Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Gastroesophageal Cancers

Part 2 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Gastrointestinal Cancers Symposium

Thursday, January 19, 2023
6:15 PM – 7:45 PM PT

Faculty

Yelena Y Janjigian, MD
Zev Wainberg, MD, MSc
Florian Lordick, MD, PhD

Moderator

Samuel J Klempner, MD

RTP RESEARCH TO PRACTICE

Faculty

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

Zev Wainberg, MD, MSc
Co-Director, GI Oncology Program
Director of Early Phase Clinical Research
Jonsson Comprehensive Cancer Center
UCLA School of Medicine
Los Angeles, California

Florian Lordick, MD, PhD
Full Professor of Medicine at the University of Leipzig
Director of the University Cancer Center
Head of Department of Oncology
Leipzig University
Leipzig, Germany

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

RTP
RESEARCH
TO PRACTICE

Commercial Support

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

Research To Practice CME Planning Committee Members, Staff and Reviewers

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

Yelena Y Janjigian, MD — Disclosures
Faculty

Consulting Agreements	AmerisourceBergen, Arcus Biosciences, AstraZeneca Pharmaceuticals LP, Basilea Pharmaceutica Ltd, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Daiichi Sankyo Inc, Geneos Therapeutics, GSK, Imugene, Lilly, Lynx Health LLC, Merck, Merck Serono, Mersana Therapeutics Inc, Michael J Hennessy Associates Inc, Pfizer Inc, Rgenix, Seagen Inc, Silverback Therapeutics, Zymeworks Inc
Contracted Research	Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Genentech, a member of the Roche Group, Lilly, Merck, Rgenix
Nonrelevant Financial Relationship	Imedex, Paradigm Medical Communications, PeerView Institute

RTP RESEARCH TO PRACTICE

Florian Lordick, MD, PhD — Disclosures
Faculty

Consulting Agreements	Amgen Inc, Astellas, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Daiichi Sankyo Inc, Lilly, Merck Sharp & Dohme LLC, Novartis, Roche Laboratories Inc
Contracted Research	Bristol-Myers Squibb Company, Gilead Sciences Inc
Data and Safety Monitoring Board/Committee	BioNTech AG
Speakers Bureau	Amgen Inc, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Daiichi Sankyo Inc, Incyte Corporation, Lilly, Merck Serono, Merck Sharp & Dohme LLC, Novartis, Roche Laboratories Inc, Servier Pharmaceuticals LLC
Nonrelevant Financial Relationship	Imedex, Medscape, MedUpdate, Streamedup

RTP
RESEARCH
TO PRACTICE

Zev Wainberg, MD, MSc — Disclosures
Faculty

Advisory Committee and Consulting Agreements	Arcus Biosciences, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Daiichi Sankyo Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Lilly, Merck, Novartis, Pfizer Inc, Roche Laboratories Inc, Seagen Inc
Contracted Research	Arcus Biosciences, Bristol-Myers Squibb Company, Plexxikon Inc
Data and Safety Monitoring Board/Committee	Daiichi Sankyo Inc, Pfizer Inc

RTP
RESEARCH
TO PRACTICE

Samuel J Klempner, MD — Disclosures
Moderator

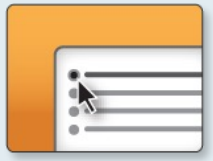
Advisory Committee	Astellas, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Daiichi Sankyo Inc, Exact Sciences Corporation, Lilly, Merck, Mersana Therapeutics Inc, Novartis, Sanofi
Data and Safety Monitoring Board/Committee	Mersana Therapeutics Inc

RTP RESEARCH TO PRACTICE

Clinicians in the Meeting Room

Networked iPads are available for you to

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



Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

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

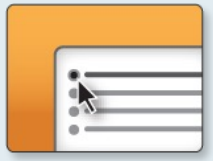
Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

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

RTP RESEARCH TO PRACTICE

Virtual Zoom Clinicians

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



Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

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

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

RTP
RESEARCH
TO PRACTICE

About the Enduring Program

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

RTP
RESEARCH
TO PRACTICE

Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Hepatobiliary Cancers

Part 3 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Gastrointestinal Cancers Symposium

Friday, January 20, 2023

6:00 PM – 7:30 PM PT

Faculty

Richard S Finn, MD

Professor Arndt Vogel, MD

Lipika Goyal, MD, MPhil

Moderator

Robin K (Katie) Kelley, MD

RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Gastroesophageal Cancers

Part 2 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Gastrointestinal Cancers Symposium

Thursday, January 19, 2023
6:15 PM – 7:45 PM PT

Faculty

Yelena Y Janjigian, MD
Zev Wainberg, MD, MSc
Florian Lordick, MD, PhD

Moderator

Samuel J Klempner, MD

RTP RESEARCH TO PRACTICE

Agenda

Module 1 – Optimizing the Selection of Therapy for Newly Diagnosed Advanced Gastric or Gastroesophageal Junction (GEJ) Cancer — Dr Klempner

Module 2 – Current Considerations in the Treatment of HER2-Positive Advanced Gastric/GEJ Adenocarcinoma — Dr Janjigian

Module 3 – Selection and Sequencing of Therapy for Relapsed/Refractory Gastric/GEJ Cancer; Novel Investigational Approaches — Prof Lordick

Module 4 – Current Approaches to the Management of Esophageal Cancer — Dr Wainberg

RTP
RESEARCH
TO PRACTICE

Warren S Brenner, MD
Lynn Cancer Institute
Boca Raton, Florida

Ranju Gupta, MD
Lehigh Valley Topper
Cancer Institute
Bethlehem, Pennsylvania

Farshid Dayyani, MD, PhD
UCI Chao Family Comprehensive
Cancer Center
Orange, California

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

Victoria Giffi, MD
Meritus Hematology and
Oncology Specialists
Hagerstown, Maryland

RTP
RESEARCH
TO PRACTICE

Namrata I Peswani, MD
Harold C Simmons Comprehensive Cancer Center
Richardson, Texas

Liudmila N Schafer, MD
Saint Luke's Cancer Institute
Kansas City, Missouri

Priya Rudolph, MD, PhD
Georgia Cancer Specialists
Athens, Georgia

Matthew R Strickland, MD
Massachusetts General Hospital Cancer Center
Boston, Massachusetts

RTP
RESEARCH TO PRACTICE

MODULE 1: Optimizing the Selection of Therapy for Newly Diagnosed Advanced Gastric or Gastroesophageal Junction (GEJ) Cancer — Dr Klempner

RTP
RESEARCH
TO PRACTICE

Case Presentation: 55-year-old man with HER2-negative gastroesophageal adenocarcinoma (PD-L1 = 100%)

Dr Victoria Giffi (Hagerstown, Maryland)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Victoria Giffi, MD

"My question with this gentleman is, if he remains in a complete response on maintenance therapy would you consider sending him for definitive surgery, particularly if we continue to have trouble with his stenosed esophagus. Is there a role for radiation therapy?"

- **What is your off-trial approach to first-line therapy for metastatic HER2-negative gastroesophageal (GE) cancer, specifically as it relates to the use of checkpoint inhibitors?**
- **What PD-L1 assay do you use? How does it factor into your decision?**
- **What about tumor location and histology?**

RTP
RESEARCH
TO PRACTICE

Dr Matthew Strickland
(Boston, Massachusetts)

81-year-old woman with a history of Stage 0 CLL, now with unresectable gastric adenocarcinoma, develops Coombs-positive hemolytic anemia after 2 cycles of FOLFOX and nivolumab

Dr Priya Rudolph
(Athens, Georgia)

61-year-old man with localized adenocarcinoma of the GEJ receives the CROSS regimen but is found at surgery to have metastatic disease. Tumor NGS demonstrates an ARID1A mutation

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Matthew R Strickland, MD

"She presents for cycle 3 of FOLFOX/nivolumab with shortness of breath and a hemoglobin of 6. Coombs test is positive with both IgG and complement. She receives prednisone and rituximab. For this patient, would you rechallenge with nivolumab?"

- **What are the common autoimmune complications you have observed in patients with GE cancers receiving checkpoint inhibitors?**
- **What in your mind are the contraindications to the use of checkpoint inhibitors in this setting in terms of prior transplant and autoimmune disease?**

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Priya Rudolph, MD, PhD

"I started him on modified FOLFOX6 with nivolumab. Sadly, he had ongoing worsening dysphagia and severe pain. I would love to know if the faculty have encountered any similar cases where they have proceeded with esophagectomy despite metastatic disease just for quality of life and debulking. I would also like to know if there are any clinical trials with the ARID1A mutation."

- **What targetable mutations are commonly identified on tumor NGS in patients with metastatic GE tumors? Do you ever do repeat mutation testing? What is the role/value of liquid biopsy?**
- **What is your experience with various local palliative procedures for obstruction in GE cancers?**

RTP
RESEARCH
TO PRACTICE

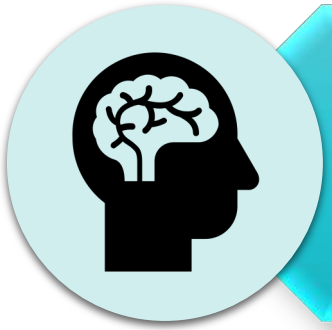
Mass General Brigham

Optimizing the Selection of Therapy for Newly Diagnosed Advanced Gastric or Gastroesophageal Junction (GEJ) Cancer

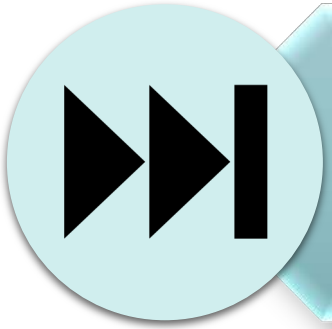
Sam Klempner, MD
Mass General Cancer Center

1/19/2023

Biomarker Overview

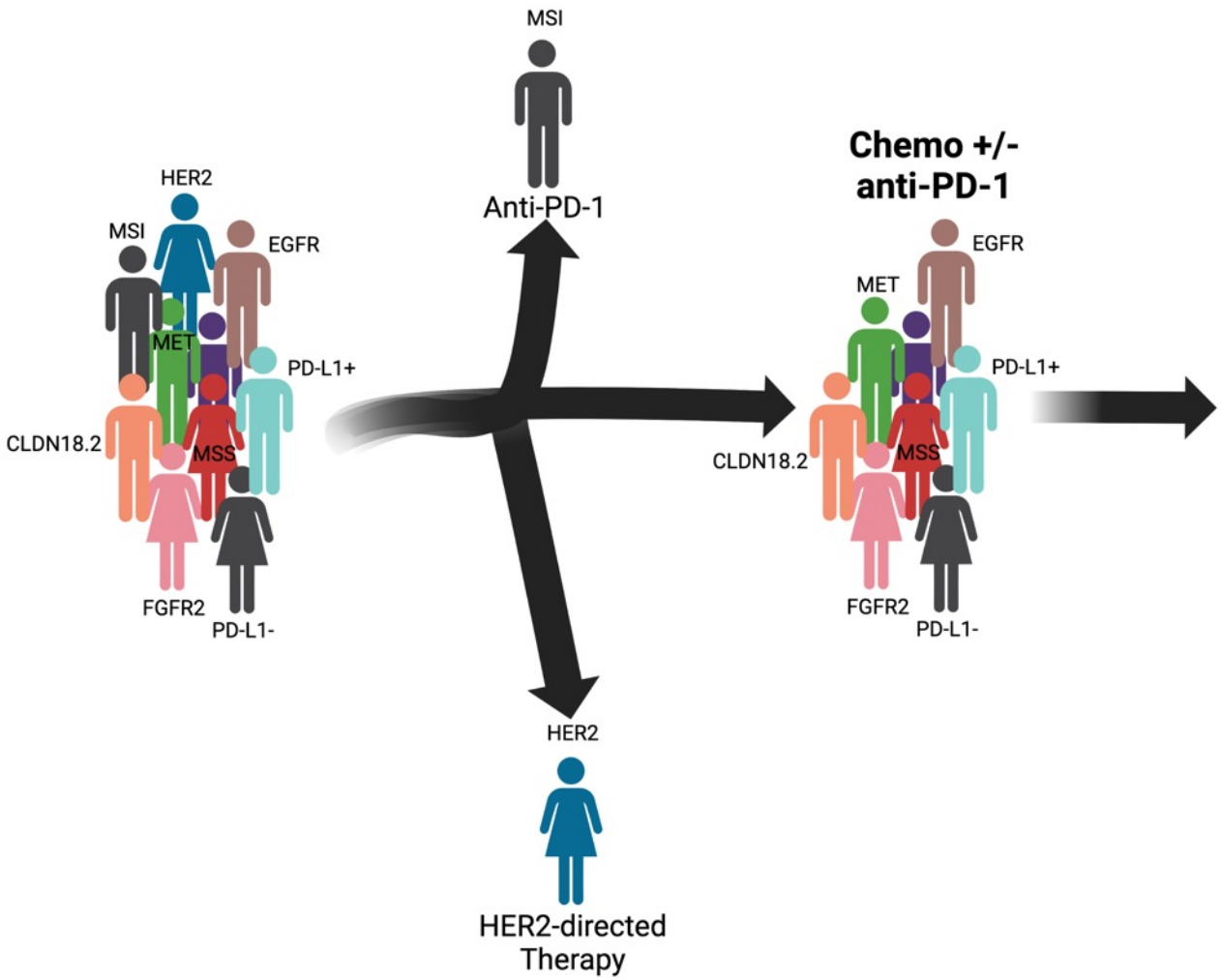


Biomarker Focus on MSI

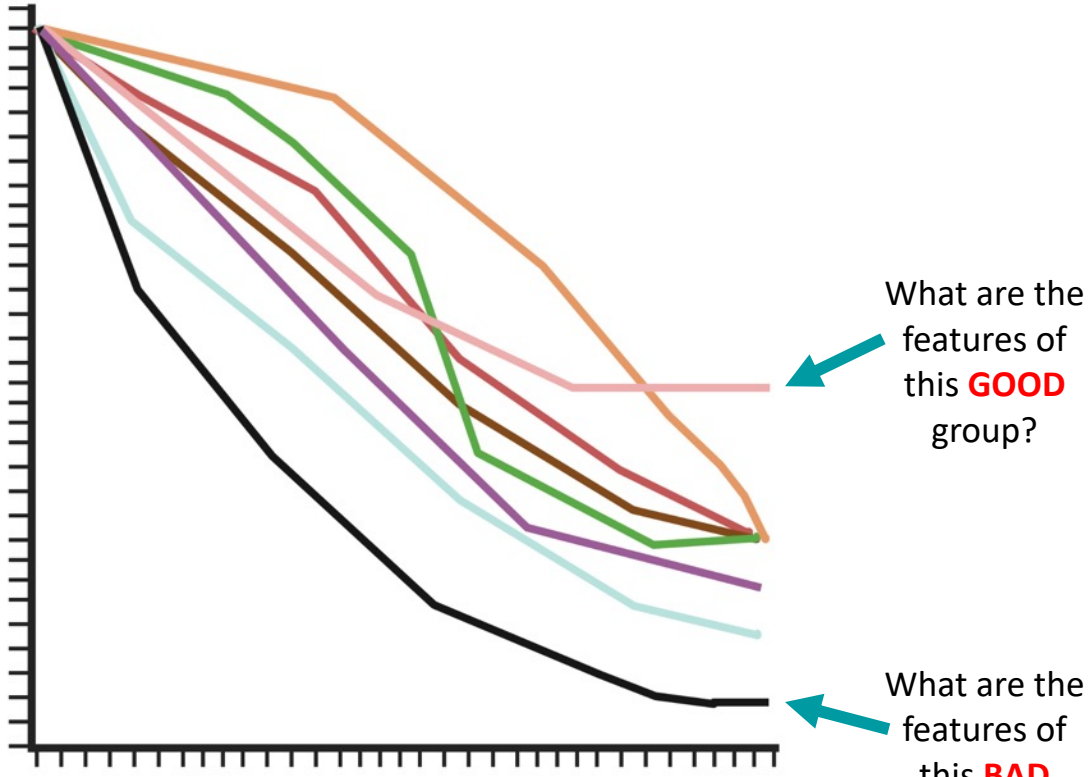


1L HER2- Standards

Gastroesophageal Adenocarcinomas are Heterogeneous



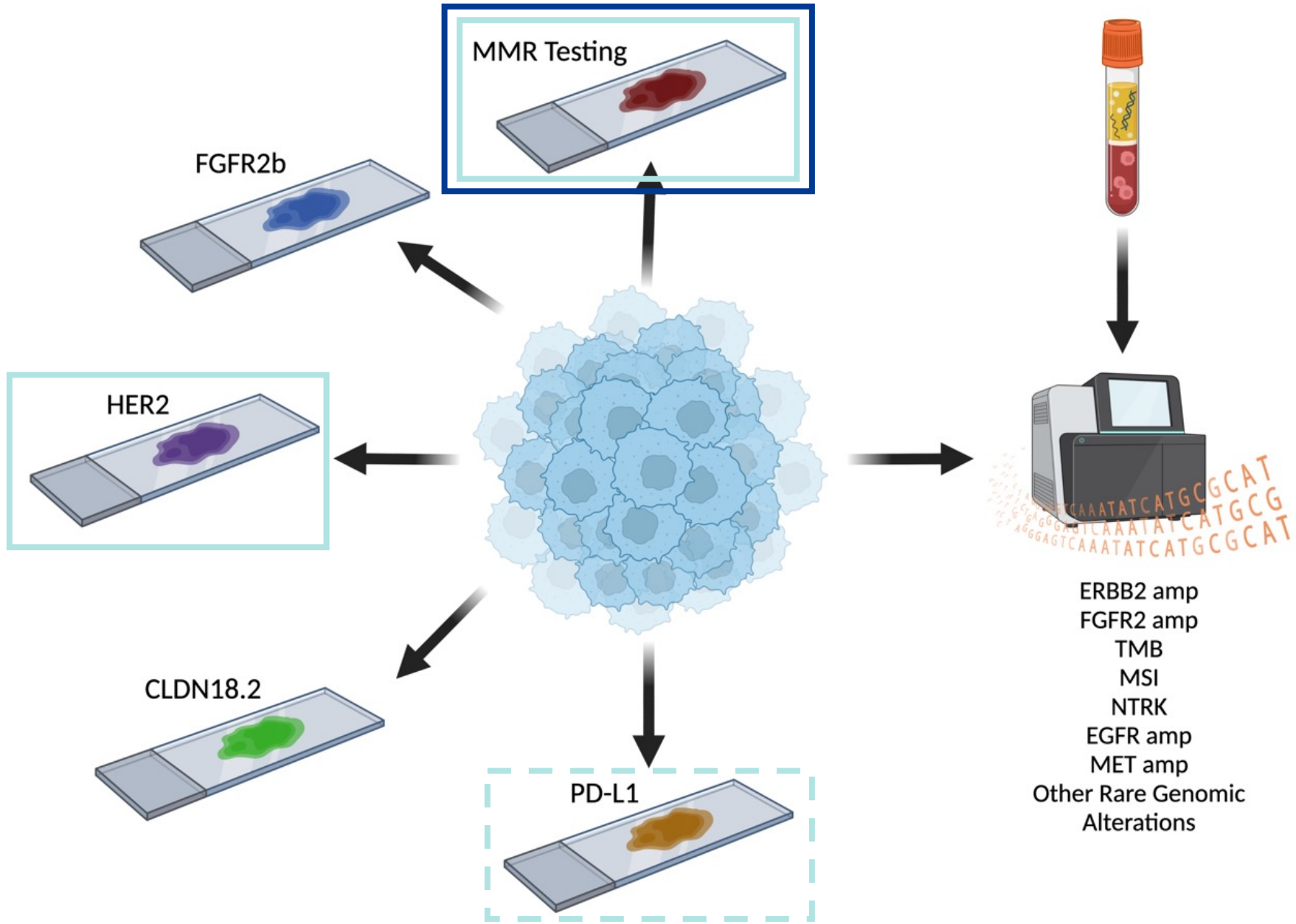
We Are Treating Different Patients the Same!



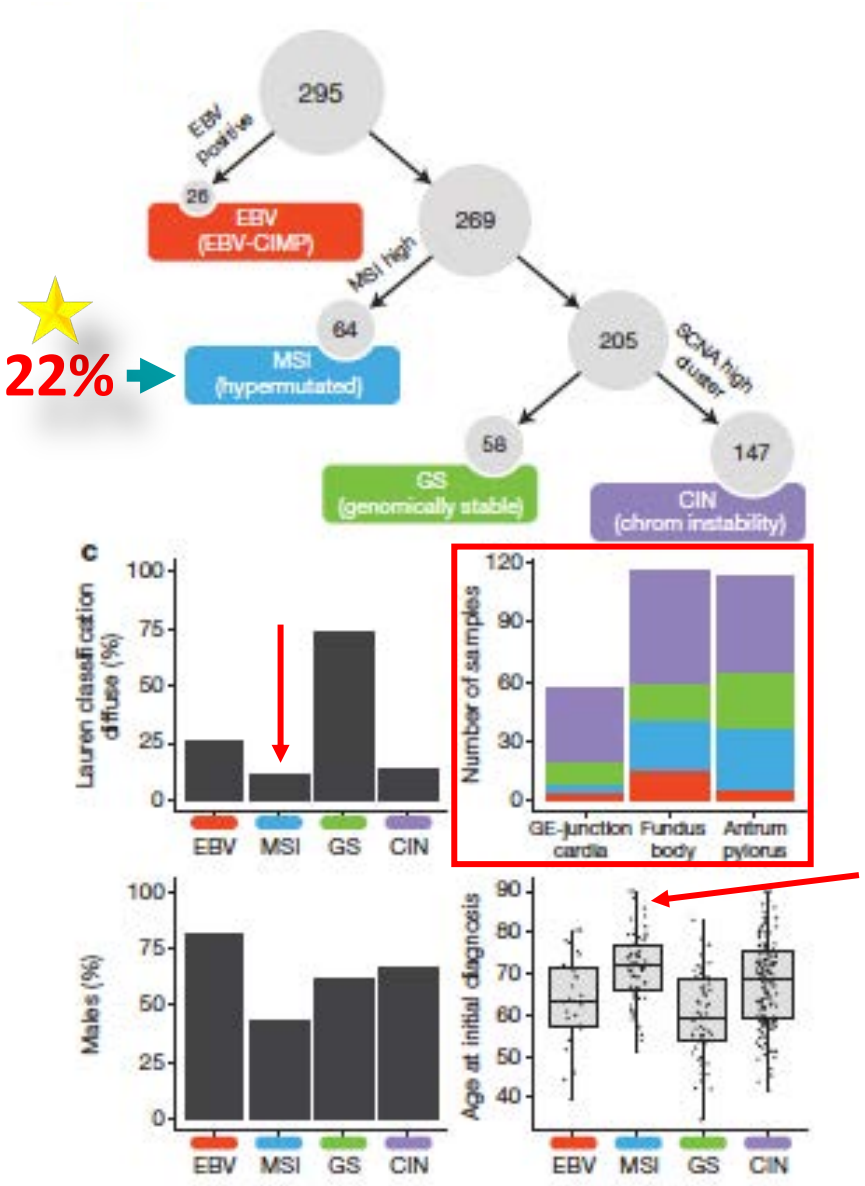
Key Biomarkers to Know

Need to Know for ALL Advanced GEA

Should Know for Localized GEA



dMMR and MSI-High GEA: Epidemiology



Nature 2014

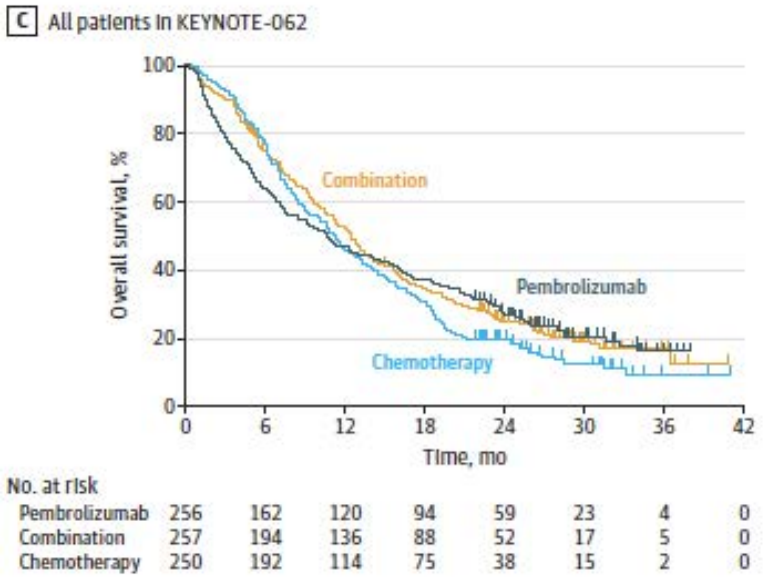
NON-METASTATIC DISEASE

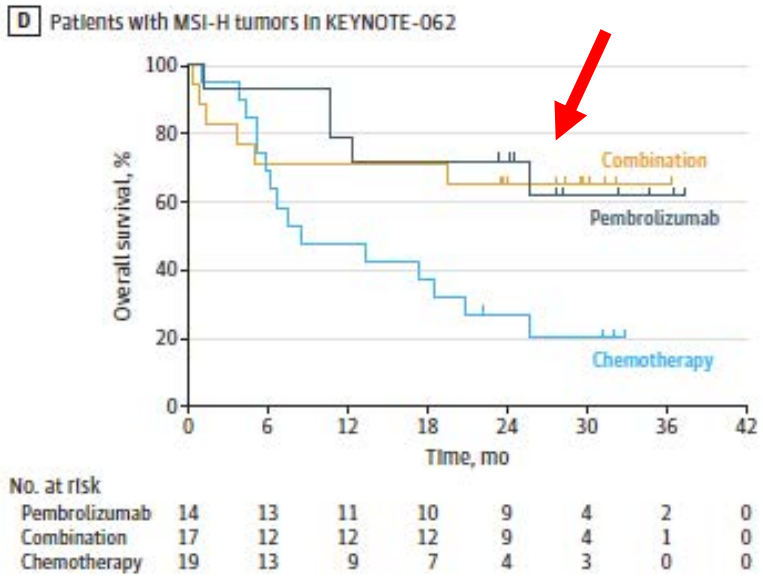
- DANTE: **7.8%** (23/295) – ASCO 2022
- Pooled meta (MAGIC, ARTIST, CLASSIC, ITACA-S): **7.8%** (121/1,556) – JCO 2019
- TCGA (mostly non-met samples): **22%** -- Nature 2014
- NEONIPIGA: N/A – JCO 2022

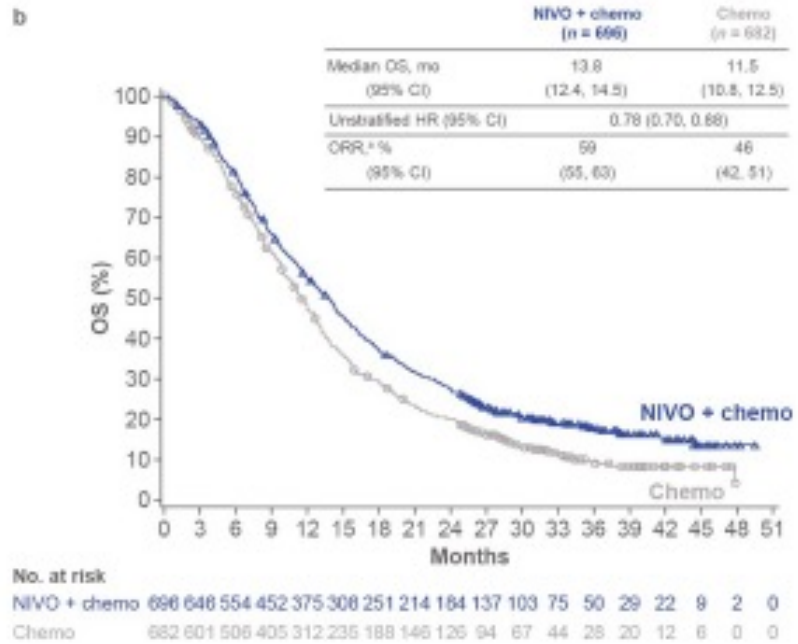
METASTATIC DISEASE

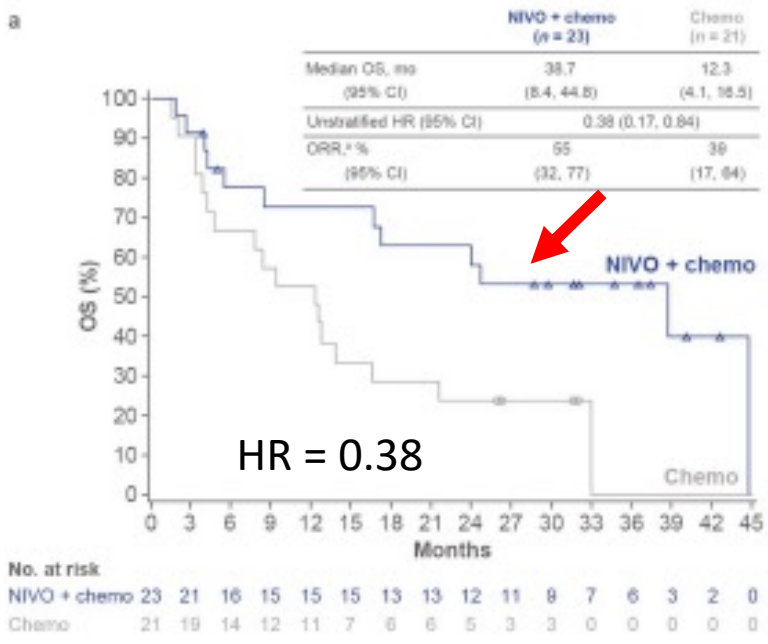
- CM-649: **3%** MSI-H – Nature 2022
- Attraction-4: Not reported – Lancet Onc 2022
- KN-061: **4.5%** (27/592) – Gastric Cancer 2021, reported as 5.3% in 2021 JAMA Meta from Keynote trials
- KN-059: **4.0%** (7/174) – JAMA Onc 2021
- KN-062: **7.3%** (50/682) – JAMA Onc 2021

ICIs Work in Advanced dMMR/MSI-H GEA







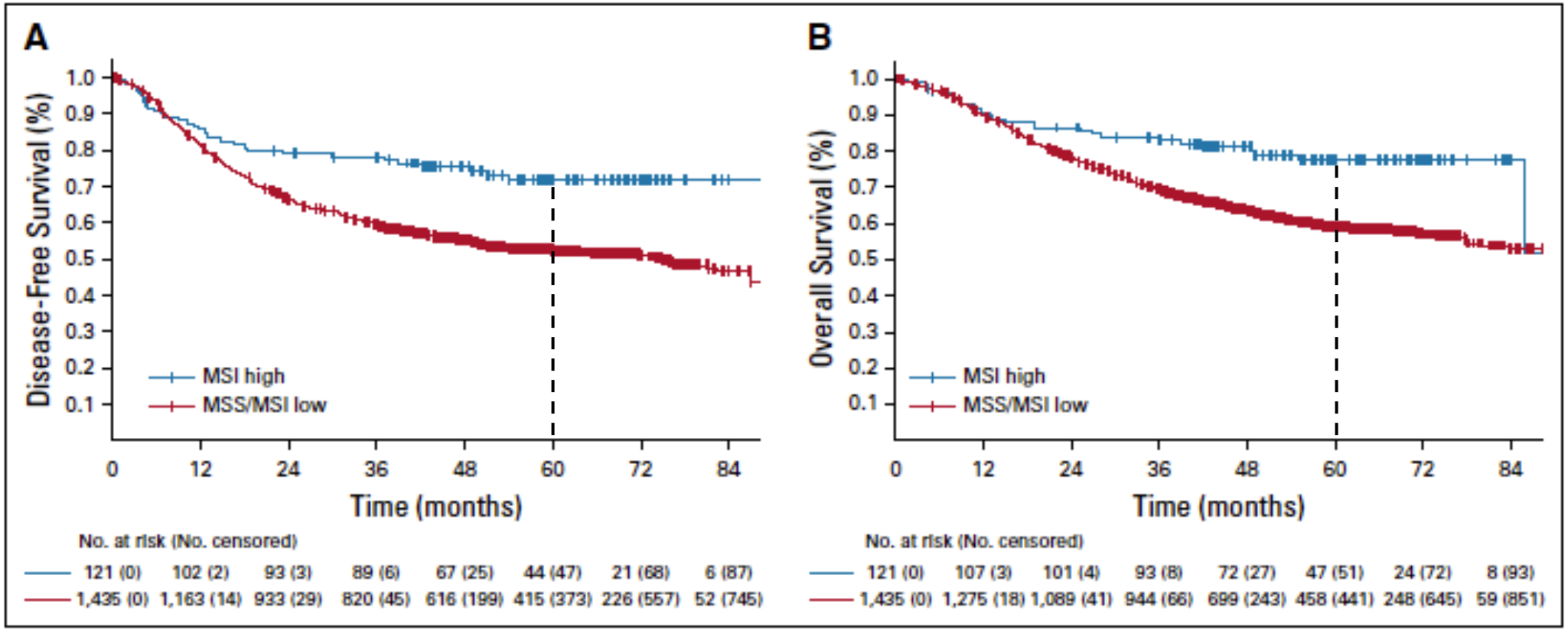


- ORR with PD-1 alone = ~55%
- ORR with Chemo-PD-1 = 55-65%
- ORR for Ipi/Nivo = 70%
- ORR for chemo = 37-39%
- 24m OS rate w/PD-1 = ~70%
- Responses are often very durable
  (median DoR = 21m with Pembro alone in KN-062)
- This is a unique biologic subgroup
- Increase enthusiasm for exploring in earlier disease

JAMA Onc 2021, Nature 2022

Why MMR/MSI Testing in Localized GEA?

Because they behave different, and it matters



Localized dMMR/MSI-H GEA have a better prognosis

5-year DFS = 72% vs. 52%

5-year OS = 78% vs 59%

JCO 2019

Periop/Adjuvant Chemo May Offer Little in dMMR/MSI

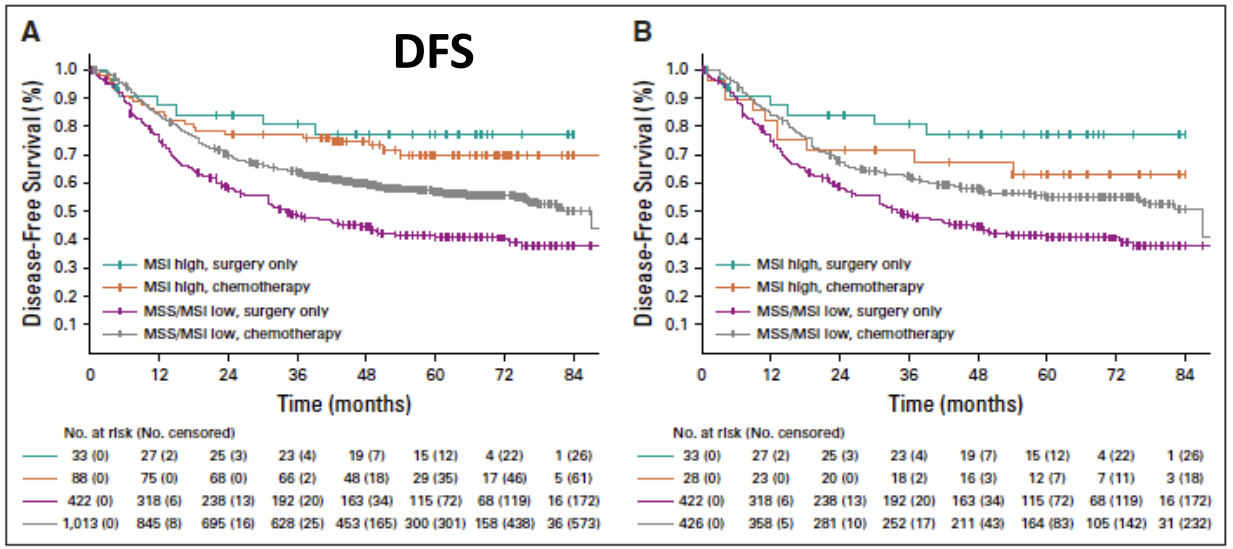


FIG 3. Kaplan-Meier curves of disease-free survival according to treatment (surgery plus chemotherapy *v* surgery only) and microsatellite-instability (MSI) status (MSI-high *v* microsatellite stable [MSS]/MSI-low) in (A) whole trial population and (B) MAGIC and CLASSIC trials only.

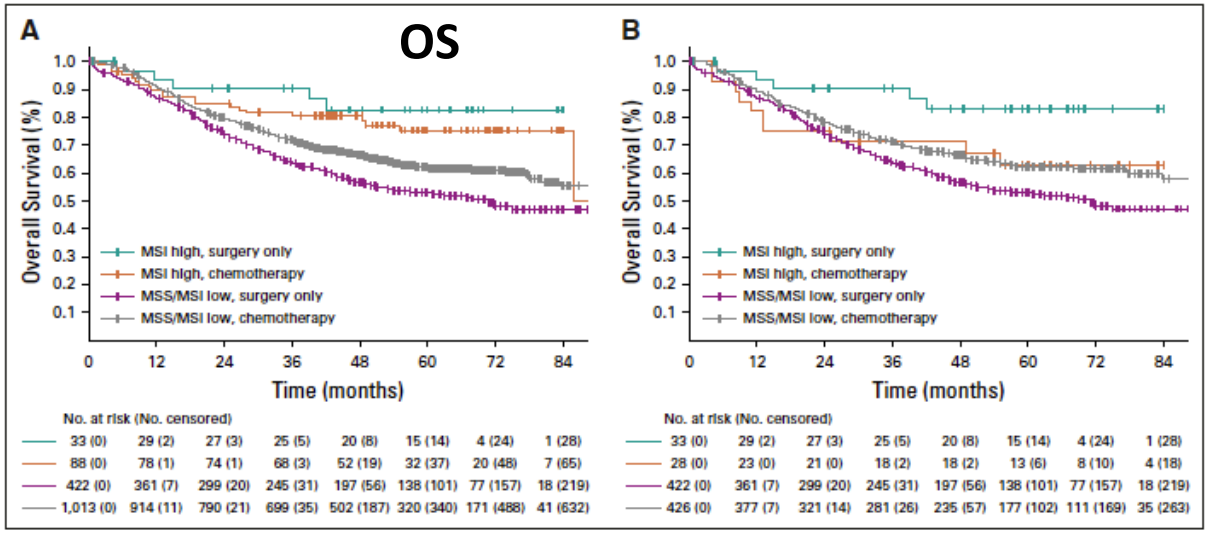
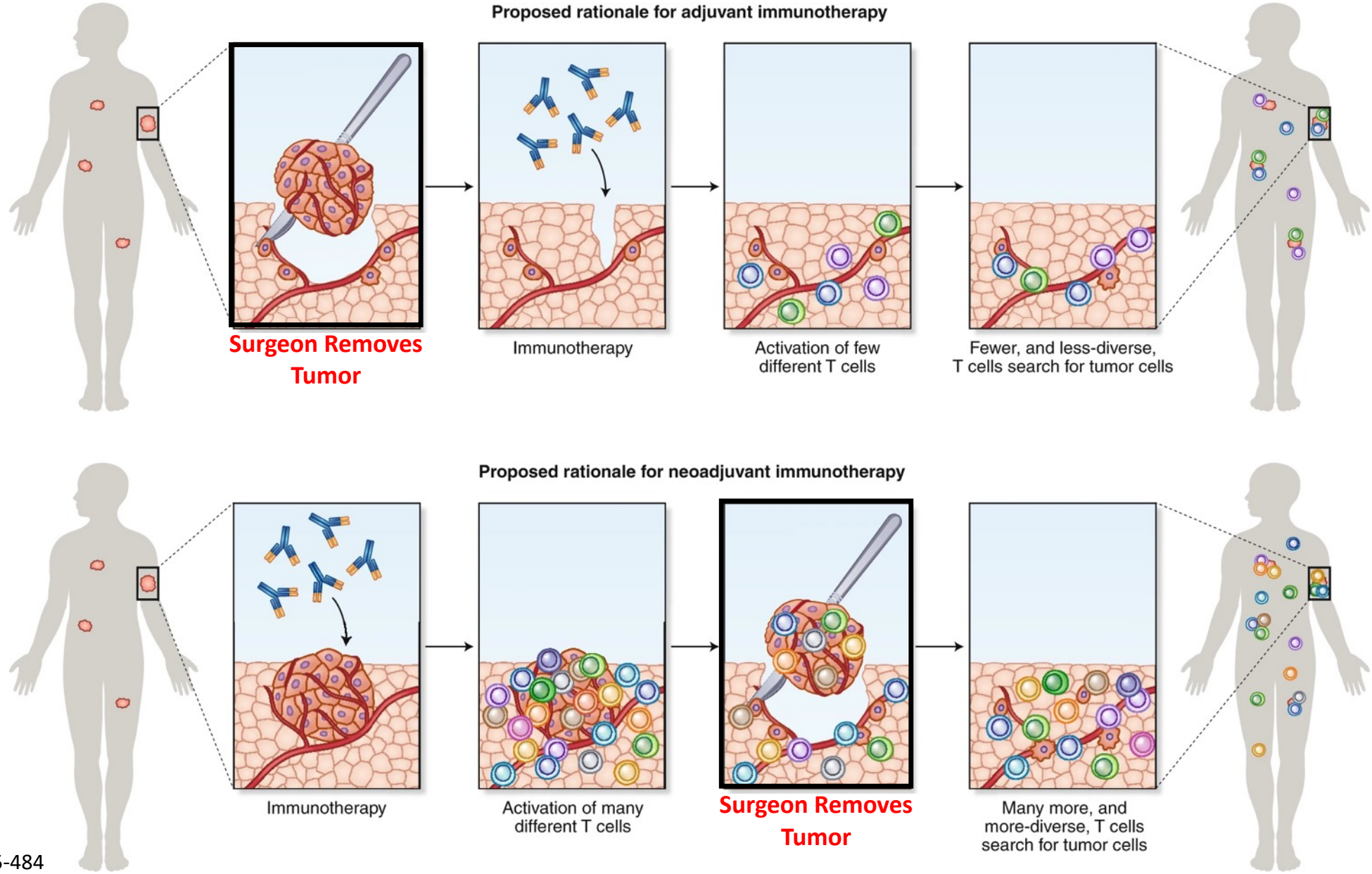


FIG 4. Kaplan-Meier curves of overall survival according to treatment (surgery plus chemotherapy *v* surgery only) and microsatellite-instability (MSI) status (MSI-high *v* microsatellite stable [MSS]/MSI-low) in (A) whole trial population and (B) MAGIC and CLASSIC trials only.

- Data suggest dMMR/MSI-H patients do not benefit from periop and/or adjuvant chemotherapy
- Suggest approach with up front resection as consideration
- Data do not include modern standard of FLOT
- Retrospective, somewhat heterogeneous datasets

JCO 2019

Rationale for ICIs in Non-Metastatic GEA



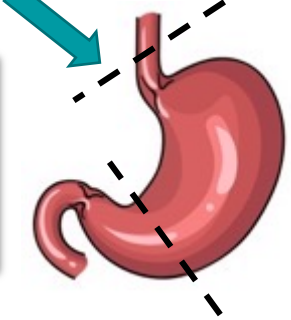
Nat Med 2020;26:475-484

Bringing ICIs Earlier in dMMR/MSI-H GEA: NEONIPIGA

- dMMR/MSI GC/GEJ
- T2-4, Nx cM0
- Phase II
- Western population

Surgery

Neoadjuvant Ipi/Nivo x 3m

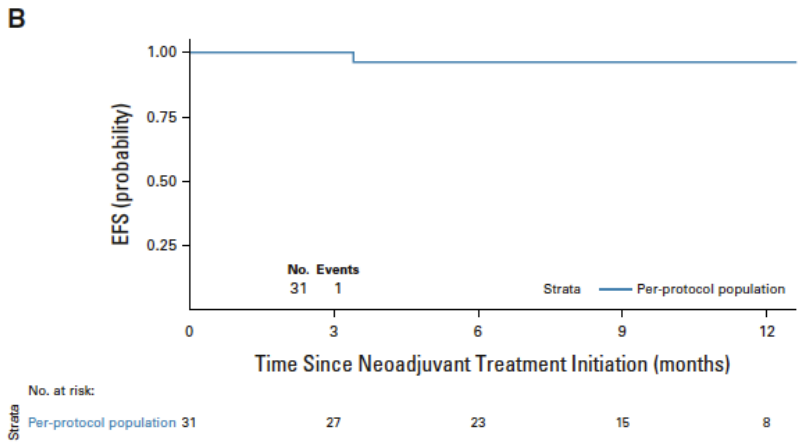


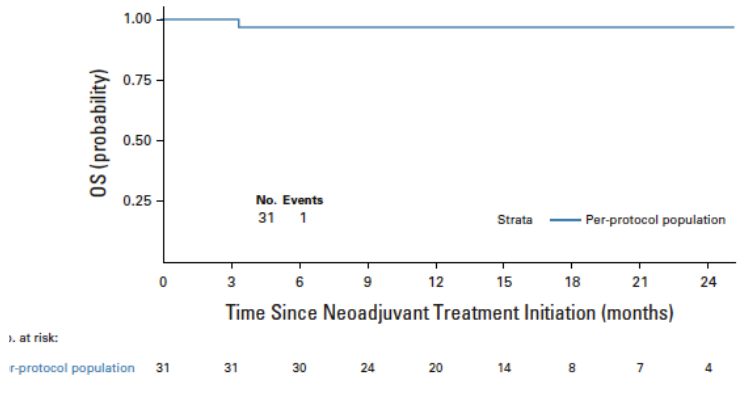
Adjuvant Nivo x 9m

Primary Endpoint = Path CR rate
29/32 (91%) Underwent surgery
pCR rate = 59%

79% with significant path response (TRG1, 2)

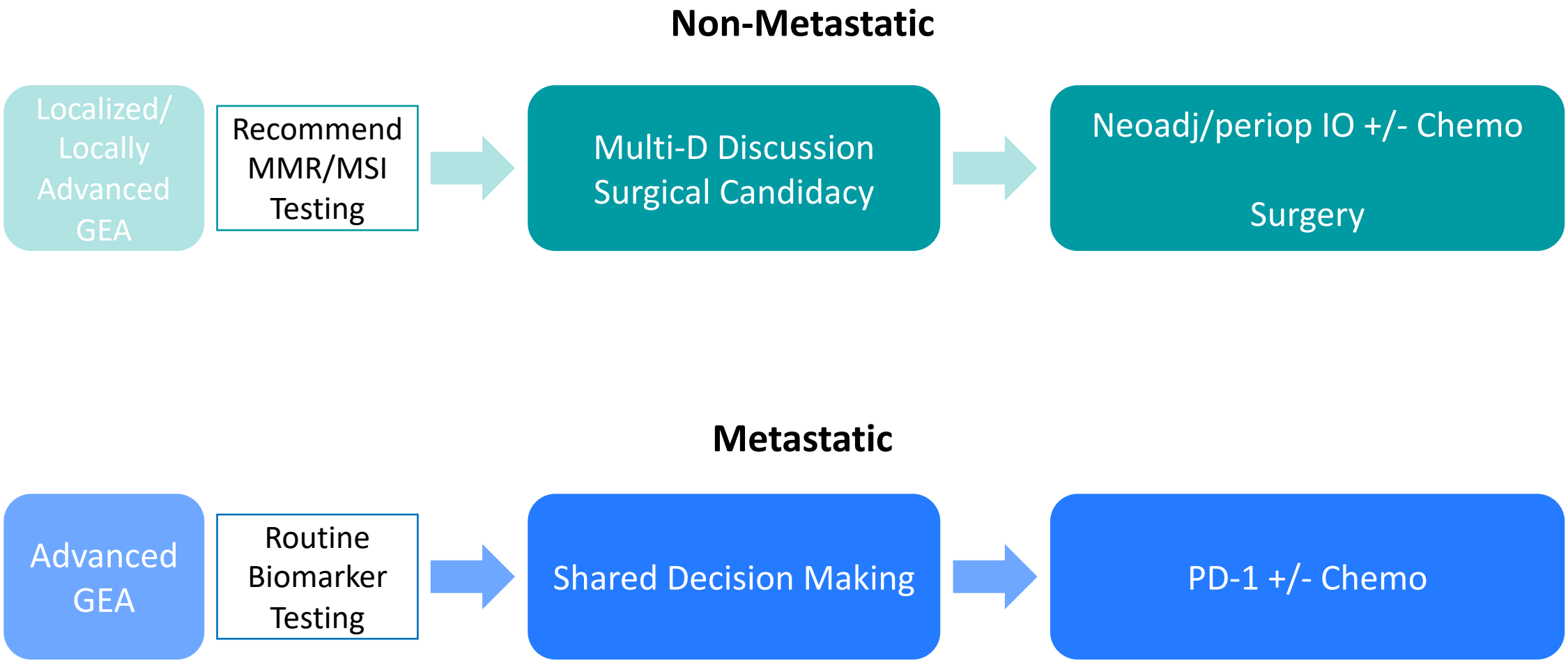
Encouraging early EFS and OS





JCO 2022

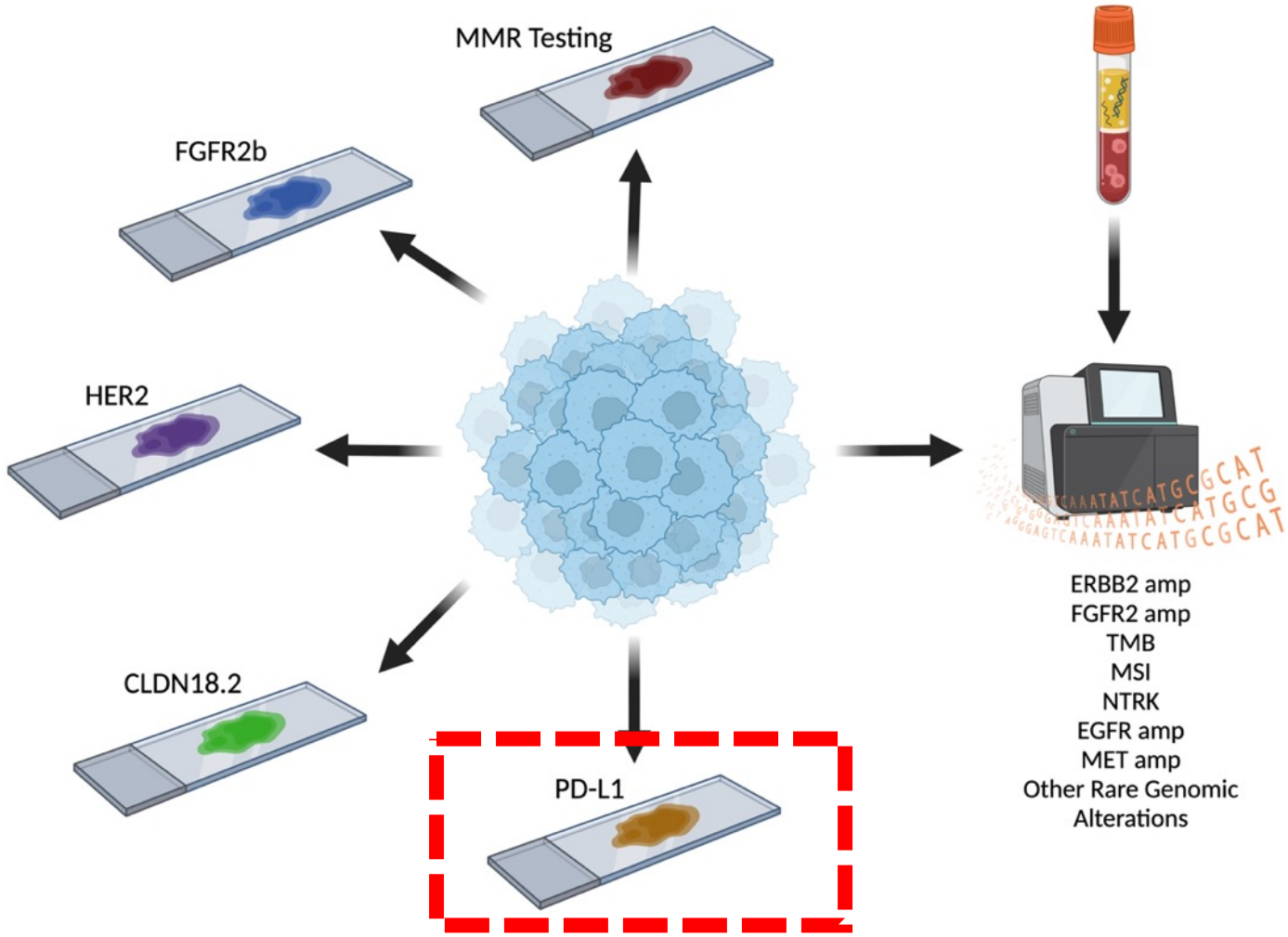
Managing dMMR/MSI-H GEA*



Focusing on Frontline Chemo-IO Approaches in HER2-, MSS

PD-L1 IHC Strata Prevalence

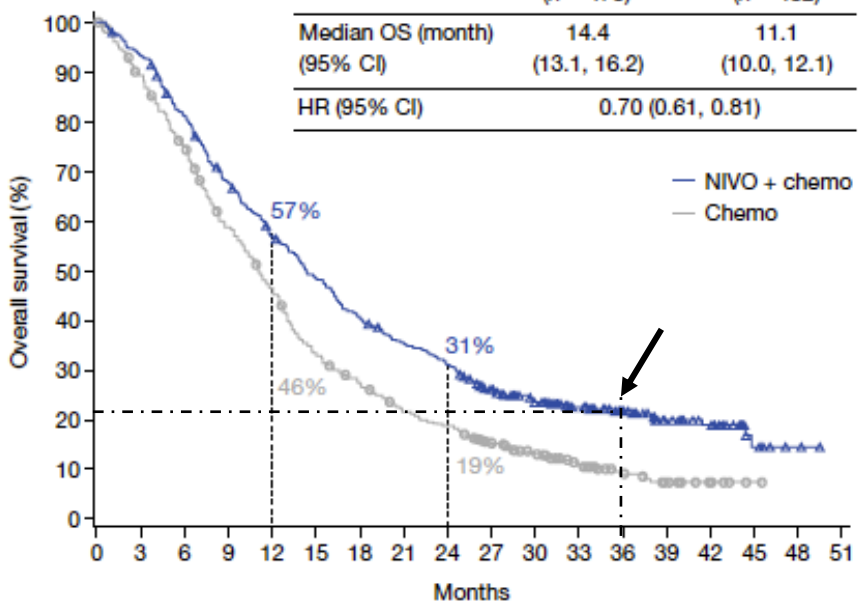
PD-L1 Strata	CM-649	ORIENT-16	ATT-4	KN-062
CPS < 1	17%	16%*	NR	0%
CPS ≥ 1	82%	84%	NR	100%
CPS 1-4	22%*	NR	NR	NR
CPS <5	38%	40%*	NR	NR
CPS ≥5	60%	60%	NR	NR
CPS 5-9	NR	NR	NR	NR
CPS 1-9	NR	NR	NR	64%*
CPS <10	50%	55%*	NR	64%*
CPS ≥10	49%	44%	NR	36%



Frontline Chemo-PD-1 is Here to Stay: CM-649

OS in CPS ≥ 5

	NIVO + chemo (*n* = 473)	Chemo (*n* = 482)
Median OS (month)	14.4	11.1
(95% CI)	(13.1, 16.2)	(10.0, 12.1)
HR (95% CI)	0.70 (0.61, 0.81)	

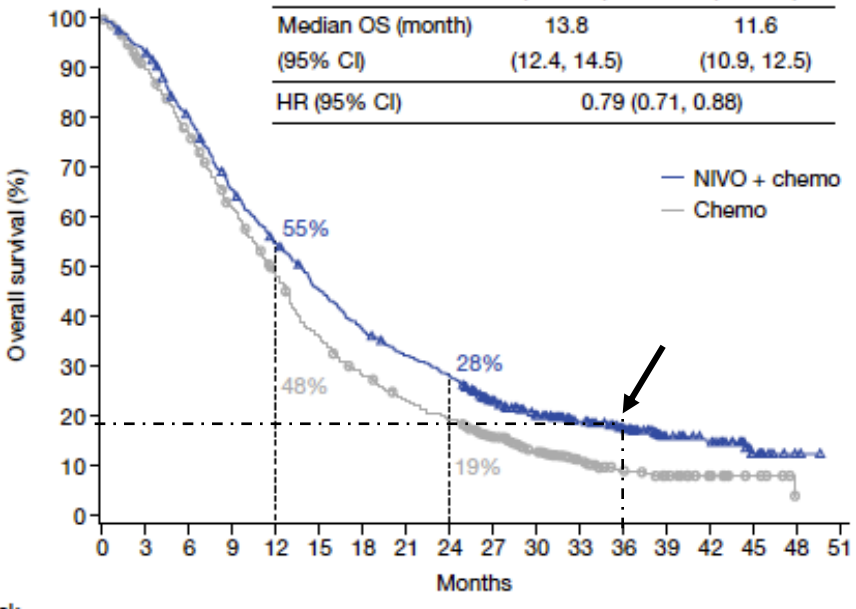


No. at risk

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

OS in CPS All Randomized

	NIVO + chemo (*n* = 789)	Chemo (*n* = 792)
Median OS (month)	13.8	11.6
(95% CI)	(12.4, 14.5)	(10.9, 12.5)
HR (95% CI)	0.79 (0.71, 0.88)	



No. at risk

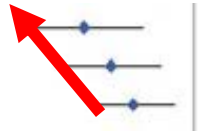
NIVO + chemo	789	733	624	508	422	349	287	246	212	156	115	84	57	33	25	9	2	0
Chemo	792	701	591	475	364	273	215	170	144	103	72	46	28	20	12	6	0	0

- CM-649 is a positive trial for CPS ≥ 5 (primary) and all randomized (secondary)
- 4/2021: Nivo FDA approved with 5FU/platinum for advanced/metastatic GEA, regardless of PD-L1
- 15% increase in G3-4 TRAEs (59% vs 44%) in nivo-chemo vs. chemo

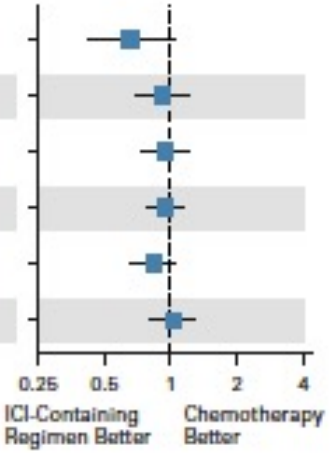
Lancet 2021, Nature 2022

PD-L1 Strata in Frontline Chemo-IO

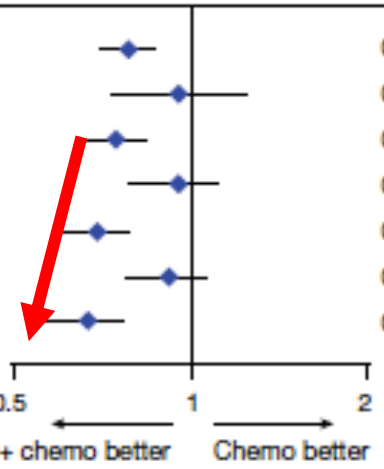
PD-L1 expression	CPS ≥10	146	142	0.56 (0.41-0.77)
	CPS ≥5	197	200	0.64 (0.49-0.84)
	CPS ≥1	275	271	0.73 (0.58-0.90)



Trial	Comparison	No.	Location	PD-L1 Expression	HR (95% CI)
KEYNOTE-590	Pembrolizumab plus chemotherapy *v* chemotherapy	54 *v* 46	Esophageal	CPS < 10	0.66 (0.42 to 1.04)
CheckMate-649	Nivolumab plus chemotherapy *v* chemotherapy	137 *v* 148	Gastric	CPS < 1	0.92 (0.70 to 1.23)
CheckMate-649	Nivolumab plus chemotherapy *v* chemotherapy	168 *v* 173	Gastric	CPS 1–4	0.95 (0.75 to 1.21)[a]
CheckMate-649	Nivolumab plus chemotherapy *v* chemotherapy	316 *v* 310	Gastric	CPS < 5	0.94 (0.78 to 1.13)
KEYNOTE-062	Pembrolizumab plus chemotherapy *v* chemotherapy	158 *v* 160	Gastric	CPS 1–9	0.84 (0.66 to 1.06)[a]
KEYNOTE-062	Pembrolizumab *v* chemotherapy	164 *v* 160	Gastric	CPS 1–9	1.03 (0.81 to 1.30)[a]



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)



- Outside dMMR/MSI-H PD-L1 CPS expression is the best predictor of ICI benefit in frontline GEA
- The magnitude of benefit differs across PD-L1 CPS subgroups
- Risk/benefit should be discussed with all patients
- PD-L1 testing remains important

ESMO 9/2021, JCO 2022, Nature 2022

Biomarker Spectrum -- Magnitude of PD-1 Benefit

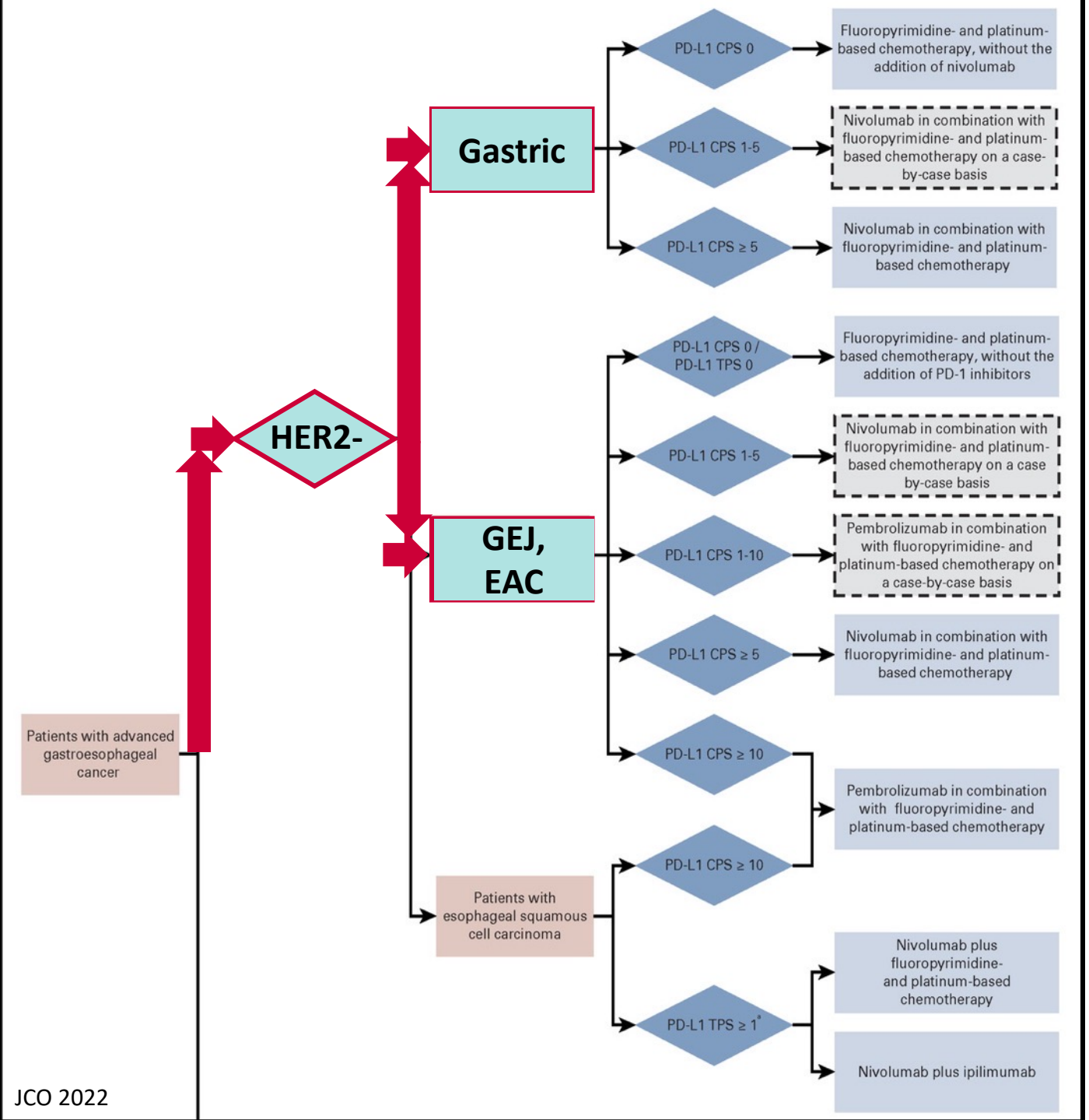
5FU/Plat + Nivo

CPS ≥ 5, HR = 0.69
MSI-H, HR = 0.38

5FU/Plat + Nivo

CPS < 1, HR = 0.95
CPS < 5, HR = 0.94

- ESMO has a scoring system
- ESMO MCBS (Magnitude of Clinical Benefit Scale)
- Scores 1-5 in advanced setting
- Scores of 4 and 5 are "high level of proven clinical benefit"
- Nivolumab score = 2 for Gastric or GEJ adeno in 1L



JCO 2022

ASCO Guidance 1L

- PD-L1 **CPS** testing helps to inform role for IO in 1L for EAC, GEJ, GC
- PD-L1 **TPS** may be better predictor in ESCC
- Approach to CPS consideration similar in GEJ adeno and GC
- ASCO guidance is somewhat divergent from FDA labels in GEJ/GC
- Shared decision making remains important

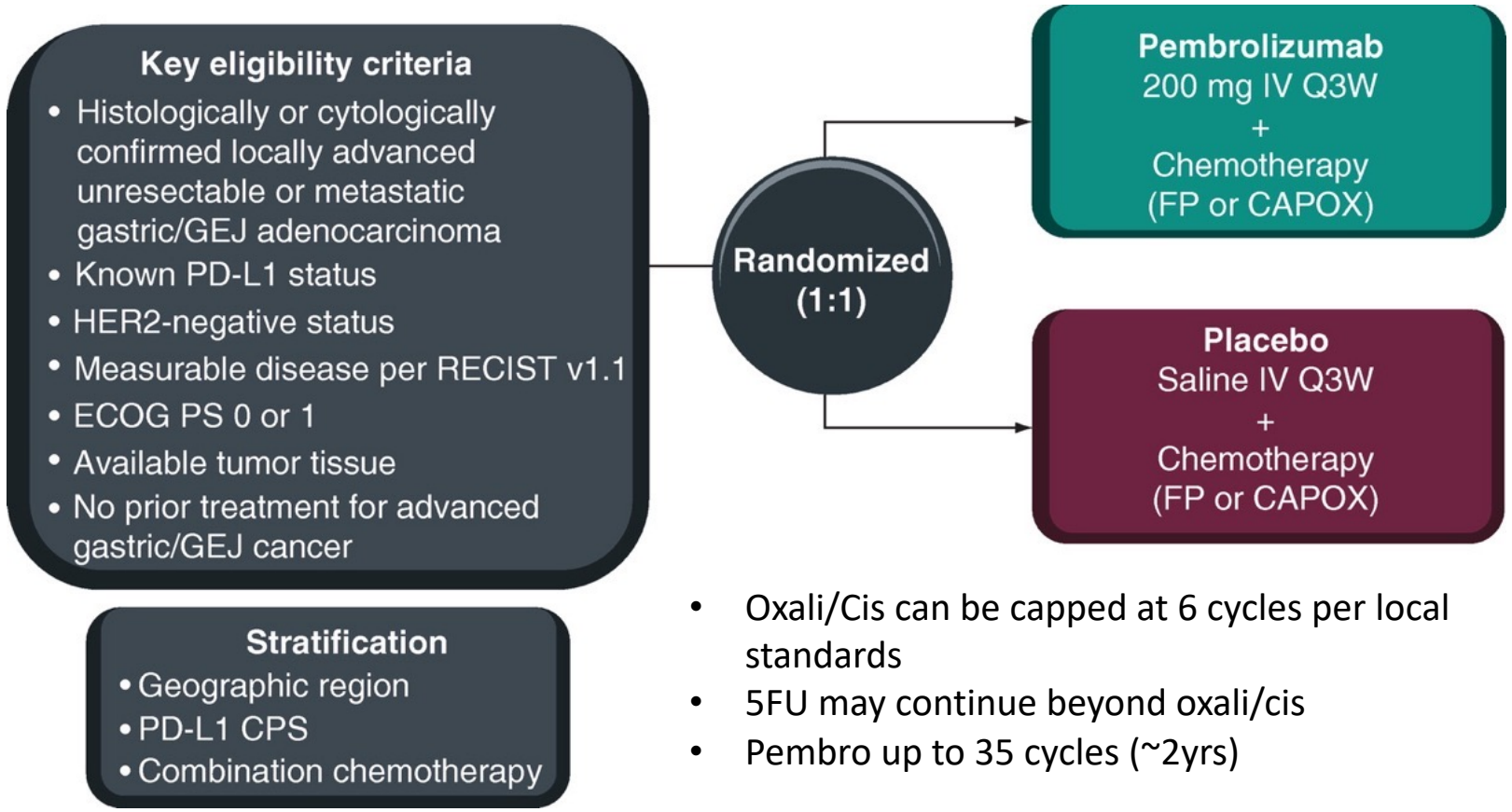

Brah, Use the Biomarkers!
Nah Brah, PD-1 for Everyone!

Check but Not Checkmate

PD-L1 CPS < 1, CPS 1-4?

PD-L1 CPS ≥ 5, dMMR/MSI-H

Other Chemo-IO Approaches: KEYNOTE-859



- Oxali/Cis can be capped at 6 cycles per local standards
- 5FU may continue beyond oxali/cis
- Pembro up to 35 cycles (~2yrs)

- Sample size = 1,579pts
- Primary Endpoint = OS
- Secondary = PFS, ORR, DOR

11/22/2022: Merck press release that KN-859 met OS in all randomized, and that PFS and ORR were improved vs chemo

Take Home Points

- Biomarker testing, including HER2, MMR/MSI, and PD-L1 are critical to informing the frontline management of advanced GEA
- There is increasing literature supporting MMR/MSI testing for non-metastatic GEA
- Neoadjuvant, and/or perioperative ICI, is a promising strategy in dMMR/MSI-H patients, likely limited role for chemo
- 5FU/oxaliplatin +/- PD-1 is the standard frontline approach for HER2-, MSS GEA

MODULE 2: Current Considerations in the Treatment of HER2-Positive Advanced Gastric/GEJ Adenocarcinoma — Dr Janjigian

RTP
RESEARCH
TO PRACTICE

Case Presentation: 31-year-old woman with newly diagnosed metastatic HER2-amplified signet cell gastric adenocarcinoma

Dr Farshid Dayyani (Orange, California)

RTP
RESEARCH
TO PRACTICE

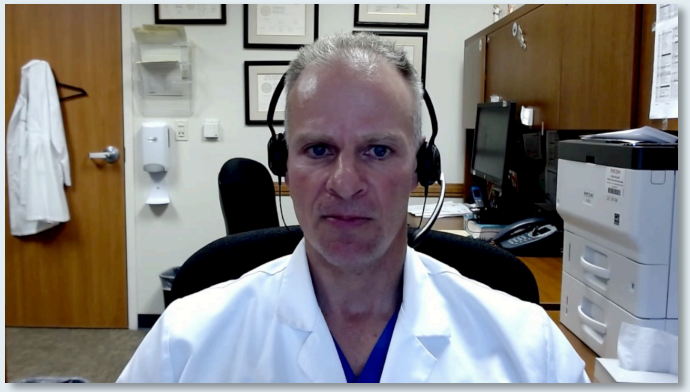
QUESTIONS FOR THE FACULTY

Farshid Dayyani, MD, PhD

"She had a great response to FLOT/trastuzumab/nivolumab — gaining weight, she's eating better, energy's better. The nodes are much smaller, marked decrease in size of the tumor. So the question is, what would the panel do? Would they attempt surgery? The surgeon was very adamant that it would improve her survival."

- **What are your diagnostic criteria for HER2 positivity for GE cancer, and how does it compare to the breast cancer definition?**
- **What is your usual first-line approach for metastatic HER2-positive GE cancer? Do you consider PD-L1 level? How flexible are you in choice of chemotherapy regimen and checkpoint inhibitor?**
- **Outside of a trial, in what situations, if any, would you add anti-HER2 treatment to neoadjuvant therapy for GE cancer?**

RTP RESEARCH TO PRACTICE



Dr Warren Brenner
(Boca Raton, Florida)

86-year-old man with newly diagnosed HER2-positive gastroesophageal cancer metastatic to the liver and lung. The tumor is 3+ by IHC for HER2 with a PD-L1 of 10

Dr Matthew Strickland
(Boston, Massachusetts)

75-year-old woman with HER2-positive esophageal adenocarcinoma and brain metastases s/p stereotactic radiosurgery

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Warren S Brenner, MD

"My question for the investigators is, is there any role for trastuzumab and pembrolizumab without chemotherapy in the elderly patient with metastatic HER2-positive GE junction cancer?

If this patient progresses on his current therapy, would the investigators use trastuzumab deruxtecan versus a taxane-based therapy?

And do they have any pearls in the management of trastuzumab deruxtecan toxicity, particularly the pneumonitis?"

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Matthew R Strickland, MD

"Should a brain MRI or CNS imaging be part of standard baseline imaging and workup for patients with gastroesophageal cancer?

Does the HER2-positive status change your approach to this question?

At the time of progression of disease, what would you recommend for this patient in the second line?"

RTP
RESEARCH
TO PRACTICE

Memorial Sloan Kettering Cancer Center

Current Considerations in the Treatment of HER2-Positive Advanced Gastric/GEJ Adenocarcinoma

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

Chief, Gastrointestinal Oncology Service
Memorial Sloan Kettering Cancer Center

Twitter: @yjanjigianMD

Thursday, January 19, 2023
San Francisco, CA I 8 Minutes I Live Talk
ASCO GI Gastroesophageal

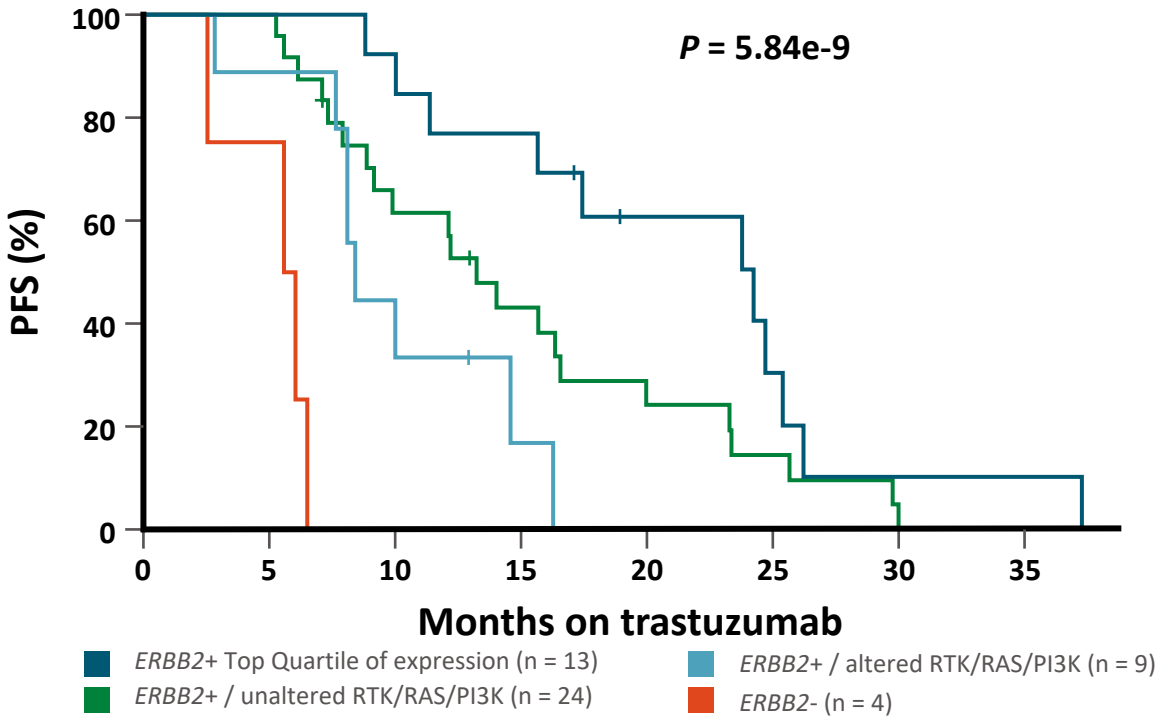
HER2 inhibition in EG adenocarcinoma

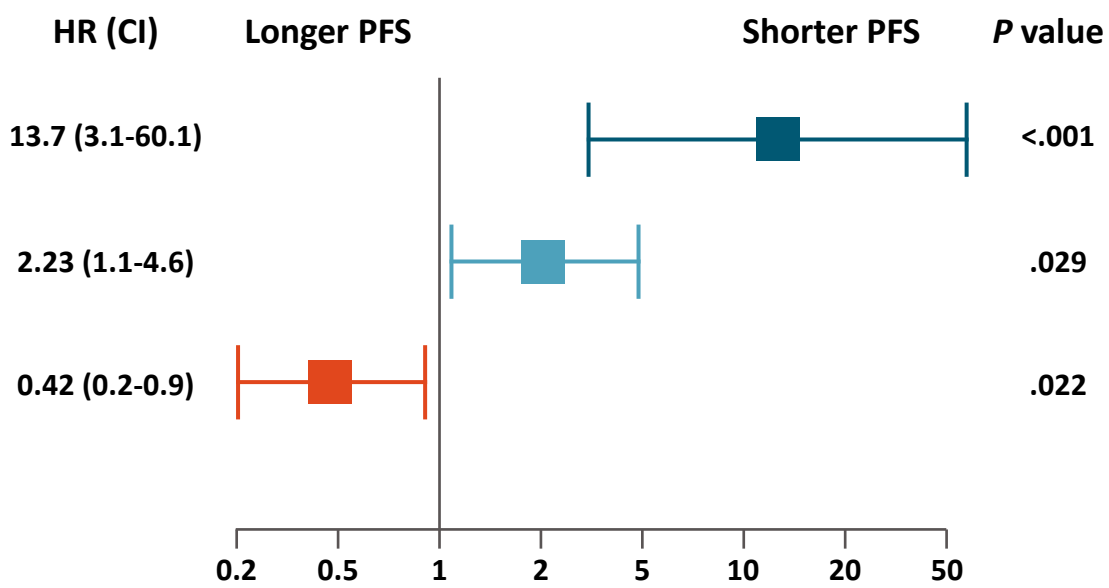
- Up to 20-30% HER2+ positive
- First-line trastuzumab/chemotherapy FDA approved mOS 13.8 mos ORR 47%
- 30% of GEJ HER2+ tumors with co-alterations of the RTK/RAS/PI3K pathway–intrinsic resistance
- HER2 inhibition alone in 1st line insufficient to overcome intrinsic resistance-several negative studies (LOGIC, JACOB, HELOISE)
- Pembrolizumab/Trastuzumab/chemotherapy FDA approved in 1st line
- Trastuzumab deruxtecan (T-DXd) is FDA approved after trastuzumab failure based on DESTINY-Gastric01

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*

PFS in Gastroesophageal Cancer with Intrinsic Trastuzumab Resistance

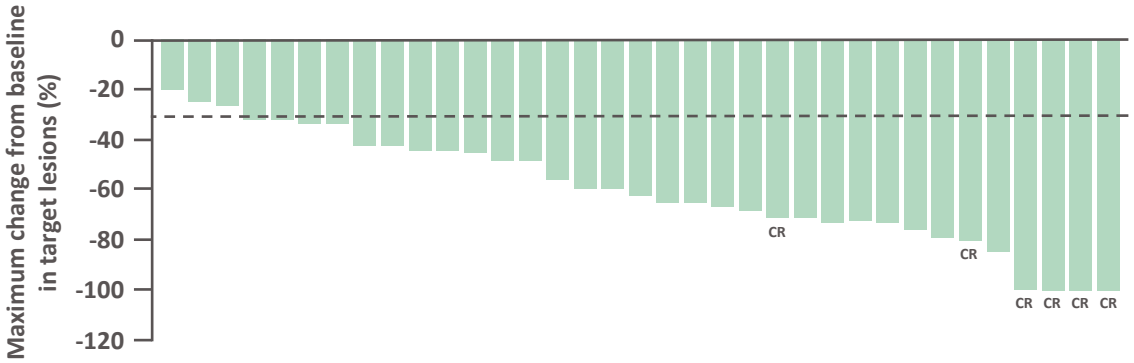
- Retrospective analysis of MSKCC cohort: predominantly younger patients with stage IV gastroesophageal cancer (N = 295)
- 30% of HER2+ tumors lacked *ERBB2* amplification or had co-mutations of the RTK/RAS/PI3K pathway; such patients had rapid progression on trastuzumab



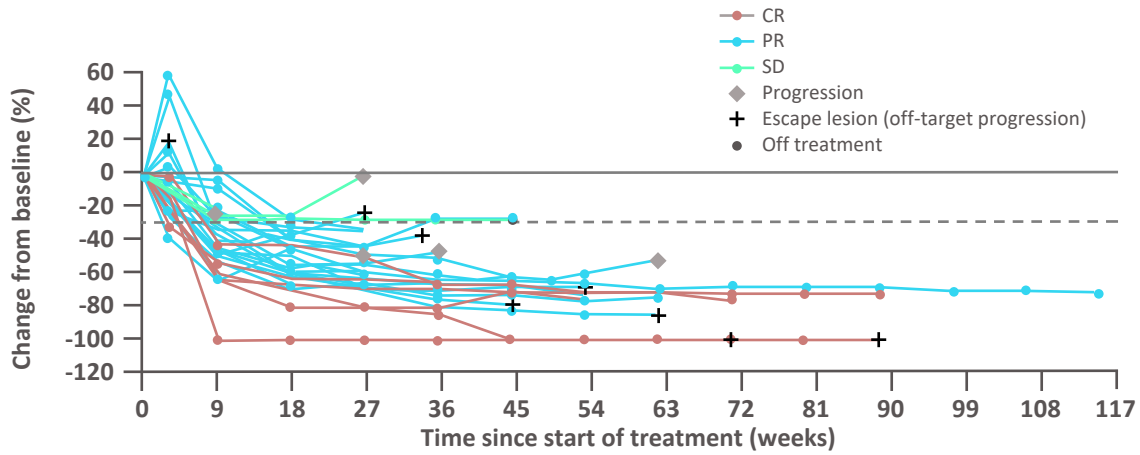


Janjigian. Cancer Discov. 2018;8:49.

Dual Anti-PD-1/Anti-HER2 Blockade in *ERBB2*+ Gastroesophageal Cancer

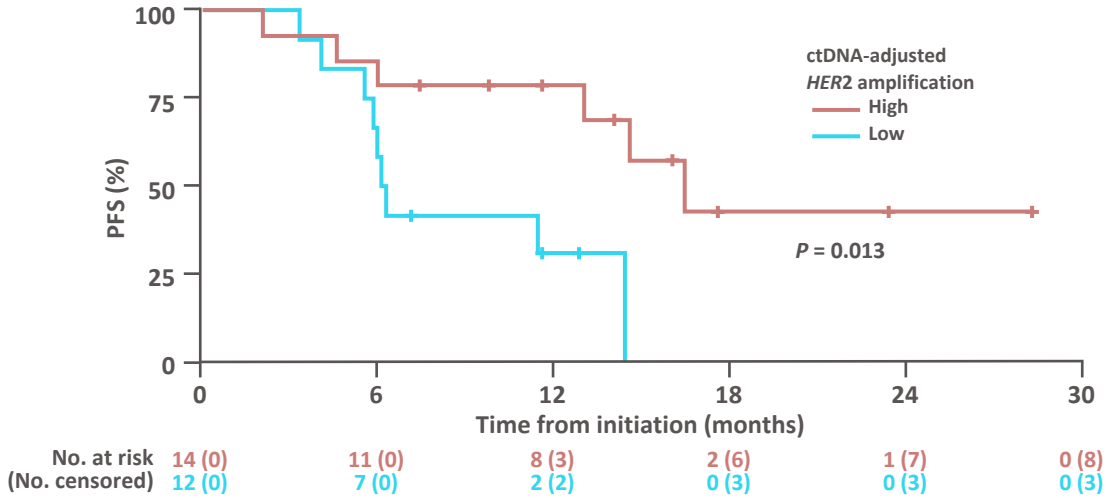


Adapted with permission from Janjigian 2020.



Adapted with permission from Janjigian 2020.

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



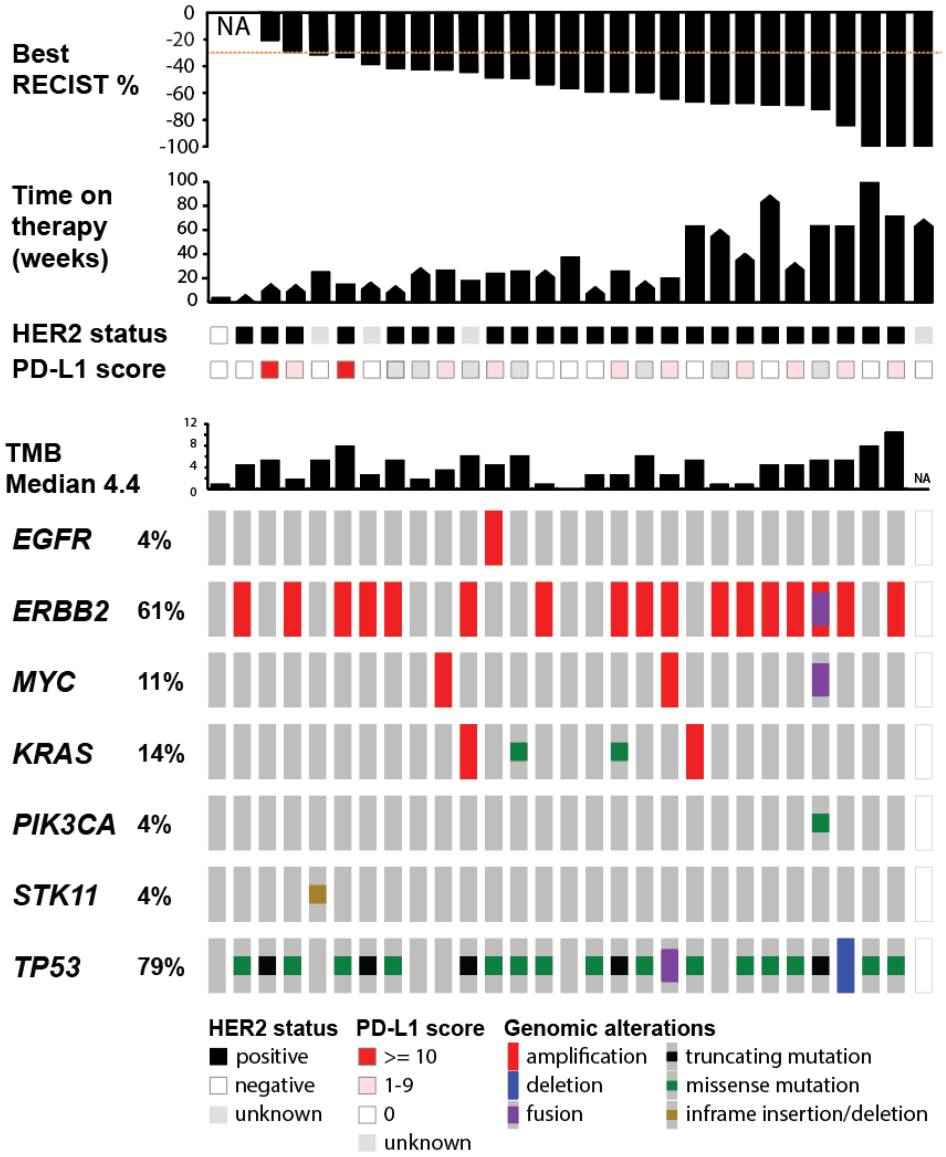
Adapted from Janjigian 2020.

- 49% of patients experienced a grade 3 TRAE; 8% experienced a grade 4 TRAE

[a]Among patients with evaluable disease (n = 35).

Janjigian YY et al. *Lancet Oncol*. 2020;21:821-831.

Biomarker Analysis from Phase II study



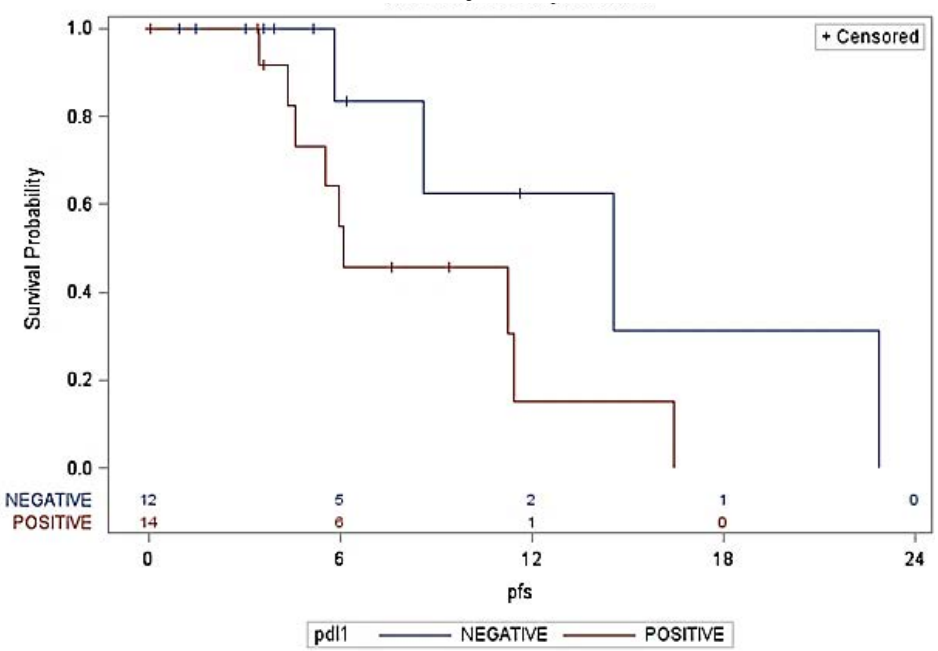
- No MSI tumors in HER2+ mEGA

  -- Median TMB 4.4 mut/MB (range 0 to 10.6)

- PDL-1 status not a predictor

  -- PFS (log-rank p=0.10) or OS (log-rank p=0.60) between PDL-1 positive and negative

PFS by PDL-1



- Low *ERBB2* may be associated with short duration of response

  -- 33% of patients with co- occurring RTK/RAS/PIK3CA alterations

[a]Among patients with evaluable tissue (n = 29).
Janjigian YY et al. *Lancet Oncol*. 2020;21:821-831.

Case

60 year old male without significant past medical history initially presented with 1 month of dysphagia and 15 pound weight loss.

EGD: Ulcerated mass, beginning 2 centimeters above and extending 3 centimeters below the gastroesophageal junction (GEJ).

EUS: Tumor invades through the adventitia and appears to abut the diaphragm. 3 pathologic appearing lymph nodes are biopsied. Stage uT4N2.

FDG PET/CT: Large, intensely avid (SUV 13.5) GEJ mass and adjacent lymphadenopathy. No distant metastases identified.

Pathology: Invasive moderately differentiated adenocarcinoma. HER2 3+. PD-L1 CPS 5. MSS. On NGS ERBB2 amp 14, negative for KRAS, MYC, MET and EGFR

ctDNA: Detected, high level of ERBB2, negative for KRAS, MYC, MET and EGFR

Diagnostic laparoscopy: Negative peritoneal washings.

Initial Tumor Board Discussion:

Unresectable primary tumor due to abutment and concern for possible invasion into diaphragm

Planned to start systemic therapy

Treatment Course

Started on trastuzumab, pembrolizumab and Capecitabine/Oxaliplatin (per Keynote 811)

Cycles 1-3: Symptoms improved. Tolerating solid foods. Gaining weight

After 4 cycles:
Clinically: Has regained 10 pounds, active, ECOG 0
ctDNA: >50% decrease, but detectable
Radiographically: Significant response at primary tumor (SUV 13. 5 reduction to 3.2). Resolution of lymphadenopathy (no longer FDG avid)

After 8 cycles:
Clinically: Feeling and eating well. Moderate neuropathy.
ctDNA: Continued decrease, but low-level detectable
Radiographically: Resolution of PET avidity SUV 2.9, on EGD dramatic response with some residual tumor cell seen on biopsy.

Presentation at DMT– and resection, ypT2N0 tumor 95% treatment response

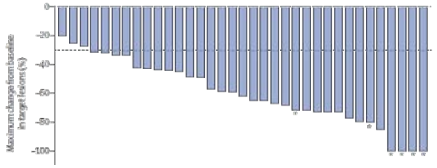
Post up ctDNA negative, patient resumed pembro/trastuzumab maintenance with serial ctDNA monitoring and CT CAP imaging, remains NED for 12 months.

Janjigian et al, Nature 2021

Background

- Standard first-line therapy for HER2-positive metastatic gastric or gastroesophageal junction (G/GEJ) cancer is trastuzumab (anti–HER2) with a fluoropyrimidine and a platinum
- Phase 2 data suggested antitumor activity and manageable safety for adding pembrolizumab (anti–PD-1) to trastuzumab and chemotherapy
  - MSKCC study (N = 37): 91% ORR, 100% DCR, 70% 6-mo PFS, 80% 12-mo OS

Janjigian YY et al. *Lancet Oncol* 2020;21:821-31.
Figure reused with permission. © 2020 Elsevier.



  - PANTHERA (N = 43): 77% ORR, 98% DCR, 77% 6-mo PFS, 77% 12-mo OS

Rha SY et al. *J Clin Oncol* 2020;38:Abstr 3081.

KEYNOTE-811 Global Cohort

Double-Blind Phase 3 Study of Pembrolizumab + Trastuzumab and Chemotherapy vs Placebo + Trastuzumab and Chemotherapy as First-Line Therapy For HER2-Positive Unresectable or Metastatic G/GEJ Cancer (NCT03615326)

Patients
- Advanced G/GEJ adenocarcinoma
- No prior therapy in advanced setting
- HER2-positive

Stratification Factors
- Geographic region
- PD-L1 CPS
- Chemotherapy choice

R 1:1
N ≈ 692

Pembrolizumab 200 mg IV Q3W
+
Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

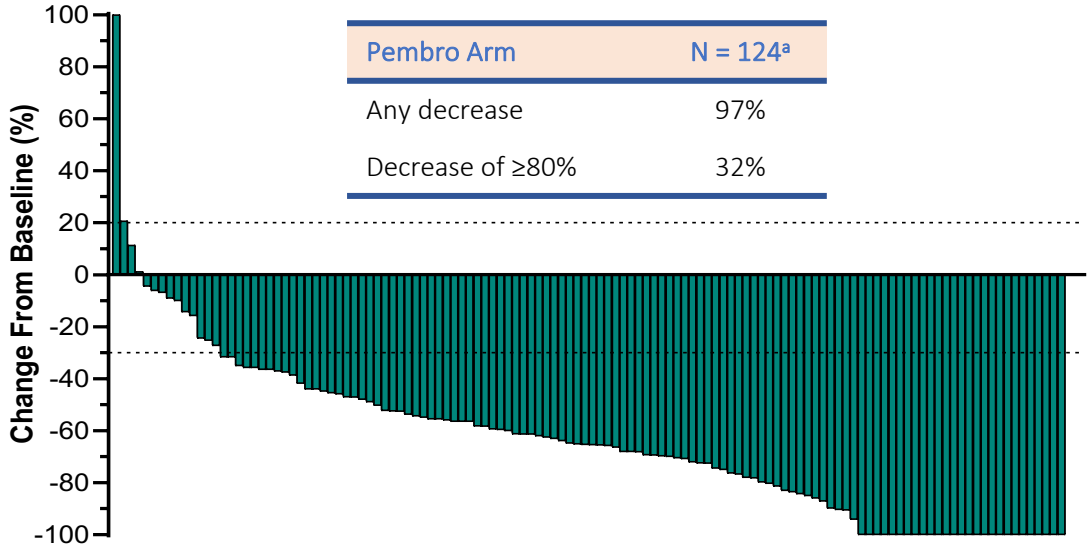
Placebo IV Q3W
+
Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Dual Primary End Points
- OS
- PFS (RECIST v1.1 per BICR)

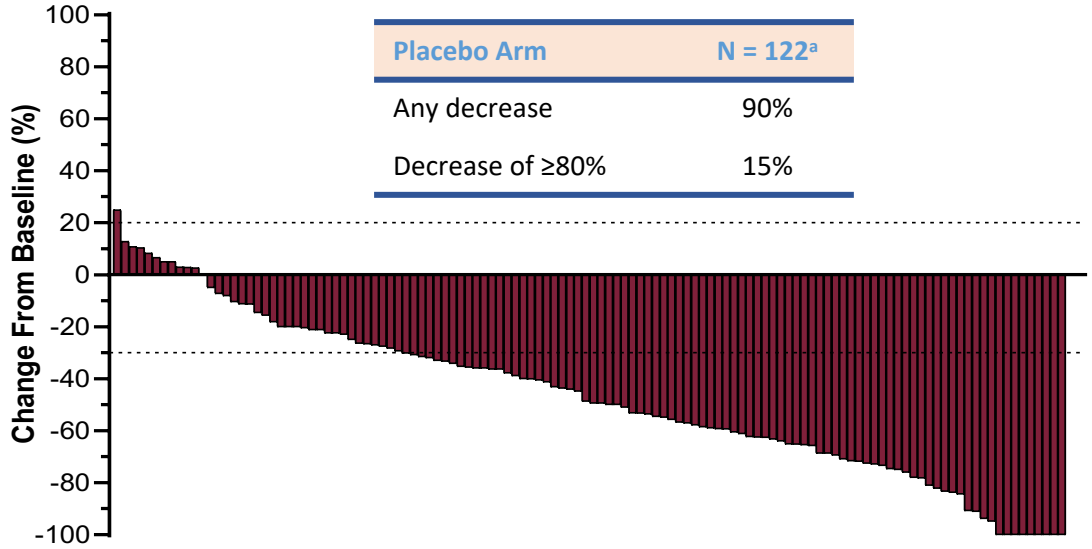
Secondary End Points
- ORR (RECIST v1.1 per BICR)
- DOR (RECIST v1.1 per BICR)
- Safety

[a]Trastuzumab dose: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP dose: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX dose: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100).

Confirmed Response at IA1



Pembro Arm	N = 124[a]
Any decrease	97%
Decrease of ≥80%	32%



Placebo Arm	N = 122[a]
Any decrease	90%
Decrease of ≥80%	15%

ORR and DCR, % (95% CI)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
ORR	74.4% (66.2-81.6)	51.9% (43.0-60.7)
ORR difference[b]	22.7% (11.2-33.7) *P* = 0.00006	
DCR	96.2% (91.4-98.8)	89.3% (82.7-94.0)

Best Response, n (%)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
CR	15 (11%)	4 (3%)
PR	84 (63%)	64 (49%)
SD	29 (22%)	49 (37%)
PD	5 (4%)	7 (5%)
Not evaluable	0	2 (2%)
Not assessed	0	5 (4%)

Duration of Response[c]	**Pembro Arm (N = 99)**	**Placebo Arm (N = 68)**
Median[d]	10.6 mo	9.5 mo
Range	1.1+ to 16.5+	1.4+ to 15.4+
≥6-mo duration[d]	70.3%	61.4%
≥9-mo duration[d]	58.4%	51.1%

[a]Participants with RECIST-measurable disease at baseline and ≥1 post-baseline measurement evaluable for change from baseline in target lesions. [b]Calculated using the Miettinen and Nurminen method stratified by the randomization stratification factors. [c]Calculated in participants with best response of CR or PR. [d]Kaplan-Meier estimation. The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

Adverse Events at IA1

All-Cause AEs

	Pembro Arm (N = 217)		Placebo Arm (N = 216)	
Summary				
Any grade	97%		98%	
Grade 3-5	57%		57%	
Serious	31%		38%	
Led to death	3%		5%	
Led to discon, any drug	24%		26%	
Incidence >20%	**Any**	**Gr 3-5**	**Any**	**Gr 3-5**
Diarrhea	53%	7%	44%	8%
Nausea	49%	5%	44%	6%
Anemia	41%	9%	44%	9%
↓ Appetite	31%	2%	32%	4%
Vomiting	31%	5%	27%	2%
↓ Platelet count	24%	8%	28%	7%
Fatigue	24%	4%	20%	3%
↓ Neutrophil count	24%	7%	25%	7%
Peripheral sensory neuropathy	23%	3%	19%	1%
↑ AST	21%	<1%	13%	<1%

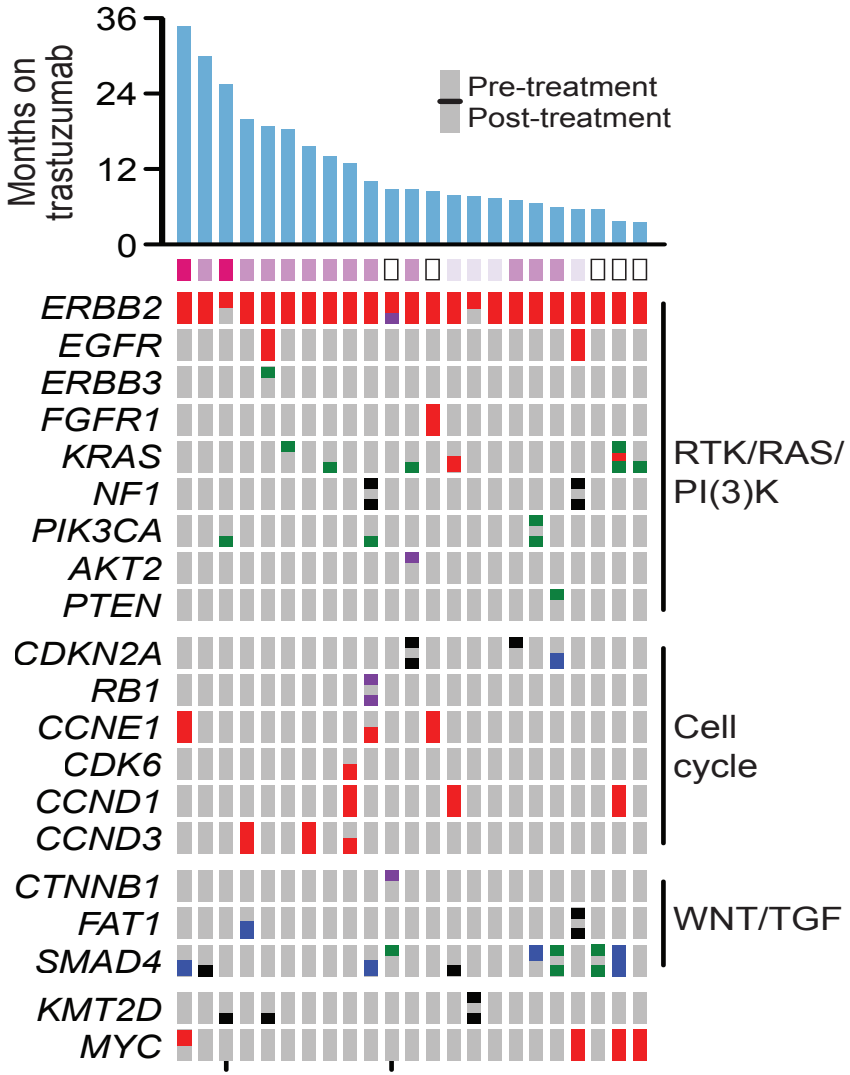
Immune-Mediated AEs and Infusion Reactions[a]

	Pembro Arm (N = 217)		Placebo Arm (N = 216)	
Summary				
Any grade	34%		21%	
Grade 3-5	10%		3%	
Serious	9%		3%	
Led to death	1%		<1%	
Led to discon, any drug	6%		2%	
Incidence ≥2 Participants	**Any**	**Gr 3-5**	**Any**	**Gr 3-5**
Infusion reactions	18%	3%	13%	1%
Pneumonitis	5%	1%	1%	0
Colitis	5%	3%	2%	2%
Hypothyroidism	5%	0	3%	0
Hyperthyroidism	4%	0	3%	0
Hypophysitis	1%	<1%	0	0
Hepatitis	1%	1%	1%	0
Severe skin reactions	1%	1%	0	0

[a]Events were considered regardless of attribution to treatment by the investigator. Related terms were included in addition to the specific terms listed.
Participants in both arms received trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

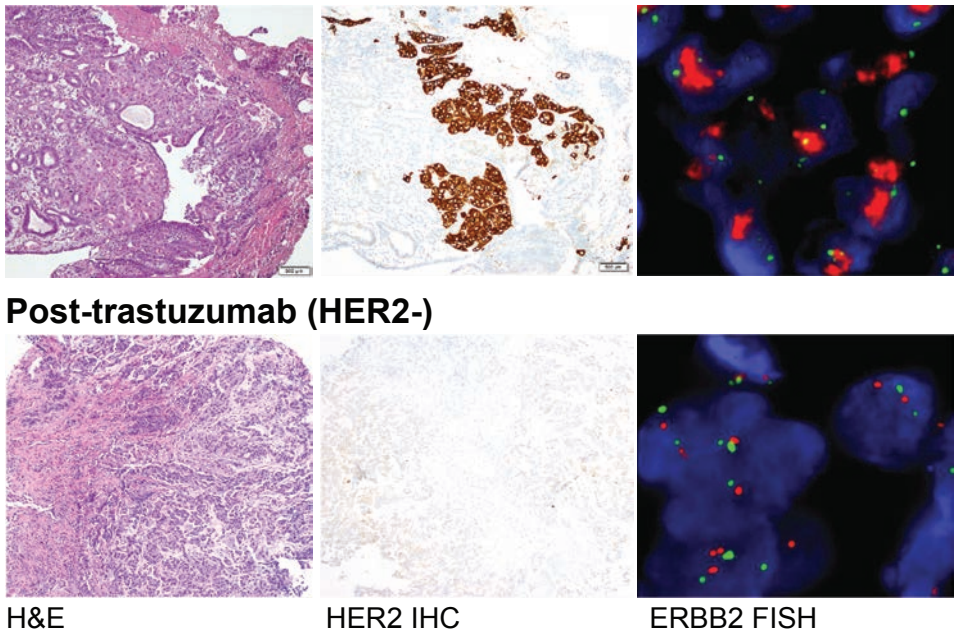
ACQUIRED TRASTUZUMAB RESISTANCE

Loss of *ERBB2* and KRAS and PIK3CA ALTERATIONS IN 20% OF CASES



Pre-trastuzumab (HER2+)

Post-trastuzumab (HER2-)



H&E HER2 IHC ERBB2 FISH

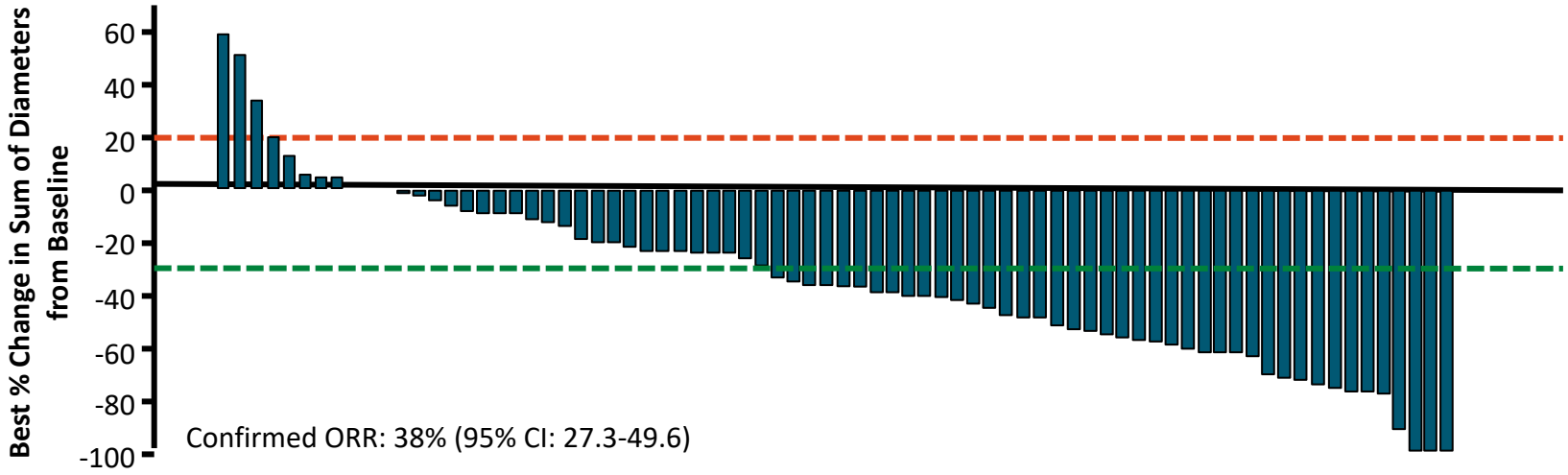
Janjigian et al *Cancer Discovery* 2018

Tumor Size Change with T-DXd in HER2+ Adv Gastric/GEJ Cancer After Trastuzumab (DESTINY-Gastric01 and 02)

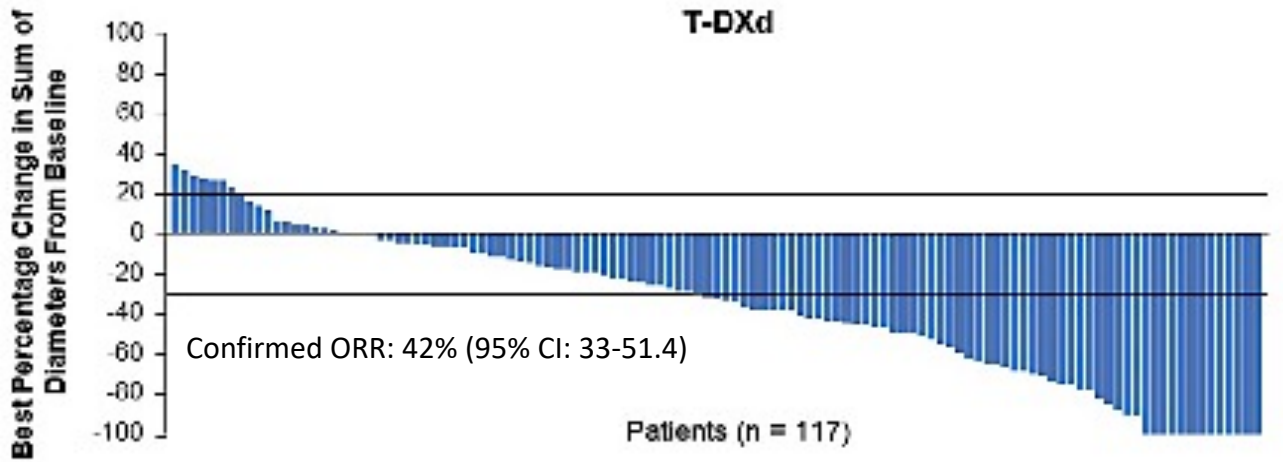
Efficacy[1,2]	T-DXd (N = 79)
ORR, % (95% CI)	38 (27.3-49.6)
Median DOR, mo	8.1
Median PFS, mo (95% CI)	5.6 (4.2-8.3)
Median OS, mo (95% CI)	12.1 (9.4-15.4)

Survival, mo (95% CI)[3,4]	T-DXd (n = 125)	Chemo (n = 62)
Median OS	12.5 (10.3 – 15.2)	8.9 (6.4-10.4)
HR for death: 0.60		
Median PFS	5.6 (4.3-6.9)	3.5 (2.0-4.3)
HR for PD or death: 0.47		

DESTINY-Gastric02 (US/Europe; progression on 1L trastuzumab)[1]



DESTINY-Gastric01 (Japan; progression on ≥2 prior regimens)[4]



1. Van Cutsem. ESMO 2021. Abstr LBA55. 2. Ku ESMO 2022. Abstr 1205MO. 3. Shitara. NEJM. 2020;382:2419. 4. Yamaguchi. ASCO GI 2022. Abstr 242.

DESTINY-Gastric01 and 02: AEs with T-DXd in HER2+ Adv Gastric/GEJ Cancer After Trastuzumab

DESTINY-Gastric02 (US/Europe; progression on 1L trastuzumab)[1]

TEAEs in ≥15% of Patients, n (%)	T-DXd (N = 79)	
	Any Grade	Grade ≥3
Patients with ≥1 TRAEs	74 (93.7)	21 (26.6)
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)

DESTINY-Gastric01 (Japan; progression on ≥2 prior regimens)[2]

TEAEs in ≥20% of Patients Treated with T-DXd[a]

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

1. Van Cutsem. ESMO 2021. Abstr LBA55. 2. Yamaguchi. ASCO GI 2022. Abstr 242

DESTINY-Gastric01 Biomarker Analysis: T-DXd in HER2+ Adv Gastric/GEJ Cancer After ≥2 Prior Regimens

- Only 30% of new tumor samples obtained after/during trastuzumab therapy
- ORR slightly higher in patients w/HER2+ tumor after/during first trastuzumab
  - ORR: 57% vs 48%
  - OS confounded by small sample size (same)
- High level of ERBB2 (mRNA or plasma) predicts high ORR
- Tissue mRNA >9.7: ORR 81% vs 23% (small sample size)
- Plasma ERBB2 detected in 64% of patients (Guardant 360)
  - ORR with *ERBB2+* ctDNA*:* 76% vs 40%
  - OS nearly doubled if ctDNA *ERBB2* >6 copy: 21 vs 12 mo median OS
- Co-occurring *EGFR/MET* amplifications associated with worse outcome

- FDA urges biopsy of all patients after trastuzumab progression
  - ~20% of patients with esophagogastric cancer have loss of HER2
- This analysis indicates that ctDNA can be used if biopsy not feasible

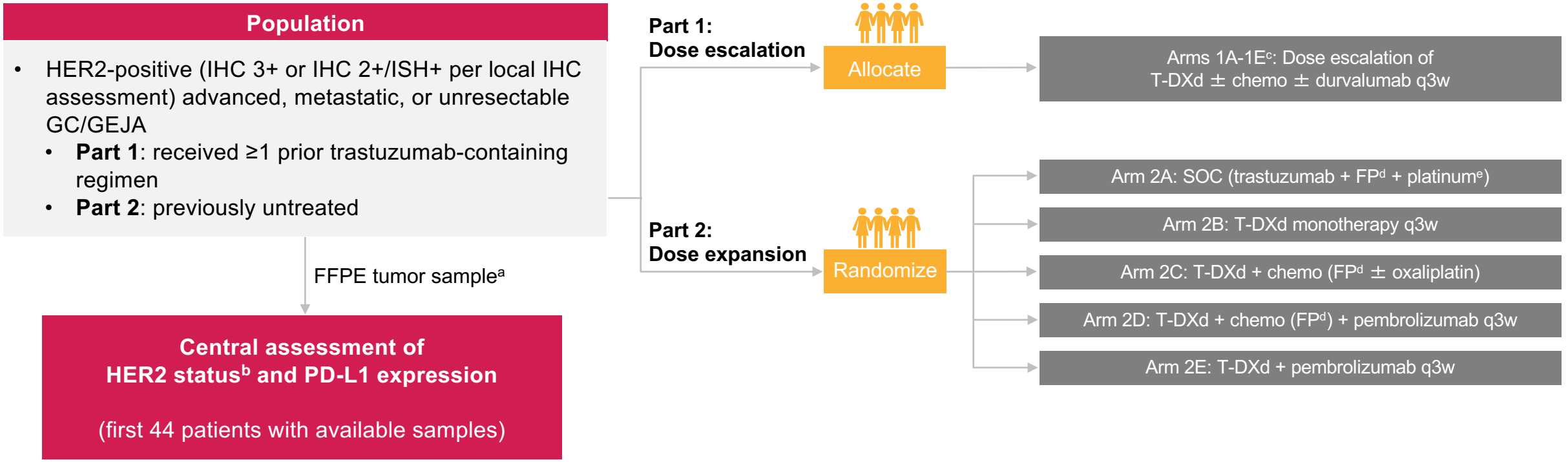
Shitara. ESMO World GI 2021. Abstract O14.

DESTINY-Gastric02: Additional T-DXd Results in HER2+ Adv Gastric/GEJ Cancer After First-Line Trastuzumab

- GEJ primary: 66%[1]
  - vs 86% in DESTINY-Gastric01[2]
- Rebiopsy for HER2 mandated for all patients and centrally reviewed[1]
  - vs 30% in DESTINY-Gastric01[2]
- ORR (primary endpoint): 38% w/median PFS 5.5 mo
  - vs 27% ORR, median PFS 4.2 mo with ramucirumab/paclitaxel[3]
- No new safety signals[1]: 7.6% ILD
  - 0 Grade 3/4 events, 1 Grade 5
- Grade ≥3 TEAEs: 27%[1]
  - Compares favorably to ramucirumab/paclitaxel[3]

1. Van Cutsem. ESMO 2021. Abstr LBA55. 2. Shitara. NEJM. 2020;382:2419. 3. Wilke. Lancet. 2014;15:1224.

DESTINY-Gastric03 (NCT04379596)

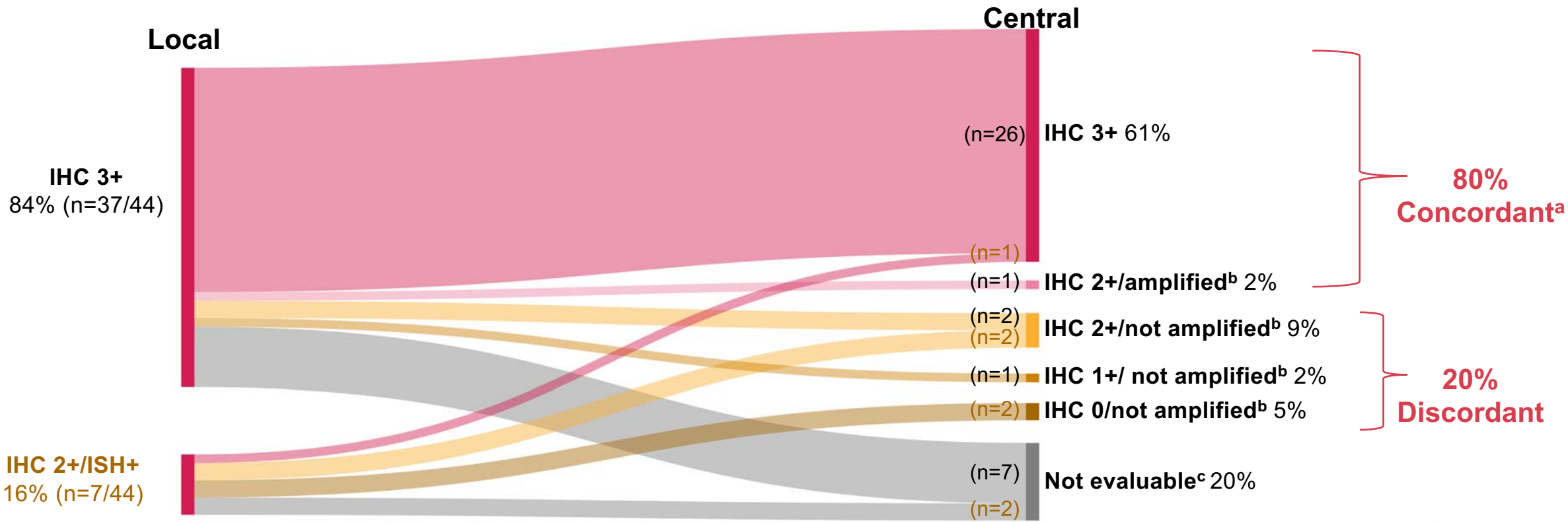


BID, twice daily; Cap, capecitabine; chemo, chemotherapy; FFPE, formalin-fixed paraffin-embedded; FP, fluoropyrimidine; 5-FU, 5-fluorouracil; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PD-L1, programmed death ligand 1; q3w, every 3 weeks; SOC, standard of care; T-DXd, trastuzumab deruxtecan.

[a] Tumor tissue may be from either the primary tumor or a metastatic biopsy. For patients in part 1, samples included recently collected tumor samples and original diagnostic biopsy samples (archival tissue); for patients in part 2, recently collected tumor samples were required. [b] *HER2* gene amplification was centrally assessed using FoundationOne® (F1CDx); this assay is not currently approved for GC. Ongoing testing using ISH is planned. [c] Arm 1A: T-DXd q3w + 5-FU on days 1-5 q3w; arm 1B: T-DXd q3w + Cap BID on days 1-14 q3w; arm 1C: T-DXd + durvalumab q3w; arm 1D(a): T-DXd + 5-FU + oxaliplatin q3w; arm 1D(b): T-DXd + Cap + oxaliplatin q3w; arm 1E(a): T-DXd + 5-FU + durvalumab q3w; arm 1E(b): T-DXd + Cap + durvalumab q3w. [d] 5-FU or Cap per investigator's choice. [e] Investigator's choice of cisplatin or oxaliplatin at SOC dose.

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

Local and Central HER2 Assessment: 20% Discordant; 80% Concordant[a]



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

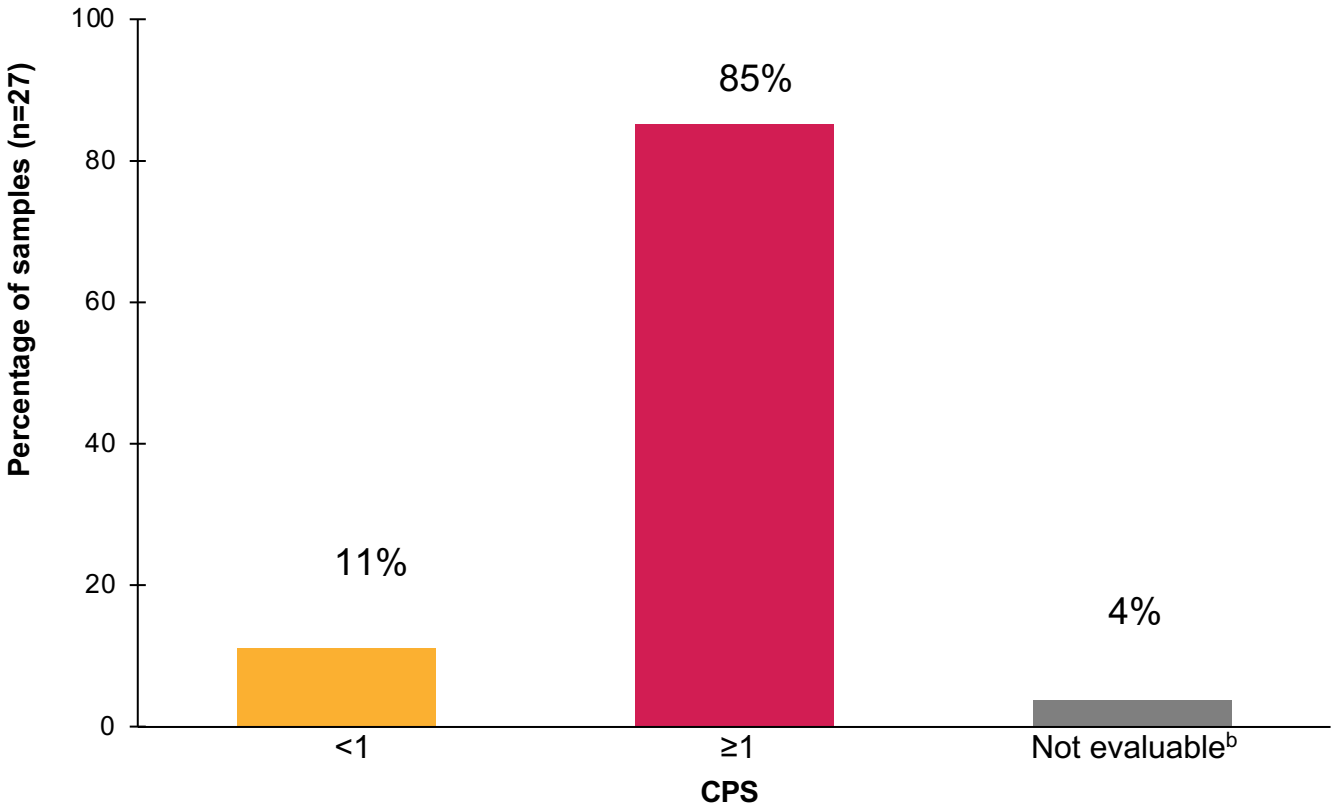
[a] Concordance rate was defined as the percentage of samples classified as HER2 positive by both local and central assessment.

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

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

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

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



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

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

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

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

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

HER2 inhibition in EG adenocarcinoma

- Up to 20-30% HER2+ positive
- Principal outcomes from the Phase III KEYNOTE-811 trial supports the use of first-line pembrolizumab/trastuzumab/chemotherapy for metastatic HER2-positive gastric/GEJ adenocarcinoma
- Published efficacy and safety data with trastuzumab deruxtecan (T-DXd) for Asian (DESTINY-Gastric01 trial) and Western (DESTINY-Gastric02 trial) patients with progressive HER2-positive gastric/GEJ cancer supports use after trastuzumab failure

MODULE 3: Selection and Sequencing of Therapy for Relapsed/Refractory Gastric/GEJ Cancer; Novel Investigational Approaches — Prof Lordick

RTP
RESEARCH
TO PRACTICE

Dr Namrata Peswani
(Richardson, Texas)

76-year-old woman with Lynch syndrome and a history of Stage III colon cancer presents with poorly differentiated GEJ carcinoma with liver and lung metastases

Dr Ranju Gupta
(Bethlehem, Pennsylvania)

61-year-old man presents with a 70-lb weight loss and locally advanced high-grade neuroendocrine carcinoma of the distal esophagus

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Namrata I Peswani, MD

"She was the first person in her family to go through genetic testing, even though there had been multiple family members with cancer before her, and she was confirmed to have Lynch syndrome."

- **What would be the best first-line therapy for this patient?**

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Ranju Gupta, MD

"What is the optimal treatment for this patient? The disease is confined to the esophagus and the upper portion of the stomach.

My plan is to start him on chemoradiation with cisplatin and etoposide, like a small cell type of regimen, and then follow with 2 more cycles of chemotherapy. But would anybody treat him differently?

If he has a good response, is there any role for surgery after?"

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 63-year-old man with metastatic gastric adenocarcinoma (PD-L1 CPS 0) with clinical and radiographic progression of disease after 4 cycles of FOLFOX

Dr Matthew Strickland (Boston, Massachusetts)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Matthew R Strickland, MD

"Would you have used immunotherapy as part of first-line therapy for this patient with a CPS of 0?

What second-line therapy would you recommend for this patient?

I started him on second-line conventional paclitaxel and ramucirumab. My plan in the third line would be for a clinical trial we have of a bispecific antibody."

RTP
RESEARCH
TO PRACTICE

Selection and Sequencing of Therapy for Relapsed/Refractory Gastric/GEJ Cancer; Novel Investigational Approaches

Prof Florian Lordick

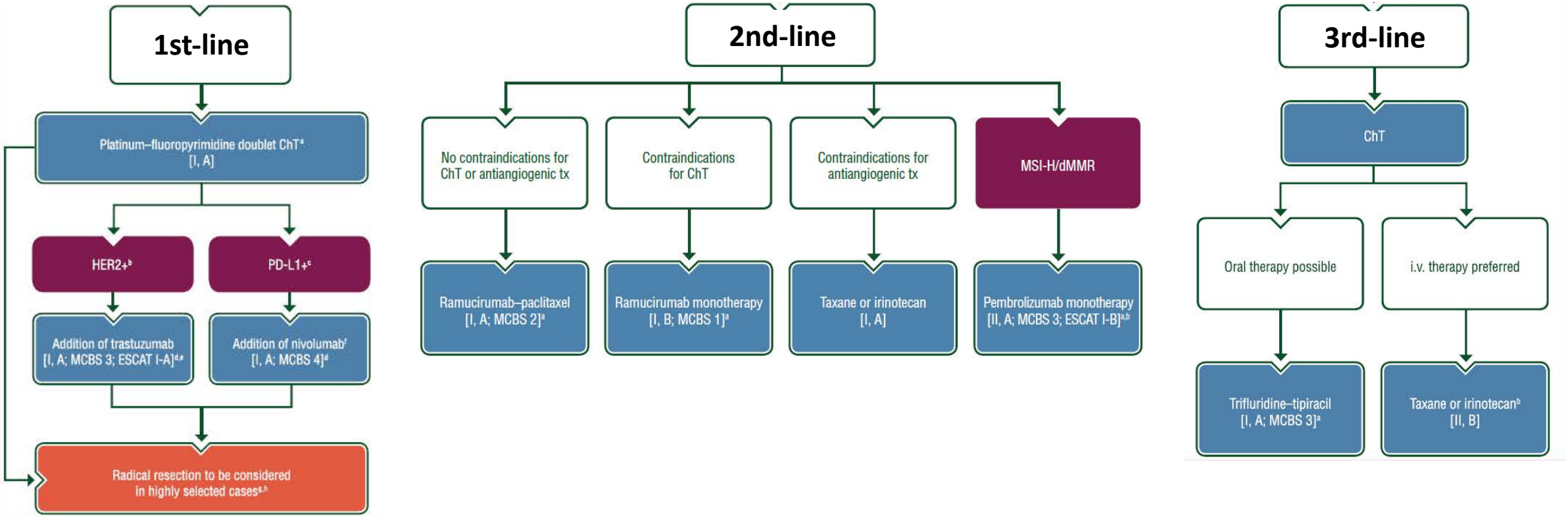
Director Comprehensive Cancer Center Central Germany (CCCG)
and Head of Department of Medicine, Leipzig Univ Hospital

Universitätsklinikum Leipzig
Medizin ist unsere Berufung.
UCCL UNIVERSITÄRES KREBSZENTRUM

UNIVERSITÄT LEIPZIG
MEDIZINISCHE FAKULTÄT

CANCER CENTER CENTRAL GERMANY
United to beat cancer

TREATMENT SEQUENCE FOR ADVANCED GE ADENOCARCINOMA



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

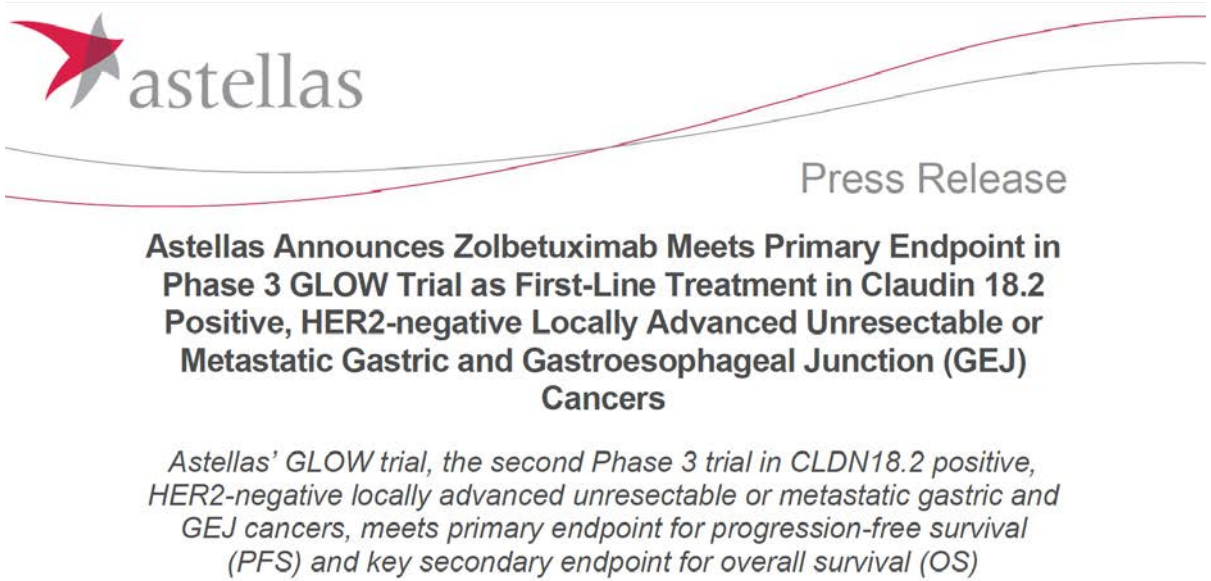
Lordick F, et al. *Ann Oncol.* 2022 Oct;33(10):1005-1020

CLAUDIN18.2 ZOLBETUXIMAB– 2 POSITIVE PHASE-3 STUDIES

SPOTLIGHT

https://www.astellas.com/en/news/26821

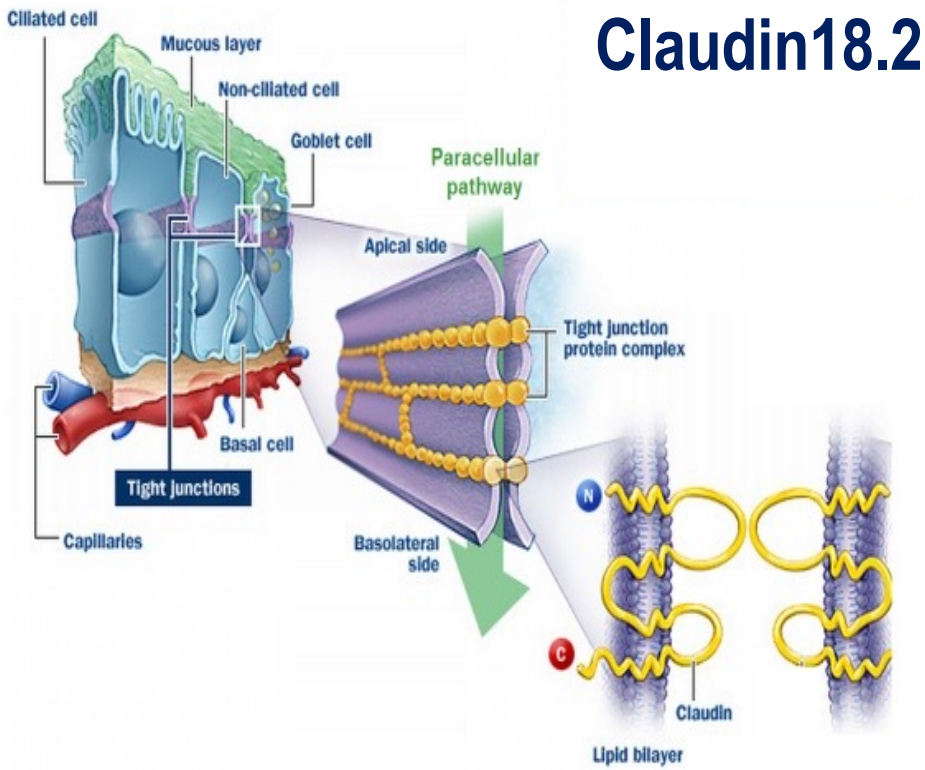
GLOW



https://www.astellas.com/en/news/26891

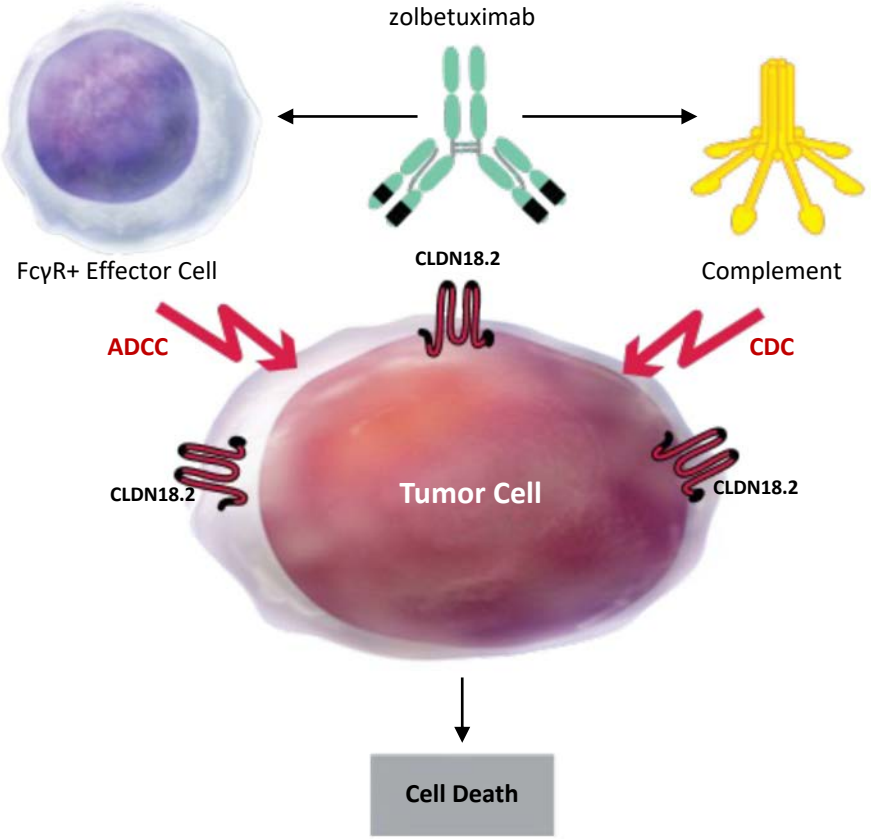
CLAUDIN18.2 – A NOVEL TARGET

Claudin18.2



- Member of the claudin family
- Major structural component of tight junctions
- Seals intercellular space in epithelial sheets
- Not expressed in any healthy tissues, except: stomach mucosa, but with limited accessibility

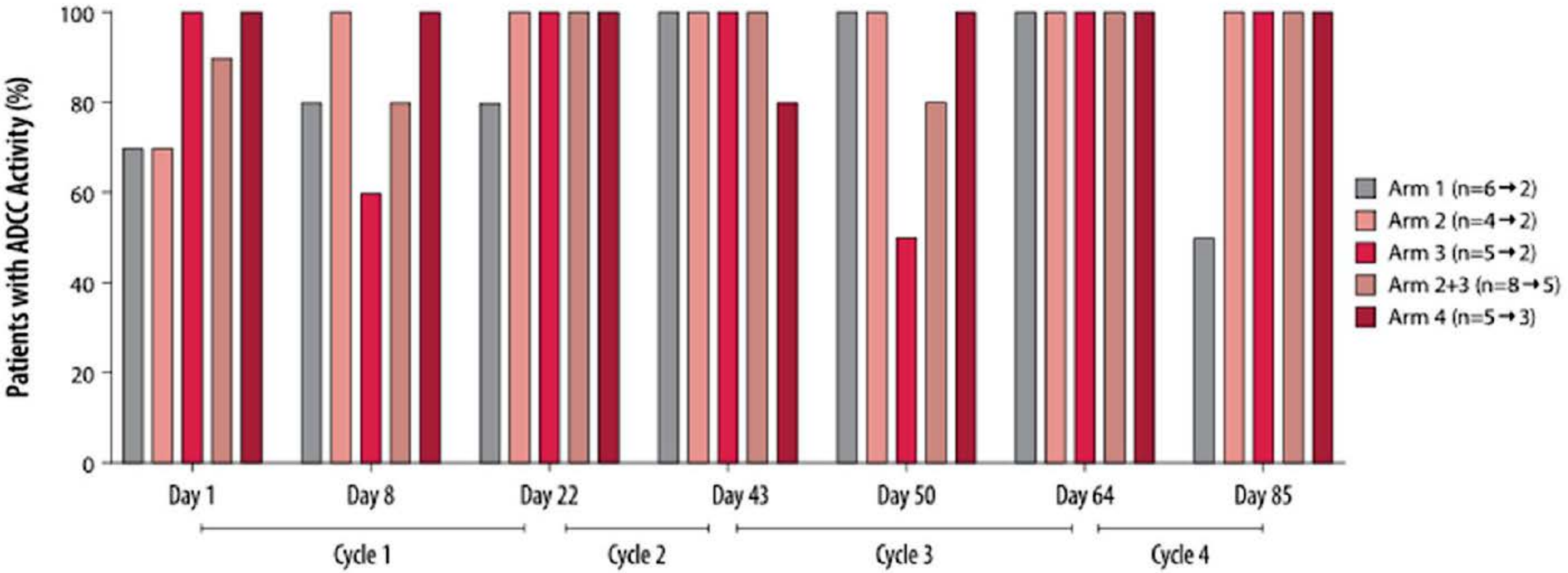
Mechanism of Action of Zolbetuximab



Sahin U et al. *Ann Oncol.* 2021 May;32(5):609-619

ZOLBETUXIMAB – IMMUNOMODULATORY EFFECTS

Proportion of patients with measurable ADCC-specific lysis (lysis > 19%) for all treatment arms on all study days until Day 85



Arm 1. Zolbetuximab (Z) + Zoledronic Acid (ZA), Arm 2: Z+ZA+ low-dose IL-2; Arm 3: Z+ZA+ intermediate dose IL-2
Arm 4: Zolbetuximab monotherapy

Lordick F et al. *J Cancer Res Clin Oncol.* 2023 Jan 6. doi: 10.1007/s00432-022-04459-3. Epub ahead of print

SPOTLIGHT – STUDY DESIGN

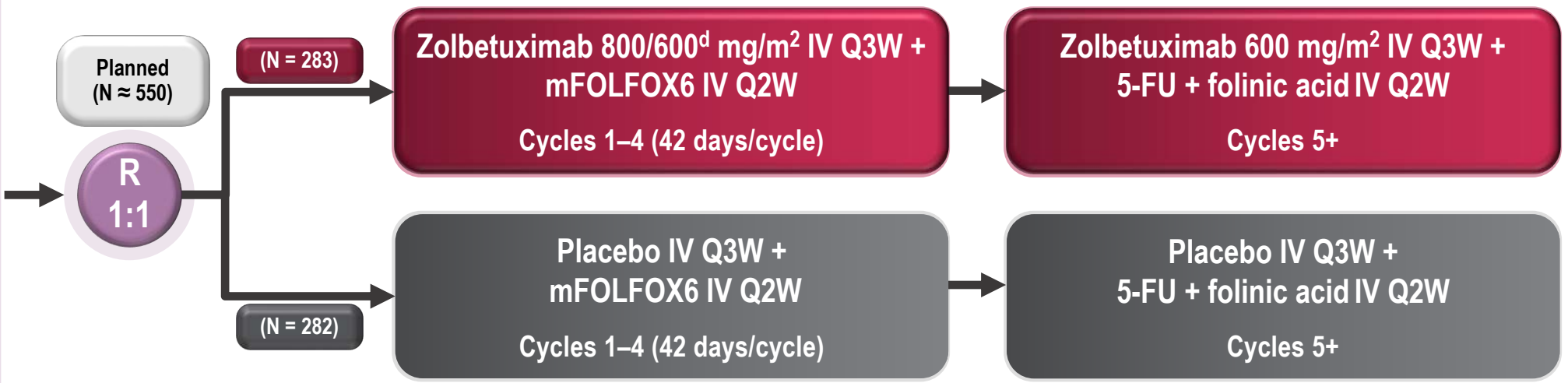
Global[a], randomized, double-blinded, placebo-controlled, phase 3 trial

Key Eligibility Criteria

- Previously untreated LA unresectable or mG/GEJ adenocarcinoma
- CLDN18.2+ (moderate-to-strong CLDN18 staining in ≥75% of tumor cells)[b]
- HER2–[c]
- ECOG PS 0–1

Stratification Factors

- Region (Asia vs non-Asia)
- Number organs w/ metastases (0–2 vs ≥3)
- Prior gastrectomy (yes vs no)



Primary End Point

- PFS[e]

Key Secondary End Points

- OS
- TTCD in GHS/QoL, PF, and OG25-Pain

Secondary End Points

- ORR[e]
- DOR[e]
- Safety
- PROs

[a]Study was conducted at 215 sites in 20 countries across Australia, Asia, Europe, N. America, and S. America; [b]By central IHC using the analytically validated VENTANA CLDN18 (43-14A) RxDx Assay; [c]By central or local HER2 testing; [d]800 mg/m² at cycle 1 day 1 followed by 600 mg/m² on cycle 1 day 22 and days 1 and 22 of subsequent cycles; [e]Per RECIST v1.1 by independent review committee.

Shitara K et al. *ASCO GI Meeting.* 2023; LBA 292

SPOTLIGHT – BASELINE CHARACTERISTICS

		Zolbetuximab + mFOLFOX6 (N = 283)	Placebo + mFOLFOX6 (N = 282)
Age, years (range)	Median	62.0 (27–83)	60.0 (20–86)
Sex, n (%)	Male	176 (62.2)	175 (62.1)
Region, n (%)	Asia	88 (31.1)	89 (31.6)
	Non-Asia	195 (68.9)	193 (68.4)
Organs with metastases, n (%)	0–2	219 (77.4)	219 (77.7)
	≥3	64 (22.6)	63 (22.3)
Prior gastrectomy, n (%)	Yes	84 (29.7)	82 (29.1)
	No	199 (70.3)	200 (70.9)
Primary site, n (%)	Stomach	219 (77.4)	210 (74.5)
	GEJ	64 (22.6)	72 (25.5)
Lauren classification, n (%)	Diffuse	82 (29.1)	117 (42.1)
	Intestinal	70 (24.8)	66 (23.7)
	Mixed/others[a]	130 (45.9)	95 (33.7)
ECOG PS[b,c], n (%)	0	125 (44.8)	115 (41.4)
	1	153 (54.8)	163 (58.6)

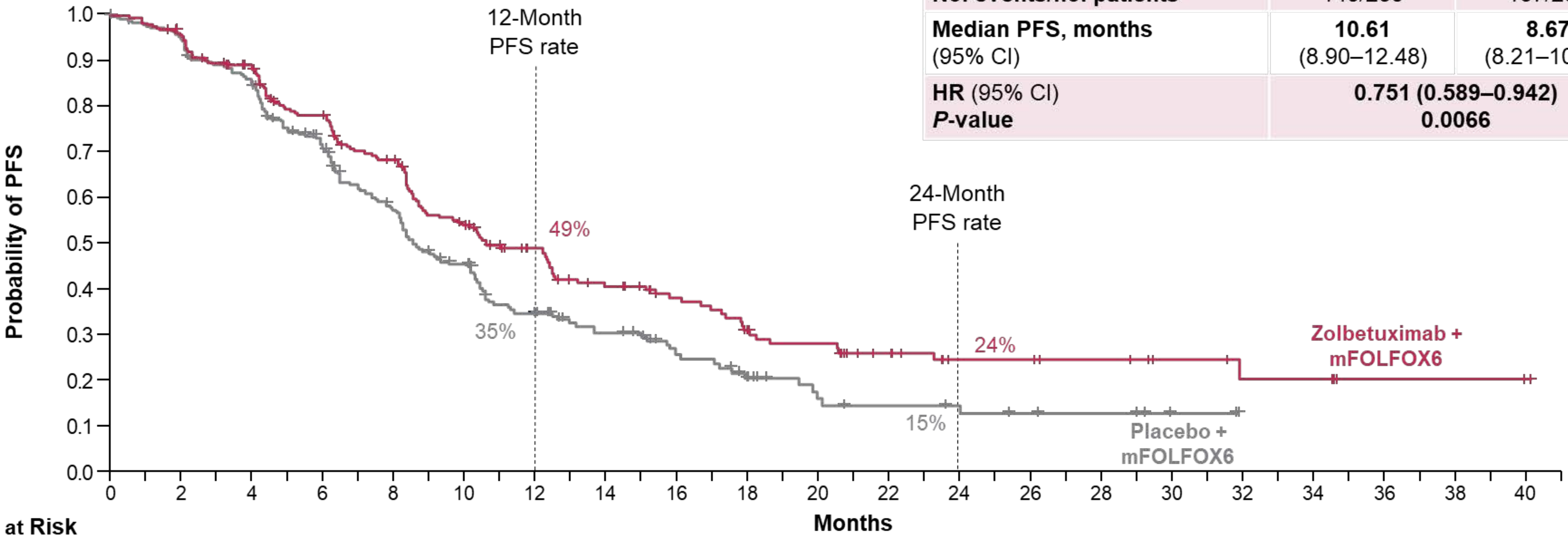
- As an ad hoc analysis, 41/311 (13.2%) of assessable patients had tumors with PD-L1 CPS ≥5[d]
- Subsequent anticancer therapies were administered to 48% of patients in the zolbetuximab arm and 53% in the placebo arm

[a]Patients with Lauren classification "Mixed/others" include those classified as "mixed," "other," or "unknown" (unknown represents patients with adenocarcinoma without Lauren classification); [b]A patient in the zolbetuximab arm with ECOG PS 2 at baseline who was enrolled with ECOG PS 1 at screening is not shown here; [c]Four patients in each arm with ECOG PS missing at baseline who were enrolled with ECOG PS 0 or 1 at screening are not shown here (did not receive treatment and therefore did not have baseline measurements at C1D1); [d]Using the Dako PD-L1 IHC 28-8 pharmDx assay for samples within test stability and with subject consent.

Shitara K et al. *ASCO GI Meeting.* 2023; LBA 292

SPOTLIGHT – PROGRESSION-FREE SURVIVAL

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



No. at Risk

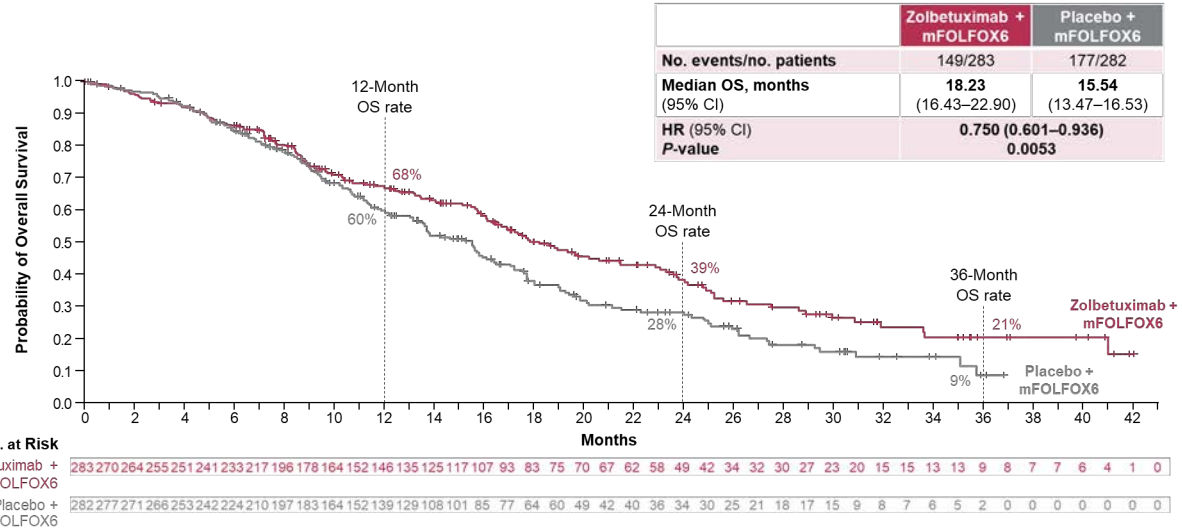
Zolbetuximab + mFOLFOX6	283	263	254	232	226	190	187	148	143	108	102	84	78	59	56	53	43	40	33	28	28	21	19	17	12	12	12	10	10	9	7	7	5	5	5	2	2	2	2	2	1	0
Placebo + mFOLFOX6	282	273	260	237	226	183	168	136	122	91	83	60	56	43	40	38	26	25	19	14	12	9	9	9	8	7	6	5	5	4	2	2	0	0	0	0	0	0	0	0	0	0

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

Data cutoff: September 9, 2022; Median follow-up = 12.94 months (zolbetuximab + mFOLFOX6) vs 12.65 months (placebo + mFOLFOX6).
[a]Per RECIST version 1.1.

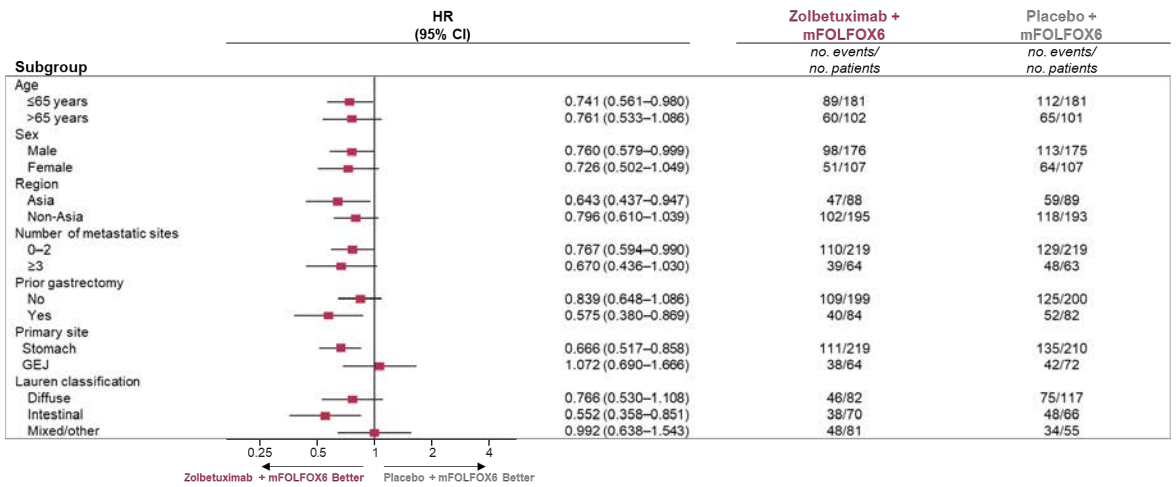
Shitara K et al. *ASCO GI Meeting.* 2023; LBA 292

SPOTLIGHT – OVERALL SURVIVAL



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

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



- OS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 across most subgroups

Data cutoff: September 9, 2022.

Shitara K et al. *ASCO GI Meeting.* 2023; LBA 292

SPOTLIGHT – OVERALL RESPONSE RATE

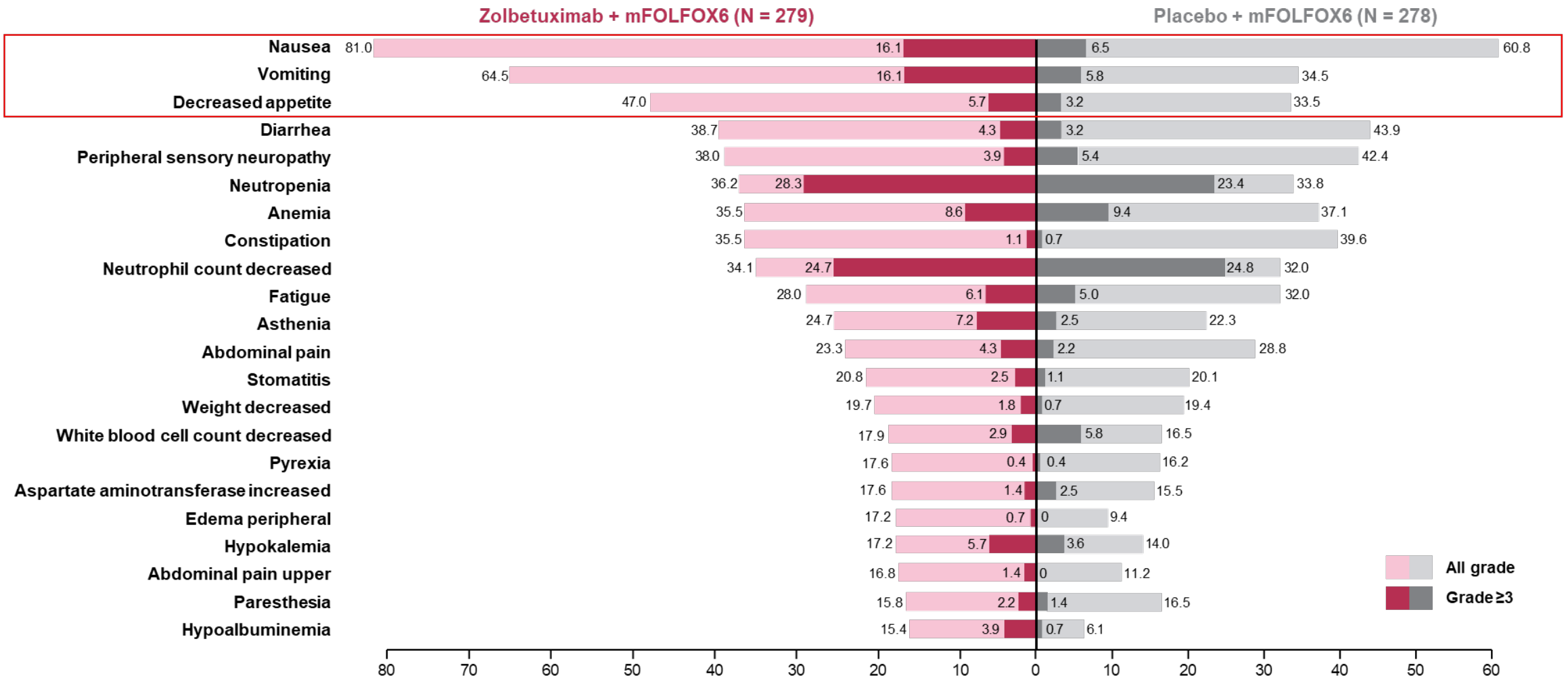
	Zolbetuximab + mFOLFOX6 (N = 211)	Placebo + mFOLFOX6 (N = 211)
Patients[a], n	128	131
ORR[b], % (95% CI)	60.7 (53.72–67.30)	62.1 (55.17–68.66)
BOR[c,d], n (%)		
CR	12 (5.7)	7 (3.3)
PR	116 (55.0)	124 (58.8)
SD	45 (21.3)	52 (24.6)
PD	14 (6.6)	14 (6.6)
Median DOR[b], months, (95% CI)	8.51 (6.80–10.25)	8.11 (6.47–11.37)
3rd quartile, months (95% CI)	29.9 (10.41–NE)	15.5 (13.27–NE)

- Response rates were similar between treatment arms
- Formal analysis of PROs is pending
  - Initial descriptive analysis did not indicate differences between treatment arms

[a]Patients with measurable disease. [b]Per RECIST version 1.1 by independent review committee; [c]Patients with non-CR/non-PD, no disease, missing data, or who could not be evaluated are not shown; [d]Patients with missing data had no post-baseline imaging assessment.

Shitara K et al. *ASCO GI Meeting.* 2023; LBA 292

SPOTLIGHT – TEAES IN ≥15% OF ALL TREATED PATIENTS

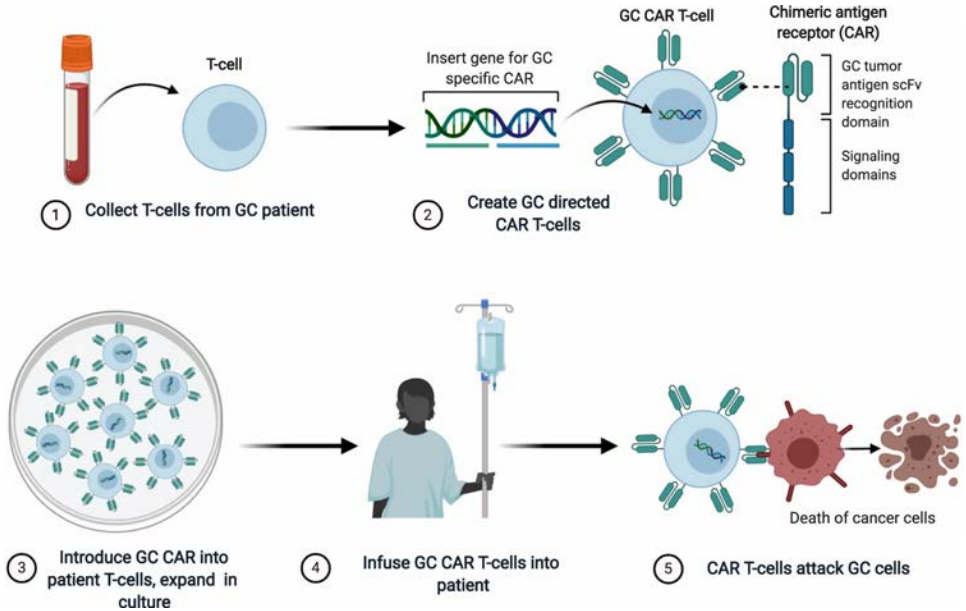


- The most common TEAEs with zolbetuximab + mFOLFOX6 were nausea and vomiting as on-target effects

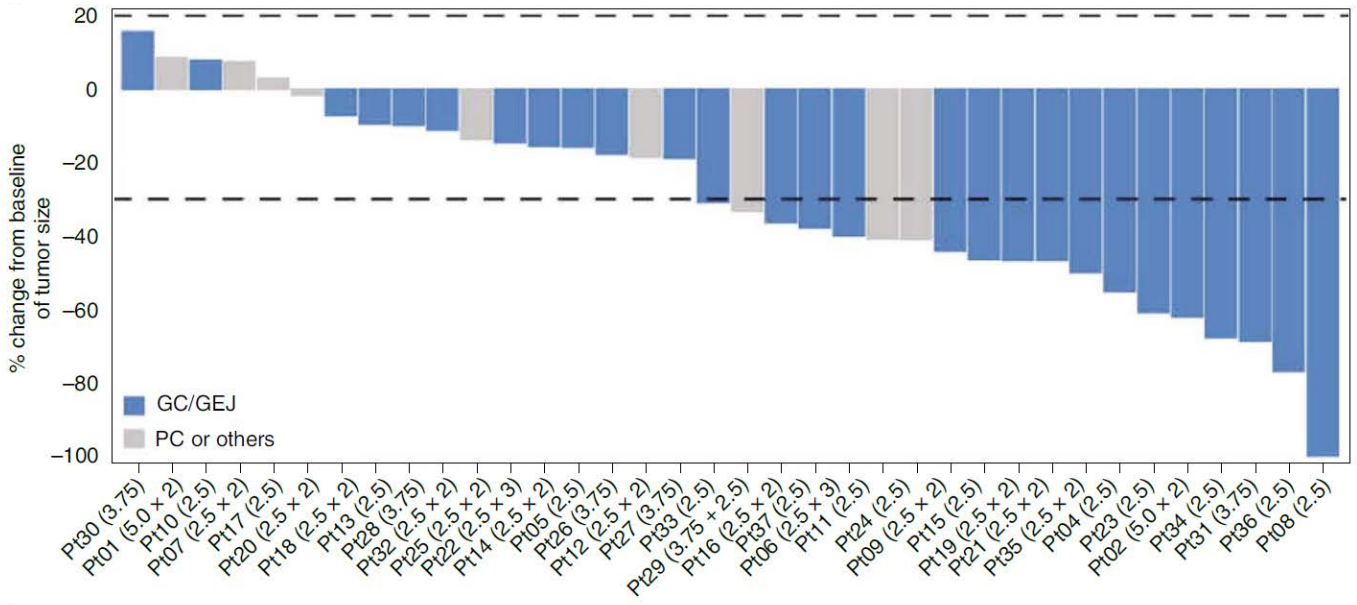
[a]Preferred terms were defined according to the Medical Dictionary for Regulatory Activities terminology version 25.0.

Shitara K et al. *ASCO GI Meeting.* 2023; LBA 292

CAR-T CELL THERAPY AGAINST GC TUMOR ANTIGENS

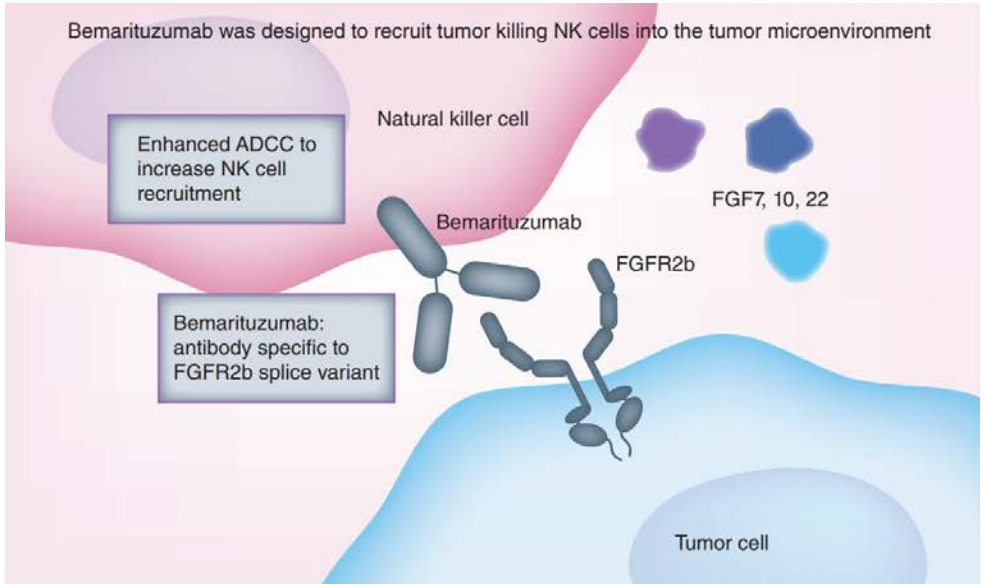


Claudin 18.2-directed CAR-T therapy



Olnes MJ, Martinson HA. *Cancer Gene Ther*. 2021 Sep;28(9):924-934
Qi C et al. *Nat Med*. 2022 Jun;28(6):1189-1198

FGFR-2B POSITIVE GASTRIC CANCER – BEMARITUZUMAB



Key Eligibility Criteria

- No prior therapy for unresectable, locally advanced or metastatic gastric/GEJ adenocarcinoma
- RECIST v1.1 evaluable disease
- FGFR2b overexpression and/or *FGFR2* gene amplification
- Not HER2-positive

Stratification Factors

- Geographic region
- Single dose of FOLFOX while screening
- Prior perioperative chemotherapy

Randomization 1:1

- Bemarituzumab* + mFOLFOX6 (n = 77)
- VS
- Placebo + mFOLFOX6 (n = 78)

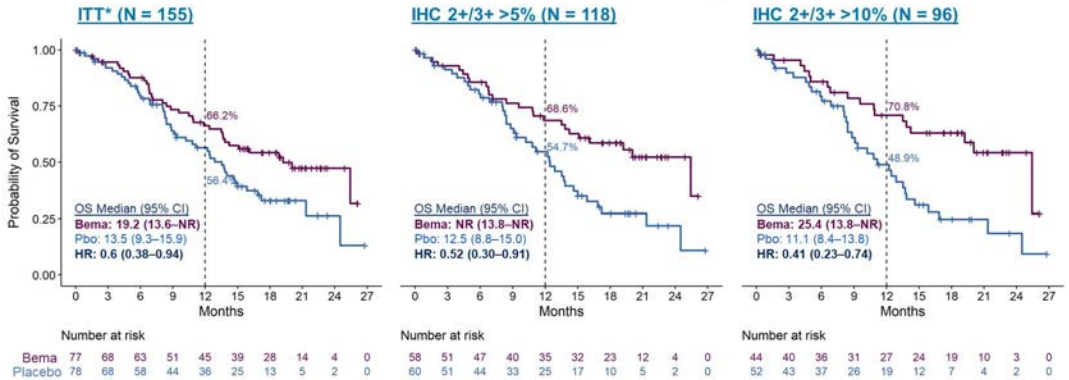
Primary endpoint
- PFS

Secondary endpoints
- OS
- Response rate

Treatment may continue until progression, unacceptable toxicity, or the patient meets other withdrawal criteria

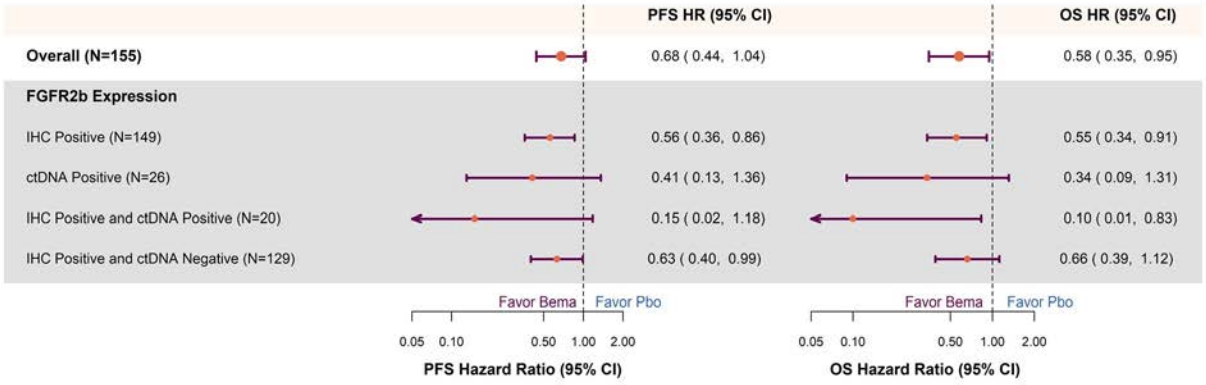
*Bemarituzumab dosing: 15 mg/kg Q2W beginning cycle 1 day 1 (plus 1 dose of 7.5 mg/kg on day 8 of cycle 1 only). FOLFOX6 dosing: standard fixed doses Q2W.
FGFR2b, fibroblast growth factor receptor 2b.

Addition of Bemarituzumab Showed a +5.7 Month Improvement in Median OS



*ITT = includes 149 patients with IHC 2+/3+ and 6 with IHC <2+ or not available who were enrolled based on ctDNA alone.
NR, not reached.

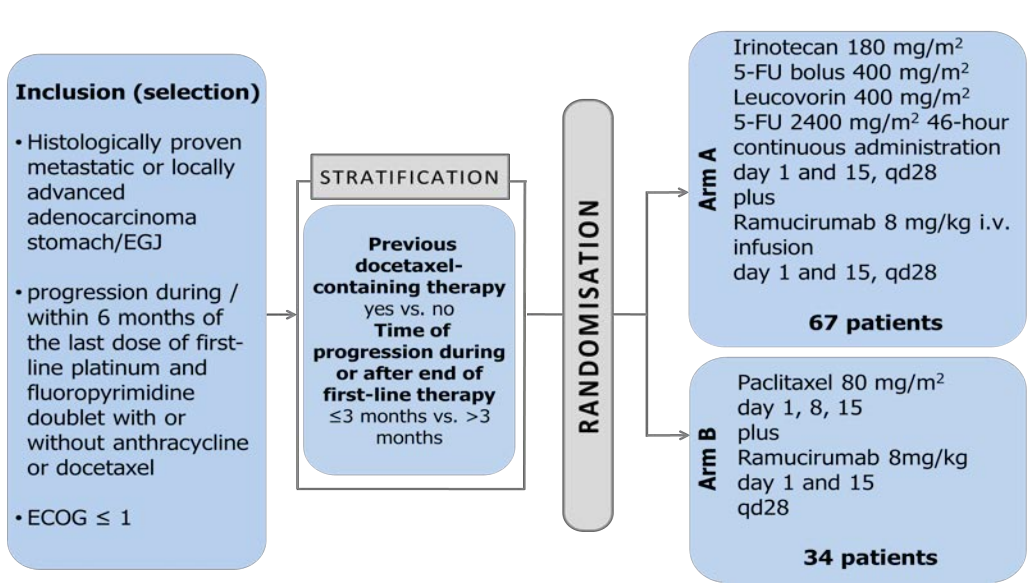
Overexpression was Sufficient, ctDNA+ with Most Pronounced Benefit

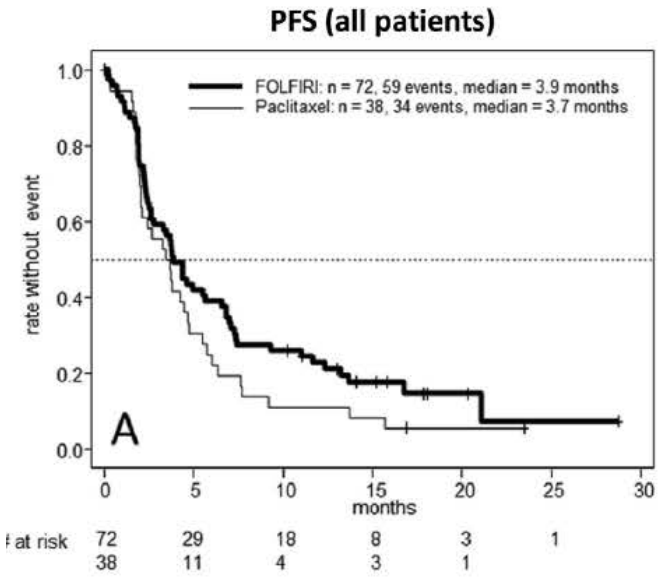


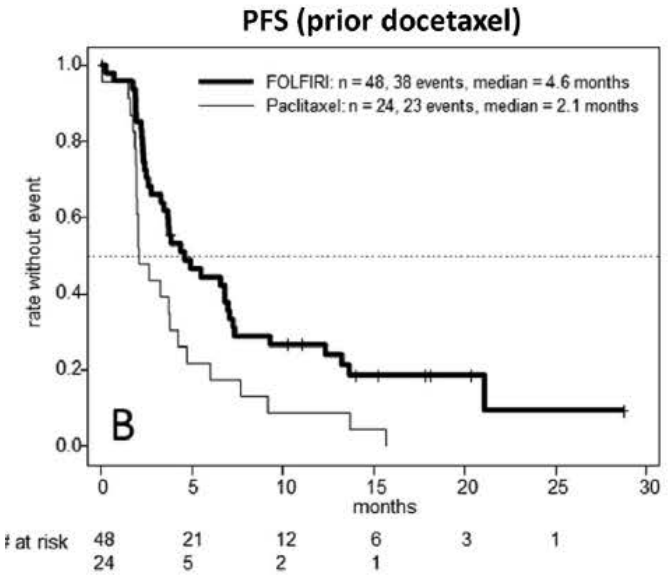
Wainberg Z et al. *Lancet Oncol.* 2022 Oct 13:S1470-2045(22)00603-9

2ND-LINE: RAMUCIRUMAB COMBINED WITH PACLITAXEL OR FOLFIRI

AIO-RAMIRIS Study – Design and primary endpoint (PFS)

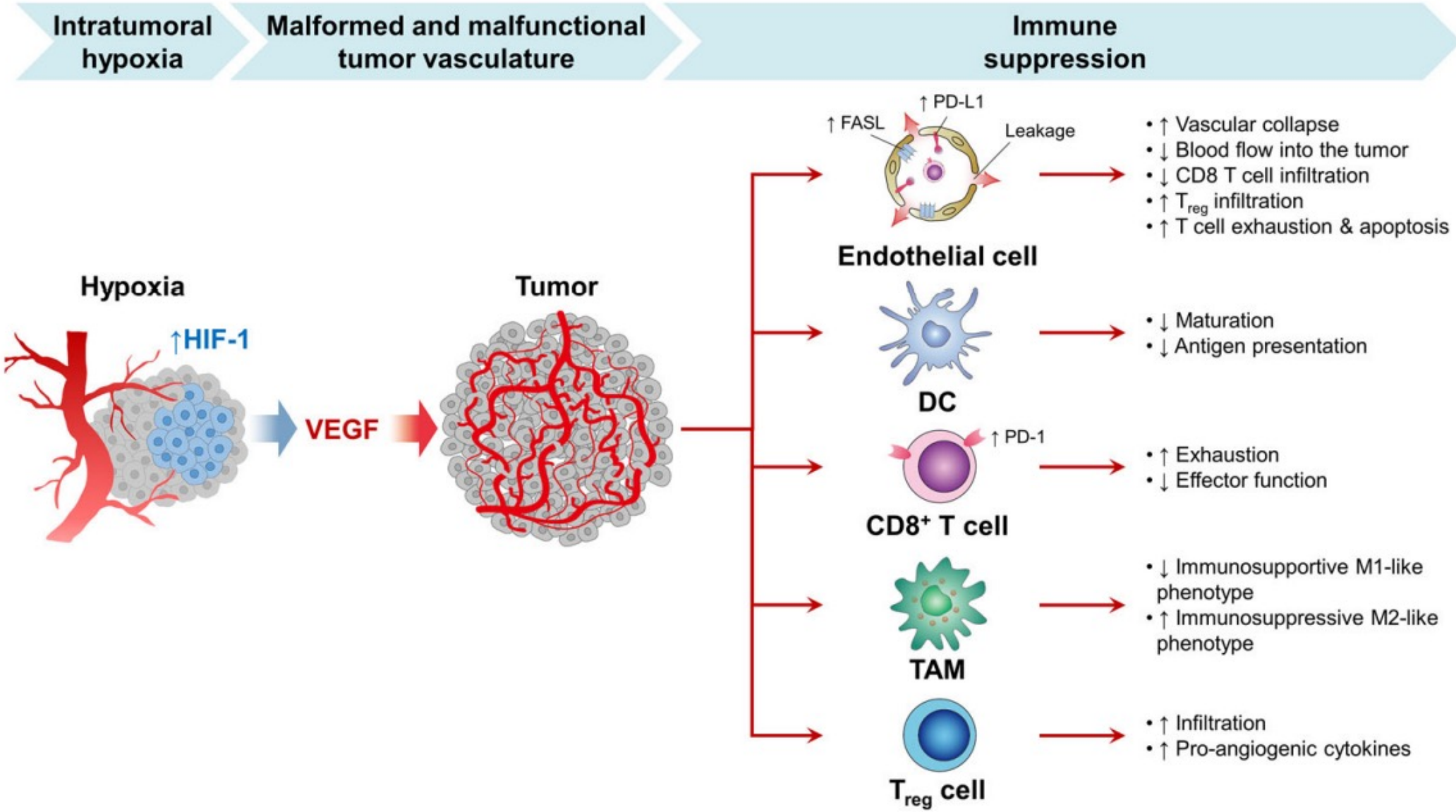






Lorenzen S et al. *European Journal of Cancer 2022; 165: 48e57*

ANGIOGENESIS AND IMMUNE PATHOPHYSIOLOGY



Lee WS et al. *Experimental & Molecular Medicine* 2020; 52:1475–1485

RAMUCIRUMAB AFTER ANTI-PD1 THERAPY

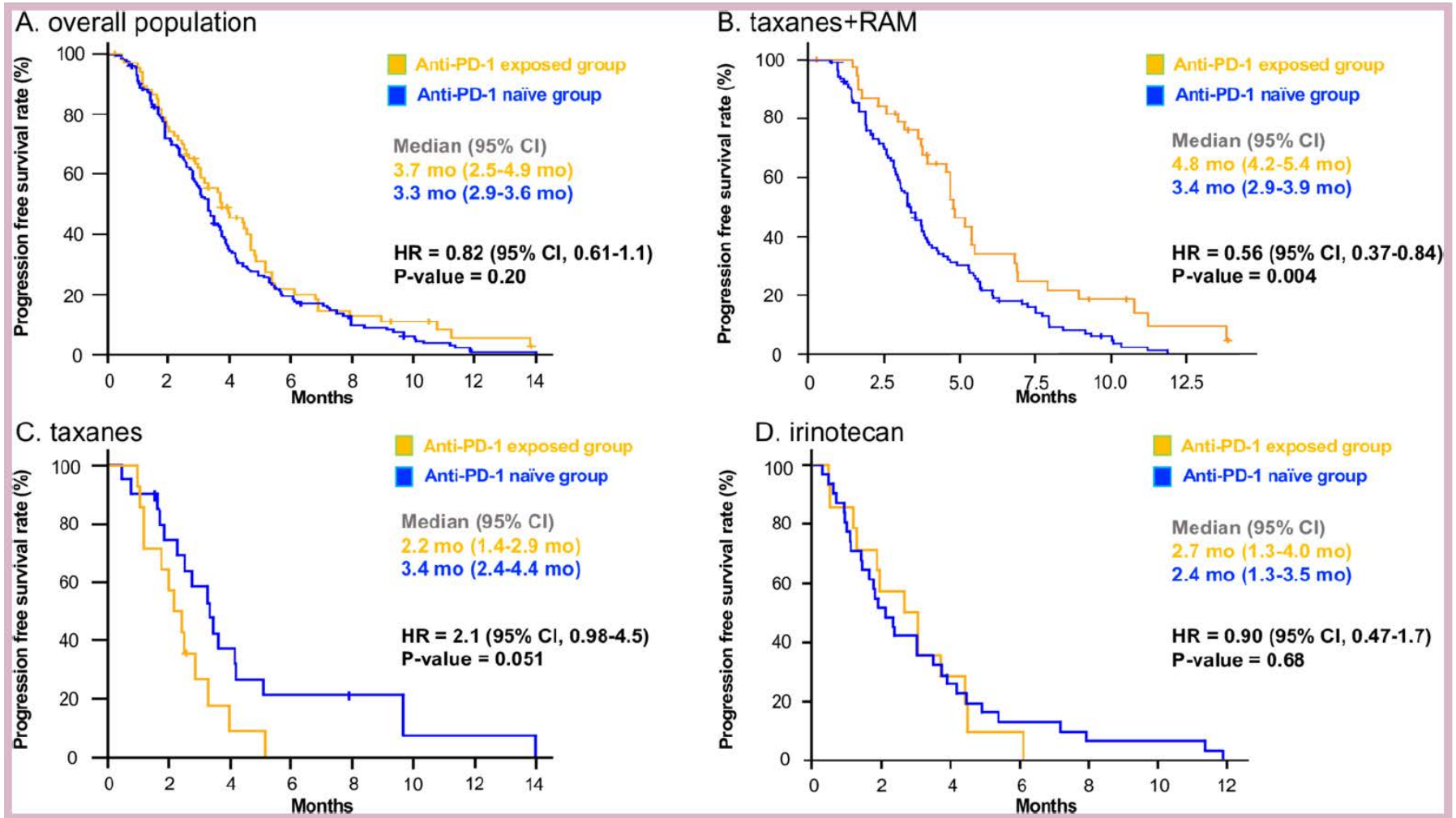


Figure 1 Kaplan-Meier estimates of progression-free survival. (A) Overall population. (B) Taxanes+RAM. (C) Taxanes. (D) Irinotecan. RAM, ramucirumab

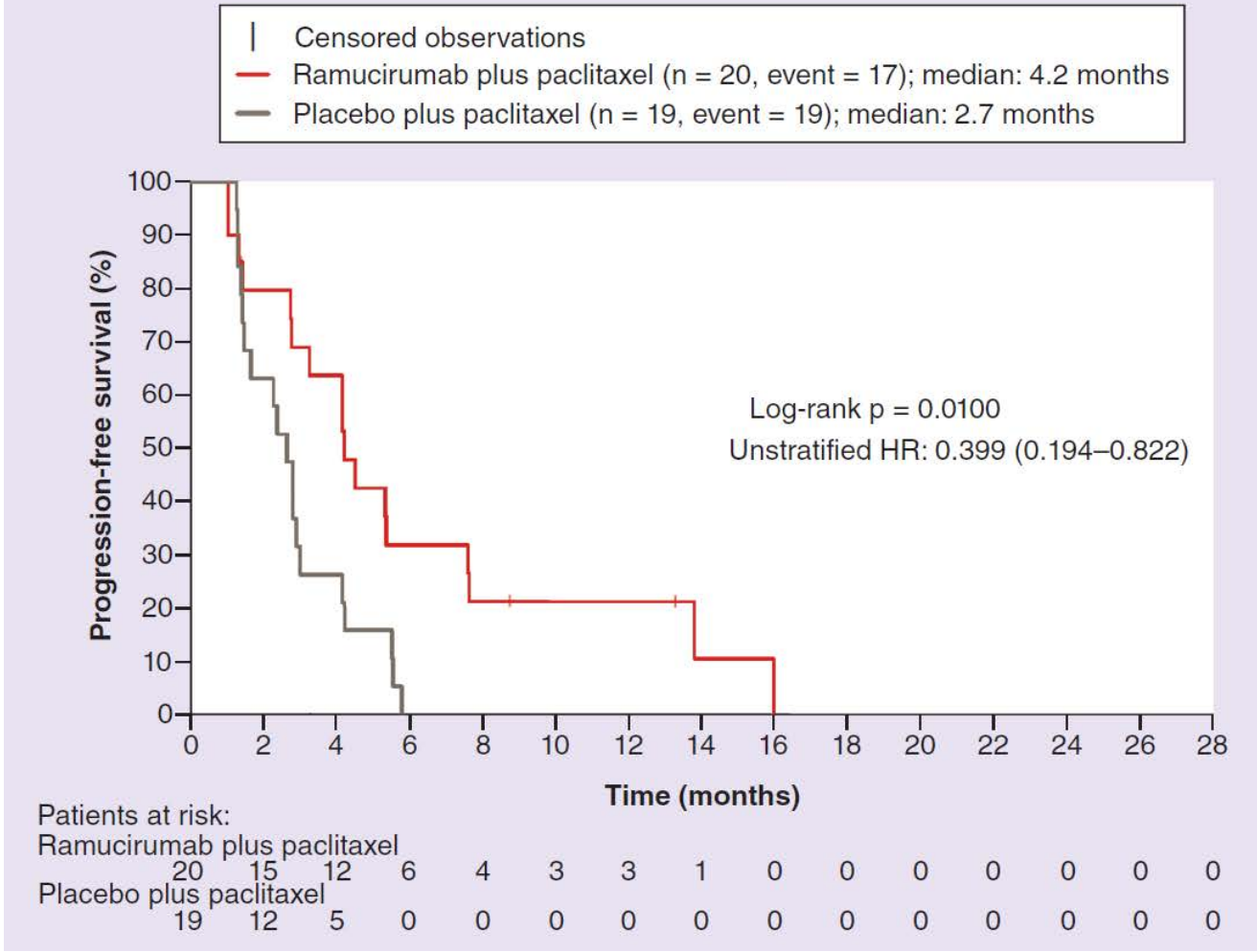
Taxane/Ramucirumab group

Response Rate (ORR)
Anti-PD-1-exposed: 60.6% (n=33)
Anti-PD1-naive: 20.0% (n=85)

Sasaki A et al. *ESMO Open.* 2020 Jul;4(Suppl 2):e000775

RAMUCIRUMAB-PACLITAXEL POST TRASTUZUMAB

Ramucirumab and paclitaxel in patients with gastric cancer and prior trastuzumab: subgroup analysis from RAINBOW study

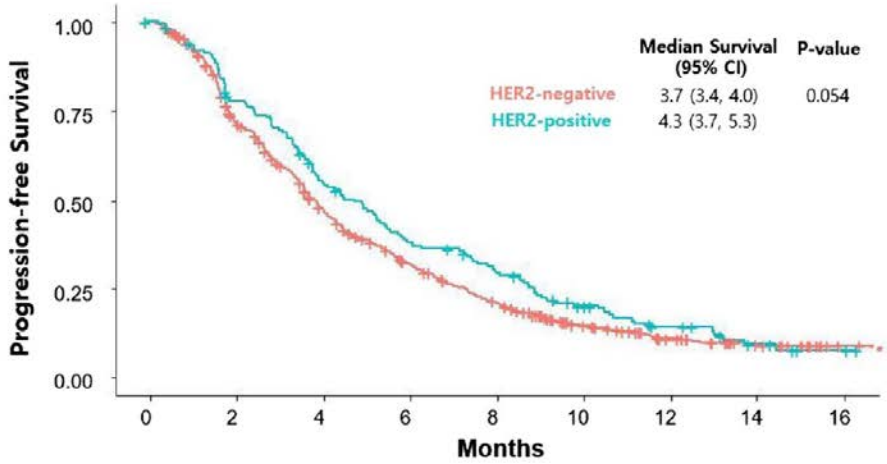


De Vita F et al. *Future Oncol* 2019; 15(23), 2723–2731

RAMUCIRUMAB-PACLITAXEL IN HER2-POSITIVE GEAC

Ramucirumab plus paclitaxel as a second-line treatment in HER2-positive gastric cancer: subgroup analysis of a nationwide, real-world study in Korea (KCSG-ST19-16)

Bum Jun Kim[1] · Hee-Jung Jee[2] · Sun Young Rha[3,17,18] · Hye Sook Han[4,5] · Min-Hee Ryu[6] · Se Hoon Park[7] · Jong Gwang Kim[8] · Woo Kyun Bae[9] · Keun-Wook Lee[10] · Do-Youn Oh[11,12] · Ji-Hye Byun[13] · Dong Sook Kim[14] · Young Ju Suh[15] · Hyonggin An[16] · Dae Young Zang[1]



	Number of patients (%) (Total number of patients with measurable disease = 755)			
	Missing *n* (%)	HER2-positive (*n* = 135)	HER2-negative (*n* = 620)	*P*-value
Best overall response	3 (0.4%)			0.04
Complete response (CR)		1 (0.7%)	2 (0.3%)	
Partial response (PR)		30 (22.2%)	91 (14.7%)	
Stable disease (SD)		56 (41.5%)	256 (41.5%)	
Progressive disease (PD)		23 (17.0%)	167 (27.1%)	
Not applicable		25 (18.5%)	101 (16.4%)	
Objective response rate[a]	3 (0.4%)	23.0% (95% CI, 15.9–30.1%)	15.1% (95% CI, 12.3–17.9%)	0.025
Disease control rate[b]	3 (0.4%)	64.4% (95% CI, 56.3–72.5%)	56.6% (95% CI, 52.7–60.5%)	0.093

Kim BJ et al. *Gastric Cancer 2022; 25:609–618*

SELECTION AND SEQUENCING OF THERAPY FOR GEAC

- **Sequential therapies** in advanced / metastatic GE cancer are standard
- **Molecular characterization** drives treatment selection
- **Claudin18.2 directed Zolbetuximab: SPOTLIGHT + GLOW** – 2 positive phase III studies
- **FGFR2+ GC** Promising phase II data for Bemarituzumab + chemo; phase III ongoing
- **Ramucirumab-Paclitaxel** 2nd-line remains standard for the majority of GE cancer
- **Ramucirumab-Paclitaxel** effective post PD-1 therapy and post Trastuzumab
- **Ramucirumab-FOLFIRI** is being explored for taxane-pretreated patients

MODULE 4: Current Approaches to the Management of Esophageal Cancer — Dr Wainberg

RTP
RESEARCH
TO PRACTICE

Gurveen Kaur
(Wheeling, West Virginia)

57-year-old man with dysphagia, weight loss and a lower esophageal adenocarcinoma (T3N3)

Dr Liudmila Schafer
(Kansas City, Missouri)

75-year-old man with dysphagia is found to have a lower esophageal adenocarcinoma with regional adenopathy and pulmonary nodules (CPS 40 by SP263)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Gurveen Kaur, MD

"He did very well on the CROSS regimen. Imaging was consistent with response. Pathology at esophagogastrectomy demonstrated residual disease, along with lymph node involvement. He is now on adjuvant nivolumab. Does CPS affect the adjuvant decision? Are experts considering immunotherapy in patients receiving neoadjuvant FLOT?"

- **How do you manage patients with GE cancers who receive the neoadjuvant CROSS regimen but then refuse to go to surgery?**
- **For how long after treatment do you continue thyroid function testing in patients receiving adjuvant immunotherapy?**

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Liudmila N Schafer, MD

"In KEYNOTE-590, they used 5-FU/cisplatin with pembrolizumab in the first line. This regimen is very toxic and really difficult for patients to tolerate.

Would the faculty approach this man differently?"

RTP
RESEARCH
TO PRACTICE

Case Presentation: 60-year-old woman with a known germline BRCA2 mutation and a history of Hodgkin lymphoma, breast and anaplastic thyroid cancers now has localized squamous cell esophageal cancer

Dr Warren Brenner (Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Warren S Brenner, MD

"My question for the investigators is, when do they use dual checkpoint inhibitor therapy in squamous cell cancer of the esophagus?

What is the role of a PARP inhibitor in patients who have BRCA mutations and underlying esophageal cancer?"

RTP
RESEARCH
TO PRACTICE

Current Approaches to the Management of Esophageal Cancer

Zev Wainberg, MD

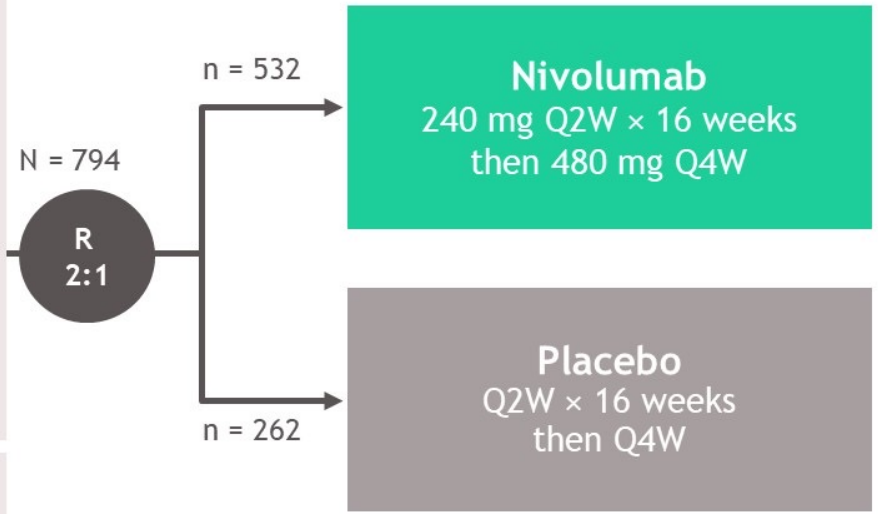
Co-Director GI Oncology Program
Director of Early Phase Clinical Research
Jonsson Comprehensive Cancer Center, UCLA School of Medicine
Los Angeles, California

CheckMate 577 study design

- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

Key eligibility criteria
- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0-1

Stratification factors
- Histology (squamous versus adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 versus ypN0)
- Tumor-cell PD-L1 expression (≥ 1% versus < 1%[c])



Total treatment duration of up to 1 year[d]

Primary endpoint:
- DFS[e]

Secondary endpoints:
- OS[f]
- OS rate at 1, 2, and 3 years

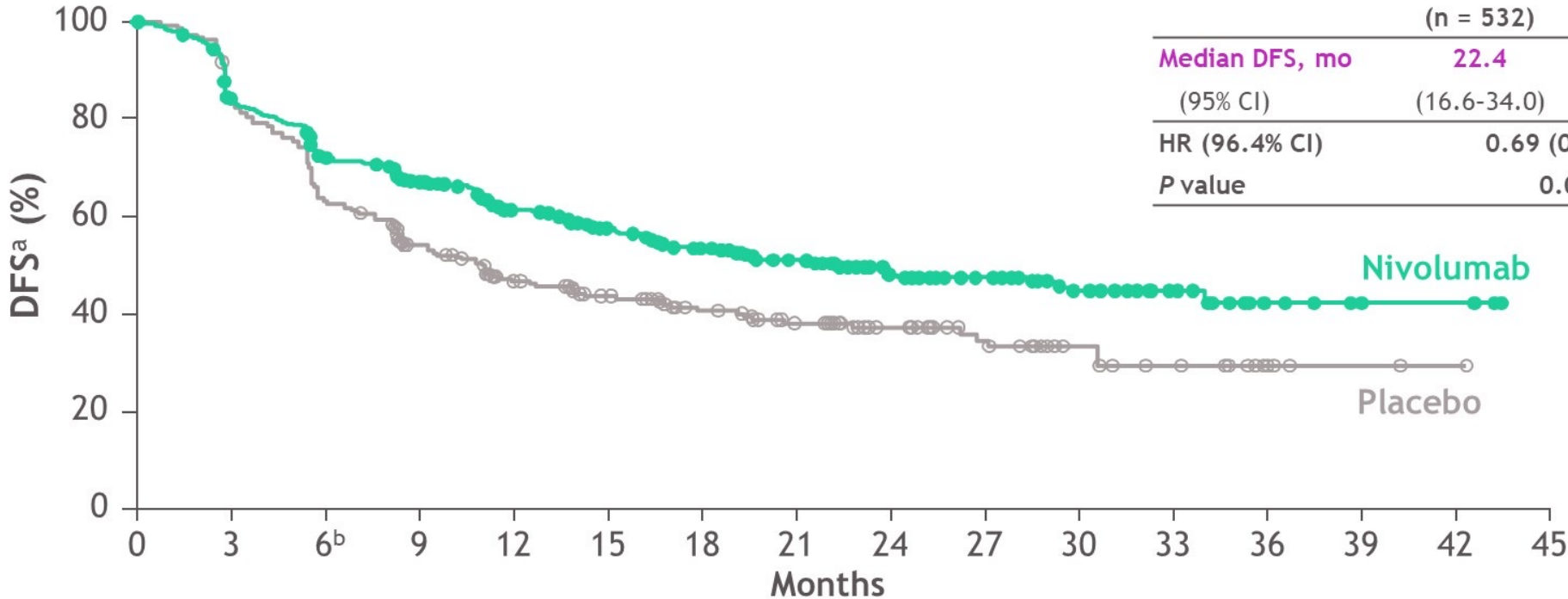
Exploratory endpoints included:
- Safety
- DMFS[g]
- PFS2[h]
- QoL

- Median follow-up was 24.4 months (range, 6.2–44.9)[i]
- Geographical regions: Europe (38%), United States and Canada (32%), Asia (13%), rest of the world (16%)

[a]ClinicalTrials.gov. NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a prespecified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]DMFS is defined as the time between randomization and the first distant recurrence or death, whichever occurs first; [h]PFS2 is defined as the time from randomization to progression after the first subsequent systemic therapy, initiation of second subsequent systemic therapy, or death, whichever is earlier; [i]Time from randomization date to clinical data cutoff (May 12, 2020).

Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203.

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

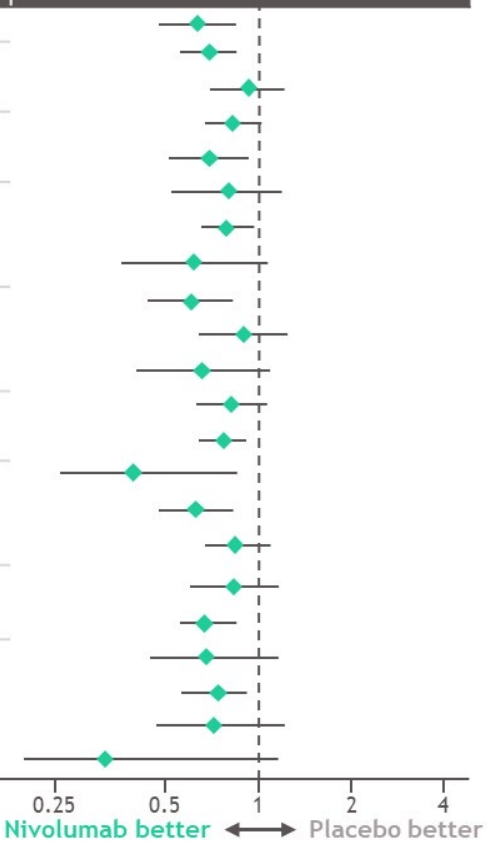
- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

[a]Per investigator assessment; [b]6-month DFS rates were 72% (95% CI, 68-76) in the nivolumab arm and 63% (95% CI, 57-69) in the placebo arm; [c]The boundary for statistical significance at the prespecified interim analysis required the *P* value to be less than 0.036.

Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203.

Disease-free survival subgroup analysis

Category	Subgroup	Median DFS, mo		Unstratified HR
		Nivolumab	Placebo	
Overall	N = 794	22.4	11.0	0.70
Tumor location at initial diagnosis	Esophagus (n = 462)	24.0	8.3	0.61
	Gastroesophageal junction (n = 332)	22.4	20.6	0.87
Histologic type	Adenocarcinoma (n = 563)	19.4	11.1	0.75
	Squamous cell carcinoma (n = 230)	29.7	11.0	0.61
Tumor cell PD-L1 expression[a]	≥ 1% (n = 129)	19.7	14.1	0.75
	< 1% (n = 570)	21.3	11.1	0.73
	Indeterminate/nonevaluable (n = 95)	Not reached	9.5	0.54
PD-L1 CPS expression[a,b]	≥ 5 (n = 371)	29.4	10.2	0.62
	< 5 (n = 295)	16.3	11.1	0.89
	Missing/nonevaluable (n = 128)	Not reached	10.8	0.61
Pathologic lymph node status	ypN0 (n = 336)	Not reached	27.0	0.74
	≥ ypN1 (n = 457)	14.8	7.6	0.67
Pathological tumor status	ypT0 (n = 47)	34.0	5.2	0.35
	ypT1 or ypT2 (n = 308)	28.3	9.3	0.60
	ypT3 or ypT4 (n = 436)	18.9	14.1	0.84
Time from complete resection to randomization	< 10 weeks (n = 256)	24.0	14.1	0.84
	≥ 10 weeks (n = 538)	21.4	10.8	0.66
Radiotherapy dosage[b,c]	< 41.4 Gray (n = 92[d])	19.7	13.8	0.69
	41.4-50.4 Gray (n = 504)	24.0	11.1	0.73
	> 50.4 Gray (n = 152)	21.4	8.3	0.72
	Not reported (n = 41)	14.4	6.1	0.41

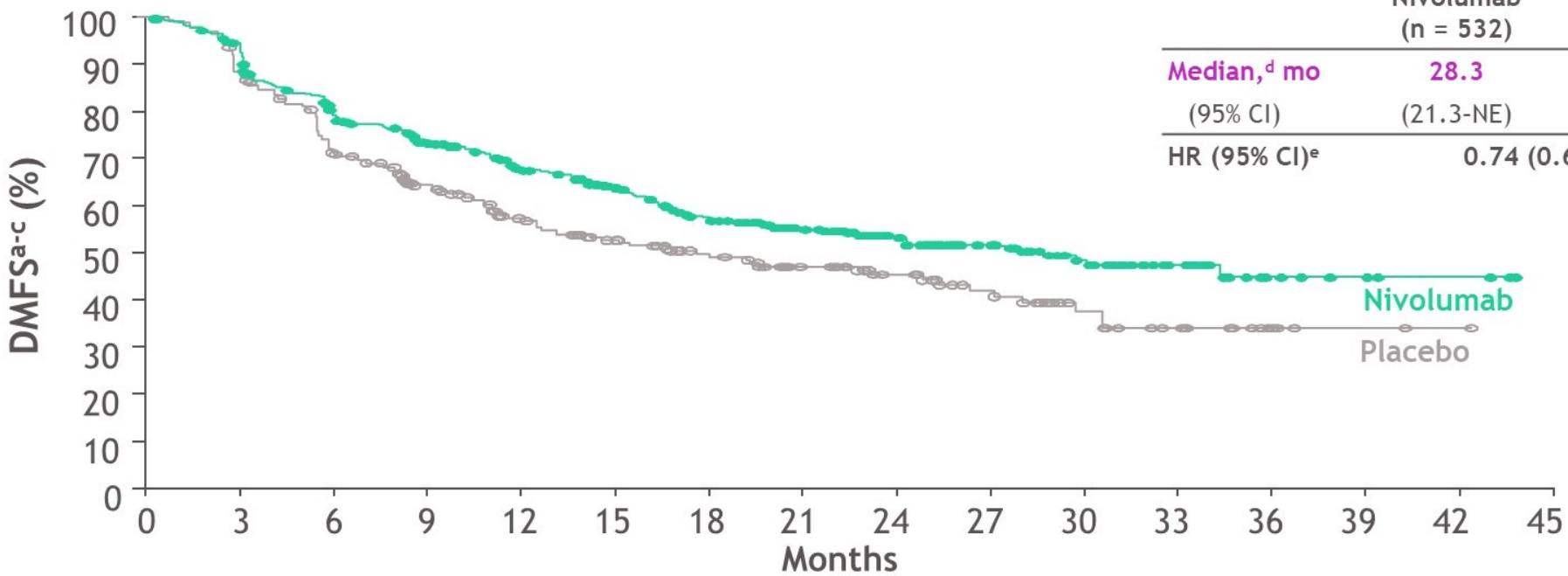


- Disease-free survival benefit was observed with nivolumab versus placebo across multiple subgroups

[a]PD-L1 expression determined from tumor tissue specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako), which for most patients, was obtained after completion of chemoradiotherapy; [b]Post hoc analysis; [c]Radiotherapies received from the start of concurrent CRT until complete resection. [d]10 patients (7 in the nivolumab group and 3 in the placebo group) received total exposure less than 40 Gray (following database lock, investigators amended the total dose of radiotherapy for 7 of these patients to 41.4-50.4 Gray).

Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203.

Distant metastasis–free survival (DMFS)



	Nivolumab (n = 532)	Placebo (n = 262)
Median,[d] mo	28.3	17.6
(95% CI)	(21.3-NE)	(12.5-25.4)
HR (95% CI)[e]	0.74 (0.60-0.92)	

No. at risk																
Nivolumab	532	449	392	332	276	235	195	160	102	75	44	23	8	4	3	0
Placebo	262	226	180	142	113	93	77	64	46	33	21	14	5	2	1	0

- Nivolumab showed a 26% reduction in the risk of distant recurrence or death versus placebo
- Distant (29% versus 39%) and locoregional (12% versus 17%) recurrences were less frequent with nivolumab versus placebo, respectively

[a]Per investigator assessment; based on Kaplan-Meier estimates; [b]DMFS is defined as the time between randomization and the first distant recurrence or death, whichever occurs first; [c]DMFS was censored on the date of last disease assessment; [d]Median DMFS time was computed using the Kaplan-Meier estimate, and a 95% CI for the median was computed based on a log-log transformation of the survivor function; [e]Stratified Cox proportional-hazards model. Hazard ratio is nivolumab over placebo.

Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203.

Table 3. Safety summary

- CheckMate 577

Patients, n (%)	Nivolumab[a] (n = 532)		Placebo[a] (n = 260)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AEs[b,c]	513 (96)	186 (35)	243 (93)	84 (32)
Serious AEs[c]	160 (30)	109 (20)	80 (31)	53 (20)
AEs leading to discontinuation[d]	71 (13)	39 (7)	21 (8)	16 (6)
Any TRAEs[b]	379 (71)	74 (14)	122 (47)	16 (6)
Serious TRAEs	41 (8)	31 (6)	7 (3)	3 (1)
TRAEs leading to discontinuation	49 (9)	26 (5)	8 (3)	7 (3)
TRAEs in ≥10% of treated patients in either arm[b]				
Fatigue	92 (17)	6 (1)	29 (11)	1 (< 1)
Diarrhea	89 (17)	2 (< 1)	39 (15)	2 (< 1)
Pruritus	53 (10)	2 (< 1)	9 (3)	0
Rash	51 (10)	4 (< 1)	10 (4)	1 (< 1)
Hypothyroidism	51 (10)	0	4 (2)	0

[a]Patients who received ≥ 1 dose of study treatment; [b]Events reported between first dose and 30 days after last dose of study drug; [c]There were 8 and 7 grade 5 AEs in the nivolumab and placebo arms, respectively; [d]There were 3 and 2 grade 5 AEs leading to discontinuation in the nivolumab and placebo arms, respectively.

Early Stage Gastro-Esophageal

- **Clinical Implications**: Nivolumab established as the SOC for patients post-esophagectomy regardless of histology (SCC and adeno), PDL1 status, and final pathological stage
- **Questions Remain**:
  - Impact on Overall Survival?
  - What about patients with complete path response?
- **Future Directions**:

  Definitive Chemoradiation: Role for Immunotherapy

  -Keynote 975 (Chemoradiation +/- Pembrolizumab), KUNLUN (chemoradiation +/- Durvalumab)
- **Early Stage Gastric Cancer:**

  -Keynote 585 (Chemo +/- Pembrolizumab), Matterhorn (FLOT +/- Durvalumab)

Updated Results From First-line Pembro + CT vs CT in Esophageal Cancer (KEYNOTE-590): Study Design

- International, randomized, placebo-controlled, phase III trial of first-line pembro

Stratified by region (Asia vs rest of world); ECOG PS (0 vs 1); ESCC vs EAC

Response assessed Wk 9 then Q9W (RECIST v1.1, by investigator)

Patients with locally advanced, unresectable or metastatic EAC or ESCC or advanced/metastatic EGJ Siewert type 1 adenocarcinoma; no prior treatment; ECOG PS 0/1; RECIST v1.1 (N = 749)

→ **Pembrolizumab** 200 mg IV Q3W for ≤35 cycles **+** **CT** (**5-FU** 800 mg/m^2 days 1-5 Q3W for ≤35 cycles **+** **Cisplatin** 80 mg/m^2 IV Q3W for ≤6 cycles)

→ **Placebo +** **CT** (**5-FU** 800 mg/m^2 days 1-5 Q3W for ≤35 cycles + **Cisplatin** 80 mg/m^2 IV Q3W for ≤6 cycles)

- **Coprimary endpoints:** OS and PFS (RECIST v1.1, by investigator)
- **Secondary endpoint:** ORR (RECIST v1.1, by investigator)

Sun. *Lancet*. 2021;10302:759. Metges. ASCO GI 2022. Abstr 241. NCT03189719.

KEYNOTE-590 Update: Baseline Characteristics in ITT

Characteristic	**Pembrolizumab + CT (n = 373)**	**Placebo + CT (n = 376)**
Median age, yr (range) ≥65	64.0 (28-94) 172 (46)	62.0 (27-89) 150 (40)
Male, n (%)	306 (82.0)	319 (84.8)
Asia, n (%)	196 (52.5)	197 (52.4)
ECOG PS 1, n (%)	223 (59.8)	225 (59.8)
Metastatic disease, n (%)	344 (92.2)	339 (90.2)
Unresectable/locally advanced, n (%)	29 (7.8)	37 (9.8)
Squamous cell carcinoma, n (%)	274 (73.5)	274 (72.9)
Adenocarcinoma, n (%) ▪ Esophageal ▪ EGJ	99 (26.5) 58 (15.5) 41 (11.0)	102 (27.1) 52 (13.8) 50 (13.3)
PD-L1 CPS ≥10%*	186 (49.9)	197 (52.4)

*PD-L1 status unavailable: n = 12 in pembrolizumab + CT arm; n = 7 in placebo + CT arm.

Data cutoff: July 9, 2021

Metges. ASCO GI 2022. Abstr 241.

KEYNOTE-590 Update: OS in Prespecified Subgroups

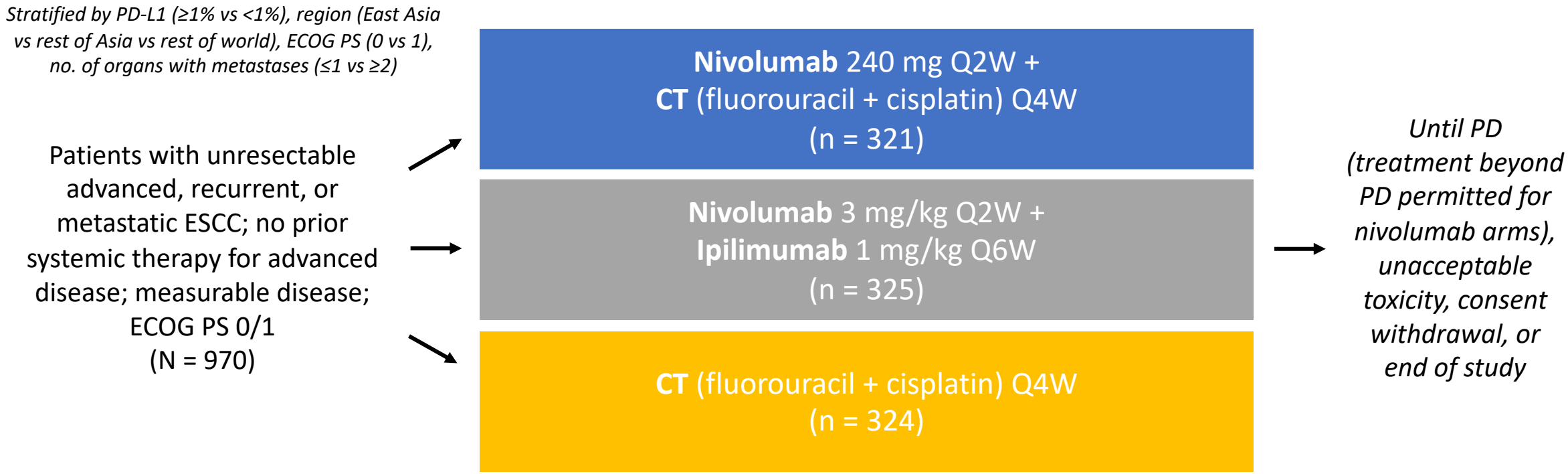
Parameter	ESCC PD-L1 CPS ≥10		ESCC		PD-L1 CPS ≥10	
	Pembro + CT	Placebo + CT	Pembro + CT	Placebo + CT	Pembro + CT	Placebo + CT
OS events, %	78	90	80	89	80	90
HR (95% CI)	0.59 (0.45-0.76)		0.73 (0.61-0.88)		0.64 (0.51-0.80)	
Median OS, mo (95% CI)	13.9 (11.1-16.0)	8.8 (7.8-10.5)	12.6 (10.2-14.12)	9.8 (8.6-11.1)	13.6 (11.1-15.2)	9.4 (8.0-10.7)
12-mo OS rate, %	55	34	51	38	54	37
24-mo OS rate, %	29	15	27	17	30	16

Median follow-up: 34.8 mo

Metges. ASCO GI 2022. Abstr 241.

CheckMate 648: First-line Nivolumab + Chemotherapy or Ipilimumab vs Chemotherapy in Advanced ESCC

- International, randomized, open-label phase III trial

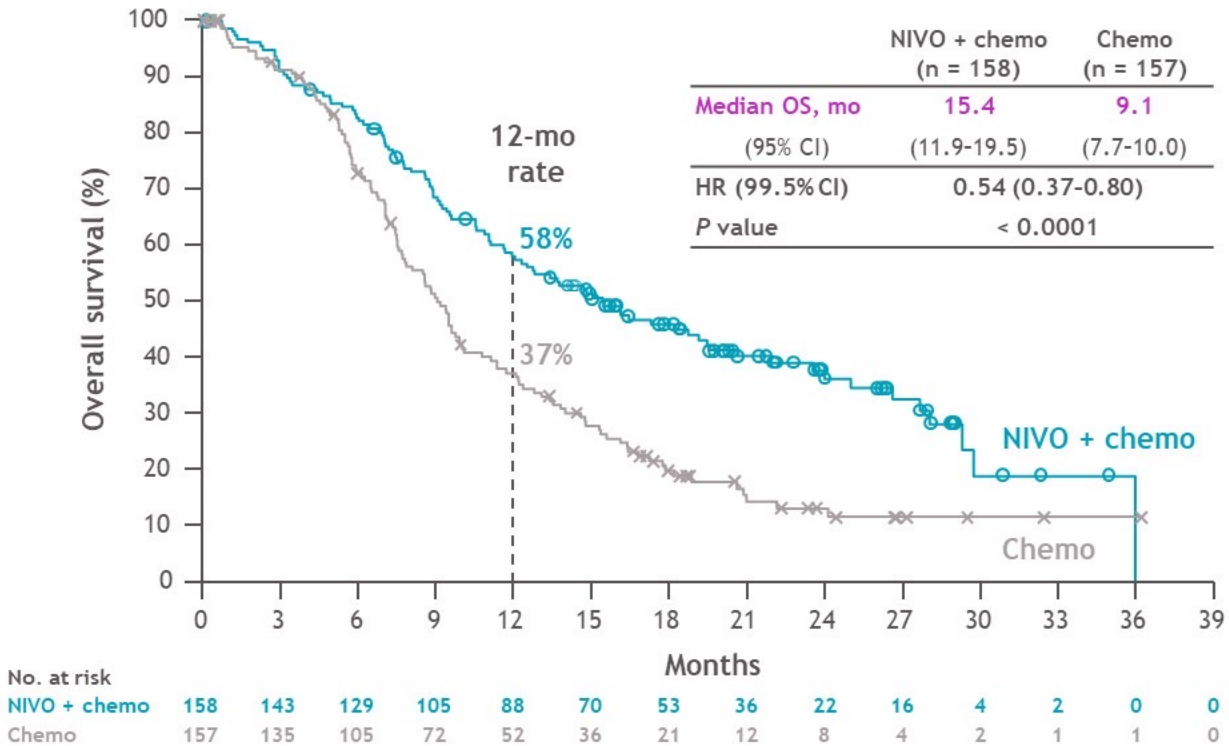


- Coprimary endpoints: OS and PFS per BICR in patients with tumor cell PD-L1 ≥1%
- Exploratory endpoints in this analysis: DoR per BICR, PFS2

Chau. ESMO World GI 2022. Abstr O-3. Chau. ASCO 2022. Abstr 4035. Doki. NEJM. 2022; 386: 449.

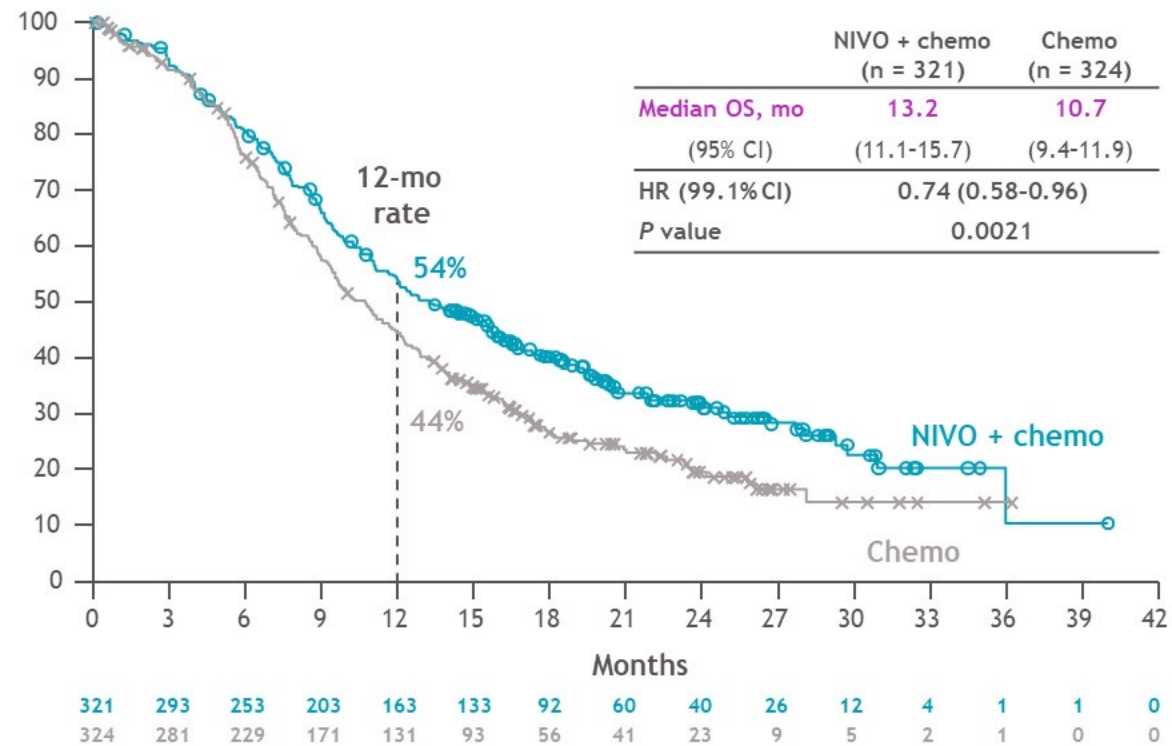
Overall survival: NIVO + chemo vs chemo

Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



	NIVO + chemo (n = 158)	Chemo (n = 157)
Median OS, mo	15.4	9.1
(95% CI)	(11.9-19.5)	(7.7-10.0)
HR (99.5% CI)	0.54 (0.37-0.80)	
P value	< 0.0001	

All randomized[a]



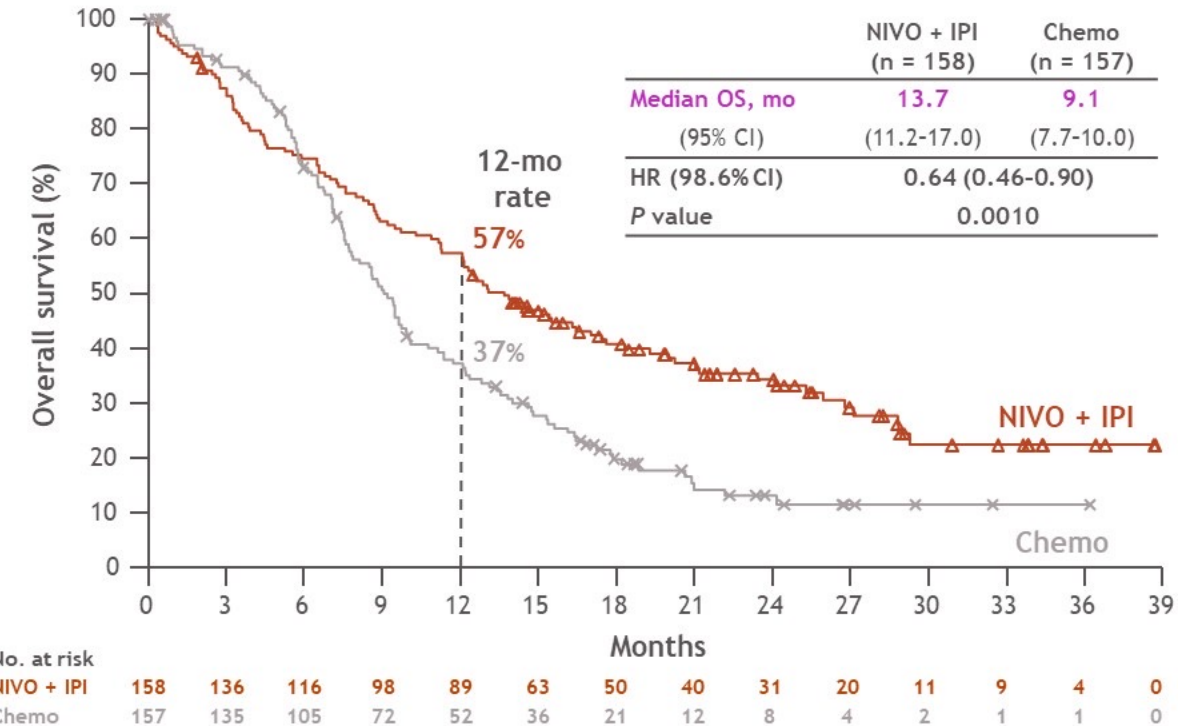
	NIVO + chemo (n = 321)	Chemo (n = 324)
Median OS, mo	13.2	10.7
(95% CI)	(11.1-15.7)	(9.4-11.9)
HR (99.1% CI)	0.74 (0.58-0.96)	
P value	0.0021	

- Superior OS with NIVO + chemo vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 46% reduction in the risk of death and a 6.3-month improvement in median OS
  - All randomized: 26% reduction in the risk of death and a 2.5-month improvement in median OS

[a]Minimum follow-up 12.9 months.

Overall survival: NIVO + IPI vs chemo

Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]

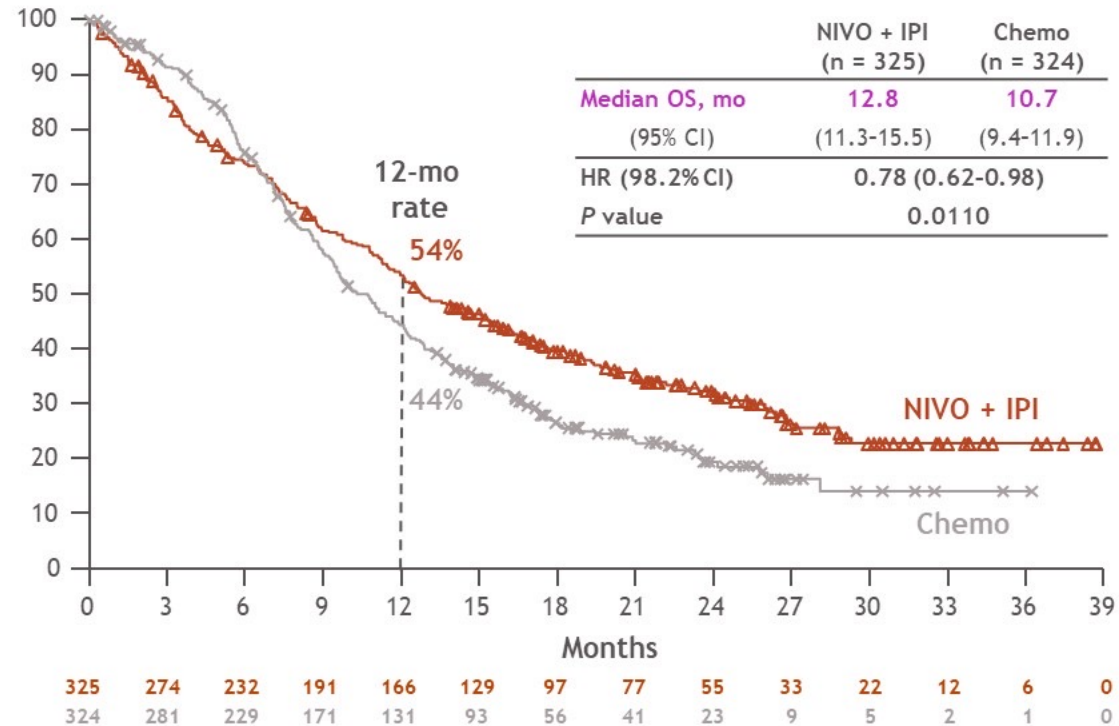


	NIVO + IPI (n = 158)	Chemo (n = 157)
Median OS, mo	13.7	9.1
(95% CI)	(11.2-17.0)	(7.7-10.0)
HR (98.6% CI)	0.64 (0.46-0.90)	
P value	0.0010	

No. at risk

NIVO + IPI	158	136	116	98	89	63	50	40	31	20	11	9	4	0
Chemo	157	135	105	72	52	36	21	12	8	4	2	1	1	0

All randomized[a]



	NIVO + IPI (n = 325)	Chemo (n = 324)
Median OS, mo	12.8	10.7
(95% CI)	(11.3-15.5)	(9.4-11.9)
HR (98.2% CI)	0.78 (0.62-0.98)	
P value	0.0110	

NIVO + IPI	325	274	232	191	166	129	97	77	55	33	22	12	6	0
Chemo	324	281	229	171	131	93	56	41	23	9	5	2	1	0

- Superior OS with NIVO + IPI vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - — Tumor cell PD-L1 ≥ 1%: 36% reduction in the risk of death and a 4.6-month improvement in median OS
  - — All randomized: 22% reduction in the risk of death and a 2.1-month improvement in median OS

[a]Minimum follow-up 12.9 months.

CheckMate 648: Baseline Characteristics

Characteristic	Nivolumab + CT (n = 321)	Nivolumab + Ipi (n = 325)	CT (n = 324)
Median age, yr (range)	64 (40-90)	63 (28-81)	64 (26-81)
Male, %	79	83	85
Asian, %	71	71	70
ECOG PS 1, %	53	54	52
ESCC, %	97	>99	98
Tumor cell PD-L1 expression ≥1%	49	49	48
Disease status at entry, % ▪ De novo metastatic ▪ Recurrent locoregional ▪ Recurrent distant ▪ Unresectable advanced	 57 7 22 14	 60 8 22 10	 58 8 19 16
No. of organs with metastases, % ▪ ≤1 ▪ ≥2	 49 51	 49 51	 49 51
Current/former smoker, %	79	82	79

Chau. ESMO World GI 2022. Abstr O-3. Chau. ASCO 2022. Abstr 4035. Doki. NEJM. 2022;386: 449.

CheckMate 648: Updated Efficacy and Safety Results

Outcome	Nivo + CT (n = 321)	Nivo + Ipi (n = 325)	CT (n = 324)
PFS2,* HR vs CT (95% CI)	0.64 (0.54-0.77)	0.74 (0.62-0.88)	--
ORR, % (95% CI)	47 (42-53)	28 (23-33)	27 (22-32)
DoR ≥12 mo, %	39	48	23

*At 13 mo of follow-up.

- TRAEs mostly grade 1/2
  - Grade 3/4 events: ≤6% in nivolumab arms
  - Any-grade select AEs
    - Nivo/CT: median 5-31 wk
    - Nivo/Ipi/CT: median 4-12 wk
- Nonendocrine select TRAEs resolved in most patients with established management algorithms
  - Nivo/CT: 57%-91%
  - Nivo/Ipi/CT: 63%-95%
  - Median time to resolution
    - Nivo/CT: 2-17 wk
    - Ipi/CT: 3-12 wk

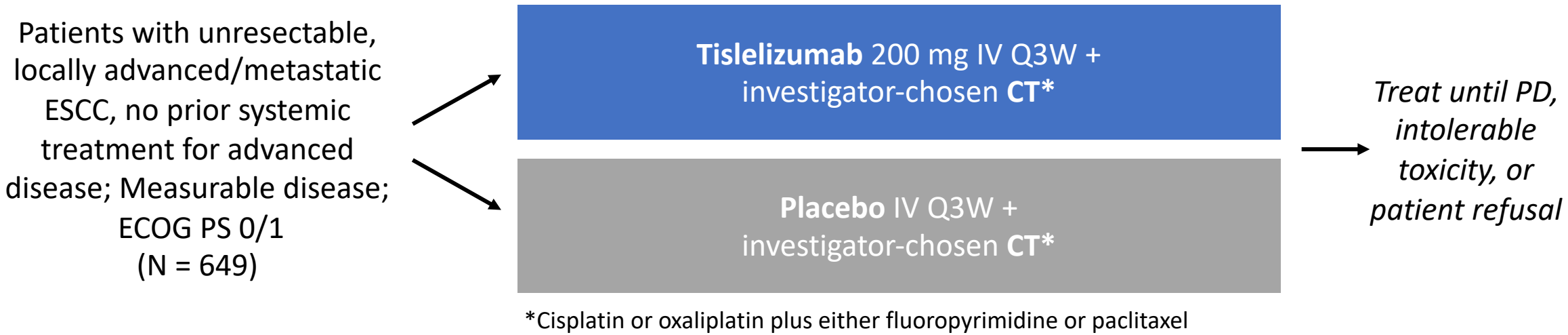
Chau. ESMO World GI 2022. Abstr O-3.

New Drugs and Targets in ESCC

RATIONALE-306: Tislelizumab + CT vs CT in Advanced/Metastatic ESCC

- Double-blind, placebo-controlled, global, randomized phase III study

Stratified by region (Asia excluding Japan vs Japan vs rest of world), prior definitive therapy (yes vs no), investigator-chosen chemotherapy (platinum/FP vs platinum/paclitaxel)

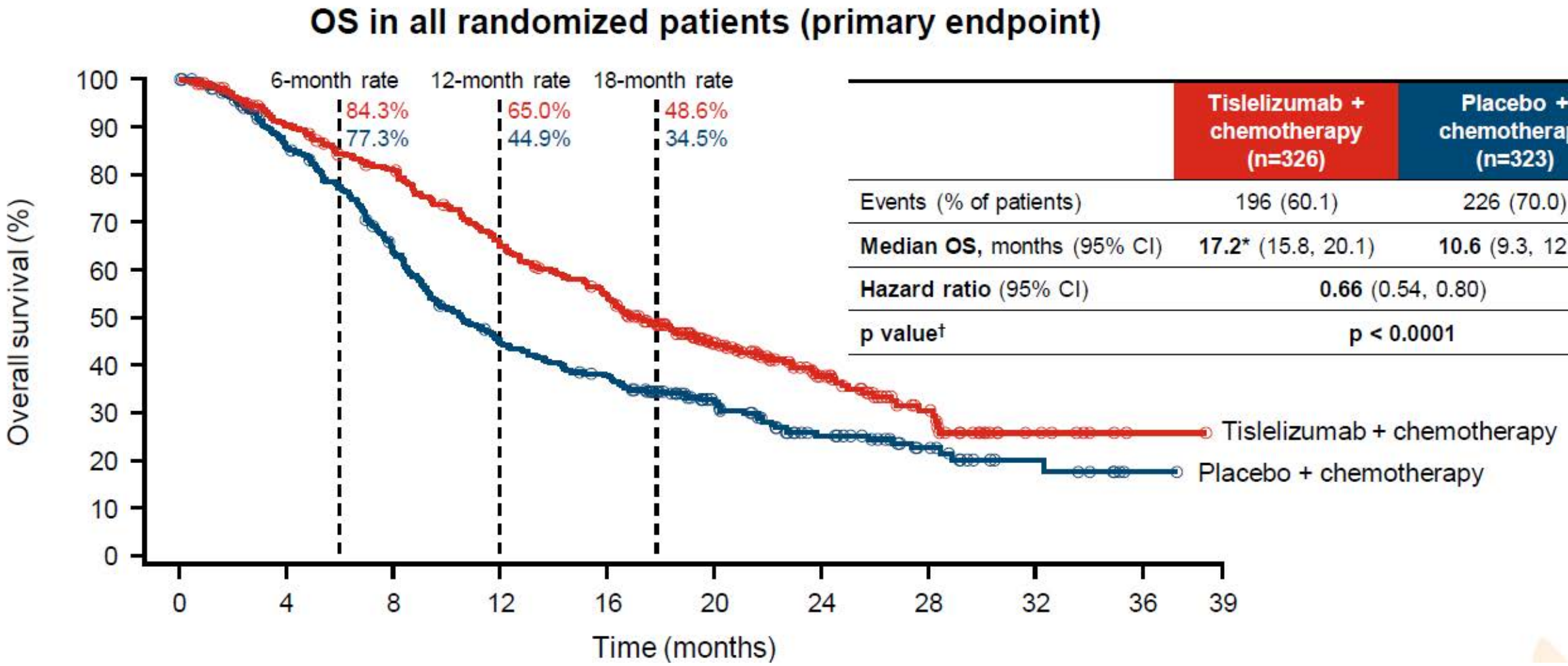


*Cisplatin or oxaliplatin plus either fluoropyrimidine or paclitaxel

- **Primary endpoint:** OS (ITT)
- **Secondary endpoints:** PFS, ORR, DoR by investigator; OS with PD-L1 ≥10%; HRQoL; safety

Yoon. ESMO WCGIC 2022. Abstr LBA-1.

RATIONALE-306



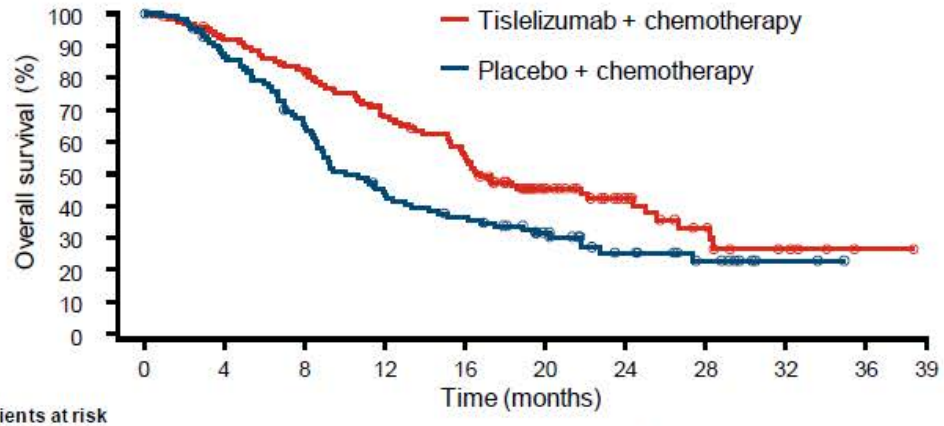
	Tislelizumab + chemotherapy (n=326)	Placebo + chemotherapy (n=323)
Events (% of patients)	196 (60.1)	226 (70.0)
Median OS, months (95% CI)	**17.2*** (15.8, 20.1)	**10.6** (9.3, 12.1)
Hazard ratio (95% CI)	**0.66** (0.54, 0.80)	
p value†	**p < 0.0001**	

Yoon et al. ESMO GI 2022

RATIONALE-306

OS by centrally-assessed baseline PD-L1 expression status

Patients with PD-L1 score ≥ 10% (secondary endpoint)

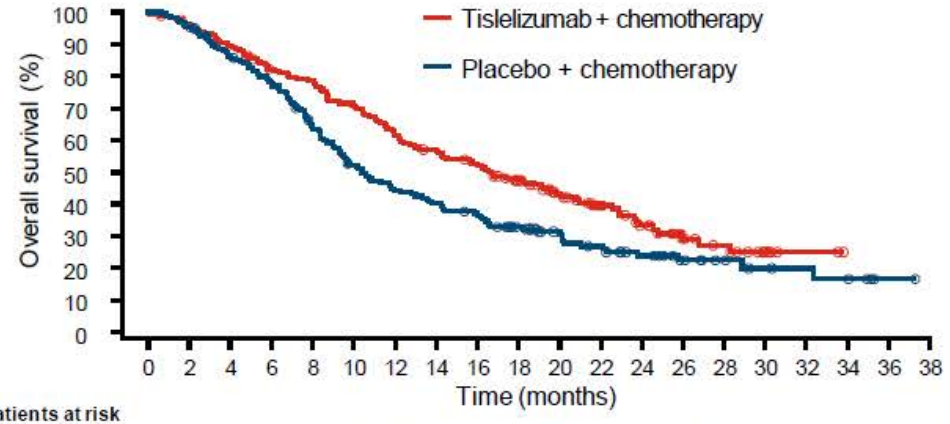


Number of patients at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38
Tislelizumab + chemotherapy	123	119	111	104	100	90	81	74	66	51	36	28	21	15	11	6	5	3	1	1
Placebo + chemotherapy	113	110	95	86	70	55	46	42	38	33	25	17	14	12	8	4	2	1	0	0

	Tislelizumab + chemotherapy (n=123)	Placebo + chemotherapy (n=113)
Events (% of patients)	73 (59.3)	79 (69.9)
Median OS, months (95% CI)	**16.6** (15.3, 24.4)	**10.0** (8.6, 13.0)
Hazard ratio* (95% CI); **p value**†	**0.62** (0.44, 0.86); **p=0.0020**‡	

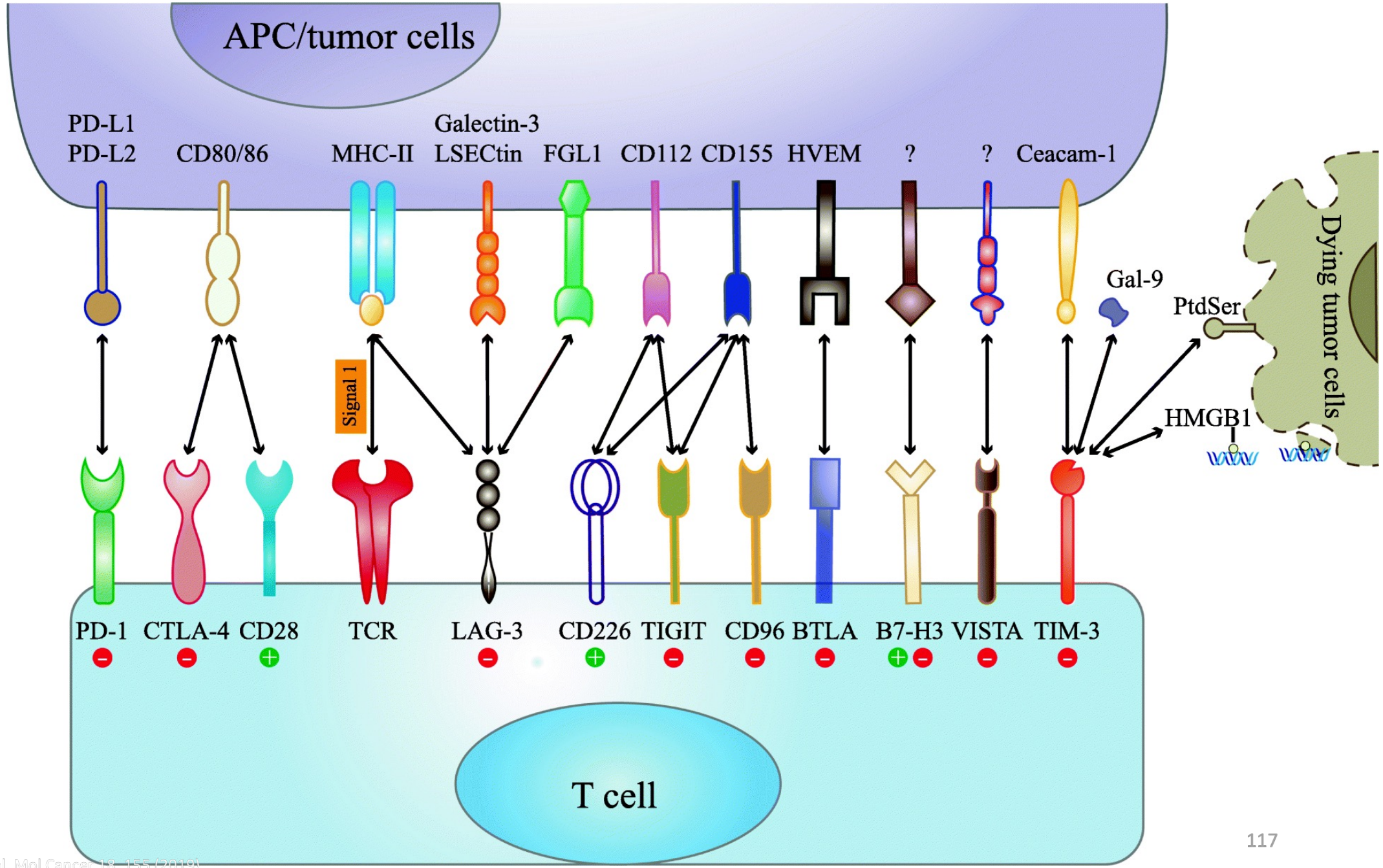
Patients with PD-L1 score < 10%



Number of patients at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38
Tislelizumab + chemotherapy	165	157	146	131	125	113	98	90	82	68	53	41	28	17	13	6	2	0	0	0
Placebo + chemotherapy	176	168	149	134	109	87	75	67	61	47	35	29	21	15	10	7	6	5	1	0

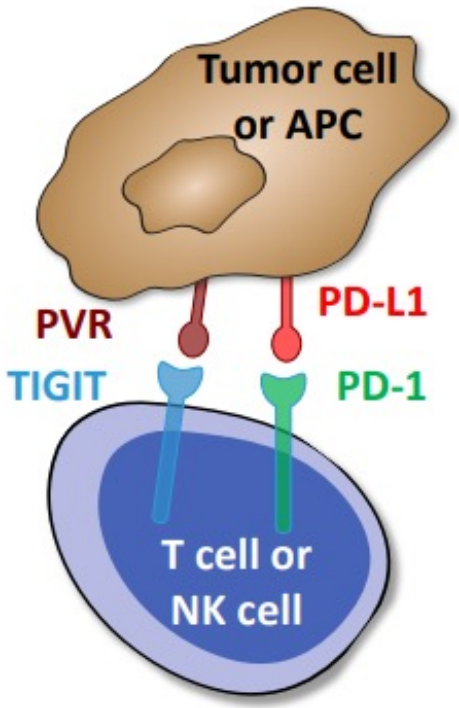
	Tislelizumab + chemotherapy (n=165)	Placebo + chemotherapy (n=176)
Events (% of patients)	105 (63.6)	127 (72.2)
Median OS, months (95% CI)	**16.7** (13.0, 20.1)	**10.4** (9.1, 13.0)
Hazard ratio* (95% CI)	**0.72** (0.55, 0.94)	



Qin et al. Mol Cancer 18, 155 (2019).

Background on TIGIT

- TIGIT (T cell immunoreceptor with Ig and ITIM domains) is a novel inhibitory immune checkpoint present on activated T cells and NK cells in multiple cancers[1–3]
- TIGIT expression correlates with PD-1, especially in tumor-infiltrating T cells
- Tiragolumab is a fully human IgG1/kappa anti-TIGIT monoclonal antibody with an intact Fc region that blocks the binding of TIGIT to its receptor PVR
- *Hypothesis*: Anti-TIGIT antibodies, such as tiragolumab, could restore the anti-tumor response and may amplify the activity of anti-PD-L1/PD-1 antibodies



APC, antigen-presenting cell; NK, natural killer; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PVR, poliovirus receptor

1. Manieri et al. Trends Immunol 2017; 2. Rotte et al. Ann Oncol 2018; 3. Yu et al. Nat. Immunol 2009

Ongoing tiragolumab studies in esophageal cancer

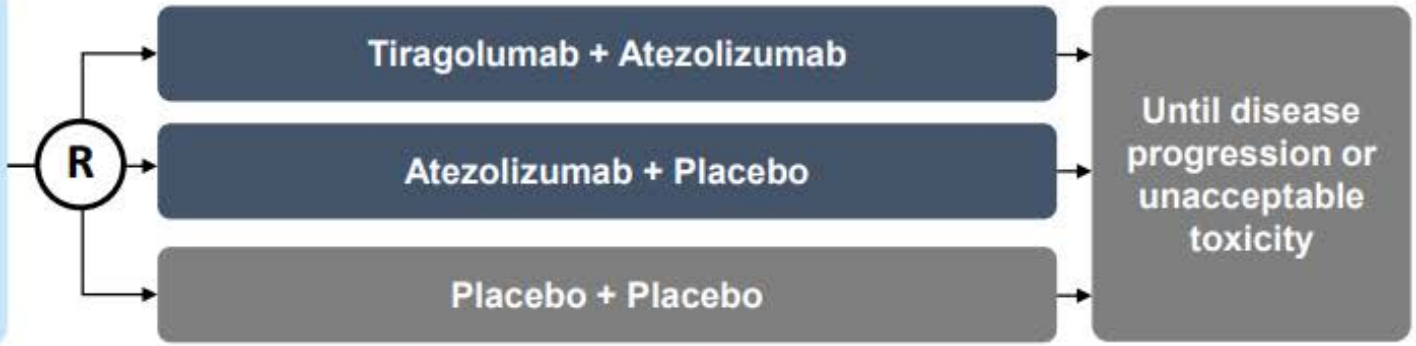
SKYSCRAPER-07

NCT04543617

Unresectable locally advanced esophageal

- Squamous
- Definitive platinum-based chemotherapy and radiation therapy and no progression
- ECOG PS 0–1

n=750



Co-primary endpoints: PFS by INV assessment and OS

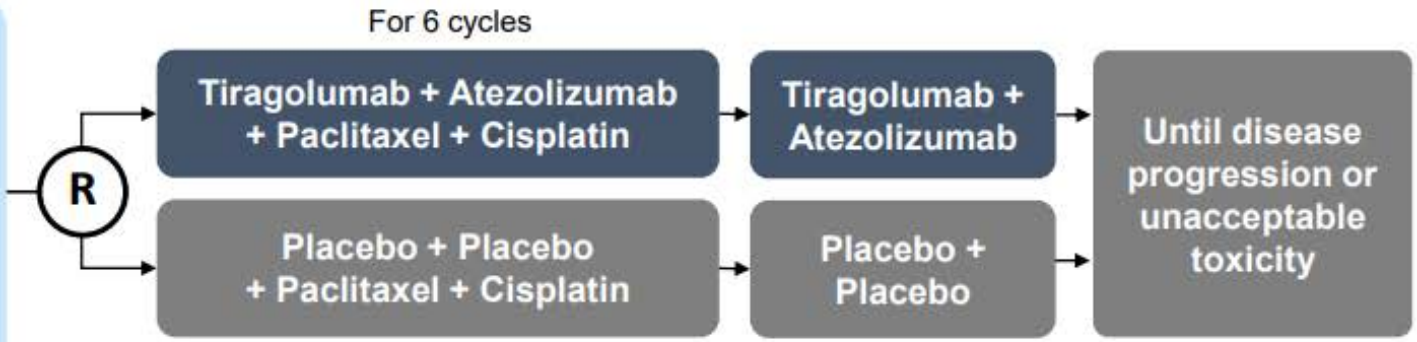
SKYSCRAPER-08

NCT04540211

Unresectable locally advanced, unresectable recurrent or metastatic esophageal

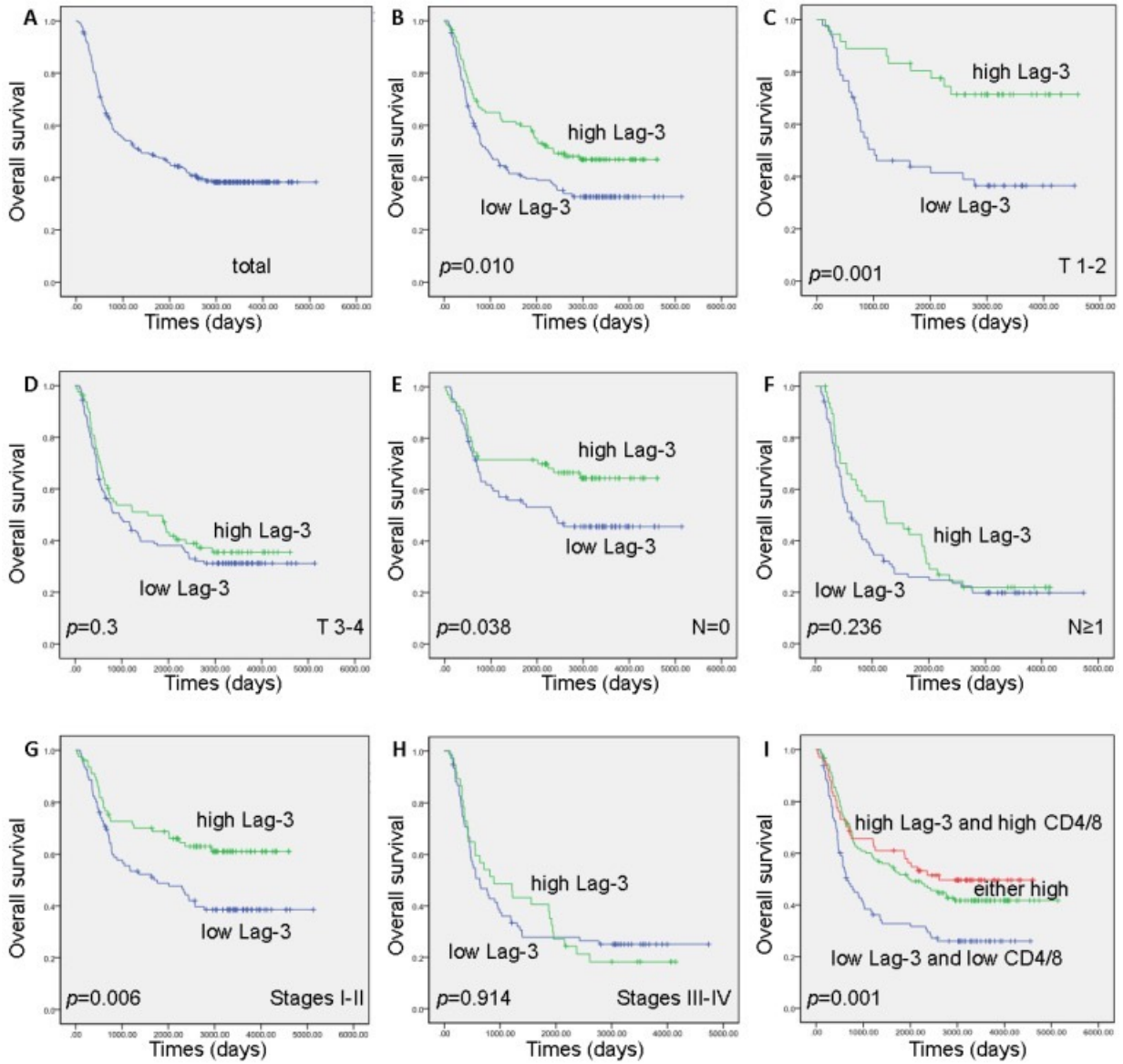
- Squamous
- Measurable metastases
- ECOG PS 0–1
- No prior systemic treatment

n=450



Co-primary endpoints: PFS by IRF assessment and OS

Association Between LAG-3 Expression and OS of ESCC patients



Zhang Y, et al. Prognostic Value of Lymphocyte Activation Gene-3 (LAG-3) Expression in Esophageal Squamous Cell Carcinoma. *J Cancer*. 2018 Oct 20;9(22):4287-4293.

Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Gastroesophageal Cancers

Part 2 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Gastrointestinal Cancers Symposium

Thursday, January 19, 2023
6:15 PM – 7:45 PM PT

Faculty

Yelena Y Janjigian, MD
Zev Wainberg, MD, MSc
Florian Lordick, MD, PhD

Moderator

Samuel J Klempner, MD

RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Hepatobiliary Cancers

Part 3 of a 3-Part CME Symposium Series Held in Conjunction with the 2023 ASCO Gastrointestinal Cancers Symposium

Friday, January 20, 2023

6:00 PM – 7:30 PM PT

Faculty

Richard S Finn, MD

Professor Arndt Vogel, MD

Lipika Goyal, MD, MPhil

Moderator

Robin K (Katie) Kelley, MD

RTP RESEARCH TO PRACTICE

Thank you for attending!

CME Credit Information

For those participating in person today, please remit your CME credit form as you exit the meeting room.

For all others, a CME credit link will be provided in the chat room at the conclusion of the program.

RTP
RESEARCH
TO PRACTICE