Immunotherapy and HER2 targeted therapies in gastroesophageal cancer
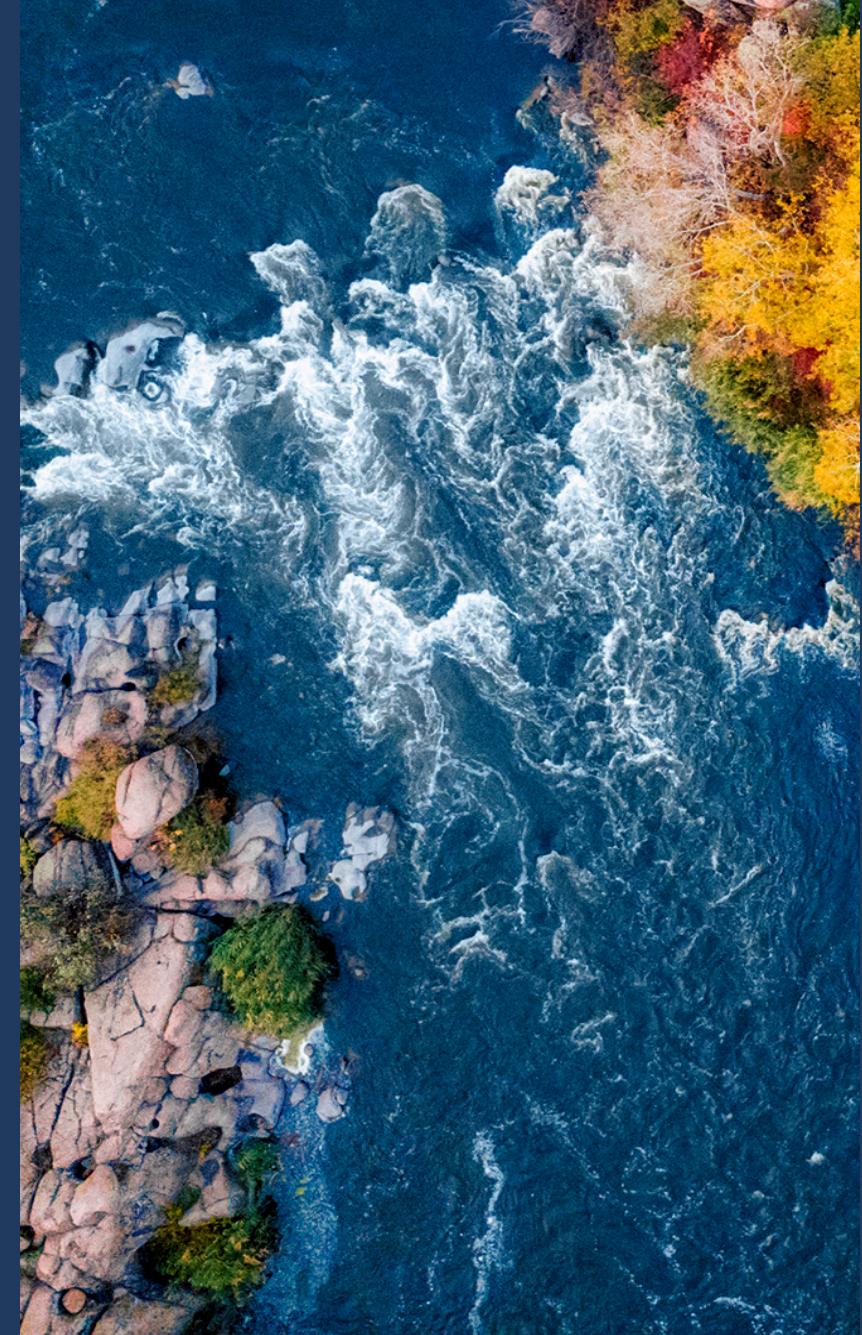
Harry H Yoon, MD MHS

Professor of Oncology
Enterprise Co-Leader, GI/Hepatobiliary/Pancreatic Cancer Research
Enterprise Vice-Chair, GI Disease Group
Mayo Clinic
Rochester, MN; Phoenix, AZ; Jacksonville, FL

MLS Cleveland: Precision Medicine and Immunotherapy Conference
Saturday, April 13, 2024
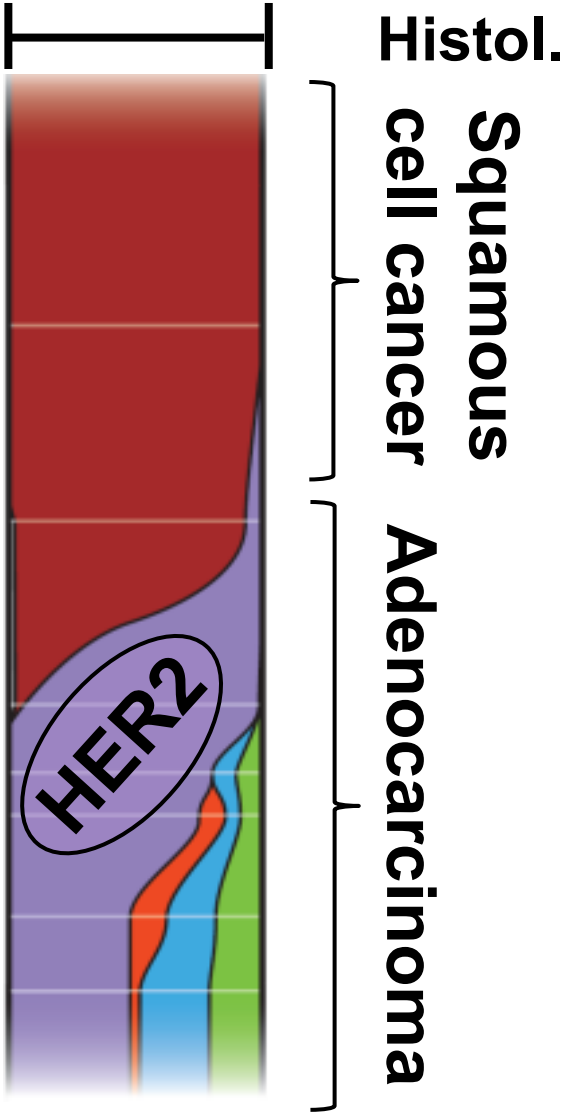Intercontinental Cleveland Hotel in Cleveland, Ohio.

Molecular landscape of gastro-esophageal cancer

TCGA,
Nature 2017

Proportion of patients
at each anatomic level

Histol.

Squamous cell cancer

Adenocarcinoma

HER2

Mol. Signature

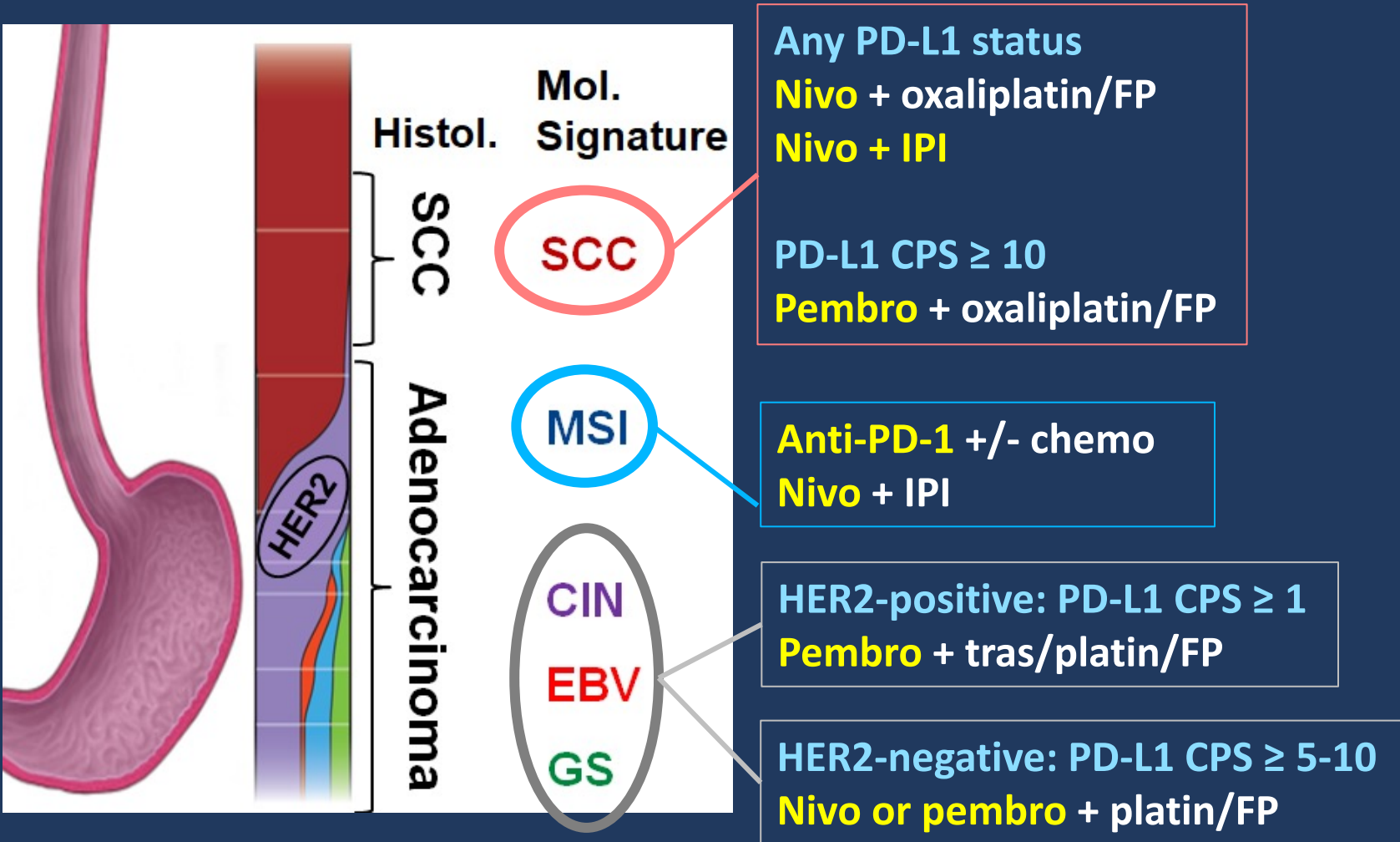**SCC signature**
~15%

MSI *~5-10%*

Chromosomal instability (CIN)
~60-70%

EBV *<5%*

Genomically stable *~5-10%*

2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal cancer (NCCN Category 1 or 2A)

Any PD-L1 status
Nivo + oxaliplatin/FP
Nivo + IPI

PD-L1 CPS ≥ 10
Pembro + oxaliplatin/FP

Anti-PD-1 +/- chemo
Nivo + IPI

HER2-positive: PD-L1 CPS ≥ 1
Pembro + tras/platin/FP

HER2-negative: PD-L1 CPS ≥ 5-10
Nivo or pembro + platin/FP

2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal cancer (NCCN Category 1 or 2A)
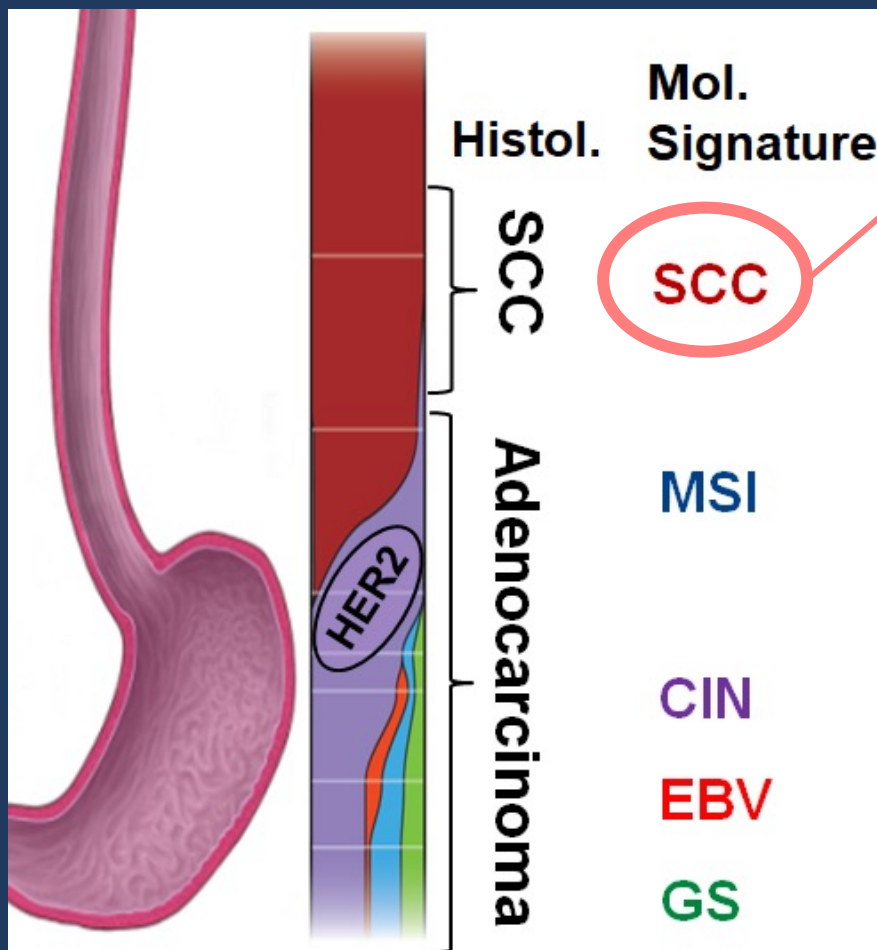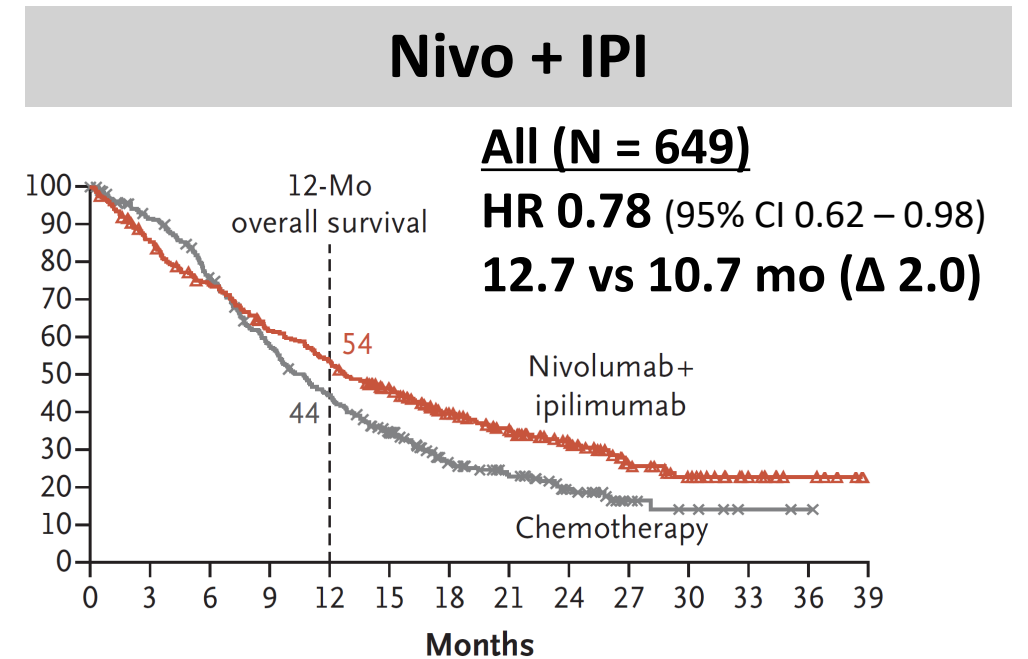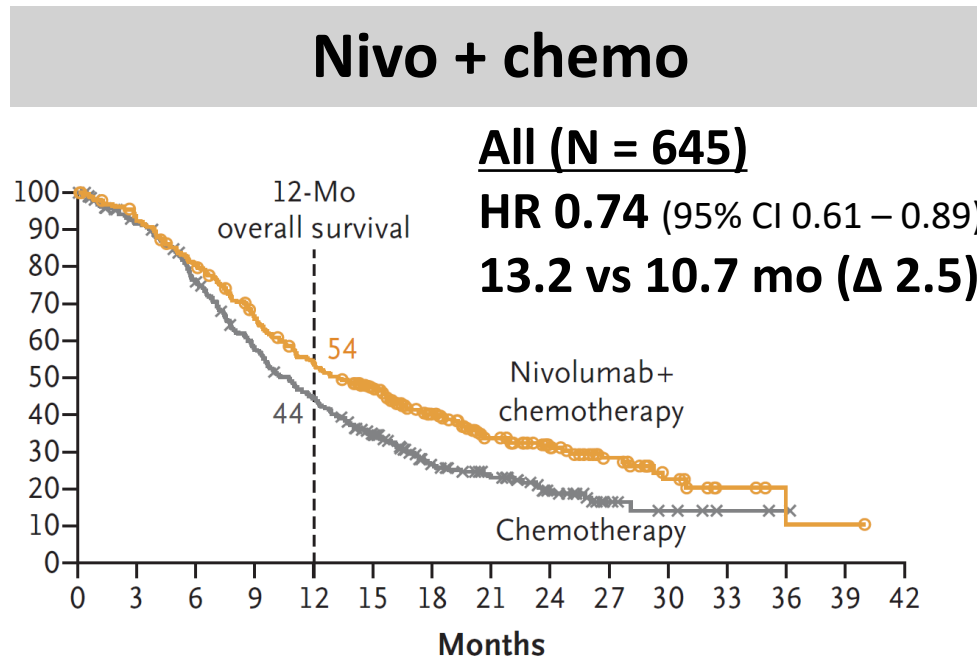

Any PD-L1 status
Nivo + oxaliplatin/FP
Nivo + IPI

PD-L1 CPS ≥ 10
Pembro + oxaliplatin/FP

Esoph SCC: Nivo improves OS in 1st-line (CM 648)

Primary endpoints: OS and PFS in TPS ≥ 1

	Nivo + chemo	Nivo + IPI
All	**All (N = 645)** HR 0.74 (95% CI 0.61 – 0.89) 13.2 vs 10.7 mo (Δ 2.5)	**All (N = 649)** HR 0.78 (95% CI 0.62 – 0.98) 12.7 vs 10.7 mo (Δ 2.0)

Doki et al, NEJM 2022

SCC, squamous cell carcinoma; TPS, tumor proportion score; OS, overall survival; PFS, progression free survival; nivo, nivolumab;; IPI, ipilumumab

Most phase 3 trials in esophageal SCC show meaningfully improved OS with ICI + chemo, even in PD-L1-low tumors

Overall Survival in CPS <10

Meta-analysis [1]

Trial	HR (95% CI)
KEYNOTE-590 ✦	0.99 (0.74 to 1.32)
CheckMate 648 ✦	0.78 (0.60 to 1.01)
JUPITER-06	0.61 (0.40 to 0.93)
ORIENT-15	0.62 (0.45 to 0.85)
TOTAL	**0.77 (0.66–0.89)**

0.1 — 1.0 — 10.0

← Combo Better   Chemo Better →

Subsequent trials [2-3]

Trial	HR (95% CI)
RATIONALE-306 ✦	0.82 (0.62 to 1.08)
ASTRUM-007 [a]	0.74 (0.54 to 1.03)

✦ Study population was global (ie, includes non-Asia)
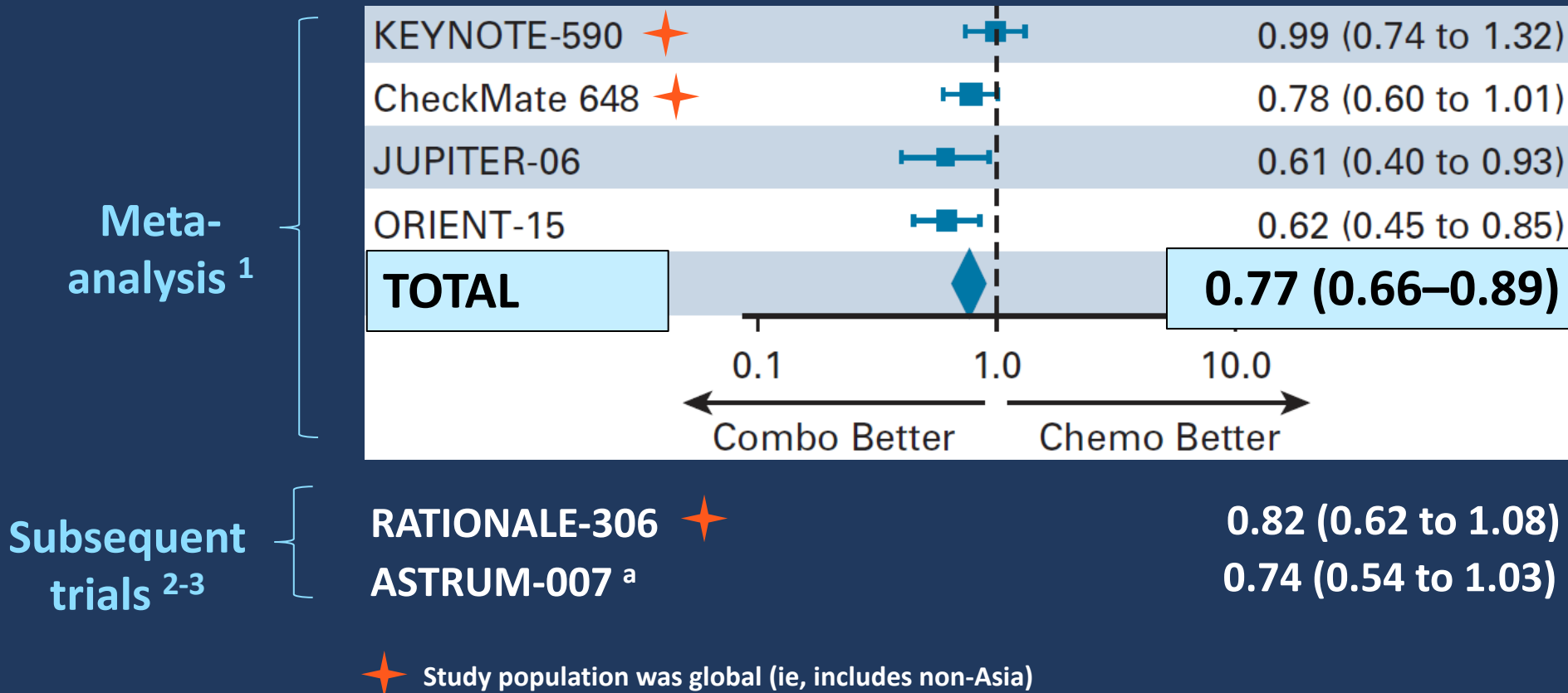
1. Wu H-X et al, JCO 2022; 2. Xu J … Yoon HH et al, Lancet Oncol 2022; 3. Song Y et al, Nat Med 2022

[a] ASTRUM-007 reported only CPS 1-9 (not CPS <10 and not TPS)

SCC, squamous cell carcinoma ICI, immune checkpoint inhibition; OS, overall survival; CPS, combined positive score

2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal cancer (NCCN Category 1 or 2A)
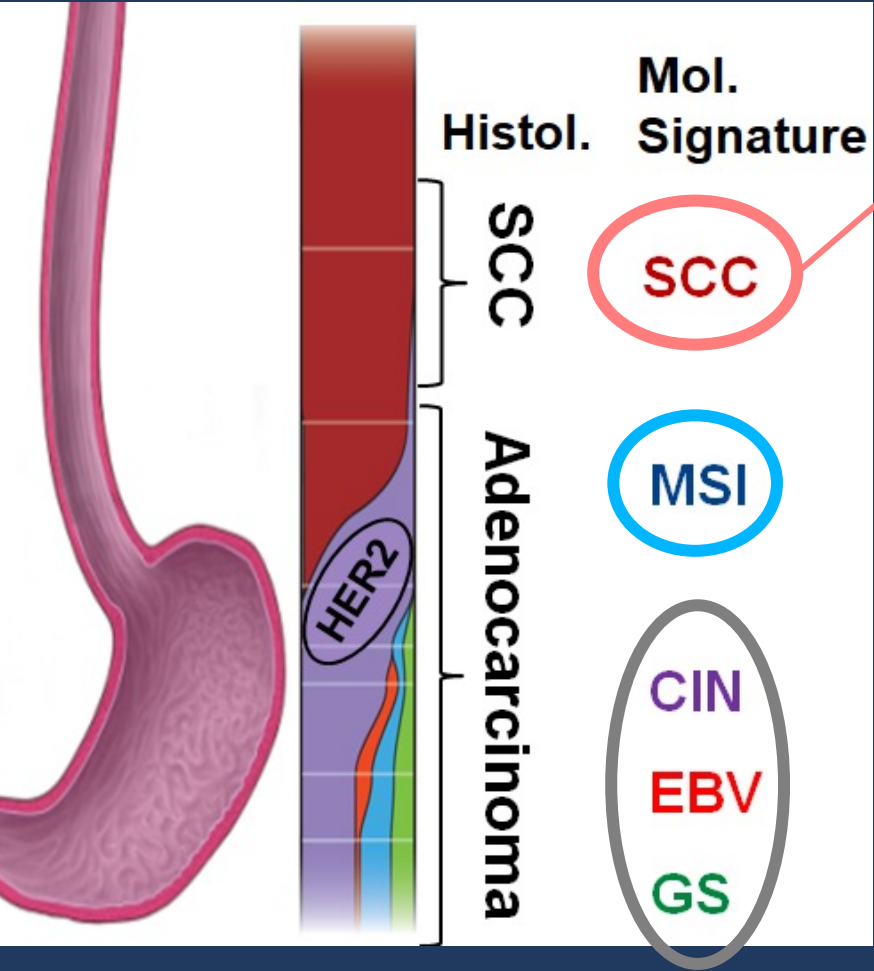
Any PD-L1 status
Nivo + oxaliplatin/FP
Nivo + IPI

PD-L1 CPS ≥ 10
Pembro + oxaliplatin/FP

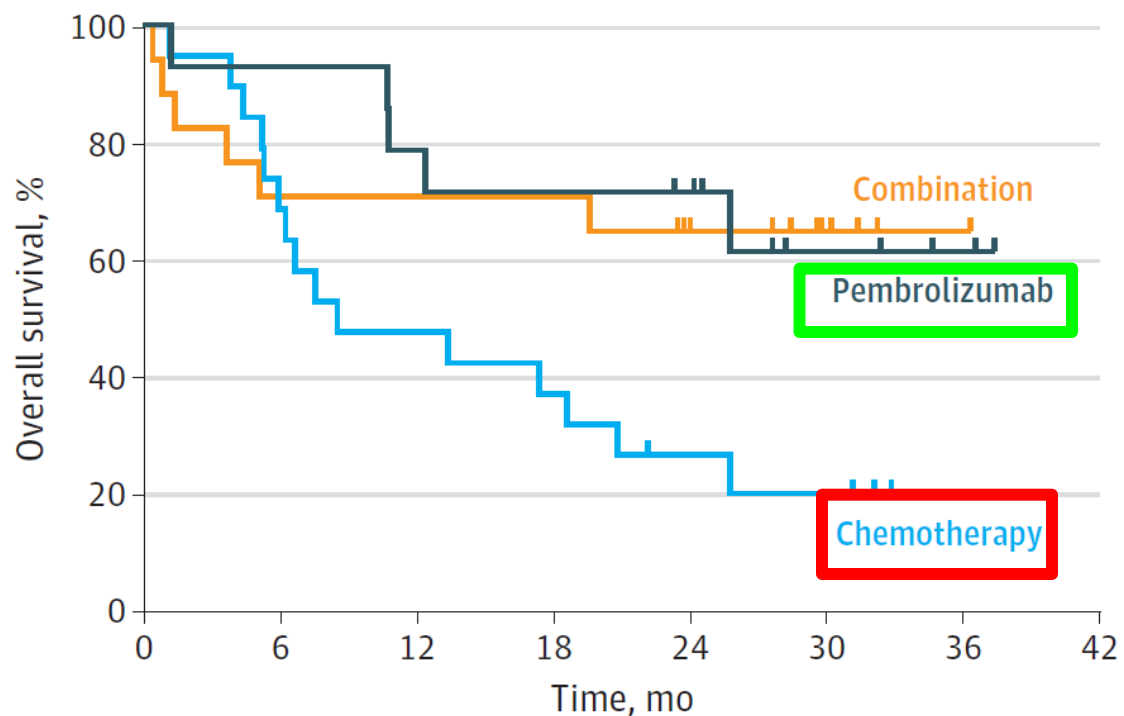# 2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal cancer (NCCN Category 1 or 2A)
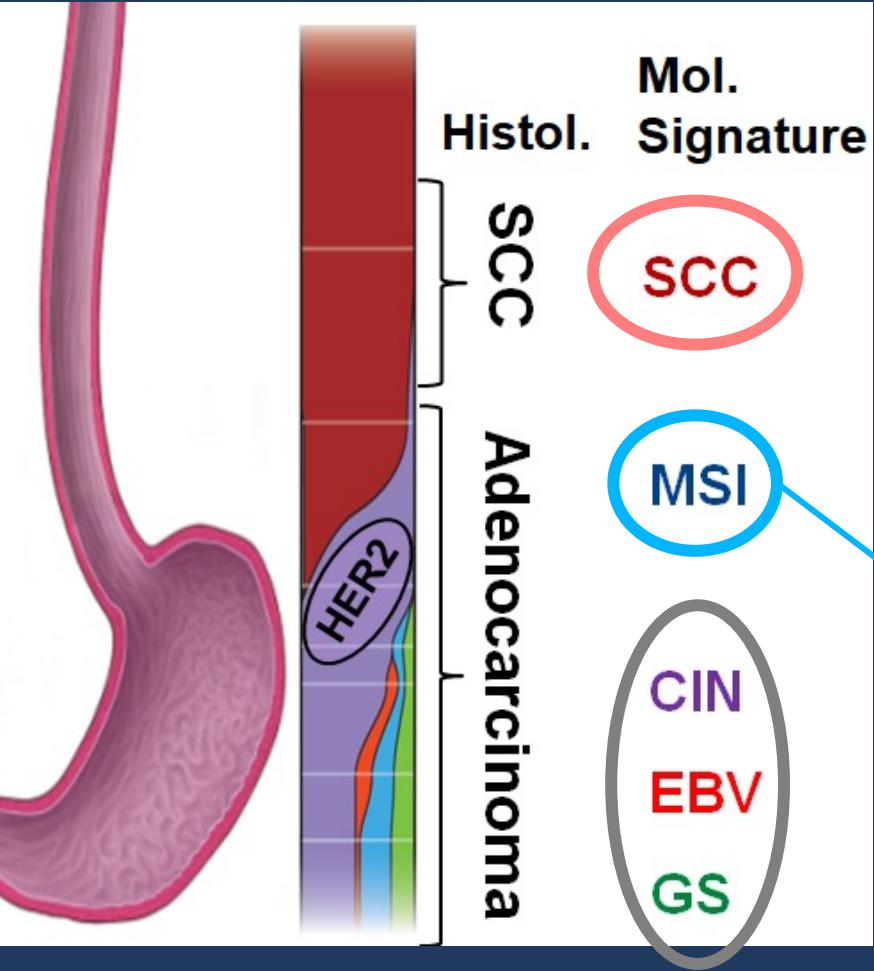
Anti-PD-1 +/- chemo
Nivo + IPI

Pembro
Dostarlimab
Nivo + ipilimumab
Nivo + FOLFOX
Pembro + chemo

CPS, Combined positive score; FP, fluoropyrimidine; nivo, nivolumab; pembro, pembrolizumab; ICI, immune checkpoint inhibition; IPI, ipilumumab

©2024 Mayo Foundation for Medical Education and Research | slide-8

MSI-high in KN-062: Benefit of IO vs chemo

Patients with MSI-H tumors in KEYNOTE-062

	Pembro	Pembro + chemo	Chemo
ORR	57%	65%	37%
CR	7%	35%	10%
DOR	21m	Not reached	7 m
PFS	11.2 m	Not reached	6.6 m
OS	Not reached	Not reached	8.5 m

DOR, duration of response

HRs were not reported

No. at risk

Pembrolizumab	14	13	11	10	9	4	2	0
Combination	17	12	12	12	9	4	1	0
Chemotherapy	19	13	9	7	4	3	0	0

Chao J et al. JAMA Oncol 2021

MSI-high in KN-062: Benefit of IO <u>+ chemo</u> vs chemo

D Patients with MSI-H tumors in KEYNOTE-062

	Pembro	Pembro + chemo	Chemo
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Chao J et al. JAMA Oncol 2021

MSI-high in KN-062: IO + chemo vs IO

D Patients with MSI-H tumors in KEYNOTE-062

	Pembro	Pembro + chemo	Chemo
ORR CR	57% 7%	65% 35%	37% 10%
DOR	21m	Not reached	7 m
PFS	11.2 m	Not reached	6.6 m
OS	Not reached	Not reached	8.5 m

DOR, duration of response

HRs were not reported

But <20% MSI-high don't seem to benefit from IO

Chao J et al. JAMA Oncol 2021

MSI-high in CM649:
Nivo + chemo or Nivo + IPI are options

Nivo + chemo	Nivo + IPI

HR 0.38
38.7 vs 12.3 mo

HR 0.28
Not reached vs 10 mo
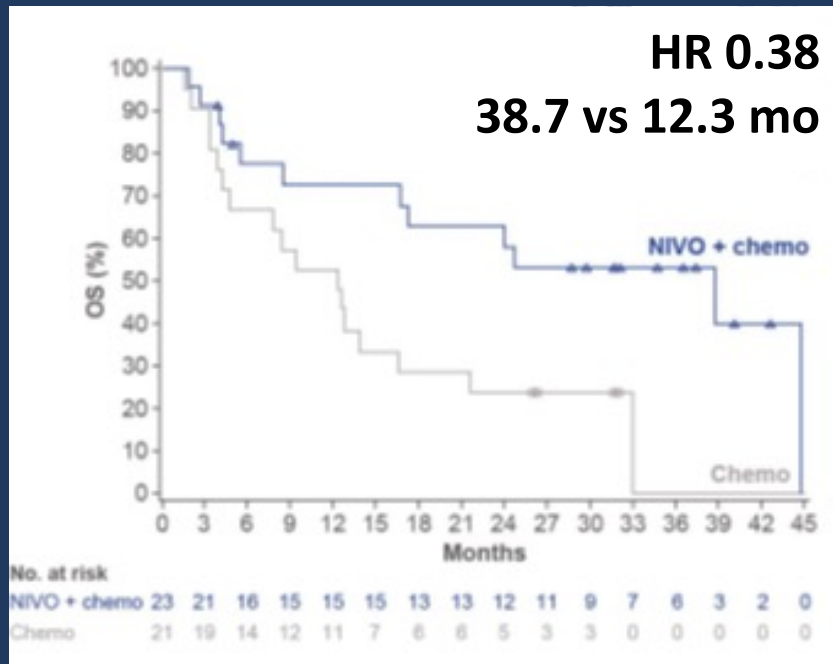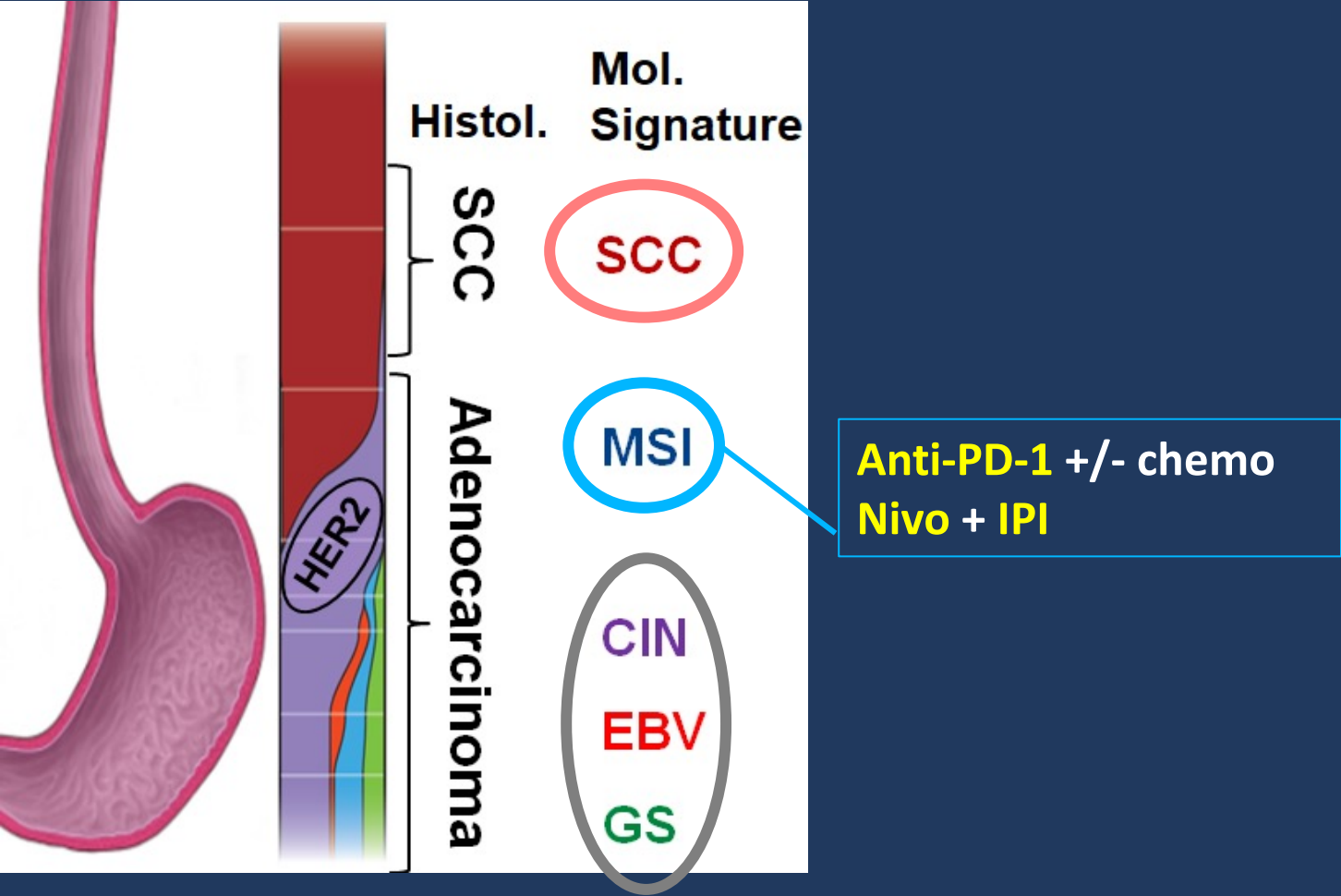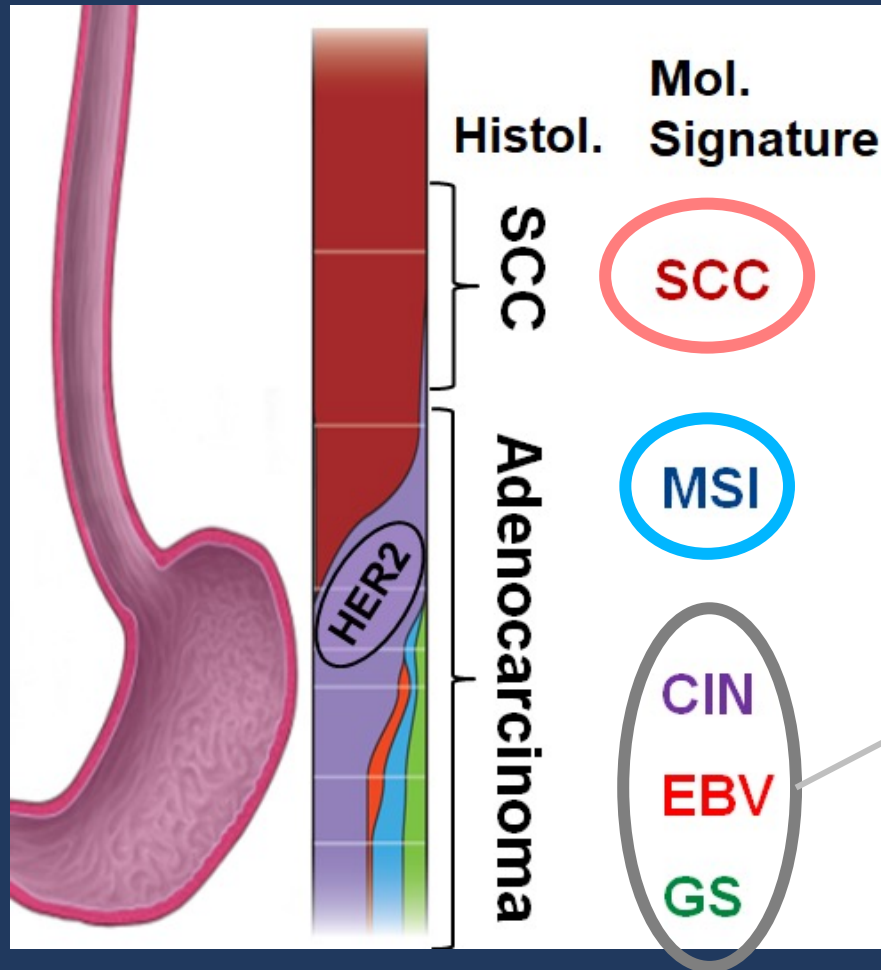
But ~20% MSI-high don't seem to benefit from IO

2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal cancer (NCCN Category 1 or 2A)

Anti-PD-1 +/- chemo
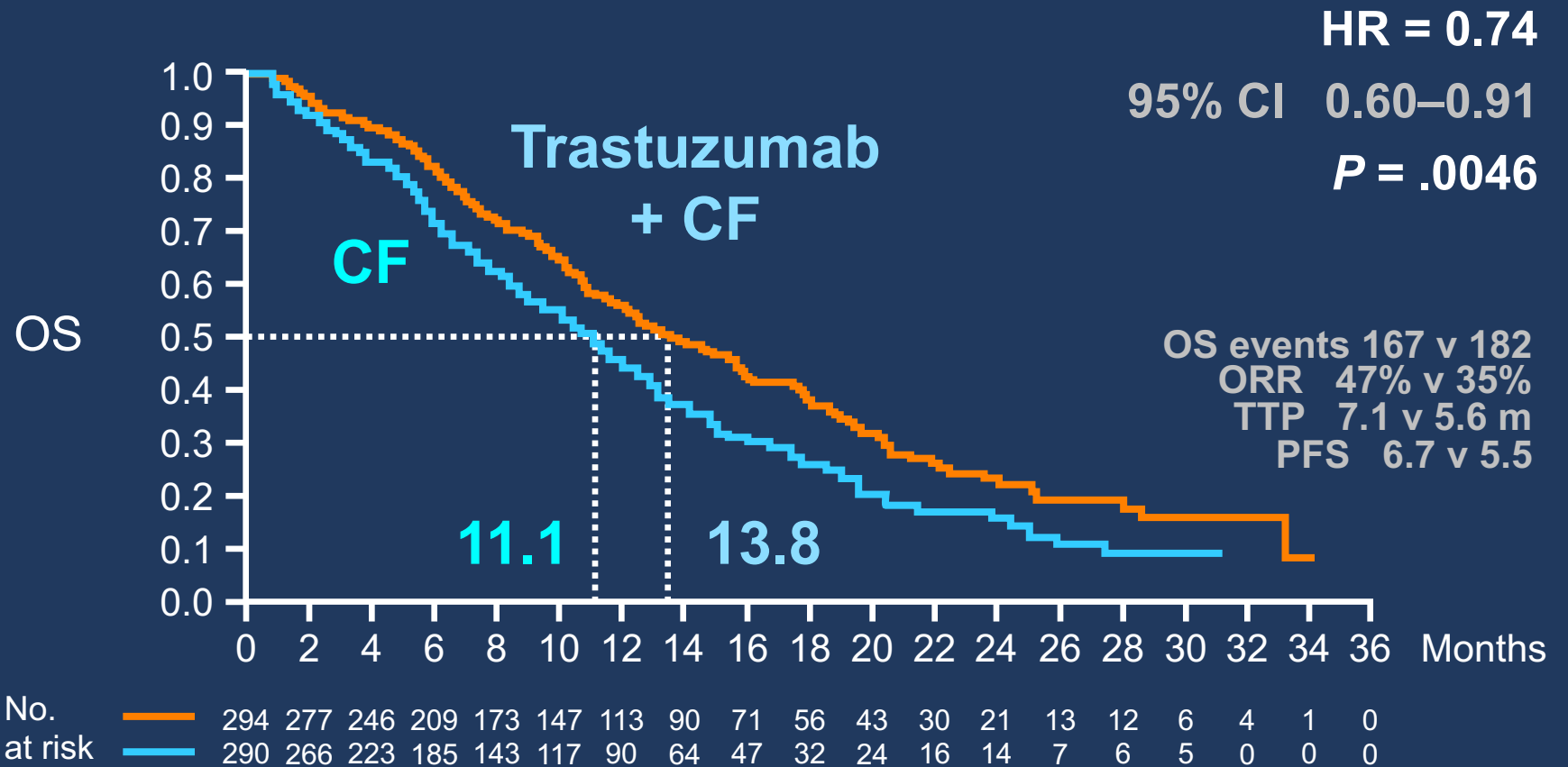**Nivo + IPI**

2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal cancer (NCCN Category 1 or 2A)

HER2-positive: PD-L1 CPS ≥ 1
Pembro + tras/platin/FP

Landmark ToGA trial: Adding trastuzumab to chemo improved OS

HR = 0.74

95% CI 0.60–0.91

***P* = .0046**

Patient population
Advanced gastric/GEJ adenocarcinoma, 1st-line setting, HER2 IHC 3+ or FISH+

OS

Trastuzumab + CF

CF

11.1   **13.8**

OS events 167 v 182
ORR   47% v 35%
TTP   7.1 v 5.6 m
PFS   6.7 v 5.5

No. at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	Months
	294	277	246	209	173	147	113	90	71	56	43	30	21	13	12	6	4	1	0	
	290	266	223	185	143	117	90	64	47	32	24	16	14	7	6	5	0	0	0	

CF = cisplatin + 5FU

Failed RCTs targeting HER2

Gastroesophageal

2010	2011 — 2019				2020
ToGA 1st-line Chemo + **Tras** *vs* Chemo	**LOGIC** 1st-line Chemo + Tras + **lapatinib** *vs* Chemo + Tras	**JACOB** 1st-line Chemo + Tras + **Pertuz** *vs* Chemo + Tras	**TyTAN** 2nd-line Chemo + **lapatinib** *vs* Chemo	**GATSBY** 2nd-line T-DM1 *vs* Chemo	**DESTINY-G-01** 3rd-line **T-deruxtecan** *vs* Chemo
HR 0.74	HR 0.91	HR 0.84	HR 0.84	HR 1.15	HR 0.59

Breast

Meta-analysis	CLEOPATRA	EGF100151	EMILIA
1st-line	1st-line	Non-1st line	1st/2nd line
HR 0.79	HR 0.69	HR 0.80	HR 0.68
(>50% crossover)		(accounting for crossover)	

Hazard ratios for overall survival are shown
Other negative RCTs in gastroesophageal adenocarcinoma: Trastuzumab beyond progression (T-ACT); chemo + trastuzumab +/- MM-111; neoadjuvant trastuzumab with CRT (RTOG-1010); neoadjuvant pertuzumab/trastuzumab with chemo (PETRARCA)

Bang et al 2010 Lancet; Hecht et al 2016 JCO; Tabernero 2018 Lancet Onc; Satoh T et al 2014 JCO; Thuss-Patience et al 2017 Lancet Onc; Shitara et al NEJM 2020; Makiyama et al 2020 JCO; Denlinger et al 2014 JCO Supp; Safran et al 2020 JCO Supp; Hofheinz et al 2020 JCO Supp; Balduzzi S et al 2014 Cochrane D Sys Rev; Swain et al 2020 Lancet Onc; Cameron et al, 2010 Oncologist; Verma et al 2012 NEJM; Krop et al 2014 Lancet Onc
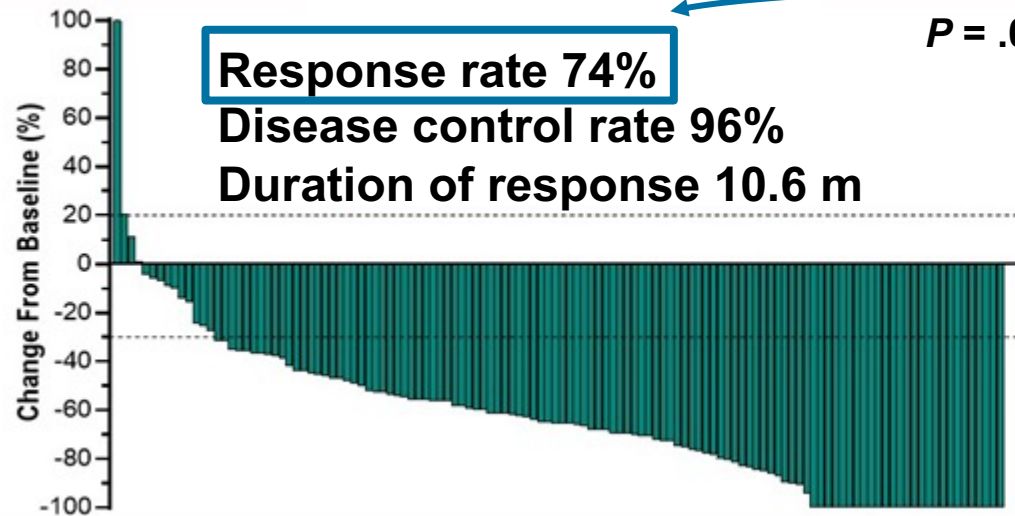
PRESENTED BY: Harry H Yoon

Early results (KN-811) that led to pembro approval in HER2-positive gastric cancer were limited to response, did not include survival
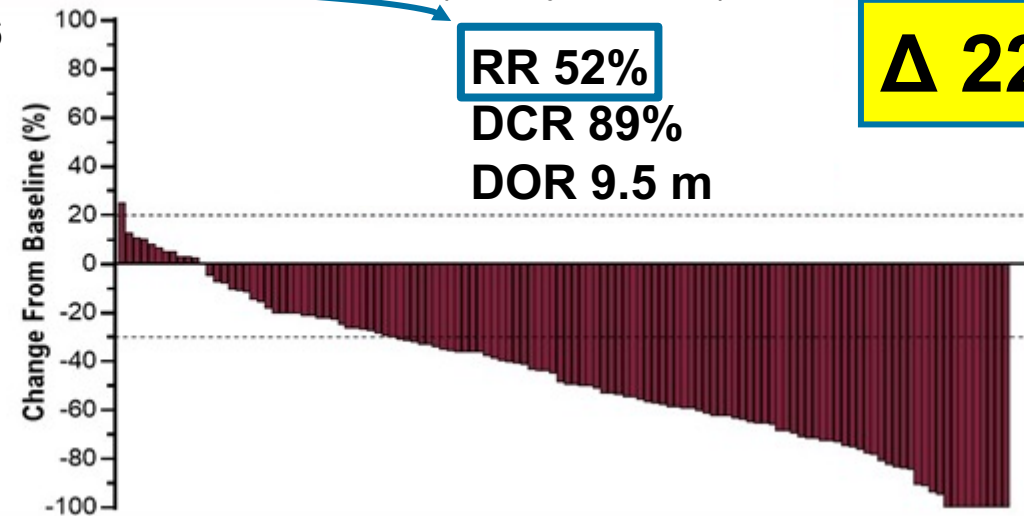
Pre-specified interim analysis of first 246 pts

Pembro + tras + platin/FP
(mostly CAPOX)

Placebo + tras + platin/FP
(mostly CAPOX)

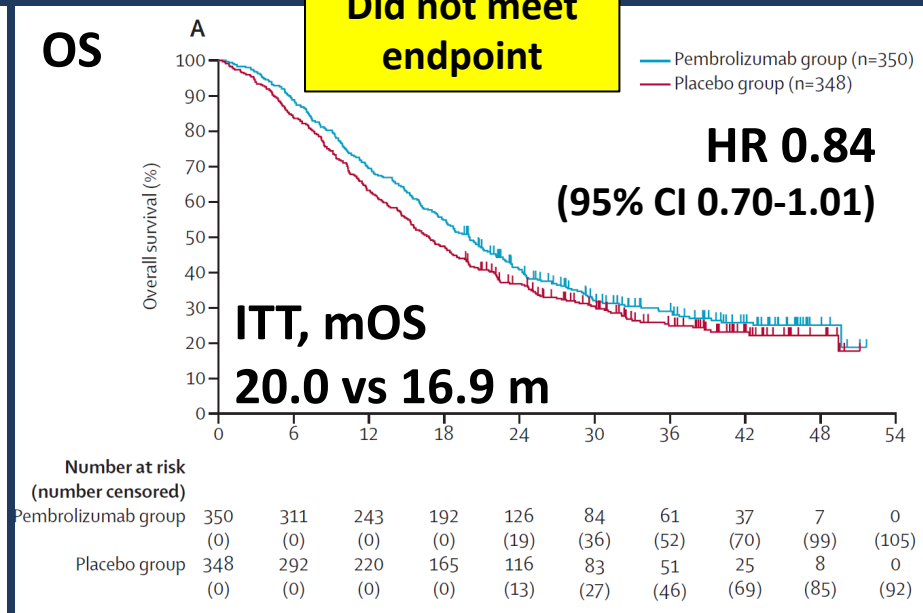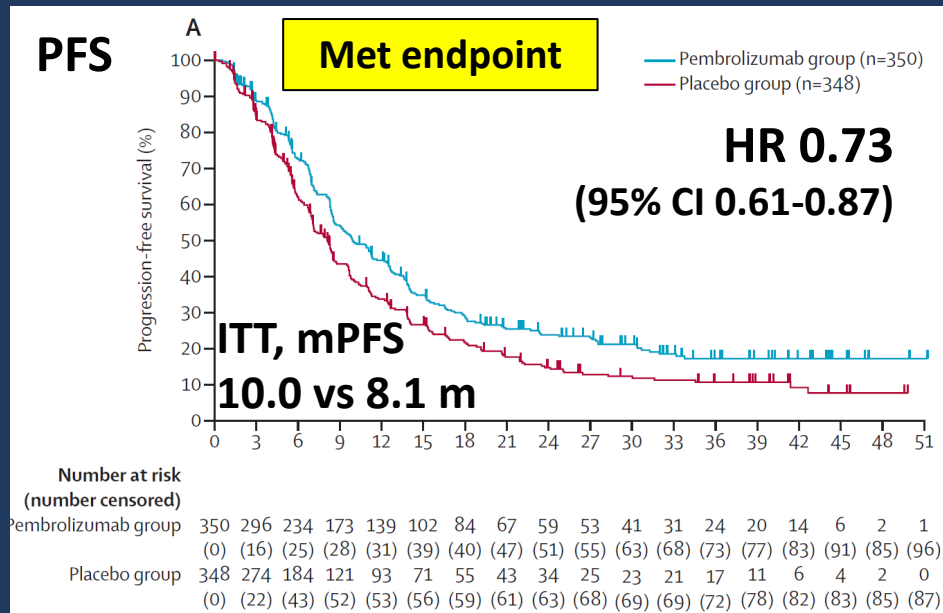**Response rate 74%**
Disease control rate 96%
Duration of response 10.6 m

P = .00006

RR 52%
DCR 89%
DOR 9.5 m

Δ 22%

Δ RR between arms by PD-L1 status
- **CPS ≥1 (n=229): 25.2%** (95% CI -12.8, 36.9)
- **CPS <1 (n=35): 4.6%** (95% CI -27.6, 35.4)

Data by HER2 status (eg 3+ vs other) not reported

Accelerated FDA approval
NCCN Cat 1 and 2A approval

Janjigian et al, Nature 2021

Mature data for Pembro + FP/oxaliplatin in HER2 positive gastroesophageal adenoca (KN-811, N = 698); ITT shown

PFS

Met endpoint

Pembrolizumab group (n=350)
Placebo group (n=348)

HR 0.73
(95% CI 0.61-0.87)

ITT, mPFS
10.0 vs 8.1 m

Progression-free survival (%)

Number at risk (number censored)

Pembrolizumab group	350	296	234	173	139	102	84	67	59	53	41	31	24	20	14	6	2	1
	(0)	(16)	(25)	(28)	(31)	(39)	(40)	(47)	(51)	(55)	(63)	(68)	(73)	(77)	(83)	(91)	(85)	(96)
Placebo group	348	274	184	121	93	71	55	43	34	25	23	21	17	11	6	4	2	0
	(0)	(22)	(43)	(52)	(53)	(56)	(59)	(61)	(63)	(68)	(69)	(69)	(72)	(78)	(82)	(83)	(85)	(87)

OS

Did not meet endpoint

Pembrolizumab group (n=350)
Placebo group (n=348)

HR 0.84
(95% CI 0.70-1.01)

ITT, mOS
20.0 vs 16.9 m

Overall survival (%)

Number at risk (number censored)

Pembrolizumab group	350	311	243	192	126	84	61	37	7	0
	(0)	(0)	(0)	(0)	(19)	(36)	(52)	(70)	(99)	(105)
Placebo group	348	292	220	165	116	83	51	25	8	0
	(0)	(0)	(0)	(0)	(13)	(27)	(46)	(69)	(85)	(92)

Improvement in response rates is smaller than at first interim analysis

- **Updated: Δ 12.8%** (72.6% vs 59.8%)
- **Prior: Δ 22.5%** (74.4% vs 51.9%)

Dual primary endpoints: PFS and OS
Study would be considered positive if positive for either endpoint
(6% in either arm received post-study anti-PD-1/-L1 therapy)
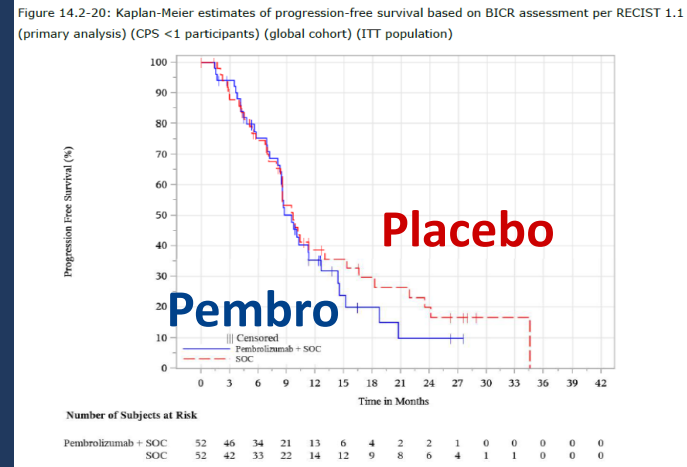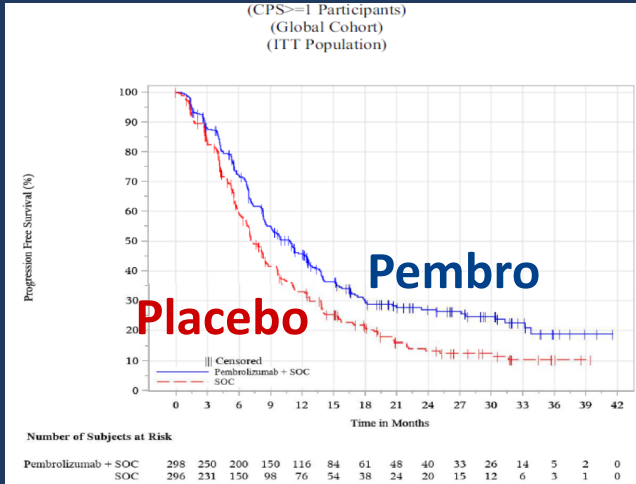
Subgroup analysis:
- **PD-L1: CPS <1 (15% of subjects) did not benefit – FDA approval withdrawn for this subset**

Janjigian et al, 2023 Lancet

By PD-L1: Pembro + FP/oxaliplatin in HER2 positive gastroesoph adenoca (KN-811, N = 698)
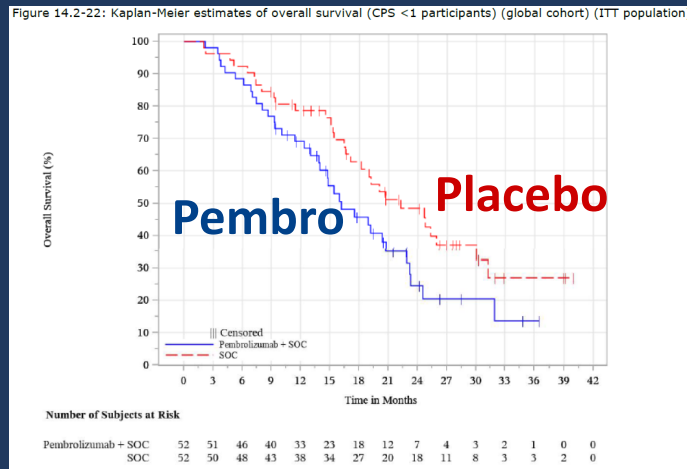

PD-L1 CPS 1+ (85%)
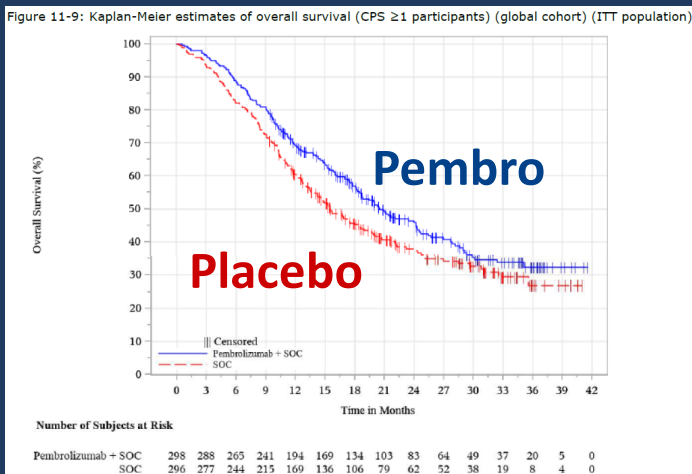
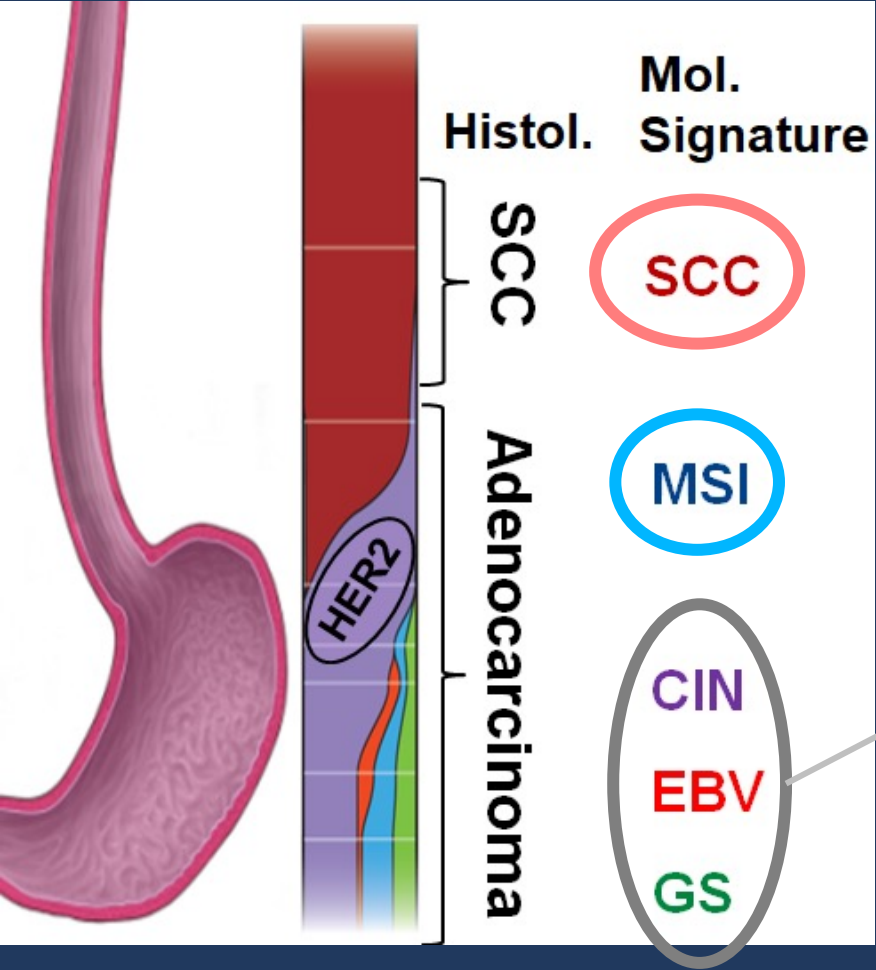**PD-L1 CPS < 1 (15%)**
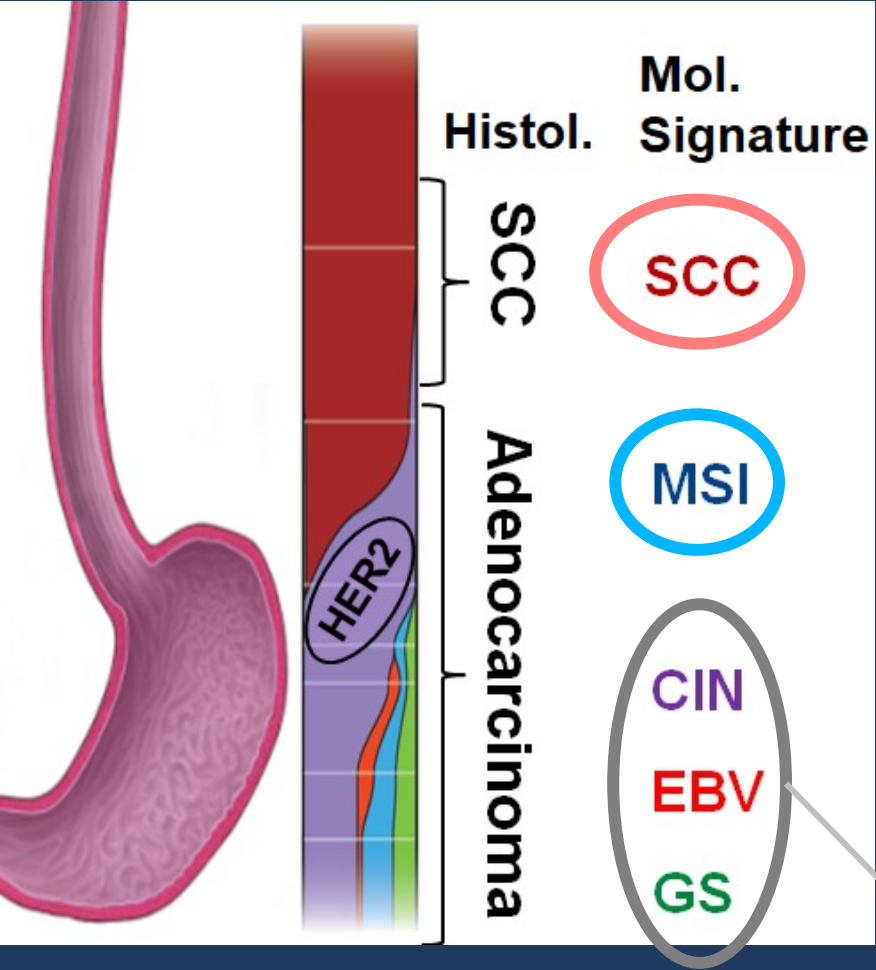
PFS

OS

RR in CPS <1
69.2% vs 67.3%

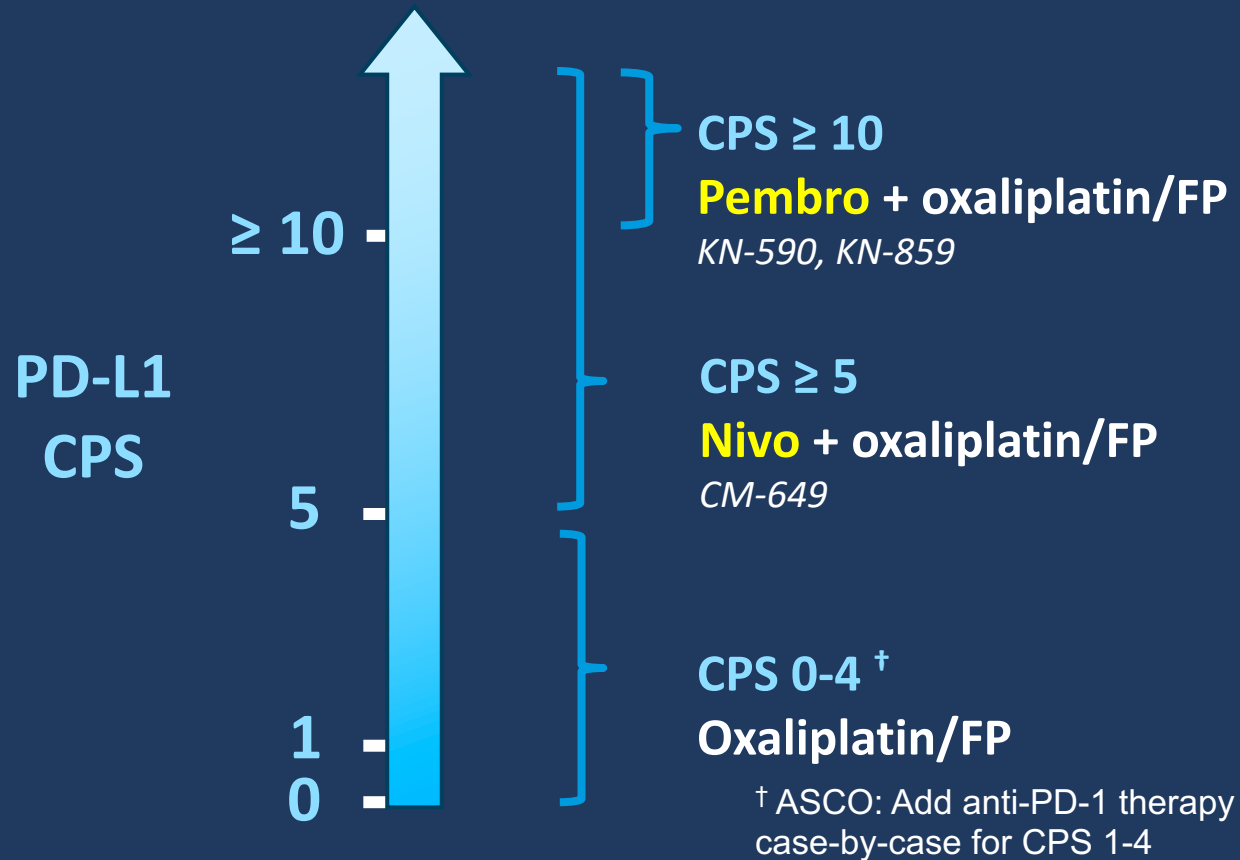# 2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal cancer (NCCN Category 1 or 2A)

HER2-positive: PD-L1 CPS ≥ 1
Pembro + tras/platin/FP

2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal cancer (NCCN Category 1 or 2A)

HER2-negative: PD-L1 CPS ≥ 5-10
Nivo or pembro + platin/FP

1L Treatment for HER2-negative MSS gastroesoph adenoca depends on PD-L1 status (NCCN Category 1 or 2A)

PD-L1 CPS

≥ 10 –

5 –

1 –

0 –

CPS ≥ 10
Pembro + oxaliplatin/FP
KN-590, KN-859

CPS ≥ 5
Nivo + oxaliplatin/FP
CM-649

CPS 0-4 [†]
Oxaliplatin/FP

[†] ASCO: Add anti-PD-1 therapy
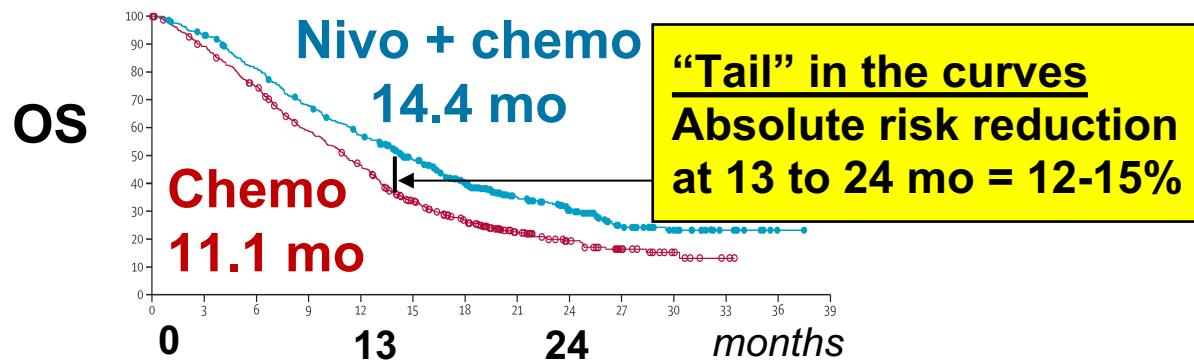case-by-case for CPS 1-4

CM-649: Nivo improves overall survival in CPS ≥ 5

Gastric/GEJ adenocarcinoma (1st-line FOLFOX/CAPOX +/- nivo)

Primary endpoints = OS in CPS ≥ 5 and PFS in CPS ≥ 5 (IHC Ab 28-8)

CPS ≥ 5 HR 0.71 (95% CI 0.59–0.86)	CPS 1-4 HR 0.95 (95% CI 0.75–1.21)

n = 955

n = 341

Nivo + chemo 14.4 mo

Chemo 11.1 mo

"Tail" in the curves
Absolute risk reduction at 13 to 24 mo = 12-15%

OS

months

Nivo + Chemo

Chemo

OS

Time (months)

PFS = 8.1 vs 6.1 mo; HR 0.70 (95% CI 0.60–0.81) [a]
ORR = 60% vs 45%
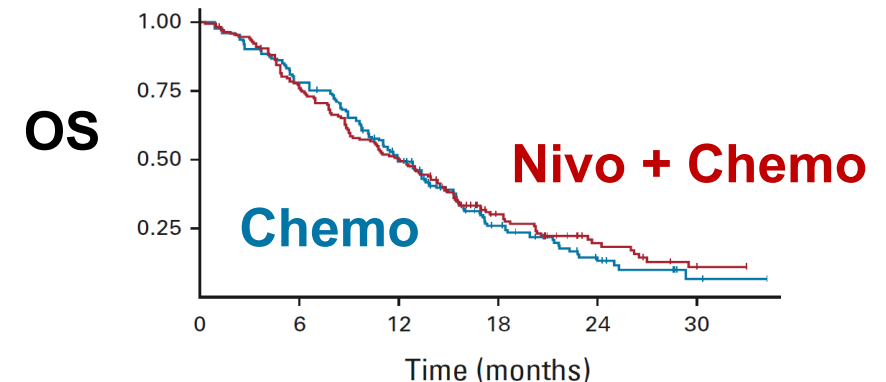
PFS = ~9 vs ~9 m; HR 0.96 (95% CI 0.74–1.24)
ORR = not reported

Janjigian YY, et al. *Lancet*. 2021;398(10294):27-40.

Zhao JJ, et al. *JCO*. 2021:40:392

[a] For PFS, maximum absolute risk reduction is at 12 months = 14%

Higher G3-5 Toxicity with nivolumab in CM649

	Nivo + Chemo	Chemo
Any G3-5	**60%** 1.3x	**44%** ref
G4-5	**14%** 2x	**7%** ref
Treatment duration	*6.8 m* 1.4x	*4.9 m* ref

Along with CM 649, data from other phase 3 trials generally reinforced PD-L1 as predictive marker

Therapeutic benefit should never be excluded based on a single exploratory (subgroup) analysis …
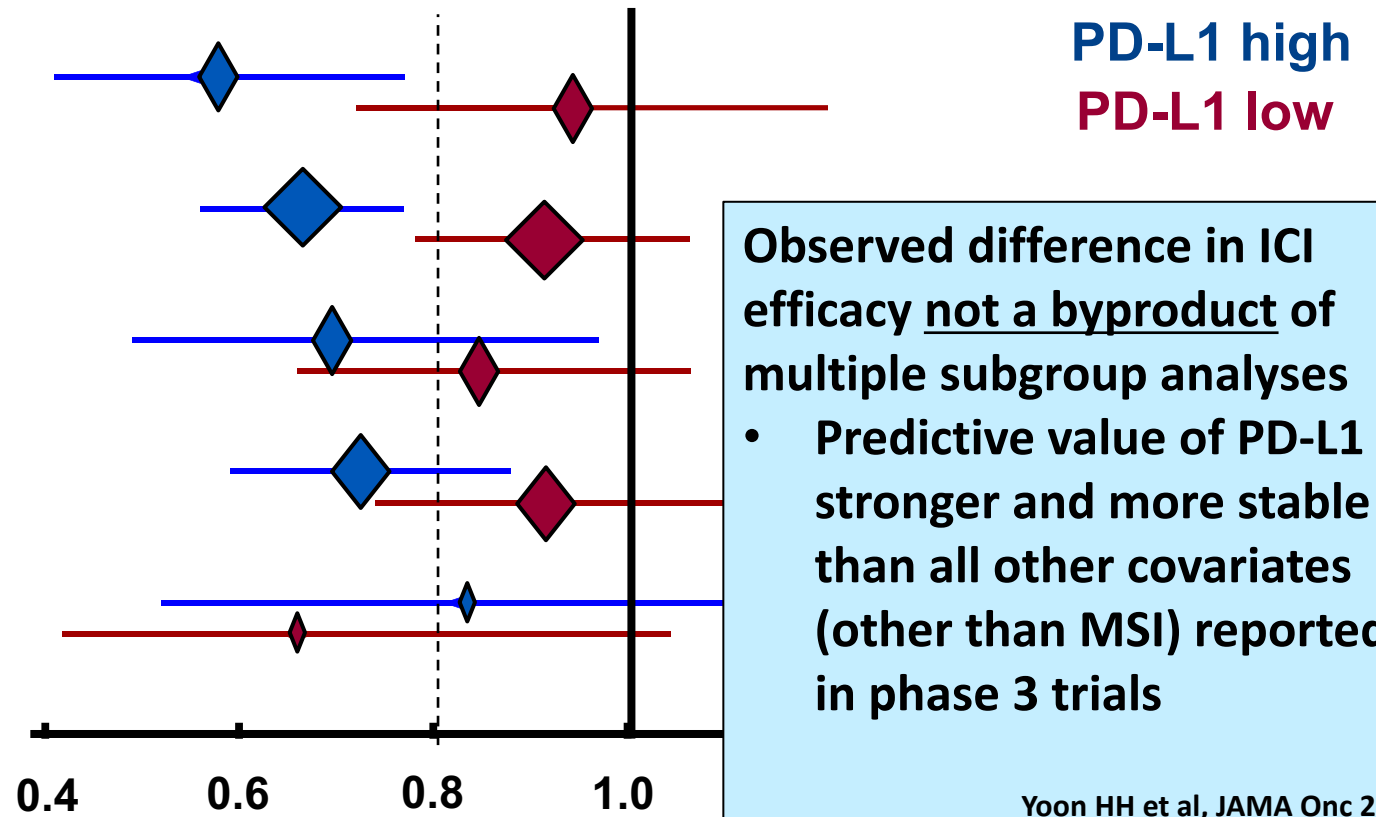
But more evidence than that has now emerged...

ICI efficacy is greater in PD-L1 high (vs low) patients in 1st-line phase 3 trials of MSS HER2-negative gastroesoph adenoca

Complex issues regarding PD-L1 assay

- **Spatiotemporal (hetero)homogeneity**
- **Detection antibodies**
- **Interpathologist (dis)agreement**
- **Ideal cutpoint**
- **Issues common to IHC**

1. Kulangara K et al, Arch Pathol Lab Med 143:330-337, 2018.
2. Kim S-W et al, Pathology 53:586-594, 2021.
3. Ahn S et al, Mod Pathol 34:1719-1727, 2021
4. Yeong J et al, Gastric Cancer 25:741-750, 2022
5. Park Y et al, Cancer Res Treat 52:661-670, 2020
6. Kim JM et al, Mol Diagn Ther 26:679-688, 2022
7. Dabbagh TZ et al, Appl Immunohisto Mol Morphol 29:462-466, 2021
8. Fernandez AI ... Rimm DL. Mod Pathol 36:100128, 2023
9. Robert ME et al, Mod Pathol 36:100154, 2023
10. Zhou KI ... Catenacci DVT, Clin Cancer Res 26:6453-6463, 2020
11. Catenacci DVT et al, Cancer Discov 11:308-325, 2021

ICI benefit in PD-L1 high

PD-L1 high
PD-L1 low
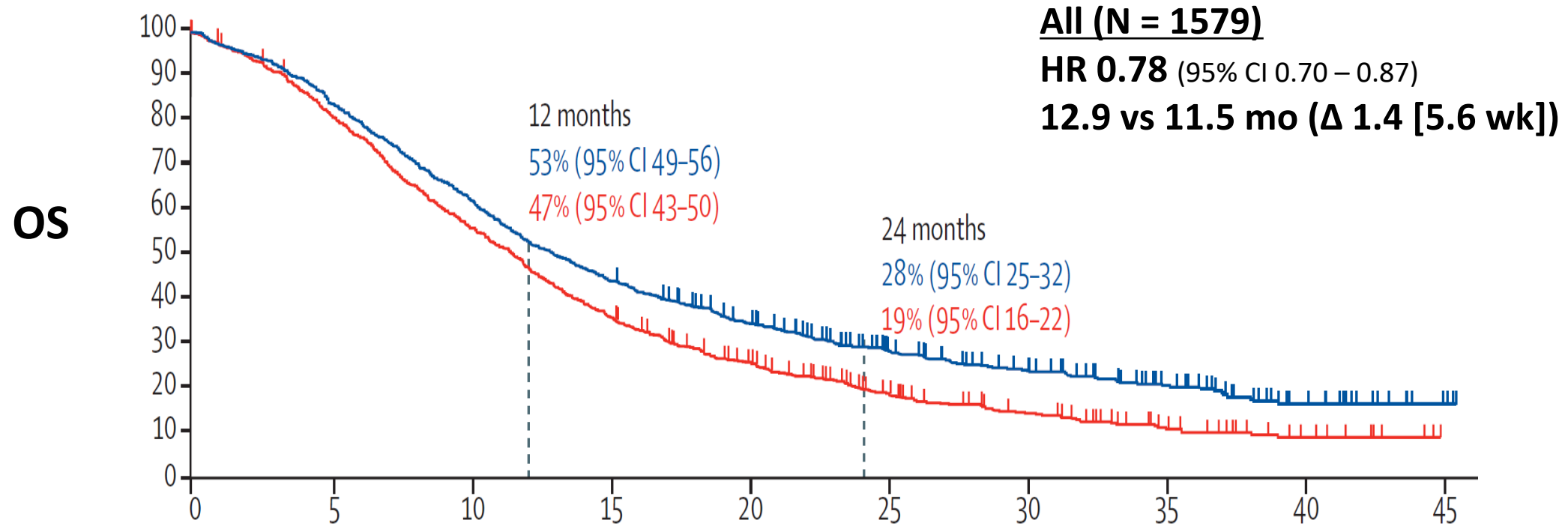
Observed difference in ICI efficacy not a byproduct of multiple subgroup analyses

- **Predictive value of PD-L1 stronger and more stable than all other covariates (other than MSI) reported in phase 3 trials**

Yoon HH et al, JAMA Onc 2022

0.4   0.6   0.8   1.0

More ICI benefit   **Less ICI benefit**

[a] **Ellis LM et al, JCO 2014**

MSS, microsatellite stable; TAP, tumor area positivity; CPS, combined positive score

KN 859: pembro improves OS in 1st-line GEA Overall population

OS

12 months
53% (95% CI 49–56)
47% (95% CI 43–50)

24 months
28% (95% CI 25–32)
19% (95% CI 16–22)

All (N = 1579)
HR 0.78 (95% CI 0.70 − 0.87)
12.9 vs 11.5 mo (Δ 1.4 [5.6 wk])

Rha SY et al, Lancet Oncol 2023

KN 859: pembro efficacy with OS by PD-L1

CPS < 1	CPS 1-4	CPS 5-9	CPS ≥ 10

Figure 16 Kaplan-Meier Plot of Overall ...
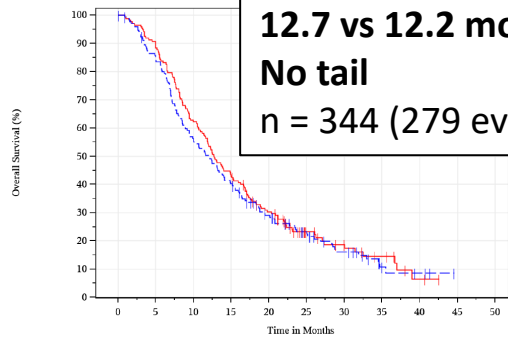
CPS < 1
HR 0.92
(95% CI 0.73 – 1.17)
12.7 vs 12.2 mo (Δ 0.5)
No tail
n = 344 (279 events)

CPS 1-4
HR 0.78
(95% CI 0.64 – 0.95)
11.5 vs 11.1 mo (Δ 0.4)
Tail ~ Δ 10%
n = 468
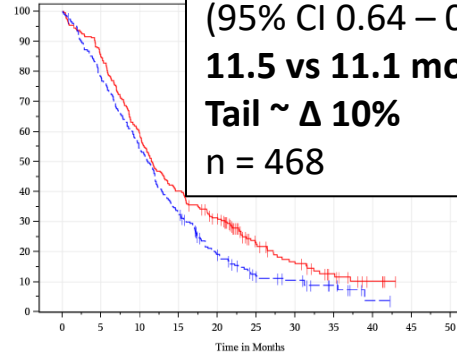
CPS 5-9
HR 0.94
(95% CI 0.71 – 1.25)
10.2 vs 10.7 mo (Δ -0.5)
Tail?
n = 231 (191 events)
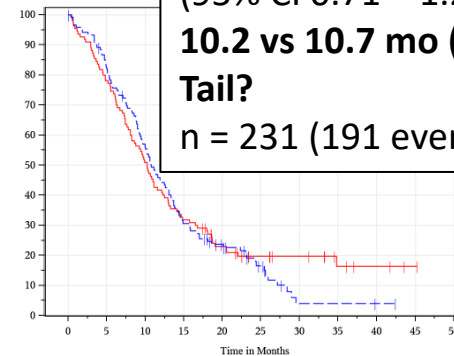
CPS ≥ 10
HR 0.65
(95% CI 0.53 – 0.79)
15.7 vs 11.8 mo (Δ 3.9)
Tail Δ 17%
n = 551

38% (95% CI 32-44)
21% (95% CI 16-26)

ORR
48.3% vs 39.5% (Δ 9%)

ORR
47.3% vs 40.2% (Δ 7.1%)

ORR
40.0% vs 47.1% (-Δ 7.1%)
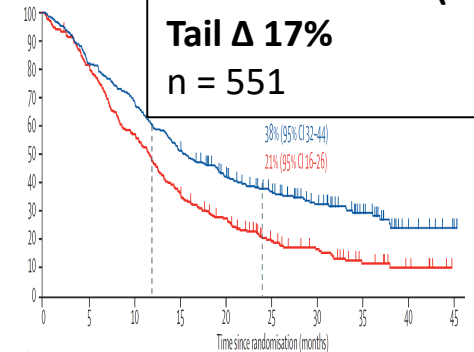
ORR
60.6% vs 43.0% (Δ 17.5%)

Grade 3-5 toxicity in overall population   **Δ 9%** (60% pembro vs 51% placebo)

1L Treatment for HER2-negative MSS gastroesoph adenoca depends on PD-L1 status (NCCN Category 1 or 2A)

PD-L1 CPS

≥ 10 –

5 –

1 –
0

CPS ≥ 10
Pembro + oxaliplatin/FP
KN-590, KN-859

CPS ≥ 5
Nivo + oxaliplatin/FP
CM-649

CPS 0-4 [†]
Oxaliplatin/FP
[†] ASCO: Add anti-PD-1 therapy case-by-case for CPS 1-4
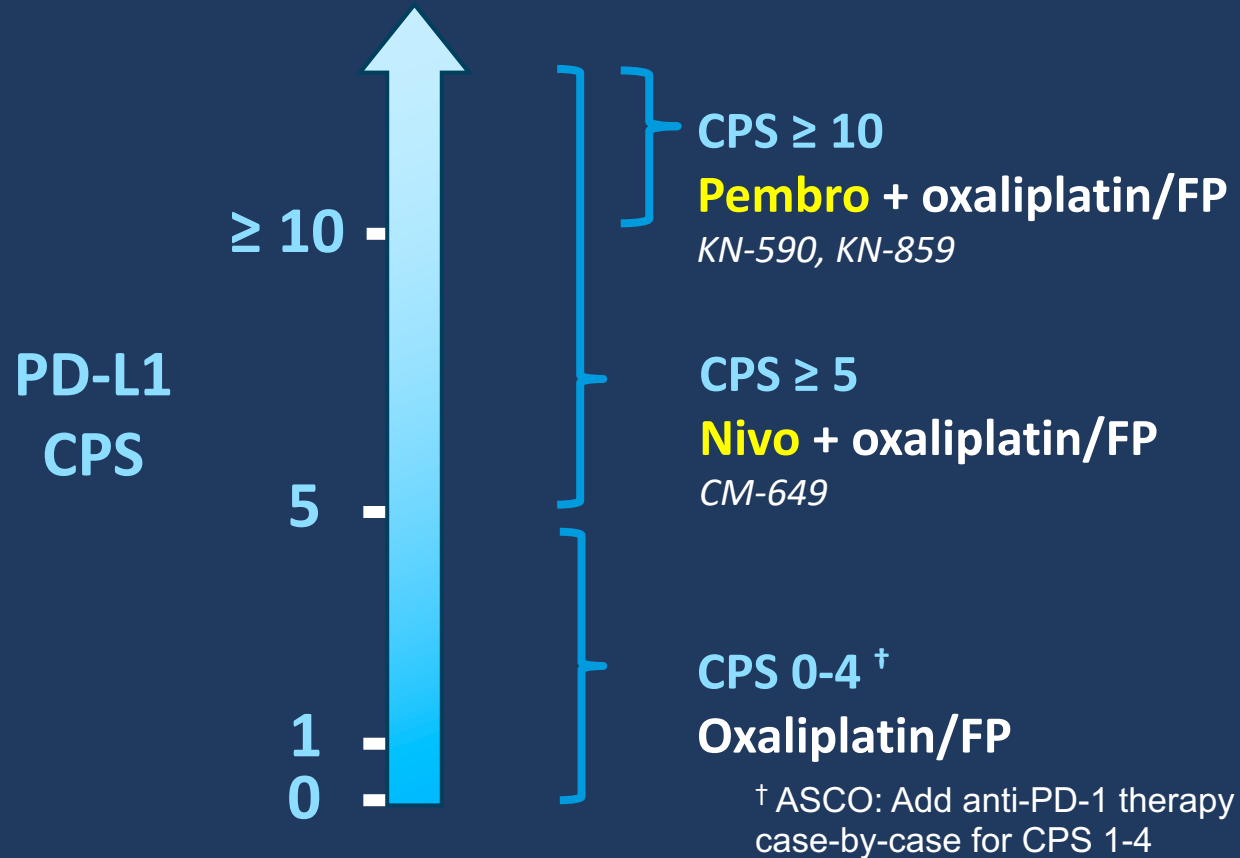
[†] Shah MA et al. JCO 2023

CPS, Combined positive score; FP, fluoropyrimidine; MSS, microsatellite stable; nivo, nivolumab; pembro, pembrolizumab; Tras, trastuzumab

2024 Simplified landscape of first-line therapy for fit patient with gastroesophageal cancer (NCCN Category 1 or 2A)

Any PD-L1 status
Nivo + oxaliplatin/FP
Nivo + **IPI**

PD-L1 CPS ≥ 10
Pembro + oxaliplatin/FP

Anti-PD-1 +/- chemo
Nivo + **IPI**

HER2-positive: PD-L1 CPS ≥ 1
Pembro + tras/platin/FP

HER2-negative: PD-L1 CPS ≥ 5-10
Nivo or pembro + platin/FP
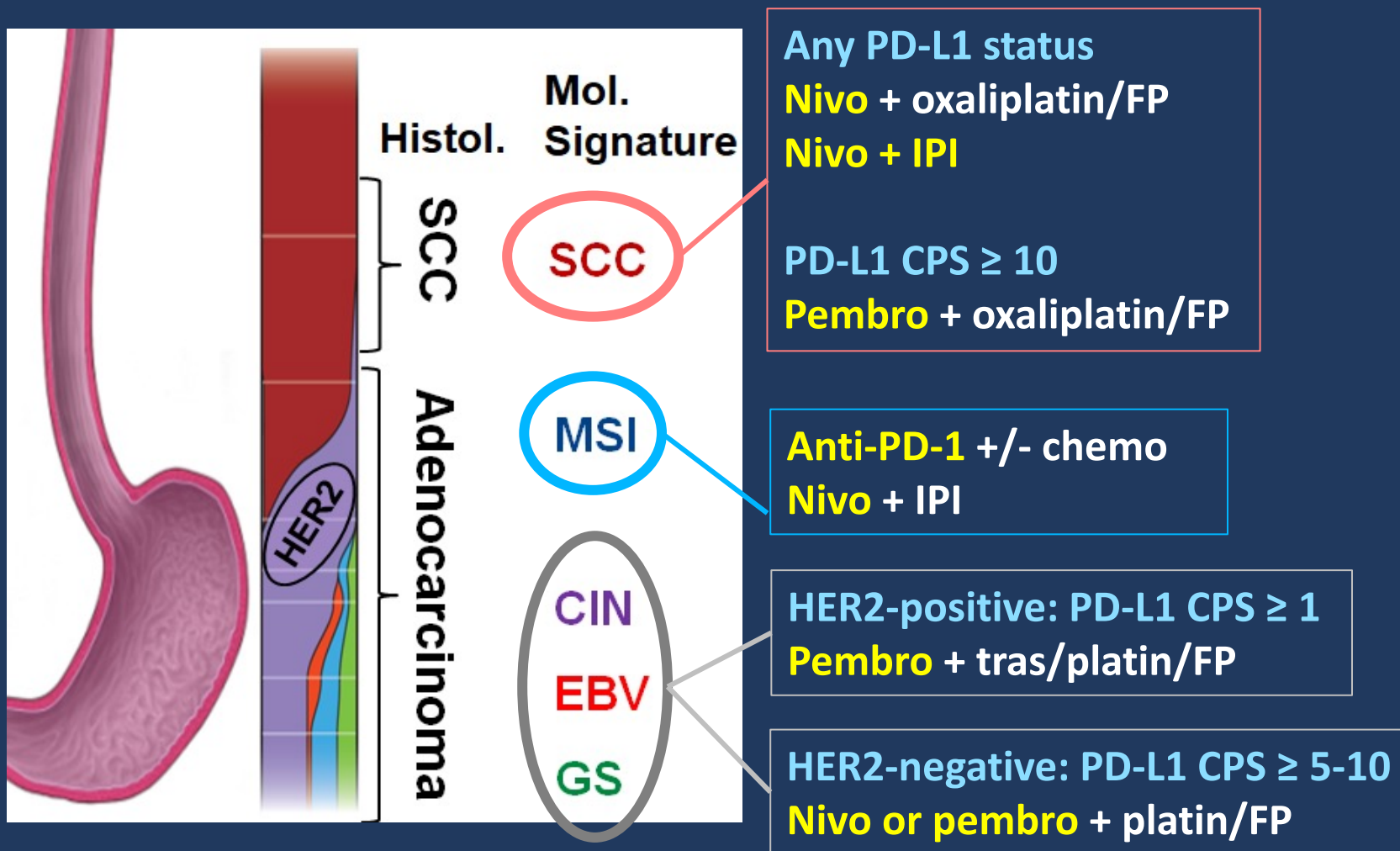
LANDSCAPE OF INVESTIGATIVE APPROACHES

Targets
- Oncogenic drivers
  - HER2 (eg, ZW25 monotherapy ORR 38%) [a]
  - EGFR amplification
- Immune checkpoints (eg, TIGIT)
- Structural (eg, CLDN18.2)

More basic understanding
- T cell trafficking in tumor microenvironment
- Targeting immunosuppressive environment
- Paradoxical impact of anti-PD-1/-L1

Method of delivery and "payload"
- Immune "payload"
  - CAR-T (eg, anti-CLAUDIN18.2)
  - Bispecific
  - Trispecific Killer Engager (TRIKE)
- ADC (cytotoxic payload)
- Nanoparticles
- Many many more

[a] bispecific Ab that binds trastuzumab-binding domain and pertuzumab-binding domain

THANK YOU