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VIRTUAL EXPERTS KNOWLEDGE SHARE

EXPLORING THE CURRENT GASTROESOPHAGEAL CANCER TREATMENT LANDSCAPE AND NEAR-FUTURE DEVELOPMENTS

Tuesday March 28th 2023

EDUCATIONAL OBJECTIVES

- Understand the current gastroesophageal cancer treatment landscape and potential near-future developments
- Discuss any difference in treatments in Europe and the US
- Using patient case examples, consider how recent clinical data and treatments with different mechanisms of action will impact gastroesophageal cancer patient management

AGENDA: TUESDAY MARCH 28TH 2023

EXPLORING THE CURRENT GASTROESOPHAGEAL CANCER TREATMENT LANDSCAPE AND NEAR-FUTURE DEVELOPMENTS

Topic	Facilitator
Welcome and introduction	Dr Yelena Janjigian (USA) / COR2ED
Overview of gastroesophageal cancer	Dr Yelena Janjigian (USA)
Treatment of non metastatic patients	Dr Sam Klempner (USA)
Treatment of metastatic patients	Dr Lizzy Smyth (UK)
Questions and answers	All
Summary and close	Dr Yelena Janjigian / COR2ED

DEVELOPED BY GI CONNECT

This programme is developed by GI CONNECT, an international group of experts in the field of gastrointestinal oncology.

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INTRODUCING THE SCIENTIFIC COMMITTEE

Elizabeth (Lizzy) Smyth

Consultant in Gastrointestinal Oncology, Addenbrooke's Hospital, Cambridge, UK

Yelena Janjigian

Associate Professor and Chief of Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, USA

Samuel Klempner

GI Medical Oncologist, Massachusetts General Hospital Cancer Center and Associate Professor, Harvard Medical School, Boston, USA

OVERVIEW OF GASTROESOPHAGEAL CANCER

Yelena Y. Janjigian, MD

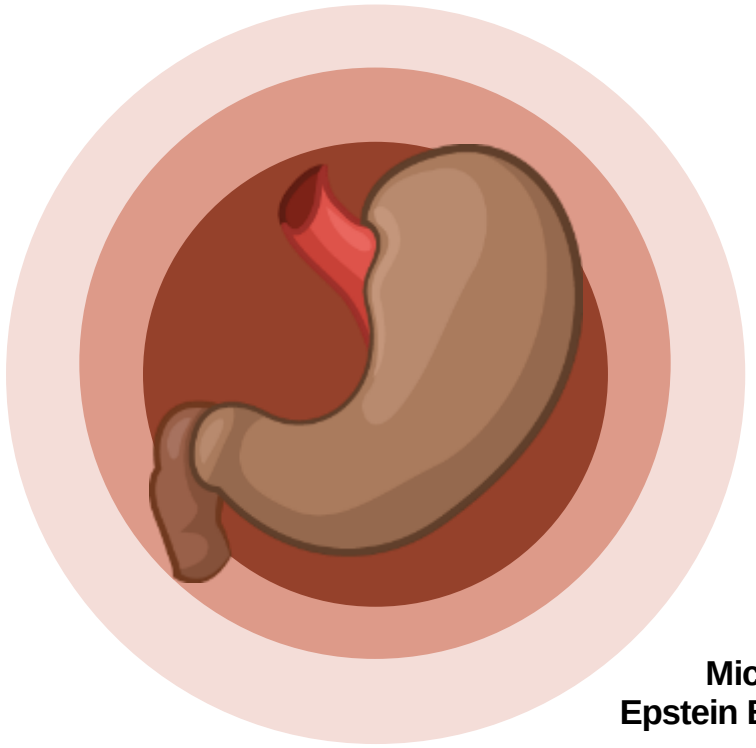
Associate Attending Physician
Associate Professor, WCMC

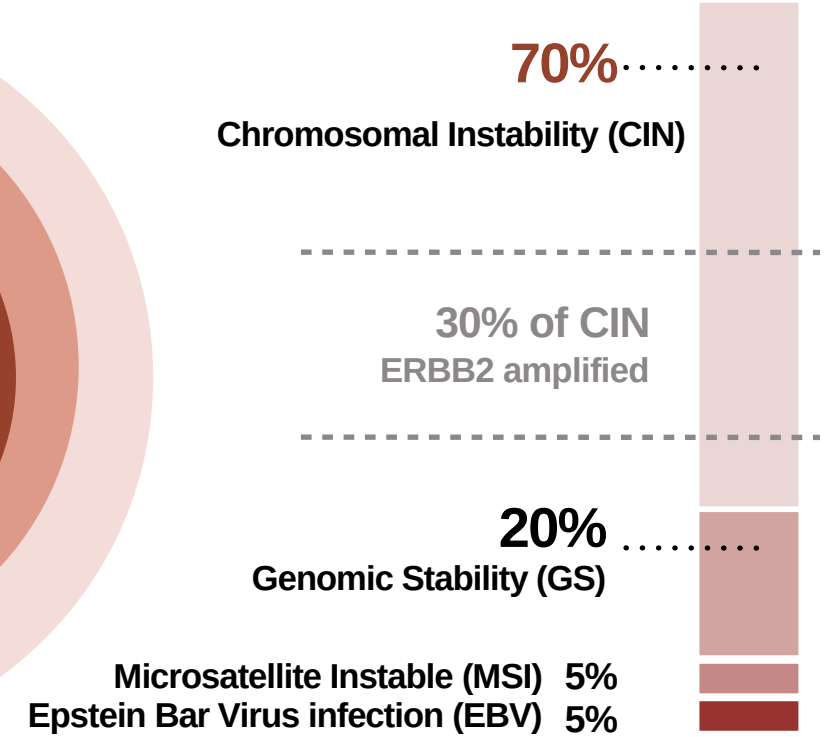
Chief, Gastrointestinal Oncology Service
Memorial Sloan Kettering Cancer Center

Twitter: @yjanjigianMD

BACKGROUND

GASTROESOPHAGEAL CANCERS





- Most common GEC subset
- No therapies addressing CIN
- Complex genomics with limited therapies
- High metastatic potential and poor survival

GEC, gastroesophageal cancer

The Cancer Genome Atlas Research Network, et al. Nature. 2017;543:378-384; Janjigian YY, et al. Cancer Discov. 2018; 8:49-58

BIOMARKER SELECTION IN ESOPHAGEAL & GASTRIC ADENOCARCINOMA

Biomarker	Prevalence in metastatic gastric cancer	Therapeutic agent(s)
ERBB2/HER2	20%	Trastuzumab + pembrolizumab
MSI-high	5% in Stage IV, 20% in Stage I-III	Pembrolizumab or nivolumab
EBV-positive	3%	Pembrolizumab or nivolumab
PD-L1 CPS	CPS ≥1 80%/ CPS ≥5 60%	Nivolumab and pembrolizumab
FGFR2b overexpression	30%	Bemarituzumab
CLDN18.2	35%	Zolbetuximab
Tumour sequencing	NTRK , EGFR, MET, RAS amplification	Larotrectinib, afatinib, etc.
Plasma DNA	Monitoring for response and resistance	Broad application

CLDN18.2, claudin 18.2; CPS, combined positive score; EBV, Epstein-Barr virus; EGFR, epidermal growth factor receptor; FGFR2b, fibroblast growth factor receptor 2b; MSI, microsatellite instability; NTRK, neurotrophic tyrosine receptor kinase; PD-L1, programmed death-ligand 1

HER2 INHIBITION IN GASTROESOPHAGEAL ADENOCARCINOMA

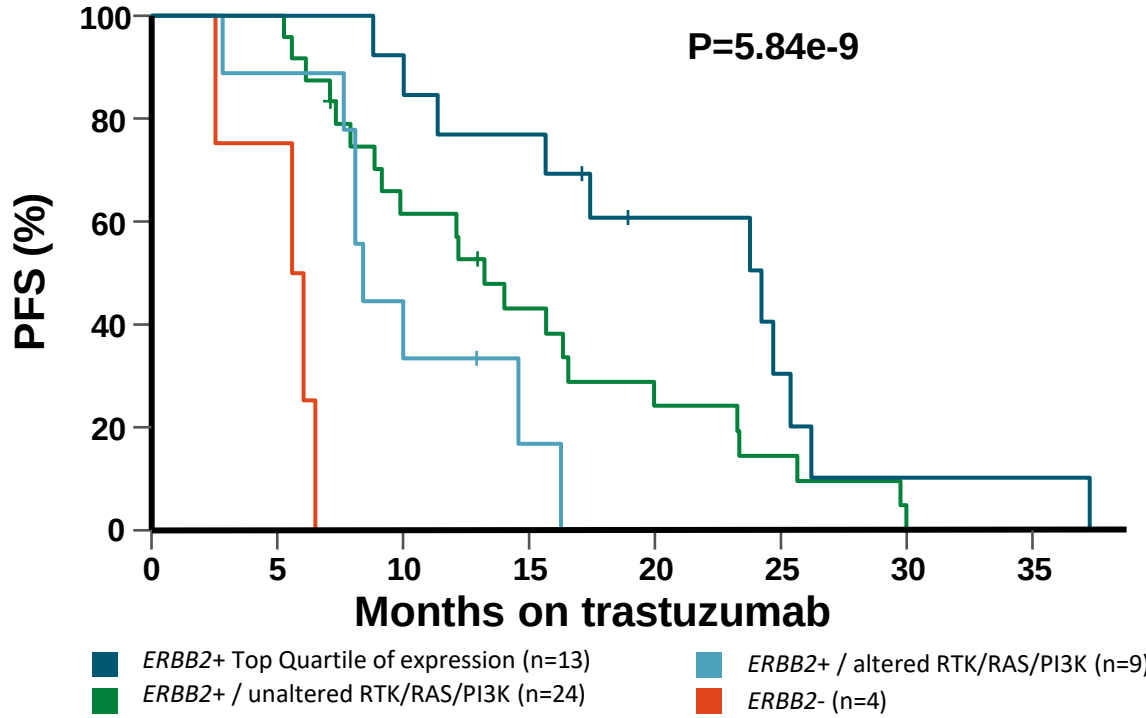
- Up to 20-30% HER2+ positive
- First-line trastuzumab/chemotherapy FDA approved mOS 13.8 mos ORR 47%
- 30% of GEJ HER2+ tumours with co-alterations of the RTK/RAS/PI3K pathway– intrinsic resistance
- HER2 inhibition alone in 1st line is insufficient to overcome intrinsic resistance- several negative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

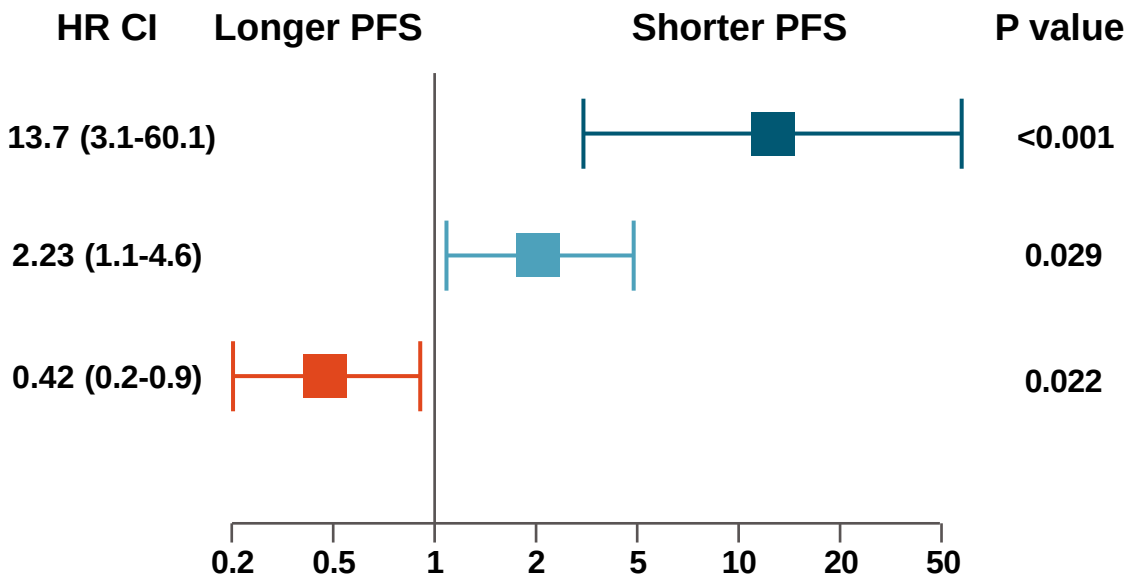
FDA, Food and Drug Administration; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; mos, months; mOS, median overall survival; ORR, objective response rate; PI3K, phosphoinositide 3-kinase; RTK, receptor tyrosine kinase

Bang Y, et al. Lancet. 2010;376:687-97; Janjigian YY, et al. Cancer Discov. 2018;8:49-58; Hecht JR, et al. J Clin Oncol. 2016;34:443-451; FDA press release https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-keytruda-pembrolizumab-combination-trastuzumab-fluoropyrimidine (accessed March 2023);Tabernero J, et al. Lancet Oncol. 2018; 9:1372-84; Shah MA, et al. J Clin Oncol. 201735:2558-67; Janjigian YY, et al. J Clin Oncol. 39(no. 15_suppl):4013-4013; Shitara, et al. N Engl J Med. 2020;382:2419-30; FDA press release https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fam-trastuzumab-deruxtecan-nxki-her2-positive-gastric-adenocarcinomas (accessed March 2023)

PFS IN GASTROESOPHAGEAL CANCER WITH INTRINSIC TRASTUZUMAB RESISTANCE

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

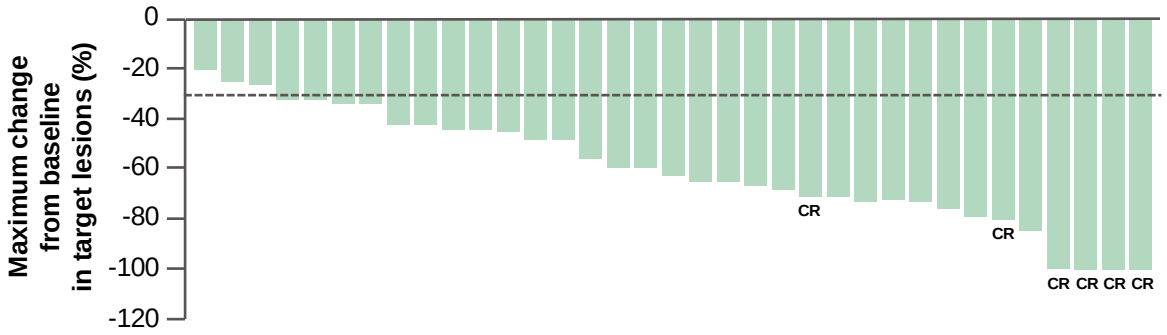




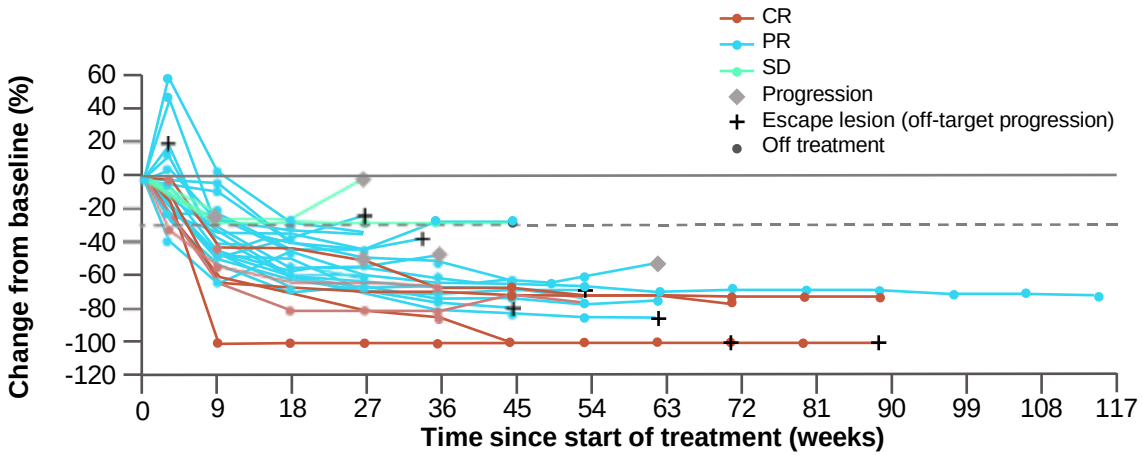
CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; MSKCC, Memorial Sloan Kettering Cancer Center; PI3K, phosphoinositide 3-kinase; PFS, progression-free survival; RTK, receptor tyrosine kinase

Janjigian YY, et al. Cancer Discov. 2018;8:49-58

DUAL ANTI-PD-1/ANTI-HER2 BLOCKADE IN *ERBB2*+ GASTROESOPHAGEAL CANCER

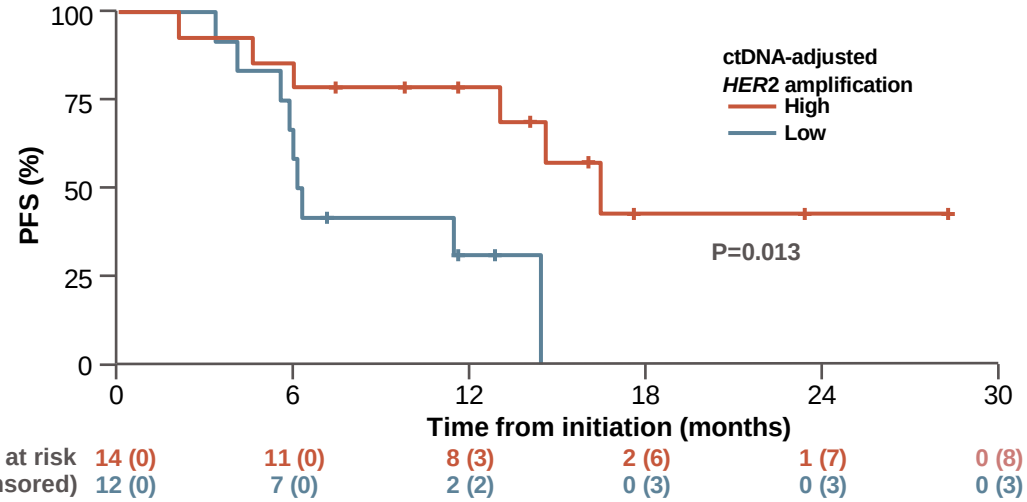


Adapted with permission from Janjigian 2020.



Adapted with permission from Janjigian 2020.

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



Adapted from Janjigian 2020.

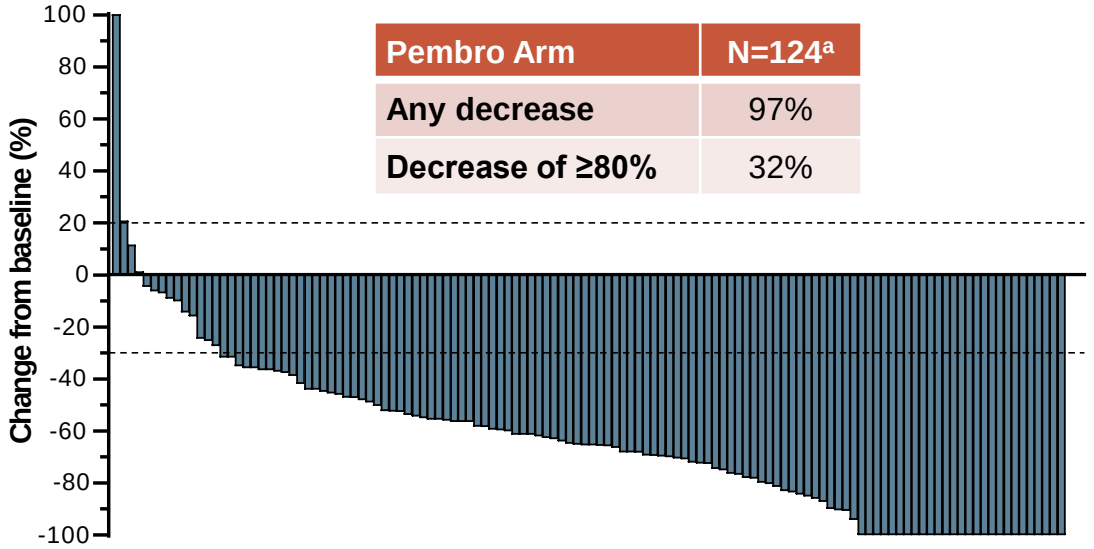
- 49% of patients experienced a grade 3 TRAE; 8% experienced a grade 4 TRAE

CI, confidence interval; CR, complete response; ctDNA, circulating tumour DNA; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PFS, progression-free survival; PR, partial response; OS, overall survival; SD, stable disease

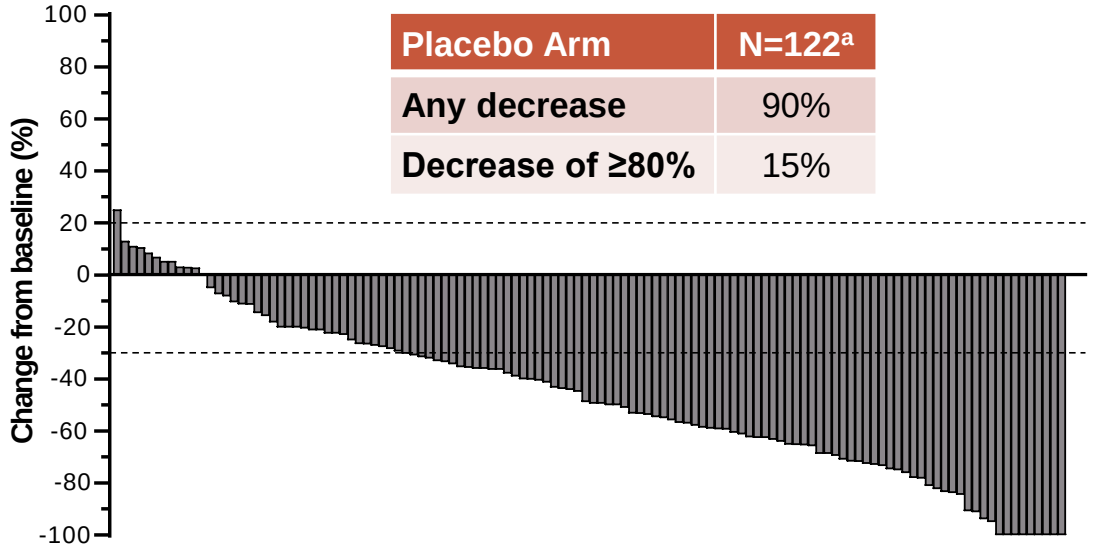
[a] Among patients with evaluable disease (n=35)

Janjigian YY, et al. Lancet Oncol. 2020;21:821-31

CONFIRMED RESPONSE AT IA1



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



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

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

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

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

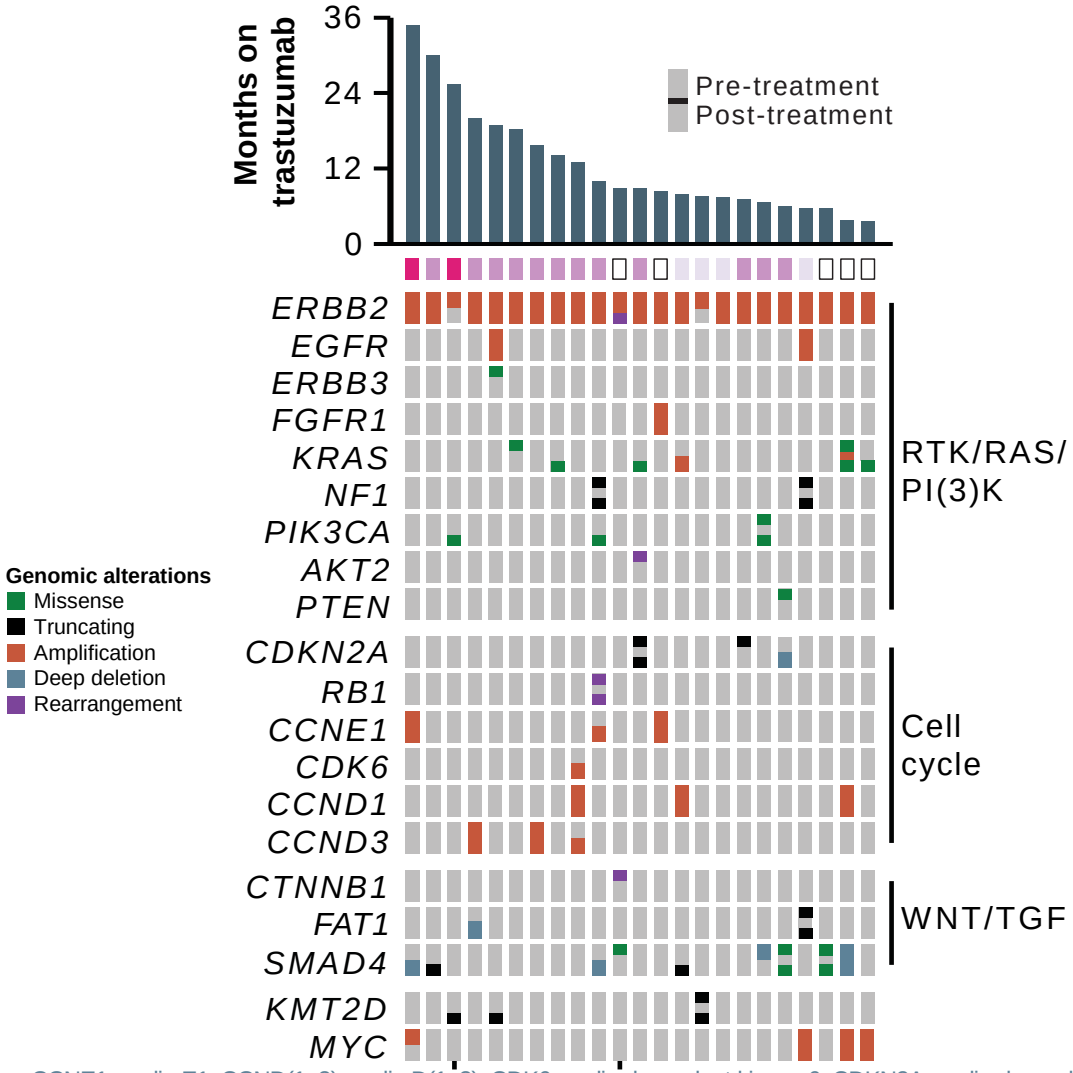
CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

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

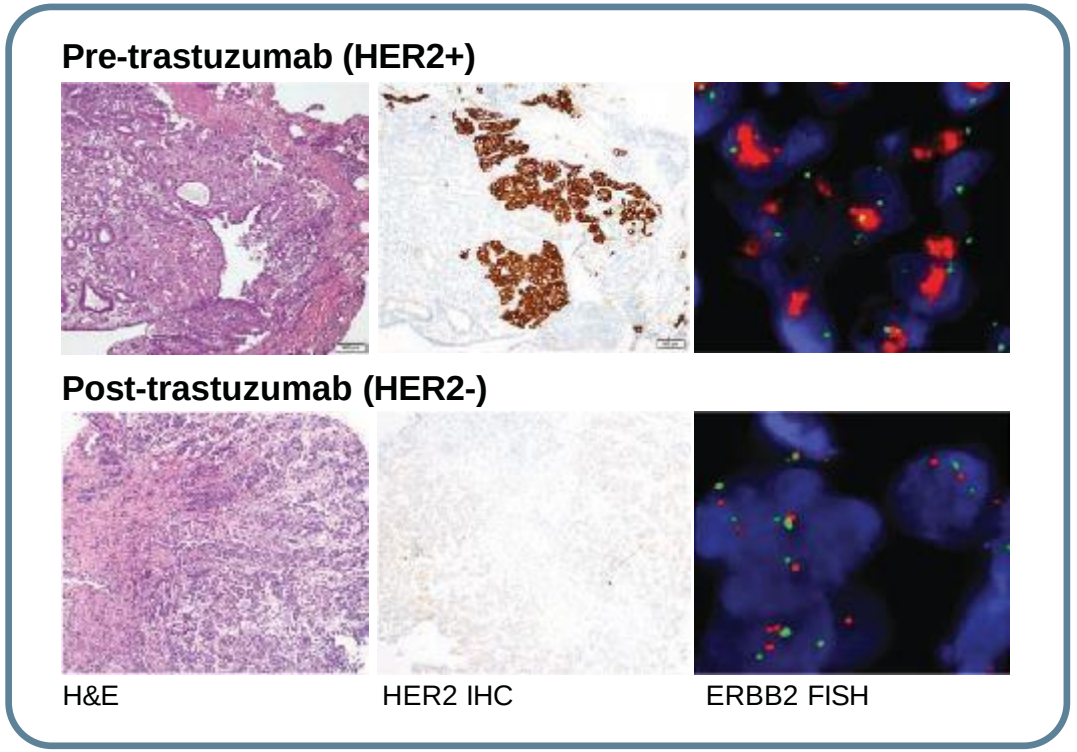
Janjigian et al. Ann Onco. 2021; 32 suppl 3: S277

ACQUIRED TRASTUZUMAB RESISTANCE

LOSS OF *ERBB2* AND KRAS AND PIK3CA ALTERATIONS IN 20% OF CASES



Loss of ERBB2 amplification and HER2 protein expression in the post treatment sample



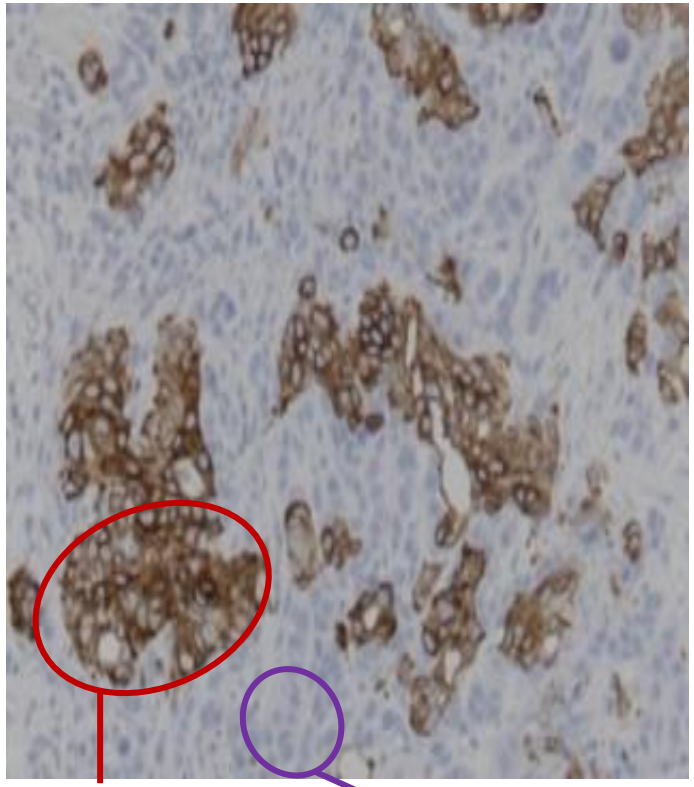
CCNE1, cyclin E1; CCND(1, 3), cyclin D(1, 3); CDK6, cyclin-dependent kinase 6; CDKN2A, cyclin-dependent kinase inhibitor 2A; CTNNB1, catenin beta 1; EGFR, epidermal growth factor receptor; FAT1, FAT atypical cadherin 1; FGFR1, fibroblast growth factor receptor 1; FISH, fluorescent in-situ hybridisation; H&E, hematoxylin and eosin; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; KMT2D, histone-lysine N-methyltransferase 2D; KRAS, Kirsten rat sarcoma virus; NF1, neurofibromin 1; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase; PTEN, phosphatase and tensin homologue; RB1, retinoblastoma gene; RTK, receptor tyrosine kinase; TGF, transforming growth factor

Janjigian YY, et al. Cancer Discov. 2018;8:49-58

BYSTANDER EFFECT OF ADCs: TRASTUZUMAB DERUXTECAN VS TRASTUZUMAB EMTANSINE

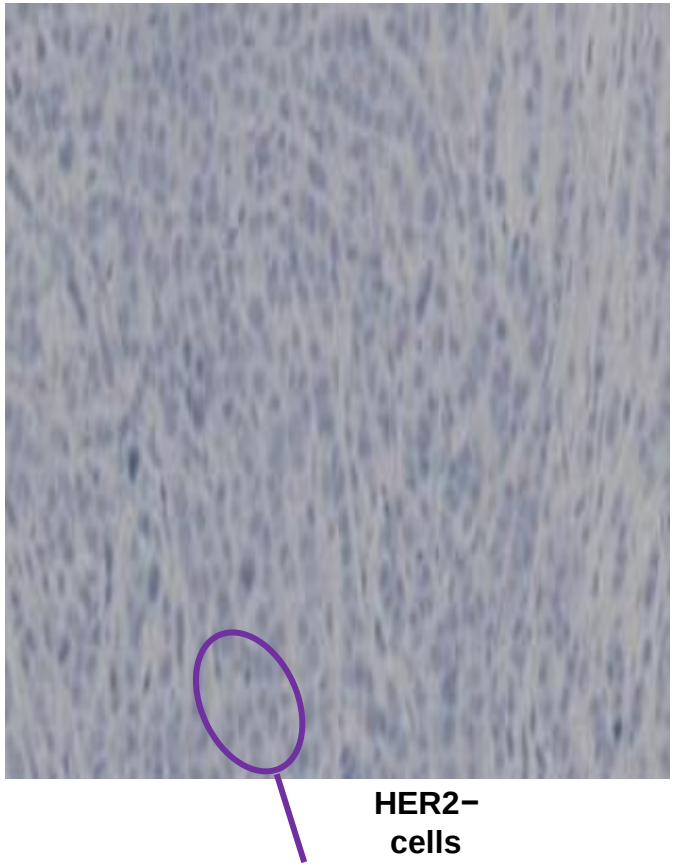
Control

Co-culture of HER2+ and HER2− tumours in vivo



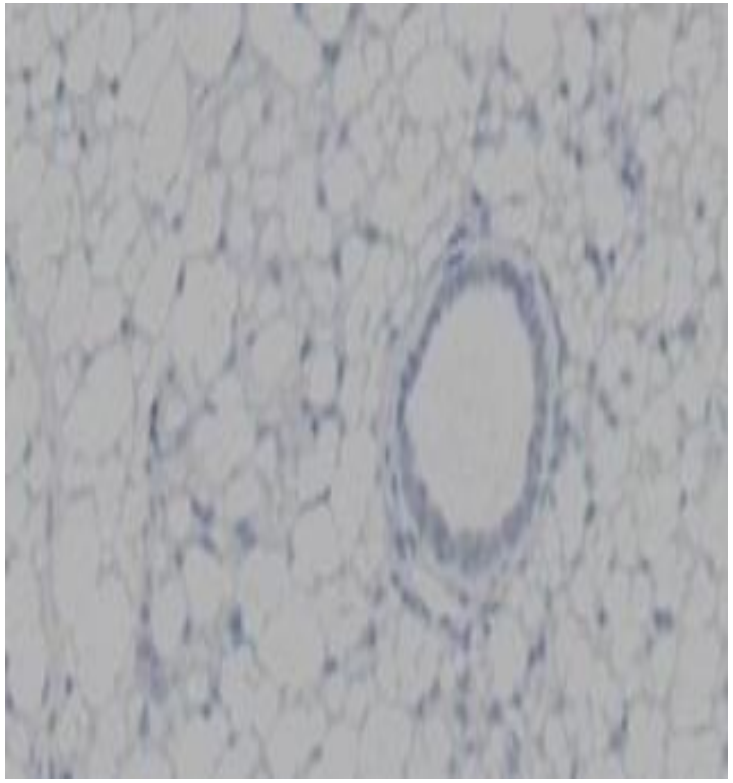
Trastuzumab Emtansine, 10 mg/kg

HER2− cells still persist



Trastuzumab Deruxtecan 3.0 mg/kg

Both HER2+ and HER2− are impacted



Tumour regression

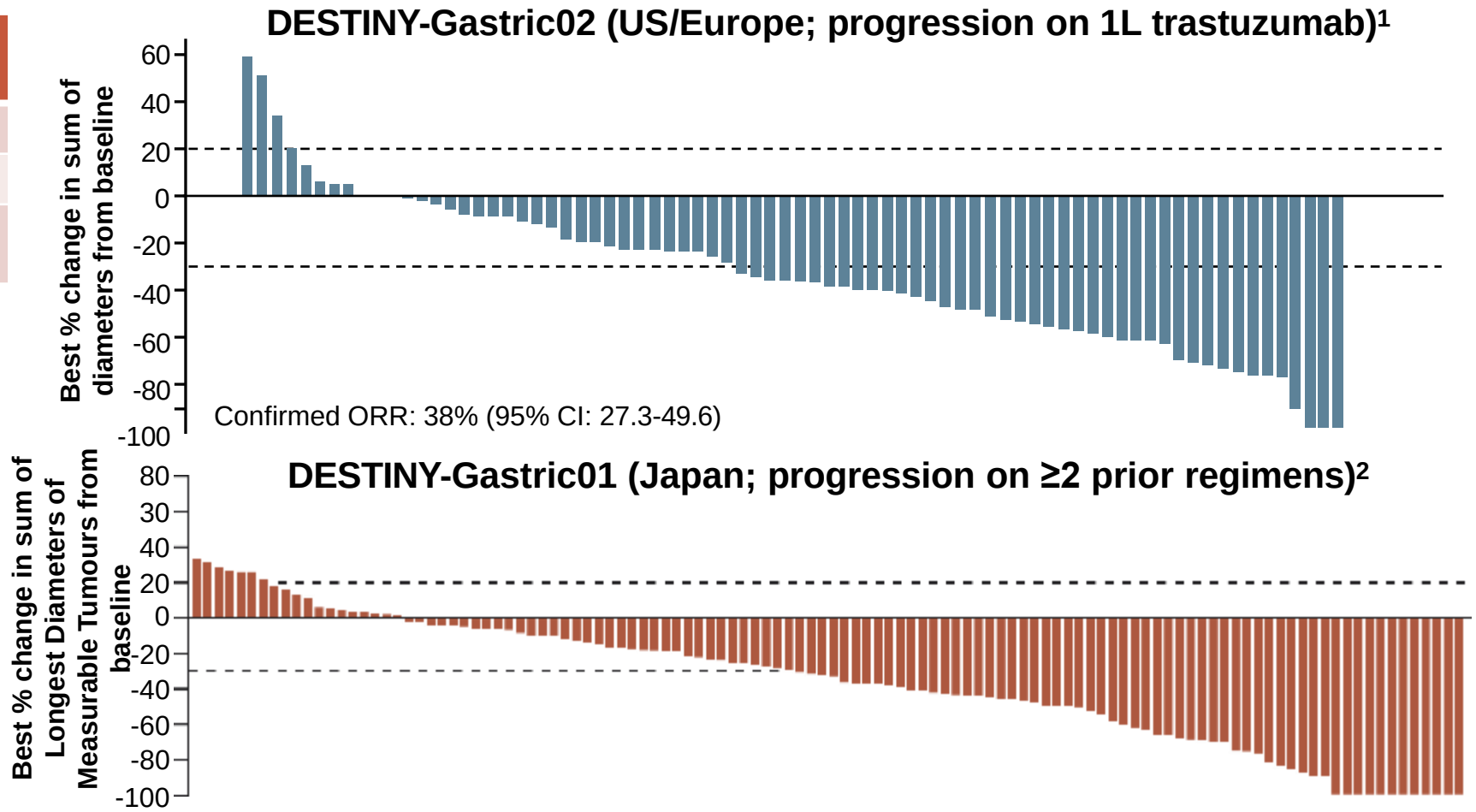
ADC, antibody drug conjugate; HER2, human epidermal growth factor receptor 2

Ogitani Y, et al. Cancer Sci. 2016;107:1039-46; Iwata H, et al. J Clin Oncol. 36;(no. 15_suppl):2501-2501

TUMOUR SIZE CHANGE WITH T-DXD IN HER2+ ADVANCED GASTRIC/GEJ CANCER AFTER TRASTUZUMAB (DESTINY-GASTRIC01 AND 02)

Efficacy[1]	T-DXd (N=79)
ORR, % (95% CI)	38 (27.3-49.6)
Median DoR, mo	8.1
Median PFS (95% CI), mo	5.5 (4.2-7.3)

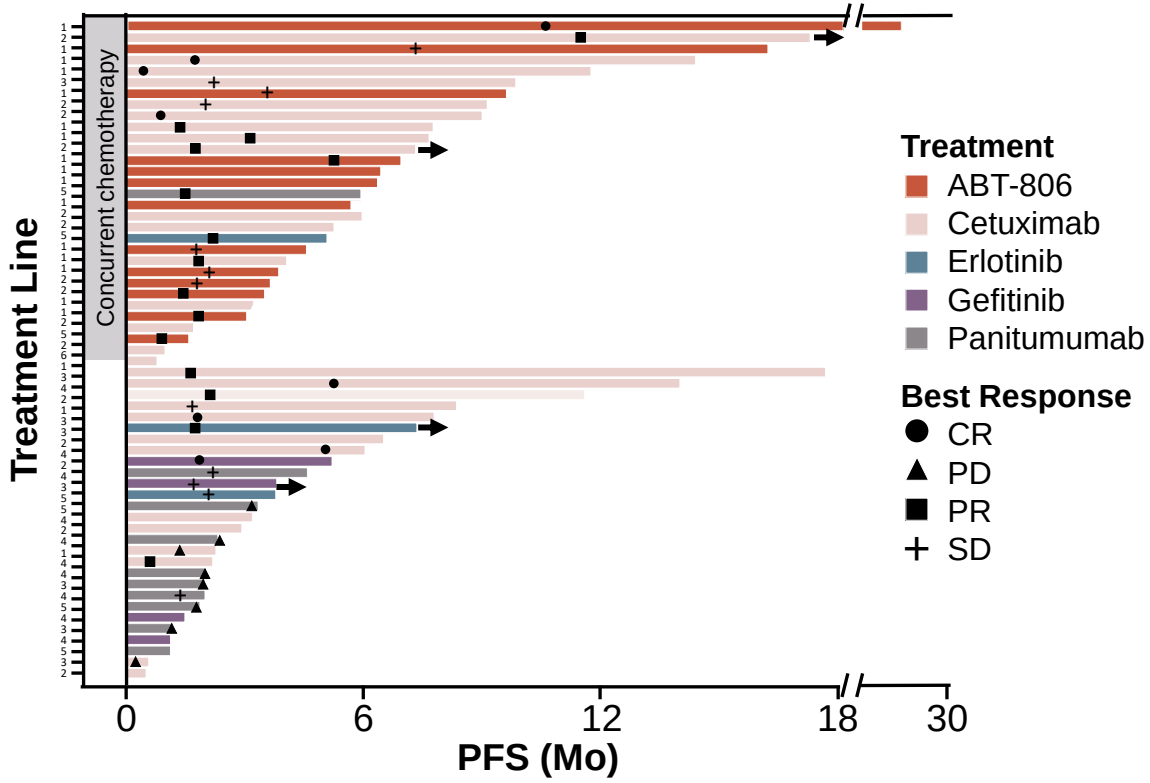
Survival, mo (95% CI)[2]	T-DXd (N=125)	Chemo (N=62)
Median OS	12.5 (9.6-14.3)	8.4 (6.9-10.7)
	HR for death: 0.59; P=0.01	
Median PFS	5.6 (4.3-6.9)	3.5 (2.0-4.3)
	HR for PD or death: 0.47	

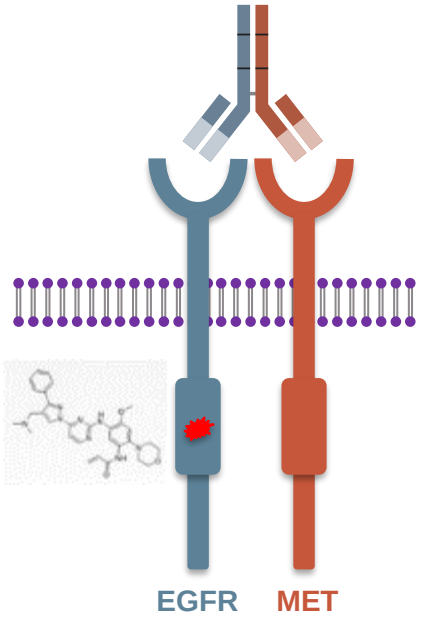


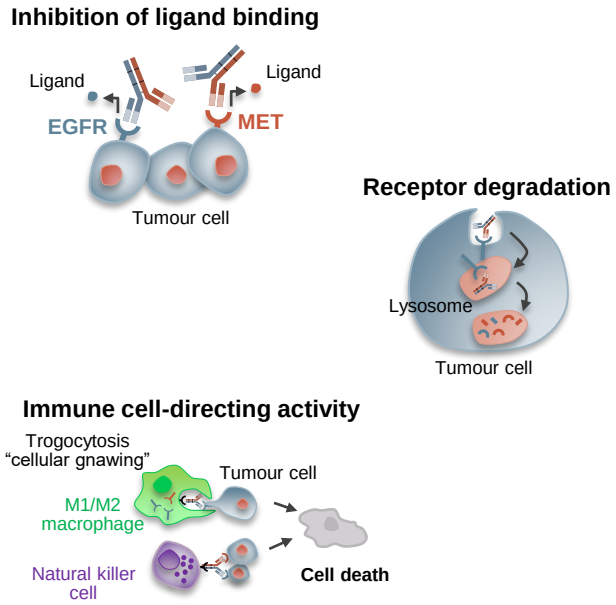
1L, first line; CI, confidence interval; DoR, duration of response; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; T-Dxd. trastuzumab deruxtecan

1. Van Cutsem. ESMO 2021. Abstr LBA55. 2. Shitara, et al. N Engl J Med. 2020;382:2419-30

EGFR AMPLIFICATION IN ~ 8% OF GASTROESOPHAGEAL ADENOCARCINOMA CO-OCCURRING ALTERATIONS A MAJOR LIMITATION







Treatment line, n/N (%)	1	2	3	4	5
Overall	11/17 (65)	7/15 (43)	28 (25)	4/16 (25)	24/56 (43)
EGFRi + chemo	9/14 (64)	5/10 (50)	0/1 (0)	2/3 (67)	16/28 (57)
EGFRi	2/3 (67)	2/5 (40)	2/7 (29)	2/13 (15)	8/28 (29)

- EGFR is a therapeutic target in EAC/GEJ
- Well suited toward combinatorial approaches
- Activity seen independent of line of therapy
- Ongoing phase 2 trials examining bispecific Ab amivantamab in EGFR and/or METamp GEA

CR, complete response; EAC, esophageal adenocarcinoma; EGFR, epidermal growth factor receptor; EGFRi, EGFR inhibitor; GEA, gastroesophageal adenocarcinoma; GEJ, gastroesophageal junction; METamp, MET amplification; mo, month; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease

Maron SB, et al. J Clin Oncol. 2022;40:2458-67

IMMUNOTHERAPY IN GASTROESOPHAGEAL ADENOCARCINOMA

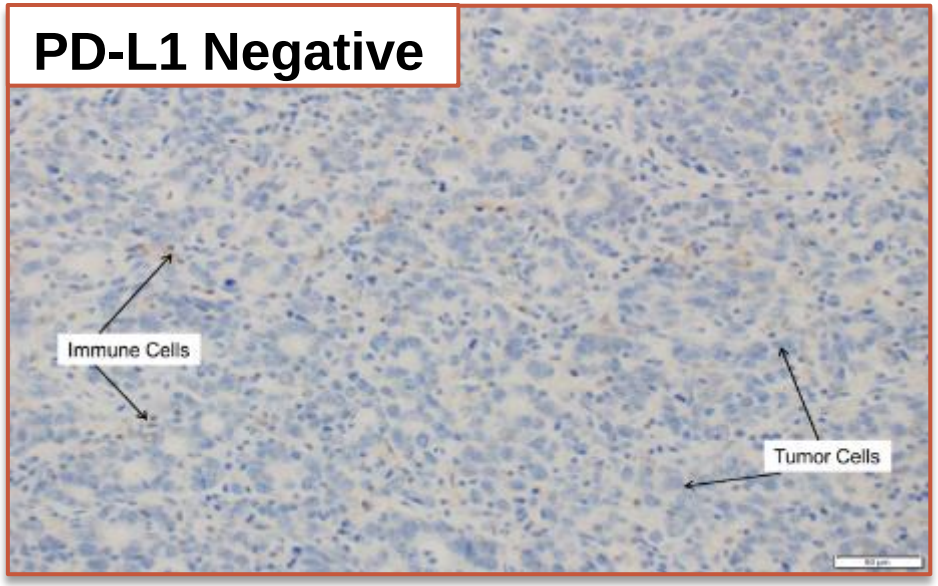
- Nivolumab with chemotherapy approved in the United States for 1st-line treatment irrespective of PD-L1 status
- Pembrolizumab, trastuzumab, and chemotherapy approved in the United States for HER2-positive disease
- Nivolumab approved in Asia irrespective of PD-L1 status for ≥3rd-line treatment
- Pembrolizumab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

HER2, human epidermal growth factor receptor 2; Mb, megabase; MSI-H, microsatellite instability-high; mut, mutation; PD-L1, programmed death-ligand 1; TMB, tumour mutational burden

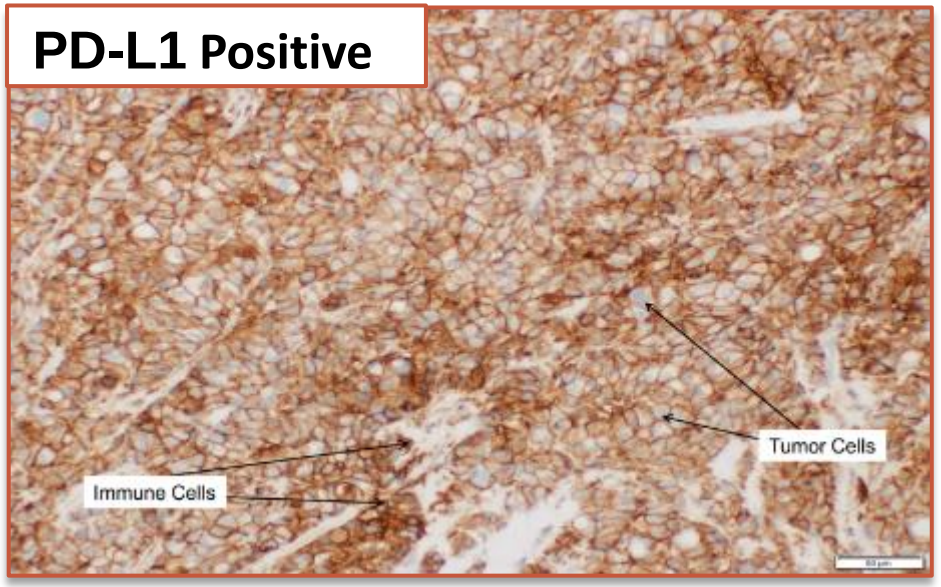
FDA press release https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approvals-trodelvy-sacituzumab-govitecan-locally-advancedmetastatic (accessed March 2023); FDA press release https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-keytruda-pembrolizumab-combination-trastuzumab-fluoropyrimidine (accessed March 2023); Högner A, Thuss-Patience P. Pharmaceuticals (Basel). 2021;14:151; Merck (press release, July 1, 2021). Accessed July 20, 2021; Merck (press release, August 24, 2020). Accessed July 20, 2021

PD-L1 EXPRESSION IHC

- PD-L1 expression in gastric cancer is determined by **c**ombined **p**ositive **s**core (CPS)
- **CPS** = [# of PD-L1 staining cells (tumour cells, lymphocytes, macrophages)/total no. of viable tumour cells] × 100
- A specimen is considered to have positive PD-L1 expression if CPS ≥1



22C3 pharmDx kit

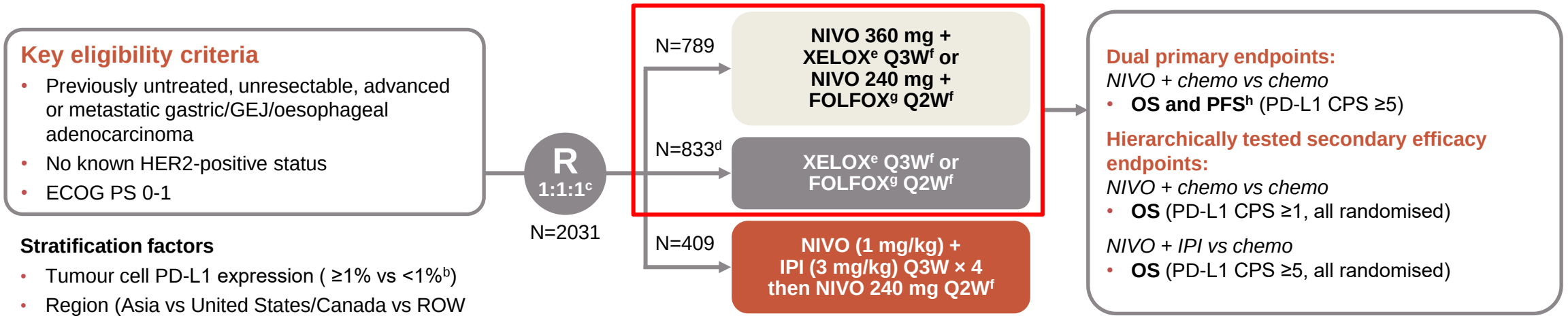


IHC, immunohistochemistry; PD-L1, programmed death-ligand 1

Park. Cancer Res Treat. 2020;52:661-70; Shitara K. Lancet. 2018;392:123-33

CHECKMATE 649 STUDY DESIGN

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



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**

[a] ClinicalTrials.gov number, NCT02872116. [b] <1% includes indeterminate tumour 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 randomised 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 randomisation of the last patient to data cutoff

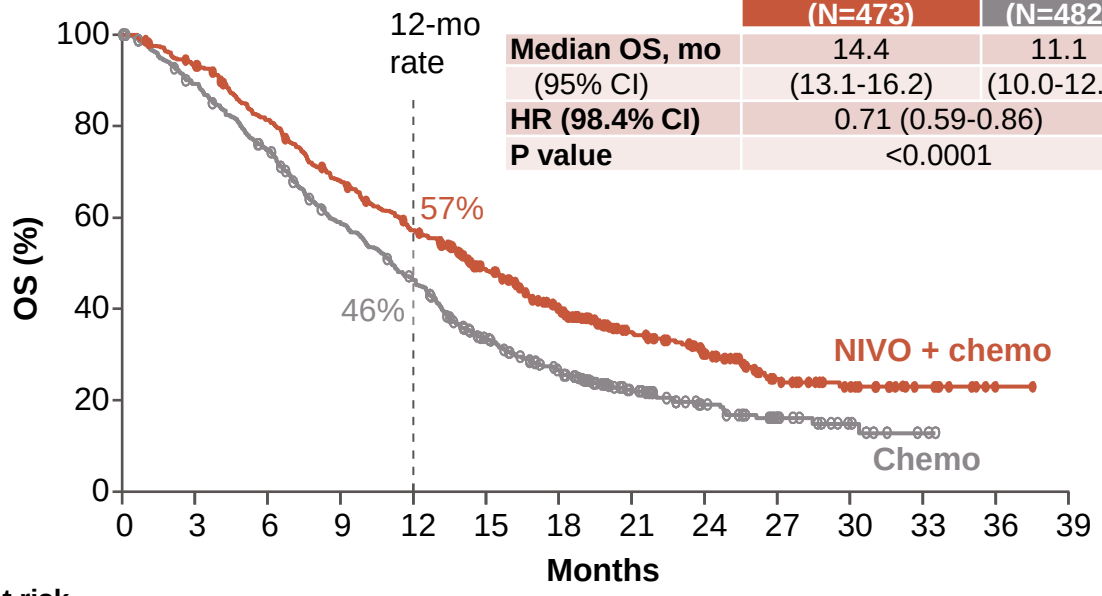
CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PFS, progression-free survival; PD-L1, programmed death-ligand 1; QXW, every X weeks; R, randomisation; RoW, rest of world

1. Janjigian YY, et al. Lancet. 2021;398:27-40; 2. Janjigian YY, et al. Ann Oncol. 2021;32 (suppl_5):S1283-S1346

CHECKMATE 649: GLOBAL PHASE 3 REGISTRATION TRIAL
NIVO + CHEMO IMPROVED SURVIVAL
FDA APPROVED APRIL 2021[1]

PD-L1 CPS ≥5

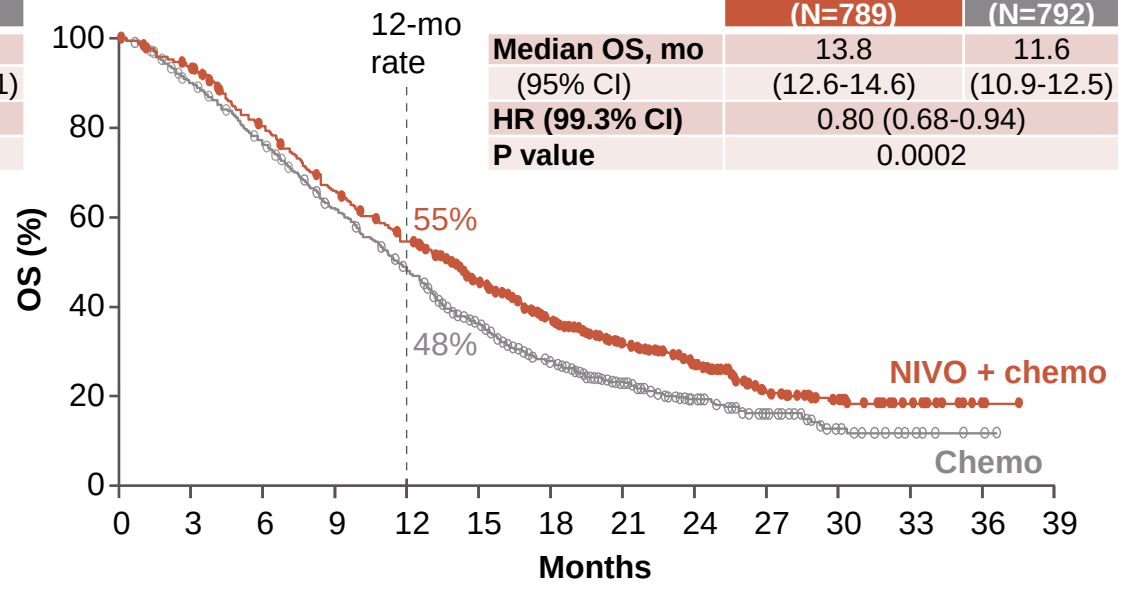
	NIVO + chemo (N=473)	Chemo (N=482)
Median OS, mo	14.4	11.1
(95% CI)	(13.1-16.2)	(10.0-12.1)
HR (98.4% CI)	0.71 (0.59-0.86)	
P value	<0.0001	



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 randomised

	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]

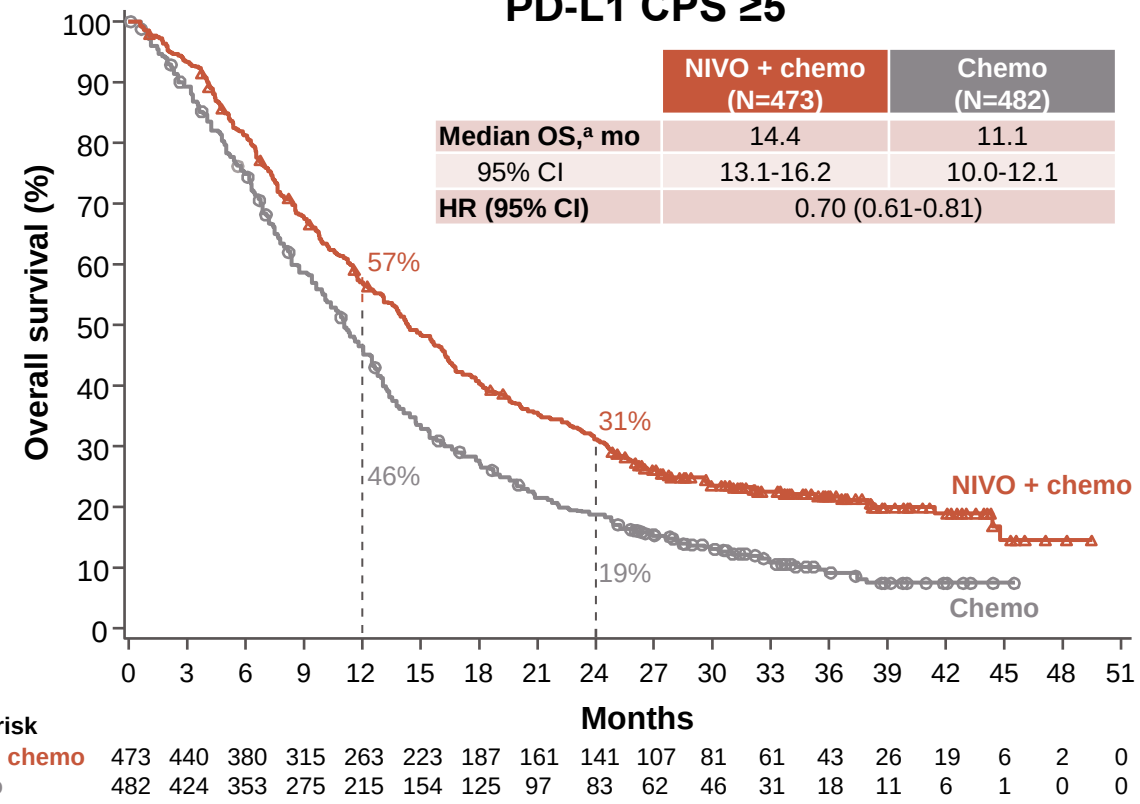
- Grade 3-4 TRAEs were reported in 59% of patients in the NIVO + chemo arm and 44% of patients in the chemo arm[1]
- Treatment-related deaths occurred in 16 (2%) and 4 (1%) of patients in the NIVO + chemo and chemo arms, respectively[1]

CI, confidence interval; CPS, combined positive score; HR, hazard ratio; mo, months; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 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

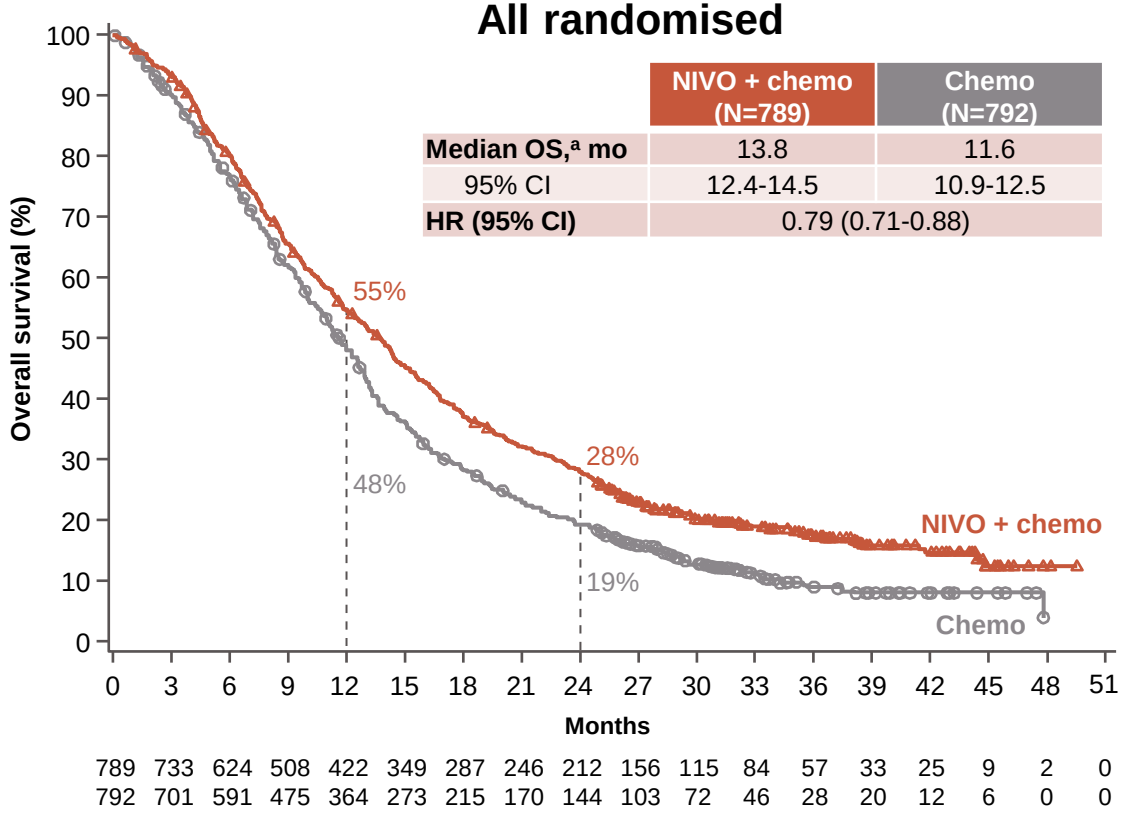
PD-L1 CPS ≥5



	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 randomised



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

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

- Clinically meaningful improvement in OS with NIVO + chemo vs chemo was maintained with longer follow-up
  - PD-L1 CPS ≥5: 30% reduction in the risk of death and 12% improvement in 24-month OS rate
  - All randomised: 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 randomised, 0.80 [99.3% CI, 0.68-0.94])[1]

[a] Minimum follow-up, 24.0 months

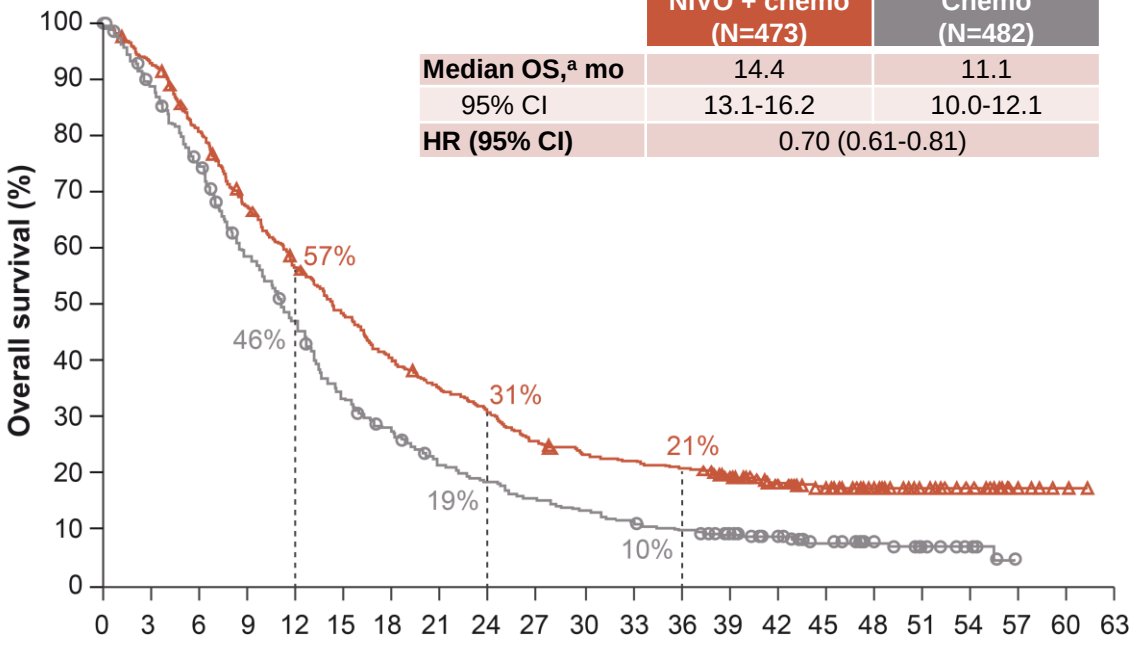
CI, confidence interval; CPS, combined positive score; HR, hazard ratio; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1

Janjigian YY, et al. Lancet 2021;398:27-40

OVERALL SURVIVAL: 36-MONTH FOLLOW-UP ALL PATIENTS

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)	

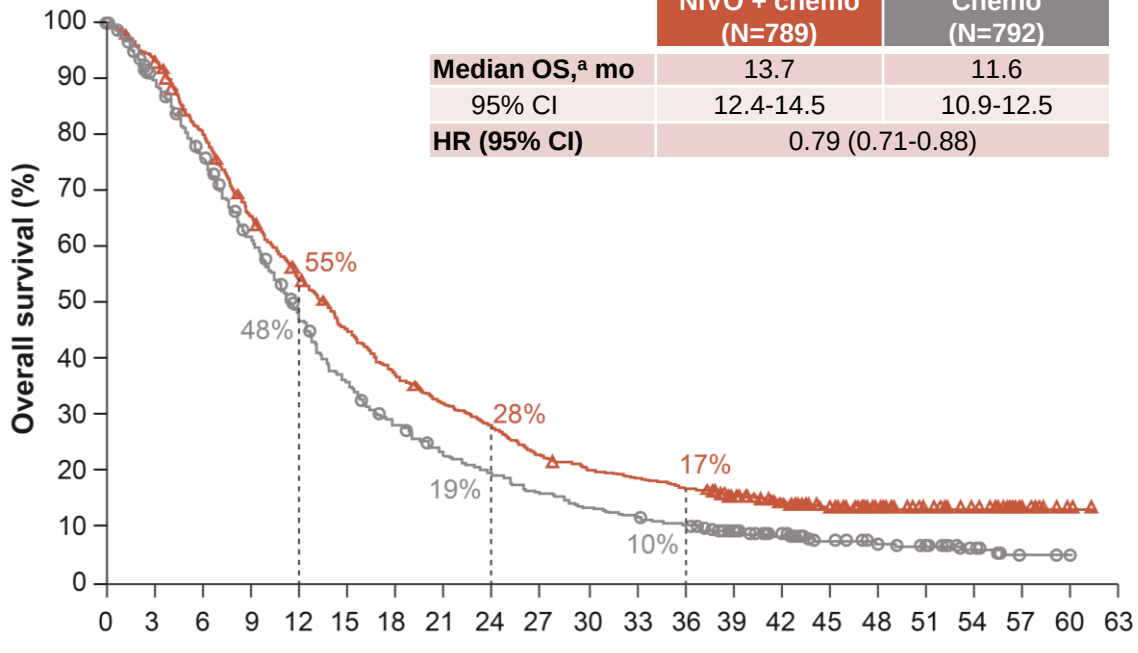


No. at risk

NIVO + chemo	473	440	380	315	263	223	187	161	141	118	105	100	94	81	66	53	37	24	17	6	2	0
Chemo	482	424	353	275	215	154	125	97	83	69	60	51	44	35	28	18	14	10	5	0	0	0

All randomised

	NIVO + chemo (N=789)	Chemo (N=792)
Median OS,[a] mo	13.7	11.6
95% CI	12.4-14.5	10.9-12.5
HR (95% CI)	0.79 (0.71-0.88)	



789	733	625	509	422	349	287	246	212	175	154	143	129	106	87	67	48	30	23	9	2	0
792	701	591	475	364	273	215	170	144	118	98	87	75	57	45	27	21	17	9	3	1	0

- Clinically meaningful improvement in OS with NIVO + chemo vs chemo was maintained with longer follow-up in PD-L1 CPS ≥5 and all randomised populations

[a] Minimum follow-up, 36.2 months

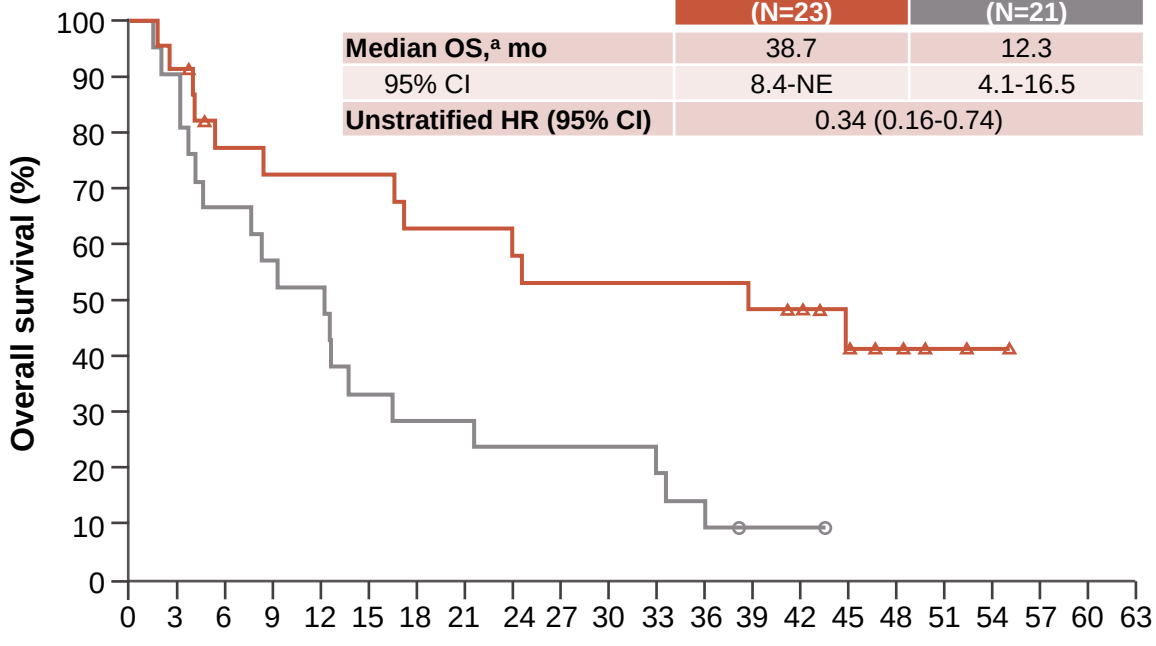
CI, confidence interval; CPS, combined positive score; HR, hazard ratio; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1

Janjigian YY, et al. J Clin Oncol. 2023;41(suppl 4; abstr 291)

OVERALL SURVIVAL BY MSI STATUS: 36-MONTH FOLLOW-UP

MSI-H

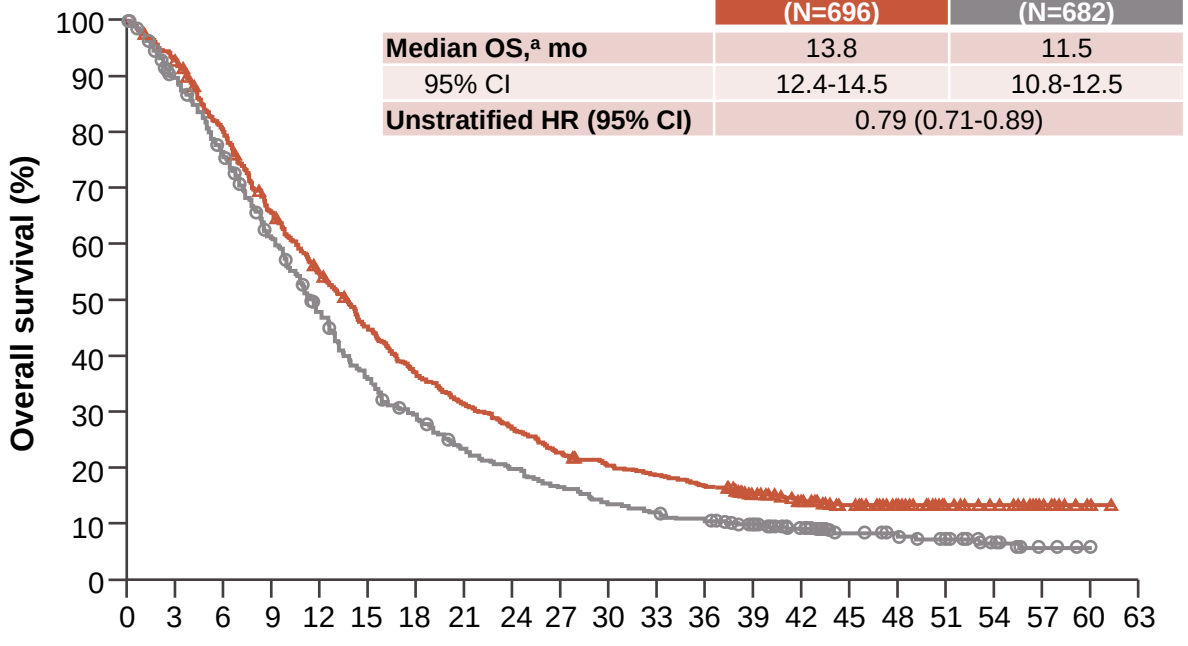
	NIVO + chemo (N=23)	Chemo (N=21)
Median OS,[a] mo	38.7	12.3
95% CI	8.4-NE	4.1-16.5
Unstratified HR (95% CI)	0.34 (0.16-0.74)	



No. at risk																							
NIVO + chemo	23	21	16	15	15	15	13	13	12	11	11	11	11	10	9	6	4	2	1	0	0	0	
Chemo	21	19	14	12	11	7	6	6	5	5	5	4	3	1	1	0	0	0	0	0	0	0	

MSS

	NIVO + chemo (N=696)	Chemo (N=682)
Median OS,[a] mo	13.8	11.5
95% CI	12.4-14.5	10.8-12.5
Unstratified HR (95% CI)	0.79 (0.71-0.89)	



NIVO + chemo	696	646	555	453	375	308	251	214	184	155	137	126	113	92	76	60	43	27	21	9	2	0	
Chemo	682	601	506	405	312	235	188	146	126	104	86	77	66	54	42	26	21	17	9	3	1	0	

- Longer median OS was observed in all randomised patients with MSI-H and MSS tumours treated with NIVO + chemo vs chemo
  - The magnitude of benefit was greater in patients with MSI-H tumours
  - Patients with MSS tumours had results similar to the all randomised population

[a] Minimum follow-up, 36.2 months

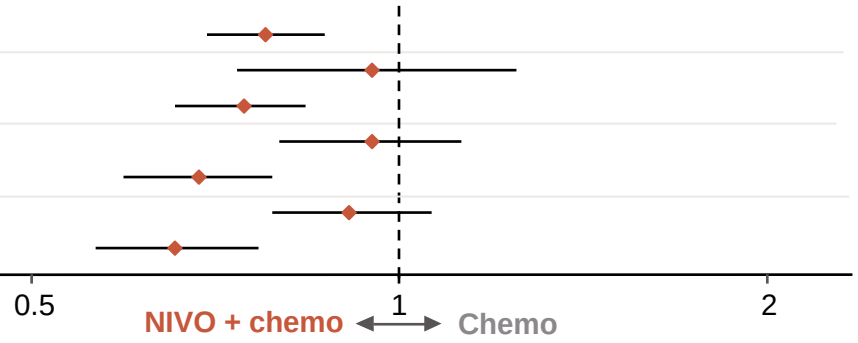
CI, confidence interval; HR, hazard ratio; MSI-(H), microsatellite instability-(high); MSS, microsatellite stable; NE, not estimable; NIVO, nivolumab; OS, overall survival

Janjigian YY, et al. J Clin Oncol. 2023;41(suppl 4; abstr 291)

EFFICACY SUBGROUP ANALYSIS BY PD-L1 CPS: 36-MONTH FOLLOW-UP

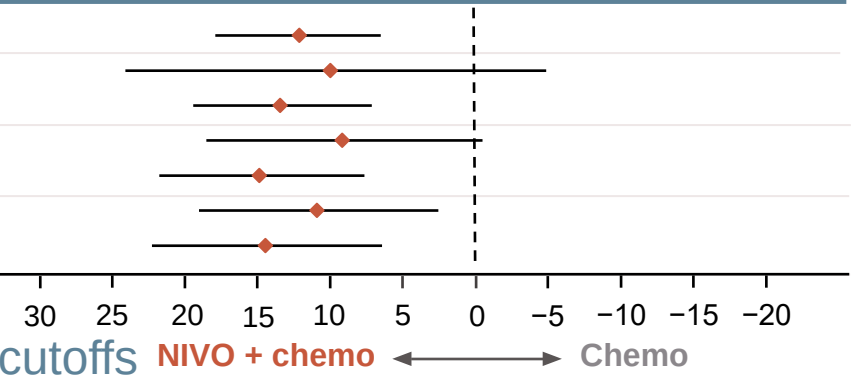
Overall survival

PD-L1 CPS[a]	Number of patients	Median OS, months		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N=1581)		13.7	11.6	0.78	
<1	265	13.1	12.5	0.95	
≥1	1297	13.8	11.3	0.75	
<5	607	12.4	12.3	0.95	
≥5	955	14.4	11.1	0.69	
<10	794	12.4	12.5	0.91	
≥10	768	15.0	10.9	0.66	



Objective response rate

PD-L1 CPS[b]	Number of patients	Objective response rate, %		Unweighted ORR difference,[c] %	Unweighted ORR difference,[c] % (95% CI)
		NIVO + chemo	Chemo		
Overall (N=1209)		58	46	12	
<1	179	51	41	10	
≥1	1016	60	46	13	
<5	427	56	46	9	
≥5	768	60	45	15	
<10	577	58	47	11	
≥10	618	59	44	14	



- OS benefit with NIVO + chemo was enriched at higher PD-L1 CPS cutoffs
- ORR was higher vs chemo across all PD-L1 CPS subgroups

[a] PD-L1 CPS expression indeterminate/nonevaluable/not reported, n=19; [b] Randomised patients who had target lesion measurements at baseline, per BICR. PD-L1 CPS expression indeterminate/nonevaluable/not reported, n=14; [c] Percentages may not reflect an exact difference due to rounding

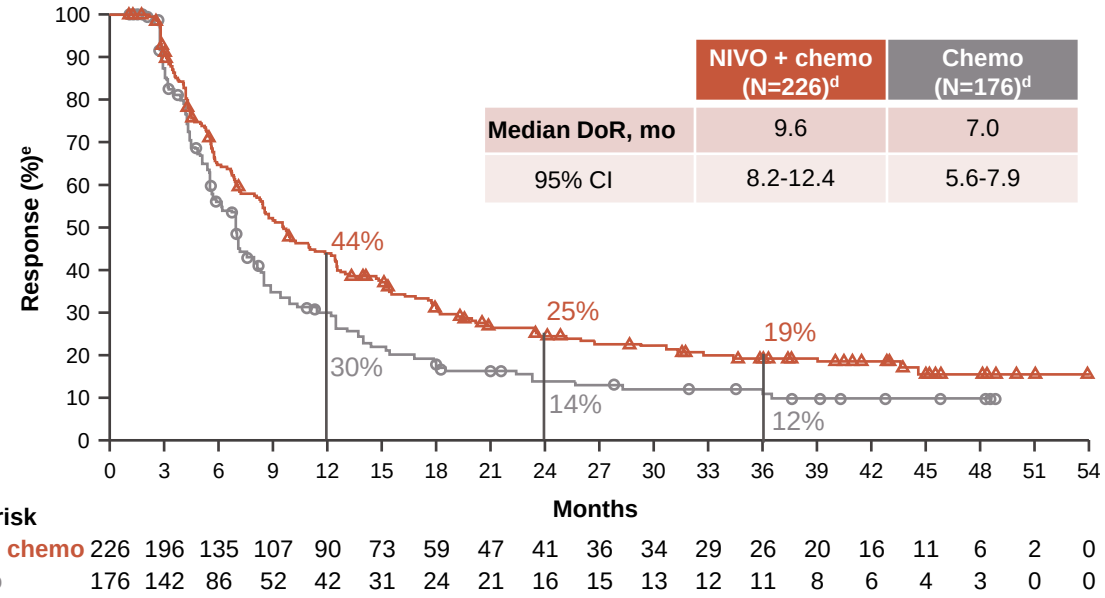
CI, confidence interval; CPS, combined positive score; HR, hazard ratio; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1

Janjigian YY, et al. J Clin Oncol. 2023;41(suppl 4; abstr 291)

RESPONSE AND DURATION OF RESPONSE: 36-MONTH FOLLOW-UP

PD-L1 CPS ≥5

Response per BICR	NIVO + chemo (N=378)[a]	Chemo (N=390)[a]
ORR,[b] % (95% CI)	60 (55-65)	45 (40-50)
CR	13	7
PR	47	38
SD	28	34
PD	7	11

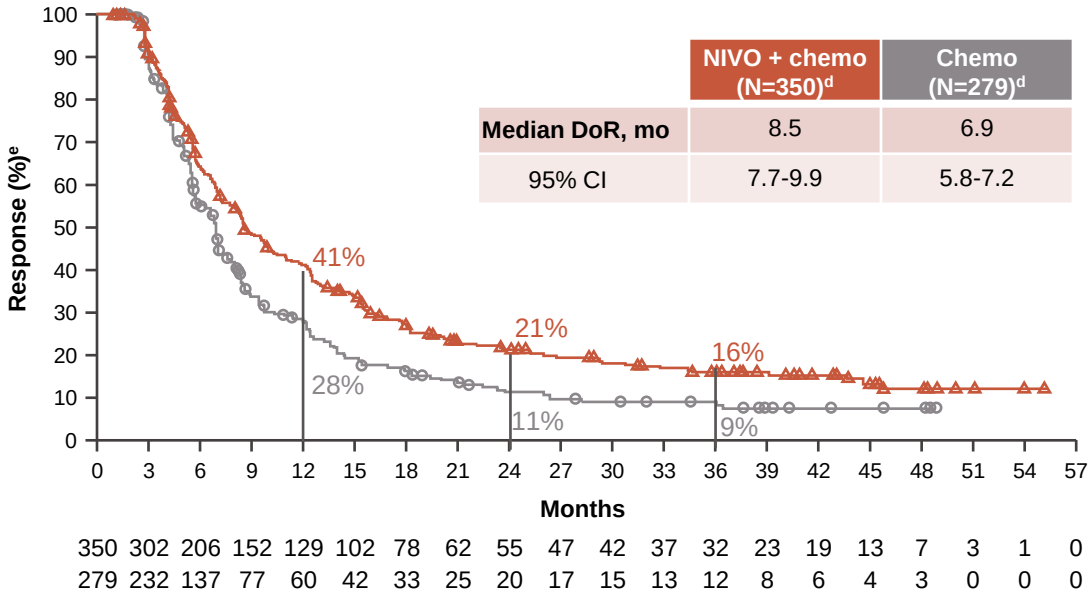


	NIVO + chemo (N=226)[d]	Chemo (N=176)[d]
Median DoR, mo	9.6	7.0
95% CI	8.2-12.4	5.6-7.9

No. at risk																			
NIVO + chemo	226	196	135	107	90	73	59	47	41	36	34	29	26	20	16	11	6	2	0
Chemo	176	142	86	52	42	31	24	21	16	15	13	12	11	8	6	4	3	0	0

All randomised

Response per BICR	NIVO + chemo (N=602)[a]	Chemo (N=607)[a]
ORR,[c] % (95% CI)	58 (54-62)	46 (42-50)
CR	11	7
PR	47	39
SD	28	33
PD	7	10



	NIVO + chemo (N=350)[d]	Chemo (N=279)[d]
Median DoR, mo	8.5	6.9
95% CI	7.7-9.9	5.8-7.2

NIVO + chemo	350	302	206	152	129	102	78	62	55	47	42	37	32	23	19	13	7	3	1	0
Chemo	279	232	137	77	60	42	33	25	20	17	15	13	12	8	6	4	3	0	0	0

- Higher ORR was maintained, and responses remained more durable with NIVO + chemo vs chemo with longer follow-up

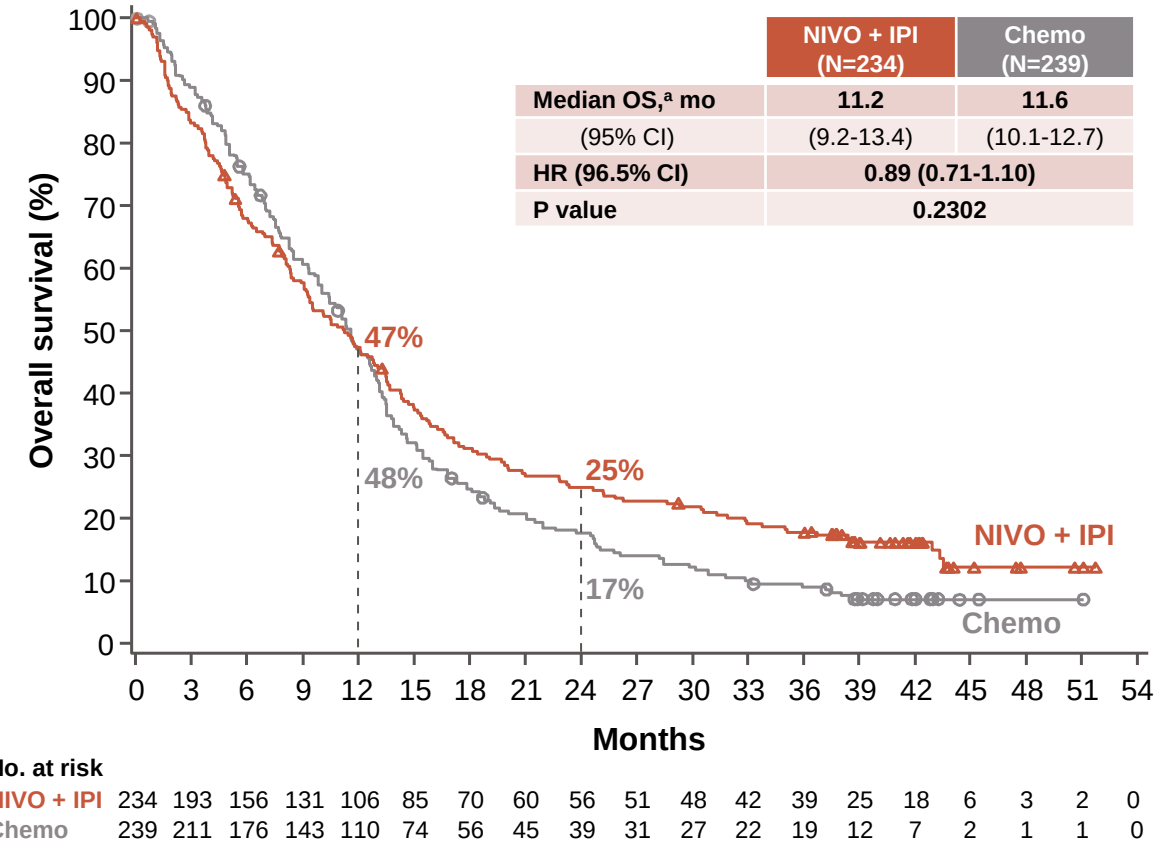
BICR, blinded independent central review; CI, confidence interval; CPS, combined positive score; CR, complete response; DoR, duration of response; NIVO, nivolumab; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease

[a] Randomised patients who had target lesion measurements at baseline per BICR assessment; [b] Unable to determine: NIVO + chemo, n=21; chemo, n=40; [c] Unable to determine: NIVO + chemo, n=40; chemo, n=66; [d] Number of responders; [e] Per BICR assessment

Janjigian YY, et al. J Clin Oncol. 2023;41(suppl 4; abstr 291)

OVERALL SURVIVAL: NIVO + IPI VS CHEMO

PD-L1 CPS ≥5

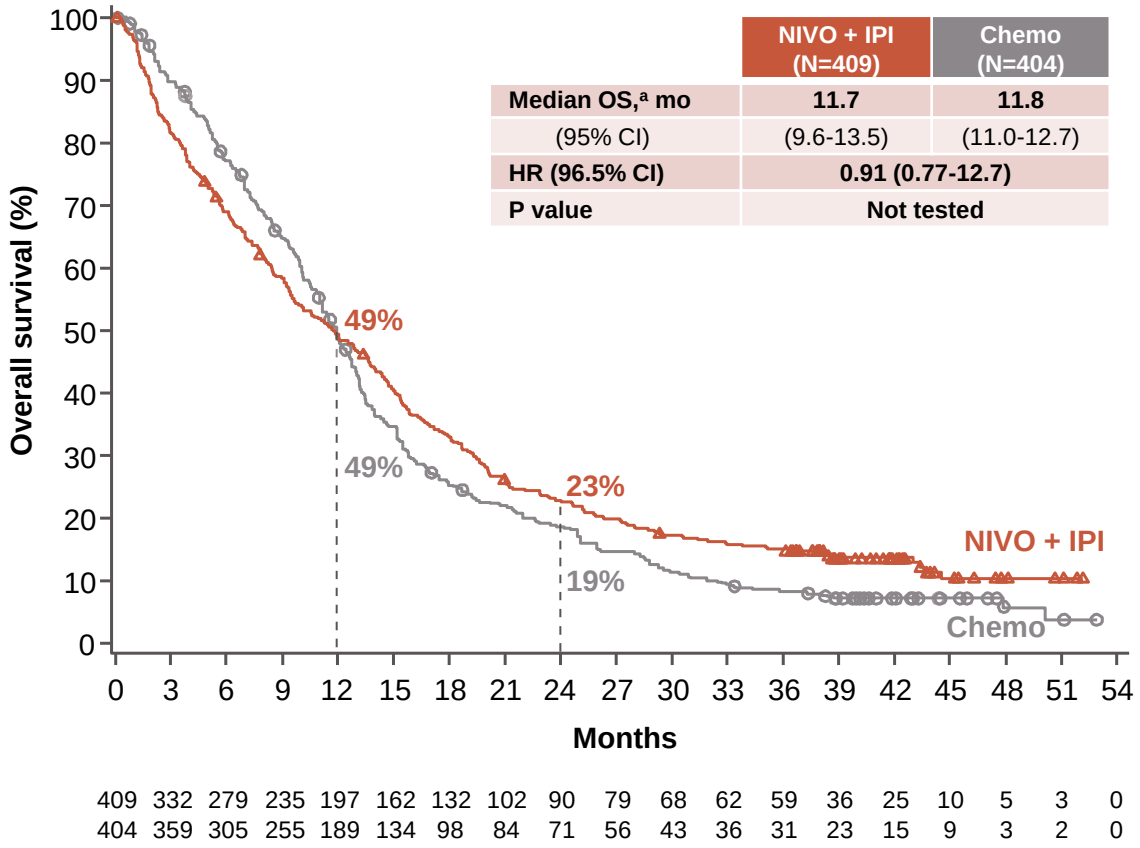


	NIVO + IPI (N=234)	Chemo (N=239)
Median OS,[a] mo	**11.2**	**11.6**
(95% CI)	(9.2-13.4)	(10.1-12.7)
HR (96.5% CI)	**0.89 (0.71-1.10)**	
P value	**0.2302**	

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 randomised



	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 (0.77-12.7)**	
P value	**Not tested**	

NIVO + IPI	409	332	279	235	197	162	132	102	90	79	68	62	59	36	25	10	5	3	0
Chemo	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 randomised patients was not statistically tested

[a] Minimum follow-up, 35.7 months

CI, confidence interval; CPS, combined positive score; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1

Janjigian YY, et al. J Clin Oncol. 2023;41(suppl 4; abstr 291)

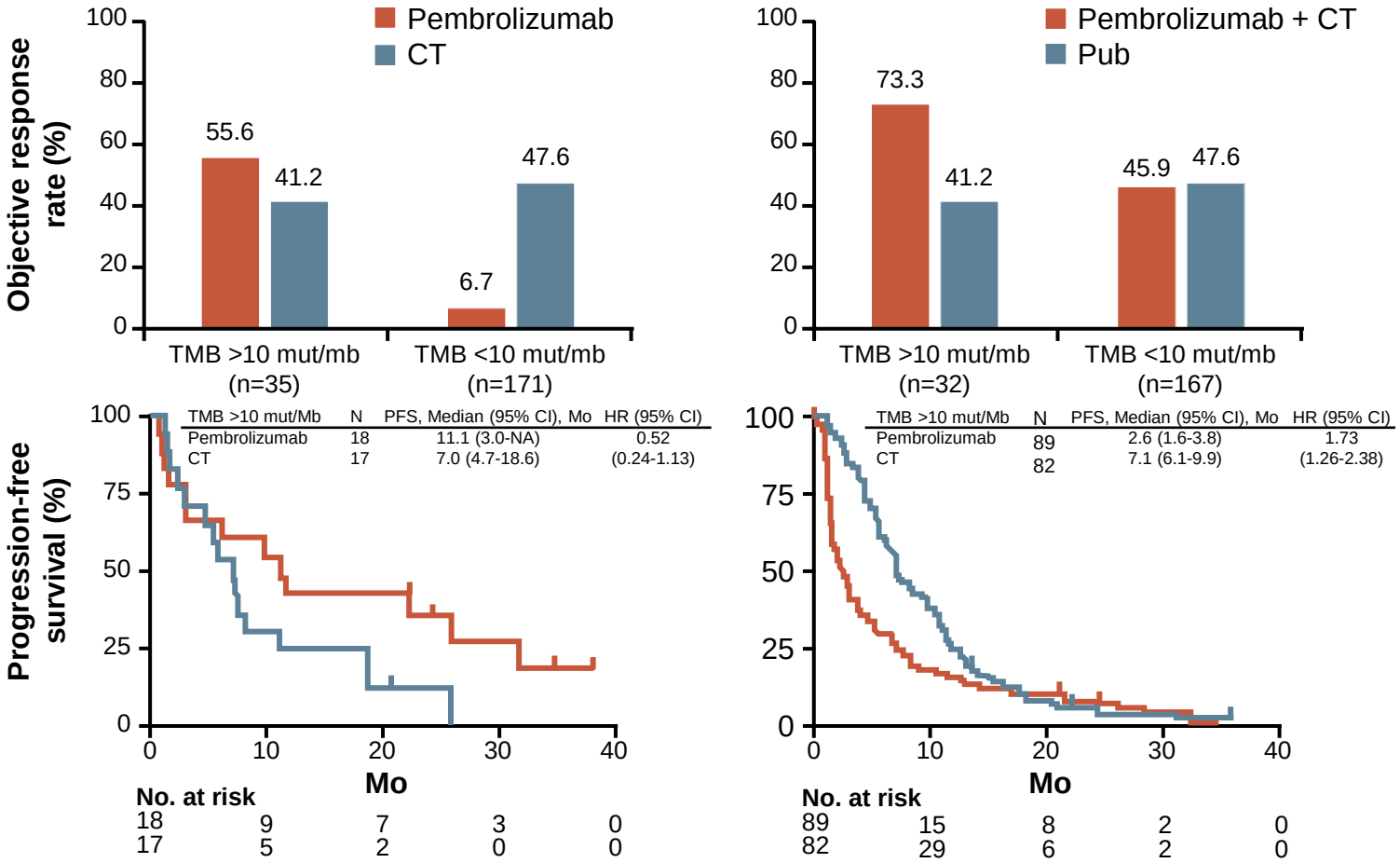
CASE 1: MSI-H GE JUNCTION ADENOCARCINOMA

- At presentation T3N1, HER2 negative, imaging negative for metastasis
- The patient treated with carboplatin/paclitaxel/radiation
- The patient developed malignant supraclavicular and retroperitoneal lymphadenopathy
- Biopsy proven metastatic adenocarcinoma
- Treated with palliative FOLFOX for four cycles with further disease progression
- **MSI-H tumour – on NGS 31 mutations including MLH1 X263 splice**

FOLFOX, fluorouracil (5-FU), leucovorin, oxaliplatin; GE, gastroesophageal; HER2, human epidermal growth factor receptor 2; MLH1, MutL protein homolog 1; MSI-H, microsatellite instability-high; N, nodal stage; NGS, next-generation sequencing; T, tumour stage

TMB IS NOT PREDICTIVE OF ICB BENEFIT IN NON-MSI-H

- FDA 6/16/2020: accelerated approval for pembrolizumab for unresectable or metastatic TMB-H (≥10mut/Mb) solid tumours, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment option



- TMB ≥10 Mut/Mb is seen in ~10%-15% of gastric cancers (KEYNOTE-062 data)
- ~45% of TMB-H also were MSI-H
- TMB and PD-L1 CPS do not have a tight correlation (r=0.23)
- After removing patients with MSI-H tumours, association between TMB-H and PFS/OS no longer significant

CI, confidence interval; CT, chemotherapy; FDA, Food and Drug Administration; HR, hazard ratio; ICB, immune checkpoint blockade; Mb, megabase; mo, month; MSI-H, microsatellite instability-high; mut, mutation; OS, overall survival; PFS, progression-free survival; TMB-(H), tumour mutational burden-(high)

Lee K-W, et al. Clin Cancer Res. 2022; 28:3489-98

53-YR-OLD WOMAN WITH STAGE IV GASTRIC ADENOCARCINOMA

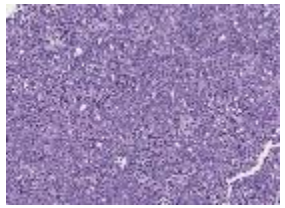
GERD, PPI

↑ gas, bloating, early satiety, weight loss (25 lbs/11 kg)

EGD: ulceration in lesser curvature
CT CAP: 2.5 cm lesion lesser curvature, peritoneal carcinomatosis

Mo

-4 -2 0



Infiltrating Adenocarcinoma
Moderately to Poorly Differentiated

7 Mutations (page 1 of 1)

Samples	Gene	Protein Change	Annotation	Mutation Type
1	PIK3CA	*G106R*		Missense
1	KRAS	*G13D*		Missense
1	CREBBP	*R1446S*		Missense
1	SMARCA4	*R1135W*		Missense
1	BCOR	*L775Vfs*42*		FS Ins
1	SETD2	*Y1605N*		Missense
1	NSD1	*S1051N*		Missense

Showing 1-7 of 7 Mutations

IHC for **HER2** (4B5, Ventana): **negative** (score 0)
IHC for **PD-L1** expression (clone E1L3N): **CPS 20 (of 100)**
Mismatch repair proteins: MLH1, MSH2, MSH6, PMS2 present

CPS, combined positive score; CREBBP, CREB binding protein; CT CAP, computed tomographic (CT) chest abdomen pelvis; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma virus; MLH1, MutL protein homolog 1; mo, month; PD-L1, programmed death-ligand 1; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase; PPI, proton pump inhibitor

PATIENT CASE: 53-YR-OLD WOMAN WITH STAGE IV GASTRIC ADENOCARCINOMA

GERD, PPI

↑ gas, bloating, early satiety, weight loss (25 lbs/11 kg)

EGD: ulcer
CT CAP: 2.5 cm lesion lesser curvature, peritoneal carcinomatosis

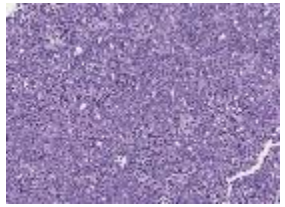
EGD: benign on bx
CT CAP: resolution of radiographic disease

FOLFOX + Nivo × 11 Cycles

5FU/Nivo Maintenance

Mo

-4 **-2** **0** **5** **9** **36**



Infiltrating Adenocarcinoma
Moderately to Poorly Differentiated

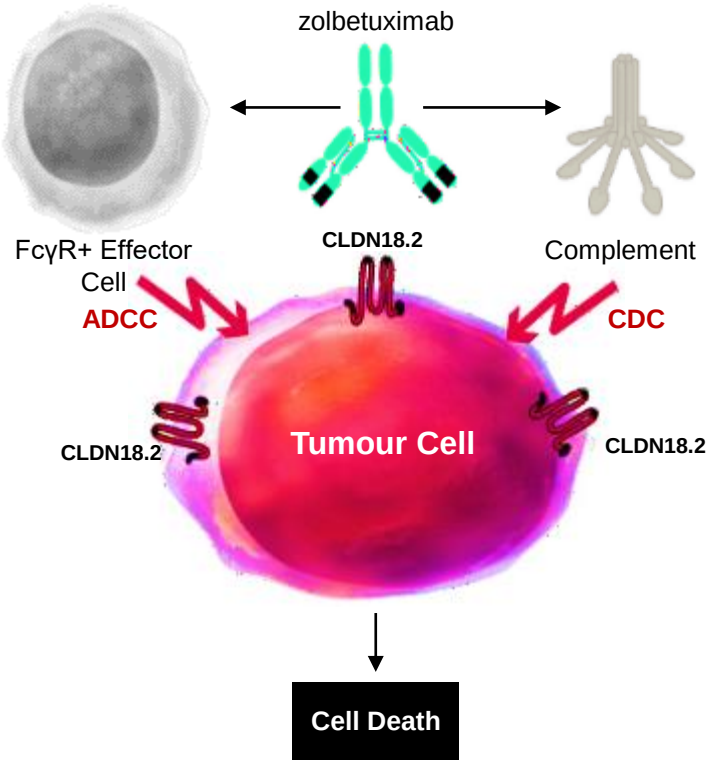
IHC for **HER2** (4B5, Ventana): **negative** (score 0)
IHC for **PD-L1** expression (clone E1L3N): **CPS 20 (of 100)**
Mismatch repair proteins: MLH1, MSH2, MSH6, PMS2 present

5-FU, fluorouracil; CPS, combined positive score; CT CAP, Computed tomographic (CT) chest abdomen pelvis; EGD, esophagogastroduodenoscopy; FOLFOX, fluorouracil (5-FU), leucovorin, oxaliplatin; GERD, gastroesophageal reflux; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MLH1, MutL protein homolog 1; mo, month; NIVO, nivolumab; PD-L1, programmed death-ligand 1; PPI, proton pump inhibitor

INTRODUCTION: ZOLBETUXIMAB TARGETS CLDN18.2

- CLDN18.2 is a tight junction protein normally expressed in gastric mucosa cells and retained in G/GEJ adenocarcinoma[1-8]
- CLDN18.2 may become exposed on the surface of G/GEJ adenocarcinoma cells, making it a promising target[2-8]
- Zolbetuximab is a first-in-class chimeric IgG1 monoclonal antibody that targets CLDN18.2 and induces ADCC/CDC[4-8]
- In the phase 2b FAST study, EOX ± zolbetuximab prolonged survival in a subgroup of patients with higher expression of CLDN18.2 in tumour cells[8]
  - mPFS: 9.0 vs 5.7 months with zolbetuximab + EOX vs EOX alone
  - mOS: 16.5 vs 8.9 months with zolbetuximab + EOX vs EOX alone

Mechanism of Action of Zolbetuximab



ADCC, antibody-dependent cellular toxicity; CDC, complement-dependent toxicity; CLDN18.2, claudin 18.2; EOX, epirubicin and oxaliplatin plus capecitabine; G/GEJ, gastric or gastroesophageal junction; OS, median overall survival; mPFS, median progression-free survival

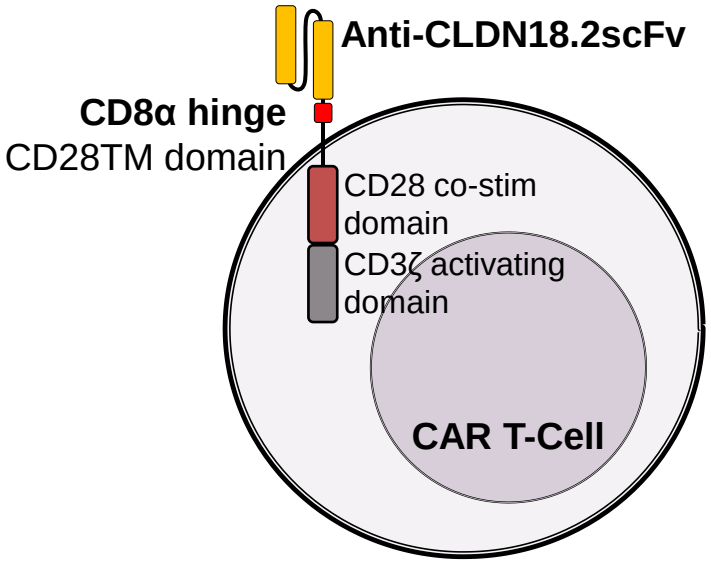
1. Nimi T, et al. Mol Cell Biol. 2001;21:7380-90; 2. Sahin U, et al. Clin Cancer Res. 2008;14:7624-34; 3. Moran D, et al. Ann Oncol. 2018;29:viii14-viii57; 4. Sahin U, et al. Eur J Cancer. 2018;100:17-26; 5. Rhode C, et al. Jpn J Clin Oncol 2019;49:870-6; Türeci Ö, et al. Ann Oncol. 2019;30:1487-95; 7. Pellino A, et al. J Pers Med. 2021;11:1095; 8. Sahin U, et al. Ann Oncol. 2021;32:609-19

MAJOR CLAUDIN18.2 STRATEGIES

Zolbetuximab (CLDN18.2 IgG1 mAb) is an advanced CLDN18.2-directed agent, awaiting phase 3 1L trial readouts (SPOTLIGHT and GLOW)

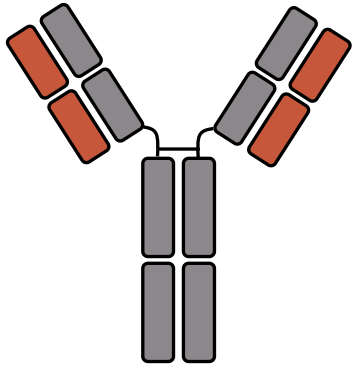
CAR T-Cell

CT041[1]



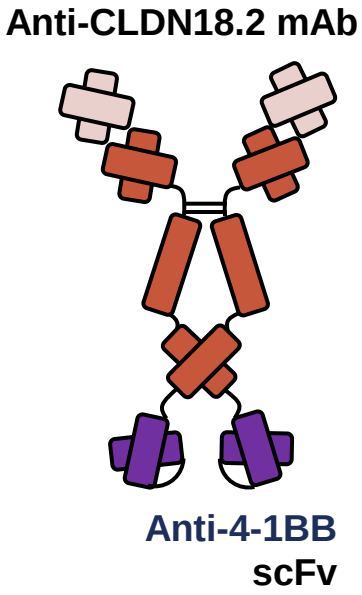
Engineered mAb

ZL-1211[2] (Humanised IgG1)



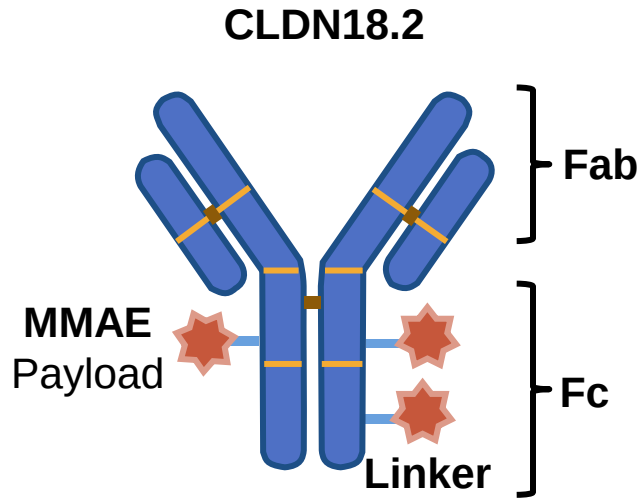
Bispecific Ab

TJ-CD4B[3]



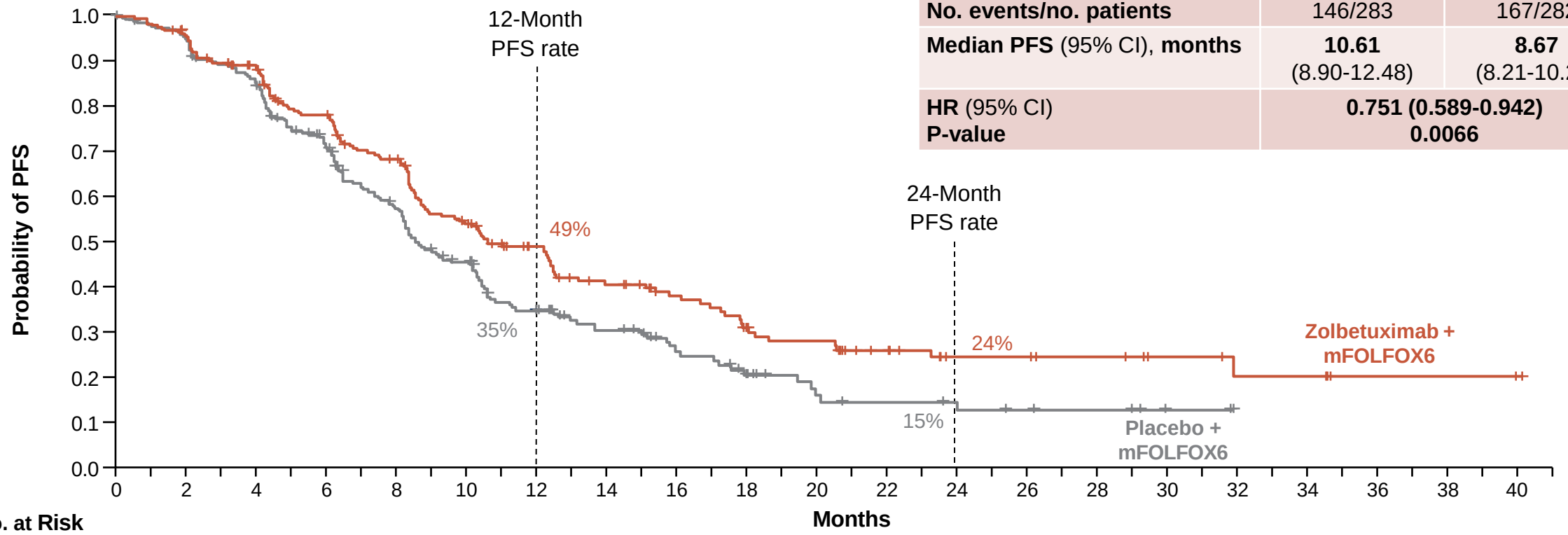
Antibody–Drug Conjugate

CMG901[1]



SPOTLIGHT PRIMARY END POINT: PFS BY INDEPENDENT REVIEW COMMITTEE[a]

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



No. at Risk

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

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

Data cutoff: September 9, 2022; Median follow-up = 12.94 months (zolbetuximab + mFOLFOX6) vs 12.65 months (placebo + mFOLFOX6).

[a] Per RECIST version 1.1

CI, confidence interval; FOLFOX, fluorouracil (5-FU), leucovorin, oxaliplatin; HR, hazard ratio; mFOLFOX6, modified FOLFOX regimen; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours

Shitara K, et al. J Clin Oncol. 2023;41(suppl 4; abstr LBA292)

BIOMARKER OVERLAP IN GASTRIC CANCER

- *Reflex testing of all tumours is critical*
- Overlap between PDL1 CPS ≥5 and CLD18.2 high in approximately 20% of patients

Term	Kubota Y 2022[1,a]	Pellino A 2021[2,a]	Jia K 2022[3,b]	SPOTLIGHT[4,a]	GLOW[5,a]
Percentage (%)	CLDN18.2+ 24%	CLDN18.2+ 33%	CLDN18.2+ 53%	CLDN18.2+ 39%	CLDN18.2+ 38%
HER2+	15	15	21	–	–
dMMR/MSI	5	13	14	–	–
PD-L1[c] CPS <1	26	74	21		
PD-L1[c] CPS ≥5	42	18	57.1	13	22
Diffuse Type	48	40	29	29	34
Intestinal Type	52	46	38	25	14
Mixed/Other	–	12	33	46	51

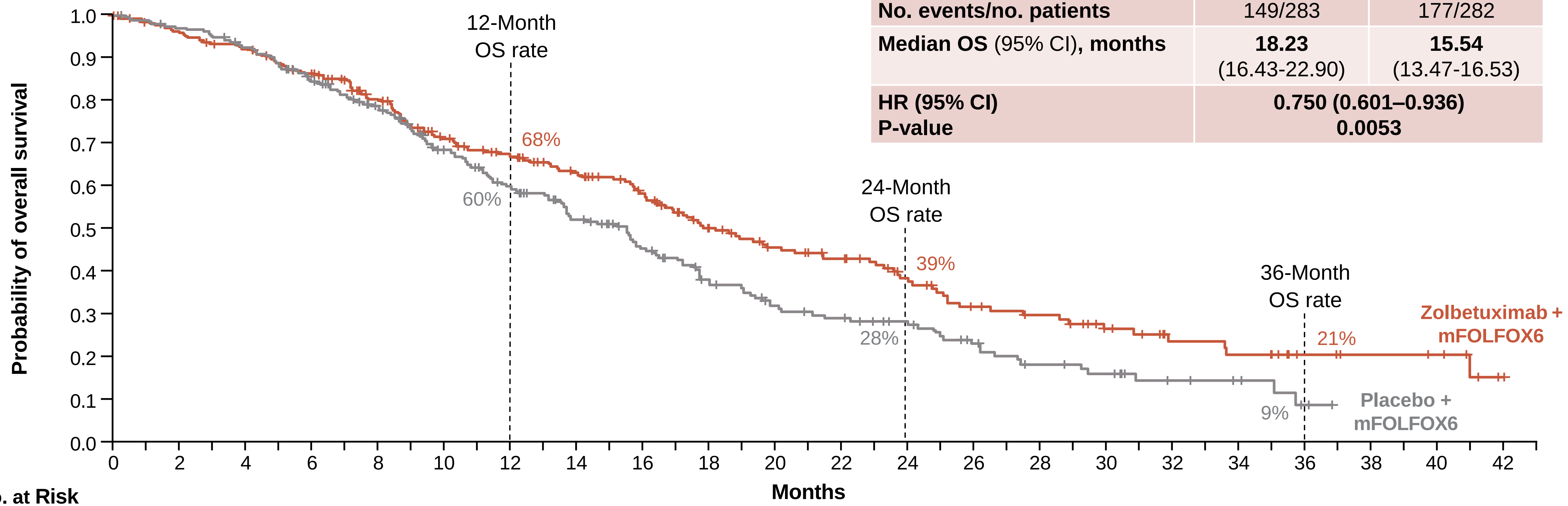
a. CLDN18.2+ as >= 75% tumor cells with 2+/3+ membrane staining, IHC Ab = Roche, clone 43-14A (Kubota and Pellino) VENTANA CLDN18 (43-14A) RxDx Assay (SPOTLIGHT and GLOW)
b. CLDN18.2+ as >=40% tumor cells with 2+ or higher membrane staining, IHC Ab = Abcam ab222512
c. PD-L1 testing antibodies; Kubota SP142 or SP263, Pellino 22C3, Jia E1L3N

Ab, antibody; CLDN18.2, claudin 18.2; CPS, combined positive score; IHC, immunohistochemistry; PD-L1, programmed death-ligand 1

1. Kubota Y, et al. ESMO Open. 2023;8:100762; 2. Pellino A, et al. J Pers Med. 2021; 3. Jia K, et al. BMC Med. 2022;20:223; 4. Shitara K, et al. J Clin Oncol 41, 2023 (suppl 4; abstr LBA292); 5. Xu R-H, et al. J Clin Oncol 41, 2023 (suppl 36; abstr 405736)

SPOTLIGHT KEY SECONDARY END POINT: OS

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	149/283	177/282
Median OS (95% CI)**, months**	**18.23** (16.43-22.90)	**15.54** (13.47-16.53)
HR (95% CI) **P-value**	**0.750 (0.601–0.936)** **0.0053**	



No. at Risk

Zolbetuximab + mFOLFOX6	283	270	264	255	251	241	233	217	196	178	164	152	146	135	125	117	107	93	83	75	70	67	62	58	49	42	34	32	30	27	23	20	15	15	13	13	9	8	7	7	6	4	1	0
Placebo + mFOLFOX6	282	277	271	266	253	242	224	210	197	183	164	152	139	129	108	101	85	77	64	60	49	42	40	36	34	30	25	21	18	17	15	9	8	7	6	5	2	0	0	0	0	0	0	0

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

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

CI, confidence interval; FOLFOX, fluorouracil (5-FU), leucovorin, oxaliplatin; HR, hazard ratio; mFOLFOX6, modified FOLFOX regimen; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumours

Shitara K, et al. J Clin Oncol. 2023;41(suppl 4; abstr LBA292)

SPOTLIGHT SECONDARY END POINTS

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

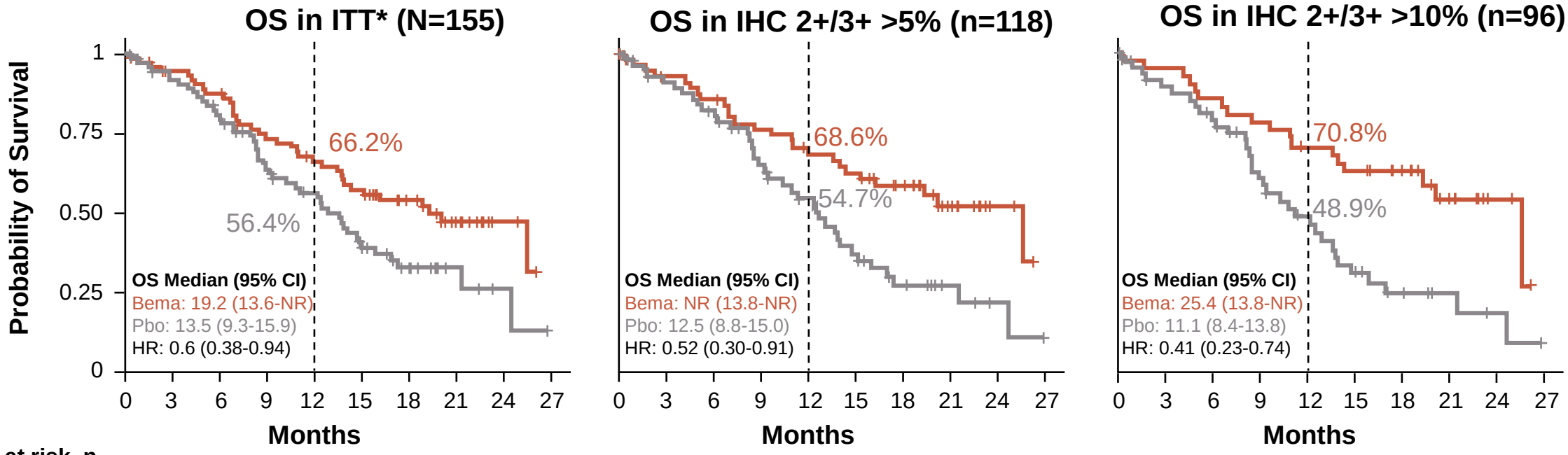
- Response rates were similar between treatment arms
- Formal analysis of PROs is pending
  - Initial descriptive analysis did not indicate differences between treatment arms

BOR, best overall response; CI, confidence interval; CR, complete response; DoR, duration of response; FOLFOX, fluorouracil (5-FU), leucovorin, oxaliplatin; mFOLFOX6, modified FOLFOX regimen; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; PRO, patient-reported outcome; SD, stable disease

Shitara K, et al. J Clin Oncol. 2023;41(suppl 4; abstr LBA292)

FIGHT: FIRST-LINE BEMARITUZUMAB + CHEMOTHERAPY IN FGFR2B-POSITIVE ADVANCED GASTRIC CANCER

- Addition of anti FGFR2b antibody to chemotherapy in FGFR2b+ gastric cancer showed 5.7-mo improvement in mOS in ITT population



Patients at risk, n

Bema	77	68	63	51	45	39	28	14	4	0		58	51	47	40	35	32	23	12	4	0		44	40	36	31	27	24	19	10	3	0
Placebo	78	68	58	44	36	25	13	5	2	0		60	51	44	33	25	17	10	5	2	0		52	43	37	26	19	12	7	4	2	0

Median follow-up 12.5; data cutoff: February 28, 2021

* ITT composed of n=149 patients with IHC 2+/3+ and n=6 with IHC <2 or not available; patients enrolled based on ctDNA results only

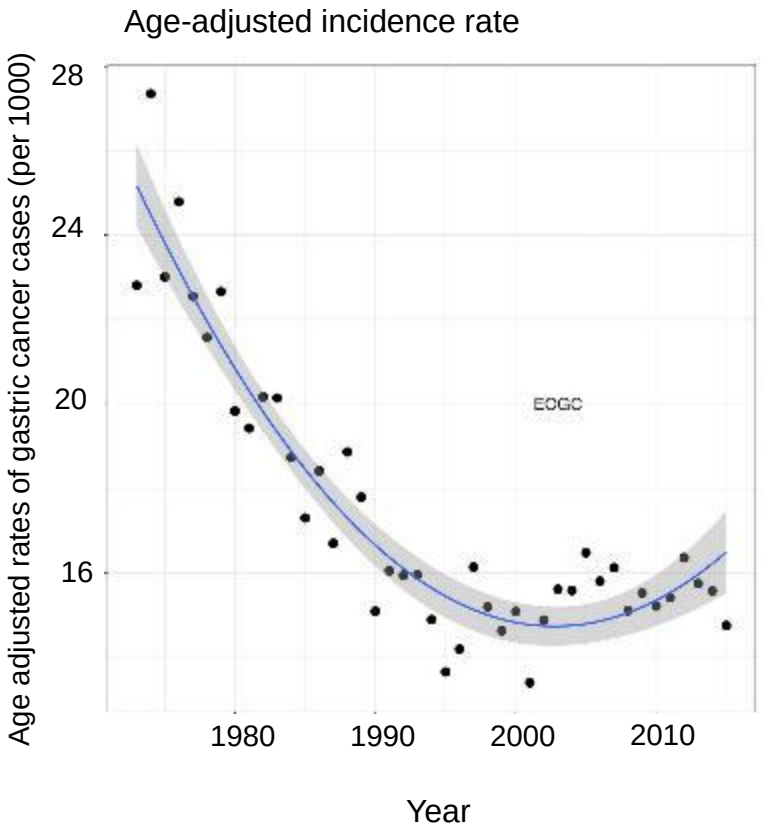
Bema, bemarituzumab; CI, confidence interval; FGFR2b, fibroblast growth factor receptor 2b; IHC, immunohistochemistry; ITT, intent to treat; mo, month; mOS, median OS; OS, overall survival; pbo, placebo

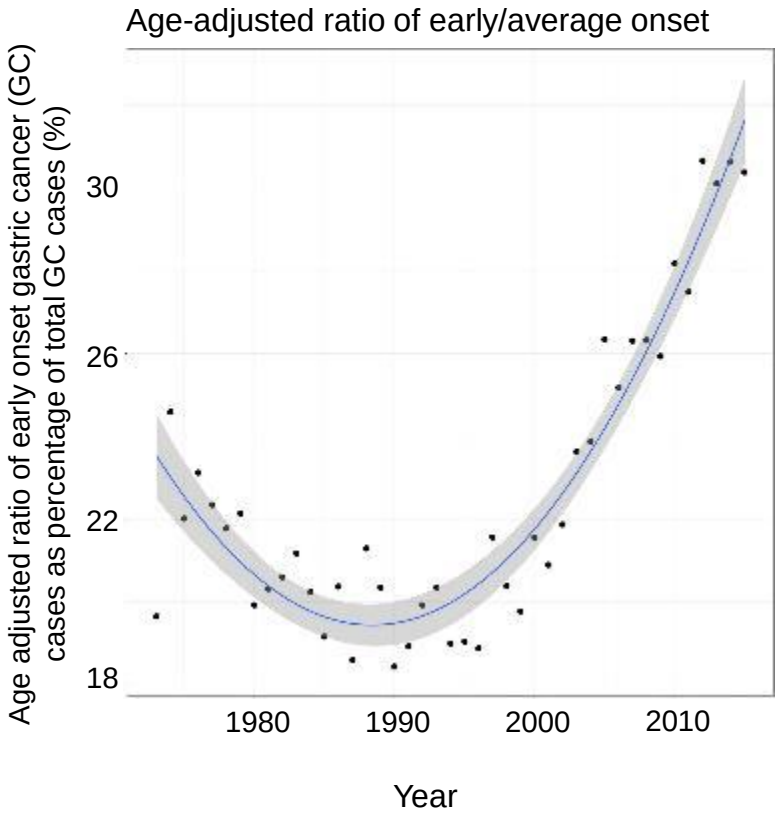
Catenacci DVT, et al. J Clin Oncol. 2021;39(no. 15_suppl):4010-4010

INCIDENCE OF EARLY ONSET ESOPHAGOGASTRIC CANCER (AGE ≤50) IS RISING

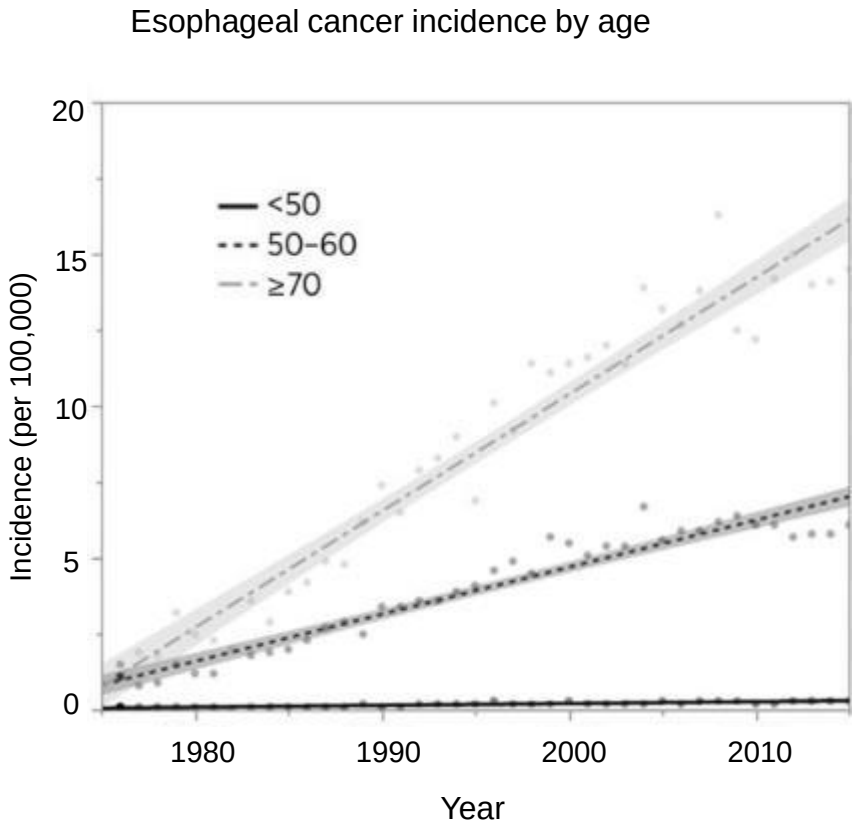
3x increase of early onset GEJ adenocarcinoma from 0.08/100,000 in 1975 to 0.27/100,000 in 2015

Gastric Cancer[1]





Esophageal Cancer[2]

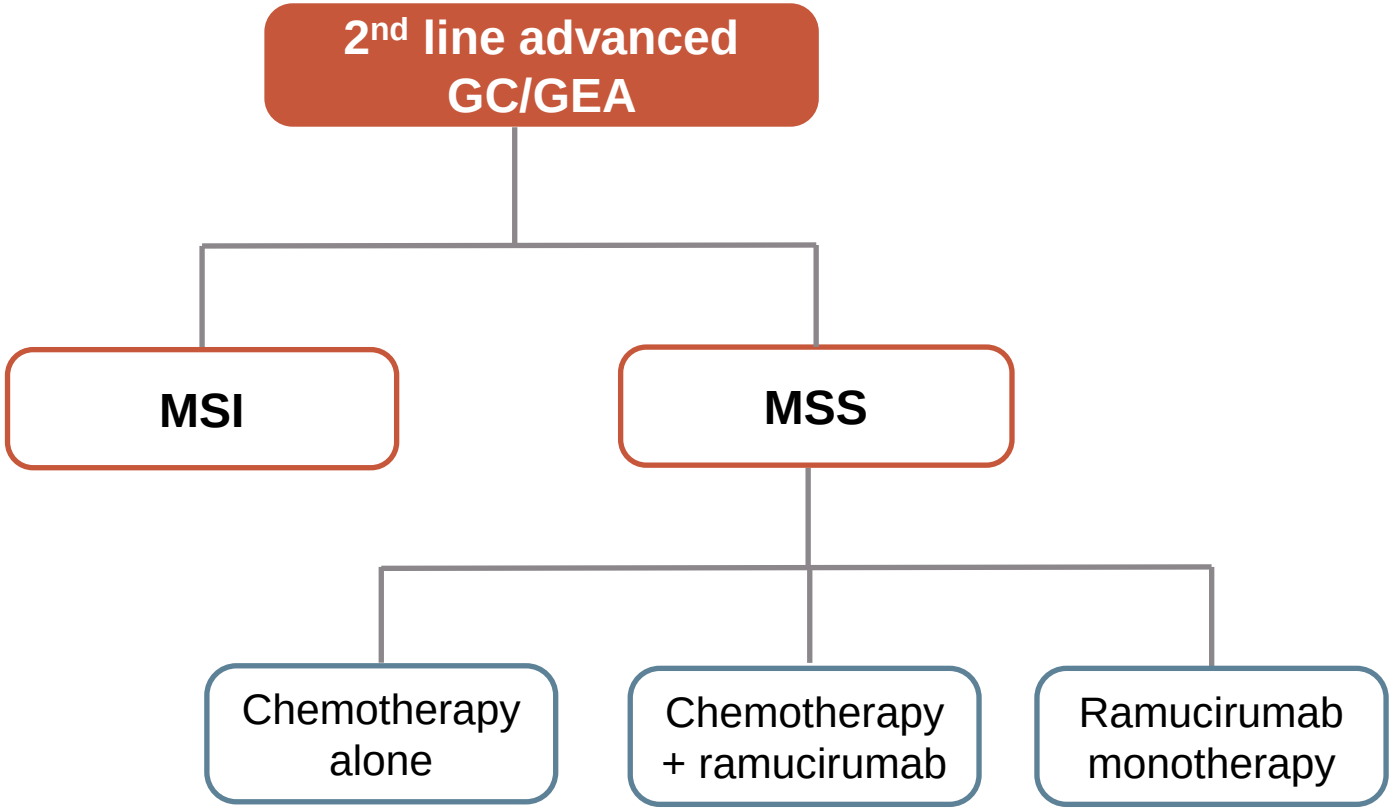


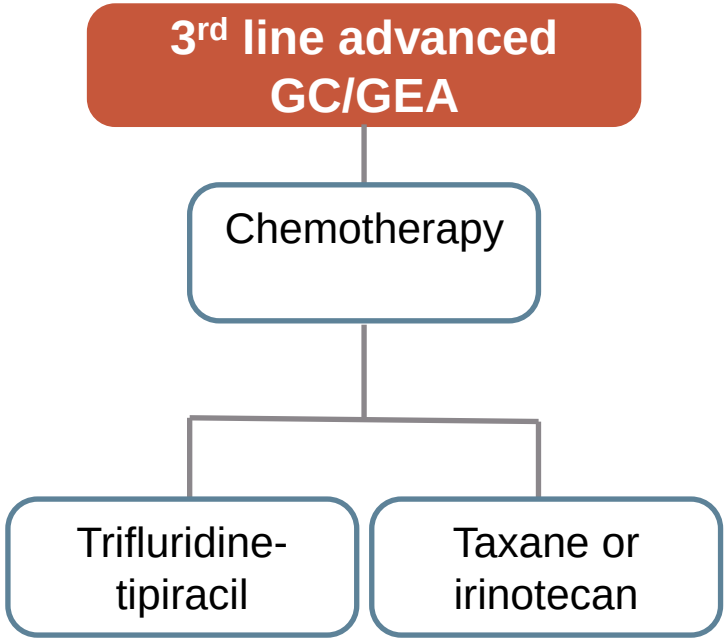
GEJ, gastroesophageal junction

1.Bergquist JR, et al. Surgery 2019;166:547-55 Codipilly DC, et al. 2.Cancer Epidemiol Biomarkers Prev. 2021; 30:142-149

SECOND- AND THIRD LINE TREATMENTS OPTIONS FOR PATIENTS WHO PROGRESS

CURRENT NCCN AND ESMO GUIDELINES ON SECOND-LINE AND FURTHER THERAPIES





Symth EC, et al. Ann Oncol. 2016;27 Suppl 5:38–49
Ajani JA, et al. JNCCN.2022; 20:167-192

GC, gastric cancer; GEA, gastroesophageal adenocarcinoma; MSI, microsatellite instability; MSS, microsatellite stable

OUTLOOK IN TO THE FUTURE

INVESTIGATIONAL SECOND- AND FURTHER-LINE TREATMENTS

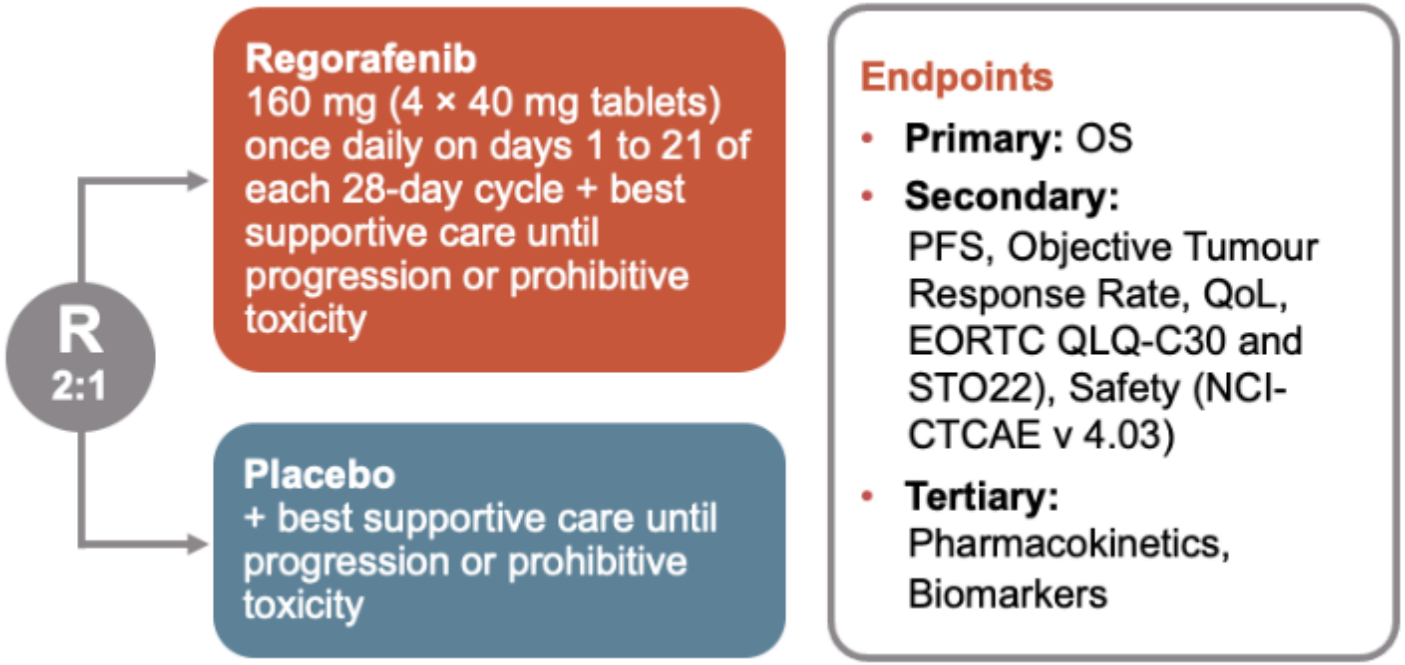
Name	Phase	Biomarker	Drug	Arms
ASPEN-06	2/3	HER2	Evorpacept (ALX148) Trastuzumab Ramucirumab Paclitaxel	• Evorpacept (ALX148), trastuzumab, ramucirumab, paclitaxel • Trastuzumab, ramucirumab, paclitaxel • Ramucirumab
LEAP-015	3	Antiangiogenic + PD-1	Lenvatinib Pembrolizumab	• Lenvatinib + pembrolizumab + chemotherapy • Chemotherapy
FORTITUDE 101	3	FGFR2b	Bemarituzuamb	• Bemarituzumab with mFOLFOX6 • Placebo with mFOLFOX6
FORTITUDE 102	1b/3	FGFR2b	Bemarituzumab	• Bemarituzumab with mFOLFOX6 and nivolumab • Placebo with mFOLFOX6 and nivolumab
INTEGRATE IIB	3	Anti-angiogenic + PD-1	Regorafenib	• Regorafenib plus nivolumab • Standard of care

https://clinicaltrials.gov/ct2/show/NCT05002127;https://clinicaltrials.gov/ct2/show/NCT04662710; https://clinicaltrials.gov/ct2/show/NCT05052801; https://clinicaltrials.gov/ct2/show/NCT05111626; https://clinicaltrials.gov/ct2/show/NCT04879368

ADVANCED REFRACTORY GASTROESOPHAGEAL CANCER

INTEGRATE IIa Phase III International, multi-centre, randomised controlled clinical trial: Regorafenib vs best supportive care

- Regorafenib improved OS:
  - HR 0.70 (95% CI: 0.56-0.87; p=0.001) in the pooled study population (INTEGRATE and INTEGRATE IIa); no heterogeneity observed (p=0.90)
  - After 238 events in INTEGRATE IIa, OS HR 0.68 with 12-month survival of 19% vs 6%
  - No statistically significant regional difference (Asia vs non-Asia), with benefit seen in all pre-specified sub-groups
- Regorafenib improved PFS: HR=0.53; 95% CI: 0.40-0.70; p<0.0001)
- Regorafenib delays deterioration in global QoL compared with PBO (p=0.0043)
- Regorafenib toxicity profile was similar to that seen in previous reports



- INTEGRATE IIb is an ongoing international Phase III study in pre-treated patients with AGOC comparing regorafenib + nivolumab to standard chemotherapy (NCT04879368)

AGOC, advanced gastro-oesophageal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; IV, intravenous; OS, overall survival; PFS, progression-free survival; QoL, quality of life; R, randomisation; RCT, randomised controlled trial; VEGF, vascular endothelial growth factor;QLQ-C30, EORTC core quality of life questionnaire; QLQ-STO22, EORTC-QLQ-stomach module; QoL, quality of life; R, randomisation; VEGF, vascular endothelial growth factor

Pavlakis N, et al. ASCO GI 2023. Abstract #LBA294; https://clinicaltrials.gov/ct2/show/NCT02773524; https://clinicaltrials.gov/ct2/show/NCT04879368

CONCLUSION

- Anti-PD-1 therapy improves survival & transforms patient lives
- Greater magnitude of benefit in biomarker enriched populations
- Critical to continue to test for HER2, MSI, PD-L1 and now CLD18.2
- Zolbetuximab + mFOLFOX6 is a new potential treatment for a biomarker-based subgroup of patients with CLDN18.2+/HER2−
- Priority remains in first-line setting
  - Immune check point blockade for MSI-H and PDL CPS ≥5 tumors
  - Dual HER2/PD-1 blockade in HER2-positive tumors
  - In patients with unknow CLD18.2 immune check point blockade
- The next generation of CLD18.2 inhibitors show potential for deeper responses and synergy with anti-PD-1 therapy
- The future is bright for gastric cancer biomarker selected strategies

CLD18.2, claudin 18.2; EGFR, epidermal growth factor receptor; FGFR2a, fibroblast growth factor receptor 2a; FOLFOX, fluorouracil (5-FU), leucovorin, oxaliplatin; HER2, human epidermal growth factor receptor 2; mFOLFOX6, modified FOLFOX regimen; MSI, microsatellite instability; PD-1, programmed cell death protein; PD-L1, programmed death-ligand 1

TWITTER: @YJANJIGIANMD

THANK YOU FOR YOUR ATTENTION

NON-METASTATIC GASTROESOPHAGEAL CANCERS

Sam Klempner, MD
MGH Cancer Center
Boston, MA, USA

CASE #1: LOCALISED GASTRIC CANCER

History of present illness : 77-year-old male presents with fatigue and anaemia and is found to have a 4 cm ulcer in the gastric fundus, biopsies with moderately differentiated adenocarcinoma. ECOG 1

- PMH: HTN, Left 5th finger amputation (lost a bet), hyperlipidaemia
- Labs: Fe-deficiency anaemia, otherwise WNL
- FH: No history GI cancers, father with lung cancer
- Physical exam: WNL
- Imaging: CT CAP with contrast with perigastric 16 mm lymph node, no other disease
- Diagnostic Laparoscopy: No peritoneal disease, washings negative

CAP, chest abdomen pelvis; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; Fe, iron; FH, family history; HTN, hypertension; PMH, past medical history; WNL, within normal limits

POLL QUESTION #1

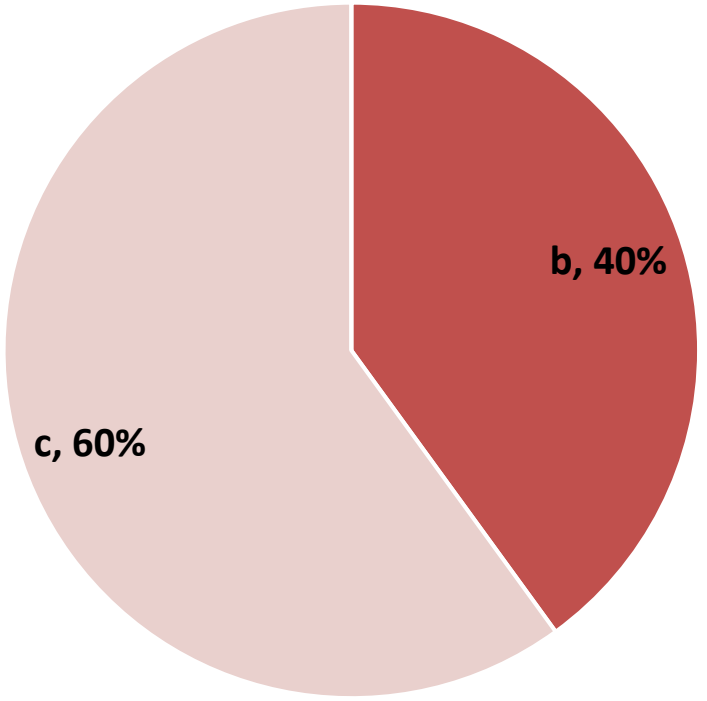
Interval History: He comes to clinic with his daughter, a practicing GI oncologist and wants to know the next steps. What do you tell him?

a) This is advanced disease and curative intent is not appropriate?

b) We will get you set up for FLOT within 2 weeks?

c) **Additional biomarker testing might help?** ☑

d) Nothing, seek advice from his specialist daughter?



FLOT, fluorouracil, leucovorin, oxaliplatin and docetaxel; GI, gastrointestinal

A CASE OF LOCALISED GASTRIC CANCER

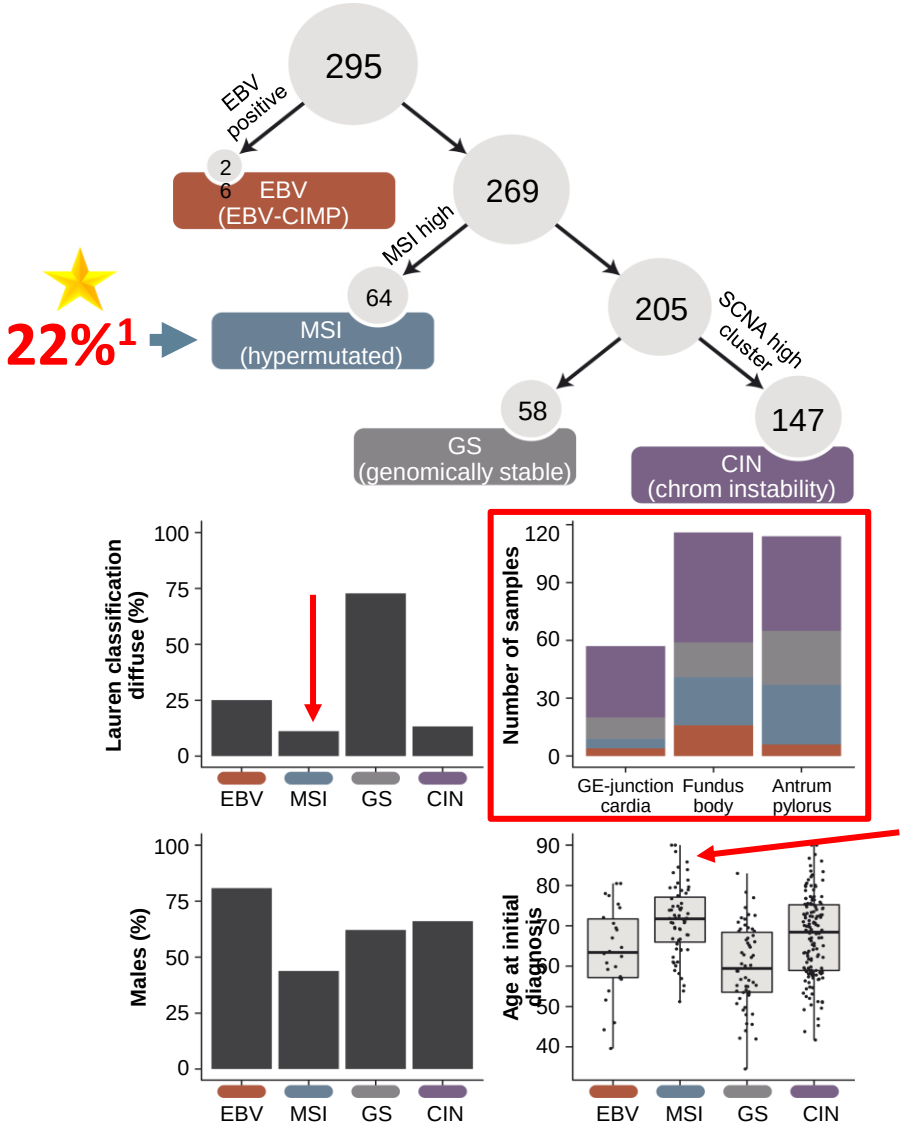
You elect for additional biomarker testing and the tumour is found to have complete loss of MLH1 and PMS2. HER2 IHC 1+. PD-L1 was not performed. The patient wants to know the implications of these results.

Is there a prognostic role for dMMR/MSI-H in localised GEA?

Do these results guide your management?

dMMR, deficient mismatch repair; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MLH1, MutL protein homologue 1; MSI-H, microsatellite instability-high; PD-L1, programmed death-ligand 1; PMS2, mismatch repair endonuclease PMS2

dMMR AND MSI IN LOCALISED GASTROESOPHAGEAL ADENOCARCINOMA



NON-METASTATIC DISEASE

- DANTE: **7.8%** (23/295) – ASCO 2022[2]
- Pooled meta (MAGIC, ARTIST, CLASSIC, ITACA-S): **7.8%** (121/1,556) – JCO 2019[3]
- TCGA (mostly non-met samples): **22%** – Nature 2014[1]
- NEONIPIGA: N/A – JCO 2022[4]

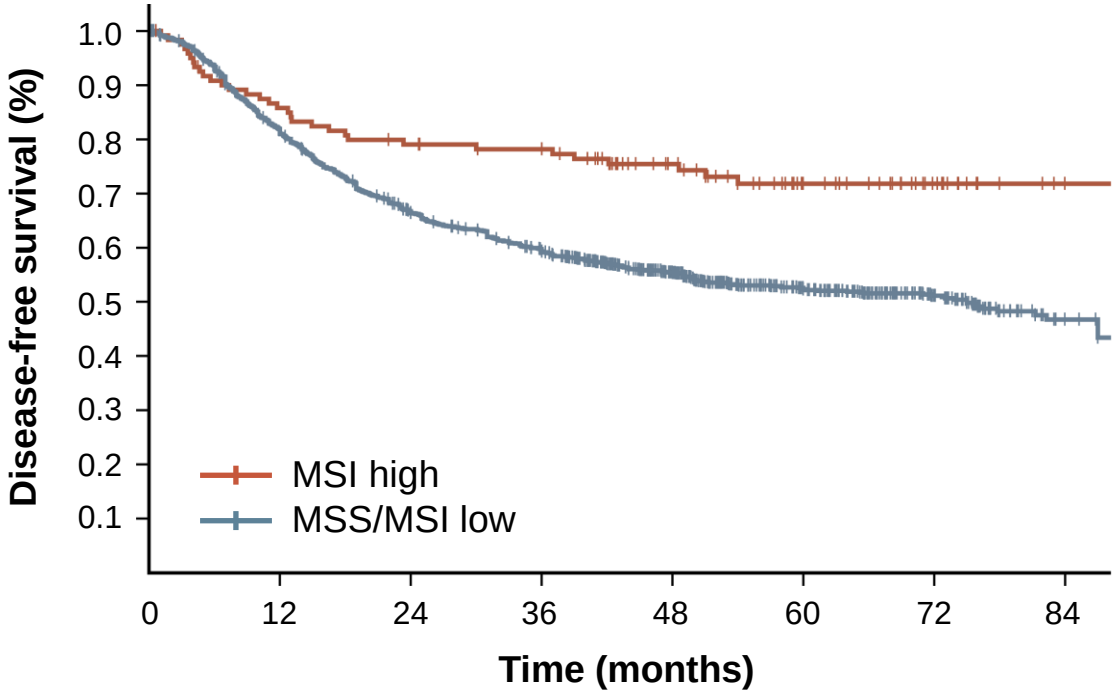
METASTATIC DISEASE

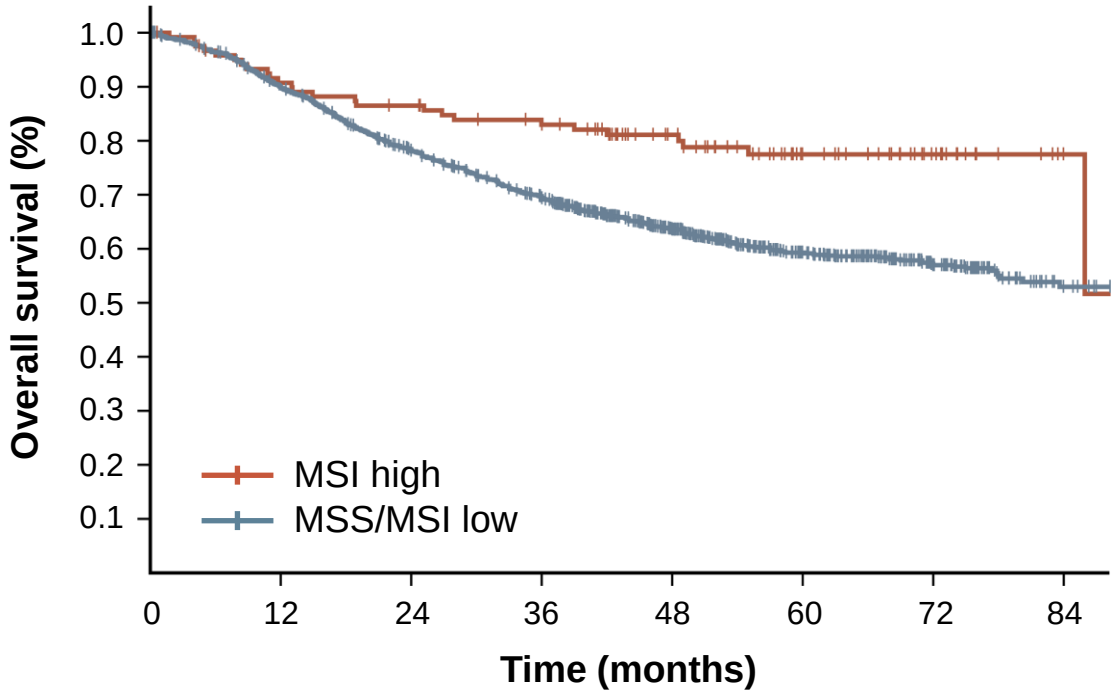
- CheckMate-649: **3%** MSI-H – Nature 2022[5]
- Attraction-4: Not reported – Lancet Onc 2022[6]
- KeyNote-061: **4.5%** (27/592) – Gastric Cancer 2021[7], reported as 5.3% in 2021 JAMA Meta from Keynote trials[8]
- KN-059: **4.0%** (7/174) – JAMA Onc 2021[8]
- KN-062: **7.3%** (50/682) – JAMA Onc 2021[8]

chrom, chromosomal; CIMP, CpG island methylator phenotype; dMMR, deficient mismatch repair; EBV, Epstein Barr virus; MSI-(H), microsatellite instability-(high); SCNA, somatic copy number alteration; TCGA, The Cancer Genome Atlas Program

1. Cancer Genome Atlas Research Network. Nature 2014;513:202-209; 2. Al-Batran S-E, et al. J Clin Oncol. 2022;40(no. 16_suppl):4003-4003 (2022 ASCO oral presentation); 3. Pietrantonio F, et al. J Clin Oncol. 2019;37:3392-3400; 4. Andre T, et al. J Clin Oncol. 2022;40(no. 4_suppl):244-244; 5. Shitara K, et al. Nature. 2022;603:942-948; 6. Kang YK, et al. Lancet Oncol. 2022:23:234-247; 7. Fuchs CS, et al. Gastric Cancer, 2022;25:197-206; 8. Chao J, et al. JAMA Oncol. 2021;7:895-902

dMMR AND MSI IN LOCALISED GEA





No. at risk (no. censored)								
MSI high	121 (0)	102 (2)	93 (3)	89 (6)	67 (25)	44 (47)	21 (68)	6 (87)
MSS/MSI low	1,435 (0)	1,163 (14)	933 (29)	820 (45)	616 (199)	415 (373)	266 (557)	52 (745)

No. at risk (no. censored)								
MSI high	121 (0)	107 (3)	101 (4)	93 (8)	72 (27)	47 (51)	24 (72)	8 (93)
MSS/MSI low	1,435 (0)	1,275 (18)	1,089 (41)	944 (66)	699 (243)	458 (441)	248 (645)	59 (851)

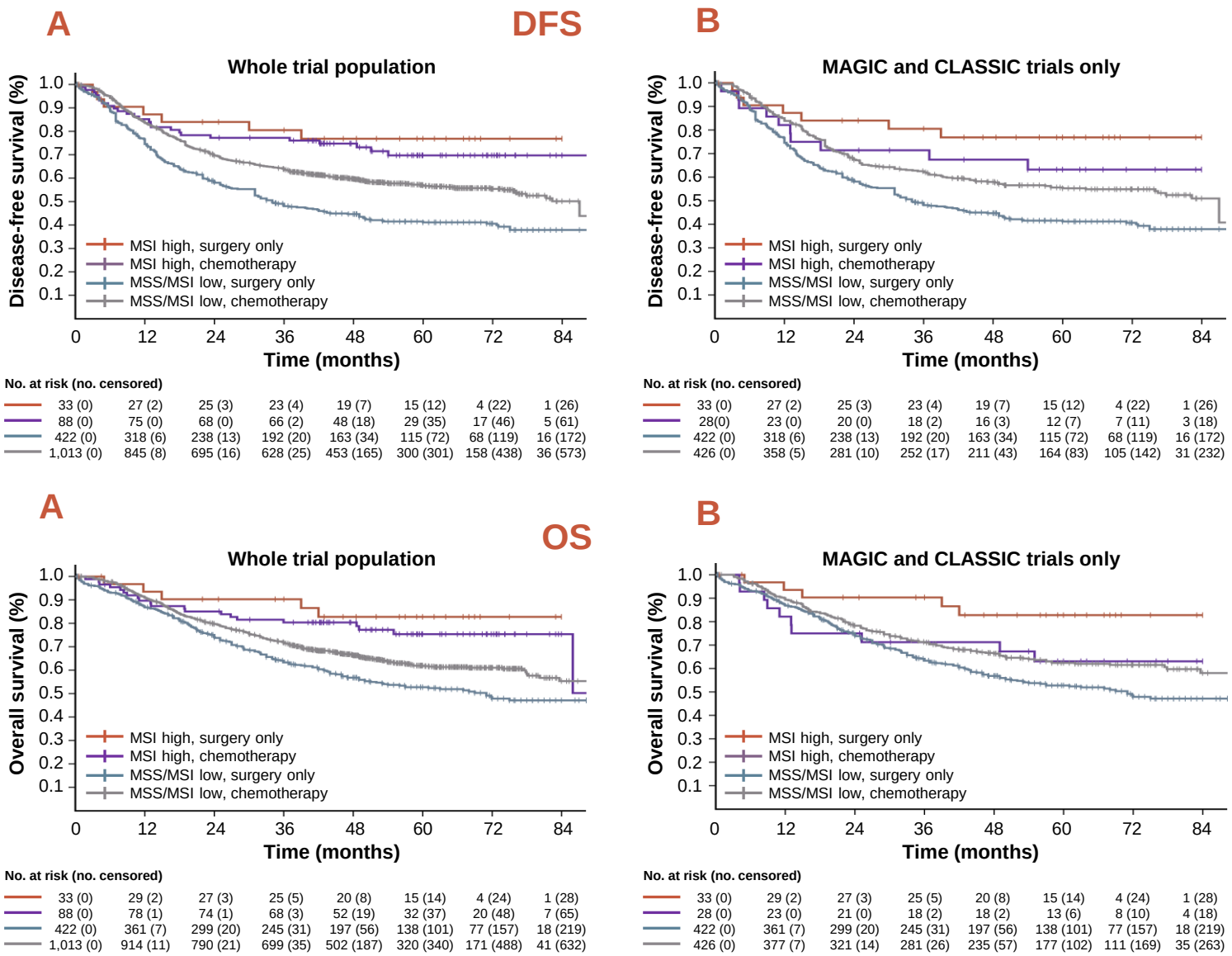
Localised dMMR/MSI-H GEA have a better prognosis

5-year DFS = 72% vs 52%
5-year OS = 78% vs 59%

DFS, disease-free survival; dMMR, deficient mismatch repair; GEA, gastroesophageal adenocarcinoma; MSI-(H), microsatellite instability-(high); MSS, microsatellite stable; OS, overall survival

Pietrantonio F, et al. J Clin Oncol. 2019;37:3392-3400

DO LOCALISED dMMR/MSI-H BENEFIT



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

DFS, disease-free survival; dMMR, deficient mismatch repair; FLOT, fluorouracil, leucovorin, oxaliplatin and docetaxel; GI, gastrointestinal; MSI-(H), microsatellite instability-(high); MSS, microsatellite stable; OS, overall survival

Pietrantonio F, et al. J Clin Oncol. 2019;37:3392-3400

A CASE OF LOCALISED GASTRIC CANCER

You convince his family that there is a prognostic role for MMR testing. He looks to his daughter and asks about strategies that might allow for non-operative management. His daughter says she has 17 trials for this situation. He declines a trial as he lives out in the country on a farm and it is too far to travel.

What do we know about immunotherapy in localised GEA?

Is there a path toward non-operative management?

GEA, gastroesophageal adenocarcinoma; MMR, mismatch repair

POLL QUESTION #2

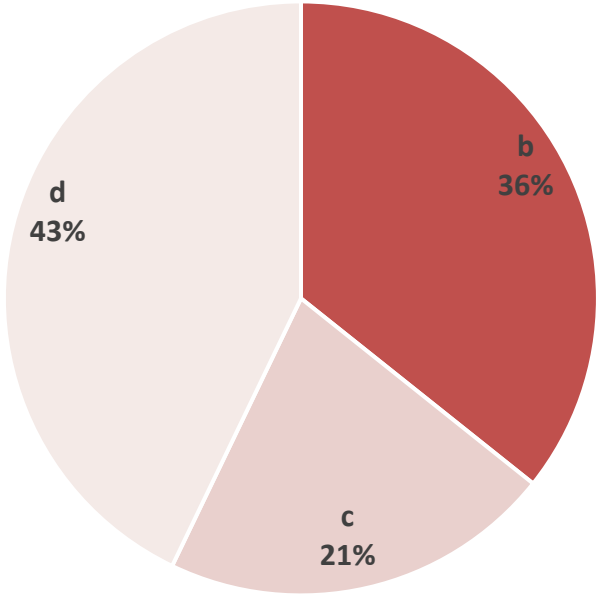
Which of the following is most accurate statement about immune checkpoint inhibitors (ICIs) in dMMR/MSI-H non-metastatic gastroesophageal adenocarcinomas?

a) Neoadjuvant ICI therapy is included in ESMO and NCCN guidelines

b) Neoadjuvant ICI therapy is associated with pathologic complete response in ~85% of patients

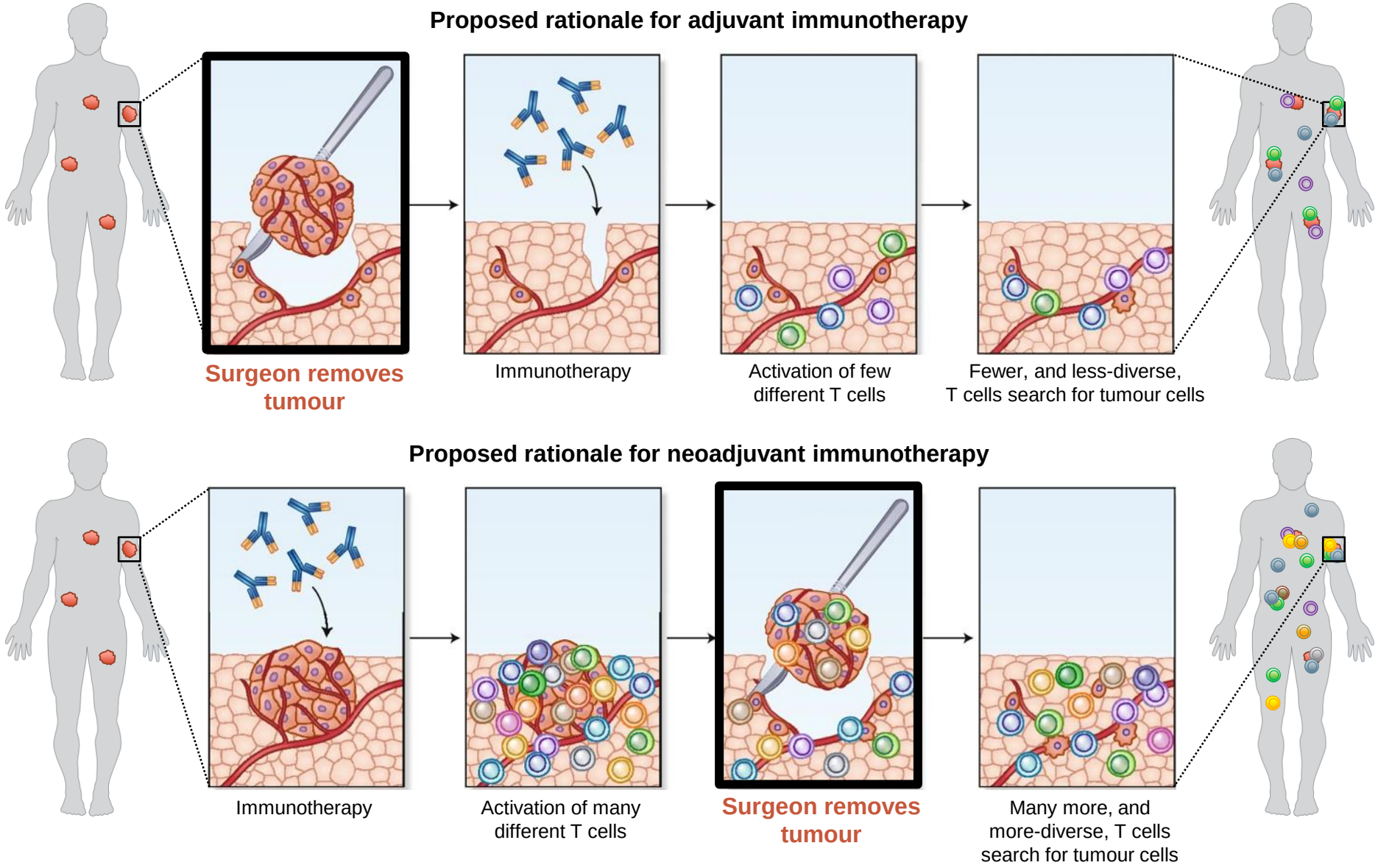
c) Randomised Phase 2 data suggest highly favourable outcomes with neoadjuvant ICIs

d) Neoadjuvant ICI therapy is associated with pathologic complete response in ~60% of patients ☑



dMMR, deficient mismatch repair; ESMO, European Medical Society for Medical Oncology; MSI-H, microsatellite instability-high; NCCN, National Comprehensive Cancer Network

WHY ICI IN dMMR AND MSI IN LOCALISED GEA



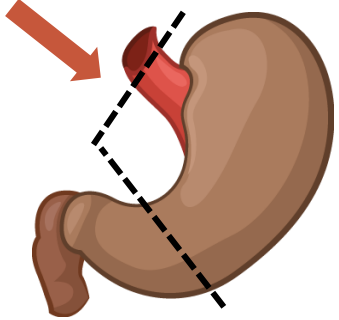
dMMR, deficient mismatch repair; GEA, gastroesophageal adenocarcinoma; ICI, immune checkpoint inhibitor; MSI, microsatellite instability

Versluis JM, et al. Nat Med. 2020;26:475-484

DATA FOR ICI-CONTAINING APPROACHES

- dMMR/MSI GC/GEJ
- T2-4, Nx cM0
- Phase 2
- Western population

Surgery



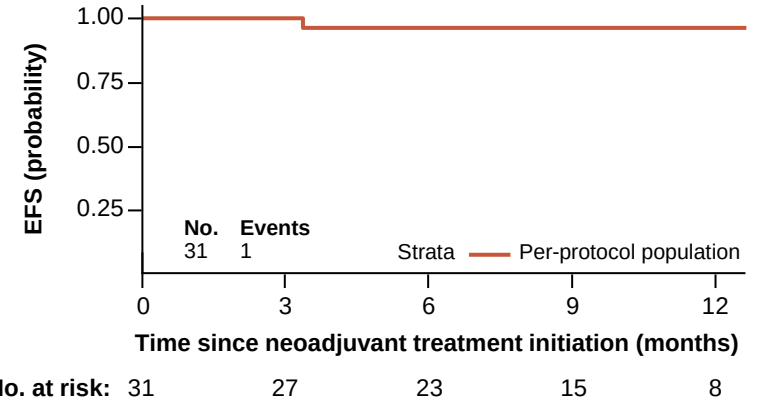
Neoadjuvant Ipi/Nivo × 3m

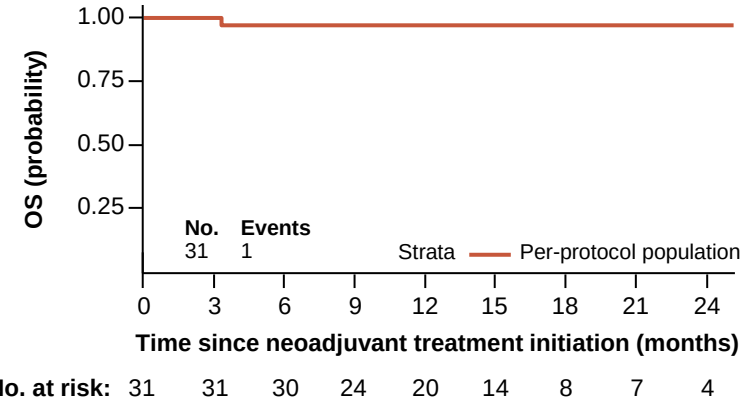
Adjuvant Nivo × 9m

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

79% with significant path response (TRG1, 2)

Encouraging early EFS and OS



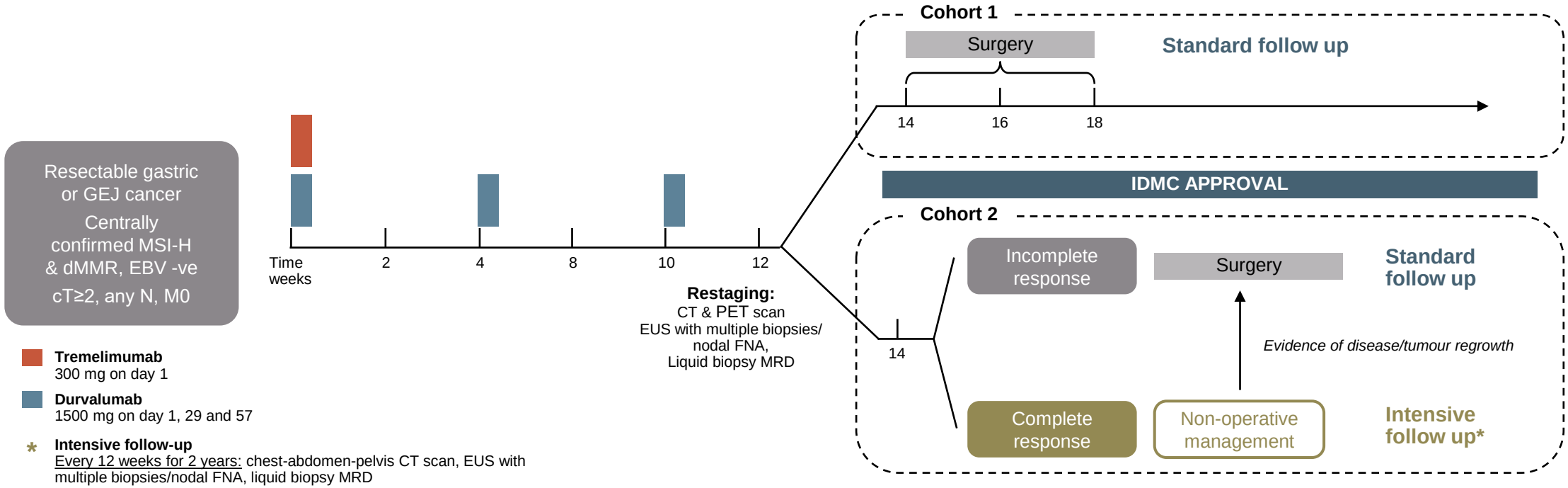


cM, clinical metastasis stage; CR, complete response; dMMR, deficient mismatch repair; EFS, event-free survival; GC, gastric cancer; GEJ, gastroesophageal junction; ICI, immune checkpoint inhibitor; Ipi, ipilimumab; N, nodal stage; Nivo, nivolumab; OS, overall survival; pCR, pathologic complete response; T, tumour stage; TRG, tumour regression grade

Andre T, et al. J Clin Oncol. 2022;40(no. 4_suppl):244-244

dMMR AND MSI IN LOCALISED GASTROESOPHAGEAL ADENOCARCINOMA

TRIAL DESIGN

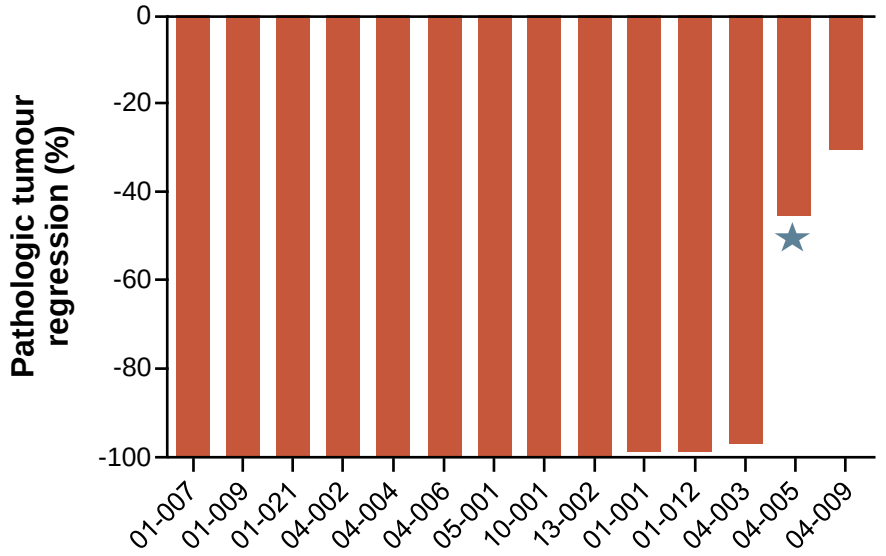


cT, clinical T stage; CT, computed tomography; dMMR, mismatch repair deficiency; EBV, Epstein-Barr virus; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; GEA, gastroesophageal adenocarcinoma; G/GEJ, gastric or gastroesophageal junction; IDMC, independent data monitoring committee; M, evaluation of distant metastasis; MRD, minimal residual disease; MSI-(H), microsatellite instability-(high); N, evaluation of regional lymph nodes; PET, positron emission tomography

Pietrantonio F, et al. J Clin Oncol 2023;41(no. 4_suppl):358-358 (2023 ASCO GI Cancer Symposium oral presentation)

dMMR AND MSI IN LOCALISED GEA

Characteristics	N=18 (%)
Age, years: median (IQR)	71.5 (65-80)
Sex	
Male	12 (67)
Female	6 (33)
ECOG PS	
0	12 (67)
1	6 (33)
Primary site	
Gastric	14 (78)
Gastroesophageal junction	2 (22)
T stage	
T2	1 (5)
T3	10 (56)
T4	7 (39)
N stage	
N0	3 (17)
N1	6 (33)
N2	9 (50)
N bulky	
Yes	4 (22)
No	14 (78)



★ Heterogeneous pMMR/dMMR status at surgery

TRG Becker	N=15	%
1a	9	60%
1b	3	20%
3	2	13%

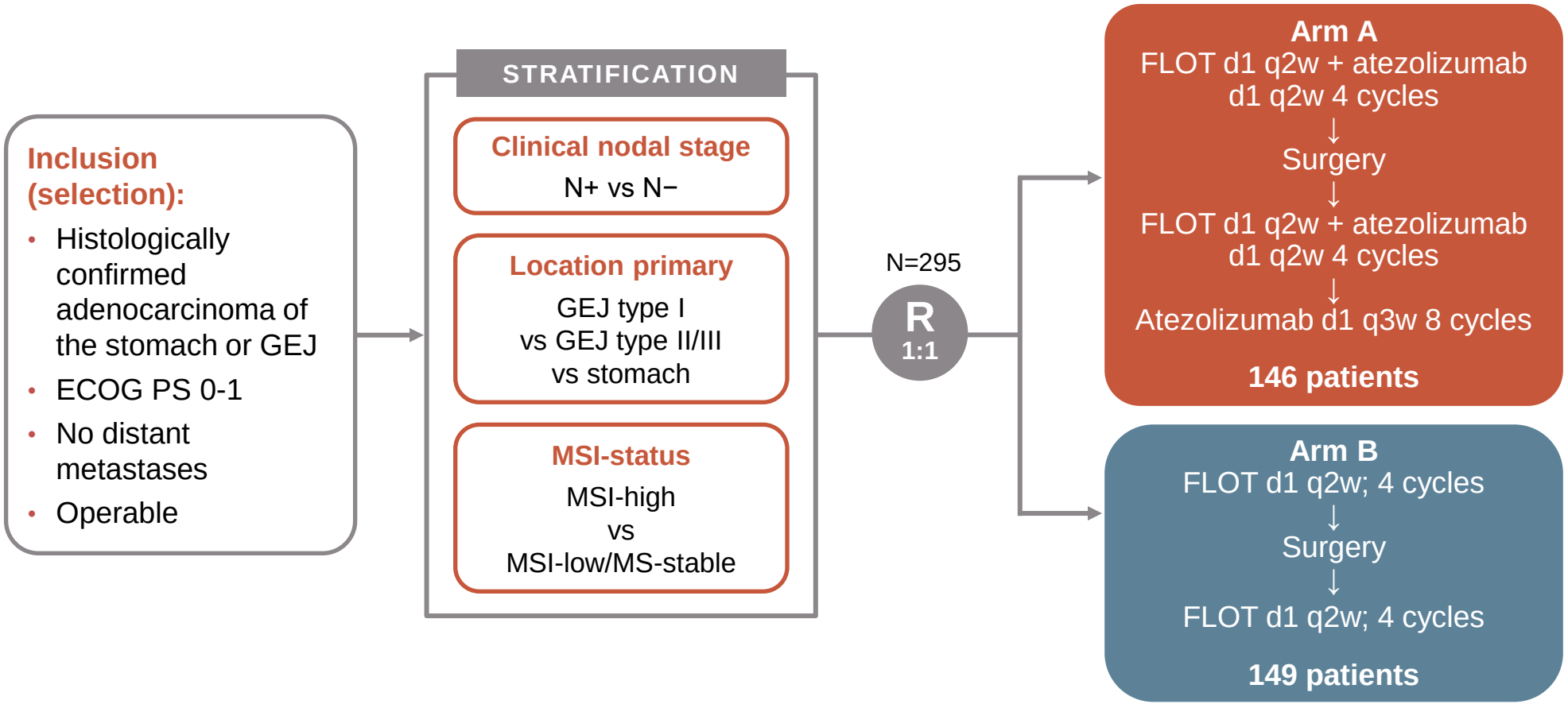
1 patient did not undergo surgery for PD

Among evaluable patients, rate of pCR was 60% and rate of major to complete pathological response (<10% viable cells) was 80%

dMMR, deficient mismatch repair; ECOG, Eastern Cooperative Oncology Group; GEA, gastroesophageal adenocarcinoma; MSI, microsatellite instability; N, node stage; IQR, interquartile range; pCR, pathologic complete response; PD, progressive disease; pMMR, proficient mismatch repair; T, tumour stage; TRG, tumour regression grade

Pietrantonio F, et al. J Clin Oncol 2023;41(no. 4_suppl):358-358 (2023 ASCO GI Cancer Symposium oral presentation)

dMMR AND MSI IN LOCALISED GEA



d, day; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group performance status; FLOT, fluorouracil, leucovorin, oxaliplatin and docetaxel; GEA, gastroesophageal adenocarcinoma; GEJ, gastroesophageal junction; MS, microsatellite; MSI, microsatellite instability; N, nodal stage; q2w, every 2 weeks; q3w, every 3 weeks; R, randomisation

Al-Batran S-E, et al. J Clin Oncol. 2022;40(no. 16_suppl):4003-4003 (2022 ASCO oral presentation)

dMMR AND MSI IN LOCALISED GEA

Pathological regression FLOT + atezolizumab (arm A) vs FLOT (arm B)	Becker classification			
	TRG1a[1]		TRG1a/b[2]	
	A	B	A	B
All patients (N=295; 146|149)	35 (24%)	23 (15%)	71 (49%)	58 (39%)
PD-L1 CPS ≥1 (N=170; 82|88)	20 (24%)	13 (15%)	42 (51%)	40 (46%)
PD-L1 CPS ≥5 (N=81; 40|41)	11 (28%)	8 (20%)	22 (55%)	18 (44%)
PD-L1 CPS ≥10 (N=53; 27|26)	9 (33%)	3 (12%)	18 (67%)	10 (39%)
MSI high (N=23; 8|15)	5 (63%)	4 (27%)	6 (75%)	7 (47%)

[1] pathological complete regression acc. to Becker
[2] pathological subtotal regression acc. to Becker

dMMR, deficient mismatch repair; CPS, combined positive score; FLOT, fluorouracil, leucovorin, oxaliplatin and docetaxel; GEA, gastroesophageal adenocarcinoma; MSI, microsatellite instability; N, nodal stage; PD-L1, programmed death-ligand 1; TRG, tumour regression grade

Al-Batran S-E, et al. J Clin Oncol. 2022;40(no. 16_suppl):4003-4003 (2022 ASCO oral presentation)

dMMR AND MSI IN LOCALISED GEA

NEO-ADJUVANT INVESTIGATOR-INITIATED TRIAL PHASE 2 WITH IO FOR LOCALISED MSI-H/dMMR GI IN PROGRESS OR UPCOMING

Type of phase 2 (number of pts planned)	Primary	Name	Coordinator group and country	Drug	Schedule before surgery or Watch and Wait strategy	Primary end-point
Mono-arm n=32 NCT05197322 In progress	Colon & rectum	NEOPRISM-CRC	Shiu KK, UCL, UK	Pembrolizumab	1 to 3 cycles depending and stratified to TMB before surgery	**Pathological complete response rate**
Mono-arm n=120 NCT04795661 In progress	All GI	IMHOTEP	De la Fouchardière C UNICANCER, France	Pembrolizumab	1 to 2 cycles before surgery	**Pathological complete response rate**
Randomised non comparative n=64 upcoming	Colon	PREMICES	Cohen R GERCOR, France	Pembrolizumab	6 cycles and W&W with salvage surgery vs surgery	**Rate of failure of strategy (surgery) at 6 months**
Mono-arm n=60 upcoming	Stomach and GEJ	DEWI	André T GERCOR, France	Dostarlimab	9 cycles and with salvage surgery	**Clinical complete response (cCR) at 1 year**
Randomised non comparative n=64 upcoming	Rectum	PREDIR	Karoui M FFCD, France	Dostarlimab	6 months of dostarlimab vs RT (5×5 Gy) then 6 months of dostarlimab	**Residual or metastatic disease at 24 months with or without surgery**

dMMR, deficient mismatch repair; GEA, gastroesophageal adenocarcinoma; GI, gastrointestinal; IO, immuno-oncology; MSI-H, microsatellite instability-high; TMB, tumour mutational burden; W&W, watch and wait

https://www.clinicaltrials.gov/ct2/show/NCT05197322; https://clinicaltrials.gov/ct2/show/NCT04795661

dMMR AND MSI IN LOCALISED GEA – TAKE HOME

- dMMR/MSI-H is seen in 8-22% of localised gastroesophageal adenocarcinomas and should be tested for
- Localised dMMR/MSI-H GEA has a favourable prognosis and lesser benefit from perioperative or adjuvant chemotherapy
- Early Phase 2 data suggests high pathCR rates and favourable outcomes with neoadjuvant ICI therapy – like other cancers
- The optimal strategy (ICI mono, ICI combo, chemo-ICI) is not definitively established

CR, complete response; pathCR, pathologic CR; dMMR, deficient mismatch repair; GEA, gastroesophageal adenocarcinoma; ICI, immune checkpoint inhibitor; MSI-(H), microsatellite instability-(high)

CASE #2: LOCALISED ESOPHAGEAL ADENOCARCINOMA

History of present illness: 67-year-old female presents with worsening dysphagia, 20 lb. weight loss and fatigue. Referred for esophagogastroduodenoscopy with 4 cm long mass from 26-30 cm. Biopsy with mod-poorly differentiated adenocarcinoma, pMMR, PD-L1+ (CPS = 3). ECOG 1

- PMH: HTN, Eczema
- Labs: Albumin 3.3, otherwise WNL
- Subjective history: Married, Computer engineer, non-smoker, enjoys judo
- Physical exam: WNL
- Imaging: PET-CT with mid-lower esophageal thickening, several sub-cm paraesophageal LN are suspicious
- EUS: T3N1 by ultrasound

CPS, combined positive score; CT, computed tomography; EUS, endoscopic ultrasound; N, nodal stage; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PMH, past medical history; T, tumour stage; WNL, within normal limits

POLL QUESTION #3

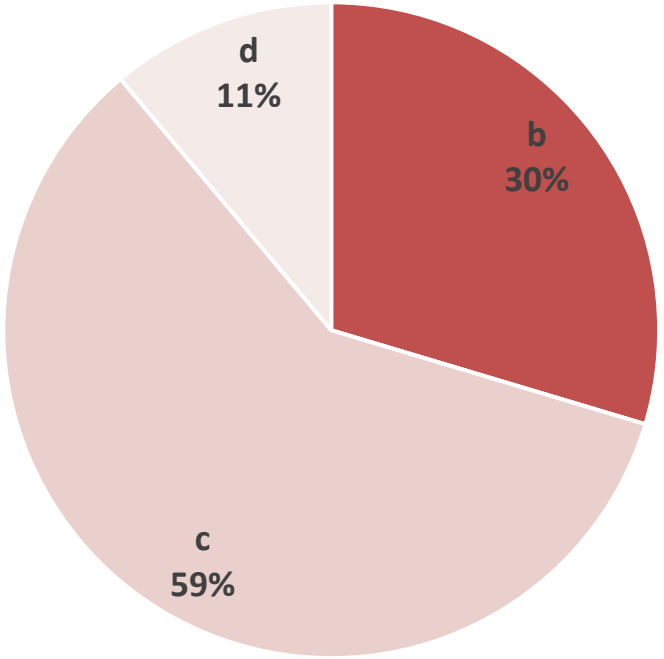
She is deemed a surgical candidate in multidisciplinary conference. What is your current approach to clinical esophageal adenocarcinoma with nodal involvement?

a) Induction chemo followed by chemoradiation

b) Chemoradiation with CROSS regimen

c) Perioperative chemotherapy with FLOT ☑

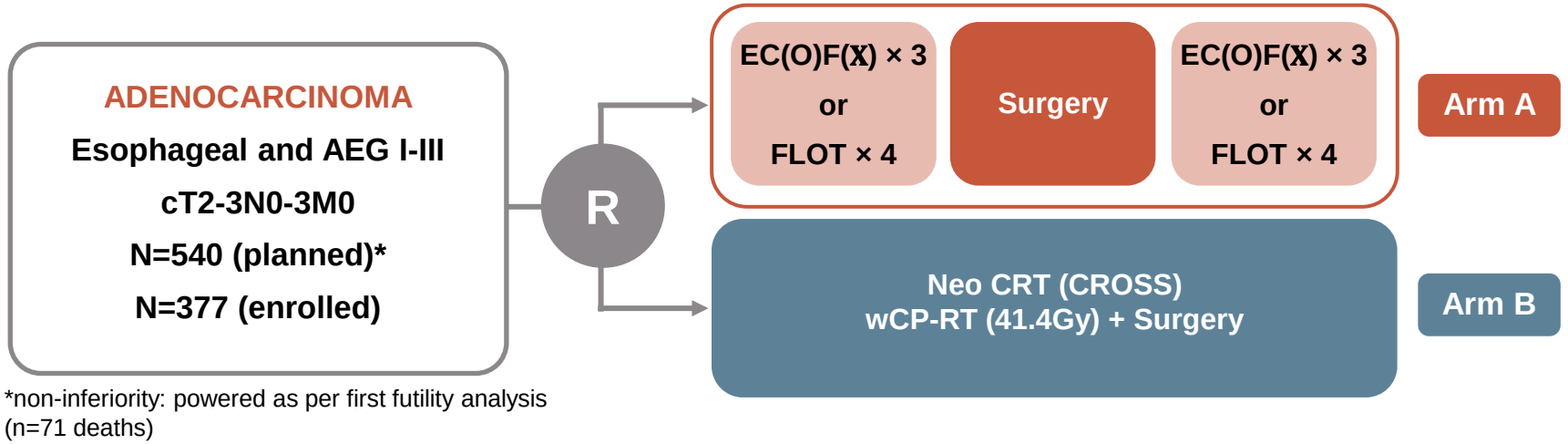
d) Chemoradiation with FOLFOX backbone



FLOT, fluorouracil, leucovorin, oxaliplatin and docetaxel; FOLFOX, folinic acid, fluorouracil and oxaliplatin, CROSS, Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study

LOCALISED EAC UPDATES: NEO-AEGIS

Neo-AEGIS (Arm A: 2013-18 MAGIC; 2018-20; FLOT or MAGIC)



*non-inferiority: powered as per first futility analysis (n=71 deaths)

Primary endpoints:

- Overall survival

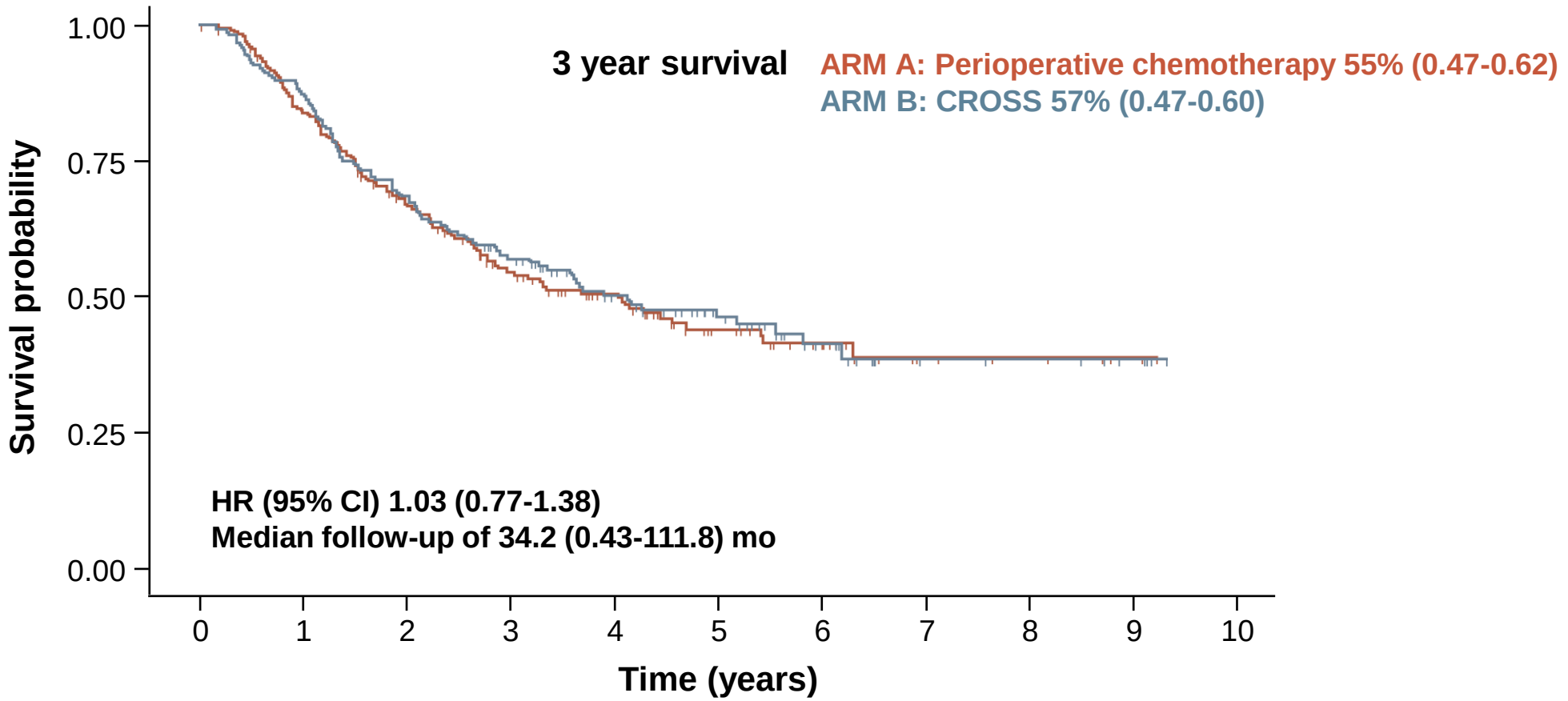
Secondary endpoints:

- Disease free survival
- Time to treatment failure
- Toxicity
- Tumour Regression Grade (TRG)
- R0 resection
- Postoperative complications (ECCG defined, Clavien-Dindo)
- Quality of life

AEG, adenocarcinoma of the esophagogastric junction; CROSS, Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study; CRT, chemoradiotherapy; cT, clinical T stage; EAC, esophageal adenocarcinoma; ECCG, Esophageal Complications Consensus Group; FLOT, docetaxel, 5-FU, leucovorin, oxaliplatin; modified MAGIC, epirubicin, cisplatin (oxaliplatin), 5-FU (capecitabine); M, evaluation of distant metastasis; N, evaluation of regional lymph nodes; R0, R0 resection; wCP, weekly carboplatin paclitaxel

Lowery M, et al. ASCO GI 2023; abstr 295

LOCALISED EAC UPDATES: NEO-AEGIS



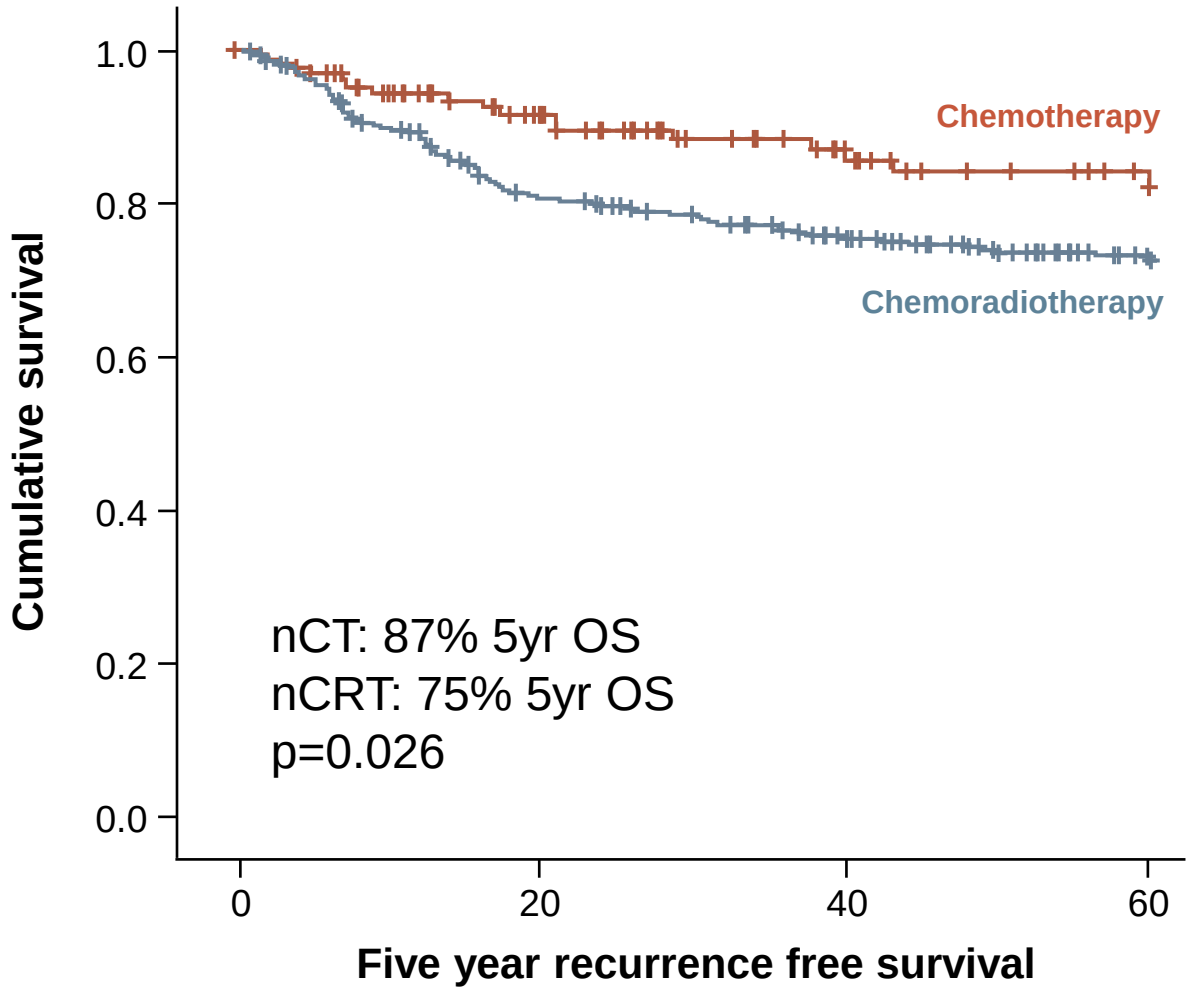
CI, confidence interval; EAC, esophageal adenocarcinoma; HR, hazard ratio; mo, months

Lowery M, et al. ASCO GI 2023; abstr 295

ANOTHER NOTE ON CT VS CRT

Comparison of patients with pathologically complete response following neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy

Variable	Chemotherapy group (n=132) (%)	Chemoradiotherapy (n=333) (%)	P
Age	64.8 ± 9.9	62.4 ± 9.4	0.016
Sex			
Female	29 (22.0)	55 (16.5)	0.168
Male	103 (78.0)	278 (83.5)	–
ECOG			
0	94 (71.2)	219 (65.8)	0.208
1	35 (26.5)	112 (33.6)	–
2	2 (1.5)	1 (0.3)	–
3	1 (0.8)	1 (0.3)	–
Tumour location			
GEJ	70 (53.0)	208 (62.5)	0.05
Distal esophagus	55 (41.7)	103 (30.9)	–
Middle esophagus	6 (4.5)	22 (6.6)	–
Upper esophagus	1 (0.8)	1 (0.2)	–
cT stage			
1	3 (2.3)	6 (1.8)	0.227
2	16 (12.1)	66 (19.8)	–
3	107 (81.1)	251 (75.4)	–
4	6 (4.5)	10 (3.0)	–
cN stage			
0	38 (28.8)	116 (34.8)	0.025
1	72 (54.5)	190 (57.1)	–
2	18 (13.6)	25 (7.5)	–
3	4 (3.0)	2 (0.6)	–
Operation			
Transhiatal	2 (1.5)	24 (7.2)	<0.001
LTA	17 (12.9)	1 (0.3)	–
ILE	97 (73.5)	247 (74.2)	–
McKeown	16 (12.1)	61 (18.3)	–
Approach			
Open	64 (48.5)	200 (60.1)	0.010
Hybrid	11 (8.3)	10 (3.0)	–
Total MIE	57 (43.2)	123 (36.9)	–
Lymph node harvest	33 ± 18	28 ± 12	0.09



5yr distant RFS with nCT = 23%
5yr distant RFS with nCRT = 8.3%

cN, clinical nodal; cT, clinical tumour stage; ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction; ILE, Ivor-Lewis esophagectomy; LTA, left thoracoabdominal; MIE, minimally invasive esophagectomy; (n)CRT, (neoadjuvant) chemoradiotherapy; (n)CT, (neoadjuvant) chemotherapy; RFS, recurrence-free survival; yr, year

Latrique CJ, et al. Ann Surg. 2022;276:799–805

POLL QUESTION #4

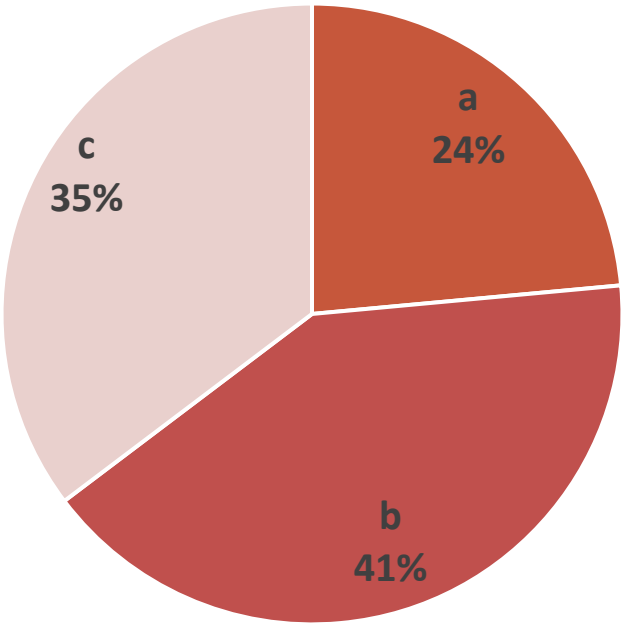
She is treated with a CROSS approach followed by R0 esophagectomy. Pathology reveals at ypT2N0 EAC, TRG2 response, LVI-, PD-L1+ (CPS = 2). She asks about expectations. Which is the most accurate thing to tell her?

a) Her median overall survival is about 5 years

b) Her median disease-free survival is about 11-12 months ☑

c) Trials show adjuvant chemotherapy improves her survival

d) The disease is most likely to recur in the remaining esophagus



CPS, combined positive score; EAC, esophageal adenocarcinoma; LVI, lymphovascular invasion; N, nodal stage; PD-L1, programmed death-ligand 1; R0, R0 resection; T, tumour stage; TRG, tumour regression grade, yp; post-treatment

CASE #2: LOCALISED ESOPHAGEAL ADENOCARCINOMA

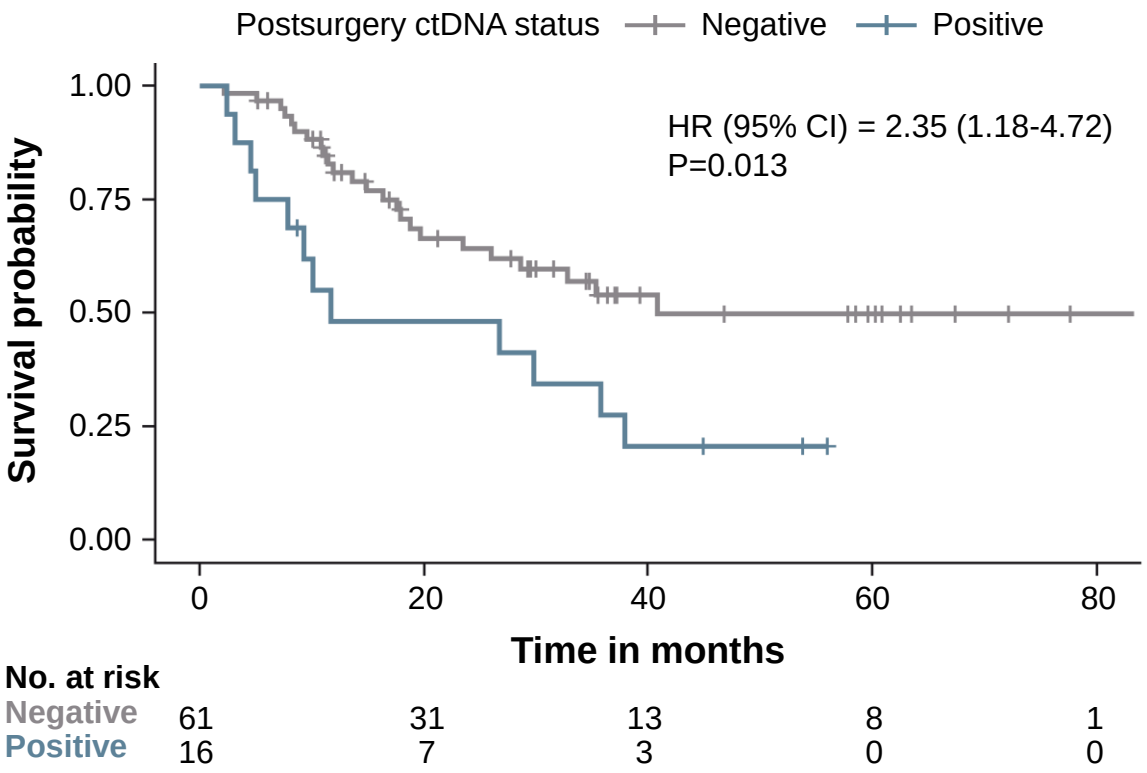
Interval History: You had forgotten you sent a ctDNA test when you saw her 5 weeks post-op to discuss adjuvant nivolumab. She now comes in at week 8 after surgery and asks you about the results.

What do we know about ctDNA in localised EAC?

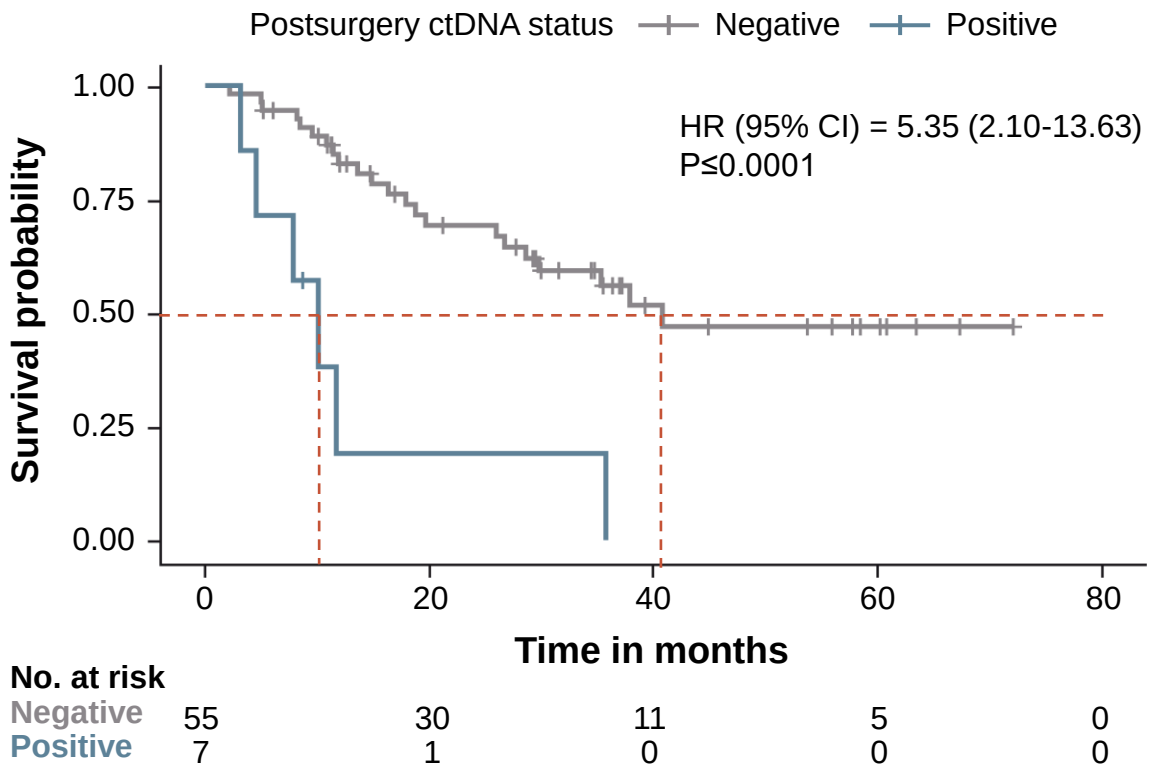
ctDNA, circulating tumour DNA; EAC, esophageal adenocarcinoma

A WORD ON ctDNA IN LOCALISED EARLY GASTRIC CANCER

DFS without CHIP filtering



DFS with CHIP filtering

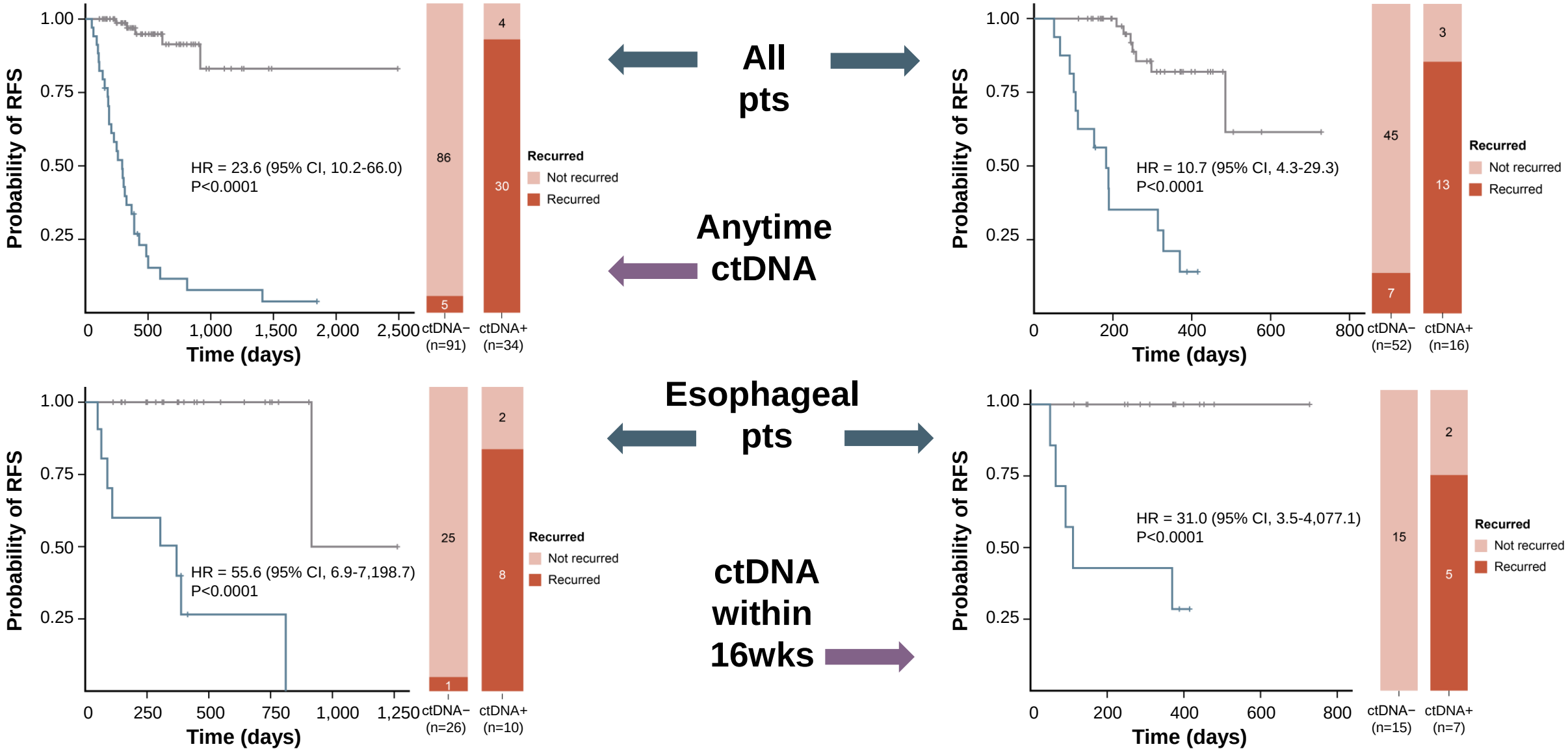


ctDNA after curative intent surgery is associated with a high recurrence rate and worse survival

CHIP, clonal haematopoiesis with indeterminate potential; CI, confidence interval; ctDNA, circulating tumour DNA; DFS, disease-free survival; EGC, early gastric cancer; HR, hazard ratio

Ococks E, et al. Ann Oncol. 2021;32:522-532

A WORD ON ctDNA IN LOCALISED EARLY GASTRIC CANCER



CI, confidence interval; ctDNA, circulating tumour DNA; EGC, early gastric cancer; HR, hazard ratio; RFS, recurrence-free survival

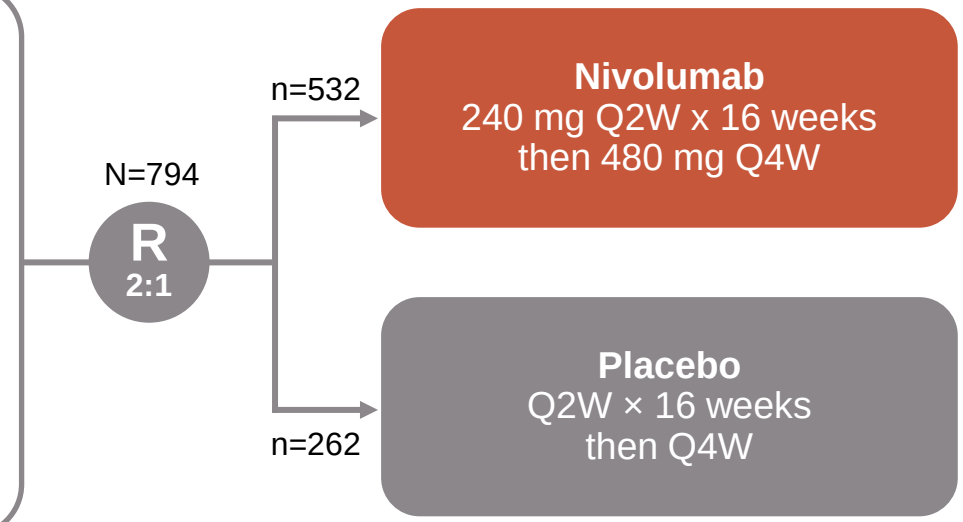
Huffman BM, et al. JCO Precis Oncol. 2022;6:e2200420

CHECKMATE-577

- CheckMate 577 is a global, Phase 3, randomised, double-blind, placebo controlled trial

Key eligibility criteria:

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



Total treatment duration of up to 1 year

Primary endpoint:

- DFS

Secondary endpoints:

- OS
- OS rate 1, 2 and 3 years

Exploratory endpoints included:

- Safety
- DMFS
- PFS2
- QoL

Stratification factors:

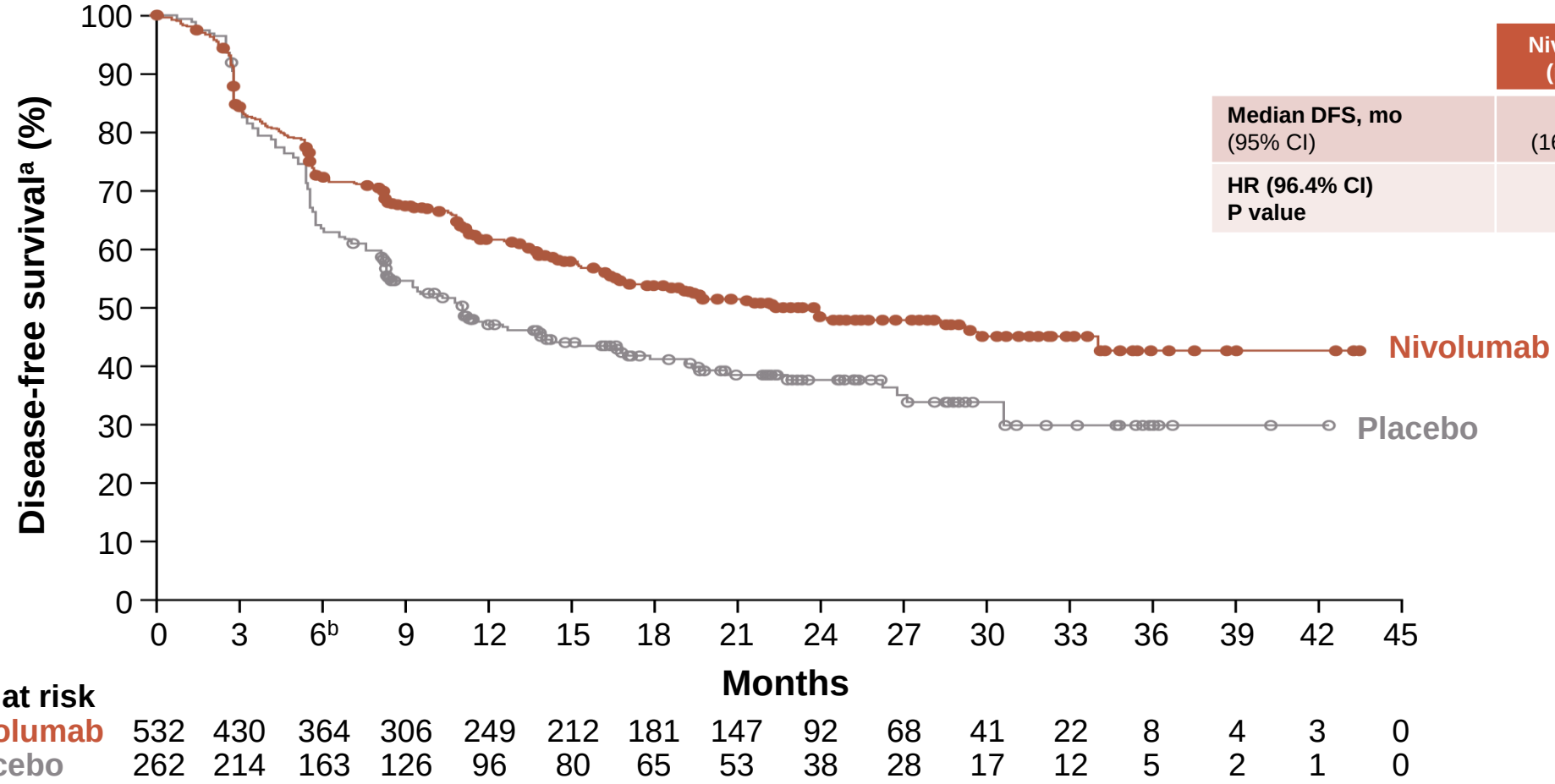
- Histology (squamous vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumour-cell PD-L1 expression (≥1% vs <1%)

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

CRT, chemoradiotherapy; DFS, disease-free survival; DMFS, distant metastasis free survival; EC, esophageal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJC, gastroesophageal junction cancer; N, nodal stage; OS, overall survival; PD-L1, programmed death-ligand 1; Q2W, every 2 weeks; Q4W, every 4 weeks; QoL, quality of life; R, randomisation; R0, R0 resection; T, tumour stage; yp, after neoadjuvant therapy

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

CHECKMATE-577



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

No. at risk

Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

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

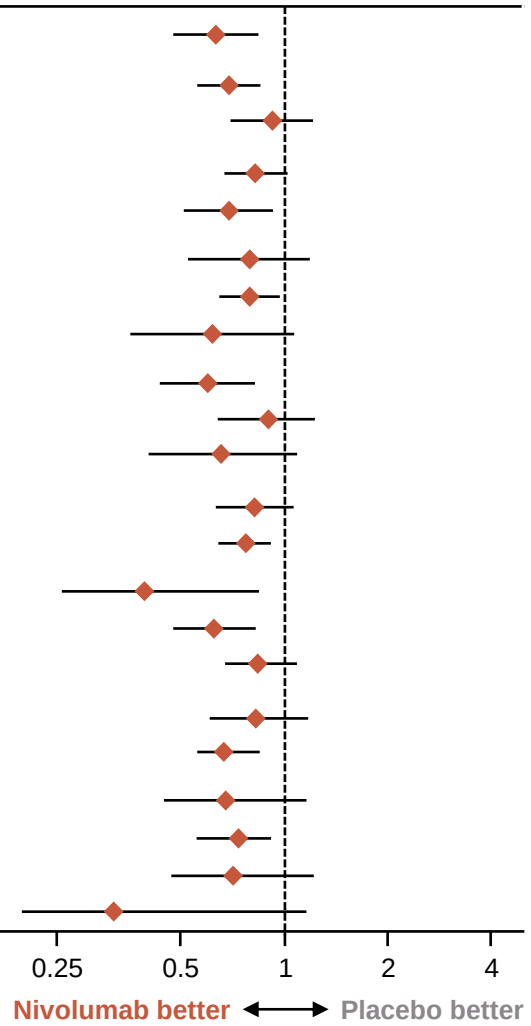
[a] The boundary for statistical significance at the prespecified interim analysis required the P value to be less than 0.036

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; mo, months

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

CHECKMATE-577

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



CI, confidence interval; CPS, combined positive score; DFS, disease-free survival; HR, hazard ratio; mo, months; N, nodal stage; PD-L1, programmed death-ligand 1; T, T stage; yp, after neoadjuvant therapy

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

CHECKMATE-577

Patients, n (%)	Nivolumab (n=532)		Placebo (n=260)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any AEs	510 (96)	183 (34)	243 (93)	84 (32)
Serious AEs	158 (30)	107 (20)	78 (30)	53 (20)
AEs leading to discontinuation[d]	68 (13)	38 (7)	20 (8)	16 (6)
Any TRAEs	376 (71)	71 (13)	119 (46)	15 (6)
Serious TRAEs	40 (8)	29 (5)	7 (3)	3 (1)
TRAEs leading to discontinuation	48 (9)	26 (5)	8 (3)	7 (3)
TRAEs in ≥10% of treated patients in either arm				
Fatigue	90 (17)	6 (1)	29 (11)	1 (<1)
Diarrhea	88 (17)	2 (<1)	39 (15)	2 (<1)
Pruritus	53 (10)	2 (<1)	9 (3)	0
Rash	52 (10)	4 (<1)	10 (4)	1 (<1)
Hypothyroidism	50 (9)	0	4 (2)	0

AE, adverse event; TRAE, treatment-related AE

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

CASE #2: LOCALISED ESOPHAGEAL ADENOCARCINOMA

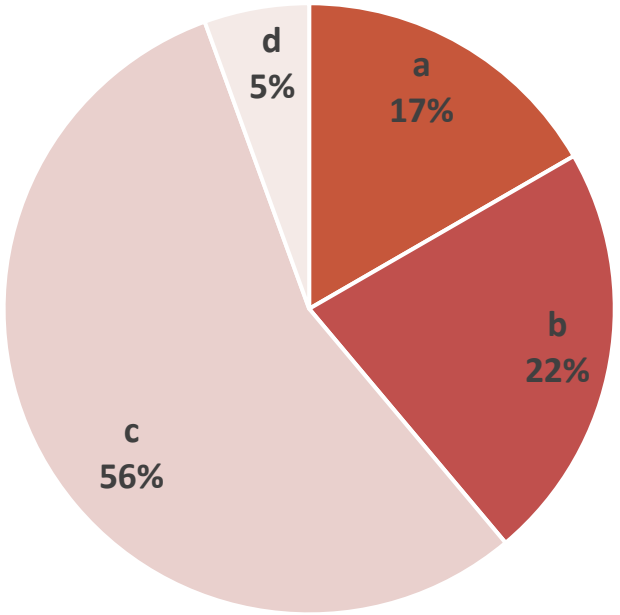
Interval History: She completes a year of adjuvant nivolumab without incident. She comes in for a CT ~5 months after completing nivolumab and is found to have RP adenopathy and four liver lesions. Biopsy confirms recurrent EAC, pMMR, HER2 neg, PD-L1+ (CPS = 1). How do you approach this clinical scenario?

a) Shared decision making, offer 5FU/oxali

b) Shared decision making, offer Ipi-Nivo

c) Shared decision making, offer 5FU/oxali + PD-1 ☑

d) Shared decision making, ask me again after Dr. Smyth's talk



5-FU, fluorouracil; CPS, combined positive score; CT, computed tomography scan; EAC, esophageal cancer; HER2, human epidermal growth factor receptor 2; Ipi, ipilimumab; Nivo, nivolumab; oxali, oxaliplatin; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; pMMR, proficient mismatch repair; RT, retropharyngeal

Thank You

Sam Klempner, MD
MGH Cancer Center
Boston, MA

sklempner@partners.org

508-954-6022

@KlempnerSam

METASTATIC GASTROESOPHAGEAL CANCERS

Dr Lizzy Smyth

Cambridge University Hospital NHS Foundation Trust

UK

CASE PRESENTATION 1: HER2-POSITIVE GEA

Initial diagnosis + staging	• 59-year-old nursing professor; male • Short history of dysphagia • Endoscopy, Siewert type II junctional adenocarcinoma • HER2 positive, MMR intact • CT and PET confirm T3N2 tumour
Medical history	• Hypertension, mild asthma, non-smoker, ECOG PS 0

CT, computerised tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; MMR, mismatch repair; N, node (stage); PET, positron emission tomography; T, tumour (stage)

POLL QUESTION #1

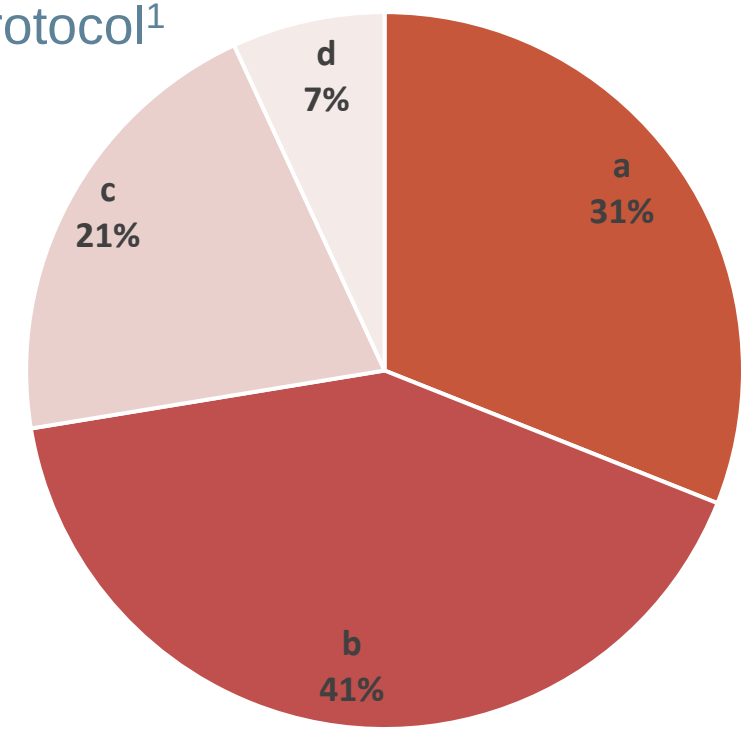
What would you do?

a) **Neoadjuvant chemotherapy with FLOT** ☑

b) Neoadjuvant chemoradiotherapy according to CROSS protocol[1]

c) Neoadjuvant chemotherapy plus trastuzumab

d) Neoadjuvant chemoradiotherapy plus trastuzumab



CROSS, Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel

1. van Hagen P, et al. N Engl J Med. 2012;366:2074-84

CASE PRESENTATION 1: HER2-POSITIVE GEA

Initial treatment	• Treated with neoadjuvant FLOT
	• Resection in January 2019
	  – ypT3N1
	  – 2/26 positive lymph nodes
	  – Tumour regression grade 3
	• Rapid development of liver metastases after surgery
	• July 2020 to September 2020: chemotherapy + trastuzumab with PD

FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; HER2, human epidermal growth factor receptor 2; N, node (stage); PD, progression of disease; T, tumour (stage); yp, pathological

POLL QUESTION #2

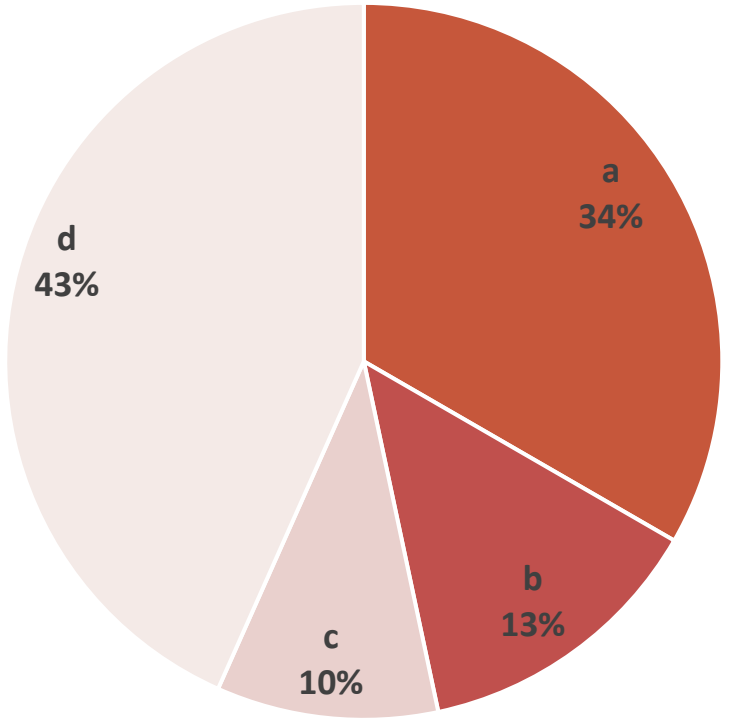
What would you do next?

a) Start taxane-based chemotherapy plus ramucirumab

b) Start irinotecan or FOLFIRI

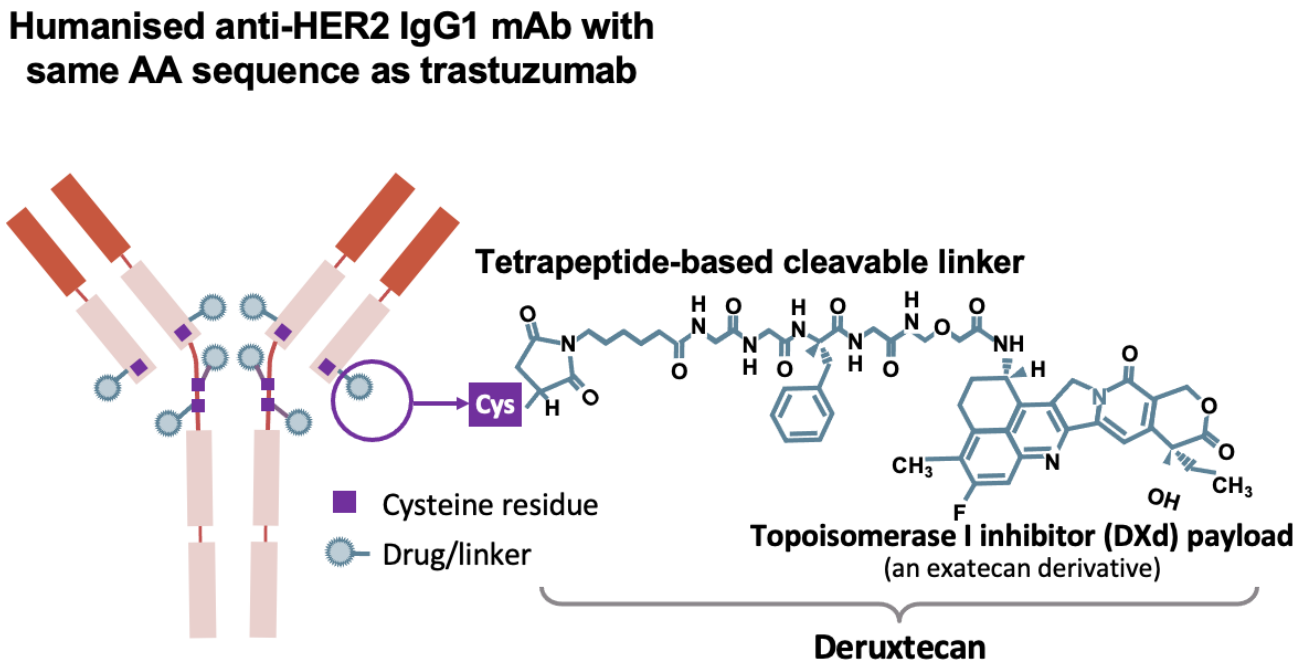
c) Start trastuzumab deruxtecan without biopsy ☑

d) Start trastuzumab deruxtecan if biopsy shows retained HER2 positivity ☑



FOLFIRI, folinic acid, fluorouracil, and irinotecan; HER2, human epidermal growth factor receptor 2

TRASTUZUMAB DERUXTECAN



Trastuzumab deruxtecan

- HER2-targeted ADC
- Membrane-permeable payload with short systemic half-life and bystander killing effect
- EMA approved in December 2022 for patients with advanced HER2-positive gastric or GEJ adenocarcinoma and who have received a prior trastuzumab-based regimen
  - Approval was based on the results of DESTINY-Gastric01 and DESTINY-Gastric02 trials
- Safety and efficacy study of trastuzumab deruxtecan vs ramucirumab/paclitaxel combination therapy in patients with HER2-positive metastatic and/or unresectable gastric or GEJ adenocarcinoma with disease progression on or after a trastuzumab-containing regimen is ongoing
  - DESTINY-Gastric04

AA, amino acid; ADC, antibody-drug conjugate; cys, cysteine; DXd, deruxtecan; EMA, European Medicines Agency; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; Ig, immunoglobulin; mAb, monoclonal antibody

Destiny-Gastric-04. Available from: https://clinicaltrials.gov/ct2/show/NCT04704934. Accessed March 2023; Nakada T, et al. Chem Pharm Bull (Tokyo). 2019;67:173-85; Ogitani Y, et al. Cancer Sci. 2016;107:1039-46; Ogitani Y, et al. Clin Cancer Res. 2016;22:5097-108; Trail PA, et al. Pharmacol Ther. 2018;181:126-42

CASE PRESENTATION 1

Diagnosis + staging	• October 2020: – Started trastuzumab deruxtecan with excellent response

ILD issue	• One year later: some weight loss noted, but cancer in PR
	• Ejection fraction noted to have declined by 15% on echocardiogram
	  – Cardio-oncology referral made
	  – Commenced ACE inhibitor + beta blocker
	• CT showed inflammatory change in left-lung apex
	• Patient is asymptomatic

ACE, angiotensin-converting enzyme; CT, computerised tomography; EF, ejection fraction; ILD, interstitial lung disease; PR, partial remission

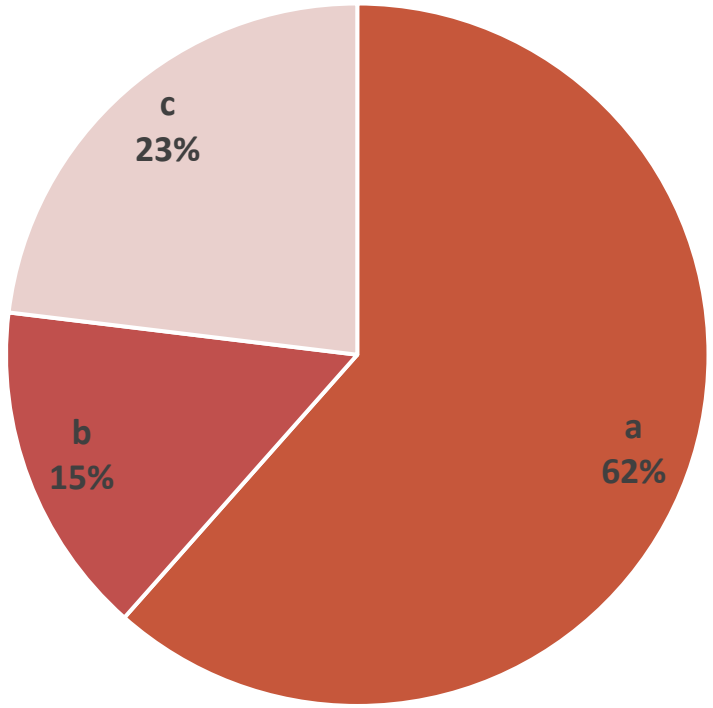
POLL QUESTION #3

What would you do next?

a) Temporarily stop treatment, repeat CT in a few weeks ☑

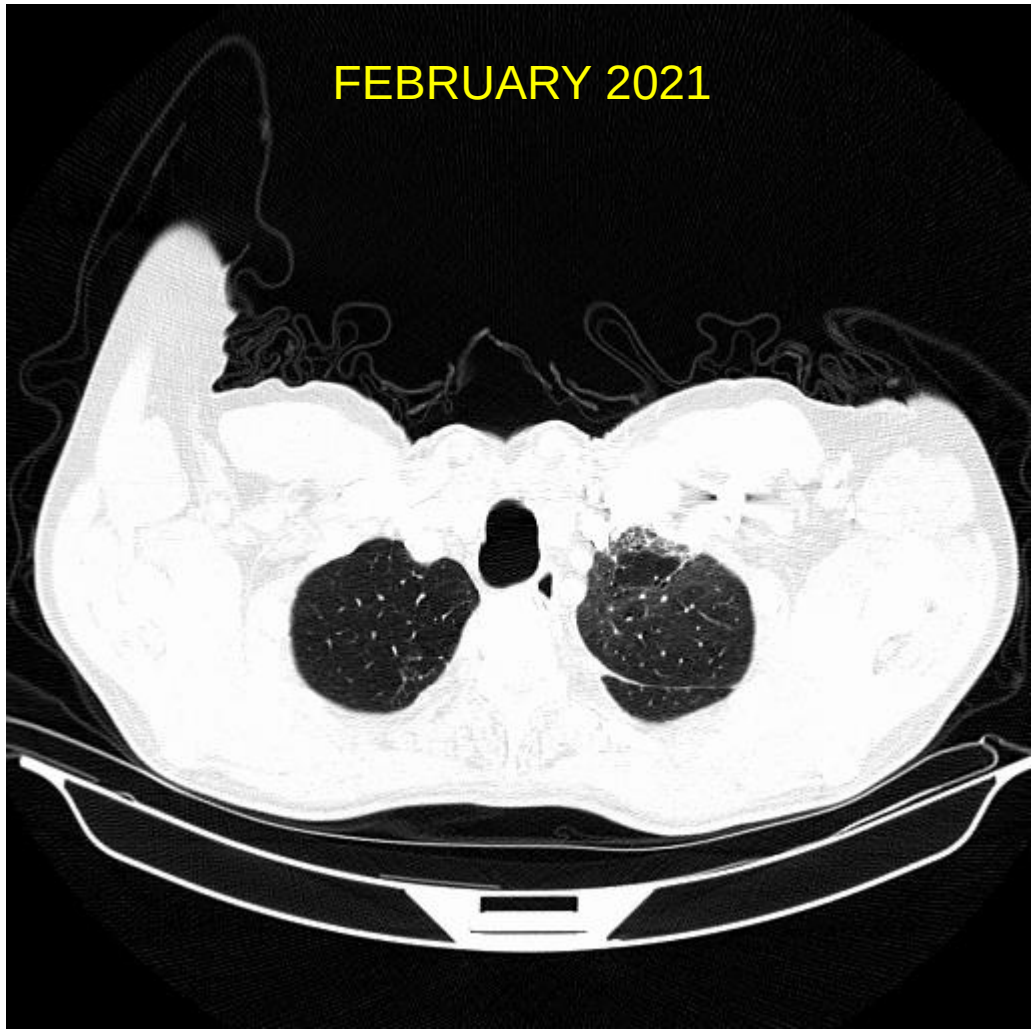
b) Discontinue treatment, start corticosteroid

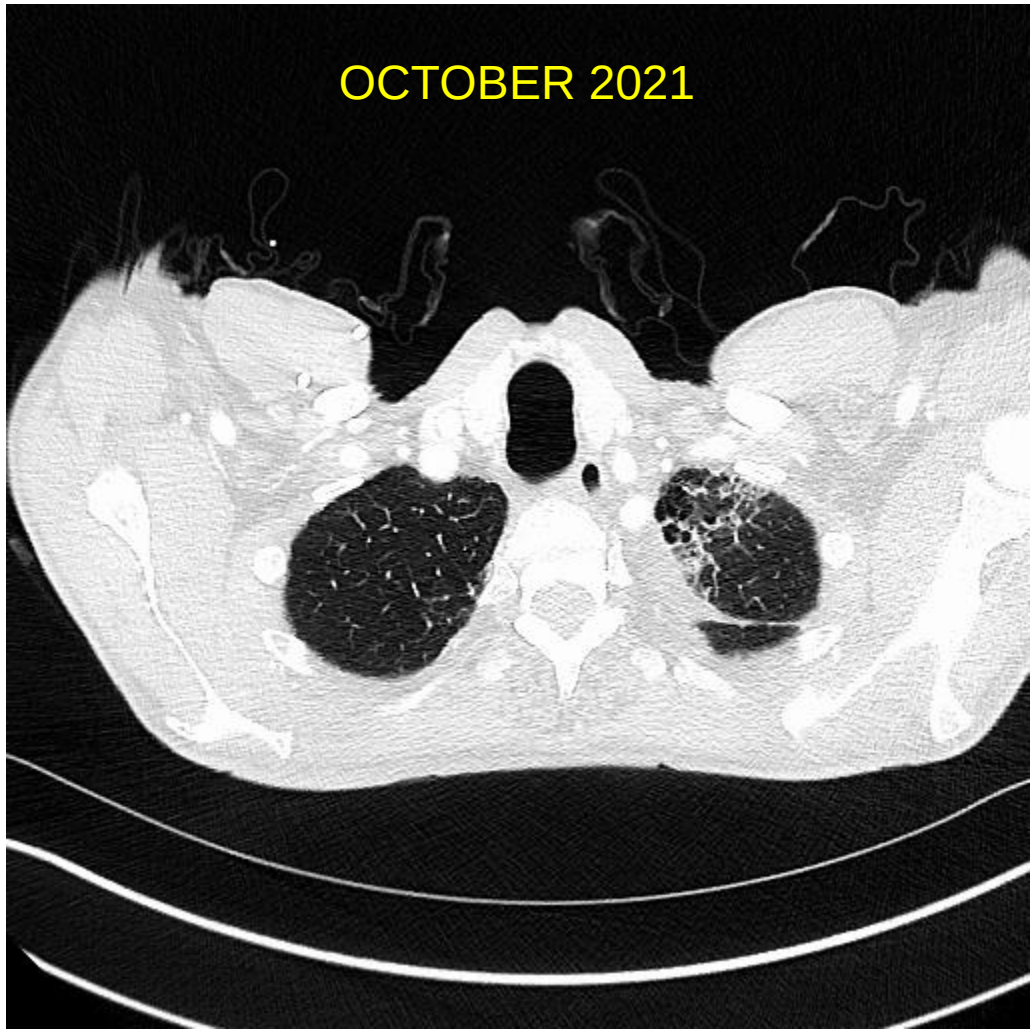
c) Continue current treatment



CT, computerised tomography

CASE PRESENTATION 1: ILD DISCUSSION





ILD, interstitial lung disease

Provided by: Dr Lizzy Smyth

CASE PRESENTATION 1

Next steps	• Temporarily stopped trastuzumab deruxtecan • Started prednisolone: 1 mg/kg/day • Patient went to France (visit)
	• November 2021 – Increased shortness of breath noted while in France; new cough – CT on return: increased opacification and volume loss in the left lung with new opacification in right-lung periphery

CT, computerised tomography

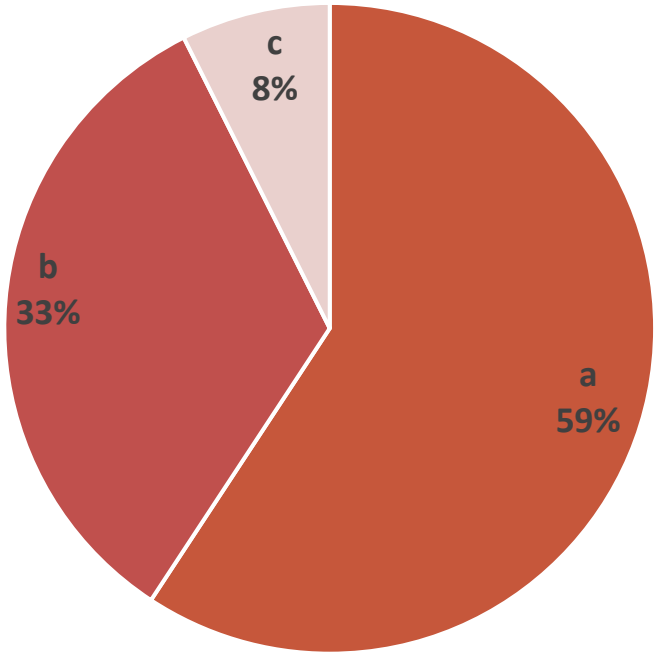
POLL QUESTION #4

What would you do next?

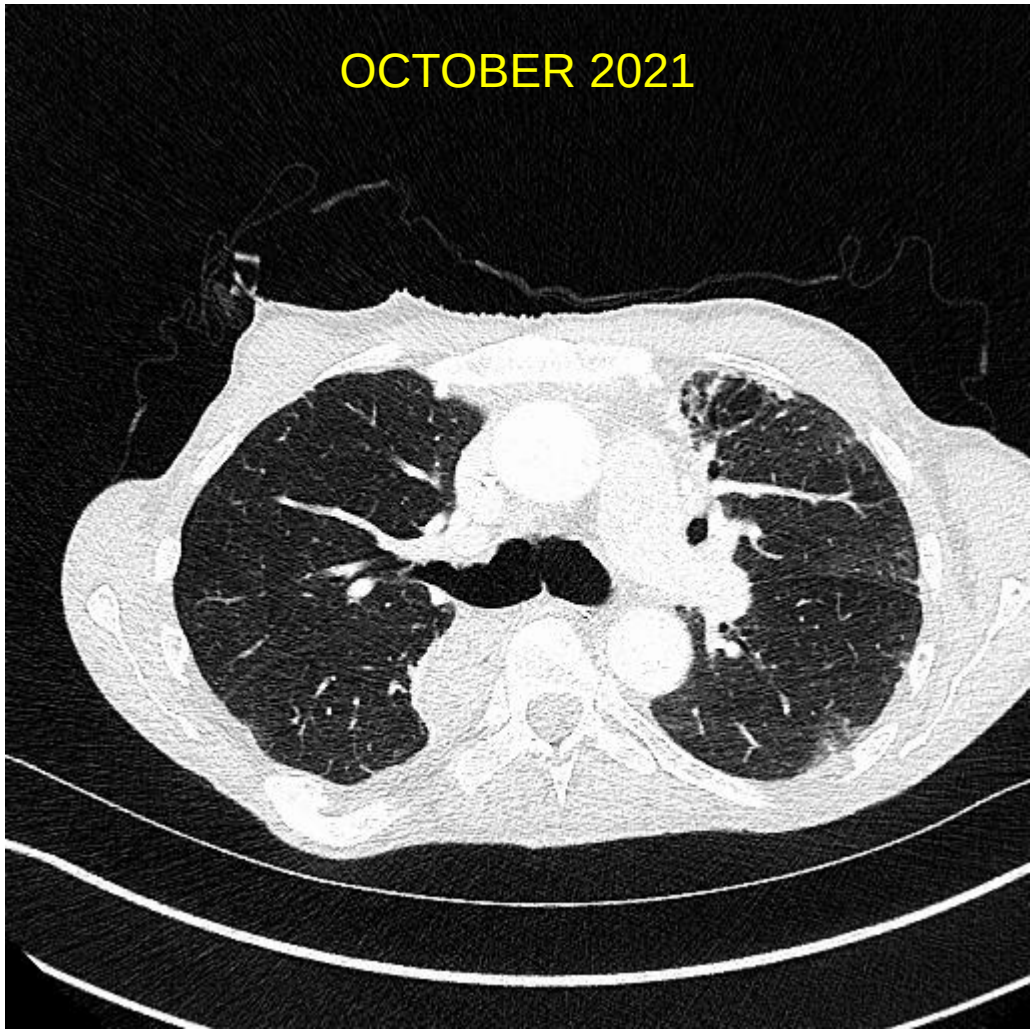
a) Admit to hospital for respiratory workup ☑

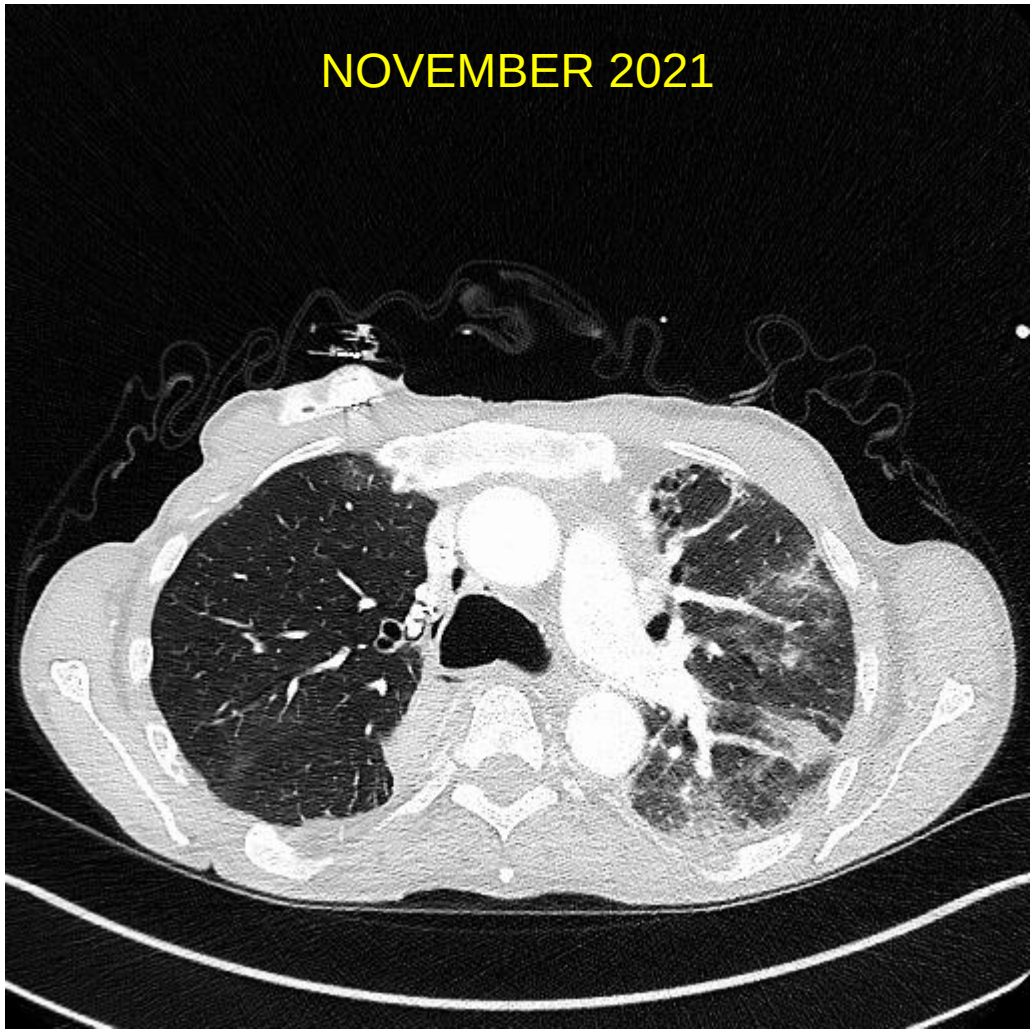
b) Increase corticosteroid dose

c) Resume treatment



CASE PRESENTATION 1





ILD, interstitial lung disease

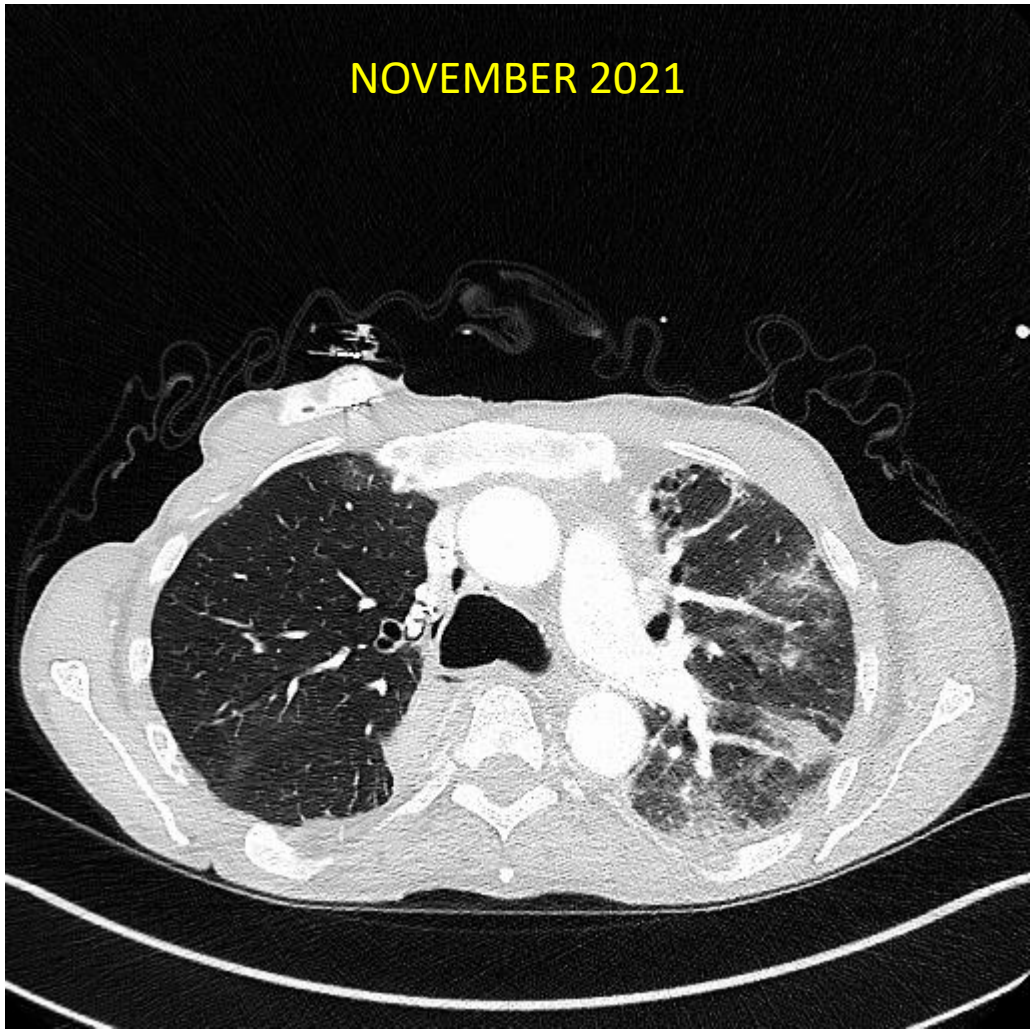
Provided by: Dr Lizzy Smyth

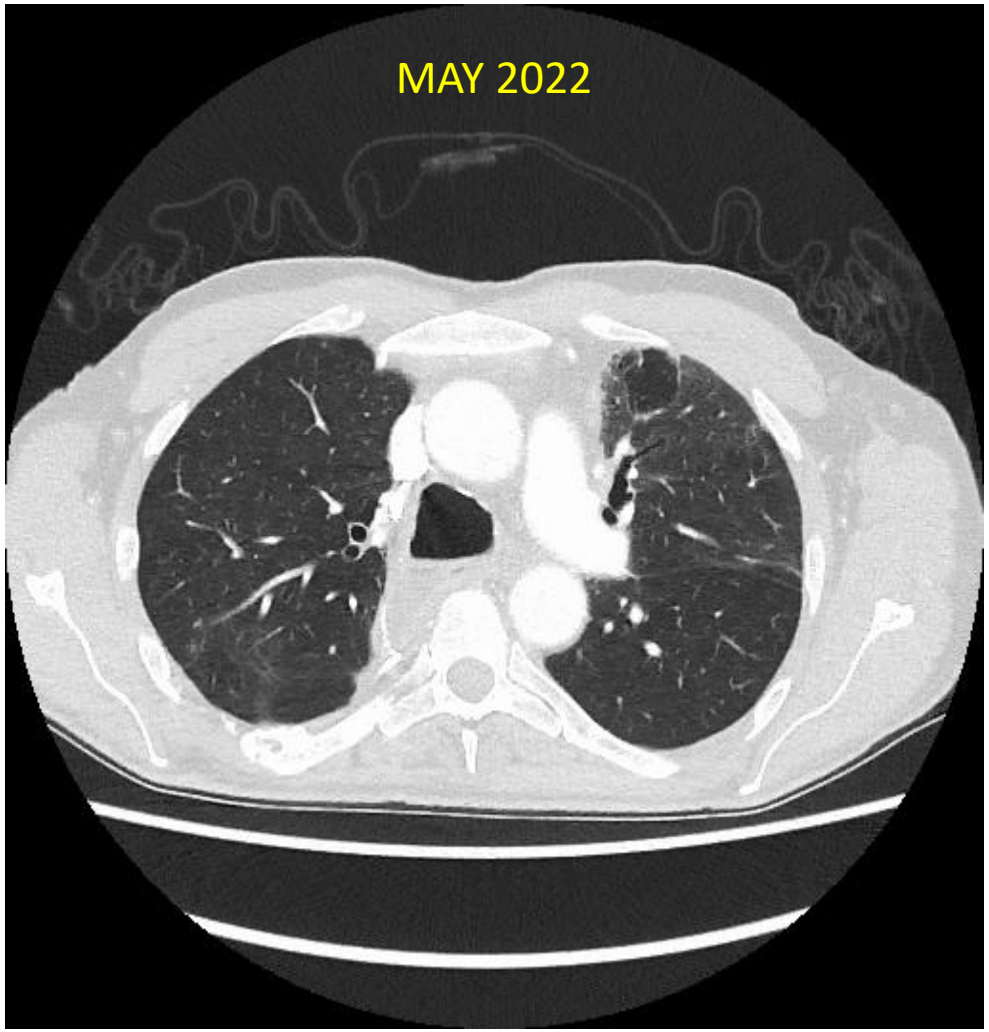
CASE PRESENTATION 1

Next steps	• Admitted for work up and treatment. • SARS-CoV-2 and respiratory virus work-up negative • Commenced IV methylprednisolone • Bronchoscopy and BAL requested • Noted to have grade 2 transaminitis • No improvement with methylprednisolone (3 days) • Anti-TNF contraindicated by liver-function test → started MMF treatment – Still minimal improvement in symptoms • BAL positive for pneumocystis pneumonia → commenced co-trimoxazole
	• Slow improvement in symptoms over 2 weeks • Discharged; tapering of MMF, co-trimoxazole, and prednisolone • Gradual recovery over next few months • CT shows gradual resolution of ILD • Oesophageal cancer stable; off treatment for 8 months before PD and third-line treatment

BAL, bronchoalveolar lavage; CT, computerised tomography; ILD, interstitial lung disease; IV, intravenous; MMF, mycophenolate mofetil; PD, progression of disease; TNF, tumour necrosis factor

CASE PRESENTATION 1: ILD DISCUSSION





ILD, interstitial lung disease

Provided by: Dr Lizzy Smyth

ADVERSE EVENTS IN DESTINY-GASTRIC01 AND 02

Adverse events occurring in at least 20% of the patients treated with trastuzumab deruxtecan[1]

Preferred term	Trastuzumab deruxtecan (N=125)			Physician's choice of chemotherapy (N=62)[a]		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
	Patients, n (%)					
Nausea	79 (63)	6 (5)	0	29 (47)	1 (2)	0
Neutrophil count decreased[b]	79 (63)	48 (38)	16 (13)	22 (35)	10 (16)	5 (8)
Decreased appetite	75 (60)	21 (17)	0	28 (45)	8 (13)	0
Anaemia[c]	72 (58)	47 (38)	0	19 (31)	13 (21)	1 (2)
Platelet count decreased[d]	49 (39)	12 (10)	2 (2)	4 (6)	1 (2)	1 (2)
White cell count decreased[e]	47 (38)	26 (21)	0	22 (35)	5 (8)	2 (3)
Malaise	43 (34)	1 (1)	0	10 (16)	0	0
Diarrhoea	40 (32)	3 (2)	0	20 (32)	1 (2)	0
Vomiting	33 (26)	0	0	5 (80	0	0
Constipation	30 (24)	0	0	14 (23)	0	0
Pyrexia	30 (24)	0	0	10 (16)	0	0
Alopecia	28 (22)	0	0	9 (15)	0	0
Fatigue	27 (22)	9 (7)	0	15 (24)	2 (3)	0
Lymphocyte count decreased[f]	27 (22)	8 (6)	6 (5)	2 (3)	0	1 (2)

Drug-related TEAEs in ≥15% of patients[2]

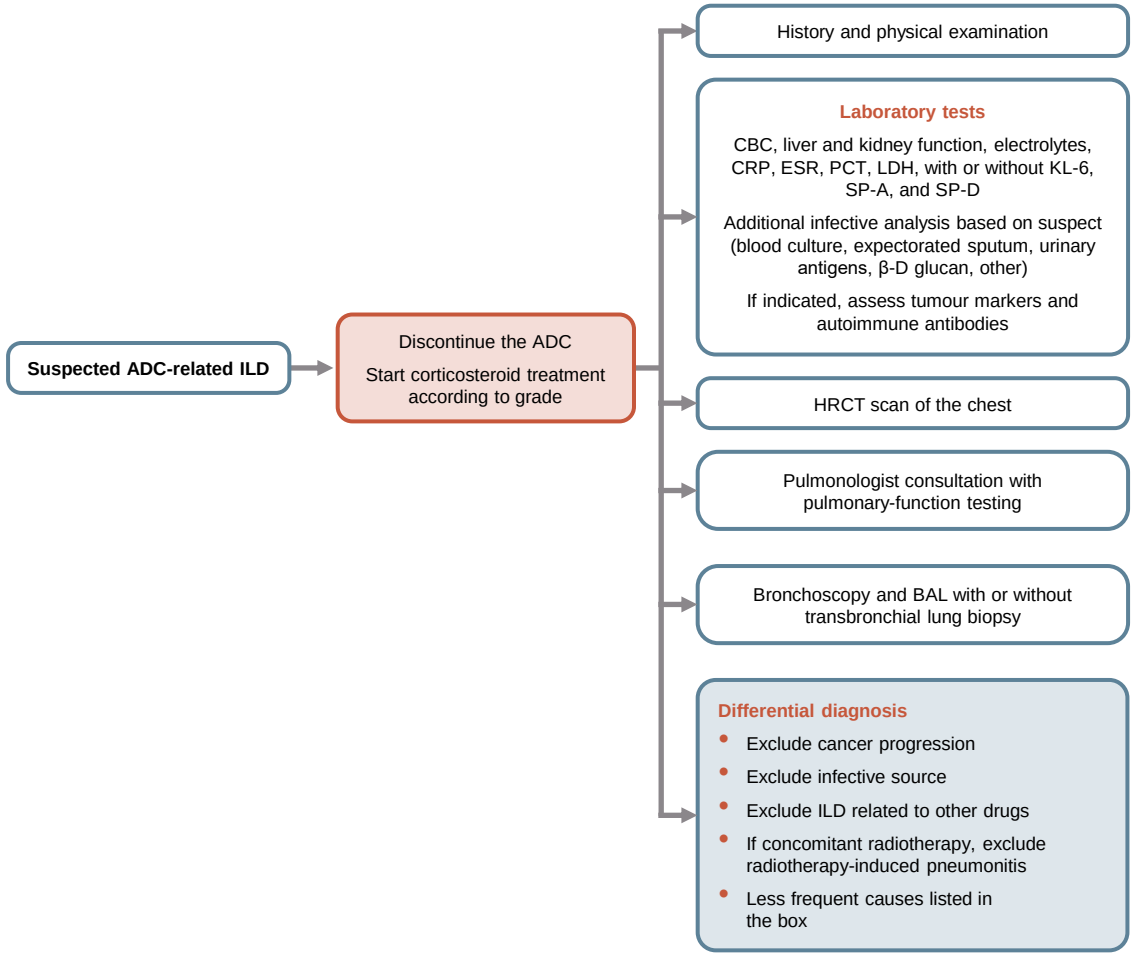
	Patients, n (%) (N=79)	
	Any grade	Grade ≥3
Patients with ≥1 drug-related TEAEs	74 (93.7)	21 (26.6)
Drug-related TEAEs with ≥15% incidence in all patients		
Nausea	46 (58.2)	3 (3.8)
Fatigue	29 (36.7)	3 (3.8)
Vomiting	26 (32.9)	1 (1.3)
Diarrhoea	22 (27.8)	1 (1.3)
Decreased appetite	18 (22.8)	1 (1.3)
Alopecia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

[a] No additional adverse events during the trial were observed in at least 20% of the patients receiving physician's choice of chemotherapy; [b] This category includes the preferred terms neutrophil count decreased and neutropenia; [c] This category includes the preferred terms haematocrit decreased, haemoglobin decreased, red cell count decreased, and anaemia; [d] This category includes the preferred terms platelet count decreased and thrombocytopenia; [e] This category includes the preferred terms white cell count decreased and leukopenia; [f] This category includes the preferred terms lymphocyte count decreased and lymphopenia

TEAE, treatment-emergent adverse event

1. Shitara K, et al. Gastric Cancer. 2021;24:780-9; 2. Van Custem E, et al. Ann Oncol. 2021; 32 suppl 5: S1283-S1346

APPROACH TO ILD



Adverse reaction	Severity	Treatment modification
ILD/pneumonitis	Asymptomatic ILD/pneumonitis (grade 1)	Interrupt trastuzumab deruxtecan until resolved to grade 0, then: • If resolved in ≤28 days from date of onset, maintain dose • If resolved in >28 days from date of onset, reduce dose one level • Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected
	Symptomatic ILD/pneumonitis (grade ≥2)	• Permanently discontinue trastuzumab deruxtecan • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected

- Multidisciplinary approach is essential
- Differentials should be excluded and treatment stopped if grade ≥2 occurs
- Corticosteroids are the mainstay of treatment

ADC, antibody-drug conjugate; BAL, bronchoalveolar lavage; CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HRCT, high-resolution computerised tomography; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; PCT, procalcitonin; SP-A/D, surfactant protein A/D

Enhertu SmPC. https://www.medicines.org.uk/emc/product/12135 ; Tarantino P, et al. JAMA Oncol. 2021;7:1873-81

MANAGEMENT OF OTHER ADVERSE EVENTS

Neutropenia	Grade 3 (<1.0-0.5 × 10^9/L)		• Interrupt trastuzumab deruxtecan until resolved to grade ≤2, then maintain dose
	Grade 4 (<0.5 × 10^9/L)		• Interrupt trastuzumab deruxtecan until resolved to grade ≤2 • Reduce dose by one level
Febrile neutropenia	Absolute neutrophil count of <1.0 × 10^9/L and temperature >38.3°C or a sustained temperature of ≥38°C for >1 hour		• Interrupt trastuzumab deruxtecan until resolved • Reduce dose by one level
LVEF decreased	LVEF >45% and absolute decrease baseline is 10-20%		• Continue treatment with trastuzumab deruxtecan
	LVEF 40-45%	And absolute decrease from baseline is <10%	• Continue treatment with trastuzumab deruxtecan Repeat LVEF assessment within 3 weeks
		And absolute decrease from baseline is 10-20%	• Interrupt trastuzumab deruxtecan • Repeat LVEF assessment within 3 weeks • If LVEF has not recovered to within 10% from baseline, permanently discontinue trastuzumab deruxtecan • If LVEF recovers to within 10% from baseline, resume treatment with trastuzumab deruxtecan at the same dose
	LVEF of <40% or absolute decrease from baseline of >20%		• Interrupt trastuzumab deruxtecan • Repeat LVEF assessment within 3 weeks • If LVEF of <40% or absolute decrease from baseline of >20% is confirmed, permanently discontinue trastuzumab deruxtecan
	Symptomatic congestive heart failure		• Permanently discontinue trastuzumab deruxtecan

LVEF, left ventricular ejection fraction

Enhertu SmPC. https://www.medicines.org.uk/emc/product/12135

CASE PRESENTATION 2: HER2-NEGATIVE/MSS GEA

Initial diagnosis + staging	• 72-year-old female; retired teacher • Epigastric pain and nausea for 3 months • 5 kg weight loss • Endoscopy, ulcer at antrum, biopsy-positive adenocarcinoma • CT shows T4N2M1 tumour with liver metastases
Medical history	• Osteoarthritis, hypothyroidism, ECOG PS 1

CT, computerised tomography; ECOG PS, Eastern Cooperative Oncology Group performance status GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; M, metastasis (stage); MSS, microsatellite stable; N, node (stage); T, tumour (stage)

POLL QUESTION #5

What biomarkers would you test?

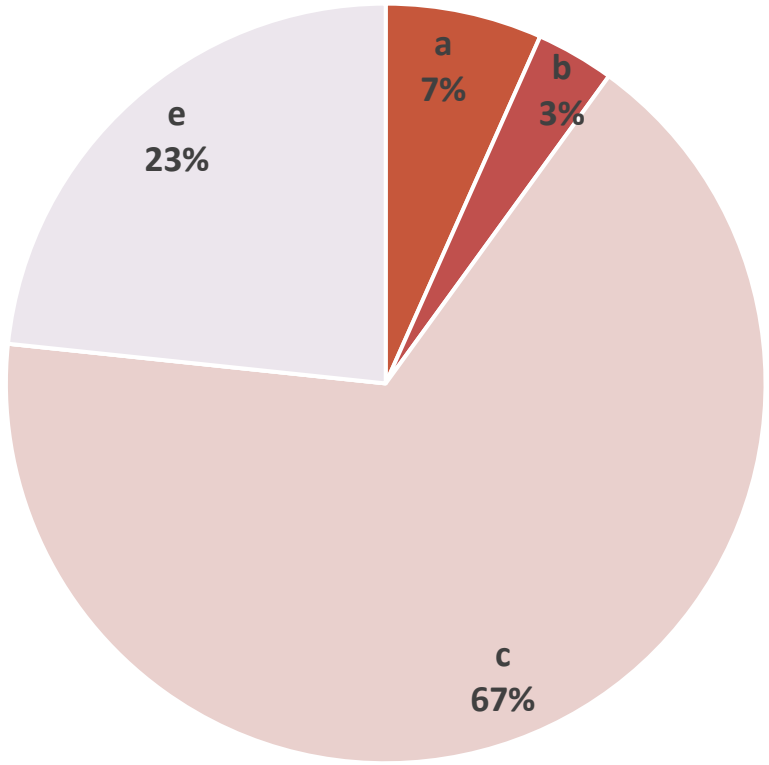
a) HER2 and PD-L1

b) HER2 and MMR/MSI

c) HER2, PD-L1, and MMR/MSI ☑

d) TMB by NGS

e) All of the above



HER2, human epidermal growth factor receptor 2; MMR, mismatch repair; MSI, microsatellite instability; NGS, next-generation sequencing; PD-L1, programmed death-ligand 1; TMB, tumour mutational burden

CASE PRESENTATION 2: BIOMARKER RESULTS

Biomarker results	• HER2 negative; FISH negative • PD-L1 CPS of 3 (223C assay) • MMR intact • NGS not done

CPS, combined positive score; FISH, fluorescence in situ hybridisation; HER2, human epidermal growth factor receptor 2; MMR, mismatch repair; NGS, next-generation sequencing; PD-L1, programmed death-ligand 1

POLL QUESTION #6

What would you do next?

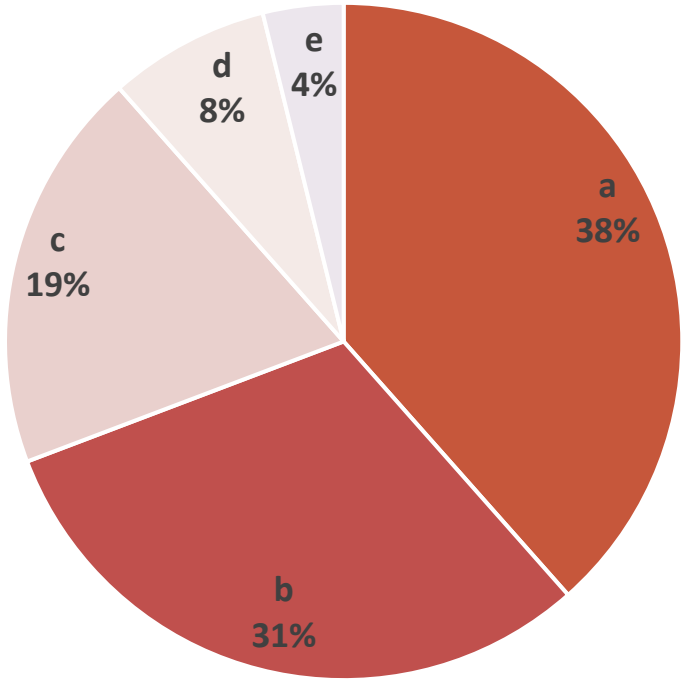
a) **Start platinum/5-FU doublet chemotherapy (FOLFOX/CAPOX/CF/CX)** ☑

b) Start platinum/5-FU/taxane-based triplet chemotherapy (mDCF/FLOT)

c) Start chemotherapy with nivolumab or pembrolizumab

d) Start nivolumab or pembrolizumab monotherapy

e) Start chemotherapy/pembrolizumab and trastuzumab



5-FU, fluorouracill; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; CAPOX, capecitabine and oxaliplatin; CF, cisplatin and fluorouracil; CX, cisplatin and capecitabine; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; mDCF, modified docetaxel, cisplatin, and fluorouracil

CASE PRESENTATION 2: TREATMENT

First-line treatment	• Anti-PD-1 not licensed for CPS of <5 in UK • Patient wished to explore clinical trials • Screened for trial of chemotherapy ± anti-CLDN-18.2 antibody • CLDN-18.2 high expression → enrolled in trial
Adverse event management	• Grade 2 nausea (cycles 1 and 2) • Hypoalbuminemia (grade 2)
Response	• PR in primary and liver metastases after 2 cycles • Oxaliplatin dropped after 4 months due to cumulative neuropathy • Maintained PR until 18 months → progression in liver metastases

CLDN, claudin; CPS, combined positive score; PD-1, programmed cell death protein 1; PR, partial remission

POLL QUESTION #7

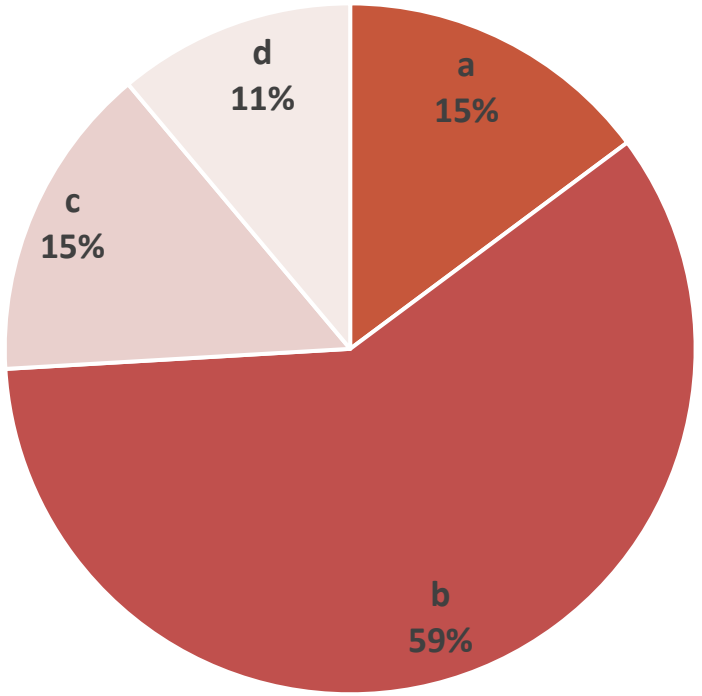
What would you do next?

a) Re-introduce oxaliplatin

b) Stop treatment, start taxane-based chemotherapy ± ramucirumab

c) Stop treatment, start irinotecan or FOLFIRI

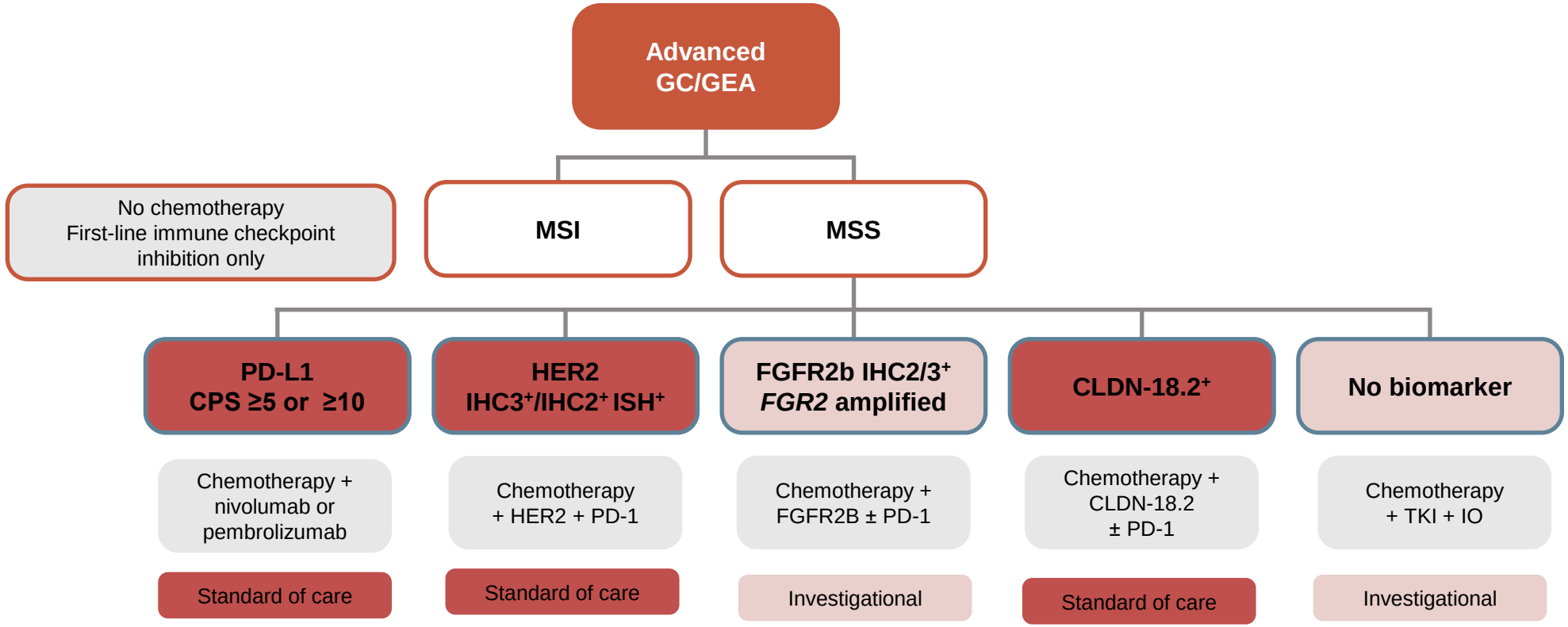
d) Consider another clinical trial



The correct answer depends on available therapies and may differ in each case

FOLFIRI, folinic acid, fluorouracil, and irinotecan

CURRENT AND EVOLVING TREATMENT OPTIONS IN GC/GEA: FIRST LINE



+, positive; CLDN, claudin; CPS, combined positive score; FGFR2B, fibroblast growth factor receptor 2B; GC, gastric cancer; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IO, immuno-oncology; ISH, in situ hybridization; MSI, microsatellite instability; MSS, microsatellite stable; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; TKI, tyrosine kinase inhibitor

INVESTIGATIONAL FIRST-LINE TREATMENTS IN THE GC/GEA SETTING

Name	Phase	Biomarker	Drug	Arms
GLOW	3	CLDN-18.2	Zolbetuximab	• Zolbetuximab plus CAPOX • Placebo plus CAPOX
ILUSTRO	2	CLDN- 18.2 PD-1	Zolbetuximab Pembrolizumab Nivolumab	• Zolbetuximab • mFOLFOX plus Zolbetuximab • Pembrolizumab plus zolbetuximab • Zolbetuximab in combination with mFOLFOX6 and nivolumab
FORTITUDE 101	3	FGFR2B	Bemarituzuamb	• Bemarituzumab with mFOLFOX6 • Placebo with mFOLFOX6
FORTITUDE 102	1b/3	FGFR2B	Bemarituzumab	• Bemarituzumab with mFOLFOX6 and nivolumab • Placebo with mFOLFOX6 and nivolumab
HERIZON	2	HER2	Zanidatamab	• Trastuzumab plus physician's choice of capecitabine plus oxaliplatin or 5-fluorouracil plus cisplatin • Zanidatamab plus physician's choice of capecitabine plus oxaliplatin or 5-fluorouracil plus cisplatin • Zanidatamab and tislelizumab plus physician's choice of capecitabine plus oxaliplatin or 5-fluorouracil plus cisplatin
LEAP-015	3	–	Levantinib Pembrolizumab	• Lenvatinib + pembrolizumab + chemotherapy • Chemotherapy

5-FU, fluorouracil; CLDN, claudin; FGFR2B, fibroblast growth factor receptor 2B GC, gastric cancer; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; mFOLFOX, modified folinic acid, fluorouracil, oxaliplatin; PD-1, programmed cell death protein 1

https://clinicaltrials.gov/ct2/show/NCT05052801; https://clinicaltrials.gov/ct2/show/NCT03505320; https://clinicaltrials.gov/ct2/show/NCT05052801; https://clinicaltrials.gov/ct2/show/NCT05111626; https://clinicaltrials.gov/ct2/show/NCT05152147; https://clinicaltrials.gov/ct2/show/NCT04662710

BIOMARKER CO-EXPRESSION IN GC/GEJC

- CLDN positivity is found in 30-33% of GC/GEJC patients and is associated with diffuse-type GC/GEJC
- The impact of the clinicopathological features of CLDN-positivity in GC/GEJC on treatment outcomes with standard chemotherapy or anti-PD-1 therapy is unclear
- A recent comprehensive clinical and molecular characterization of CLDN-18.2 expression in advanced GC/GEJC sheds light on this

Methods:

- Patients with advanced GC/GEJC who received systemic chemotherapy
- Clinicopathological features of CLDN-18.2 expression with four molecular subtypes:
  - MMR deficient
  - EBV-positive
  - HER2 positive
  - Others (all negative)
- PD-L1 CPS and other molecular alterations in Japanese patients with advanced GC/GEJC were included
- Clinical outcomes of standard first- or second-line chemotherapy and subsequent anti-PD-1 therapy were also investigated according to CLDN-18.2 expression

CLDN, claudin; CPS, combined positive score; EBV, Epstein Barr virus; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; MMR, mismatch repair; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1

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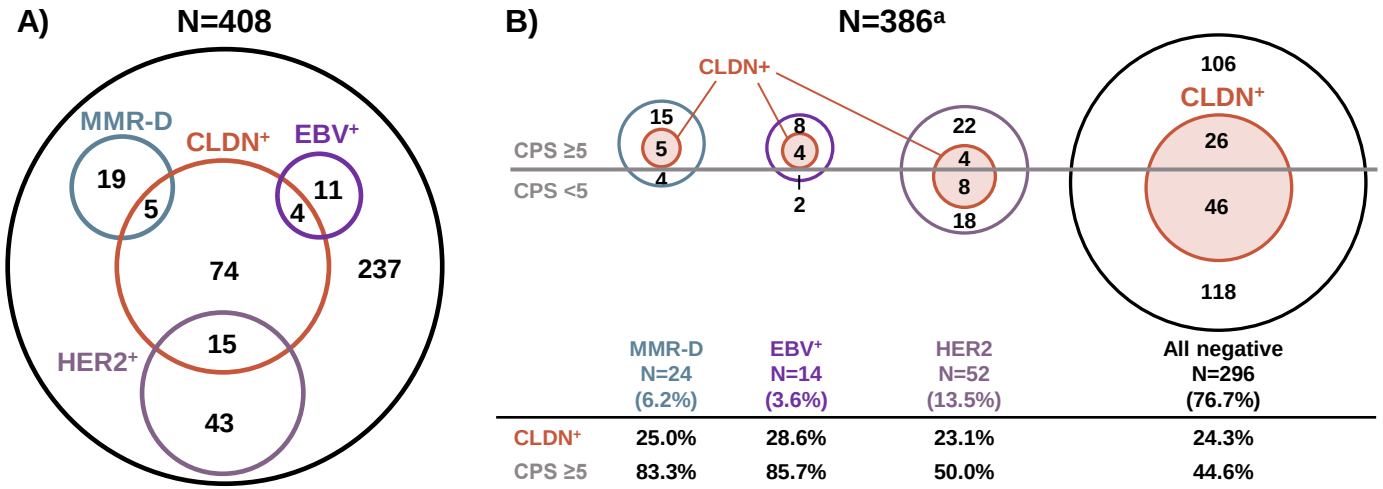
OUTCOME AND RESULTS

- Tumour response, PFS, and OS were evaluated
- Moderate to strong CLDN-18.2 expression in 98/408 patients with equal distribution in the four molecular subtypes or CPS subgroups
- CLDN-18.2 positivity was associated with Borrmann type 4, *KRAS* amplification, low CD16, and high CD68 expression



- Relationship between CLDN and other biomarkers (A) and PD-L1 CPS (B)
- All-negative:
- Negative for neither MMR-D, EBV nor HER2

[a] Patients with available CPS results

+, positive; CD, cluster of differentiation; CLDN, claudin; CPS, combined positive score; EBV, Epstein Barr virus; HER2, human epidermal growth factor receptor 2; MMR-D, mismatch repair deficient; MMR-P, mismatch repair proficient; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival

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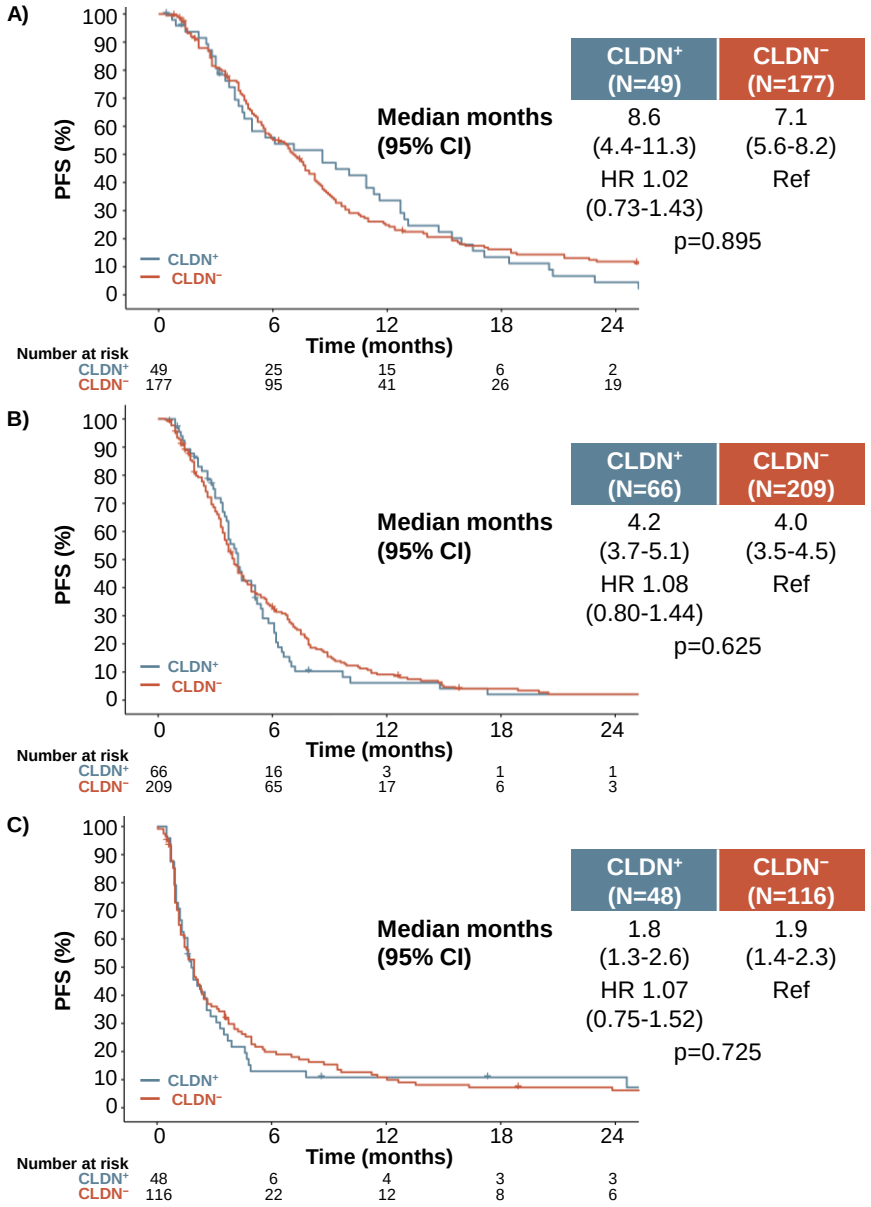
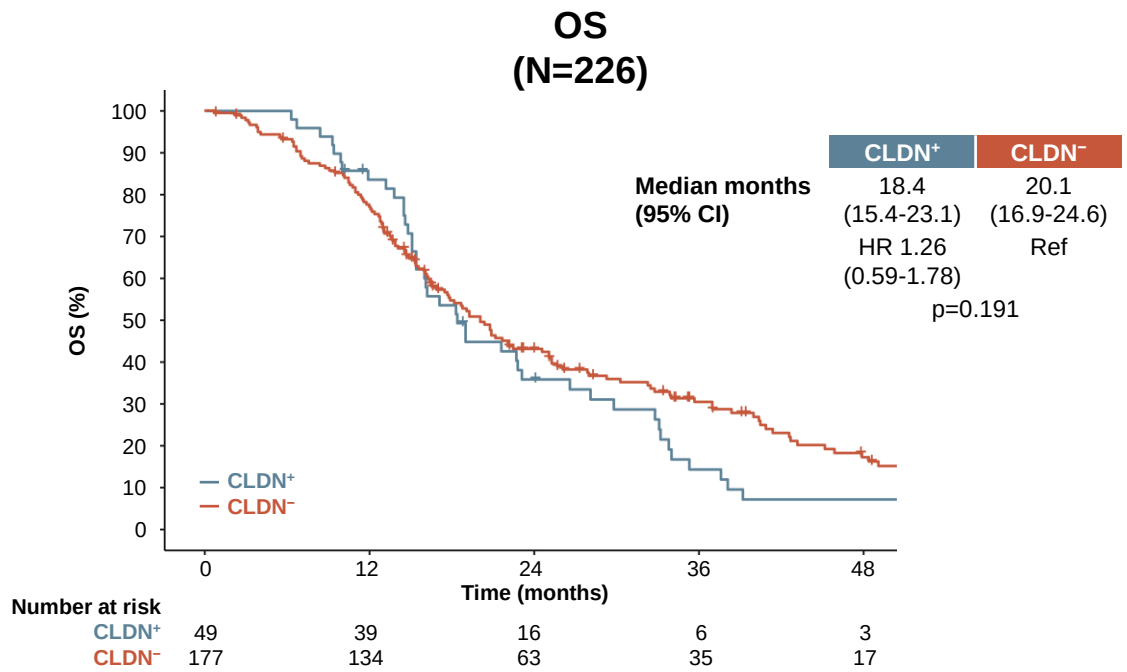
OS AND PFS



	CLDN⁺ (N=49)	CLDN⁻ (N=177)
Median months (95% CI)	8.6 (4.4-11.3)	7.1 (5.6-8.2)
	HR 1.02 (0.73-1.43)	Ref
	p=0.895	

	CLDN⁺ (N=66)	CLDN⁻ (N=209)
Median months (95% CI)	4.2 (3.7-5.1)	4.0 (3.5-4.5)
	HR 1.08 (0.80-1.44)	Ref
	p=0.625	

	CLDN⁺ (N=48)	CLDN⁻ (N=116)
Median months (95% CI)	1.8 (1.3-2.6)	1.9 (1.4-2.3)
	HR 1.07 (0.75-1.52)	Ref
	p=0.725	



	CLDN⁺	CLDN⁻
Median months (95% CI)	18.4 (15.4-23.1)	20.1 (16.9-24.6)
	HR 1.26 (0.59-1.78)	Ref
	p=0.191	

- OS with first-line chemotherapy was not significantly different between CLDN-18.2-positive and CLDN-18.2-negative groups (median 18.4 vs 20.1 months; HR 1.26 [95% CI 0.89-1.78]; p=0.191) regardless of stratification by PD-L1 CPS ≥5
- PFS and objective response rates of first- and second-line chemotherapy and anti-PD-1 therapy also showed no significant differences according to CLDN-18.2 status

+, positive; ⁻, negative; CI, confidence interval; CLDN, claudin; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand 1; PD-L1, programmed death ligand 1; PFS, progression-free survival ; Ref, reference

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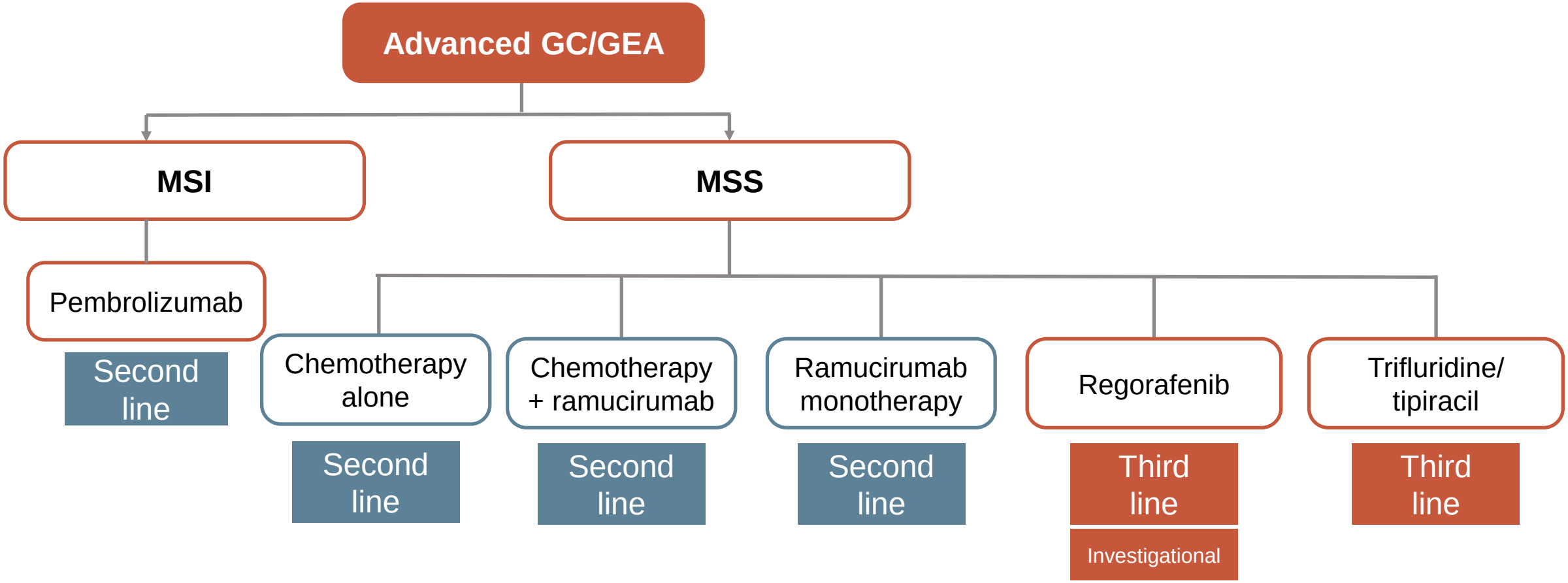
CASE PRESENTATION 2: TREATMENT AFTER FIRST LINE

Second-line treatment	• Enrolled in anti-TIGIT monotherapy trial with PD after 6 weeks • NGS panel sent
NGS results	• Pathogenic ATM mutation
Third-line treatment	• Explored PARP and ATR inhibitor trials: none currently available • Commenced FOLFIRI chemotherapy with response at 3 months • Treatment ongoing

ATR, ataxia telangiectasia and Rad3-related; FOLFIRI, folinic acid, fluorouracil, irinotecan; NGS, next-generation sequencing; PARP, poly ADP ribose polymerase; PD, progression of disease; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains

CURRENT AND EVOLVING TREATMENT OPTIONS IN GC/GEA: SECOND- AND THIRD-LINE



GC, gastric cancer; GEA, gastroesophageal adenocarcinoma; MSI, microsatellite instability; MSS, microsatellite stable

REFRACTORY ADVANCED GASTROESOPHAGEAL CANCER

Name	Phase	Drug	Arms
INTEGRATE IIB	3	Regorafenib	• Regorafenib plus nivolumab • Standard of care
LOGICAN	2	Trifluridine/tipiracil	• Trifluridine/tipiracil + oxaliplatin • FOLFOX

Lam LL, et al. BMC Cancer. 2023;23:180; https://clinicaltrials.gov/ct2/show/NCT05476796. Accessed March 2023.

FOLFOX, folinic acid, fluorouracil, and oxaliplatin

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