Immunoterapia: novità, sviluppi e problematiche

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Agenda

- Current evidence supporting immunotherapy development in GC

- Hottest news in immunotherapy for GC

- How to optimally select candidates for ICIs in GC

- Main ongoing trials with ICIs in GC

- Conclusions

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- **Current evidence supporting immunotherapy development in GC**

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Phase 3 studies with ICIs in pretreated GC

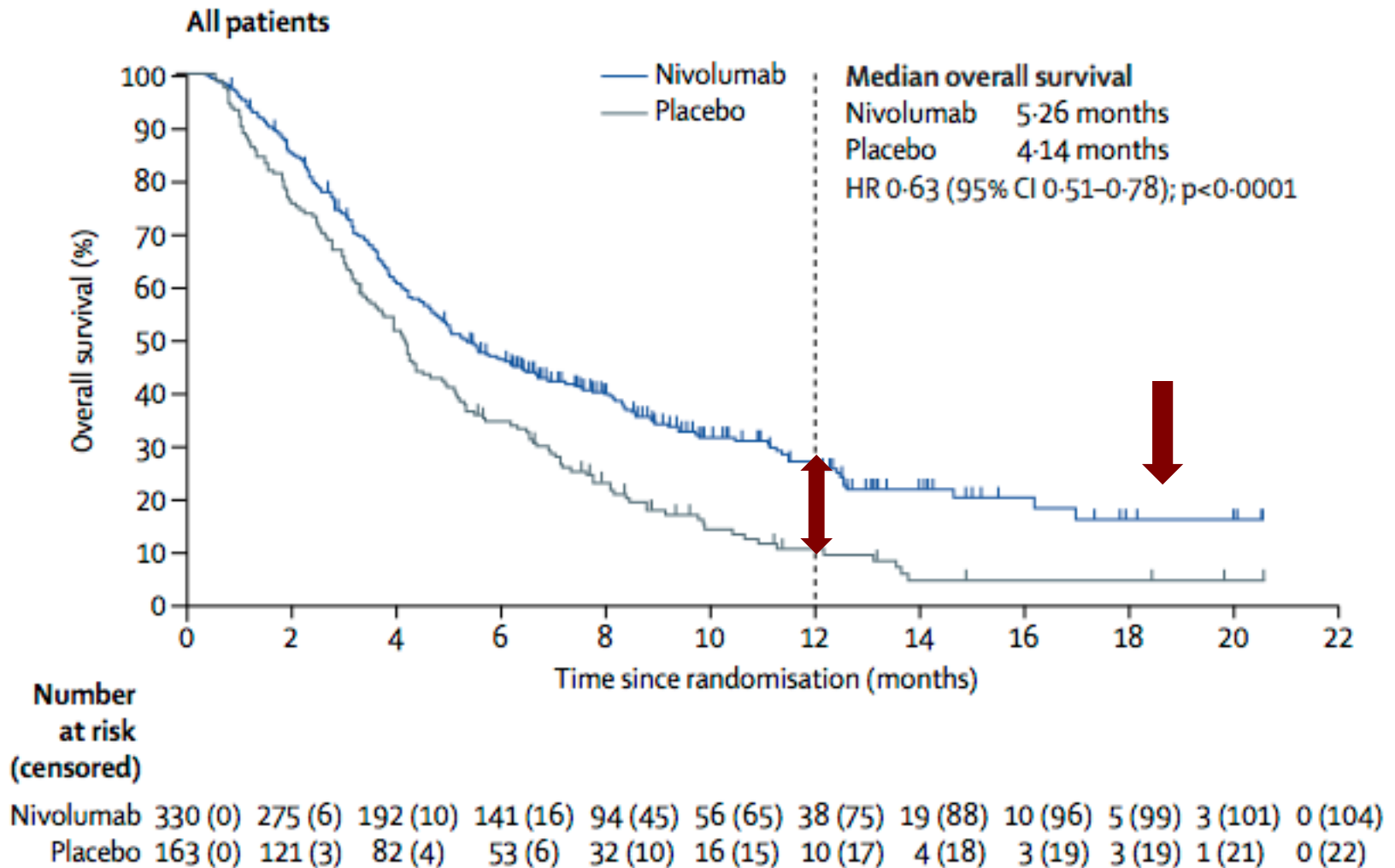|	ATTRACTION-2[1] n=330 *vs.* 163	KEYNOTE-061[2] n=296 *vs.* 296	JAVELIN Gastric 300[3] n=185 *vs.* 186
Setting	≥3L unselected	2L CPS≥1 (n=395)	3L unselected
Treatment arms	Nivolumab *vs.* Placebo	Pembrolizumab *vs.* Paclitaxel	Avelumab *vs.* CT (inv's choice)
Response rate	11% *vs.* 0%	15.8% *vs.* 13.6%	2.2% *vs.* 4.3%
Median PFS, mos	1.61 *vs.* 1.45	1.5 *vs.* 4.1	1.4 *vs.* 2.7
Median OS, mos	5.26 *vs.* 4.14	9.1 *vs.* 8.3	4.6 *vs.* 5.0
HR (95%CI) **P-value**	0.63 (0.51-0.78) p<0.0001	0.82 (0.66-1.03) p=0.0421*	1.1 (0.9-1.4) p=0.81

* significance threshold for OS set at p=0.0135 (one-sided)

[1]Kang YK et al. Lancet 2017
[2]Shitara K et al. Lancet 2018
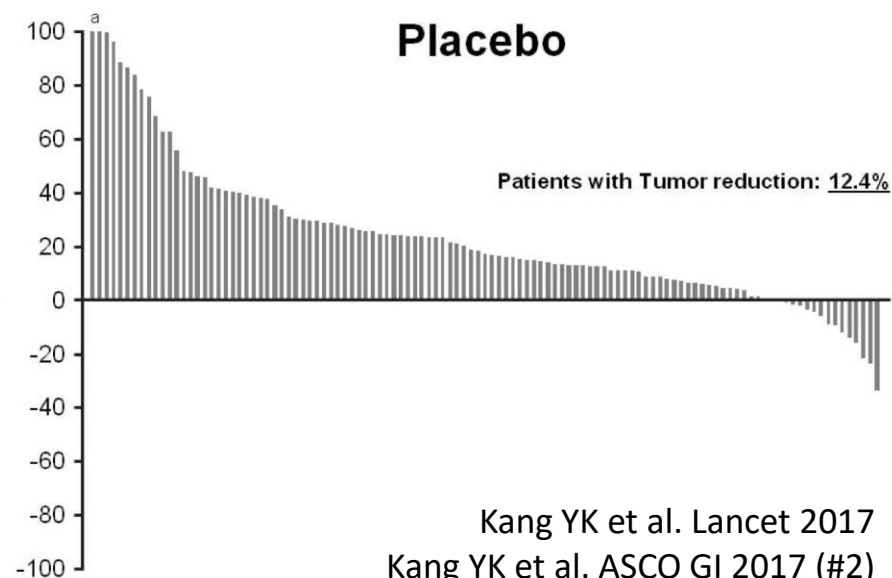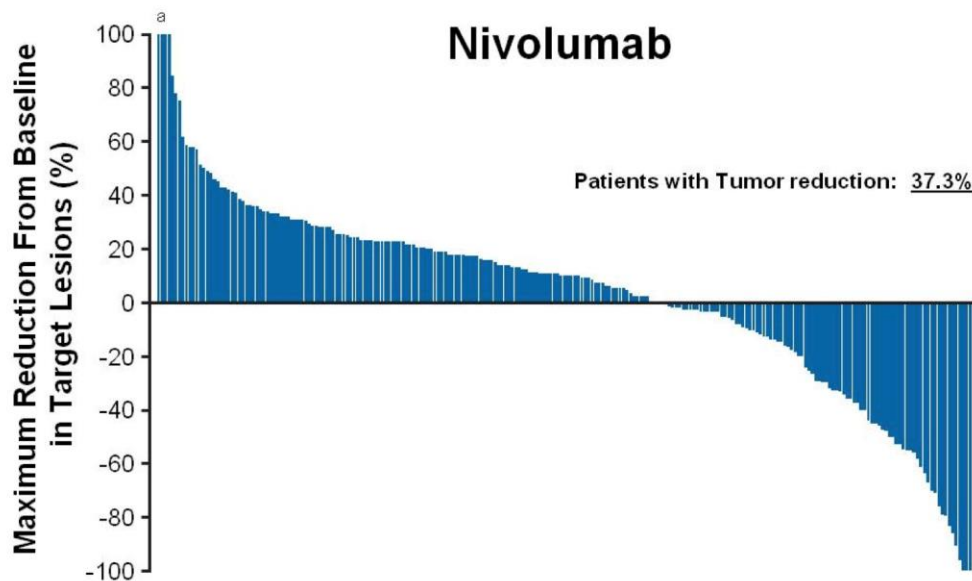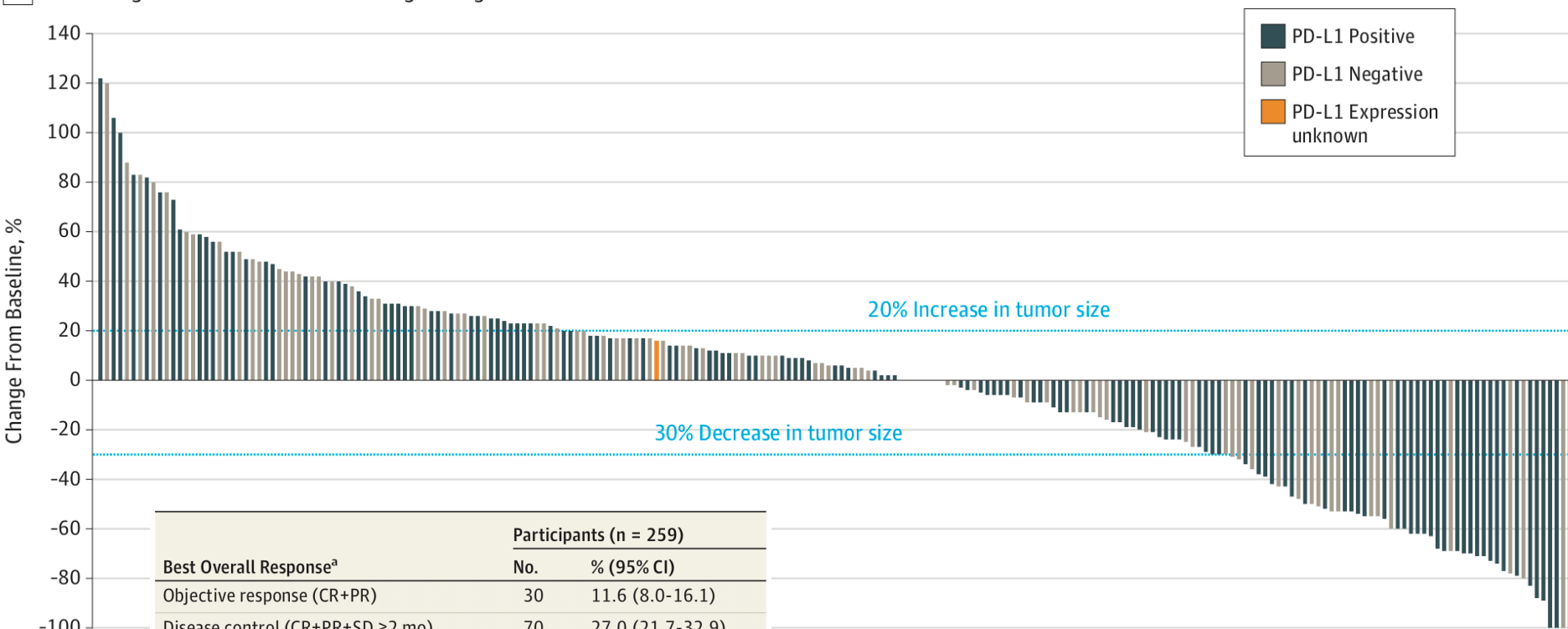[3]Bang YJ et al. Ann Oncol 2018

ATTRACTION-2: OS

All patients

Median overall survival
Nivolumab 5·26 months
Placebo 4·14 months
HR 0·63 (95% CI 0·51–0·78); p<0·0001

Number at risk (censored)											
Nivolumab	330 (0)	275 (6)	192 (10)	141 (16)	94 (45)	56 (65)	38 (75)	19 (88)	10 (96)	5 (99)	3 (101)	0 (104)
Placebo	163 (0)	121 (3)	82 (4)	53 (6)	32 (10)	16 (15)	10 (17)	4 (18)	3 (19)	3 (19)	1 (21)	0 (22)

Kang YK et al. Lancet 2017

ATTRACTION-2: RR

RECIST Response and Disease Control

	Nivolumab 3 mg/kg (n = 268)	Placebo (n = 131)
ORR, n (%)	30 (11.2)	0
[95% CI]	[7.7–15.6]	[0–2.8]
P value	< 0.0001	—
DCR, n (%)	108 (40.3)	33 (25.2)
[95% CI]	[34.4–46.4]	[18.0–33.5]
P value	0.0036	—
Median TTR (range), months	1.61 (1.4–7.0)	—
Median DOR, months	9.53	—
[95% CI]	[6.14–9.82]	

Nivolumab — Patients with Tumor reduction: 37.3%

Placebo — Patients with Tumor reduction: 12.4%

Kang YK et al. Lancet 2017
Kang YK et al. ASCO GI 2017 (#2)

KEYNOTE-059: RR

A Best change from baseline in sum of longest target lesion diameters

Legend:
- PD-L1 Positive
- PD-L1 Negative
- PD-L1 Expression unknown

20% Increase in tumor size

30% Decrease in tumor size

Best Overall Response[a]	Participants (n = 259)	
	No.	% (95% CI)
Objective response (CR+PR)	30	11.6 (8.0-16.1)
Disease control (CR+PR+SD ≥2 mo)	70	27.0 (21.7-32.9)
CR	6	2.3 (0.9-5.0)
PR	24	9.3 (6.0-13.5)
SD	42	16.2 (11.9-21.3)
Progressive disease	145	56.0 (49.7-62.1)
Nonevaluable	7	2.7 (1.1-5.5)
No assessment[b]	35	13.5 (9.6-18.3)
Duration of response, median (range), mo		8.4 (1.6+ to 17.3+)[c]

Fuchs CS et al. JAMA Oncol 2018

KEYNOTE-059: RR

C Longitudinal change in sum of longest target lesion diameters

Fuchs CS et al. JAMA Oncol 2018

KEYNOTE-061: OS

A

Median OS
Pembrolizumab   9.1 months
Paclitaxel   8.3 months

HR 0·82 (95% CI 0·66–1·03); one-sided p=0·0421
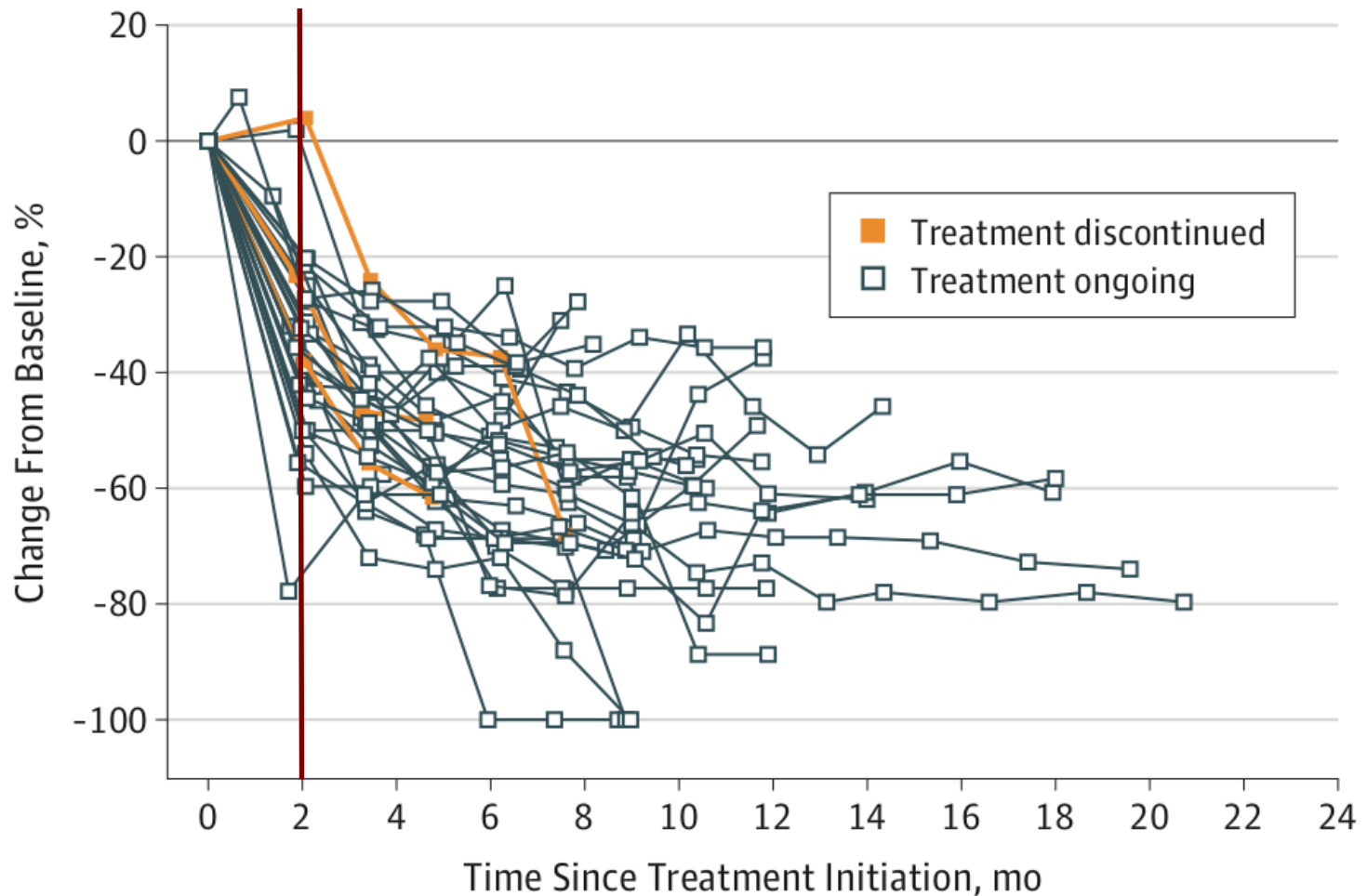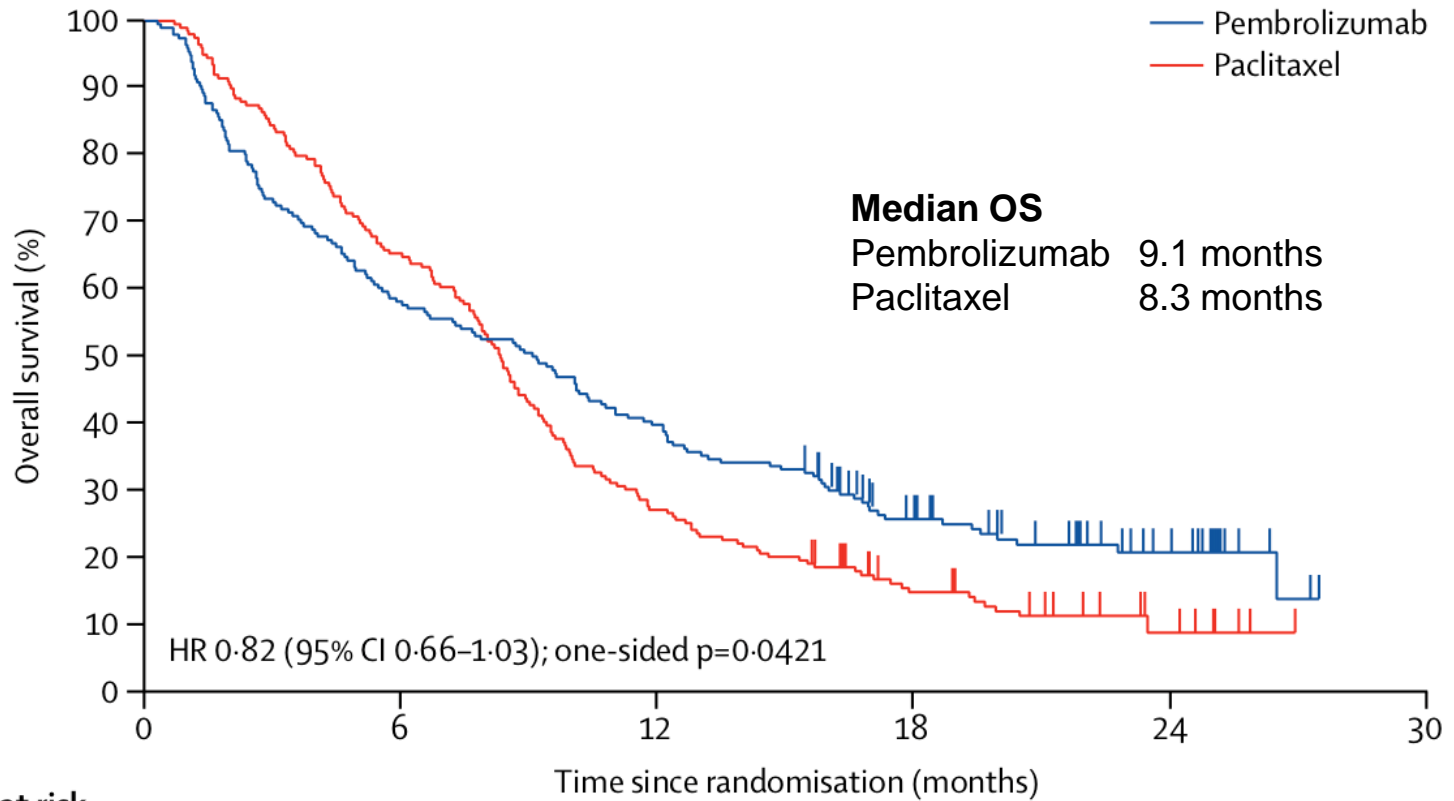
Number at risk (censored)						
Pembrolizumab	196 (0)	114 (0)	78 (0)	39 (12)	14 (31)	0 (45)
Paclitaxel	199 (0)	130 (0)	54 (0)	23 (8)	7 (17)	0 (24)

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KEYNOTE-062

KEYNOTE-062 Study Design (NCT02494583)

Key Eligibility Criteria
- Locally advanced, unresectable or metastatic gastric or gastroesophageal adenocarcinoma
- HER2/neu negative, PD-L1-positive disease (CPS ≥1)
- ECOG PS 0 or 1

Stratification Factors
- Region[a]
- Locally advanced or metastatic disease
- 5-FU or Capecitabine

N = 763

R (1:1:1)

N = 256 → Pembrolizumab 200 mg Q3W for up to 35 cycles[b]

N = 257 → Pembrolizumab 200 mg Q3W (to 35 cycles) + Chemotherapy[c]

N = 250 → Placebo + Chemotherapy

Until unacceptable toxicity, disease progression, or patient/physician withdrawal decision

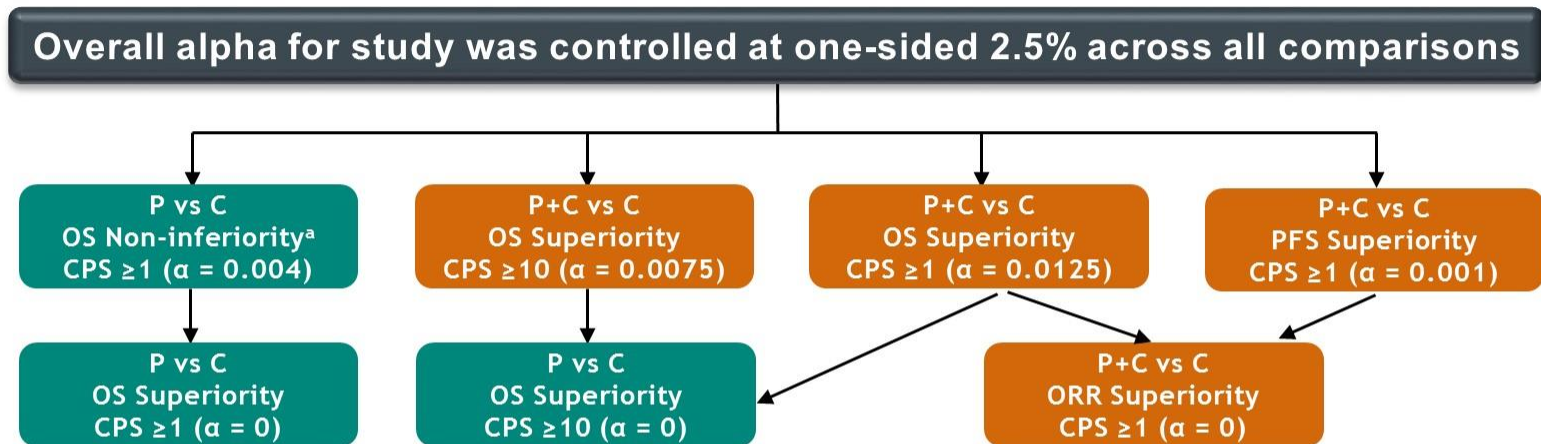**Primary endpoints: OS and PFS**
Secondary endpoints: ORR, Safety

[a]EU/North America/Australia, Asia (South Korea, Hong Kong, Taiwan, Japan), Rest of World (including South America).
[b]Administration of pembrolizumab monotherapy was not blinded.
[c]Chemotherapy: Cisplatin 80 mg/m^2 Q3W + 5-FU 800 mg/m^2/d for 5 days Q3W or capecitabine BID d1-14 Q3W (Cisplatin may be capped at 6 cycles as per country guidelines).

Tabernero J et al. ASCO 2019 (#LBA4007)

KEYNOTE-062: Statistics

Statistical Considerations

Overall alpha for study was controlled at one-sided 2.5% across all comparisons

| P vs C OS Non-inferiority[a] CPS ≥1 (α = 0.004) | P+C vs C OS Superiority CPS ≥10 (α = 0.0075) | P+C vs C OS Superiority CPS ≥1 (α = 0.0125) | P+C vs C PFS Superiority CPS ≥1 (α = 0.001) |

| P vs C OS Superiority CPS ≥1 (α = 0) | P vs C OS Superiority CPS ≥10 (α = 0) | P+C vs C ORR Superiority CPS ≥1 (α = 0) |

- Hypotheses in top row tested first and in parallel
  - Remaining hypotheses tested only if preceding hypothesis was positive
  - Prespecified analysis plan allowed alpha passing from successful hypotheses
- Final analysis: planned to occur ≥22 months after last patient was randomized and ~415 OS events observed in P+C and C treatment groups in patients with PD-L1 CPS ≥1

[a]Alpha passed from non-inferiority to superiority test; Median follow-up, 11.3 months (range, 0.2-41.2); Data cutoff: March 26, 2019.
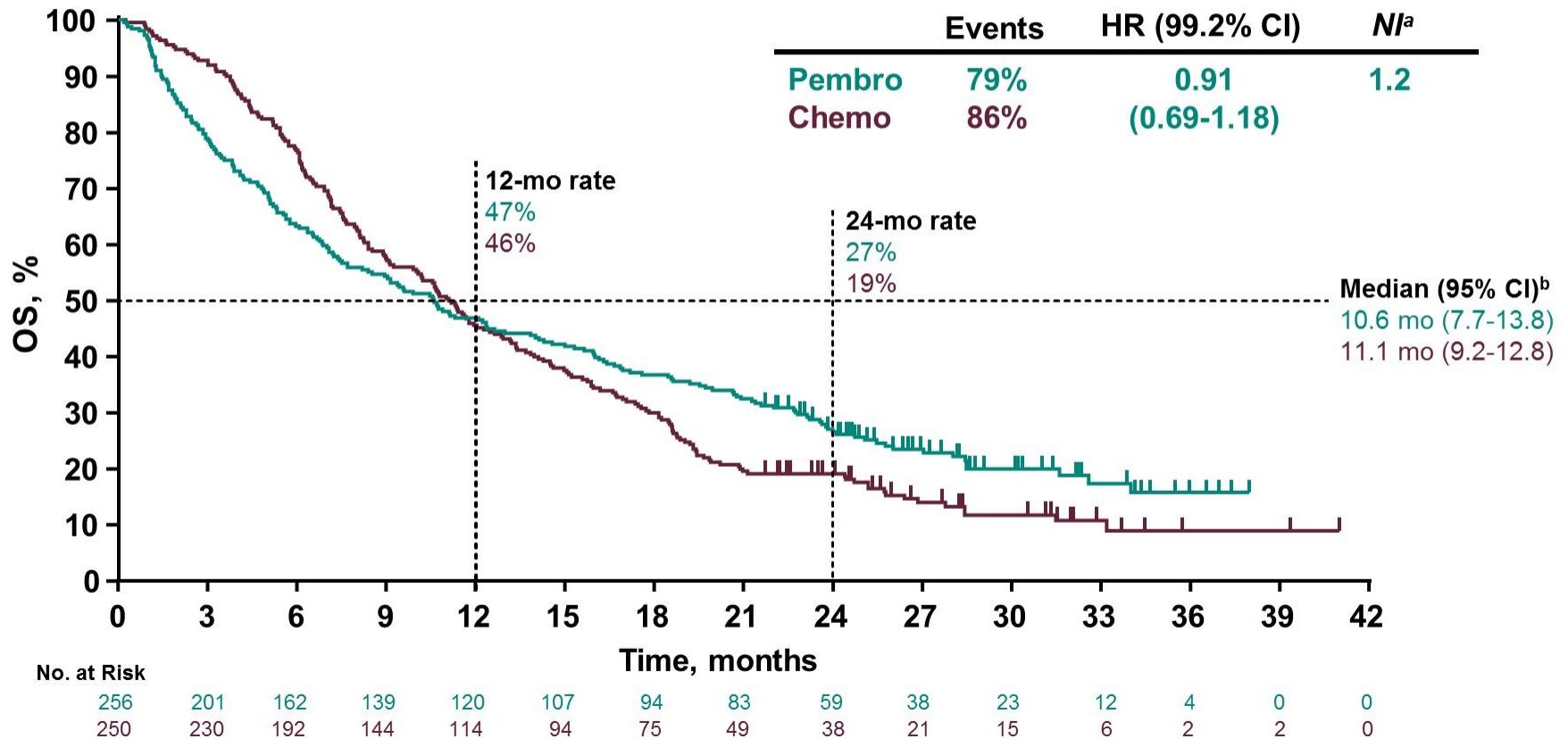
Tabernero J et al. ASCO 2019 (#LBA4007)

KEYNOTE-062: Patients

Baseline Characteristics (CPS ≥1)

Characteristic, n (%)	Pembro N = 256	Pembro + Chemo N = 257	Chemo N = 250
Age, median (range), years	61.0 (20-83)	62.0 (22-83)	62.5 (23-87)
Male	180 (70)	195 (76)	179 (72)
ECOG PS 1	125 (49)	138 (54)	135 (54)
Metastatic disease	245 (96)	243 (95)	235 (94)
CPS ≥10	92 (36)	99 (39)	90 (36)
MSI-H	14 (5)	17 (7)	19 (8)
Region			
Europe/North America/Australia	148 (58)	148 (58)	147 (59)
Asia	62 (24)	64 (25)	61 (24)
Rest of World	46 (18)	45 (18)	42 (17)
Primary tumor location			
Stomach	176 (69)	170 (66)	181 (72)
GEJ	79 (31)	85 (33)	67 (27)
Backbone therapy[a]			
5-FU	-	98 (38)	95 (38)
Capecitabine	-	159 (62)	155 (62)

[a]Per stratification; Data cutoff: March 26, 2019.

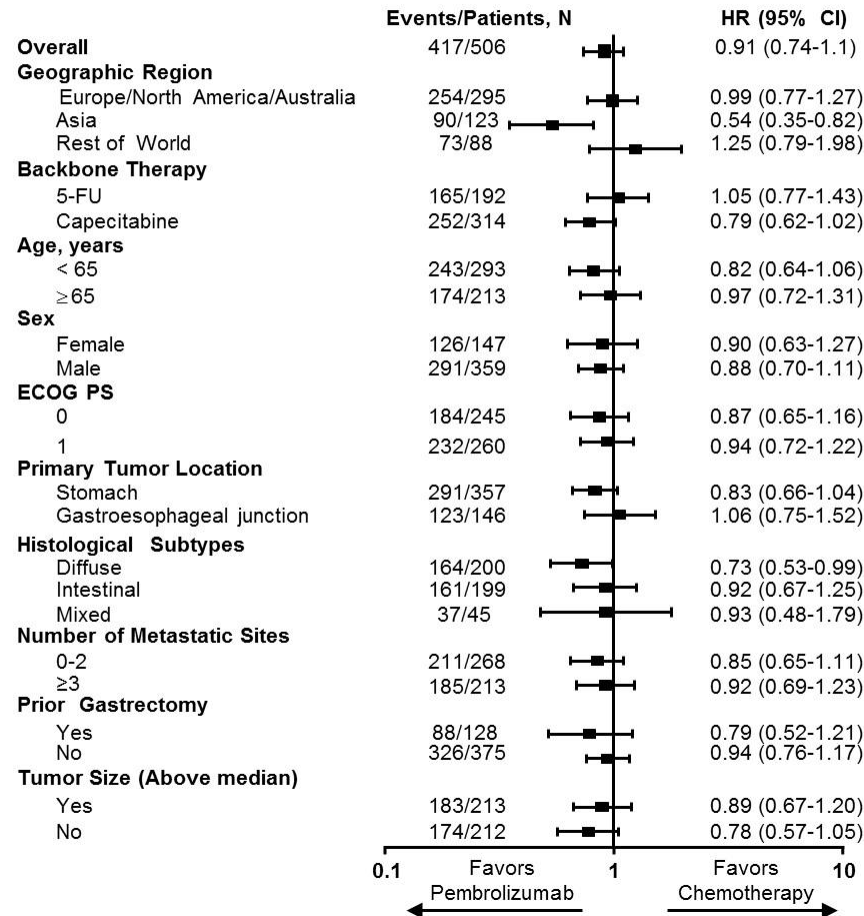# Pembrolizumab *vs.* CT: OS

Overall Survival: P vs C (CPS ≥1)

	Events	HR (99.2% CI)	*NI*[a]
Pembro	79%	0.91	1.2
Chemo	86%	(0.69-1.18)	

12-mo rate
47%
46%

24-mo rate
27%
19%

Median (95% CI)[b]
10.6 mo (7.7-13.8)
11.1 mo (9.2-12.8)

No. at Risk

| 256 | 201 | 162 | 139 | 120 | 107 | 94 | 83 | 59 | 38 | 23 | 12 | 4 | 0 | 0 |
| 250 | 230 | 192 | 144 | 114 | 94 | 75 | 49 | 38 | 21 | 15 | 6 | 2 | 2 | 0 |

[a]NI, non-inferiority margin; [b]HR (95% CI) = 0.91 (0.74-1.10), *P* = 0.162 for superiority of P vs C; Data cutoff: March 26, 2019.

Tabernero J et al. ASCO 2019 (#LBA4007)

Pembrolizumab *vs*. CT: OS (subgroups)

Overall Survival in Key Subgroups: P vs C

CPS ≥1

	Events/Patients, N		HR (95% CI)
Overall	417/506		0.91 (0.74-1.1)
Geographic Region			
Europe/North America/Australia	254/295		0.99 (0.77-1.27)
Asia	90/123		0.54 (0.35-0.82)
Rest of World	73/88		1.25 (0.79-1.98)
Backbone Therapy			
5-FU	165/192		1.05 (0.77-1.43)
Capecitabine	252/314		0.79 (0.62-1.02)
Age, years			
< 65	243/293		0.82 (0.64-1.06)
≥65	174/213		0.97 (0.72-1.31)
Sex			
Female	126/147		0.90 (0.63-1.27)
Male	291/359		0.88 (0.70-1.11)
ECOG PS			
0	184/245		0.87 (0.65-1.16)
1	232/260		0.94 (0.72-1.22)
Primary Tumor Location			
Stomach	291/357		0.83 (0.66-1.04)
Gastroesophageal junction	123/146		1.06 (0.75-1.52)
Histological Subtypes			
Diffuse	164/200		0.73 (0.53-0.99)
Intestinal	161/199		0.92 (0.67-1.25)
Mixed	37/45		0.93 (0.48-1.79)
Number of Metastatic Sites			
0-2	211/268		0.85 (0.65-1.11)
≥3	185/213		0.92 (0.69-1.23)
Prior Gastrectomy			
Yes	88/128		0.79 (0.52-1.21)
No	326/375		0.94 (0.76-1.17)
Tumor Size (Above median)			
Yes	183/213		0.89 (0.67-1.20)
No	174/212		0.78 (0.57-1.05)

0.1 — Favors Pembrolizumab — 1 — Favors Chemotherapy — 10

Data cutoff: March 26, 2019.

Tabernero J et al. ASCO 2019 (#LBA4007)

Pembrolizumab *vs*. CT: OS

Overall Survival: P vs C (CPS ≥10)

	Events	HR (95% CI)
Pembro	66%	0.69
Chemo	83%	(0.49-0.97)

12-mo rate
57%
47%

24-mo rate
39%
22%

Median (95% CI)
17.4 mo (9.1-23.1)
10.8 mo (8.5-13.8)

OS, %

Time, months

No. at Risk

| 92 | 71 | 62 | 56 | 52 | 50 | 45 | 40 | 32 | 22 | 13 | 9 | 4 | 0 | 0 |
| 90 | 82 | 70 | 53 | 42 | 33 | 28 | 20 | 16 | 8 | 7 | 3 | 0 | 0 | 0 |

Data cutoff: March 26, 2019.

Pembrolizumab *vs*. CT: DoR

Response Summary: P vs C

CPS ≥1

	ORR, %	Median DOR, mo (range)
Pembro	14.8	13.7 (1.4+ to 33.6+)
Chemo	37.2	6.8 (1.4+ to 30.4+)

No. at Risk
38 30 27 18 16 15 15 8 4 4 3 2 0 0 0
93 80 43 24 14 9 8 7 5 4 2 0 0 0 0

CPS ≥10

	ORR, %	Median DOR, mo (range)
Pembro	25.0	19.3 (1.4+ to 33.6+)
Chemo	37.8	6.8 (1.5+ to 30.4+)

No. at Risk
23 19 18 13 12 11 11 7 4 4 3 2 0 0 0
34 30 16 8 6 3 3 3 3 2 1 0 0 0 0
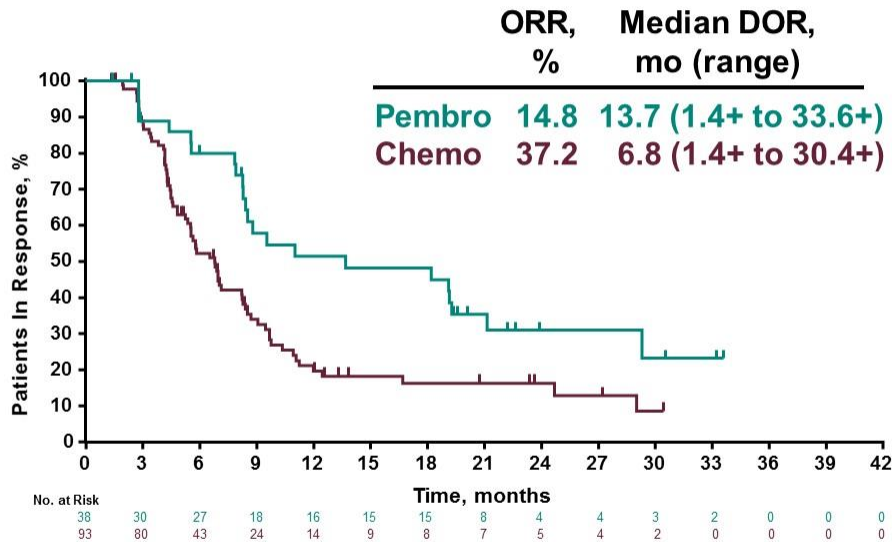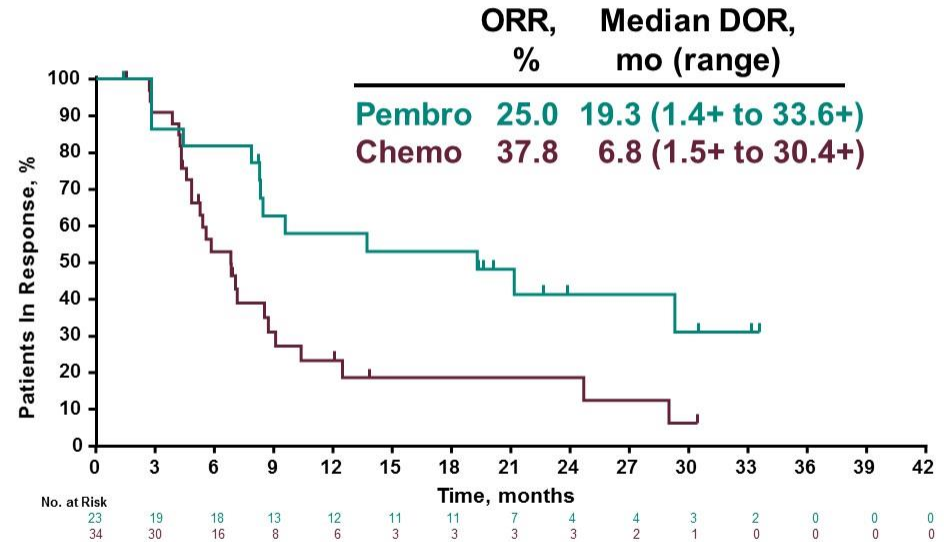
Response assessed per RECIST v1.1 by blinded independent central review. Data cutoff: March 26, 2019.

Tabernero J et al. ASCO 2019 (#LBA4007)

CT *vs.* CT + Pembrolizumab: OS

Overall Survival: P+C vs C (CPS ≥1)

	Events	HR (95% CI)	P
Pembro + Chemo	80%	0.85	0.046
Chemo	86%	(0.70-1.03)	

12-mo rate
53%
46%

24-mo rate
24%
19 %

Median (95% CI)
12.5 mo (10.8-13.9)
11.1 mo (9.2-12.8)

No. at Risk

| 257 | 229 | 194 | 165 | 136 | 105 | 88 | 74 | 52 | 33 | 17 | 8 | 5 | 1 | 0 |
| 250 | 230 | 192 | 144 | 114 | 94 | 75 | 49 | 38 | 21 | 15 | 6 | 2 | 2 | 0 |

Data cutoff: March 26, 2019.

Tabernero J et al. ASCO 2019 (#LBA4007)

CT *vs.* CT + Pembrolizumab: OS

Overall Survival: P+C vs C (CPS ≥10)

	Events	HR (95% CI)	P
Pembro + Chemo	76%	0.85	0.158
Chemo	83%	(0.62-1.17)	

12-mo rate
51%
47%

24-mo rate
28%
22%

Median (95% CI)
12.3 mo (9.5-14.8)
10.8 mo (8.5-13.8)

No. at Risk

| 99 | 89 | 74 | 64 | 50 | 40 | 35 | 30 | 21 | 11 | 7 | 3 | 3 | 0 | 0 |
| 90 | 82 | 70 | 53 | 42 | 33 | 28 | 20 | 16 | 8 | 7 | 3 | 0 | 0 | 0 |
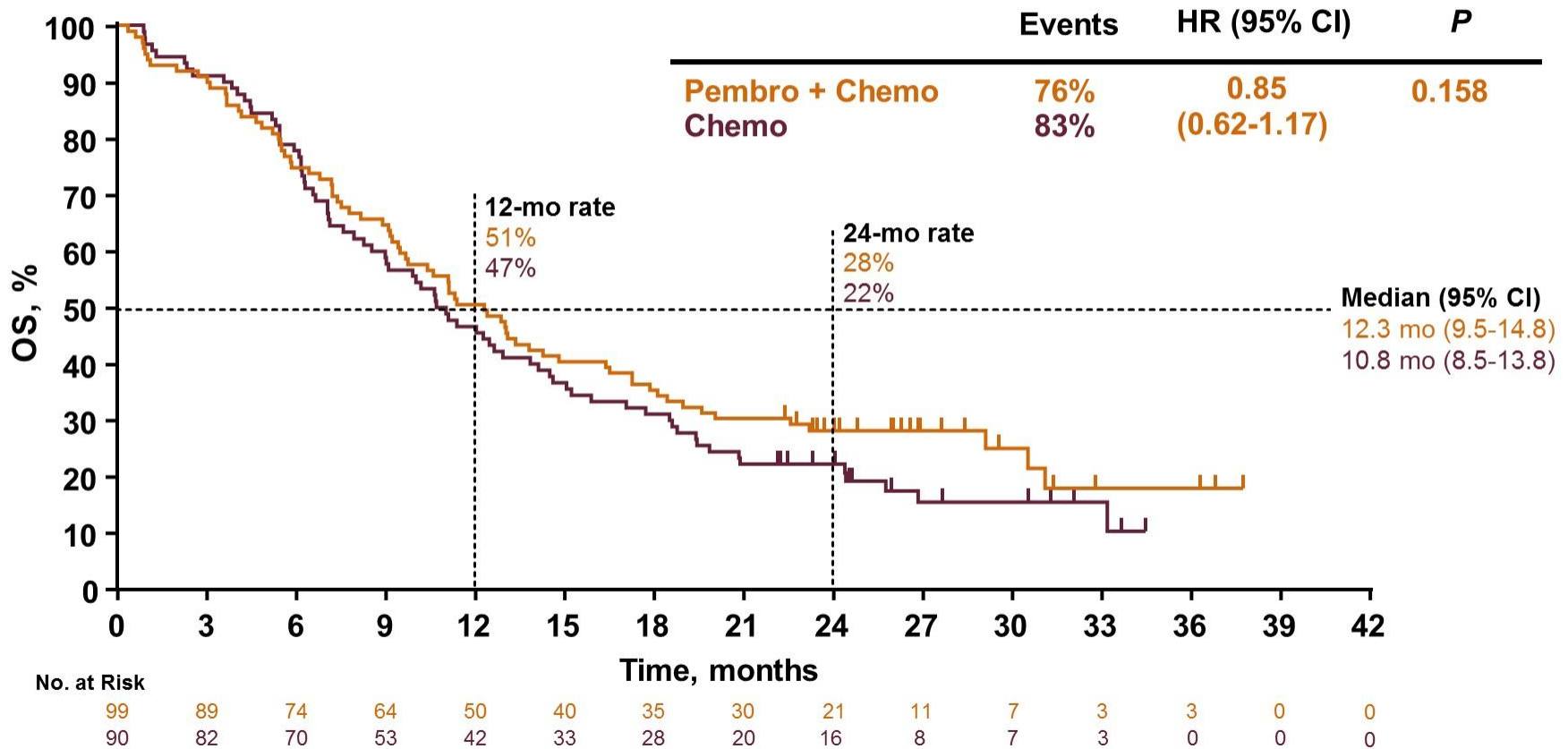
Data cutoff: March 26, 2019.

CT *vs*. CT + Pembrolizumab: DoR

Response Summary: P+C vs C

CPS ≥1

	ORR, %	Median DOR, mo (range)
Pembro + Chemo	48.6	6.8 (1.4+ to 34.7+)
Chemo	37.2	6.8 (1.4+ to 30.4+)

CPS ≥10

	ORR, %	Median DOR, mo (range)
Pembro + Chemo	52.5	8.3 (1.6+ to 34.7+)
Chemo	37.8	6.8 (1.5+ to 30.4+)

No. at Risk

125	107	61	43	35	26	24	18	10	8	4	2	0	0	0
93	80	43	24	14	9	8	7	5	4	2	0	0	0	0

No. at Risk

52	47	26	22	19	16	14	12	5	4	3	2	0	0	0
34	30	16	8	6	3	3	3	3	2	1	0	0	0	0
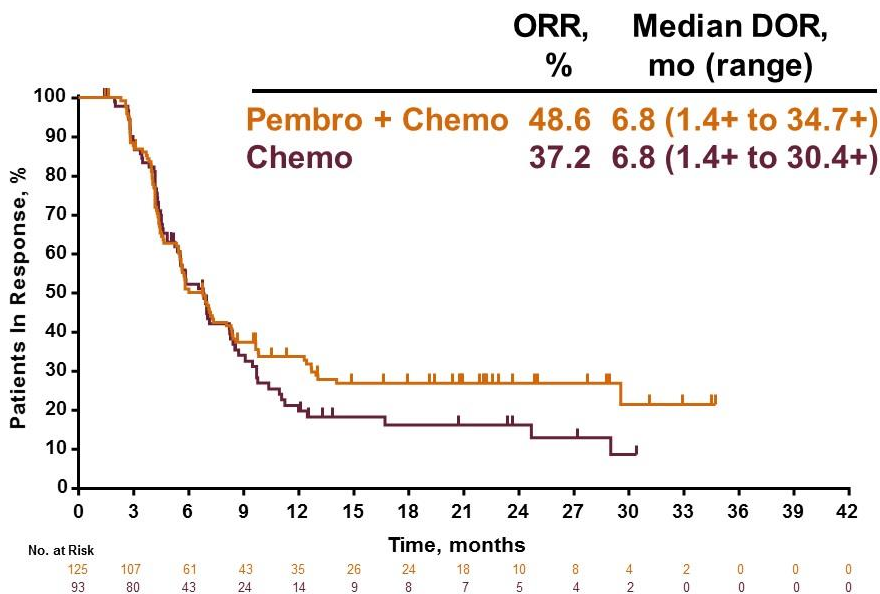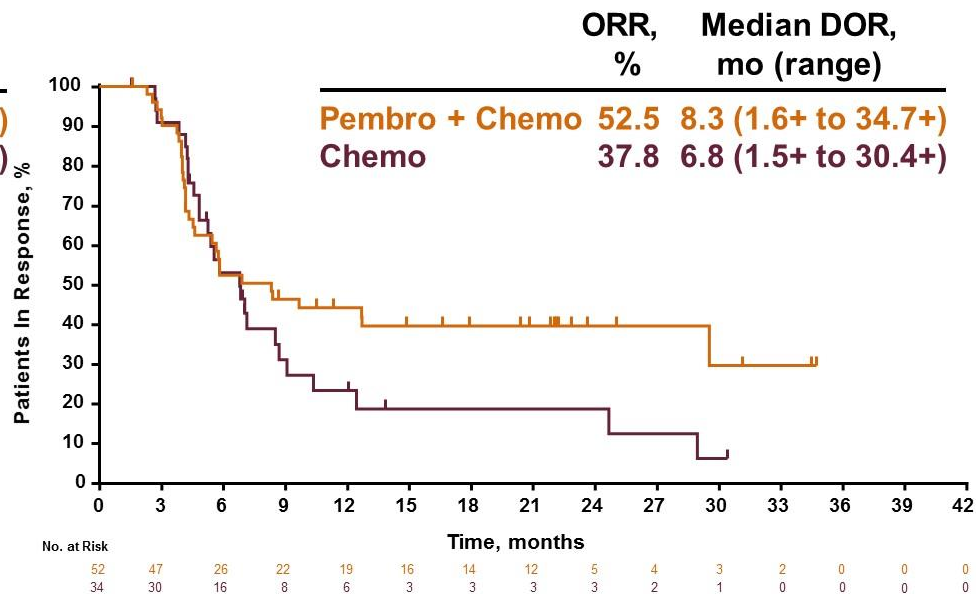
Response assessed per RECIST v1.1 by blinded independent central review; DOR, duration of response; Data cutoff: March 26, 2019.

Tabernero J et al. ASCO 2019 (#LBA4007)

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PD-L1 in gastric cancer: Tumour *vs*. immune cells
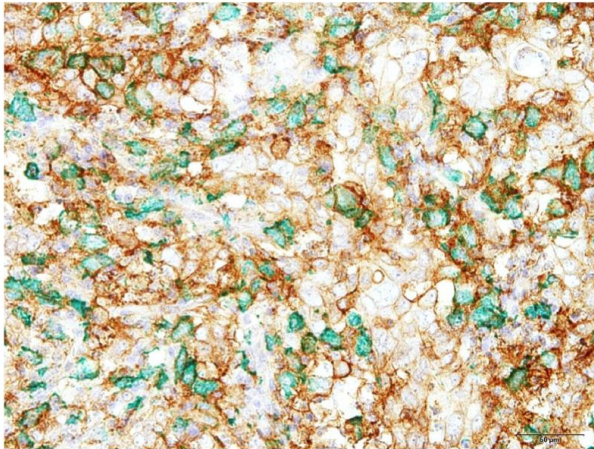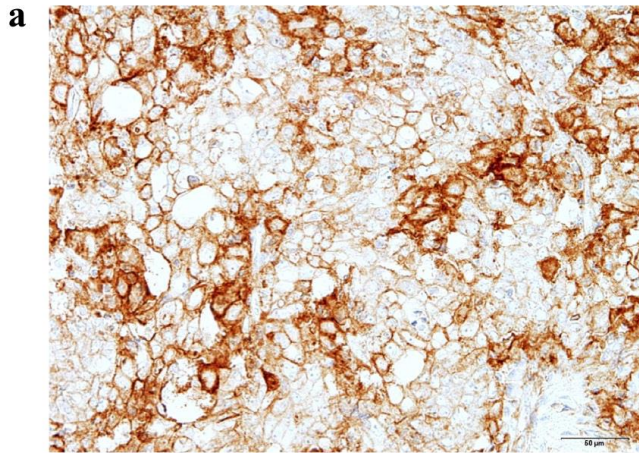
TPS: PD-L1 (+) CPS:PD-L1 (+)
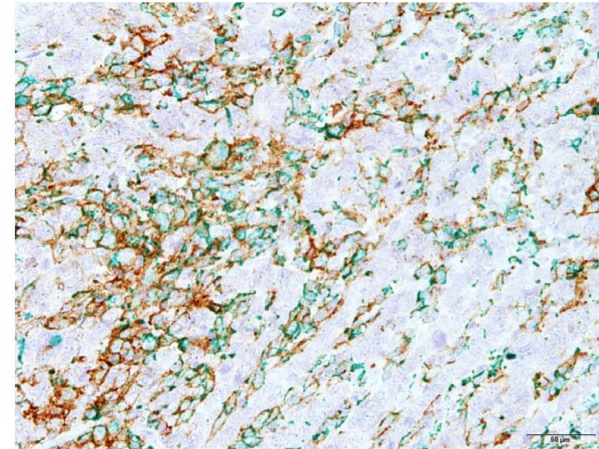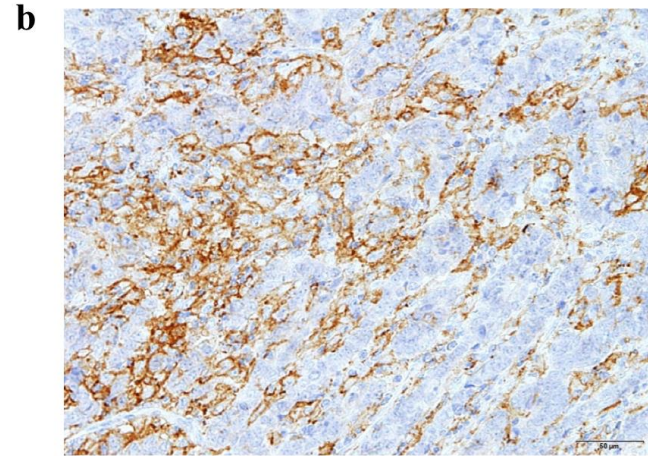
TPS: PD-L1 (–) CPS:PD-L1 (+)

PD-L1 assessment: Biopsy *vs*. resection specimen

Table 1. Comparison of PD-L1 positivity between biopsy and resected specimens

	Resected specimen		Total
	Positive (≥1%)	Negative (<1%)	
Biopsy specimen			
Positive (≥1%)	78	11	89
Negative (<1%)	57	45	102
Total	135	56	191
Accordance rate (%)		64.4	
Kappa coefficient (value)		0.31	
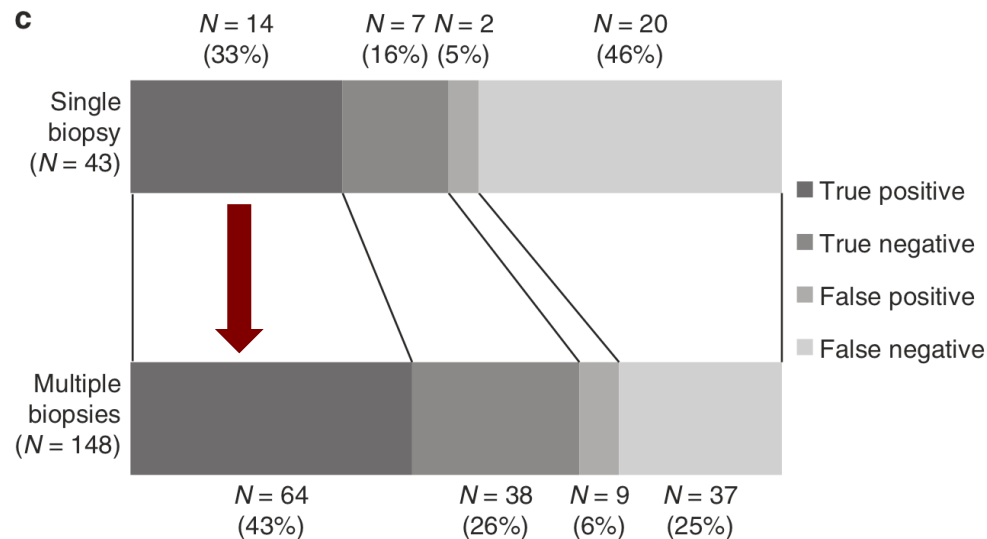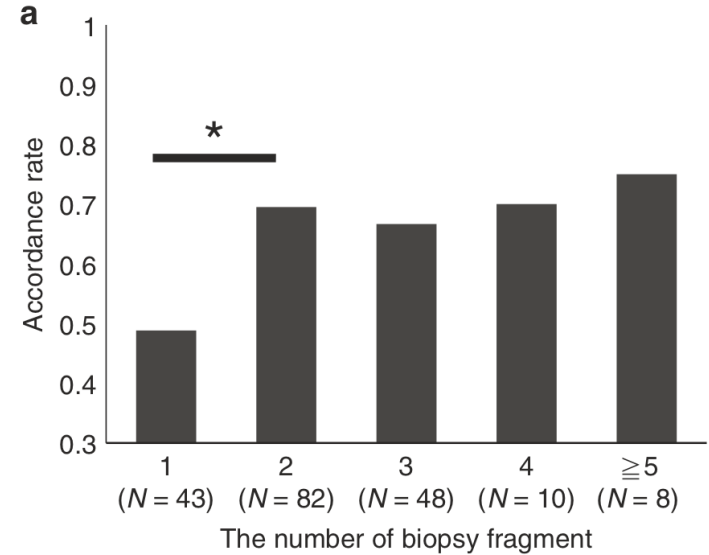
a

Accordance rate vs. The number of biopsy fragment
- 1 (N = 43)
- 2 (N = 82)
- 3 (N = 48)
- 4 (N = 10)
- ≥5 (N = 8)

c

Single biopsy (N = 43):
- N = 14 (33%)
- N = 7 (16%)
- N = 2 (5%)
- N = 20 (46%)

Multiple biopsies (N = 148):
- N = 64 (43%)
- N = 38 (26%)
- N = 9 (6%)
- N = 37 (25%)

Legend:
- True positive
- True negative
- False positive
- False negative

Yamashita K et al. Br J Cancer 2019

PD-L1: A reliable biomarker?
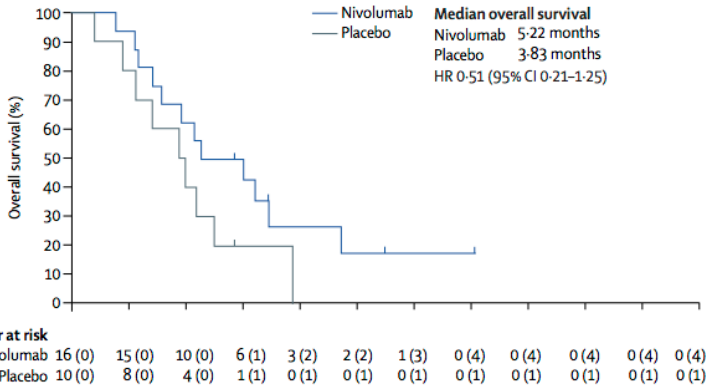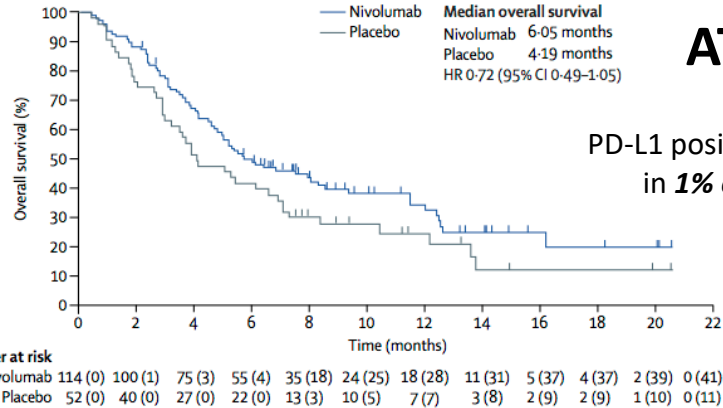
ATTRACTION-2

PD-L1 positivity defined as staining in *1% or more of tumour cells*
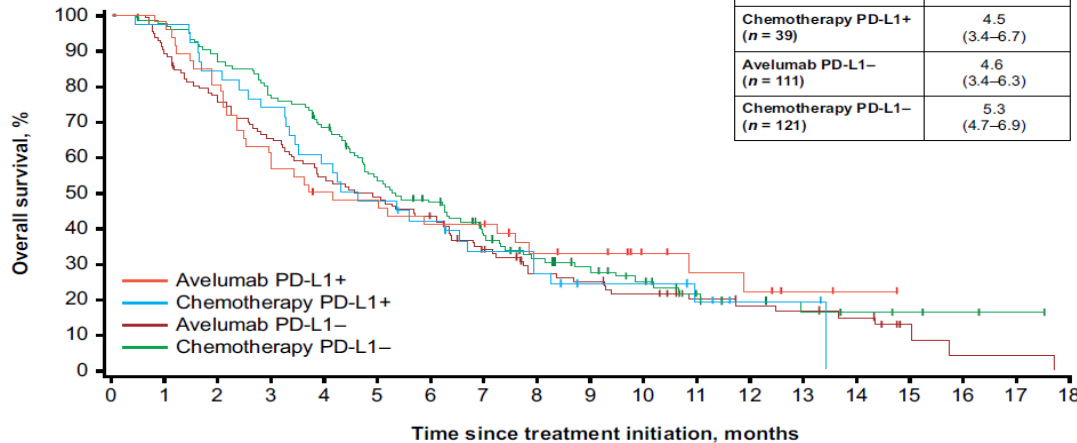
JAVELIN Gastric 300

PD-L1 status *assessed on tumour cells, with a cutoff of ≥1% expression*. Comparable results were obtained when PD-L1 expression was measured in *both tumour and immune cells*

Kang YK et al. Lancet 2017
Bang YJ et al. Ann Oncol 2018

PD-L1: A reliable biomarker?

Overall Survival by PD-L1 CPS

Shitara K et al. Lancet 2018
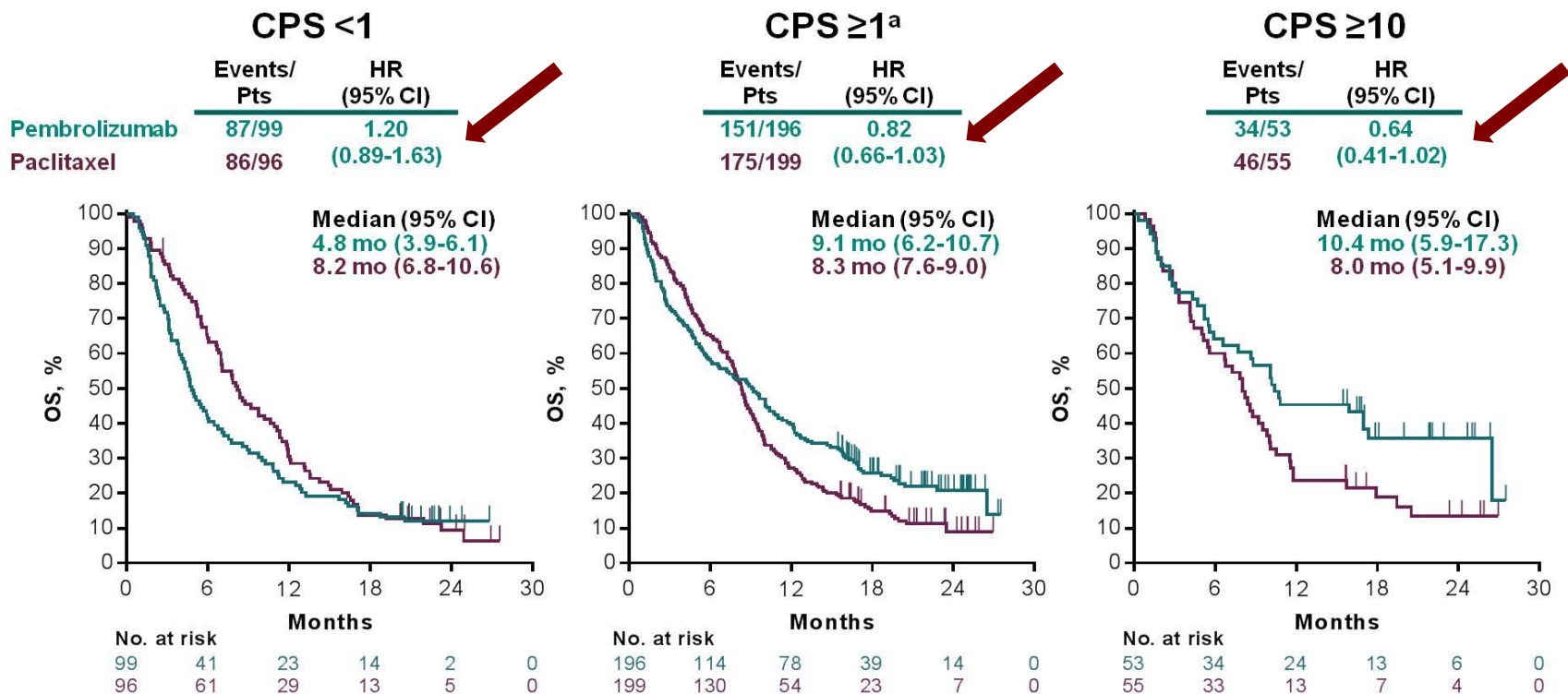
TCGA: Gastric cancer molecular subgroups

CIN
- Intestinal histology
- *TP53* mutation
- RTK-RAS activation

EBV
- *PIK3CA* mutation
- *PD-L1/2* overexpression
- EBV-CIMP
- *CDKN2A* silencing
- Immune cell signalling

MSI
- Hypermutation
- Gastric-CIMP
- *MLH1* silencing
- Mitotic pathways

GS
- Diffuse histology
- *CDH1, RHOA* mutations
- *CLDN18–ARHGAP* fusion
- Cell adhesion

Cardia
GE Junction
Fundus
Body
Pylorus
Antrum

b

295
EBV positive
26
EBV (EBV-CIMP)
9%

269
MSI high
64
MSI (hypermutated)
22%

205
SCNA high cluster
58
GS (genomically stable)
20%

147
CIN (chrom instability)
50%

Does TCGA help in molecular selection for ICIs?

Response to Pembrolizumab according to TCGA subtype

Kim ST et al. Nat Med 2018
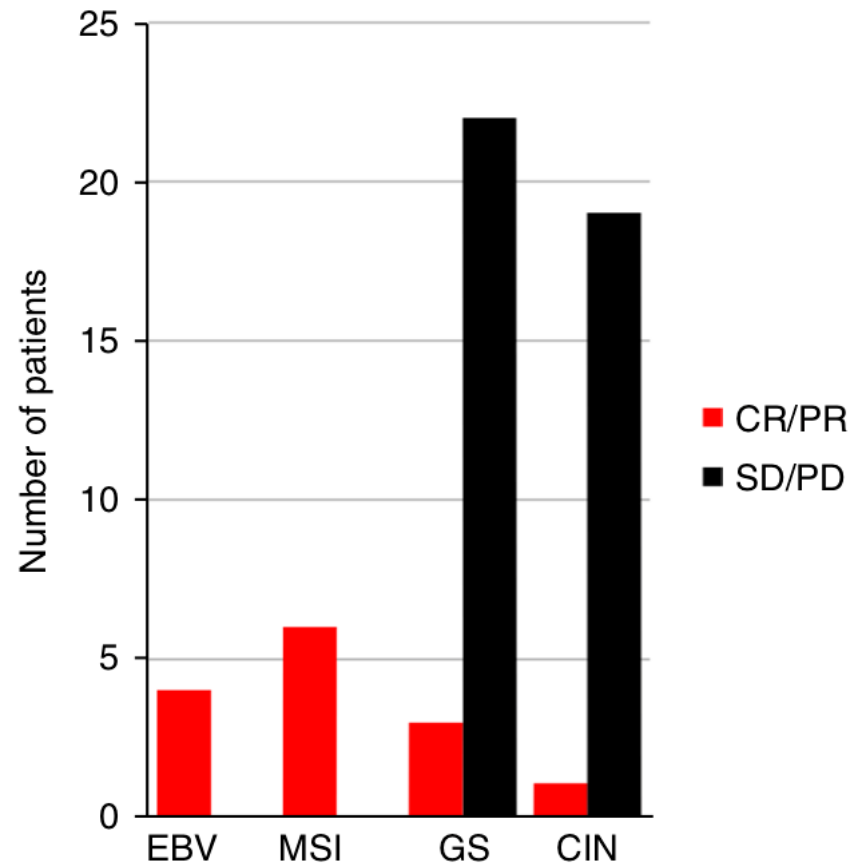
EBV carcinogenesis

Mechanisms of immune evasion in EBVaGC.

Mechanism of Immune Evasion	Description
Overexpression of IL- 1β	• Nonspecific lymphocytes are recruited by IL- 1β to prevent direct contact between EBV-specific cytotoxic T cells and tumor cells [34] • IL- 1β also inhibits stomach acid secretion and promotes EBVaGC growth [86]
Overexpression of IFN-ϒ	• IFN-ϒ activates IDO1 [34], which depletes tryptophan, and inhibits proliferation and activation of CTLs and natural killer cells which are sensitive to tryptophan [87]
PD-L1 amplification	• PD-L1 interacts with its co-inhibitory molecule, PD-1 receptor on T cells, leading to inhibition of T cell proliferation, cytotoxicity and cytokine release [34] • Induces apoptosis of CTLs and promote differentiation of CD4+ T cells into Treg cells [34] • Increases tumor resistance to CTLs [34]
Expression of early lytic gene- BNLF2α	• BNLF2α blocks antigen presentation to CTLs through inhibition of peptide loading onto major histocompatibility complex (MHC) class I molecules [87]
LMP2A mutations	• LMP2A gene mutations on exons 1–9 impair detection by CTLs [43]
EBNA1 repeats and polymorphisms	• EBNA1 contains glycine-alanine repeat sequences and polymorphisms which impede antigen presentation and processing, facilitating tumor growth and immune evasion [88]

EBVaGC frequencies around the world listed in ascending order.

Country	EBVaGC frequency (%)	Reference
Papa New Guinea	1.3	[89]
Pakistan	1.9	[90]
Peru	4	[83]
China- Guangzhou	6.7	[88]
Japan	6.9	[87]
Brazil	7	[19]
China-Beijing	7.3	[91]
Denmark	8.5	[53]
Malaysia	10	[92]
China- Tangshan	10.6	[48]
Iran	11.1	[93]
Colombia	16	[83]
United States	16	[94]
Chile	17	[87]
Zambia	23	[47]
Brunei	30.9	[92]

Naseem M et al. Cancer Treat Rev 2018

Predictive role of MSI and EBV status

Waterfall plot according to MSI/EBV status

Response rate:
85.7% MSI-high
100% EBV+

*New lesion

MSI-H ■   EBV(+) ■   MSS/EBV(−) ■

Enrolled patients
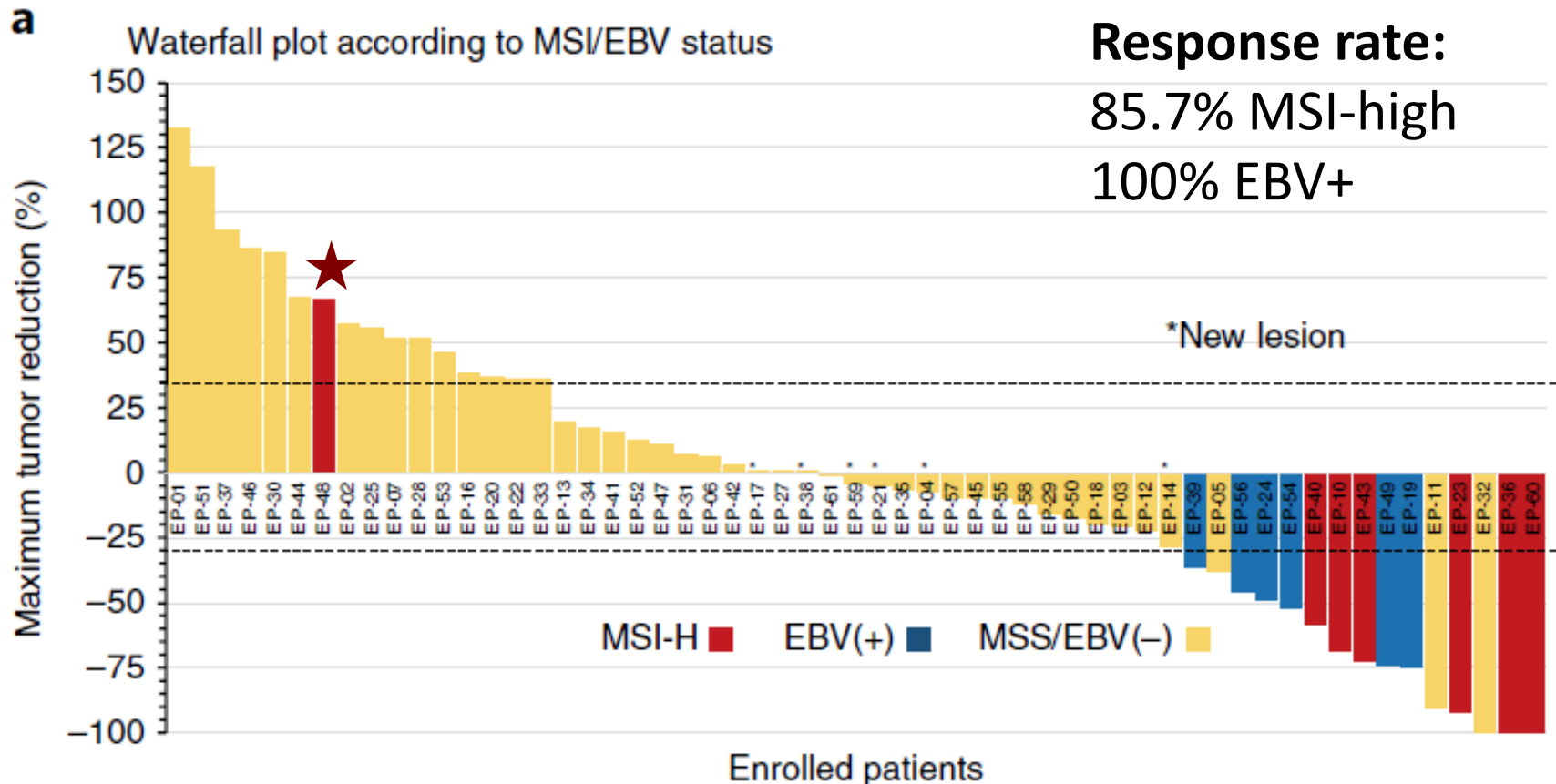
★ 1 MSI-high tumour had marked heterogeneity in MSH1 expression

Kim ST et al. Nat Med 2018

KEYNOTE-061: MSI-high subgroup

OS, ORR, and DOR for MSI-H Tumors[a]
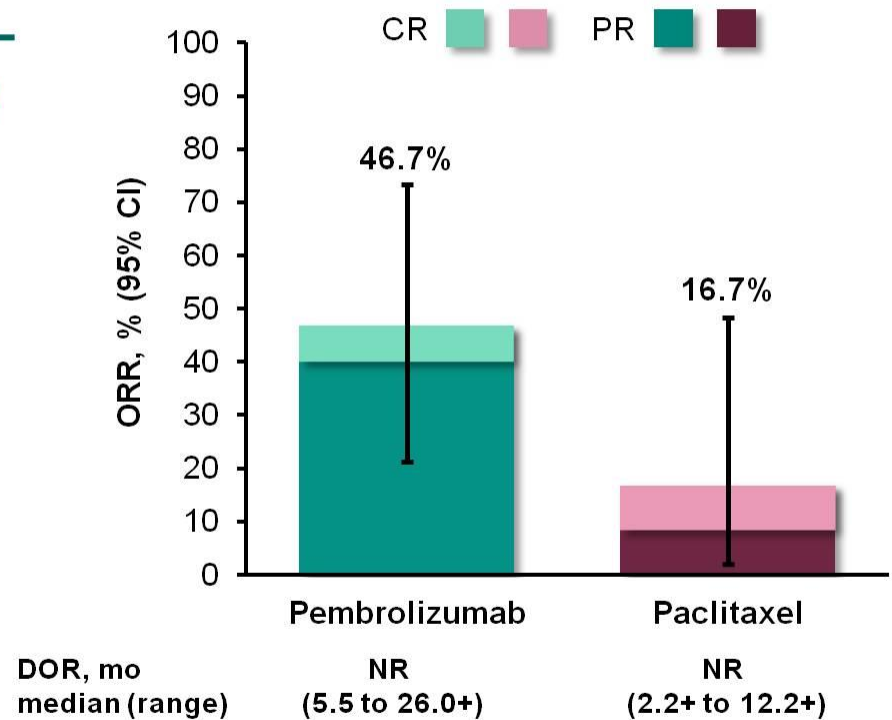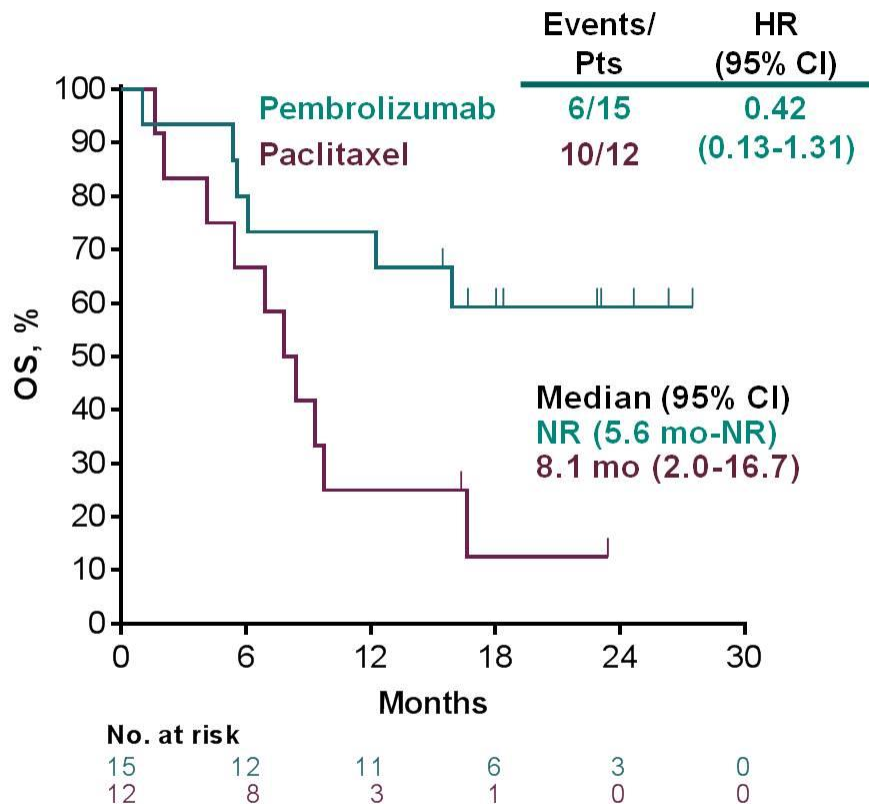
Shitara K et al. ASCO 2018

KEYNOTE-062: MSI-high (OS)


Pembro vs Chemo: OS in MSI-H Group

CPS ≥1

	Events	HR (95% CI)
Pembro	36%	0.29
Chemo	79%	(0.11-0.81)

12-mo rate
79%
47%

24-mo rate
71%
26%

Median (95% CI)
NR (10.7-NR)
8.5 mo (5.3-20.8)

No. at risk
14 13 13 13 11 10 10 10 9 6 4 3 2 0 0
19 18 13 9 9 8 7 5 4 3 3 0 0 0 0

CPS ≥10

	Events	HR (95% CI)
Pembro	27%	0.21
Chemo	80%	(0.06-0.83)

12-mo rate
82%
50%

24-mo rate
82%
30%

Median (95% CI)
NR (10.7-NR)
13.6 mo (3.8-25.8)

No. at risk
11 10 10 10 9 9 9 9 8 5 3 3 2 0 0
10 10 8 5 5 5 5 3 2 1 1 0 0 0 0

Data cutoff: March 26, 2019.

Shitara K et al. ESMO 2019 (#LBA44)
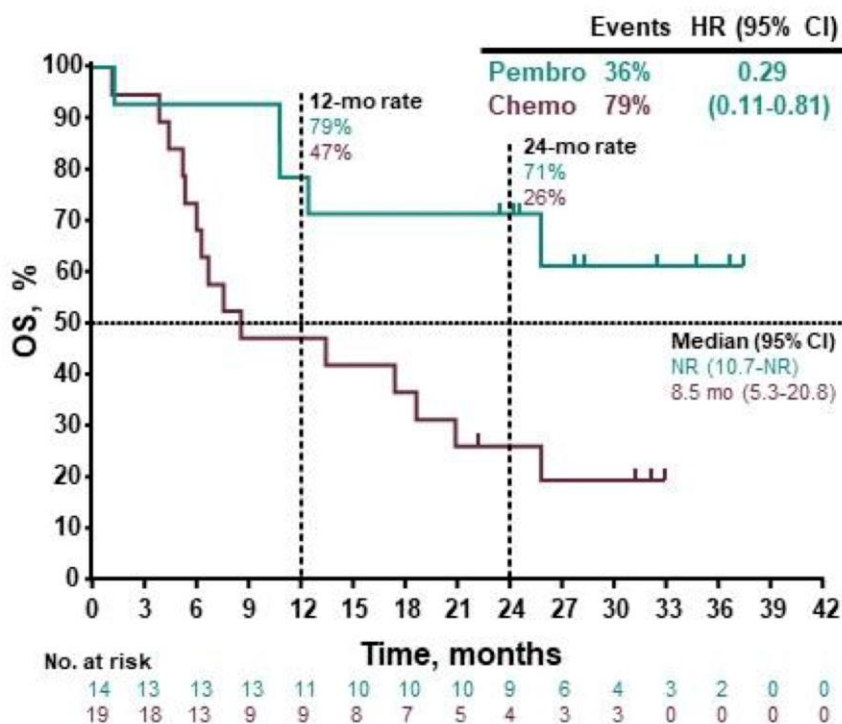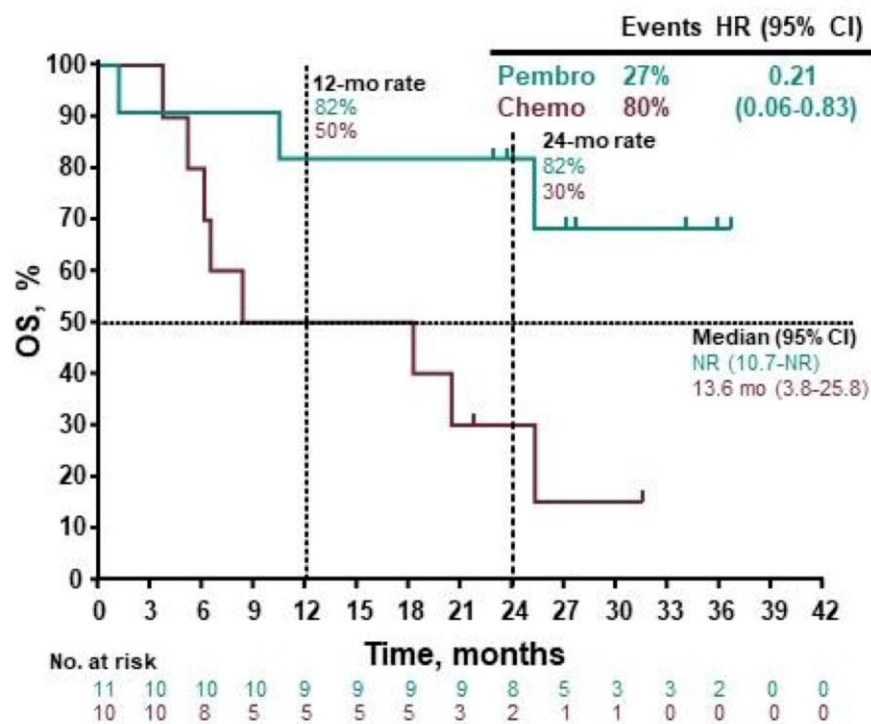
KEYNOTE-062: non-MSI-high (OS)

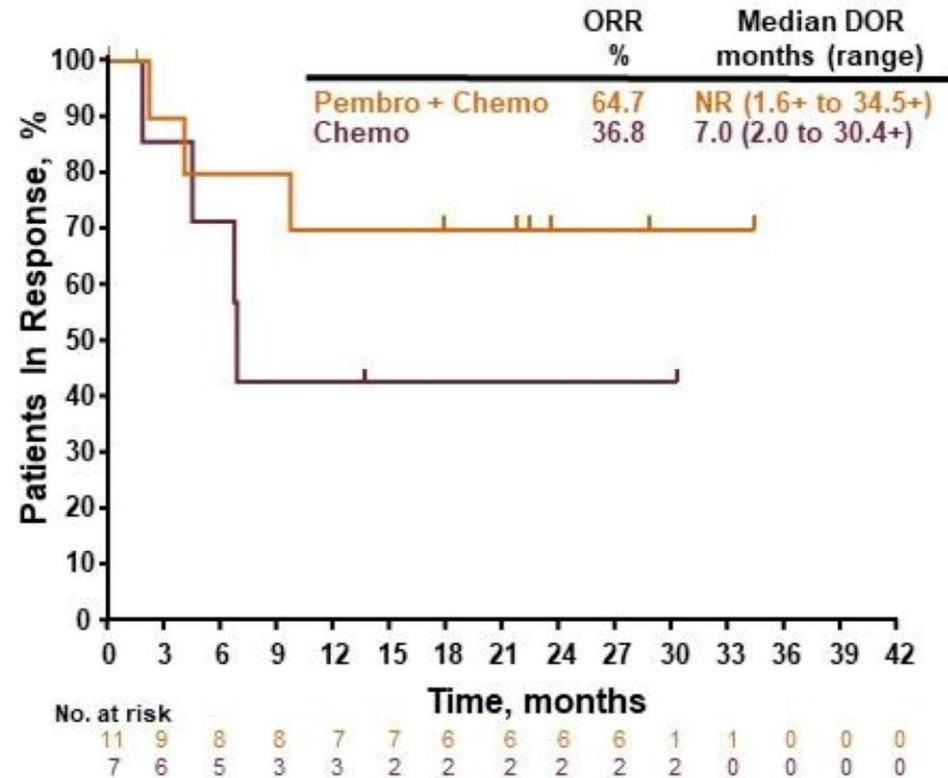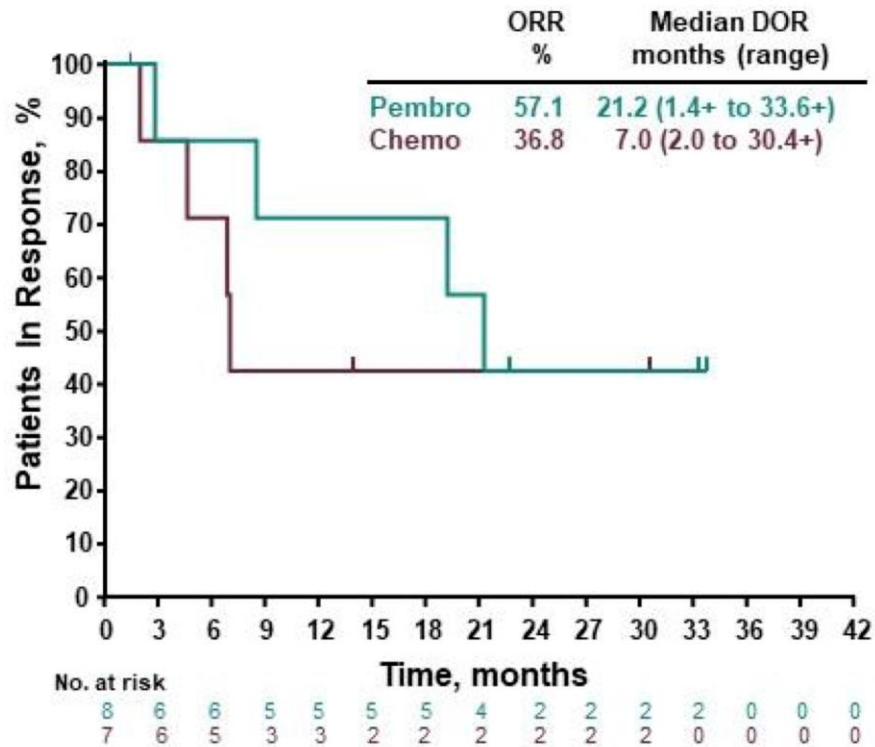Pembro vs Chemo: OS in Non-MSI-H Group
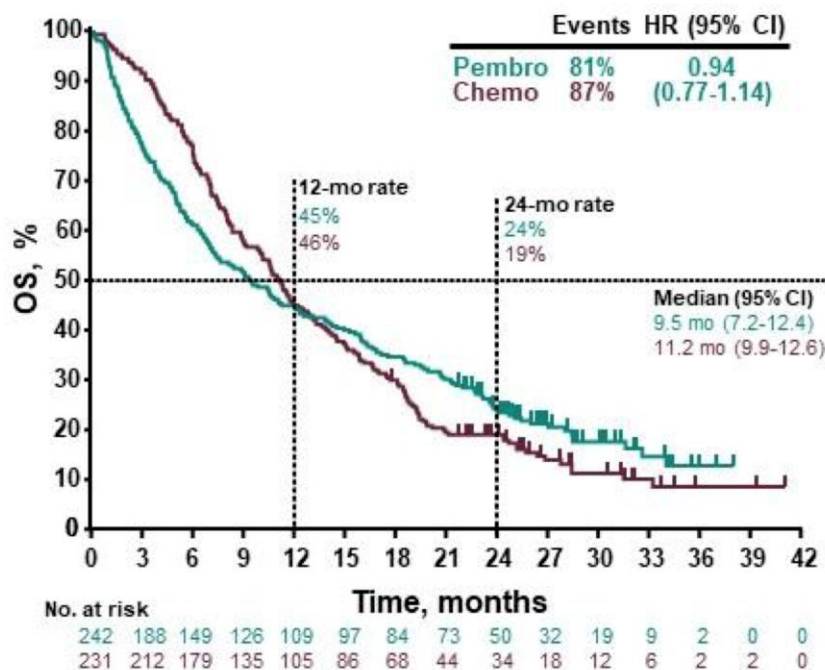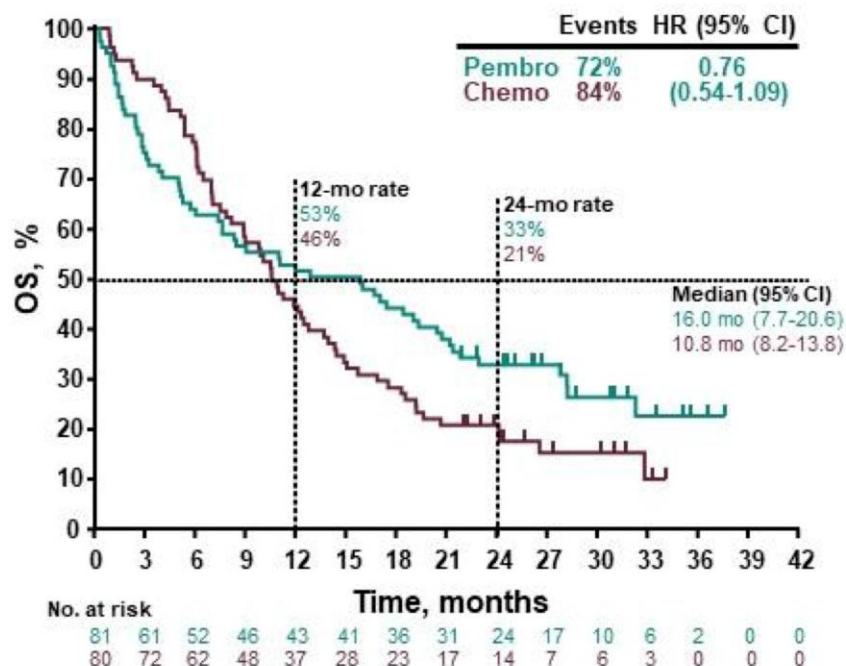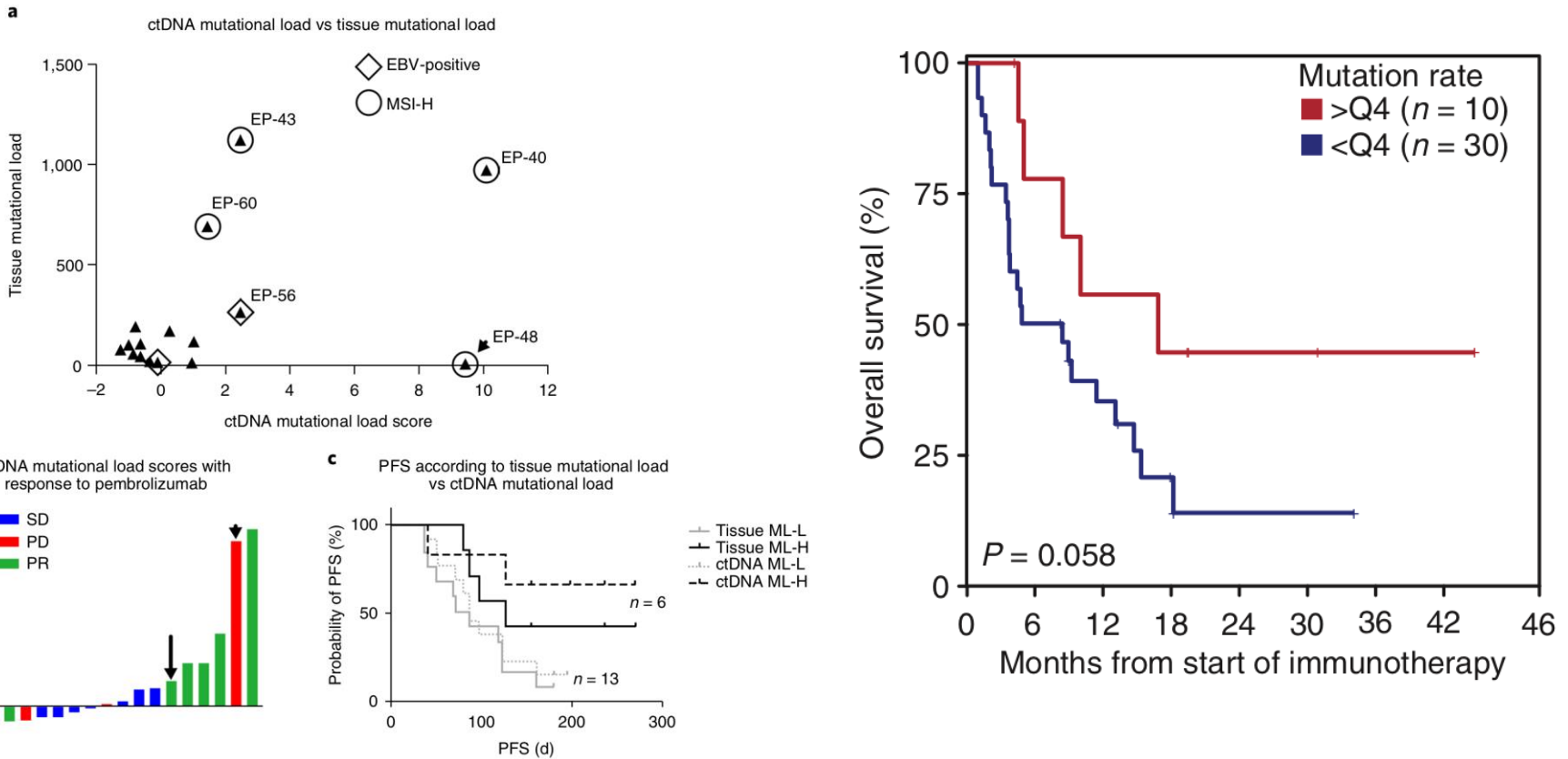
KEYNOTE-062: MSI-high (OS)

Pembro + Chemo vs Chemo: OS in MSI-H Group
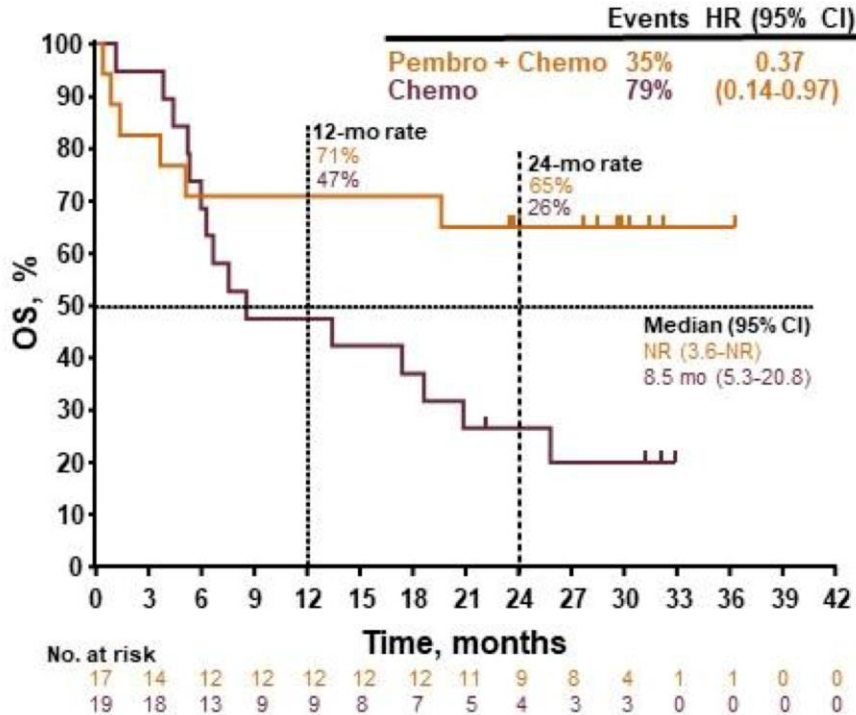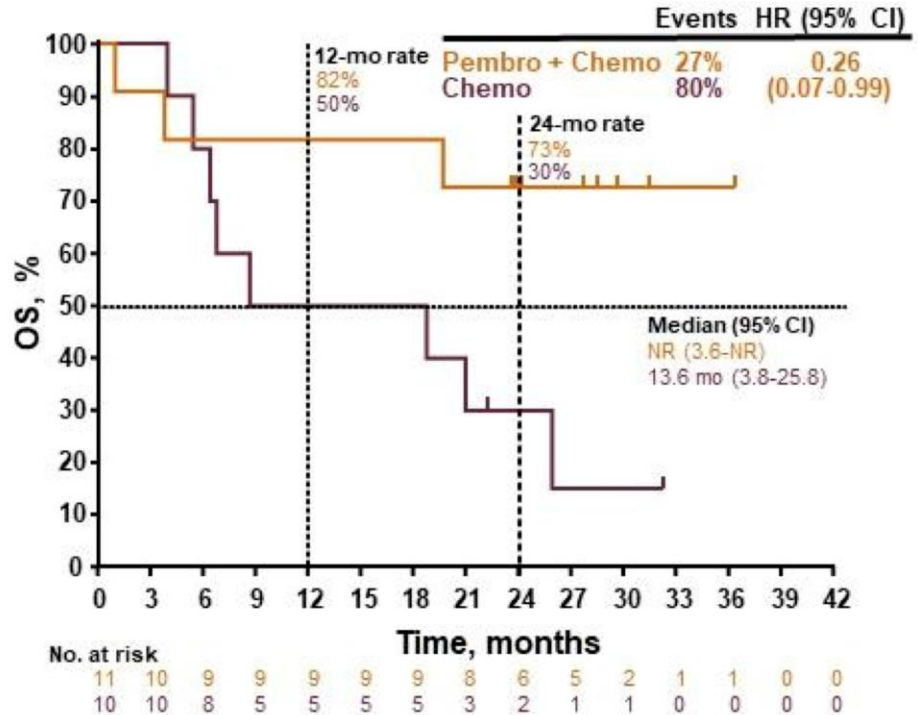
MSI-high (OS): Do we really need CT?

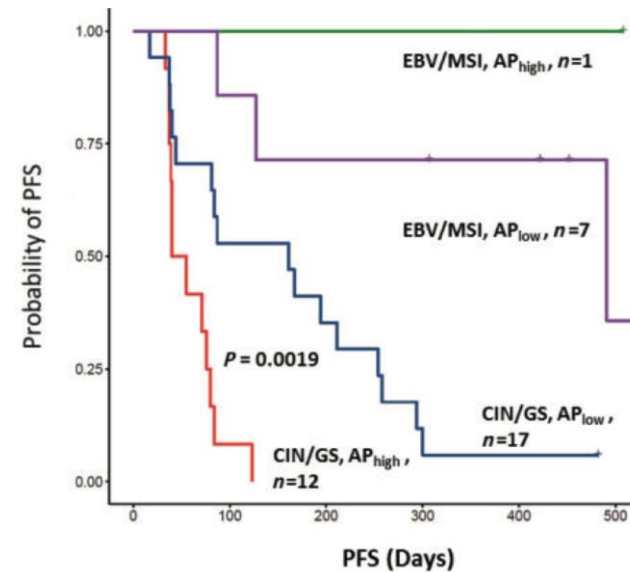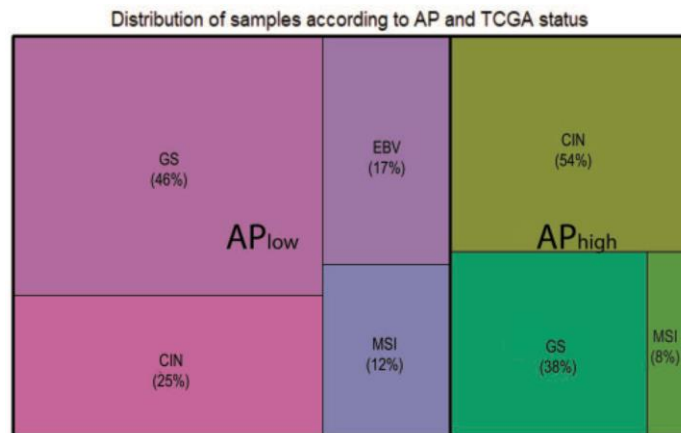Shitara K et al. ESMO 2019 (#LBA44)
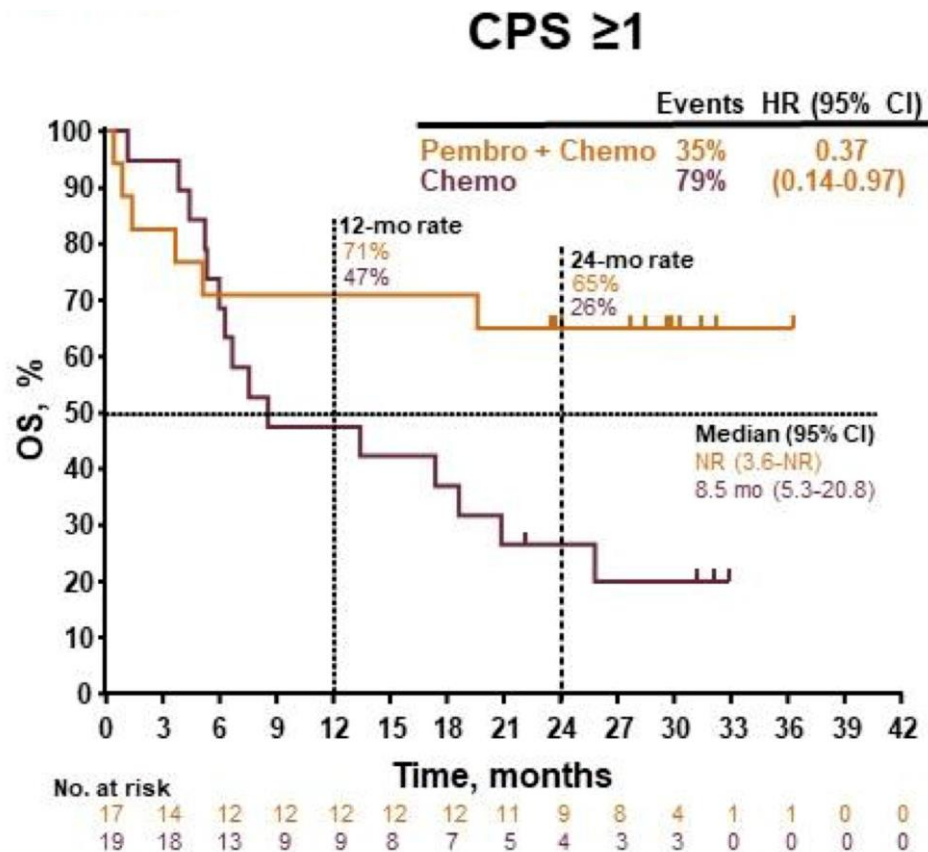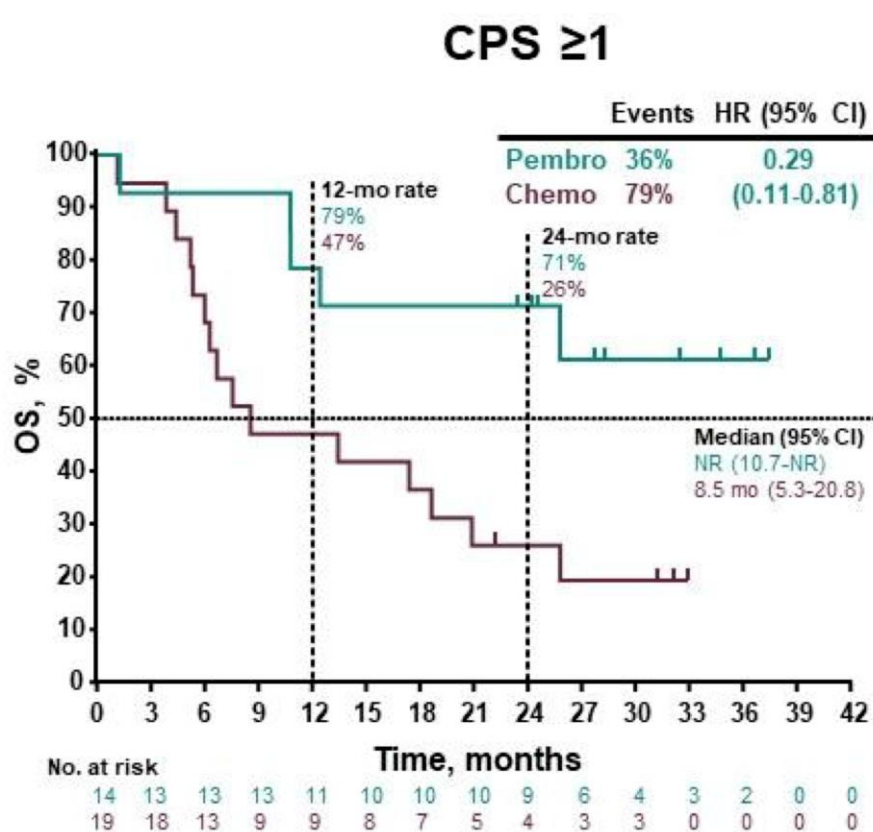
MSI-high (RR and DoR): Do we really need CT?
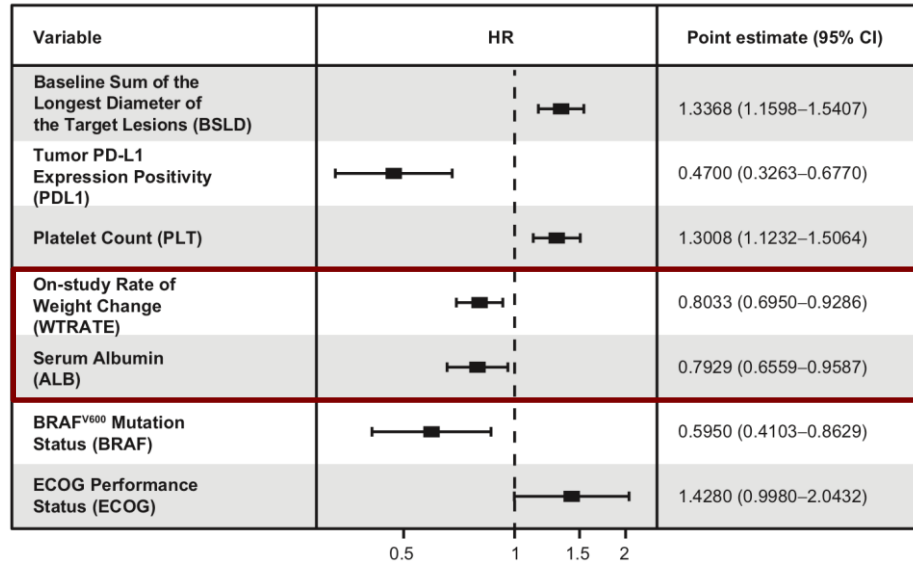
Is TMB a potential predictive biomarker?

Kim ST et al. Nat Med 2018
Janjigian YY et al. Cancer Discovery 2018

Epigenomic promoter alterations and IO in GC

MSI[high]

Sundar R et al. Ann Oncol 2019
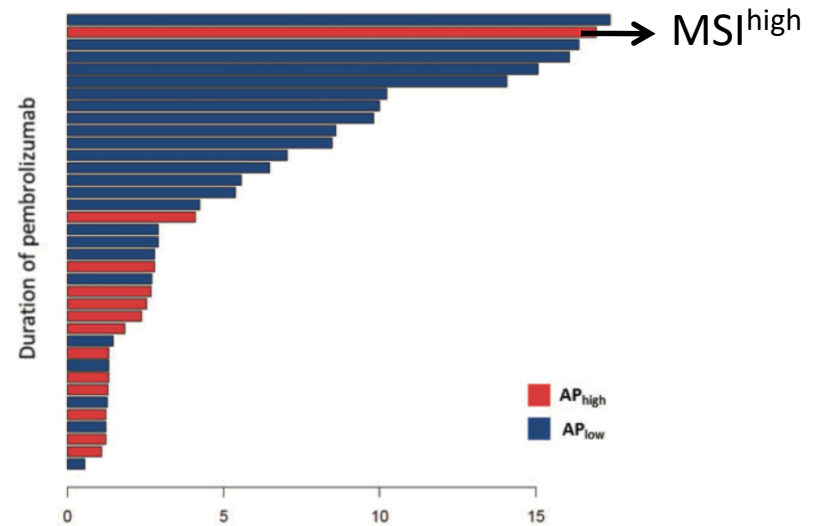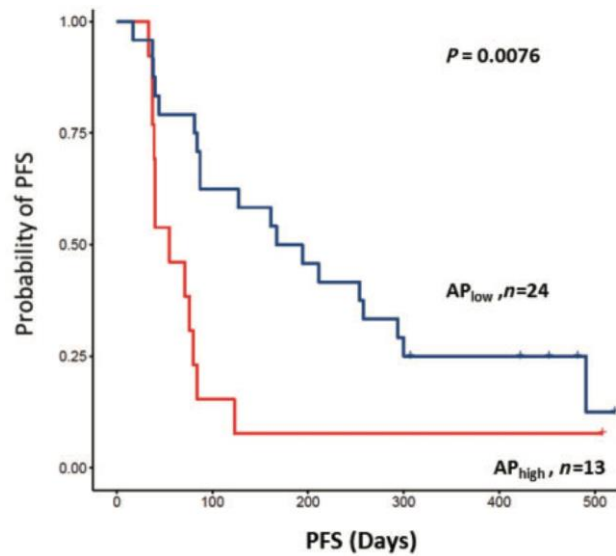
Nutritional status and response to ICIs

Melanoma

Variable	HR	Point estimate (95% CI)
Baseline Sum of the Longest Diameter of the Target Lesions (BSLD)		1.3368 (1.1598–1.5407)
Tumor PD-L1 Expression Positivity (PDL1)		0.4700 (0.3263–0.6770)
Platelet Count (PLT)		1.3008 (1.1232–1.5064)
On-study Rate of Weight Change (WTRATE)		0.8033 (0.6950–0.9286)
Serum Albumin (ALB)		0.7929 (0.6559–0.9587)
BRAF^{V600} Mutation Status (BRAF)		0.5950 (0.4103–0.8629)
ECOG Performance Status (ECOG)		1.4280 (0.9980–2.0432)

NSCLC

| Variable	HR	Point estimate (95% CI)
On-study Rate of Albumin Change (ALBRATE)		0.2793 (0.2117–0.3684)
Serum Albumin (ALB)		0.7030 (0.6207–0.7962)
On-study Rate of Weight Change (WTRATE)		0.7306 (0.6467–0.8254)
Lactate Dehydrogenase (LDH)		1.1697 (1.0941–1.2505)
Squamous Histology (SQUAM)		1.9428 (1.4454–2.6113)
Male Gender (MALE)		0.7094 (0.5450–0.9233)
Baseline Sum of the Longest Diameter of the Target Lesions (BSLD)		1.1551 (1.0188–1.3097)
ECOG Performance Status (ECOG)		1.2952 (0.9782–1.7149)

Model	KEYNOTE-002; advanced melanoma (complete-case dataset $n = 211$)			KEYNOTE-010; advanced, previously treated NSCLC (complete-case dataset $n = 537$)		
Univariate pooled $AUC_{6weeks,CL0}$ HR across 2 and 10 mg/kg	0.71 (0.59–0.87)			0.77 (0.67–0.88)		
	CL_0 HR (95% CI for HR)	CL_0 P value	$\Delta OBJV$ with CL_0 included[a]	CL_0 HR (95% CI for HR)	CL_0 P value	$\Delta OBJV$ with CL_0 included[a]
Unadjusted univariate or "crude" Cox model	2.56 (1.72–3.80)	<0.001	−20.67	2.64 (1.94–3.57)	<0.001	−33.21
Adjusted for time-varying on-study proxy factors of cancer cachexia and baseline clinical risk factors[b]	1.60 (1.04–2.47)	0.031	−4.49	1.53 (0.97–2.41)	0.068	−3.18
Adjusted for baseline clinical risk factors only[c]	1.64 (1.06–2.52)	0.025	−4.89	1.88 (1.22–2.89)	0.004	−7.58

Turner DC et al. Clin Cancer Res 2018

Nutritional status: From 1982 to 2018

Synthesis of Information

The information summarized and partially documented indicates that: (*a*) malnutrition is closely related to late-stage malignant disease and is, in the absence of therapy, a poor prognostic sign; (*b*) nutritional therapy can induce reversal of malnutrition independent of cancer therapy; (*c*) cancer-directed therapy can aggravate or precipitate malnutrition; and (*d*) nutritional support aids in delivery of antineoplastic therapy. Therefore, all parts of an independent effect of nutritional state on the course of cancer morbidity exist. Whether the cancer is treated or not, nutritional support can avert or revert malnutrition in most cases. In that sense, the hypothesis posed is answered in the affirmative.

What is not possible is making ineffective or marginally effective therapy effective by nutritional support.
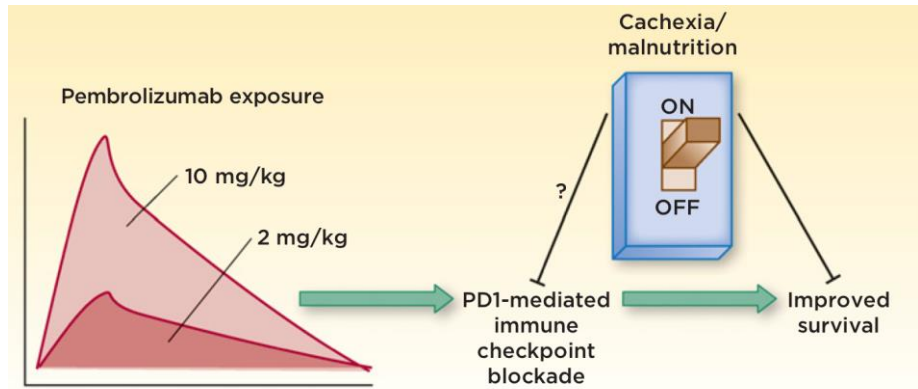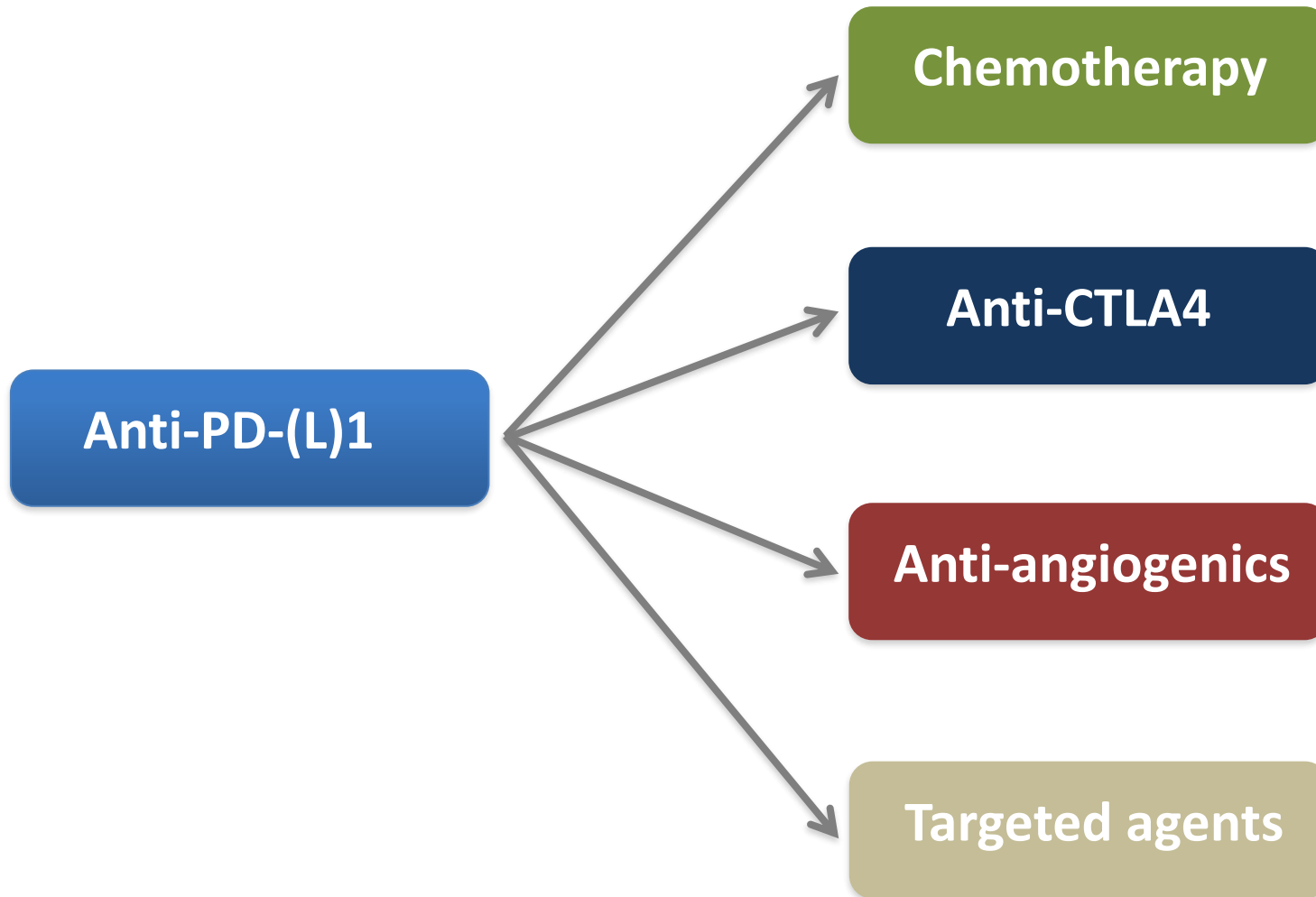
However, nutritional support is, at least in pediatrics, not counterproductive; rather the converse is true. Children feel better, have fewer complications, and tolerate a course of chemotherapy better. We must be careful to avoid posing nonquestions and we must feed starving children when they need it.

Van Eys J. Cancer Res 1982
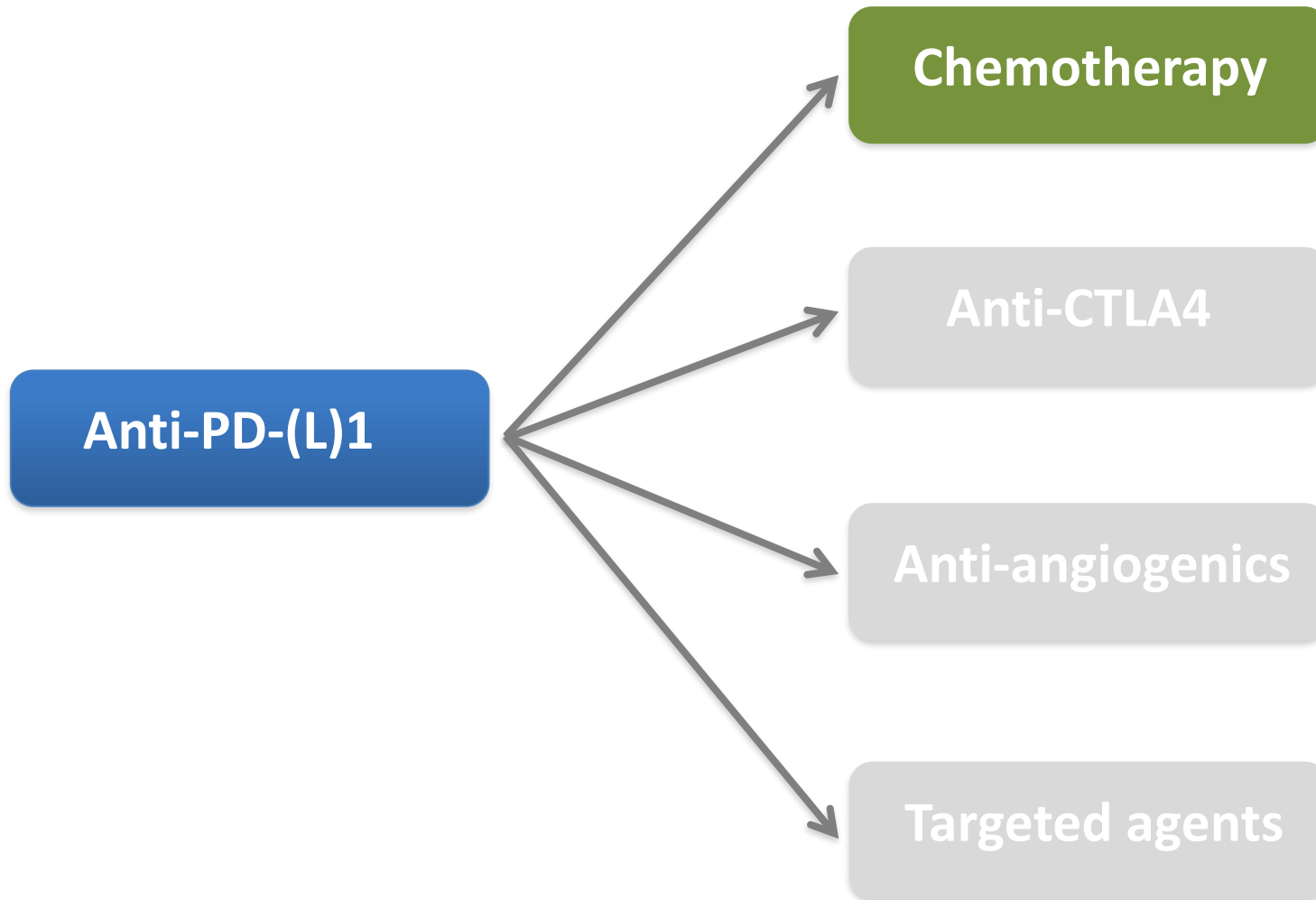Coss CC et al. Clin Cancer Res 2018

Agenda

- Current evidence supporting immunotherapy development in GC

- Hottest news in immunotherapy for GC

- How to optimally select candidates for ICIs in GC

- **Main ongoing trials with ICIs in GC**

- Conclusions

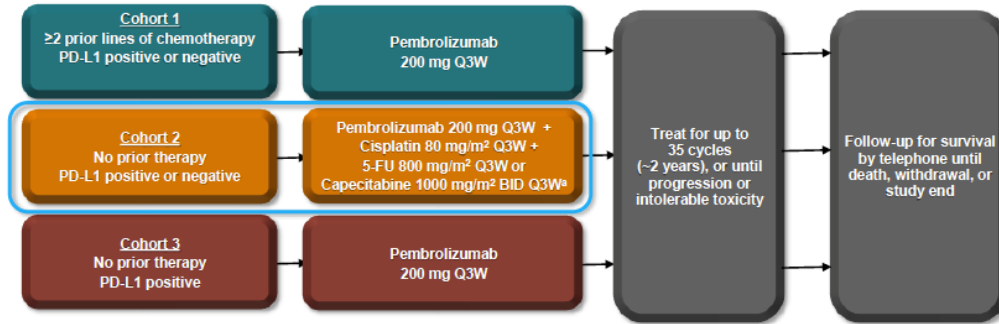# Main research directions: Combinations

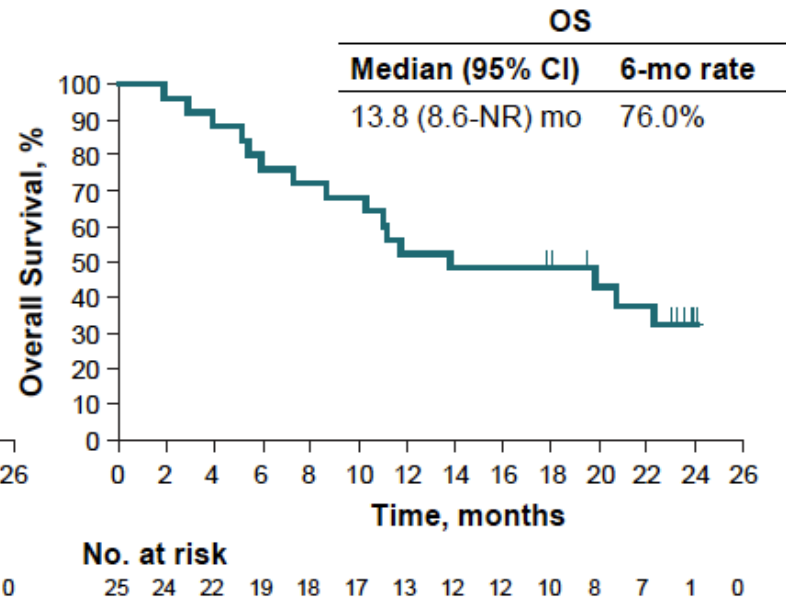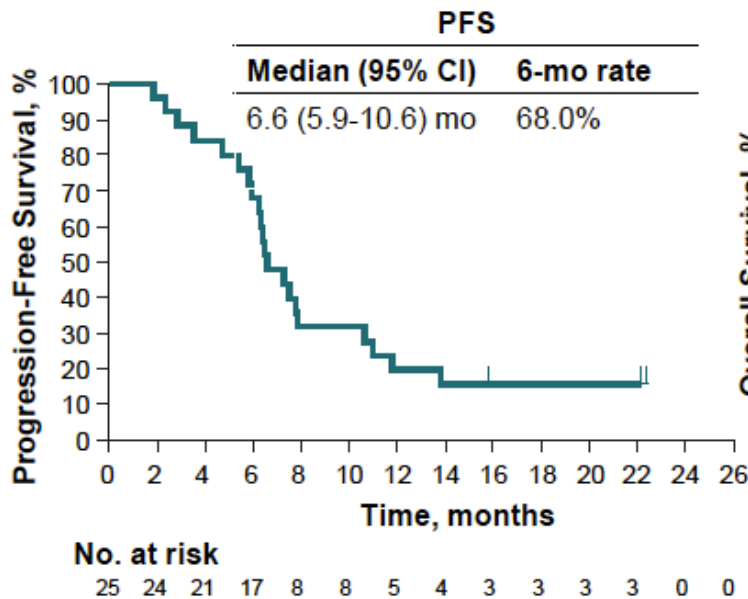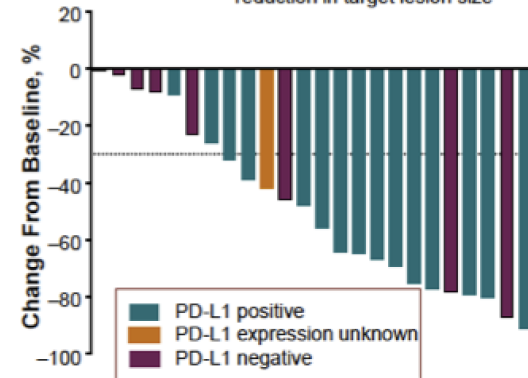# Main research directions: Combinations

KEYNOTE-059: CT + Immunotherapy
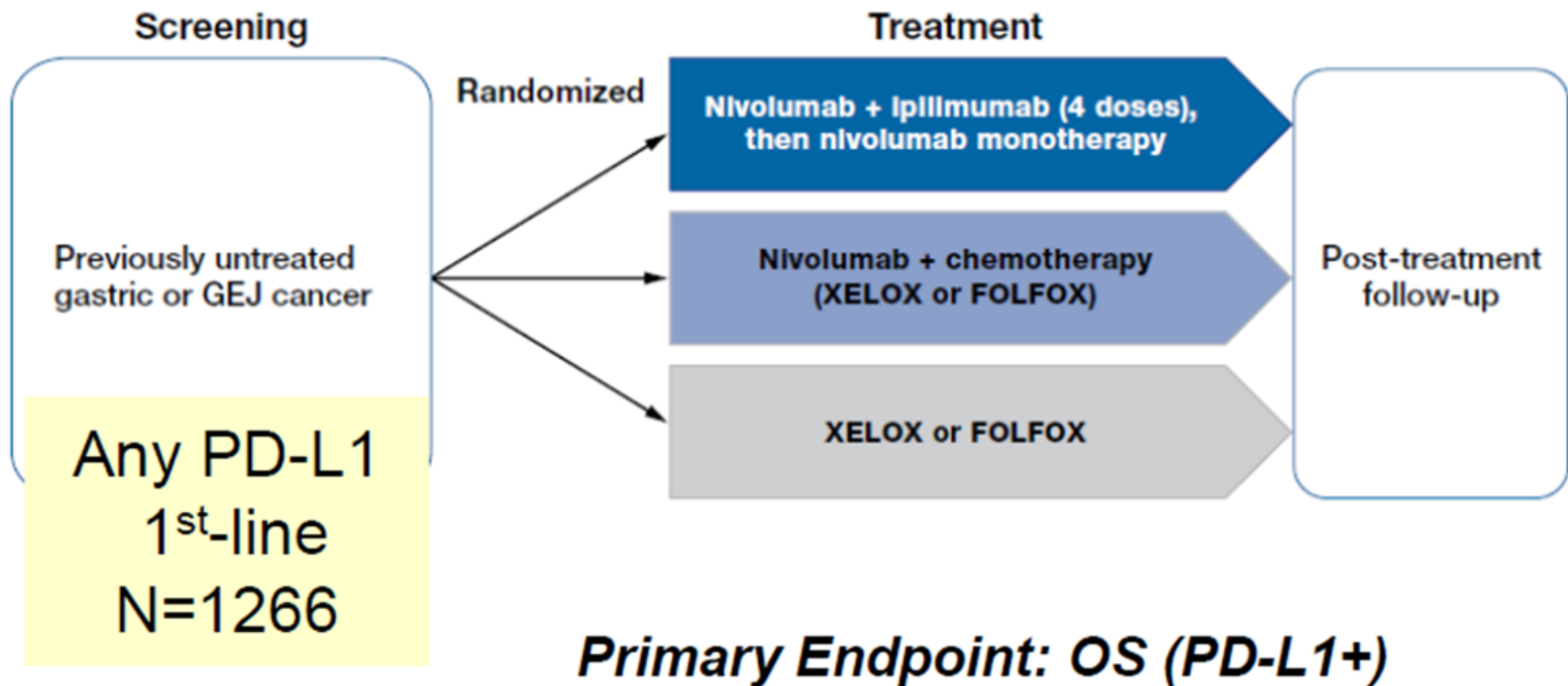
KEYNOTE-059 Study Design

Cohort 1	Pembrolizumab 200 mg Q3W
≥2 prior lines of chemotherapy PD-L1 positive or negative	

Cohort 2	Pembrolizumab 200 mg Q3W + Cisplatin 80 mg/m² Q3W + 5-FU 800 mg/m² Q3W or Capecitabine 1000 mg/m² BID Q3Wª
No prior therapy PD-L1 positive or negative	

Cohort 3	Pembrolizumab 200 mg Q3W
No prior therapy PD-L1 positive	

Treat for up to 35 cycles (~2 years), or until progression or intolerable toxicity

Follow-up for survival by telephone until death, withdrawal, or study end

Best Percentage Change in All Patients (n = 24)ª

24 patients (96%) experienced a reduction in target lesion size

- PD-L1 positive
- PD-L1 expression unknown
- PD-L1 negative

PFS

	Median (95% CI)	6-mo rate
	6.6 (5.9-10.6) mo	68.0%

No. at risk
25 24 21 17 8 8 5 4 3 3 3 3 0 0

OS

	Median (95% CI)	6-mo rate
	13.8 (8.6-NR) mo	76.0%

No. at risk
25 24 22 19 18 17 13 12 12 10 8 7 1 0

Weinberg Z et al. ESMO 2017 (LBA28)

Phase 3 CheckMate-649

Screening

Previously untreated gastric or GEJ cancer

Any PD-L1 1st-line N=1266

Randomized

Treatment

Nivolumab + Ipilimumab (4 doses), then nivolumab monotherapy

Nivolumab + chemotherapy (XELOX or FOLFOX)

XELOX or FOLFOX

Post-treatment follow-up

Primary Endpoint: OS (PD-L1+)

Phase 3 JAVELIN Gastric 100

Moehler M et al. Future Oncol 2019
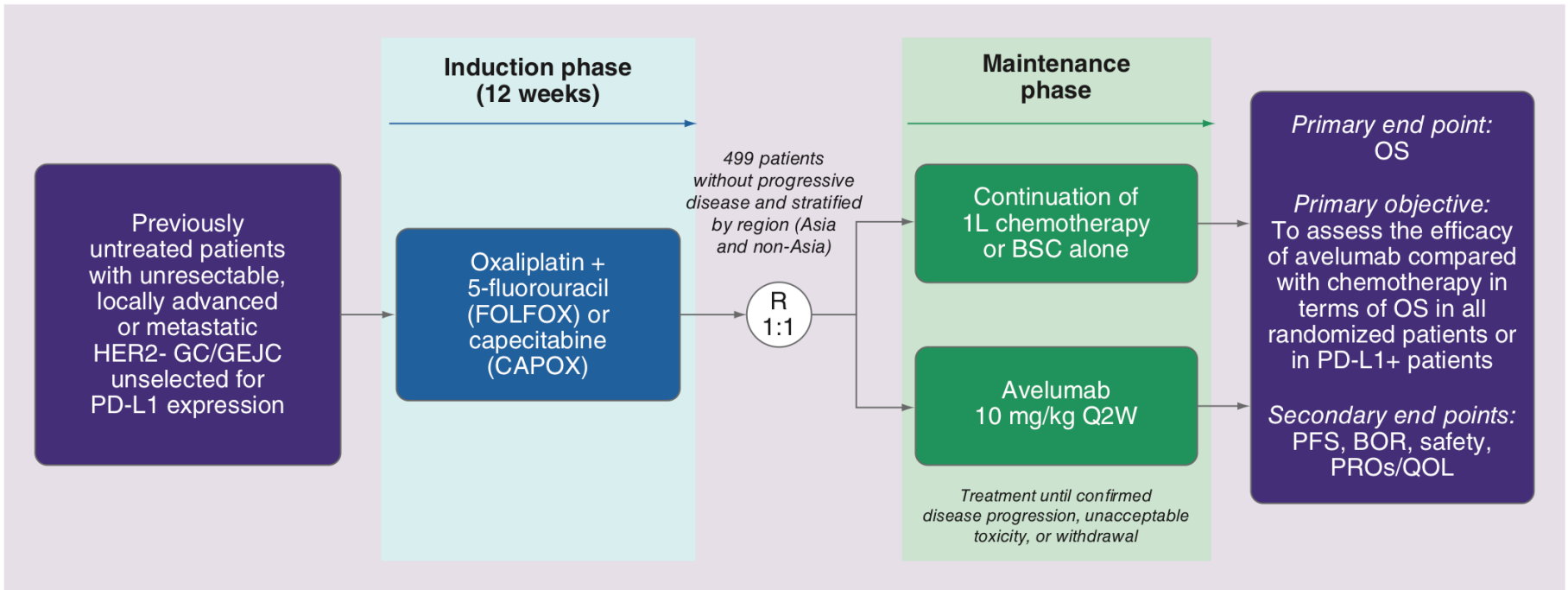
Main research directions: Combinations
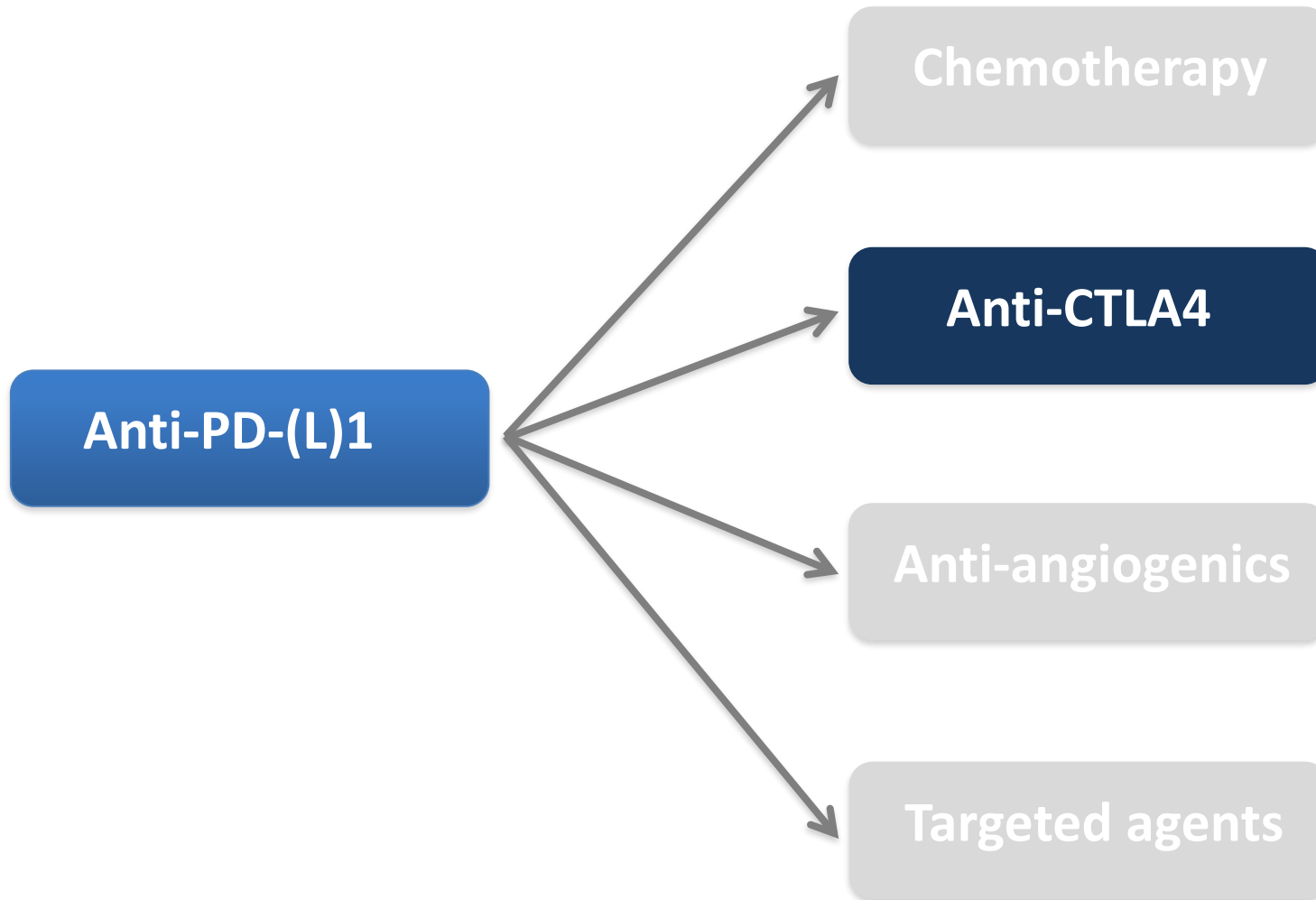
CheckMate-032: Nivolumab +/- Ipilimumab

D

Maximum Change From Baseline in Target Lesions (%)

RR 12%
PD-L1+: 19%
PD-L1-: 12%

RR 24%
PD-L1+: 40%
PD-L1-: 22%

RR 8%
PD-L1+: 23%
PD-L1-: 0%

NIVO3
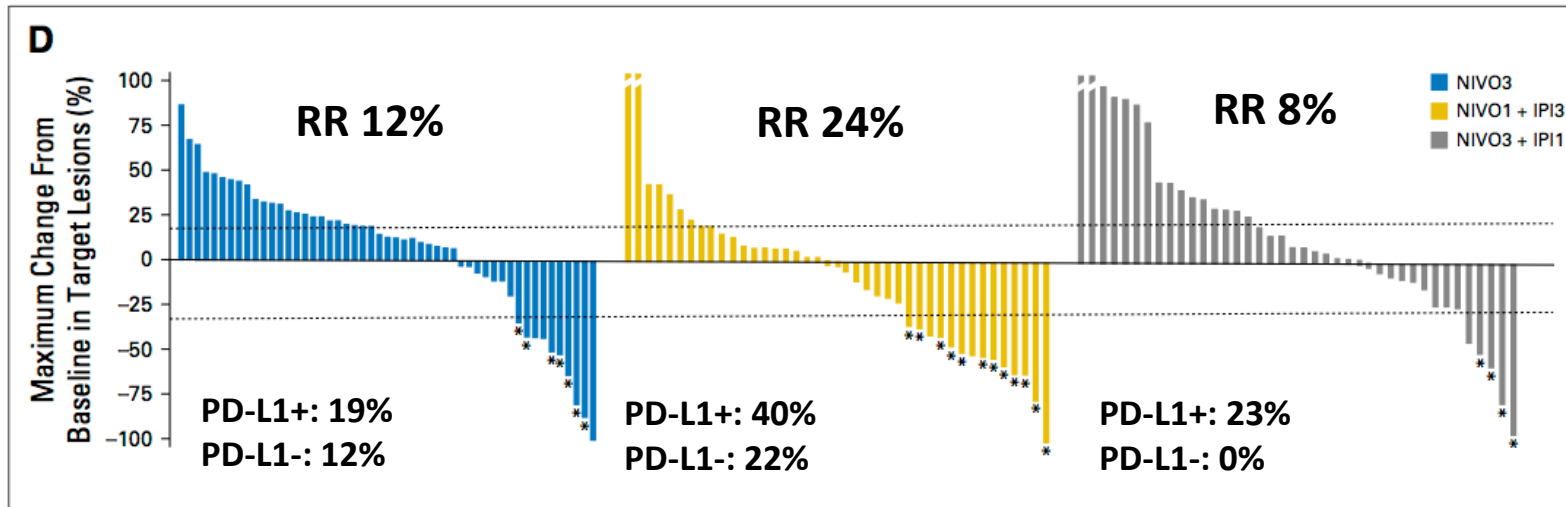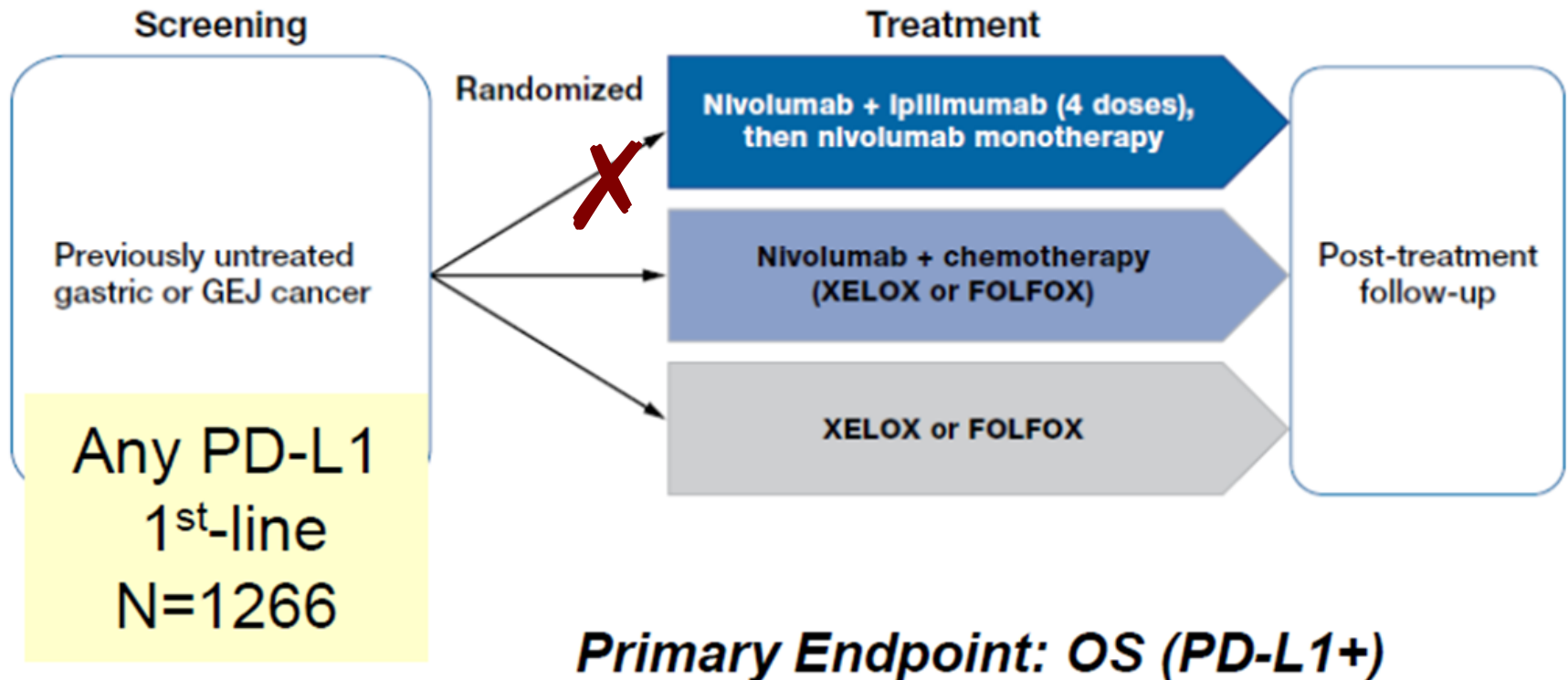NIVO1 + IPI3
NIVO3 + IPI1

Table 4. Treatment-Related Adverse Events

TRAE	NIVO3, No. (%) (n = 59)		NIVO1 + IPI3, No. (%) (n = 49)		NIVO3 + IPI1, No. (%) (n = 52)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any TRAE	41 (69)	10 (17)	41 (84)	23 (47)	39 (75)	14 (27)
Serious TRAEs*	6 (10)	3 (5)	21 (43)	17 (35)	13 (25)	9 (17)
TRAEs leading to treatment discontinuation	2 (3)	2 (3)	10 (20)	10 (20)	7 (13)	5 (10)
TRAEs in ≥ 15% of patients in any treatment group						
ALT increased	5 (8)	2 (3)	8 (16)	7 (14)	5 (10)	2 (4)
AST increased	7 (12)	3 (5)	8 (16)	5 (10)	2 (4)	1 (2)
Decreased appetite	9 (15)	0	5 (10)	0	3 (6)	0
Diarrhea	9 (15)	1 (2)	15 (31)	7 (14)	5 (10)	1 (2)
Fatigue	20 (34)	1 (2)	14 (29)	3 (6)	10 (19)	0
Pruritus	10 (17)	0	9 (18)	1 (2)	12 (23)	0
Rash	5 (8)	0	10 (20)	0	8 (15)	0

Abbreviations: IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; TRAE, treatment-related adverse event.
*The most common (≥ 5%) serious TRAEs in the NIVO1 + IPI3 group included diarrhea (8%), adrenal insufficiency (8%), fatigue (6%), increased ALT (6%), increased AST (6%), and colitis (6%). In the NIVO3 + IPI1 group, pneumonitis was reported as a serious TRAE in 8% of patients. No serious TRAEs ≥ 5% were reported in the NIVO3 group.
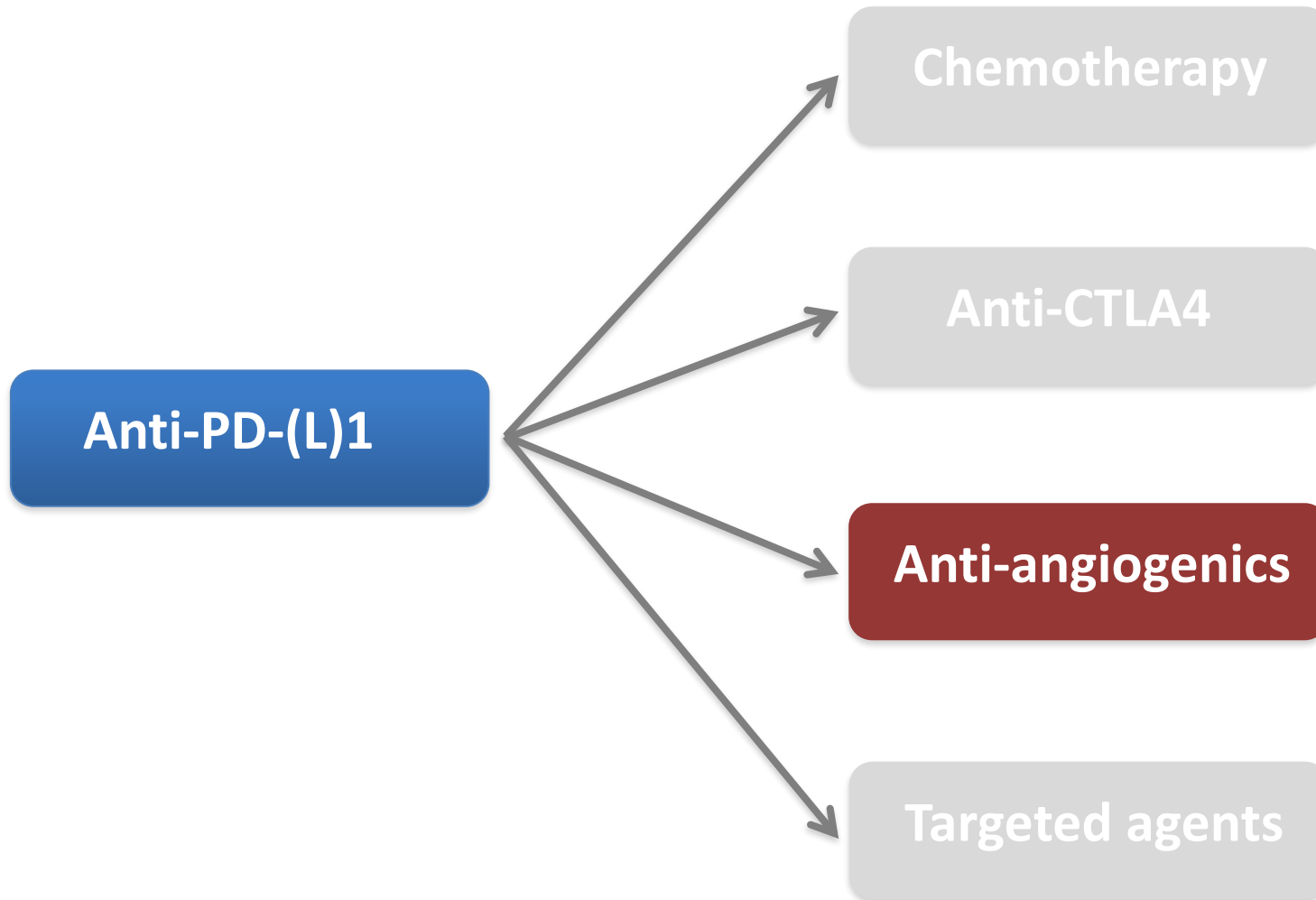
Janjigian YY et al. J Clin Oncol 2018

Caution against IO-combo in unselected patients

Phase 3 CheckMate-649

Screening

Treatment

Randomized

Nivolumab + Iplimumab (4 doses), then nivolumab monotherapy

Previously untreated gastric or GEJ cancer

Nivolumab + chemotherapy (XELOX or FOLFOX)

XELOX or FOLFOX

Post-treatment follow-up

Any PD-L1
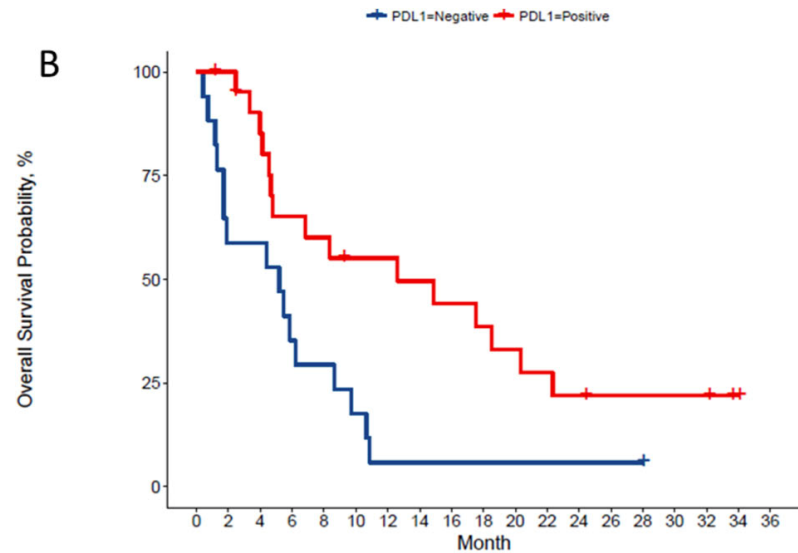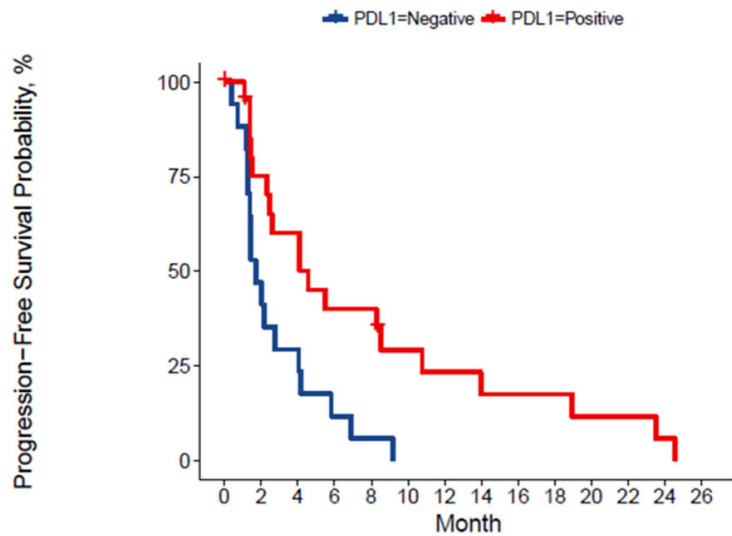1st-line
N=1266
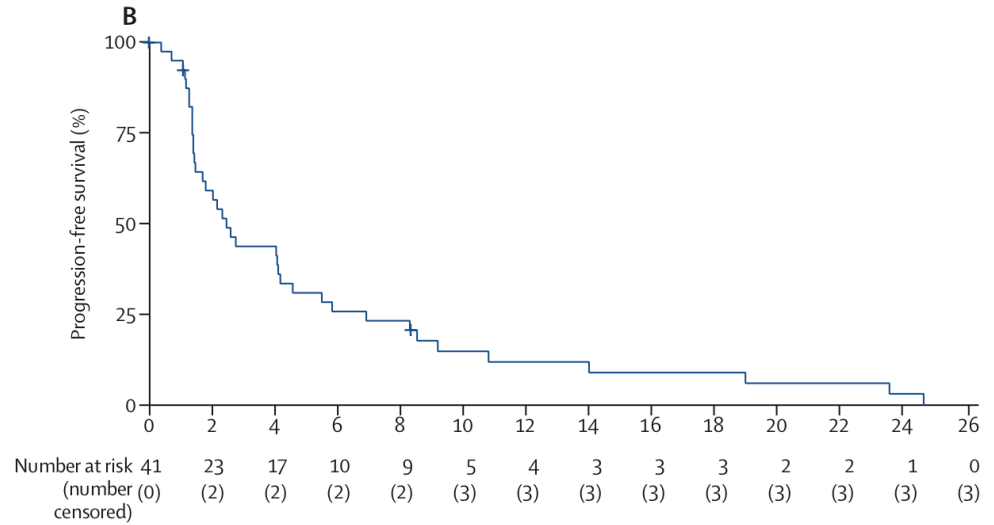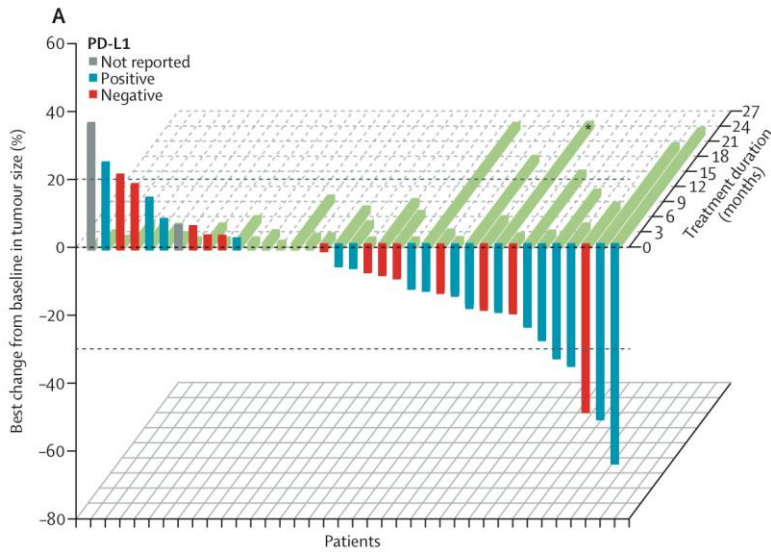
Primary Endpoint: OS (PD-L1+)

Nivo + Ipi arm closed *"due to an observed increased early death rate, as well as an increased toxicity rate"*

Main research directions: Combinations
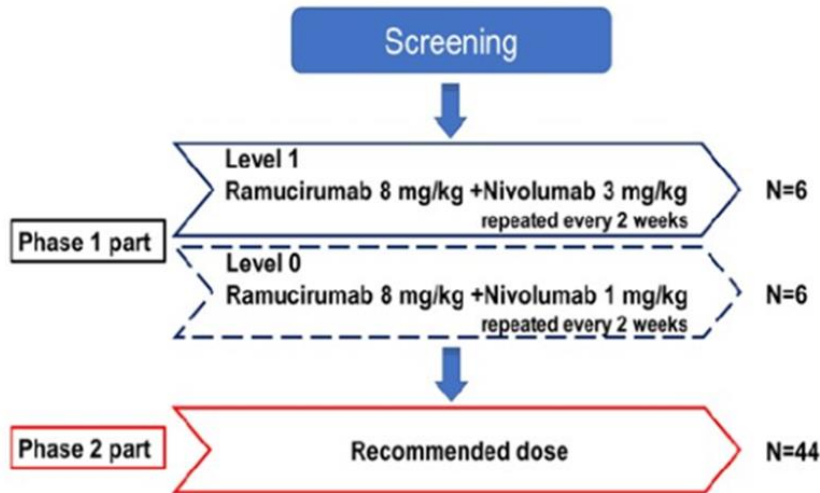
JVDF Phase 1a/b: Pembrolizumab + Ramucirumab

Herbst RS et al. Lancet Oncol 2019

NivoRam: Nivolumab + Ramucirumab

Figure 6. Progression free survival

PFS by all patients (N=45)

Median PFS	6 m PFS % (90%CI)	12 m PFS %
2.89 month	37.0% (25.2-48.8)	9.6%

No. at risk: 45, 22, 15, 6, 2
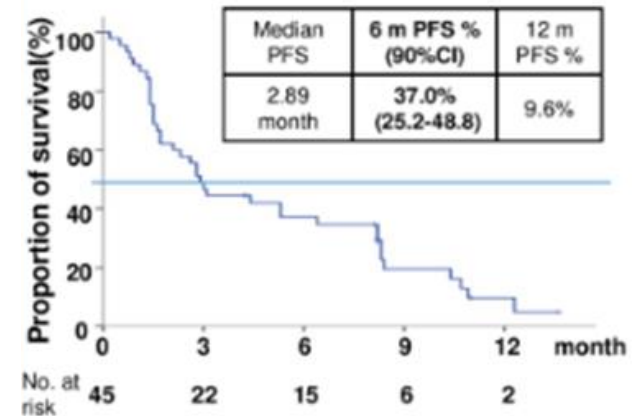
Figure 7. Overall survival

OS by all patients (N=45)

MST	6m OS%	12m OS%
17.05 m	86.4 %	58.6 %

No. at risk: 45, 43, 38, 30, 22, 15

Table 2. Tumor response data by PD-L1 expression

	All		CPS ≥1		CPS <1	
	N=45	%	N=26	%	N=16	%
Complete Response (CR)	0	0	0	0	0	0
Partial Response (PR)	12	26.7	8	30.8	2	12.5
Stable Disease (SD)	16	35.6	7	26.9	9	56.3
Progressive Disease (PD)	17	37.8	11	42.3	5	31.3
ORR (95% CI)	26.7(14.6-41.9)		30.8(14.3-51.8)		12.5(1.6-38.4)	
DCR (95% CI)	62.2(46.5-76.2)		57.7(36.9-76.7)		68.8(41.3-89.0)	

Hara H et al. ASCO GI 2019 (#129)

REGONIVO, EPOC1603: Regorafenib + Nivolumab

STUDY DESIGN

Dose escalation cohort: "3+3" design

Regorafenib Level 1: 80 mg/day 21 on 7 days off + Nivolumab 3 mg/kg q2w
n=3~6

Regorafenib Level 2: 120 mg/day 21 on 7 days off + Nivolumab 3 mg/kg q2w
n=3~6

Regorafenib Level 3: 160 mg/day 21 on 7 days off + Nivolumab 3 mg/kg q2w
n=3~6

Expansion cohort

Colorectal cancer
Gastric cancer
Total 36 cases
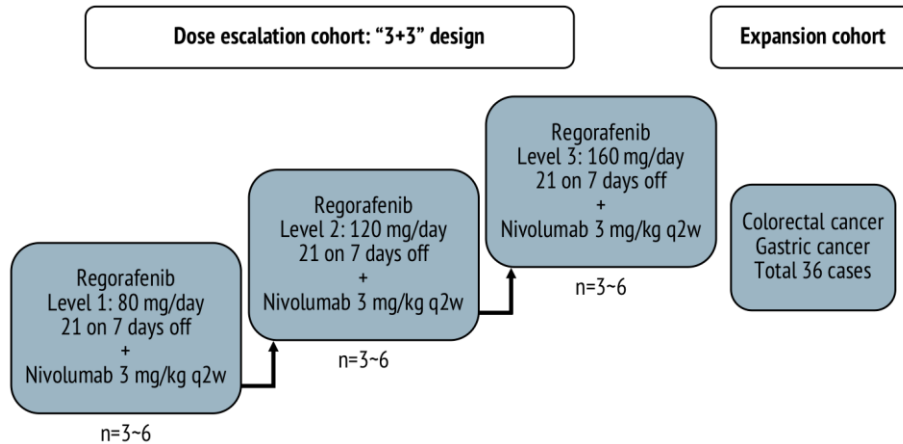
Primary outcome

Dose-limiting toxicity

Secondary outcomes

• ORR, DCR, PFS, OS

POPULATION CHARACTERISTICS

Characteristics	Total (n=50)	Dose escalation (n=14)	Dose expansion (n=36)
Median age, years (range)	61 (31–80)	61 (31–77)	61 (41–80)
Male sex	40 (80)	12 (86)	28 (78)
ECOG PS 0	49 (98)	14 (100)	35 (97)
Cancer Type			
Gastric cancer	25 (50)	9 (64)	16 (44)
Colorectal cancer	25 (50)	5 (36)	20 (56)
Site of metastases			
Lymph node	35 (70)	12 (86)	23 (64)
Liver	28 (56)	10 (71)	18 (50)
Lung	22 (44)	5 (36)	17 (47)
Peritoneum	10 (20)	0	10 (28)
Prior regimens, median (range)	3 (2–8)	3 (2–8)	3 (2–8)
Angiogenesis inhibitors	48 (96)	13 (93)	35 (97)
Anti-PD1/PD-L1	7 (14)	4 (29)	3 (9)
HER2 positive in gastric cancer	6 (24)	2 (22)	4 (25)
MSI status			
MSI-H	1 (2)	1 (7)	0
MSS	49 (98)	13 (93)	36 (100)
PD-L1 CPS*			
Positive (CPS≥1)	18 (41)**	3 (25)**	15 (47)**
Negative (CPS<1)	26 (59)**	9 (75)**	17 (53)**

*PD-L1 IHC 28–8 pharmDx   CPS; Combined positive score
**Percentage among evaluable patients
Data are n (%) unless otherwise specified

Fukuoka S et al. ASCO 2019 (#2522)

REGONIVO, EPOC1603: Regorafenib + Nivolumab

Waterfall plots showing change from baseline (%) for Colorectal cancer and Gastric cancer.

Colorectal cancer:
ORR 36%
(33% with MSS pts)
◆ MSI-H (all other patients were MSS)

Gastric cancer:
ORR 44%
(all responders were MSS)
◆ Anti-PD-1/PD-L1 refractory

Kaplan-Meier curve:
- Colorectal: Median 6.3 months
- Gastric: Median 5.8 months
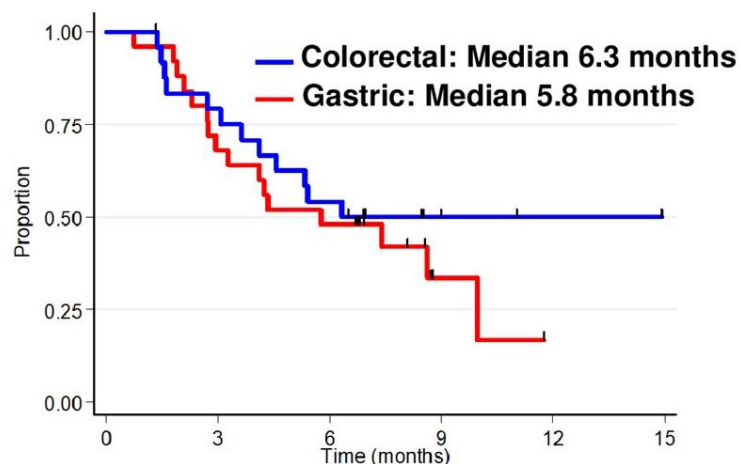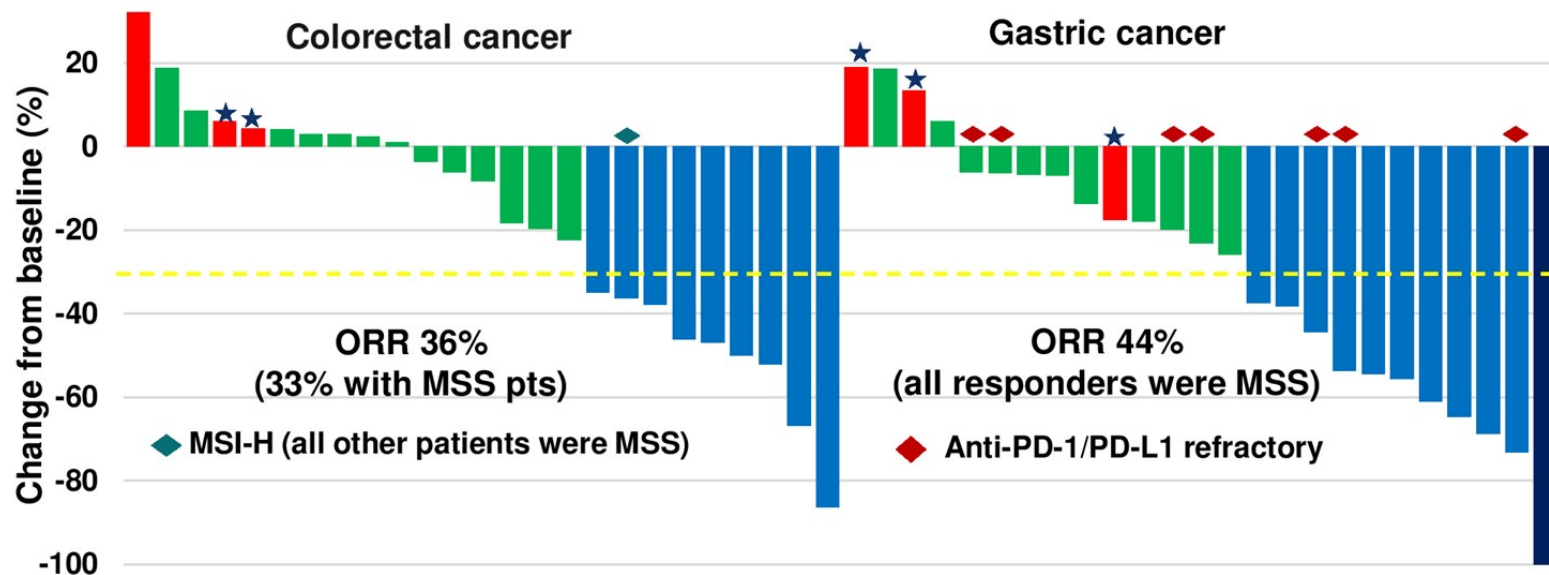
Number at risk
Gastric: 25, 17, 12, 2, 0, 0
Colorectal: 25, 19, 13, 2, 1, 0

Outcome	Colorectal	Gastric
ORR (%)	36	44
Median PFS (months)	6.3	5.8
DCR (%)*	88	88
≥ Grade 3 toxicity (%)		
80 mg		27
120 mg		44
160 mg		100

*DCR values are for the overall cohort and not stratified by tumor type

Fukuoka S et al. ASCO 2019 (#2522)

REGONIVO, EPOC1603: Regorafenib + Nivolumab

	Gastric cancer			Colorectal cancer		
	CPS 0	$1 \leq CPS < 5$	$5 \leq CPS$	CPS 0	$1 \leq CPS < 5$	$5 \leq CPS$
CR, PR	5	4	2	5	0	2
SD	5	3	1	8	5	0
PD	2	0	0	1	1	0

- 67-year-old male with HER2-negative gastric cancer
- Disease progression after Nivo monotherapy · MSS, PD-L1 CPS0, EBV negative
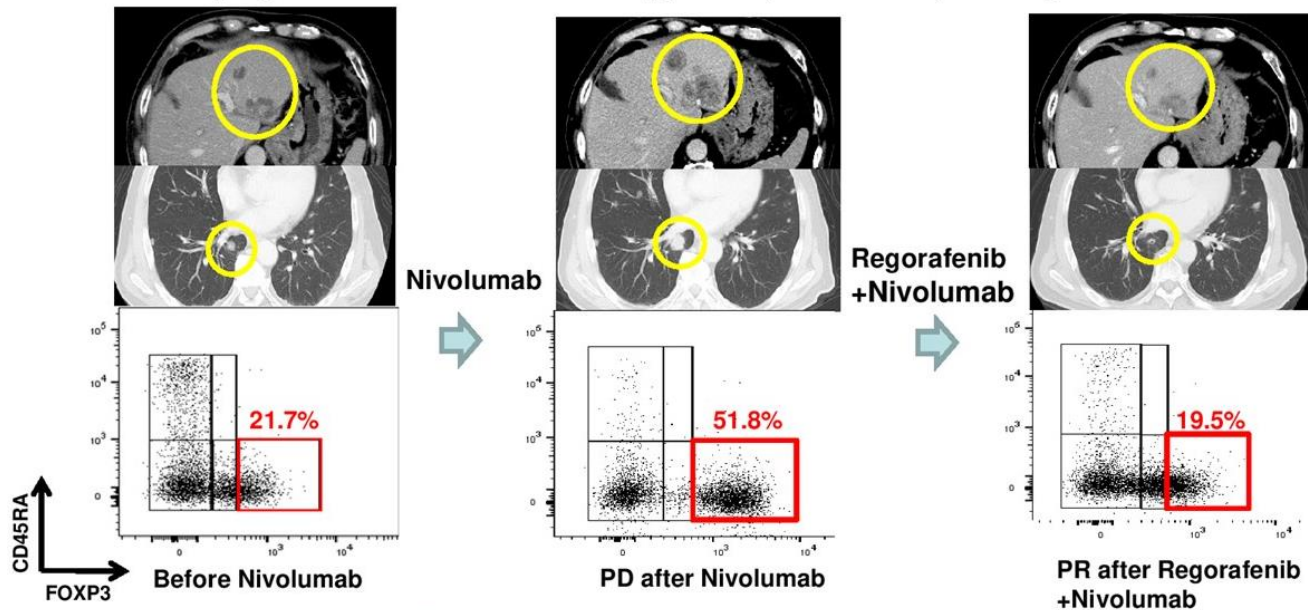
CD45RA⁻FoxP3ʰⁱ effector Tregs increased at PD state after nivolumab treatment, which decreased after regorafenib+nivolumab

Fukuoka S et al. ASCO 2019 (#2522)

Main research directions: Combinations
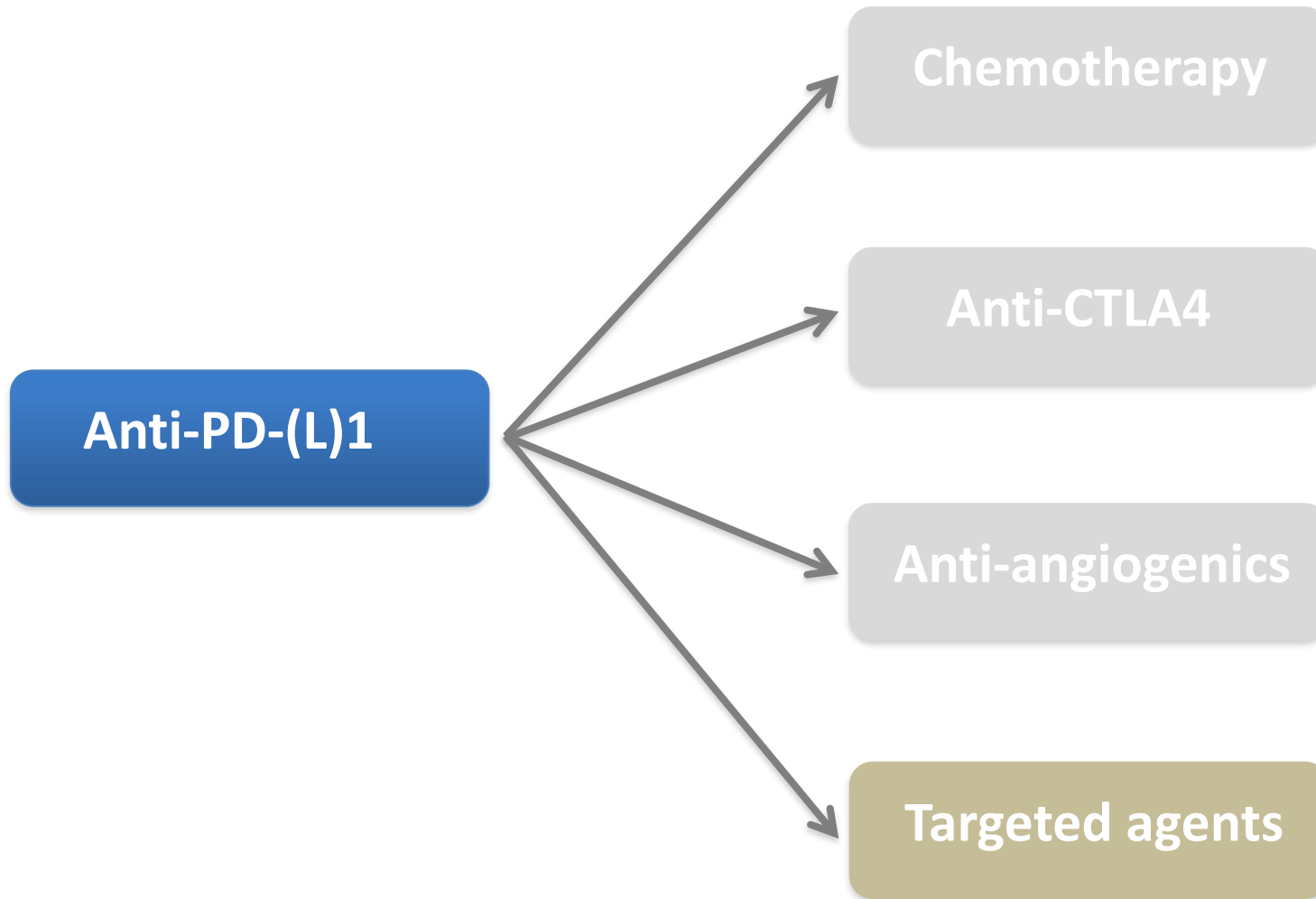
CAPOX + Trastuzumab + Pembrolizumab: Phase 2

Baseline Characteristics (n=35)

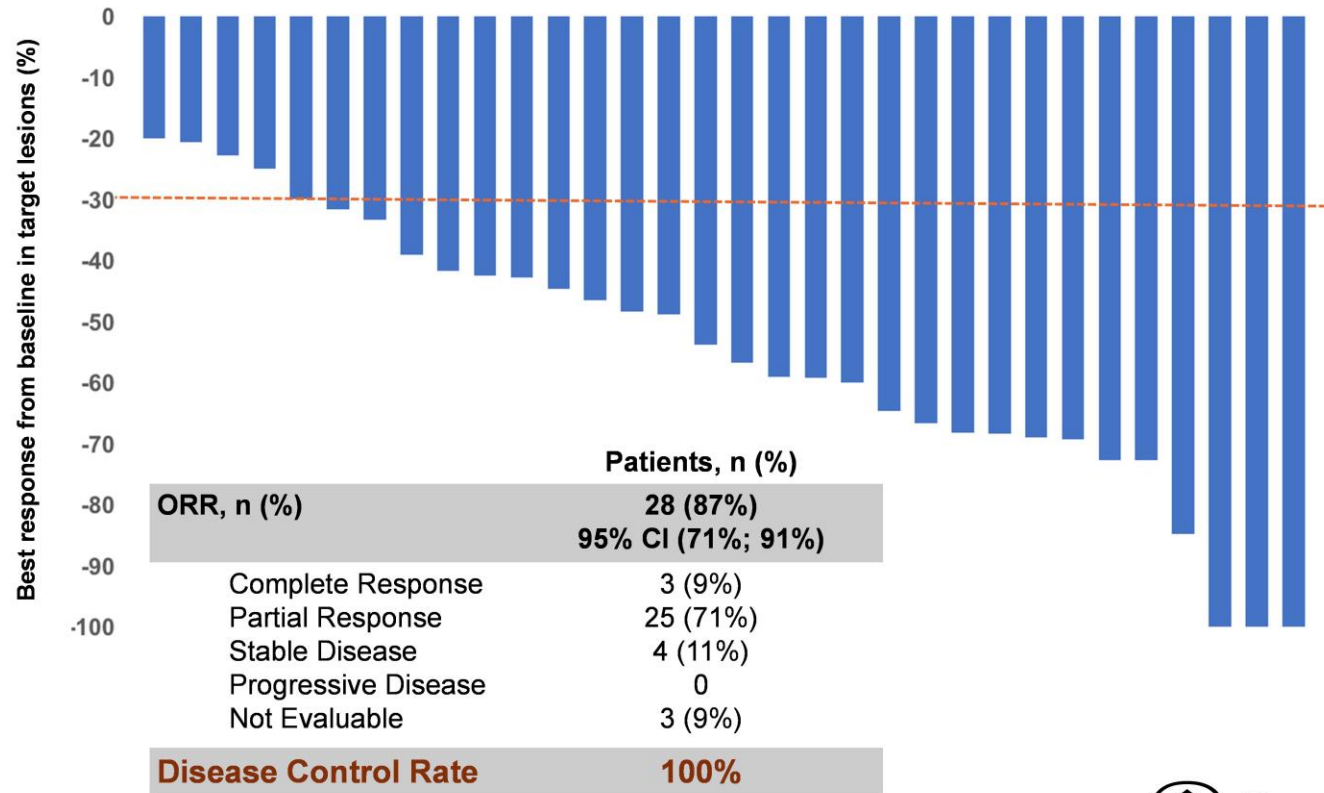| Pembrolizumab/Trastuzumab/Chemo	Patients, n (%)
Age, median (range), years	61 (20-83)
Male	27 (77)
Race	
White	29 (82)
Asian	2 (6)
Black	1 (3)
Hispanic/Other	3 (9)
Primary site	
Esophageal	14 (40)
GEJ	12 (34)
Gastric	9 (26)
HER2 MSK confirmation	
Positive	28 (80)
Negative	6 (17)
Not available	1 (3)
Pretreatment PD-L1 status	
CPS <1 (negative)	12 (34)
CPS >=1	14 (40)
Not available	9 (26)

Memorial Sloan Kettering Cancer Center

Janjigian YY et al. ASCO GI 2019 (#62)

CAPOX + Trastuzumab + Pembrolizumab: Phase 2

Janjigian YY et al. ASCO GI 2019 (#62)

CAPOX + Trastuzumab + Pembrolizumab: Phase 2

Progression-Free Survival (n=35)
Pembrolizumab/Trastuzumab/Chemotherapy

Median PFS 11.4 months (95%CI; 6.0 to 16.4)
67% of patients progression free at 6 months
Median follow up 6.6 months (0.03 to 23.5)

CAPOX + Trastuzumab + Pembrolizumab: Phase 2

Biomarker Analysis (n=29)
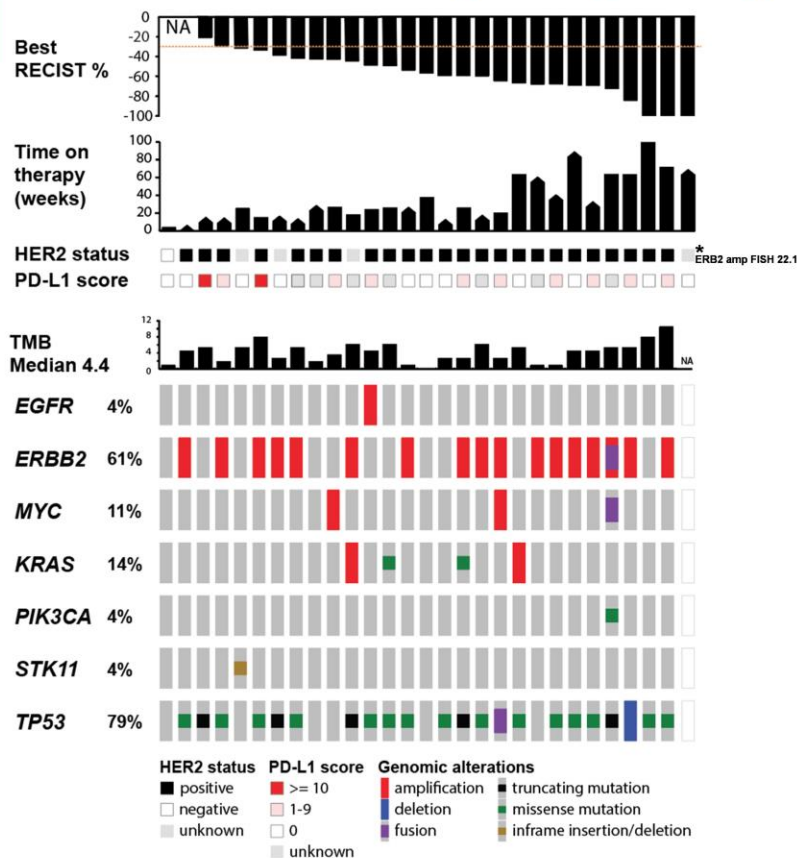
- **No MSI tumors in HER2+ mEGA**
  - -- Median TMB 4.4 mut/MB (range 0 to 10.6)
- **PDL-1 status is not a predictor**
  - -- PFS (log-rank p=0.10) or OS (log-rank p=0.60) between PDL-1 + vs PDL-1-
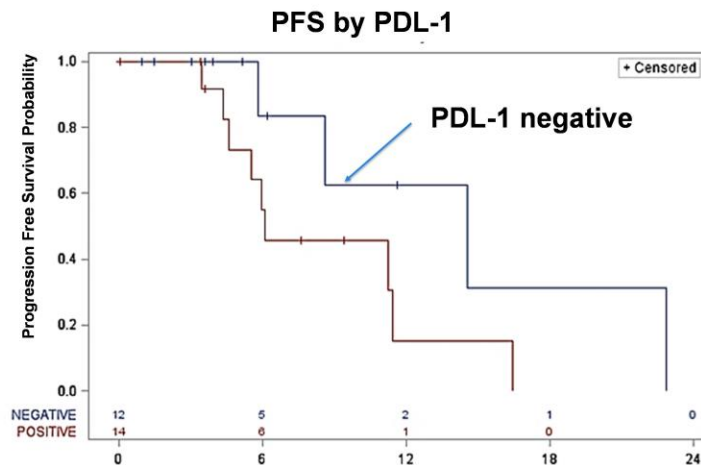
- **ERBB2 non-amp by NGS is associated with short duration of response**
  - -- 33% of patients with co- occurring RTK/RAS/PIK3CA alterations

Janjigian YY et al. ASCO GI 2019 (#62)

Phase 3 KEYNOTE 811

Patients

- Advanced G/GEJ adenocarcinoma
- No prior therapy for advanced disease
- HER2-positive

Randomization 1:1 N = 692

Pembrolizumab 200 mg q3w + Trastuzumab + FP or CAPOX

Placebo + Trastuzumab + FP or CAPOX

Treat for up to 35 cycles (2 years) or until progression or intolerable toxicity

Stratification

- Geographic region
- PD-L1 status
- Chemo regimen (FP or CAPOX)

Janjigian YY et al. ASCO 2019 (#TPS4146)

Agenda

- Current evidence supporting immunotherapy development in GC

- Hottest news in immunotherapy for GC

- How to optimally select candidates for ICIs in GC

- Main ongoing trials with ICIs in GC

- **Conclusions**

Conclusions

• Beyond ATTRACTION-2 in Eastern population, no definitive phase 3 evidence confirmed the role of ICIs in unselected advanced GC

• KEYNOTE-062 proved Pembrolizumab non-inferior to CT in PD-L1 CPS 1 or higher, but what about at risk-patients in ICI arm?

• Biomarkers might help refining patient selection
  • PD-L1: conflicting data, CPS vs. TPS, optimal sample debated
  • EBV: strong rationale, preliminary data, no post-hoc analyses
  • MSI: testing recommended (screening, prognosis, prediction)

• Ongoing trials exploring multiple combinations, but still no prospective validation of molecular selection on the horizon

Thank you!

lorenzo.fornaro@gmail.com

BACK UP SLIDES
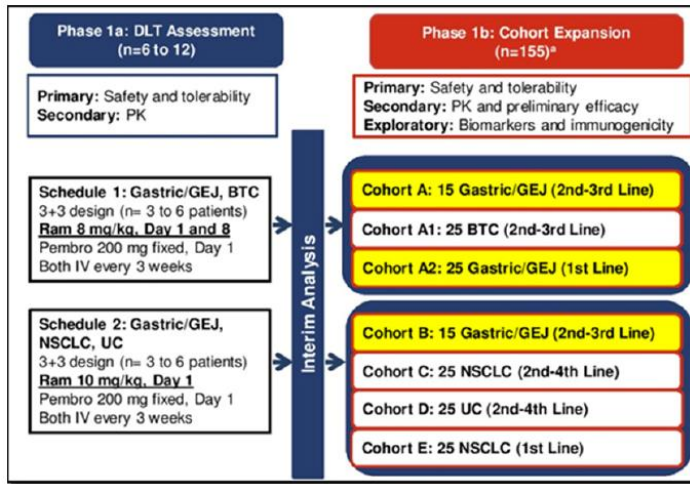
JVDF: Pembrolizumab + Ramucirumab

Phase 1a: DLT Assessment (n=6 to 12)

Primary: Safety and tolerability
Secondary: PK

Schedule 1: Gastric/GEJ, BTC
3+3 design (n= 3 to 6 patients)
Ram 8 mg/kg, Day 1 and 8
Pembro 200 mg fixed, Day 1
Both IV every 3 weeks

Schedule 2: Gastric/GEJ, NSCLC, UC
3+3 design (n= 3 to 6 patients)
Ram 10 mg/kg, Day 1
Pembro 200 mg fixed, Day 1
Both IV every 3 weeks

Interim Analysis

Phase 1b: Cohort Expansion (n=155)[a]

Primary: Safety and tolerability
Secondary: PK and preliminary efficacy
Exploratory: Biomarkers and immunogenicity

Cohort A: 15 Gastric/GEJ (2nd-3rd Line)
Cohort A1: 25 BTC (2nd-3rd Line)
Cohort A2: 25 Gastric/GEJ (1st Line)
Cohort B: 15 Gastric/GEJ (2nd-3rd Line)
Cohort C: 25 NSCLC (2nd-4th Line)
Cohort D: 25 UC (2nd-4th Line)
Cohort E: 25 NSCLC (1st Line)

Table 6. Efficacy Outcomes in Evaluable Patients (PD-L1 All Comers)

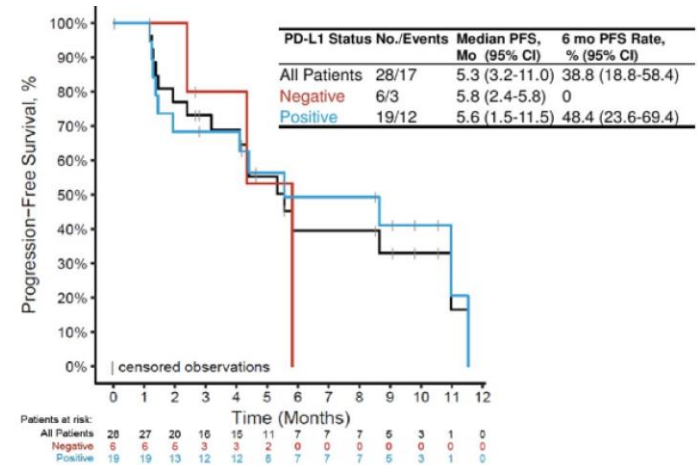| All treated patients	1st-Line Cohort A2 n=28
Median follow-up duration, mo (95% CI)	8.1 (5.7-9.9)
Best overall response, n (%)	
Complete response (CR)	-
Partial response (PR)	7 (25)
Stable disease (SD)	12 (43)
Progressive disease (PD)	6 (21)
Not Evaluable	3 (11)
Objective response rate	25%
Disease control rate[a]	68%
Median duration of response, mo (95%CI)	10 (9.7-10.3)[b]
Median time to response, mo (95% CI)	2.7 (1.3-2.8)
Duration of stable disease, mo (95% CI)	5.4 (3.2-8.6)

[a] patients with best response of CR, PR, or SD;
[b] As of the data cutoff, 5 (71%) of 7 patients with a confirmed response were still on treatment.
NR= not reached

Efficacy by PD-L1 (2nd-3rd line)

PD-L1	pts/events	Median PFS, Mo (95% CI)
Negative	17/17	1.7 (1.3-4.0)
Positive	22/19	4.6 (2.3-8.5)

PD-L1	pts/events	Median OS, Mo (95% CI)
Negative	17/16	5.2 (1.3-8.6)
Positive	22/15	12.6 (4.7-20.3)

Pts=patients
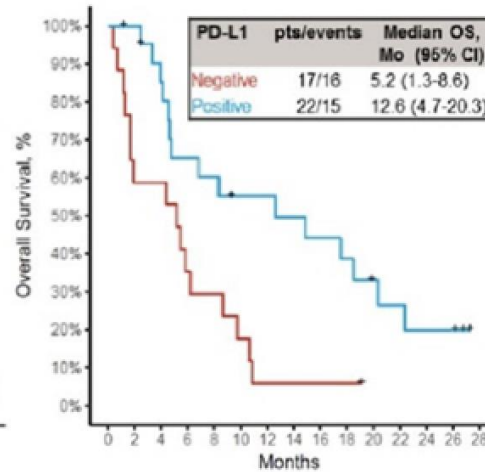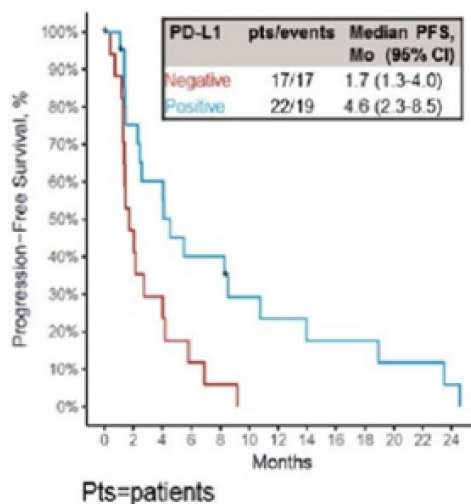
Efficacy by PD-L1 (1st line)

PD-L1 Status	No./Events	Median PFS, Mo (95% CI)	6 mo PFS Rate, % (95% CI)
All Patients	28/17	5.3 (3.2-11.0)	38.8 (18.8-58.4)
Negative	6/3	5.8 (2.4-5.8)	0
Positive	19/12	5.6 (1.5-11.5)	48.4 (23.6-69.4)

| censored observations

Patients at risk:
All Patients 28 27 20 16 15 11 7 7 5 3 1 0
Negative 6 6 6 3 3 2 0 0 0 0 0 0
Positive 19 19 13 12 12 8 7 7 5 3 1 0

Chau I et al. ASCO GI 2018 (abstr. 101); Herbst RS et al. ASCO 2018 (abstr 3059)

Ongoing phase 3 trials in 1-line

Study	Endpoint	Arms
Keynote-811	OS, PFS	PF-Trastuzumab +/- Pembrolizumab
Keynote-859	OS, PFS	PF +/- Pembrolizumab
Checkmate-649	OS, PFS	PF +/- Nivolumab
Javelin Gastric 100	OS	PF *vs*. PF ➜ Avelumab

ClinicalTrials.gov (accessed: 20/Feb/2019)

MEDIOLA: Olaparib + Durvalumab

Table 3. Objective response rate, onset of response and duration of response

Best response	n (%) (N=39)	First dose to onset of response	Duration of response from onset of response
Objective response rate	10.3% (95% CI: 2.9, 24.2)		
CR	2 (5.1)	84, 85 days	51, 339 days
PR	2 (5.1)	84, 197 days	225, 225 days*
SD	6 (15.4)	NA	NA
PD	26 (66.7)	NA	NA
NE	3 (7.7)	NA	NA

*Patients without a progression event are censored using date last known to be progression-free

Figure 3. a) Progression-free survival. b) Overall survival
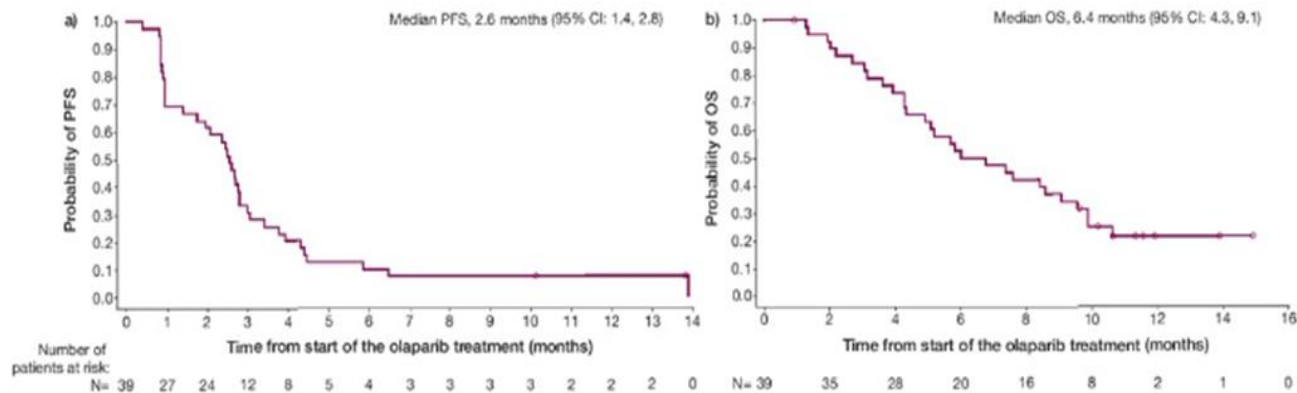
A circle represents a censored event. Patients who have not died are censored at their last known date alive
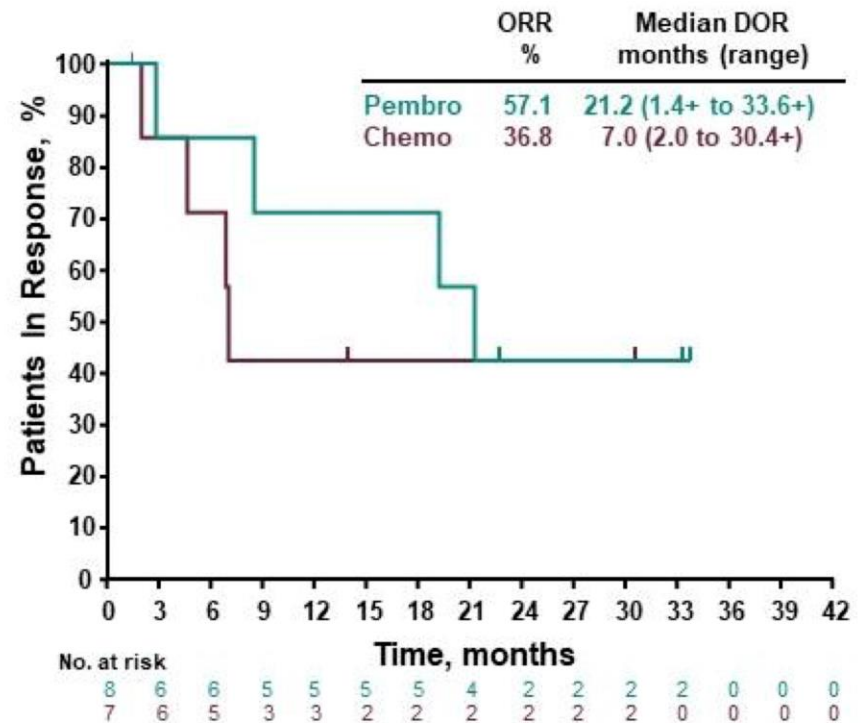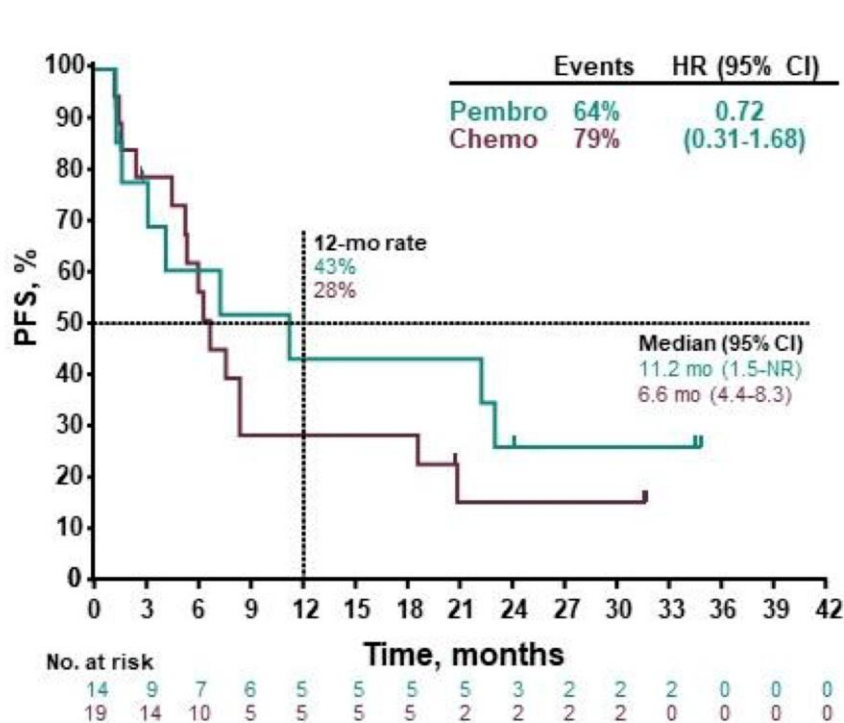
Bang YJ et al. ASCO GI 2019 (abstr. 140)

Results according to BRCA and platinum sensitivity

Swimmer plot by last known survival day, platinum sensitivity and genomic data

No molecular data available
PD during or <6 mos from platinum
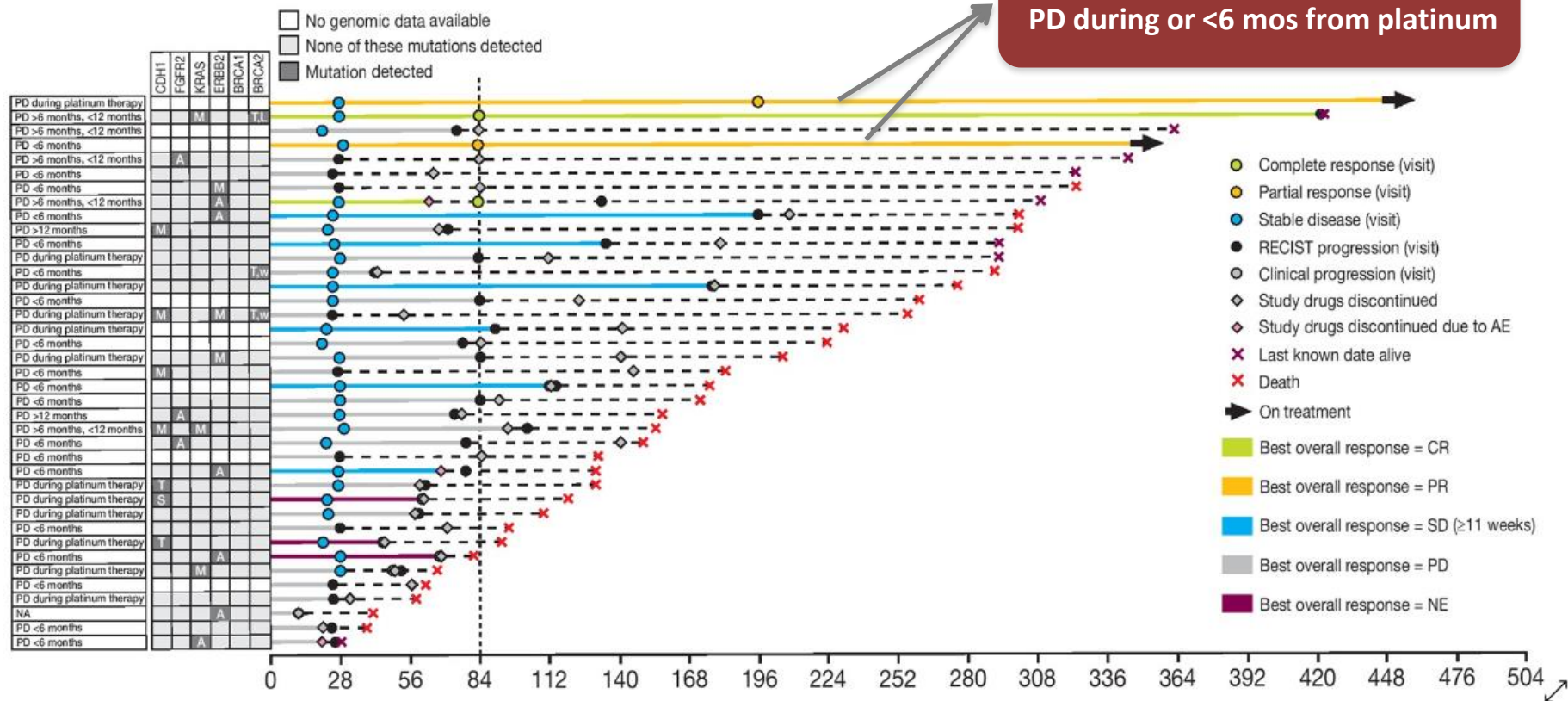
KEYNOTE-062: MSI-high (PFS and DoR)

Pembro vs Chemo: PFS and DOR in MSI-H Group (CPS ≥1)

MSI status and benefit from CT

Janjigian YY et al. Cancer Discovery 2018
Pietrantonio F et al. JCO 2019