or NIVO + IPI), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [f]Time from concurrent randomization of the last patient to data cutoff. 1. Janjigian YY, et al. *Lancet* 2021;398:27-40.

Janjigian YY et al. ESMO 2021;Abstract LBA7.

Overall survival: NIVO + chemo vs chemo

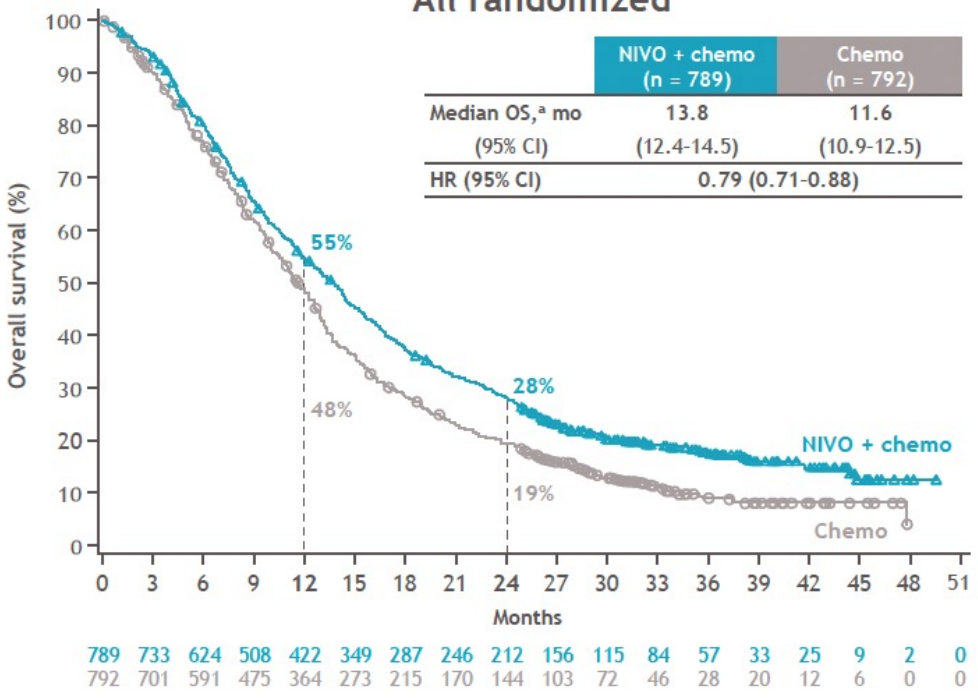
PD-L1 CPS ≥ 5



	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS,[a] mo	14.4	11.1
(95% CI)	(13.1-16.2)	(10.0-12.1)
HR (95% CI)	0.70 (0.61-0.81)	

No. at risk																		
NIVO + chemo	473	440	380	315	263	223	187	161	141	107	81	61	43	26	19	6	2	0
Chemo	482	424	353	275	215	154	125	97	83	62	46	31	18	11	6	1	0	0

All randomized



	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS,[a] mo	13.8	11.6
(95% CI)	(12.4-14.5)	(10.9-12.5)
HR (95% CI)	0.79 (0.71-0.88)	

NIVO + chemo	789	733	624	508	422	349	287	246	212	156	115	84	57	33	25	9	2	0
Chemo	792	701	591	475	364	273	215	170	144	103	72	46	28	20	12	6	0	0

- Clinically meaningful improvement in OS with NIVO + chemo vs chemo was maintained with longer follow-up
  - PD-L1 CPS ≥ 5: 30% reduction in the risk of death and 12% improvement in 24-month OS rate
  - All randomized: 21% reduction in the risk of death and 9% improvement in 24-month OS rate
  - Directionally improved HRs relative to the 12-month follow-up (PD-L1 CPS ≥ 5, 0.71 [98.4% CI, 0.59-0.86]; all randomized, 0.80 [99.3% CI, 0.68-0.94])[1]

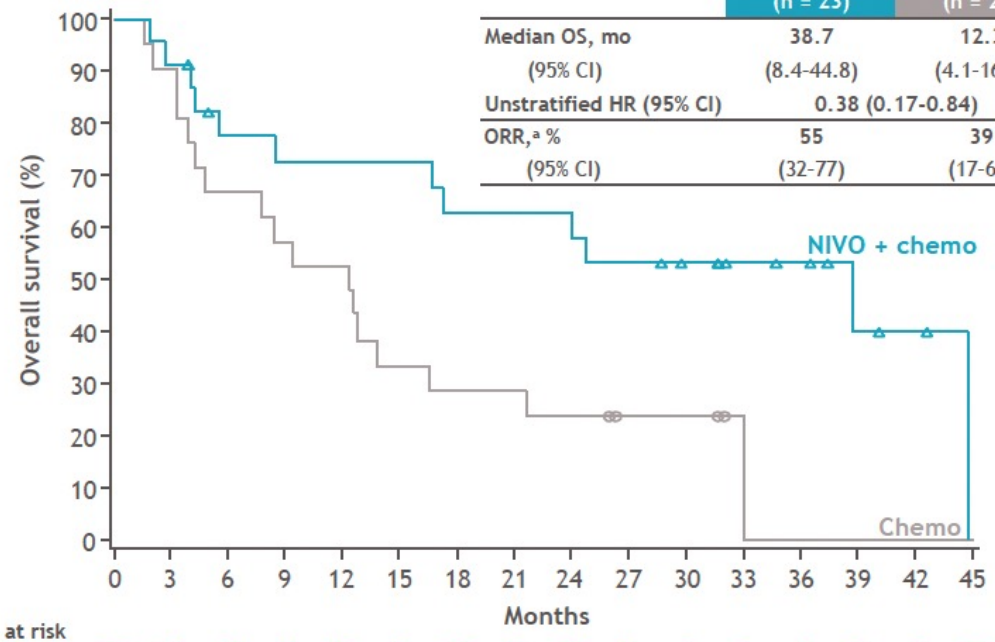
[a]Minimum follow-up, 24.0 months. 1. Janjigian YY, et al. *Lancet* 2021;398:27-40.

Janjigian YY et al. ESMO 2021;Abstract LBA7.

Efficacy by MSI status: NIVO + chemo vs chemo

MSI-H

	NIVO + chemo (n = 23)	Chemo (n = 21)
Median OS, mo	38.7	12.3
(95% CI)	(8.4-44.8)	(4.1-16.5)
Unstratified HR (95% CI)	0.38 (0.17-0.84)	
ORR,[a] %	55	39
(95% CI)	(32-77)	(17-64)

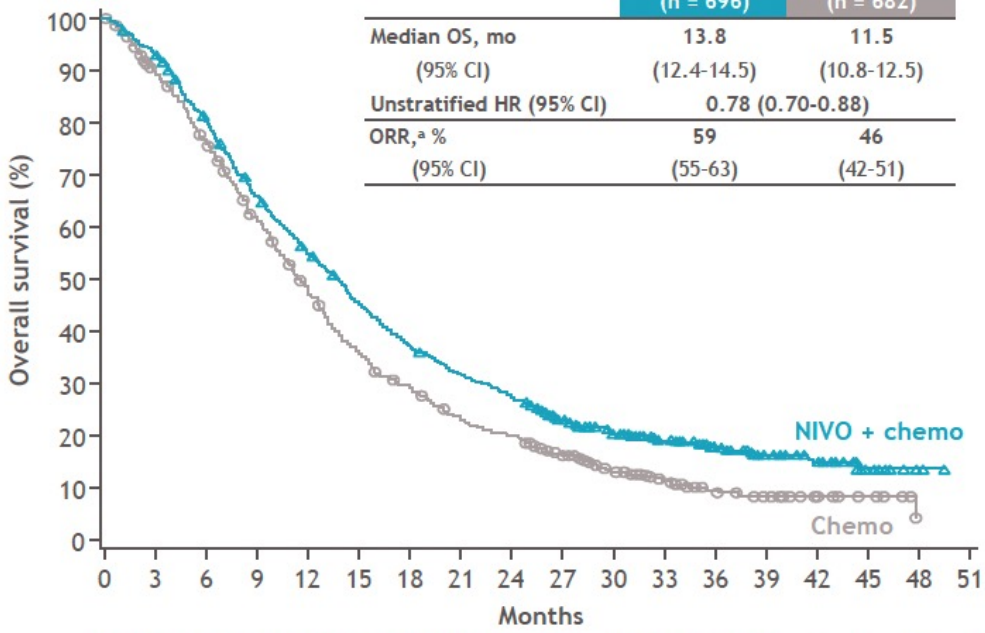


No. at risk

NIVO + chemo	23	21	16	15	15	15	13	13	12	11	9	7	6	3	2	0
Chemo	21	19	14	12	11	7	6	6	5	3	3	0	0	0	0	0

MSS

	NIVO + chemo (n = 696)	Chemo (n = 682)
Median OS, mo	13.8	11.5
(95% CI)	(12.4-14.5)	(10.8-12.5)
Unstratified HR (95% CI)	0.78 (0.70-0.88)	
ORR,[a] %	59	46
(95% CI)	(55-63)	(42-51)



NIVO + chemo	696	646	554	452	375	308	251	214	184	137	103	75	50	29	22	9	2	0
Chemo	682	601	506	405	312	235	188	146	126	94	67	44	28	20	12	6	0	0

- Longer median OS and higher ORR were observed in all randomized patients with MSI-H and MSS tumors with NIVO + chemo vs chemo
  - The magnitude of benefit was greater in patients with MSI-H tumors, and patients with MSS tumors had results similar to the all randomized population

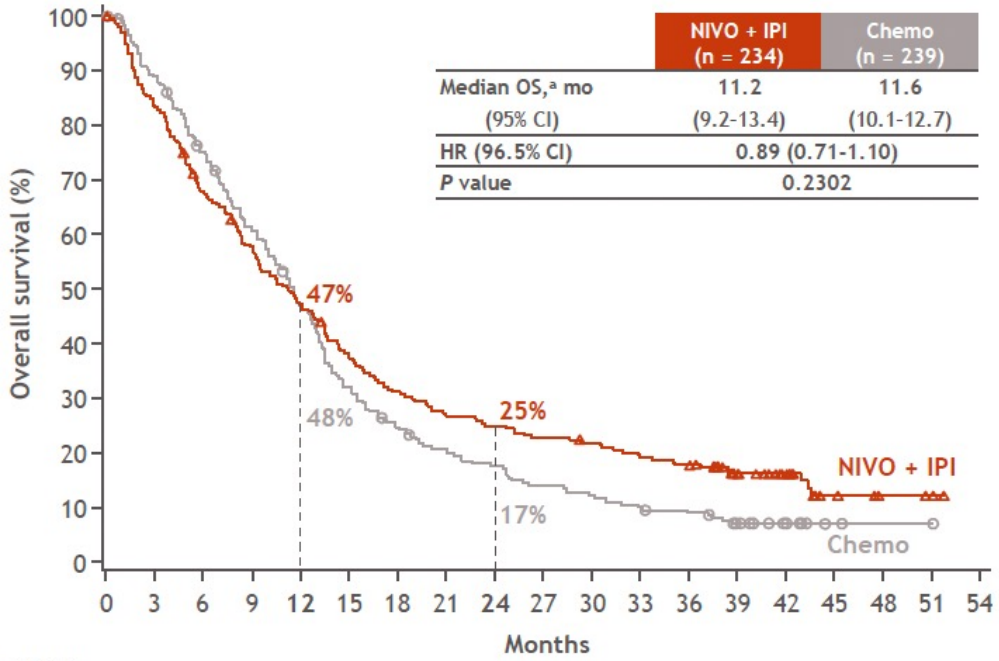
[a]Randomized patients who had target lesion measurements at baseline per BICR assessment. MSI-H: NIVO + chemo, n = 20; chemo, n = 18, patients with MSS: NIVO + chemo, n = 535; chemo, n = 533.

Janjigian YY et al. ESMO 2021;Abstract LBA7.

Overall survival: NIVO + IPI vs chemo

PD-L1 CPS ≥ 5

	NIVO + IPI (n = 234)	Chemo (n = 239)
Median OS,[a] mo	11.2	11.6
(95% CI)	(9.2-13.4)	(10.1-12.7)
HR (96.5% CI)	0.89 (0.71-1.10)	
P value	0.2302	

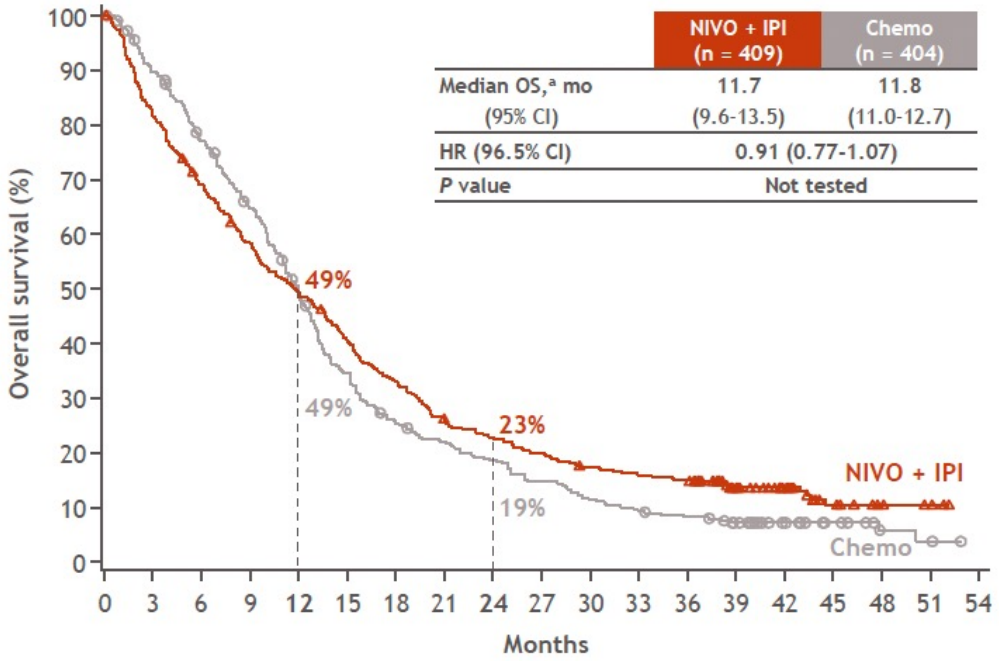


No. at risk

NIVO + IPI	234	193	156	131	106	85	70	60	56	51	48	42	39	25	18	6	3	2	0
Chemo	239	211	176	143	110	74	56	45	39	31	27	22	19	12	7	2	1	1	0

All randomized

	NIVO + IPI (n = 409)	Chemo (n = 404)
Median OS,[a] mo	11.7	11.8
(95% CI)	(9.6-13.5)	(11.0-12.7)
HR (96.5% CI)	0.91 (0.77-1.07)	
P value	Not tested	



	409	332	279	235	197	162	132	102	90	79	68	62	59	36	25	10	5	3	0
	404	359	305	255	189	134	98	84	71	56	43	36	31	23	15	9	3	2	0

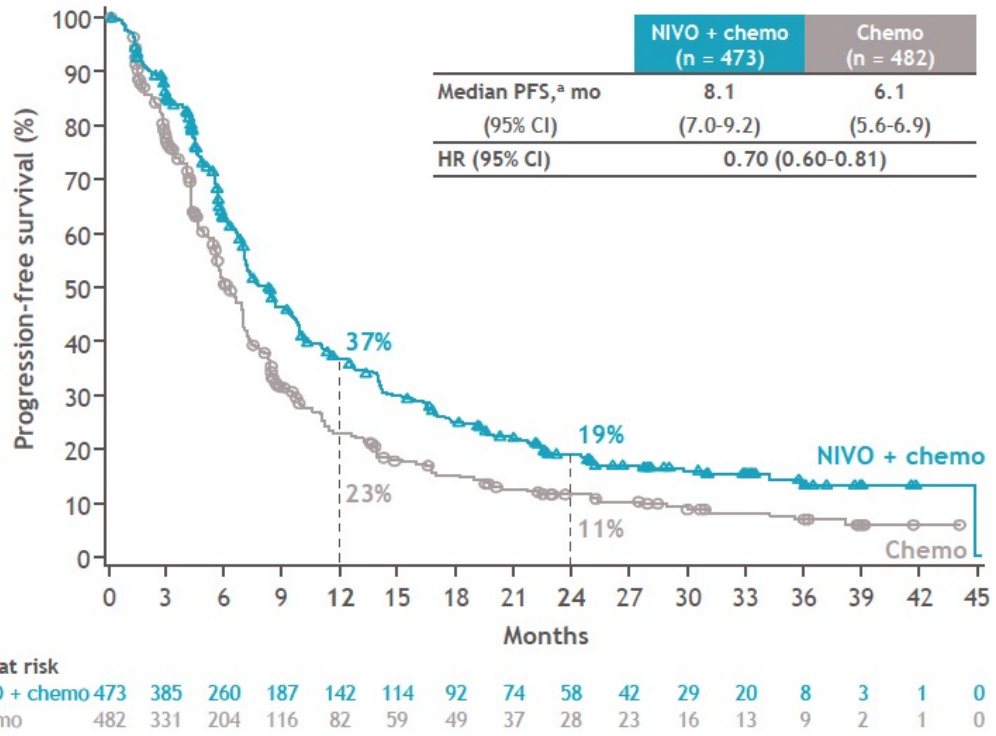
- The hierarchically tested secondary endpoint of OS with NIVO + IPI vs chemo in patients with PD-L1 CPS ≥ 5 was not met; OS in all randomized patients was not statistically tested

[a]Minimum follow-up, 35.7 months.

Janjigian YY et al. ESMO 2021;Abstract LBA7.

Progression-free survival: NIVO + chemo vs chemo

PD-L1 CPS ≥ 5

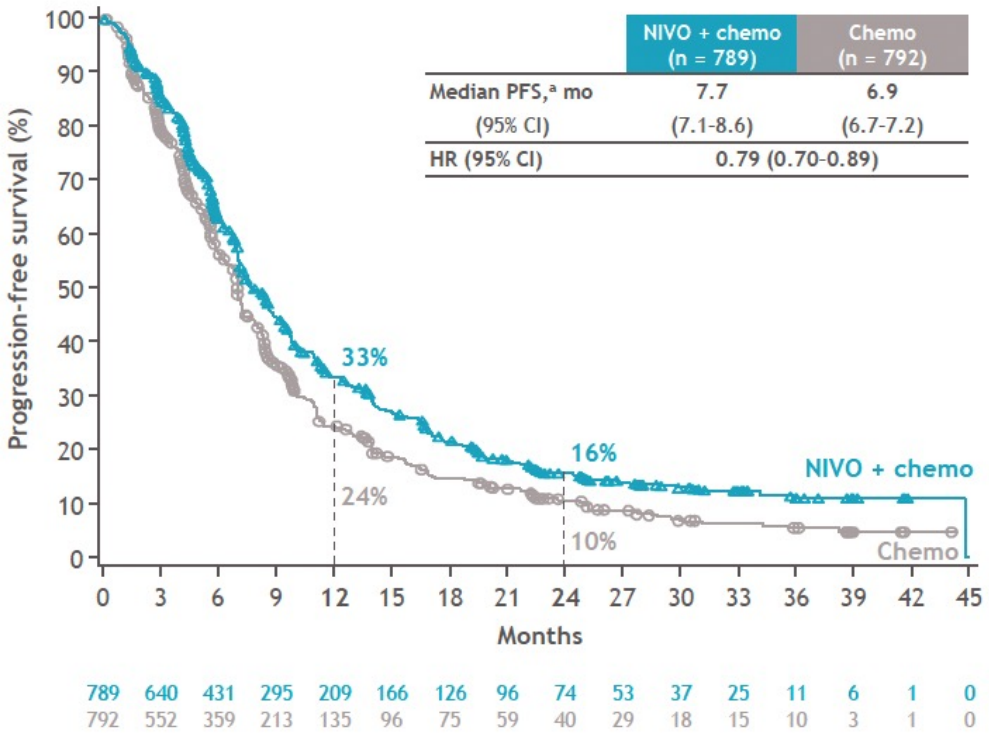


	NIVO + chemo (n = 473)	Chemo (n = 482)
Median PFS,[a] mo	8.1	6.1
(95% CI)	(7.0-9.2)	(5.6-6.9)
HR (95% CI)	0.70 (0.60-0.81)	

No. at risk

NIVO + chemo	473	385	260	187	142	114	92	74	58	42	29	20	8	3	1	0
Chemo	482	331	204	116	82	59	49	37	28	23	16	13	9	2	1	0

All randomized



	NIVO + chemo (n = 789)	Chemo (n = 792)
Median PFS,[a] mo	7.7	6.9
(95% CI)	(7.1-8.6)	(6.7-7.2)
HR (95% CI)	0.79 (0.70-0.89)	

789	640	431	295	209	166	126	96	74	53	37	25	11	6	1	0
792	552	359	213	135	96	75	59	40	29	18	15	10	3	1	0

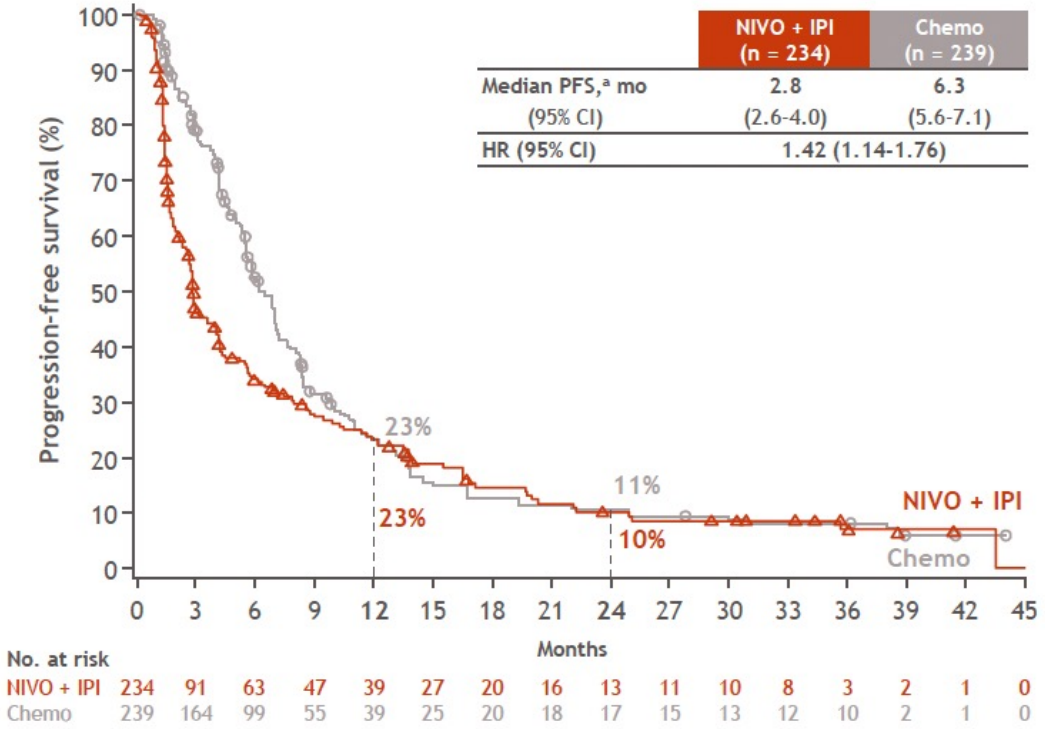
- PFS benefit was maintained with NIVO + chemo vs chemo with longer follow-up in both PD-L1 CPS ≥ 5 and all randomized populations

[a]Per BICR assessment; minimum follow-up, 24.0 months.

Janjigian YY et al. ESMO 2021;Abstract LBA7.

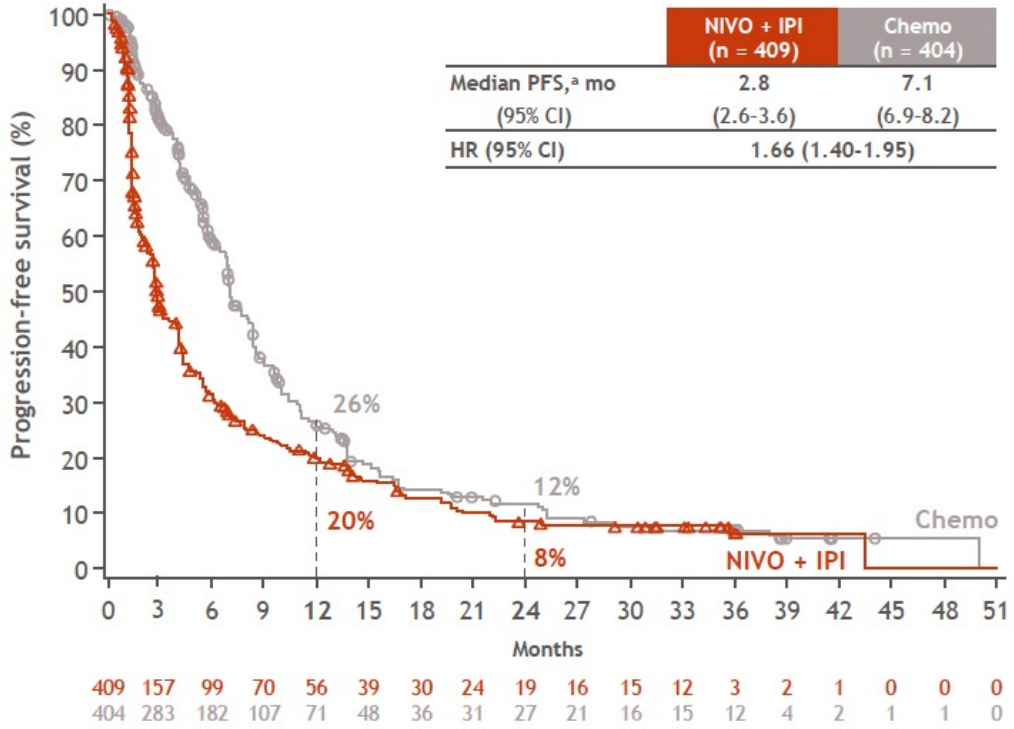
Progression-free survival: NIVO + IPI vs chemo

PD-L1 CPS ≥ 5



	NIVO + IPI (n = 234)	Chemo (n = 239)
Median PFS,[a] mo	2.8	6.3
(95% CI)	(2.6-4.0)	(5.6-7.1)
HR (95% CI)	1.42 (1.14-1.76)	

All randomized



	NIVO + IPI (n = 409)	Chemo (n = 404)
Median PFS,[a] mo	2.8	7.1
(95% CI)	(2.6-3.6)	(6.9-8.2)
HR (95% CI)	1.66 (1.40-1.95)	

- No PFS benefit was observed with NIVO + IPI vs chemo in either the PD-L1 CPS ≥ 5 or all randomized population

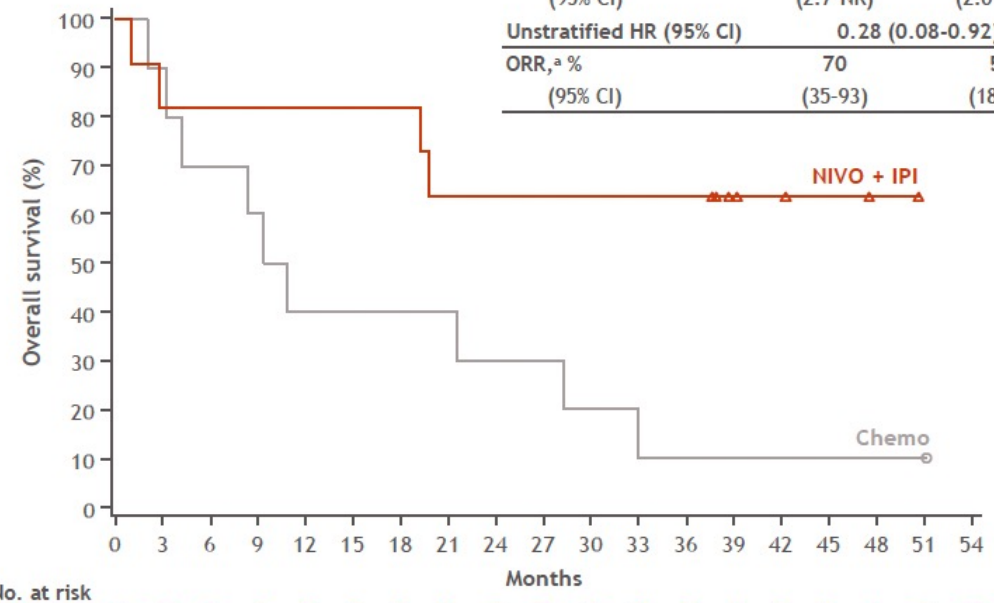
[a]Per BICR assessment; minimum follow-up, 35.7 months.

Janjigian YY et al. ESMO 2021;Abstract LBA7.

Efficacy by MSI status: NIVO + IPI vs chemo

MSI-H

	NIVO + IPI (n = 11)	Chemo (n = 10)
Median OS, mo	NR	10.0
(95% CI)	(2.7-NR)	(2.0-28.2)
Unstratified HR (95% CI)	0.28 (0.08-0.92)	
ORR,[a] %	70	57
(95% CI)	(35-93)	(18-90)

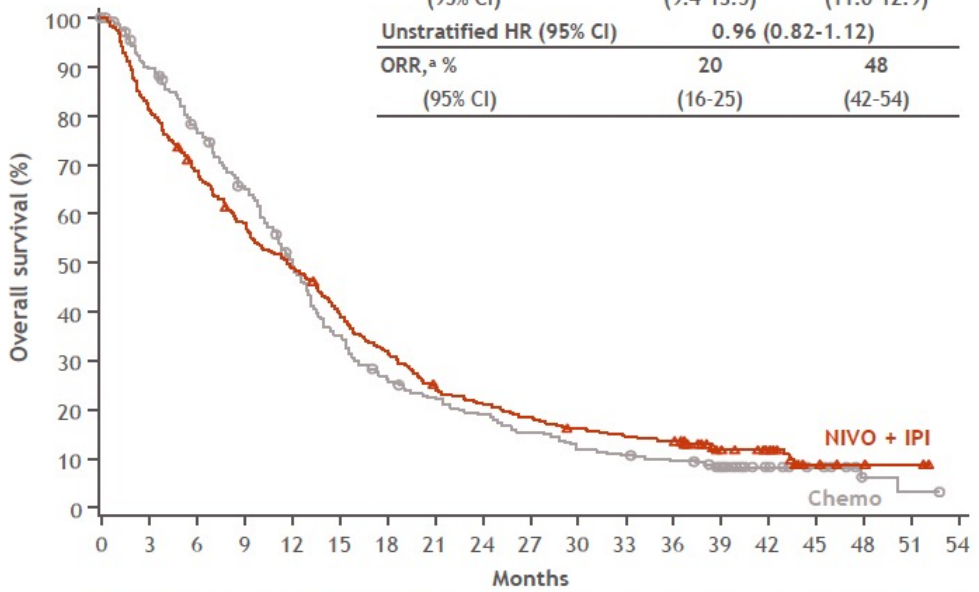


No. at risk

NIVO + IPI	11	9	9	9	9	9	9	7	7	7	7	7	7	4	3	2	1	0	0
Chemo	10	9	7	6	4	4	4	4	3	3	2	1	1	1	1	1	1	1	0

MSS

	NIVO + IPI (n = 355)	Chemo (n = 344)
Median OS, mo	11.6	12.0
(95% CI)	(9.4-13.5)	(11.0-12.9)
Unstratified HR (95% CI)	0.96 (0.82-1.12)	
ORR,[a] %	20	48
(95% CI)	(16-25)	(42-54)



NIVO + IPI	355	286	240	202	170	137	110	83	72	63	54	48	45	25	18	5	3	2	0
Chemo	344	303	257	216	162	116	85	72	61	49	39	34	30	22	14	8	2	1	0

- Longer median OS and higher ORR observed in all randomized patients with MSI-H tumors with NIVO + IPI vs chemo, although sample size was small

[a]Randomized patients who had target lesion measurements at baseline per BICR assessment. Patients with MSI-H: NIVO + IPI, n = 10; chemo, n = 7, patients with MSS: NIVO + IPI, n = 292; chemo, n = 257.

Janjigian YY et al. ESMO 2021;Abstract LBA7.

Summary

- NIVO + chemo continued to demonstrate improvement in OS, PFS, and objective responses vs chemo in previously untreated patients with advanced GC/GEJC/EAC with an additional 12-month follow-up
  - Clinically meaningful long-term OS and PFS benefit with sustained separation of the KM curves
  - Higher ORR and more durable responses
  - Deepening of response with additional complete responses with longer follow-up
- NIVO + IPI did not significantly improve OS vs chemo in patients with PD-L1 CPS ≥ 5
- No new safety signals were identified with NIVO + chemo or NIVO + IPI
- **Longer follow-up data for NIVO + chemo further support its use as a new standard 1L treatment in patients with advanced GC/GEJC/EAC**

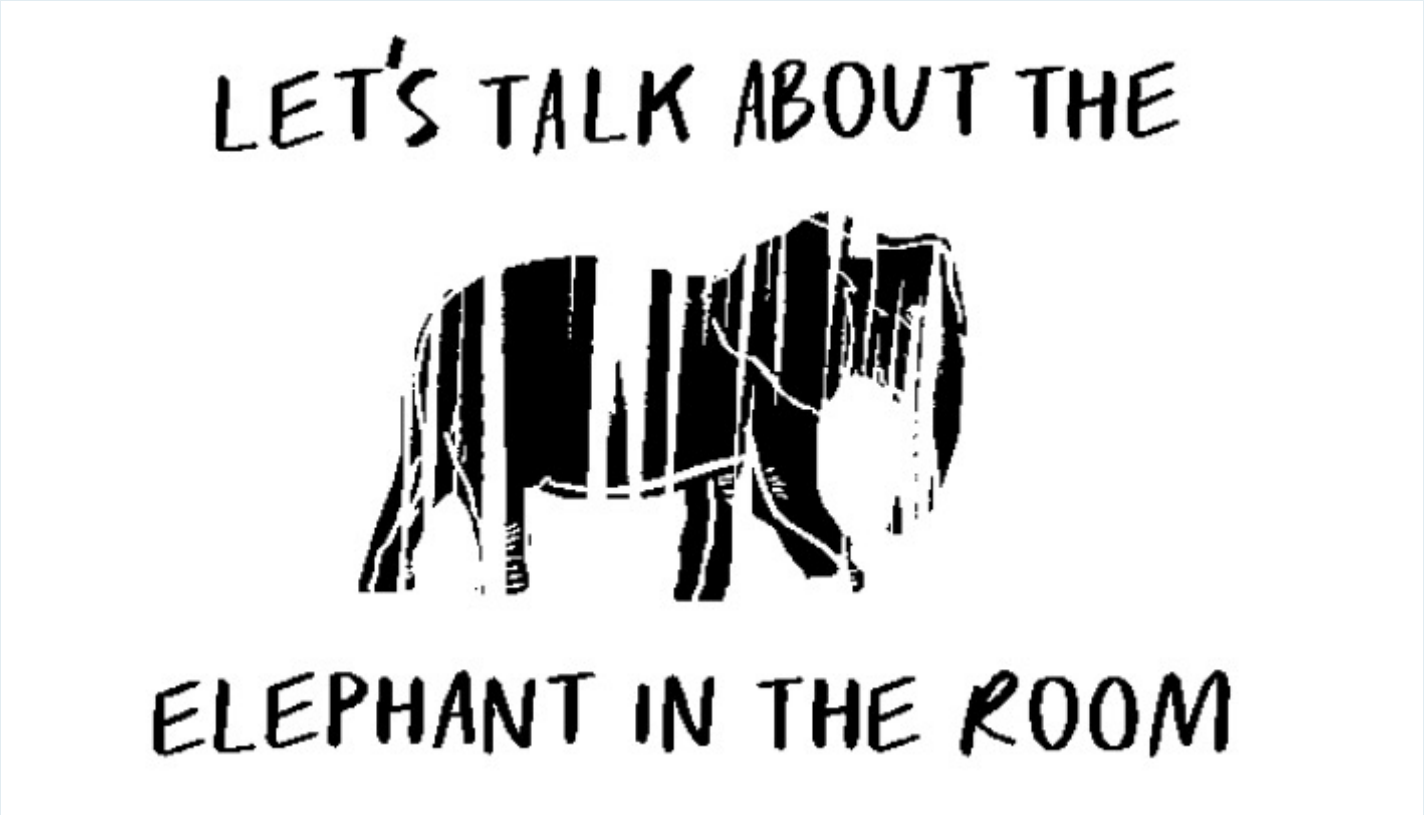
Janjigian YY et al. ESMO 2021;Abstract LBA7.

Take Home Message from CheckMate 649

Nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy should be **new standard of care** for the first-line treatment of patients with HER2-negative **advanced or metastatic gastric, gastro-esophageal junction or esophageal adenocarcinoma** whose tumors express **PD-L1** with a **combined positive score (CPS) ≥ 5**

Lordick F. ESMO 2021;Discussant.

CheckMate 649 – Nivolumab with Ipilimumab



Lordick F. ESMO 2021;Discussant.

Checkmate-649 – Nivolumab plus Ipilimumab in Gastric Ca.

Why did Nivolumab plus Ipilimumab NOT show improved OS over chemotherapy?

- Underpowered?
- Second-line /cross-over effects?
- PD-L1-CPS-based patient selection?
- Treatment tolerabilty?
- Early progression / Early deaths?

Lordick F. ESMO 2021;Discussant.

PD-L1 Expression in Gastric Cancer

Pooled data from clinical studies

Combined positive score (CPS) ≥ 1:
prevalence 57.6% (148 of 257 patients)
enrichment of responses to pembrolizumab (OR, 2.8).

Tumor proportion score (TPS) ≥ 1:
prevalence 12.5% (32 of 257 patients)
minimal enrichment of responses to pembrolizumab (OR, 1.4)

Reproducibility:
interpathologist overall agreement of 96.6%
intrapathologist overall agreement of 97.2%

Lordick F. ESMO 2021;Discussant.

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

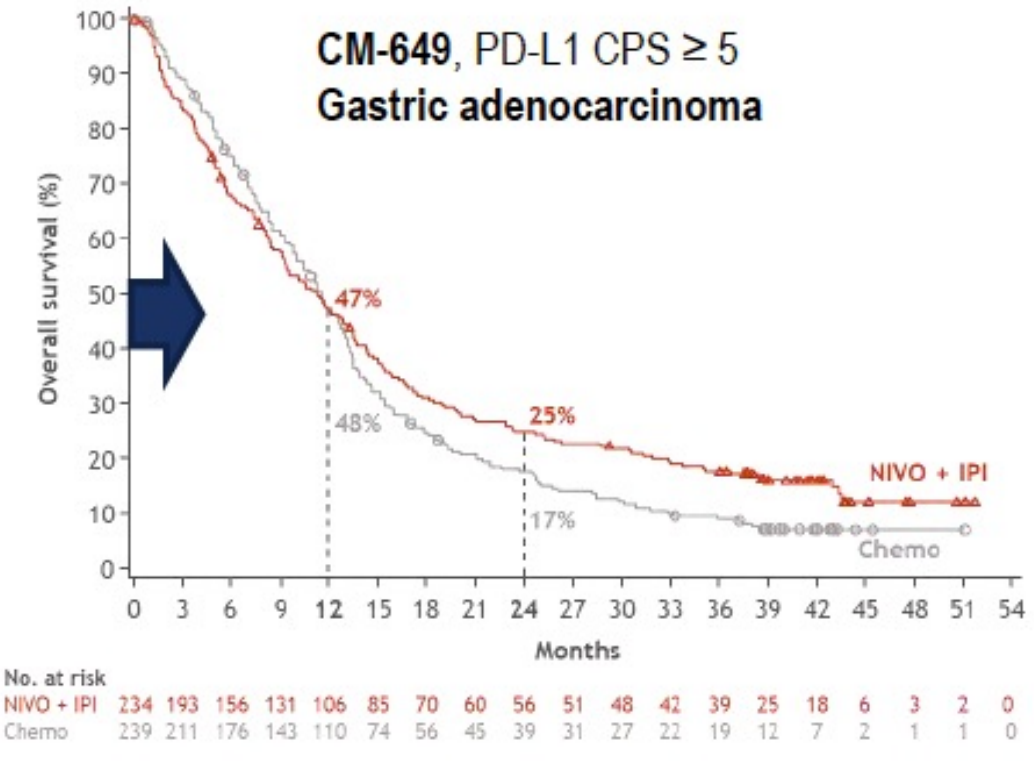
CM-649: Treatment-related Adverse Events

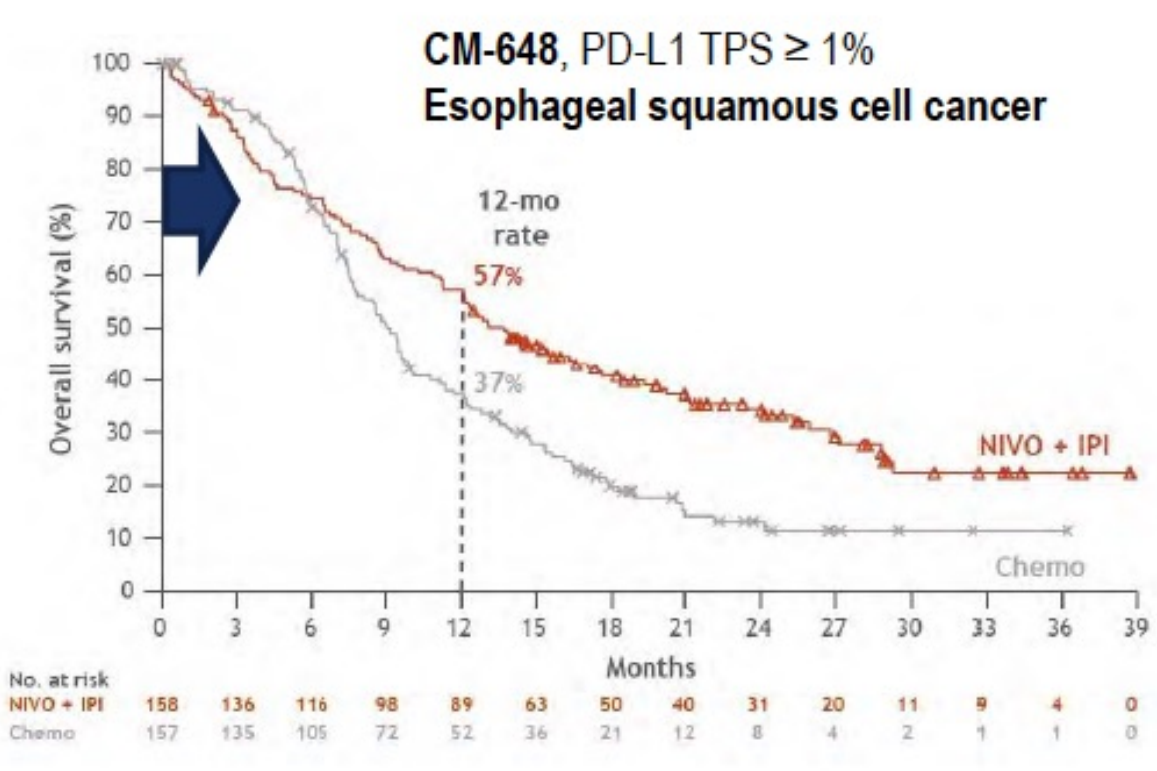
All treated,[a] n (%)	NIVO + chemo (n = 782)[b]		Chemo (n = 767)[b]		NIVO + IPI (n = 403)[c]		Chemo (n = 389)[c]	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAEs[d]	739 (95)	471 (60)	682 (89)	344 (45)	323 (80)	155 (38)	356 (92)	180 (46)
Serious TRAEs[d]	175 (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.

Checkmate-649 – Nivolumab plus Ipilimumab in Gastric Ca.

Early progression / early deaths?

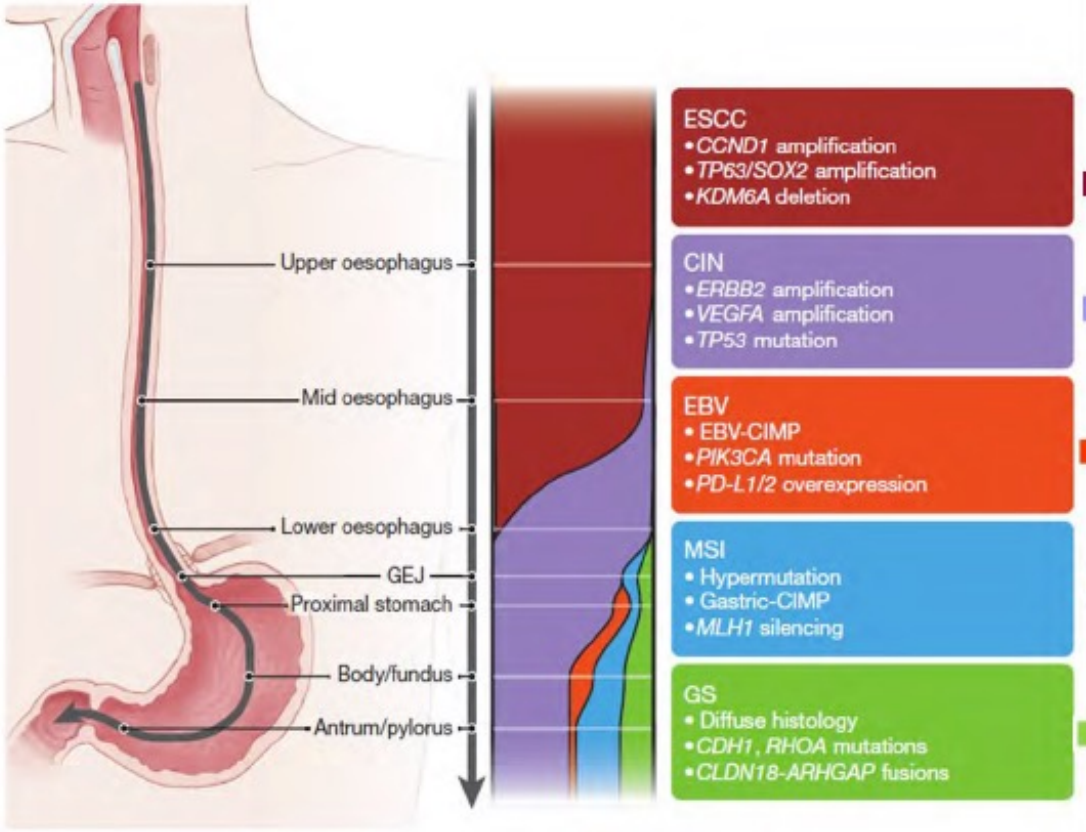




Lordick F. ESMO 2021;Discussant.

RTP RESEARCH TO PRACTICE

Tumor Biology Is Key



ESCC
- *CCND1* amplification
- *TP63/SOX2* amplification
- *KDM6A* deletion

CIN
- *ERBB2* amplification
- *VEGFA* amplification
- *TP53* mutation

EBV
- EBV-CIMP
- *PIK3CA* mutation
- *PD-L1/2* overexpression

MSI
- Hypermutation
- Gastric-CIMP
- *MLH1* silencing

GS
- Diffuse histology
- *CDH1*, *RHOA* mutations
- *CLDN18-ARHGAP* fusions

ESCC - Similarities with Head-Neck Cancer

CIN – Immunogenic ?
HER2 / VEGF amplications

EBV - Immunogenic
Immune infiltrates, PD-L1 high

MSI - Immunogenic
High mutational burden

Genomic stable (silent)
Lower mutational burden

Adopted from: **The Cancer Genome Atlas Research Network**. *Nature*. 2017;541:169-175.

Lordick F. ESMO 2021;Discussant.

RTP RESEARCH TO PRACTICE

Which adjuvant systemic therapy would you currently recommend to a patient with HER2-negative, microsatellite-stable (MSS) squamous cell carcinoma of the esophagus who receives neoadjuvant carboplatin/paclitaxel and concurrent radiation therapy and has residual disease at surgery?

 Dr Enzinger	Nivolumab	 Dr Shah	Nivolumab
 Dr Janjigian	Nivolumab	 Dr Strickler	Nivolumab
 Dr Klempner	Nivolumab	 Dr Yoon	Nivolumab

RTP RESEARCH TO PRACTICE

For a patient with esophageal/gastroesophageal junction (GEJ) cancer to whom you opt to administer adjuvant nivolumab, how long do you continue treatment, assuming the patient is responding and tolerating it well?

 Dr Enzinger	1 year	 Dr Shah	1 year
 Dr Janjigian	1 year	 Dr Strickler	1 year
 Dr Klempner	1 year	 Dr Yoon	1 year

RTP RESEARCH TO PRACTICE

Outside of a clinical trial, have you or would you attempt to access an anti-PD-1/PD-L1 antibody as part of adjuvant therapy for a patient with MSS esophageal cancer who receives neoadjuvant carboplatin/paclitaxel and concurrent radiation therapy and has no evidence of residual disease at surgery?

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

RTP RESEARCH TO PRACTICE

An older, frail patient with MSS esophageal cancer (PD-L1 CPS = 0) who is not a candidate for surgical resection has a good response to definitive chemoradiation therapy. Regulatory and reimbursement issues aside, would you offer an adjuvant anti-PD-1/PD-L1 antibody?

CPS = combined positive score

An older, frail patient with MSS esophageal cancer (PD-L1 CPS = 10) who is not a candidate for surgical resection has a good response to definitive chemoradiation therapy. Regulatory and reimbursement issues aside, would you offer an adjuvant anti-PD-1/PD-L1 antibody?

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 0?

 Dr Enzinger	FOLFOX	 Dr Shah	Chemotherapy
 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 1?

 Dr Enzinger	FOLFOX	 Dr Shah	Chemotherapy
 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

Regulatory and reimbursement issues aside, what would you currently recommend as second-line therapy for a patient with metastatic HER2-negative, MSS adenocarcinoma of the GEJ (PD-L1 CPS ≥5) who has experienced disease progression on first-line FOLFOX/nivolumab or FOLFOX/pembrolizumab?

 Dr Enzinger	Ramucirumab/ paclitaxel	 Dr Shah	Ramucirumab/ paclitaxel
 Dr Janjigian	Ramucirumab/ paclitaxel	 Dr Strickler	Ramucirumab/ paclitaxel
 Dr Klempner	Ramucirumab/ paclitaxel	 Dr Yoon	Ramucirumab/ paclitaxel

RTP RESEARCH TO PRACTICE

Beyond paclitaxel, are there any other chemotherapeutic agents that you are comfortable combining with ramucirumab for your patients with relapsed gastroesophageal cancer?

 Dr Enzinger	FOLFIRI + ramucirumab	 Dr Shah	Irinotecan
 Dr Janjigian	FOLFIRI	 Dr Strickler	No
 Dr Klempner	FOLFIRI	 Dr Yoon	FOLFIRI

RTP RESEARCH TO PRACTICE

Lancet 2021;398:27-40.

First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial

Yelena Y Janjigian, Kohei Shitara*, Markus Moehler, Marcelo Garrido, Pamela Salman, Lin Shen, Lucjan Wyrwicz, Kensei Yamaguchi, Tomasz Skoczylas, Arinilda Campos Bragagnoli, Tianshu Liu, Michael Schenker, Patricio Yanez, Mustapha Tehfe, Ruben Kowalyszyn, Michalis V Karamouzis, Ricardo Bruges, Thomas Zander, Roberto Pazo-Cid, Erika Hitre, Kynan Feeney, James M Cleary, Valerie Poulart, Dana Cullen, Ming Lei, Hong Xiao, Kaoru Kondo, Mingshun Li, Jaffer A Ajani*

ASCO Gastrointestinal Cancers Symposium 2022

Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: expanded analyses from 24-month follow-up of CheckMate 649

Kohei Shitara,[1] Yelena Y. Janjigian,[2] Markus Moehler,[3] Marcelo Garrido,[4] Carlos Gallardo,[5] Lin Shen,[6] Kensei Yamaguchi,[7] Lucjan Wyrwicz,[8] Tomasz Skoczylas,[9] Arinilda Bragagnoli,[10] Tianshu Liu,[11] Mustapha Tehfe,[12] Elena Elimova,[13] Samira Soleymani,[14] Ming Lei,[14] Kaoru Kondo,[14] Mingshun Li,[14] Jaffer A. Ajani[15]

[1]National Cancer Center Hospital East, Kashiwa, Japan; [2]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [3]Johannes-Gutenberg University Clinic, Mainz, Germany; [4]Clinica San Carlos de Apoquindo, Pontificia Universidad Católica, Santiago, Chile; [5]Fundacion Arturo Lopez Perez, Santiago, Chile; [6]Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; [7]Cancer Institute Hospital of JFCR, Tokyo, Japan; [8]Klinika Onkologii i Radioterapii, Narodowy Instytut Onkologii, Warszawa, Poland; [9]II Klinika Chirurgii Ogólnej, Gastroenterologicznej i Nowotworów Układu Pokarmowego, Medical University of Lublin, Lublin, Poland; [10]Fundacao Pio Xii Hosp Cancer De Barretos, Barretos, Brazil; [11]Zhongshan Hospital Fudan University, Shanghai, China; [12]Oncology Center - Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; [13]Princess Margaret Cancer Centre, Toronto, ON, Canada; [14]Bristol Myers Squibb, Princeton, NJ, USA; [15]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract number 240

Nature 2022;603(7903):942-8.

Article

Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer

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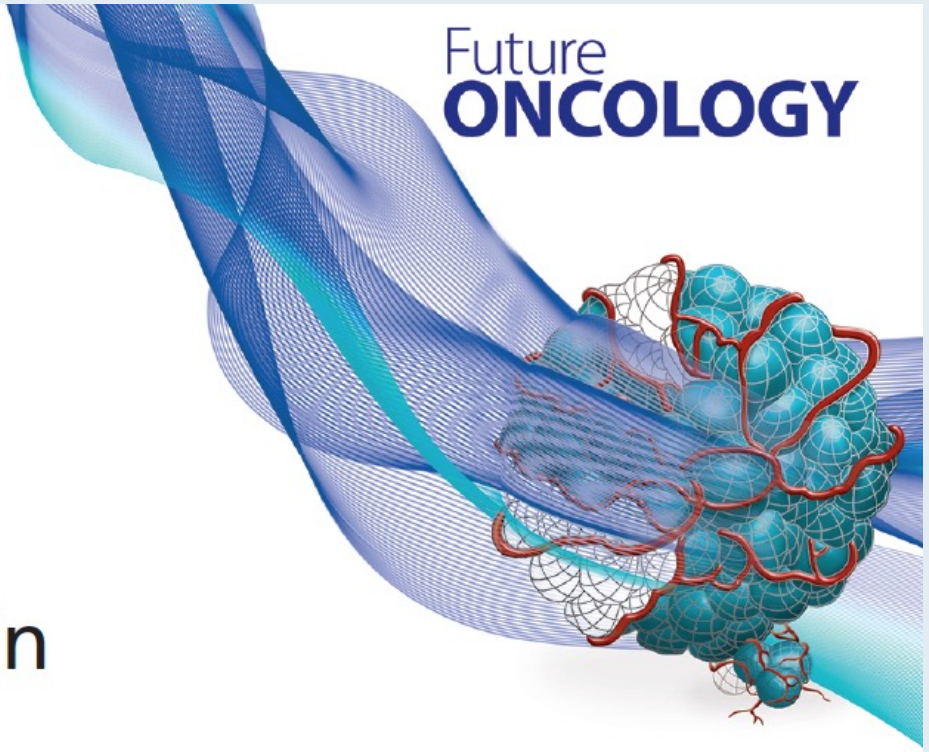
Kohei Shitara[1], Jaffer A. Ajani[2], Markus Moehler[3], Marcelo Garrido[4], Carlos Gallardo[5], Lin Shen[6], Kensei Yamaguchi[7], Lucjan Wyrwicz[8], Tomasz Skoczylas[9], Arinilda Campos Bragagnoli[10], Tianshu Liu[11], Mustapha Tehfe[12], Elena Elimova[13], Ricardo Bruges[14], Thomas Zander[15], Sergio 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]✉

Future Oncol 2021;17(22):2847-55.

Clinical Trial Protocol



KEYNOTE-859: a Phase III study of pembrolizumab plus chemotherapy in gastric/gastroesophageal junction adenocarcinoma

Josep Tabernero*,[1], Yung-Jue Bang[2], Eric Van Cutsem[3], Charles S Fuchs[4], Yelena Yuriy Janjigian[5], Pooja Bhagia[6], Kan Li[6], David Adelberg[6] & Shu Kui Qin[7]

A Randomized Phase 3 Study Evaluating the Efficacy and Safety of First-Line Pembrolizumab plus Lenvatinib plus Chemotherapy versus Chemotherapy in Patients with Advanced/Metastatic Gastroesophageal Adenocarcinoma: LEAP-015

Cohen DJ et al.

Gastrointestinal Cancer Symposium 2022;Abstract TPS369

2021 ESMO congress

Mini Oral Discussion: LBA52, LBA53, LBA 54, and LBA55

Yelena Y. Janjigian, MD
Associate Attending Physician, Associate Professor, WCMC

Chief, Gastrointestinal Oncology
Memorial Sloan Kettering Cancer Center

Immunotherapy in EG adenocarcinoma

- Nivolumab with chemotherapy approved in the United States for 1st-line treament irrespective of PD-L1 status[1]
- Pembrolizumab, trastuzumab, and chemotherapy approved in the United States for HER2-positive disease[2]
- Nivolumab approved in Asia irrespective of PD-L1 status for ≥ 3rd-line treament[3]
- Pembrolizumab approval for ≥ 3rd-line treatment in the United States to be withdrawn (announced in July 2021)[4]
- Pembrolizumab approved in TMB ≥ 10 mut/Mb (United States) or MSI-H tumors (United States and Japan)[2,5]

1. OPDIVO (nivolumab) [package insert]. Princeton, NJ: Bristol Myers Squibb; 2021. 2. KEYTRUDA (pembrolizumab) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2021. 3. Högner A, Thuss-Patience P. *Pharmaceuticals (Basel)*. 2021;14:151. 4. Merck (press release, July 1, 2021). Accessed July 20, 2021. 5. Merck (press release, August 24, 2020). Accessed July 20, 2021.

Janjigian YY. ESMO 2021 Discussant for LBA52, LBA53, LBA54 and LBA55.

Immunotherapy in EG adenocarcinoma

	Keynote 62	Checkmate 649	Orient 16
Design	Chemo/PD-1 vs chemo PD-1 vs chemo	Chemo/PD-1 vs chemo	Chemo/PD-1 vs chemo
Major enrollment	US/ Europe/ Australia 58%	US 17%, Asia 23%, rest 60%	China
CPS ≥ 5	NA (37% CPS ≥ 10)	60%	62%
OS HR ITT; CPS ≥ 5; CPS ,<5	NA; CPS ≥1 0.85*; NA; NA and 0.91; NA;NA	0.80; 0.71; 0.94	0.76; 0.66; NA
ITT PFS	0.84* and 1.66*	0.77	0.63
ITT ORR	49% vs 37% and 15% vs 37%	58% vs 46%	58%/vs 48%
Grade 3-5 AEs	73% vs 69% and 17% vs 69%	60% vs 44%	60% vs 52%

Shitara K et al. JAMA Oncol, 2020.; Janjigian Y et al. Lancet, 2021. Xuet al. ESMO 2021, LBA53.

Janjigian YY. ESMO 2021 Discussant for LBA52, LBA53, LBA54 and LBA55.

Research

JAMA Oncology | Original Investigation

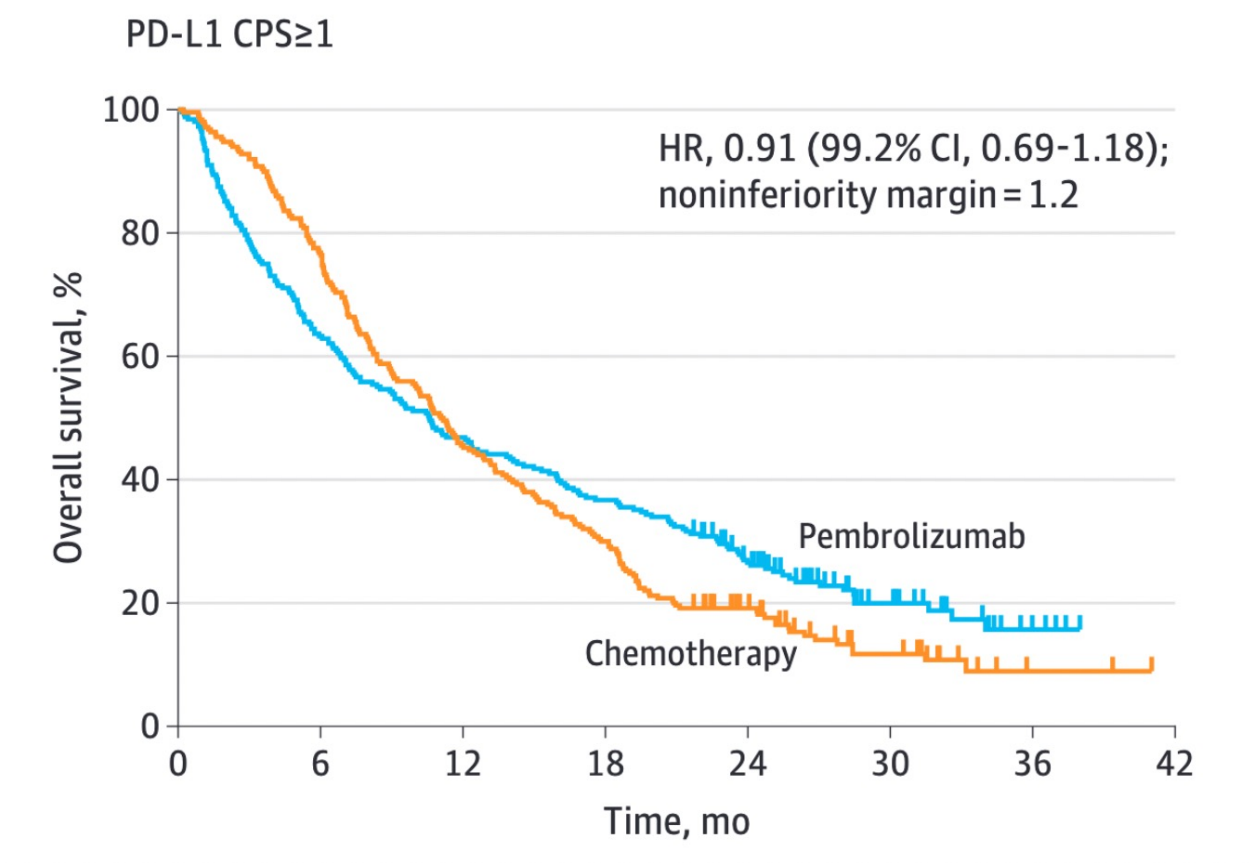
Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer

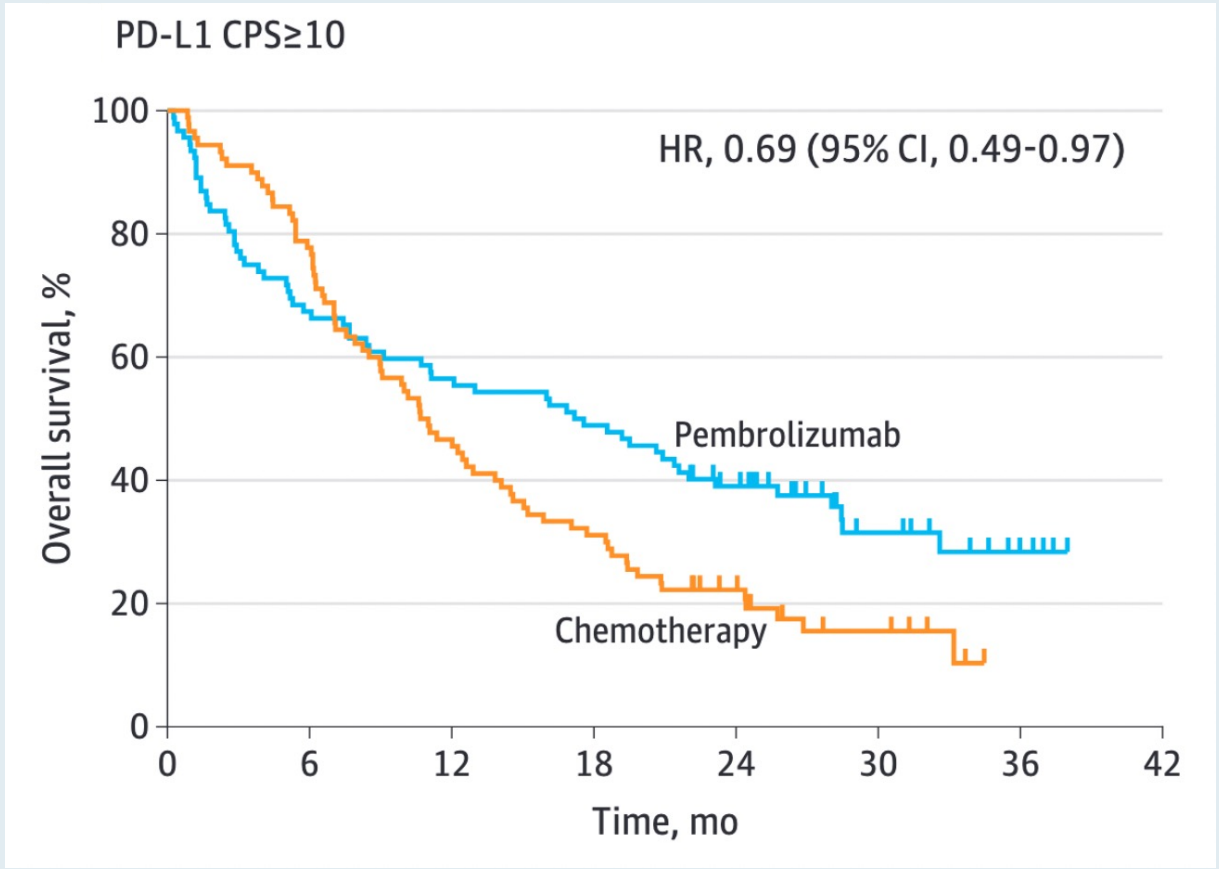
The KEYNOTE-062 Phase 3 Randomized Clinical Trial

Kohei Shitara, MD; Eric Van Cutsem, MD; Yung-Jue Bang, MD; Charles Fuchs, MD; Lucjan Wyrwicz, MD; Keun-Wook Lee, MD; Iveta Kudaba, MD; Marcelo Garrido, MD; Hyun Cheol Chung, MD; Jeeyun Lee, PhD; Hugo Raul Castro, MD; Wasat Mansoor, MD; Maria Ignez Braghiroli, MD; Nina Karaseva, MD; Christian Caglevic, MD; Luis Villanueva, MD; Eray Goekkurt, MD; Hironaga Satake, MD; Peter Enzinger, MD; Maria Alsina, MD; Al Benson, MD; Joseph Chao, MD; Andrew H. Ko, MD; Zev A. Wainberg, MD; Uma Kher, MS; Sukrut Shah, PhD; S. Peter Kang, MD; Josep Tabernero, MD, PhD, MSc

2020; 6(10):1571–1580.

KEYNOTE 062: Pembrolizumab Monotherapy

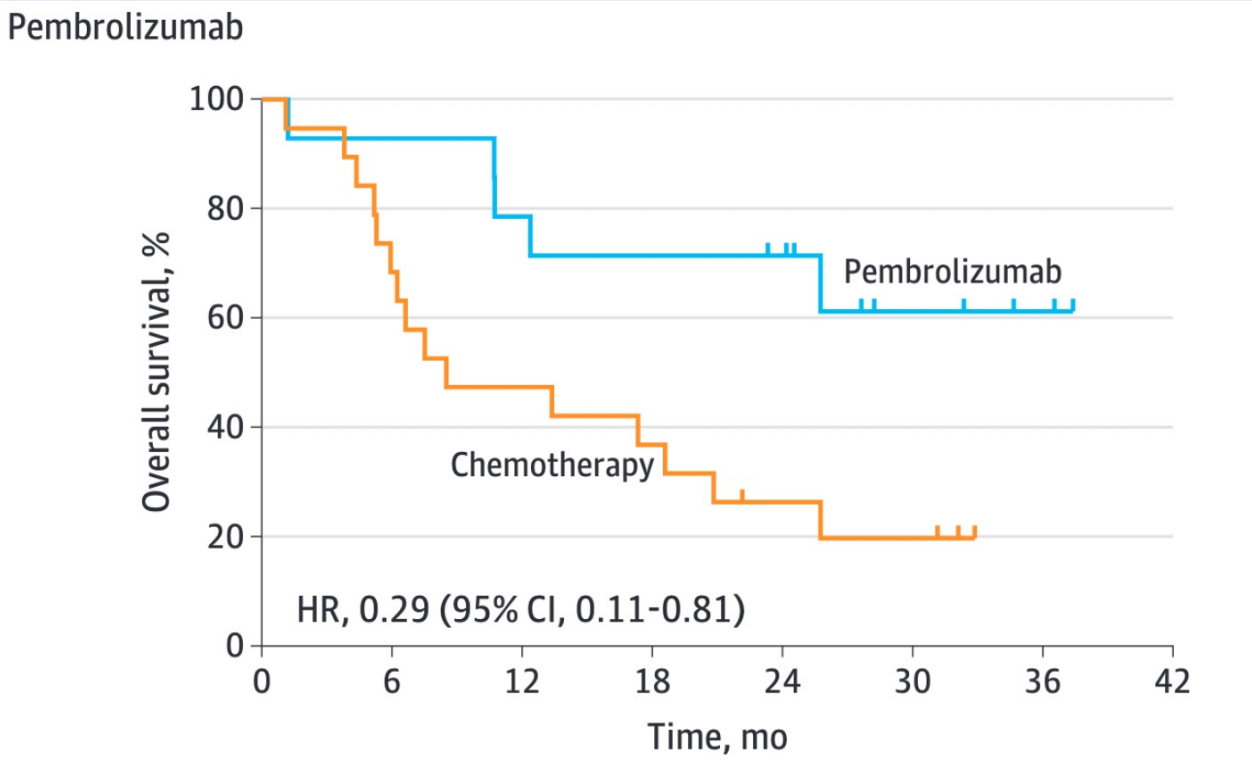


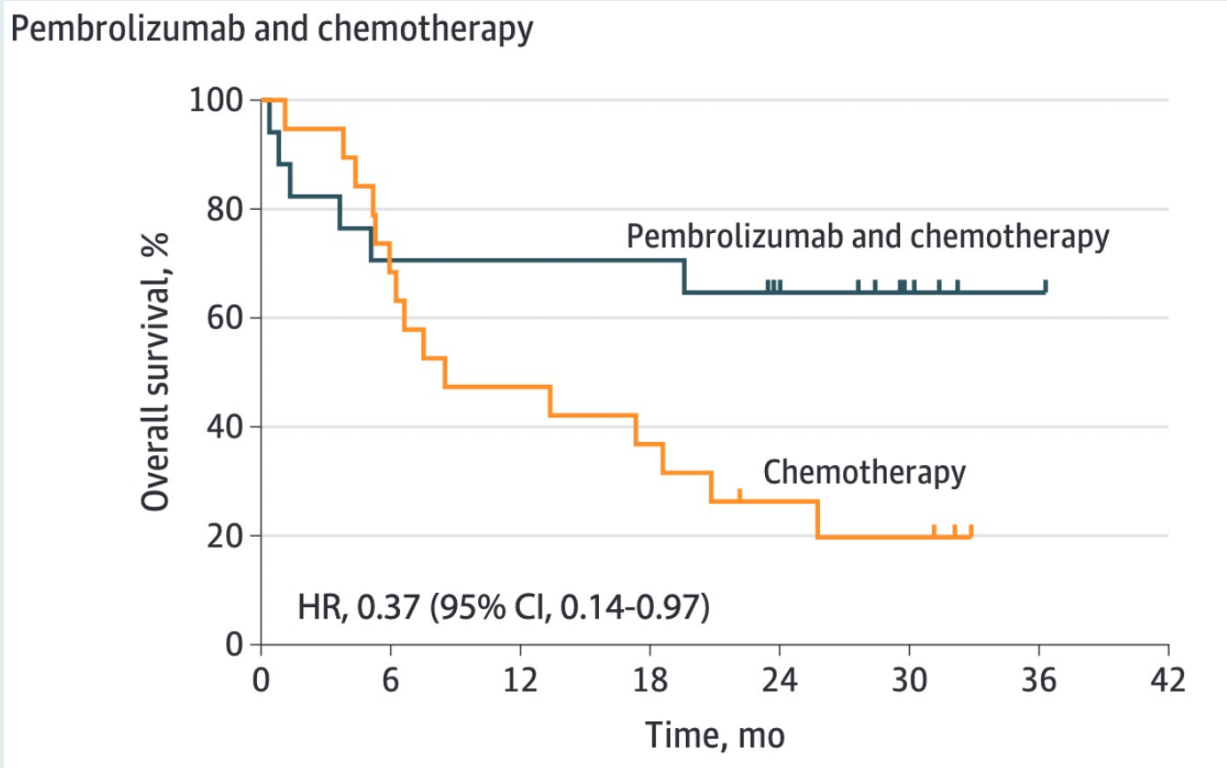


Shitara K et al. *JAMA Oncol.* 2020;6(10):1571-80.

RTP RESEARCH TO PRACTICE

KEYNOTE 062: Overall Survival in MSI-H, CPS ≥1





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

RTP RESEARCH TO PRACTICE

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

European Journal of Cancer 165 (2022) 48–57

Available online at www.sciencedirect.com

ScienceDirect

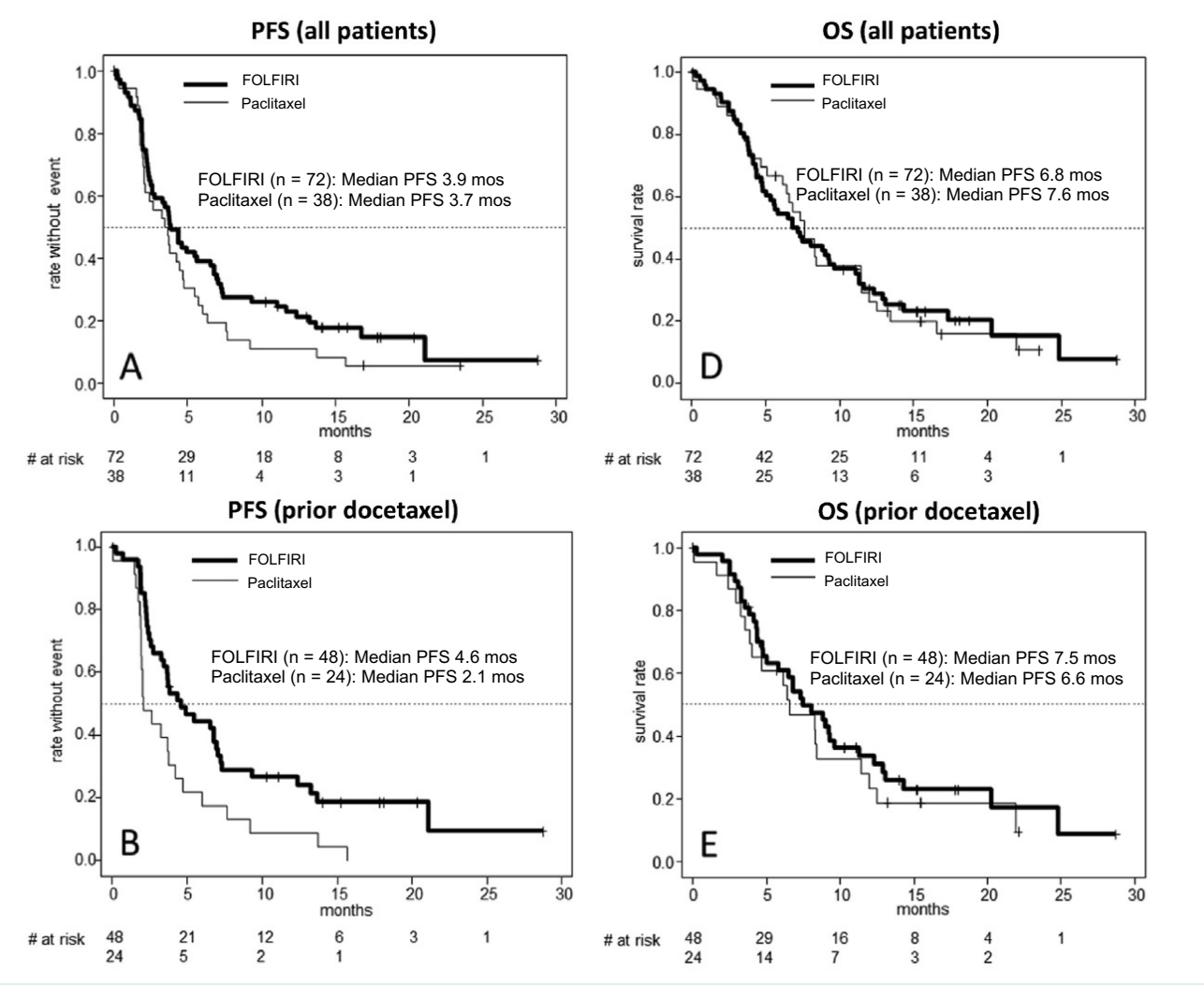
journal homepage: www.ejcancer.com

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.

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

Al-Batran SE et al.

ASCO 2022;Abstract 4003

Primary Track: Gastrointestinal Cancer—Gastroesophageal, Pancreatic, and Hepatobiliary
Oral Session: June 5, 2022, 9:12 AM

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

The Role of the TP53 Pathway in Predicting Response to Neoadjuvant Therapy in Esophageal Adenocarcinoma

Smita Sihag[1], Samuel C. Nussenzweig[1], Henry S. Walch[2], Meier Hsu[3], Kay See Tan[3], Sergio De La Torre[1], Yelena Y. Janjigian[4], Steven B. Maron[4], Geoffrey Y. Ku[4], Laura H. Tang[5], Pari M. Shah[4], Abraham Wu[6], David R. Jones[1], David B. Solit[2], Nikolaus Schultz[2], Karuna Ganesh[4], Michael F. Berger[2], and Daniela Molena[1]

Published online ahead of print 2022; CCR-21-4016.

Meet The Professor with Dr Janjigian

Introduction

MODULE 1: HER2-Negative Gastroesophageal Cancers

MODULE 2: HER2-Positive Gastroesophageal Cancers

- Dr Kaur: A 66-year-old woman with metastatic esophageal adenocarcinoma – PD-L1 CPS 5, HER2 amplification
- Dr Morganstein: A 62-year-old man with HER2-positive metastatic gastric cancer
- Dr Markowski: A 62-year-old man with diffuse metastatic HER2-positive esophageal adenocarcinoma

MODULE 3: Journal Club with Dr Janjigian

MODULE 4: Appendix of Key Publications

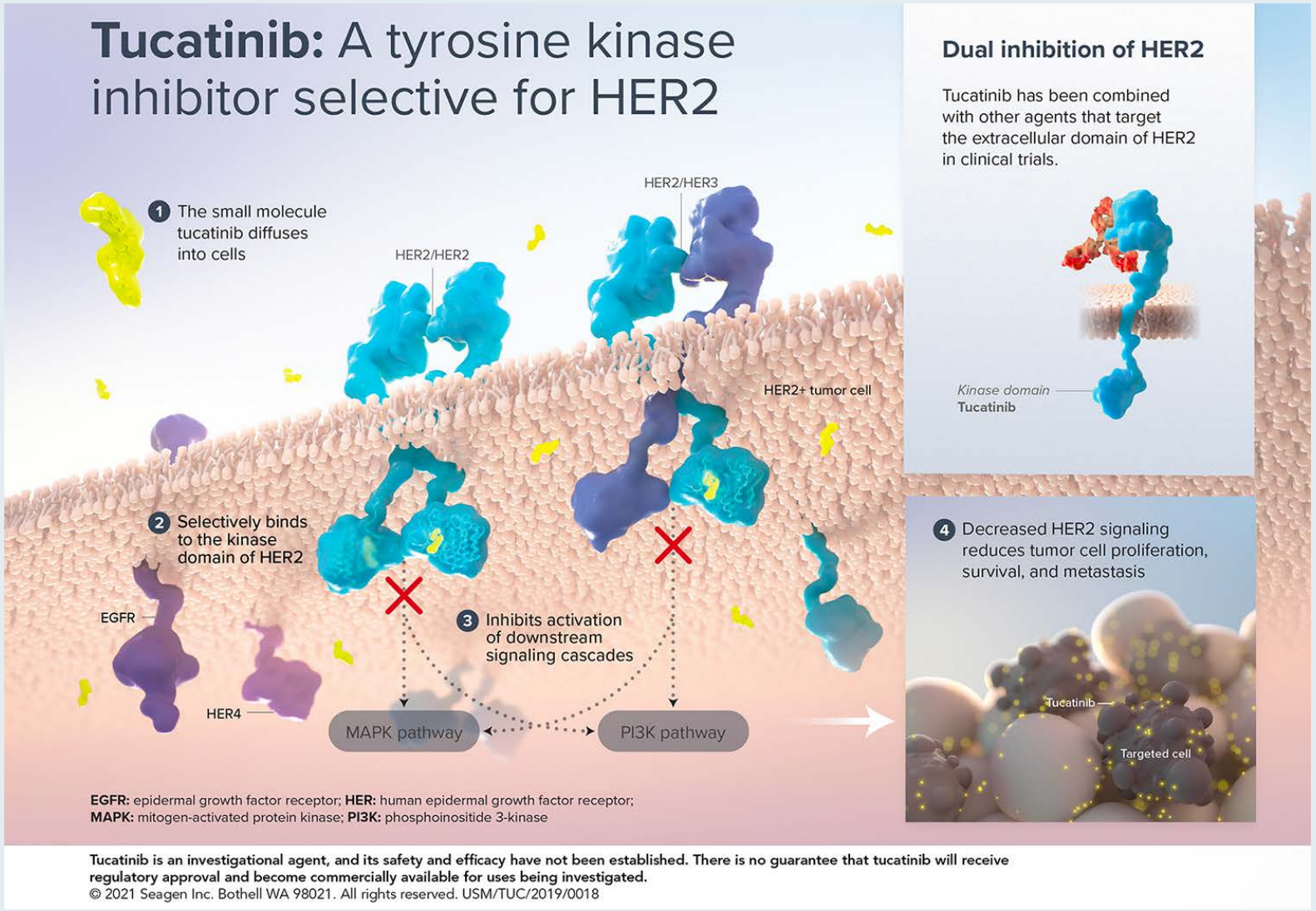
RTP RESEARCH TO PRACTICE

MOUNTAINEER-02: Phase II/III Study of Tucatinib, Trastuzumab, Ramucirumab, and Paclitaxel in Previously Treated HER2+ Gastric or Gastroesophageal Junction Adenocarcinoma (GEC): Trial in Progress

Catenacci DV et al.

ESMO 2021;Abstract 1434TiP

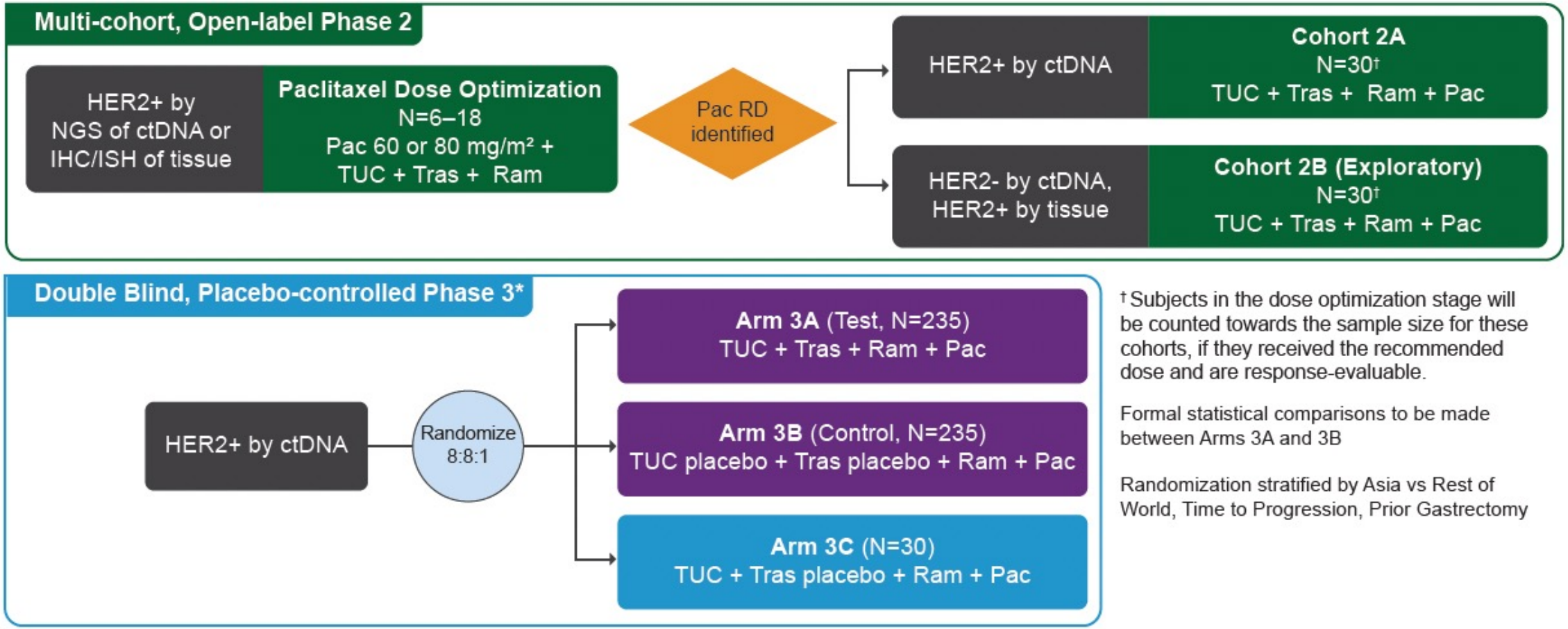
Tucatinib Proposed Mechanism of Action



Tucatinib is an investigational agent, and its safety and efficacy have not been established. There is no guarantee that tucatinib will receive regulatory approval and become commercially available for uses being investigated.

Catenacci DV et al. ESMO 2021;Abstract 1434TiP.

MOUNTAINEER-02 Phase II/III Study Design



† Subjects in the dose optimization stage will be counted towards the sample size for these cohorts, if they received the recommended dose and are response-evaluable.

Formal statistical comparisons to be made between Arms 3A and 3B

Randomization stratified by Asia vs Rest of World, Time to Progression, Prior Gastrectomy

* The SMC may recommend proceeding to phase 3 if the regimen is safe and tolerable and an ORR ≥36% is observed in all response-evaluable patients treated at the Pac RD who have HER2+ disease by NGS assay of ctDNA.

Catenacci DV et al. ESMO 2021;Abstract 1434TiP.

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

1. FOLFOX/trastuzumab
2. Trastuzumab/chemotherapy/anti-PD-1/PD-L1 antibody
3. Trastuzumab/nivolumab + ipilimumab
4. Trastuzumab deruxtecan
5. Anti-PD-1/PD-L1 antibody/chemotherapy
6. Nivolumab + ipilimumab
7. Anti-PD-1/PD-L1 antibody monotherapy
8. Other

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

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, PD-L1-positive (CPS >1), MSS gastric adenocarcinoma?

1. FOLFOX/trastuzumab
2. Trastuzumab/chemotherapy/anti-PD-1/PD-L1 antibody
3. Trastuzumab/nivolumab + ipilimumab
4. Trastuzumab deruxtecan
5. Anti-PD-1/PD-L1 antibody/chemotherapy
6. Nivolumab + ipilimumab
7. Anti-PD-1/PD-L1 antibody monotherapy
8. Other

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

RTP RESEARCH TO PRACTICE

Case Presentation: A 66-year-old woman with metastatic esophageal adenocarcinoma – PD-L1 CPS 5, HER2 amplification

Dr Gurveen Kaur (Wheeling, West Virginia)

RTP RESEARCH TO PRACTICE

Case Presentation: A 62-year-old man with HER2-positive metastatic gastric cancer

Dr Neil Morganstein (Summit, New Jersey)

Case Presentation: A 62-year-old man with diffuse metastatic HER2-positive esophageal adenocarcinoma and high PD-L1 CPS

Dr Paul Markowski (Summit, New Jersey)

RTP RESEARCH TO PRACTICE

Have you or would you administer HER2-targeted therapy as a component of (neo)adjuvant therapy to a patient with HER2-positive gastric/GEJ adenocarcinoma outside of a clinical trial?

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

RTP RESEARCH TO PRACTICE

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

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

RTP RESEARCH TO PRACTICE

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

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

RTP RESEARCH TO PRACTICE

Have any of your patients receiving trastuzumab deruxtecan for advanced gastric/GEJ adenocarcinoma developed interstitial lung disease (ILD)?

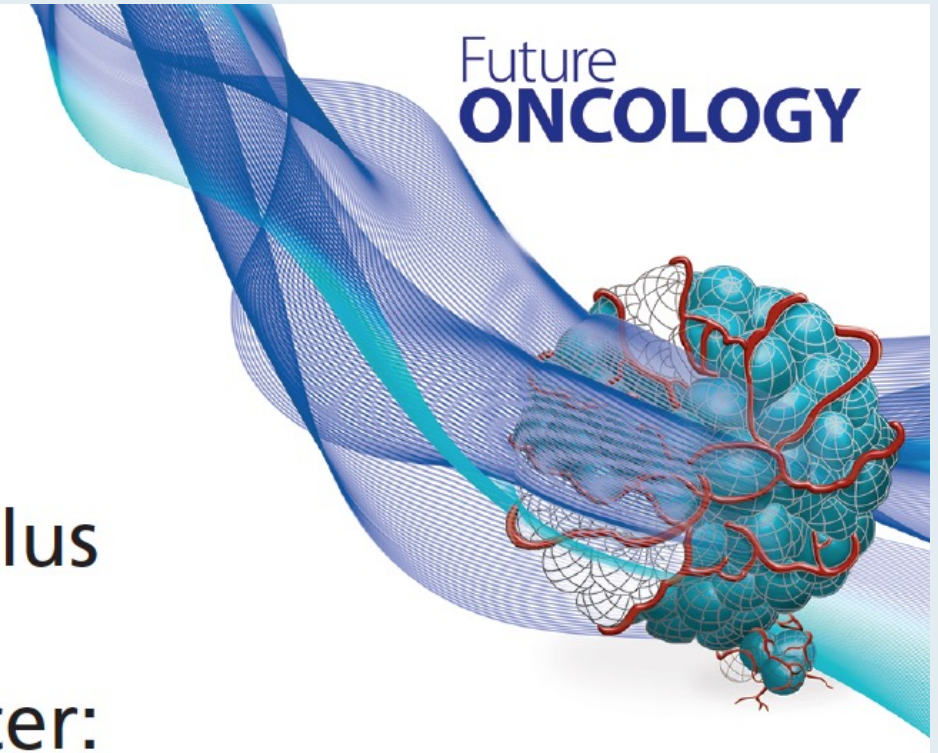
 Dr Enzinger	Yes	 Dr Shah	No
 Dr Janjigian	Yes	 Dr Strickler	No
 Dr Klempner	No	 Dr Yoon	No

RTP RESEARCH TO PRACTICE

Clinical Trial Protocol

For reprint orders, please contact: reprints@futuremedicine.com

***Future Oncol* 2021;17(5):491-501.**



First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer: KEYNOTE-811

Hyun Cheol Chung*,[1], Yung-Jue Bang[2], Charles S Fuchs[3], Shu-Kui Qin[4], Taroh Satoh[5], Kohei Shitara[6], Josep Tabernero[7], Eric van Cutsem[8], Maria Alsina[7], Zhu Alexander Cao[9], Jia Lu[9], Pooja Bhagia[9], Chie-Schin Shih[9] & Yelena Y Janjigian[10]

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

Article

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

https://doi.org/10.1038/s41586-021-04161-3

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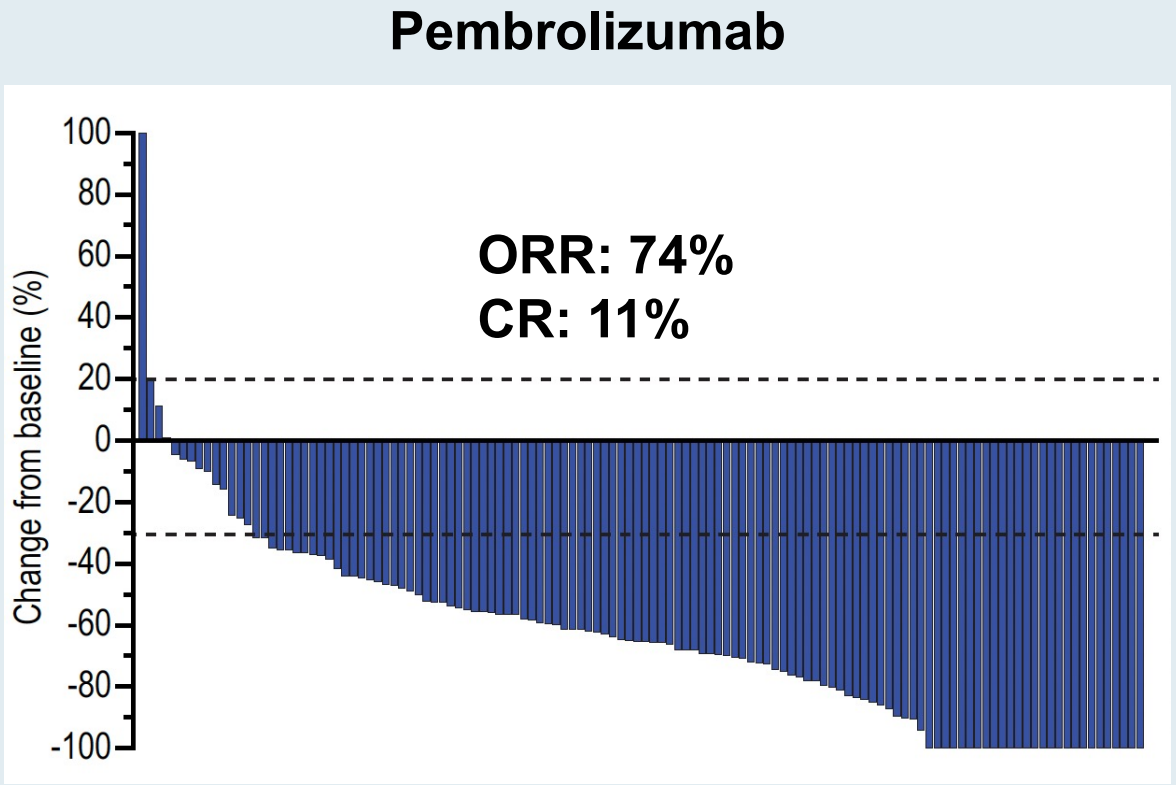
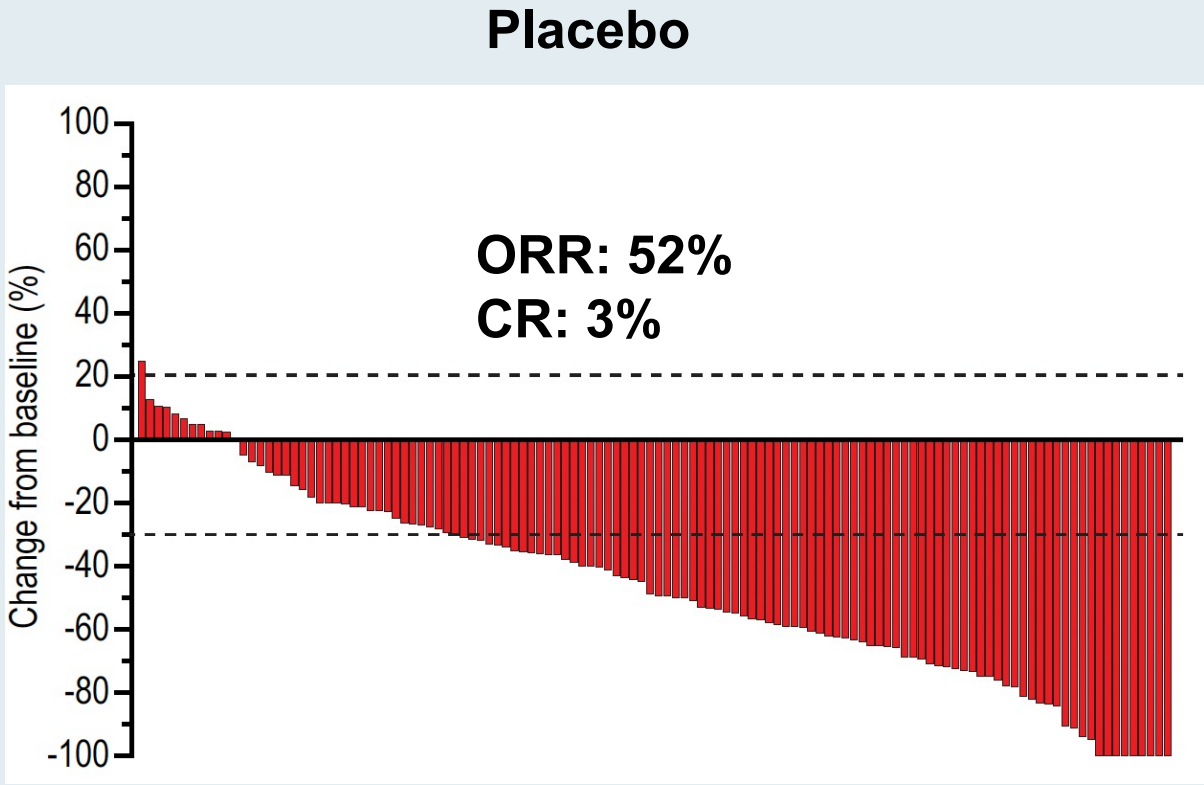
Yelena Y. Janjigian[1]✉, Akihito Kawazoe[2], Patricio Yañez[3], Ning Li[4], Sara Lonardi[5], Oleksii Kolesnik[6], Olga Barajas[7], Yuxian Bai[8], Lin Shen[9], Yong Tang[10], Lucjan S. Wyrwicz[11], Jianming Xu[12], Kohei Shitara[2], Shukui Qin[13], Eric Van Cutsem[14], Josep Tabernero[15], Lie Li[16], Sukrut Shah[16], Pooja Bhagia[16] & Hyun Cheol Chung[17]

KEYNOTE-811: Overall Response Rate (ORR)





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

2021 ESMO congress

Mini Oral Discussion: LBA52, LBA53, LBA 54, and LBA55

Yelena Y. Janjigian, MD
Associate Attending Physician, Associate Professor, WCMC

Chief, Gastrointestinal Oncology
Memorial Sloan Kettering Cancer Center

HER2 inhibition in EG adenocarcinoma

- Up to 20-30% HER2+ positive
- First-line trastuzumab/chemotherapy FDA approved mOS 13.8mos ORR 47%
- 30% of GEJ HER2+ tumors with co-alterations of the RTK/RAS/PI3K pathway– intrinsic resistance
- HER2 inhibition alone in 1st line insufficient to overcome intrinsic resistance- several negative studies (LOGIC, JACOB, HELOISE)
- Pembrolizumab/Trastuzumab/chemotherapy FDA approved in 1st line
- Trastuzumab deruxtecan (T-DXd) is FDA approved after trastuzumab failure based on Destiny Gastric 01

Bang Y et al. *Lancet*. 2010;376:687-697 ; Janjigian YY et al. *Cancer Discov*. 2018;8:49-58.*Hecht JR et al. J Clin Oncol, 2016. Tabernero J et al. Lancet Oncol, 2018. Shah MA et al. J Clin Oncol, 2017; Janjigian et al, ASCO 2021; Shitara et al. NEJM 2020*

Janjigian YY. ESMO 2021 Discussant for LBA52, LBA53, LBA54 and LBA55.

2021 ESMO congress

LBA54

Ipilimumab or FOLFOX in combination with Nivolumab and Trastuzumab in previously untreated HER2 positive Esophago Gastric Adenocarcinoma – the randomized AIO INTEGA trial.

Alexander Stein

Hematology-Oncology Practice Hamburg-Eppendorf

University Cancer Center Hamburg

Janjigian YY. ESMO 2021 Discussant for LBA52, LBA53, LBA54 and LBA55.

JC JOURNAL CLUB

RTP RESEARCH TO PRACTICE

AIO-Intega notable facts

- Relatively large phase II (n=82) with translation research
- Chemotherapy free arm nivo1/ipi3/trastuzumab
- Patients enrolled irrespective PDL1 status; PDL1 is not predictive
- Trast/Nivo/FOLFOX ORR 56% (74% in Phase III w/ pembro/traz/chemo))
- ctDNA decline after 1st cycle predictive of outcome mOS 8.5 vs. 31.2 months
- Grade ≥ 3 TRAE higher with chemo by 20% , QOL favored the chemotherapy arm likely due to better efficacy

	PEMBRO + trastuzumab + capecitabine + oxaliplatin
ORR, n (%; 95% CI)[a]	32 (91; 78-97)
Best response, n (%)[a] CR PR SD PD	 6 (17) 26 (74) 3 (8) 0
Disease control rate, %	100
Median PFS, months 6-month rate, %	13.0 75
Median OS, months 12-month rate, %	27.3 80

[a]Among patients with evaluable disease (n = 35).
Janjigian YY et al. *Lancet Oncol*. 2020;21:821-831.

	All (n=88) ITT AIO-Intega	
	Trast/Nivo/ Ipi	Trast/Nivo/FOLFOX
ORR	32%	56%
mPFS	3.2 mo	10.7 mo
PFSR@12	15%	37%
mDOR	5.8 mo	9.2 mo
mOS	16.4 mo	21.8 mo
OSR@12	57%	70%

Janjigian YY. ESMO 2021 Discussant for LBA52, LBA53, LBA54 and LBA55.

2021 ESMO congress

LBA55

Primary Analysis of a Phase 2, Open-Label, Single Arm Trial of Trastuzumab Deruxtecan in Western Patients With HER2-Positive Unresectable or Metastatic Gastric or Gastroesophageal Junction Cancer 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

Janjigian YY. ESMO 2021 Discussant for LBA52, LBA53, LBA54 and LBA55.

JC JOURNAL CLUB

RTP RESEARCH TO PRACTICE

Conclusions: HER2 in EG adenocarcinoma

- First-line trastuzumab/anti-PD1/chemotherapy important option
  - CTLA4 blockade w/ dual HER2/PD-1 inhibition not enough
- Second-line HER2 remains a viable therapeutic target
  - T-Dxd has similar ORR in 2nd Western patients (despite mandatory biopsies) and ≥3rd line Eastern patients
  - Co-occurring activation in GEJ/E CIN tumors likely driving the resistance

Janjigian YY. ESMO 2021 Discussant for LBA52, LBA53, LBA54 and LBA55.

Dose-Escalation and Dose-Expansion Study of Trastuzumab Deruxtecan (T-DXd) Monotherapy and Combinations in Patients (pts) with Advanced/Metastatic HER2+ Gastric Cancer (GC)/Gastroesophageal Junction Adenocarcinoma (GEJA): DESTINY-Gastric03

Janjigian YY et al.

Gastrointestinal Cancer Symposium 2022;Abstract 295

The First Report of K-Umbrella Gastric Cancer Study: An Open Label, Multi-Center, Randomized, Biomarker-Integrated Trial for Second-Line Treatment of Advanced Gastric Cancer (AGC)

Rha SY et al.

ASCO 2022;Abstract 4001

Primary Track: Gastrointestinal Cancer—Gastroesophageal, Pancreatic, and Hepatobiliary
Oral Session: June 5, 2022, 9:00 AM

Meet The Professor with Dr Janjigian

Journal of Geriatric Oncology 13 (2022) 100–103

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

A nutritional management algorithm in older patients with locally advanced esophageal cancer

Ryan H. Moy [a], Shalom Sabwa [a], Steven B. Maron [a], Marina Shcherba [a], Arlyn Apollo [a], Yelena Y. Janjigian [a], Geoffrey Y. Ku [a], William P. Tew [b], Abraham J. Wu [c], David R. Jones [d], Daniela Molena [d], David H. Ilson [a], Elizabeth Won [a,*]

GENERAL THORACIC SURGERY: *Ann Thorac Surg* 2021;112(6):1775-81.

The Annals of Thoracic Surgery CME Program is located online at http://www.annalsthoracicsurgery.org/cme/home. To take the CME activity related to this article, you must have either an STS member or an individual non-member subscription to the journal.

Oligometastases After Curative Esophagectomy Are Not One Size Fits All

Tamar B. Nobel, MD, Smita Sihag, MD, Xin Xing, BA, Mahmoud Eljalby, BA, Meier Hsu, MS, Kay See Tan, PhD, David B. Sewell, MA, Manjit S. Bains, MD, Yelena Janjigian, MD, Abraham Wu, MD, Geoffrey Ku, MD, David R. Jones, MD, and Daniela Molena, MD

JCO Clin Cancer Inform 2021;5:221-30.

review articles

SPECIAL SERIES: CANCER CLASSIFICATION SYSTEMS

OncoTree: A Cancer Classification System for Precision Oncology

Ritika Kundra, MS[1]; Hongxin Zhang, MS[1]; Robert Sheridan, MS[1]; Sahussapont Joseph Sirintrapun, MD[2]; Avery Wang, MS[1]; Angelica Ochoa, MS[1]; Manda Wilson, MS[1]; Benjamin Gross, MS[1]; Yichao Sun, MS[1]; Ramyasree Madupuri, MS[1]; Baby A. Satravada, MS[1]; Dalicia Reales, MPH[3]; Efsevia Vakiani, MD, PhD[1]; Hikmat A. Al-Ahmadie, MD[2]; Ahmet Dogan, MD, PhD[2]; Maria Arcila, MD[4]; Ahmet Zehir, PhD[2]; Steven Maron, MD, MSc[5]; Michael F. Berger, PhD[6,1,2]; Cristina Viaplana, MS[7]; Katherine Janeway, MD, MMSc[8]; Matthew Ducar, MS[9]; Lynette Sholl, MD[10,11]; Snjezana Dogan, MD[2]; Philippe Bedard, MD[12,13]; Lea F. Surrey, MD[14,15]; Iker Huerga Sanchez, MS[16]; Aijaz Syed, MS[2]; Anoop Balakrishnan Rema, MS[2]; Debyani Chakravarty, PhD[1]; Sarah Suehnholz, PhD[1]; Moriah Nissan, PhD[1]; Gopakumar V. Iyer, MD[5]; Rajmohan Murali, MD[2]; Nancy Bouvier, BA[17]; Robert A. Soslow, MD[2]; David Hyman, MD[18]; Anas Younes, MD[19]; Andrew Intlekofer, MD, PhD[6]; James J. Harding, MD[5,20]; Richard D. Carvajal, MD[21]; Paul J. Sabbatini, MD[5,20]; Ghassan K. Abou-Alfa, MD[5]; Luc Morris, MD, MSc[6,22,23]; Yelena Y. Janjigian, MD[5]; Meighan M. Gallagher, MPH[24]; Tara A. Soumerai, MD[25]; Ingo K. Mellinghoff, MD[5,6]; Abraham A. Hakimi, MD[26]; Matthew Fury, MD[27]; Jason T. Huse, MD, PhD[28]; Aditya Bagrodia, MD[29]; Meera Hameed, MD[2]; Stacy Thomas, MS[30]; Stuart Gardos, BA[30]; Ethan Cerami, PhD[31]; Tali Mazor, PhD[32]; Priti Kumari, MS[32]; Pichai Raman, PhD[33]; Priyanka Shivdasani, MS[34]; Suzanne MacFarland, MD[35,36]; Scott Newman, PhD[37]; Angela Waanders, MD, MPH[38]; Jianjiong Gao, PhD[1]; David Solit, MD[1,5,6,20]; and Nikolaus Schultz, PhD[1,6,39]

Meet The Professor with Dr Janjigian

Introduction

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RTP
RESEARCH
TO PRACTICE

HER2-Negative Gastroesophageal Cancers

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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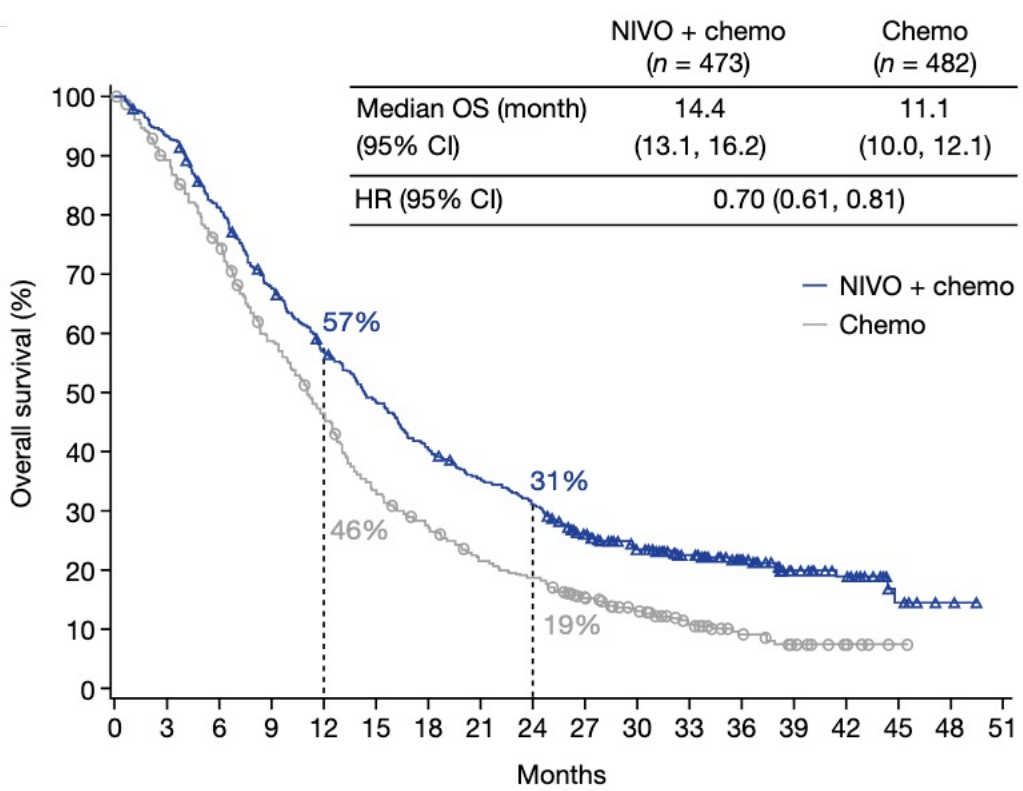
Open access

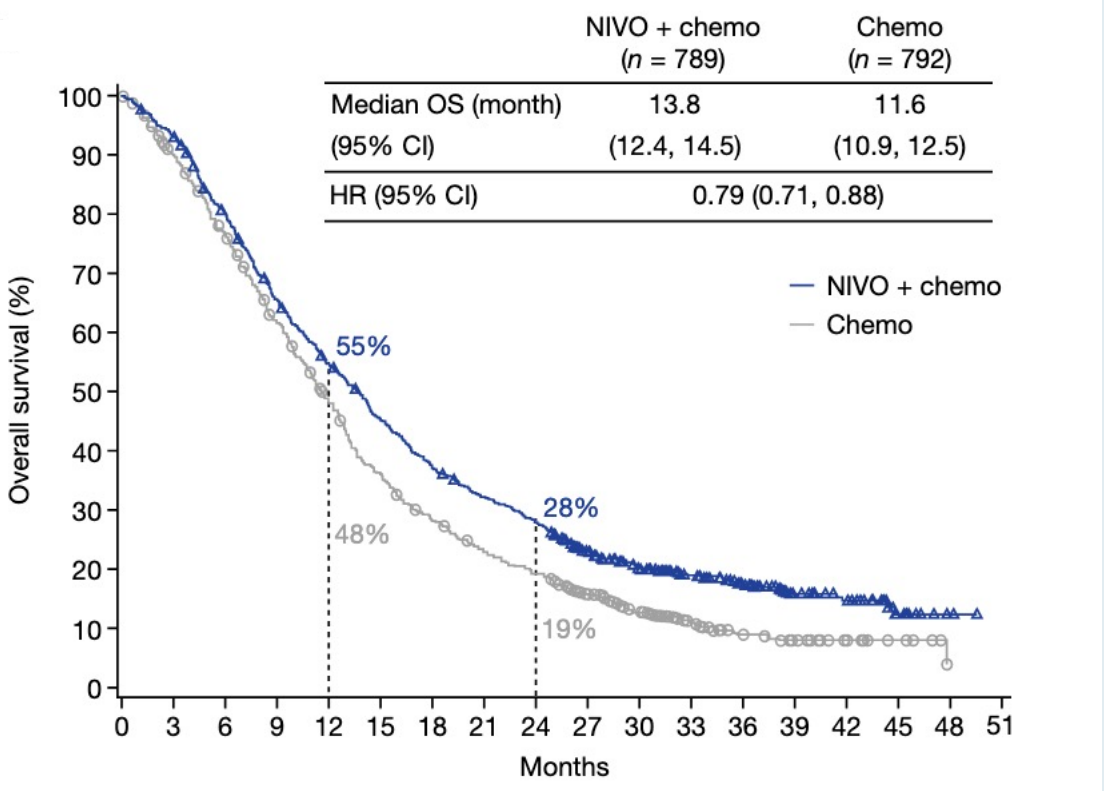
Kohei Shitara[1], Jaffer A. Ajani[2], Markus Moehler[3], Marcelo Garrido[4], Carlos Gallardo[5], Lin Shen[6], Kensei Yamaguchi[7], Lucjan Wyrwicz[8], Tomasz Skoczylas[9], Arinilda Campos Bragagnoli[10], Tianshu Liu[11], Mustapha Tehfe[12], Elena Elimova[13], Ricardo Bruges[14], Thomas Zander[15], Sergio 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

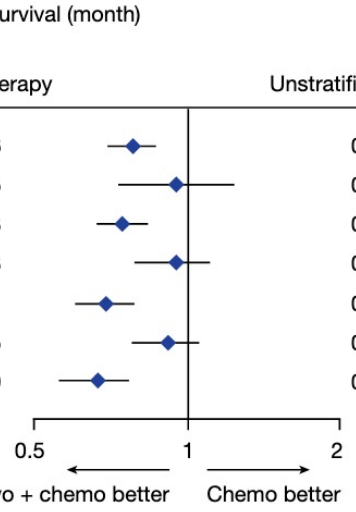
Shitara K et al. *Nature* 2022;[Online ahead of print].

RTP RESEARCH TO PRACTICE

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

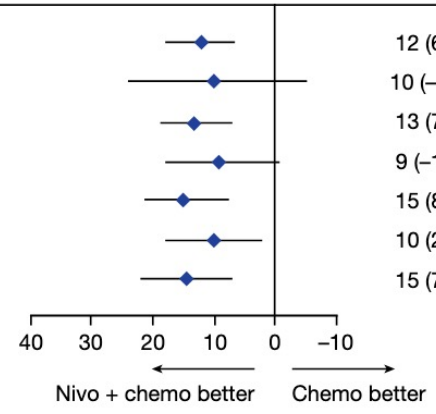
Median overall survival (month)

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

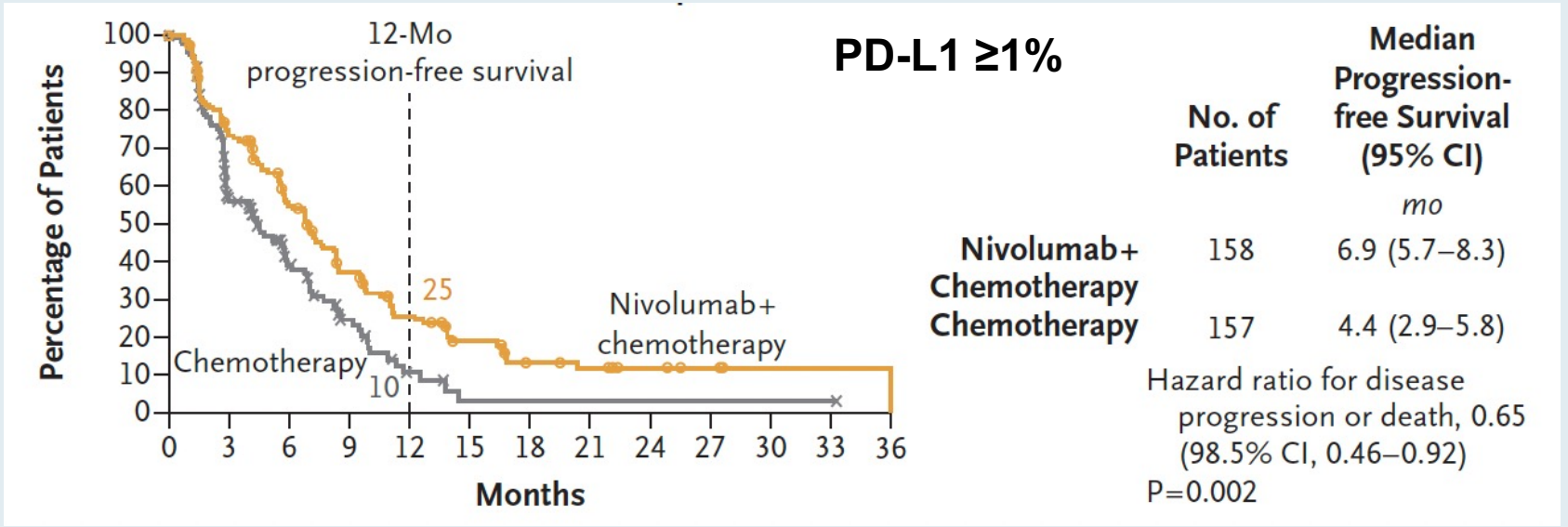
ORIGINAL ARTICLE

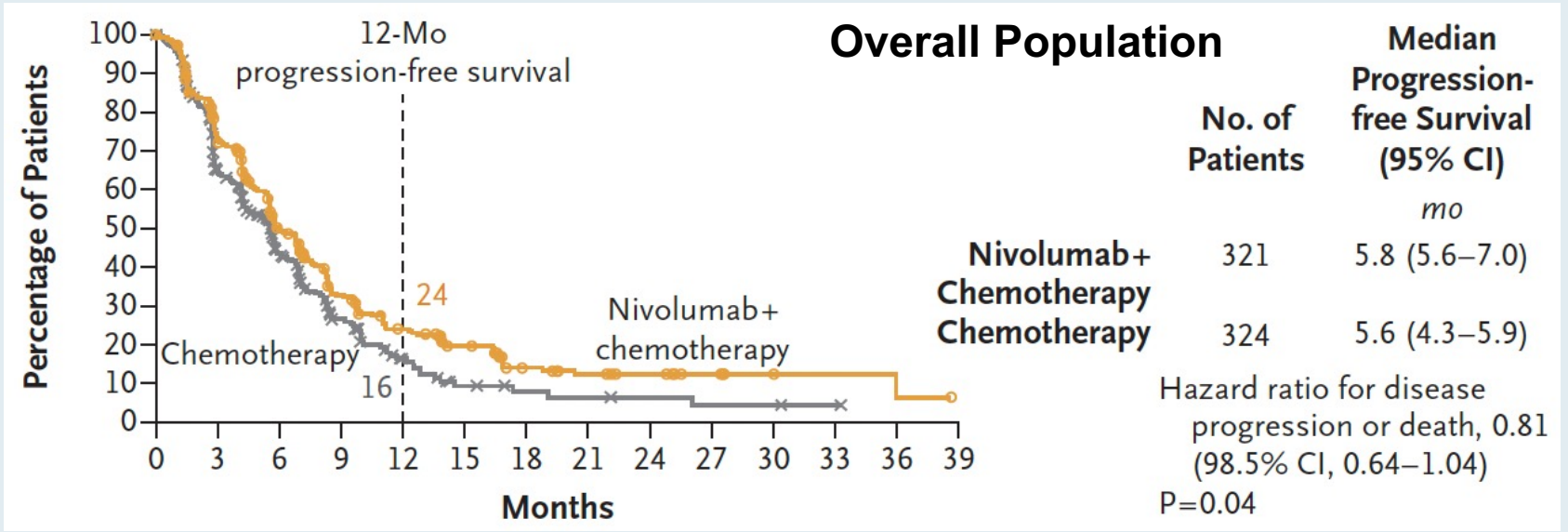
Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma

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*

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

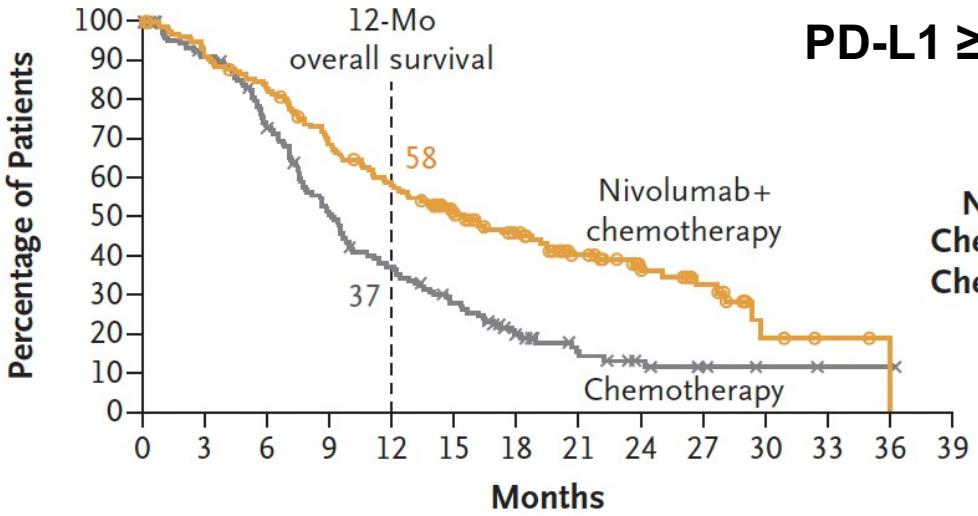
CheckMate 648: Progression-Free Survival for PD-L1 ≥1% and in the Overall Population





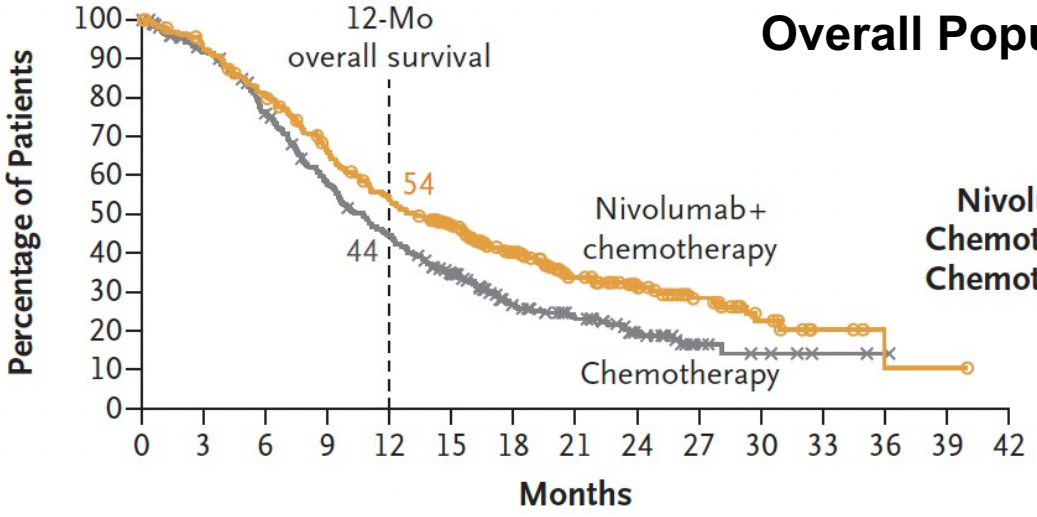
Doki Y et al. *N Engl J Med* 2022;386(5):449-62.

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



	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



	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.

RTP RESEARCH TO PRACTICE

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.

2021 ASCO ANNUAL MEETING

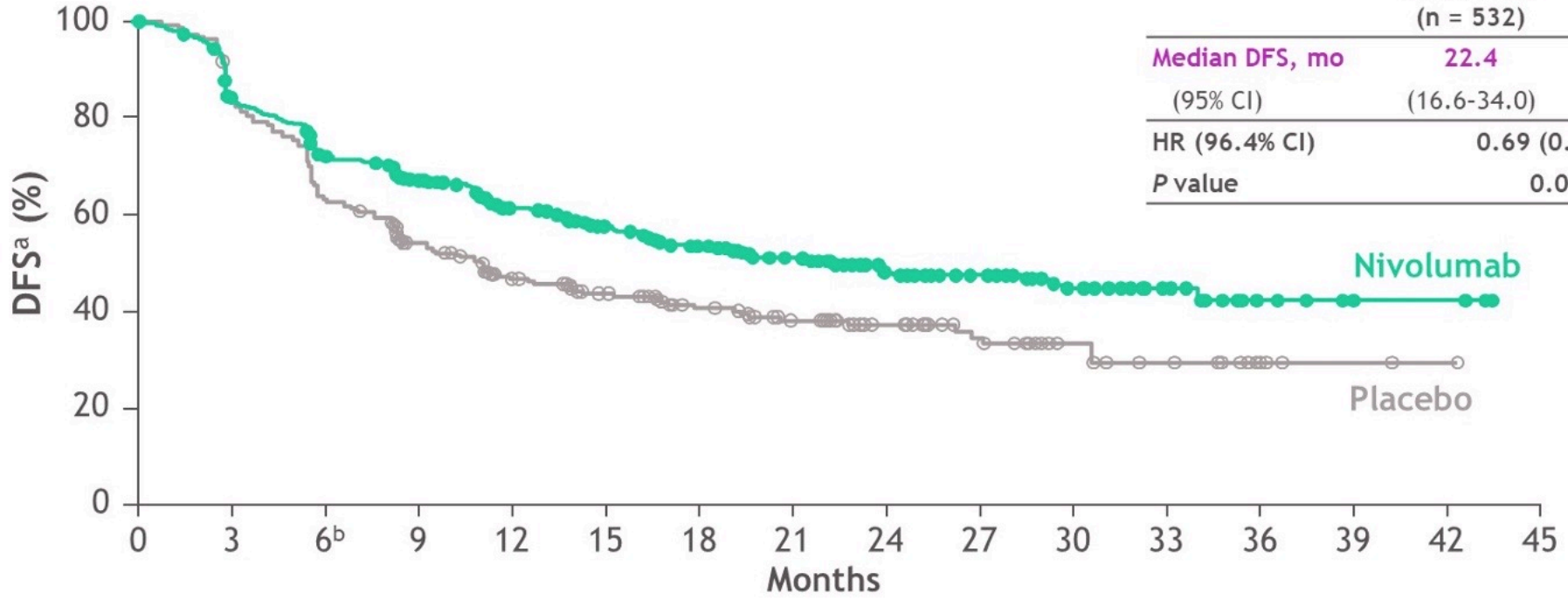
Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiotherapy: expanded efficacy and safety analyses from CheckMate 577

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.

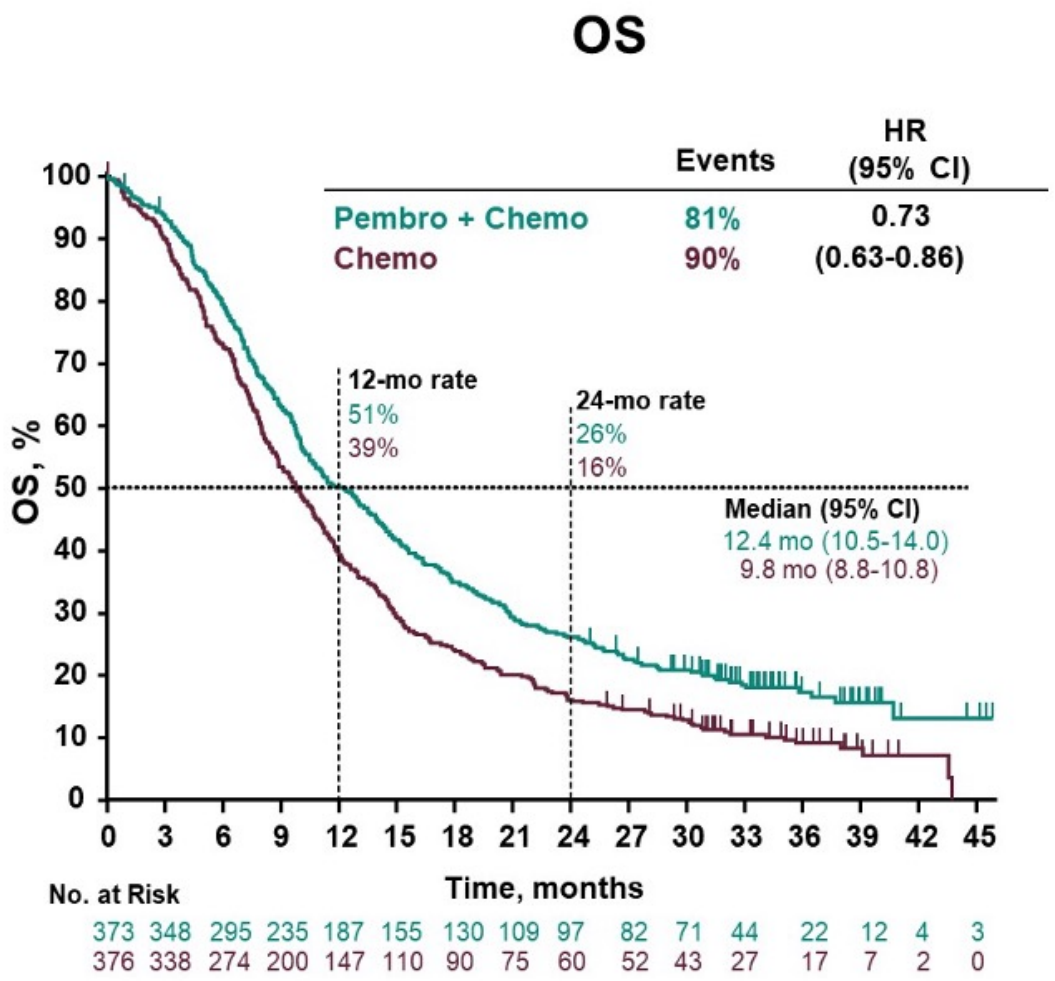
First-line Pembrolizumab Plus Chemotherapy Versus Chemotherapy in Advanced Esophageal Cancer: Longer-term Efficacy, Safety, and Quality-of-life Results From the Phase 3 KEYNOTE-590 Study

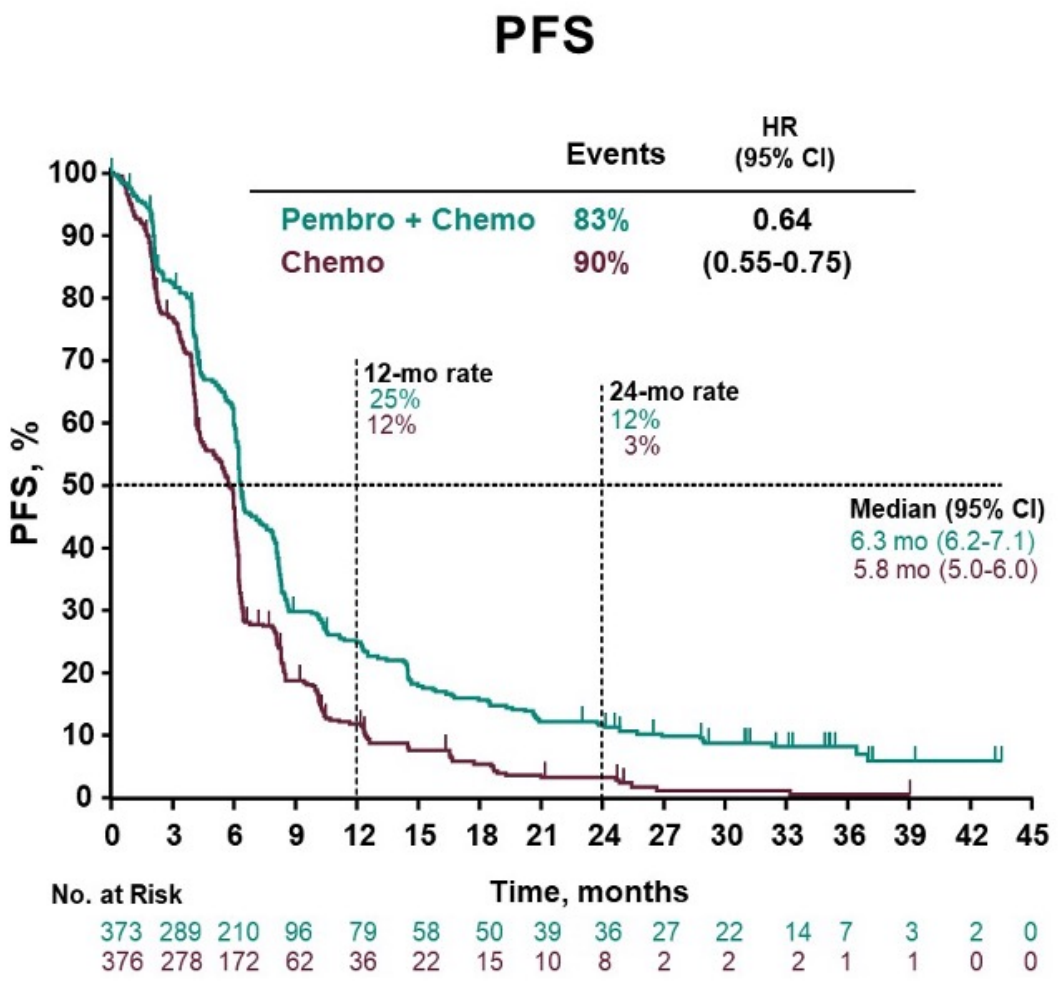
Jean-Philippe Metges,[1] Ken Kato,[2] Jong-Mu Sun,[3] Manish A. Shah,[4] Peter Enzinger,[5] Antoine Adenis,[6] Toshihiko Doi,[7] Takashi Kojima,[7] Zhigang Li,[8] Sung-Bae Kim,[9] Byoung Chul Cho,[10] Wasat Mansoor,[11] Shau-Hsuan Li,[12] Patrapim Sunpaweravong,[13] Maria Alsina Maqueda,[14] Gary L.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



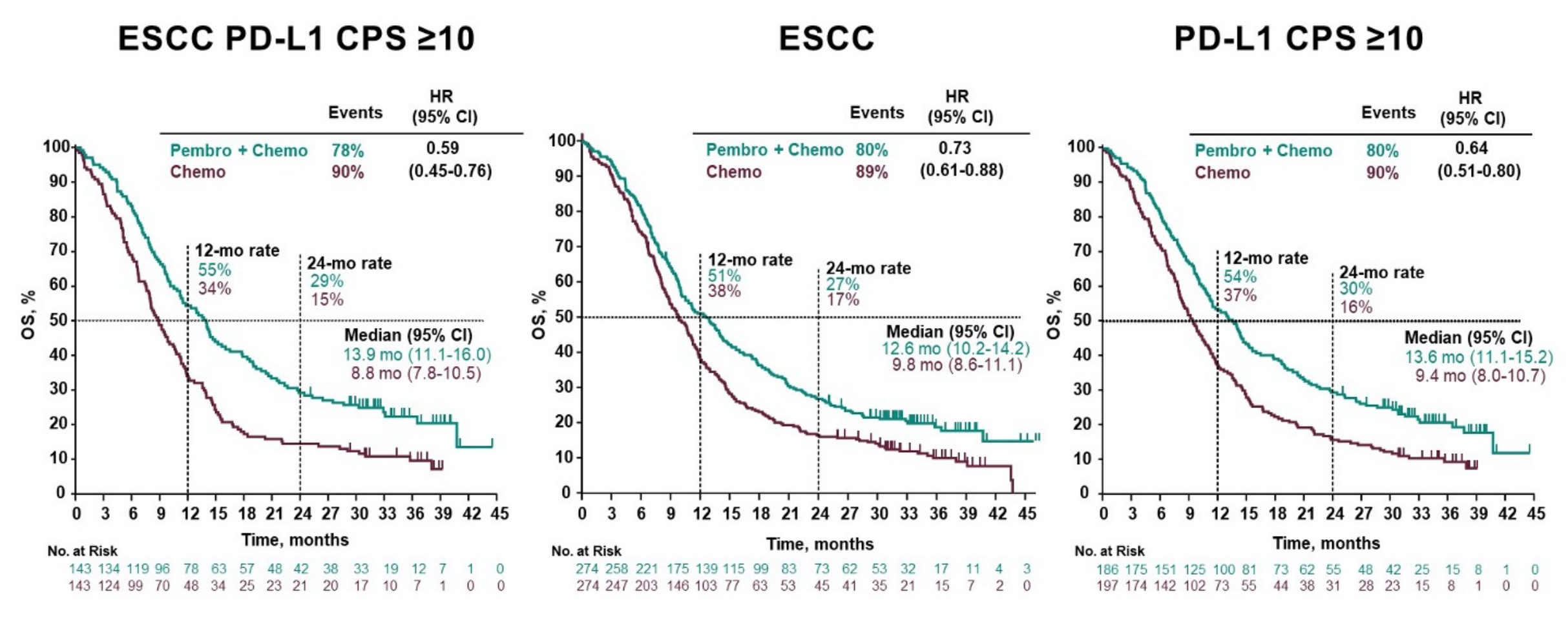


OS = overall survival; PFS = progression-free survival

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

RTP RESEARCH TO PRACTICE

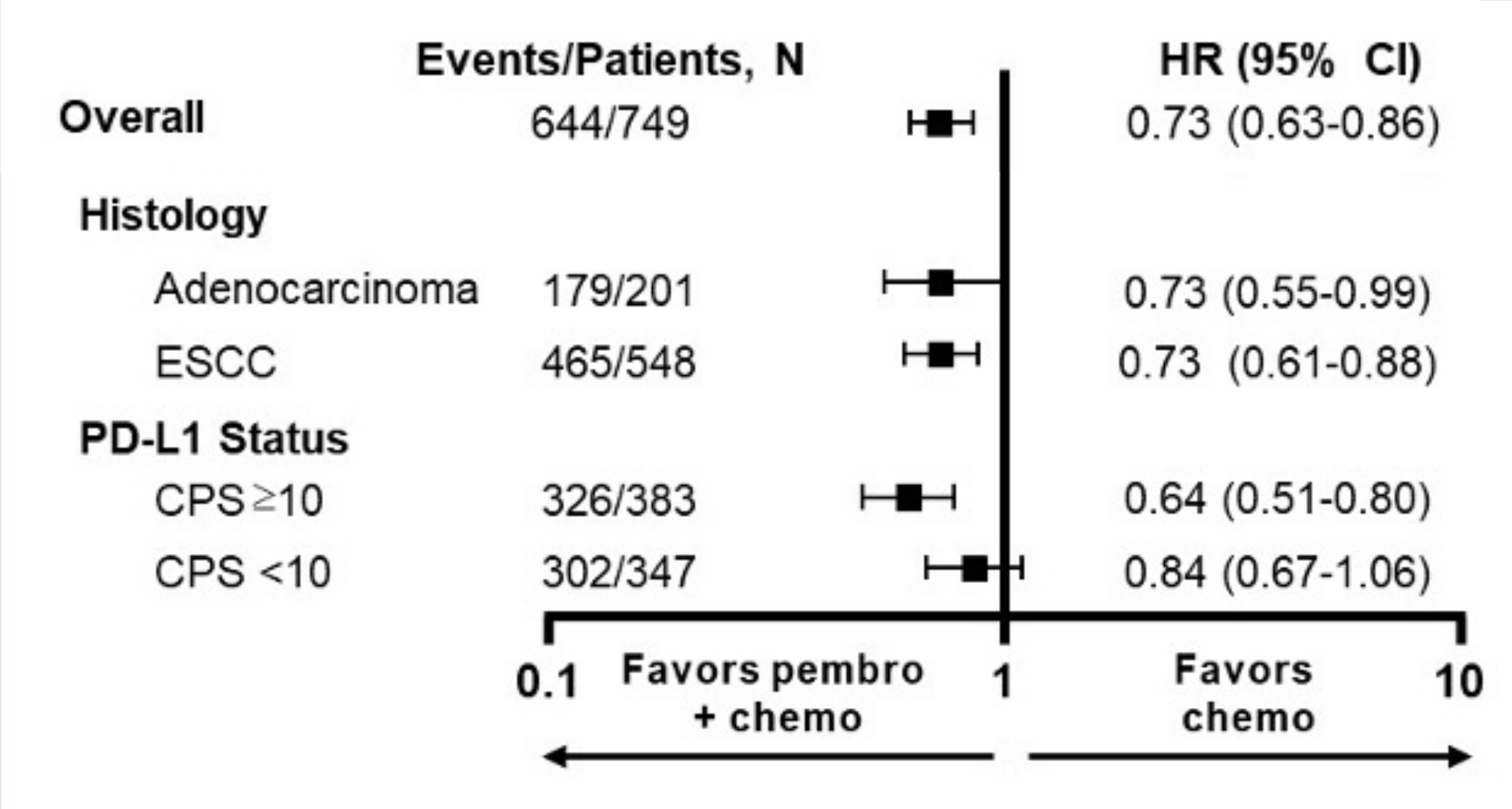
KEYNOTE-590: Overall Survival (OS) in Prespecified Subgroups



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.

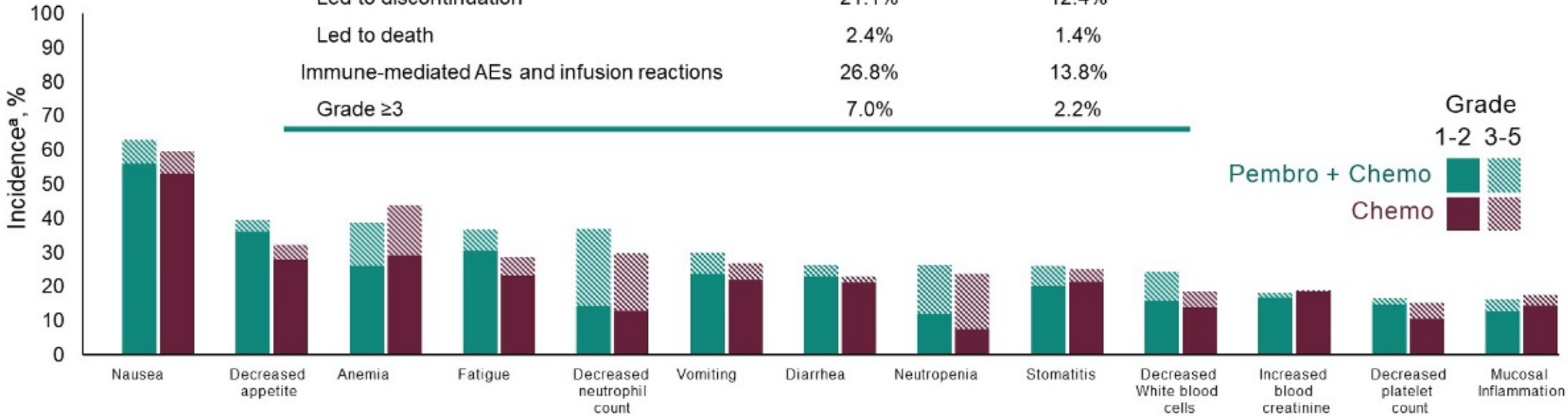
KEYNOTE-590: Antitumor Response

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.

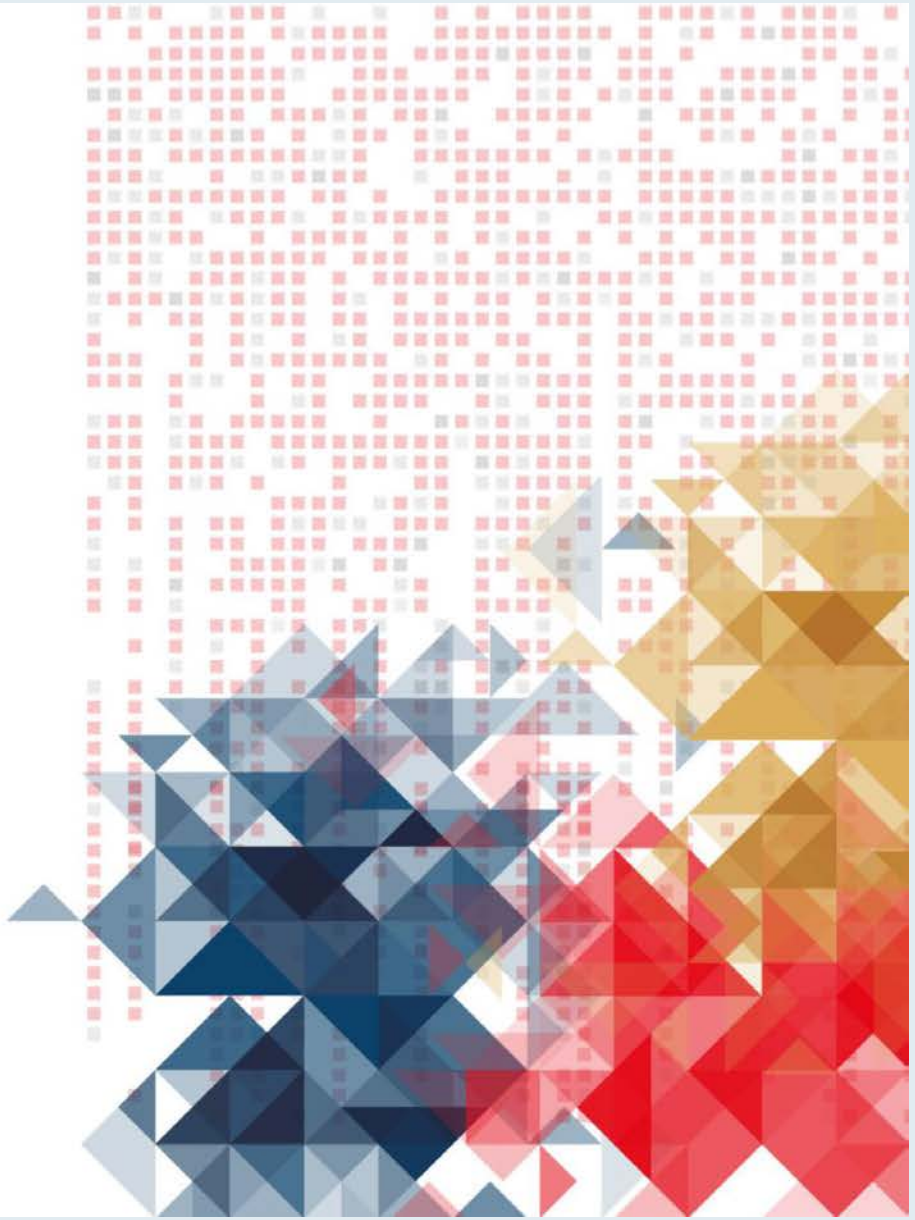
RTP RESEARCH TO PRACTICE

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

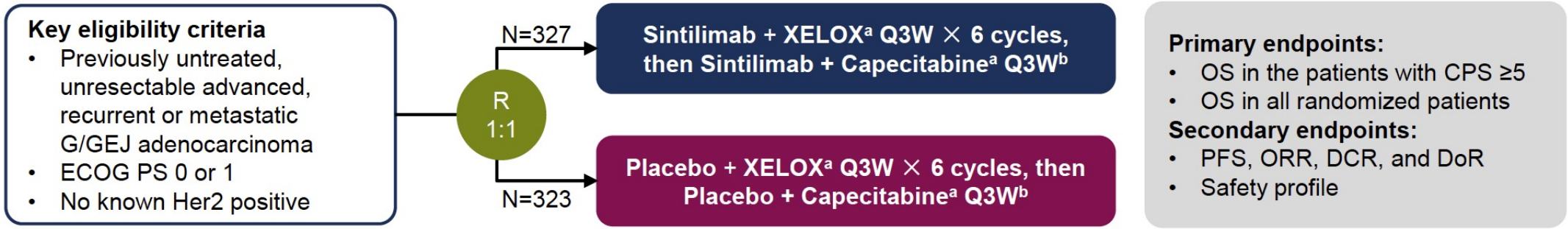
RTP RESEARCH TO PRACTICE

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



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).

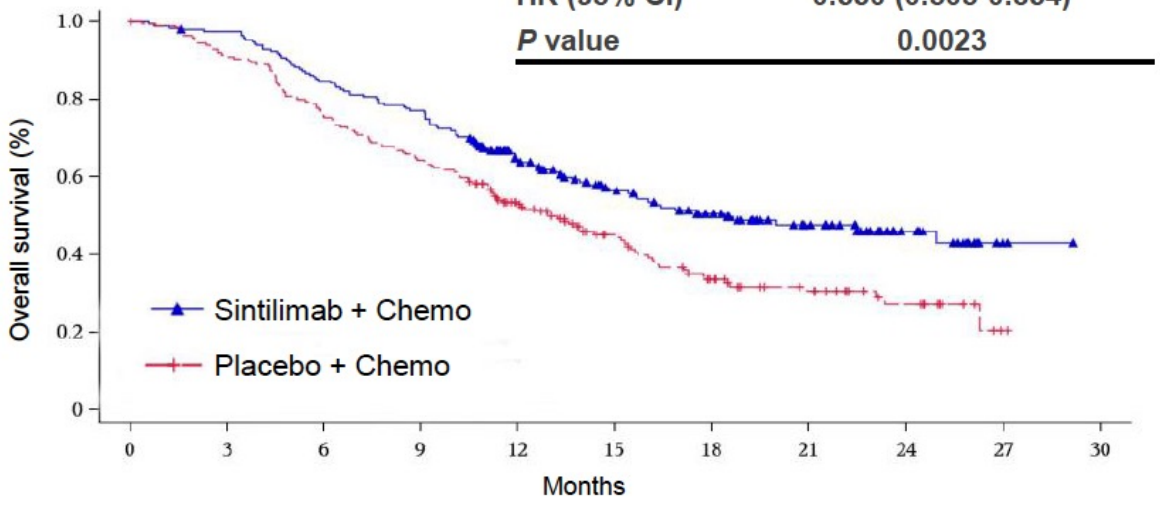
[a] ClinicalTrial.gov number, NCT03745170; [b] Sintilimab 3 mg/kg for body weight <60 kg, 200 mg for ≥60 kg; Oxaliplatin 130 mg/m^2 IV; Capecitabine 1000 mg/m^2 PO Bid d1-14;
[c] Until progressive disease, intolerable toxicity, withdrawal of consent. Treatment is given for a maximum of 2 years.

Xu J et al. ESMO 2021;Abstract LBA53.

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

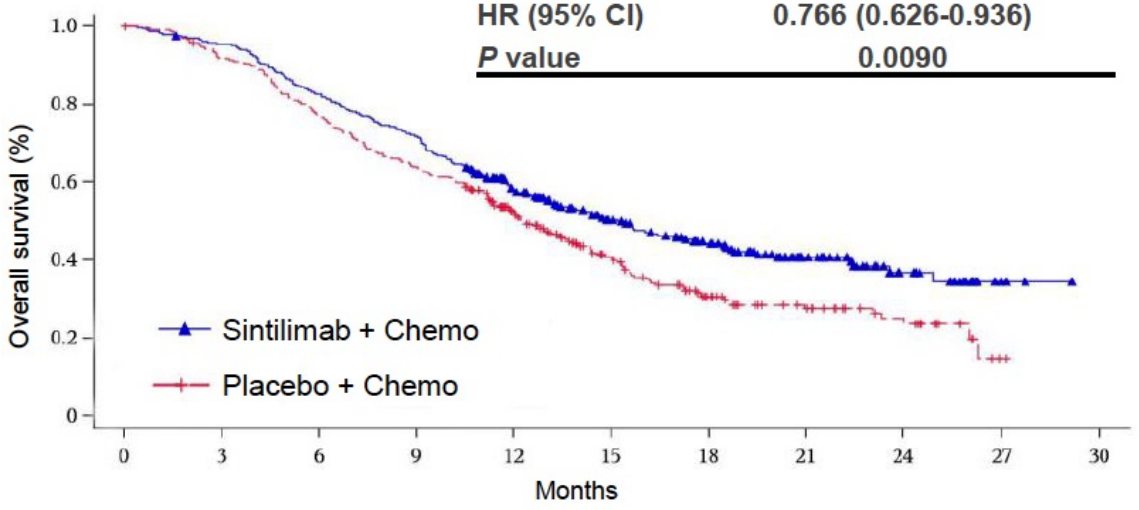
PD-L1 CPS ≥5

	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]

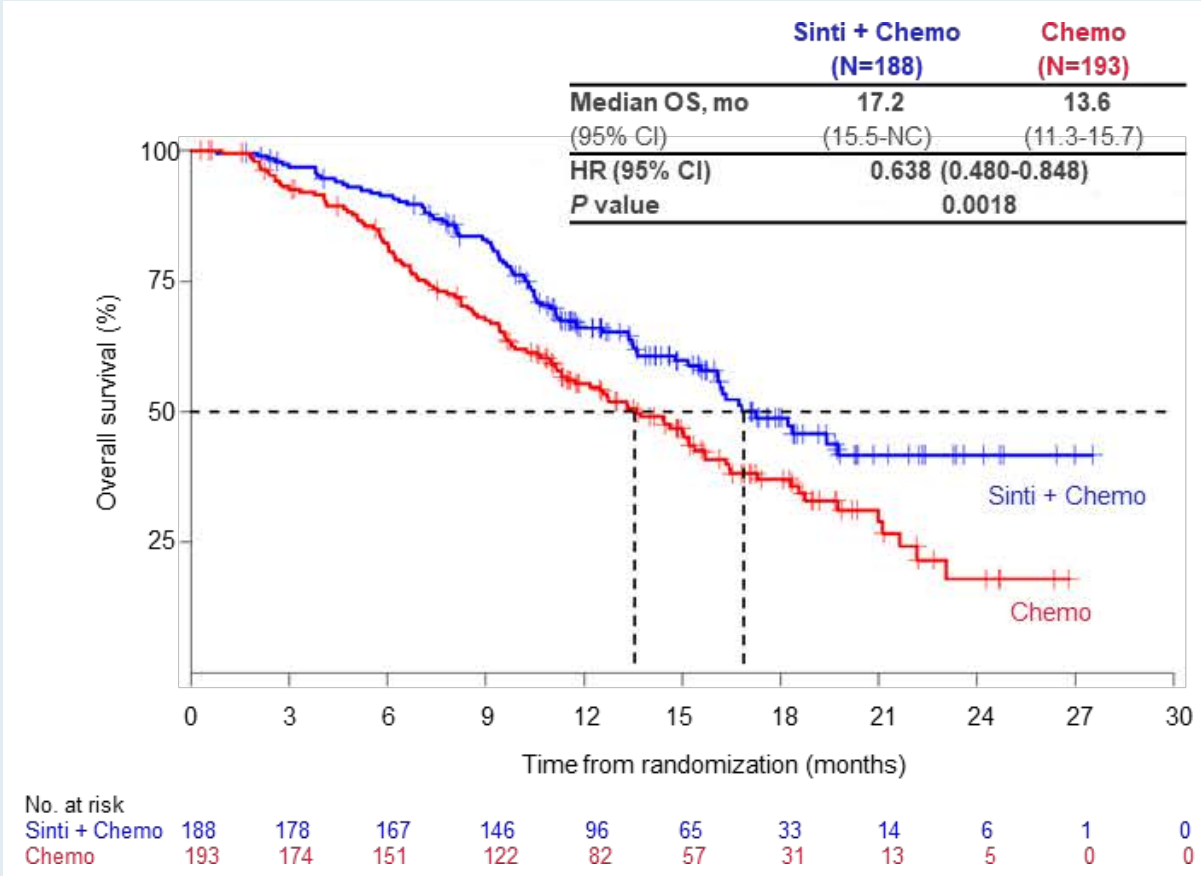
[1]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital and Institute, Beijing, China, [2]Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China, [3]Department of Oncology, The Affiliated 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.

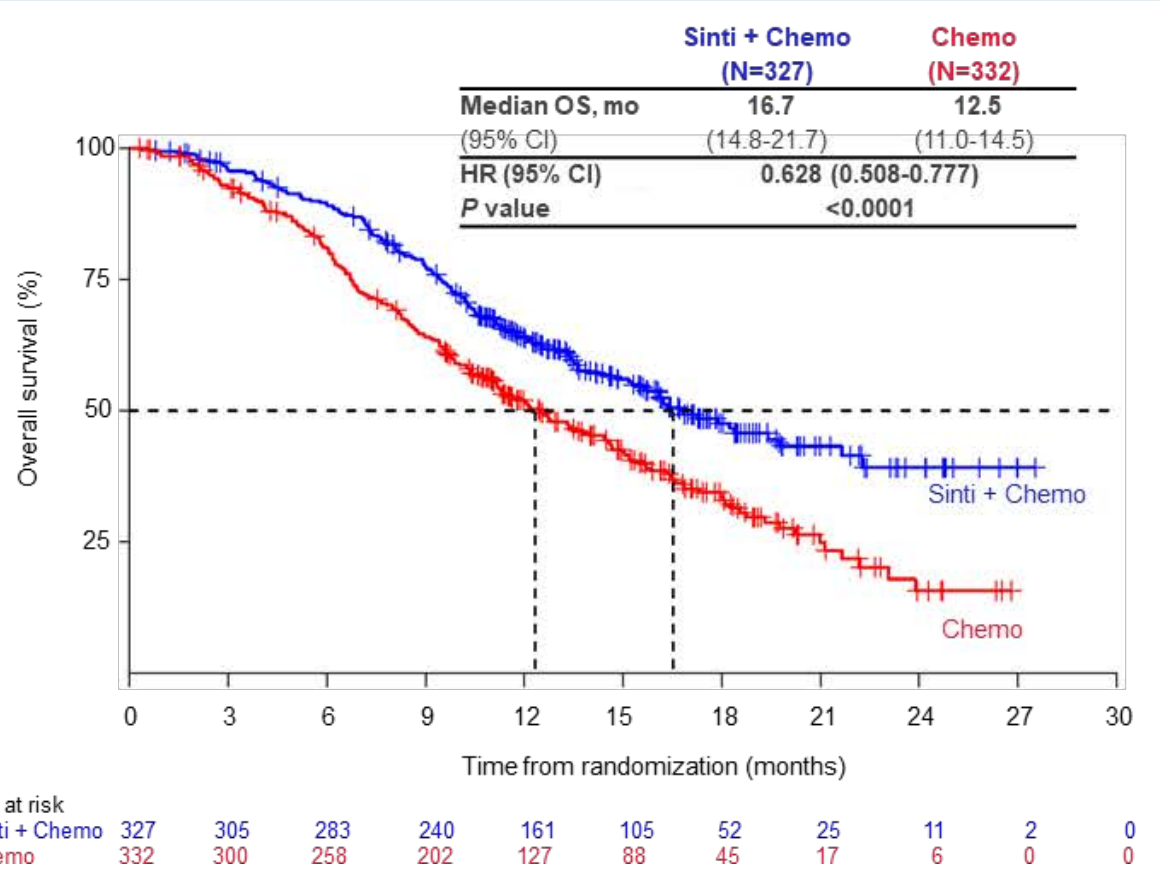
RTP RESEARCH TO PRACTICE

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

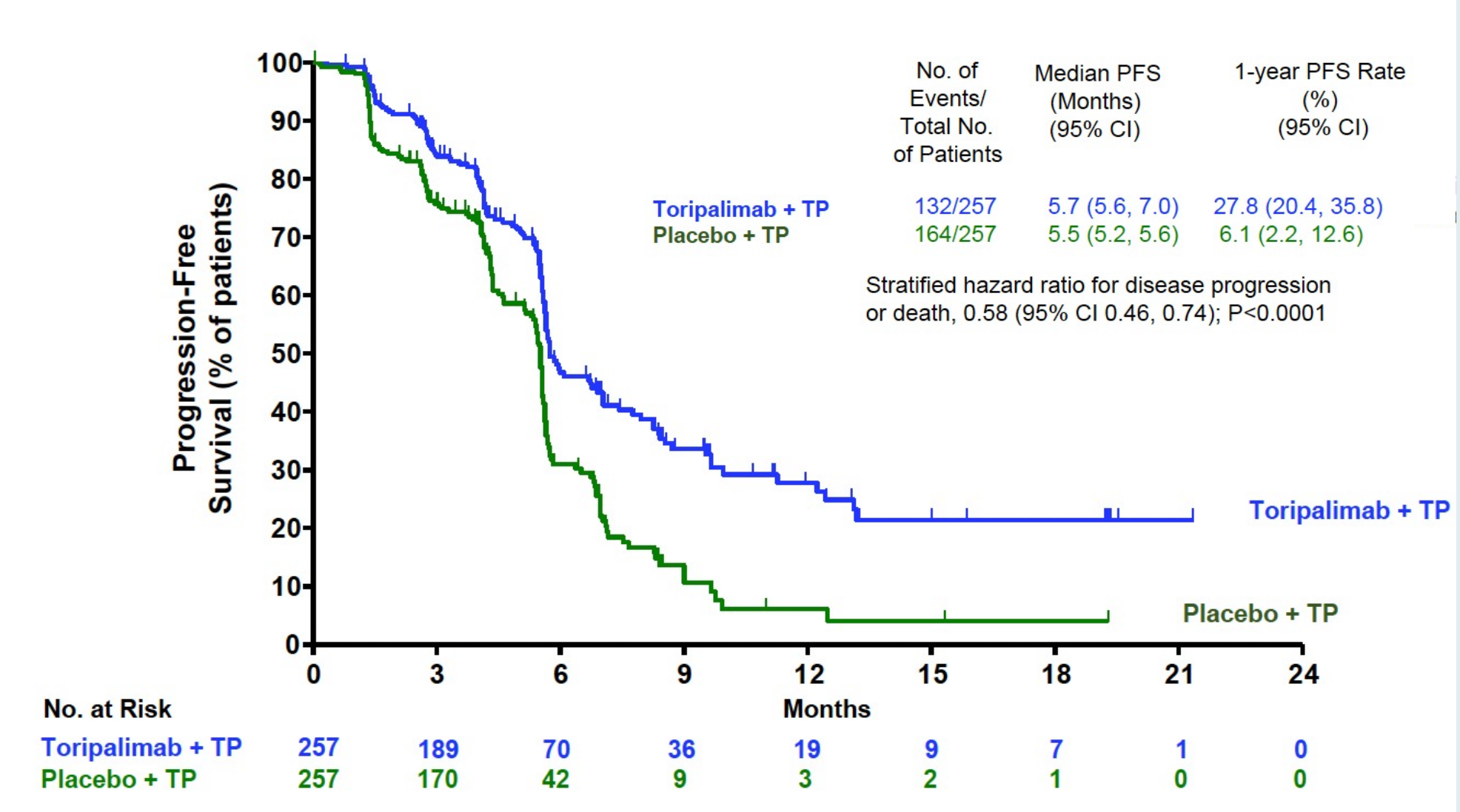
CellPress

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

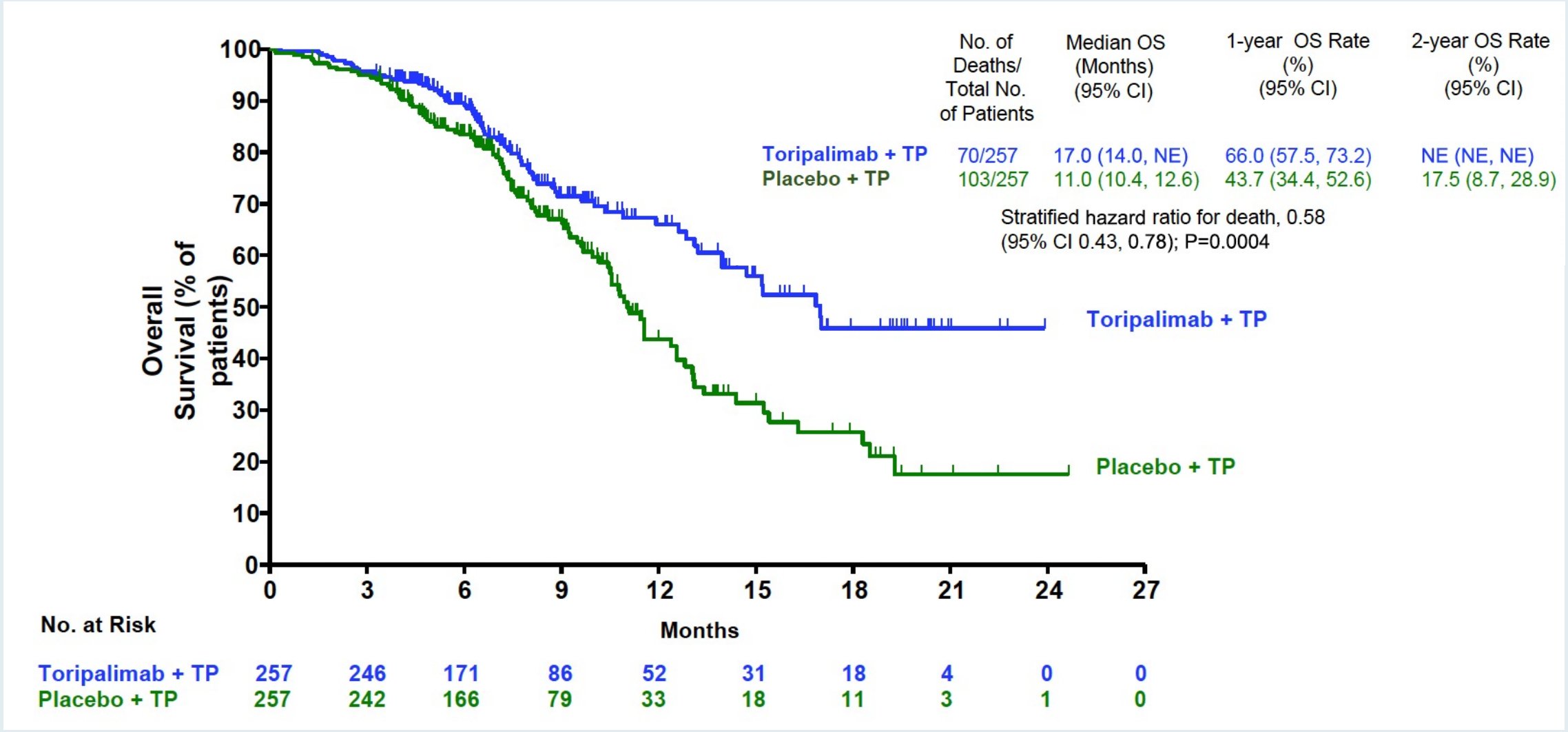
JUPITER-06: Progression-Free Survival (BICR, ITT Population)



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

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.

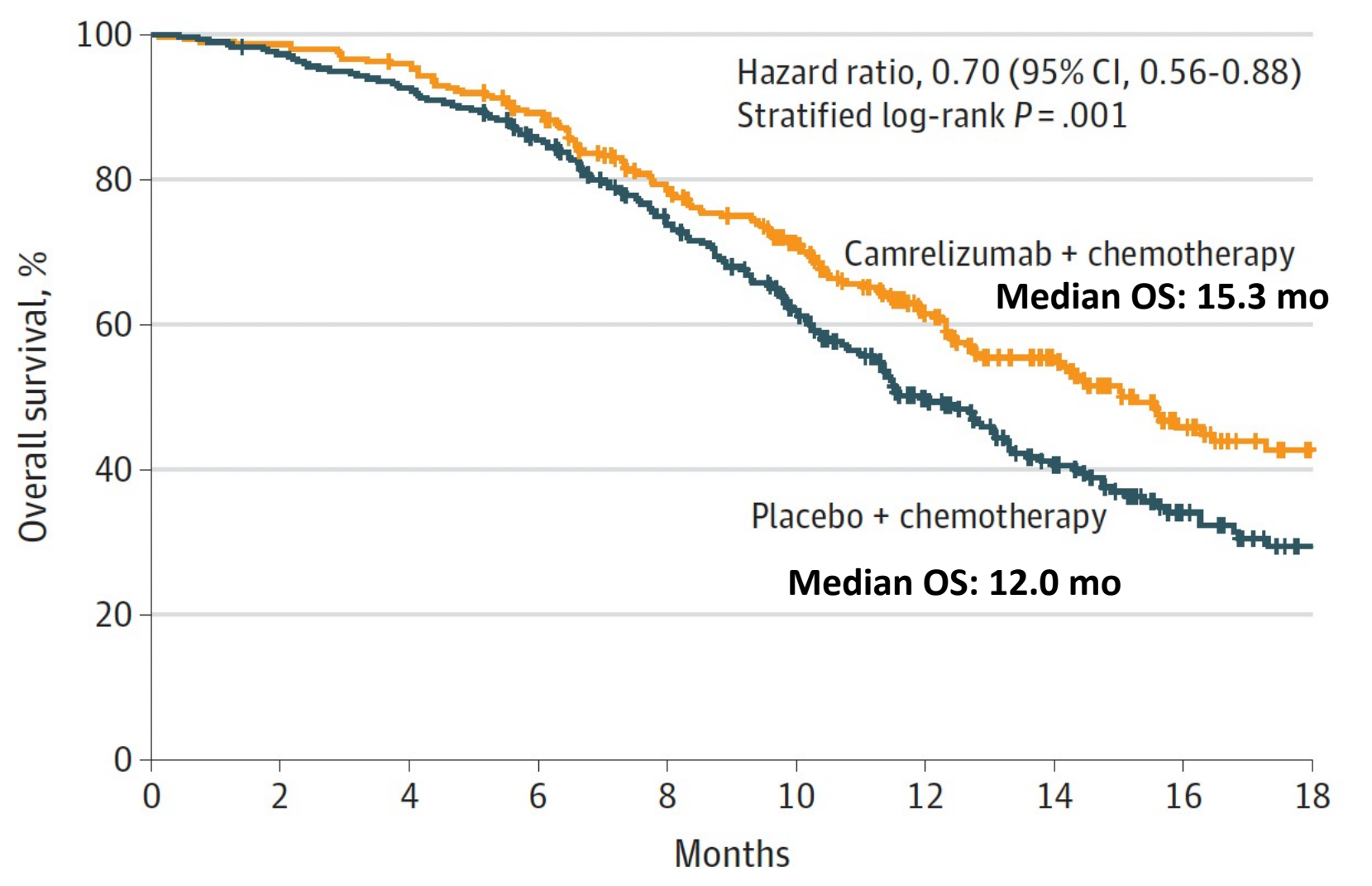
JAMA | Original Investigation

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

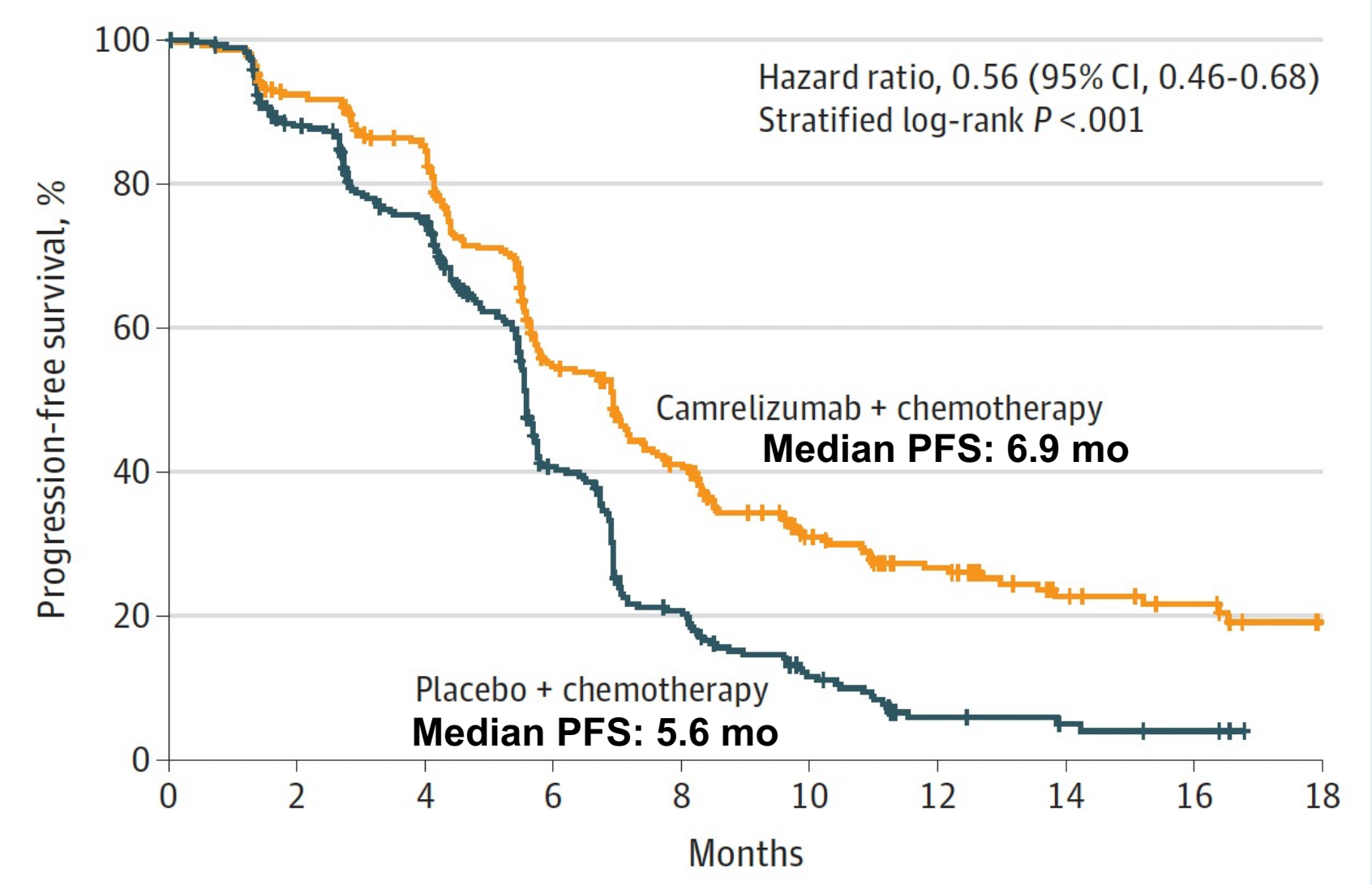
ESCORT-1st: Overall Survival (Coprimary Endpoint)



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

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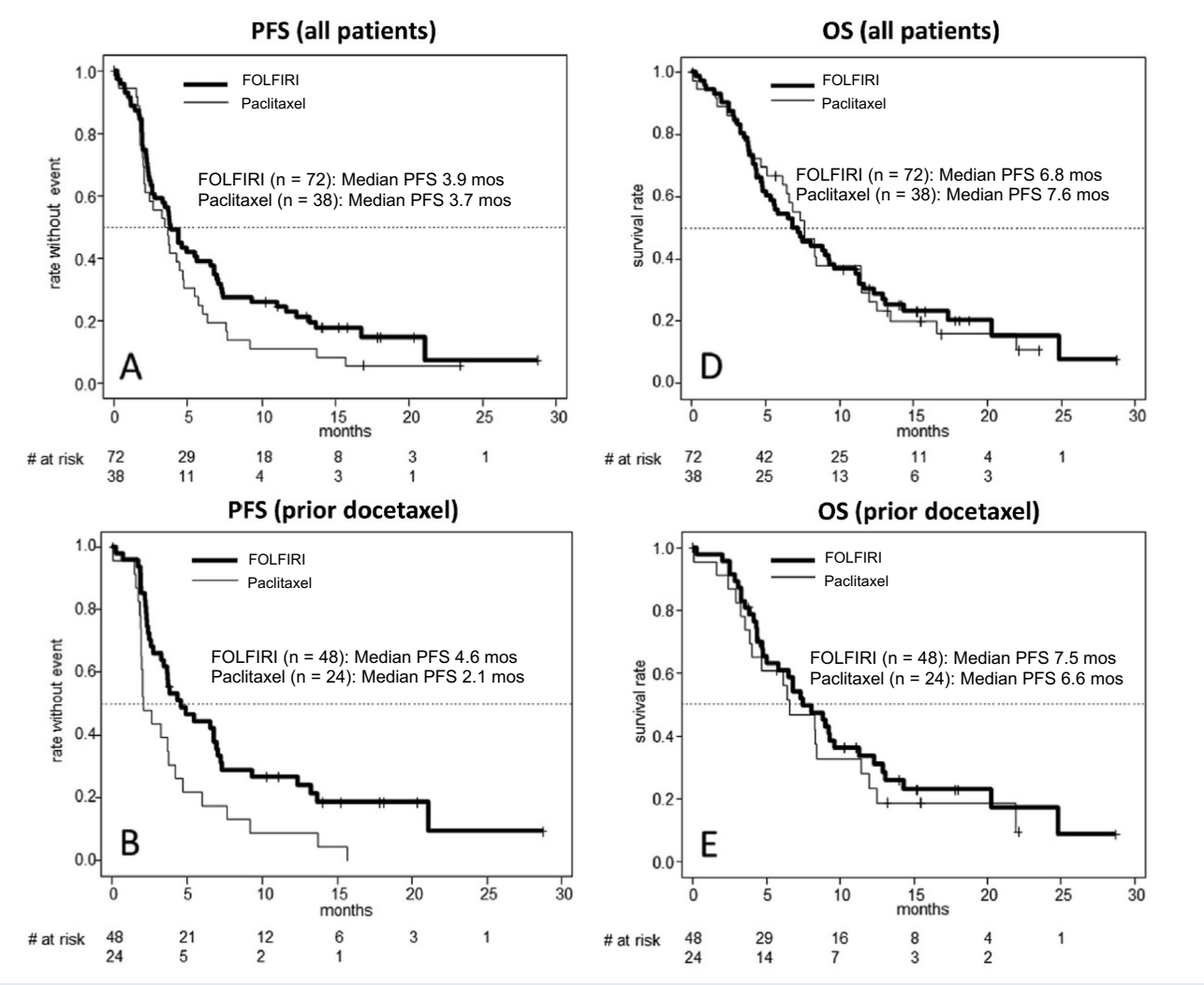
journal homepage: www.ejcancer.com

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



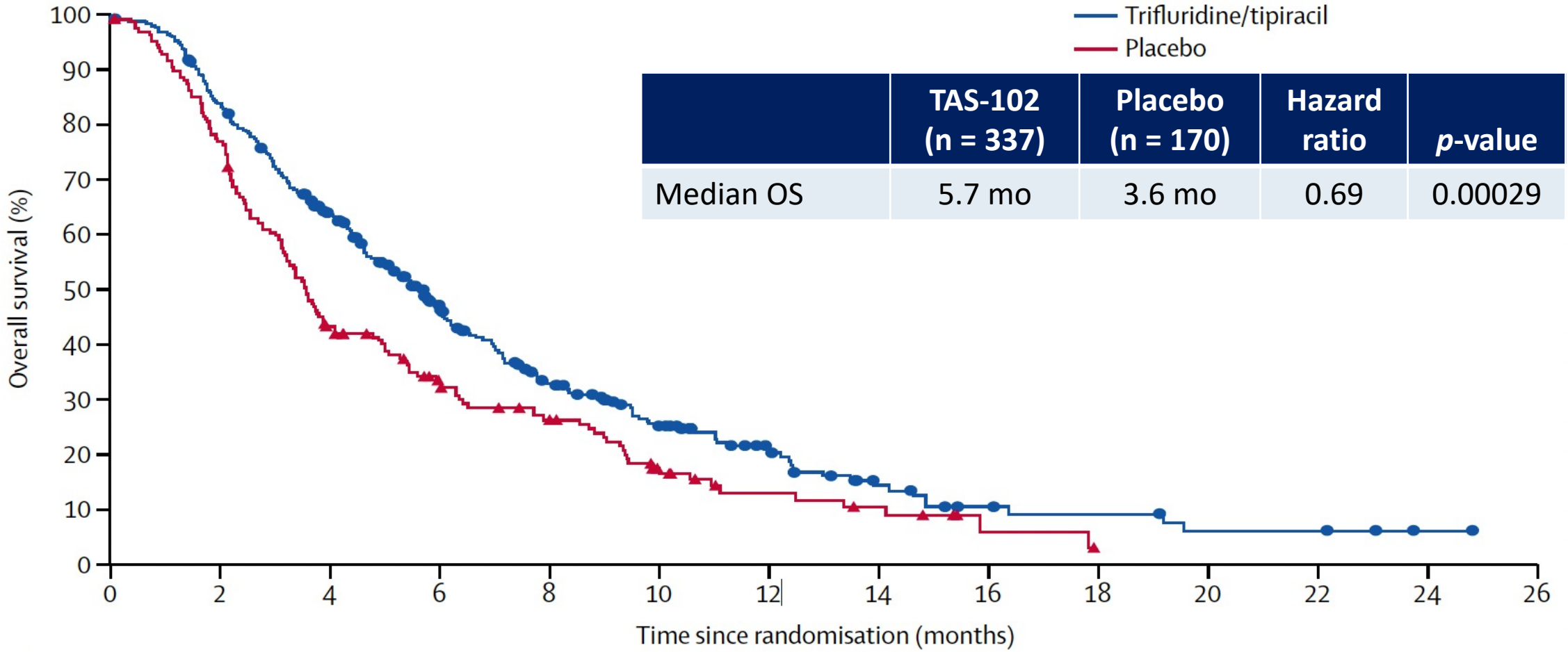
Lorenzen S et al. *Eur J Cancer* 2022;165:48-57.

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.

HER2-Positive Gastroesophageal Cancers

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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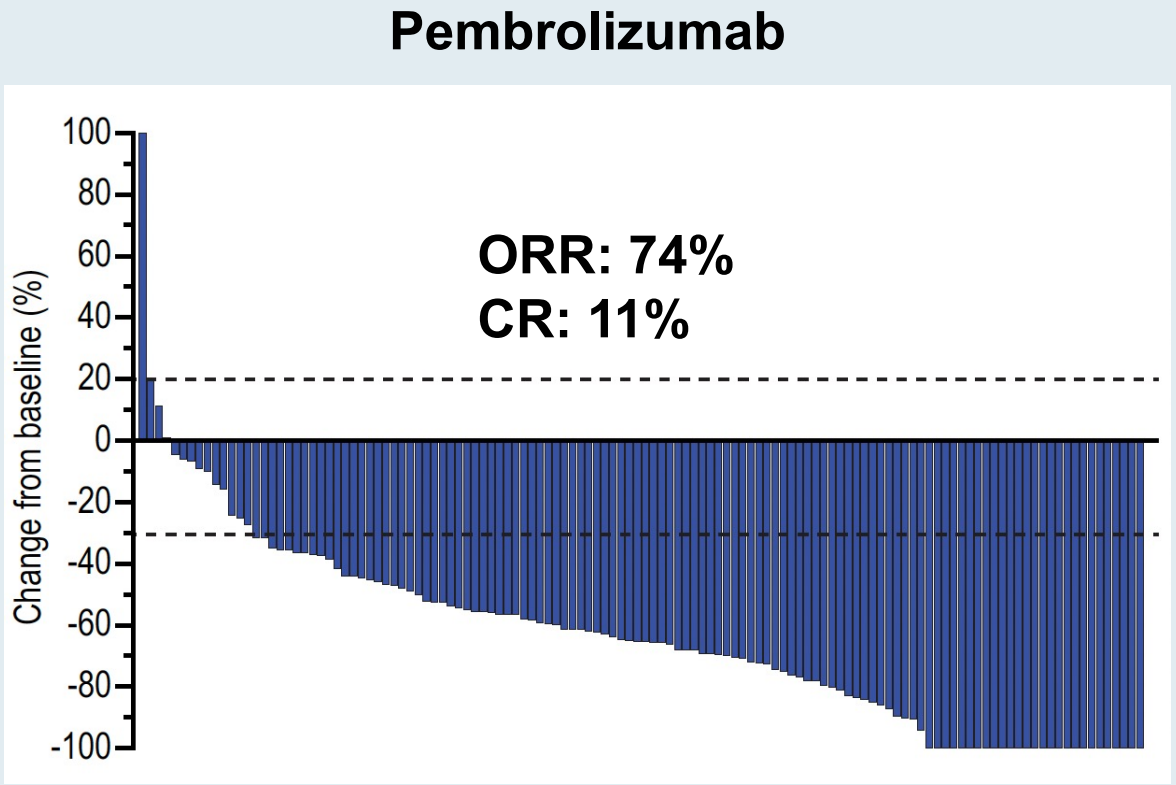
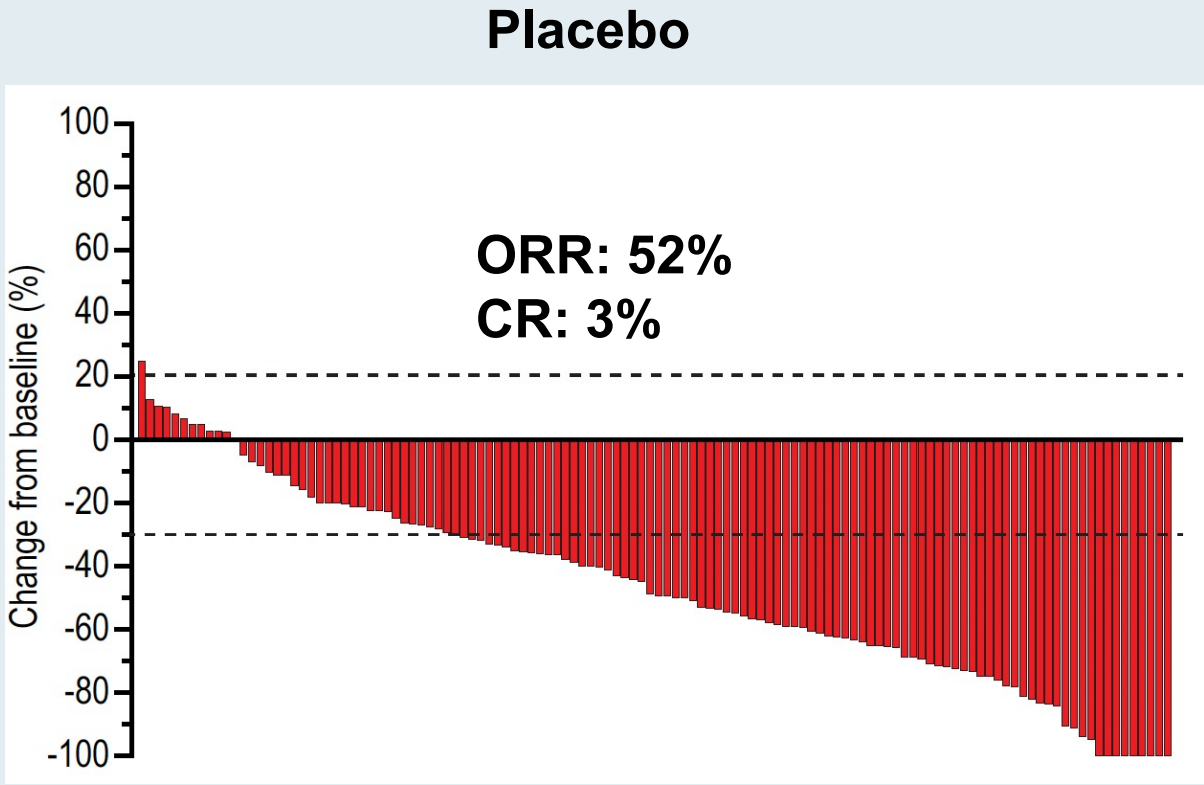
Yelena Y. Janjigian[1]✉, Akihito Kawazoe[2], Patricio Yañez[3], Ning Li[4], Sara Lonardi[5], Oleksii Kolesnik[6], Olga Barajas[7], Yuxian Bai[8], Lin Shen[9], Yong Tang[10], Lucjan S. Wyrwicz[11], Jianming Xu[12], Kohei Shitara[2], Shukui Qin[13], Eric Van Cutsem[14], Josep Tabernero[15], Lie Li[16], Sukrut Shah[16], Pooja Bhagia[16] & Hyun Cheol Chung[17]

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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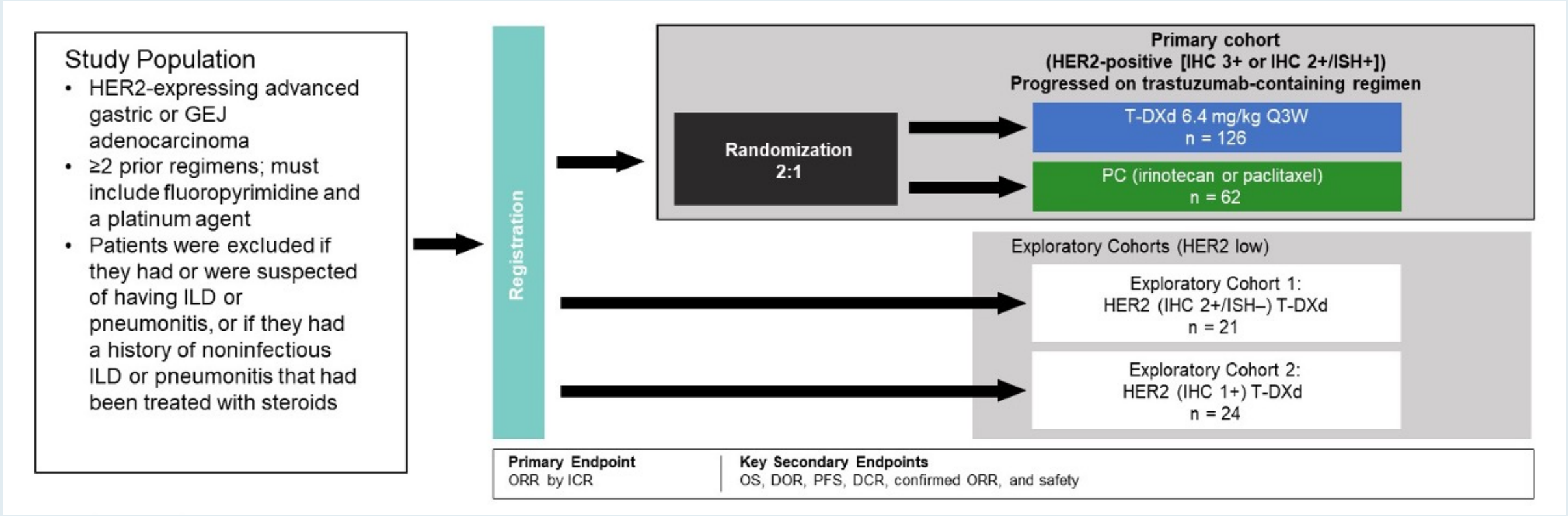
The Cancer Institute Hospital of JFCR, Tokyo, Japan

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

DESTINY-Gastric01 Randomized, Phase II Study Design

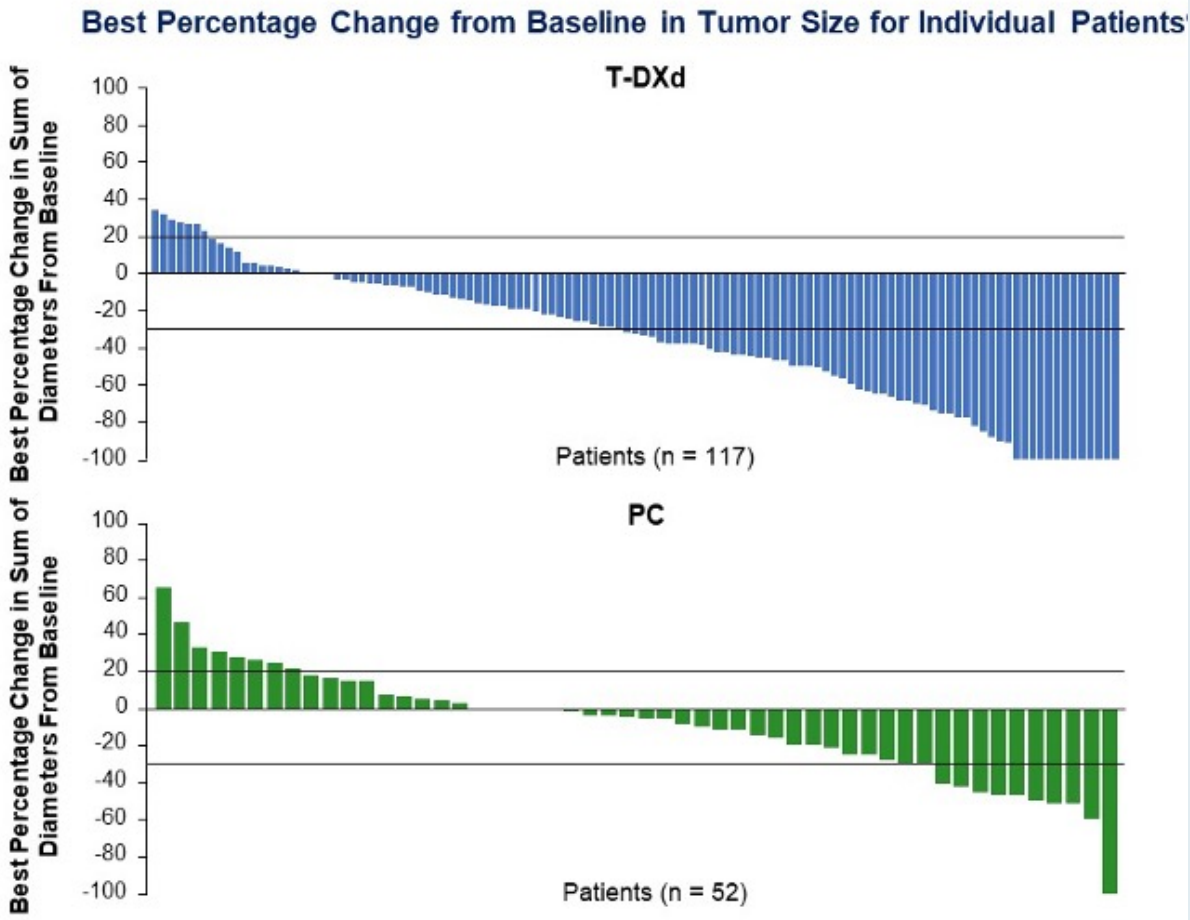


PC = physician's choice

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

DESTINY-Gastric01: Antitumor Activity

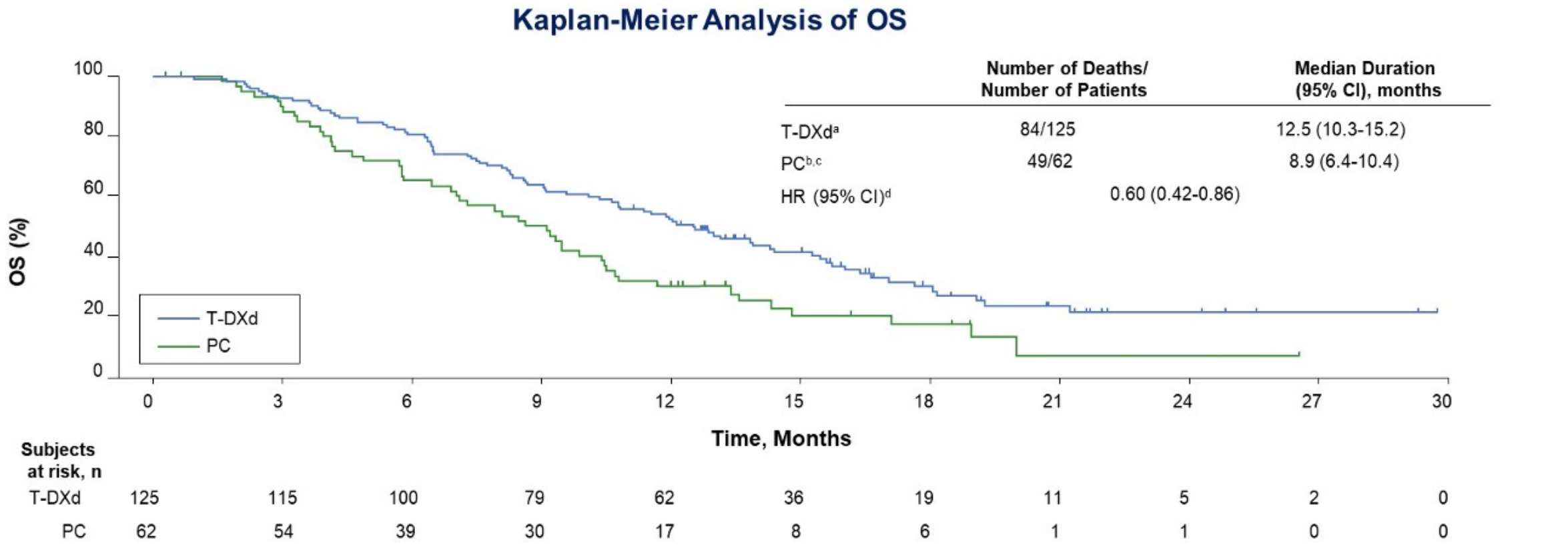
	T-DXd n = 119	PC Overall n = 56
ORR (CR + PR) by ICR, n (%)[a]	**61 (51.3) 95% CI, 41.9-60.5**	**8 (14.3) 95% CI, 6.4-26.2**
	P < 0.0001[b]	
CR	11 (9.2)	0
PR	50 (42.0)	8 (14.3)
SD	42 (35.3)	27 (48.2)
PD	14 (11.8)	17 (30.4)
Not evaluable	2 (1.7)	4 (7.1)
Confirmed ORR (CR + PR) by ICR, n (%)[a]	50 (42.0) 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.

RTP RESEARCH TO PRACTICE

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.

RTP RESEARCH TO PRACTICE

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.

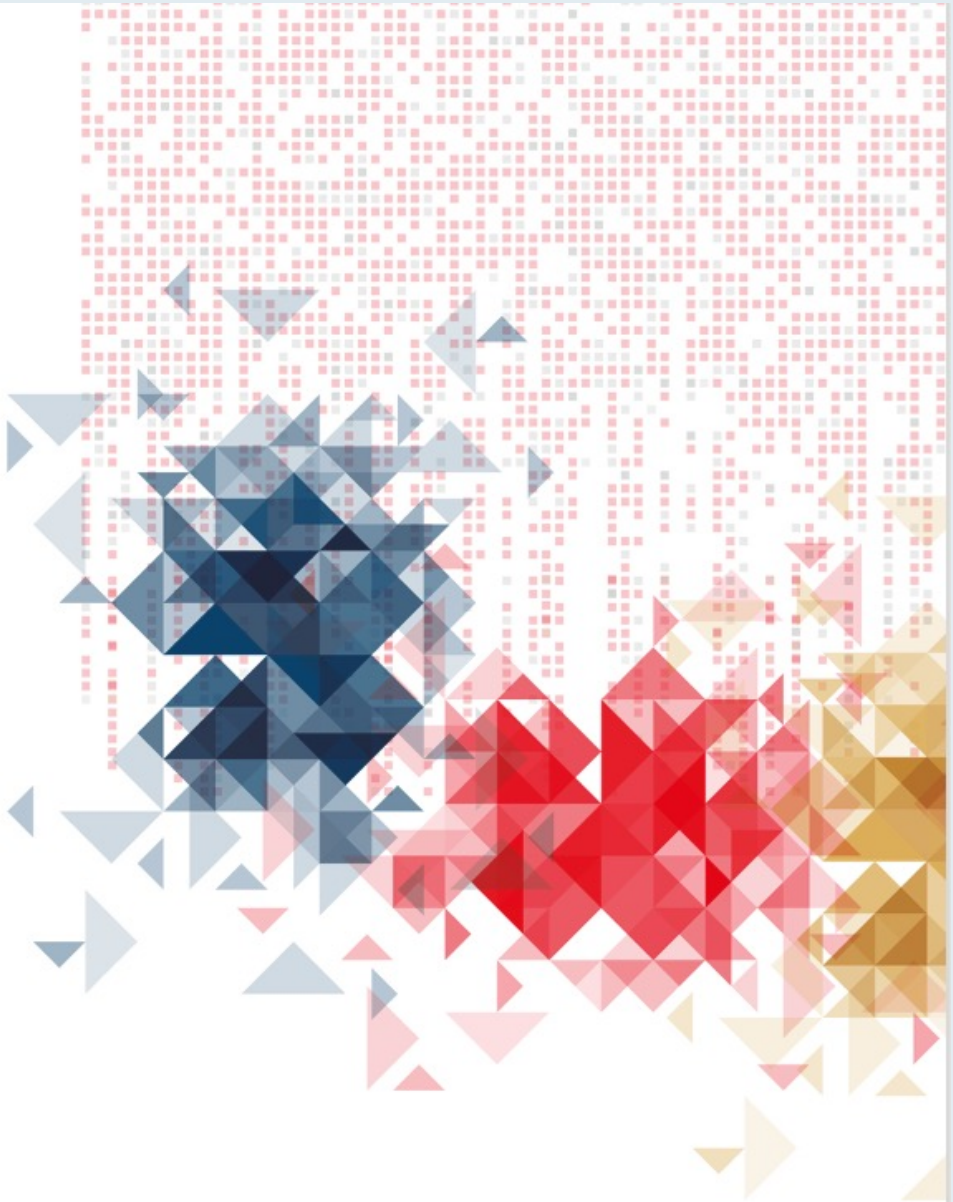
2021 ESMO congress

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

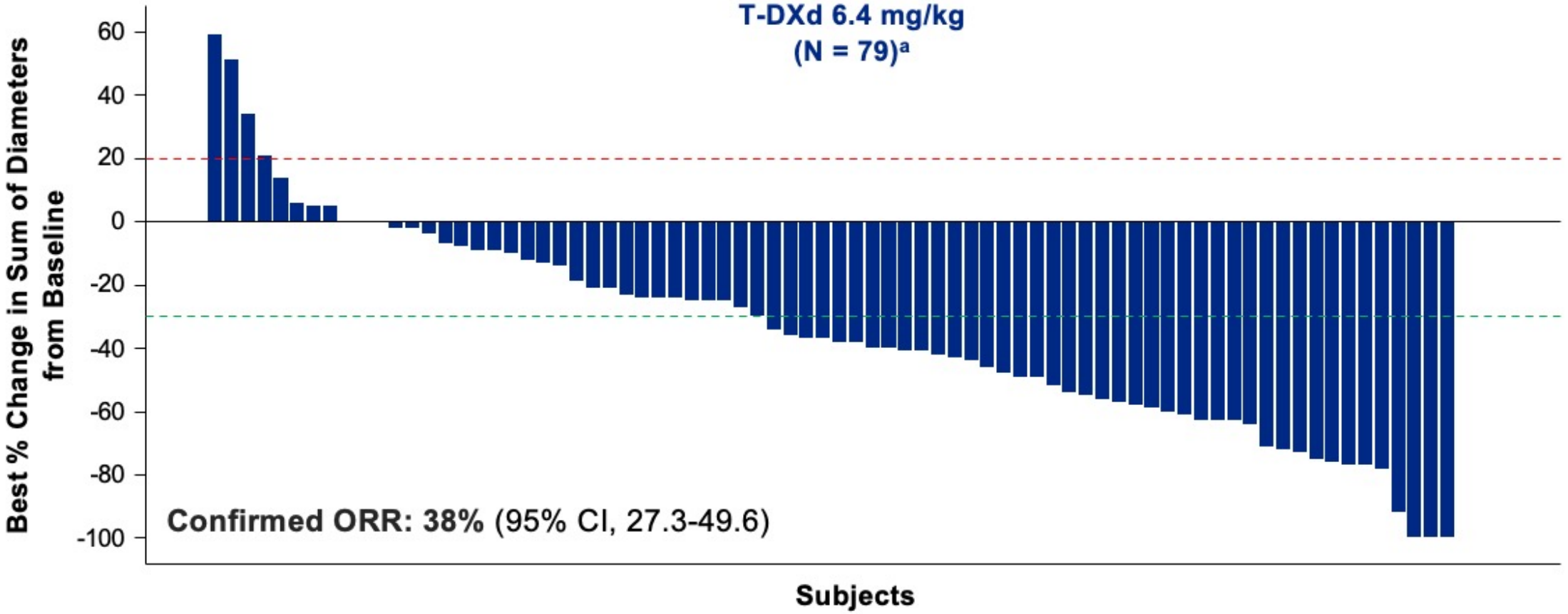
Secondary endpoints[b]

- 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.

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.

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)

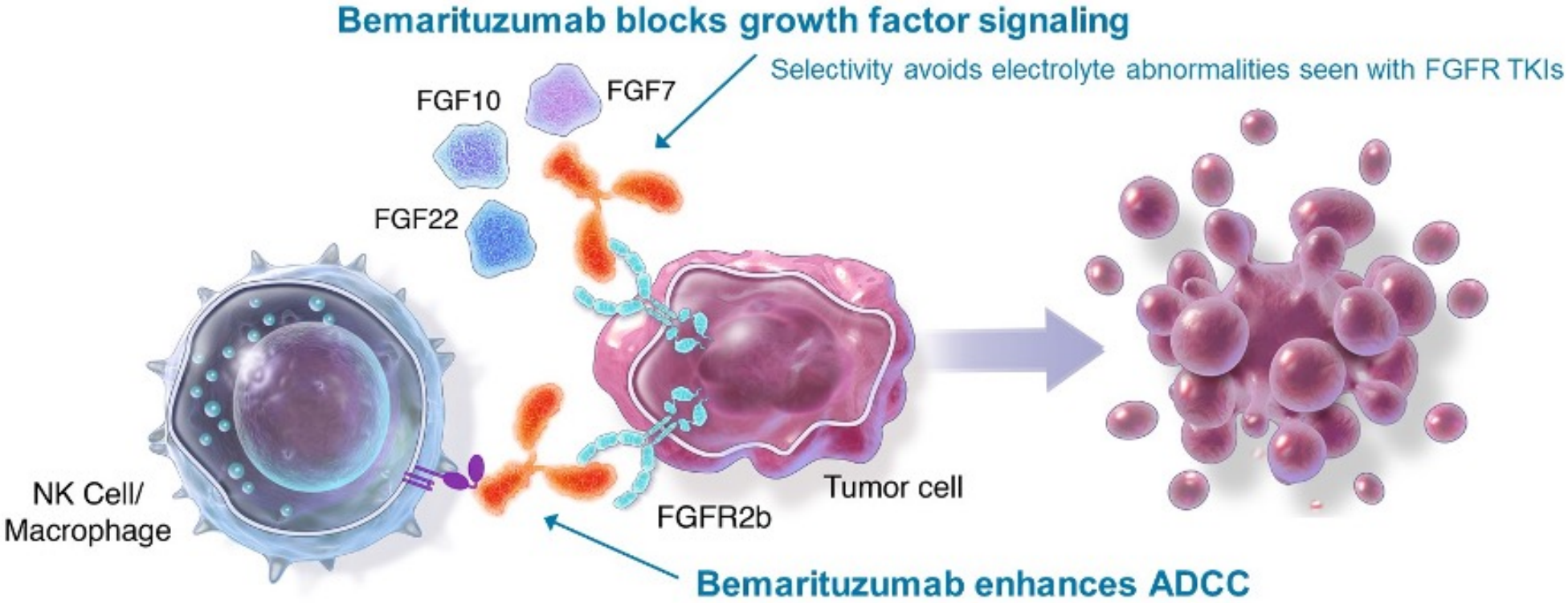
Presenter: Daniel Catenacci, MD
University of Chicago

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.

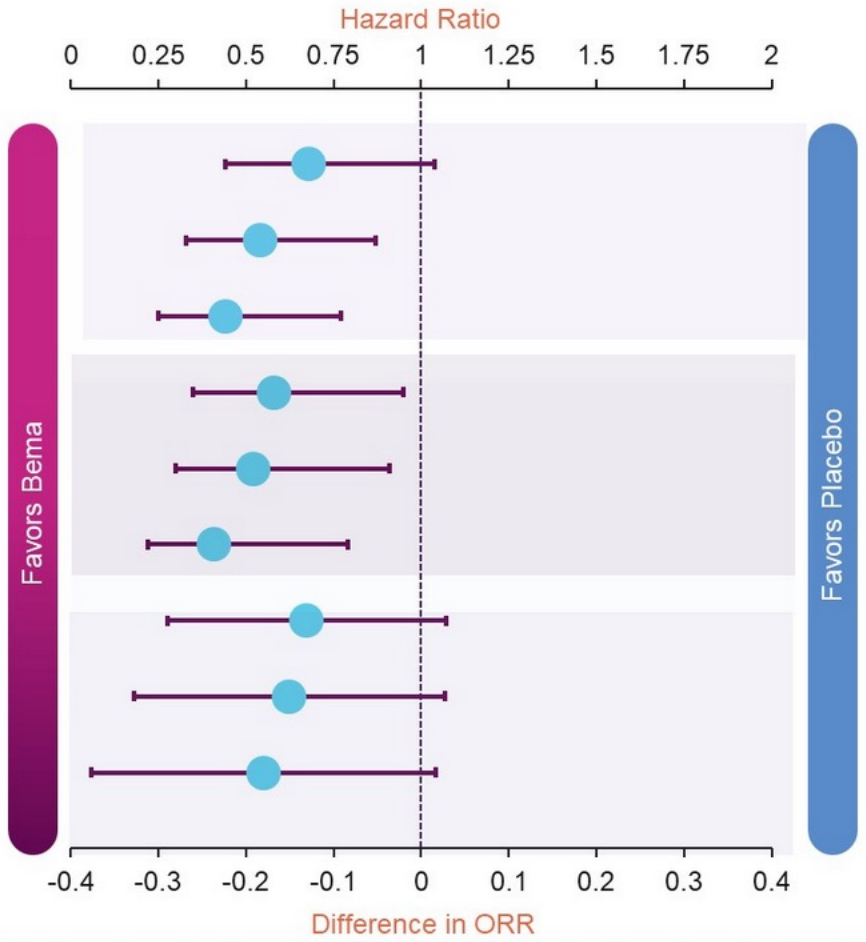
1. Catenacci D, et al. *J Clin Oncol*. 2020.

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

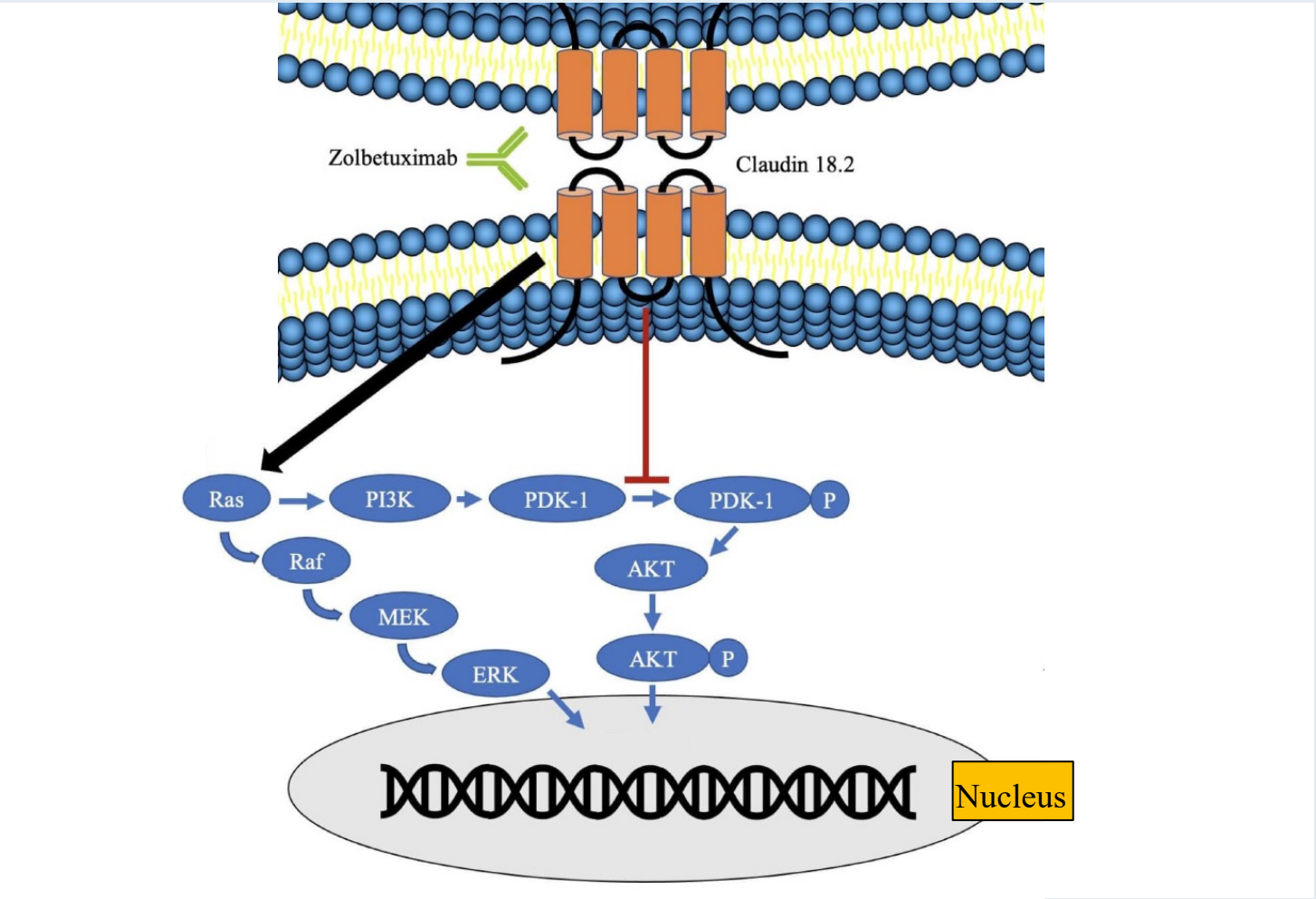
Selected AE (Preferred term)	Any Grade		Grade ≥3	
	Bema (N = 76)	Placebo (N = 77)	Bema (N = 76)	Placebo (N = 77)
Total Events	**76 (100.0%)**	**76 (98.7%)**	**63 (82.9%)**	**57 (74.0%)**
Nausea	36 (47.4%)	41 (53.2%)	0	3 (3.9%)
Vomiting	22 (28.9%)	24 (31.2%)	2 (2.6%)	2 (2.6%)
Diarrhea	31 (40.8%)	24 (31.2%)	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

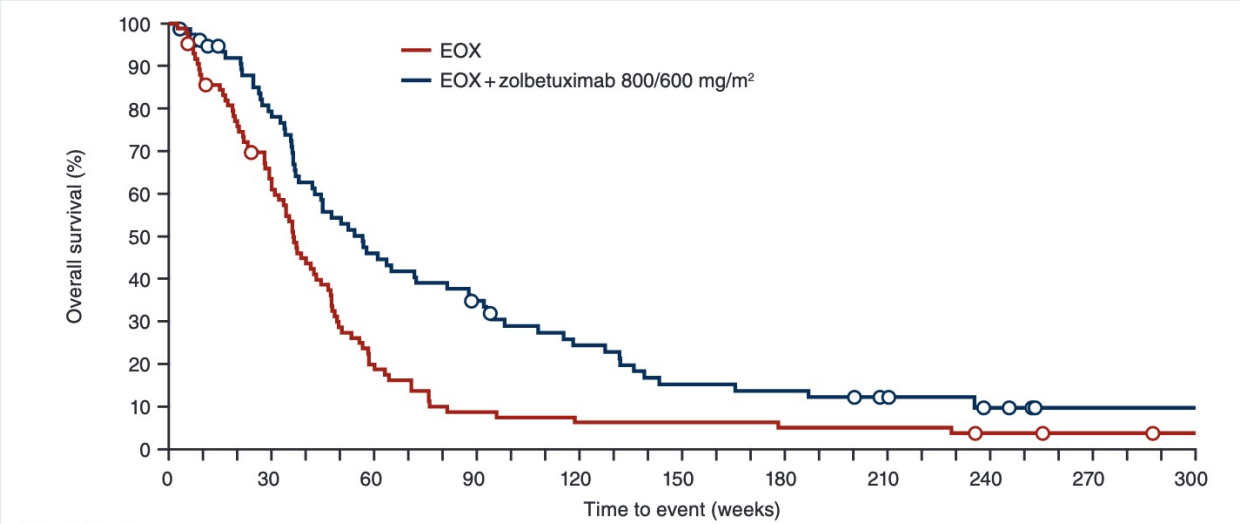
FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EOX versus EOX alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma

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

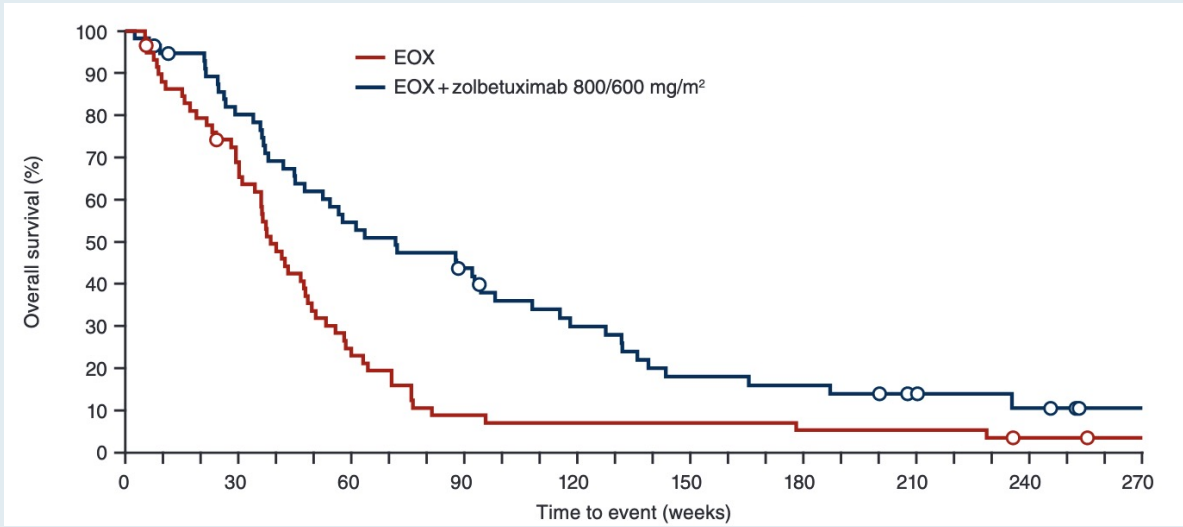
FAST: Overall Survival with Zolbetuximab in Combination with Chemotherapy for Advanced CLDN18.2-Positive Gastric and Gastroesophageal Adenocarcinoma

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.

RTP RESEARCH TO PRACTICE

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

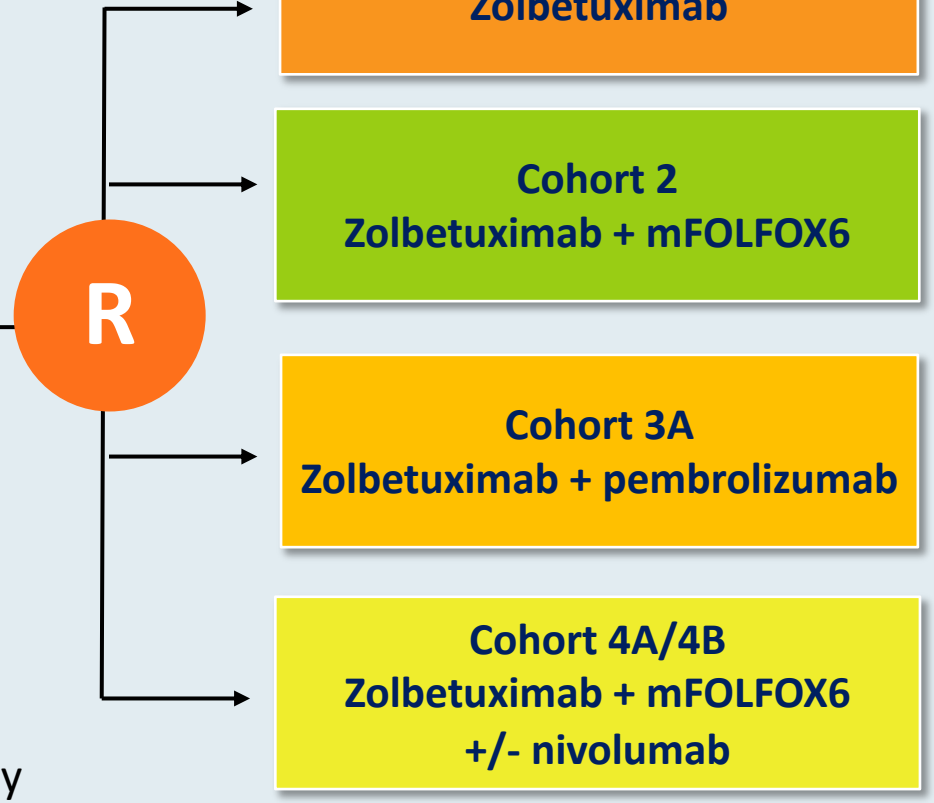
www.clinicaltrials.gov. Accessed March 2022.

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



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

www.clinicaltrials.gov; Accessed March 2022.

Cases from the Community: Urologic Oncology Investigators Provide Perspectives on the Optimal Management of Prostate Cancer and Urothelial Bladder Cancer

Friday, May 13, 2022

Prostate Cancer

8:00 AM – 10:00 AM CT (9:00 AM – 11:00 AM ET)

Faculty

Raoul S Concepcion, MD
Fred Saad, MD
Matthew R Smith, MD, PhD

Moderator

Emmanuel S Antonarakis, MD

Urothelial Bladder Cancer

6:00 PM – 8:00 PM CT (7:00 PM – 9:00 PM ET)

Faculty

Matthew D Galsky, MD
Ashish M Kamat, MD, MBBS
Stephen B Williams, MD, MS

Moderator

Sumanta Kumar Pal, MD

Thank you for joining us!

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

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