Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Gastroesophageal Cancers (Part 2 of a 3-Part Series)

Thursday, January 20, 2022
6:15 PM – 7:45 PM PT

Faculty

Yelena Y Janjigian, MD
Eric Van Cutsem, MD, PhD
Harry H Yoon, MD

Moderator

Samuel J Klempner, MD

RTP
RESEARCH
TO PRACTICE

Faculty

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

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

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

Moderator

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

RTP
RESEARCH
TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Hepatobiliary Cancers (Part 3 of a 3-Part Series)

Friday, January 21, 2022
6:15 PM – 7:45 PM PT

Faculty

Ghassan Abou-Alfa, MD, MBA
Richard S Finn, MD
Robin K Kelley, MD

Moderator

Tanios Bekaii-Saab, MD

RTP
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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.

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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.

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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.
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Agenda

Module 1 – Current and Future Front-Line Management of Advanced Gastric and Gastroesophageal Junction (GEJ) Cancer — Dr Janjigian

Module 2 – Contemporary Management of HER2-Positive Advanced Gastric and GEJ Cancer — Prof Van Cutsem

Module 3 – Selection and Sequencing of Therapy for Relapsed Gastric and GEJ Cancer — Dr Klempner

Module 4 – Key Findings Informing the Treatment of Localized and Advanced Esophageal Cancer — Dr Yoon

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ASCO GI 2022 Gastroesophageal Cancers Clinical Investigator Survey Respondents

Ghassan Abou-Alfa, MD, MBA

Thomas A Abrams, MD

Jaffer A Ajani, MD

Dirk Arnold, MD, PhD

Tanios Bekaii-Saab, MD

Joseph Chao, MD

Kristen K Ciombor, MD, MSCI

Dustin Deming, MD

Peter C Enzinger, MD

Tim Greten, MD

J Randolph Hecht, MD

Andrew E Hendifar, MD

Yelena Y Janjigian, MD

Pashtoon M Kasi, MD, MS

Samuel J Klempner, MD

Christopher Lieu, MD

Jeffrey A Meyerhardt, MD, MPH

Stacey M Stein, MD

Eric Van Cutsem, MD, PhD

Harry H Yoon, MD

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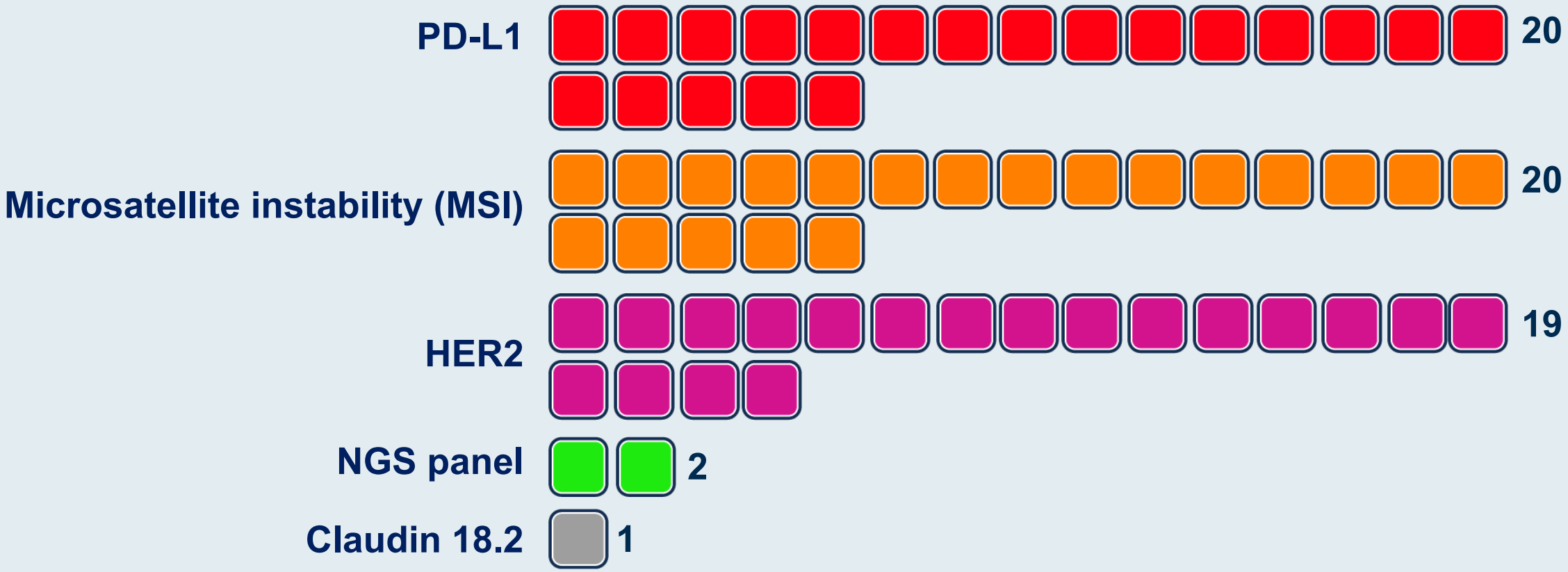
In general, which biomarkers, if any, do you believe oncologists in community practice should evaluate in patients with newly diagnosed advanced gastric cancer? (Select all that apply)



Survey of US-based clinical investigators

MODULE 1: Current and Future Front-Line Management of Advanced Gastric and Gastroesophageal Junction Cancer — Dr Janjigian

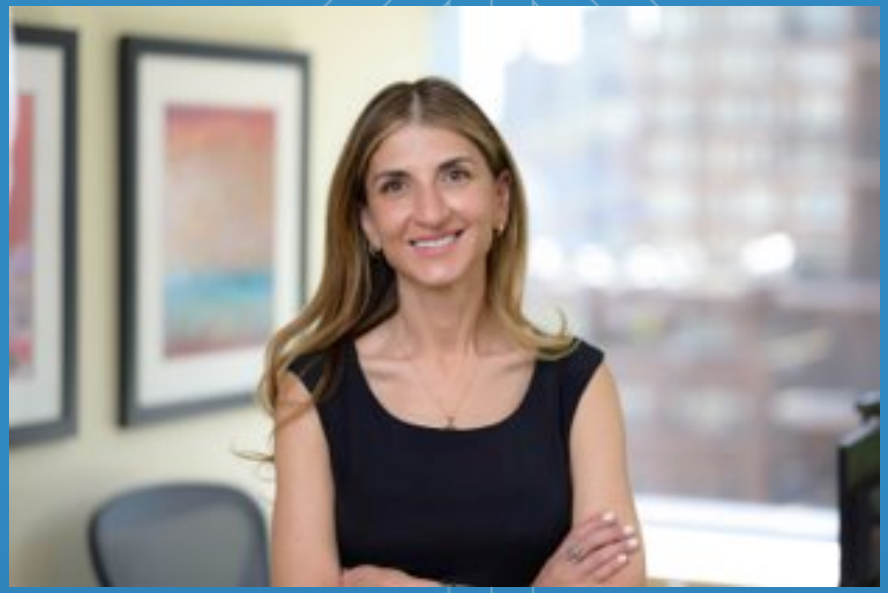
Memorial Sloan Kettering Cancer Center

Current and Future Front-Line Management of Advanced Gastric & Gastroesophageal Junction (GEJ) Cancer

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

Chief, Gastrointestinal Oncology Service
Memorial Sloan Kettering Cancer Center

Twitter: @yjanjigianMD



10 Minute Talk I 20 Slides I Thursday, January 20th I

Immunotherapy in Gastric Cancers (Adenocarcinoma)

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

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

CheckMate 649 Study Design

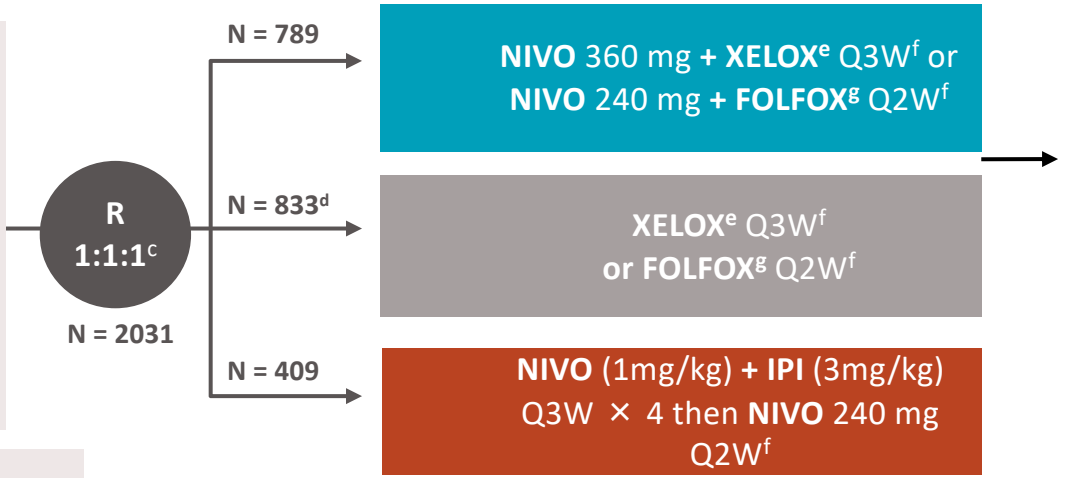
- CheckMate 649 is a randomized, open-label, phase 3 study[a]

Key eligibility criteria

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

Stratification factors

- Tumor cell PD-L1 expression (≥ 1% vs. < 1%[b])
- Region (Asia vs. US/Canada vs. ROW)
- ECOG PS (0 vs. 1)
- Chemo (XELOX vs. FOLFOX)



Dual primary endpoints

NIVO + chemo vs. chemo
- **OS** and **PFS**[h] (PD-L1 CPS ≥ 5)

Hierarchically tested secondary efficacy endpoints

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

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

PD-L1 CPS ≥ 5:

- **955/1581 (60%) patients in the NIVO + chemo vs chemo comparison**
- **473/813 (58%) patients in the NIVO+IPI vs chemo comparison**

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

[a]ClinicalTrials.gov number, NCT02872116. [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako). [c]After NIVO + chemo arm was added and before new patient enrollment in the NIVO + IPI arm was closed. Upon DMC recommendation (31-May-2018), enrollment to the NIVO + IPI arm was stopped early due to an observed increase in rates of early death and toxicity. Patients already in the NIVO+IPI arm were allowed to remain on study based on the DMC recommendation. [d]Includes patients that were concurrently randomized to receive chemo versus NIVO + IPI (October 2016–June 2018) and NIVO + chemo (June 2018-Apr 2019). [e]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1–14). [f]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo or NIVO + IPI), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years.
[g]Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1–2). [h]BICR assessed. [i]Time from concurrent randomization of the last patient to data cutoff

1. Janjigian YY et al. *Lancet*. 2021;398:27-40. 2. Janjigian YY et al. Presented at ESMO 2021.

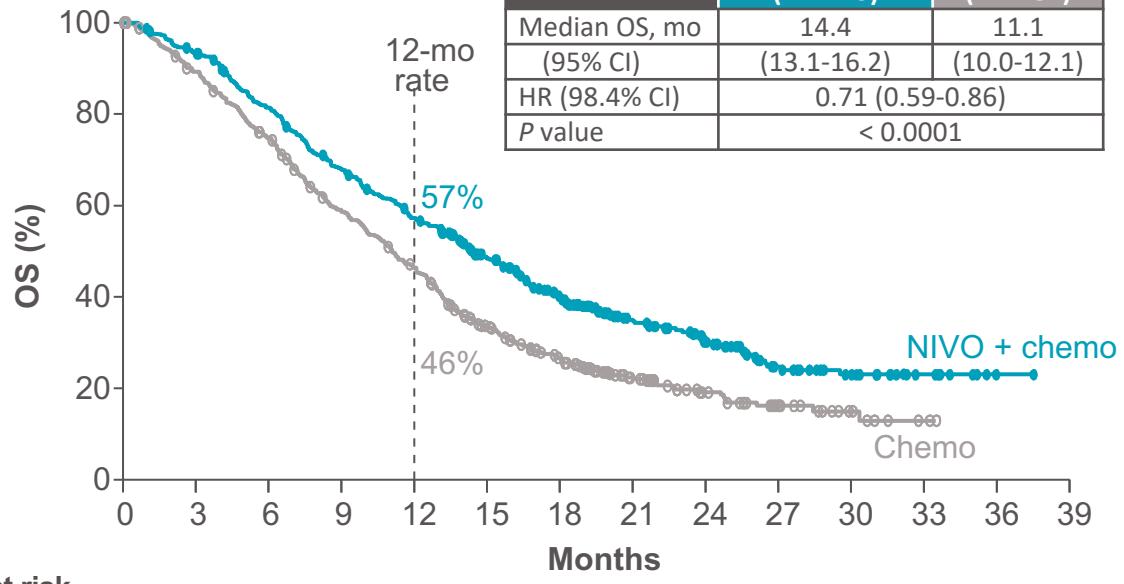
CheckMate 649: Global Phase 3 Registration Trial

NIVO + Chemo Improved Survival

FDA approved April 2021[1]

PD-L1 CPS ≥ 5

	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS, mo	14.4	11.1
(95% CI)	(13.1-16.2)	(10.0-12.1)
HR (98.4% CI)	0.71 (0.59-0.86)	
P value	< 0.0001	

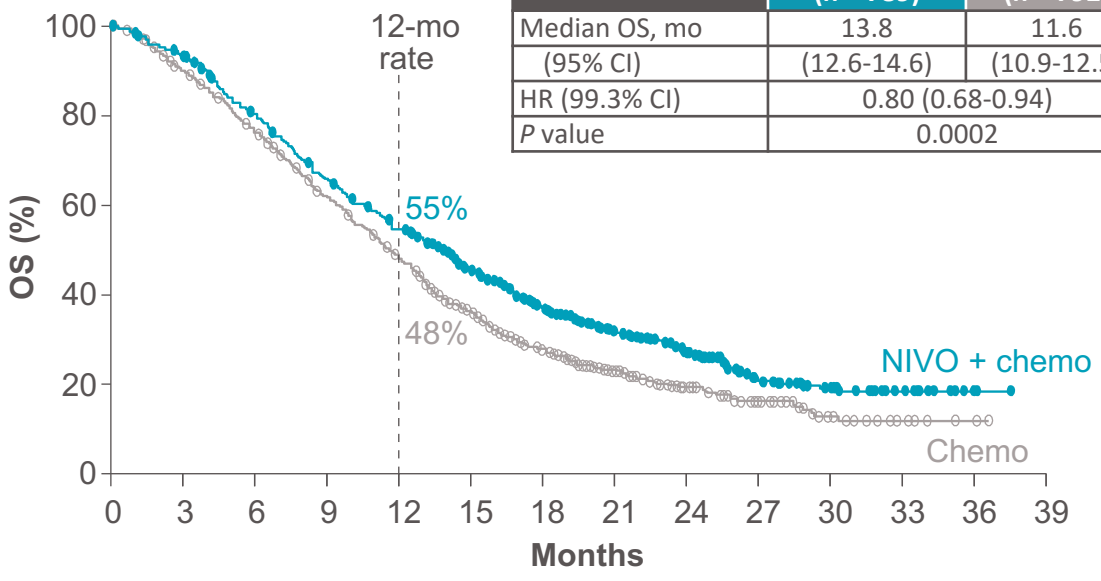


No. at risk

NIVO + chemo	473	438	377	313	261	198	149	96	65	33	22	9	1	0
Chemo	482	421	350	271	211	138	98	56	34	19	8	2	0	0

All randomized

	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS, mo	13.8	11.6
(95% CI)	(12.6-14.6)	(10.9-12.5)
HR (99.3% CI)	0.80 (0.68-0.94)	
P value	0.0002	



NIVO + chemo	789	731	621	506	420	308	226	147	100	49	34	14	2	0
Chemo	792	697	586	469	359	239	160	94	59	35	15	7	2	0

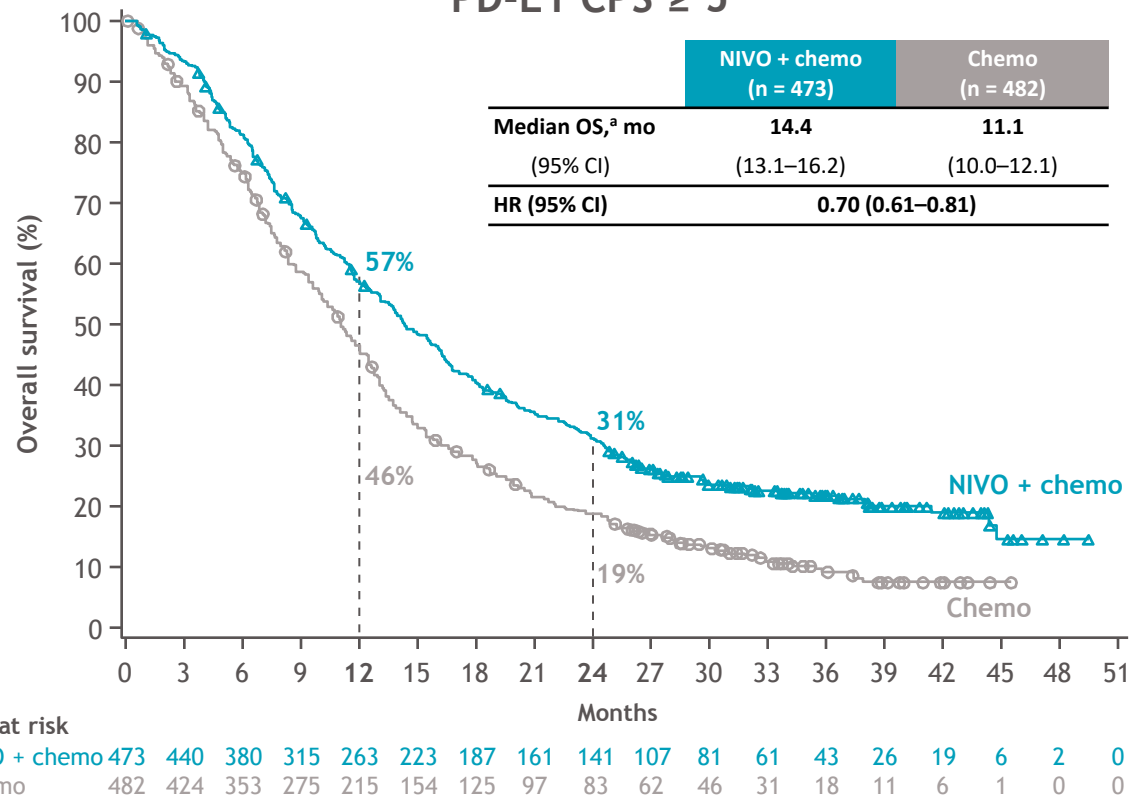
Adapted from Janjigian 2021.[2]

- Grade 3-4 TRAEs were reported in 59% of patients in the NIVO + chemo arm and 44% of patients in the chemo arm[1]
- Treatment-related deaths occurred in 16 (2%) and 4 (1%) of patients in the NIVO + chemo and chemo arms, respectively[1]

1. OPDIVO (nivolumab) [package insert]. Princeton, NJ: Bristol Myers Squibb; 2021. 2. Janjigian YY et al. *Lancet*. 2021;398:27-40.

Overall survival: NIVO + chemo vs chemo

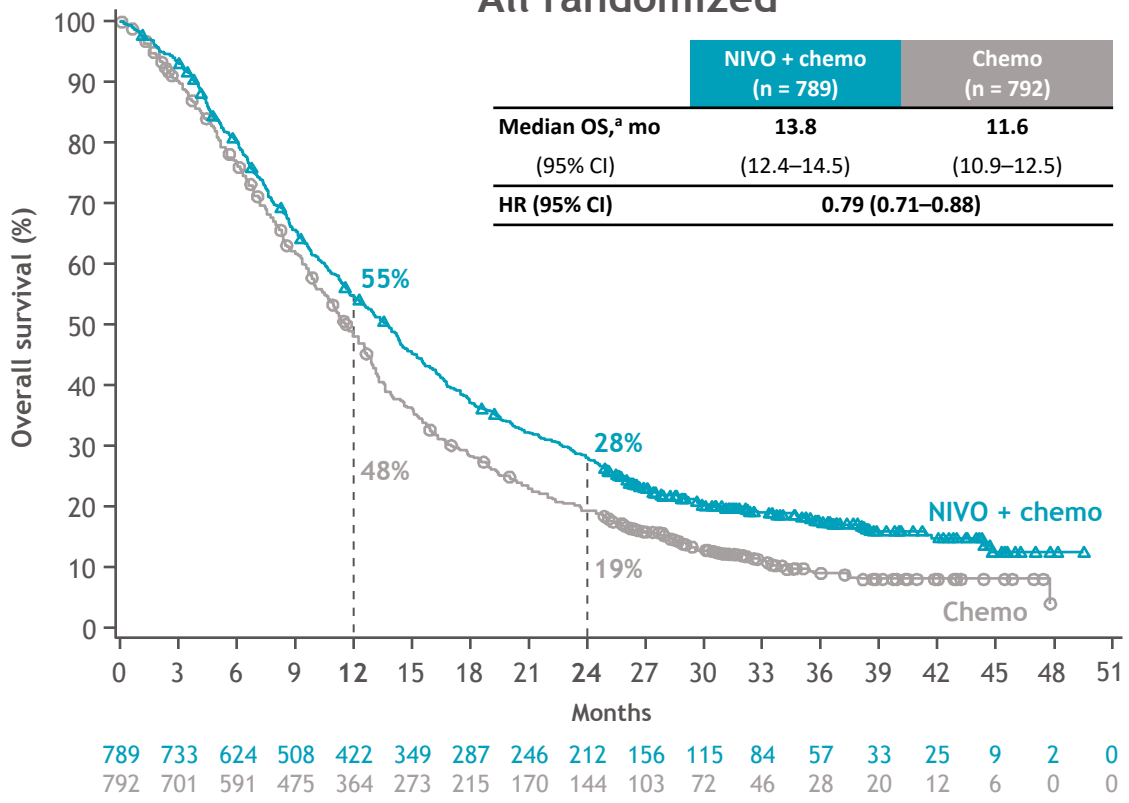
PD-L1 CPS ≥ 5



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

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

All randomized



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

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

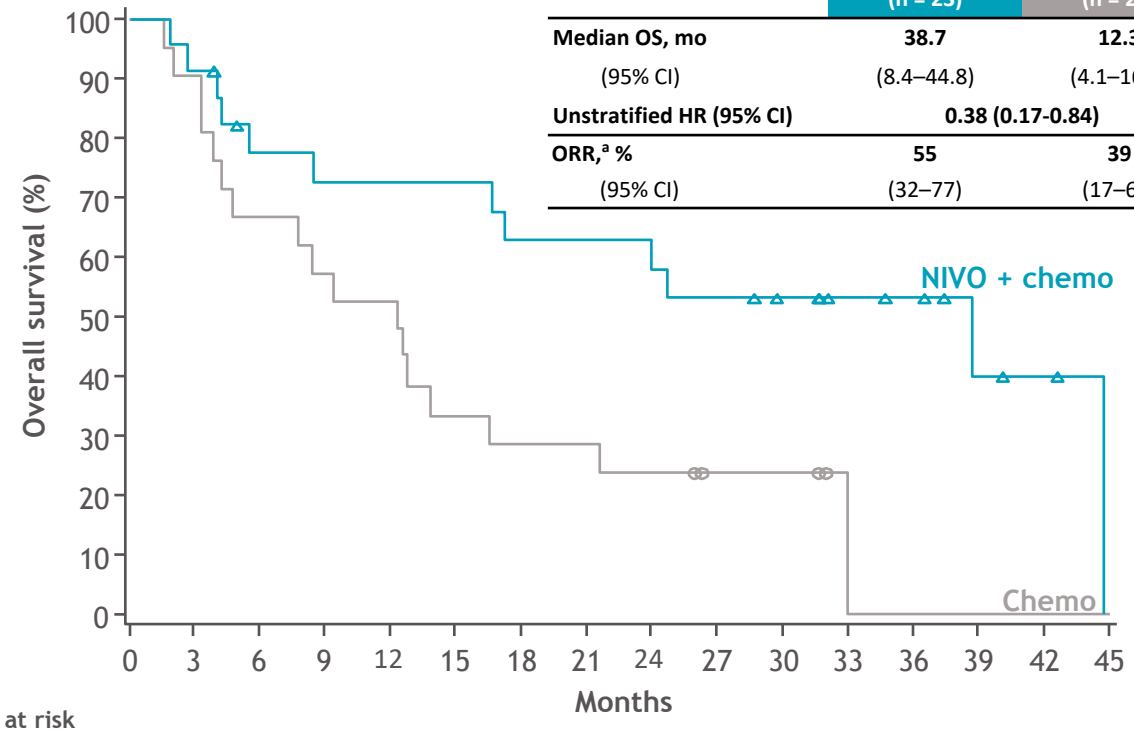
- Clinically meaningful improvement in OS with NIVO + chemo vs chemo was maintained with longer follow-up
  - PD-L1 CPS ≥ 5: 30% reduction in the risk of death and 12% improvement in 24-month OS rate
  - All randomized: 21% reduction in the risk of death and 9% improvement in 24-month OS rate
  - Directionally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

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

Efficacy by MSI status: NIVO + chemo vs chemo

MSI-H

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

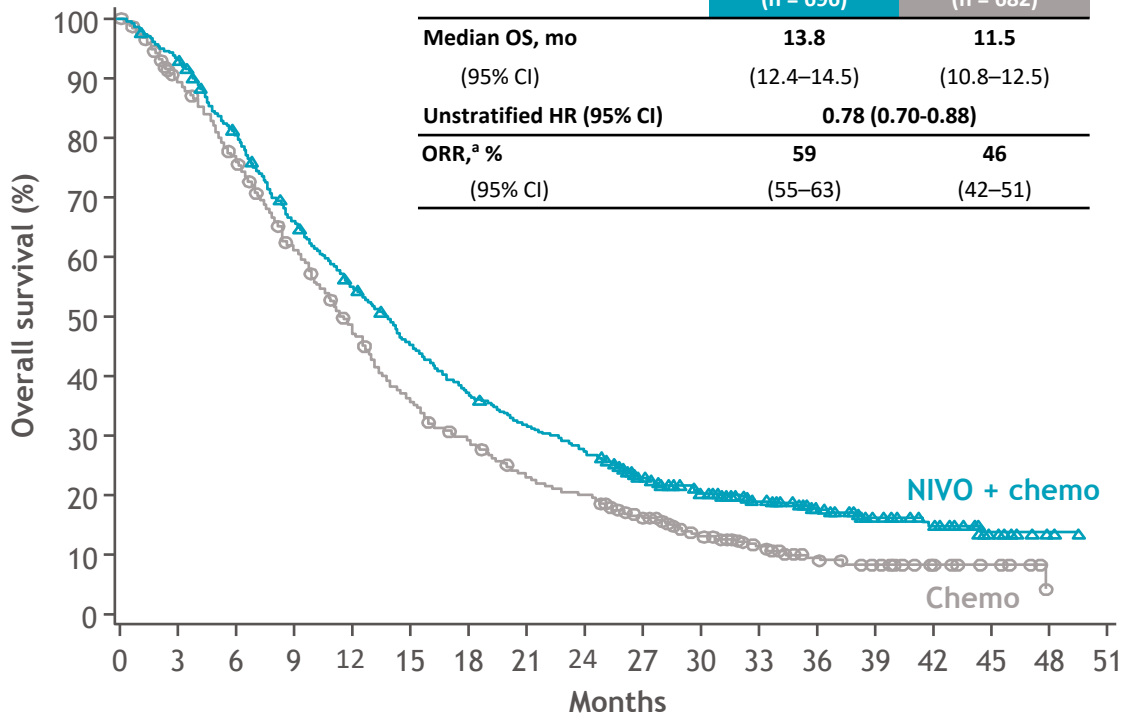


No. at risk

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

MSS

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



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

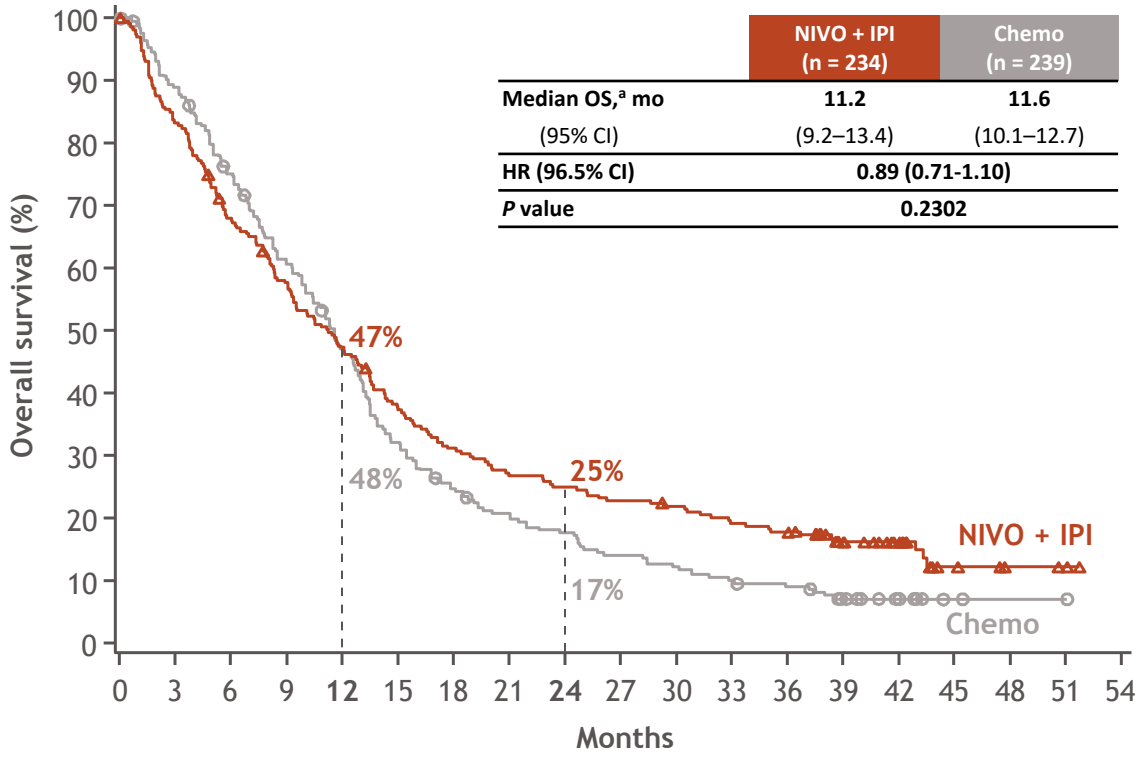
- Longer median OS and higher ORR were observed in all randomized patients with MSI-H and MSS tumors with NIVO + chemo vs chemo
  - The magnitude of benefit was greater in patients with MSI-H tumors, and patients with MSS tumors had results similar to the all randomized population

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

Overall survival: NIVO + IPI vs chemo

PD-L1 CPS ≥ 5

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

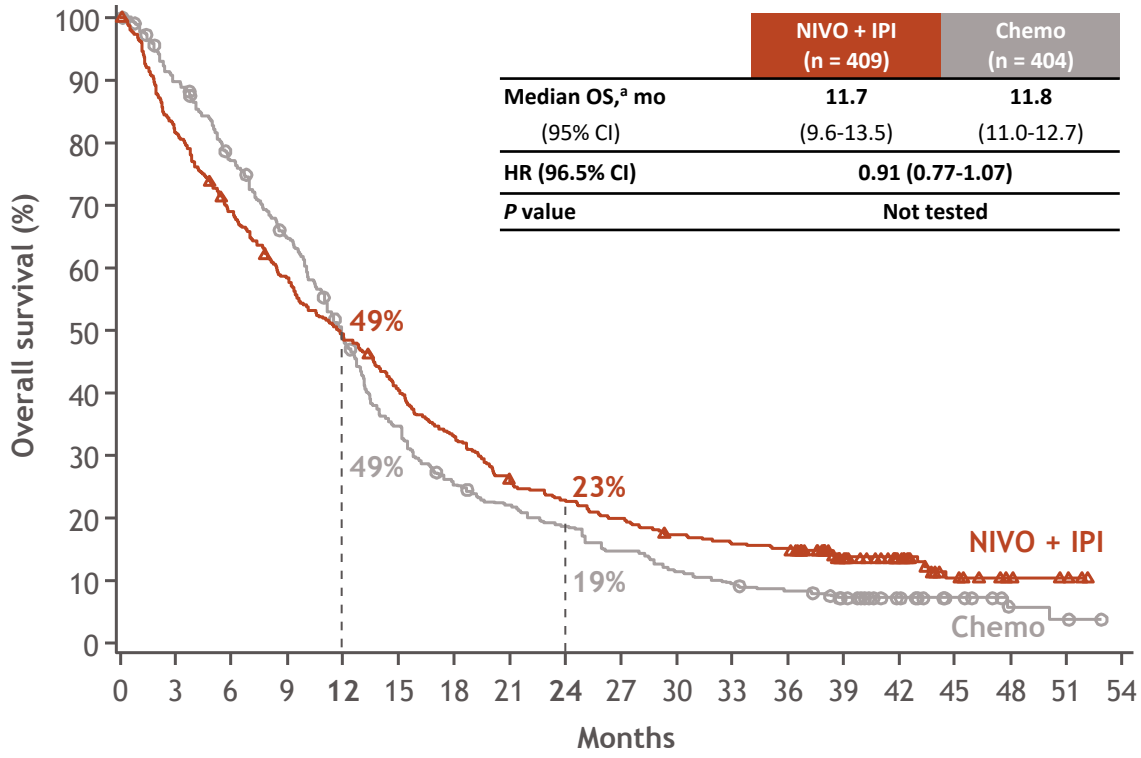


No. at risk

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

All randomized

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



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

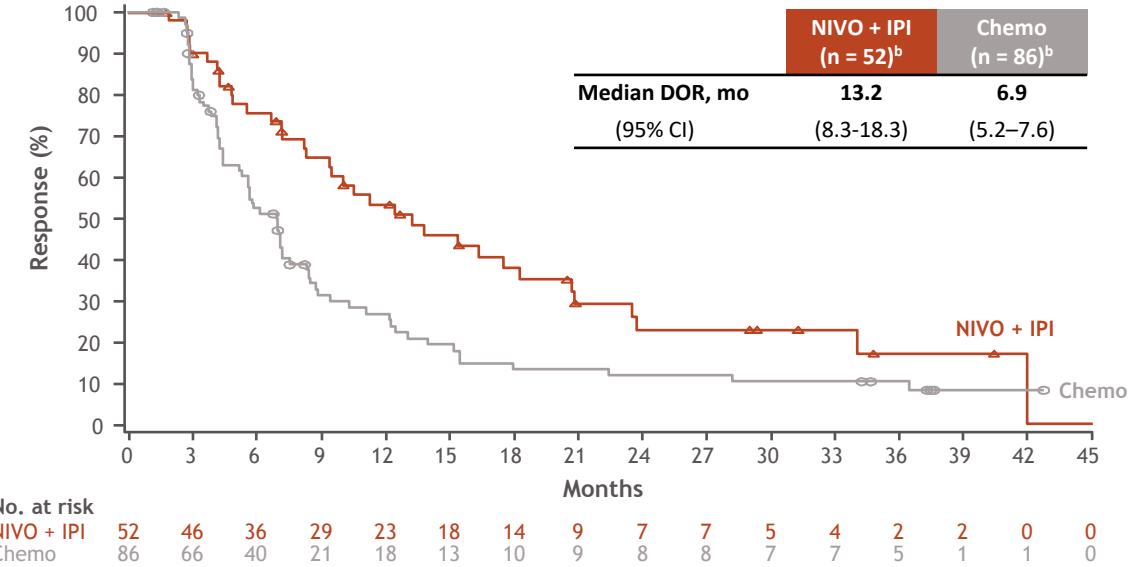
- The hierarchically tested secondary endpoint of OS with NIVO + IPI vs chemo in patients with PD-L1 CPS ≥ 5 was not met; OS in all randomized patients was not statistically tested

- [a]Minimum follow-up, 35.7 months.

Response and duration of response: NIVO + IPI vs chemo

PD-L1 CPS ≥ 5

Response per BICR	NIVO + IPI (n = 196)[a]	Chemo (n = 183)[a]
ORR, % (95% CI)	**27 (20–33)**	**47 (40–54)**
CR	5	8
PR	21	39
SD	27	35
PD	32	10



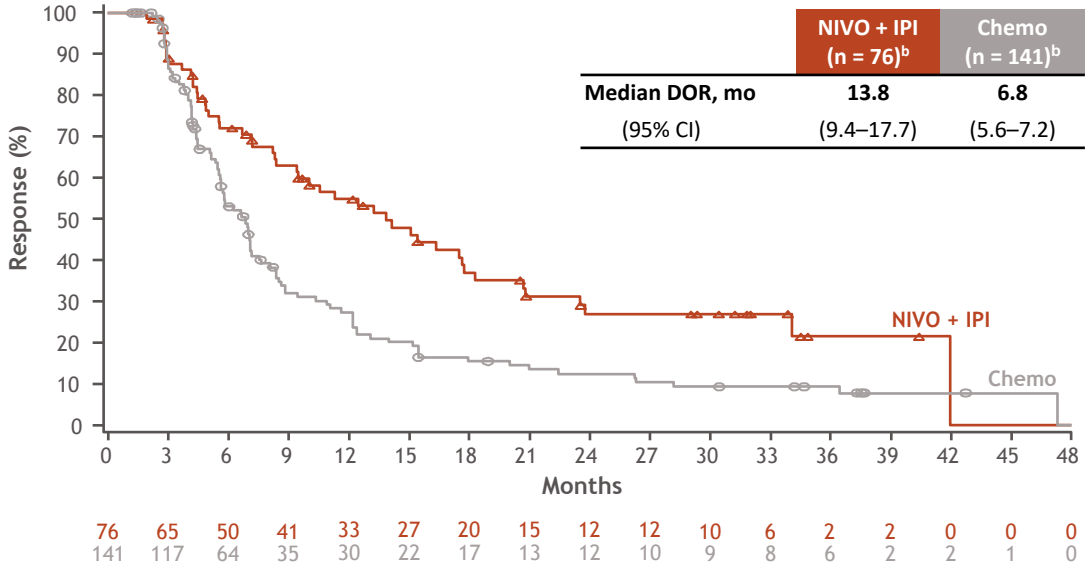
	NIVO + IPI (n = 52)[b]	Chemo (n = 86)[b]
Median DOR, mo	**13.2**	**6.9**
(95% CI)	(8.3-18.3)	(5.2–7.6)

No. at risk

NIVO + IPI	52	46	36	29	23	18	14	9	7	7	5	4	2	2	0	0
Chemo	86	66	40	21	18	13	10	9	8	8	7	7	5	1	1	0

All randomized

Response per BICR	NIVO + IPI (n = 333)[a]	Chemo (n = 299)[a]
ORR, % (95% CI)	**23 (18-28)**	**47 (41–53)**
CR	6	8
PR	17	39
SD	27	34
PD	34	9



	NIVO + IPI (n = 76)[b]	Chemo (n = 141)[b]
Median DOR, mo	**13.8**	**6.8**
(95% CI)	(9.4–17.7)	(5.6–7.2)

76	65	50	41	33	27	20	15	12	12	10	6	2	2	0	0	0
141	117	64	35	30	22	17	13	12	10	9	8	6	2	2	1	0

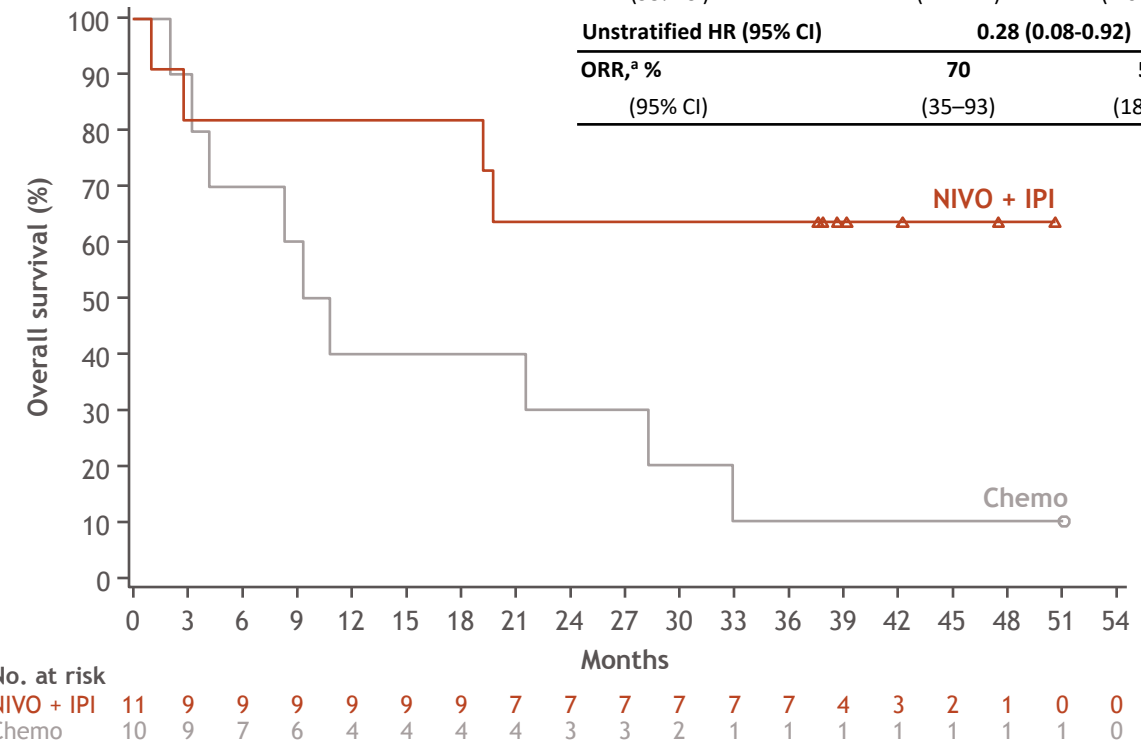
- Although response rates were lower with NIVO + IPI vs chemo, duration of response was longer in both PD-L1 CPS ≥ 5 and all randomized populations

- [a]Randomized patients who had target lesion measurements at baseline per BICR assessment; [b]Number of responders.

Efficacy by MSI status: NIVO + IPI vs chemo

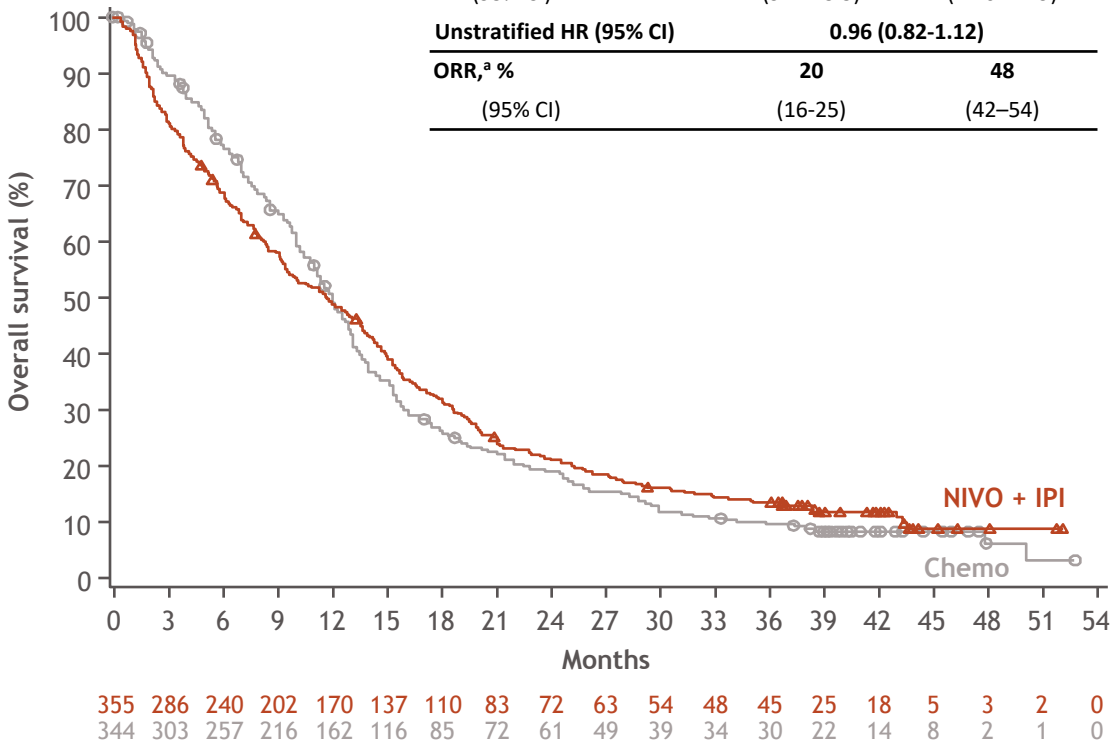
MSI-H

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



MSS

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



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

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

PD-L1 Testing

Anti-PD-1 drug and PD-L1 assessment			
mAb	*Drug*	*Cancer type*	*Scoring assessment*
22C3 pharmDx	Pembrolizumab	NSCLC	• TPS < 1%: No PD-L1 expression • TPS = 1~49%: PD-L1 expression • TPS ≥ 50%: High PD-L1 expression
		Gastric or GEJ adenocarcinoma	• CPS < 1: No PD-L1 expression • CPS ≥ 1: PD-L1 expression
28-8 pharmDx	Nivolumab	Melanoma	• TC < 1%: No PD-L1 expression • TC ≥ 1%: PD-L1 expression
		Non-squamous NSCLC	• TC < 1%: No PD-L1 expression • TC ≥ 1%: PD-L1 expression
SP142 assay	Atezolizumab	NSCLC	• TC ≥ 50%: PD-L1 expression • IC ≥ 10% PD-L1 expression • TC < 50% and IC < 10%: No PD-L1 expression
SP263 assay	Durvalumab	UC	• TC ≥ 25%: High PD-L1 expression • ICP > 1% and IC+ ≥ 25%: High PD-L1 • expression • ICP = 1% and IC+ = 100%: High PD-L1 expression • None of the criteria for PD-L1 High Status are • met: Low/negative PD-L1 expression

Adapted from Ma 2018.[1]

- A recent study of 55 patients with gastric cancer showed that PD-L1 22C3 and 28-8 pharmDx assays was found to be comparable at CPS cutoffs of 1, 10, and 50[2]

1. Ma J et al. *Diagn Pathol*. 2018;13:91. 2. Ahn S, Kim KM. *Mod Pathol*. 2021 May 17. doi: 10.1038/s41379-021-00823-9.

2021 ESMO congress

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

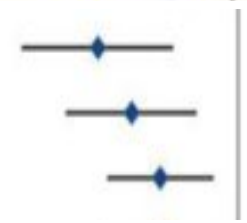
Jianming Xu*, Haiping Jiang, Yueyin Pan, Kangsheng Gu, Sundong Cang, Lei Han, Yongqian Shu, Jiayi Li, Junhui Zhao, Hongming Pan, Suxia Luo, Yanru Qin, Qunyi Guo, Yuxian Bai, Yang Ling, Yingmei Guo, Ziran Li, Ying Liu, Yan Wang, Hui Zhou

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

ORIENT-16 notable facts

- Gastric/GEJ, no esophagus adeno (Gastric do better than GEJ/esophagus)
- Dual primary endpoints OS in CPS ≥5 and ITT - both met
- XELOX/Sinti ITT mOS 15.2 mos HR .76; mPFS 7.1 HR .63; ORR 58%
- No new safety signals 59% Grade 3-4 AEs w/ XELOX/Sinti

Category	Subgroup	Sin + Chemo (N)	Chemo (N)	HR (95% CI)	HR (95% CI)
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)	



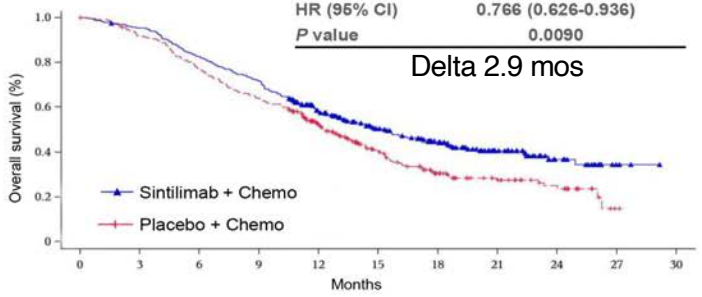
Overall Survival ORIENT-16 and CM 649

ORIENT-16 ITT

All Randomized

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

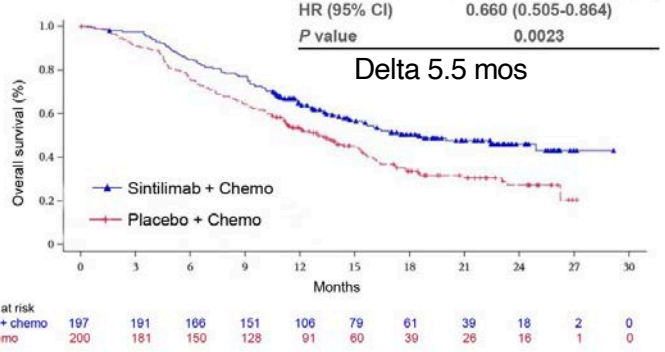
Delta 2.9 mos



PD-L1 CPS ≥5

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

Delta 5.5 mos

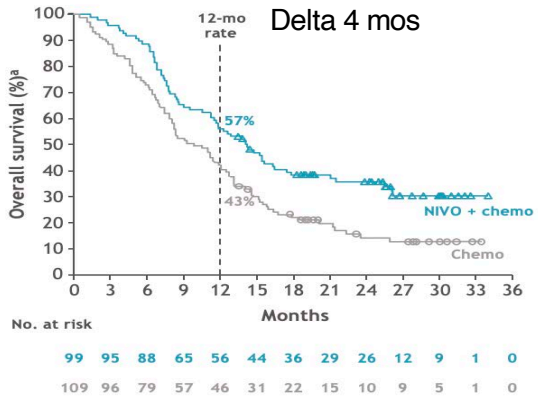


CM 649 CHINA

All randomized

	NIVO + chemo (n = 99)	Chemo (n = 109)
Median OS, mo	14.3	10.3
(95% CI)	(11.5-17.5)	(8.1-12.1)
HR (95% CI)	0.61 (0.44-0.85)	

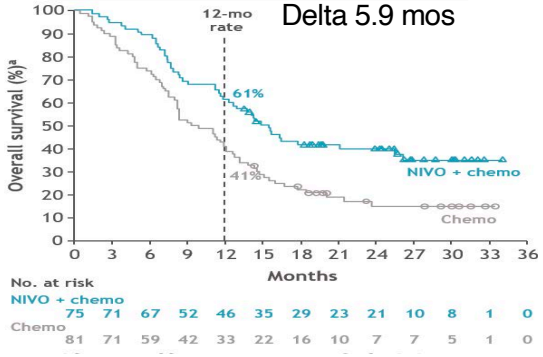
Delta 4 mos



PD-L1 CPS ≥ 5

	NIVO + chemo (n = 75)	Chemo (n = 81)
Median OS, mo	15.5	9.6
(95% CI)	(11.9-25.5)	(8.0-12.1)
HR (95% CI)	0.54 (0.36-0.79)	

Delta 5.9 mos

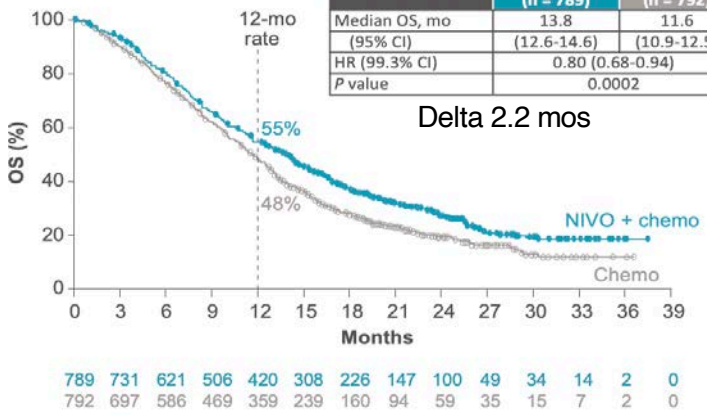


CM 649 ITT

All randomized

	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS, mo	13.8	11.6
(95% CI)	(12.6-14.6)	(10.9-12.5)
HR (99.3% CI)	0.80 (0.68-0.94)	
P value	0.0002	

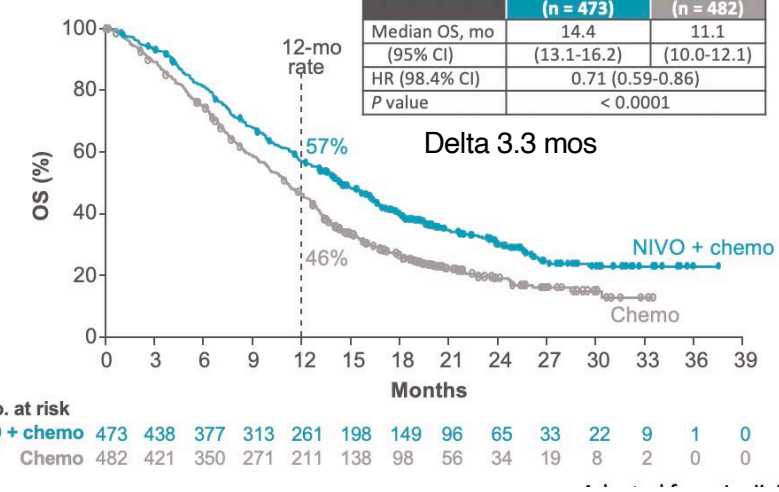
Delta 2.2 mos



PD-L1 CPS ≥ 5

	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS, mo	14.4	11.1
(95% CI)	(13.1-16.2)	(10.0-12.1)
HR (98.4% CI)	0.71 (0.59-0.86)	
P value	< 0.0001	

Delta 3.3 mos



Xu et al, ESMO 2021; Shen et al, AACR 2021; Janjigian et al, Lancet 2021

Immunotherapy in EG adenocarcinoma

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

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

KEYNOTE-811 –HER2 Positive Gastric Cancer

Key eligibility criteria

- Unresectable or metastatic gastric or GEJ adenocarcinoma
- No prior systemic therapy in advanced setting
- HER2-positive tumor by central review (IHC 3+ or IHC 2+ in combination with ISH+ (or FISH+)
- ECOG PS 0–1

Stratification factors

- Geographic region (Australia/Europe/ Israel/North America vs. Asia vs. ROW)
- PD-L1 CPS (≥ 1 vs. < 1)
- Chemotherapy choice (FP vs. CAPOX)

R 1:1

PEMBRO 200 mg IV Q3W
+ Trastuzumab
+ FP or CAPOX[b] × ≤ 35

Placebo IV Q3W
+ Trastuzumab
+ FP or CAPOX[b] × ≤ 35

Dual primary endpoints:

- **OS** and **PFS[c]**

Key secondary endpoints:

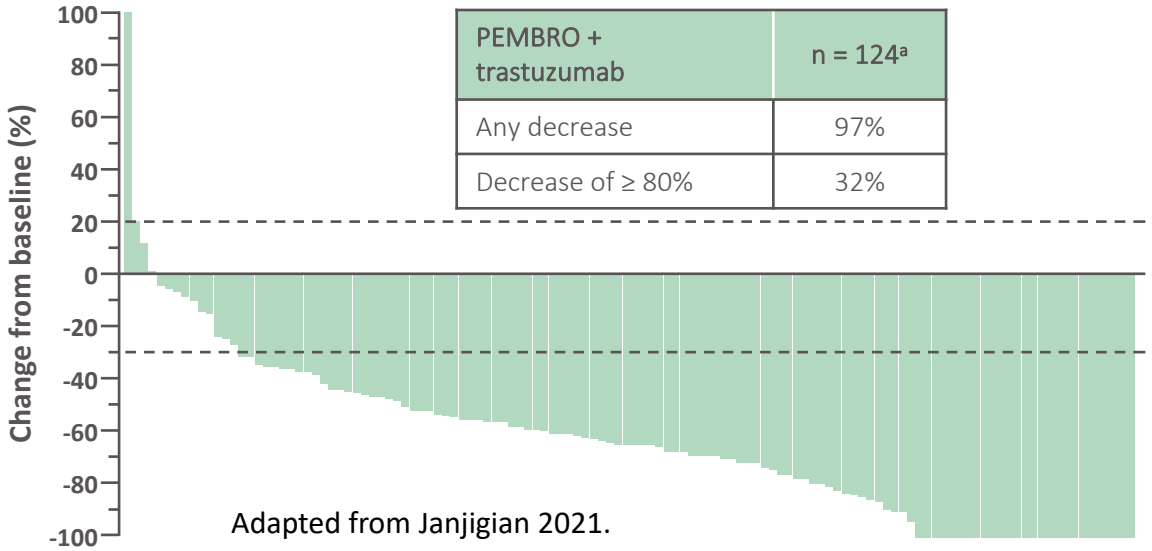
- **ORR** and **DOR[c]**
- **Safety**

[a]ClinicalTrials.gov number, NCT03615326. [b]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W. [c]Per RECIST v1.1 by BICR.

1. ClinicalTrials.gov. NCT03615326. Accessed July 2021. 2. Janjigian YY et al. Presentated at ASCO, 2021. Abstract 4013. 3. Chung HC et al. *Future Oncol*. 2021;17:491-501.

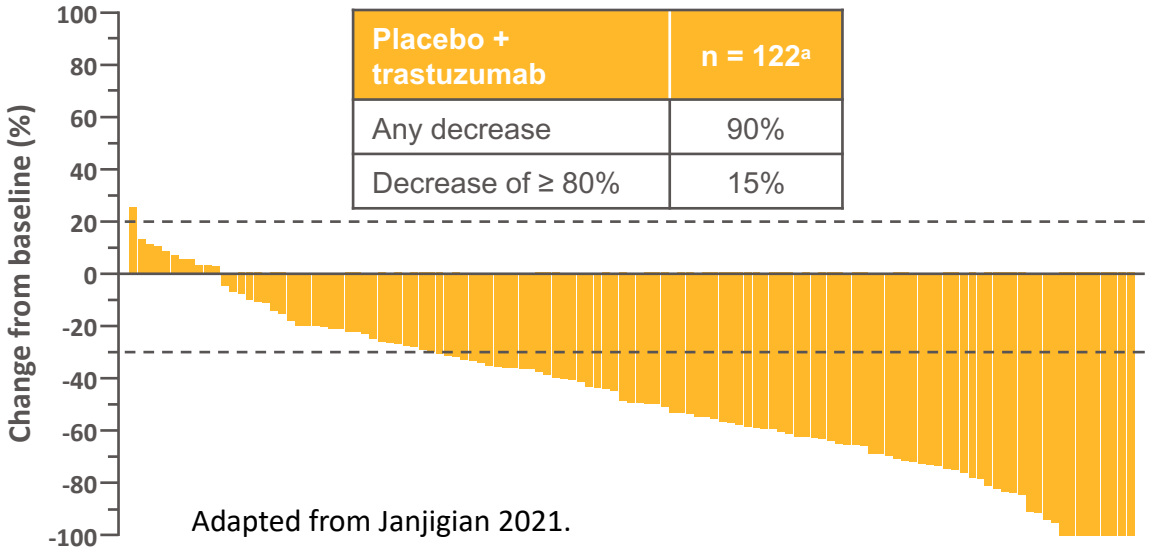
Pembrolizumab/Trastuzumab/Chemotherapy

FDA approved May 2021



PEMBRO + trastuzumab	n = 124[a]
Any decrease	97%
Decrease of ≥ 80%	32%

Adapted from Janjigian 2021.



Placebo + trastuzumab	n = 122[a]
Any decrease	90%
Decrease of ≥ 80%	15%

Adapted from Janjigian 2021.

ORR and DCR, % (95% CI)	PEMBRO + trastuzumab (n = 133)	Placebo + trastuzumab (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 + trastuzumab (n = 133)	Placebo + trastuzumab (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	PEMBRO + trastuzumab (n = 133)	Placebo + trastuzumab (n = 131)
Median[c]	10.6 mo	9.5 mo
Range	1.1+ to 16.5+	1.4+ to 15.4+
≥ 6-mo duration[c]	70.3%	61.4%
≥ 9-mo duration[c]	58.4%	51.1%

- Grade 3-5 AE rates did not differ between treatment arms (57%)

[a]Participants with RECIST-measurable disease at baseline and ≥1 evaluable post-baseline measurement. [b]Calculated using the Miettinen and Nurminen method stratified by the randomization stratification factors. [c]Kaplan-Meier estimation. The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

Janjigian YY et al. *J Clin Oncol*. 2021;39(15_suppl):4013. Presented at ASCO 2021.

FIGHT Phase 2 Study Design

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

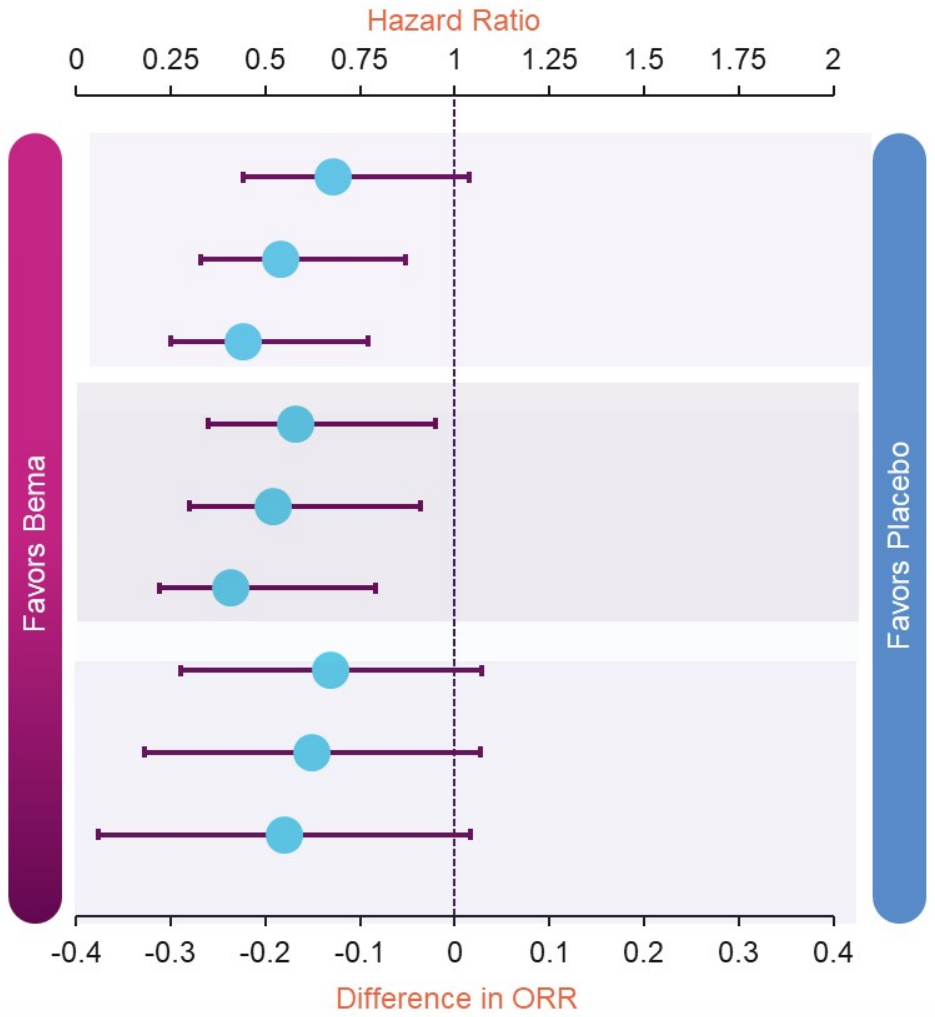
Treatment may continue until progression, unacceptable toxicity, or the patient meets other withdrawal criteria

*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.

Higher Bemarituzumab Efficacy With Higher % FGFR2b+

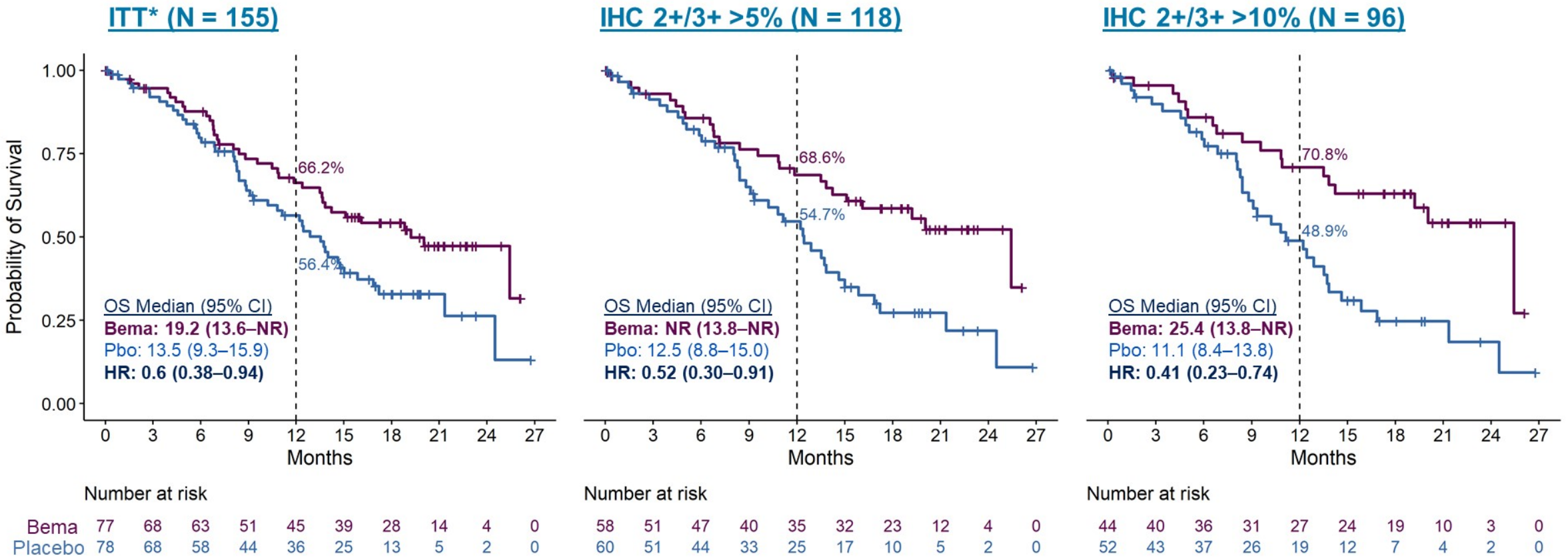
Endpoint	Subgroup	Median PFS/OS (months) Response rate	HR (95% CI) Difference in ORR (95% CI)
PFS	Overall*	Bema: 9.5 Placebo: 7.4	0.68 (0.44, 1.04)
	IHC 2+ or 3+ ≥5%†	Bema: 10.2 Placebo: 7.3	0.54 (0.33, 0.87)
	IHC 2+ or 3+ ≥10%‡	Bema: 14.1 Placebo: 7.3	0.44 (0.25, 0.77)
OS	Overall	Bema: NR Placebo: 12.9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

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



Median OS Reached With Longer Follow-up

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.
Median Follow-up 12.5 months

*Based on February, 28th 2021 data cut

Selected Treatment-Emergent Adverse Events Summary

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

AE, adverse event.

Summary of Corneal Adverse Events

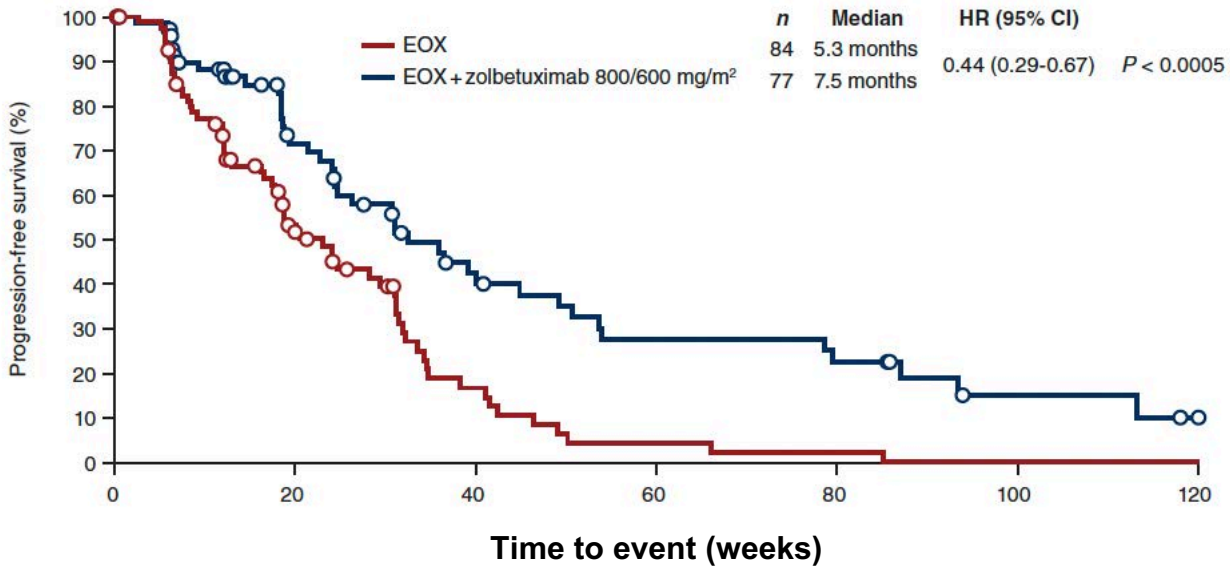
Patients with corneal AEs*	Bema (N = 76)	Placebo (N = 77)
Any corneal AE	51 (67.1%)	8 (10.4%)
Grade 1 corneal AE	16 (21.1%)	6 (7.8%)
Grade 2 corneal AE	17 (22.4%)	2 (2.6%)
Grade 3 corneal AE	18 (23.7%)	0
Grade 4 corneal AE	0	0
SAE	0	0
Time to onset (grades 2 and 3) (weeks)		
N	35	2
Median	23.7	12.8
Q1, Q3	15.9, 33.1	9.0, 16.6
Time to resolution or downgraded to grade 1 (grades 2 and 3) (weeks)		
N	21†	1
Median	19.1	2.0
Q1, Q3	9.1, 25.1	2.0, 2.0

*Duration of exposure was comparable for the two arms; †loss of follow-up of 6 patients due to death and 1 patient due to consent withdrawal.
No association with frequency or severity of corneal AE and tumor FGFR2b positivity. Corneal AEs are defined by Standardised MedDRA Queries (SMQ) of corneal disorders.

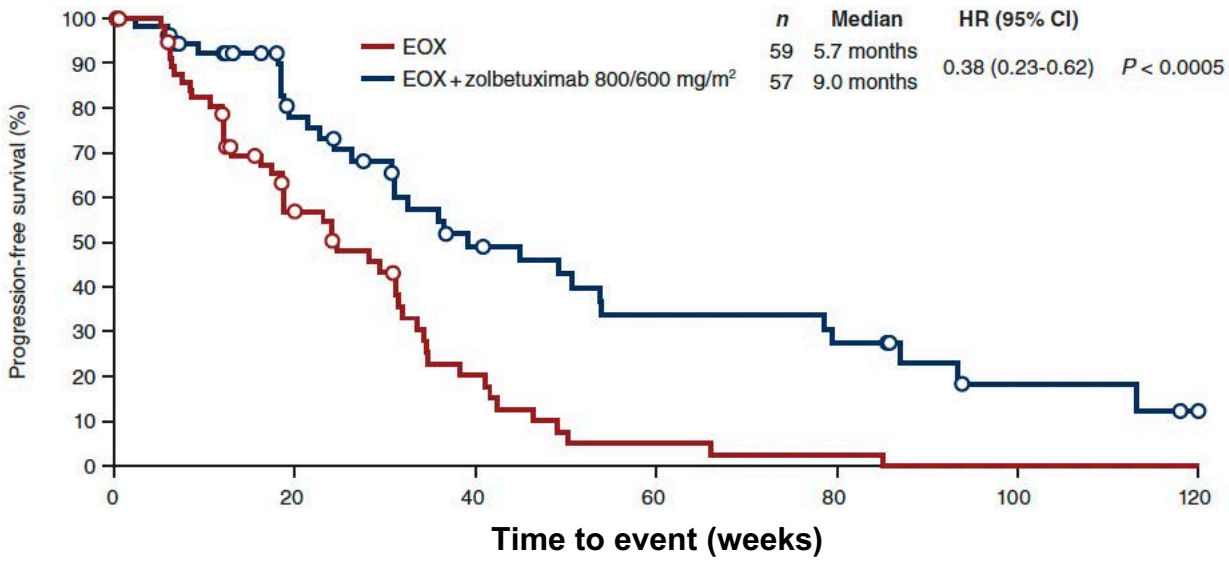
Randomized Phase II FAST Study of Zolbetuximab (IMAB362) plus EOX versus EOX Alone as First-Line Therapy for Advanced VLDN18.2-Positive Gastric and Gastroesophageal Adenocarcinoma

Progression-Free Survival

Overall Population



Patients with ≥70% of tumor cells positive for CLDN18.2

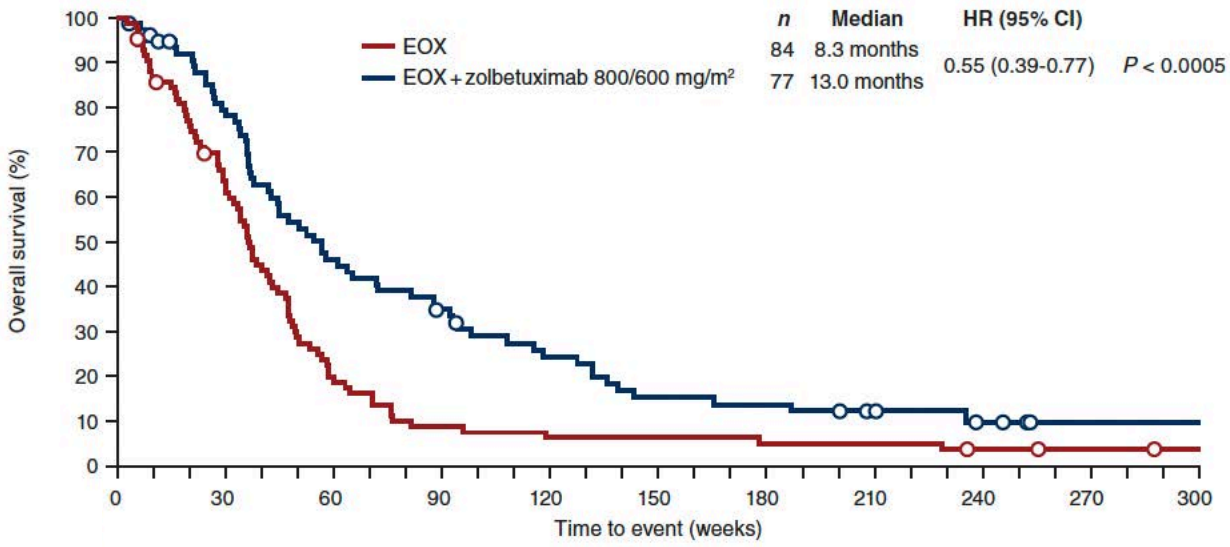


Sahin U et al. *Ann Oncol* 2021;32(5):609-19

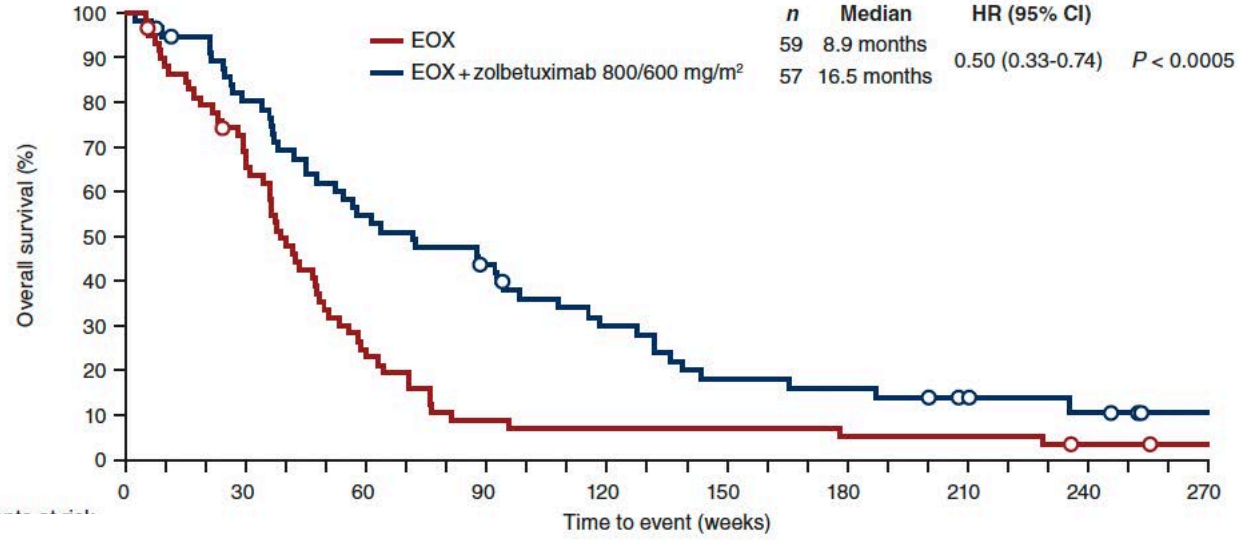
Randomized Phase II FAST Study of First-Line Zolbetuximab (IMAB362) plus EOX versus EOX Alone

Overall Survival

Overall Population



Patients with ≥70% of tumor cells positive for CLDN18.2



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

FAST: Summary of Adverse Events

Table 3. Summary of adverse events occurring ≥10% of patients in arms 1 or 2

	EOX (*N* = 84)		Zolbetuximab + EOX (*N* = 77)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Treatment-emergent adverse events, *n* (%)				
Any adverse event	84 (100)	54 (64.3)	74 (96.1)	54 (70.1)
Nausea	64 (76.2)	4 (4.8)	63 (81.8)	5 (6.5)
Vomiting	46 (54.8)	3 (3.6)	52 (67.5)	8 (10.4)
Anaemia	30 (35.7)	6 (7.1)	35 (45.5)	9 (11.7)
Neutropenia	29 (34.5)	18 (21.4)	34 (44.2)	25 (32.5)
Weight loss	26 (31.0)	3 (3.6)	25 (32.5)	9 (11.7)
Fatigue	17 (20.2)	3 (3.6)	24 (31.2)	5 (6.5)
Alopecia	17 (20.2)	1 (1.2)	22 (28.6)	0
Asthenia	19 (22.6)	2 (2.4)	19 (24.7)	2 (2.6)
Decreased appetite	19 (22.6)	2 (2.4)	15 (19.5)	0
Abdominal pain	10 (11.9)	2 (2.4)	14 (18.2)	1 (1.3)
Diarrhoea	31 (36.9)	3 (3.6)	14 (18.2)	3 (3.9)
Headache	18 (21.4)	2 (2.4)	12 (15.6)	0
Leucopoenia	14 (16.7)	5 (6.0)	12 (15.6)	6 (7.8)
Thrombocytopaenia	9 (10.7)	3 (3.6)	12 (15.6)	0
Palmar-plantar syndrome	6 (7.1)	0	10 (13.0)	0
Paraesthesia	9 (10.7)	0	10 (13.0)	0
Peripheral oedema	6 (7.1)	0	10 (13.0)	0
Increased GGT	6 (7.1)	3 (3.6)	9 (11.7)	5 (6.5)
Pyrexia	17 (20.2)	0	9 (11.7)	0
Increased AST	11 (13.1)	1 (1.2)	7 (9.1)	2 (2.6)
Upper abdominal pain	18 (21.4)	1 (1.2)	7 (9.1)	0
Increased ALT	9 (10.7)	1 (1.2)	6 (7.8)	2 (2.6)

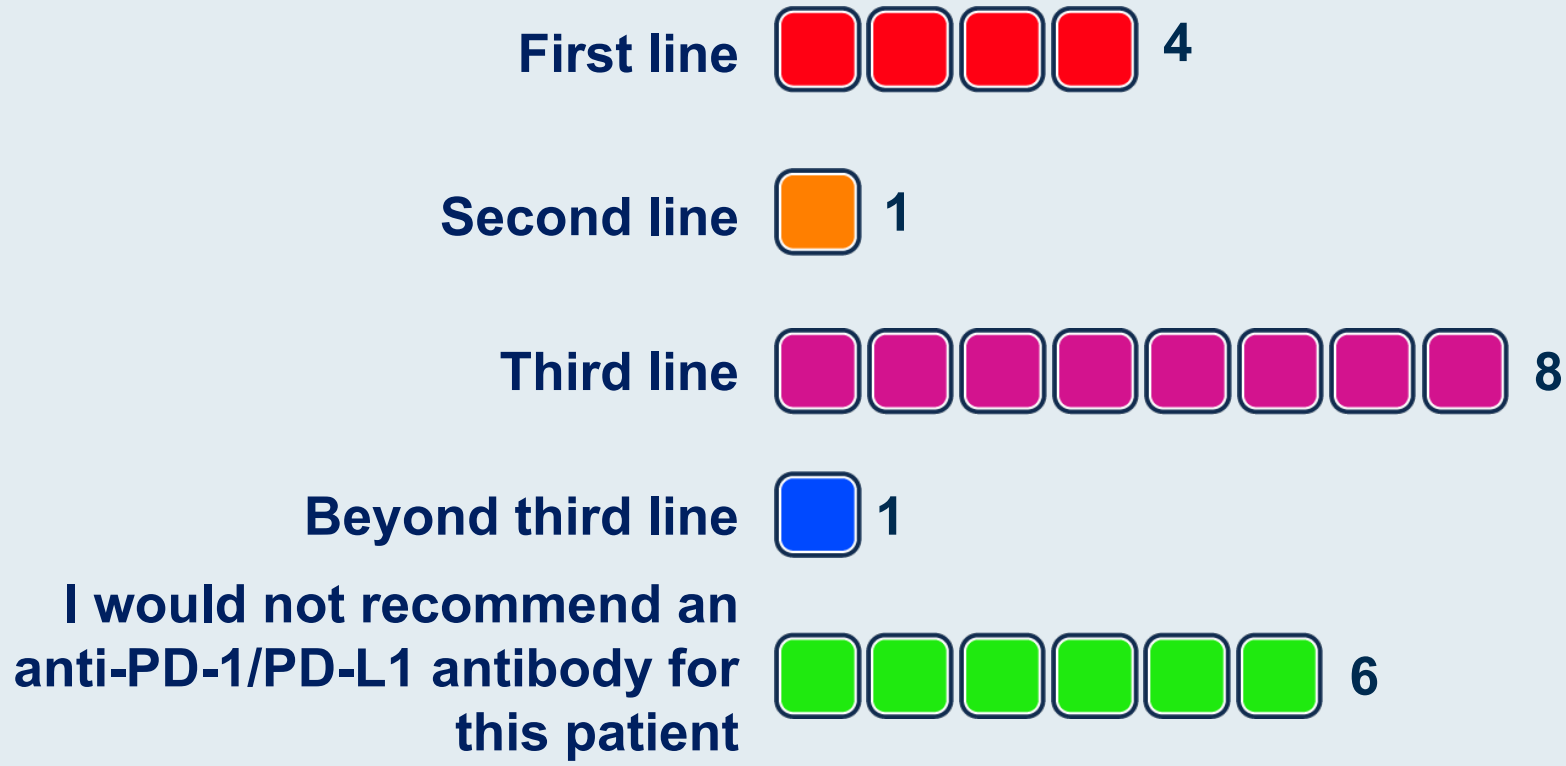
Median duration of exposure was 3.6 months (range, 0.03-6.0) in the EOX arm and 4.4 months (range, 0.03-58.7) in the zolbetuximab + EOX arm.
Although no patient in arm 1 or arm 2 had a fatal sepsis adverse event, one patient in arm 3 died from a non-treatment-related sepsis event.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOX, epirubicin, oxaliplatin, and capecitabine; GGT, gamma-glutamyl transferase.

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

Firs-line therapy for GEJ and Gastric Adenocarcinoma)

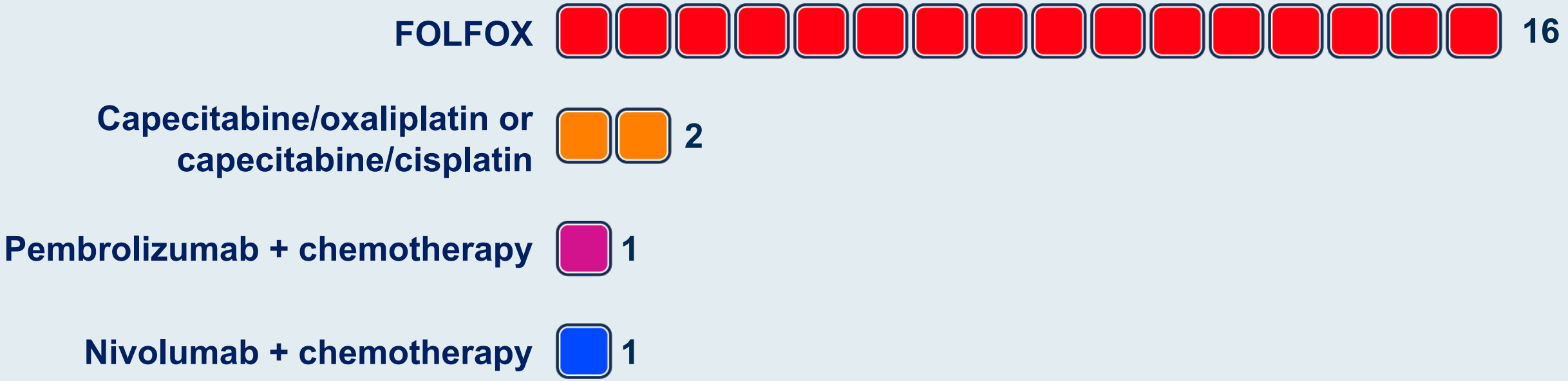
- Nivolumab with chemotherapy approved in the United States for 1st-line treament irrespective of PD-L1 status
- Pembrolizumab, trastuzumab, and chemotherapy approved in the United States for HER2-positive disease
- Biomarker selection for future strategies
- Berituzumab/FOLFOX for FGFR2+
- Zolbetuximab/FOLFOX for Claudin 18.2+

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



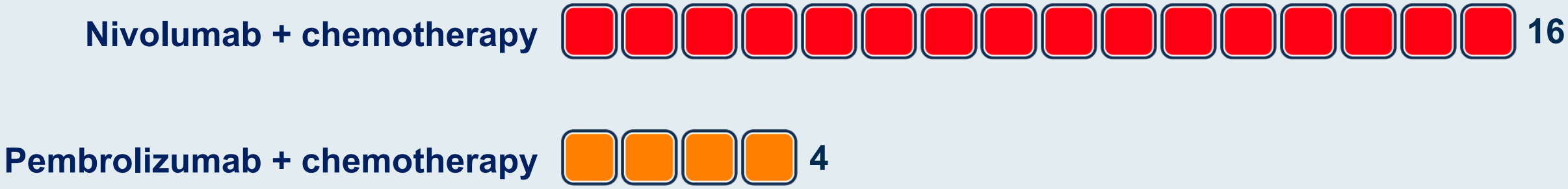
Survey of US-based clinical investigators

Regulatory and reimbursement issues aside, which first-line therapy would you most likely recommend for a 65-year-old patient with metastatic HER2-negative, microsatellite-stable (MSS) gastric adenocarcinoma with a PD-L1 combined positive score (CPS) of 1?



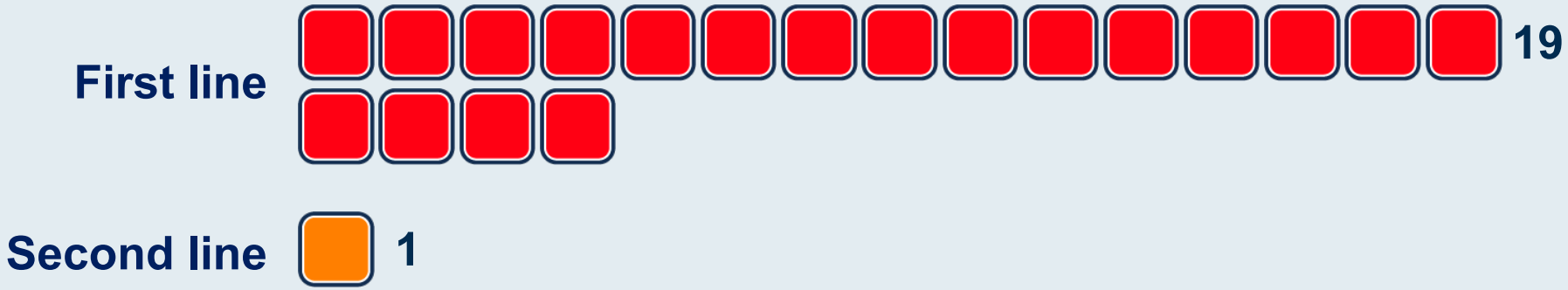
Survey of US-based clinical investigators

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



Survey of US-based clinical investigators

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



Survey of US-based clinical investigators

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

Survey of US-based clinical investigators

MODULE 2: Contemporary Management of HER2-Positive Advanced Gastric and GEJ Cancer — Prof Van Cutsem

RTP
RESEARCH
TO PRACTICE

UZ LEUVEN

Recent Advances in the Management of HER2-Positive Advanced Gastric Cancer

Prof Eric Van Cutsem, MD, PhD
Digestive Oncology
Leuven, Belgium
Eric.VanCutsem@uzleuven.be

Herestraat 49
B - 3000 Leuven
www.uzleuven.be
tel. +32 16 33 22 11
UNIVERSITY HOSPITALS LEUVEN

HER2 targeted therapy and testing in first line treatment of gastric cancer

TOGA study: chemo ± trastuzumab

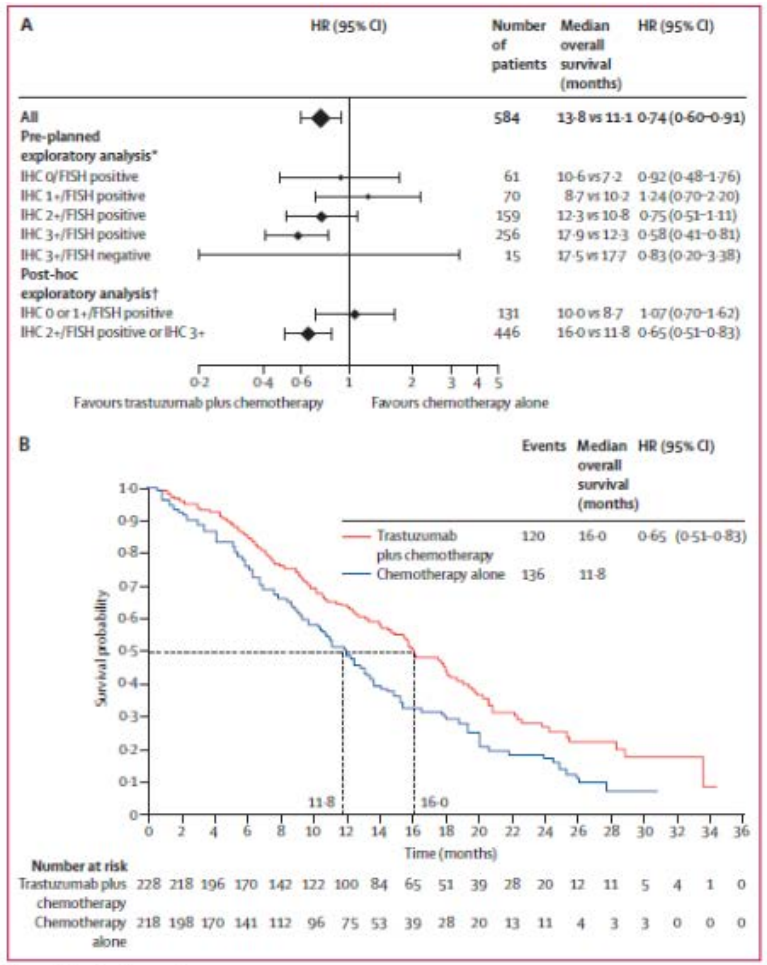


Figure 4: **Exploratory analyses**
HR=hazard ratio. (A) Pre-planned exploratory and post-hoc exploratory analyses of patients stratified by human epidermal growth factor receptor 2 (HER2) status. *n=561; patients with no immunohistochemistry (IHC) data (n=7) or IHC 3+ tumours with no fluorescence in-situ hybridisation (FISH) data (n=16) were excluded from this analysis. †n=577; patients with no IHC data (n=7) were excluded from this analysis. (B) Overall survival according to the post-hoc exploratory analysis (FISH and IHC) in patients with IHC 2+ and FISH-positive tumours or IHC 3+ tumours.

Bang Y, Van Cutsem E et al, Lancet 2010

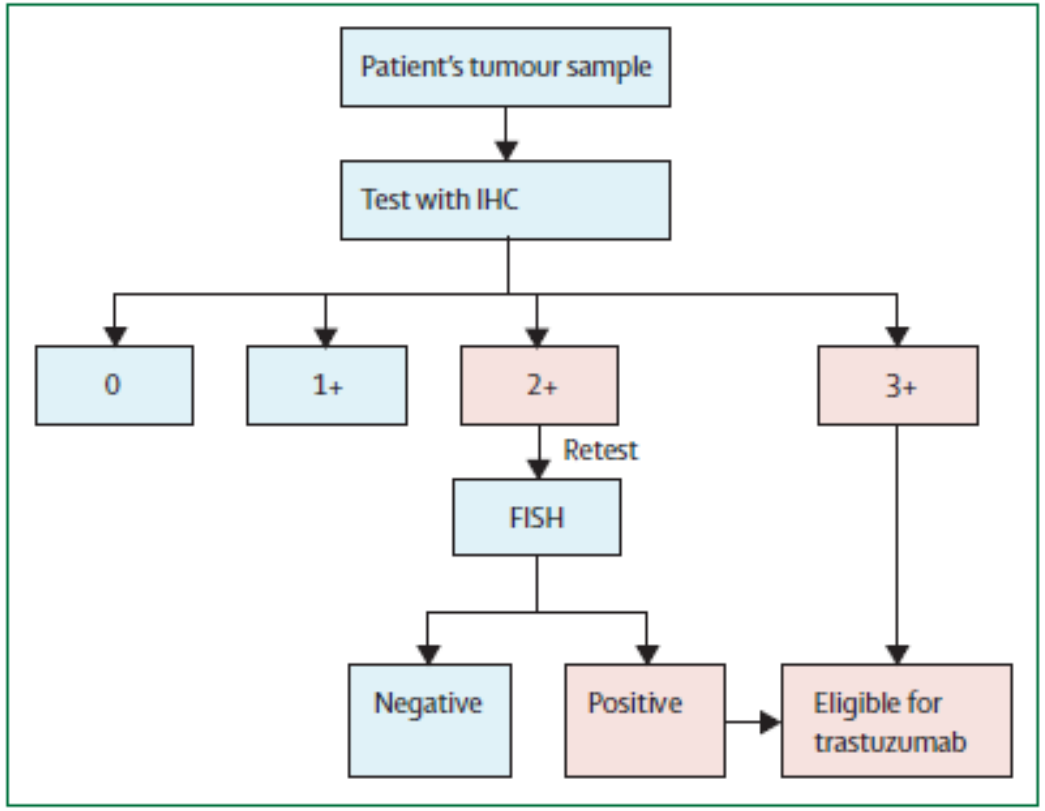
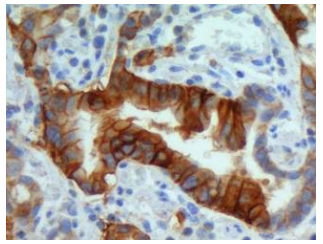
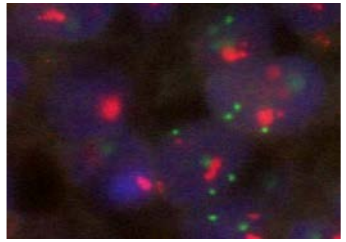


Figure 2: **Testing algorithm for *HER2* status in gastric and gastro-oesophageal-junction adenocarcinomas**
IHC=immunohistochemistry. FISH=fluorescence in-situ hybridisation.



IHC 3+



FISH +

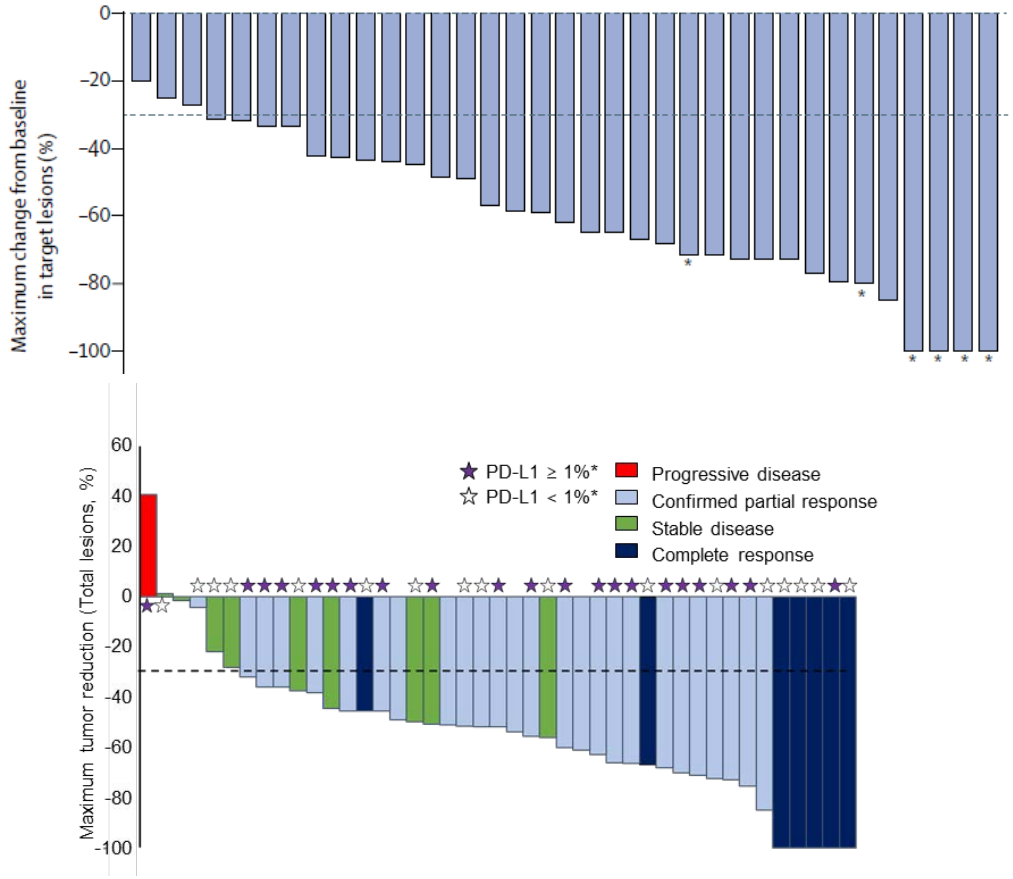
Van Cutsem E et al, Lancet 2016

Available Phase II Clinical Data in HER2 + Gastric/GEJ Adenocarcinoma

Phase 2 data suggest antitumor activity and manageable safety for adding pembrolizumab (anti–PD-1) to trastuzumab and chemotherapy

- ✓ MSKCC study (N = 37)[1]: 91% ORR, 100% DCR, 70% 6-mo PFS, 80% 12-mo OS

- ✓ PANTHERA (N = 43)[2]: 77% ORR, 98% DCR, 77% 6-mo PFS, 77% 12-mo OS



1. Janjigian YY et al. *Lancet Oncol* 2020;21:821-31.
2. Rha SY et al. Abstr 30831 presented at ASCO Gastrointestinal Cancers Symposium 2021..

ESMO WORLD CONGRESS ON Gastrointestinal Cancer

Pembrolizumab Plus Trastuzumab and Chemotherapy for HER2+ Metastatic Gastric or Gastroesophageal Junction Cancer: Initial Findings of the Global Phase 3 KEYNOTE-811 Study

Yelena Y. Janjigian,[1] Akihito Kawazoe,[2] Patricio Yañez,[3] Suxia Luo,[4] Sara Lonardi,[5] Oleksii Kolesnik,[6] Olga Barajas,[7] Yuxian Bai,[8] Lin Shen,[9] Yong Tang,[10] Lucjan S. Wyrwicz,[11] Kohei Shitara,[2] Shukui Qin,[12] Eric Van Cutsem,[13] Josep Tabernero,[14] Lie Li,[15] Chie-Schin Shih,[15] Pooja Bhagia,[15] Hyun Cheol Chung,[16] on behalf of the KEYNOTE-811 Investigators

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]National Cancer Center Hospital East, Kashiwa, Japan; [3]Universidad de La Frontera, James Lind Cancer Research Center, Temuco, Chile; [4]Henan Cancer Hospital, the Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; [5]Istituto Oncologico Veneto IOV-IRCCS, Padova, Italy; [6]Medical Center "Oncolife", Zaporizhzhia, Ukraine; [7]Arturo López Pérez Foundation, Santiago, Chile; [8]Harbin Medical University Cancer Hospital, Harbin, China; [9]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China; [10]Cancer Hospital Affiliated to Xinjiang Medical University, Xinjiang, China; [11]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; [12]Cancer Center of People's Liberation Army, Nanjing, China; [13]University Hospitals Gasthuisberg and KU Leuven, Leuven, Belgium; [14]Vall d'Hebron Hospital Campus and Institute of Oncology (VHIO), IOB-Quiron, UVic-UCC, Barcelona, Spain; [15]Merck & Co., Inc., Kenilworth, NJ, USA; [16]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

KEYNOTE-811 Global Cohort: Randomized, Double-Blind, Phase 3 Study

Key Eligibility Criteria

- Unresectable or metastatic gastric or GEJ adenocarcinoma
- No prior systemic therapy in advanced setting
- HER2-positive tumor by central review (IHC 3+ or IHC 2+ ISH+)
- ECOG PS 0 or 1

Stratification Factors

- Geographic region (Australia/Europe/ Israel/North America vs Asia vs ROW)
- PD-L1 CPS (≥1 vs <1)
- Chemotherapy choice (FP vs CAPOX)

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

End Points

- **Dual primary:** OS and PFS per RECIST v1.1 by BICR
- **Key secondary:** ORR and DOR per RECIST v1.1 by BICR and safety

[a]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: 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). KEYNOTE-811 ClinicalTrials.gov identifier, NCT03615326.

ESMO GI/WCIGC Ann Onc 2021,LBA4

KEYNOTE-811 Global Cohort:
Phase 3 Study in HER2 pos. Gastric Adenocarcinoma

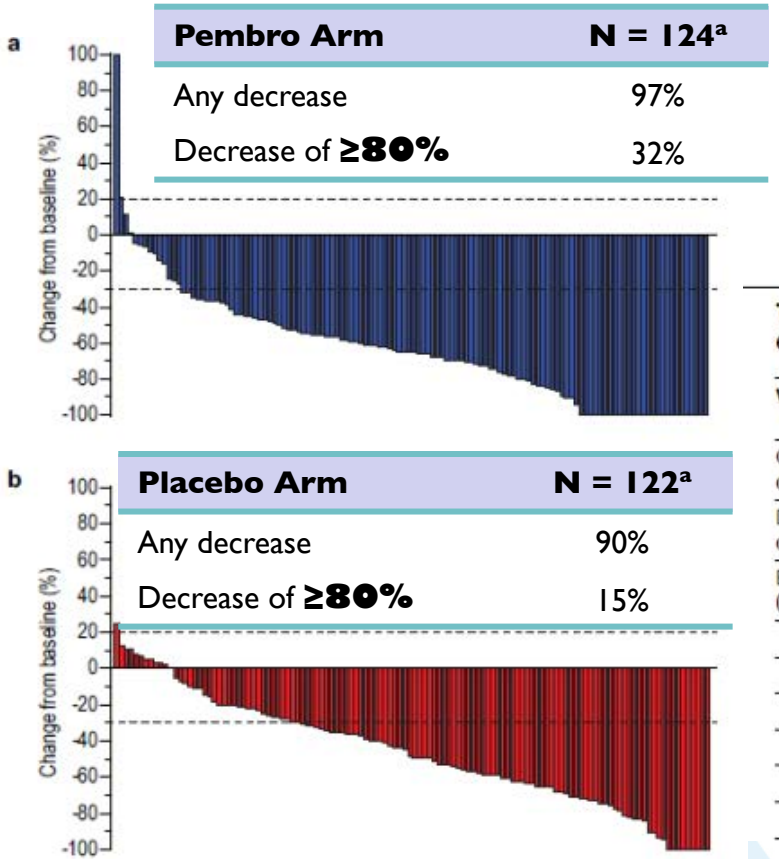
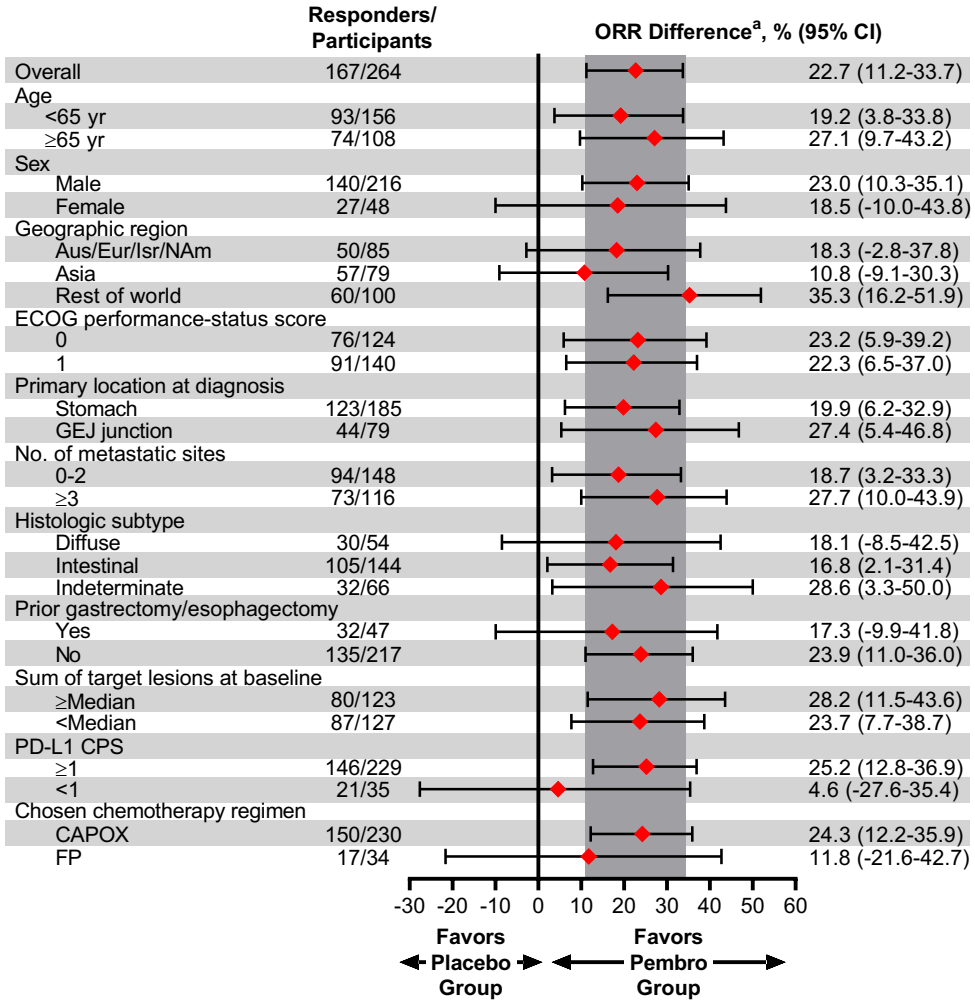


Fig. 1 | Best percentage change from baseline in the size of target lesions among participants in the efficacy population. a, Pembrolizumab group. **b**, Placebo group. Only those participants in the efficacy population who had RECIST-measurable disease at baseline and at least one evaluable post-baseline measurement are evaluable for change from baseline ($n = 124$ in the pembrolizumab group, $n = 122$ in the placebo group). The treatment regimen included trastuzumab and chemotherapy in both groups. Increases from baseline greater than 100% were truncated at 100%.

Table 1 | Summary of confirmed objective response in the efficacy population

Variable	Pembrolizumab group ($n = 133$)	Placebo group ($n = 131$)
Objective response (% (95% confidence interval))[a]	74.4 (66.2–81.6)	51.9 (43.0–60.7)
Disease control (% (95% confidence interval))[b]	96.2 (91.4–98.8)	89.3 (82.7–94.0)
Best overall response (number (%))		
Complete response	15 (11.3)	4 (3.1)
Partial response	84 (63.2)	64 (48.9)
Stable disease	29 (21.8)	49 (37.4)
Progressive disease	5 (3.8)	7 (5.3)
Not evaluable[c]	0 (0.0)	2 (1.5)
Not assessed[c]	0 (0.0)	5 (3.8)

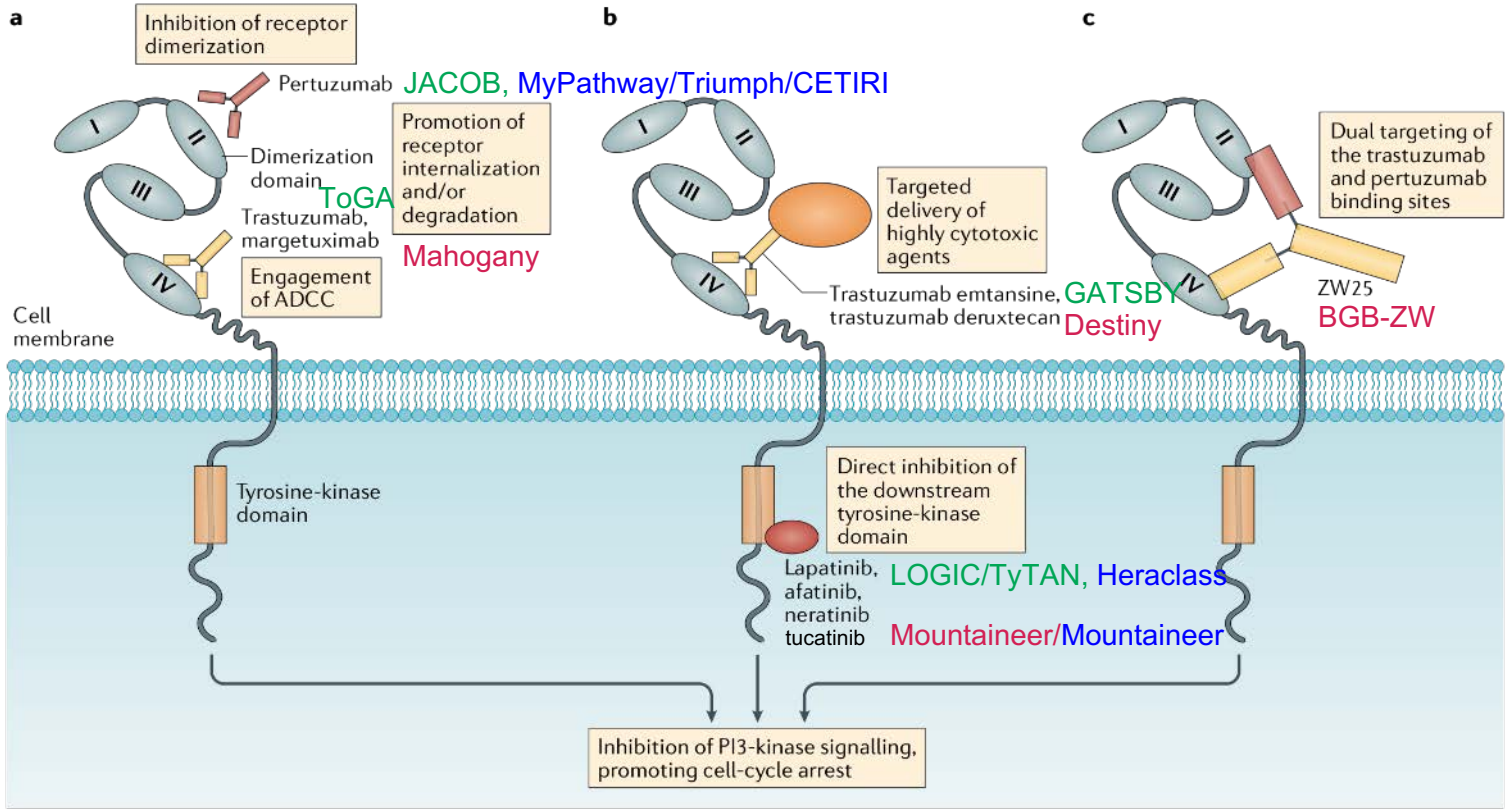


Janjigian Y, …Van Cutsem E et al Nature 2021 & ESMO GI/WCIGC Ann Onc 2021,LBA4

Armamentarium Against Resistance

- Trastuzumab beyond PD
- Chemotherapy backbone change
- High-dose trastuzumab
- Other HER2 directed treatment: ADC
- Heterodimerization with HER3
- HER2-HER3 pathways
- Combination with Antiangiogenesis
- Combination with IO
- New agents

Myriad of HER2 Directed Drugs



; Huynh JC, et al. *Cancers (Basel)*. 2020;6:1168; Khalil HS, et al. *Oxid Med Cell Longev*. 2016;2016:4148791; Macrogenics. Accessed October 25, 2020. https://clinicaltrials.gov/ct2/show/NCT04082364; Nakamura Y et al. 2019 ESMO Annual Meeting; abstract 1057; Novotny CJ, et al. *Nat Chem Biol*. 2016;12:923-930; Oh DY, Bang YJ. *Nat Rev Clin Oncol*. 2020;17:33-48; Russi S, et al. *Int J Mol Sci*. 2019;20:3736; Sartore-Bianchi A, et al. *Lancet Oncol*. 2016;17:738-746; Shitara K, et al. *N Engl J Med*. 2020;382:2419-2430; Sidaway P. *Nat Rev Clin Oncol*. 2020;17:133; Southwest Oncology Group. Accessed October 25, 2020. https://clinicaltrials.gov/ct2/show/NCT03365882; Stein A, et al. *World J Gastroenterol*. 2014;20:899-907; Strickler JH, et al. 2019 ESMO Annual Meeting; abstract 4975; Xie YH, et al. *Signal Transduct Target Ther*. 2020;5:22. https://clinicaltrials.gov/ct2/show/NCT04276493

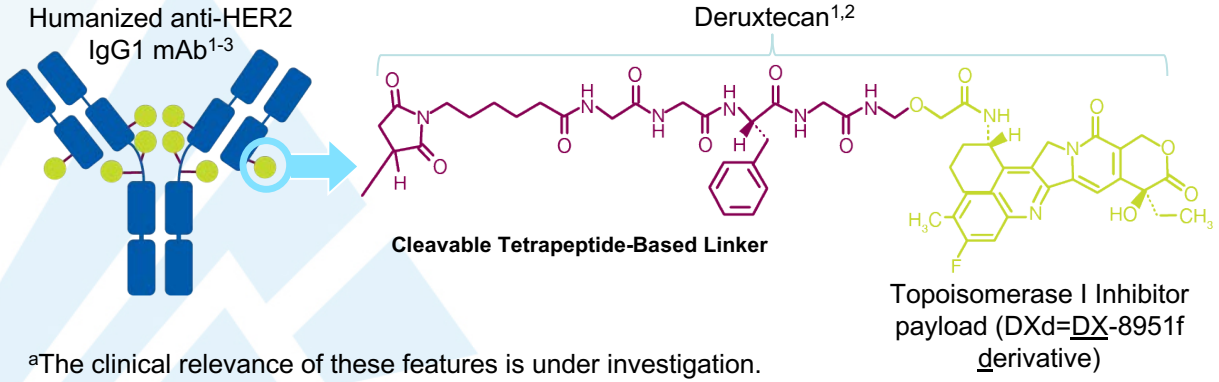
Trastuzumab-deruxtecan (T-DXd), a novel a ADC (Antibody-Drug-Conjugate)

An ADC composed of 3 components[1,2]:

A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab, covalently linked to:

A topoisomerase I inhibitor payload, an exatecan derivative, via

A tetrapeptide-based cleavable linker



[a]The clinical relevance of these features is under investigation.

Characteristics

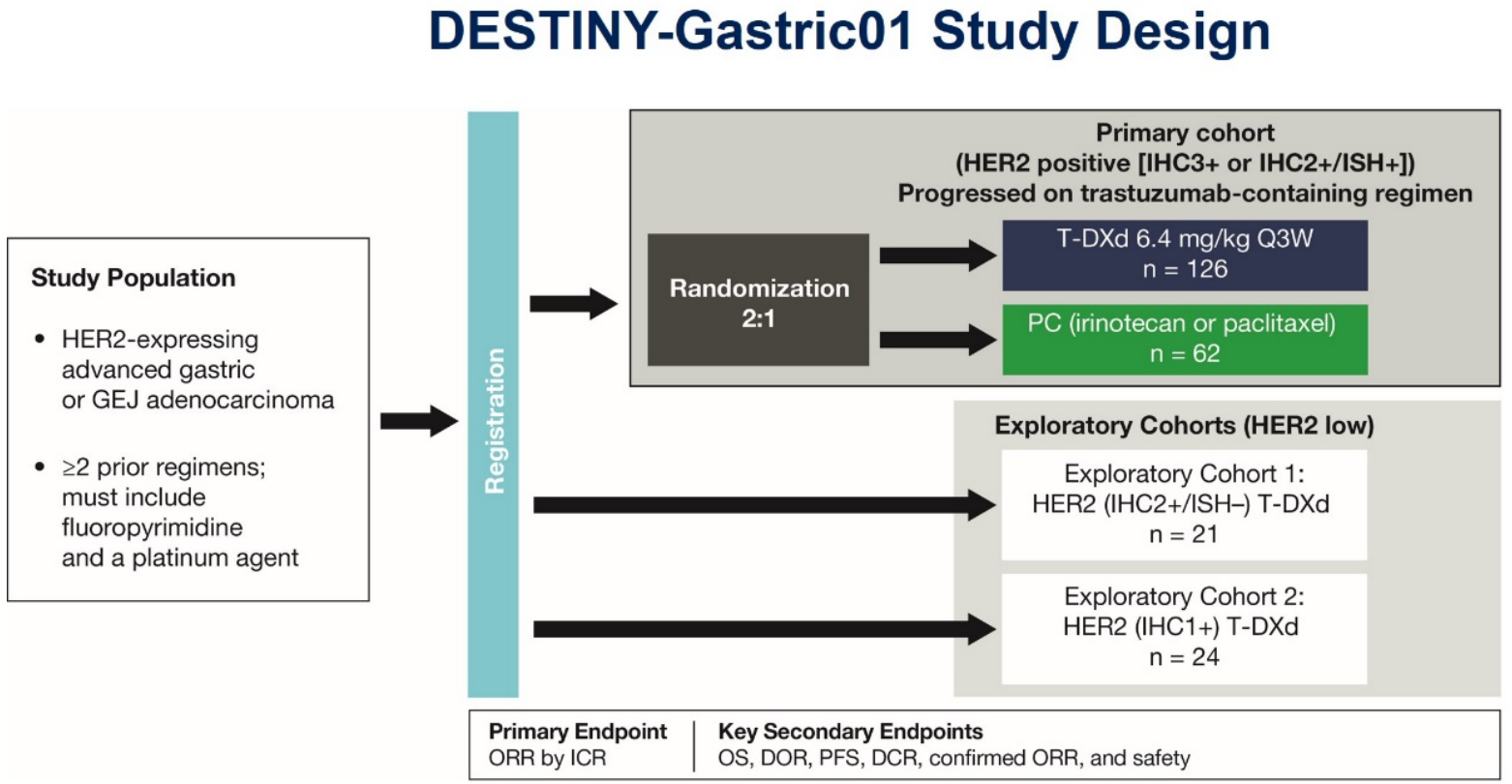
- Payload MOA: topoisomerase I **inhibitor**[1,2,a]
- High potency of payload[1,2,a]
- High DAR ≈8[1,2,a]
- Payload with short systemic half-life[1,2,a]
- Stable linker-payload[1,2,a]
- Tumor-selective cleavable linker[1,2,a]
- Membrane permeable payload[1,4,a]

1. Nakada T, et al. Chem Pharm Bull (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. Clin Cancer Research. 2016;22(20):5097-5108. 3. Trail PA, et al. Pharmacol Ther. 2018;181:126-142. 4. Ogitani Y, et al. Cancer Sci. 2016;107(7):1039-1046.

DESTINY-Gastric01

An open-label, multicenter, randomized, phase 2 study

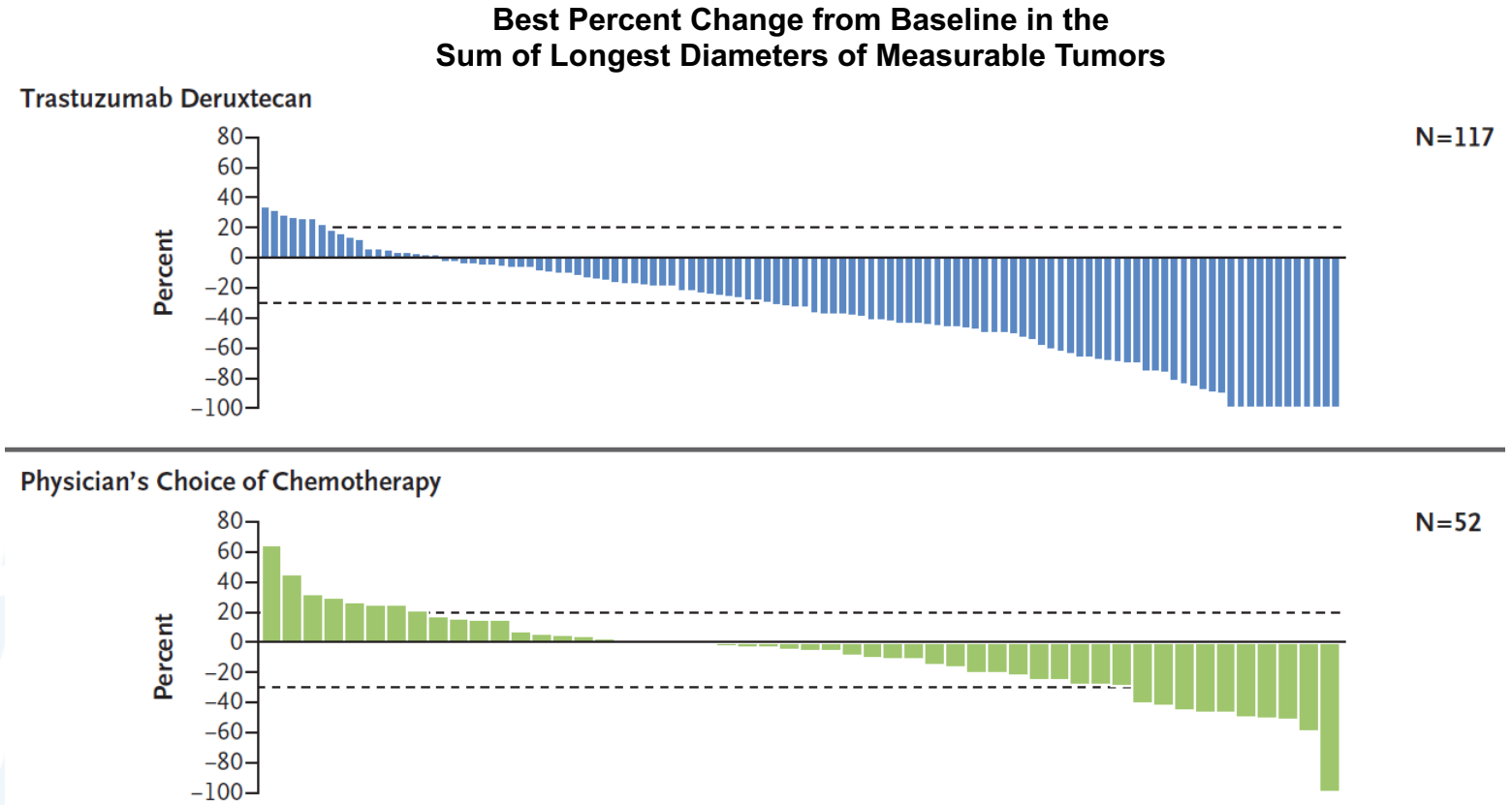
- ✓ Patients had a median of 2 prior lines of therapy (range, 2-9); 44.4% of patients had ≥3 previous lines
- ✓ As of June 3, 2020, 10 patients (8%) receiving T-DXd and no patients receiving PC remained on treatment



Key secondary endpoint of OS was to be statistically evaluated hierarchically if the primary endpoint was statistically significant

Yamaguchi K, et al. Presented at ASCO 2021 Virtual Meeting; June 4-8, 2021.

DESTINY-Gastric01: Response Rate IHC3+ or IHC2+/ISH+

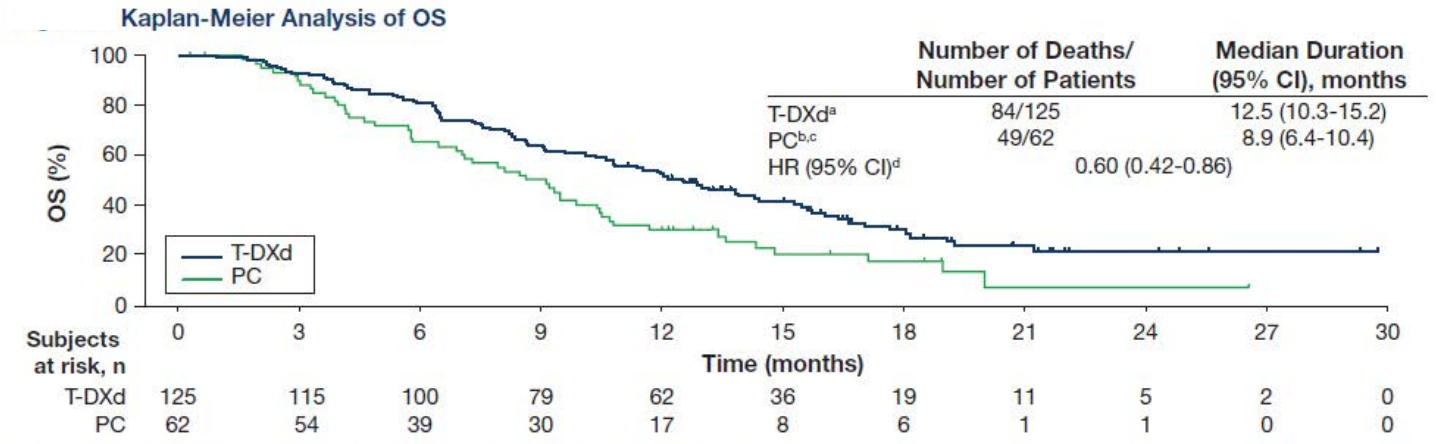


	T-DXd (n=119)	PC (n=56)
ORR[a]	**51.3%**	**14.3%**
CR	9.2%	0
PR	42.0%	14.3%
SD	35.3%	48.2%
PD	11.8%	30.4%
NE	1.7%	7.1%
Confirmed ORR[a]	**42.0%**	**12.5%**

Data cutoff: June 3, 2020. The line at 20% indicates progressive disease, and the line at −30% indicates a partial response. The analyses included patients who had both baseline and postbaseline target-lesion assessments according to independent central review. Six patients (two in the trastuzumab deruxtecan group and four in the physician's choice group) were excluded from this analysis because they did not undergo postbaseline tumor assessment. [a]Includes data for the response-evaluable set: all randomized patients who received ≥1 dose of study drug and had measurable tumors based on ICR at baseline (T-DXd, n = 119; PC overall, n = 56; irinotecan, n = 51; paclitaxel, n = 5). [b]According to the procedure of the ICR, the adjudicator assessment was changed from PR to SD in 1 patient at data cutoff of the final OS analysis.

Shitara K, et al. *N Engl J Med*. 2020;382(25):2419-2430. Yamaguchi K, et al. Presented at ASCO 2021 Virtual Meeting; June 4-8, 2021.

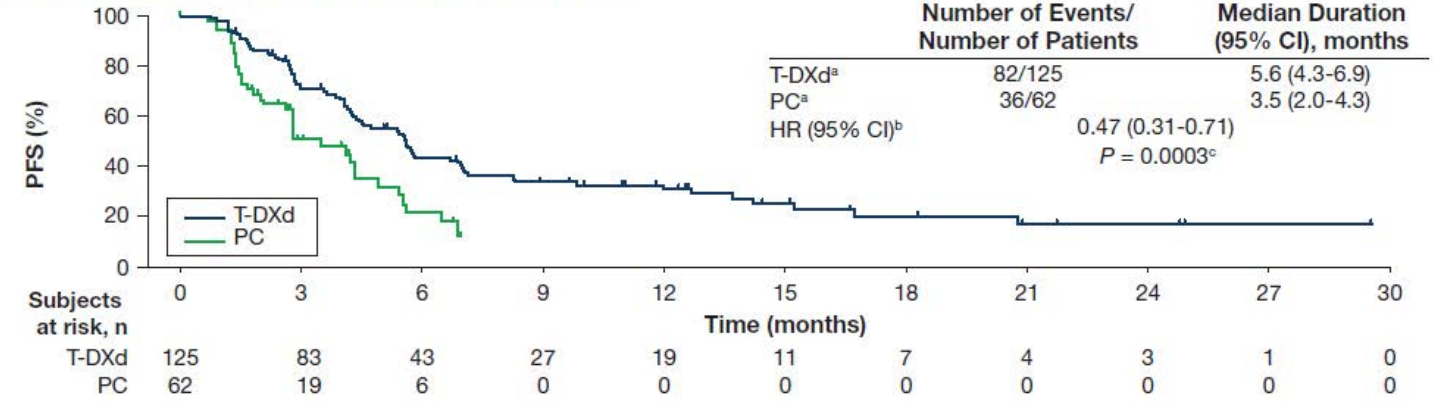
DESTINY-Gastric01: Survival



HR, hazard ratio; OS, overall survival; PC, physician's choice; T-DXd, trastuzumab deruxtecan.

[a]In the T-DXd arm, 41 patients (32.8%) were censored.
[b]In the PC arm, 13 patients (21.0%) were censored.
[c]One patient in the PC arm received crossover treatment of T-DXd.
[d]HI onding 95% CI were estimated using Cox proportional hazards model stratified by region.

Figure 5. Kaplan-Meier Analysis of PFS Based on ICR



HR, hazard ratio; ICR, independent central review; PC, physician's choice; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

[a]In the T-DXd arm, 71 patients (56.8%) had PD and 11 (8.8%) had death as the first event. In the PC arm, 34 patients (54.8%) had PD and two (3.2%) had death as the first event. 43 (34.4%) and 26 (41.9%) patients were censored in the T-DXd and PC arms, respectively, for no baseline (T-DXd [n = 0]; PC [n = 2]) or postbaseline tumor assessment (n = 1; n = 3), receiving new anticancer therapy (n = 14; n = 14), and missing two consecutive tumor assessments (n = 5; n = 1); the remaining patients were censored without an event.
[b]HR and corresponding 95% CI were estimated using Cox proportional hazards model stratified by region.
[c]Comparison between T-DXd and PC overall using a stratified log-rank test with region as a stratification factor.

Data cutoff: June 3, 2020

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Yamaguchi K, et al. Presented at ASCO 2021 Virtual Meeting; June 4-8, 2021.

2021 ESMO congress

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

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

On behalf of the DESTINY-Gastric02 investigators

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

Van Cutsem E et al. Presented at: ESMO Virtual Congress 2021; September 17-21, 2021, Ann Oncol 2021, LBA

DESTINY-Gastric02 Study Design

An open-label, multicenter phase 2 study in Western patients with HER2+ gastric or GEJ cancer (NCT04014075)

Key eligibility criteria

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

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

Primary endpoint

- Confirmed ORR by ICR

Secondary endpoints[b]

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

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

[a]Enrollment of 80 patients was planned; actual enrollment was 79 patients.
[b]Other secondary endpoints were ORR, PFS, and DOR by investigator assessment, pharmacokinetics, anti-drug antibodies, and patient-reported outcomes.

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

DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; Q3W, every 3 weeks.

Van Cutsem E et al. Presented at: ESMO Virtual Congress 2021; September 17-21, 2021, Ann Oncol 2021, LBA

Patient Demographics and Disease Characteristics

Demographics	Patients N = 79
Age	
Median (range), years	60.7 (20.3 – 77.8)
<65, %	58.2
≥65, %	41.8
Male, %	72.2
Race, %	
White	87.3
Black or African American	1.3
Asian	5.1
American Indian or Alaskan native	0
Native Hawaiian or Pacific Islander	1.3
Other	3.8
Missing	1.3

Disease characteristics	Patients N = 79
ECOG PS, %	
0	36.7
1	63.3
HER2 expression, %	
IHC 3+	86.1
IHC 2+/ISH+	12.7
Not evaluable	1.3[a]
Adenocarcinoma, %	98.7
Intestinal	24.1
Diffuse	1.3
Mixed	1.3
Unknown	72.2[b]
Cancer type, %	
Gastric	34.2
GEJ	65.8
Number of metastatic sites, %	
<2	6.3
≥2	93.7
Liver metastasis at baseline, %	63.3
Time from diagnosis, median (range), mo	14.2 (3.6 – 88.5)

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[a]Patient's enrollment was based on local laboratory testing.
[b]One patient had non-adenocarcinoma histological subtype.

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Efficacy Endpoints

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

Cutoff date: April 9, 2021.

[a]Primary endpoint. [b]Secondary endpoint analysis based on responders (n=30); 21 patients were censored (reasons: initiating new anticancer therapy, adequate tumor assessment no longer available, and ongoing without occurrence of progressive disease or death). [c]Exploratory endpoint. [d]Secondary endpoint analysis in the full analysis set based on 42 events (36 PD, 6 deaths).

BOR, best overall response; CR, complete response; DCR, disease control rate; mo, months; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response.

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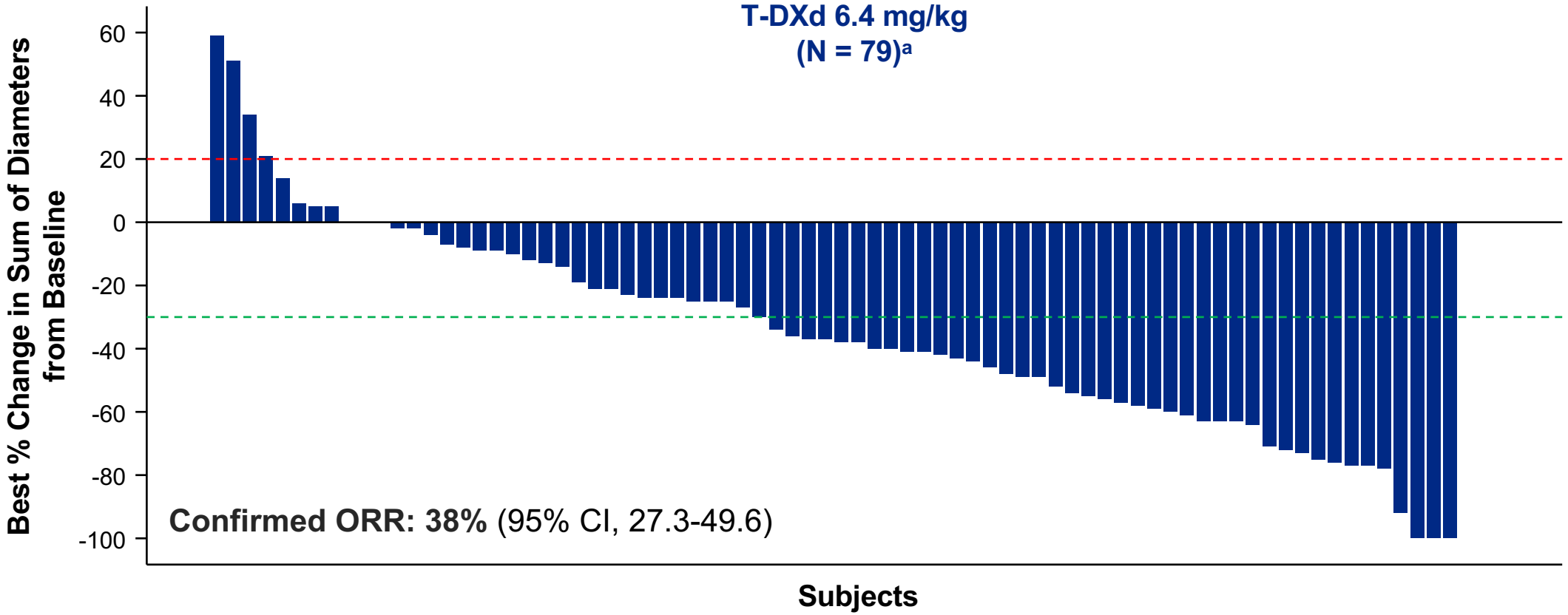
Best Percentage Change of Tumor Size from Baseline



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[a]3 patients were missing baseline or post-baseline target lesion assessment.
Red line at 20% indicates progressive disease; green line at -30% indicates partial response.
Analysis conducted in the full analysis set.

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Drug-related TEAEs in ≥15% of Patients

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

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

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Adjudicated Drug-Related ILD/Pneumonitis

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

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

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Margetuximab

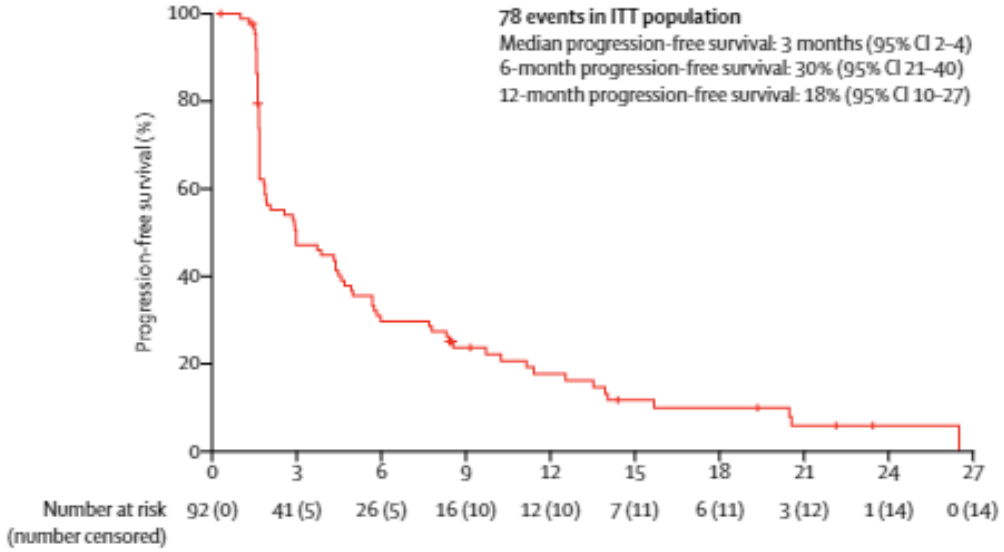
Study Design and Patients

- Single-arm, open-label, phase 1b–2 dose-escalation and cohort expansion study
- Unresectable, locally advanced or metastatic, HER2-positive, PD-L1-unselected gastro-oesophageal adenocarcinoma
- **Progressed after at least one previous line of therapy with trastuzumab plus chemotherapy**
- **Received 10-15 mg/kg margetuximab plus a flat dose of pembrolizumab 200 mg**
- **N = 95**

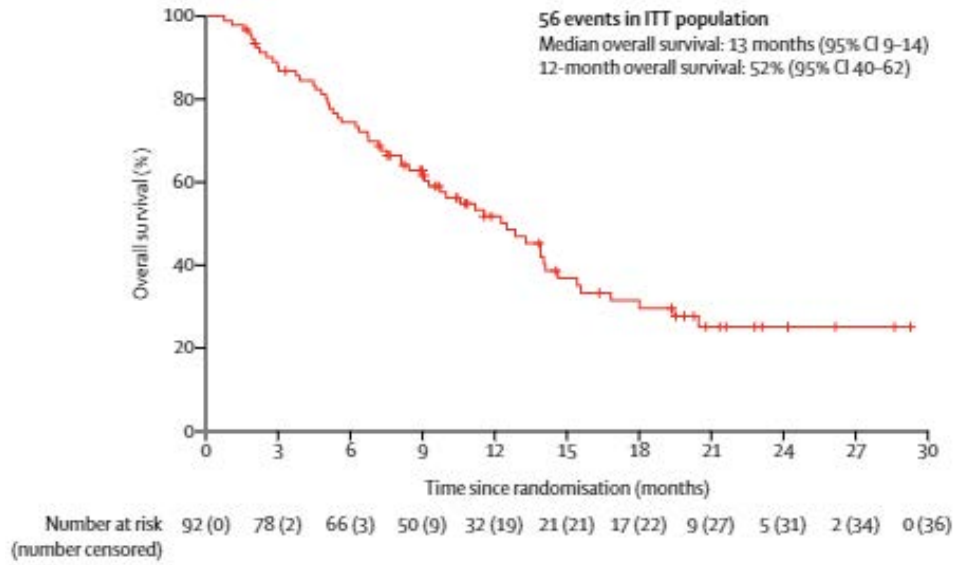
Safety: Primary Endpoint

- TRAEs occurred in 63% of patients
- 20% experienced ≥ Grade 3 TEAEs
- Most common grade 3–4 TRAEs were: anaemia (4%) and infusion-related reactions (3%)
- 8 pts discontinued treatment due TEAEs; 4 due to TRAEs
- No deaths due to TRAEs were reported

PFS



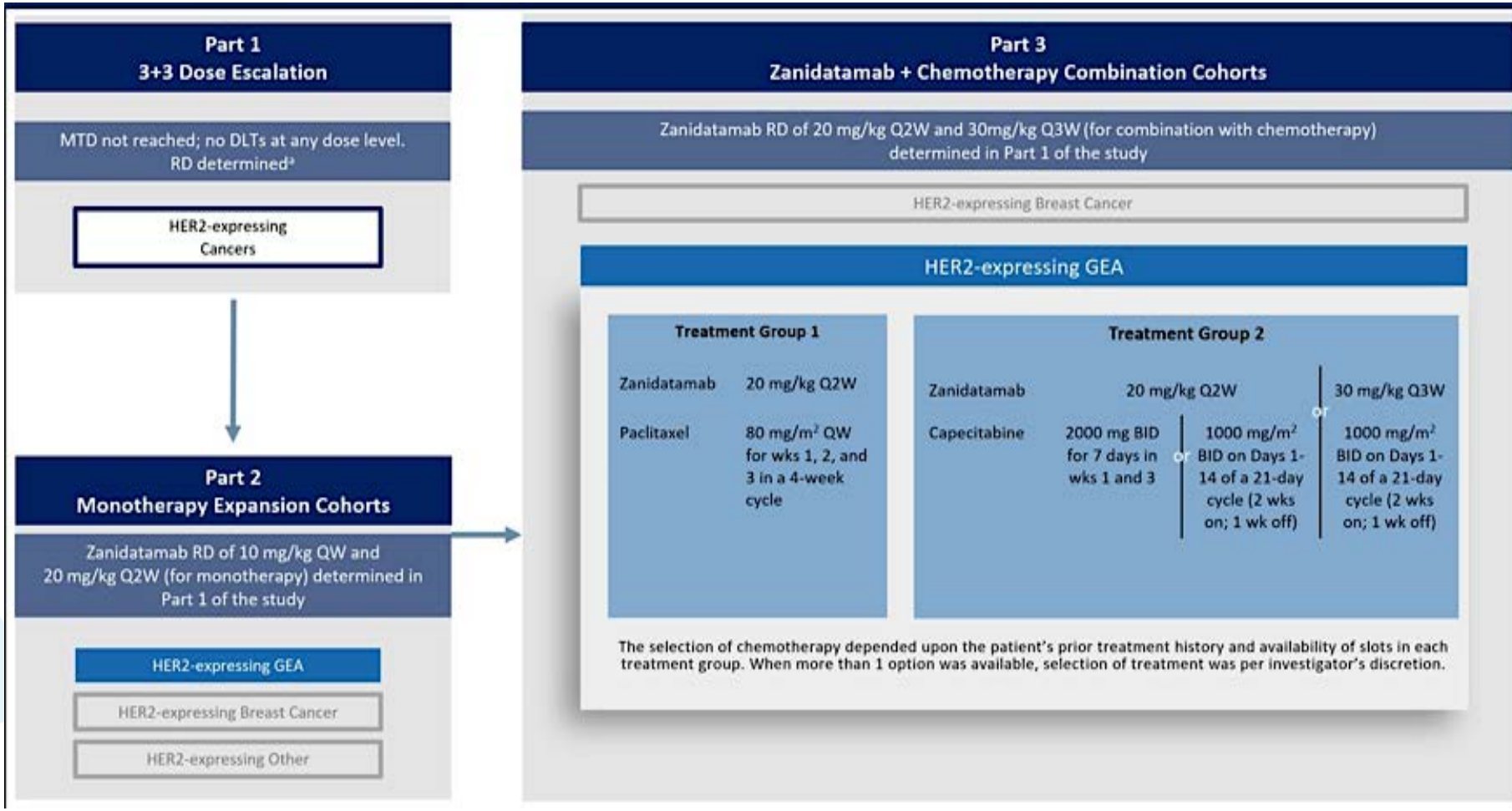
OS



Catenacci D et al. *Lancet Oncol.* 2020;21(8):1066-1076

Zanidatamab (ZW25)
ZW25-101 (NCT02892123)

- An antibody that binds two distinct sites on HER2: ECD4 (trastuzumab-targeted domain) and ECD2 (pertuzumab-targeted domain)
- Study Design and Patients
  - Phase 1 study
  - N = 63; n = 35 zanidatamab monotherapy; n = 28 zanidatamab + chemo
  - Primary endpoint: Safety and tolerability
  - Median number of prior therapies was 3 for zanidatamab monotherapy and zanidatamab + paclitaxel and 2 for zanidatamab + capecitabine



Meric-Bernstam et al. ASCO GI 2021. Presentation 164

Zanidatamab (ZW25)
ZW25-101 (NCT02892123)

- Response
  - Zanidatamab monotherapy:
    - Confirmed ORR: 33%
    - DCR: 61%
    - Median DOR: 6 mos
    - Median PFS: 3.6 mos
  - Zanidatamab + Chemo
    - Confirmed ORR: 54%
    - DCR: 79%
    - Median DOR: 8.9 mos
    - Median PFS: 5.6 mos

	Zanidatamab Monotherapy (N = 35)		Zanidatamab + Chemotherapy Combination			
			Zanidatamab + Pac (N = 11)		Zanidatamab + Cape (N = 17)	
	Any Grade	Grade 3 or higher	Any Grade	Grade 3 or higher	Any Grade	Grade 3 or higher
Patients with treatment-emergent AEs, n (%)	34 (97)	17 (49)	11 (100)	9 (82)	17 (100)	10 (59)
Patients with treatment-related AEs	25 (71)	4 (11)	11 (100)	7 (64)	15 (88)	2 (12)
Most common AEs[c]						
Diarrhea	16 (46)	1 (3)	7 (64)	0	10 (59)	0
Infusion-related reaction	12 (34)	0	3 (27)	0	0	0
Nausea	4 (11)	0	4 (36)	0	3 (18)	0
Fatigue	4 (11)	0	7 (64)	2 (18)	3 (18)	0

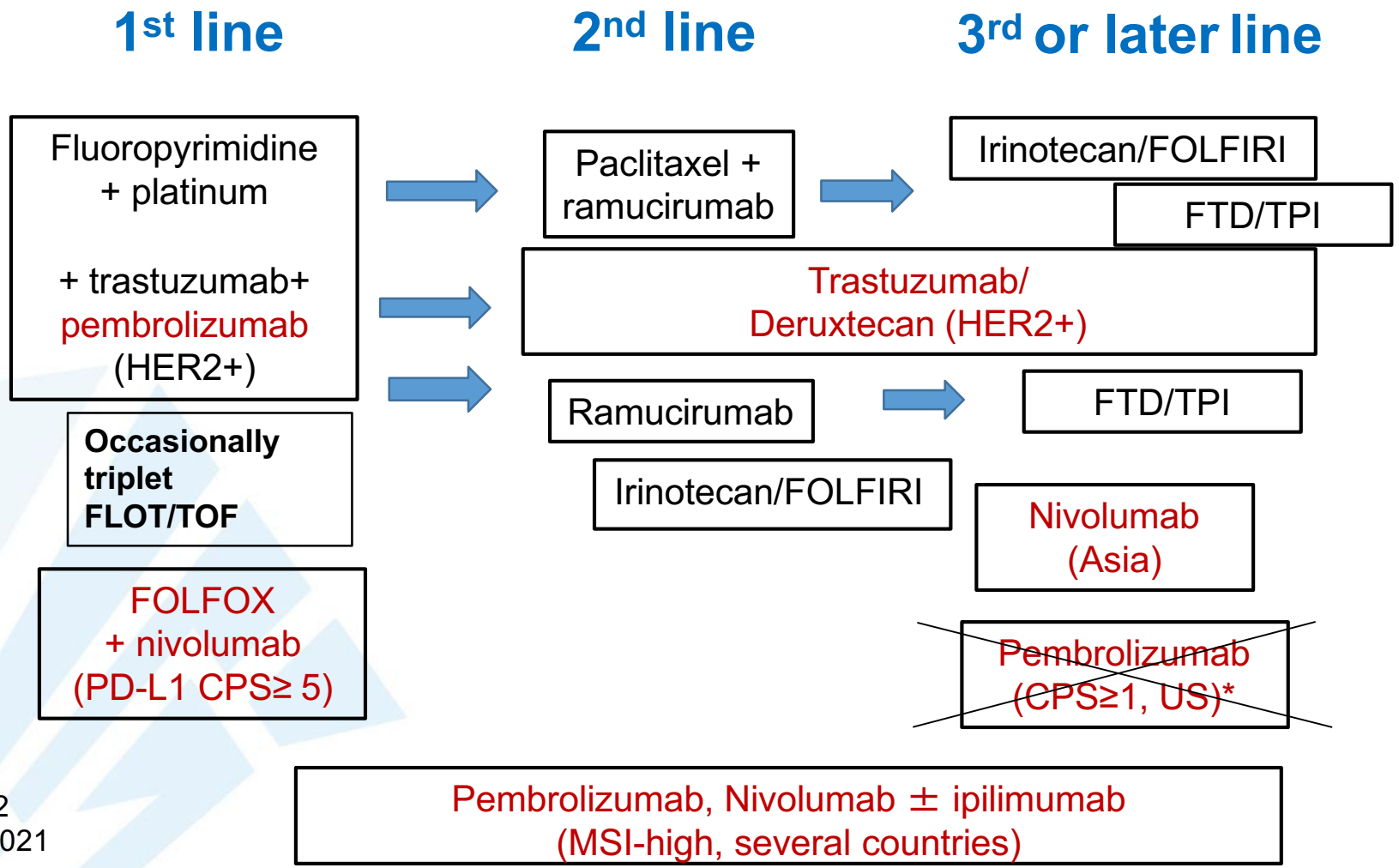
Meric-Bernstam et al. ASCO GI 2021. Presentation 164

Ongoing studies with HER2 targeting agents

- Keynote 811 - Ongoing
- DESTINY-Gastric03 phase 2 study of novel combinations with DS8201a (chemo, ICI) is now open [NCT04379596]
- DESTINY-Gastric04 phase III (N=490) study of 2nd-line DS8201a pending opening. [NCT04704934]
- Simultaneous targeting of HER2 and PD-1 (margetuximab plus retifanlimab) or HER2 and PD-1 plus LAG-3 (margetuximab plus tebotelimab) (NCT04082364)
- Tucatinib and Zanidatamab (ZW25) trials ongoing/ planned

Updated algorithm for metastatic gastric cancer in 2022 (personal opinion EVC based on evidence)

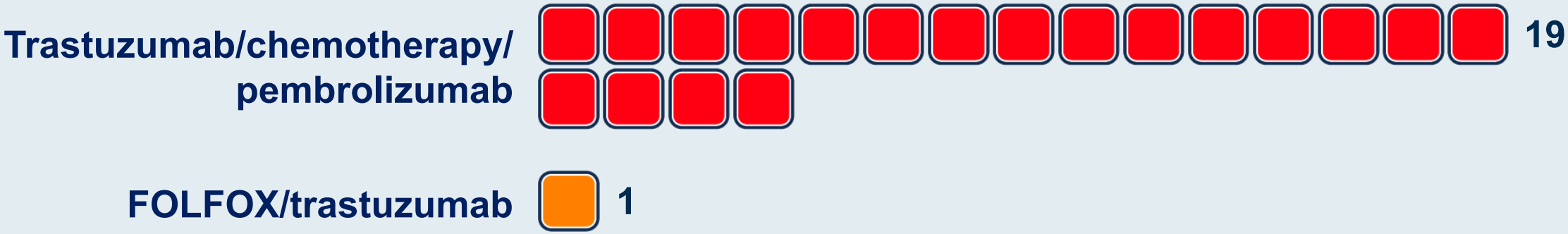
New data are discussed on drugs, including data for which an approval is not yet granted



FTD/TPI = TAS-102
* Withdrawn May 2021

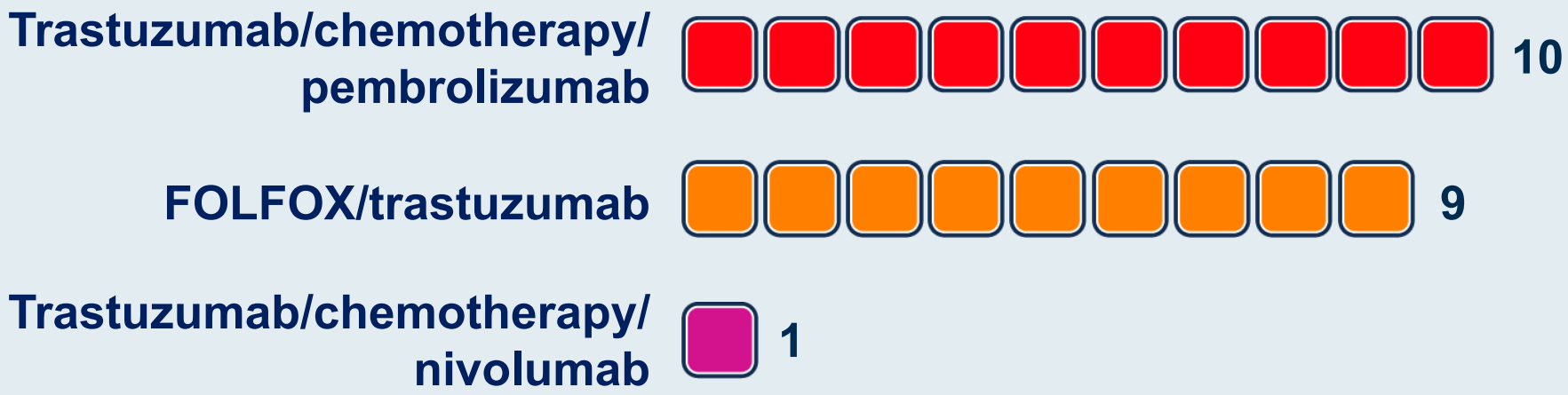
MODIFIED by Eric Van Cutsem from Muro K, Van Cutsem E et al. JSMO-ESMO guidelines. *Ann Onc* 2019;30(1):19-33.

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



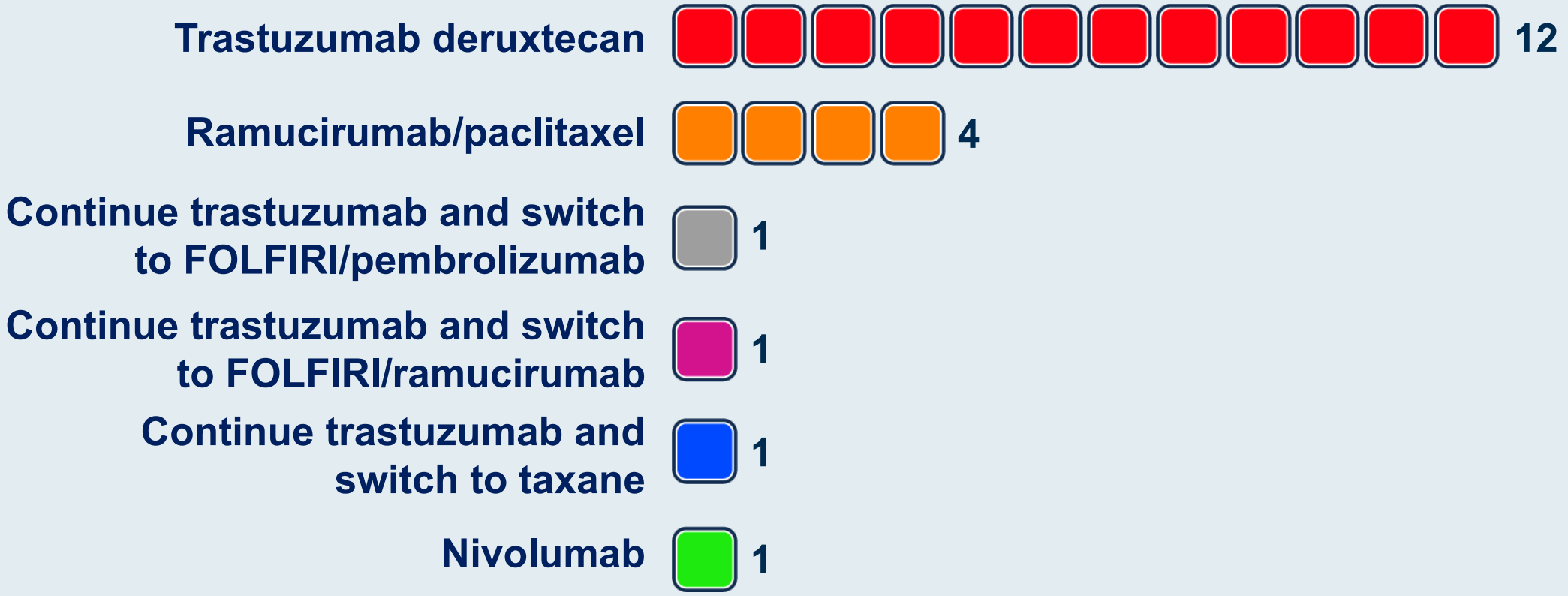
Survey of US-based clinical investigators

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



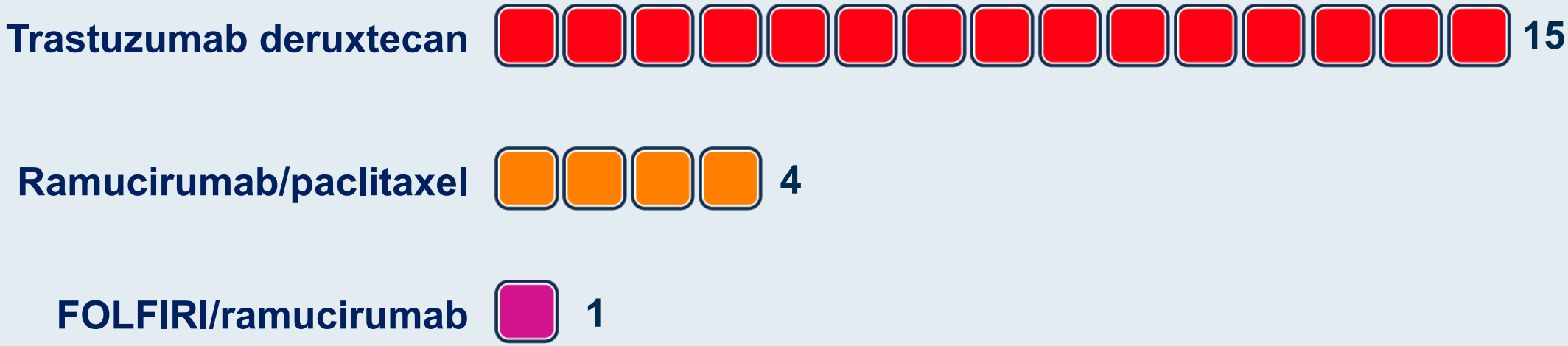
Survey of US-based clinical investigators

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



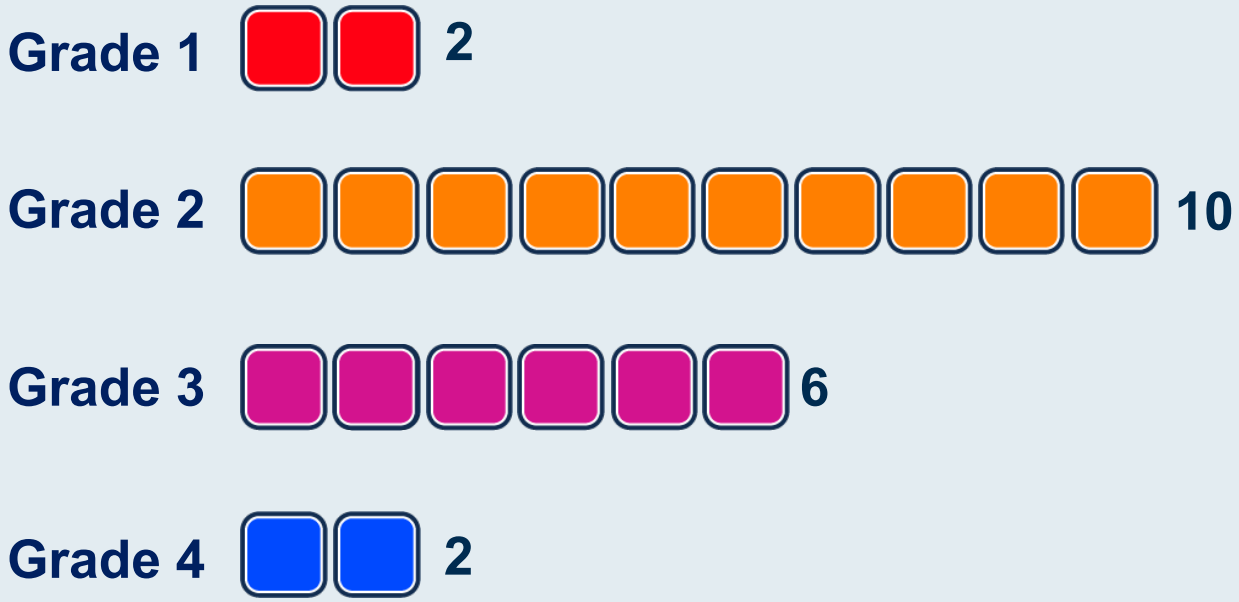
Survey of US-based clinical investigators

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



Survey of US-based clinical investigators

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



Survey of US-based clinical investigators

MODULE 3: Selection and Sequencing of Therapy for Relapsed Gastric and GEJ Cancer — Dr Klempner

Refractory and Late Line Therapy for Gastroesophageal Cancers

Samuel J. Klempner

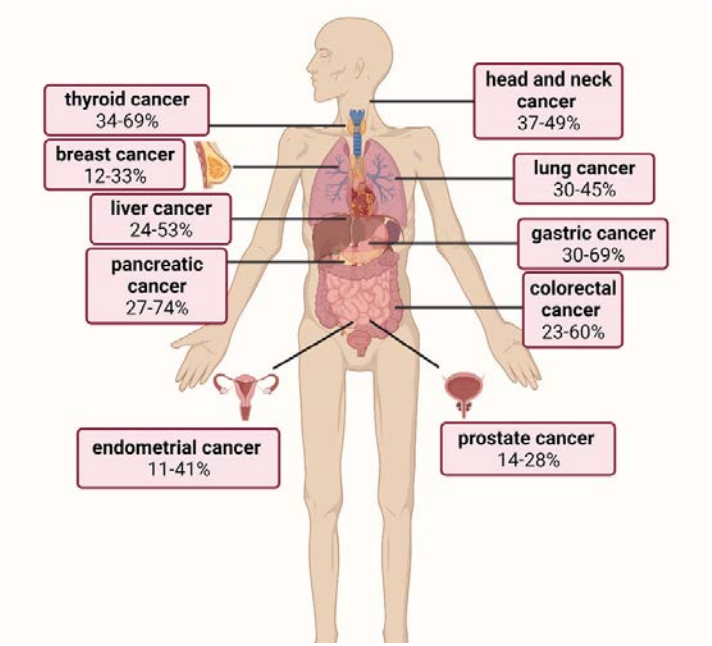
Associate Professor

MGH Cancer Center

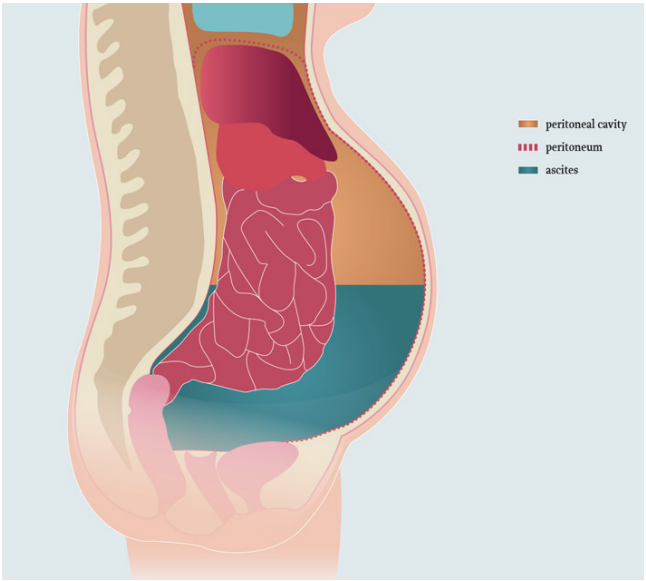
Gastroesophageal Cancers Are Bad: A Reminder

Among Phase III 1L trials only ~38-55% get subsequent therapy

High Symptom Burden, declining ECOG

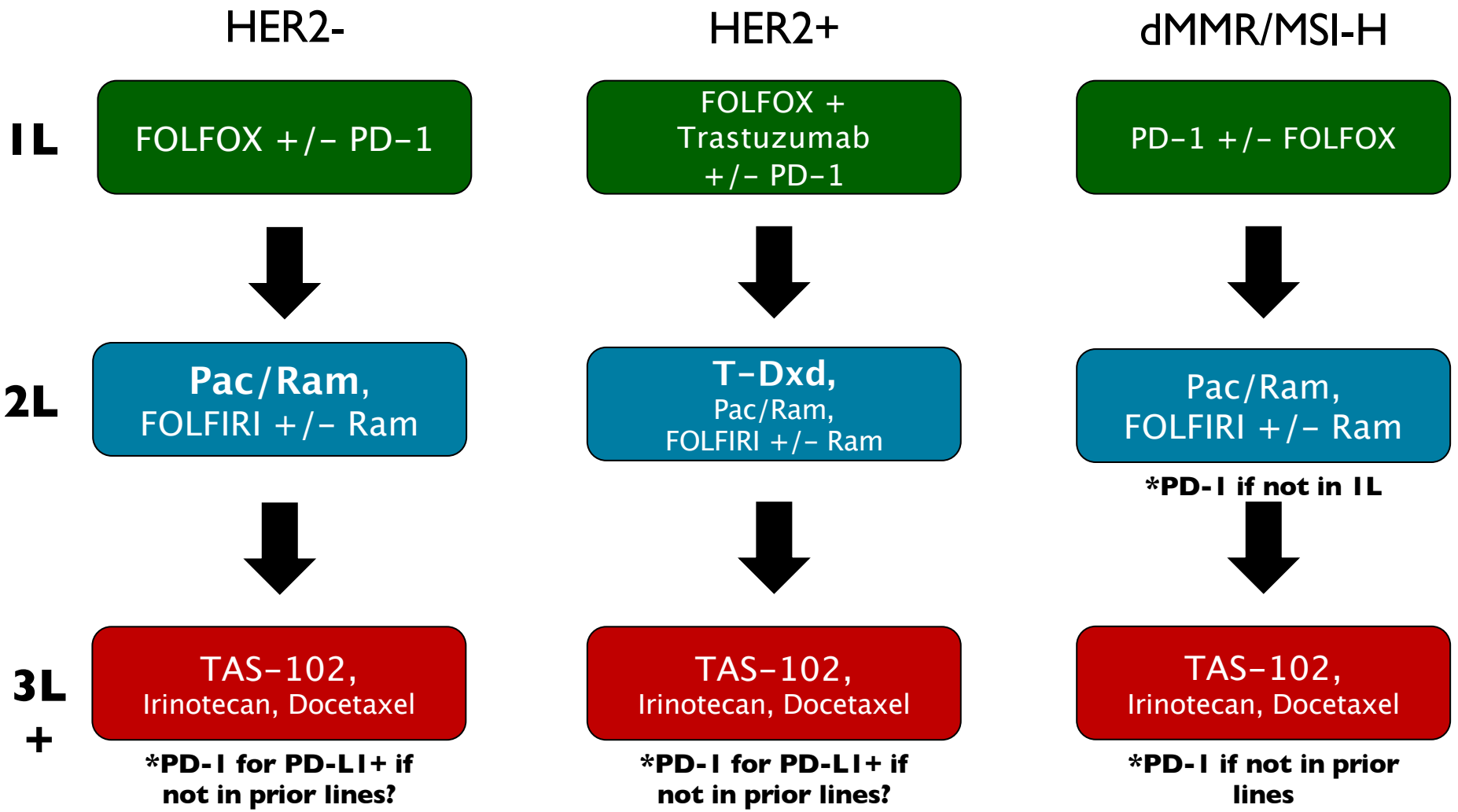


Cancer Cachexia (30-69%), malnutrition

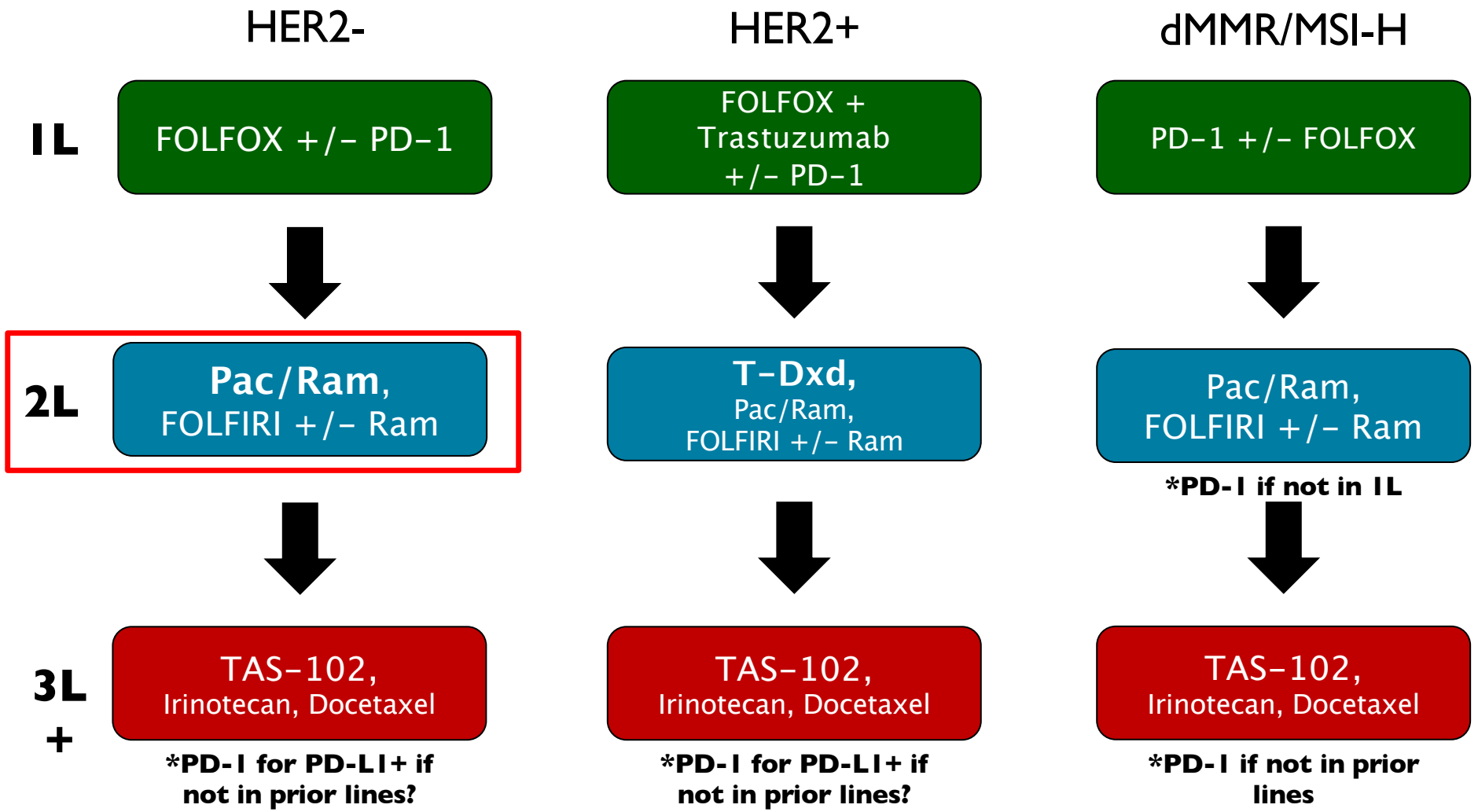


Increasing rates of peritoneal disease and ascites

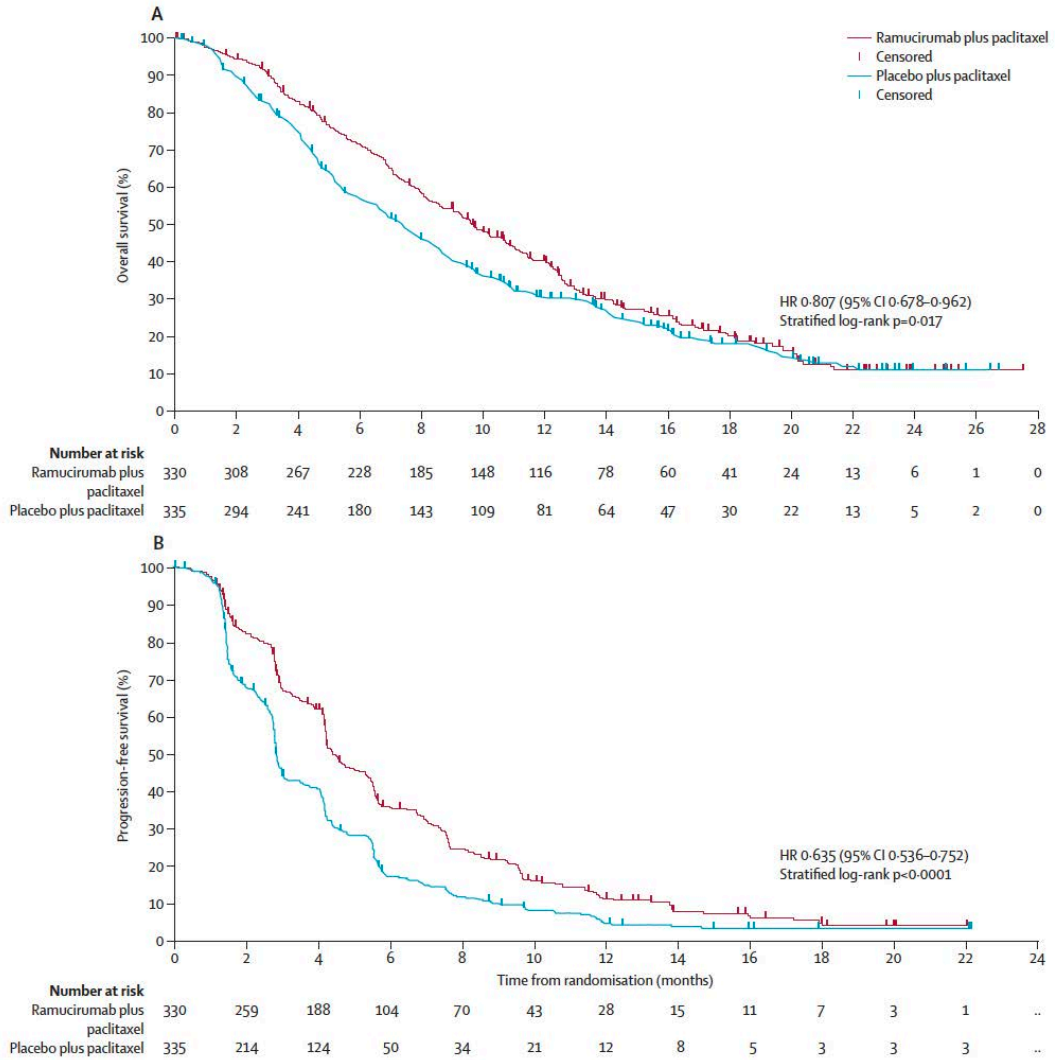
Current Paradigms – The Toolbox



Current Paradigms – The Toolbox



Level Setting: Paclitaxel and Ramucirumab is a Global 2L Standard



- **Phase III 2L RCT of Pac/Ram vs Pac (RAINBOW) in Gastric/GEJ**
- **Primary endpoint = OS**
- **Median OS 9.6m vs 7.4m (HR 0.80)**
- **Median PFS 4.4m vs 2.9m (HR 0.63)**
- **Overall response rate 27% vs 16%**

There is no phase III trial to beat this

Lancet Oncol 2014;15:1224-35

Taxane-Free Ramucirumab-based Therapy is a 2L and Later Option

Second-Line or Subsequent Therapy
- Dependent on prior therapy and PS

Preferred Regimens
- Ramucirumab and paclitaxel (category 1)[35]
- Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[36]
- Docetaxel (category 1)[28,29]
- Paclitaxel (category 1)[24,25,37]
- Irinotecan (category 1)[37-40]
- Fluorouracil[b,i] and irinotecan[38,41,42]
- Trifluridine and tipiracil for third-line or subsequent therapy (category 1)[43]

Other Recommended Regimens
- Ramucirumab (category 1)[44]
- Irinotecan and cisplatin[14,45]
- Fluorouracil and irinotecan + ramucirumab[b,i,46]
- Irinotecan and ramucirumab[47]
- Docetaxel and irinotecan (category 2B)[48]

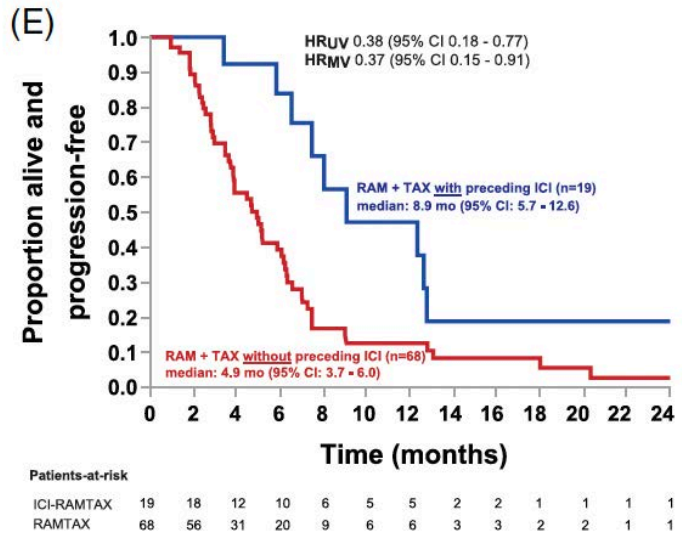
Useful in Certain Circumstances
- Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[49,50]
- Pembrolizumab[g,h] for MSI-H or dMMR tumors[51-53]
- Pembrolizumab[g,h] for TMB high (≥10 mutations/megabase) tumors[54]
- Dostarlimab-gxly[g,h,k] for MSI-H or dMMR tumors[55]

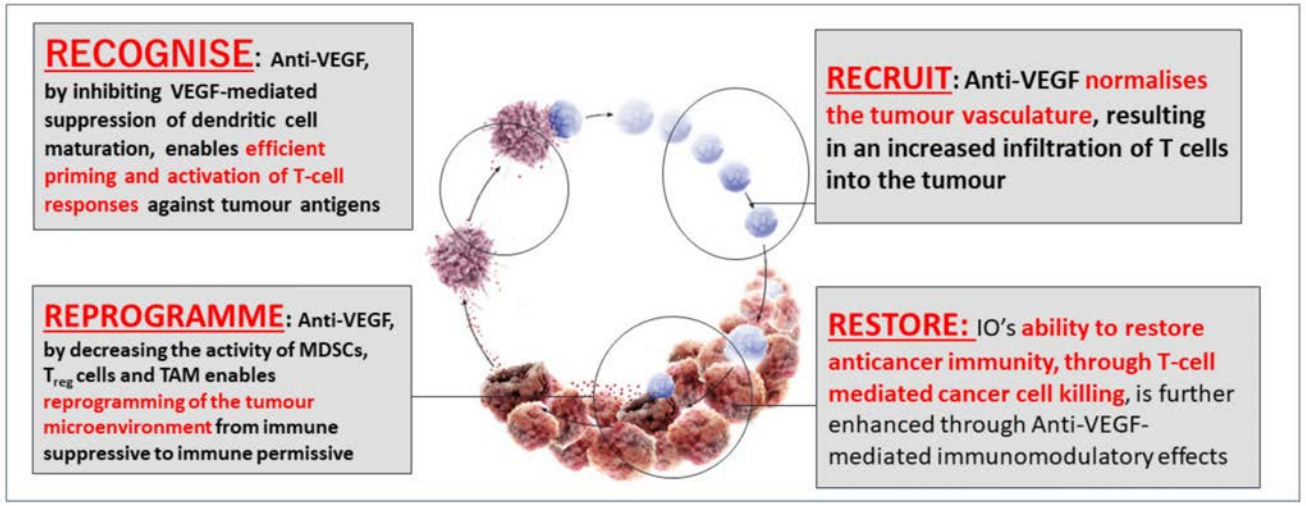
2L FOLFIRI-Ram

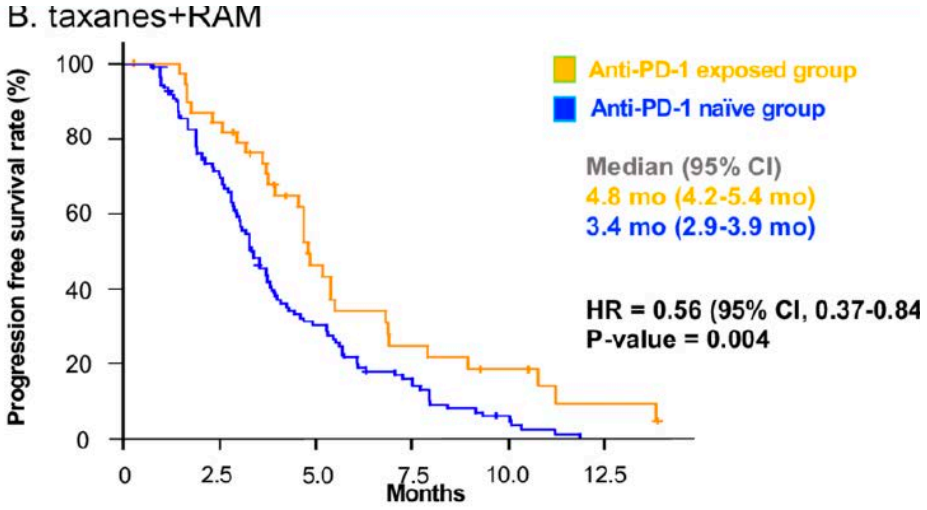
- RAMIRIS phase II/III ongoing
- ORR ~22% (25% in prior taxane)
- mPFS 4.6 months in docetaxel pre-treated
- Consideration in significant neuropathy

J Clin Oncol 38: 2020 (suppl; abstr 4514)

Ramucirumab after PD-1: More than an Observation?





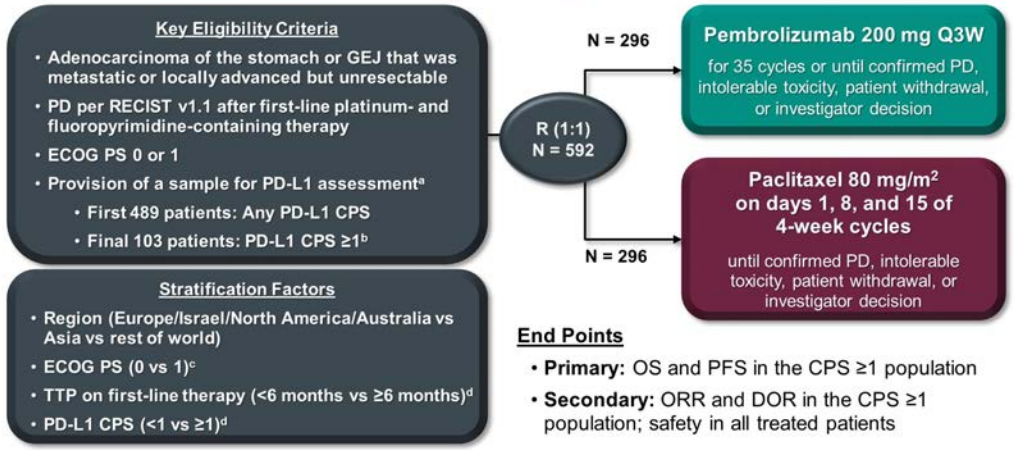


Pac-Ram post-PD-1

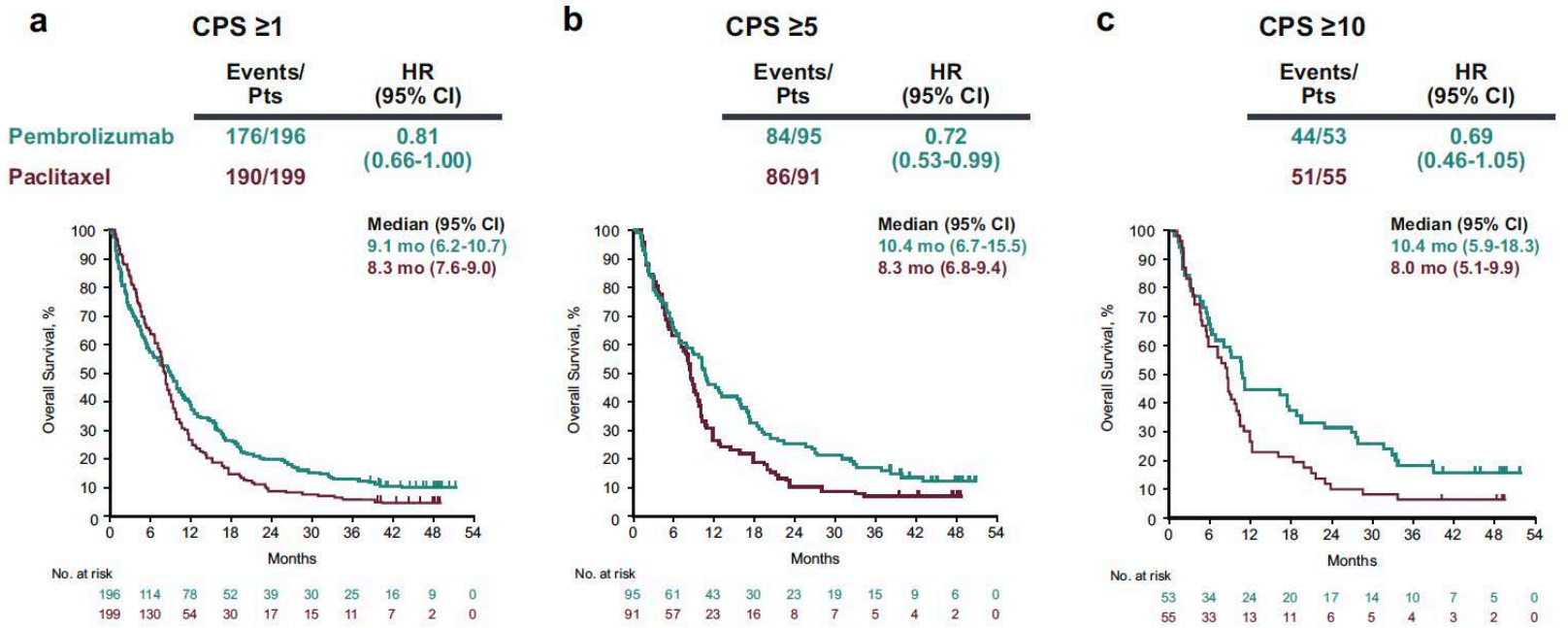
- Retrospective work in USA and Asia
- ORR 58-60% in patients with PD-1 prior to Pac + Ram
- mPFS 5-12m
- Ongoing prospective trials

Cancers 2020;12:1089, Int J Cancer. 2021;149(2):378-386, ESMO Open. 2020 Jul;4:e000775

PD-1 is Not a 2L Therapy in GEJ/GC Adenocarcinomas

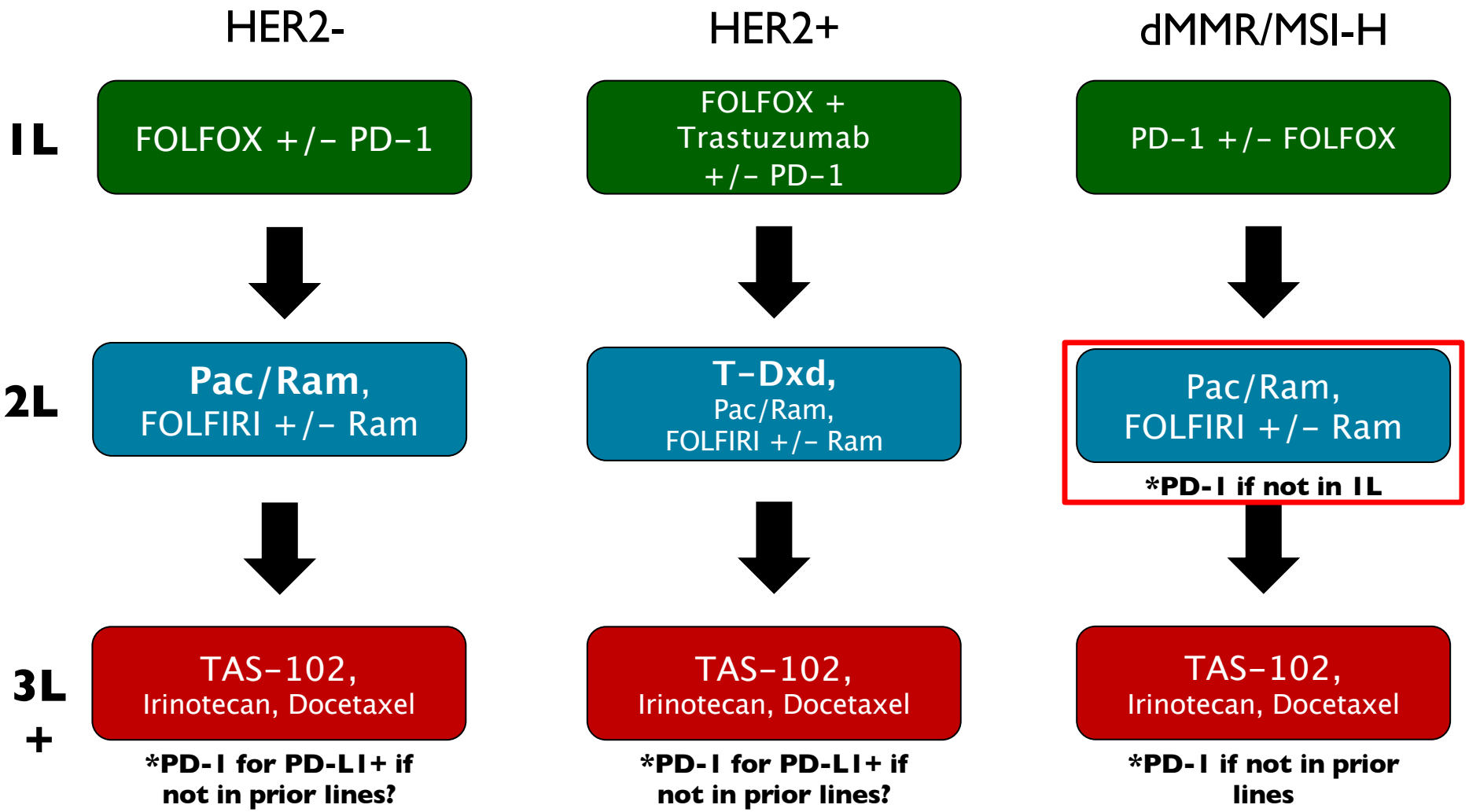


- Keynote-061 was a negative phase III trial.
- Post-hoc higher CPS cutoff c/w earlier line date

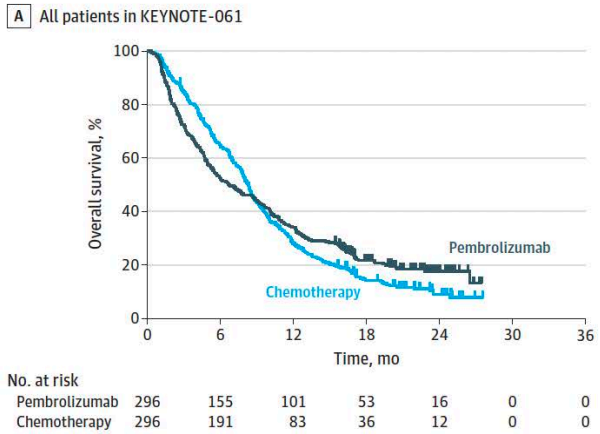


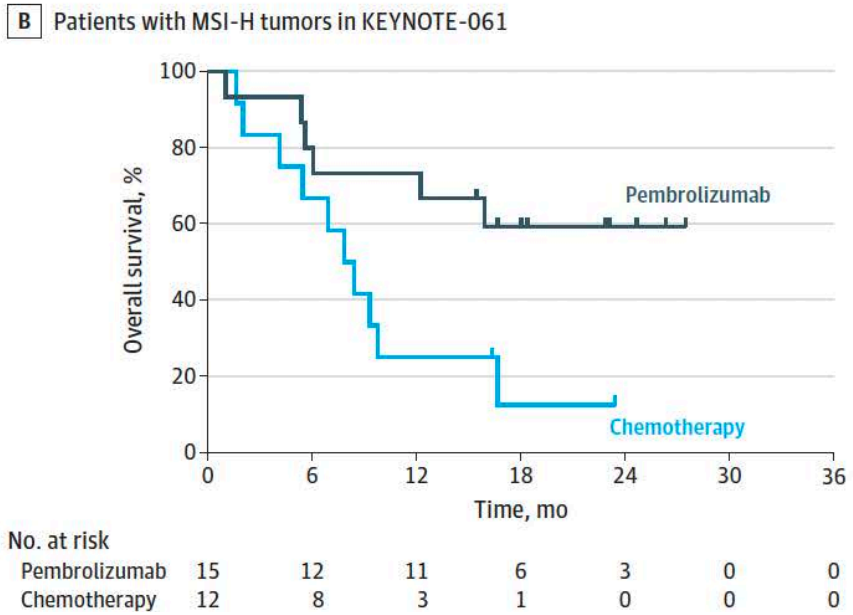
Lancet. 2018;392:123–33., Gastric Cancer. 2022;25:197-206.

Current Paradigms – The Toolbox



A Caveat to 2L PD-1: MSI-High/dMMR Tumors

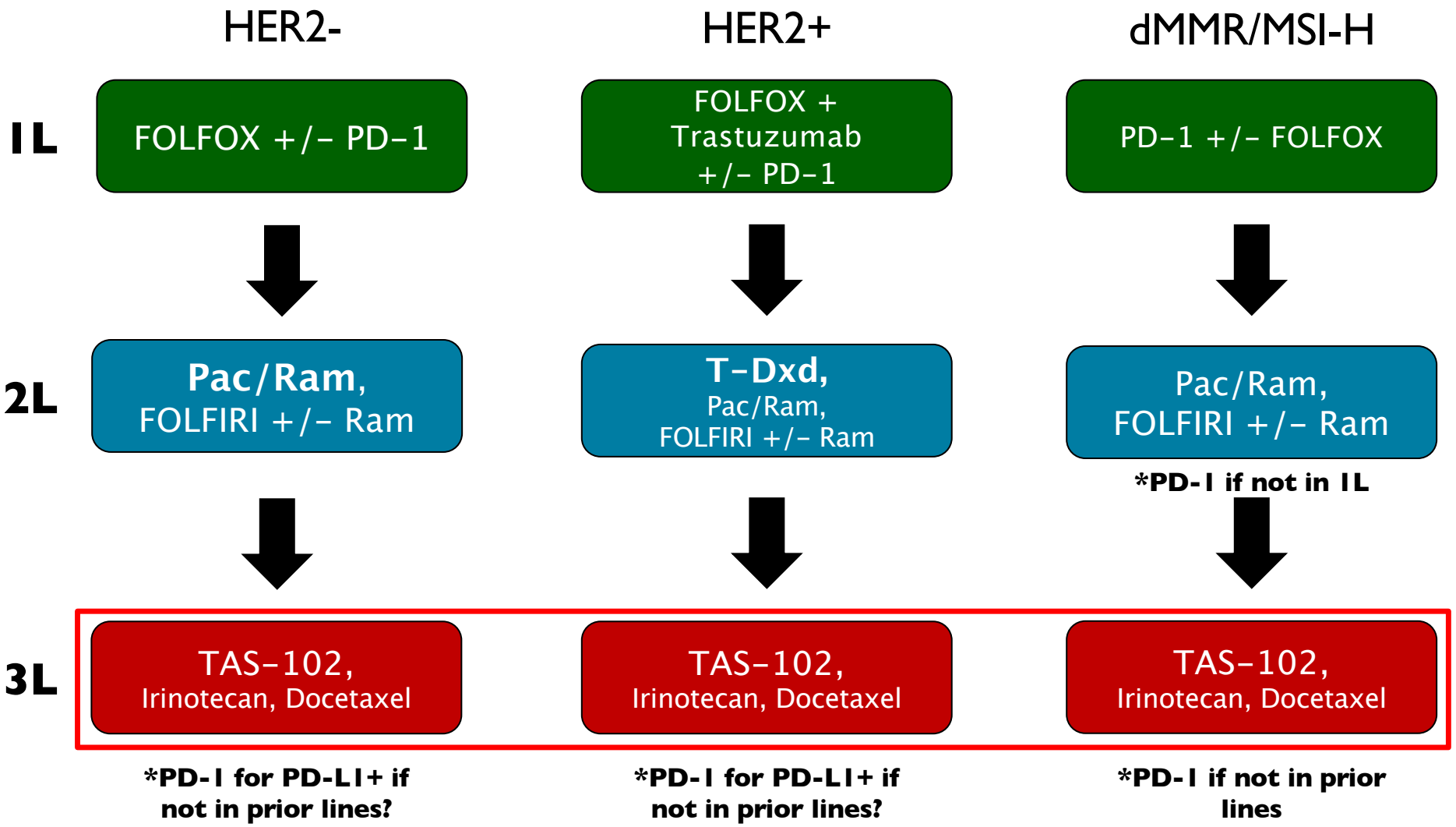




- 3-5% of stage IV patients are MSI-H/dMMR.
- Vast majority of MSI-H/dMMR are also PD-L1 high (>50% are CPS 10 or higher)
- ORR ~47-60% for PD-1 monotherapy
- mPFS 17.8m, mOS not reached
- A 2L and beyond option in MSI-H/dMMR without prior PD-1

JAMA Oncol. 2021;7:895-902

Current Paradigms – The Toolbox

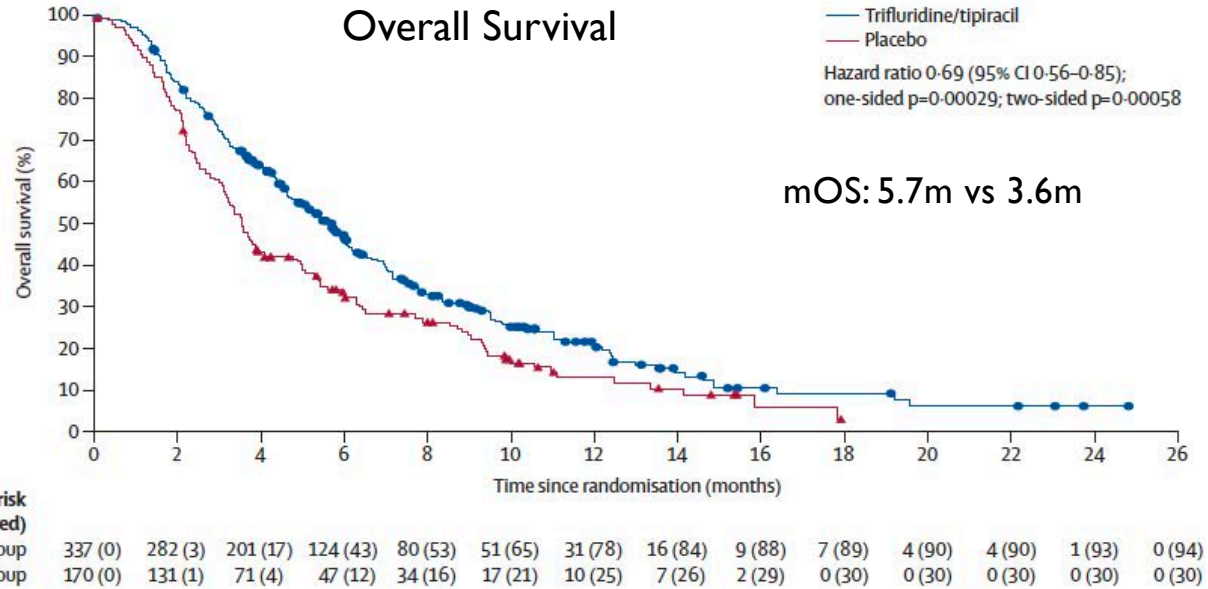


3L and Beyond: TAS-102 and the Phase III TAGS Trial

~70% GC, 30% GEJ

	Trifluridine/tipiracil group (n=337)	Placebo group (n=170)
(Continued from previous column)		
HER2 status		
Positive	67 (20%)	27 (16%)
Negative	207 (61%)	106 (62%)
Not assessed or unknown	63 (19%)	37 (22%)
Number of metastatic sites		
1–2	155 (46%)	72 (42%)
≥3	182 (54%)	98 (58%)
Peritoneal metastases	87 (26%)	53 (31%)
Previous gastrectomy	147 (44%)	74 (44%)
Number of previous chemotherapy regimens		
2	126 (37%)	64 (38%)
3	134 (40%)	60 (35%)
≥4	77 (23%)	46 (27%)
Previous systemic anticancer agents		
Platinum	337 (100%)	170 (100%)
Fluoropyrimidine	336 (>99%*)	170 (100%)
Taxane†	311 (92%)	148 (87%)
Irinotecan†	183 (54%)	98 (58%)
Ramucirumab	114 (34%)	55 (32%)
Anti-HER2 therapy	60 (18%)	24 (14%)
Immunotherapy (anti-PD-1 or anti-PD-L1)	25 (7%)	7 (4%)
Other	77 (23%)	41 (24%)

Overall Survival



mOS: 5.7m vs 3.6m

mPFS: 2.0 vs 1.8 months
ORR: 4% vs 2%
DCR: 44% vs 14%

FDA 2/2019: Trifluridine/tipiracil for 3L and beyond in gastric or gastroesophageal junction (GEJ) adenocarcinoma previously treated a fluoropyrimidine, a platinum, either a taxane or irinotecan

Lancet Oncol. 2018;19:1437-48.

Later Line TAS-102 and Ramucirumab-Containing Regimens

- Ramucirumab with Paclitaxel remains a global standard for 2L therapy.
- Ramucirumab has demonstrated clinical activity in combination with FOLFIRI
- Trifluridine/tiperacil plus bevacizumab demonstrated activity in colorectal cancers

Phase 2 TAS-102 + Ram

Overall Population

	2L, no prior Ram	≥3L, prior Ram
	Cohort A (n=33)	Cohort B (n=31)
Complete response	0	0
Partial response	3 (9%)	5 (16%)
Stable disease	25 (76%)	19 (61%)
Progressive disease	3 (9%)	7 (23%)
Not evaluable	2 (6%)	0
Overall response rate*	3 (9%, 2–24)	5 (16%, 6–34)
Disease control rate†	28 (85%, 68–95)	24 (77%, 59–90)

Data are n (%) or n (%, 95% CI). *Complete response plus partial response. †Complete response plus partial response plus stable disease.

Table 2: Investigator-assessed best overall response (full analysis set)

Prior IO exposed

	2L, no prior Ram		≥3L, prior Ram	
	Cohort A (n=33)		Cohort B (n=31)	
	Previous use (n=7)	No previous use (n=26)	Previous use (n=15)	No previous use (n=16)
Overall response rate*	2 (29%, 4–71)	1 (4%, 0–20)	5 (33%, 12–62)	0 (0%, 0–21)
Disease control rate†	7 (100%, 59–100)	21 (81%, 61–93)	10 (67%, 38–88)	14 (88%, 62–98)
Progression-free survival, months	6·1 (4·1–NA)	5·3 (3·6–7·9)	5·4 (1·4–NA)	5·0 (2·1–6·1)
Event	3 (43%)	15 (58%)	9 (60%)	12 (75%)
Censored	4 (57%)	11 (42%)	6 (40%)	4 (25%)

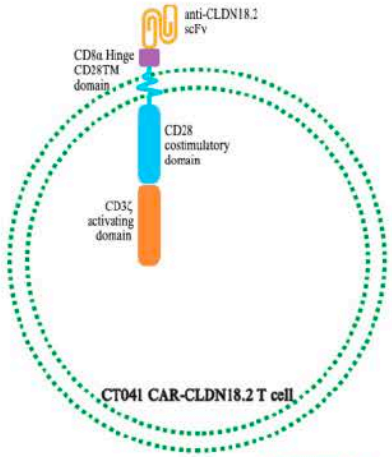
Data are n (%, 95% CI), n (95% CI), or n (%). NA=not available. *Complete response plus partial response. †Complete response plus partial response plus stable disease.

Table 3: Antitumour endpoints according to previous use of an immune checkpoint inhibitor (full analysis set)

Lancet Gastroenterol Hepatol. 2021 Mar;6(3):209-217.

Emerging Targets in 2L and Beyond: CAR-T

CT041: CLDN18.2 CAR-T



Characteristics of all patients	Total (N = 37)
Median age (range), year	53.0 (25–74)
Disease Type, n(%)	
GC/GEJ	28 (75.7)
PC	5 (13.5)
Other	4 (10.8)
ECOG, n (%)	
0	2 (5.4)
1	35 (94.6)
Bridging therapy, n (%)	28(75.7)
Expression intensity and rate of CLDN 18.2 in tumor tissue, n (%)	
Low expression	5 (13.5)
Medium expression	13 (35.1)
High expression	19 (51.4)
Numbers of metastatic organs	
Median	3.0
Min, Max	1.0, 7.0
Median no. of previous lines, n (%)	
1	6 (16.2)
2	19 (51.4)
≥ 3	12 (32.4)

Characteristics of GC	Total (N = 28)
Histological classification(WHO classification), n (%)	
Mucinous adenocarcinoma	1 (3.6)
Signet ring cell carcinoma	12 (42.9)
Other	14 (50.0)
Expression intensity and rate of CLDN 18.2 in tumor tissue, n (%)	
Low expression	2 (7.1)
Medium expression	7 (25.0)
High expression	19 (67.9)
Numbers of metastatic organs	
Median	2.5
Min, Max	1.0, 7.0
Peritoneal metastases, n (%)	19 (67.9)
Liver metastases, n (%)	10 (35.7)
Lauren classification, n (%)	
Intestinal type	10 (35.7)
Diffuse type	9 (32.1)
Mixed type	7 (25.0)
Previous systemic therapies, n (%)	
Fluorouracil	28 (100)
Platinum	27 (96.4)
Taxanes	21 (75.0)
Paclitaxel	18 (64.3)
Albumin paclitaxel	7 (25.0)
Anti-PD-(L)1 antibody	12 (42.9)
Polykinase inhibitor	10 (35.7)

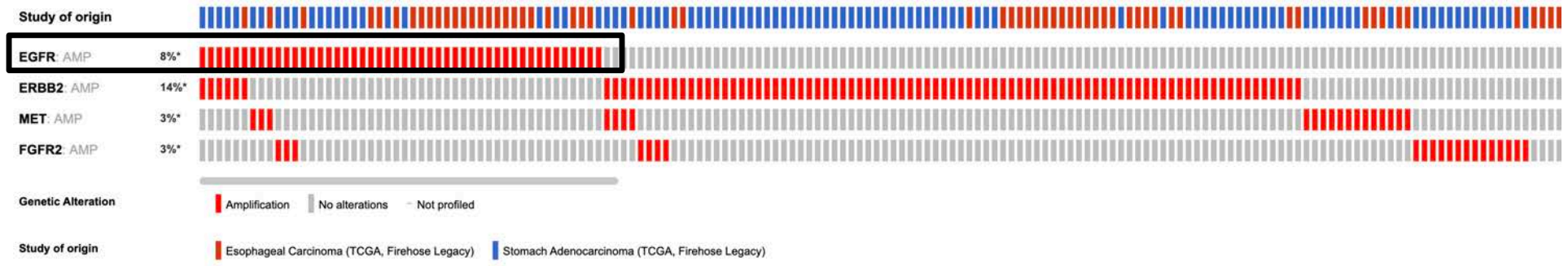
GC/GEJ ≥2 prior lines

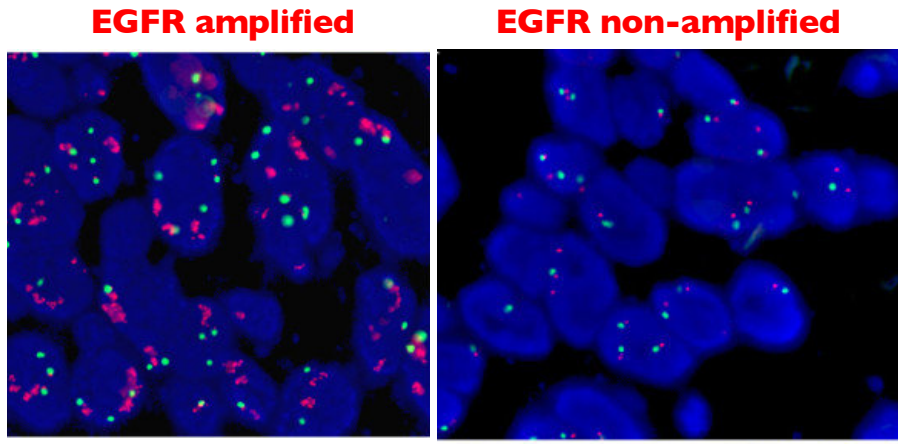
ORR [95% CI]	**11 (61.1%)** [35.75, 82.70]
DCR [95% CI]	**15 (83.3%)** [58.58, 96.42]
mPFS*	**5.6m** [2.6, 9.2]
mOS*	**9.5m** [5.2, NE]
mDOR	**6.4m** [2.7, NE]

*PFS, OS and follow up duration were calculated from CAR-T infusion date.

- Encouraging activity in previously treated patients
- Toxicity consistent with prior CAR-T
- Ongoing US trial (NCT04404595)

Revisiting A Neglected Target: EGFR

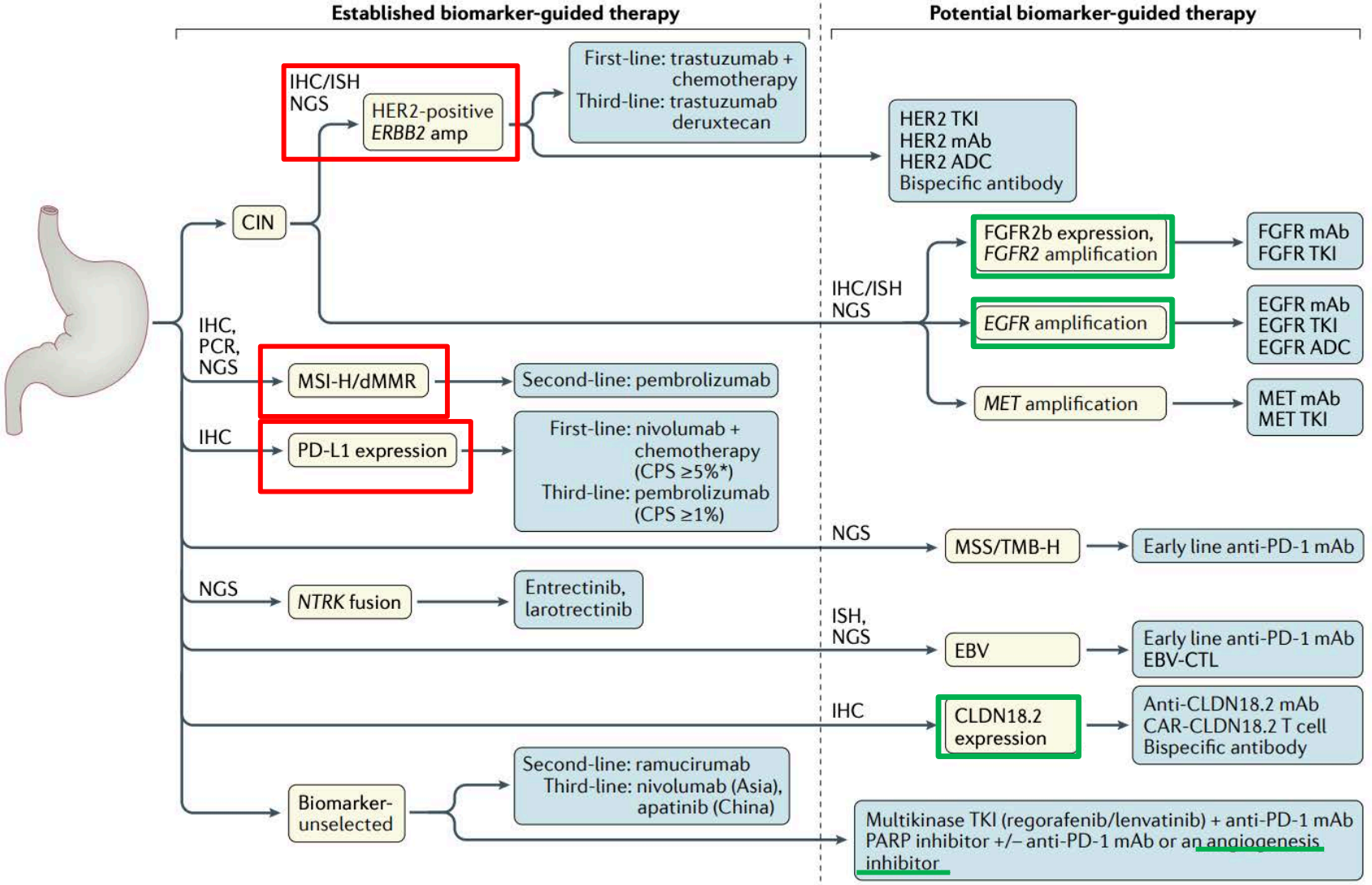




5-8% of gastroesophageal adenocarcinomas

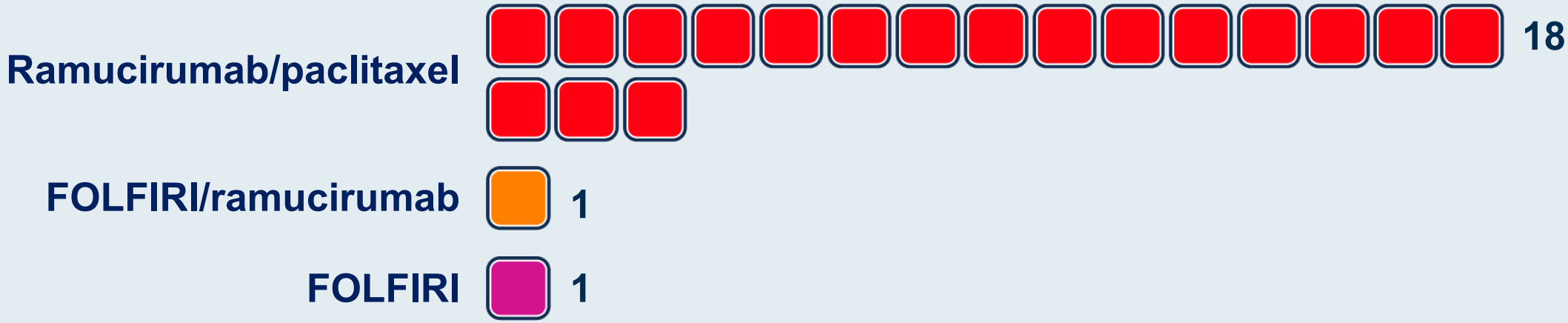
- Prior negative trials impacted by patient selection and perhaps drug choice
- Several series suggesting $EGFR_{amp}$ benefit from EGFR-directed therapies
- Perhaps most effective where $EGFR_{amp}$ does not co-exist with other RTK amplifications
- Trials ongoing, Amivantamab for example (NCT05117931)

Looking Forward: Right Tool for the Job



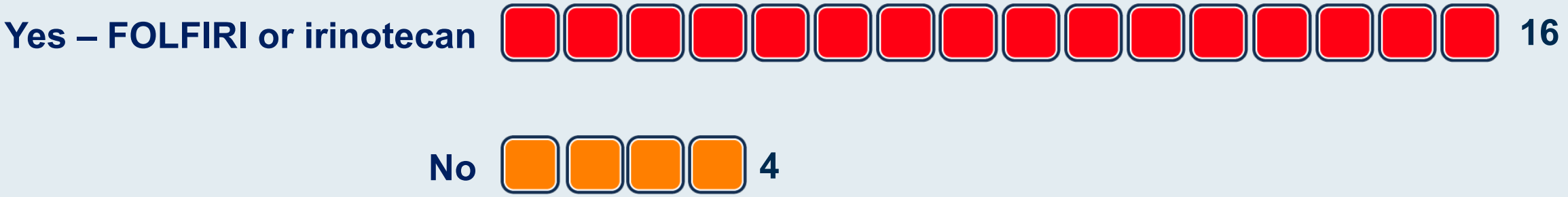
Nat Rev Clin Oncol. 2021 Aug;18(8):473-487.

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



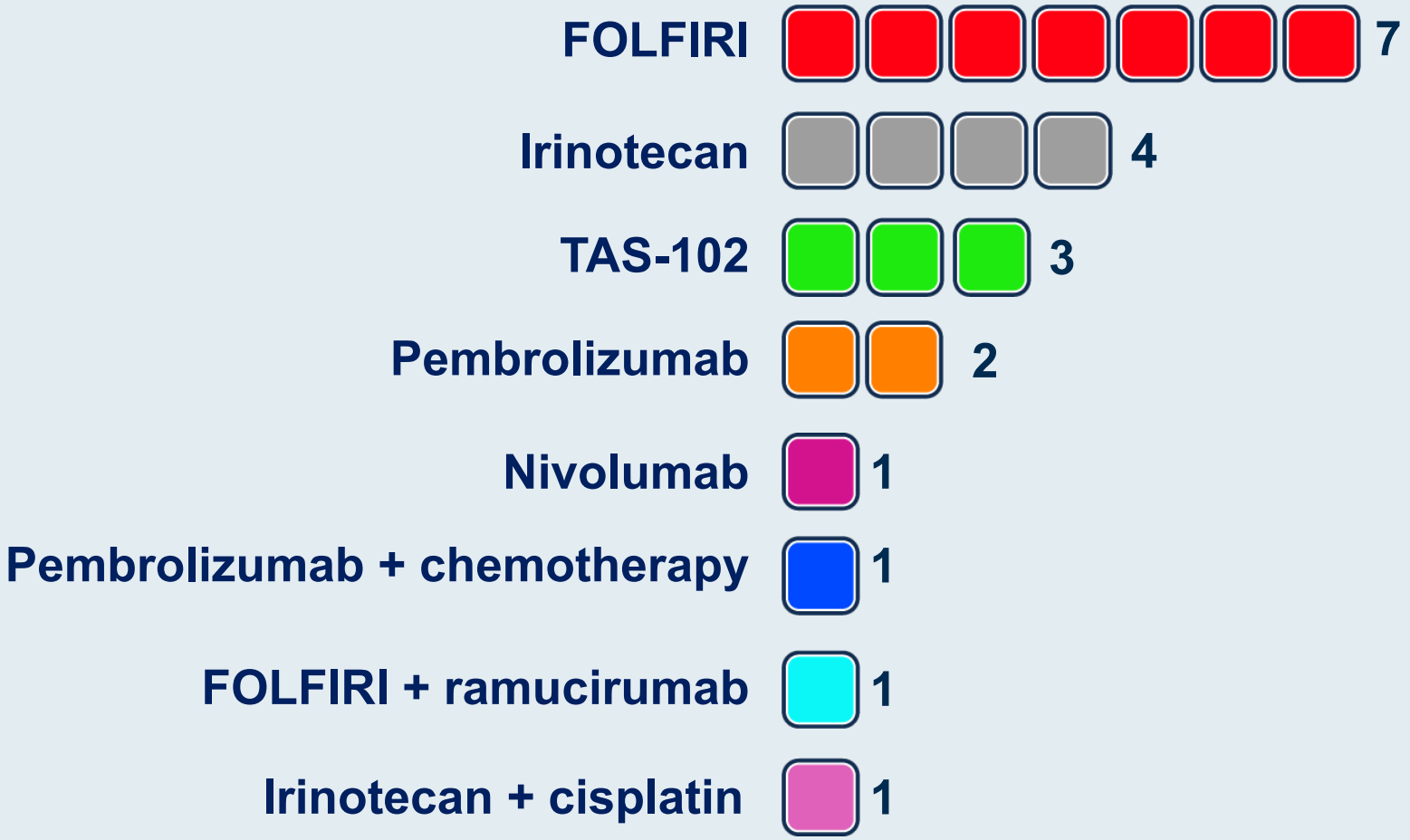
Survey of US-based clinical investigators

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



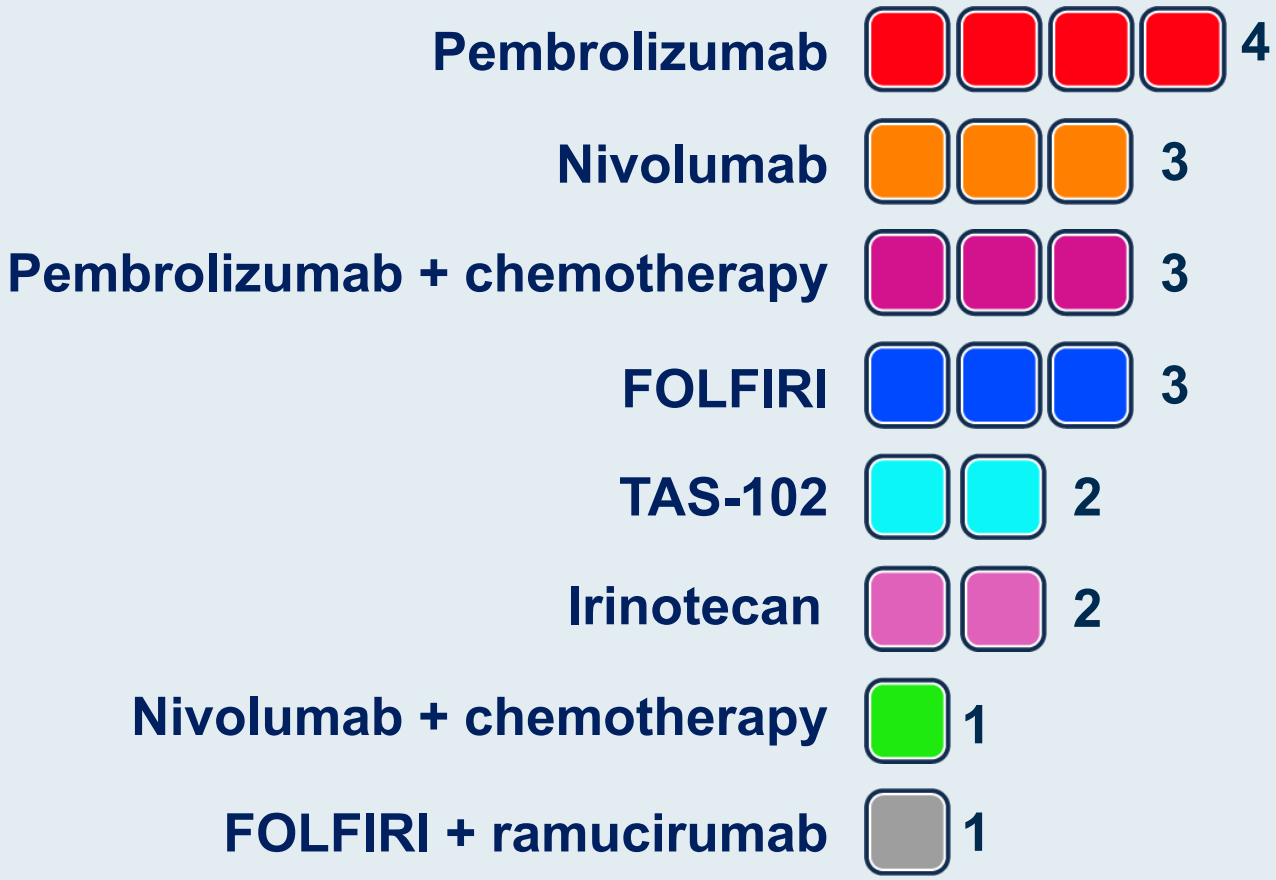
Survey of US-based clinical investigators

What is your usual third-line treatment for a younger patient (PS 0) with metastatic HER2-negative, MSS adenocarcinoma of the GEJ (PD-L1 CPS <1) who has experienced disease progression on FOLFOX and paclitaxel/ramucirumab?



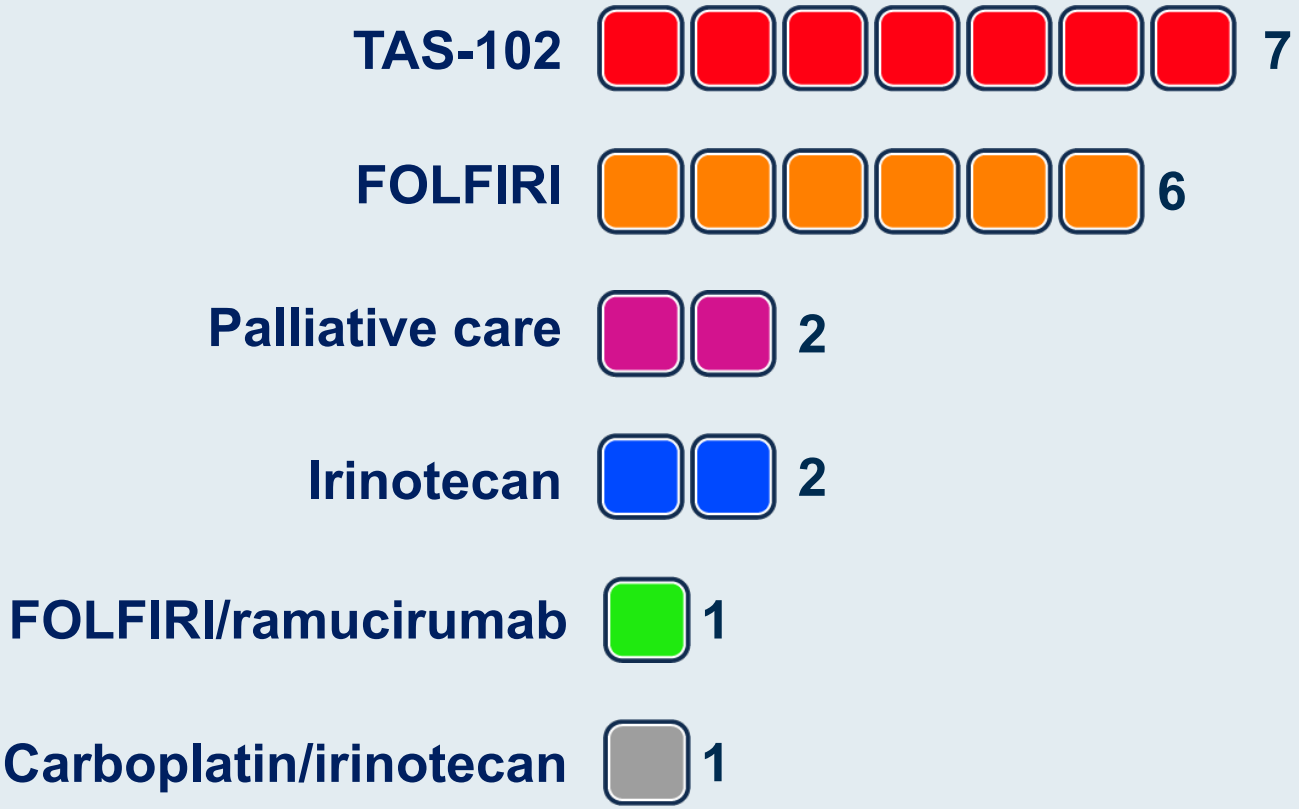
Survey of US-based clinical investigators

What is your usual third-line treatment for a younger patient (PS 0) with metastatic HER2-negative, MSS adenocarcinoma of the GEJ (PD-L1 CPS ≥1) who has experienced disease progression on FOLFOX and paclitaxel/ramucirumab?



Survey of US-based clinical investigators

What is your usual next treatment for a younger patient (PS 0) with metastatic HER2-negative, MSS adenocarcinoma of the GEJ who has experienced disease progression on FOLFOX, paclitaxel/ramucirumab and an anti-PD-1/PD-L1 antibody?



Survey of US-based clinical investigators

MODULE 4: Key Findings Informing the Treatment of Localized and Advanced Esophageal Cancer — Dr Yoon

RTP
RESEARCH
TO PRACTICE

MAYO CLINIC

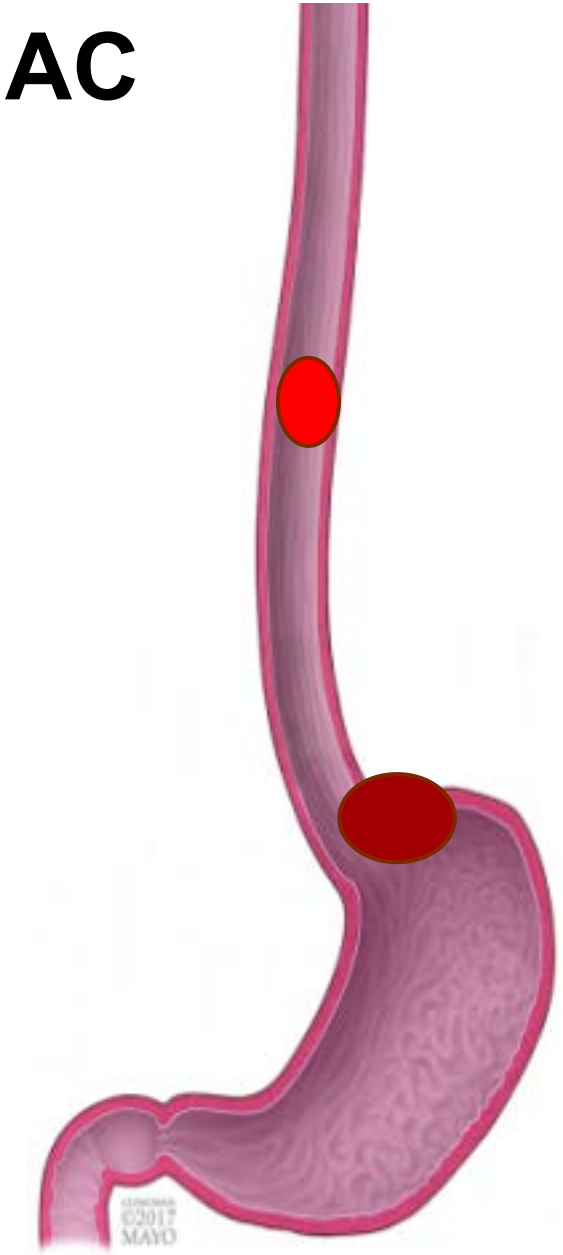
Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Patients with Gastroesophageal Cancers

KEY FINDINGS INFORMING THE TREATMENT OF LOCALIZED AND ADVANCED ESOPHAGEAL CANCER

Harry H Yoon, MD MHS
Co-Chair, Gastroesophageal Cancer Disease Group
Mayo Clinic
Rochester MN

An Independent Satellite Symposium (ISS) Held as a Premium Ancillary Educational Event During the 2022 Gastrointestinal Cancers Symposium
Thursday, January 20th, 2022
6:15 PM – 7:45 PM PST

SCC vs AC



Esophageal squamous cell carcinoma (SCC)

- East/Central Asia, southeastern Africa
- Smoking & ETOH
- Proximal anatomic location
- ~ 50% of patients have tumor cell expression of PD-L1 (ie, TPS 1+) [1-7]

Adenocarcinoma (AC)

- Western
- Reflux & obesity
- Distal esophagus
- ~ 15% of patients have TPS 1+ [1, 8-12]

1. Salem et al. 2018. *The Oncologist.* 2. ORIENT-15. 3. ESCORT _1st. 4. ESCORT_2L. 5. CM648. 6. ATTRACTION-03. 7. CM648. 8. ATTRACTION-02. 9. CM649. 10. JAV-300. 11. ATTRACTION-04. 12. JAV100_maintenance

2021 TREATMENT LANDSCAPE FOR FIT PATIENT WITH ESOPHAGEAL SQUAMOUS CELL CARCINOMA (SCC)

Advanced, 1st-line

PD-L1-CPS ≥ 10

Pembro + platin/FP (KN590)
(NCCN 1-2A and FDA)

PD-L1-TPS ≥ 1

Consider Nivo + FOLFOX (CM648)
(Await FDA & NCCN)

PD-L1-CPS 0-9 & TPS < 1

FOLFOX
(NCCN 2A)

Pembro + platin/FP
(NCCN 2B and FDA)

After chemoradiation & surgery

SCC or AC if non-pCR

Adjuvant nivolumab x 1 yr (CM-577)
(NCCN 1-2A and FDA)

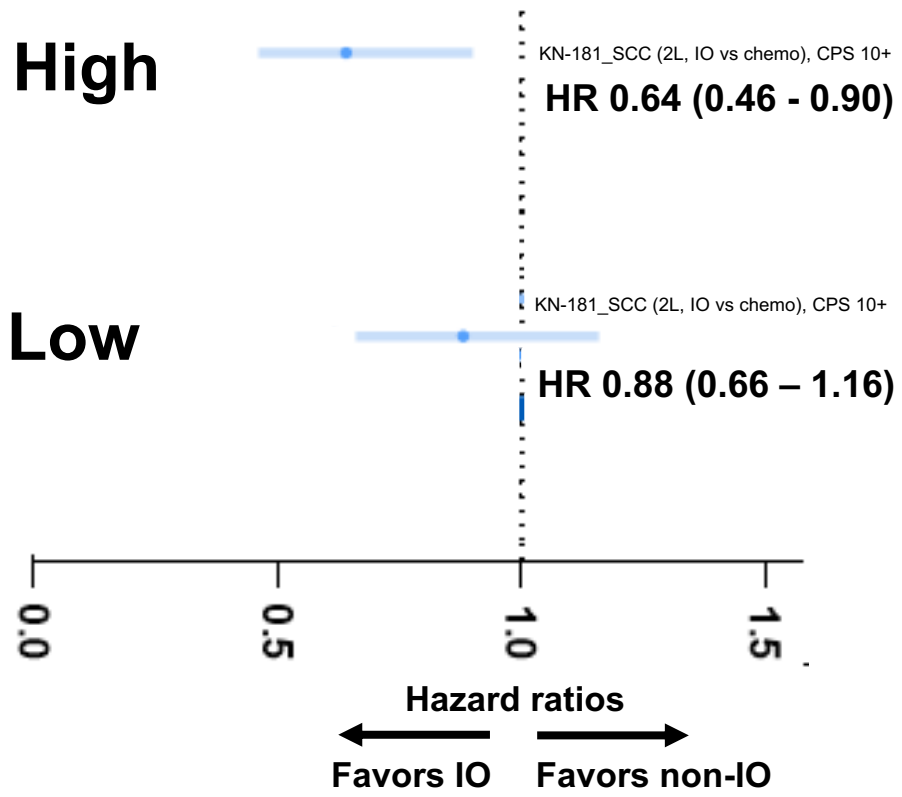
CPS, Combined positive score; **FP**, fluoropyrimidine; **nivo**, nivolumab; **pCR,** pathologic complete response; **pembro,** pembrolizumab; **TPS,** Tumor proportion score

Before 2021, available phase 3 data in SCC suggested PD-L1 expression level correlated with anti-PD-1 efficacy

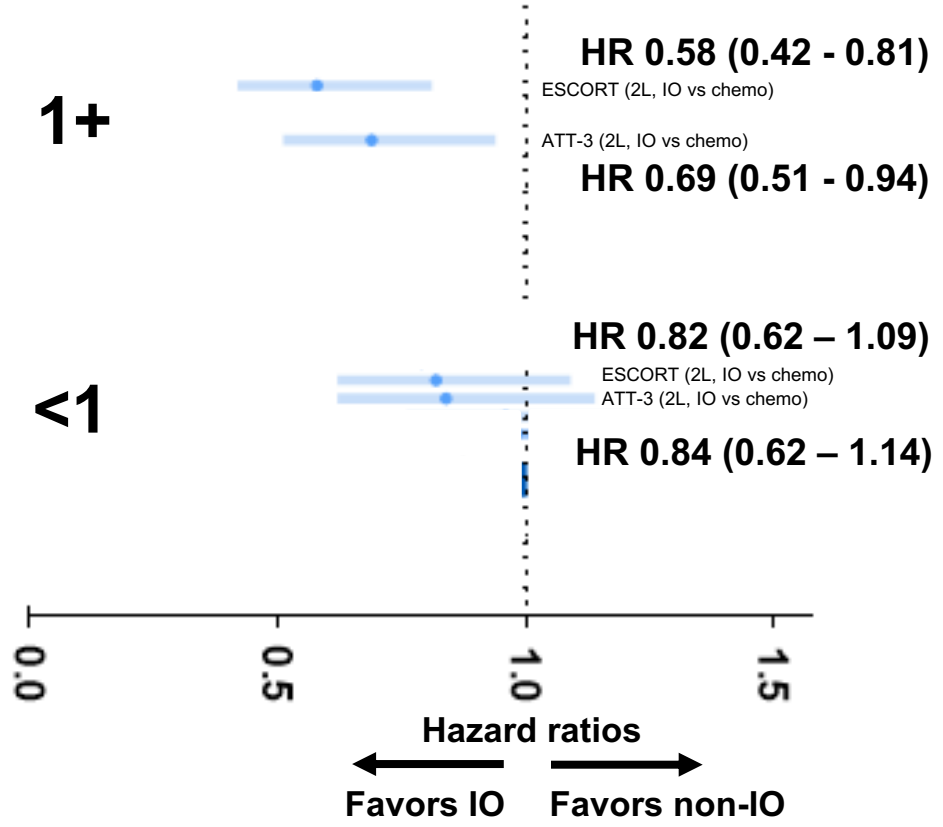
Hazard ratios for overall survival with 95% CI's shown

N = 1,268 (3 trials)

Overall survival by CPS



Overall survival by TPS



Yoon HH et al. ASCO GI 2022

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CPS, Combined positive score; **FP**, fluoropyrimidine; **nivo**, nivolumab; **pCR,** pathologic complete response; **pembro,** pembrolizumab; **TPS,** Tumor proportion score

KN-590

Patients [1]

- **ESCC (73%)** and AC Siewert 1 (26%)
- 1st-line
- Asia + Non-Asia
- **Any CPS, including CPS <10**

R

- Cisplatin/FP + **pembrolizumab**
- Cisplatin/FP + **placebo**

Primary endpoints

- PFS in ESCC
- OS in ESCC CPS ≥ 10
- OS in ESCC

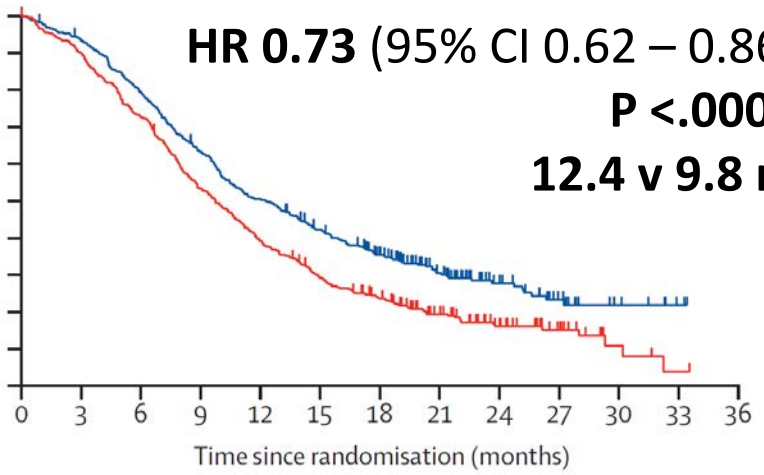
1. Not reported regarding HER2 status

Sun J-M et al et al. Lancet 2021

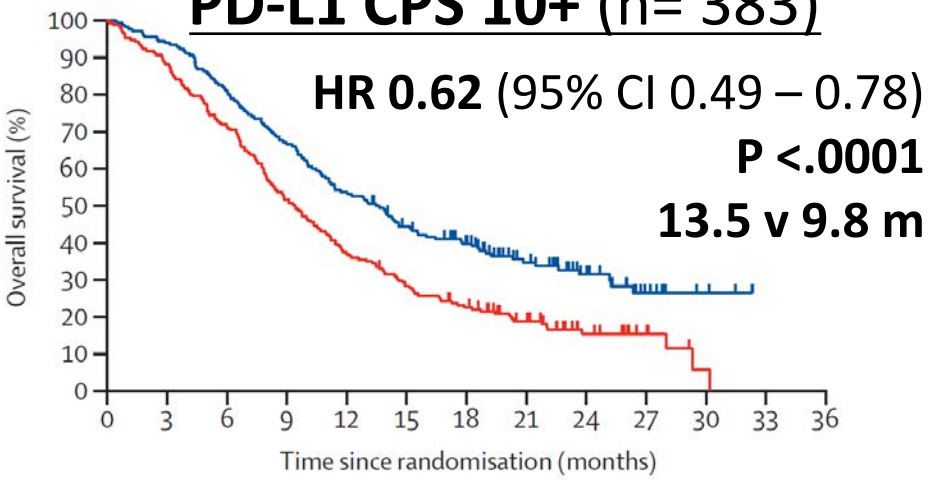
Pembro improves OS in PD-L1 CPS 10+, but unclear evidence of benefit in PD-L1 CPS <10 (KN-590)

OS

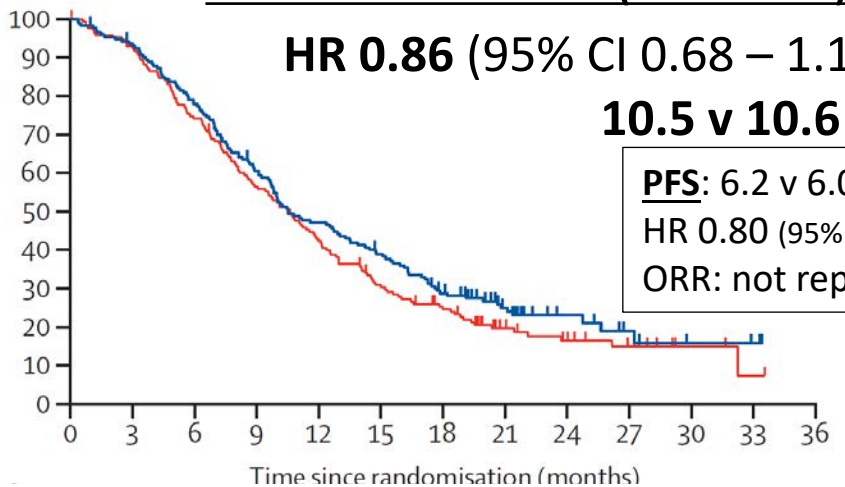
Overall (SCC and AC; N = 749)



PD-L1 CPS 10+ (n= 383)



PD-L1 CPS <10 (n = 347)



PFS: 6.2 v 6.0 m
HR 0.80 (95% CI 0.64 – 1.01)
ORR: not reported

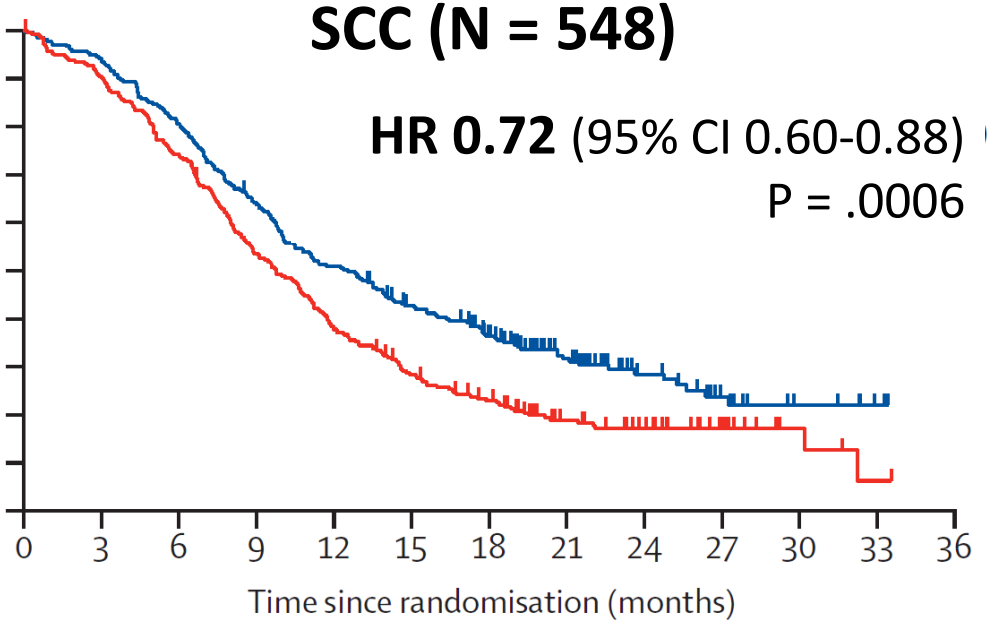
$P_{interaction}$ for CPS 10+ vs CPS <10 not reported

MAYO CLINIC

Sun J-M et al et al. Lancet 2021

Within SCC, results similar: Improved OS in CPS 10+, but unclear evidence of benefit in CPS <10 (KN-590 cont.)

OS



SCC PD-L1 CPS 10+

n = 286

13.9 m vs 8.8 m

HR 0.57 (0.43-0.75)

SCC PD-L1 CPS <10 [a]

n = 247

10.5 m vs 11.1 m

HR 0.99 (0.74-1.32)

[a] Survival curves not reported.

PFS: 6.2 v 6.0 m
HR 0.83 (95% CI 0.64 – 1.10)
ORR: not reported

G3-4 toxicities were similar between arms

Sun J-M et al et al. Lancet 2021

2021 TREATMENT LANDSCAPE FOR FIT PATIENT WITH ESOPHAGEAL SQUAMOUS CELL CARCINOMA (SCC)

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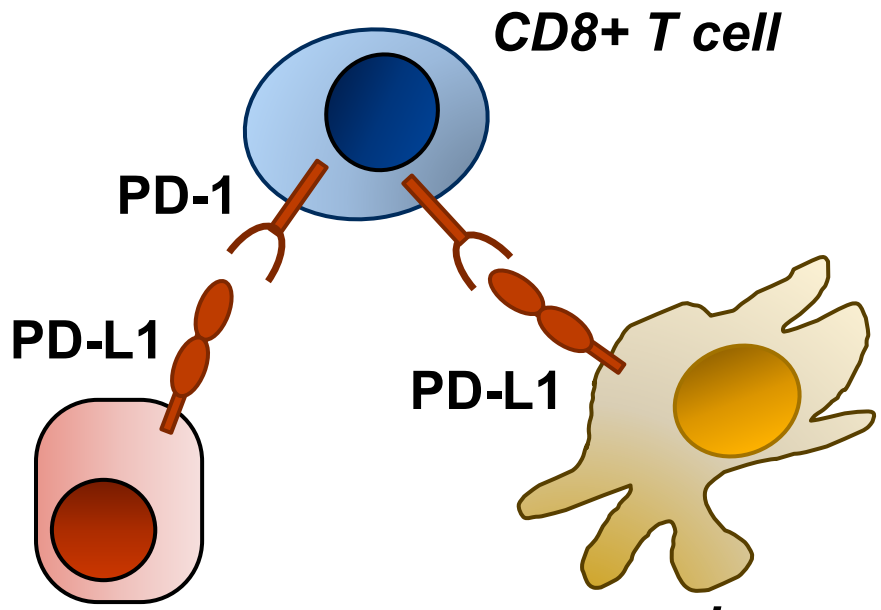
TPS *vs* CPS

$$\text{CPS} = \frac{\text{PD-L1-expressing tumor cells or } \mathbf{\text{immune cells}}}{\text{tumor cells}}$$

$$\text{TPS} = \frac{\text{PD-L1-expressing tumor cells}}{\text{tumor cells}}$$



tumor cell

PD-L1 expression by tumor cells is induced by IFN-gamma secreted by CD8 T cells

macrophage

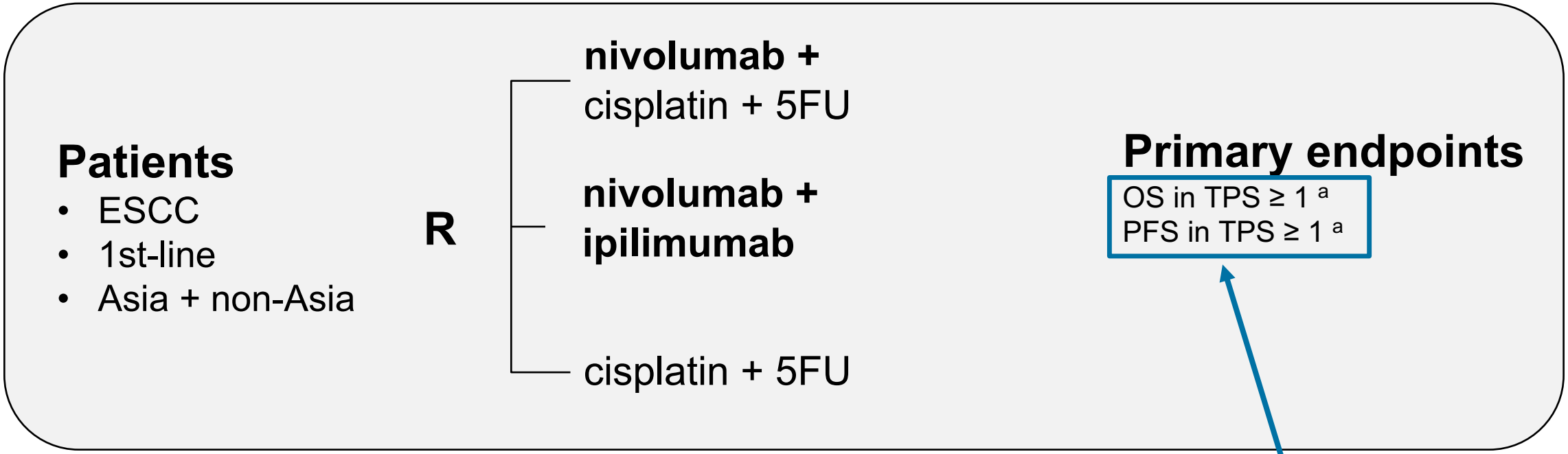
PD-L1 expression by macrophages can be IFN-independent, induced by IL-10 or IL32-gamma

- More common to have PD-L1 expressing immune cells than tumor cells
- In AC, CPS seems more predictive than TPS [1-9]
- In SCC, data on TPS or CPS were limited prior to summer 2021

1. ORIENT-15. 2. KN-061. 3. KN-062. 4. KN590_AC. 5. JAV100. 6. CM649. 7. ATT-2. 8. JAV300. 9. ATT-4.

Noguchi T et al 2017 *Cancer Immunol Res*; Taube JM et al 2015 *Clin Cancer Res*

CM-648



TPS, tumor proportion score

[a] For nivo + chemo vs chemo, *and* nivo + ipi vs chemo

Stratification: PD-L1 TPS ≥ 1 vs <1, region, ECOG PS, number of organs with metastasis

Chau I et al. ASCO annual meeting 2021

CM-648: Benefit appears to be in only TPS ≥ 1

Nivo + chemo *vs* chemo		TPS ≥ 1 n=315	TPS < 1 n=329	TPS ≥ 0 N=645
OS	Median, *months*	15.4 vs 9.1 **Δ 6.3**	12.0 vs 12.2 **Δ -0.2**	13.2 vs 10.7 **Δ 2.5**
	HR 95% CI	**0.54** 0.37-0.80	**0.98** NR	**0.74** (0.58–96)
PFS	Median, *months*	6.9 vs 4.4 **Δ 2.5**	NR	5.8 vs 5.6 **Δ 0.2**
	HR 95% CI	**0.65** 0.46-0.92	NR	**0.81** 0.64-1.04

Probably contains CPS ≥ 1 patients

NR, not reported
RR and duration of response not reported, to date, within TPS <1

Chau I et al. ASCO annual meeting 2021

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Nivo + chemo *vs* chemo		TPS ≥ 1 n=315	TPS < 1 n=329	TPS ≥ 0 N=645
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	HR 95% CI	**0.65** 0.46-0.92	NR	**0.81** 0.64-1.04

Nivo + Ipi *vs* chemo		TPS ≥ 1 n=314	TPS < 1 n=330	TPS ≥ 0 N=644
OS	Median, *months*	13.7 vs 9.1 **Δ 4.6**	12.0 vs 12.2 **Δ -0.2**	12.8 vs 10.7 **Δ 2.1**
	HR 95% CI	**0.64** 0.46-0.90	**0.96** NR	**0.78** 0.62–98
PFS	Median, *months*	4.0 vs 4.4 **Δ -0.4**	NR	2.9 vs 5.6 **Δ -2.7**
	HR 95% CI	**1.02** 0.73-1.43	NR	**1.26** 1.04-1.52

NR, not reported
RR and duration of response not reported, to date, within TPS <1

G3-4 toxicity seems higher with nivo + chemo

	Nivo + Chemo	Nivo + Ipi	Chemo
Any G3-4	**47%** *1.3x*		**36%** *ref*
Serious G3-4	**18%** *1.4x*		**13%** *ref*
G3-4 AE leading to treatment discontinuation	**9%** *1.8x*		**5%** *ref*
Treatment duration	**5.7 m** *1.7x*		**3.4 m** *ref*

Chau I et al. ASCO annual meeting 2021

G3-4 toxicity seems even higher with nivo + ipi

	Nivo + Chemo	Nivo + Ipi	Chemo
Any G3-4	**47%** *1.3x*	**32%** *0.9x*	**36%** *ref*
Serious G3-4	**18%** *1.4x*	**23%** *1.8x*	**13%** *ref*
G3-4 AE leading to treatment discontinuation	**9%** *1.8x*	**13%** *2.6x*	**5%** *ref*
Treatment duration	**5.7 m** *1.7x*	**2.8 m** *0.8x*	**3.4 m** *ref*

Chau I et al. ASCO annual meeting 2021

CM-648 CONCLUSIONS

- Nivo + chemo and nivo + ipi show promise as options for 1L treatment of ESCC
  - Benefit appears limited to TPS 1+
  - Pending review by FDA and NCCN

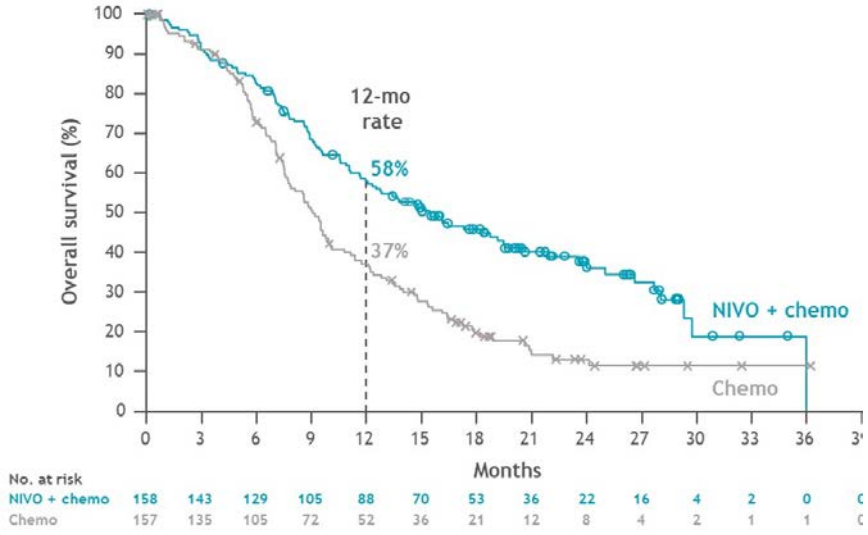
- Which nivo regimen to choose?

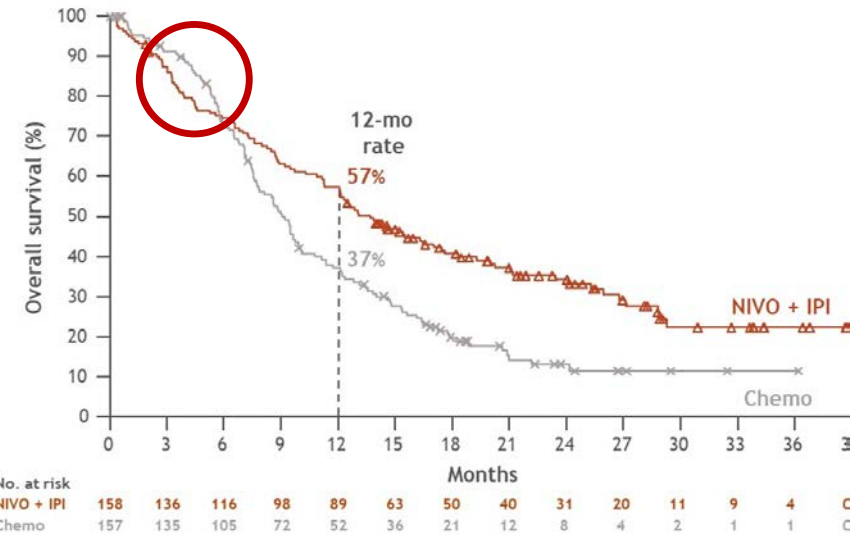
EARLY DEATH WITH NIVO + IPI

Nivo + chemo *vs* chemo

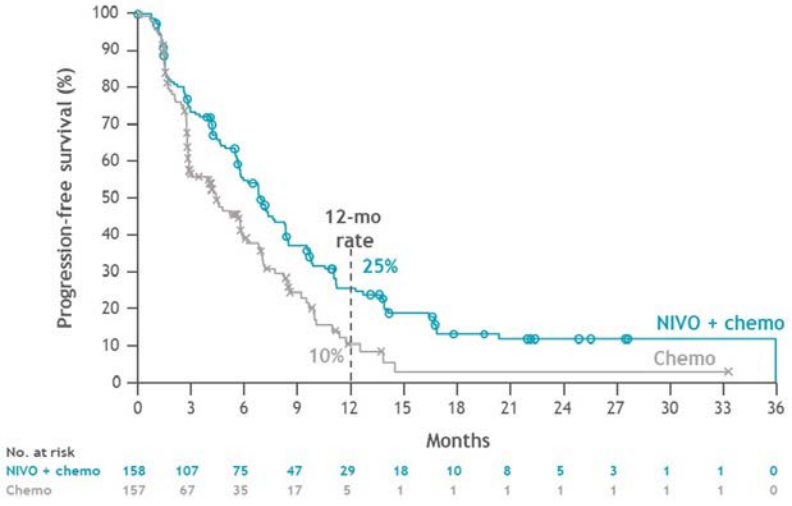
Nivo + Ipi *vs* chemo

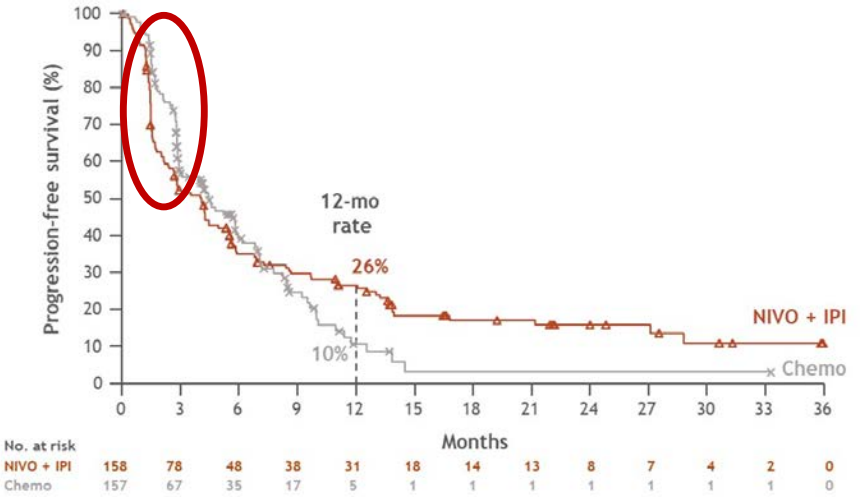
OS





PFS





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Advanced, 1st-line

PD-L1-CPS ≥ 10

Pembro + platin/FP (KN590)

(NCCN 1-2A and FDA)

PD-L1-TPS ≥ 1

Consider Nivo + FOLFOX (CM648)

(Await FDA & NCCN)

Would be helpful to see data according to CPS.

PD-L1-CPS 0-9 & TPS < 1

FOLFOX

(NCCN 2A)

Pembro + platin/FP (KN590)

(NCCN 2B and FDA)

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FOLFOX
(NCCN 2A)

Pembro + platin/FP (KN590)
(NCCN 2B and FDA)

Phase 3 data of investigational anti-PD-1 Abs

- camrelizumab (ESCORT_1st)
- sintilimab (ORIENT-15)
- toripalimab (JUPITER-06)

Asia-only
1st-line
IO + chemo vs chemo

- tislelizumab (RATIONALE-302)

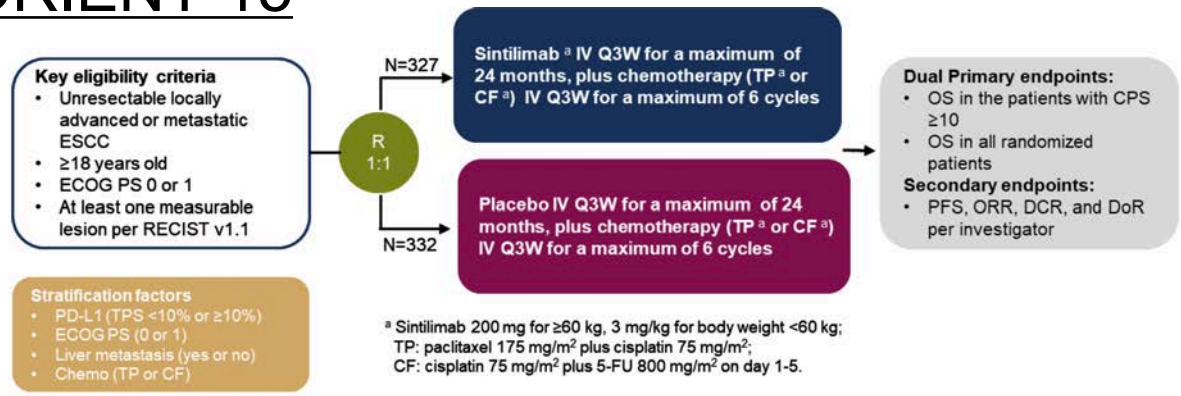
Asia + non-Asia
2nd-line
IO vs chemo

All 4 trials reported positive OS results in overall SCC population

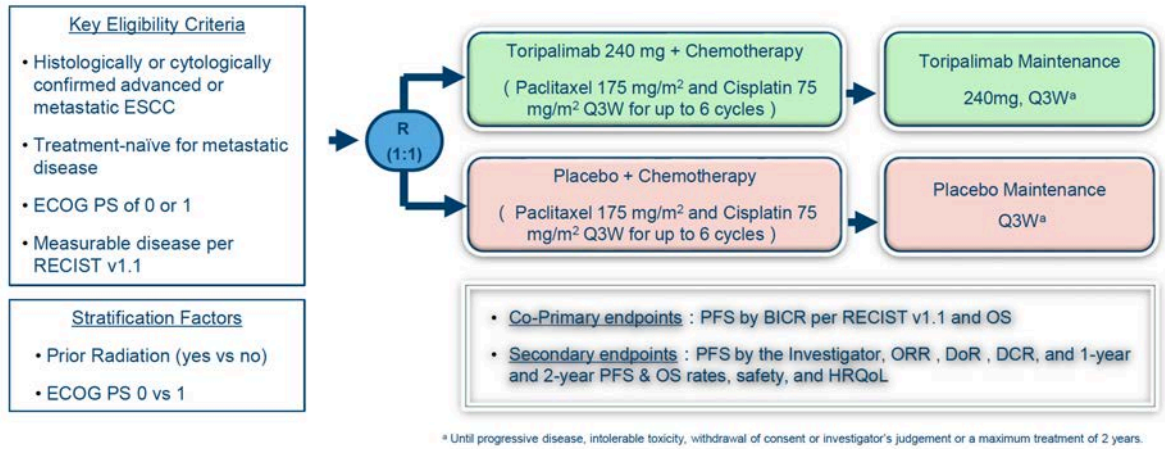
CPS, Combined positive score; **FP**, fluoropyrimidine; **nivo**, nivolumab; **pCR,** pathologic complete response; **pembro,** pembrolizumab; **TPS,** Tumor proportion score

PHASE III TRIALS OF INVESTIGATIONAL PD-1 ANTIBODIES

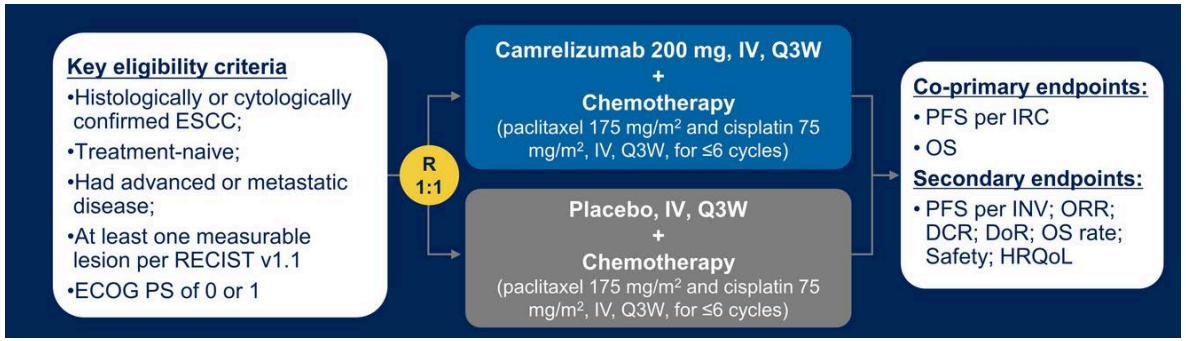
ORIENT-15



JUPITER-06



ESCORT-1st

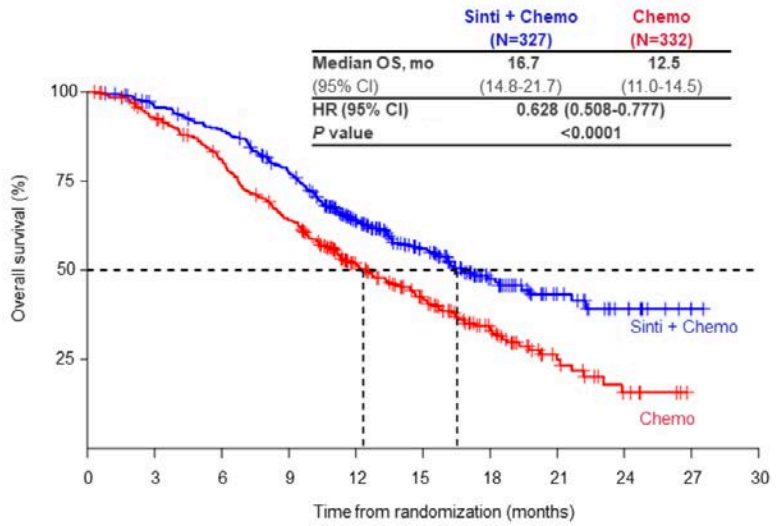


RATIONALE-302

Shen L et al. ESMO 2021; Xu R-H et al. ESMO 2021; Xu R-H et al. ASCO 2021; Ajani J et al. ESMO GI 2021

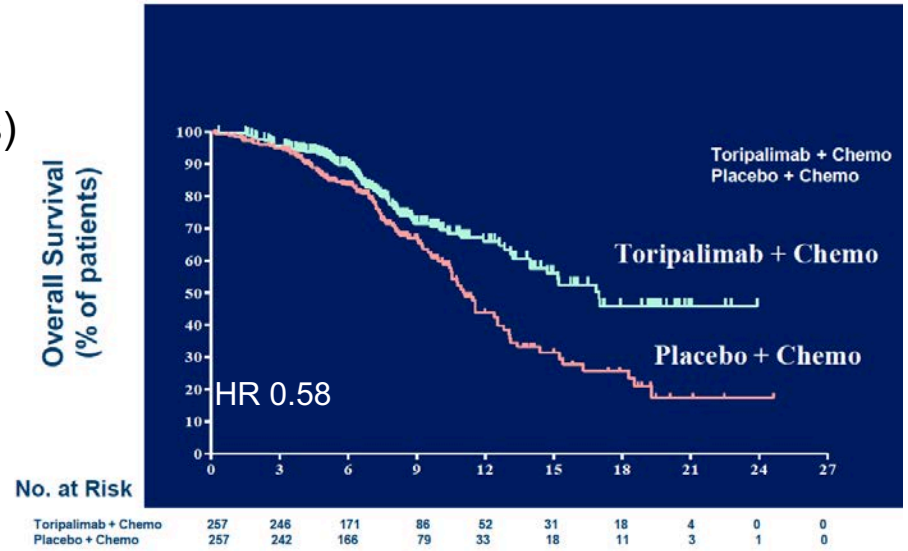
PHASE III TRIALS OF INVESTIGATIONAL PD-1 ANTIBODIES: OS IN OVERALL POPULATION

ORIENT-15

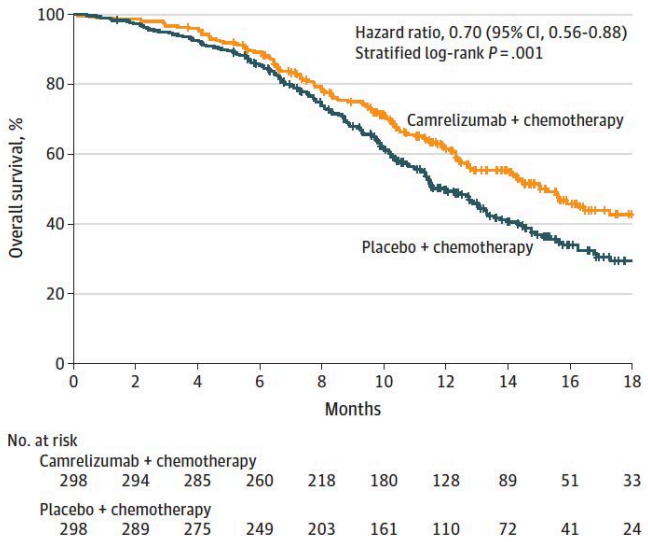


JUPITER-06

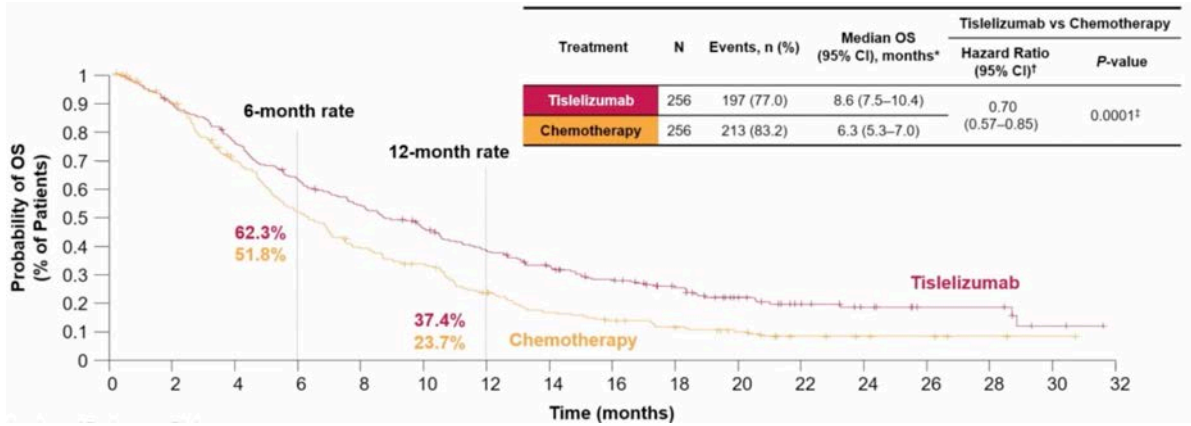
(interim analysis)



ESCORT-1st



RATIONALE-302



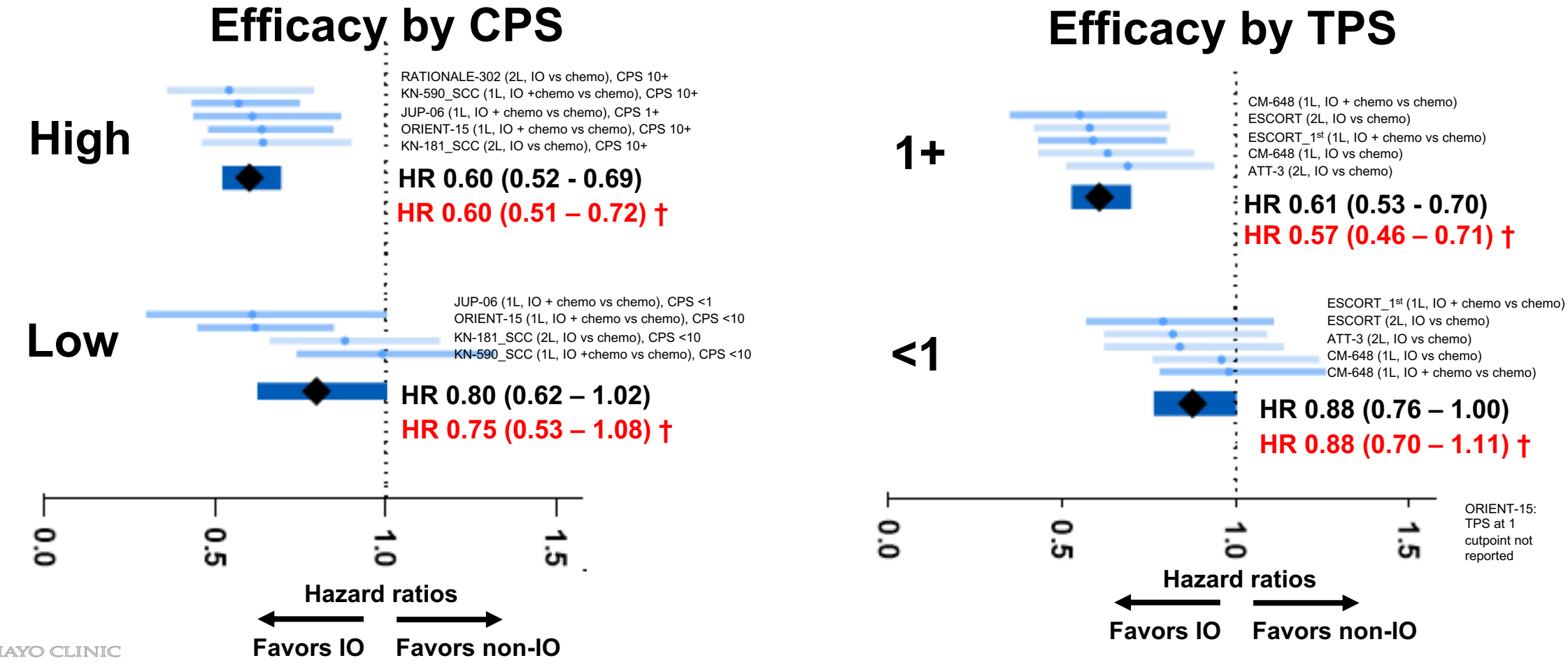
Shen L et al. ESMO 2021; Xu R-H et al. ESMO 2021; Luo H et al. JAMA 2021; Ajani J et al. ESMO GI 2021

With more data in 2021, anti-PD-1/-L1 efficacy in SCC appears to differ by PD-L1 expression

† IO + chemo *vs* chemo

Hazard ratios with 95% CI's shown

N = 3,817 (10 trials)



Yoon HH et al. ASCO GI 2022

2021 TREATMENT LANDSCAPE FOR FIT PATIENT WITH ESOPHAGEAL SQUAMOUS CELL CARCINOMA (SCC)

Advanced, 1st-line

PD-L1-CPS ≥ 10

Pembro + platin/FP (KN590)
(NCCN 1-2A and FDA)

PD-L1-TPS ≥ 1

Consider Nivo + FOLFOX (CM648)
(Await FDA & NCCN)

PD-L1-CPS 0-9 & TPS < 1

FOLFOX
(NCCN 2A)

Pembro + platin/FP (KN590)
(NCCN 2B and FDA)

After chemoradiation & surgery

SCC or AC if non-pCR

Adjuvant nivolumab x 1 yr (CM-577)
(NCCN 1-2A and FDA)

CPS, Combined positive score; **FP**, fluoropyrimidine; **nivo**, nivolumab; **pCR,** pathologic complete response; **pembro,** pembrolizumab; **TPS,** Tumor proportion score

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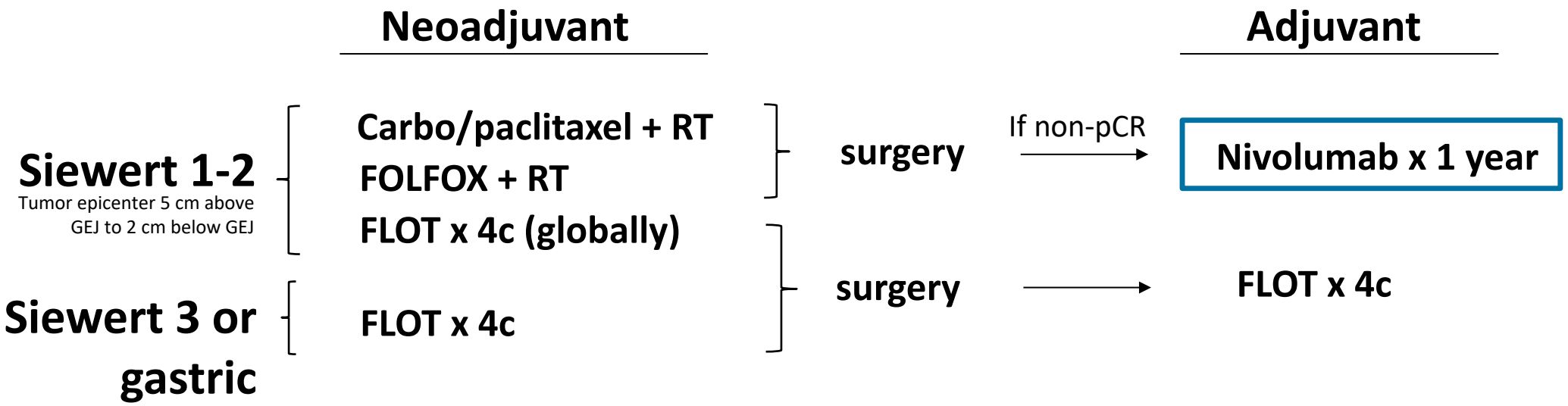
2021 TREATMENT FOR LOCALLY ADVANCED GE CA

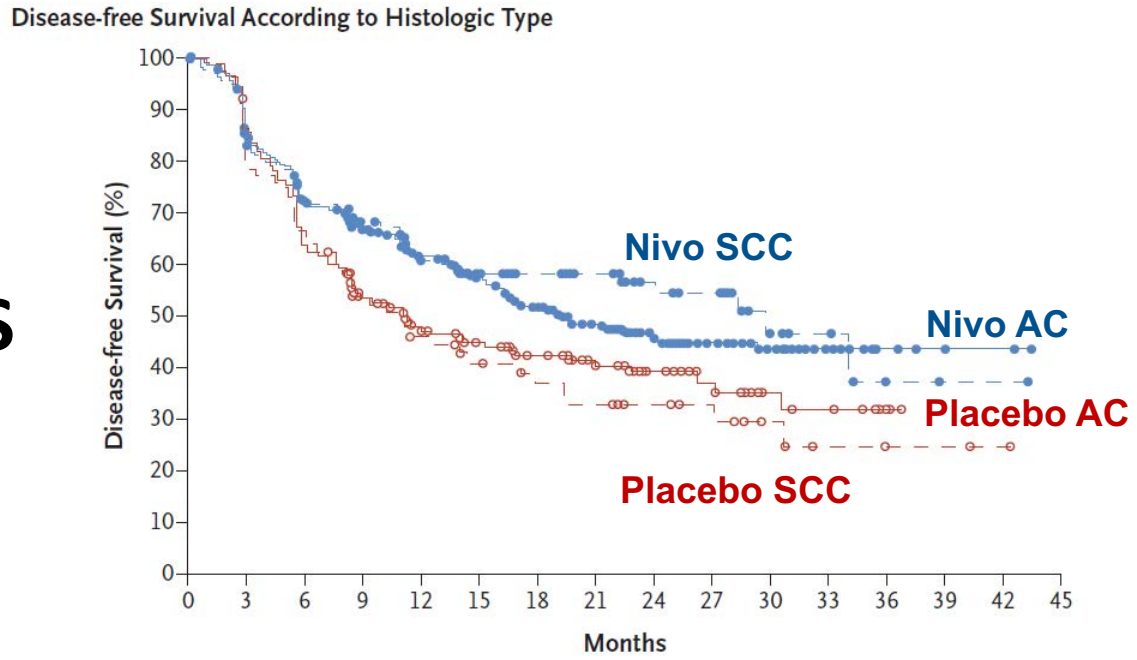
RESECTABLE LOCALLY ADVANCED



carbo, carboplatin; **pCR**, pathologic complete response; **RT**, radiation

Adjuvant nivo x 12 m in esoph/GEJ carcinoma if residual tumor after neoadjuvant CRT and surg (CM-577)

DFS



No. at Risk

Nivolumab, AC	376	305	257	219	178	151	125	99	65	45	32	16	6	3	2	0
Nivolumab, SCC	155	124	106	87	71	61	56	48	27	23	9	6	2	1	1	0
Placebo, AC	187	156	114	92	68	57	47	37	26	18	11	9	3	0	0	0
Placebo, SCC	75	58	49	34	28	23	18	16	12	10	6	3	2	2	1	0

SCC, HR 0.61 (95% CI 0.42-0.88)

AC, HR 0.75 (95% CI 0.59-0.96)

Study treatment was initiated within 4 to 16 weeks after R0 resection

Toxicity
- G3-4 34% vs 32%
- Leading to discontinuation 7% vs 6%

Treatment exposure
10.1 vs 9.0 months

FDA and NCCN Cat 1 approved

MAYO CLINIC

Ronan Kelly et al CM 577, NEJM 2021

ONGOING RCTS IN LOCALLY ADV DISEASE

	N	Tumor	Treatment arms	Primary endpoint
ESOPEC	438	E/GEJ	carbo/Taxol + **RT** → S FLOT x 4 → S → FLOT x 4	OS
RACE	340	Siew 1-3	FLOT x 2 then **FU/Ox/RT** [a] → S → FLOT x 4 FLOT x 4 → S → FLOT x 4	PFS
TOPGEAR	752	G	ECF x 2 then **RT** → S → ECF x 3 ECF x 3 → S → ECF x 3	OS
KN-585	800	G Siew 2-3	CF/FLOT x 3 + **pembro** → S → CF/FLOT x 3 + **pembro** CF/FLOT x 3 → S → CF/FLOT x 3 [b]	OS, EFS, pCR
MATTER-HORN	900	G/GEJ	FLOT + **durva** → S → FLOT + **durva** FLOT → S → FLOT	EFS
DANTE/ FLOT8	295	G/GEJ	FLOT x 4 + **atezo** → S → FLOT x 4 + **durva** FLOT x 4 → S → FLOT x 4	PFS/DFS
EA2174	278	E Siew 1-2	carbo/Taxol/RT + **Nivo** → S → **Nivo +/- IPI** carbo/Taxol/RT → S	pCR, DFS

Atezo, atezolizumab**; durva,** durvalumab; **E** = esophagus; **EFS,** event free survival; **FU**, 5-fluorouracil; **G** = gastric; **Ox**, oxaliplatin; **Siew** = Siewert

[a] oxaliplatin 45 mg/m2 weekly (d1, 8, 15, 22, 29) and continuous infusional 5-FU 225 mg/m2 + RT 45 Gy over 5 weeks

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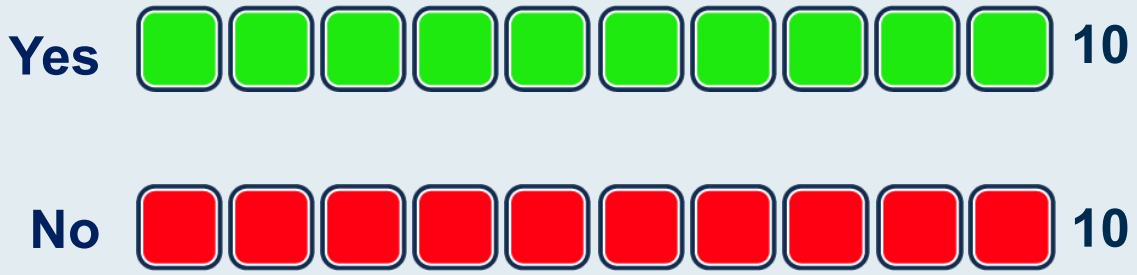
Which adjuvant systemic therapy would you currently recommend to a patient with HER2-negative, MSS squamous cell carcinoma of the esophagus who receives neoadjuvant carboplatin/paclitaxel and concurrent radiation therapy and has residual disease at surgery?

Survey of US-based clinical investigators

Regulatory and reimbursement issues aside, would you consider adding an anti-PD-1/PD-L1 antibody as a component of adjuvant treatment for a patient with HER2-negative, MSS adenocarcinoma of the GEJ who receives preoperative FLOT (docetaxel, oxaliplatin, leucovorin and 5-fluorouracil), undergoes resection and has residual disease at surgery?

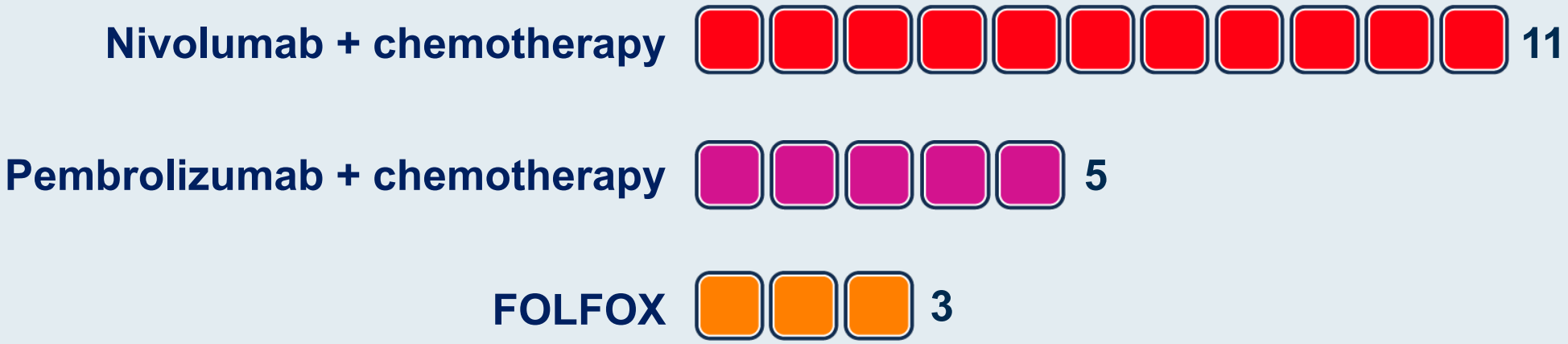


Survey of US-based clinical investigators

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

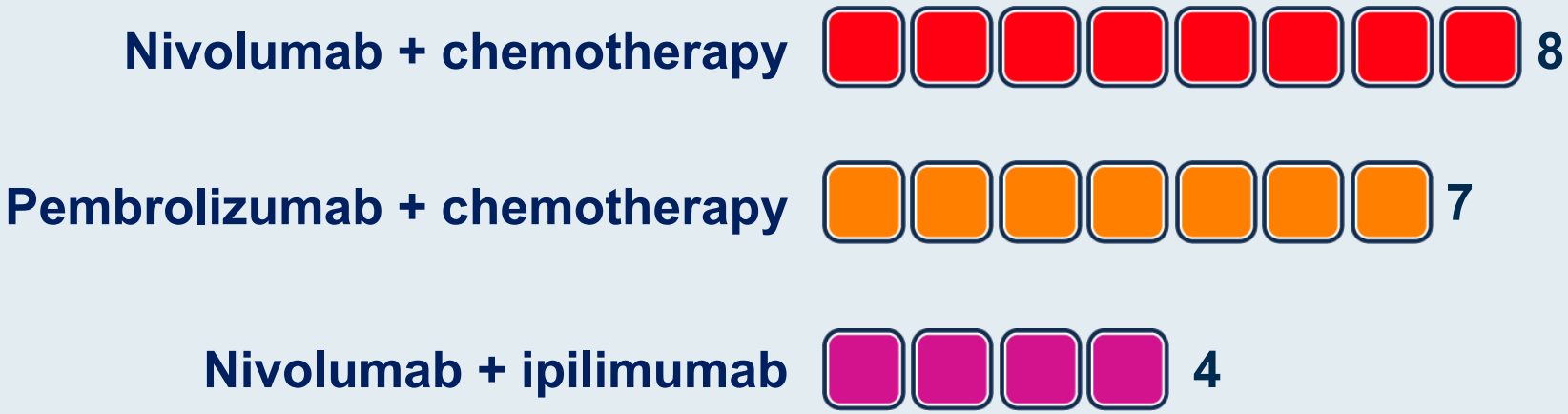
Survey of US-based clinical investigators

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



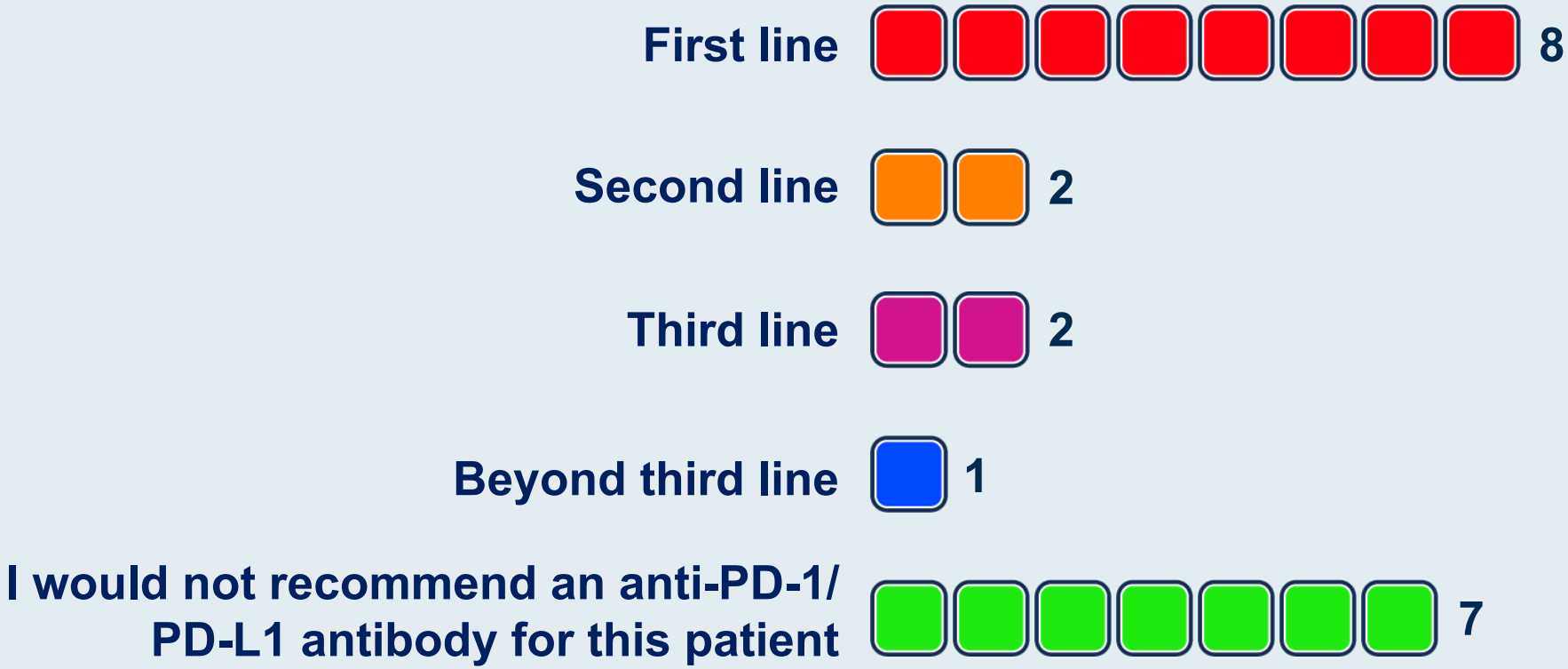
Survey of US-based clinical investigators

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



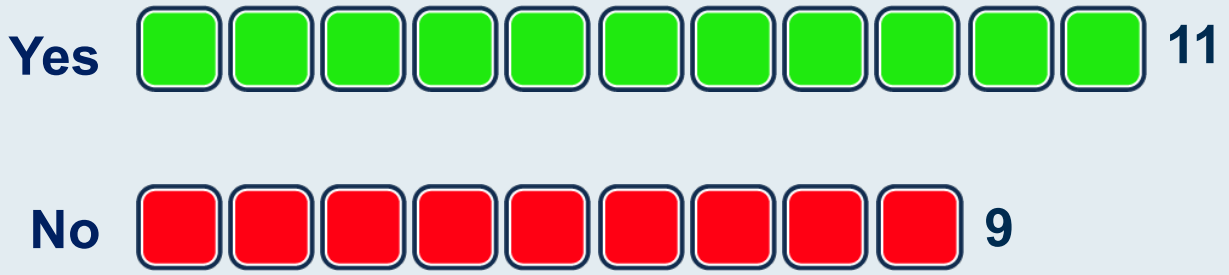
Survey of US-based clinical investigators

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



Survey of US-based clinical investigators

If the novel anti-PD-1 antibodies (eg, sintilimab, toripalimab) under investigation in esophageal cancer were available, would you consider substituting them for currently available agents?



Survey of US-based clinical investigators

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Hepatobiliary Cancers (Part 3 of a 3-Part Series)

Friday, January 21, 2022
6:15 PM – 7:45 PM PT

Faculty

Ghassan Abou-Alfa, MD, MBA
Richard S Finn, MD
Robin K Kelley, MD

Moderator

Tanios Bekaii-Saab, MD

RTP
RESEARCH TO PRACTICE

Thank you for attending!

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

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