Memorial Sloan Kettering Cancer Center

Evolving Front-Line Management of Advanced Gastric/Gastroesophageal Junction (GEJ) Cancer

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ASCO GI - *Cases from the Community*
1/19 11:30

Overview

- Summary outcomes for recent studies
  - CheckMate 649 and ATTRACTION-4 vs KEYNOTE-062
- Immunotherapy and HER2 directed therapy
- Review molecular features that affect response and inform treatment selection and timing
- Anti-PD-1 based combination strategies

Courtesy of Yelena Y Janjigian, MD

Immunotherapy in Esophagus & Gastric Cancers

Adenocarcinoma

Nivolumab approved in Asia irrespective of PD-L1 status in ≥3rd-line

Pembrolizumab approved in ≥ 3rd line the U.S.
PD-L1 CPS ≥ 1, TMB ≥10 or MSI-H tumors

Minimal benefit in PD-L1 CPS <1 patients

Squamous cell cancer

Nivolumab approved ≥2nd-line irrespective of PD-L1 status
Pembrolizumab approved in PD-L1 CPS≥10

ESMO 2020: Practice changing studies

Courtesy of Yelena Y Janjigian, MD

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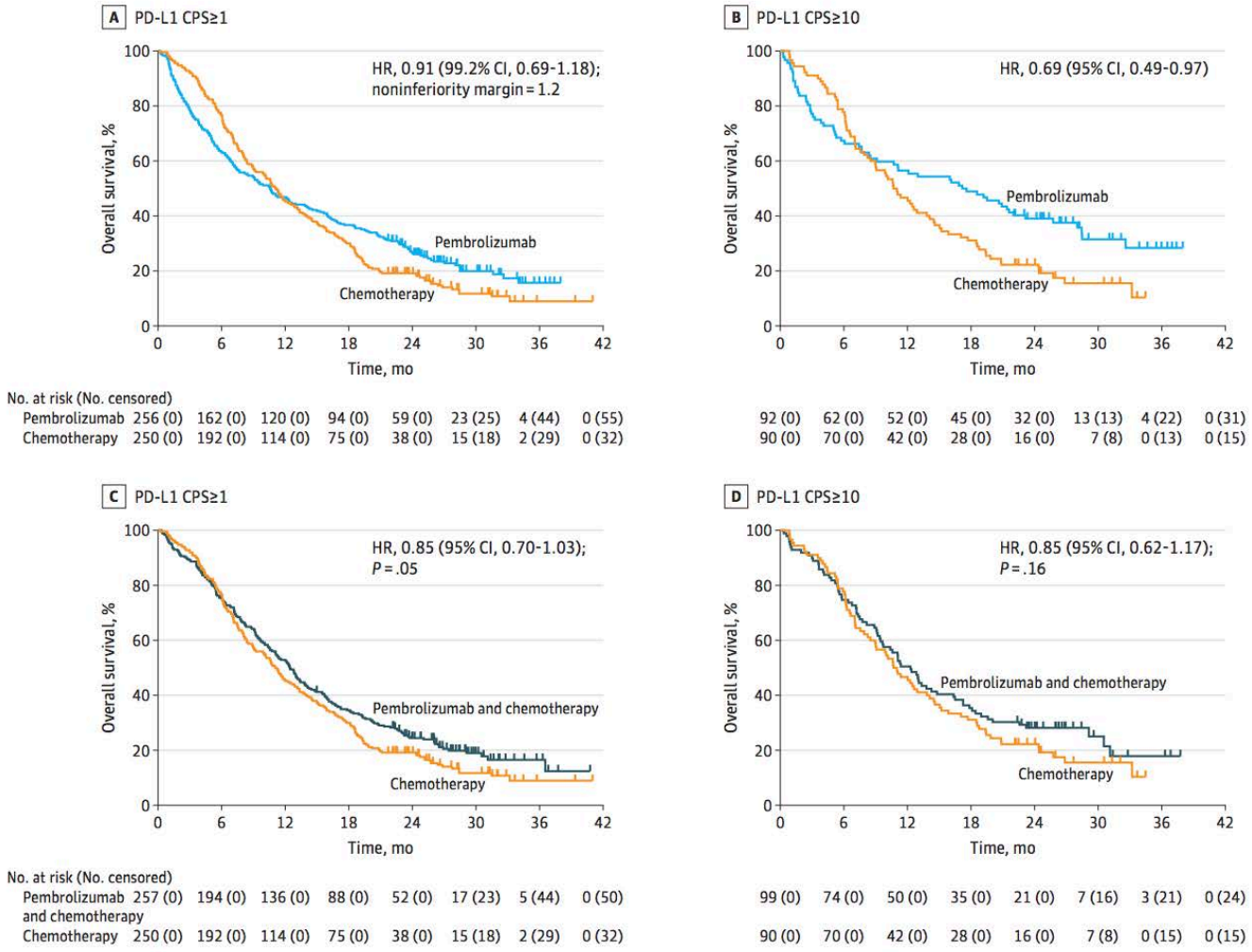
Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer

The KEYNOTE-062 Phase 3 Randomized Clinical Trial

No benefit for pembrolizumab; CPS ≥10 is a unique population



Shitara et al JAMA Onc 2020

Courtesy of Yelena Y Janjigian, MD

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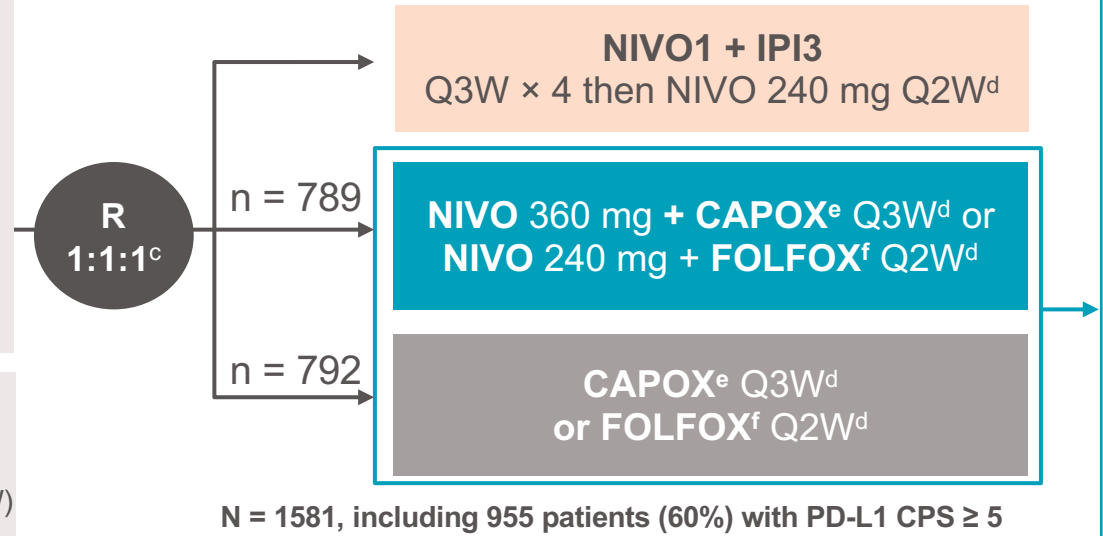
CheckMate 649 study design

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

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

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (CAPOX vs FOLFOX)



Dual primary endpoints:
- **OS** and **PFS**[g] (PD-L1 CPS ≥ 5)

Secondary endpoints:
- **OS** (PD-L1 CPS ≥ 1 or all randomized)
- **OS** (PD-L1 CPS ≥ 10)
- **PFS**[g] (PD-L1 CPS ≥ 10, 1, or all randomized)
- **ORR**[g]

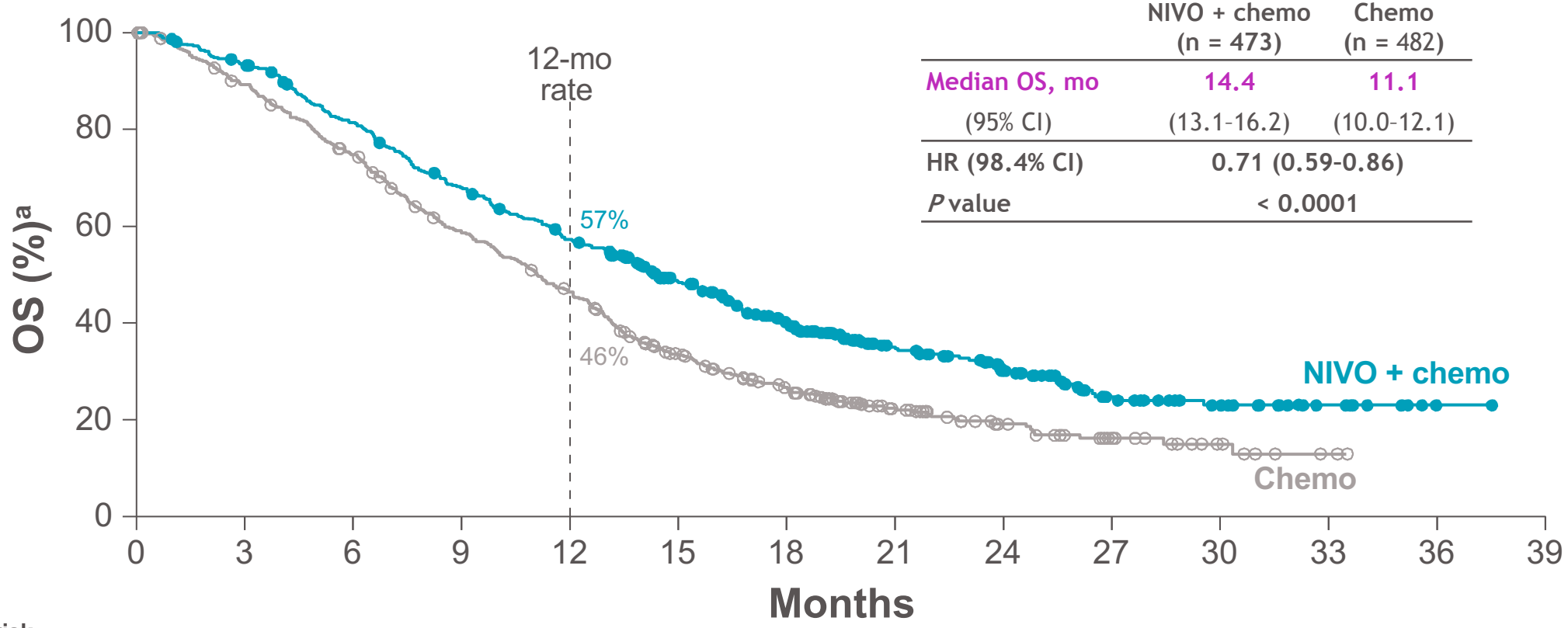
- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]

[a]ClinicalTrials.gov number, NCT02872116; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay; [c]After NIVO + chemo arm was added and before new patient enrollment in the NIVO1+IPI3 group was closed; [d]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [e]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1–14); [f]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); [g]BICR assessed; [h]Time from concurrent randomization of the last patient to NIVO + chemo vs chemo to data cutoff.

Courtesy of Yelena Y Janjigian, MD

Overall survival

Primary endpoint (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

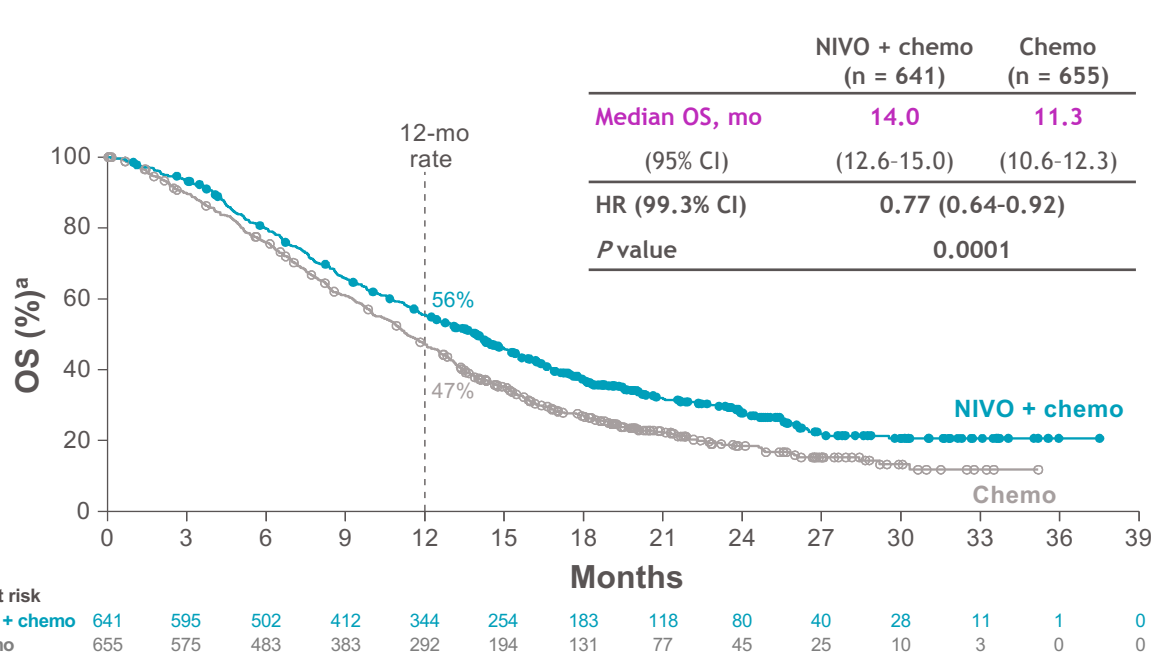
- Superior OS, 29% reduction in the risk of death, and a 3.3-month improvement in median OS with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5

[a]Minimum follow-up 12.1 months.

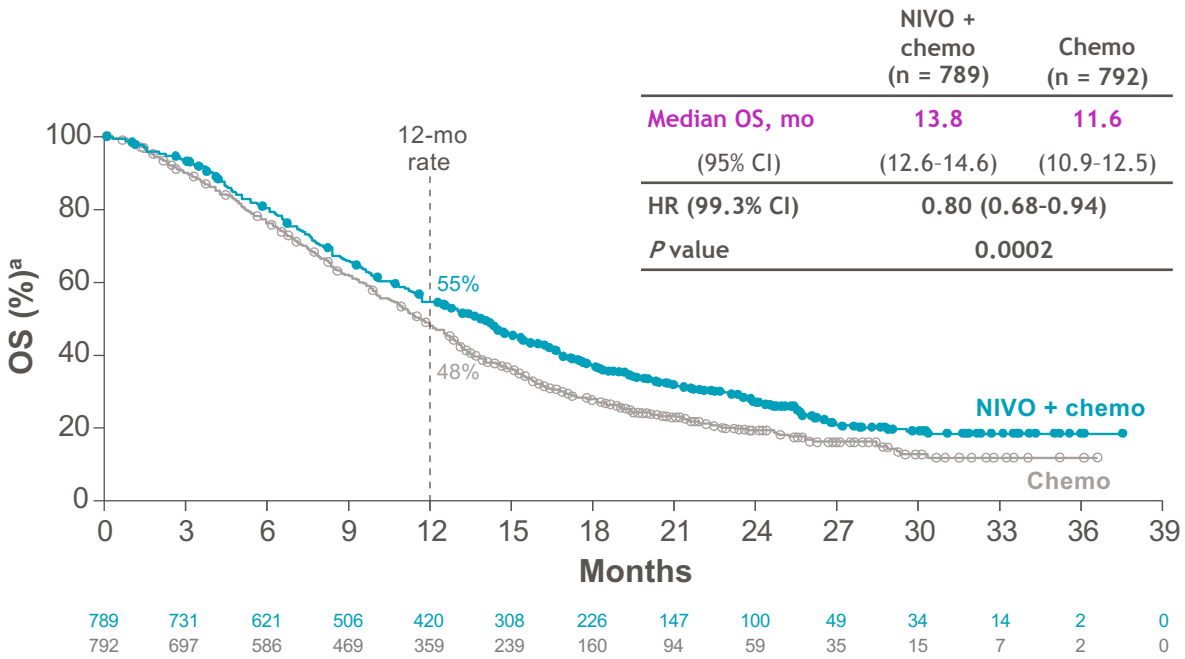
Courtesy of Yelena Y Janjigian, MD

Overall survival

PD-L1 CPS ≥ 1



All randomized



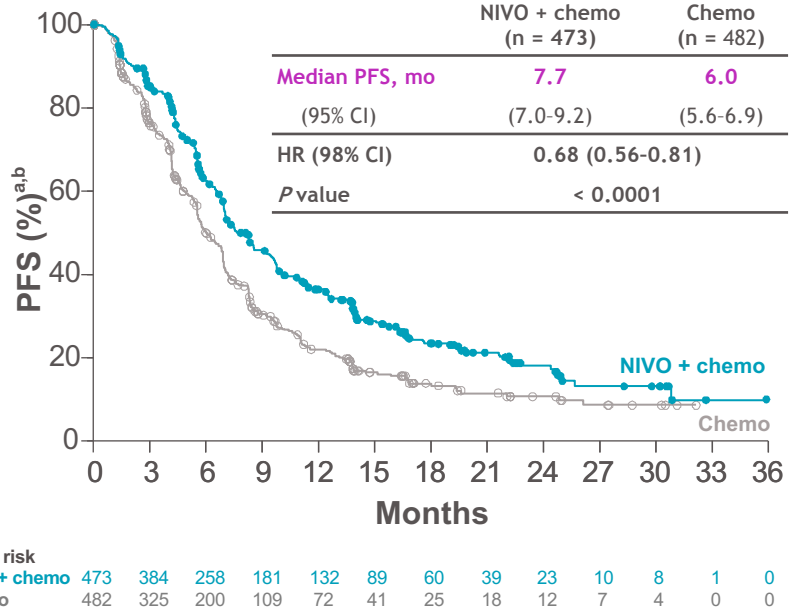
- Superior OS benefit in PD-L1 CPS ≥ 1 and all randomized patients with NIVO + chemo versus chemo

[a]Minimum follow-up 12.1 months.

Courtesy of Yelena Y Janjigian, MD

Progression-free survival

Primary endpoint (PD-L1 CPS ≥ 5)



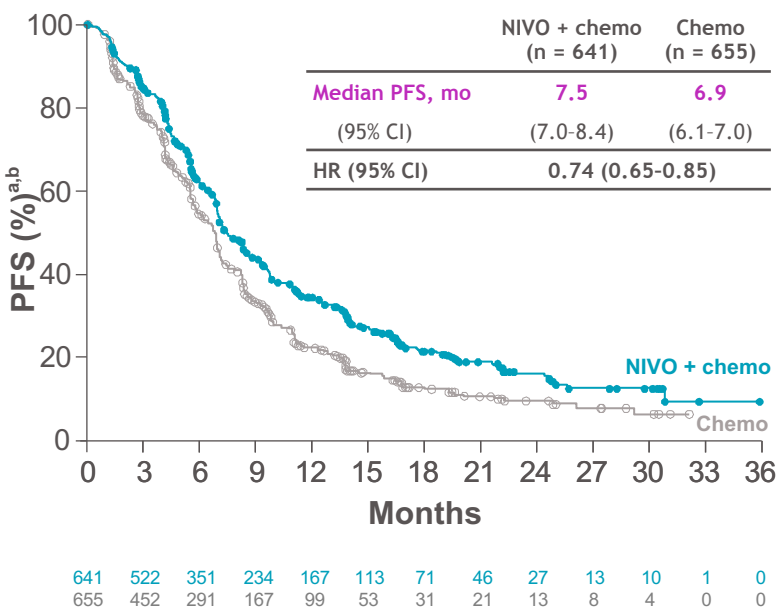
	NIVO + chemo (n = 473)	Chemo (n = 482)
Median PFS, mo	7.7	6.0
(95% CI)	(7.0-9.2)	(5.6-6.9)
HR (98% CI)	0.68 (0.56-0.81)	
P value	< 0.0001	

No. at risk

NIVO + chemo	473	384	258	181	132	89	60	39	23	10	8	1	0
Chemo	482	325	200	109	72	41	25	18	12	7	4	0	0

12-mo rate: NIVO + chemo, 36%; chemo, 22%

PD-L1 CPS ≥ 1

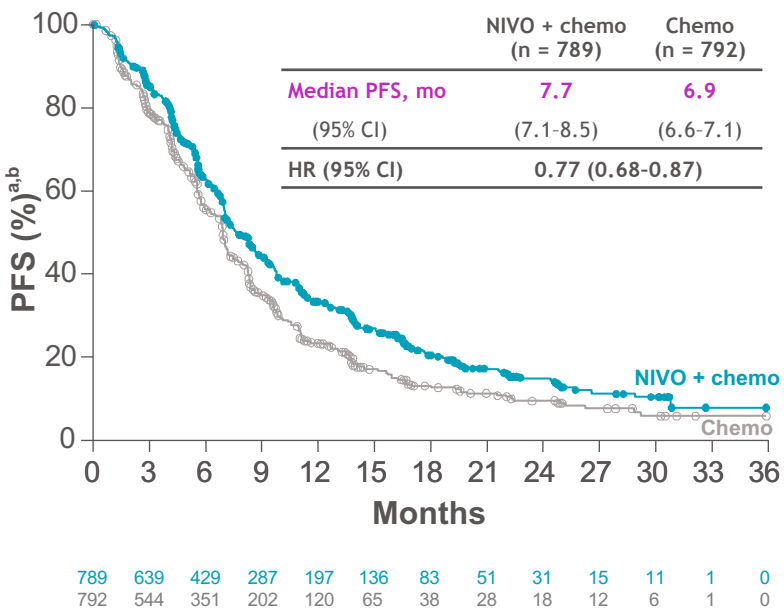


	NIVO + chemo (n = 641)	Chemo (n = 655)
Median PFS, mo	7.5	6.9
(95% CI)	(7.0-8.4)	(6.1-7.0)
HR (95% CI)	0.74 (0.65-0.85)	

NIVO + chemo	641	522	351	234	167	113	71	46	27	13	10	1	0
Chemo	655	452	291	167	99	53	31	21	13	8	4	0	0

NIVO + chemo, 34%; chemo, 22%

All randomized



	NIVO + chemo (n = 789)	Chemo (n = 792)
Median PFS, mo	7.7	6.9
(95% CI)	(7.1-8.5)	(6.6-7.1)
HR (95% CI)	0.77 (0.68-0.87)	

NIVO + chemo	789	639	429	287	197	136	83	51	31	15	11	1	0
Chemo	792	544	351	202	120	65	38	28	18	12	6	1	0

NIVO + chemo, 33%; chemo, 23%

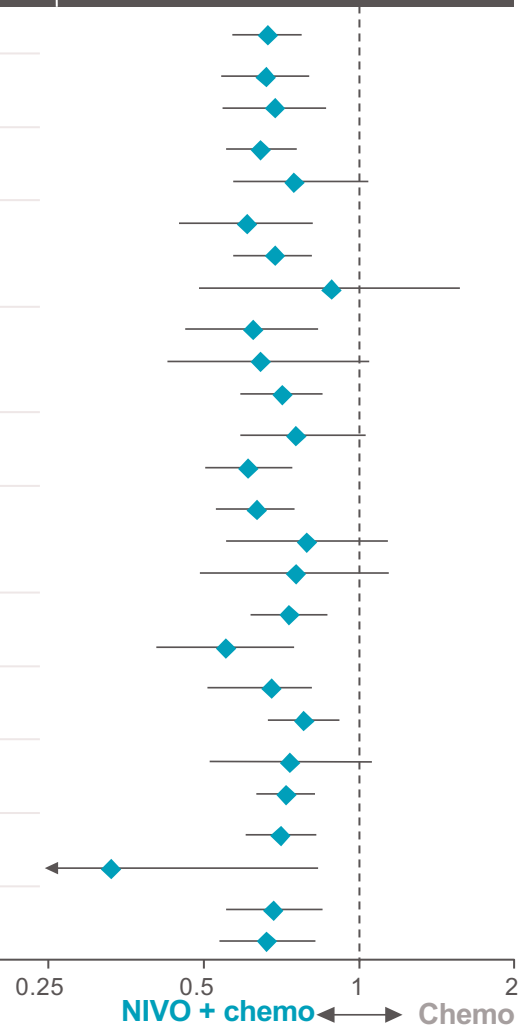
- Superior PFS, 32% reduction in the risk of progression or death with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5
- PFS benefit with NIVO + chemo versus chemo in PD-L1 CPS ≥ 1 and all randomized patients

[a]Per BICR assessment; [b]Minimum follow-up 12.1 months.

Courtesy of Yelena Y Janjigian, MD

Overall survival subgroup analysis and safety

Category (PD-L1 CPS ≥ 5)	Subgroup	Median OS, months		Unstratified HR for death
		NIVO + chemo	Chemo	
Overall (N = 955)		14.4	11.1	0.70
Age, years	< 65 (n = 552)	14.8	11.0	0.69
	≥ 65 (n = 403)	14.3	11.2	0.72
Sex	Male (n = 680)	14.4	10.8	0.67
	Female (n = 275)	14.4	12.1	0.78
Race	Asian (n = 236)	16.1	11.5	0.63
	White (n = 655)	14.0	11.1	0.71
	Other (n = 64)	9.8	10.6	0.93
Region	Asia (n = 228)	15.6	11.8	0.64
	US/Canada (n = 137)	16.8	12.6	0.67
	ROW (n = 590)	13.6	10.4	0.74
ECOG PS[a]	0 (n = 397)	17.6	13.8	0.79
	1 (n = 557)	12.6	8.8	0.63
Primary tumor location	GC (n = 667)	15.0	10.5	0.66
	GEJC (n = 170)	14.2	13.1	0.84
	EAC (n = 118)	11.2	11.3	0.78
Tumor cell PD-L1[b] expression	< 1% (n = 724)	14.2	11.6	0.75
	≥ 1% (n = 230)	16.2	8.8	0.56
Liver metastases	Yes (n = 408)	13.1	9.8	0.63
	No (n = 518)	15.5	12.0	0.76
Signet ring cell carcinoma	Yes (n = 141)	12.1	9.0	0.71
	No (n = 814)	15.1	11.3	0.69
MSI status[c]	MSS (n = 846)	14.4	11.1	0.73
	MSI-H (n = 34)	Not reached	8.8	0.33
Chemotherapy regimen	FOLFOX (n = 479)	14.3	11.3	0.71
	XELOX (n = 454)	15.0	11.0	0.69



- OS consistently favored NIVO + chemo versus chemo across multiple pre-specified subgroups
- Grade 3-4 select treatment-related TRAEs occurred in ≤5% of pts and there were no grade 5 events
- The incidence of select TRAEs in pts whose tumors expressed PD-L1 CPS ≥5 was consistent with all treated pts across both arms

[a]Not reported, n = 1; [b]Unknown, n = 1; [c]Not reported/invalid, n = 75.

Courtesy of Yelena Y Janjigian, MD

KEY DIFFERENCES: KEYNOTE-062 VS. CheckMate 649

	KN062	CM 649
Population	CPS1, Gastric/GEJ adenocarcinoma	All comers, EAC/Gastric/GEJ adenocarcinoma
Chemo backbone	FP/XP	FOLFOX/CAPOX
N	~250/group	~790/group
Minimum follow-up	22 months	12 months

	KN062 (based on screened patients with PD-L1 status)	KN062 All CPS1	CM649 (all comers)
CPS1	72%	100%	82%
CPS 5	29%	61%	60%
CPS10	17%	37%	--

Courtesy of Yelena Y Janjigian, MD

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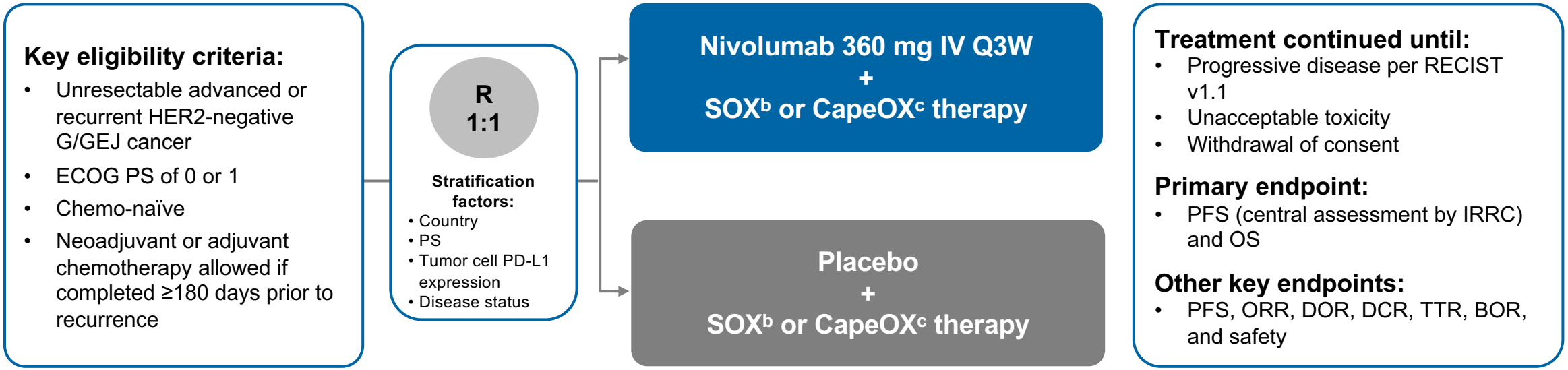
Phase 3 part of ATTRACTION-4

- Phase 3 part of ATTRACTION-4 is a double-blind, randomized (1:1) controlled study conducted at 130 centers in Japan, Korea, and Taiwan from Mar 2017[a]

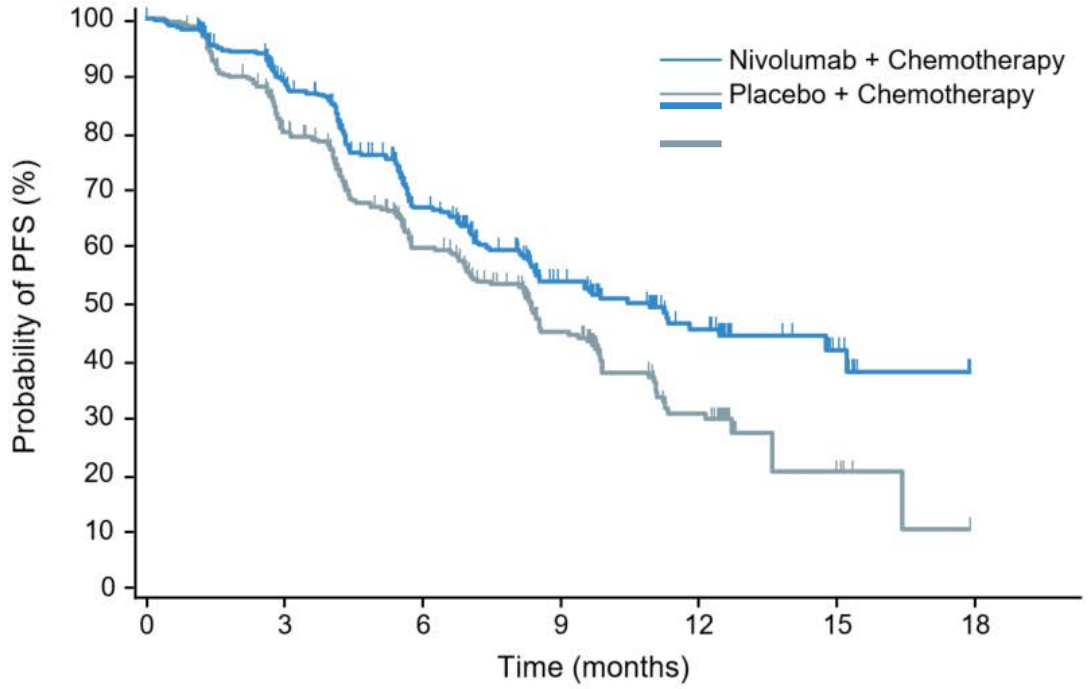


- At data cutoff for interim analysis of PFS (31 Oct 2018), the median follow-up period was 11.6 months
- At data cutoff for final analysis of OS (31 Jan 2020), the median follow-up was 26.6 months
- A total of 724 patients were randomized

[a]ClinicalTrials.gov Identifier: NCT02746796,
[b]SOX : S-1 (tegafur-gimeracil-oteracil potassium) 40 mg/m^2 orally twice daily (days 1–14) and Oxaliplatin 130 mg/m^2 IV (day 1), q3w
[c]CapeOX : Capecitabine 1000 mg/m^2 orally twice daily (days 1–14) and Oxaliplatin 130 mg/m^2 IV (day 1), q3w

Courtesy of Yelena Y Janjigian, MD

Progression-Free Survival (Interim Analysis)



At Risk							
Nivolumab + Chemotherapy	362	274	168	94	46	13	0
Placebo + Chemotherapy	362	259	160	80	30	5	0

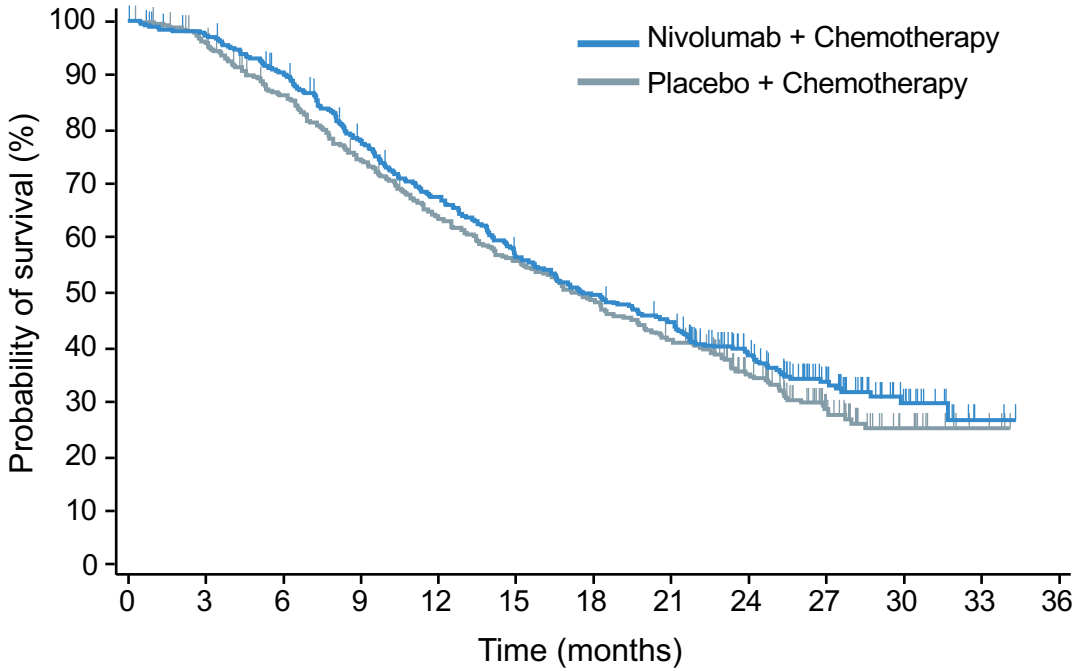
	Nivolumab + chemotherapy N = 362	Placebo + chemotherapy N = 362
Median PFS, months (95% CI)	10.45 (8.44-14.75)	8.34 (6.97-9.40)
Hazard ratio (98.51% CI)	0.68 (0.51 – 0.90)	
P value	0.0007	
1yr PFS rate (%)	45.4	30.6

Cut off: 31 Oct 2018 for Interim analysis

- PFS was continuously longer in NIVO + Chemo than in Chemo at the final analysis (NIVO+Chemo vs. Chemo: HR 0.70; mPFS 10.9 vs. 8.4 mo)

Courtesy of Yelena Y Janjigian, MD

Overall Survival (Final Analysis)



At Risk													
Nivolumab + Chemotherapy	362	346	318	269	232	193	169	150	102	58	23	2	0
Placebo + Chemotherapy	362	342	301	259	219	192	167	141	97	48	16	5	0

	Nivolumab + chemotherapy N = 362	Placebo + chemotherapy N = 362
Median OS, months (95% CI)	17.45 (15.67-20.83)	17.15 (15.18-19.65)
Hazard ratio (95% CI)	0.90 (0.75 – 1.08)	
P value	0.257	

Cut off: 31 Jan 2020 for final analysis

Courtesy of Yelena Y Janjigian, MD

PD-L1 TESTING

Table 1 The FDA-approved anti-PD1 drug and PD-L1 assessment

mAb	Drug	FDA approval	Scoring assessment	Overall response rate
22C3 pharmDx	Pembrolizumab	NSCLC	TPS[a] < 1%: No PD-L1 expression TPS = 1~ 49%: PD-L1 expression TPS ≥ 50%: High PD-L1 expression	NCT02007070 TPS ≥ 1%:15.4% (95% CI: 4.4–34.9%) TPS ≥ 50%:27.3% (95% CI: 6.0–61.0%)
		Gastric or GEJ adenocarcinoma	CPS[b] < 1: No PD-L1 expression CPS≥: PD-L1 expression	NCT02335411 CPS ≥ 1: 13.3% (95% CI: 8.2–20.0%)
28–8 pharmDx	Nivolumab	Melanoma	TC < 1%[c]: No PD-L1 expression TC ≥ 1%[d]: PD-L1 expression	NCT01721746 PD-L1 ≥ 5%: 5.49% (95% CI: 1.92–19.08%) PD-L1 < 5%: 1.13% (95% CI: 0.44–3.16%)
		Non-squamous NSCLC	TC < 1%[e]: No PD-L1 expression TC ≥ 1%[f]: PD-L1 expression	NCT01673867 PD-L1 ≥ 1%: 30.9% (95% CI: 22.9–39.9%) PD-L1 < 1%: 9.3% (95% CI: 4.5–16.4%)
SP142 Assay	Atezolizumab	NSCLC	TC ≥ 50%[g]: PD-L1 expression IC ≥ 10%: PD-L1 expression TC < 50% and IC < 10%[6]: PD-L1 expression	NCT01846416 PD-L1 expression: 16.1% (95% CI:9.32 to 25.2%)
SP263 Assay	Durvalumab	Urothelial Carcinoma	TC ≥ 25%: High PD-L1 expression ICP[7] > 1% and IC + [7] ≥ 25%: High PD-L1 expression ICP = 1% and IC+ = 100%: High PD-L1 expression None of the criteria for PD-L1 High Status are met low/negative PD-L1 expression	NCT01693562 High PD-L1: 27.6% (95% CI: 19–37.5%) Low/negative PD-L1: 5.1% (1.4–12.5%)

E1L3N IHC with PD-L1 clone E1L3N has been validated against clone 22C3 and found to be comparable.

Courtesy of Yelena Y Janjigian, MD

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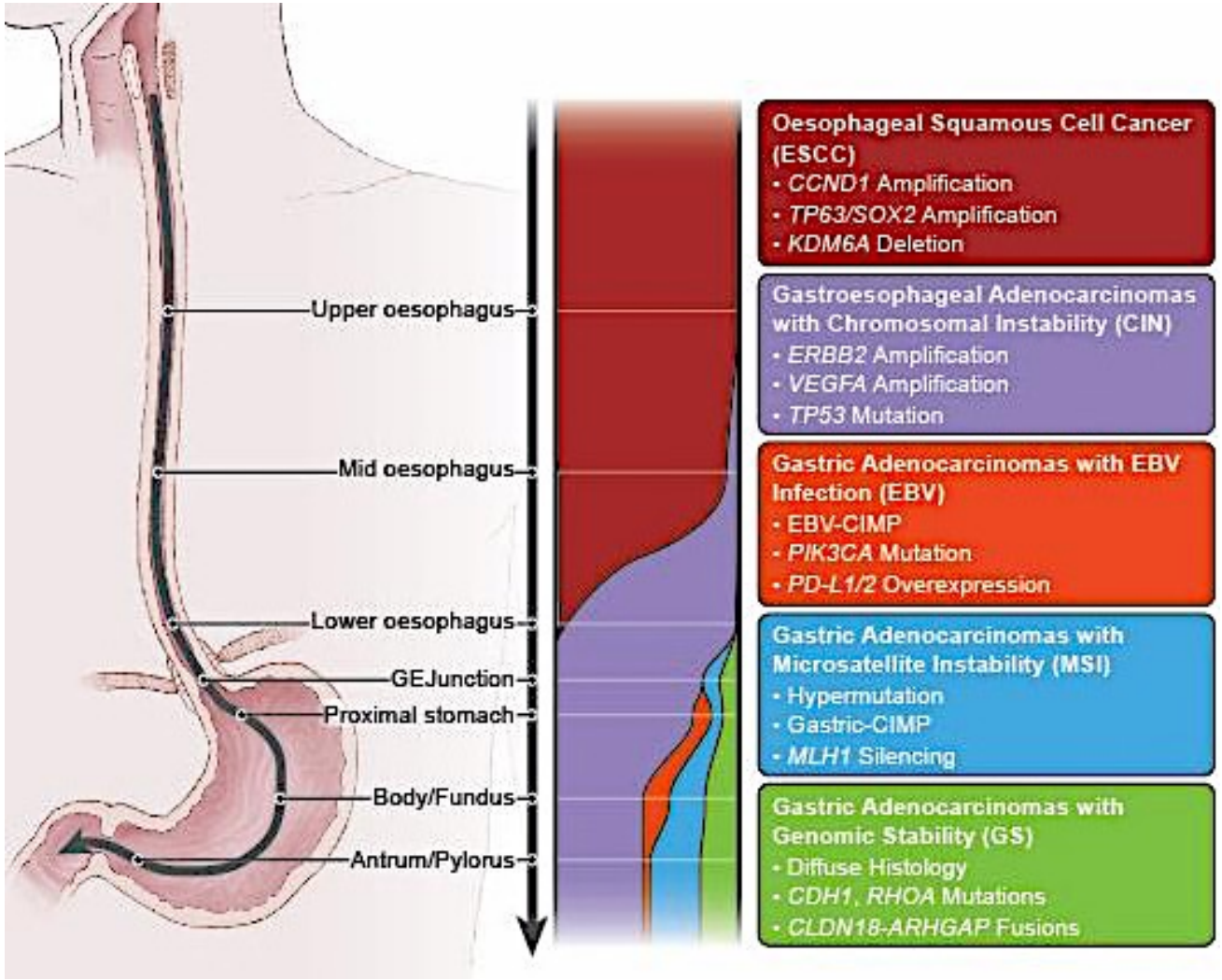
THE GENOMIC SPECTRUM OF EG CANCER

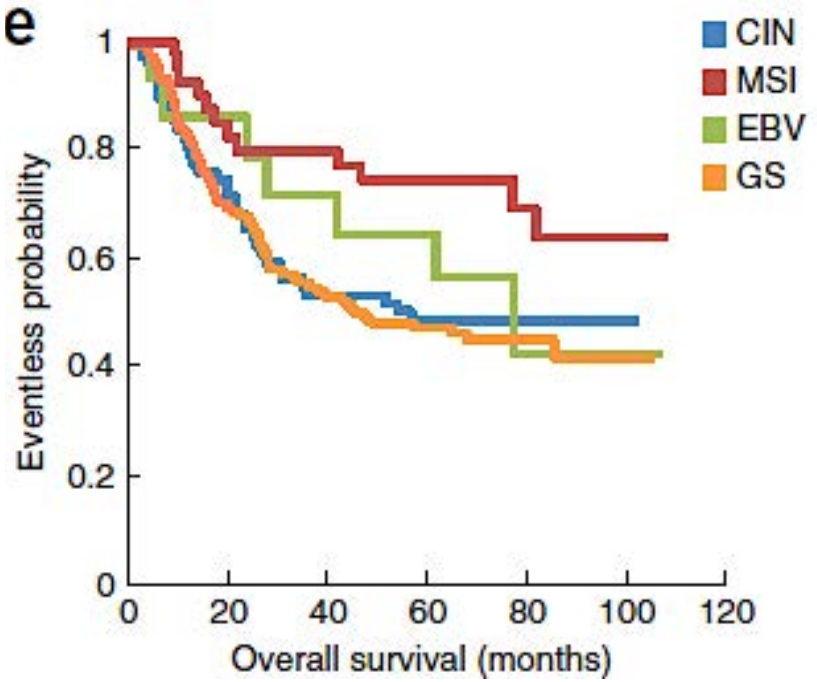


69%

5%

13%

13%



EG TCGA *Nature* 2017
Cristescu et al. *Nature Medicine* 2015

Courtesy of Yelena Y Janjigian, MD

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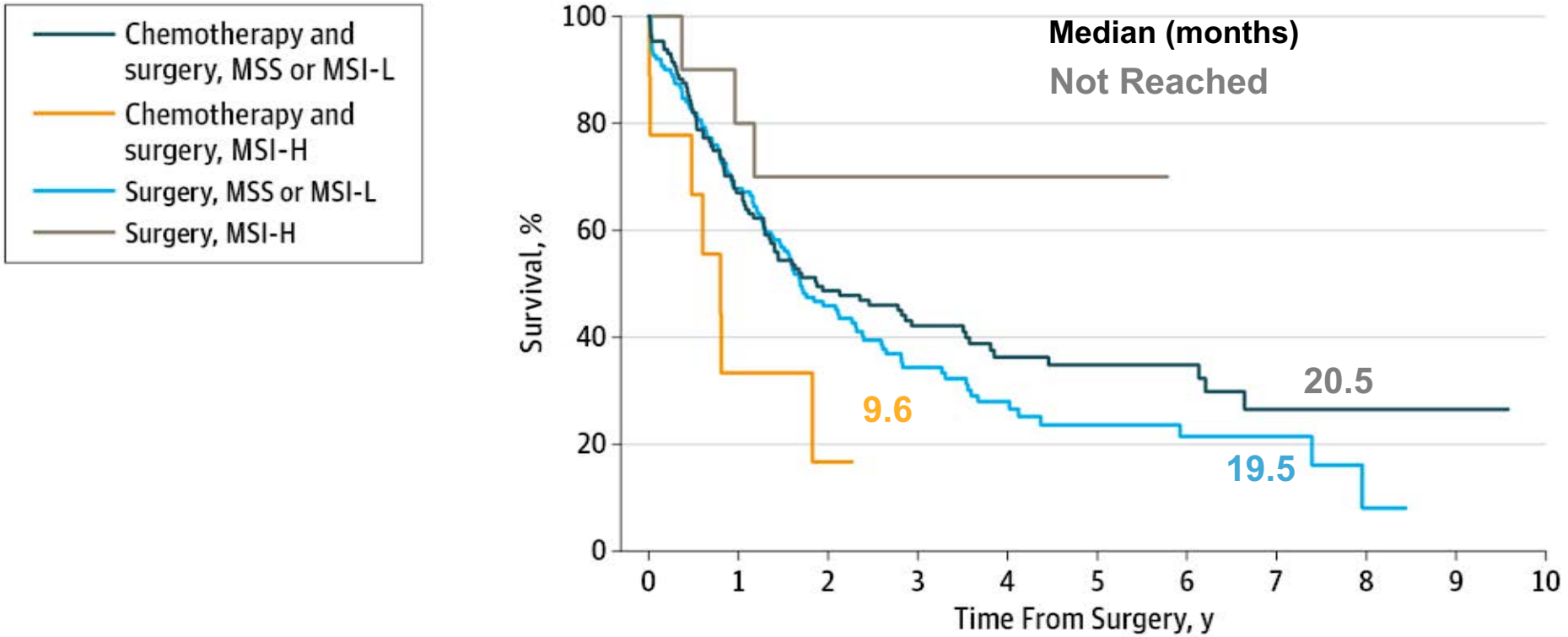
MSI-H EG TUMORS ARE CHEMOTHERAPY RESISTANT

OS in ADJUVANT MAGIC STUDY



No. at risk

Chemotherapy and surgery, MSI-negative patients	129	85	58	42	27	22	15	6	3	1
Chemotherapy and surgery, MSI-positive patients	9	3	1							
Surgery, MSI-negative patients	151	100	58	37	21	13	9	7	1	
Surgery, MSI-positive patients	10	8	6	3	1	1				

Smyth et al. *JAMA Oncology* 2017

Courtesy of Yelena Y Janjigian, MD

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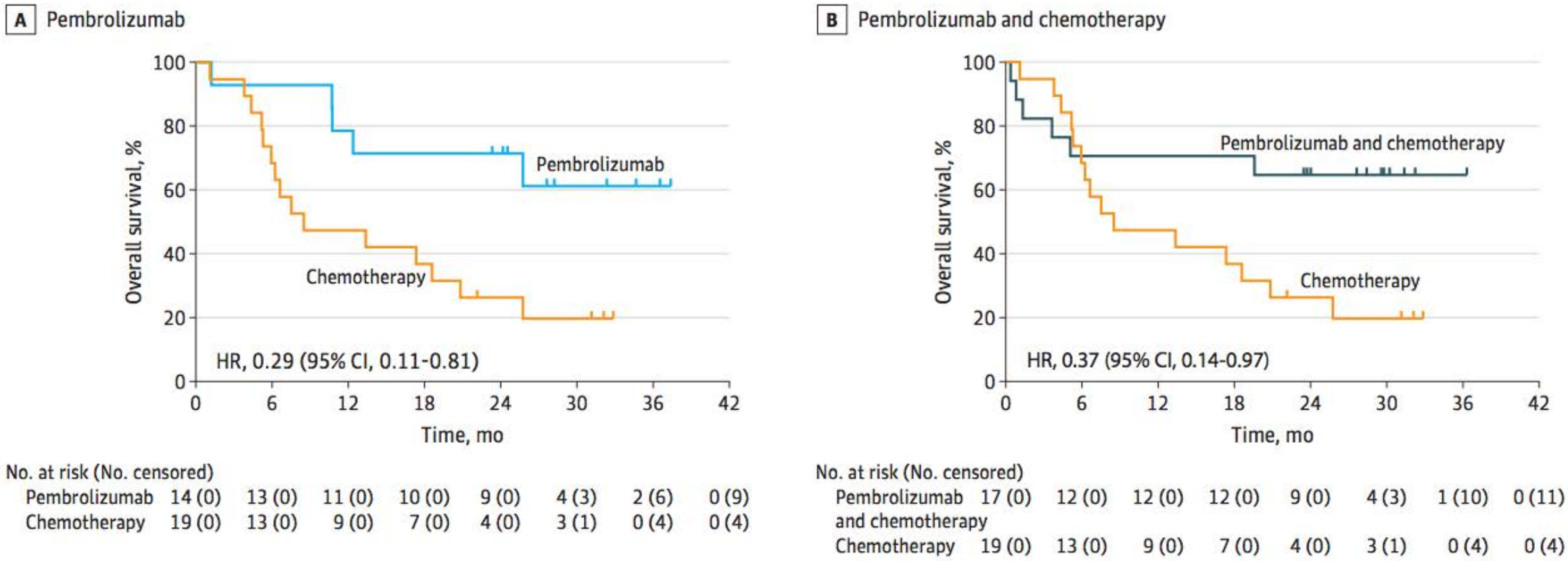
The KEYNOTE-062 Phase 3 Randomized Clinical Trial

Overall Survival in Patients With MSI-H Tumors and PD-L1 CPS of 1 or Greater



Courtesy of Yelena Y Janjigian, MD

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A Randomized Double-Blind Study of Adjuvant Pembrolizumab vs. Placebo In Patients with MSI-H Tumors with Persistent ctDNA Following Surgery NCT03832569

Patient with MSI-H TUMOR

R0 Surgical Resection

Tumor Sequencing

SOC Adjuvant Therapy

ctDNA Analysis

ctDNA+ CT -

Pembrolizumab N=24

ctDNA-

Observation

***Year 1 Objective*: To demonstrate clearance of ctDNA at 6 months.**

***Year 2, 3 and 5 Objectives*: To demonstrate DFS and OS.**

PI Janjigian

Courtesy of Yelena Y Janjigian, MD

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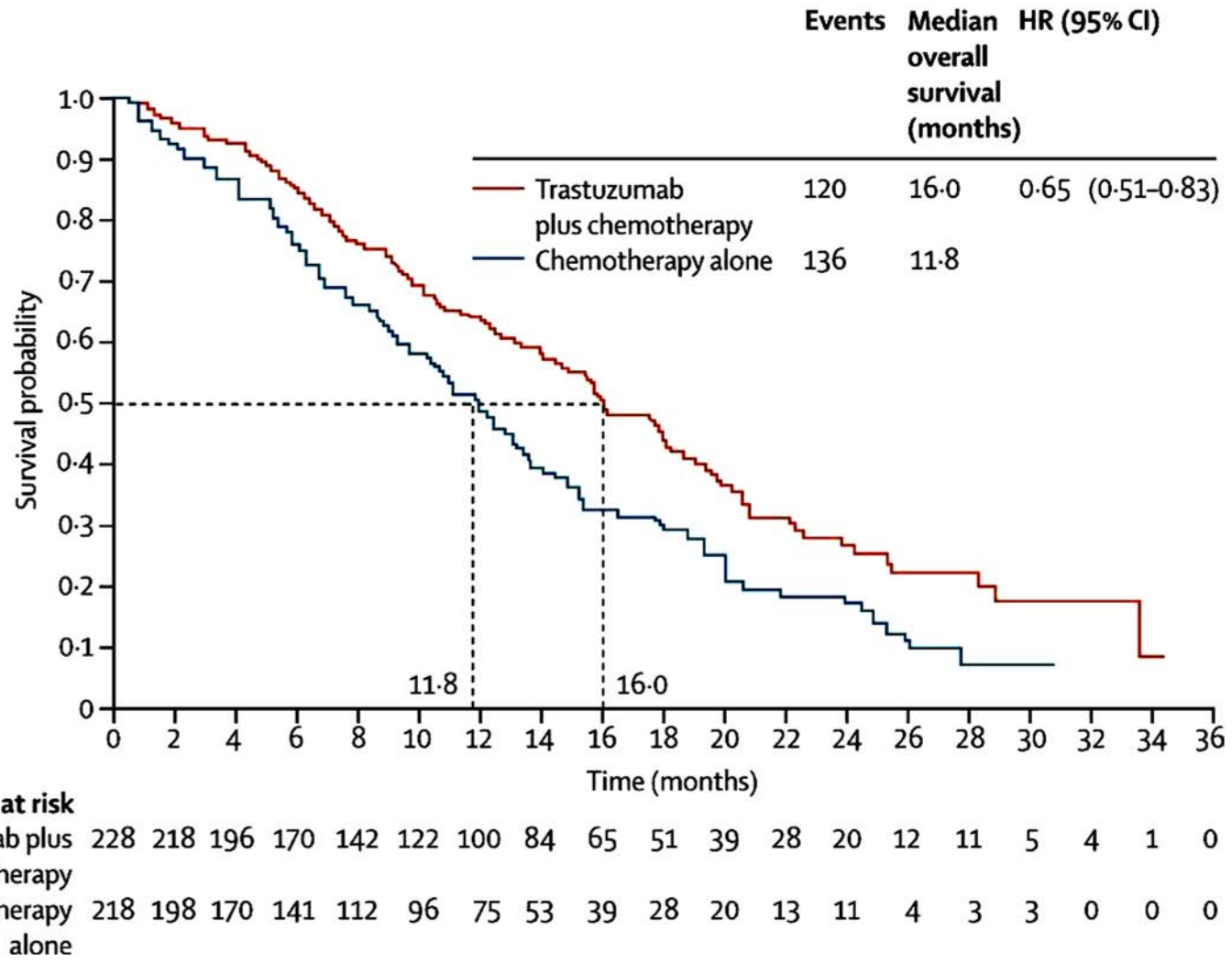
ToGA Overall Survival
IHC 2+/FISH+ or IHC 3+



Bang et al Lancet 2010

Courtesy of Yelena Y Janjigian, MD

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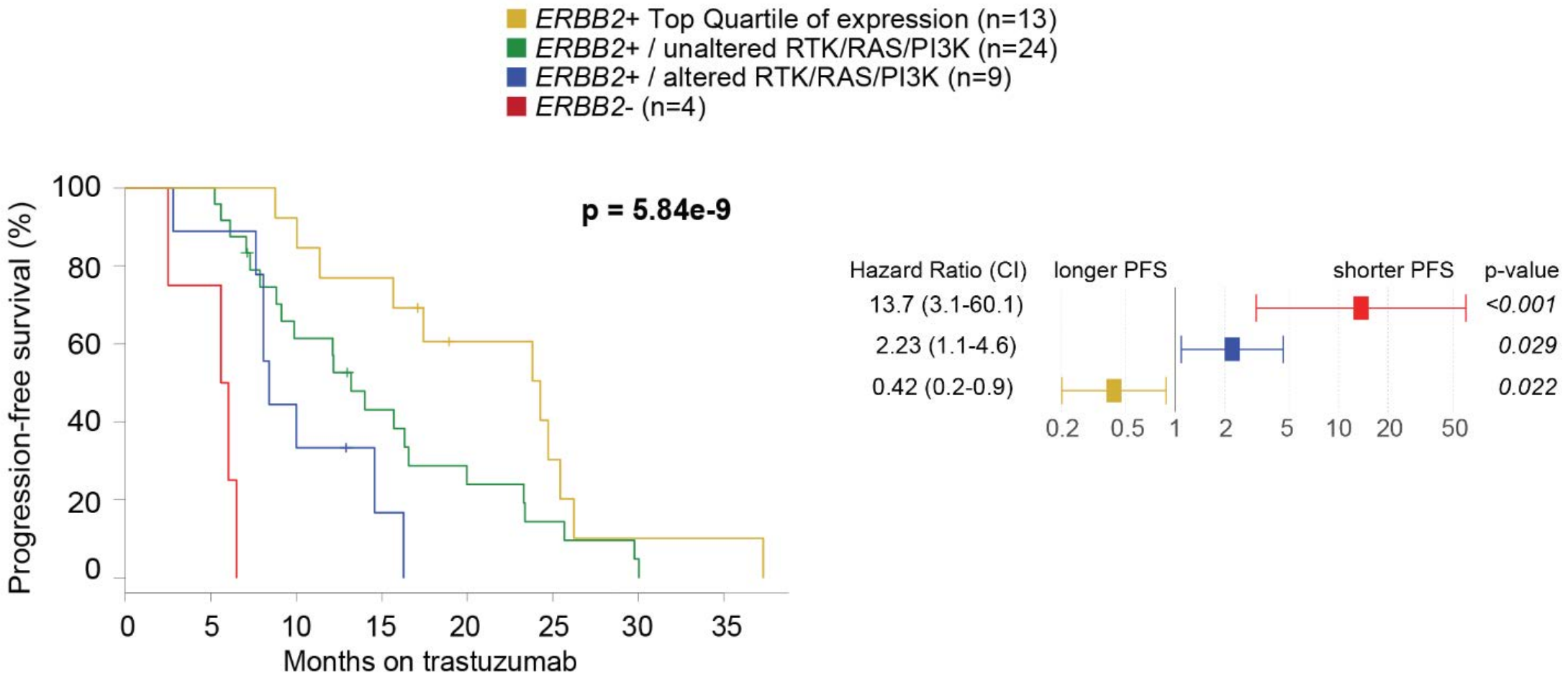
INTRINSIC TRASTUZUMAB RESISTANCE

30% of HER2+ tumors lack ERBB2 amp or had co-mutations of RTK-RAS-PIK3K pathway, and such patients had rapid progression on trastuzumab



Janjigian et al *Cancer Discovery* 2017

Courtesy of Yelena Y Janjigian, MD

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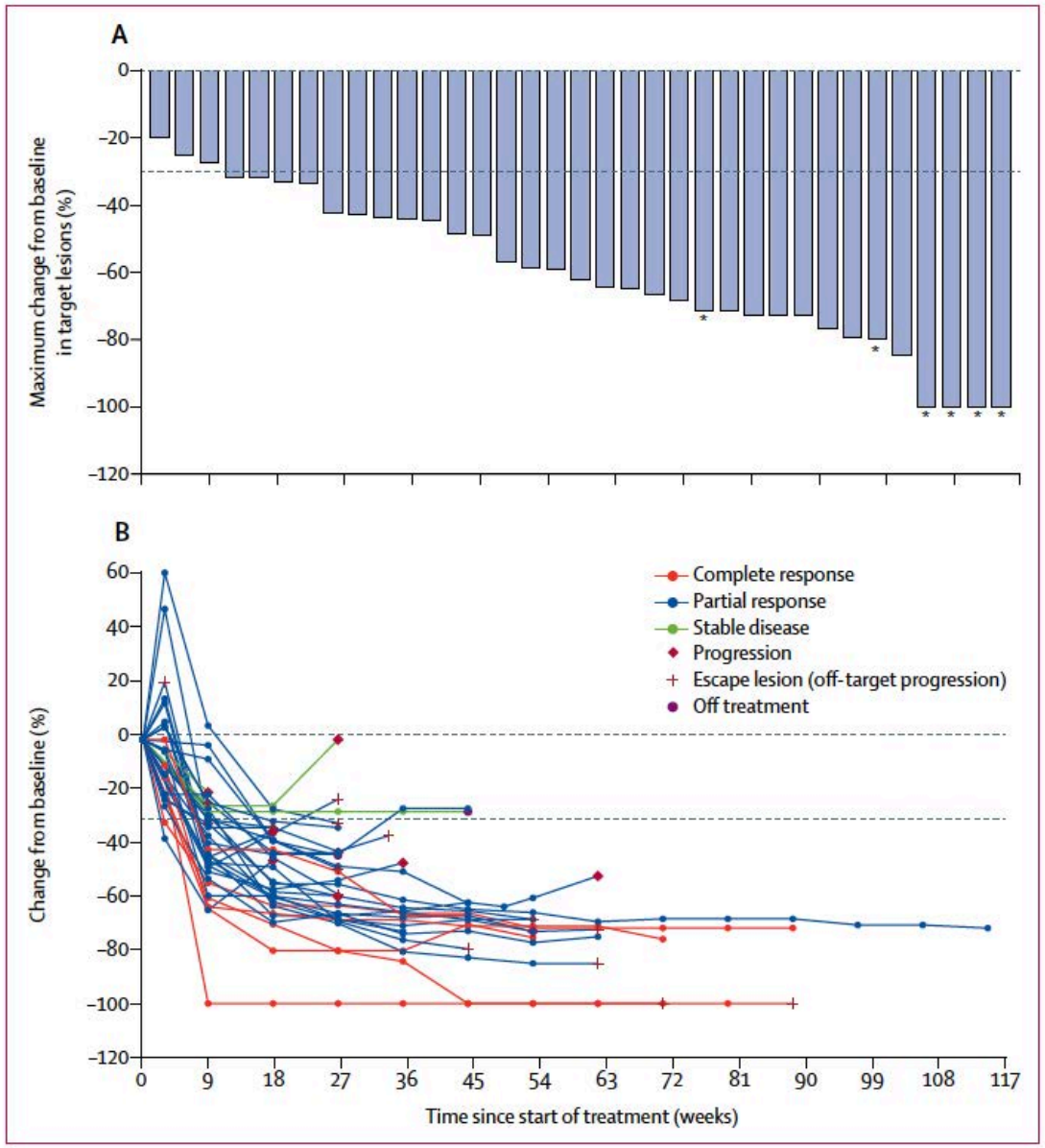
First Line Capecitabine/Oxaliplatin/Pembrolizumab/Trastuzumab



Best Response (n=37)	Patients, n (%)
ORR, n (%)	32 (91%) 95% CI (78%, 97%)
CR PR SD PD	6 (17) 26 (74) 3 (9) 0
Disease Control Rate	100%

Janjigian et al Lancet Oncology 2020

Courtesy of Yelena Y Janjigian, MD

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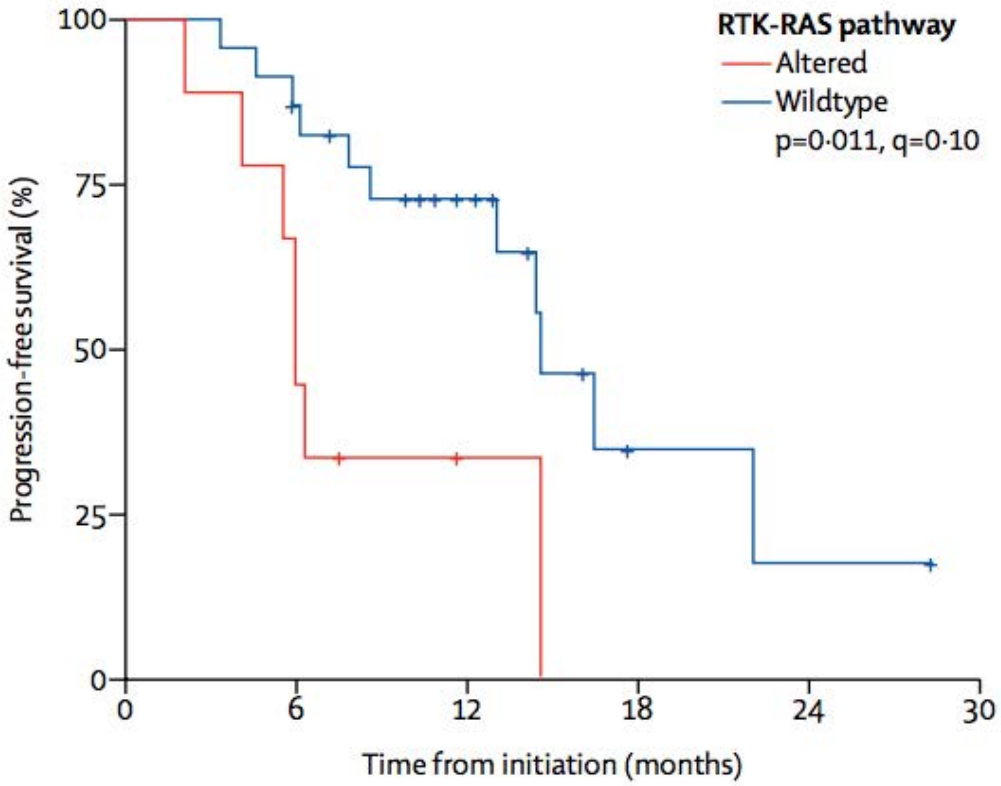
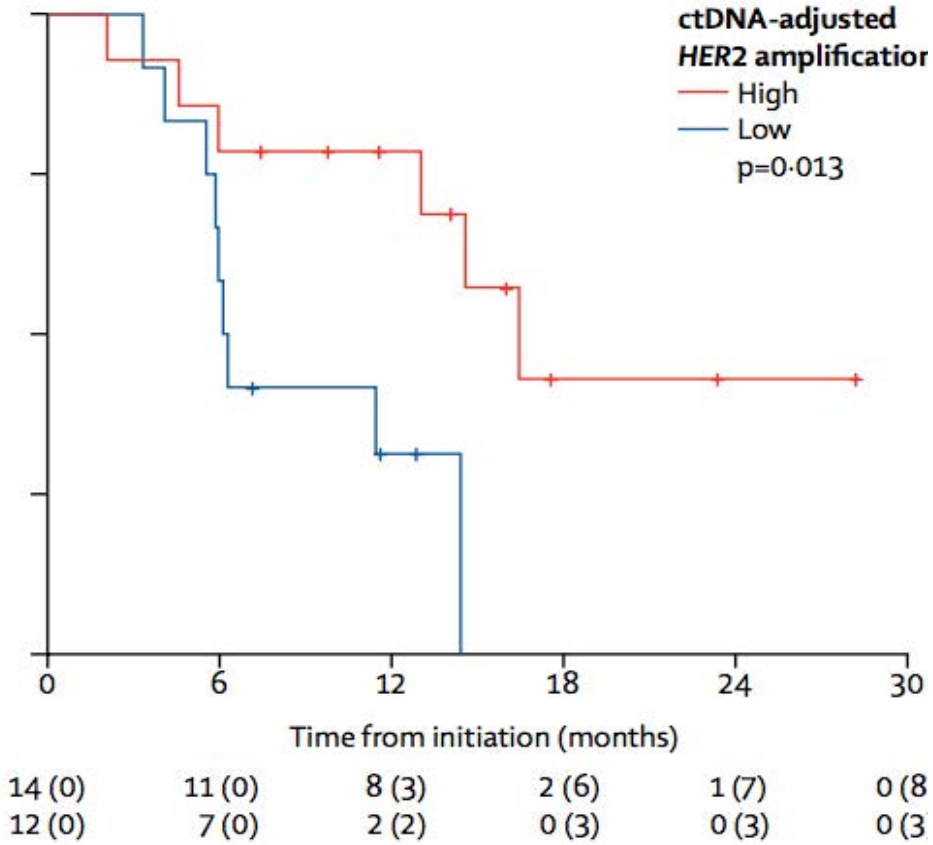
First line Capecitabine/Oxaliplatin/Pembrolizumab/Trastuzumab
HER2 heterogeneity, RTK-RAS co-alterations contribute to outcome





Janjigian et al Lancet Oncology 2020

Courtesy of Yelena Y Janjigian, MD

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Summary

- 5FU/Oxaliplatin + Nivolumab is likely to replace SOC
- Adjuvant nivolumab DFS benefit irrespective of PD-L1 and histology
- Order HER2, MSI and PD-L1 on all patients
- NGS approved in stage III/IV patients
- Lots of research potential for tumor matched ctDNA analysis

Courtesy of Yelena Y Janjigian, MD

Twitter: @yjanjigianMD

Thank you for your attention

Courtesy of Yelena Y Janjigian, MD

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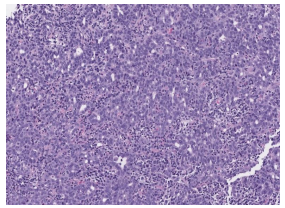
Case 1: 53-year-old woman with Stage IV gastric adenocarcinoma

GERD, PPI

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

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

Months: - 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	*S1061N*		Missense

Showing 1-7 of 7 Mutations

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

Courtesy of Yelena Y Janjigian, MD

Case 1: Patient comorbidities and additional history

- **PMH**
  - Type 1 diabetes
  - Hypothyroidism
  - Psoriasis
- **Social Hx**
  - Never smoker
  - 2 children
- **Family Hx** (Irish descent)
  - Mother – ovarian cancer age 65
  - Paternal grandfather – colon cancer

- **Home medications (at dx)**
  - Ranitidine, lansoprazole
  - Metformin, insulin glulisine
  - Pancreatin oral tablet
  - Synthroid
  - Lisinopril
  - Atorvastatin

Courtesy of Yelena Y Janjigian, MD

Case 1: 53-year-old woman with Stage IV gastric adenocarcinoma

GERD, PPI

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

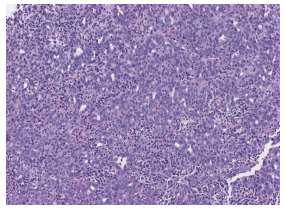
EGD: ulcer
CT CAP: 2.5cm lesion lesser curvature, peritoneal carcinomatosis

FOLFOX + nivolumab x 11 cycles

5FU/Nivolumab maintenance

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

Months: - 4, - 2, 0, 5, 9, 22



Infiltrating adenocarcinoma
moderately to poorly differentiated

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

Courtesy of Yelena Y Janjigian, MD

Case 2: 60 y/o woman with Stage IV gastric adenocarcinoma

- Epigastric discomfort, early satiety and back pain, 18 lb weight loss
- EGD: a large fungating mass in the proximal body
- Pathology shows moderately to poorly differentiated adenocarcinoma, HER2 **Negative**, PD-L1+
- **PD-L1** expression (clone E1L3N): **Combined Positive Score (CPS) 7 (of 100)**
- Mismatch repair proteins: **MSH2 absent**, MLH1, MSH6, PMS2 present

Courtesy of Yelena Y Janjigian, MD

Case 2

Past Medical History:

- HLD, Hypothyroidism, Lynch syndrome.

Social History:

- Single, no children
- Originally from Italy

Family History:

- Mother died at 85 of a malignant brain tumor
- Father died at 93 of natural causes
- 2 sisters alive and well
- Maternal cousin died of stomach cancer at 48
- Brother with Lynch syndrome and colorectal cancer (dx in 2013, surgery in 2014), currently reportedly NE

Courtesy of Yelena Y Janjigian, MD

Case 2: Tumor and Liquid biopsy ctDNA profile
MSI-H TUMOR & HNPCC

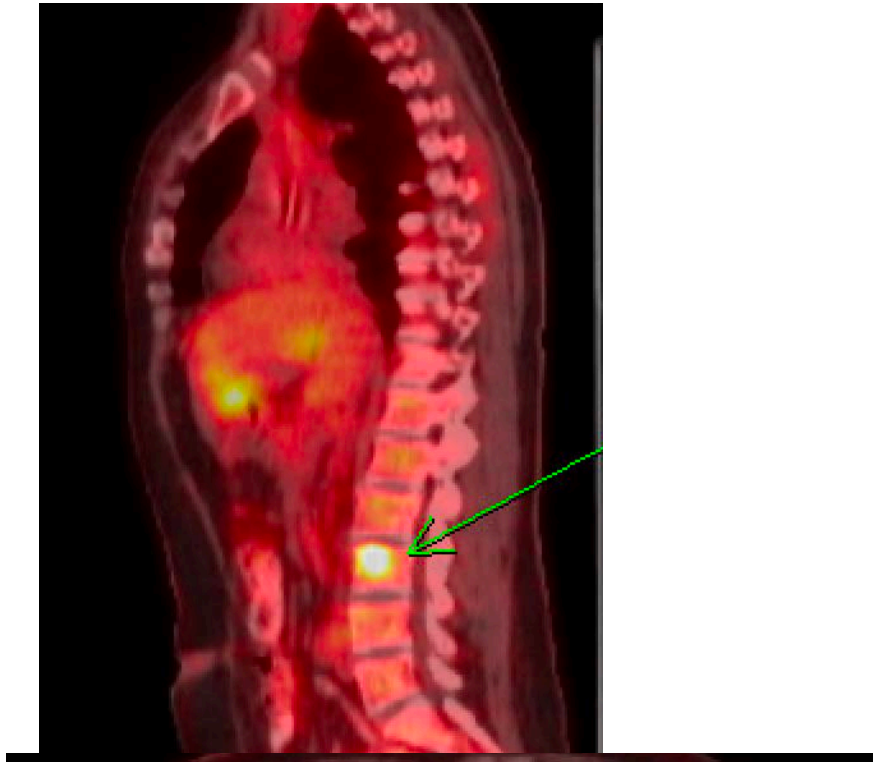
2	MLH1	*K196Nfs*6*		FS del	<1%
1	MSH2	*MSH2-intragenic loss* Germline		Fusion	
2 3	MSH2	*L559**		FS del	1%

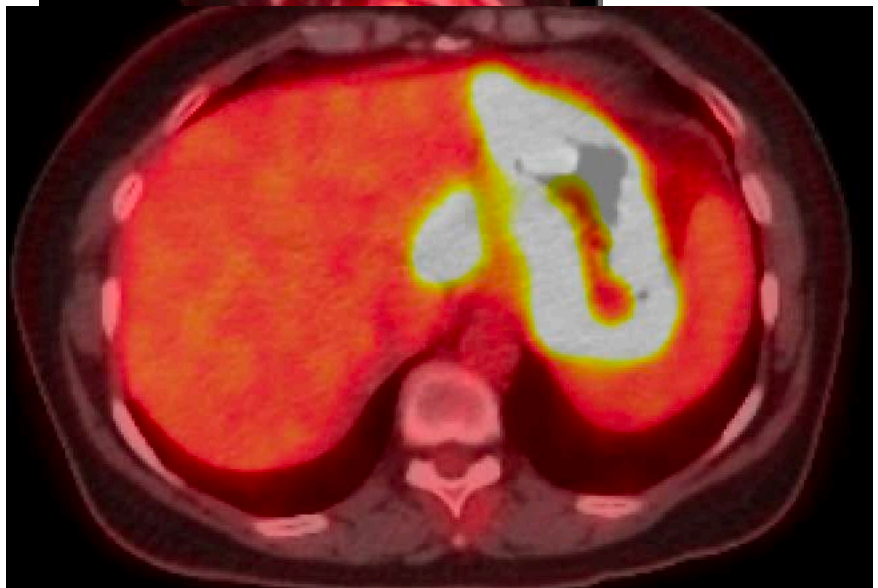
Sample	Baseline	Pembro x 2 cycles
GEJ	107 mutations	
ctDNA	35 mutations	17 mutations

Courtesy of Yelena Y Janjigian, MD

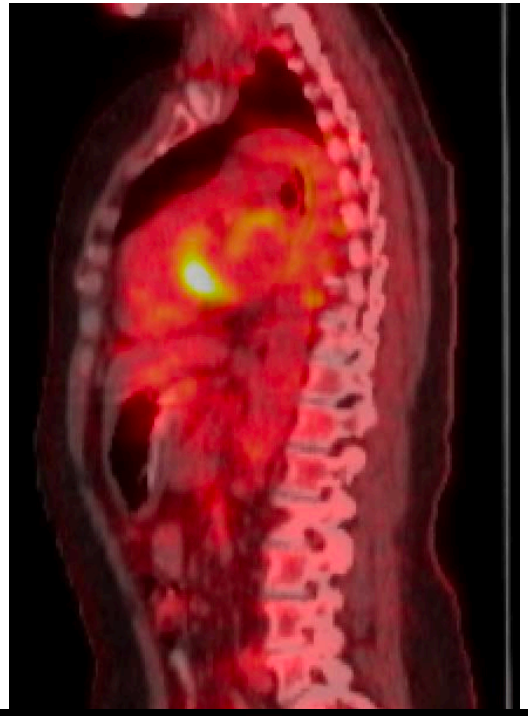
Case 2

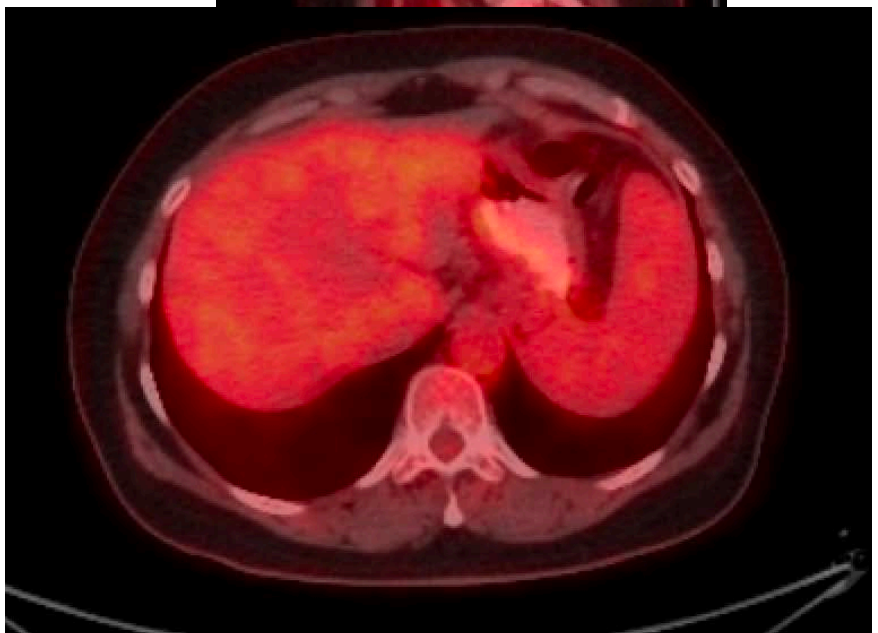
Baseline





After 8 months of pembrolizumab





EGD: - Congested, erythematous, eroded mucosa;
All biopsies: benign

Courtesy of
Yelena Y Janjigian, MD