PARIS 2022 ESMO congress

Controversy session:
PD-L1 is a good enough for now predictive biomarker for anti-PD-1 therapy in oesophagogastric cancer

Yelena Y. Janjigian, MD

Twitter: @yjanjigianMD

Memorial Sloan Kettering Cancer Center, United States of America

Disclosures

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- Bristol Myers Squibb
- Merck Serono, RGENIX
- Eli Lilly
- Daiichi Sankyo
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- Bristol Myers Squibb
- Eli Lilly
- Merck

Argument *for* biomarker selection in gastric cancer

Biomarker	Prevalence in metastatic gastric cancer	Therapeutic agent(s)
ERBB2/HER2	20%	Dual ani-HER2 and Anti-PD-1
MSI-high	5%	Anti-PD-1
EBV-positive	3%	Anti-PD-1
PD-L1 CPS	CPS ≥1 = 80%; CPS ≥5 = 60%	Anti-PD-1
FGFR2b overexpression	30%	bemarituzumab
CLDN18.2	35%	zolbetuximab
Tumor sequencing	NTRACK , EGFR, MET, RAS amp	TKIs and EGFR mabs
Plasma DNA	Monitoring for response and resistance	Broad application

PD-L1: Multiple Drugs With Multiple Assays

- PD-L1 expression in gastric cancer is determined by **c**ombined **p**ositive **s**core (**CPS**)

$$\textbf{CPS} = \frac{\text{No. of PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total no. of viable tumor cells}} \times 100$$

- A specimen is considered to have positive PD-L1 expression if CPS ≥1

Assay	Agent
PD-L1 IHC 22C3 PharmDX[1,2]	Pembrolizumab
PD-L1 IHC 28-8 PharmDX[3,4]	Nivolumab
PD-L1 (SP142) assay[5,6]	Atezolizumab
PD-L1 (SP263) assay[7,8]	Durvalumab Pembrolizumab Nivolumab

PD-L1 testing -E1L3N Cellsignaling at MSKCC

[a] 22C3 pharmDx kit, Agilent Technologies, Carpinteria, CA.

Immunotherapy in Gastric Adenocarcinoma

- Nivolumab with chemotherapy approved in the United States for 1st-line treatment irrespective of PD-L1 status[1]
- Pembrolizumab, trastuzumab, and chemotherapy approved in the United States for HER2-positive disease[2]
- Sintilimab approved in China for 1st-line treatment irrespective of PD-L1 status[3]
- Nivolumab approved in Asia irrespective of PD-L1 status for ≥ 3rd-line treament[4]
- Pembrolizumab approval for ≥ 3rd-line treatment in the United States withdrawn July 2021[5]
- Pembrolizumab approved in TMB ≥10 mut/Mb (United States) or MSI-H tumors (United States and Japan)[2,6]

1. OPDIVO (nivolumab) [package insert]. Princeton, NJ: Bristol Myers Squibb; 2021.
2. KEYTRUDA (pembrolizumab) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2021.
3. TYVYT (Sintilimab). Eli Lilly; Jun 2022
4. Högner A, Thuss-Patience P. *Pharmaceuticals (Basel).* 2021;14:151.
5. Merck (press release, July 1, 2021). Accessed July 20, 2021.
6. Merck (press release, August 24, 2020). Accessed July 20, 2021.

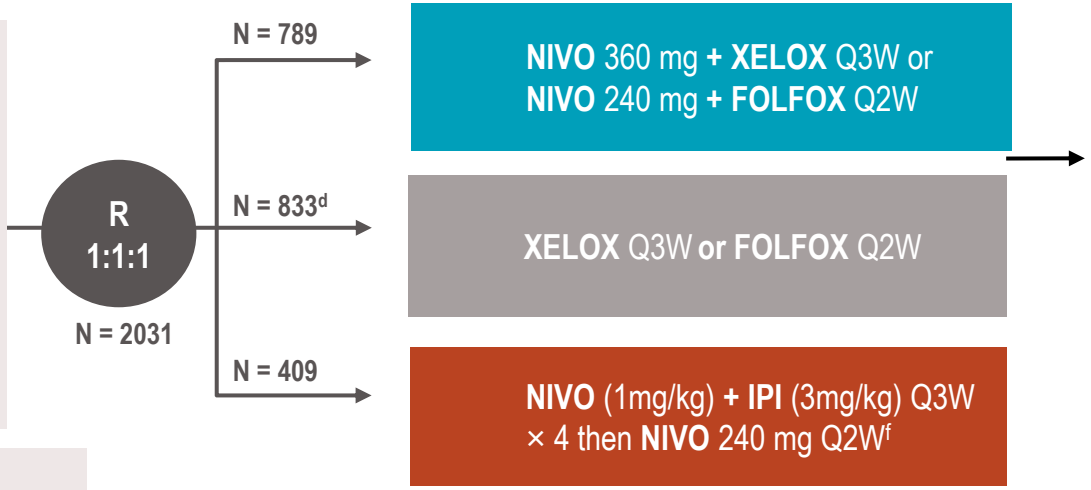
CheckMate 649 Study Design

Key eligibility criteria

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

Stratification factors

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



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**

Dual primary endpoints

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

Hierarchically tested secondary efficacy endpoints

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

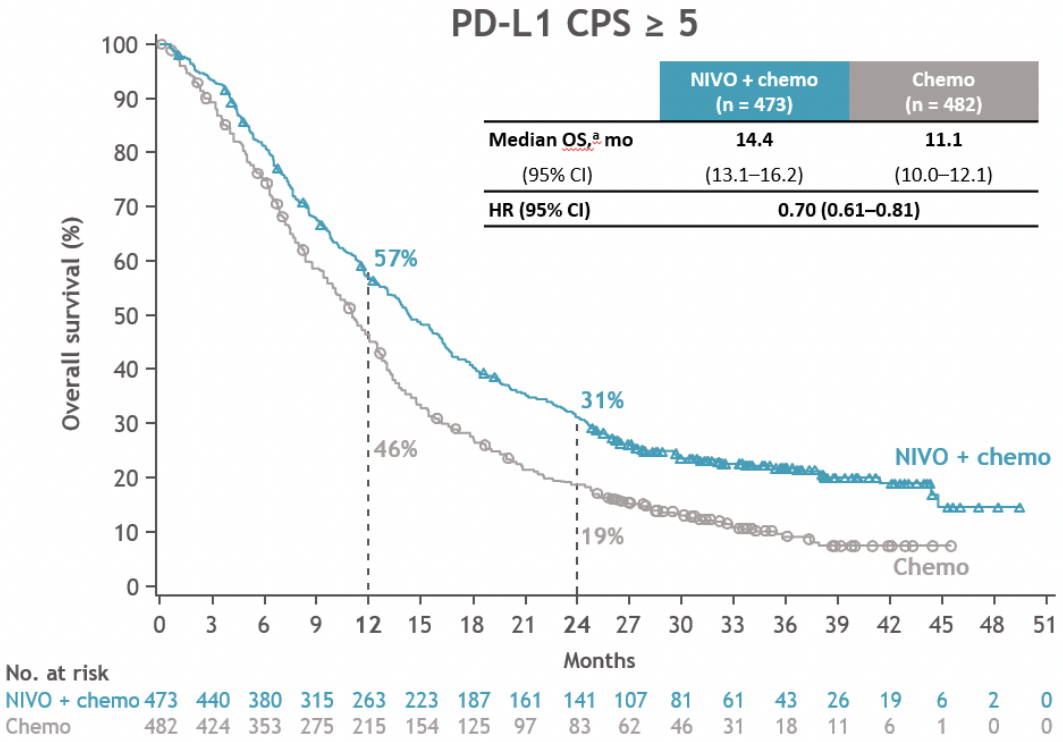
NIVO + IPI vs. chemo
- **OS** (PD-L1 CPS ≥ 5, all randomized)

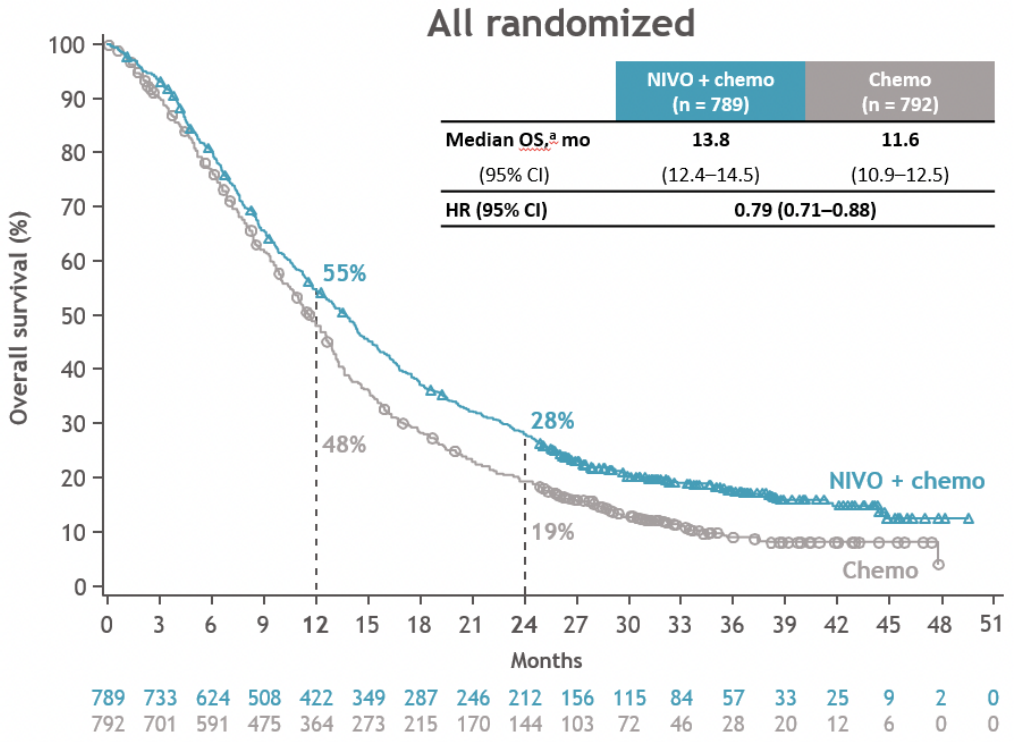
- At data cutoff (May 27, 2021) the minimum follow-up was 24.0 months in the NIVO + chemo arm and 35.7 months in the NIVO + IPI arm

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

CheckMate 649 Established a New Standard of Care:

Nivo + Chemo improved overall survival; FDA approved April 2021[1]





Clinically meaningful improvement in OS with NIVO + chemo vs chemo was maintained with longer follow-up

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

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

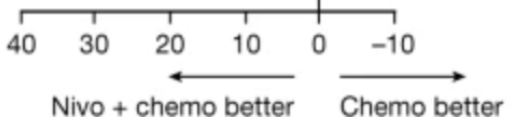
Efficacy outcomes by PD-L1 CPS with nivolumab plus chemotherapy versus chemotherapy.

a Median overall survival (month)

Population	Nivolumab plus chemotherapy	Chemotherapy	Unstratified HR for death (95% CI)
Overall (*n* = 1,581)	13.8	11.6	0.78 (0.70, 0.87)
PD-L1 CPS <1 (*n* = 265)	13.1	12.5	0.95 (0.73, 1.24)
PD-L1 CPS ≥1 (*n* = 1,297)	13.8	11.3	0.74 (0.66, 0.84)
PD-L1 CPS <5 (*n* = 607)	12.4	12.3	0.94 (0.79, 1.11)
PD-L1 CPS ≥5 (*n* = 955)	14.4	11.1	0.69 (0.60, 0.79)
PD-L1 CPS <10 (*n* = 795)	12.4	12.5	0.91 (0.78, 1.06)
PD-L1 CPS ≥10 (*n* = 767)	15.0	10.9	0.66 (0.56, 0.77)

b Objective response rate (%)

Population	Nivolumab plus chemotherapy	Chemotherapy	Unweighted ORR difference (%) (95% CI)
Overall (*n* = 1,210)	58	46	12 (6, 18)
PD-L1 CPS <1 (*n* = 179)	51	41	10 (–5, 24)
PD-L1 CPS ≥1 (*n* = 1,017)	59	46	13 (7, 19)
PD-L1 CPS <5 (*n* = 428)	55	46	9 (–1, 18)
PD-L1 CPS ≥5 (*n* = 768)	60	45	15 (8, 22)
PD-L1 CPS <10 (*n* = 579)	58	47	10 (2, 18)
PD-L1 CPS ≥10 (*n* = 617)	59	44	15 (7, 22)



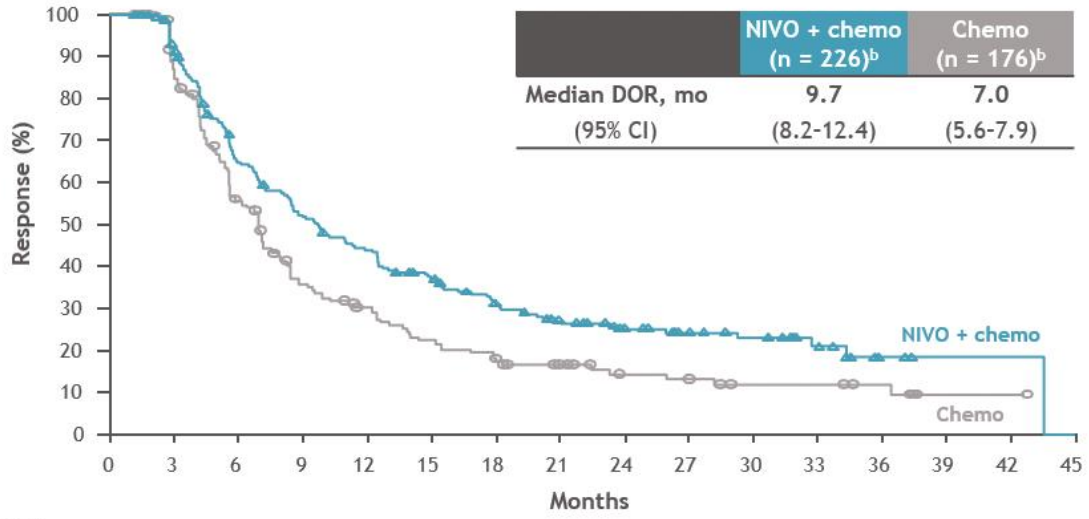
Shitara…. Janjigian et al Nature 2022

Response and duration of response

PD-L1 CPS ≥ 5[1]

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

	NIVO + chemo (n = 226)[b]	Chemo (n = 176)[b]
Median DOR, mo	9.7	7.0
(95% CI)	(8.2-12.4)	(5.6-7.9)



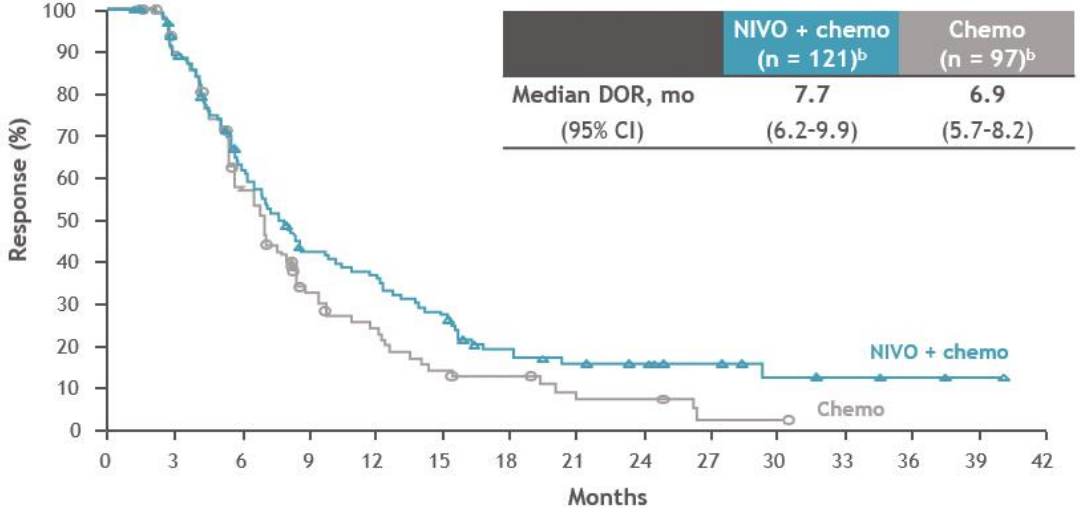
No. at risk

NIVO + chemo	226	196	135	107	90	73	58	45	34	25	20	10	3	1	1	0
Chemo	176	142	87	53	42	31	24	19	12	11	7	7	5	1	1	0

PD-L1 CPS < 5

Response per BICR	NIVO + chemo (n = 219)[a]	Chemo (n = 209)[a]
ORR, % (95% CI)	55 (48-62)	46 (40-53)
CR	7	4
PR	48	42
SD	30	32
PD	7	10

	NIVO + chemo (n = 121)[b]	Chemo (n = 97)[b]
Median DOR, mo	7.7	6.9
(95% CI)	(6.2-9.9)	(5.7-8.2)

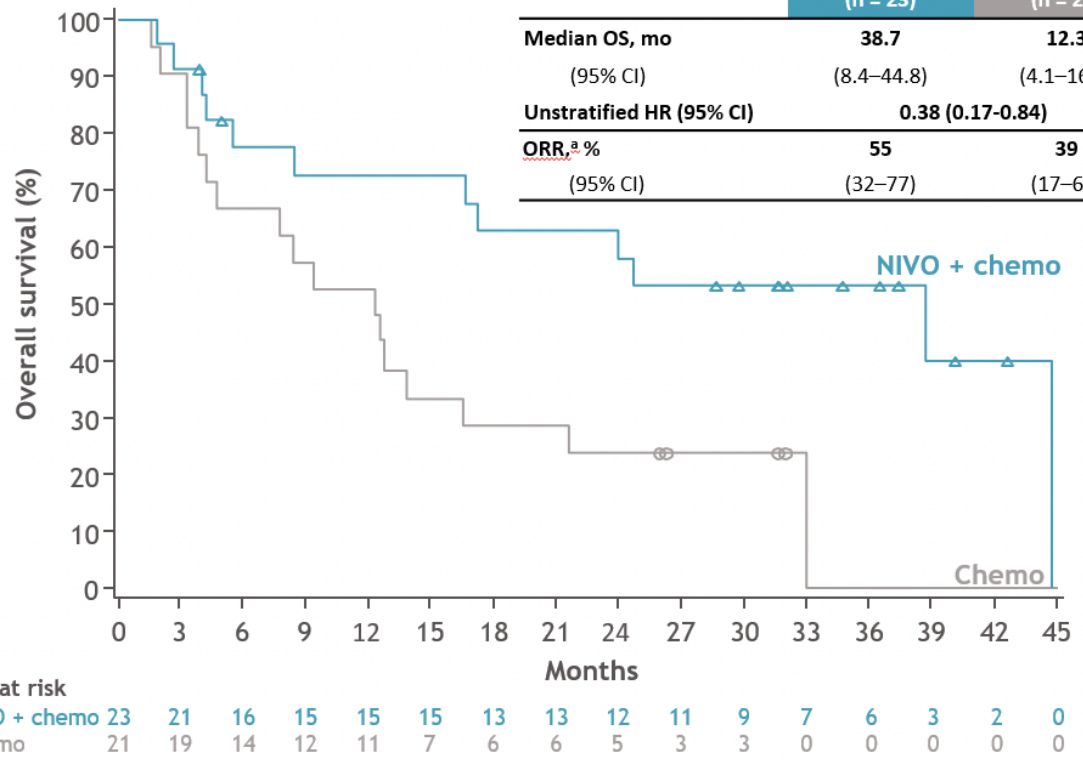


NIVO + chemo	121	104	70	45	39	29	17	13	10	7	4	3	2	1	0
Chemo	97	84	49	24	17	10	8	4	4	1	1	0	0	0	0

Efficacy by MSI Status: NIVO + Chemo vs Chemo

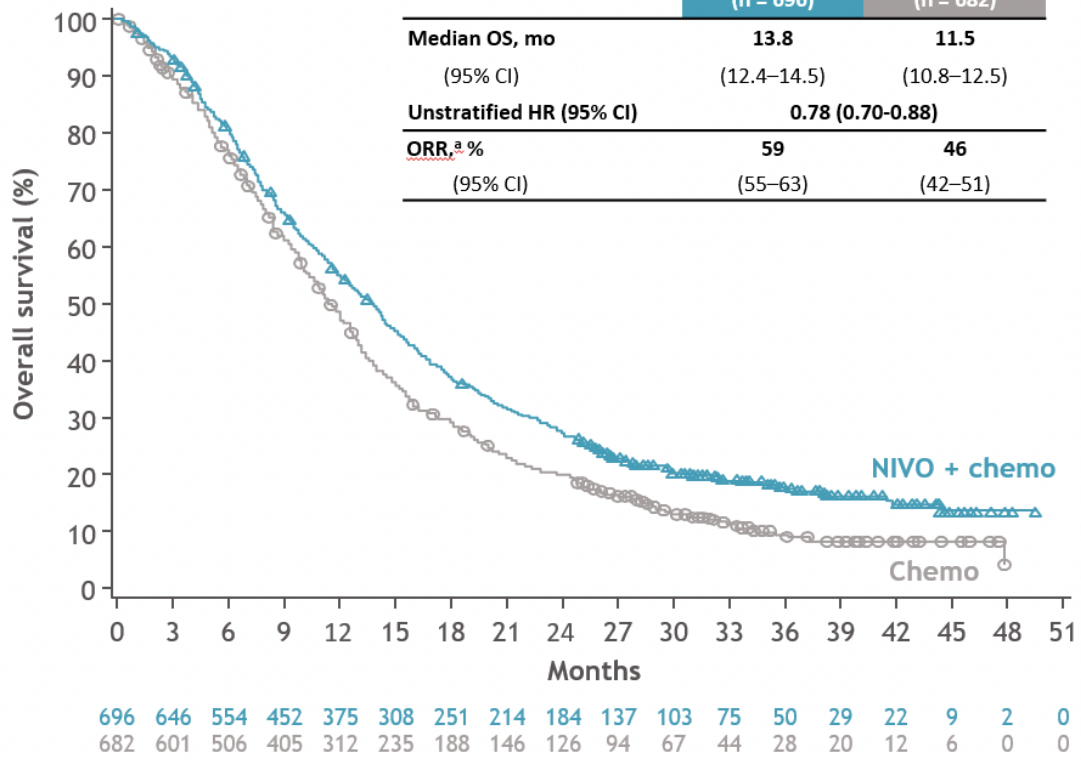
MSI-H

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



MSS

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



Longer median OS and higher ORR were observed in all randomized patients with MSI-H and MSS tumors with NIVO + chemo vs chemo

- The magnitude of benefit was greater in patients with MSI-H tumors
- Patients with MSS tumors had results similar to all randomized population

Treatment-related adverse events

All treated,[a] n (%)	NIVO + chemo (n = 782)		Chemo (n = 767)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TRAEs[b]	739 (95)	471 (60)	682 (89)	344 (45)
Serious TRAEs[b]	175 (22)	133 (17)	94 (12)	77 (10)
TRAEs leading to discontinuation[b,c]	300 (38)	141 (18)	188 (25)	70 (9)
Treatment-related deaths[d]	16 (2)[e]		4 (< 1)[f]	

- No new safety signals were identified with NIVO + chemo
- The most common grade 3/4 TRAEs included:
  - NIVO + chemo: neutropenia (15%), decreased neutrophil count (11%), anemia (6%)
  - Chemo: neutropenia (13%), decreased neutrophil count (9%), diarrhea (3%)

[a]Patients who received ≥ 1 dose of study drug; [b]Assessed in all treated patients during treatment and for up to 30 days after the last dose of study treatment; [c]TRAEs leading to discontinuation of any drug in the regimen; [d]Treatment-related deaths were reported regardless of timeframe; [e]Included 4 events of pneumonitis, 2 events of febrile neutropenia or neutropenic fever, and 1 event each of acute cerebral infarction, disseminated intravascular coagulation, GI bleeding, GI toxicity, infection, intestinal mucositis, mesenteric thrombosis, pneumonia, septic shock, and stroke; [f]Included 1 event each of asthenia and severe hyporexia, diarrhea, pneumonitis, and pulmonary thromboembolism.

Janjigian YY et al. Oral presentation at ESMO; September 16–21, 2021; Virtual. Abstract LBA7.

TRAEs with potential immunologic etiology

All treated,[a-c] n (%)	NIVO + chemo (n = 782)					
	Any grade	Grade 3/4[d]	Median time to onset (range), weeks	Median time to resolution (range), weeks	Resolved, n (%)	Patients receiving IMM, n (%)
Endocrine	109 (14)	6 (<1)	15.3 (2.0–124.3)	NR (0.4 to 191.3+)	41 (38)	17 (16)
Gastrointestinal	266 (34)	43 (5)	4.3 (0.1–97.3)	1.6 (0.1 to 155.7+)	233 (88)	29 (11)
Hepatic	207 (26)	31 (4)	8.0 (0.1–193.7)	10.1 (0.4 to 203.7+)	156 (76)	24 (12)
Pulmonary	41 (5)	14 (2)	24.0 (1.6–96.9)	10.4 (0.3+ to 174.4+)	30 (73)	31 (76)
Renal	29 (4)	7 (<1)	18.9 (1.7–65.7)	2.9 (0.1 to 67.7+)	22 (76)	7 (24)
Skin	218 (28)	27 (3)	9.9 (0.1–139.4)	23.4 (0.1 to 206.7+)	135 (62)	85 (39)

- TRAEs with potential immunologic etiology[b,c]:
  - Grade 3/4 events occurred in ≤ 5% of patients with NIVO + chemo across organ categories
  - The majority of non-endocrine events with NIVO + chemo resolved (62%-88% across organ categories) with a median time to resolution of 1.6-23.4 weeks

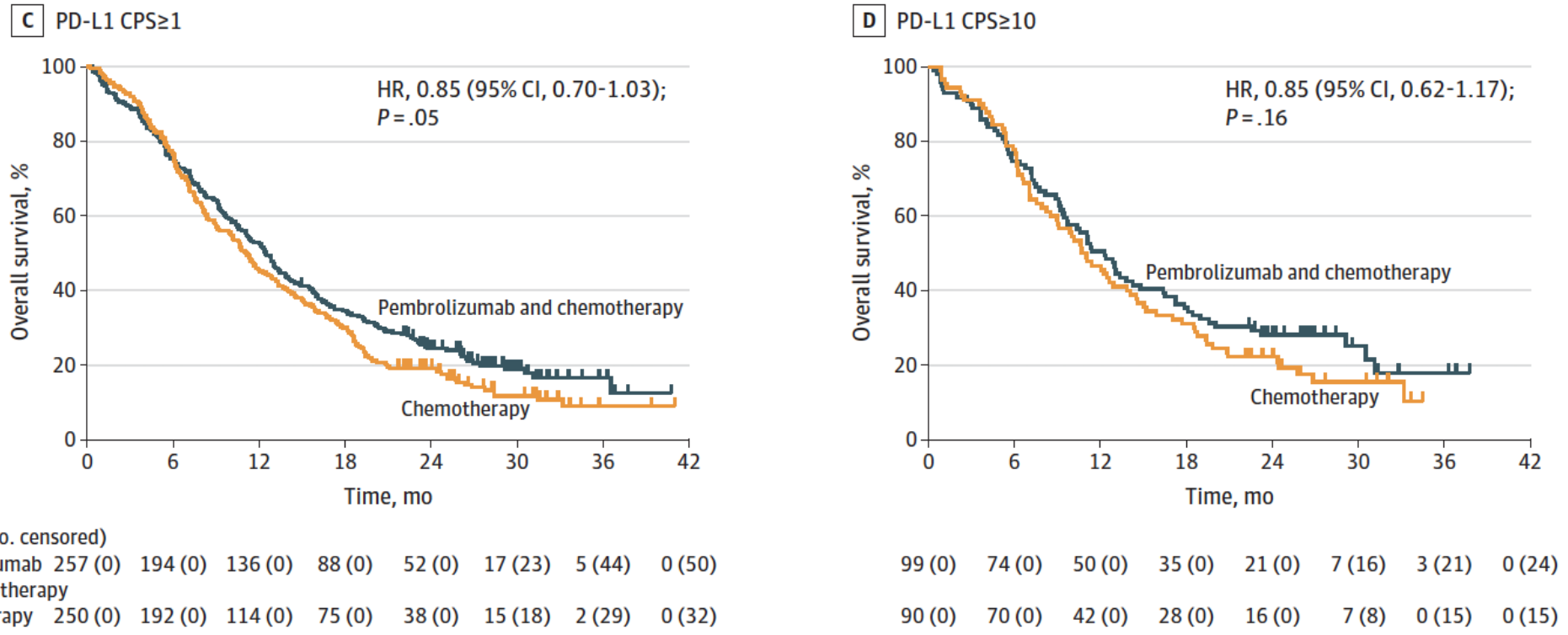
[a]Patients who received ≥ 1 dose of study drug; [b]TRAEs with potential immunologic etiology that require frequent monitoring/intervention; [c]Assessed in all treated patients during treatment and for up to 30 days after the last dose of study treatment; [d]The most common grade 3/4 events (≥ 2%) in the NIVO + chemo arm were diarrhea (n = 35), aspartate aminotransferase increased (n = 13), palmar-plantar erythrodysesthesia syndrome (n = 12), and pneumonitis (n = 12). There were no grade 5 events.

PD-L-1 rate consistent in Phase III studies in EG adenocarcinoma

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

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

Keynote 62 Pembrolizumab + Chemo vs Chemo:
No improvement in OS



No. at risk (No. censored)

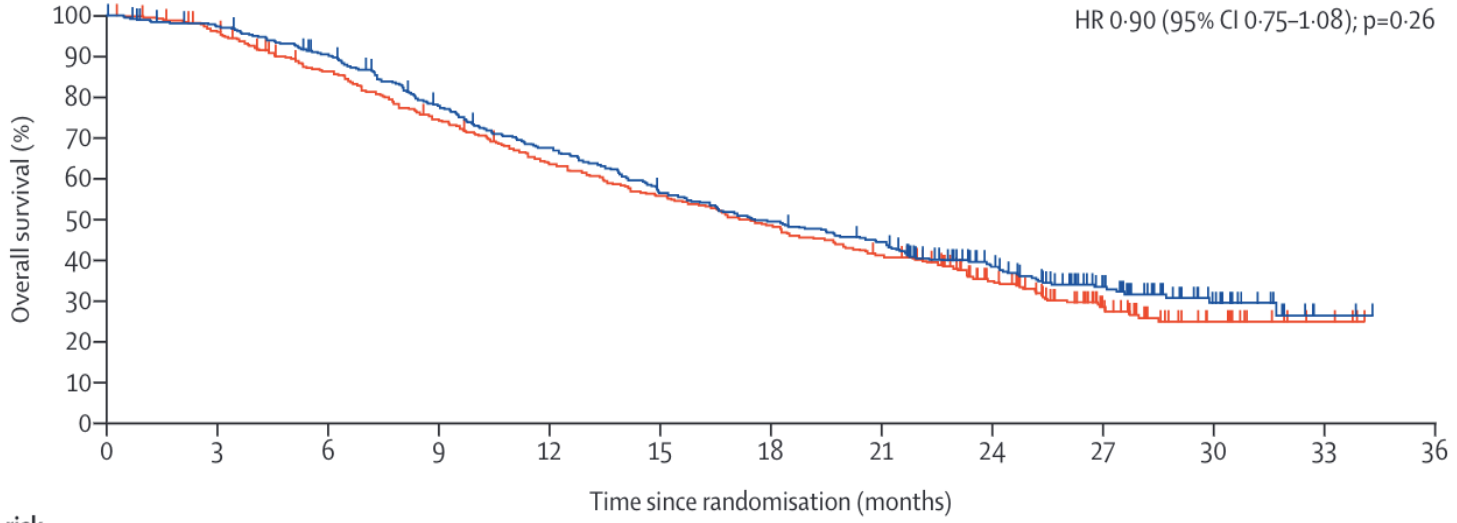
Pembrolizumab and chemotherapy	257 (0)	194 (0)	136 (0)	88 (0)	52 (0)	17 (23)	5 (44)	0 (50)
Chemotherapy	250 (0)	192 (0)	114 (0)	75 (0)	38 (0)	15 (18)	2 (29)	0 (32)

Pembrolizumab and chemotherapy	99 (0)	74 (0)	50 (0)	35 (0)	21 (0)	7 (16)	3 (21)	0 (24)
Chemotherapy	90 (0)	70 (0)	42 (0)	28 (0)	16 (0)	7 (8)	0 (15)	0 (15)

Shitara JAMA Onc 2020

ATTRACTION 4: Nivolumab + Chemo vs Chemo

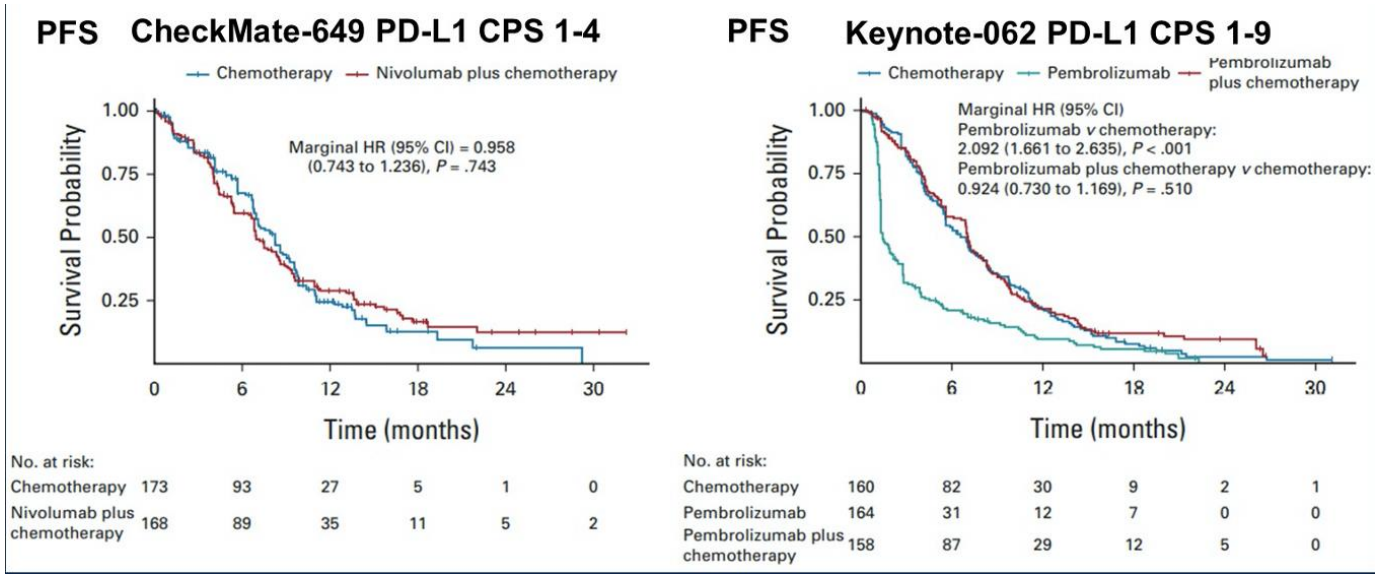
No improvement in OS in Asia

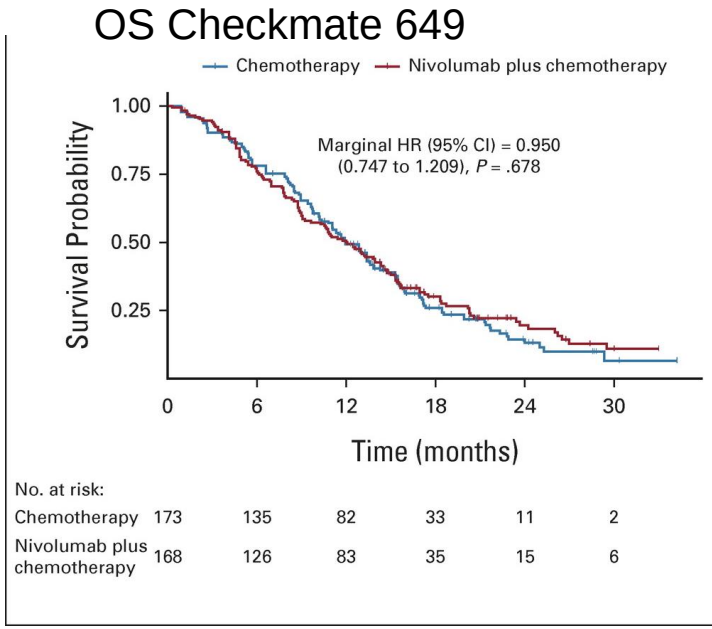


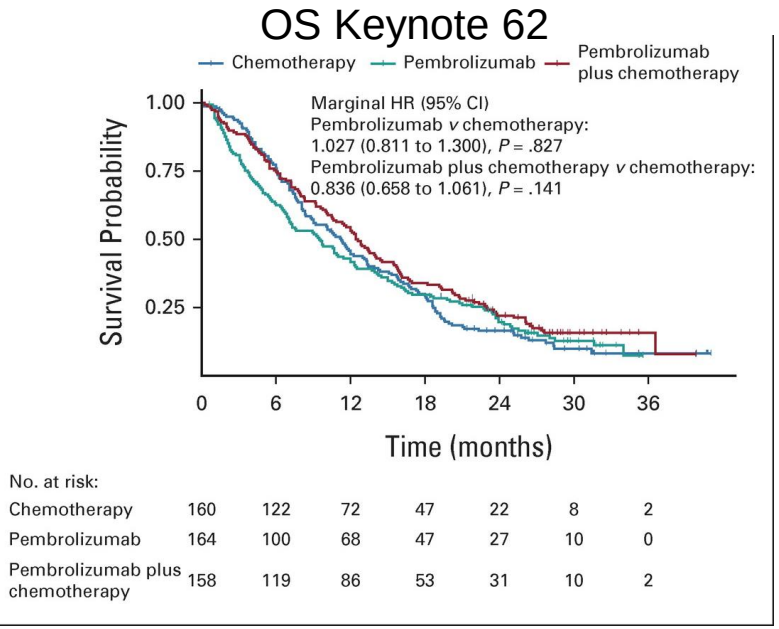
Number at risk (number censored)													
Nivolumab plus chemotherapy	362 (0)	346 (6)	318 (10)	269 (15)	232 (16)	193 (17)	169 (17)	150 (19)	102 (48)	58 (80)	23 (110)	2 (130)	0 (132)
Placebo plus chemotherapy	362 (0)	342 (5)	301 (12)	259 (13)	219 (15)	192 (15)	167 (15)	141 (16)	97 (40)	48 (74)	16 (101)	5 (112)	0 (117)

Kang Lancet Onc 2022

Minimal Survival benefit with anti-PD1 and chemo in PD-L1 low subgroups



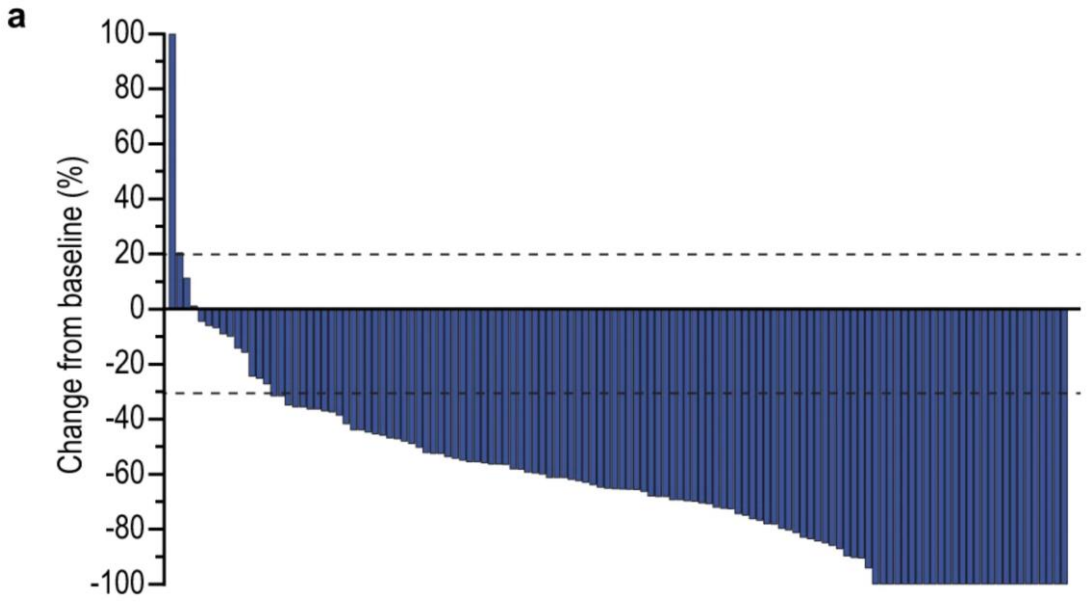


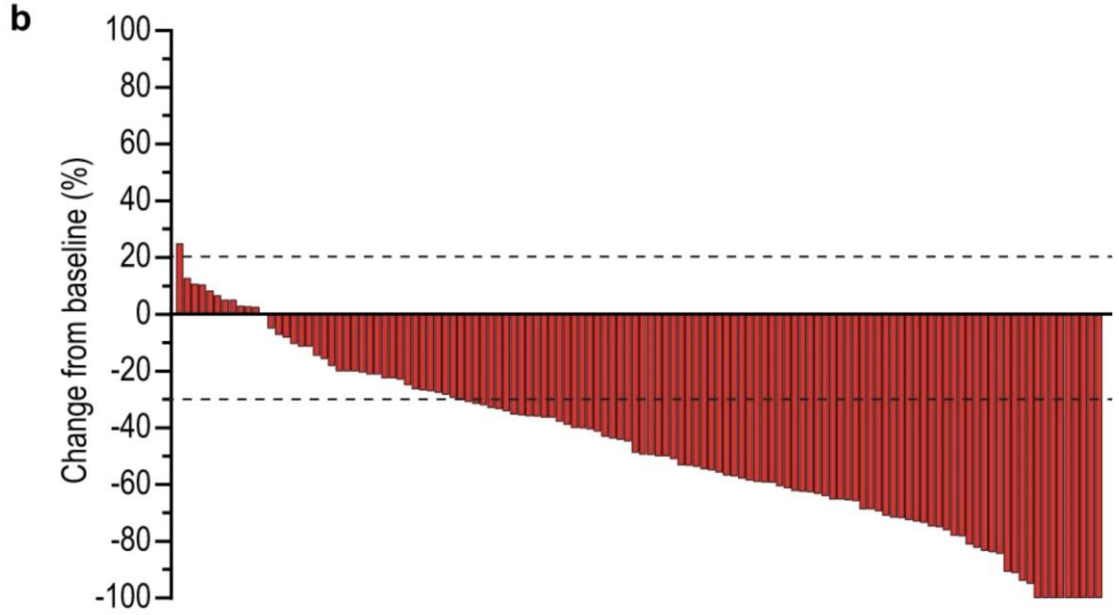


Zhao JCO 2021

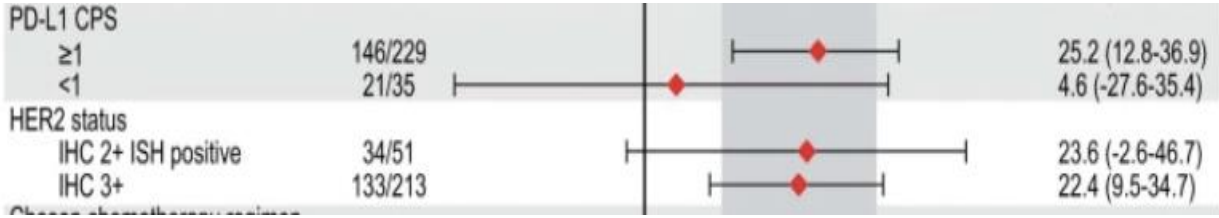
Keynote 811: Pembrolizumab/Trastuzumab/Chemotherapy

23% improvement in response rate FDA approved May 2021





ORR and DCR, % (95% CI)	PEMBRO + trastuzumab (n = 133)	Placebo + trastuzumab (n = 131)
ORR	74.4% (66.2-81.6)	51.9% (43.0-60.7)
ORR Difference[b]	22.7% (11.2-33.7) *P* = 0.00006	
DCR	96.2% (91.4-98.8)	89.3% (82.7-94.0)
Complete response	15 (11%)	4 (3%)



Janjigian Nature 2021

Biomarker Analysis Phase II PEMBRO/TRAZ

Steve Maron MSKCC

Level of ERBB2 and co-occurring alterations Not PDL-L1 predict PFS

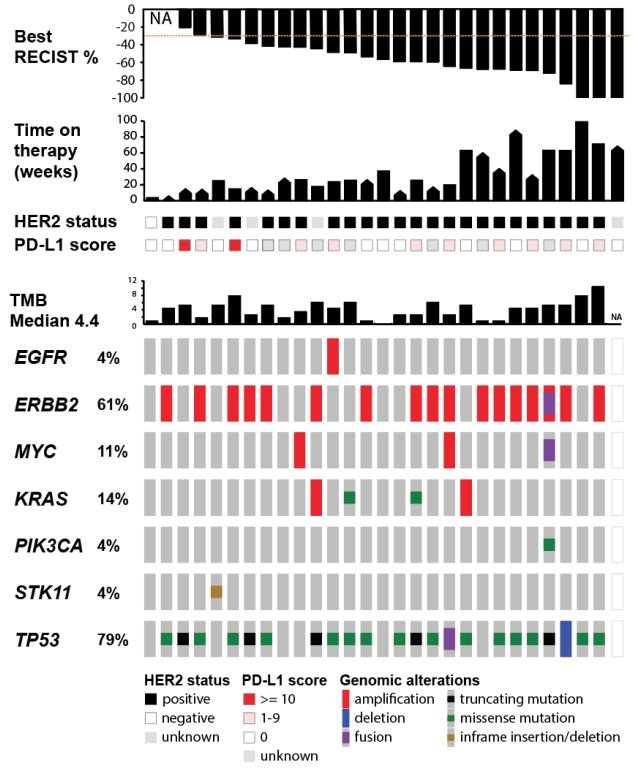
- No MSI tumors in HER2+ mEGA

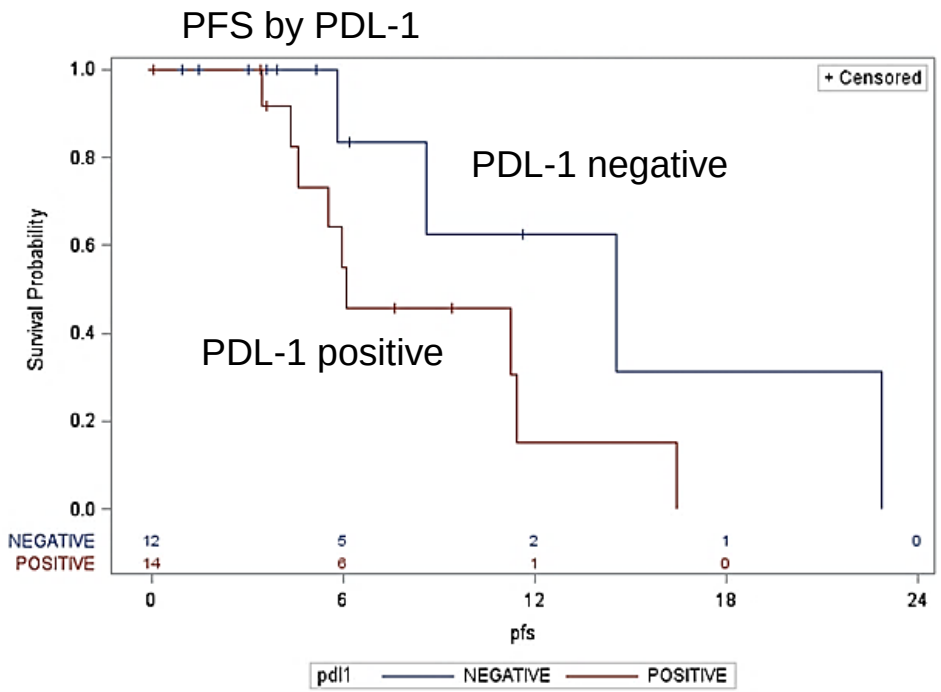
  -- Median TMB 4.4 mut/MB (range 0 to 10.6)

- PDL-1 status not a predictor

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

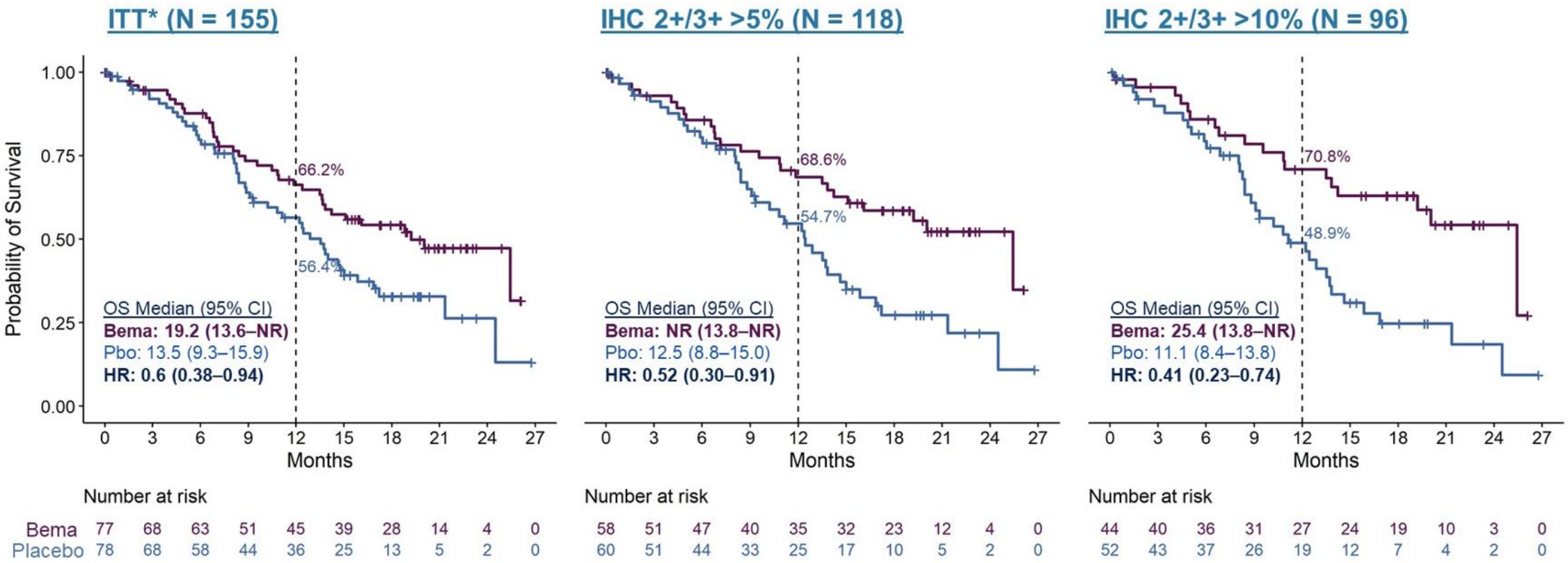
*





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

Anti-FGFR2b antibody with chemotherapy in FGFR2b+ gastric cancer:
5.7 months improvement in median OS



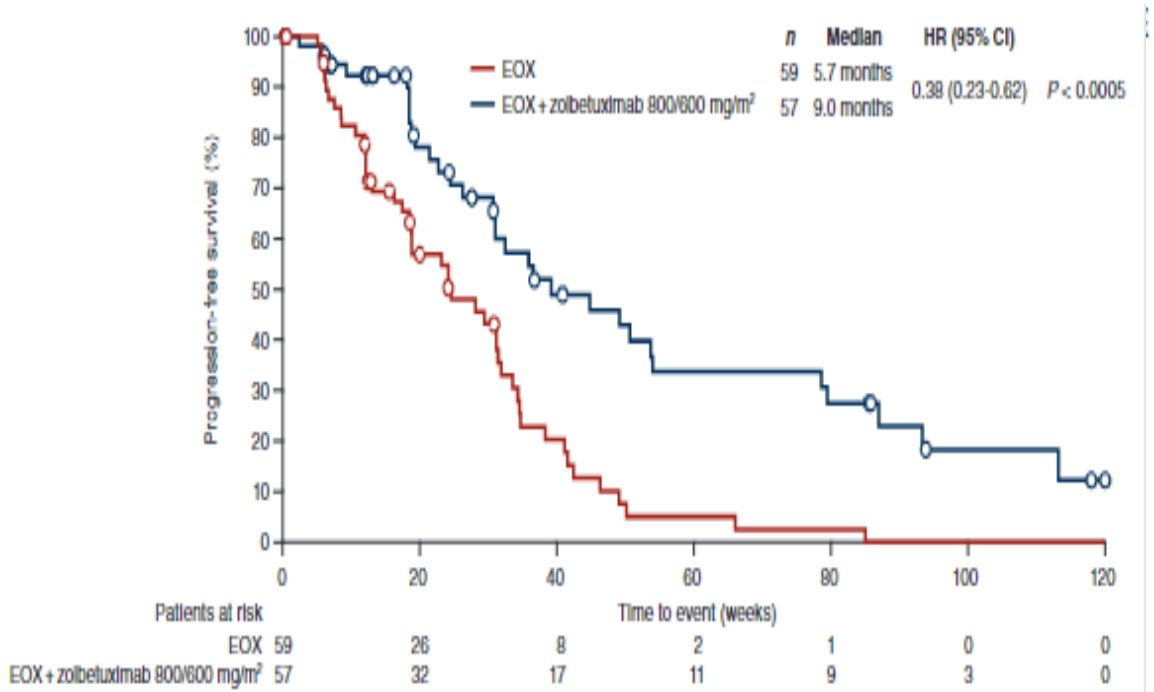
*ITT = includes 149 patients with IHC 2+/3+ and 6 with IHC <2+ or not available who were enrolled based on ctDNA alone.
NR, not reached.
Median Follow-up 12.5 months

*Based on February, 28th 2021 data cut

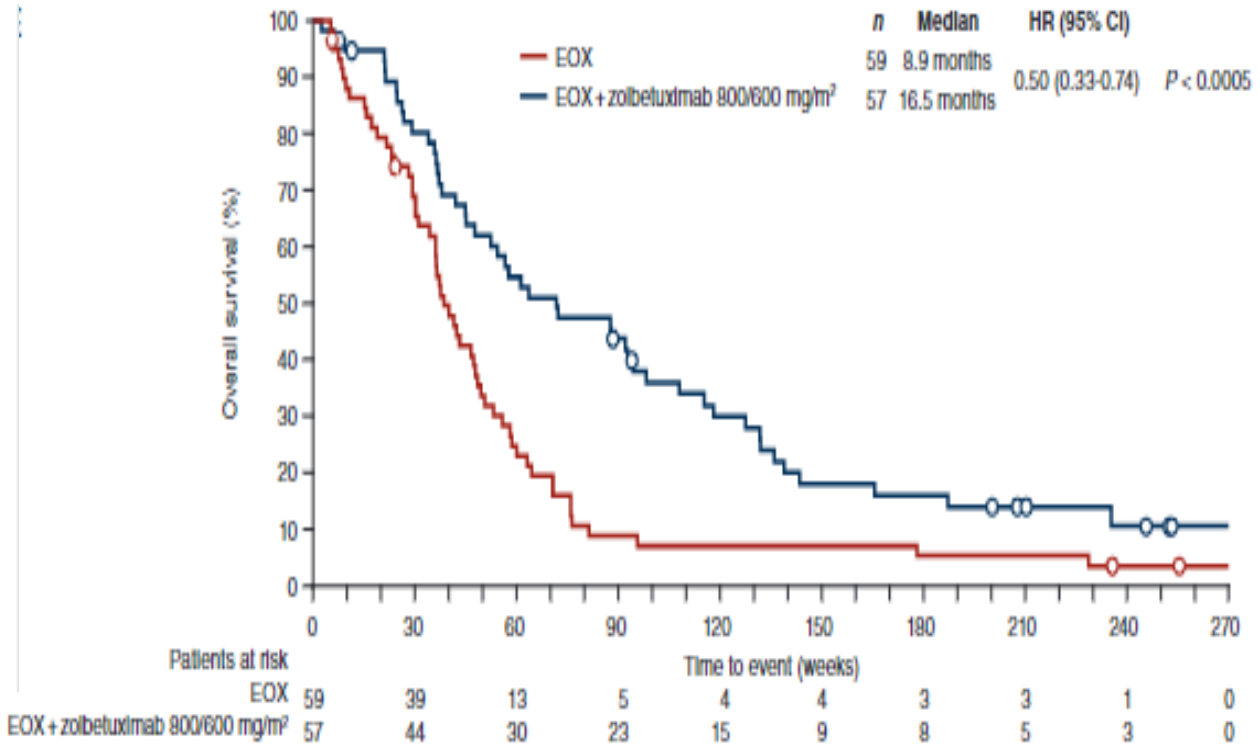
Wainberg et al ASCO 2021

Anti-CLDN18.2 antibody with chemotherapy in CLD18.2+ gastric cancer:
7.6 months improvement in median OS

Progression Free Survival



Overall Survival



Shahin Annals of Oncology 2021

Regorafenib/Nivolumab/FOLFOX

Phase II MSKCC IST

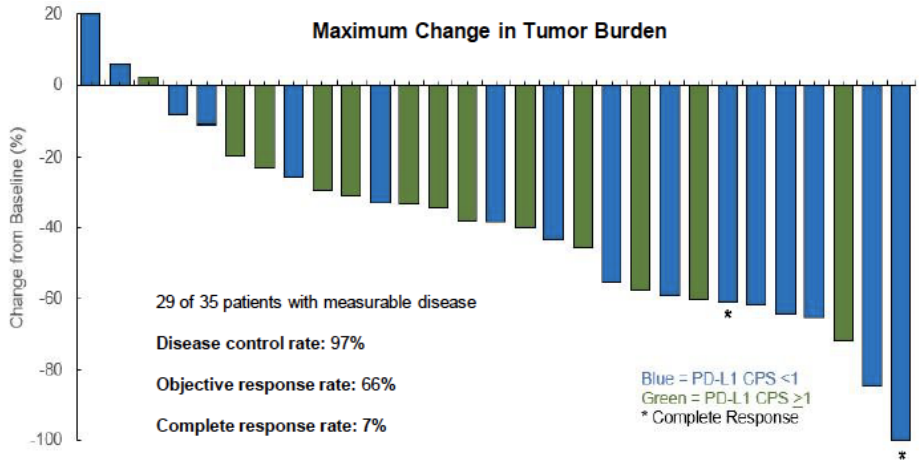
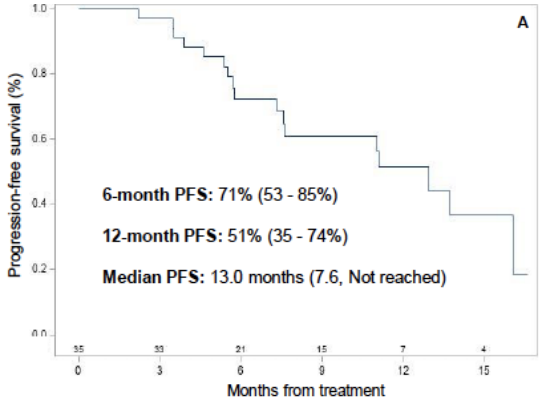
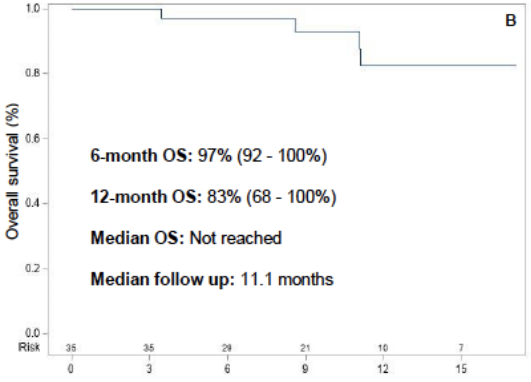


Figure 1 (left): Best percentage change from baseline in size of target lesions among participants with measurable disease as defined by RECIST v1.1

Table 1 (below): Objective response rates and 6-month progression free survival stratified by PD-L1 CPS status

	Total	PD-L1 CPS <1	PD-L1 CPS ≥1	PD-L1 CPS 1-4	PD-L1 CPS ≥5
Number (percent) patients with measurable disease	29 (100%)	16 (55%)	13 (45%)	6 (21%)	7 (24%)
ORR	66%	69%	62%	50%	71%
Number (percent) patients with evaluable disease	34 (100%)	20 (59%)	14 (41%)	5 (15%)	9 (27%)
6-month PFS	71%	75%	64%	100%	44%





Samuel Cytryn, MD
MSKCC Research Fellow

Conclusions

PDL1 testing is mandatory to improve outcomes and minimize adverse events

- Anti-PD-1 therapy improves survival & transforms patient lives
- We can do better with combination therapies for PDL1 low/negative tumors
- Greater magnitude of benefit in biomarker enriched populations
- Critical to continue to test for HER2, MSI, EBV, and PD-L1
- Prioritize biomarker selected subgroups in HER2, EGFR, FGFR2a, CLD18.2, PD-L1 over unselected approaches
- The future is bright for gastric cancer biomarker selected strategies

Twitter: @yjanjigianMD

Thank you for your attention