How I Treat Metastatic Esophageal and Gastric Cancer in 2023

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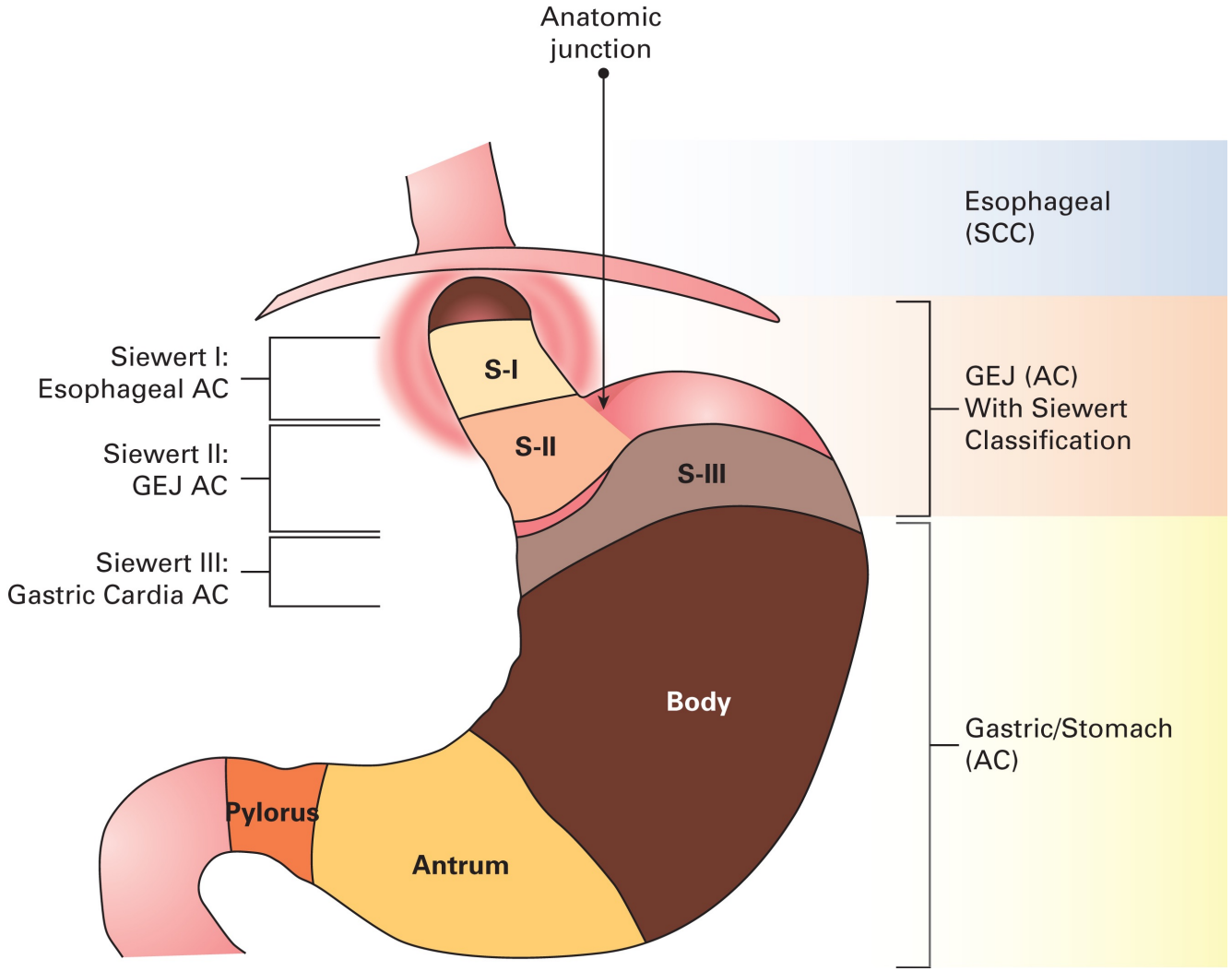
MLS Cleveland

Outline

- Overview of Gastroesophageal Cancers
- Staging approach
- Treatment Metastatic disease By subtype
- Oligometastatic disease

Overview

- 3 histological subtypes
  - Esophageal SCC
  - Distal Esophageal/GEJ AC
  - Gastric AC
- Personalized therapies
  - HER2/ERBB2 overexpressing
  - MMR/MSI
  - Anti-PD-1
  - (Claudin 18.2)



N.A. Dasari, C.D. Weekes, ASCO SEP 2022

Diagnostic W/U

Esophageal

- CT C/A with oral/IV contrast
- EUS in absence of overt metastatic disease
- Laparoscopy for GEJ in absence of overt metastatic disease
- Consideration for nutrition (PEG vs SEMS)

Gastric

- CT C/A/P with oral/IV contrast
- Laparoscopy in absence of overt metastatic disease

Metastatic disease statistics

Esophagus Cancer and GEA

- 50+% present with metastatic disease
- Locations
  - Liver (56%)
  - Distant LN (53%)
  - Lung (50%)
  - Peritoneum, adrenals, bone (20-30%)

Gastric Cancer

- >40% present with metastatic disease
- Locations
  - Peritoneum (53-60%)
  - Liver (48%)
  - Lung /plerua (21%)
  - Bone (12%)
  - CNS (3%)

Pathology Primer

- HER2/ERBB2 (7-34% overexpressed)
  - IHC 0-1+ = Negative
    - 2+ = Equivocal **needs ISH**
    - 3+ = Positive
  - Amplification measured by NGS
- MMR/MSI (8-20% deficient/high)
  - MMR: IHC for MLH1, MSH2, MSH6, PMS2
  - MSI: PCR or NGS for (BAT25, BAT26, MONO27, NR21, NR24)
- PD-L1 (>50%)
  - Combined Positive Score (CPS): PD-L1 + cells divided by total viable tumor cells x 100.

Oligometastatic disease

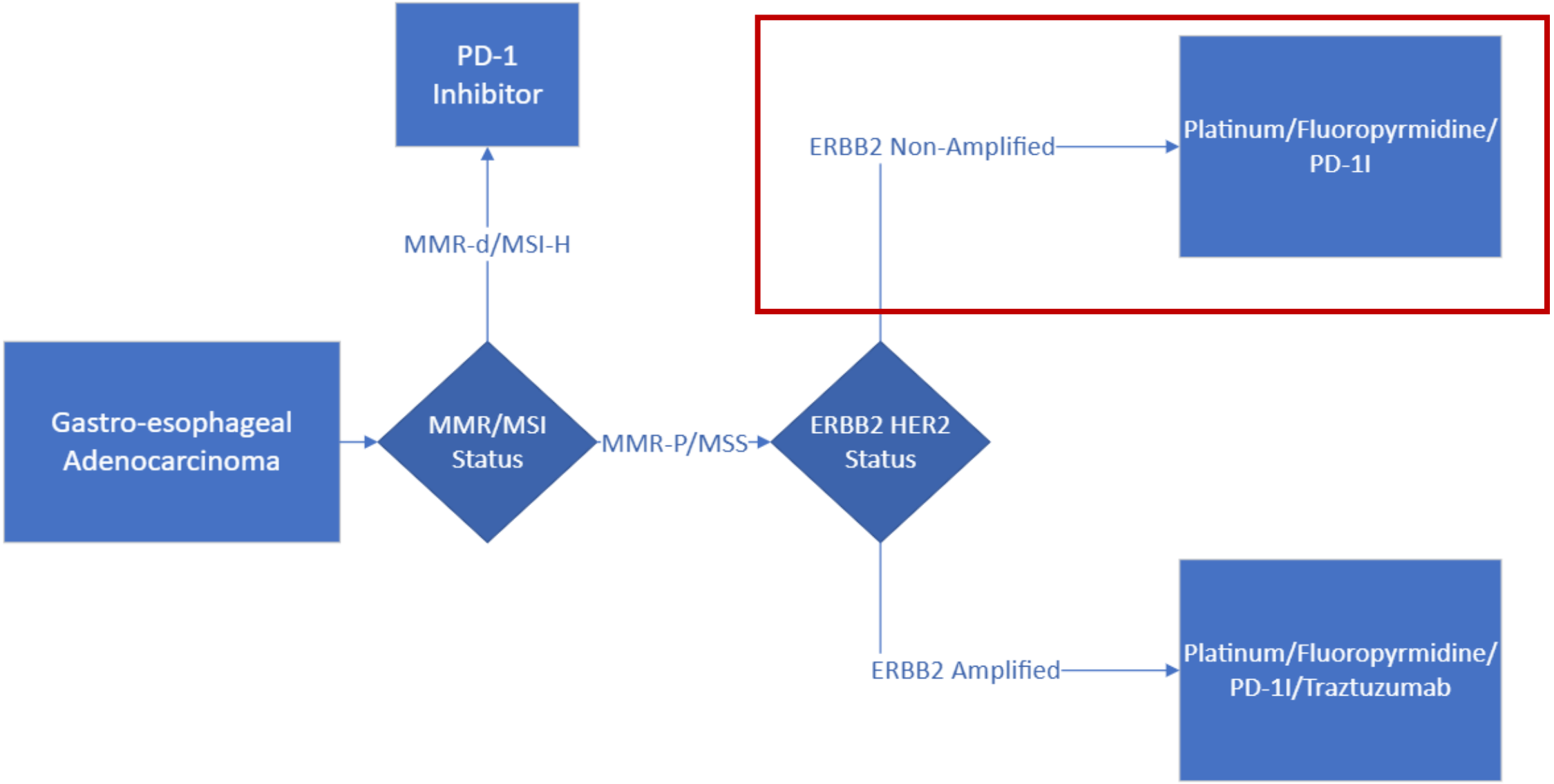
Gastric

- AIO-FLOT3 Phase 2
- Limited metastasis (1 site, =/- RP LN)= Arm B n=60
- FLOT x 4 then chemo vs surgery
- mOS 22.9mo
- RENAISSANCE (AIO-FLOT5)
- Results pending…

Esophagogastric

- L. Puckett et al Cohort study (GI ASCO 2022)
- 77 pts, 35 with oligomet ds (≤5)
- 18 with dCRT, 17 palliative tx
- mOS 91.4 v 8.2 mo

Treatment algorithm for mGEA

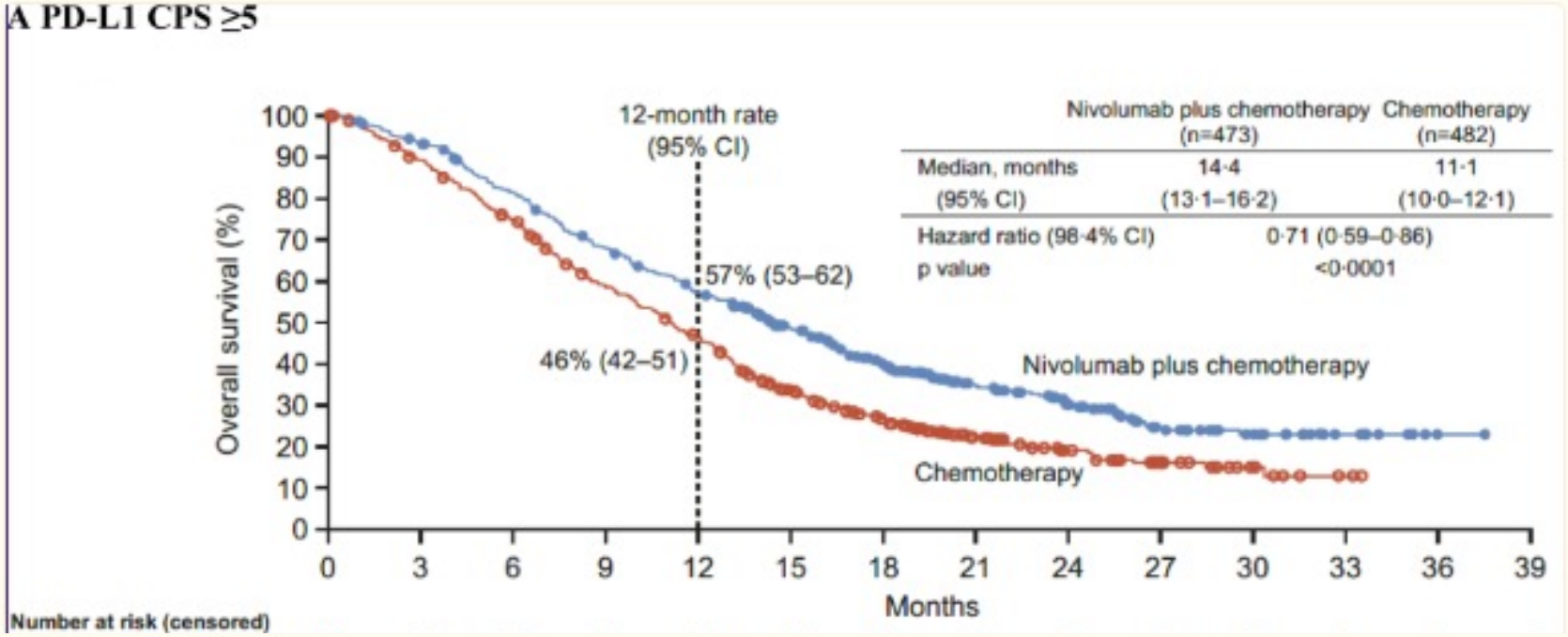


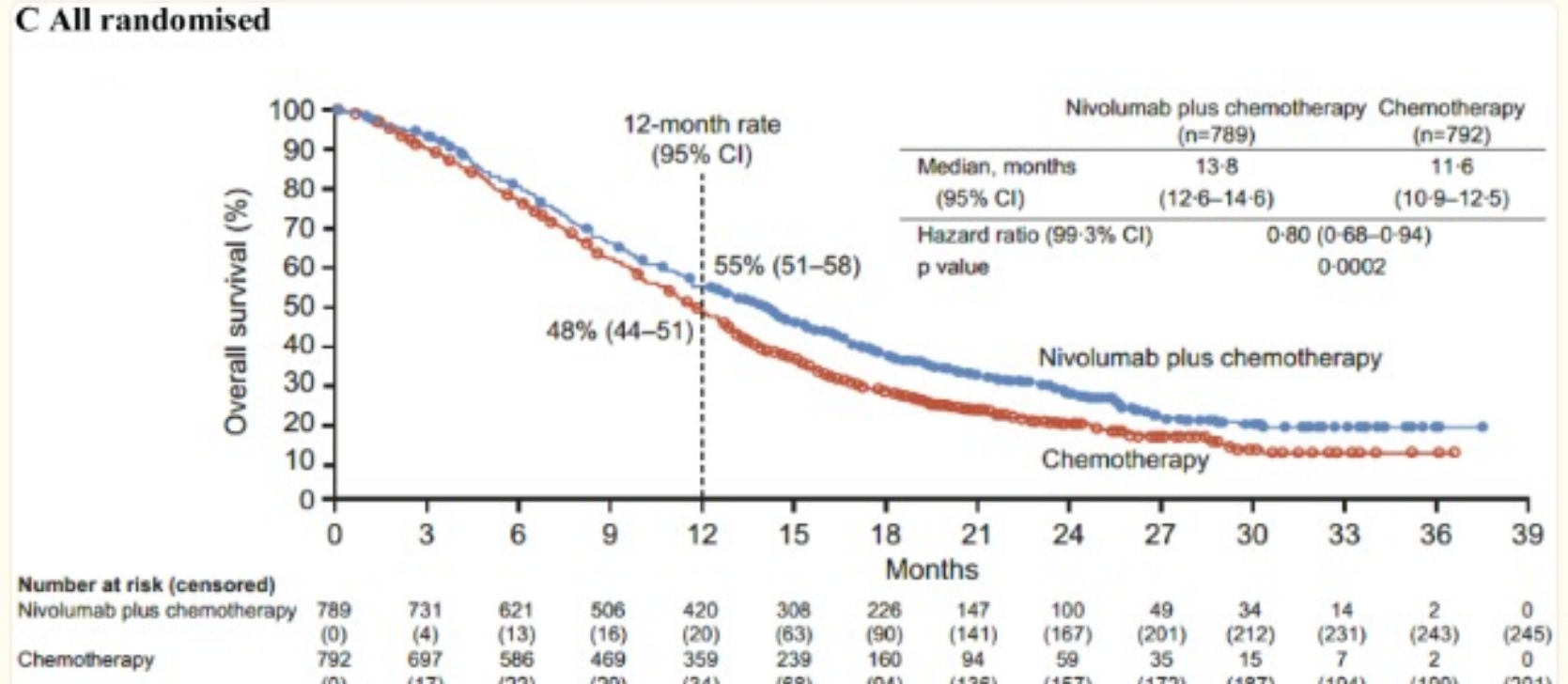
Trials of chemo + PD-1 inhibition in mGEA

- Checkmate 649
- Chemo + nivo / ipi+nivo/ chemo (1:1:1)
- Adeno only
- Chemo = FOLFOX or CAPEOX
- ~800 pts per group

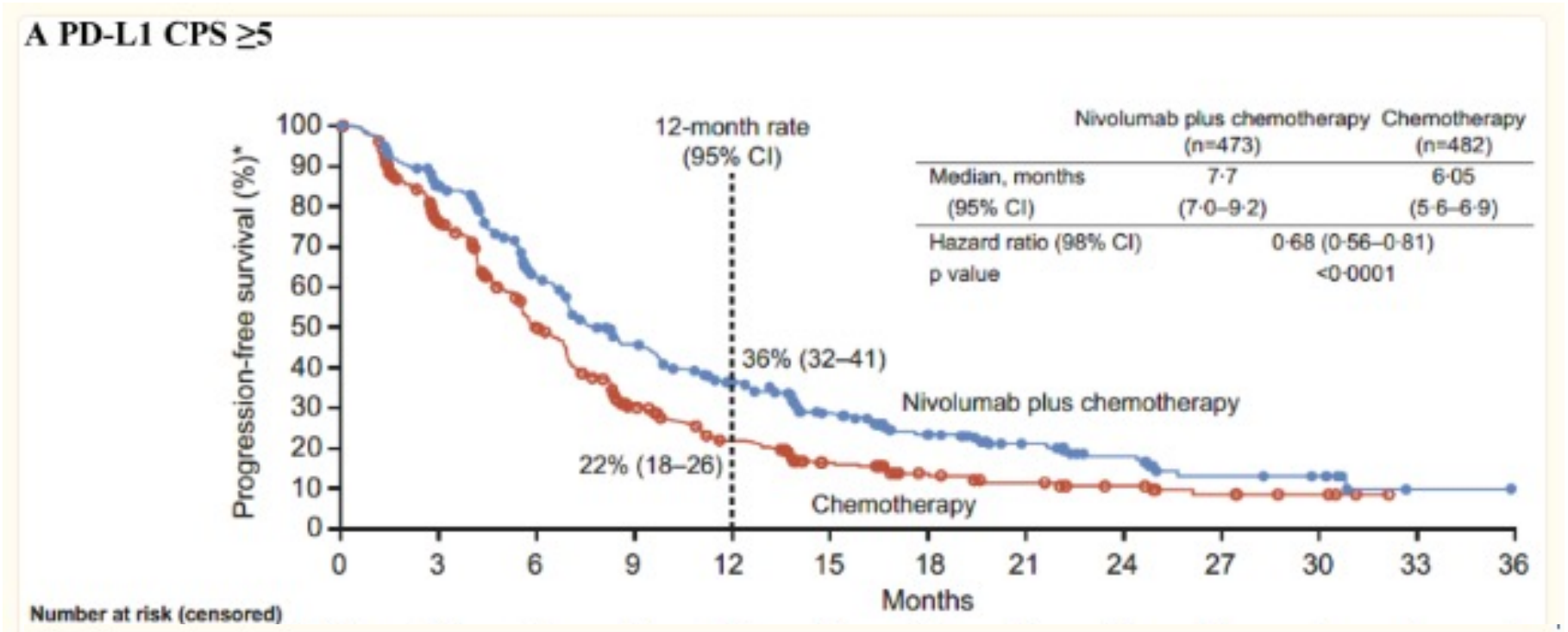
- Keynote 590
- No gastric pts
- Adeno (30%) and SCC (70%)
- 5FU + Cisplatin +/- Pembolizumab (1:1)
- ~375 pts per group

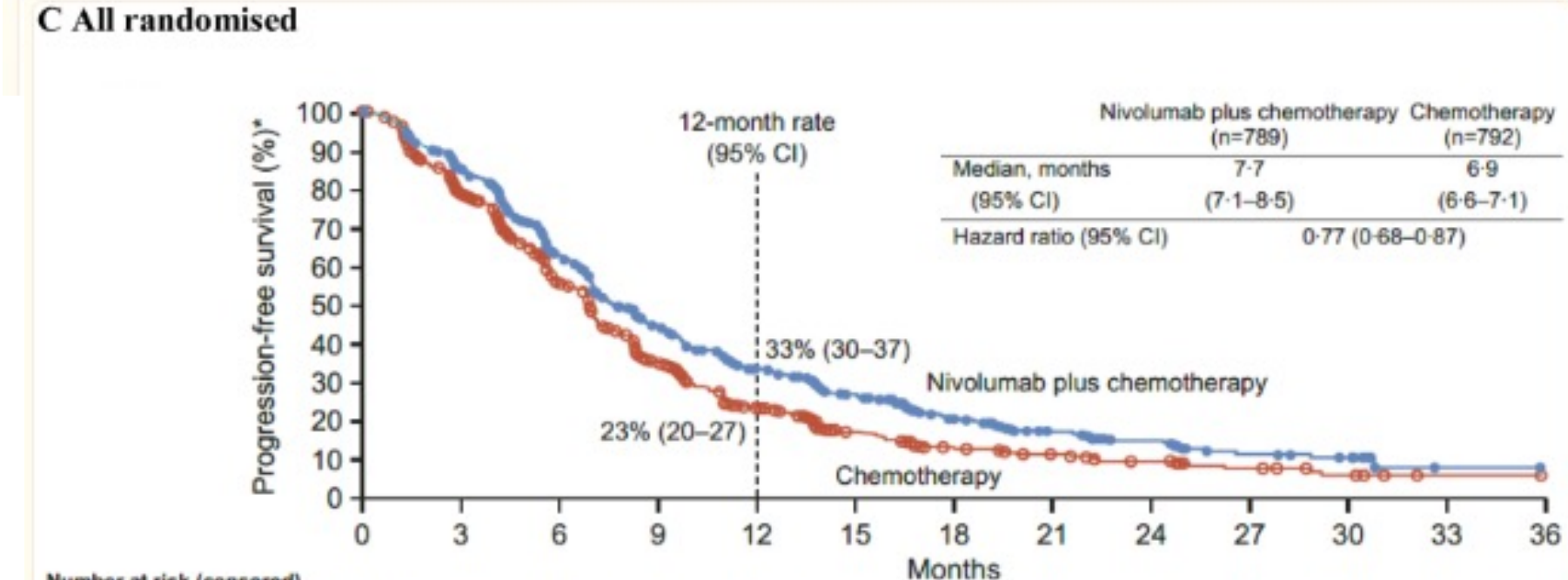
OS

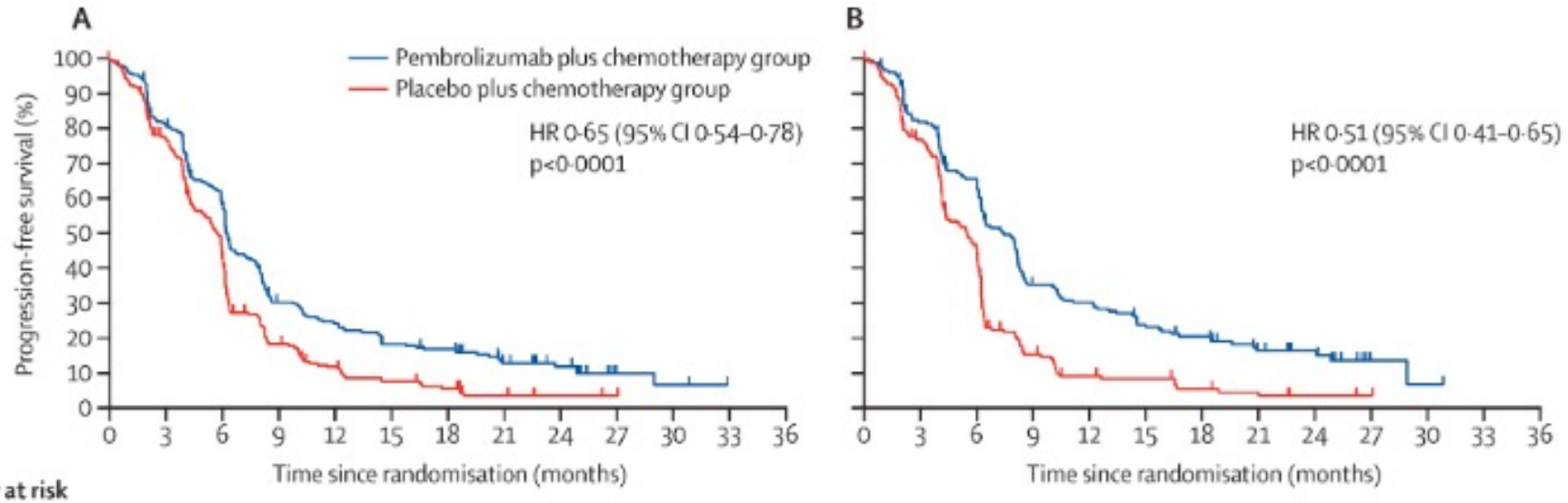

A PD-L1 CPS ≥5
12-month rate
(95% CI)
57% (53–62)
46% (42–51)
Nivolumab plus chemotherapy
Chemotherapy
Overall survival (%)
Months
Nivolumab plus chemotherapy (n=473)
Chemotherapy (n=482)
Median, months (95% CI) 14·4 (13·1–16·2) 11·1 (10·0–12·1)
Hazard ratio (98·4% CI) 0·71 (0·59–0·86)
p value <0·0001
Number at risk (censored)


C All randomised
12-month rate
(95% CI)
55% (51–58)
48% (44–51)
Nivolumab plus chemotherapy
Chemotherapy
Overall survival (%)
Months
Nivolumab plus chemotherapy (n=789)
Chemotherapy (n=792)
Median, months (95% CI) 13·8 (12·6–14·6) 11·6 (10·9–12·5)
Hazard ratio (99·3% CI) 0·80 (0·68–0·94)
p value 0·0002
Number at risk (censored)
Nivolumab plus chemotherapy 789 (0) 731 (4) 621 (13) 506 (16) 420 (20) 308 (63) 226 (90) 147 (141) 100 (167) 49 (201) 34 (212) 14 (231) 2 (243) 0 (245)
Chemotherapy 792 697 586 469 359 239 160 94 59 35 15 7 2 0

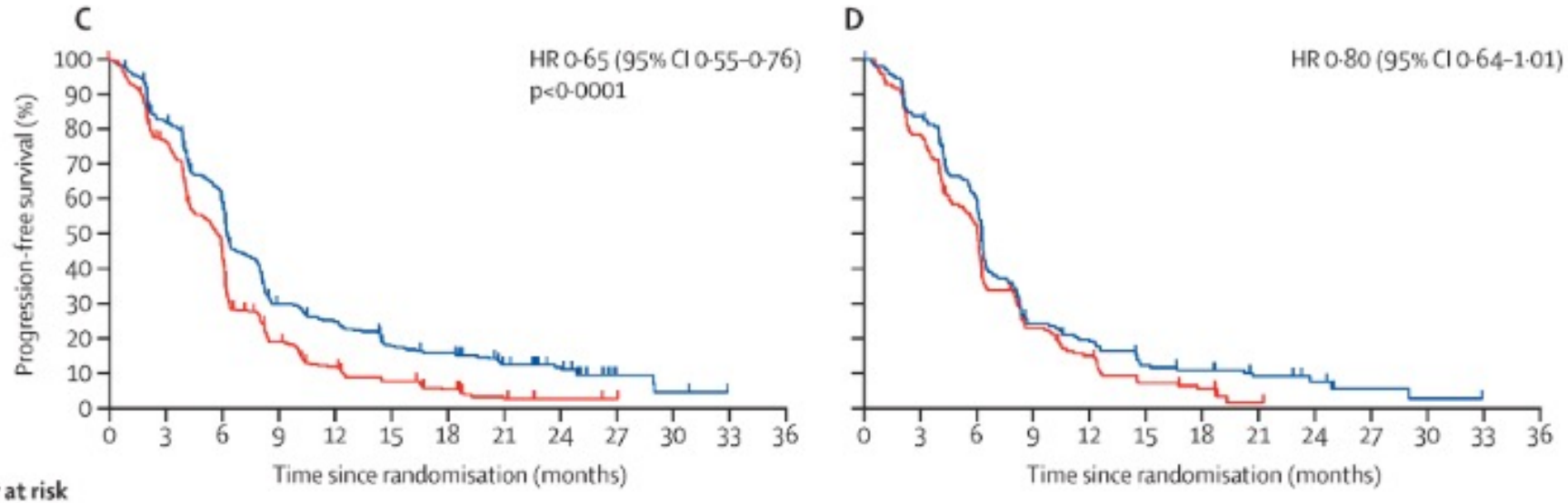
PFS


A PD-L1 CPS ≥5
12-month rate
(95% CI)
Progression-free survival (%)*
100
90
80
70
60
50
40
30
20
10
0
0
3
6
9
12
15
18
21
24
27
30
33
36
Months
36% (32–41)
22% (18–26)
Nivolumab plus chemotherapy
Chemotherapy
Nivolumab plus chemotherapy (n=473)
Chemotherapy (n=482)
Median, months 7·7 6·05
(95% CI) (7·0–9·2) (5·6–6·9)
Hazard ratio (98% CI) 0·68 (0·56–0·81)
p value <0·0001
Number at risk (censored)


C All randomised
12-month rate
(95% CI)
Progression-free survival (%)*
100
90
80
70
60
50
40
30
20
10
0
0
3
6
9
12
15
18
21
24
27
30
33
36
Months
33% (30–37)
23% (20–27)
Nivolumab plus chemotherapy
Chemotherapy
Nivolumab plus chemotherapy (n=789)
Chemotherapy (n=792)
Median, months 7·7 6·9
(95% CI) (7·1–8·5) (6·6–7·1)
Hazard ratio (95% CI) 0·77 (0·68–0·87)



Number at risk (number censored)																									
Pembrolizumab plus chemotherapy group	274 (0)	211 (15)	156 (20)	71 (26)	57 (26)	41 (28)	35 (31)	19 (40)	13 (45)	3 (53)	2 (53)	0 (55)	0 (55)	186 (0)	143 (11)	109 (17)	56 (21)	48 (21)	36 (23)	29 (25)	17 (32)	12 (37)	2 (45)	1 (45)	0 (46)	0 (46)
Placebo plus chemotherapy group	274 (0)	205 (9)	127 (11)	45 (16)	26 (20)	16 (21)	11 (22)	5 (25)	2 (28)	1 (29)	0 (30)	0 (30)	0 (30)	197 (0)	145 (7)	85 (9)	26 (14)	14 (16)	12 (17)	7 (18)	5 (19)	2 (21)	1 (22)	0 (23)	0 (23)	0 (23)



Number at risk (number censored)

Toxicity of chemo/PD-1 Inhibition

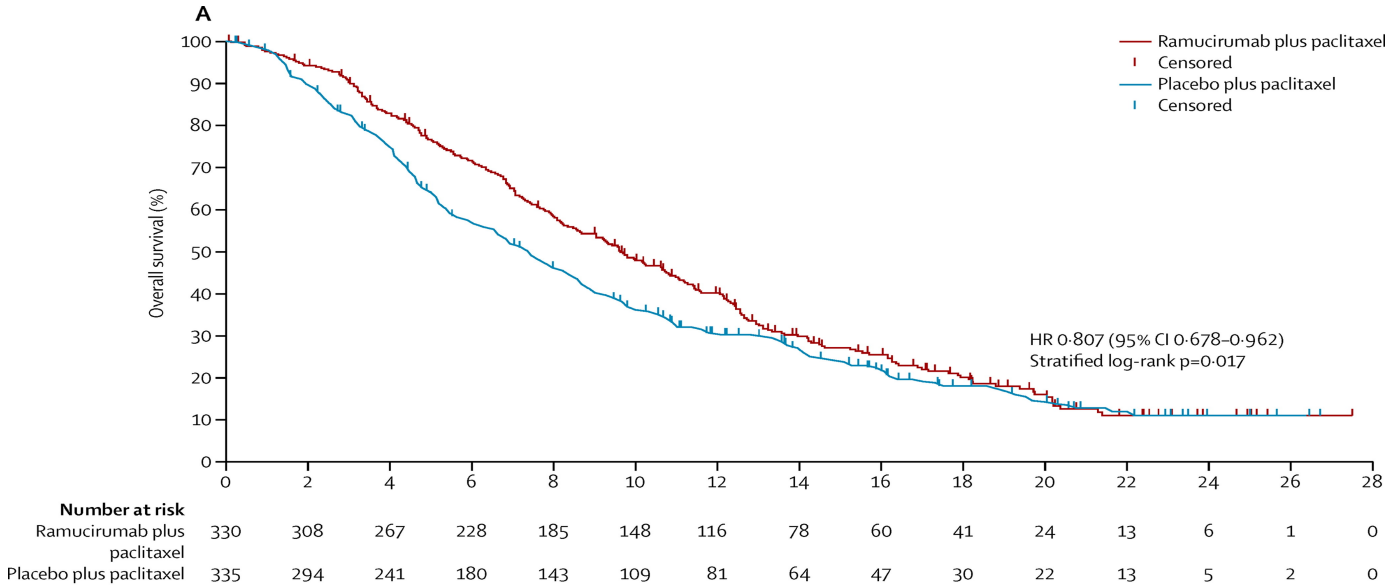
	Nivolumab plus chemotherapy (n=782) *			Chemotherapy alone (n=767) *		
	Grade 3	Grade 4	Grade 5 †	Grade 3	Grade 4	Grade 5
All events	358 (46%)	104 (13%)	4 (1%)	285 (37%)	56 (7%)	0
Serious events	97 (12%)	34 (4%)	4 (1%)	63 (8%)	14 (2%)	0
Events leading to discontinuation	109 (14%)	23 (3%)	4 (1%)	58 (8%)	9 (1%)	0
Any-grade events in 10% or more of treated patients						
Diarrhoea	33 (4%)	2 (<1%)	0	23 (3%)	1 (<1%)	0
Fatigue	30 (4%)	0	0	16 (2%)	1 (<1%)	0
Anaemia	44 (6%)	3 (<1%)	0	20 (3%)	1 (<1%)	0
Neutropenia	87 (11%)	31 (4%)	0	70 (9%)	23 (3%)	0
Lipase increased	34 (4%)	11 (1%)	0	14 (2%)	2 (<1%)	0

Second line ERBB2/HER2-

- Paclitaxel (pac) + Ramucirumab (ram) (RAINBOW)
- 665 pts, double blind randomized, 1:1 Pac+placebo vs Pac+Ram
- Previously treated pts 5FU + platinum +/- anthracycline
- Excluded: non-adeno, gastric perforation/fistula, thromboembolic events w/in 6 mo, uncontrolled HTN

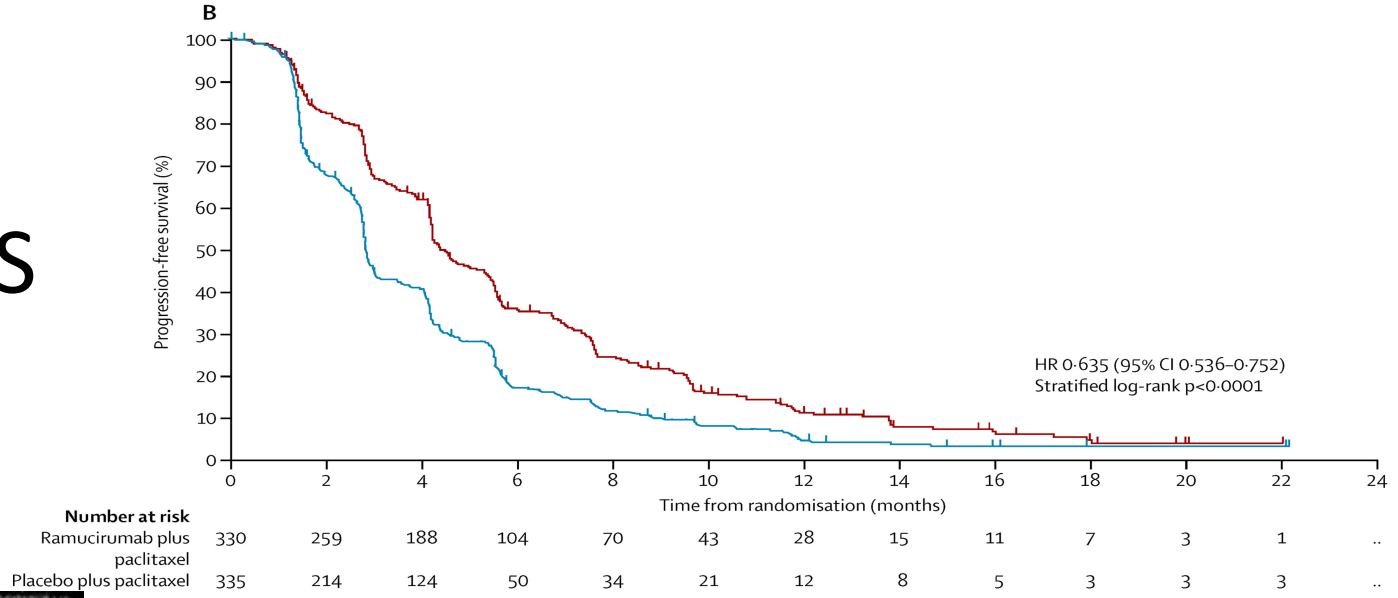
H. Wilke et al Lancet Oncol 2014

OS



mOS: 9.6 mo v 7.4 mo
12 mo OS 40% v 30%

PFS



mPFS: 4.4 mo v 2.9 mo
6 mo PFS 36% v 17%

The Lancet Oncology 2014 151224-1235DOI: (10.1016/S1470-2045(14)70420-6)

Toxicity Summary Pac/Ram

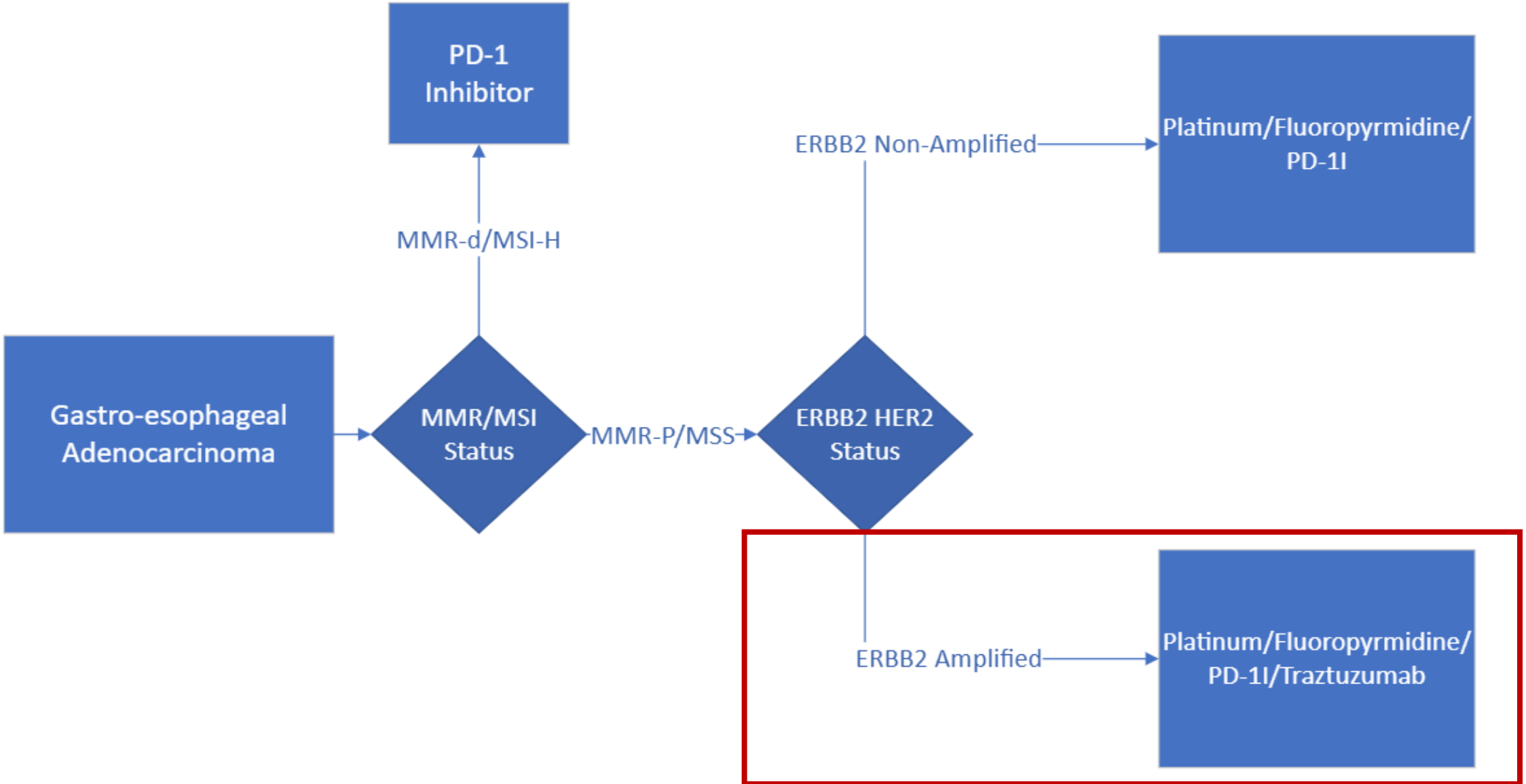
<u>Gr 3 or higher toxicities</u>

- neutropenia 41% v 19%
- HTN 14% v 2%
- Fatigue 12% v 5%
- Abd pain 6% v 3%
- Gastric perforation 4 events vs 1 event

After Second Line

- Irinotecan or FOLFIRI
- Trifluridine and tipiracil
- Other appropriate targeted therapies or clinical trials

Treatment algorithm for mGEA



ERBB2/HER2 amplified GEA

- ToGA Trial 2010 Lancet
- 600 pts 1:1 Chemo +/- traztuzumab
- 5FU (or Cape) + cisplatin
- ~80% Gastric 20% GEJ
- ~50% Asian ~30% White
- LVEF every 12 weeks

YJ Bang et al Lancet 2010

ToGA Responses

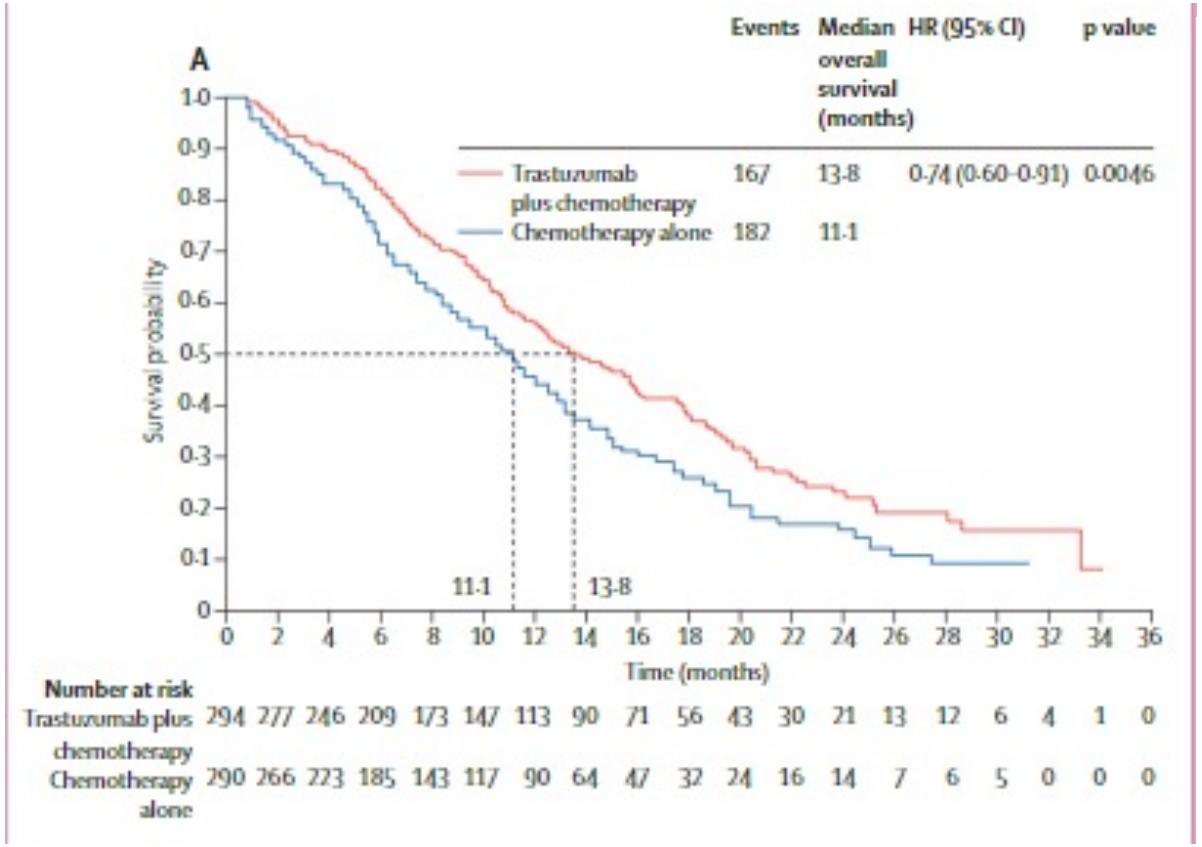
	Trastuzumab plus chemotherapy (n=294)	Chemotherapy alone (n=290)	Non-stratified effect size		Stratified effect size*		Odds ratio	p value
			Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value		
Progression-free survival (months)	6·7 (6–8)	5·5 (5–6)	0·71 (0·59–0·85)	0·0002	0·71 (0·59–0·86)	0·0004	..	..
Time to progression (months)	7·1 (6–8)	5·6 (5–6)	0·70 (0·58–0·85)	0·0003	0·69 (0·57–0·84)	0·0003	..	..
Duration of response (months)	6·9 (6–8)†	4·8 (4–6)‡	0·54 (0·40–0·73)	<0·0001	0·53 (0·39–0·73)	<0·0001	..	..
Tumour response								
Overall tumour response rate	139 (47%)	100 (35%)	..	..	..	..	1·70 (1·22–2·38)	0·0017§
Complete response	16 (5%)	7 (2%)	..	..	..	..	2·33 (0·94–5·74)	0·0599§
Partial response	123 (42%)	93 (32%)	..		..	..	1·52 (1·09–2·14)	0·0145§
Stable disease	93 (32%)	101 (35%)	..	..	..	..	..	..
Progressive disease	35 (12%)	53 (18%)	..	..	..	..	..	..
Missing	27 (9%)	36 (12%)	..	..	..	..	..	..

Data are median (95% CI) or number (%). *Stratified by extent of disease (local vs metastatic), primary tumour site (stomach vs gastro-oesophageal junction), measurability (measurable vs non-measurable), Eastern Cooperative Oncology Group performance status (0–1 vs 2), and fluoropyrimidine regimen (fluorouracil vs capecitabine). †n=139. ‡n=100. §χ^2 test.

Table 3: Secondary efficacy endpoints

YJ Bang et al Lancet 2010

ToGA Survival Curves



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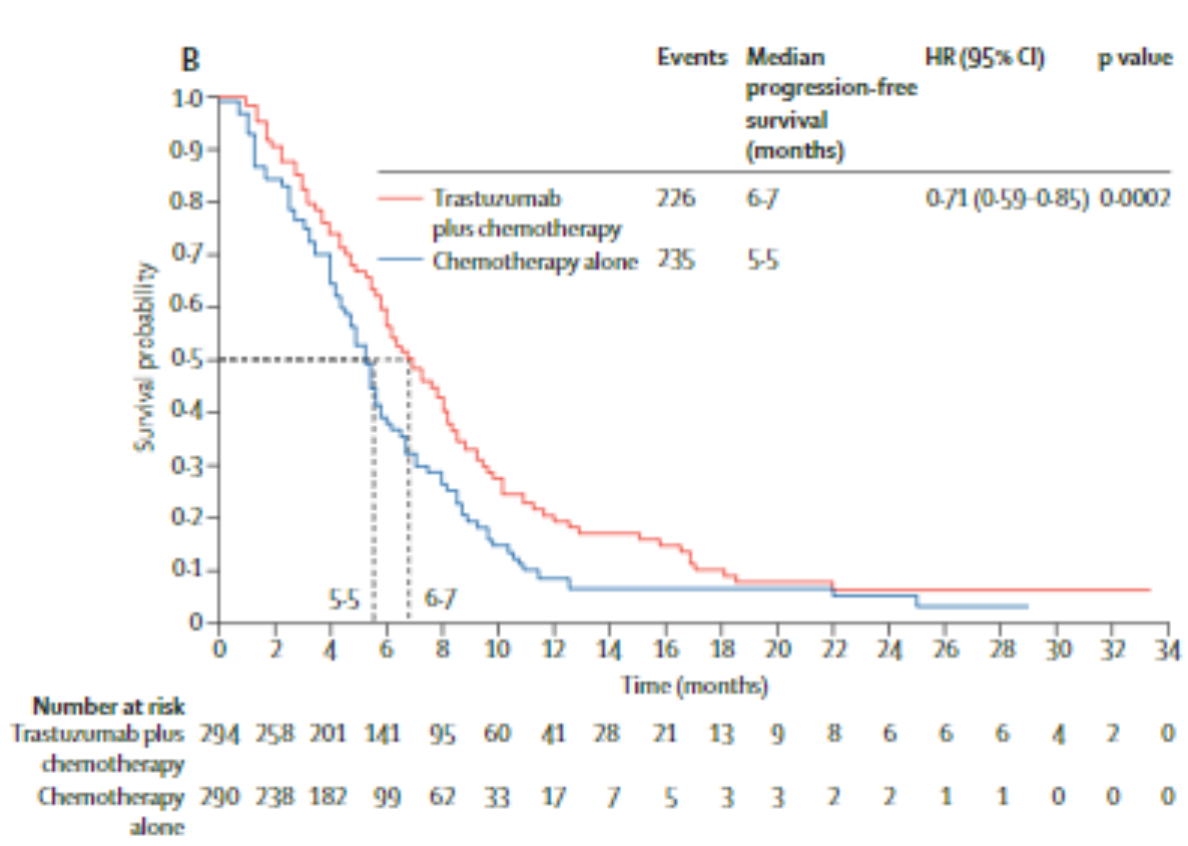


PFS

YJ Bang et al Lancet 2010

Immunotherapy in HER2+ GEA

Keynote 811

- 692 patients
- Chemo/traztuzumab +/- pembrolizumab
- Chemo = Cis/5FU or Cape/ox

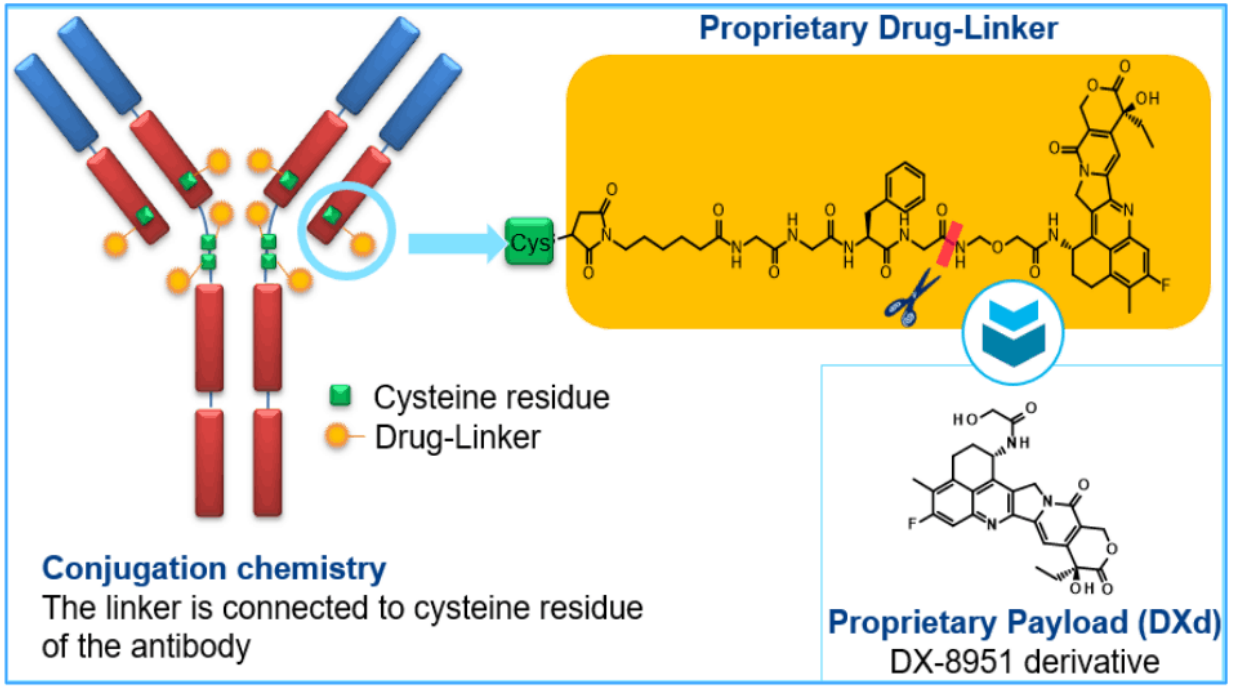
Results (interim)

- ORR: 74 v 52%
  - CR 11 v 3%
  - Duration resp: 10.6 v 9.5
  - OS/PFS: NR

Janjigian et al, Nature 2021

Second Line ERBB2/HER2 amplified

- DESTINY – gastric 01 study
- Trastuzumab deruxtecan (TD) 6.4mg/kg
- 187 pts, TD vs chemo 2:1
- ORR 51% v 14%



Website: ADC Review: www.adcreview.com/trastuzumab-deruxtecan-drug-description/

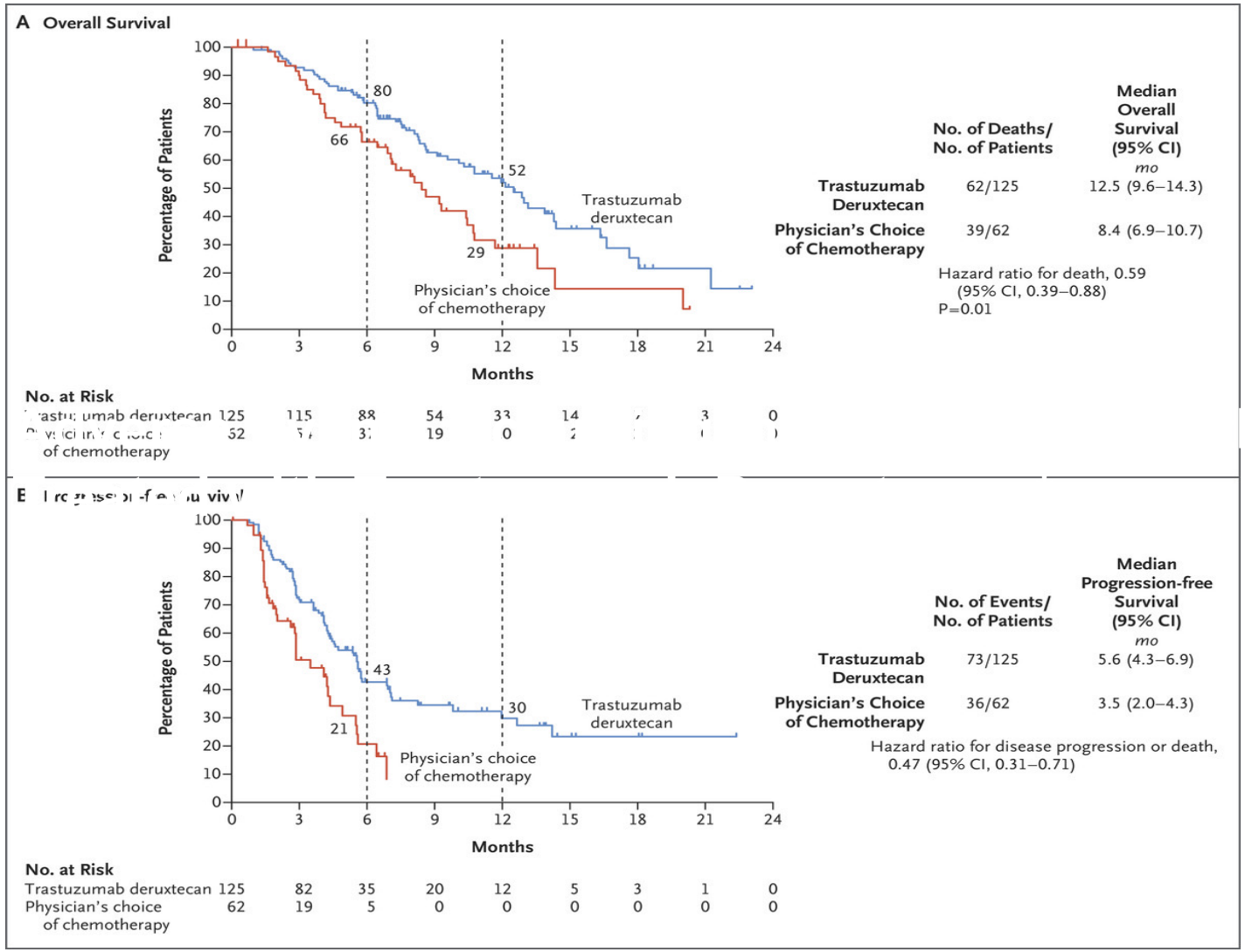
Summary of Efficacy

Table 2. Summary of Efficacy.*

Variable	Trastuzumab Deruxtecan (N = 119)	Physician's Choice of Chemotherapy (N = 56)
Objective response†		
No. of patients	61	8
Percent of patients (95% CI)	51 (42–61)	14 (6–26)
Best response — no. (%)		
Complete response	11 (9)	0
Partial response	50 (42)	8 (14)
Stable disease	42 (35)	27 (48)
Progressive disease	14 (12)	17 (30)
Could not be evaluated	2 (2)	4 (7)
Confirmed objective response‡		
No. of patients	51	7
Percent of patients (95% CI)	43 (34–52)	12 (5–24)
Confirmed best response — no. (%)		
Complete response	10 (8)	0
Partial response	41 (34)	7 (12)
Stable disease	51 (43)	28 (50)
Progressive disease	14 (12)	17 (30)
Could not be evaluated	3 (3)	4 (7)
Confirmed disease control§		
No. of patients	102	35
Percent of patients (95% CI)	86 (78–91)	62 (49–75)

K Shitara et al. N Engl J Med 2020;382:2419-2430.

Overall Survival and Progression-free Survival



mOS: 12.5 v 8.4
12m OS: 52% v 29%

mPFS: 5.6 v 3.5
12m PFS 30% v 0%

K Shitara et al. N Engl J Med 2020;382:2419-2430.

Common Adverse Events

Table 3. Adverse Events Occurring in at Least 20% of the Patients Treated with Trastuzumab Deruxtecan.*

Preferred Term	Trastuzumab Deruxtecan (N=125)			Physician's Choice of Chemotherapy (N=62)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Nausea	79 (63)	6 (5)	0	29 (47)	1 (2)	0
Neutrophil count decreased†	79 (63)	48 (38)	16 (13)	22 (35)	10 (16)	5 (8)
Decreased appetite	75 (60)	21 (17)	0	28 (45)	8 (13)	0
Anemia‡	72 (58)	47 (38)	0	19 (31)	13 (21)	1 (2)
Platelet count decreased§	49 (39)	12 (10)	2 (2)	4 (6)	1 (2)	1 (2)
White-cell count decreased¶	47 (38)	26 (21)	0	22 (35)	5 (8)	2 (3)
Malaise	43 (34)	1 (1)	0	10 (16)	0	0
Diarrhea	40 (32)	3 (2)	0	20 (32)	1 (2)	0
Vomiting	33 (26)	0	0	5 (8)	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‖	27 (22)	8 (6)	6 (5)	2 (3)	0	1 (2)

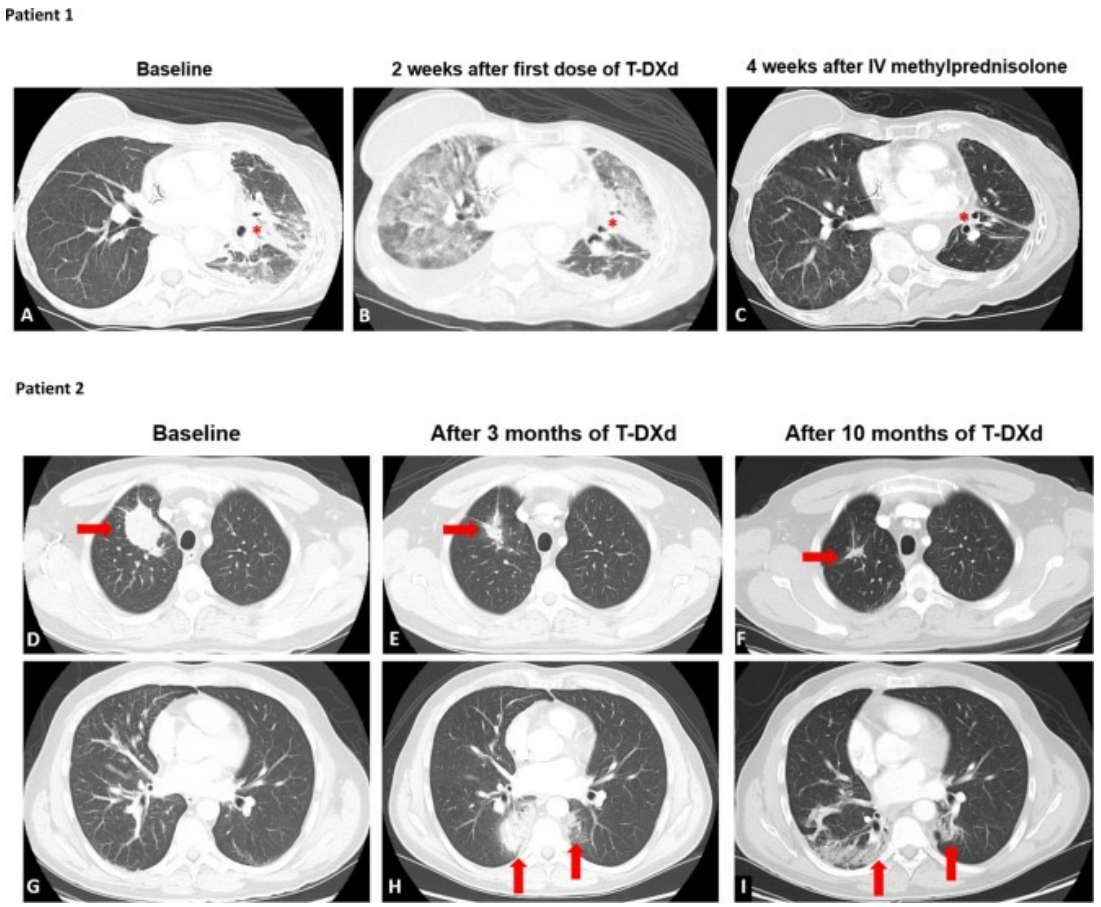
K Shitara et al. N Engl J Med 2020;382:2419-2430.

Uncommon AEs

- Febrile Neutropenia 6 events v 2
- 10% rate of pneumonitis/ILD
  - Median onset 84 days
    - 8/12 cases resolved within 57 days
- No changes in LVEF seen

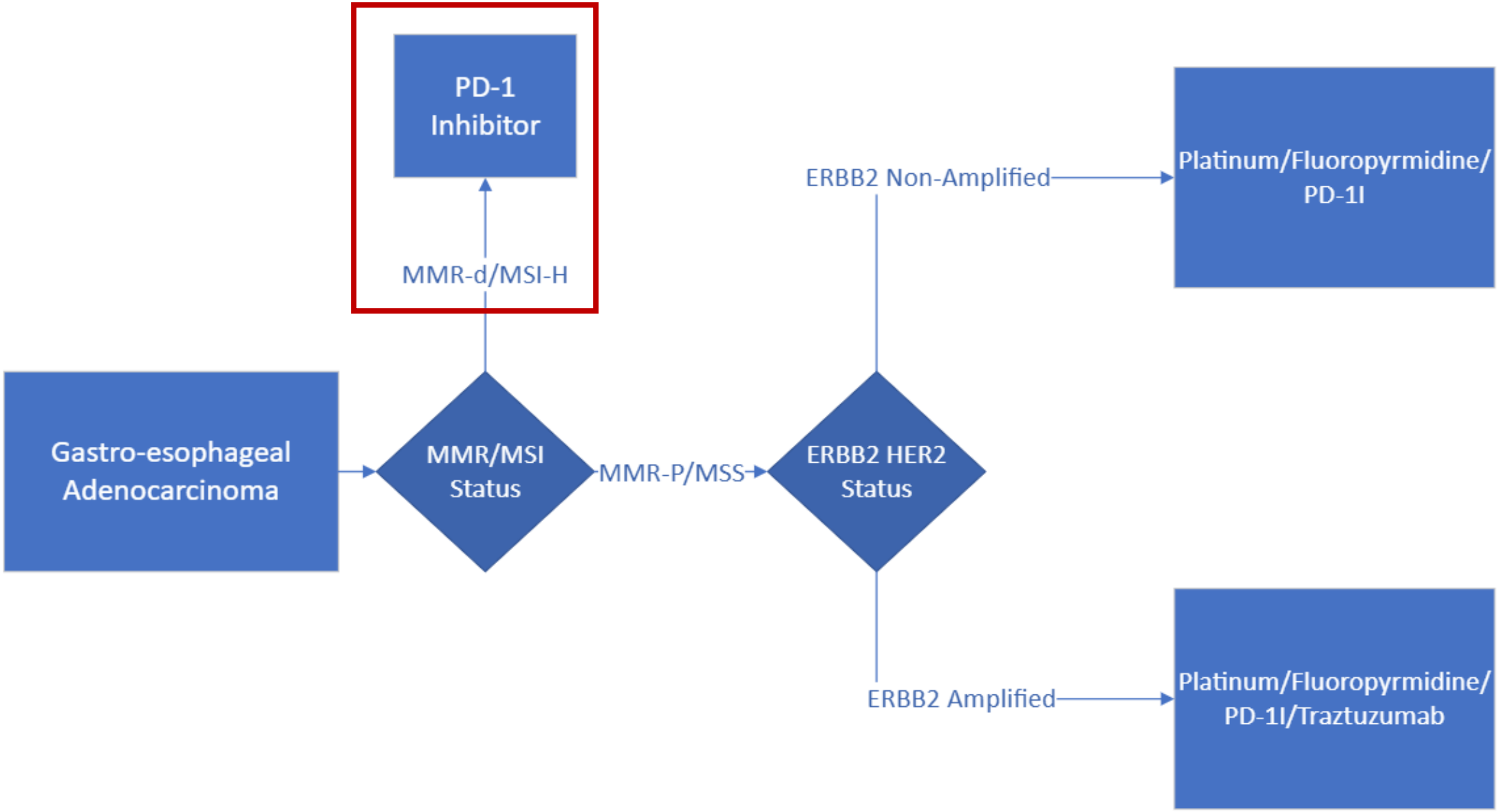
T-DXd related ILD/pneumonitis

- Early diagnosis
  - Patient education (cough, DOE)
  - Checking SpO2
  - H & P q 4-6 weeks
  - CT q 9-12 weeks as allowed by payor
- Early treatment
  - Hold T-DXd
  - Gr1: hold
  - Gr2: D/C and PO steroids w/ long taper
  - Gr3/4: D/C and hospitalization



SM Swain Et al Cancer Treatment Rev 2022

Treatment algorithm for mGEA



MMR-D/MSI-H GEA

	KN059 (3L+)	KN061 (2L)		KN062 (1L)[a]	
	Pembro N = 259	Pembro N = 296	Paclitaxel N = 296	Pembro N = 256	Cisplatin+5-FU/cape N = 250
MSI-H, n (%)	7 (3)	15 (5)	12 (4)	14 (5)	19 (8)
mOS, mo (95% CI)	NR (1.1-NR)	NR (5.6-NR)	8.1 (2.0-16.7)	NR (10.7-NR)	8.5 (5.3-20.8)
mPFS, mo (95% CI)	NR (1.1-NR)	17.8 (2.7-NR)	3.5 (2.0-9.8)	11.2 (1.5-NR)	6.6 (4.4-8.3)
ORR, %	4 (57.1)	7 (46.7)	2 (16.7)	8 (57.1)	7 (36.8)

m, median, NR, not reached; [a]Only pembro monotherapy & chemo alone arms included.

J Chao et al JCO, ASCO-GI, 2020

Future Options

- SPOTLIGHT trial
- CLDN18.2 + (≥ 75% tumor cells moderate+ staining)
- 565 pts 1:1 mFOLFOX +/- zolbetuximab
- mPFS: 10.6 v 8.7 months
- Overall SAE similar in groups but Vomiting 64.5% v 34.5%, Anorexia 47% v 34%
- Other combinations (esp immunotherapy combos) being studied

Thank You