October 10, 2019

Check-Point Inhibitors in Gastric Cancer: KEYNOTE-061 trial and beyond it

NCC EPOC
Exploratory Oncology Research & Clinical Trial Center

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Standard treatment for GC

1st line

Fluorpimidines +Platinum

+Trastuzumab (HER2+)

2nd line

Paclitaxel+ Ramucirumab

3rd or later line

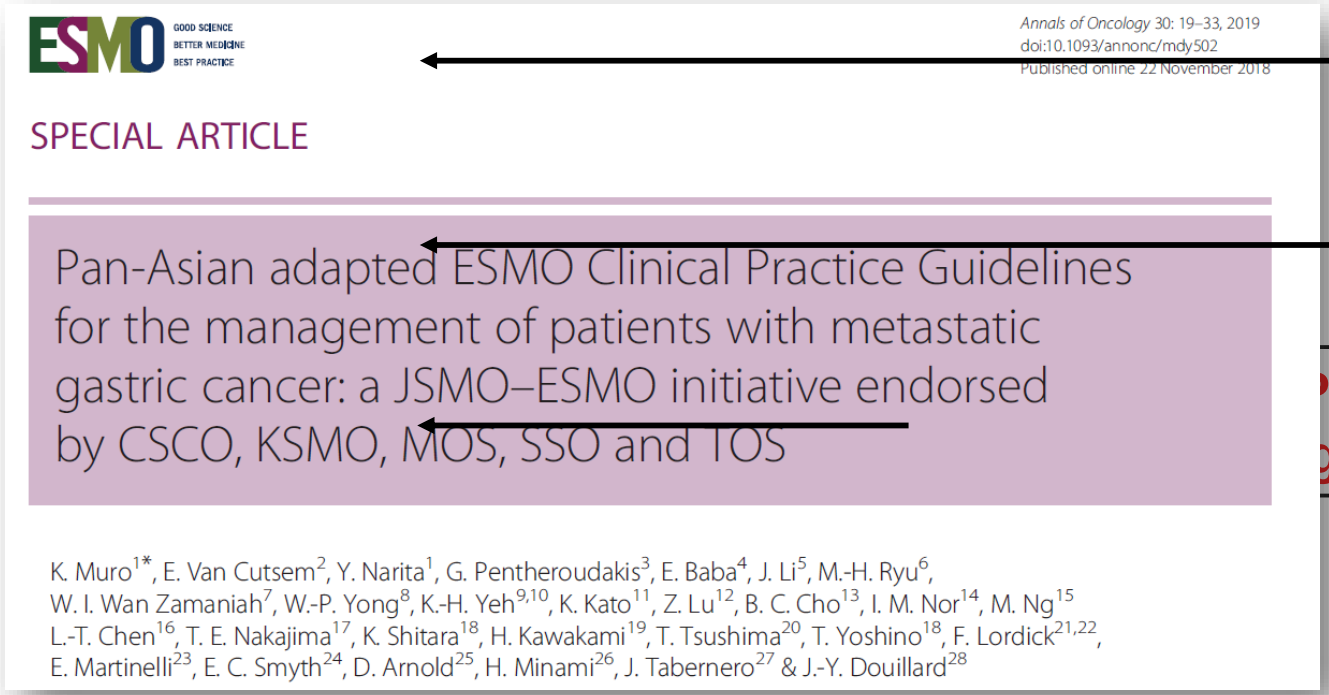
Irinotecan

FTD/TPI (US, EU,Japan)

Nivolumab (Asia)

Pembrolizumab (CPS≥1, US)

embrolizumab
gh, several countries)


ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 19–33, 2019
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SPECIAL ARTICLE

Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic gastric cancer: a JSMO–ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS

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() approved countries

KEYNOTE-061: Phase 3 Study of Pembrolizumab vs Paclitaxel for Previously Treated Advanced Gastric or Gastroesophageal Junction Cancer

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KEYNOTE-061 Study Design (NCT02370498)

Key Eligibility Criteria

- Adenocarcinoma of the stomach or GEJ that was metastatic or locally advanced but unresectable
- PD per RECIST v1.1 after first-line platinum- and fluoropyrimidine-containing therapy
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment[a]
  - First 489 patients: any PD-L1 CPS
  - Final 103 patients: PD-L1 CPS ≥1[b]

Stratification Factors

- Region (Eur/Israel/N America/Australia vs Asia vs rest of the world)
- ECOG PS (0 vs 1)[c]
- TTP on first-line therapy (<6 mo vs ≥6 mo)[d]
- PD-L1 CPS (<1 vs ≥1)[d]

R (1:1)

N = 296

Pembrolizumab

200 mg Q3W

for 35 cycles or until confirmed PD, intolerable toxicity, patient withdrawal, or investigator decision

N = 296

Paclitaxel 80 mg/m^2 on days 1, 8, and 15 of 4-week cycles

until confirmed PD, intolerable toxicity, patient withdrawal, or investigator decision

End Points

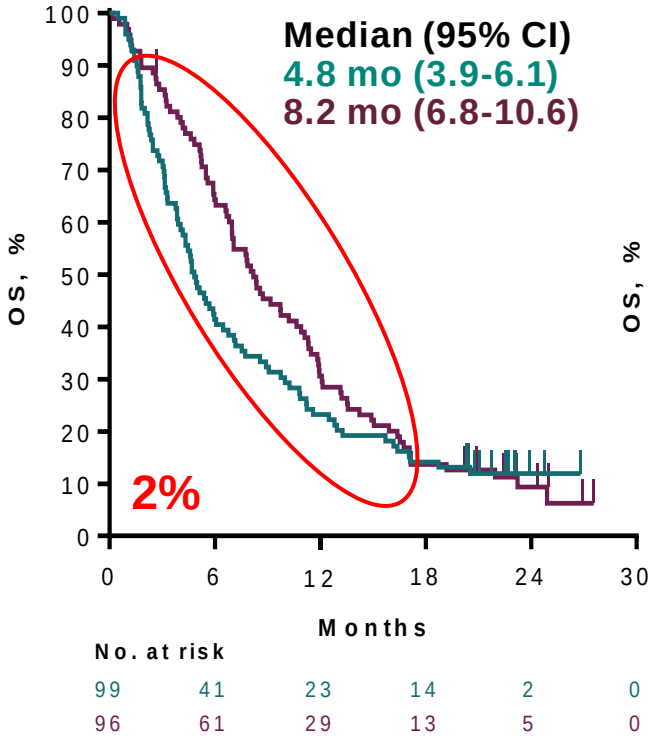
- **Primary:** OS and PFS in the CPS ≥1 population
- **Secondary:** ORR and DOR in the CPS ≥1 population; safety in all treated patients

[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay. Measured as CPS, defined as the number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) out of the total number of tumor cells × 100. [b]At the recommendation of the independent, external monitoring committee. [c]First 125 patients only. [d]Final 467 patients only.

KEYNOTE-061: Pembrolizumab vs wPTX as 2nd-line for GC: Overall Survival by PD-L1 CPS or MSI-H

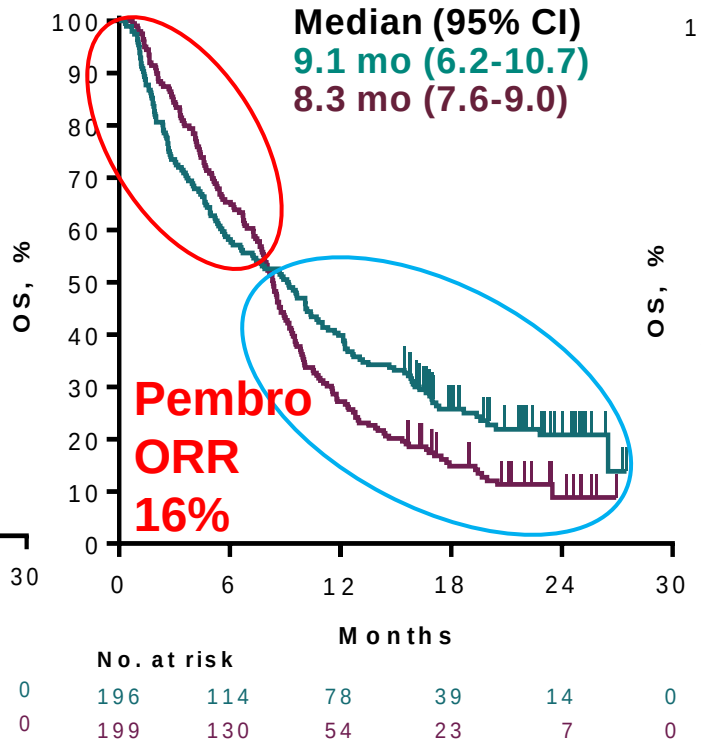
CPS <1

	Events/ Pts	HR (95% CI)
Pembrolizumab	87/99	1.20 (0.89-1.63)
Paclitaxel	86/96	



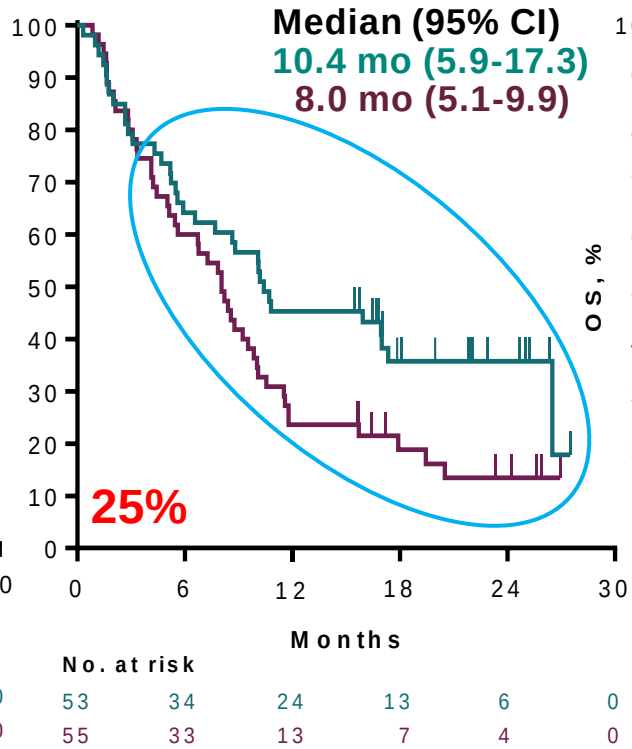
CPS ≥1 (primary cohort)

	Events/ Pts	HR (95% CI)
Pembrolizumab	151/196	0.82 (0.66-1.03)
Paclitaxel	175/199	



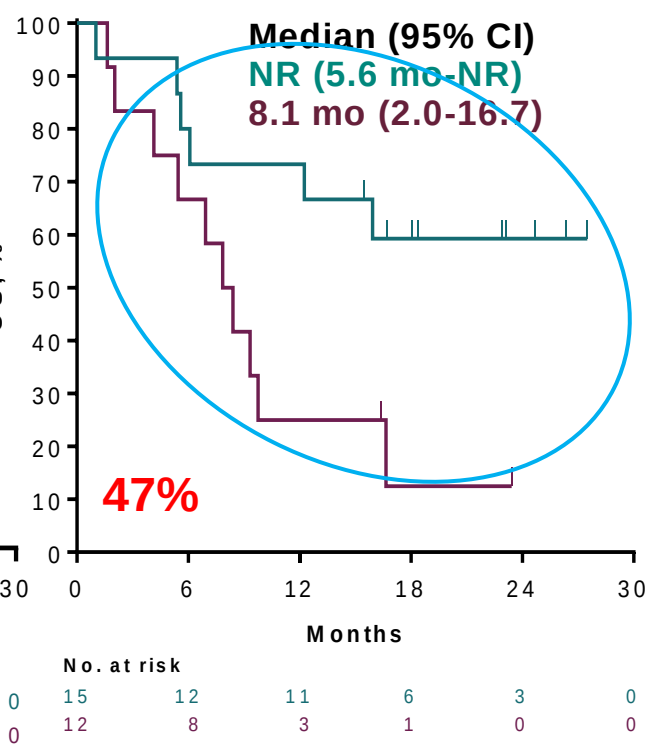
CPS ≥10

	Events/ Pts	HR (95% CI)
Pembrolizumab	34/53	0.64 (0.41-1.02)
Paclitaxel	46/55	



MSI-H

	Events/ Pts	HR (95% CI)
Pembrolizumab	6/15	0.42 (0.13-1.31)
Paclitaxel	10/12	

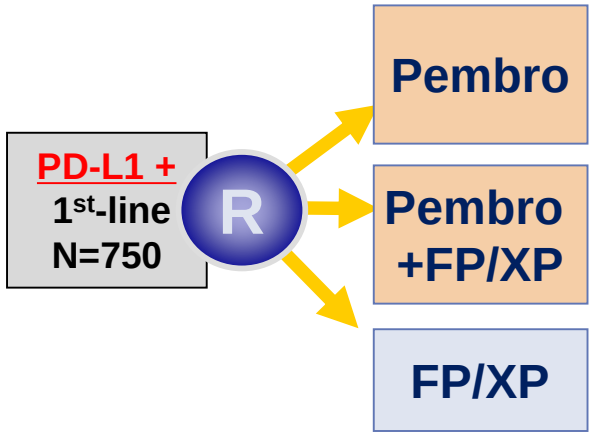


Shitara K et al. Lancet 2018

Pembrolizumab did not significantly improve OS and PFS among PDL1+ (CPS≥1) GC pts
Different treatment effect of pembrolizumab according to CPS or MSI-H status

Phase 3 trials in 1st-line for GC with completed enrollment

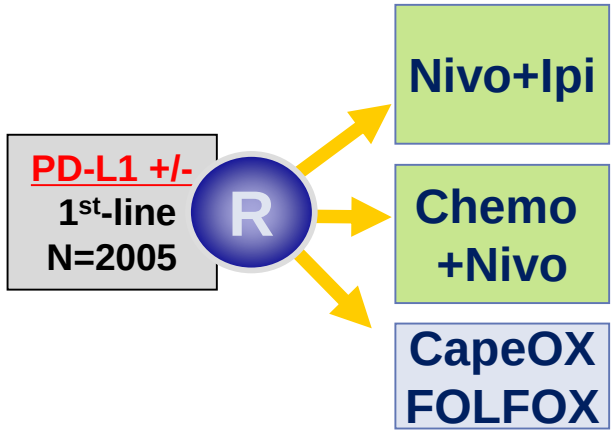
KEYNOTE-062
NCT02494583



Primary endpoint:
PFS and OS in CPS≥1
OS in CPS ≥ 10

Active, not recruiting
July 31, 2015 ~

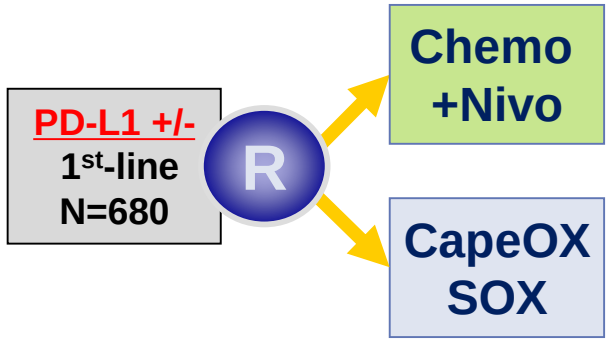
CheckMate-649
NCT02872116



Primary endpoint:
PFS and OS
in PD-L1+

Active, not recruiting
Oct.4, 2016 ~

ONO-4538-37
ATTRACTION-04
NCT02746796



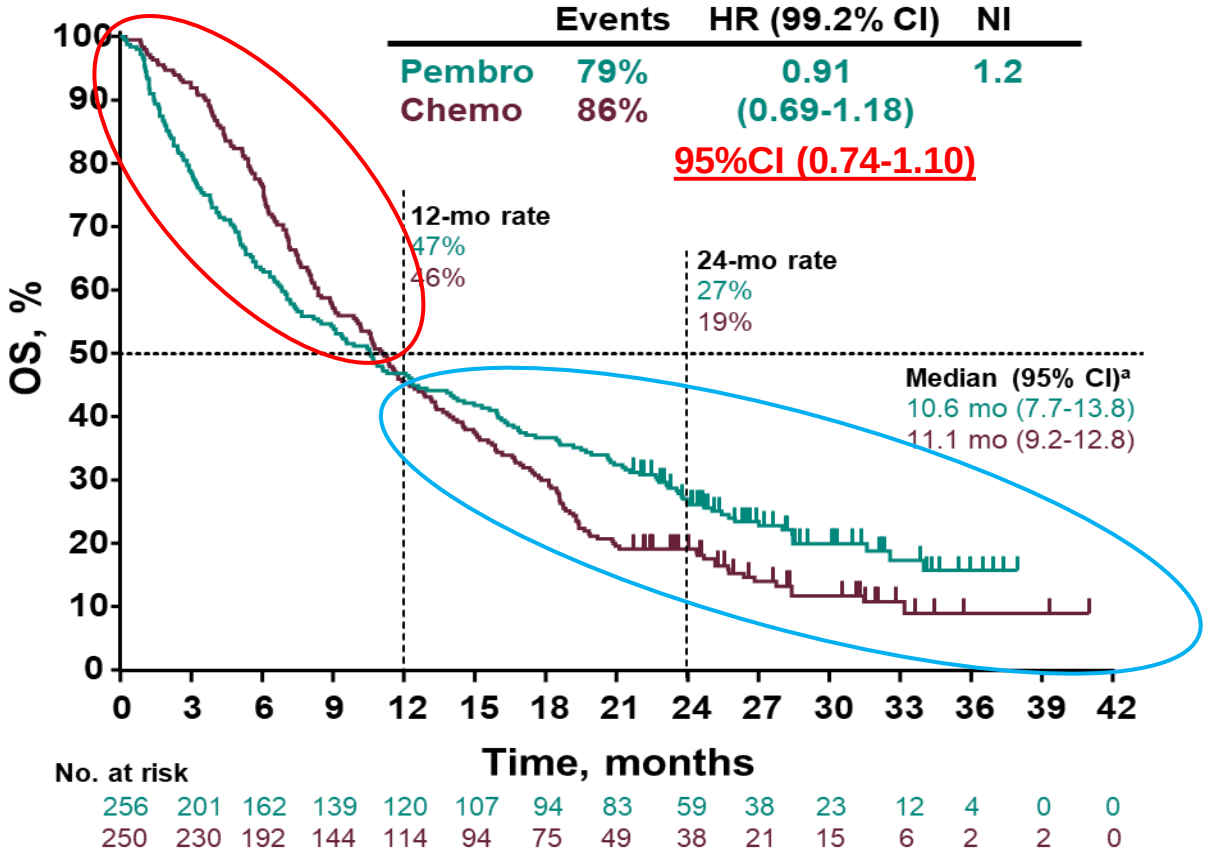
Primary endpoint:
PFS and OS

Active, not recruiting
March 2016 (part1)~

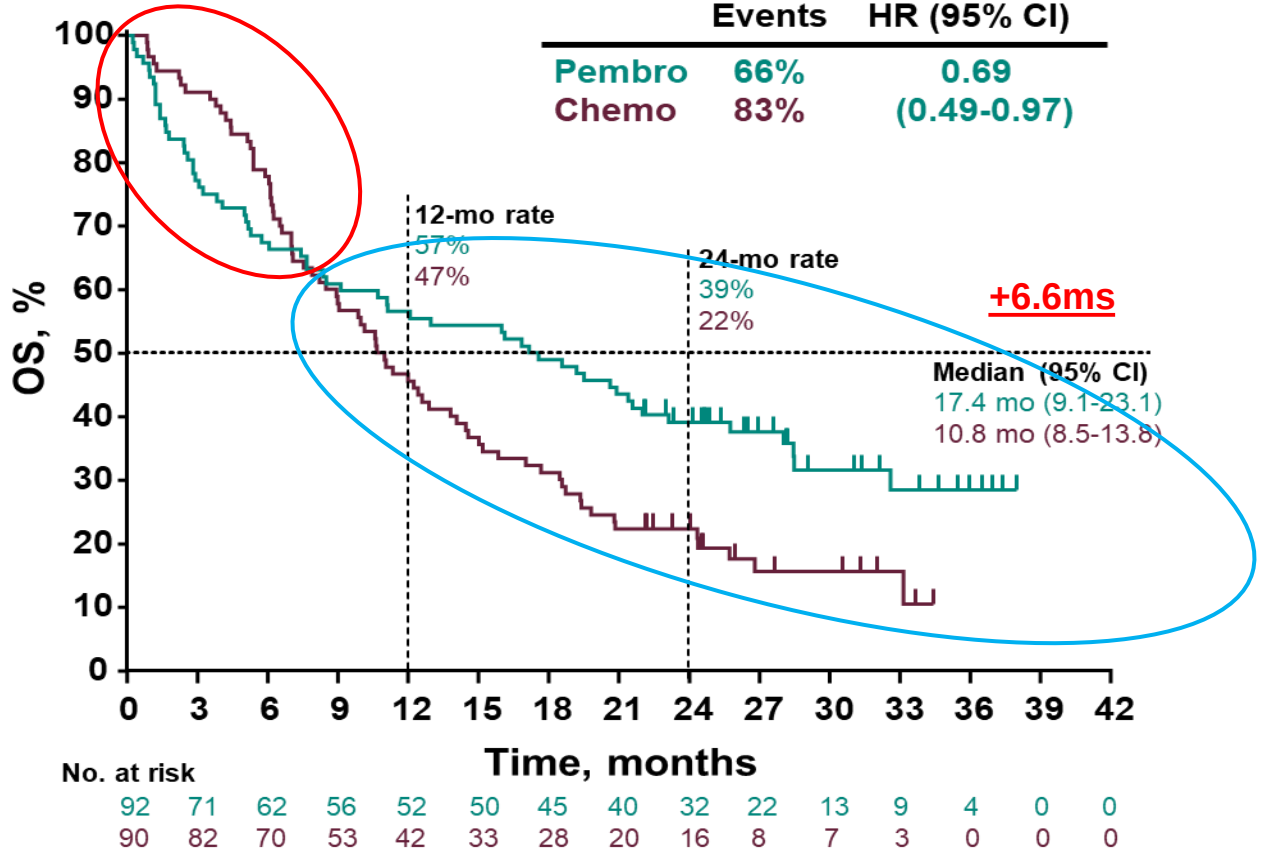
https://clinicaltrials.gov

KEYNOTE-062: Pembrolizumab vs 1st-line chemo: OS

CPS ≥1



CPS ≥10

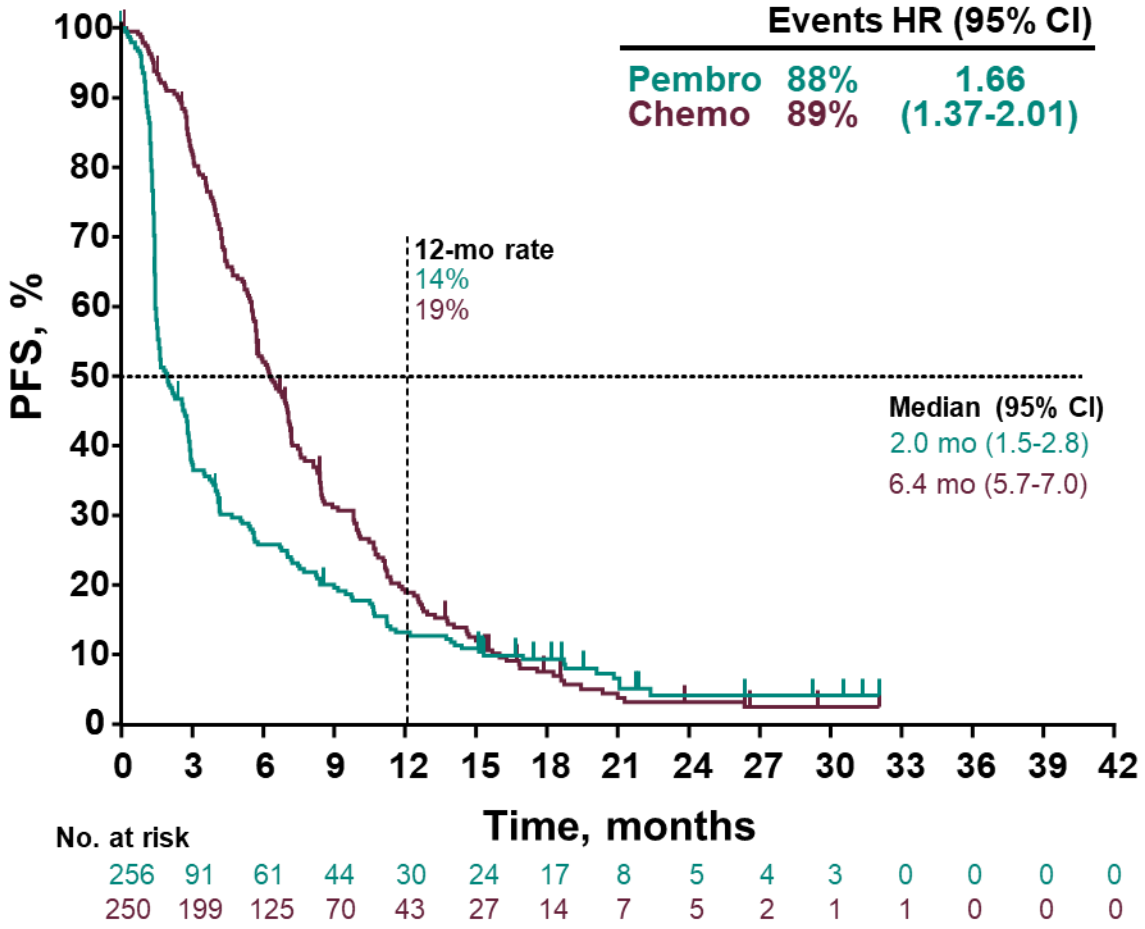


Tabernero J,et al. ASCO 2019; ESMO-GI 2019
Shitara K et al. ESMO 2019

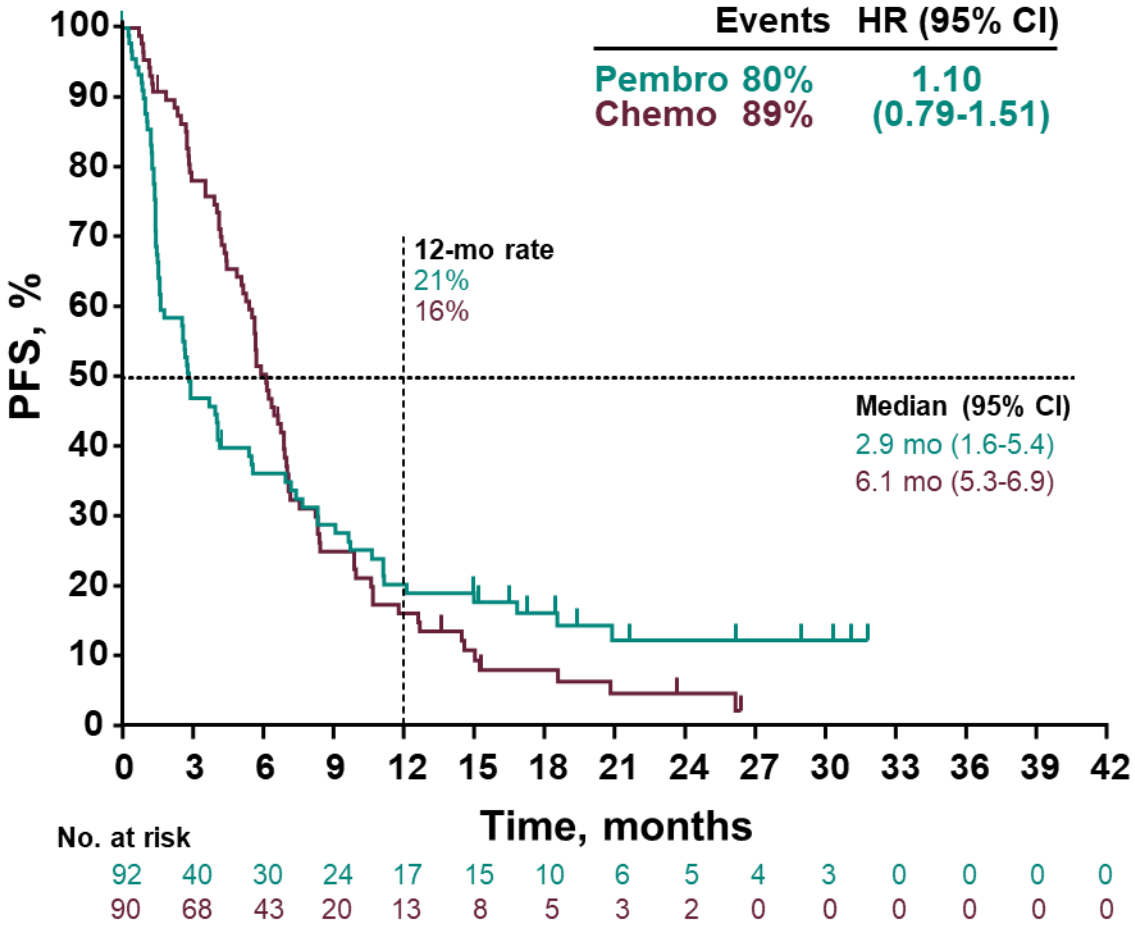
Non-inferiority of pembrolizumab was shown in OS of CPS≥1 pts
Greater effect in CPS10
Crossed OS curve (as same as KN061)
Lower Grade 3 AE (17% vs. 69%) and d/c of drugs by AE (11% vs. 24%)

KEYNOTE-062: Pembrolizumab vs 1st-line chemo: PFS

CPS ≥1



CPS ≥10



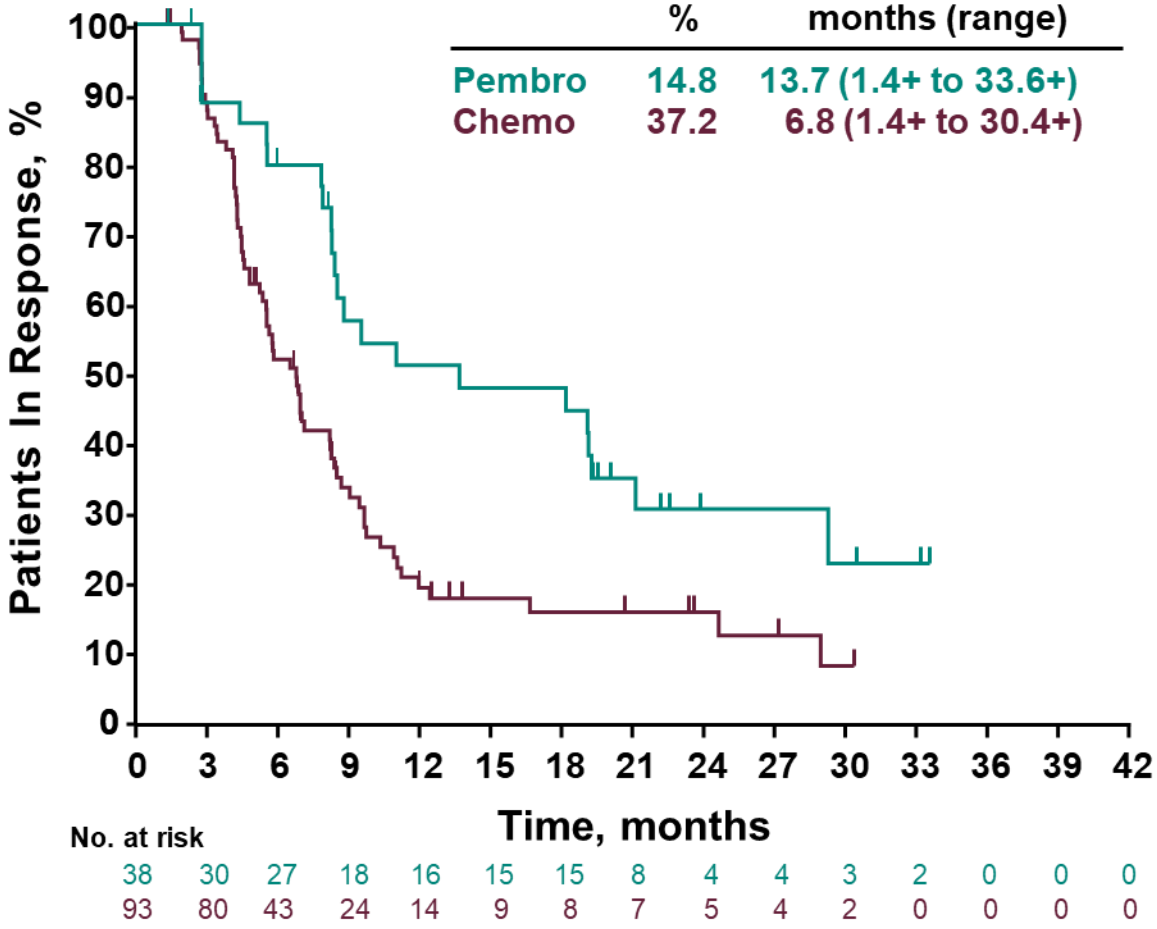
Tabernero J,et al. ASCO 2019; ESMO-GI 2019
Shitara K et al. ESMO 2019

PFS showed a shorter trend with pembro than chemo
Crossed PFS curve in CPS10

KEYNOTE-062: Pembrolizumab vs 1st-line chemo: ORR

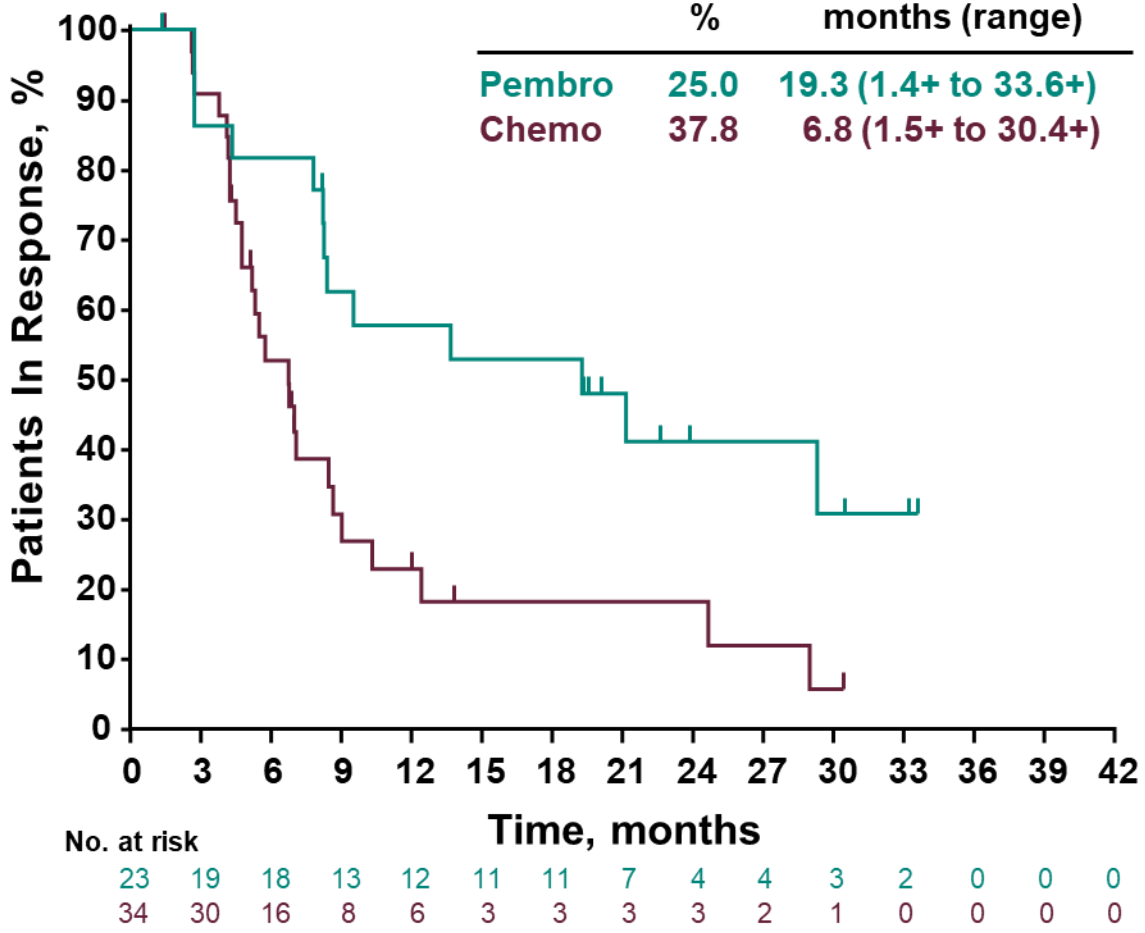
CPS ≥1

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



CPS ≥10

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

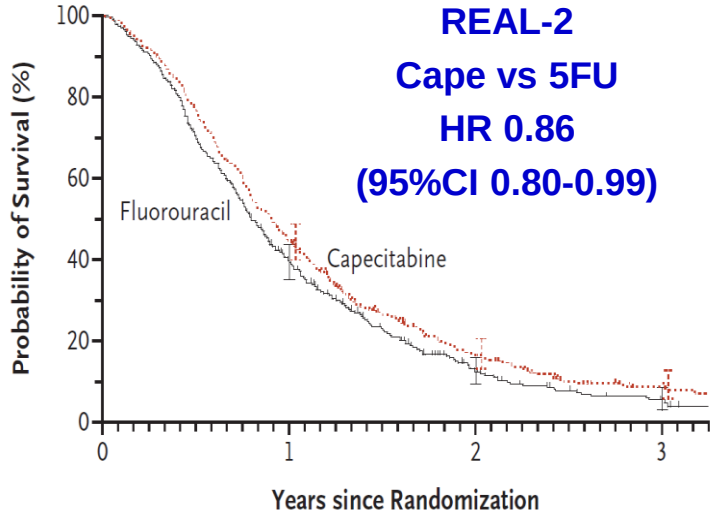


Tabernero J,et al. ASCO 2019; ESMO-GI 2019
Shitara K et al. ESMO 2019

ORR lower but longer duration of response

Non-inferiority: change clinical practice?

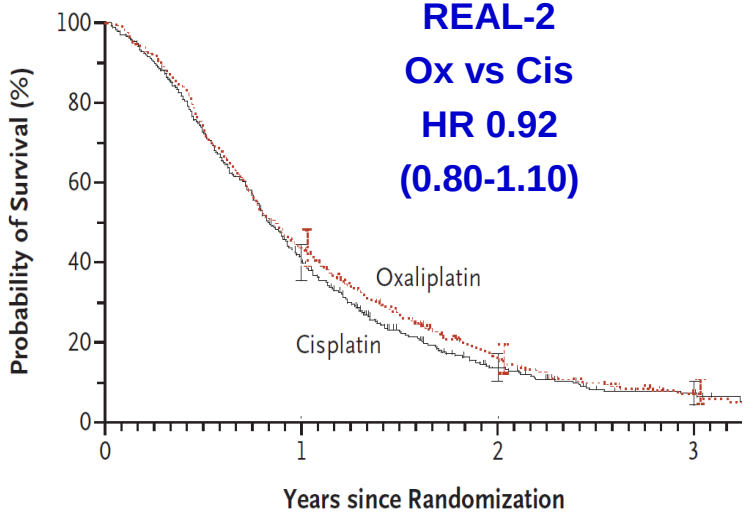
Fluoropyrimidine Comparison



REAL-2
Cape vs 5FU
HR 0.86
(95%CI 0.80-0.99)

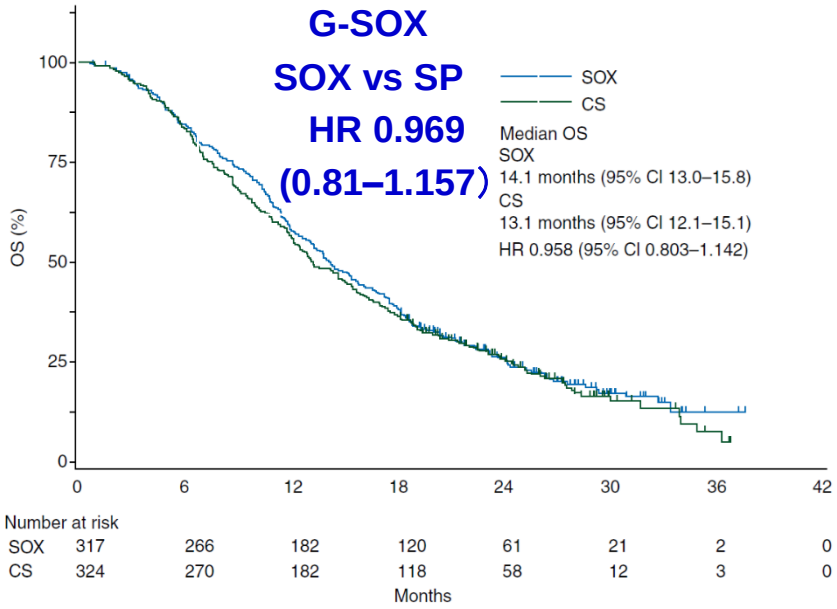
No. at Risk				
Fluorouracil	484	178	37	8
Capecitabine	480	206	52	12

Platinum Comparison



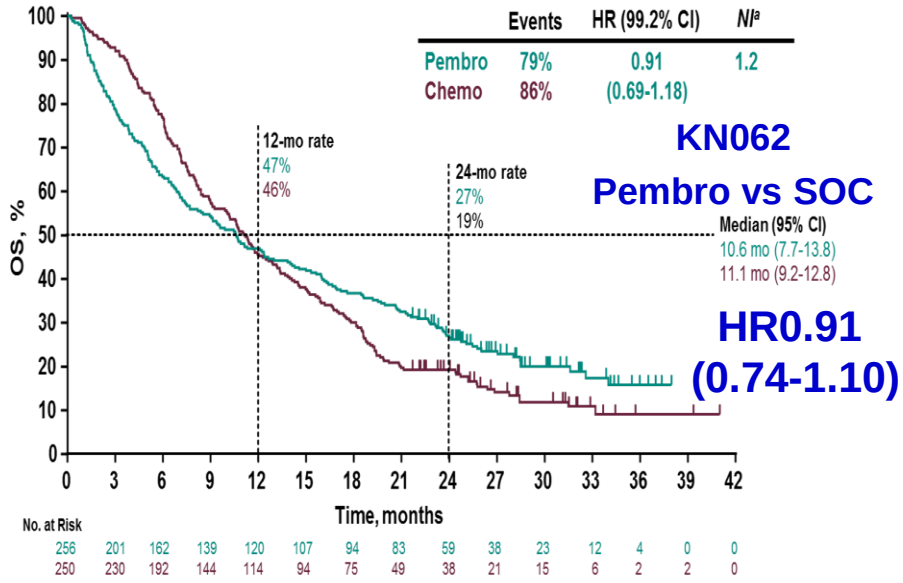
REAL-2
Ox vs Cis
HR 0.92
(0.80-1.10)

No. at Risk				
Cisplatin	490	187	41	10
Oxaliplatin	474	198	48	10



G-SOX
SOX vs SP
HR 0.969
(0.81–1.157)

Cunningham D, et al. NEJM 2008; Yamada Y, Annals of Oncol 2015
Tabernero J,et al. ASCO 2019; ESMO-GI 2019



KN062
Pembro vs SOC
HR0.91
(0.74-1.10)

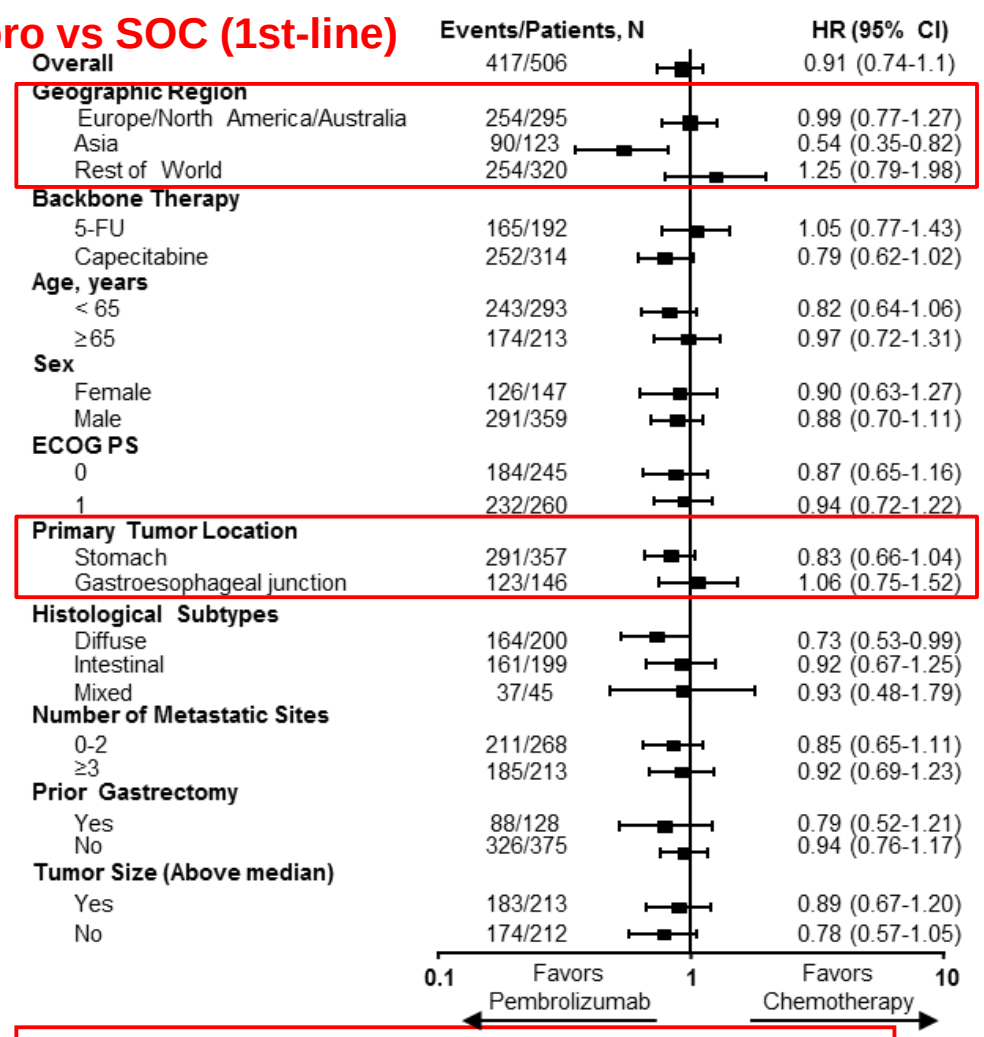
[a]NI, non-inferiority margin; Data cutoff: March 26, 2019.

Non-inferiority trials have changed practices in GC
However, crossed OS curves looks different from others
Patients selection must be important

Non-inferiority: Consistent across clinical subgroups?

KN062

Pembro vs SOC (1st-line)

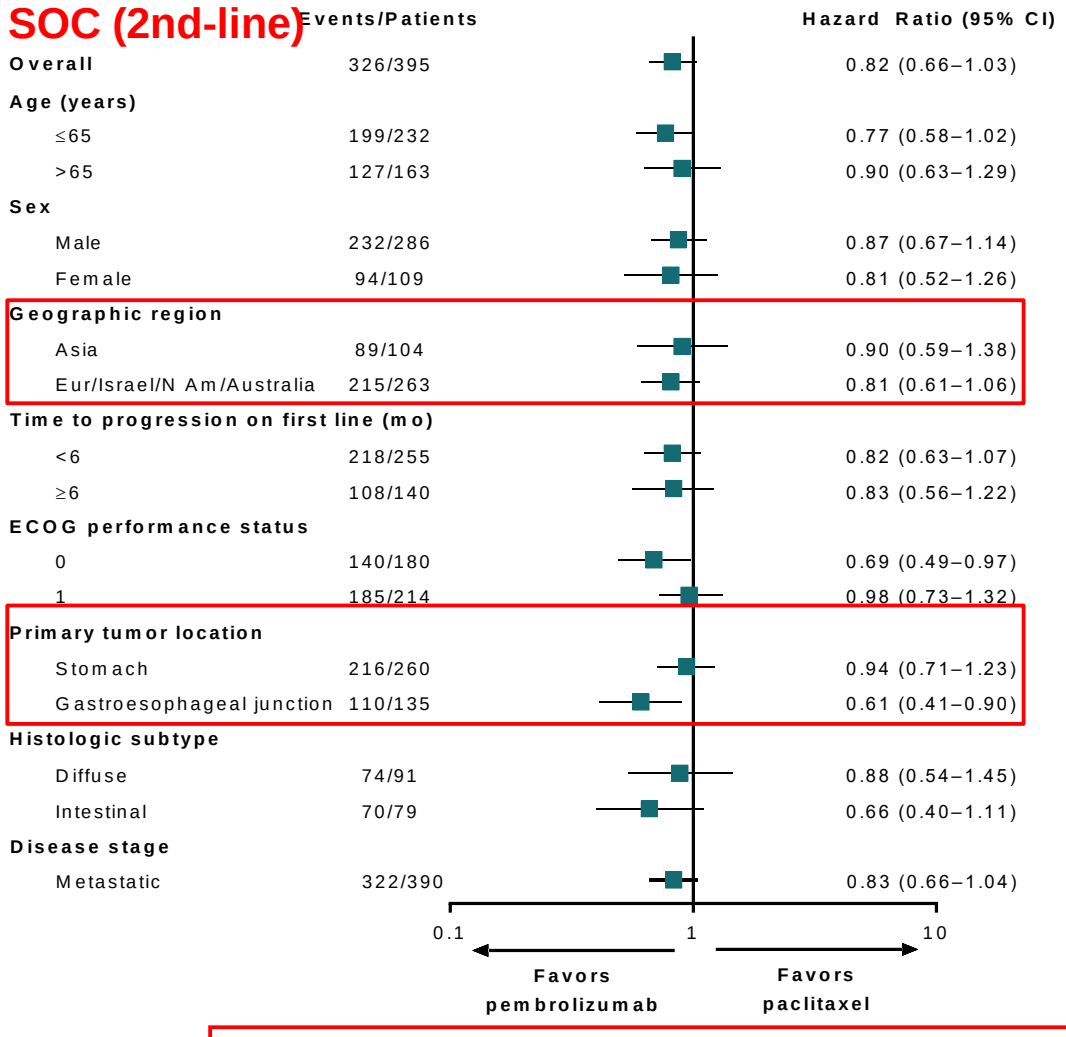


KN062
HR<1 in most predefined subgroups
HR>1 in GEJ (1.06) and ROW (1.25)

-confounded by other factors?-

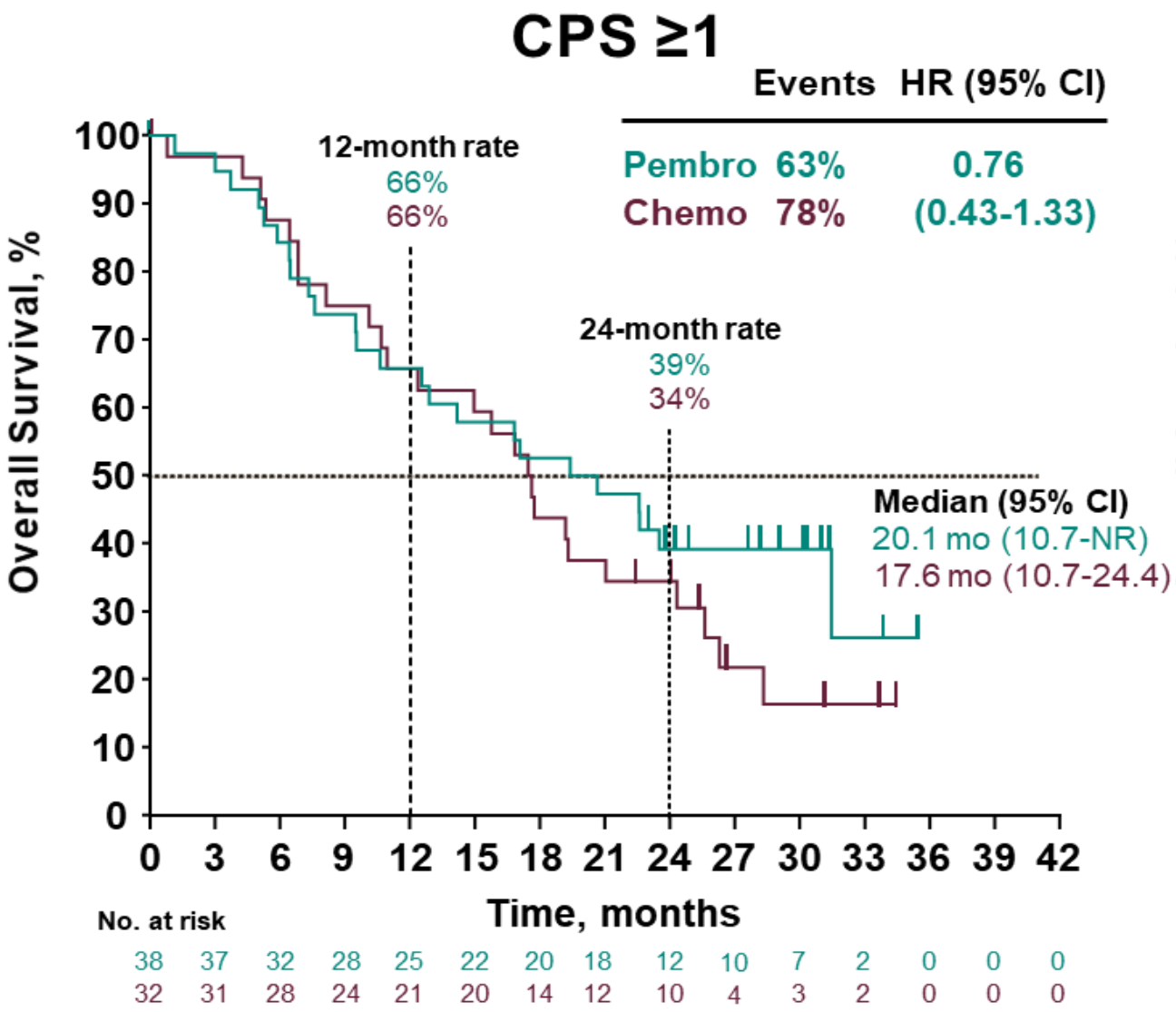
KN061

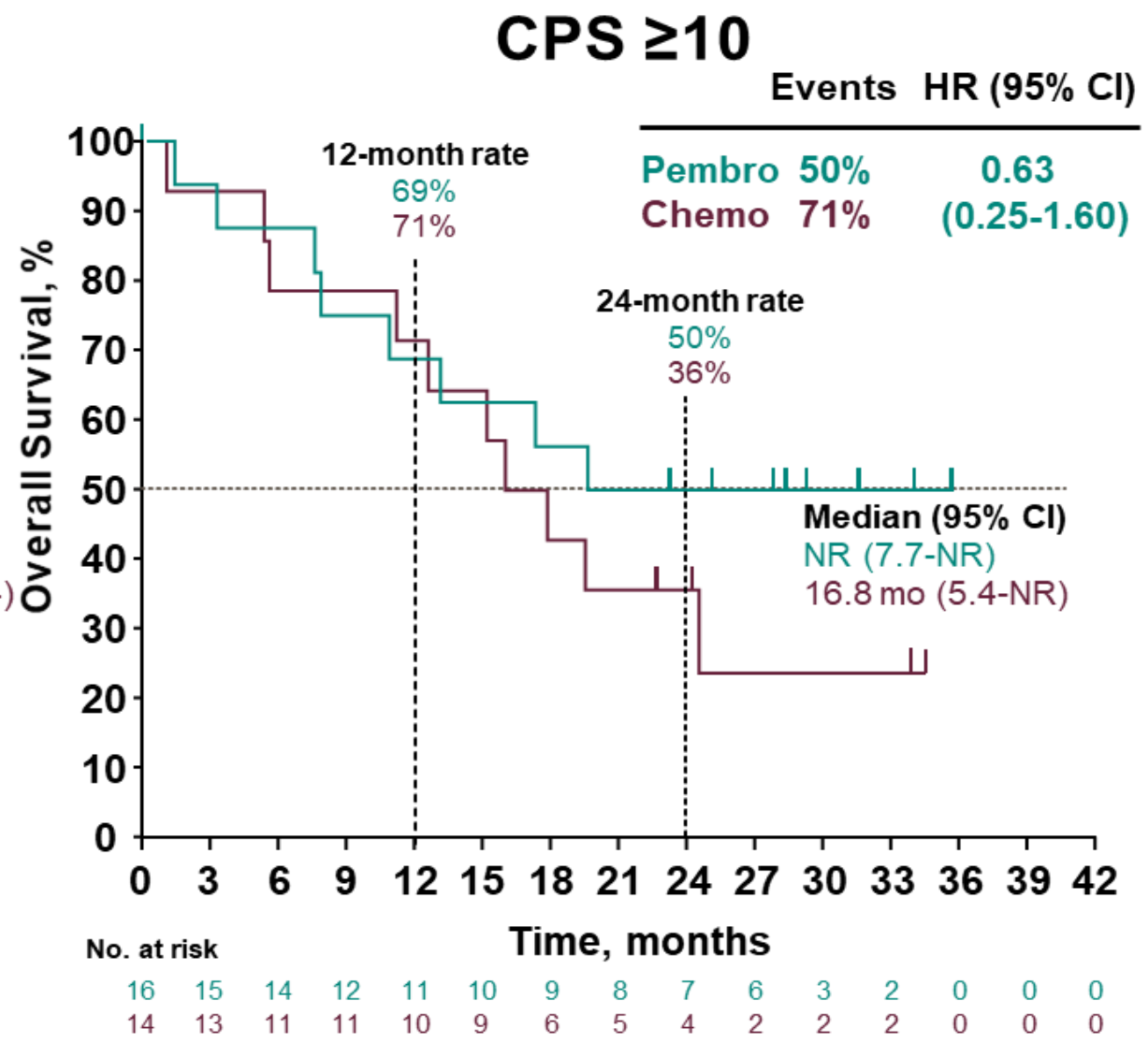
Pembro vs SOC (2nd-line)



KN061
HR<1 in most predefined subgroups
HR<1 in GEJ (0.61), non Asia (0.81)

KEYNOTE-062: Japanese subgroup analysis



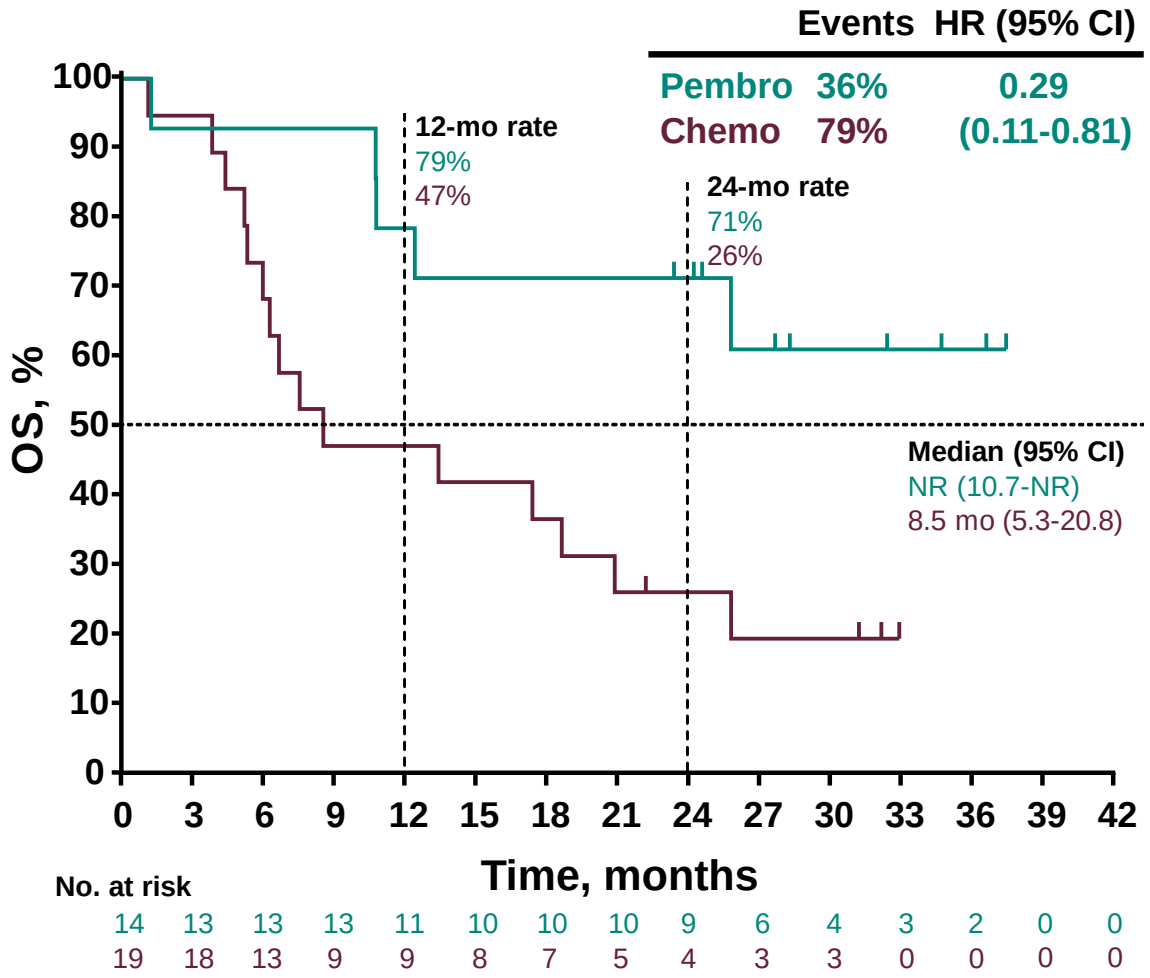


Pembro showed better trend in Japanese subgroup
OS HR 0.63 in CPS10 pts

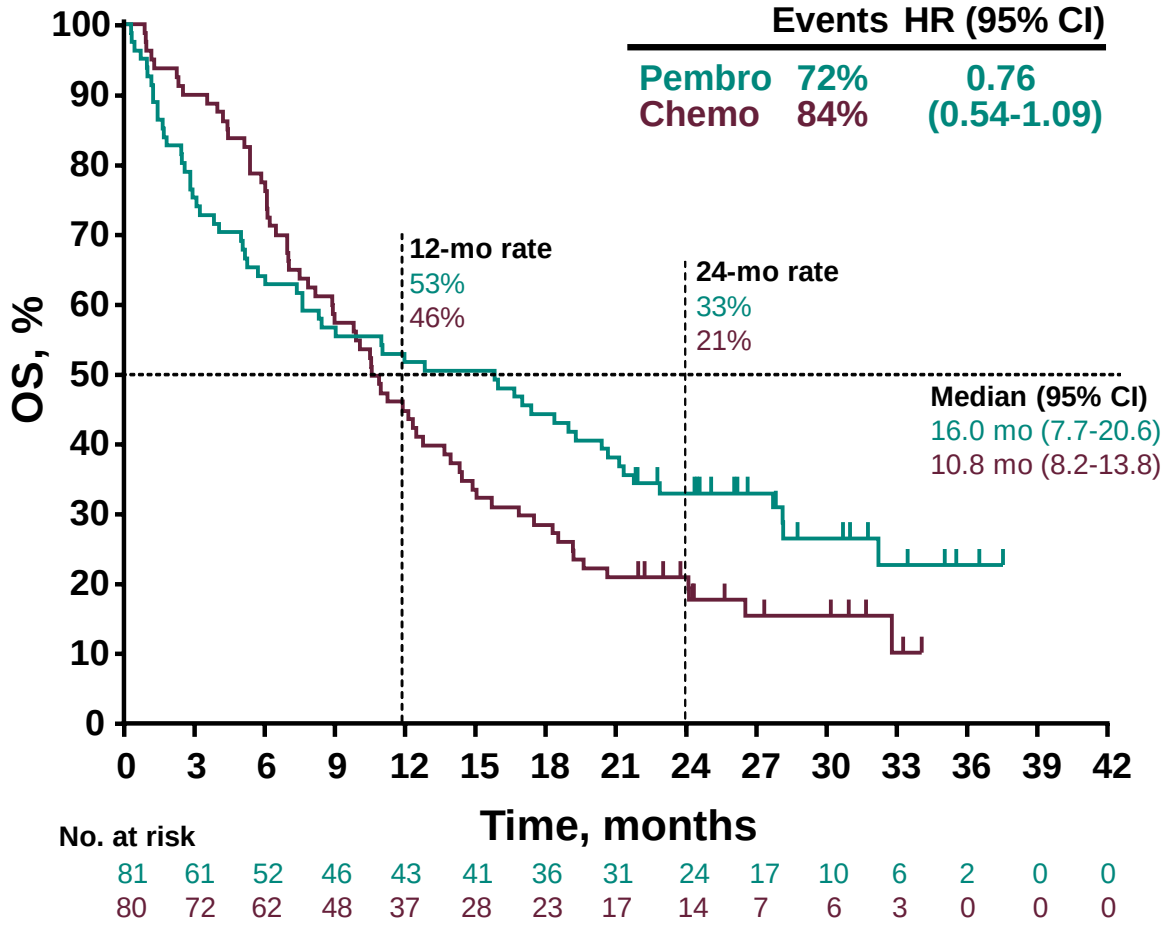
Shitara K et al. JSMO 2019

KEYNOTE-062: Pembro vs Chemo: OS in MSI-H Group

MSI-H pts



CPS ≥10 in MSS pts

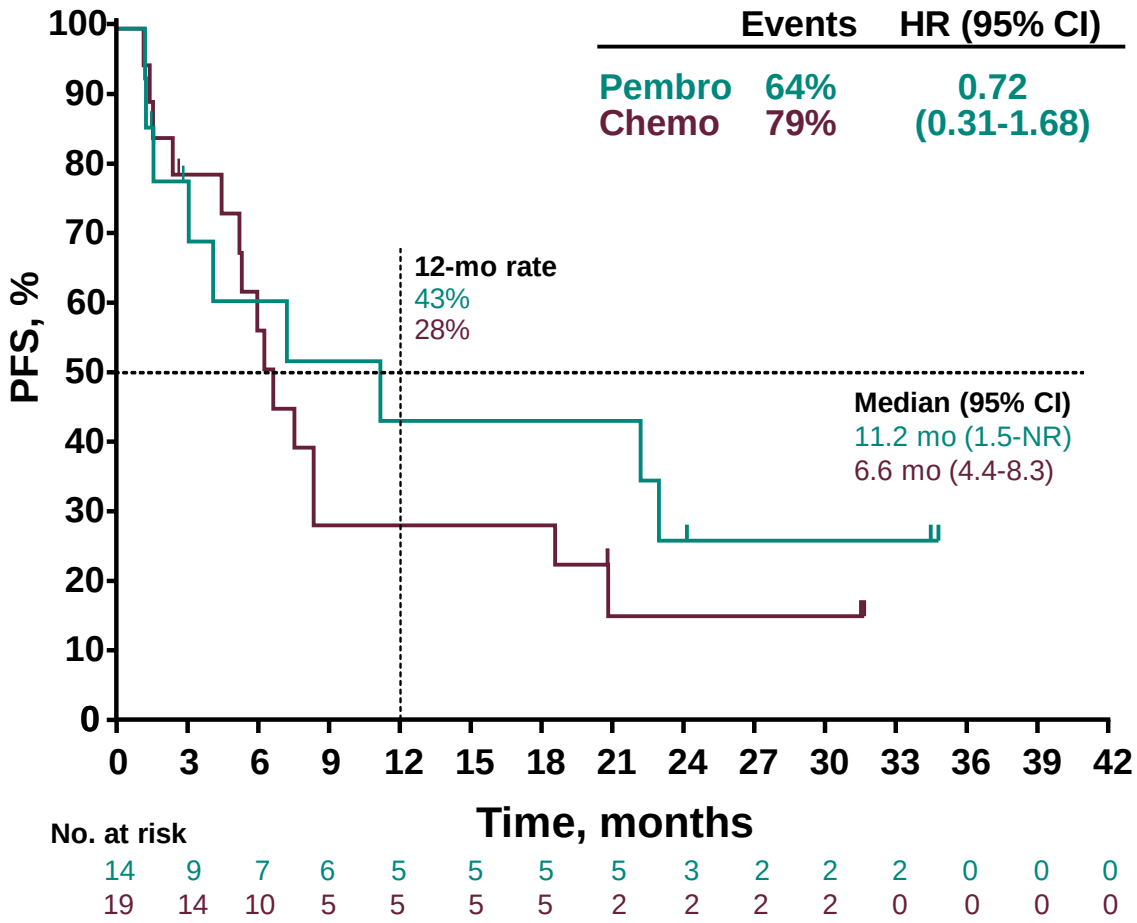


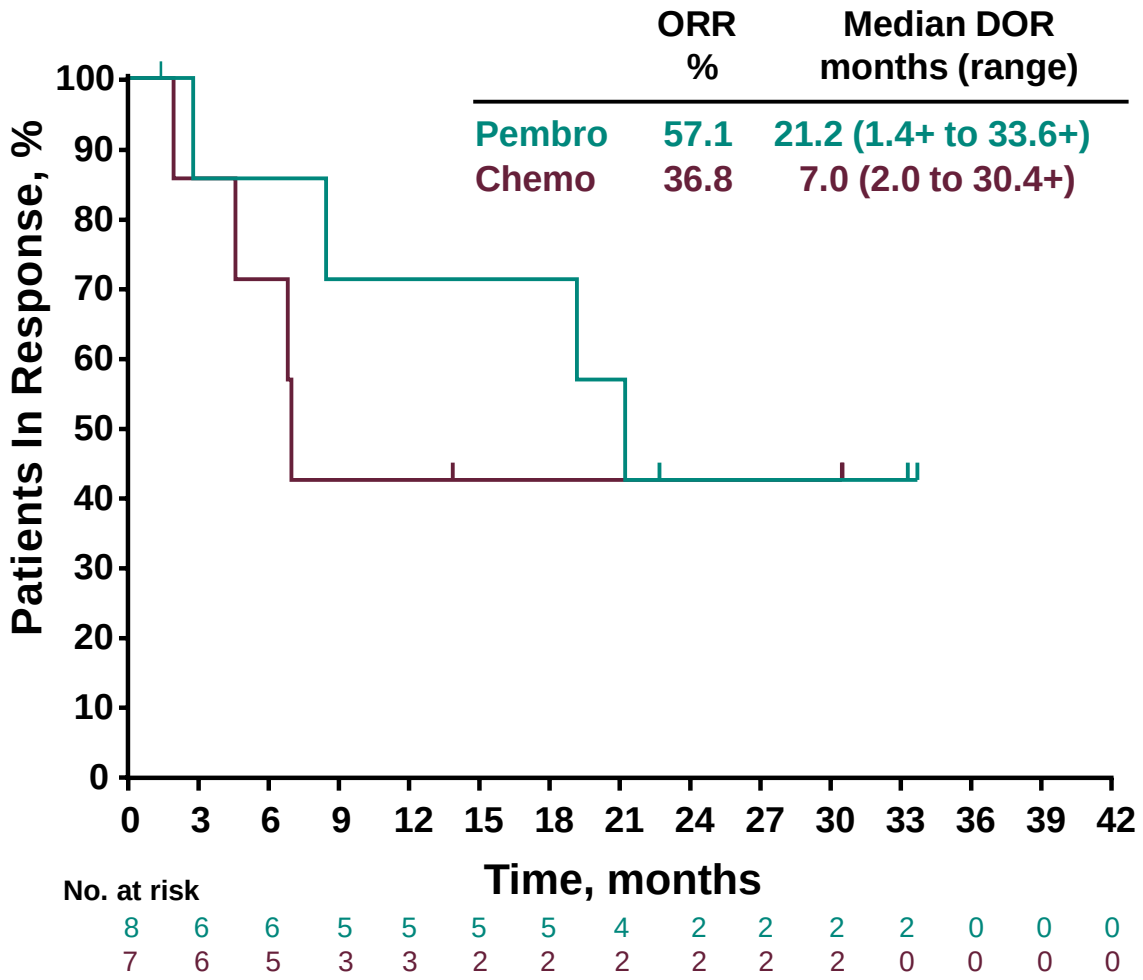
Data cutoff: March 26, 2019.

Remarkable OS benefit in MSI-H pts
Long term OS benefits in CPS10 minus MSI-Hpts

Shitara K et al. ESMO 2019

KEYNOTE-062: Pembro vs Chemo: PFS and DOR in MSI-H





PFS and response assessed per RECIST v1.1 by blinded independent central review; Data cutoff: March 26, 2019.

Shitara K et al. ESMO 2019

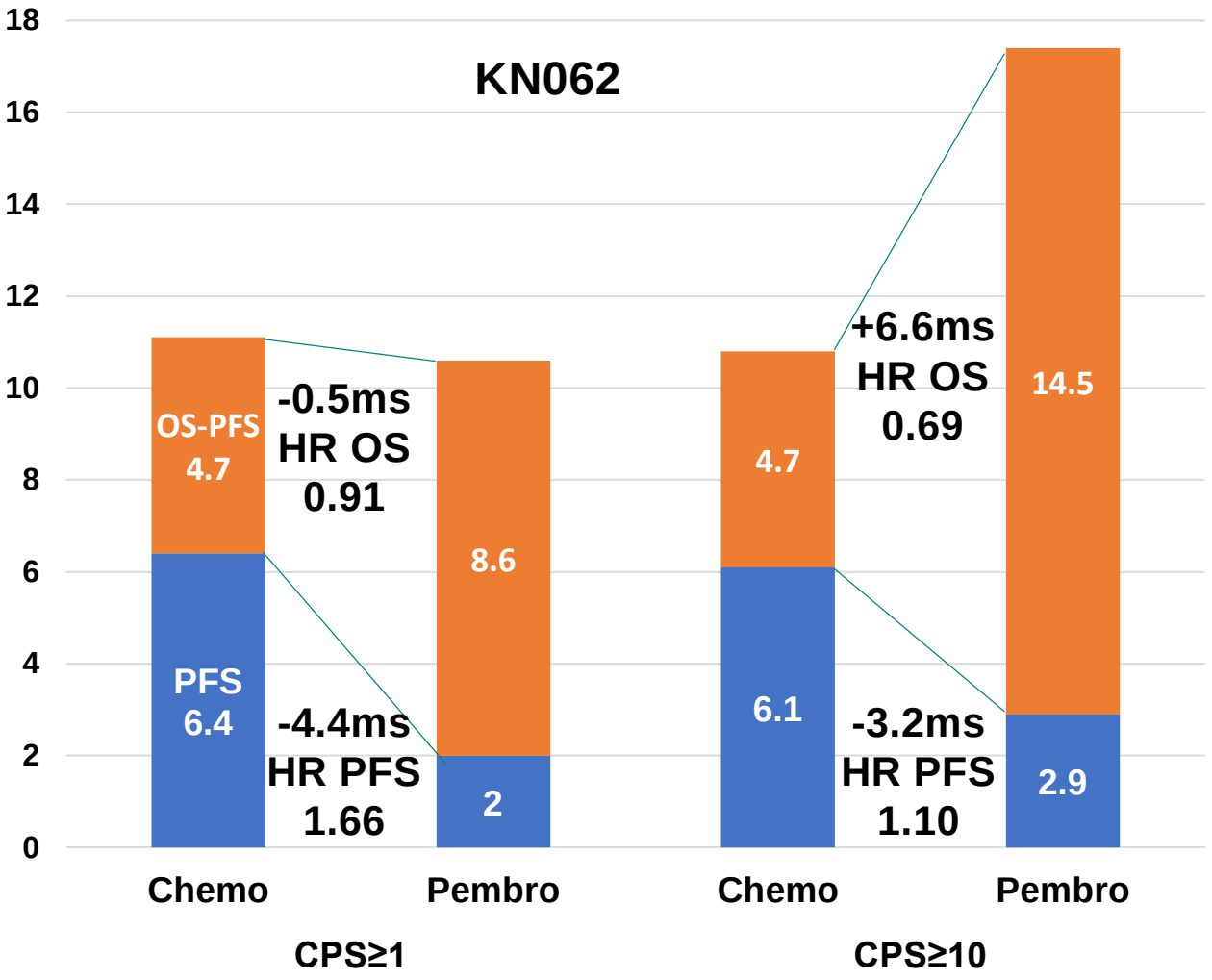
Better PFS and OS in MSI-H pts

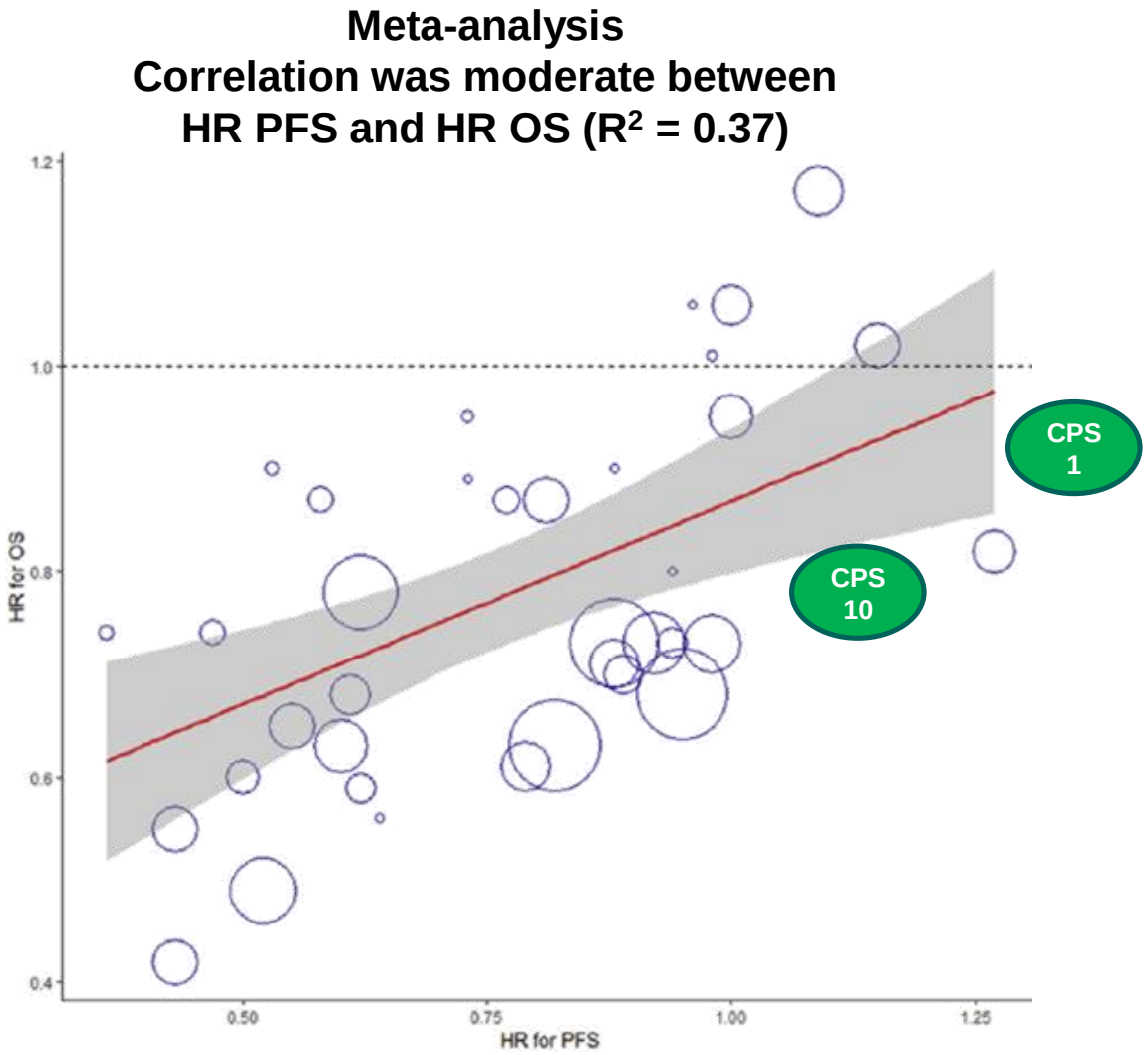
Check-Point Inhibitors in Esophageal and Gastric Cancer: Pembrolizumab monotherapy

- **KN-062 showed pre-planned non-inferiority of Pembro vs SOC**
  - **Lower AE or discontinuation rate may support non-inferiority**
- **Crossed OS curve necessitate optimal patients' selection**
  - **MSI-H or CPS10 pts may have greater treatment effects**

- **Missing pieces**
  - **1. Survival post PD or PFS2 (What happened after 1st PD?)**
  - **2. Additional biomarkers! (TMB, and EBV etc. How to exclude non-responder?)**

Discrepancy of HR for PFS and OS during A-PD1 trials





Nie RC, et al. EJC 2019

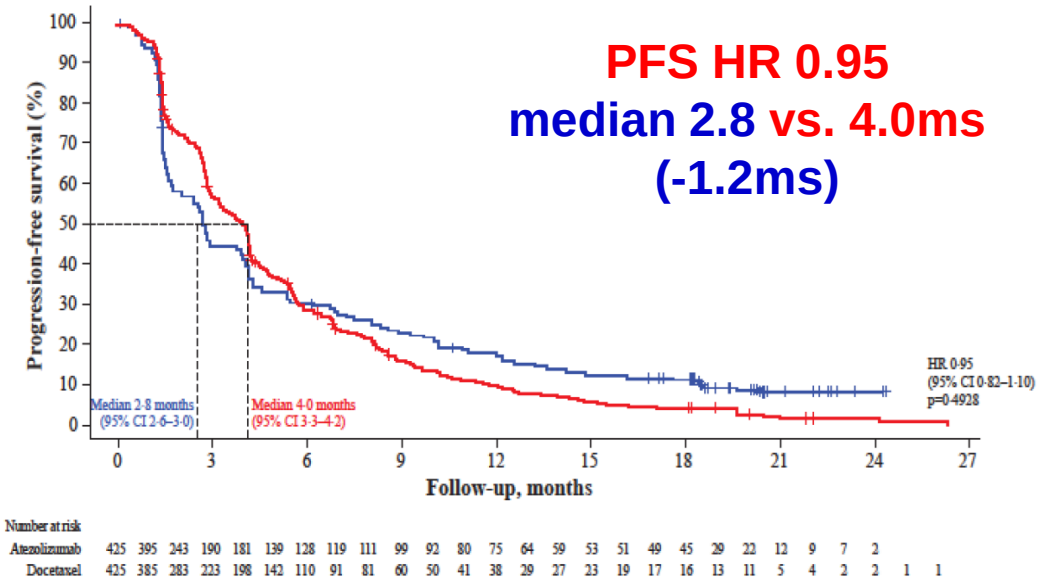
Better effect on OS rather than PFS (similar trend in not a few trials)

Duration of Treatment and Post Study Treatment (CPS ≥1)

	Pembro N = 254	Chemo N = 244
PFS Median(95% CI), months	**2.0** (1.5-2.8)	**6.4** (5.7-7.0)
Treatment duration mean (SD), months	**5.4** (7.12)	**6.0** (5.5)
Post study treatment, (%)		
All 2L	52.8	54.1
All 3L	27.2	23.8
Immunotherapy 2L	1.2	4.9
Immunotherapy 3L	0.4	4.5

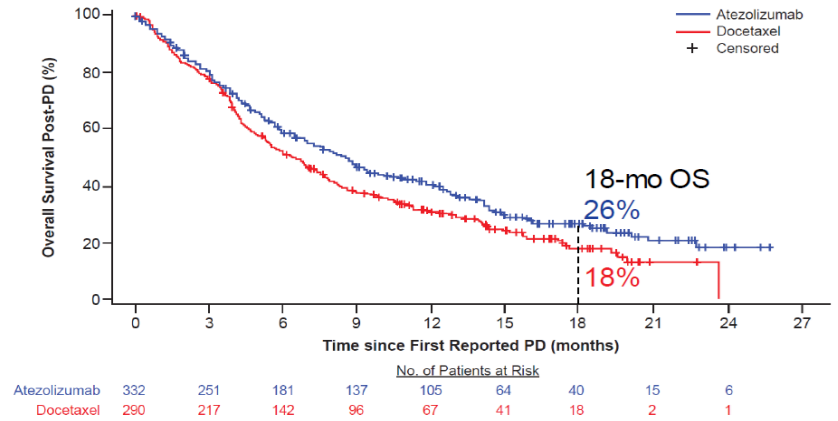
Mean treatment duration (5.4ms) > Median PFS (2.0ms)
-----How was effect of pembro beyond PD?
No difference of N pts with 2ndline
-----How was effect of post-study chemo?

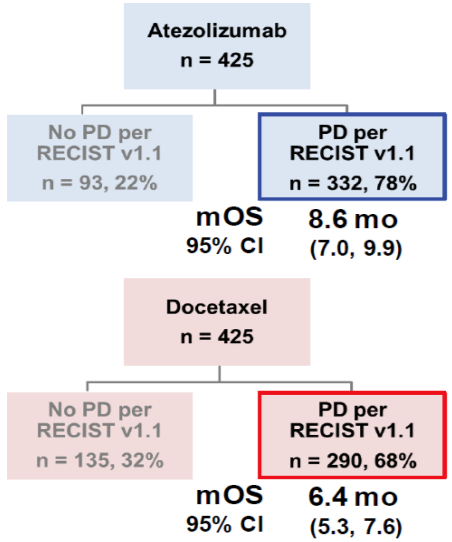
Survival-post PD in OAK study in NSCLC

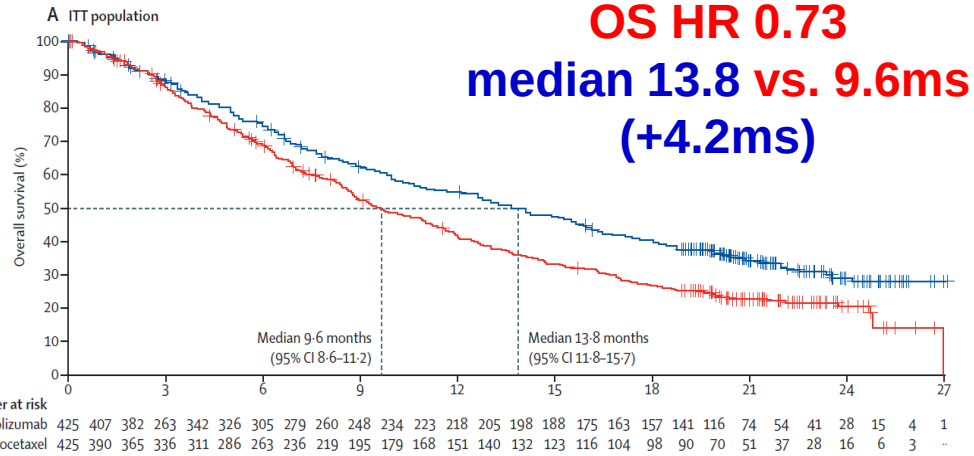


PFS HR 0.95
median 2.8 vs. 4.0ms
(-1.2ms)

OS Post-PD: By Treatment Arm

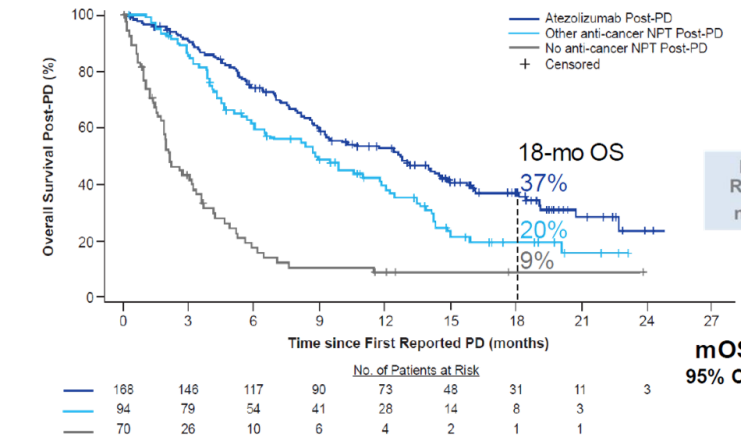


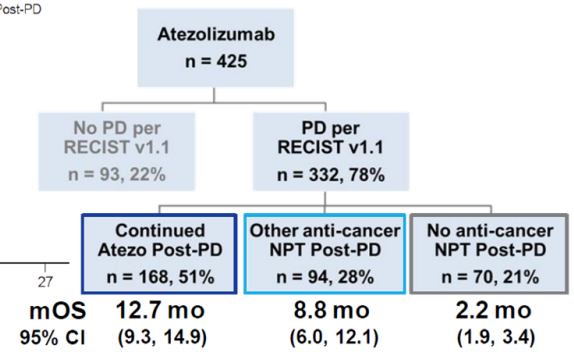




OS HR 0.73
median 13.8 vs. 9.6ms
(+4.2ms)

OS Post-PD in Atezolizumab Arm: By Post-PD Treatment





Types of subsequent treatment affect OS post-PD?
Carry over effects? Enhance activity of post-study chemo?

Rittmeyer A, et al. Lancet 2017
Gandara DR, et al. ASCO 2017; JTO 2018

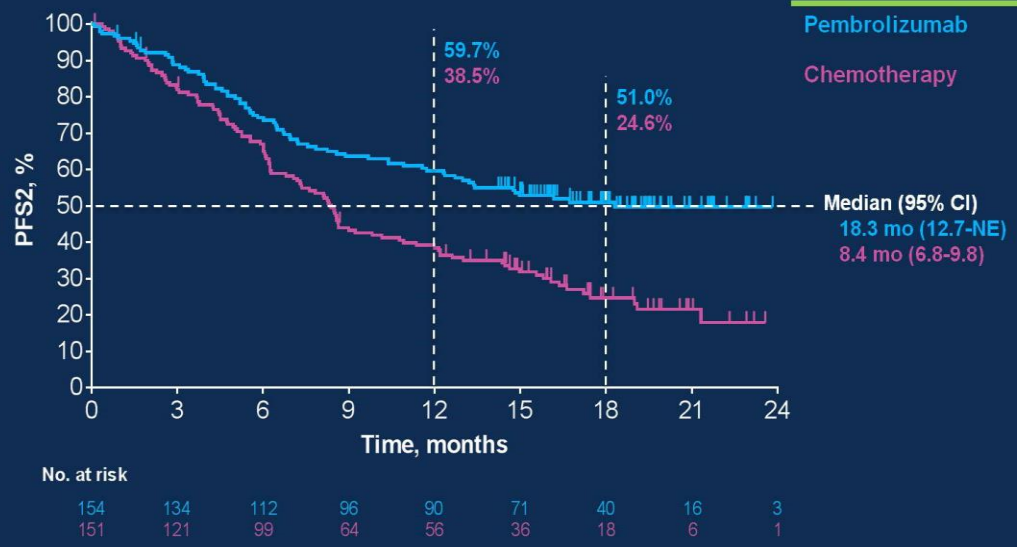
PFS2 in KEYNOTE-024: Pembro vs chemo in 1stline PDL1+NSCLC

Progression-Free Survival In the Second Line: PFS2

- As first defined by the EMA in 2012[1]: time from randomization to objective tumor progression on next-line treatment or death from any cause, whichever occurs first

1. EMA guideline on the evaluation of anticancer medicinal products in man. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/03/WC500203320.pdf.

Kaplan-Meier Estimate of PFS2



	Events, n	HR (95% CI)
Pembrolizumab	74	0.54 (0.40-0.72)
Chemotherapy	110	$P < 0.001$[a]

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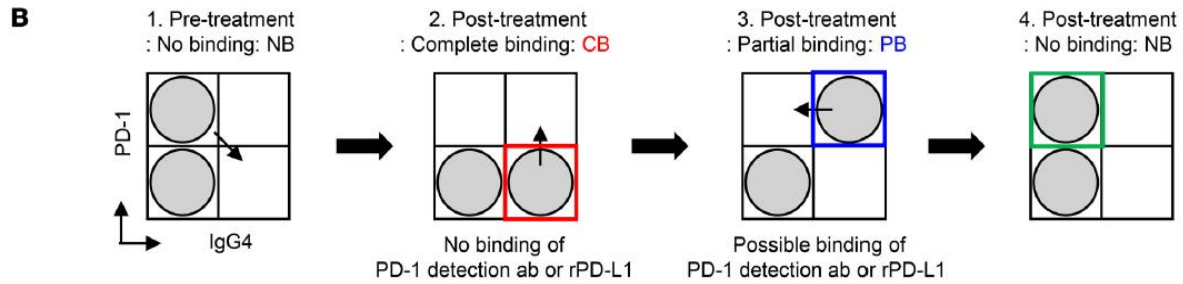
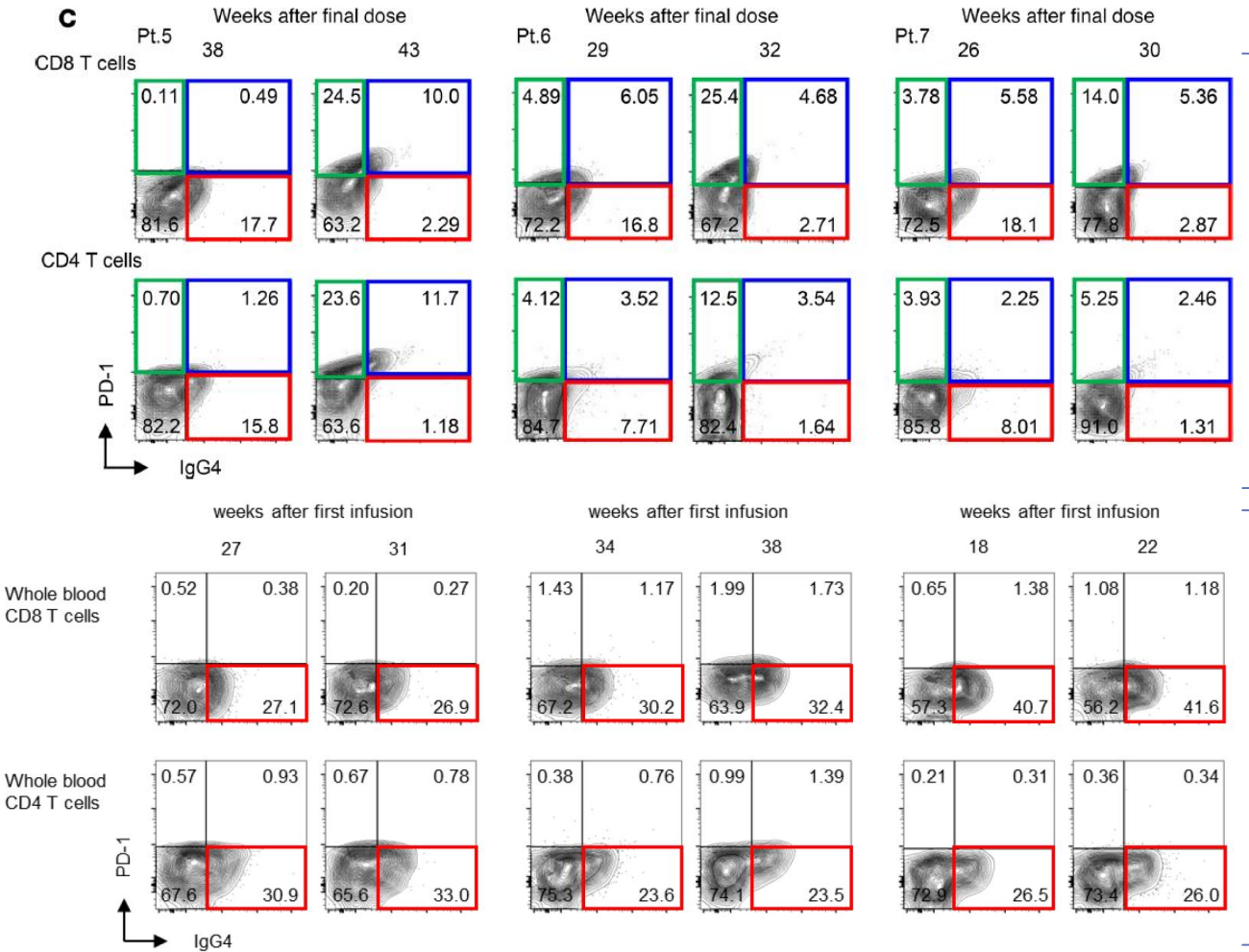
[a]Nominal *P* value. Assessed per RECIST v1.1 by investigator review. Data cutoff: Jan 5, 2017.

Pembro→Chemo (31%)
Chemo→Pembro/A-PD1 (59%)
PFS2 difference +9.9ms (HR0.54)

What happen after discontinuation of anti-PD1?

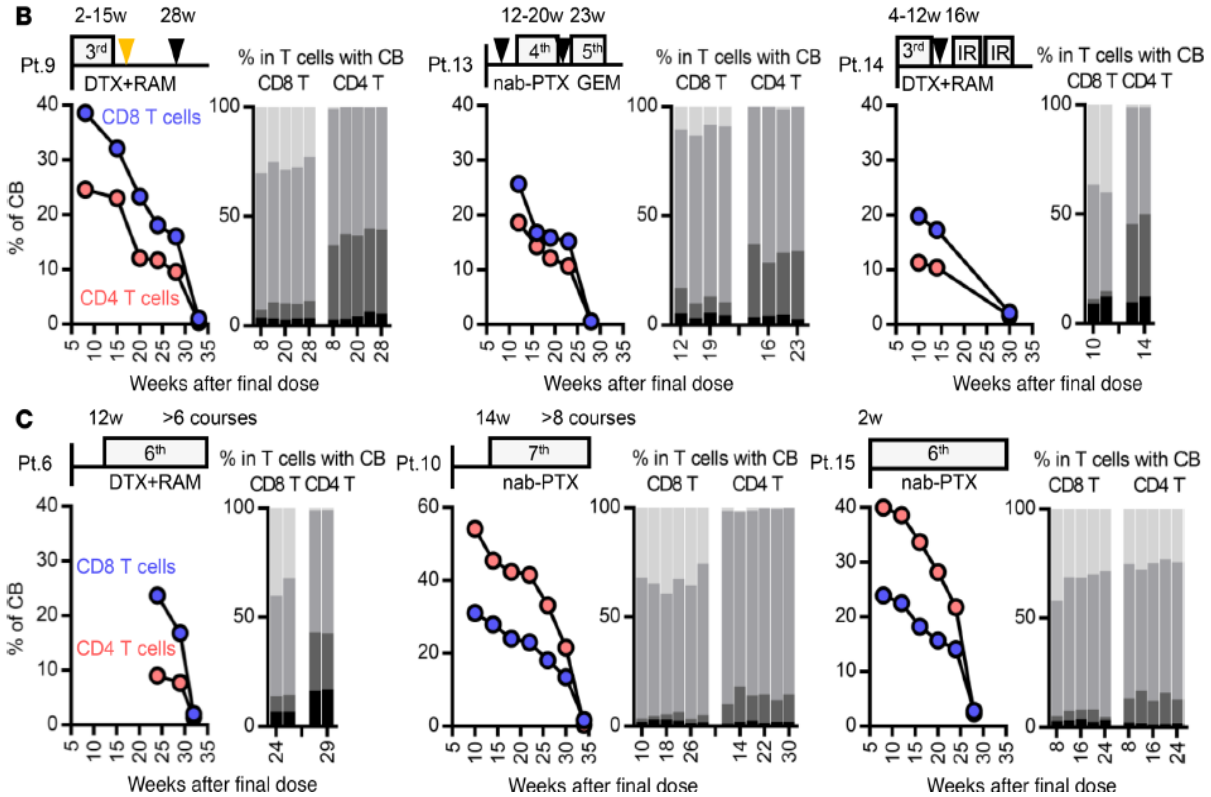




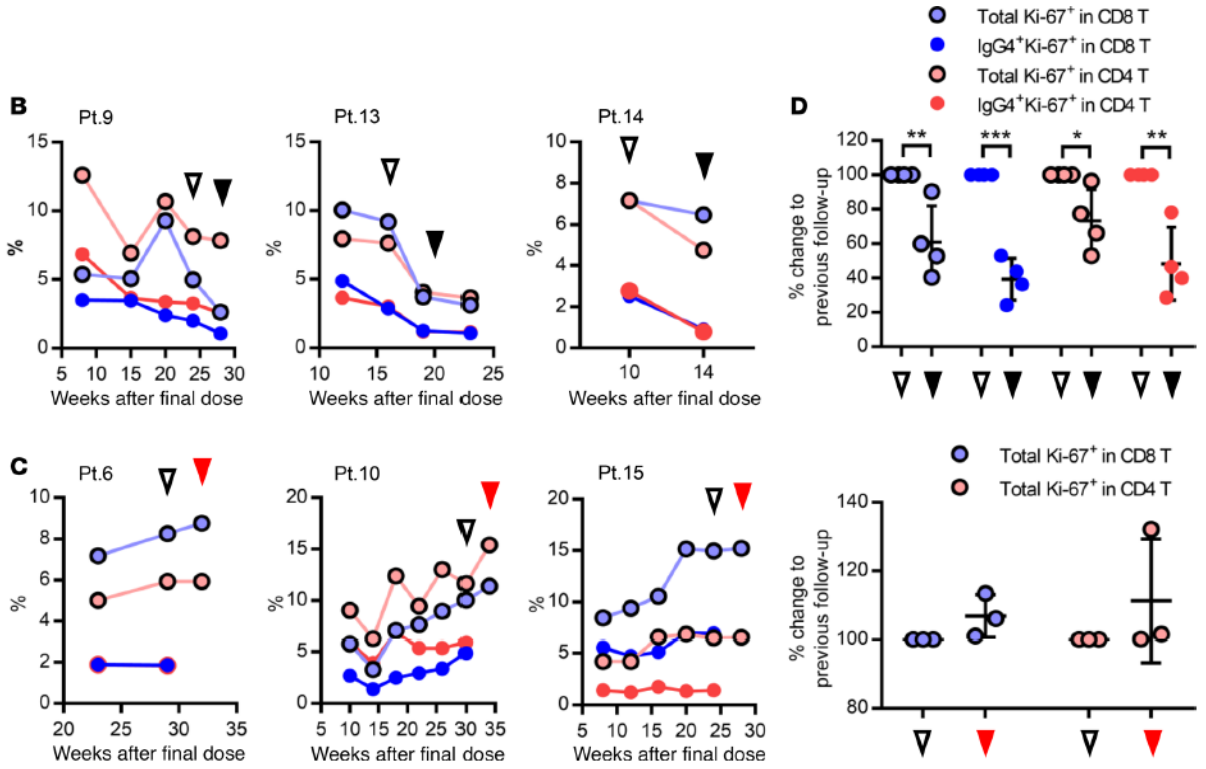
- **Monitoring nivolumab immunokinetics in NSCLC pts**
- **Classification: Nivo-complete binding-, partial binding-, and no binding cells**
- **Nivolumab binding on memory T cells is detectable more than 20 weeks after discontinuation**
- **Long-term nivolumab binding is due to sustained circulation of residual nivolumab in plasma.**

Osa A, et al. JCI insight 2018

What happen after discontinuation of anti-PD1?



Responder in Subsequent Tx



Ki-67 positivity in T cells might reflect the residual efficacy of PD-1 blockade

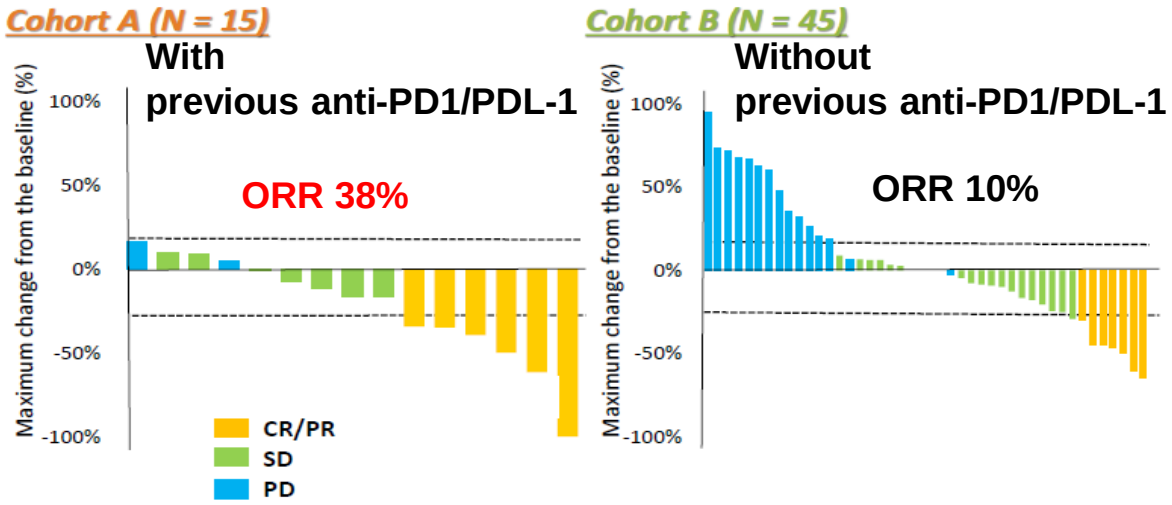
Osa A, et al. JCI insight 2018

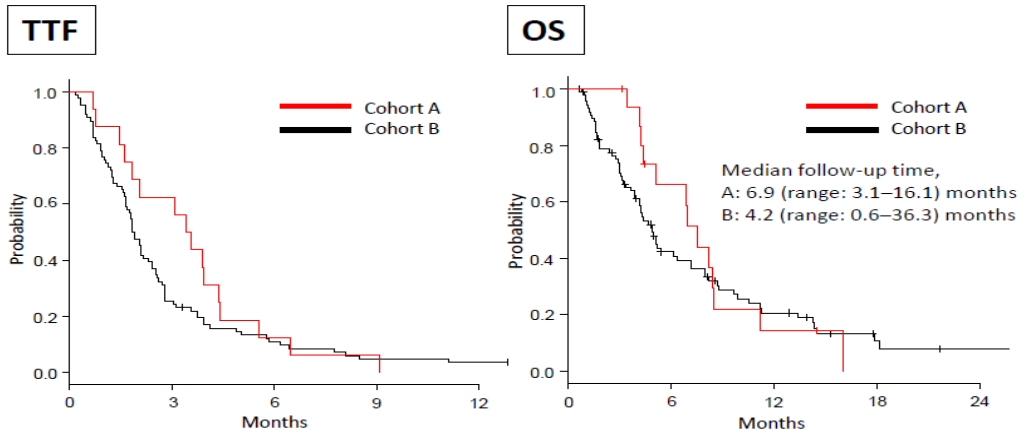
- Nivolumab binding on memory T cells is detectable **even after subsequent CTx**
- **Ki-67 positivity in T cells** might reflect the residual efficacy of PD-1 blockade, even during the period of subsequent chemotherapy (Ki67+ decreased on PD)
- Several studies suggested **enhanced activity of chemo after anti-PD1***

**Kato K, et al. ASCO-GI 2018; Shiono A, et al. Thoracic Cancer 2019; Drakaki A,et al. ASCO GU 2019; Nadal R, et al. Annals of Oncol 2016;*

Efficacy of subsequent treatment after PD-1 blockade

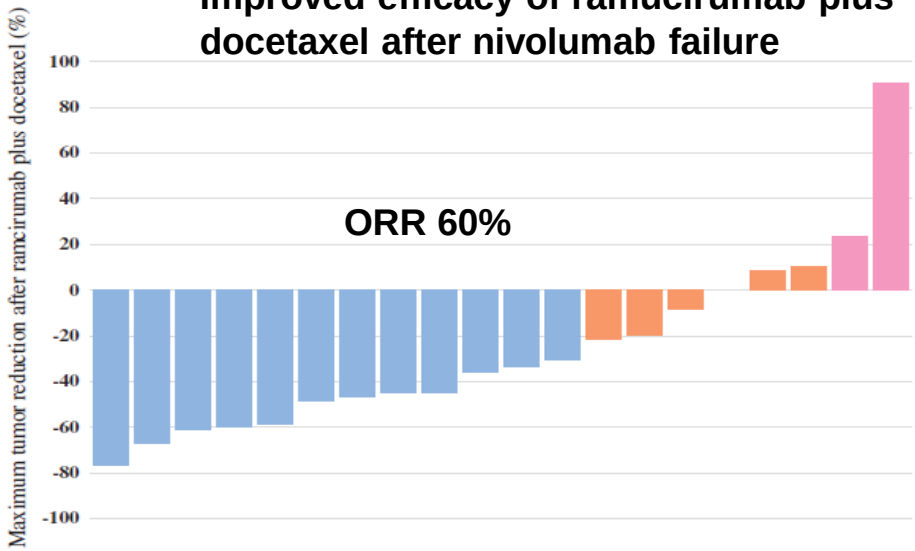
Efficacy of cytotoxic agents after progression on anti-PD-(L)1 antibody



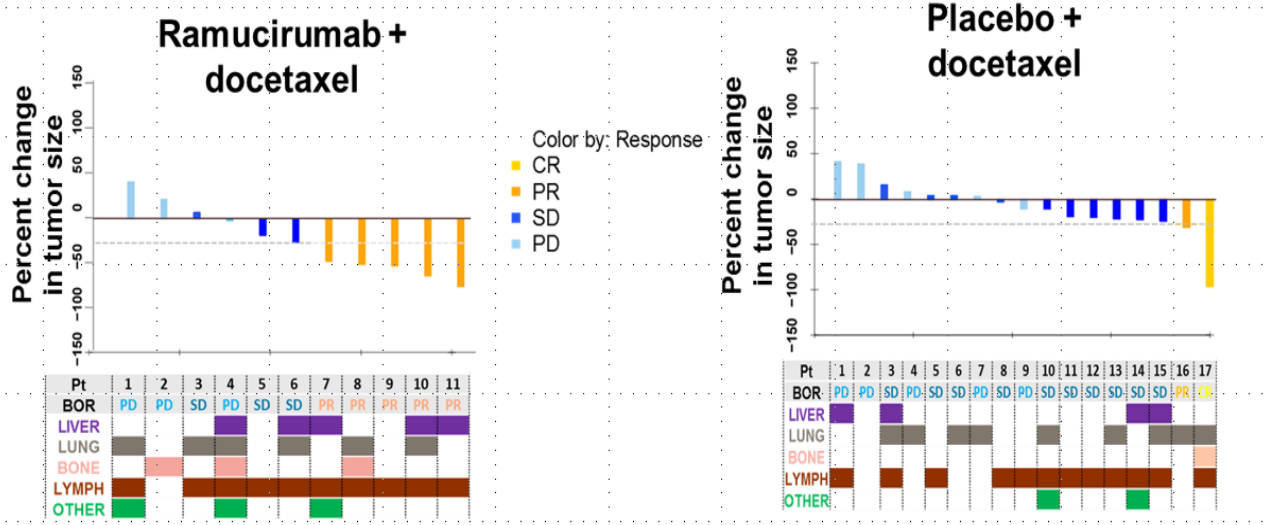


Several studies suggested enhanced activity of chemo after PD1 blockade

Improved efficacy of ramucirumab plus docetaxel after nivolumab failure



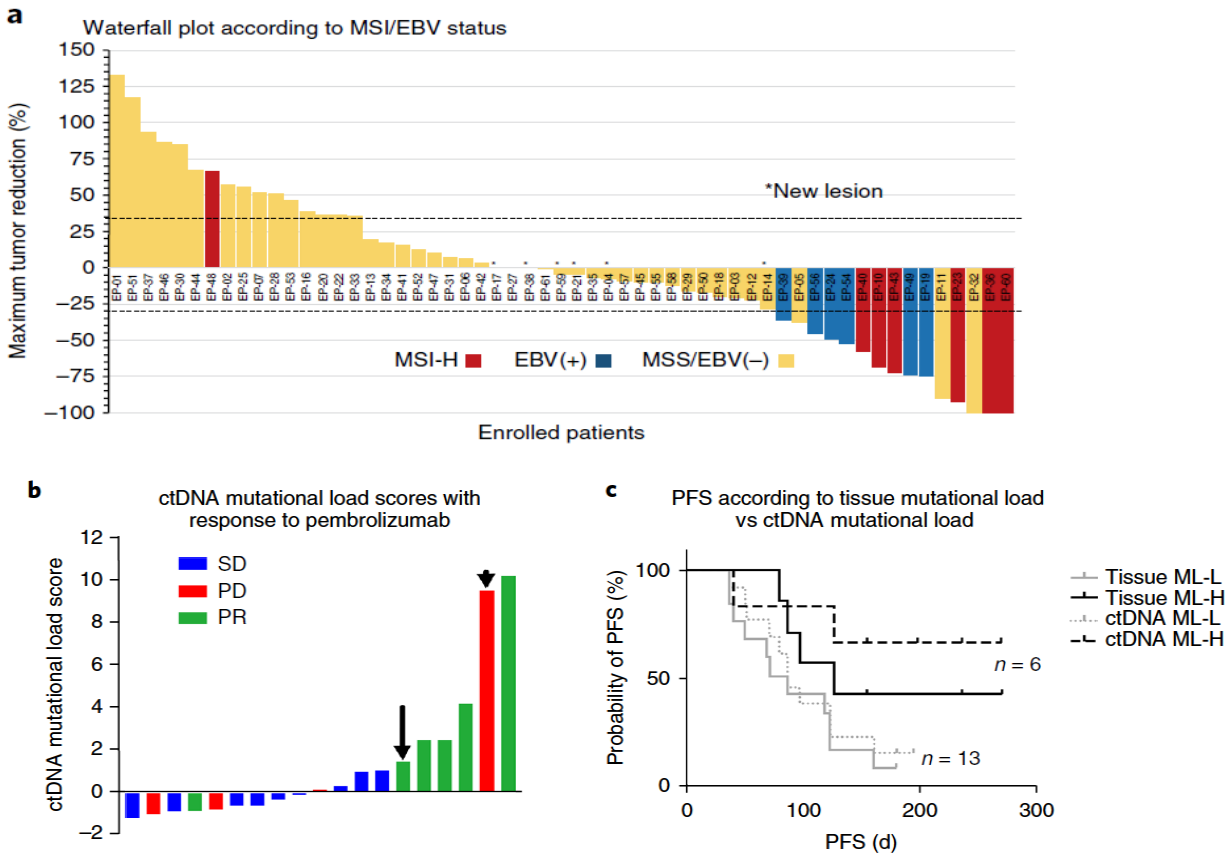
Docetaxel with or without ramucirumab after CPI in platinum-refractory metastatic urothelial carcinoma



Kato K, et al. ASCO-GI 2018; Shiono A, et al. Thoracic Cancer 2019; Drakaki A,et al. ASCO GU 2019

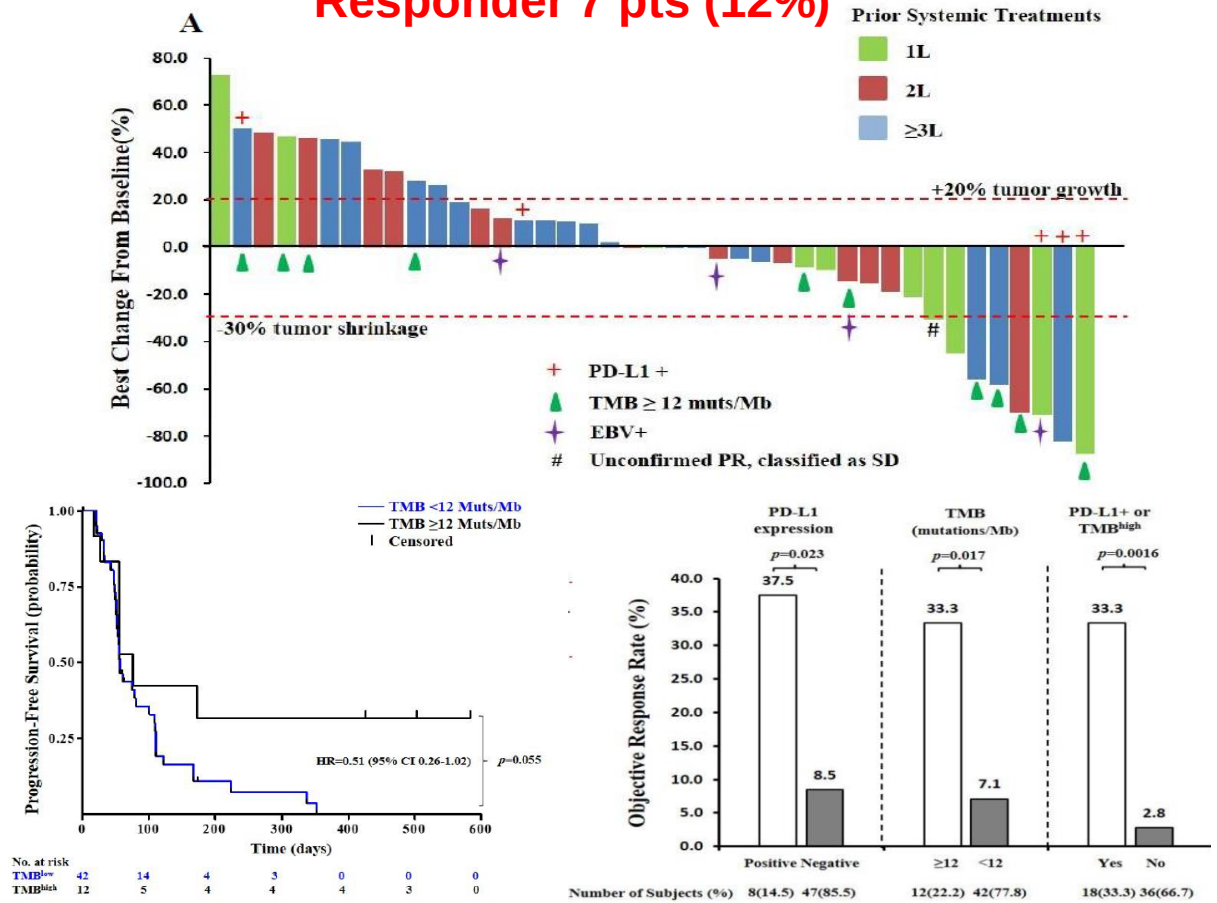
Additional biomarkers for monotherapy use: TMB? EBV?

Pembrolizumab in IIT
Responder 15 pts (20%)



Kim ST, et al. Nature Medicine 2018

Toripalimab treatment
Responder 7 pts (12%)



Xu R, et al. ASCO 2019; Wang F,et al.Annals of Oncol 2019

4 PR of 6 EBV pts
High TMB correlated with better outcomes (TMB by WES)

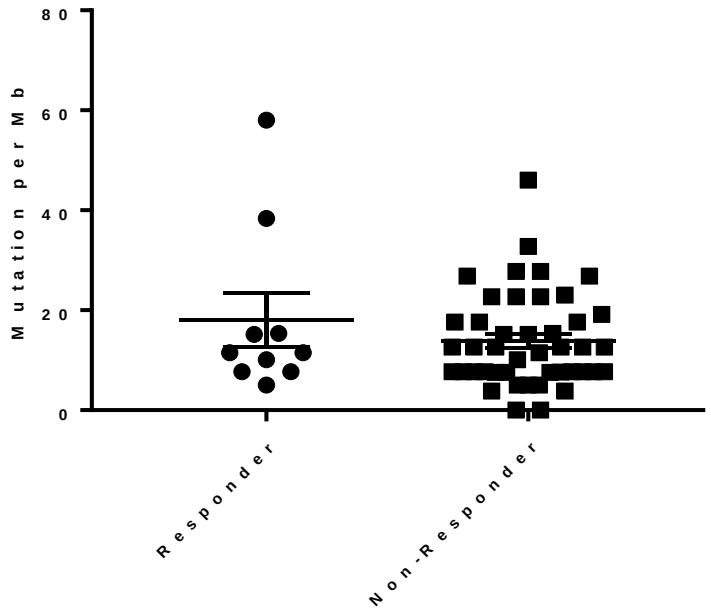
1 PR of 4 EBV pts
ORR 33% with TMB-high and 7% with TMB lowTMB（TMB by WES)

GC Pts treated with Nivolumab in practice in NCCHE

N=136 received nivolumab after approval with tumor evaluation; Responder 21 pts (15%)

Age	PS	Genomic alteration		TMB/Mb	PD-L1+ in TC	CPS 10	CPS 1	EBV	MMR
		Mutation	Amplification						
63	0	NE	NE	NE	-	+	+	-	MMR-D
63	0	NE	NE	NE	+	+	+	-	MMR-D
66	0	*PIK3CA, TP53*	None	38.3	+	-	+	-	MMR-D
62	0	*PIK3CA*	None	11.5	-	-	+	-	MMR-D
53	1	None	None	7.7	+	+	+	-	MMR-D
79	0	*MET, PIK3CA, TP53*	None	58	+	-	+	-	MMR-D
77	1	*KRAS*	None	10.1	+	NE	+	-	MMR-D
43	0	*TP53*	None	7.7	-	-	+	+	MMR-P
72	0	*TP53, ATM*	None	NE	-	NE	+	+	MMR-P
64	0	*PIK3CA*	None	15.3	+	+	+	-	MMR-P
74	0	*ARID1A, TP53*	CCNE1	15.1	-	-	+	-	MMR-P
80	0	*TP53*	CCNE1	11.5	-	-	+	-	MMR-P
76	0	None	None	10.1	-	-	+	-	MMR-P
73	0	*TP53*	None	5	+	+	+	-	MMR-P
65	0	NE	NE	NE	+	+	+	-	MMR-P
53	0	NE	NE	NE	+	-	+	-	MMR-P
64	0	None	None	2.5	+	NE	+	-	MMR-P
78	1	*TP53, IDH2*	None	NE	-	NE	+	-	MMR-P
66	0	*STK11*	None	NE	-	NE	+	-	MMR-P
49	0	NE	NE	NE	-	NE	-	-	MMR-P
41	0	*TP53*	CCNE1	12.6	-	NE	-	-	MMR-P

Response by tumor mutation burden



Mishima S, ,,Shitara K. J Immunother Cancer. 2019
Updated

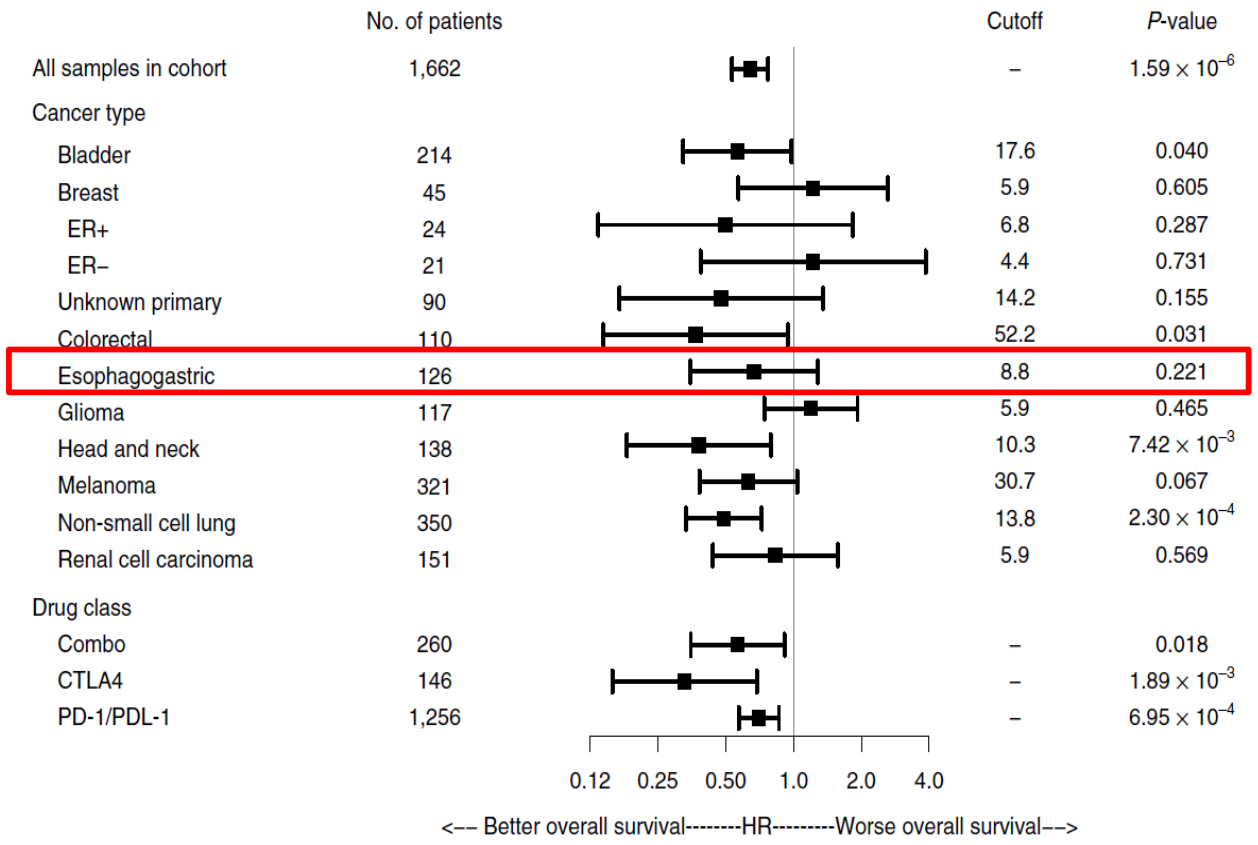
2 of 6 EBV pts showed response
TMB by NGS panel do not clearly correlate with outcomes

TMB as predictive marker in GC is still controversial

Exploratory analysis in ATTRACTION-2 trial

	Nivolumab (N=330)	Placebo (N=163)	OS HR [95% CI]
PD-L1 expression in tumor cell, n (%)	**n=130**	**n=62**	
<1%	114 (87.7)	52 (83.9)	0.72 [0.49, 1.05]
≥1%	16 (12.3)	10 (16.1)	0.51 [0.21, 1.25]
TMB analysis, n (%)	**n=91**	**n=45**	
≥0 and <5 mutation/Mb	48 (52.7)	23 (51.1)	0.78 [0.46, 1.34]
≥5 and <10 mutation/Mb	33 (36.3)	14 (31.1)	0.47 [0.24, 0.94]
≥10 mutation/ Mb	9 (9.9)	6 (13.3)	0.52 [0.16, 1.62]
Not detected	1 (1.1)	2 (4.4)	-
MSI status, n (%)	**n=91**	**n=45**	
MSI-H	1 (1.1)	3 (6.7)	-
MSS	82 (90.1)	33 (73.3)	0.61 [0.40, 0.94]
Unknown	8 (8.8)	9 (20.0)	-

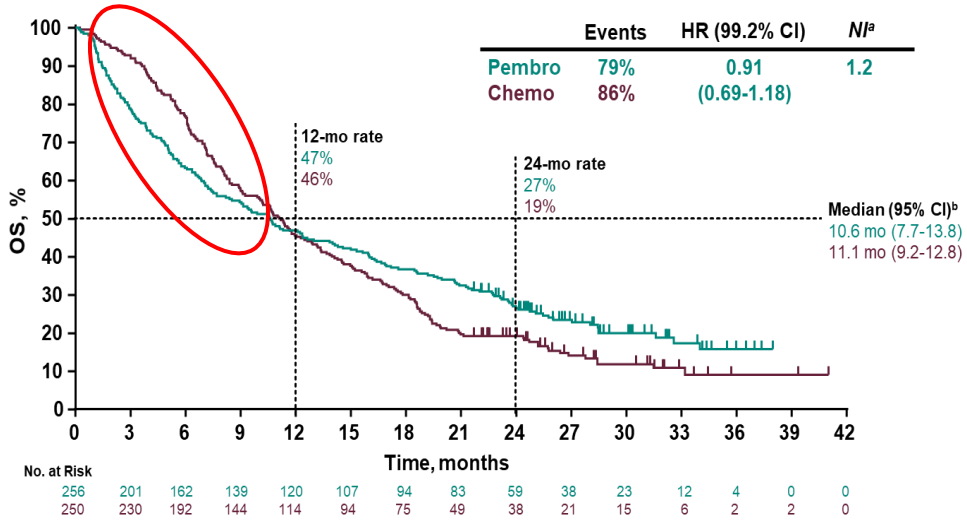
MSK-IMPACT



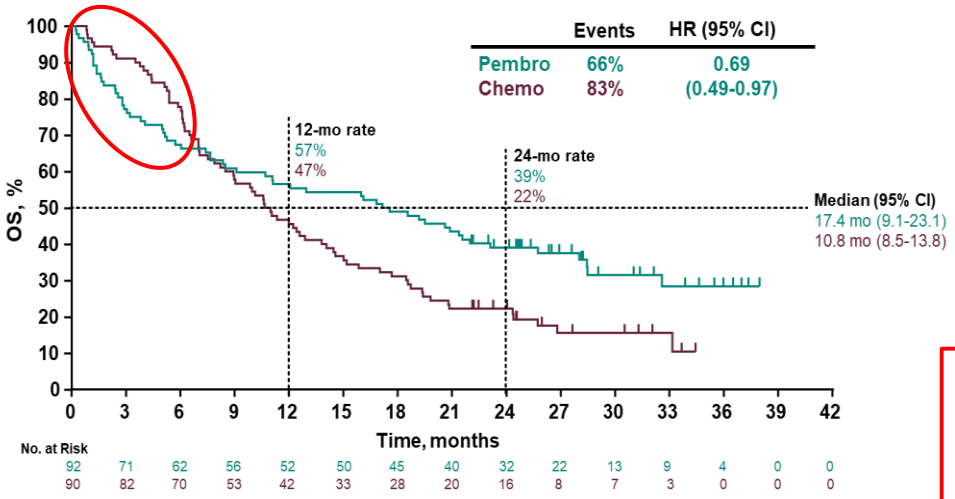
Controversial results between TMB-NGS and outcomes
Further analysis of TMB-WES in larger cohorts or RCT for GC are necessary

Crossed OS curve: Hyper progressive disease ?

Overall Survival: P vs C (CPS ≥1)

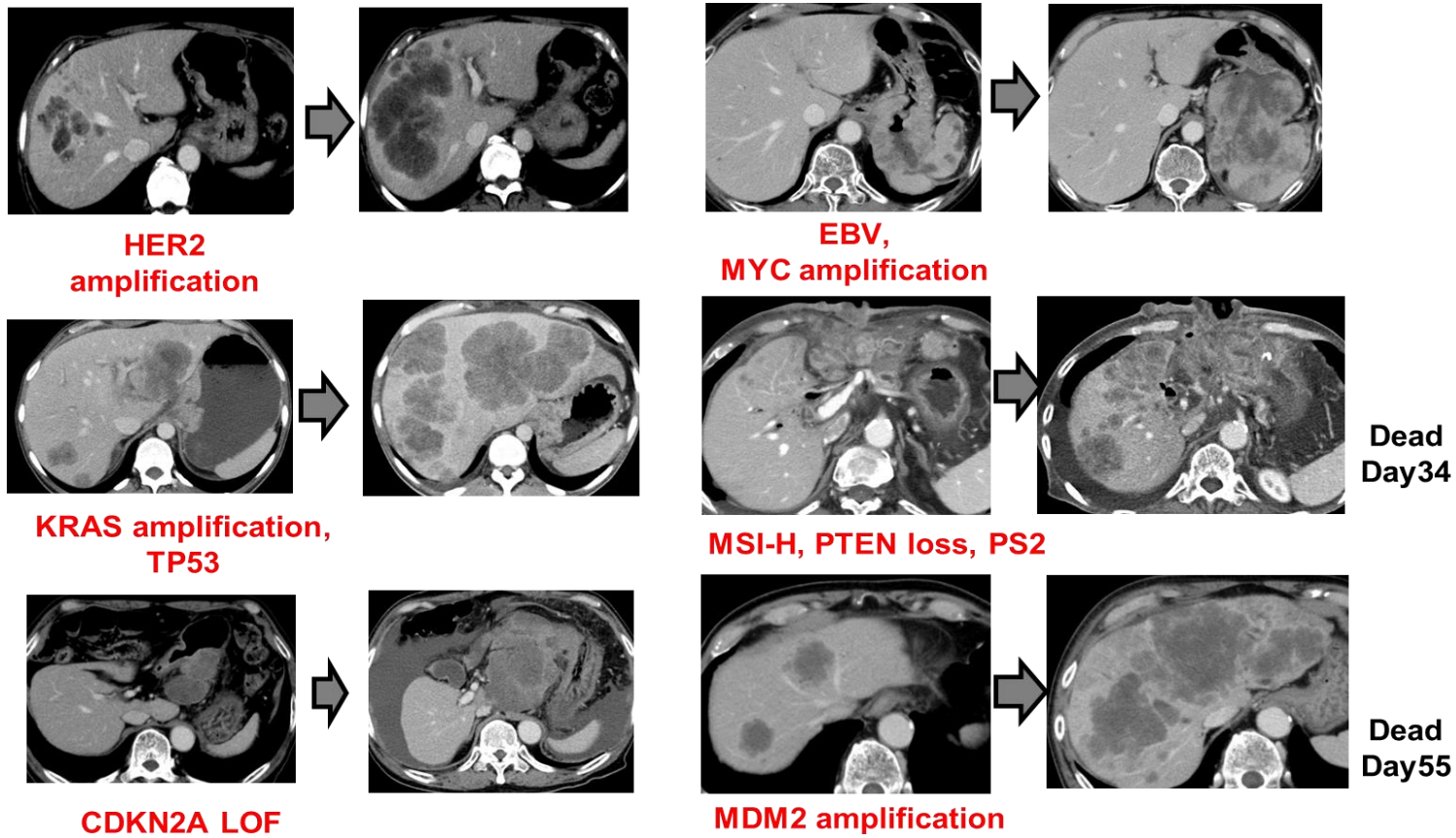


Overall Survival: P vs C (CPS ≥10)



Tabernero J,et al. ASCO 2019; ESMO-GI 2019

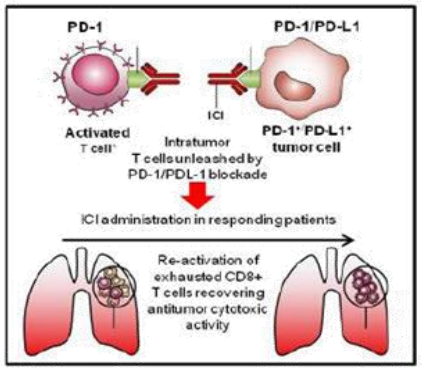
Hyper progressive disease in NCCHE

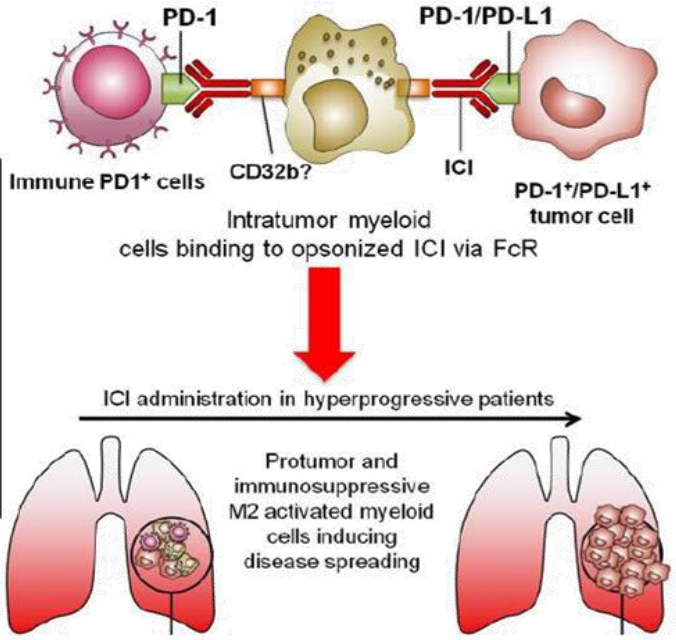


Sasaki A, Nakamura Y,,Shitara K. Gastric cancer 2019

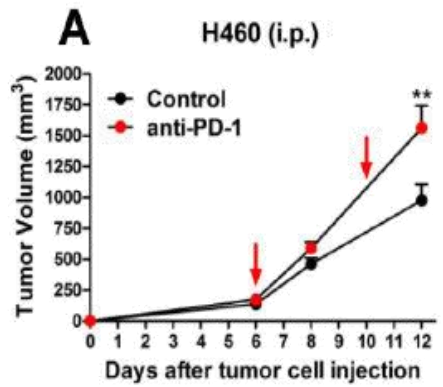
21% pts showed HPD in NCCHE experience
- Higher trend in pts with large tumor size and liver metastasis
- poor OS with few chance to receive subsequent Tx

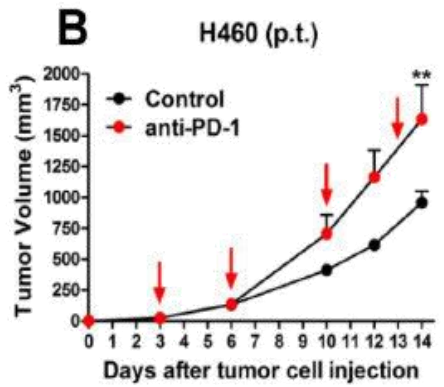
CD163+CD33+PD-L1+ Macrophage and HPD

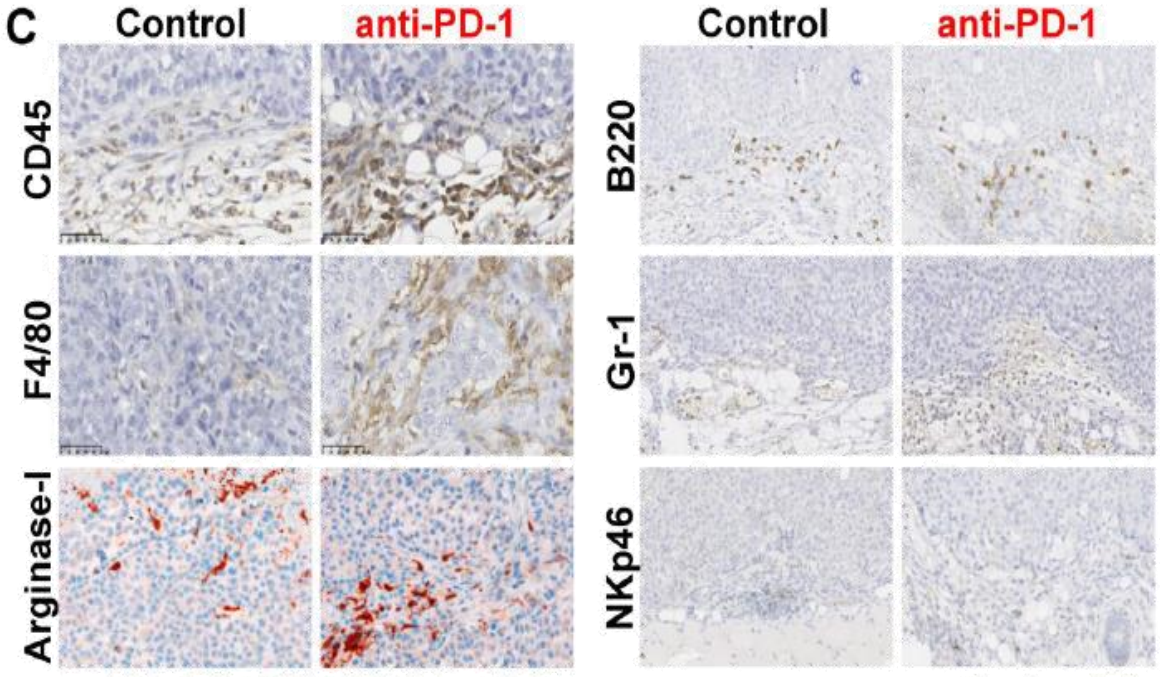




PATIENTS NUMBER	TREATMENT RESPONSE	EPITHELIOID MORPHOLOGY	PD-L1	CD163	CD33	COMPLETE PHENOTYPE
4	HP	+	+	+	+	+
5	HP	+	+	+	+	+
9	HP	+	+	+	+	+
20	HP	+	+	+	+	+
30	HP	+	+	+	+	+
34	HP	+	+	+	+	+
35	HP	+	+	+	+	+
46	HP	+	+	+	+	+
82	HP	+	+	+	+	+
116	HP	+	+	+	+	+
120	HP	+	+	+	+	+



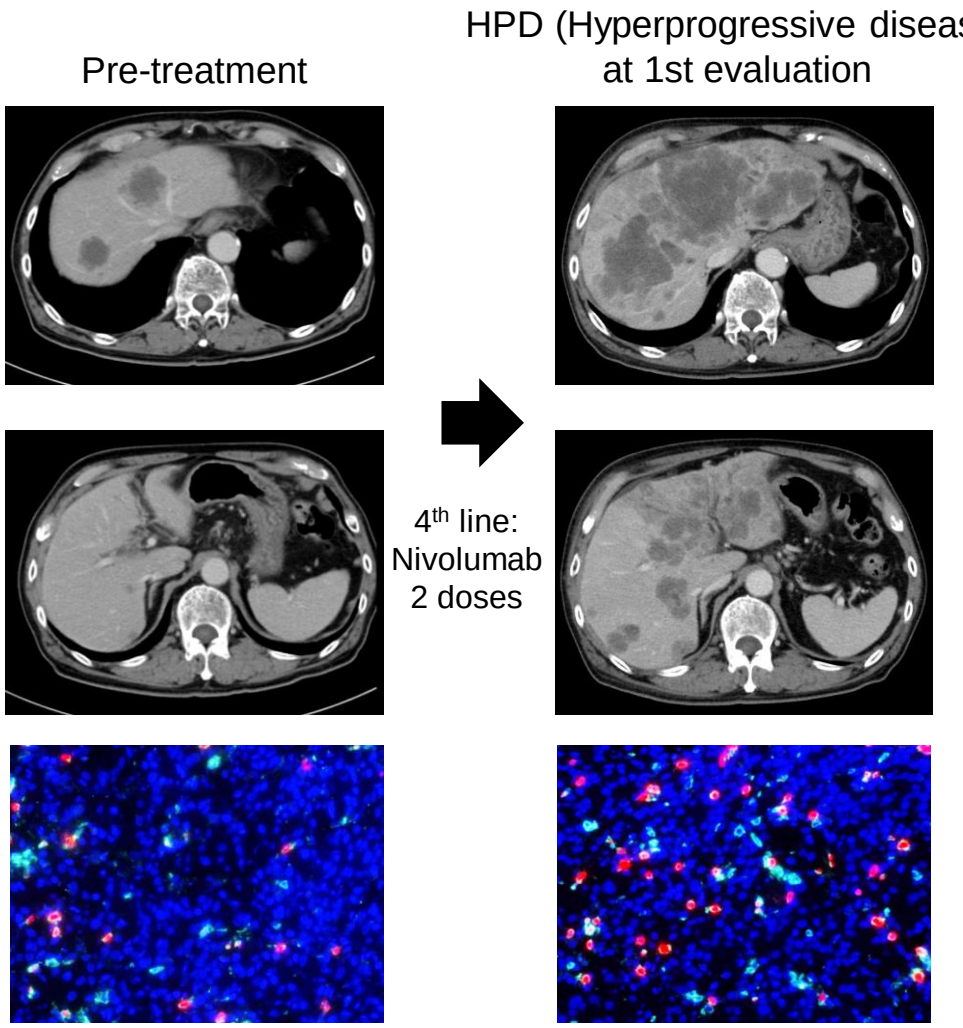


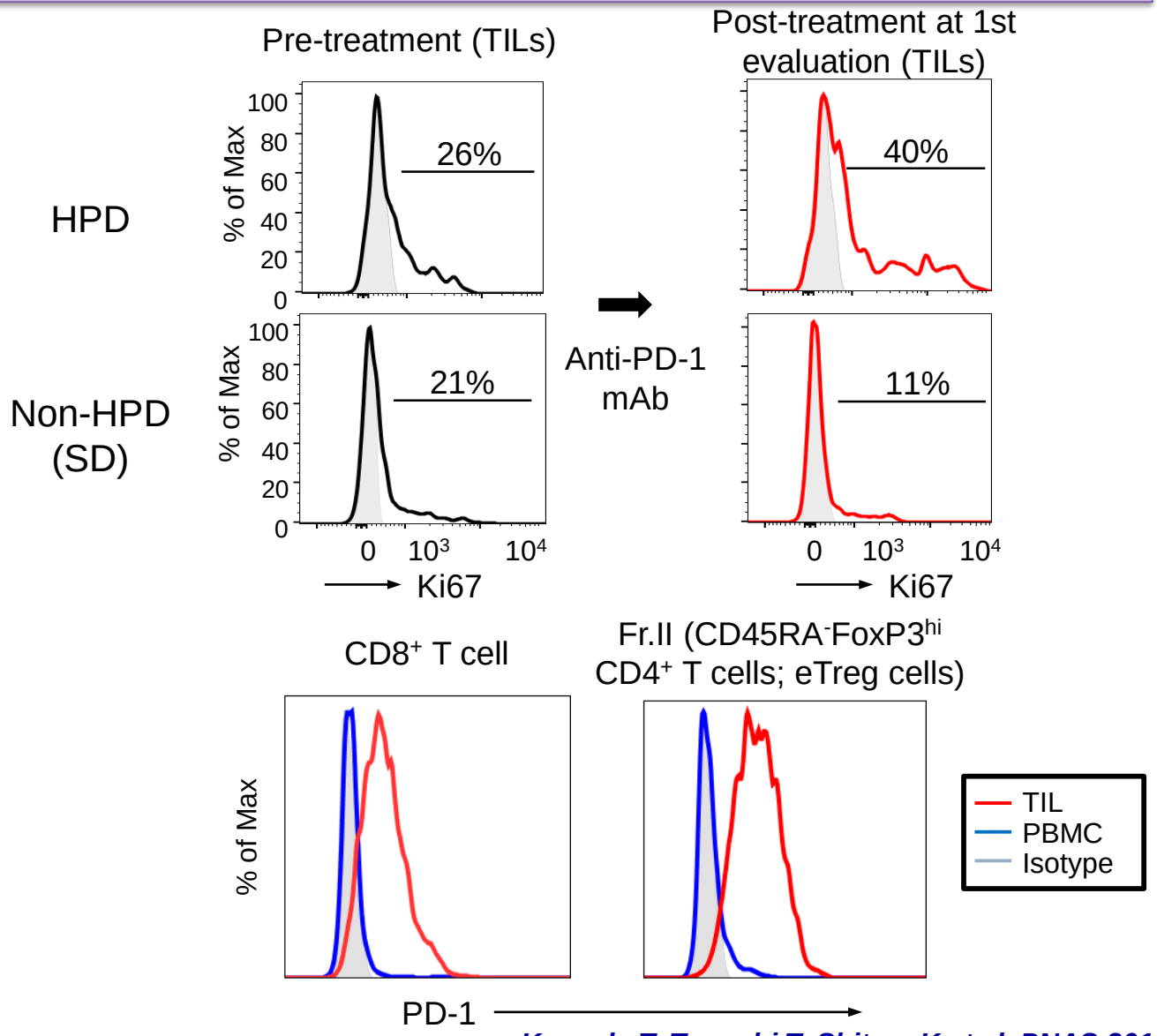


26% developed HPD after A-PD1 for NSCLC
Higher CD163+CD33+PD-L1+ macrophage in HPD case
Fc portion of A-PD1 may activate macrophage

Lo Russo G, et al. Clin Cancer Res. 2019

PD-1^{+} Tregs are activated by PD-1 blockade and contribute to HPD

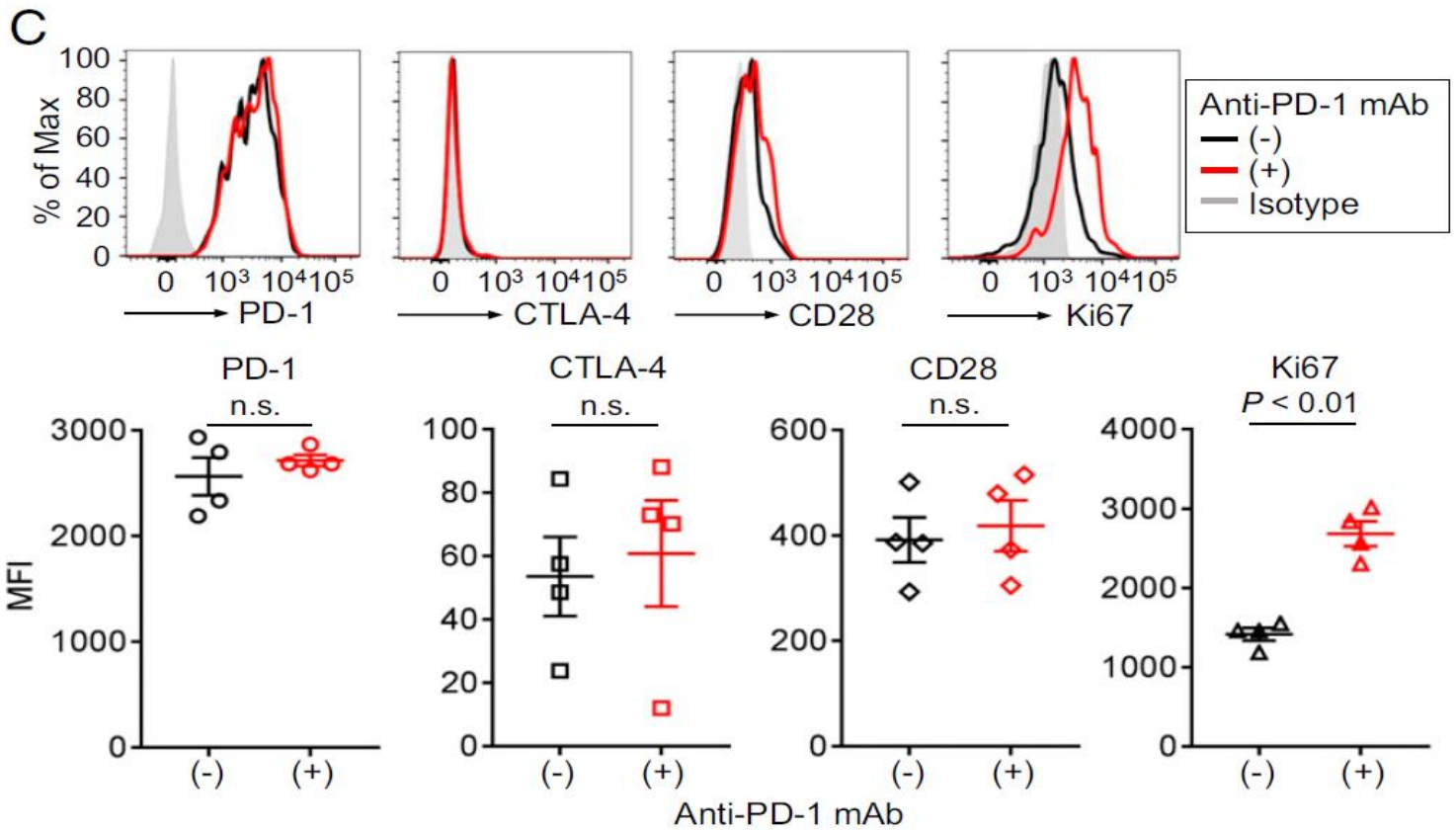




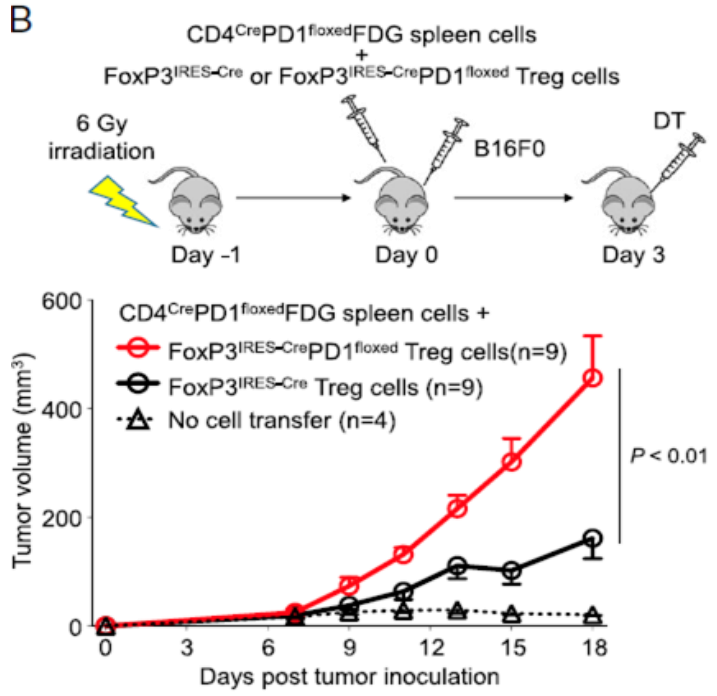
Kamada T, Togashi T, Shitara K et al. PNAS 2019

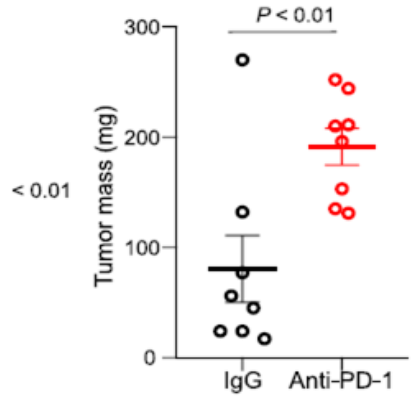
HPD cases showed increasing infiltration of KI-67+ Tregs

PD-1+ Tregs are activated by PD-1 blockade and contribute to HPD



Ki67+ Treg↑ After A-PD1



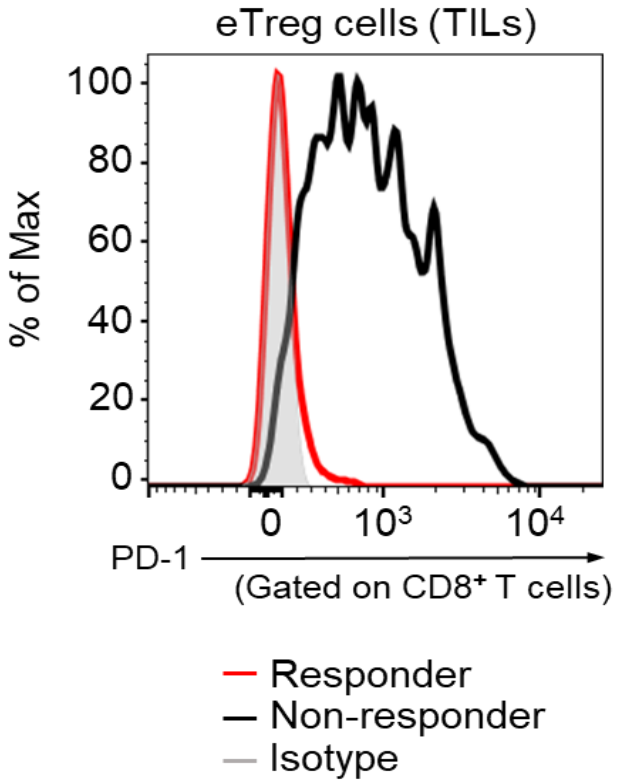


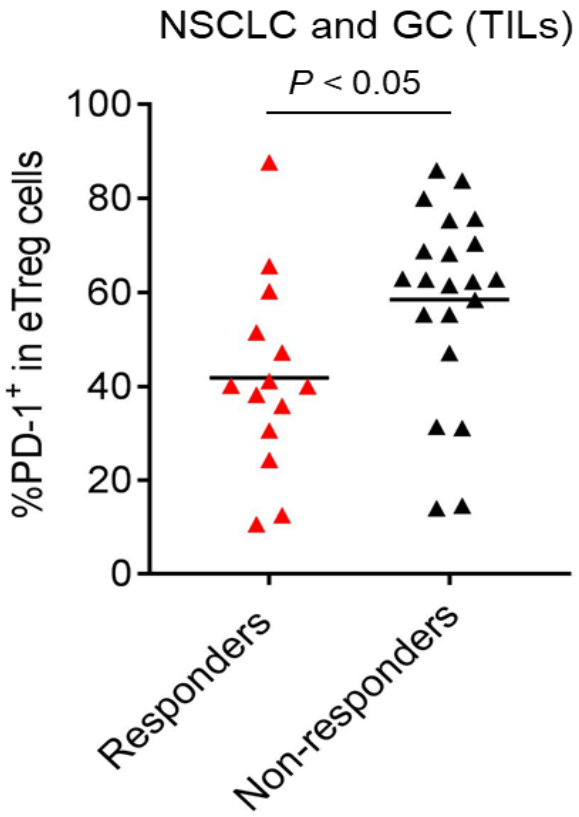
A-PD1 induce Tumor growth

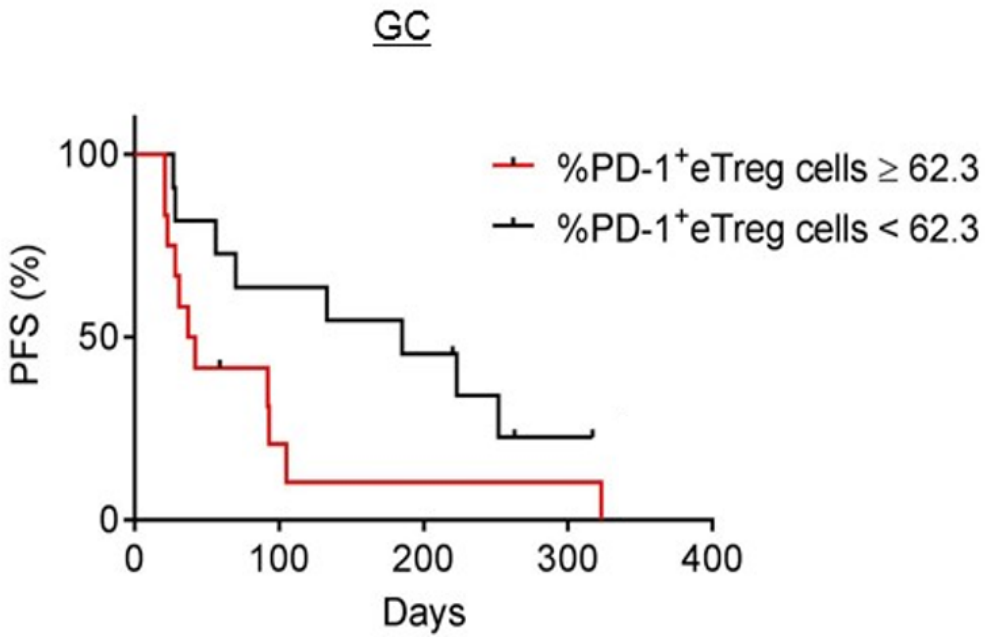
A-PD1 increase Ki67+Tregs in vitro analysis
Activated PD1+Treg strongly suppress CD8+ T cells
A-PD1 induce tumor growth in Treg enriched mouse model

Kamada T, Togashi T, Shitara K et al. PNAS 2019

PD-1^{+}Treg is associated with non-responders after Anti-PD1/PD-L1



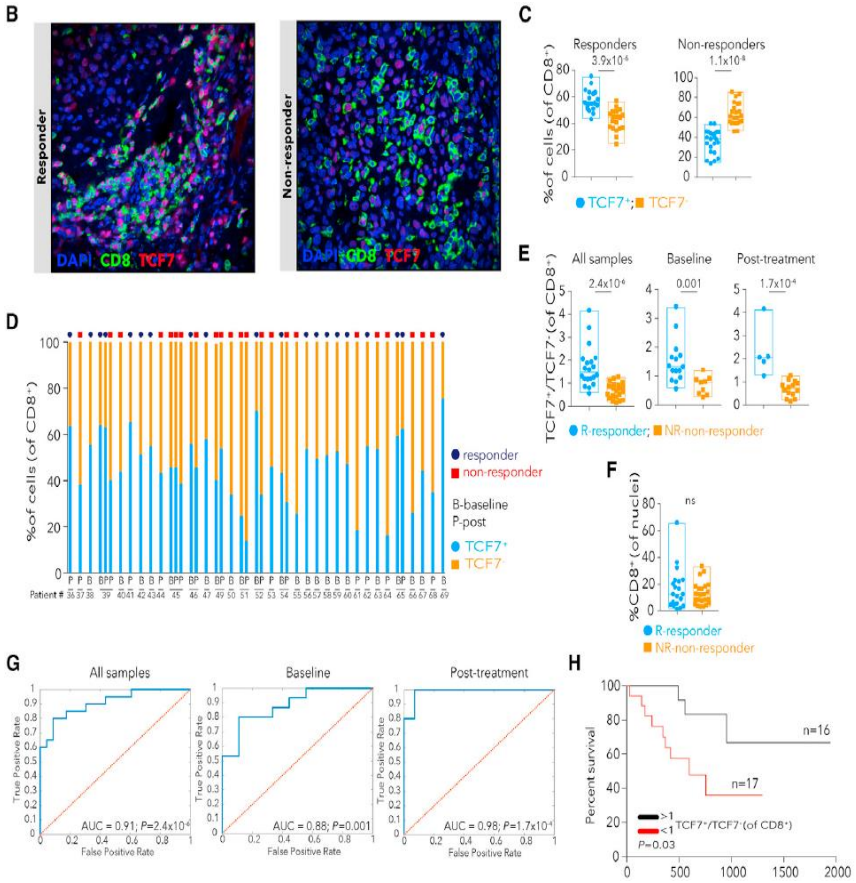




Kamada T, Togashi T, Shitara K et al. Submitted

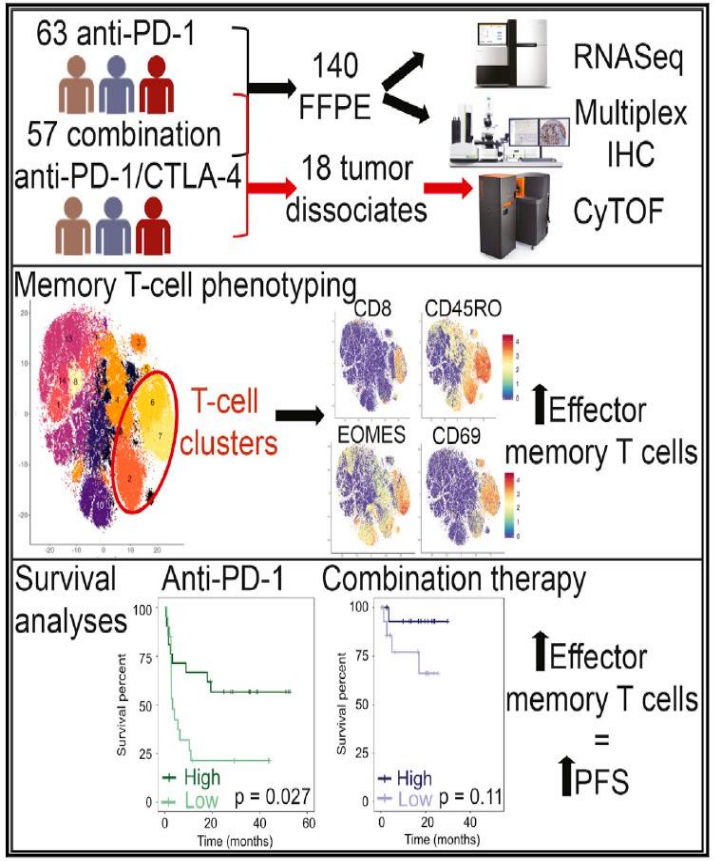
TIL analysis in GC and NSCLC pts treated by A-PD1
PD-1+Treg was apparently enriched in non-responder after A-PD1
Related to poor outcomes after A-PD1

Defining T Cell States Associated with Response to A-PD1 by ScRNAseq



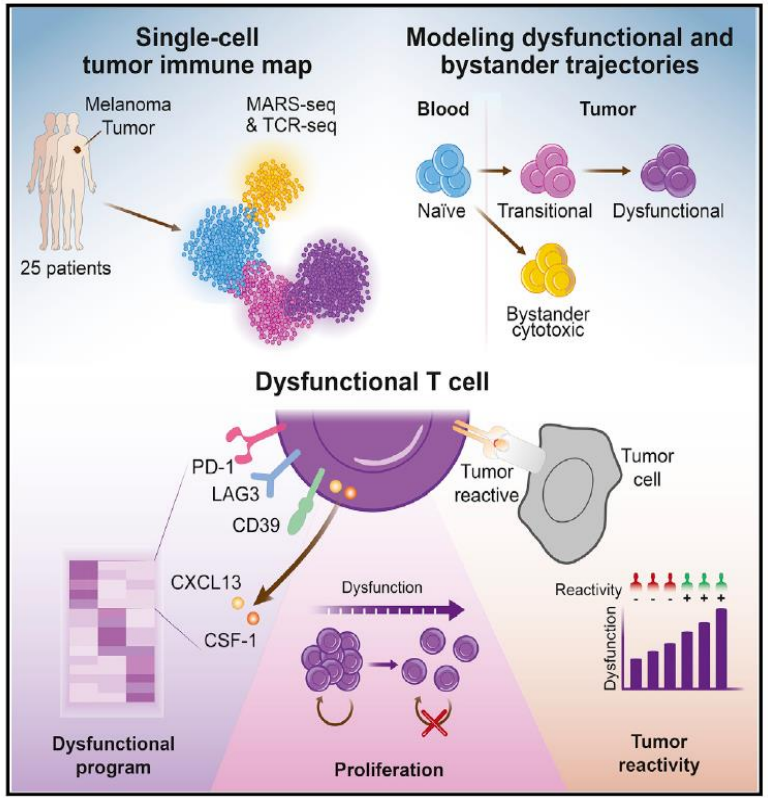
Sade-Feldman M, et al. Cell. 2019

TCF7$^+$CD8$^+$ Stem-like T Cells in TIL predict better outcome after A-PD1
CD39 and TIM3 discriminated exhausted from memory and/or effector cells



Gide TN, et al. Cancer Cell. 2019

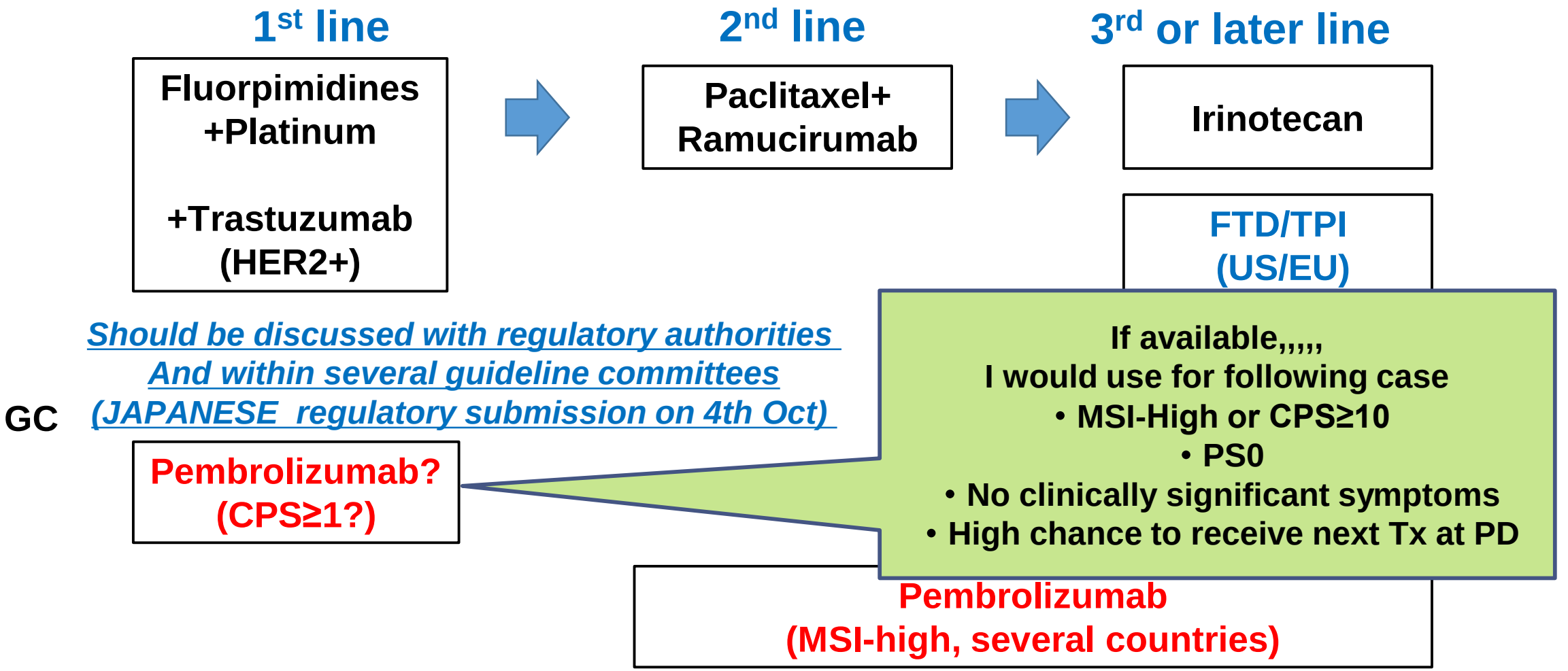
EOMES$^+$CD69$^+$CD45RO$^+$ effector memory T cells Predict A-PD-1 response



Li H, et al. Cell. 2019;176:775-789.e718.

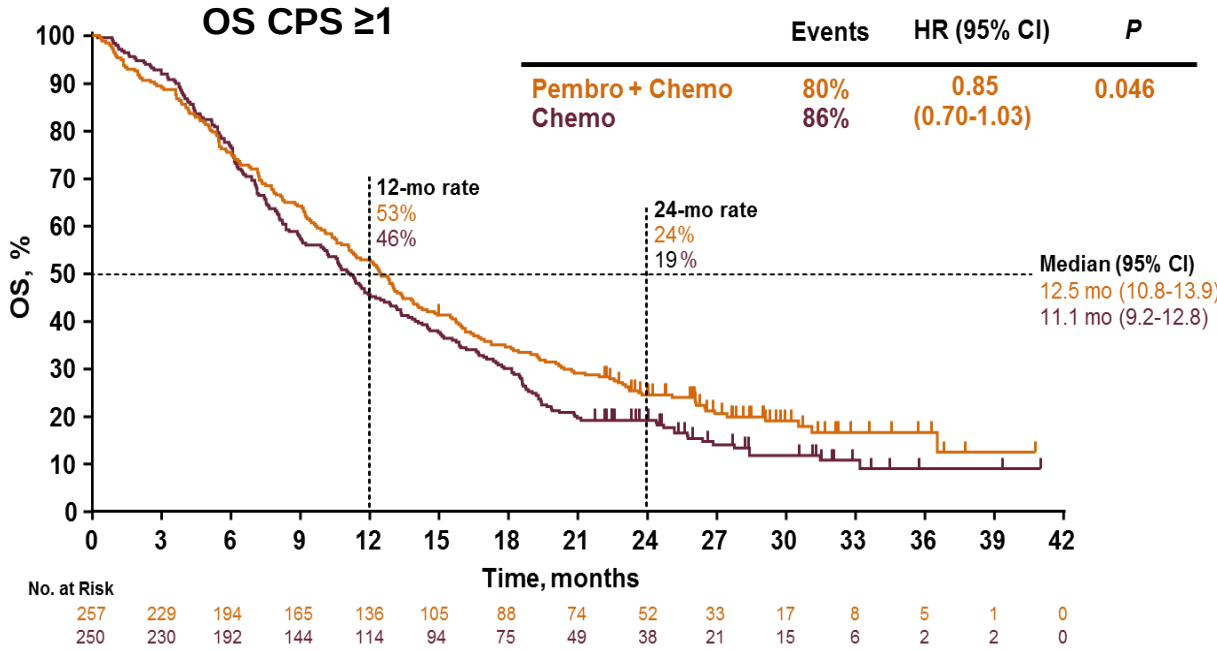
CD39$^+$PD1$^+$CD8 cells (Bystander CD8 lack CD39)

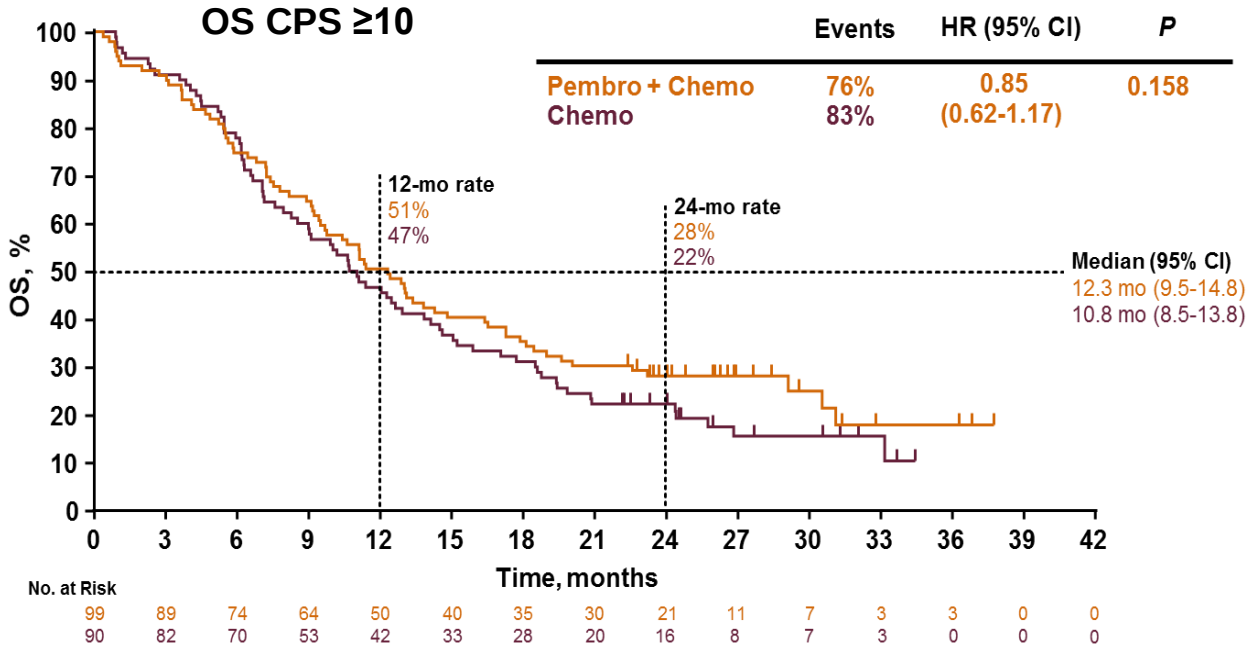
Standard treatment for GC

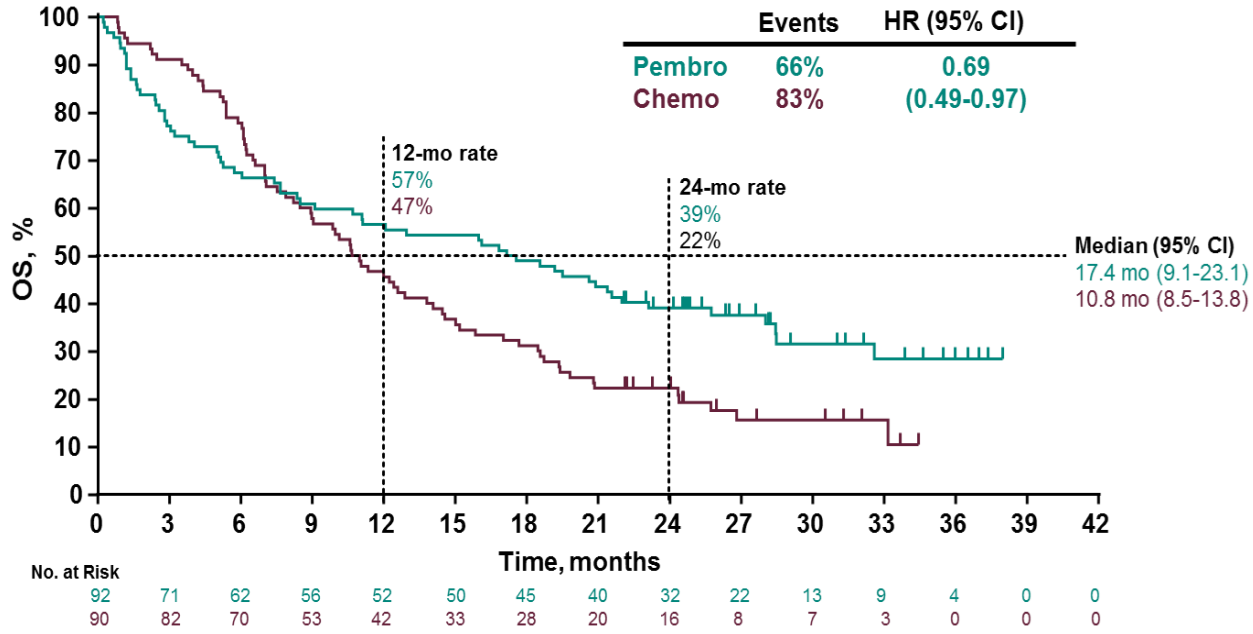


() approved countries

KEYNOTE-062: Pembrolizumab+Chemo vs 1st-line chemo



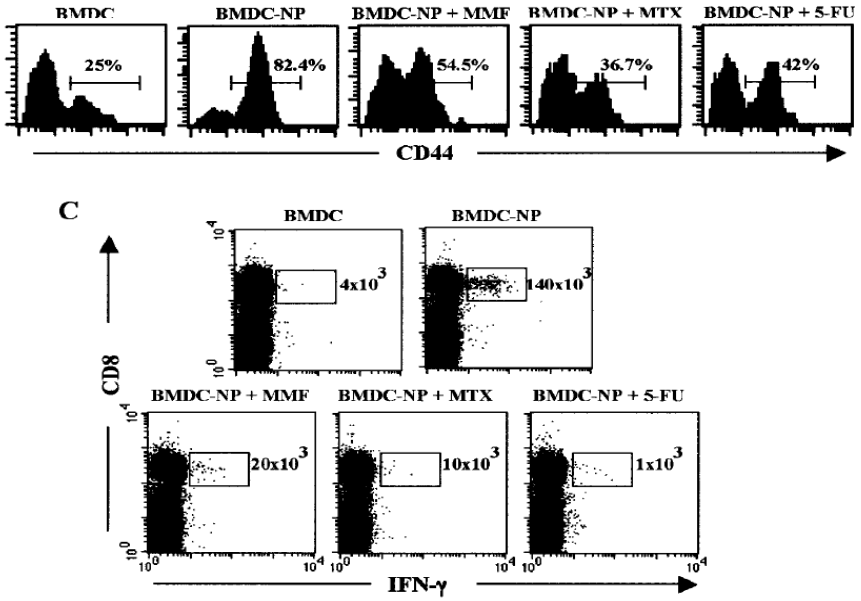




Pembrolizumab+Chemo combination
-not improve OS
-CPS10 did not predict benefit of Pembro when combined with chemo?
(detrimental effect of chemo?)

Tabernero J,et al. ASCO 2019; ESMO-GI 2019

Types of backbone chemo matter? Repeated 5-FU (capecitabine)



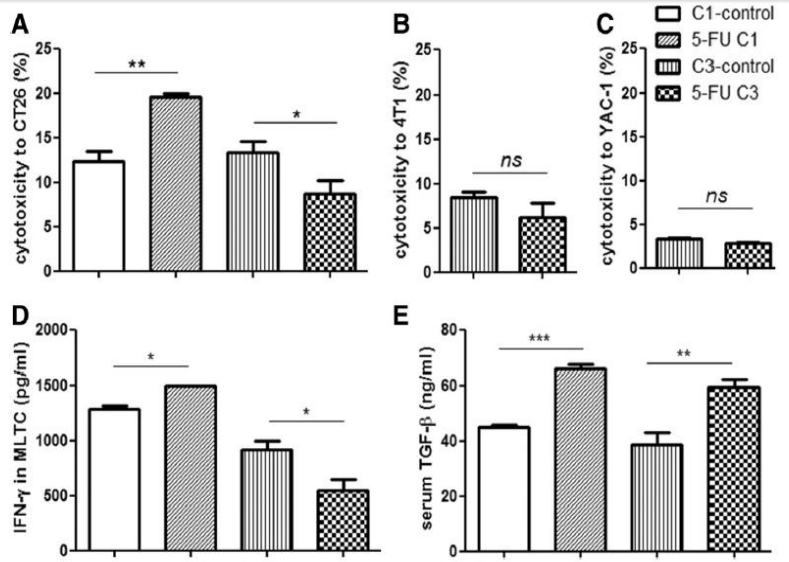


Fig. 5 Cytotoxicity and cytokine production after 5-FU C1 and C3 treatment. **a** Cytotoxicity against CT26 using CFSE-PI staining-based flow cytometry. Spleen cells from treatment and control groups as effectors were incubated with CFSE-stained CT26 cells (Fig. 5a) at an effector:target (E:T) ratio of 25:1. CFSE and PI positive cells represent killed target cells, and the cytotoxicity was calculated. **b** Cytotoxicity against 4T1 cells, and **c** cytotoxicity against YAC-1 cells at the E:T ratio of 25:1. **d** IFN-γ production by spleen cells in the MLTC assay. The supernatant of MLTC was collected on day 3, and the IFN-γ concentration was analyzed by ELISA. **e** Serum TGF-β was quantified by ELISA. Serum was collected from C1, C3 and control groups ($n = 3$) on day 7 after the last 5-FU injection. Student's *t*-test was used to analyze the significance between groups. The experiments were replicated at least twice with similar results

- **5-FU(FP) lead to depletion of nucleotide**
  - **prevent the acquisition of effector functions, such as IFN-γ, granzyme B expression, and cytotoxic function following antigenic stimulation.**
  - **Interfere with the differentiation of naïve cells into memory CD8 Tcells**
- **But, 5FU is unable to inhibit the development of improvement cytotoxic functions already displayed by memory CD8)**

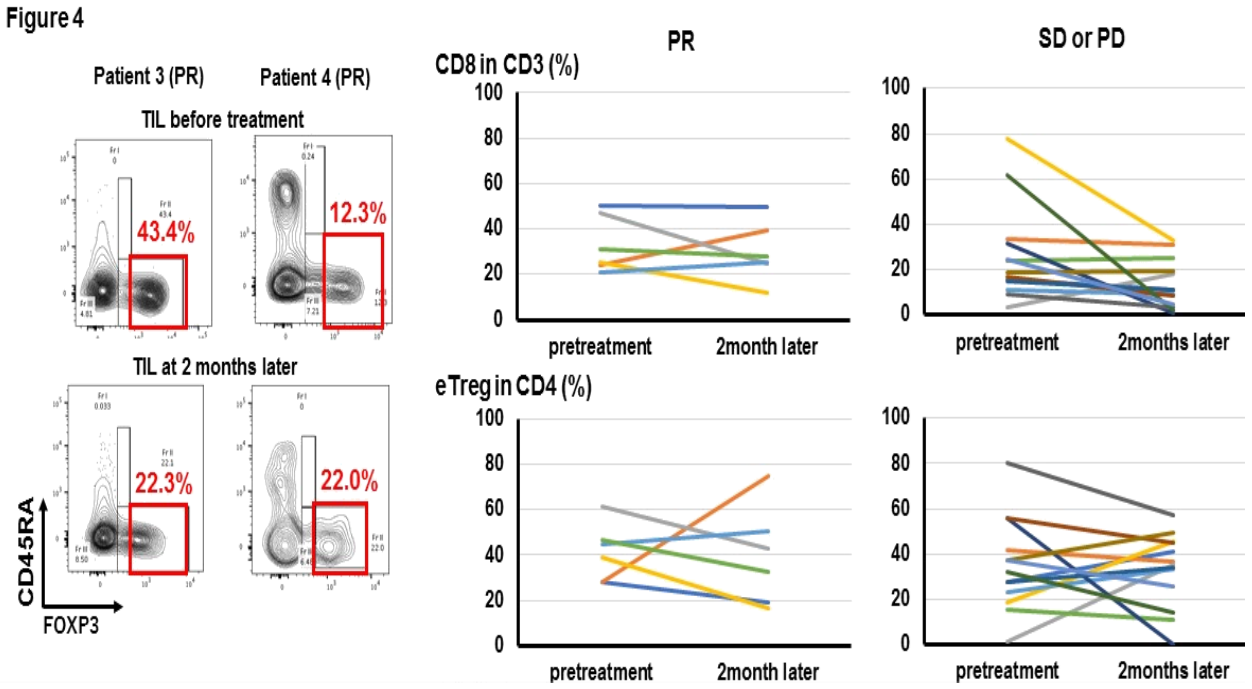
- **Repeated cycles of 5-FU impair T cell cytotoxic functions**
- **Repeated 5-FU decrease proliferated CD8 T-cells. CT26-specific cytotoxicity and IFN-γ secretion of spleen cells were also impaired in vitro**

Repeated 5FU/Cape (maintenance) affect OS?
Stay tune for ATTRACTION-4 and Checkmate649

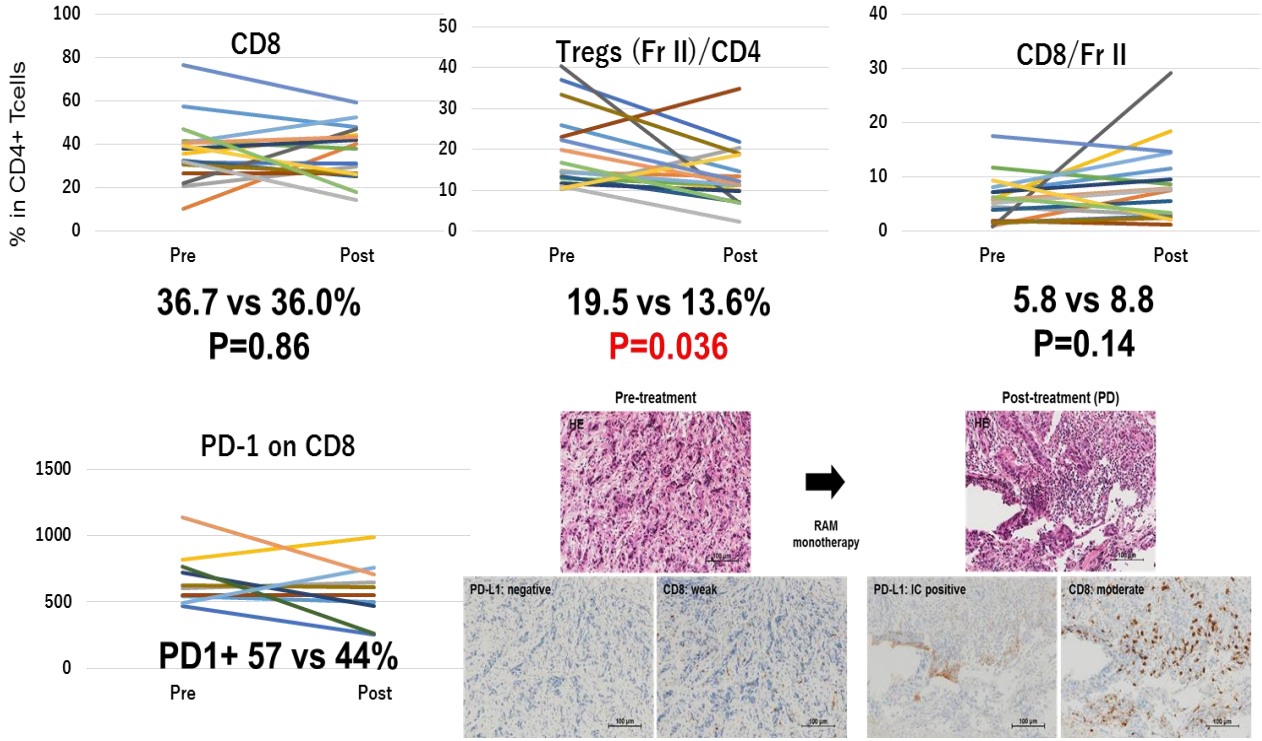
Quéméneur L, et al. J Immunology 2004
Wu Y, et al. BMC Immunology 2016

TILs change after cytotoxic chemotherapy or RAM for GC

N=20, 1stline FU+oxaliplatin, 8 PR, 11 SD, 1 PD



N=18, 2ndline RAM(+chemo)



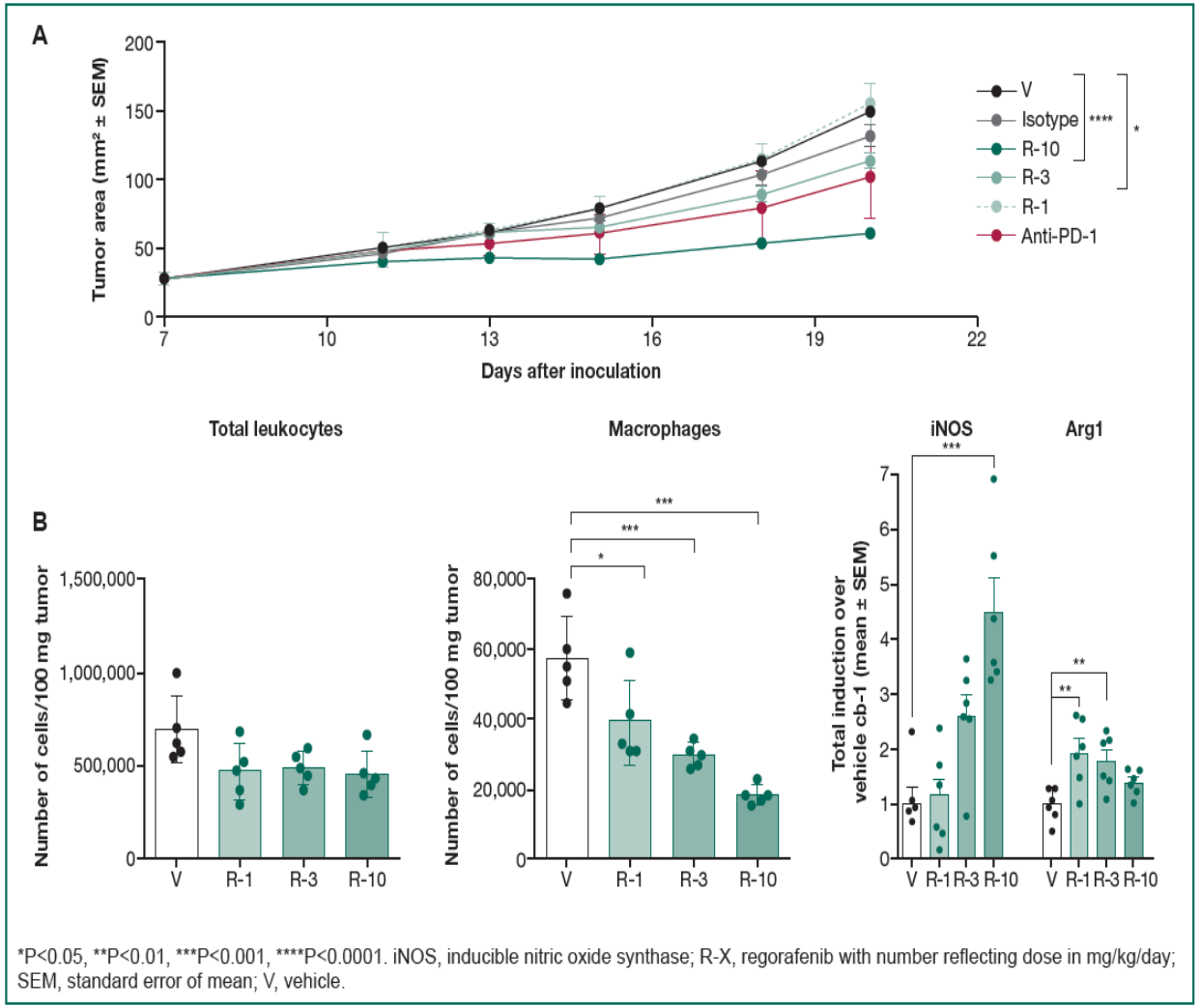
Unpublished

Toda Y,,Shitara K.
J of ImmunoTherapy of Cancer 2018

Treg or CD8 did not show consistent change after cytotoxic chemotherapy
Reduced fraction of Tregs after RAM treatment
VEGFR-2 expression is high in Tregs

Targeting immune suppressive cells : multi-kinase inhibitors

Figure 3. (A) Regorafenib dose-dependently inhibited growth of subcutaneous murine MC38 CRC tumors. (B) Dose-dependent effects of regorafenib on tumor-associated macrophages



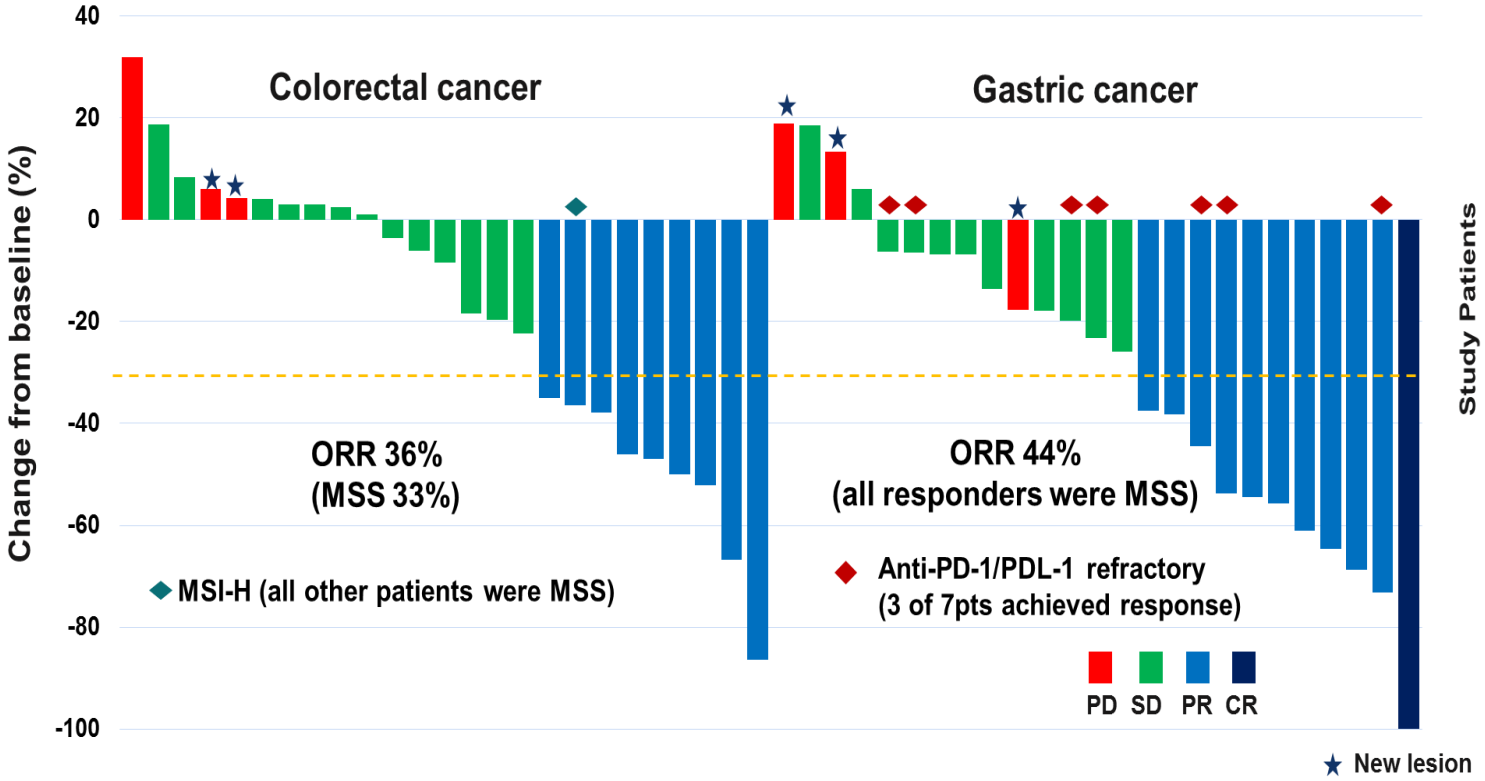
*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. iNOS, inducible nitric oxide synthase; R-X, regorafenib with number reflecting dose in mg/kg/day; SEM, standard error of mean; V, vehicle.

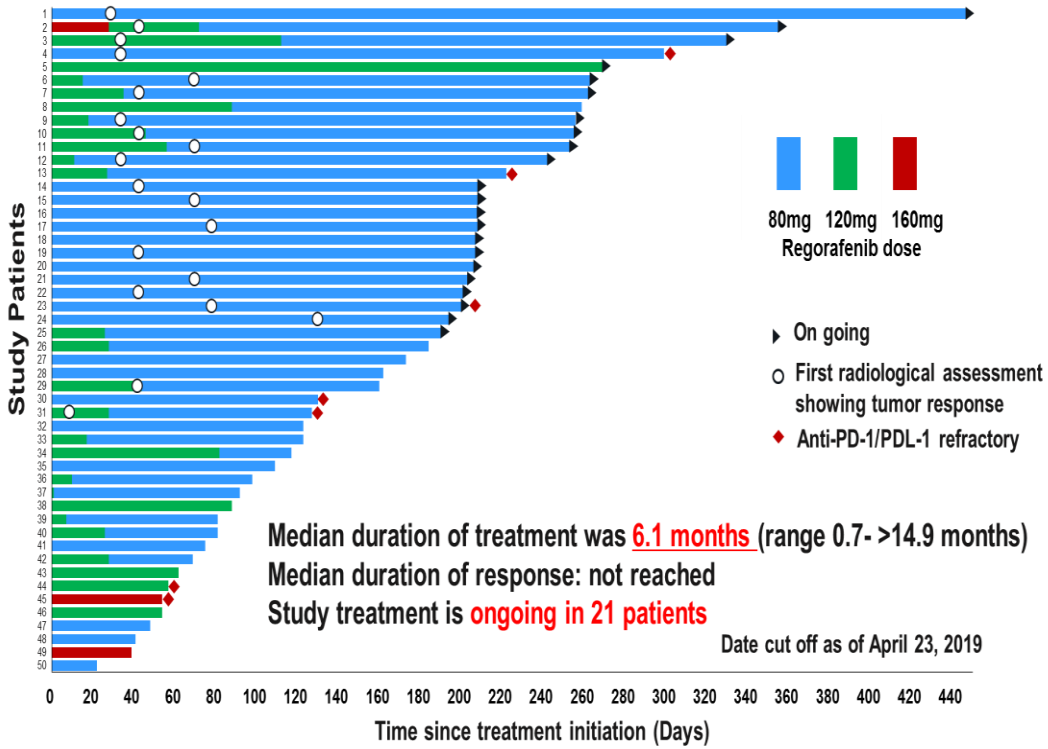
- Regorafenib multi-kinase inhibitor for multi-target inhibitor for VEGFR1, VEGFR2, VEGFR3, PDGFRβ, Kit, RET, Raf-1 as well as CSF1R
- In vivo analysis showed Regorafenib decreased TAM via CSF1R inhibition[1]
- Increased CD8 and decreased M2 macrophage is more efficiently observed in lower dose of Rego[2]
- Combination activity with A-PD1[1]
- In CRC pts, regorafenib showed decreased Tregs
- Investigator initiated trial of phase 1 of Regorafenib+Nivolumab (EPOC1603) was conducted

PI: K Shitara
SC: S Fukuoka

1.Hoff S, et al. ESMO 2018
2.Chen CW,,,Hsu C. 2019 EASL

Targeting immune suppressive cells : P1 of Regorafenib+Nivo (EPOC1603)



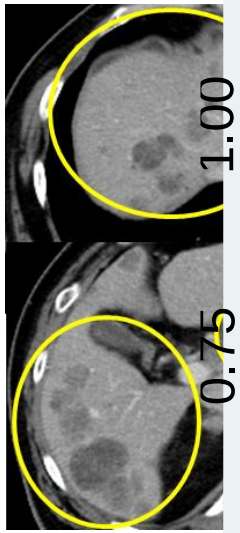


- 3DLTs in Rego 160mg and frequent skin toxicities in 120mg
- Rego 80 mg plus nivolumab is the optimal dose for future study
- Encouraging anti-tumor activities for GC and CRC in heavily treated pts (median 3 lines of previous chemo)
- Median PFS 5.8 months for GC and 6.3 months for CRC

PI: K Shitara
SC: S Fukuoka

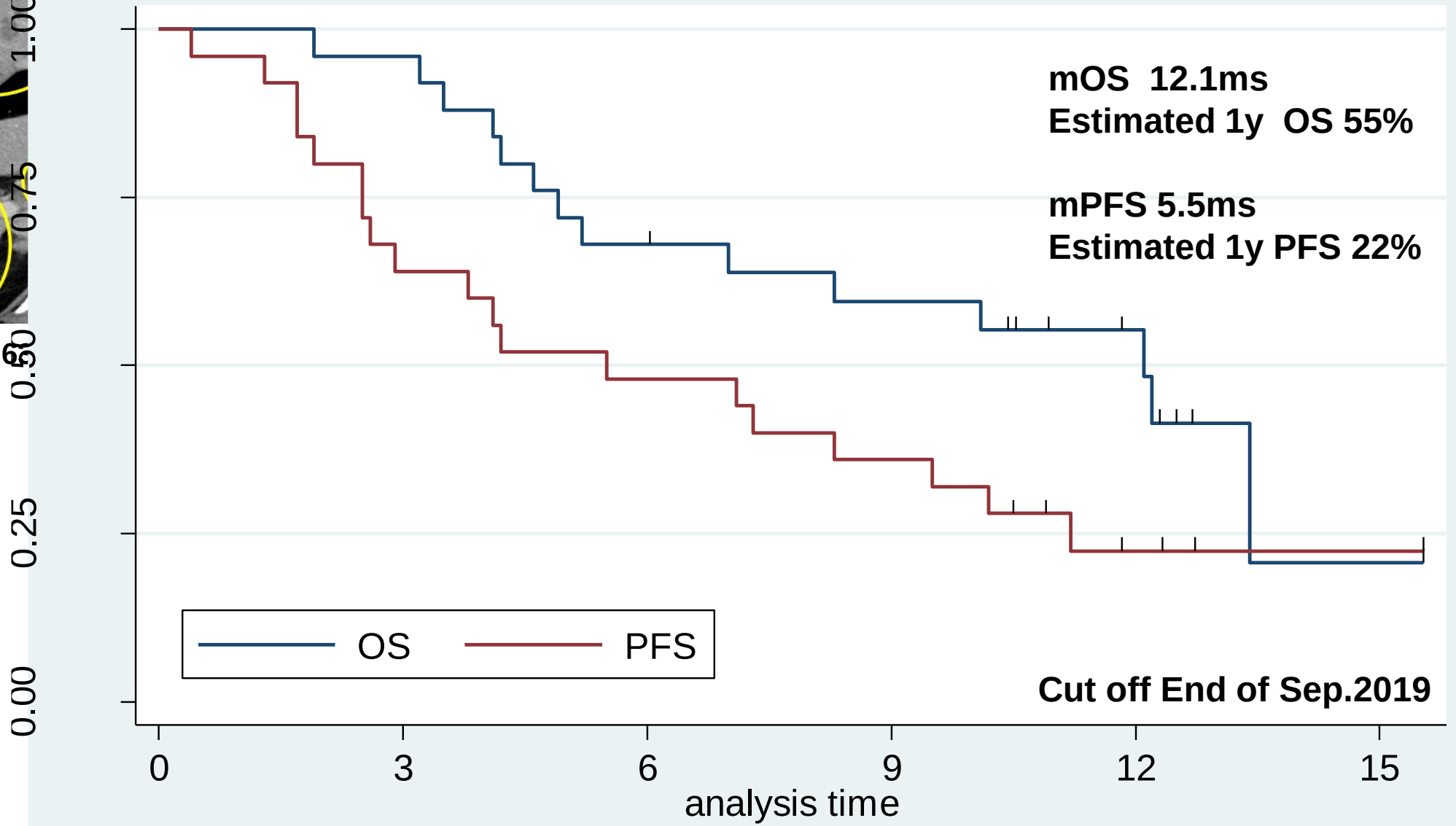
Fukuoka S,,,Shitara K. ASCO2019
Hara H,, Shitara K. ESMO-GI 2019

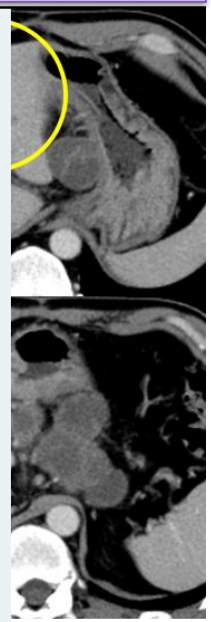
Phase 1 of Regorafenib+Nivo (EPOC1603)



Case 17: 6

Updated PFS and OS for GC (N=25)





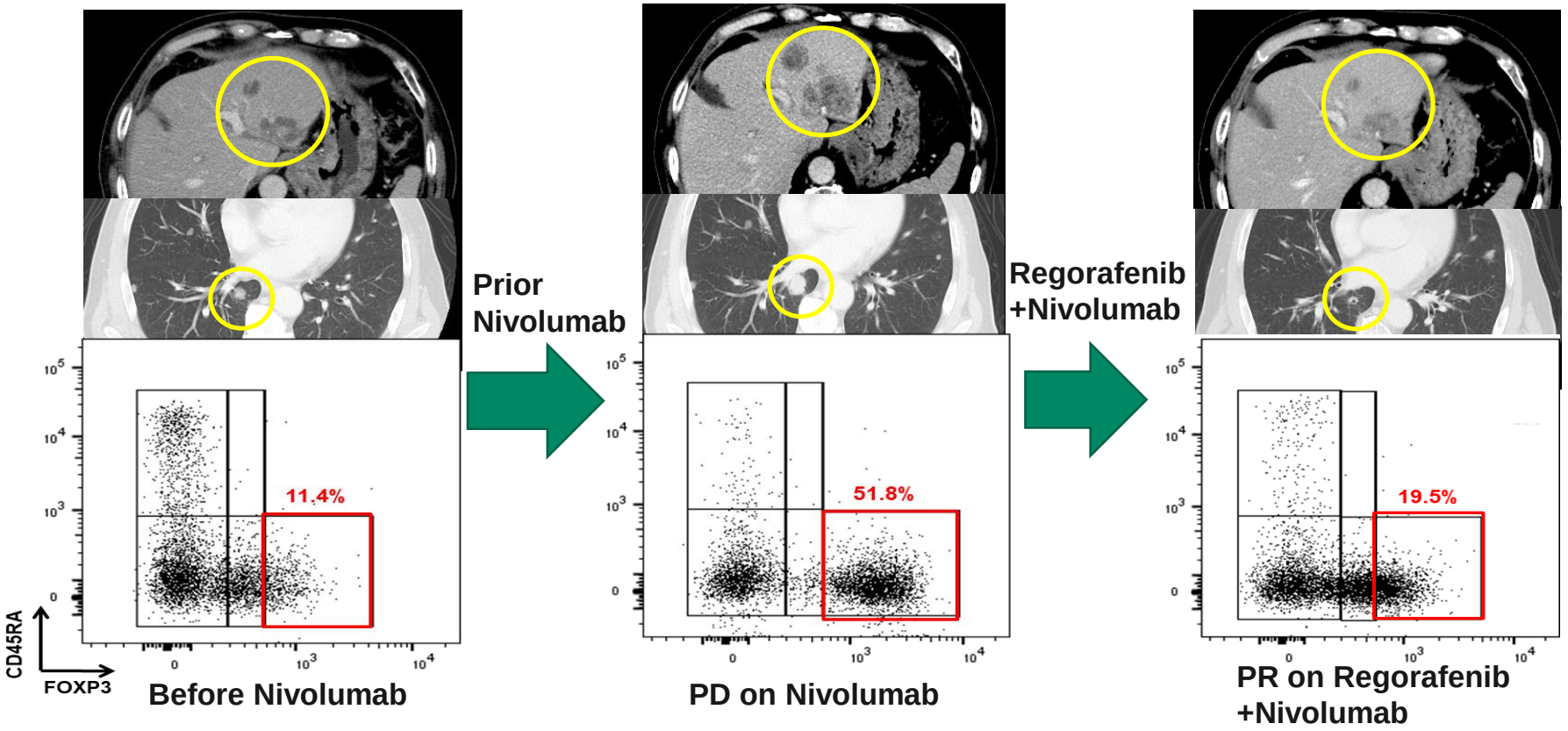
IRIRAM

ra K. ASCO2019

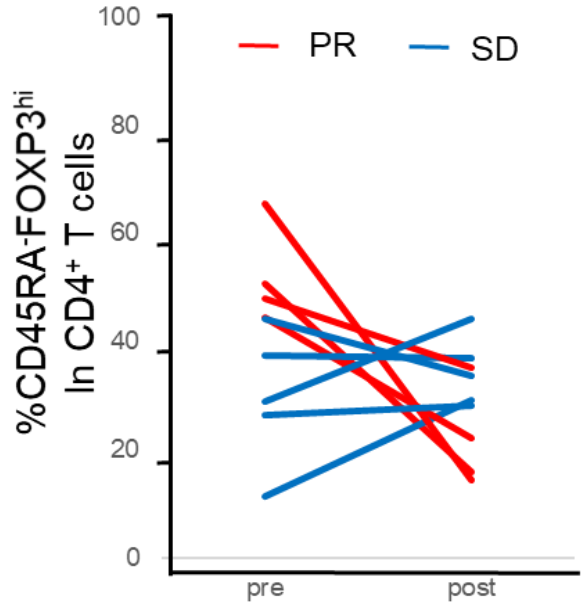
Phase 1 of Regorafenib+Nivo (EPOC1603)

- Pre-and post-treatment biopsied samples in 9 patients were analyzed using flow cytometry.

Case 2, 67 year old male with MSS GC, PDL1 CPS0
- Disease progression after Nivo monotherapy



Fraction of Treg within tumor infiltrating lymphocytes



FoxP3^{hi}CD45RA^{-}Tregs increased on PD with nivolumab, then decreased after regorafenib+nivolumab

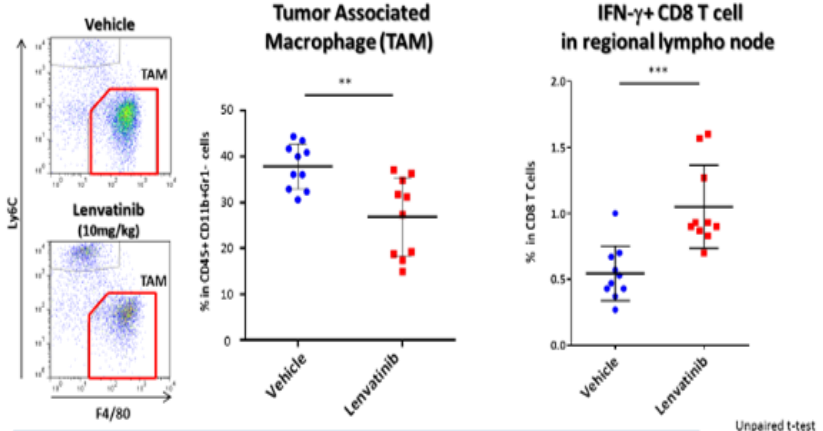
PR cases showed decrease FoxP3^{hi}CD45RA^{-}Tregs

Fukuoka S,,,Shitara K. ASCO2019

Targeting immune suppressive cells : Lenvatinib as one of multi-kinase inhibitors

Fig. 2 Immune Population Analysis in Tumors or regional LN Treated with Lenvatinib

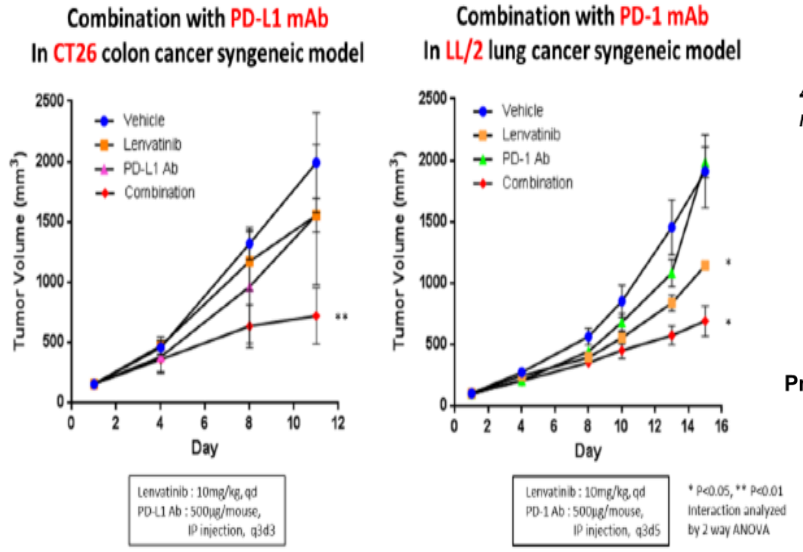
BNL 1ME A.7R.1 (Mouse HCC cell line) syngeneic model



- TAM population was decreased, and IFN-γ-producing CD8 T cells were up-regulated by lenvatinib treatment.

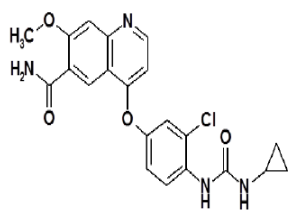
Lenvatinib decrease TAMs

Fig. 4 Combination Effect of Lenvatinib and Anti-PD-1/L1 mAb



Kato Y, et al. AACR-NCI-EORTC 2015

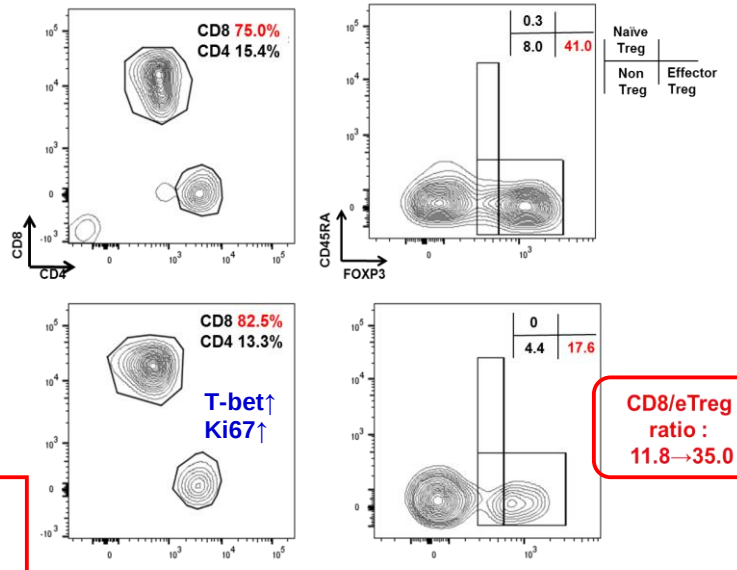
Chemical Structure of Lenvatinib



4-[3-Chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide

Cell free kinase	IC_{50} <nmol/L>	Cell free kinase	IC_{50} <nmol/L>
VEGFR1	4.7	RET	6.4
VEGFR2	3.0	KIT	85
VEGFR3	2.3	PDGFRα	29
FGFR1	61	PDGFRβ	160
FGFR2	27	RAF1	1600
FGFR3	52	$BRAF^{V600E}$	>10,000
FGFR4	43	P70S6K	>10,000

Lenvatinib treated GCpt

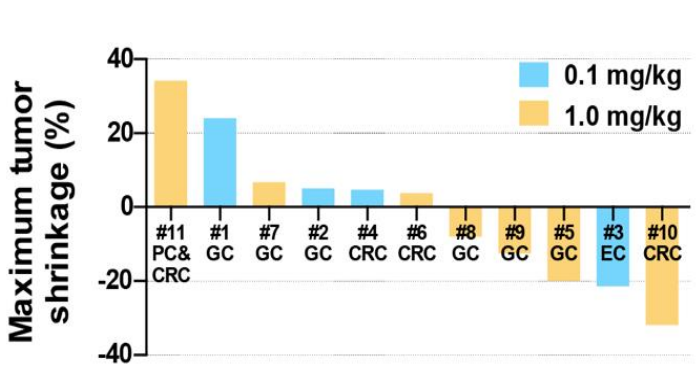


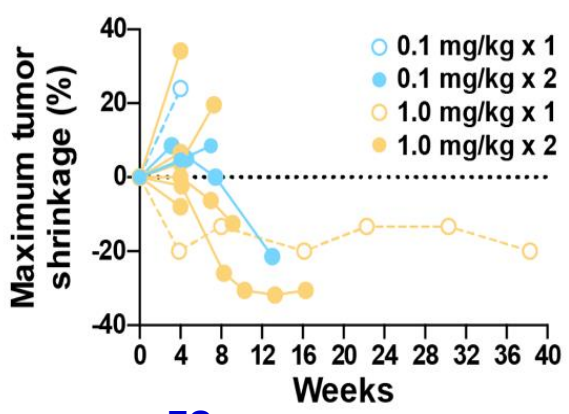
Unpublished

IIT Phase 2 of Lenvatinib+Pembro for GC (EPOC1706)
Enrollment was completed
Will be presented in near future

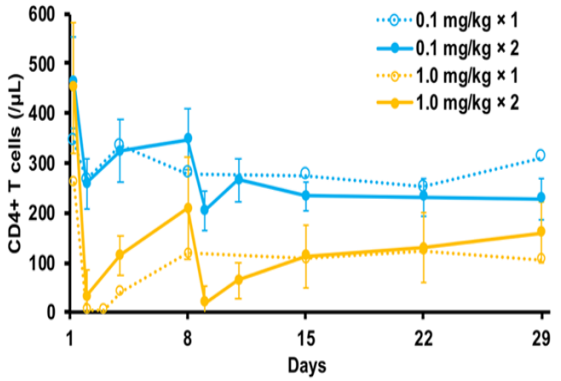
PI: K Shitara
SC: A Kawazoe, S Fukuoka

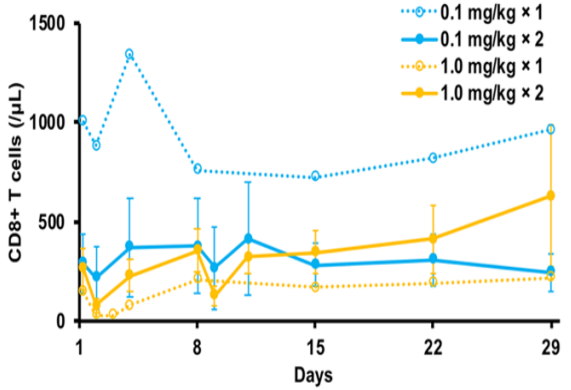
Targeting immune suppressive cells: CD4+T depletion by IT1208

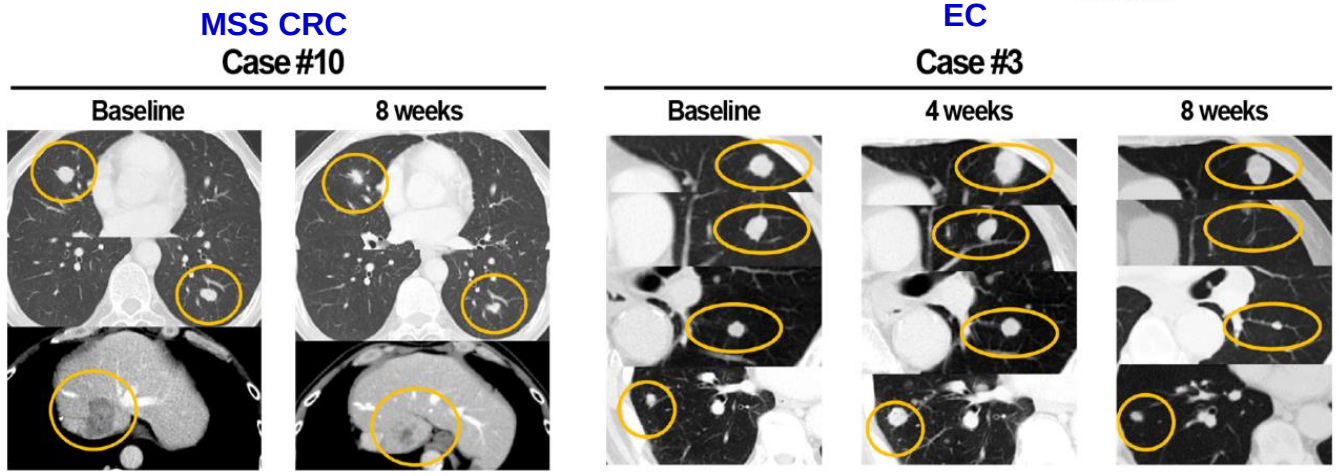


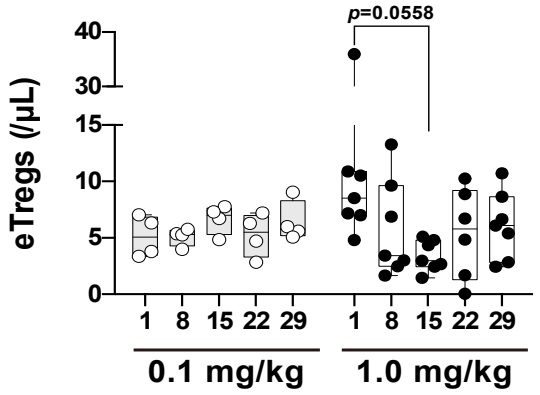


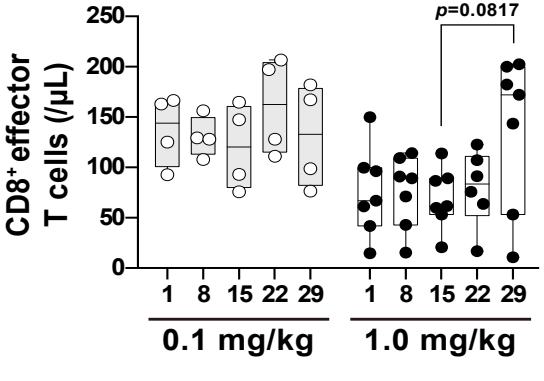
CD4 and CD8 cell in PBMC







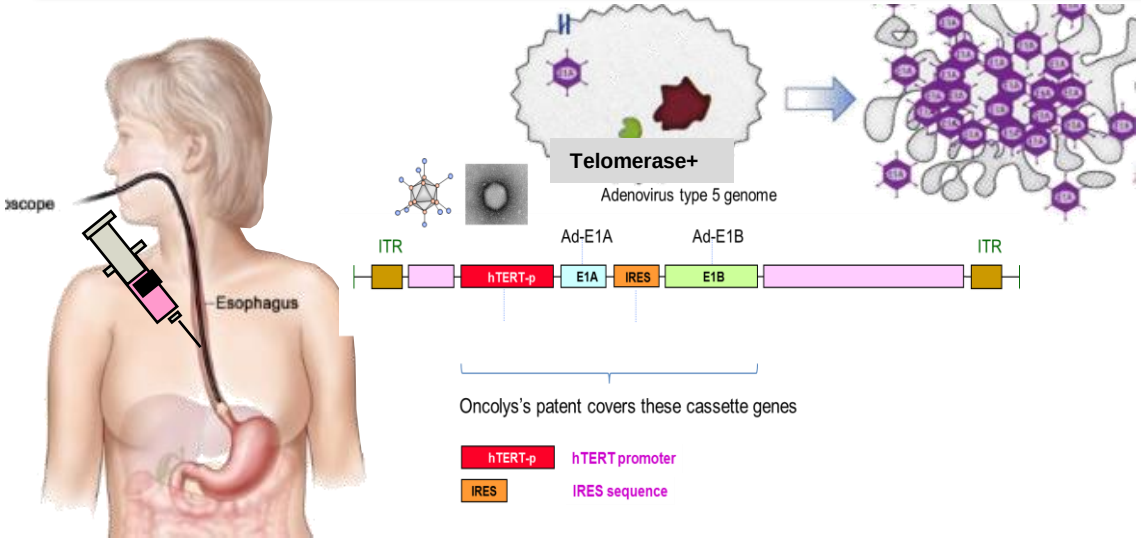




Shitara K, et al. J of ImmunoTherapy of Cancer 2019

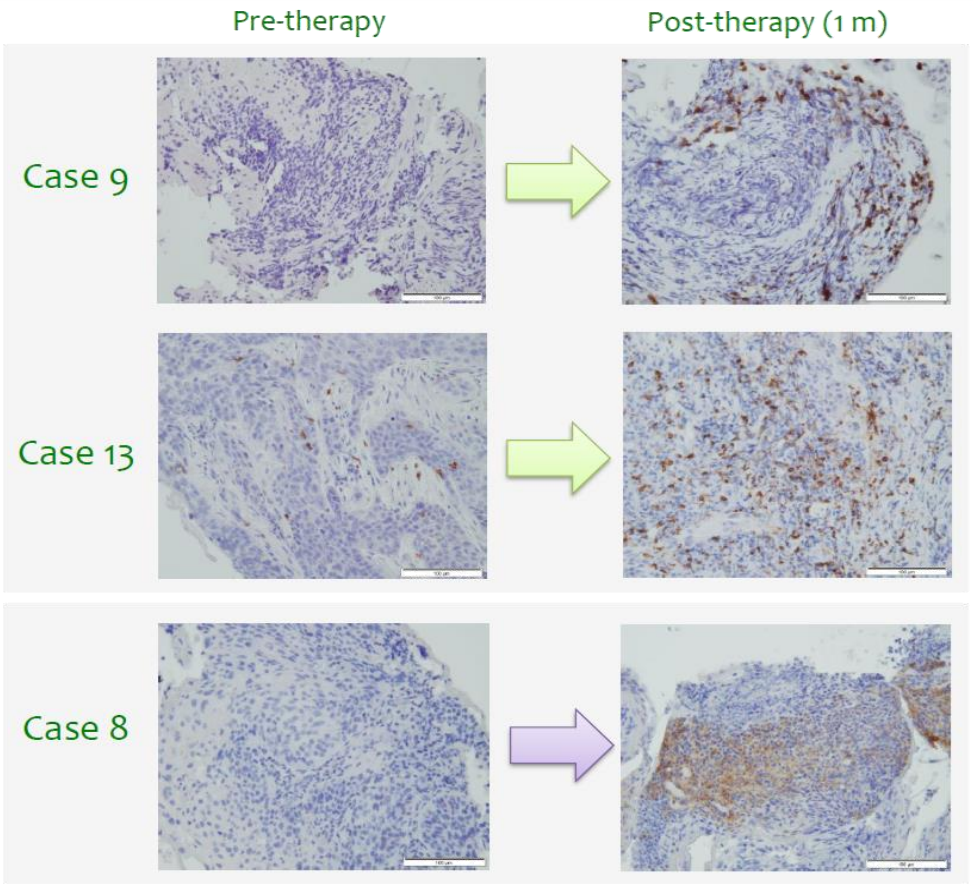
- IT1208 deplete CD4+ cells with acceptable safety profile
- Trend of decreased Treg on day15 and increased effector CD8 on day29
- Upregulation of the interferon-stimulated genes, T cell activating genes, and antigen presentation-related genes were also observed

To turn cold tumor to hot: OBP-301 (Telomelysin):
Telomerase-specific Replication Competent Oncolytic Adenovirus

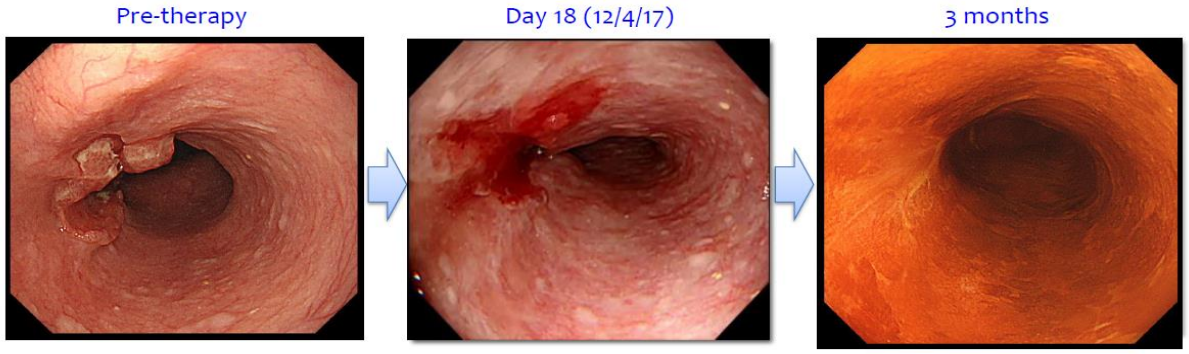


CD8

PD-L1



OBP301+RT for eso Ca (at Okayama Univ.): 8 of 11 pts CR



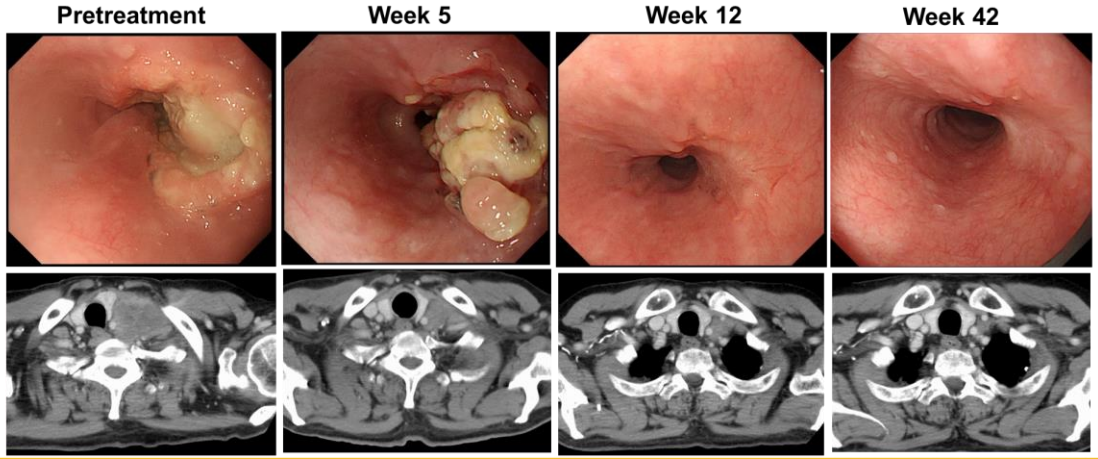
Fujiwara T, et al. AACR 2019

Telomelysin received SAKIGAKE Designation by Japanese MHLW
It also active APC and CD8+ cells
Pembro+OBP301 for GC/EC is investigated (EPOC1505)

To turn cold tumor to hot: OBP-301 (Telomelysin)+Pembro (EPOC1505)

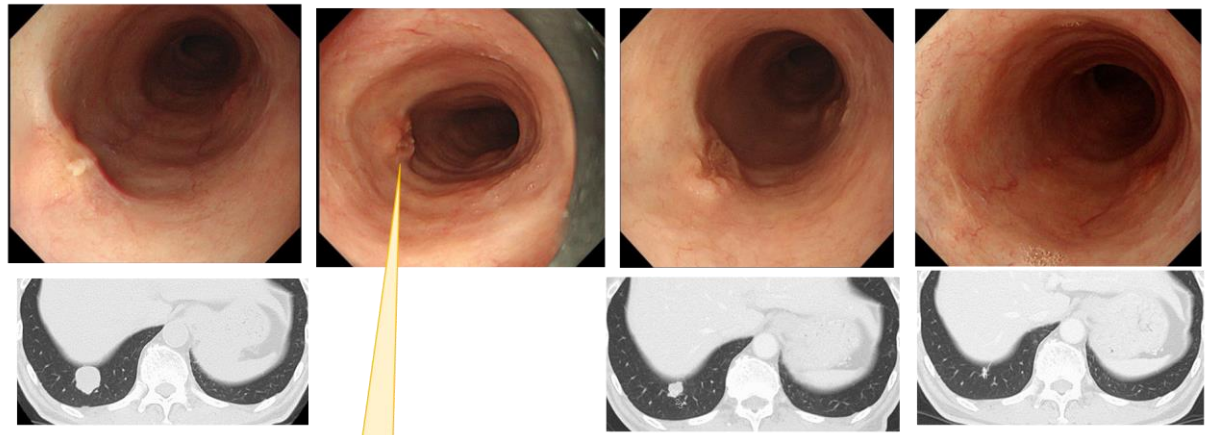
Telomerase-specific Replication Competent Oncolytic Adenovirus

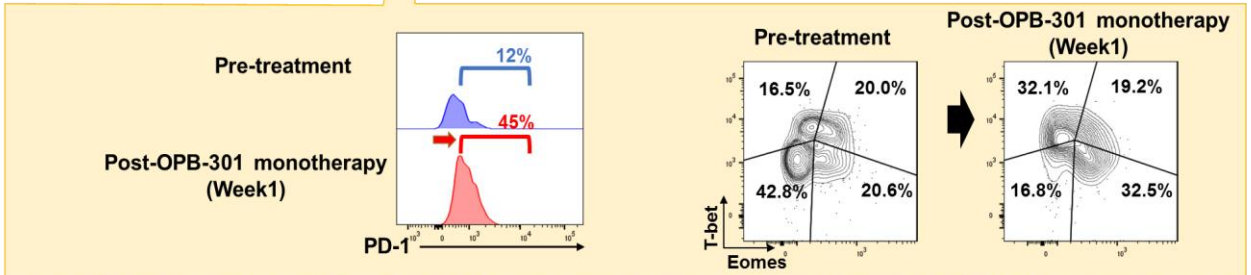
Case report: 68 year-old male (No. #1), Previous treatment: FP, PTX



No.	Cohort	Age	Sex	Cancer types	Path.	Previous treatment	RR	Adverse event
#1	1 ($1x10^{10}$)	68	M	Esophageal cancer	SCC	FP, PTX	PR	No ADR
#2	1 ($1x10^{10}$)	52	M	Gastric cancer	Adeno	SOX, CPT-11 nab-PTX+RAM	SD	No ADR
#3	1 ($1x10^{10}$)	41	F	Esophageal cancer	SCC	FP	SD	No ADR
#4	2 ($1x10^{11}$)	61	M	Esophageal cancer	SCC	FP-RT, PTX	SD	Pleural Effusion: Gr.1
#5	2 ($1x10^{11}$)	72	M	Esophageal cancer	SCC	FP-RT, PTX	PR*	No ADR
#6	2 ($1x10^{11}$)	55	M	Esophageal cancer	SCC	FP+/- PD1	PD	Fever: Gr.1
#7	3 ($1x10^{12}$)	56	M	Esophageal cancer	SCC	DCF, PTX	PR*	Fever: Gr.2 Hepatic disorder: Gr.1 Neutropenia: Gr.2 Pain: Gr.1
#8	3 ($1x10^{12}$)	75	F	Esophageal cancer	SCC	FP	NE	Hepatic disorder: Gr.3 Fever: Gr.2
#9	3 ($1x10^{12}$)	59	M	Esophageal cancer	SCC	FP+RT, PTX, PD1	SD	No ADR

Case report: 72 year-old male (No. #5), Previous treatment: FP-RT, PTX



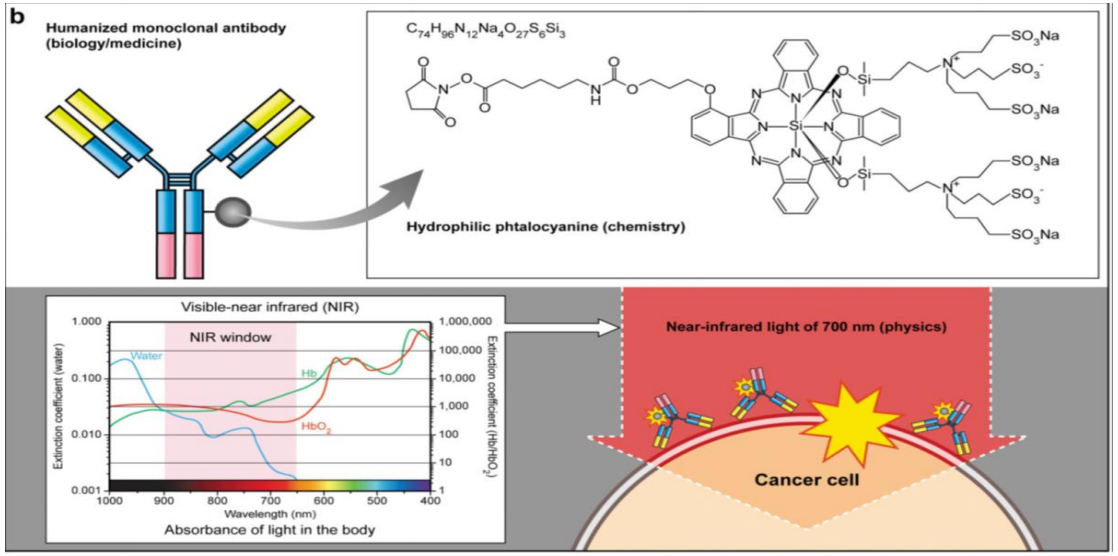


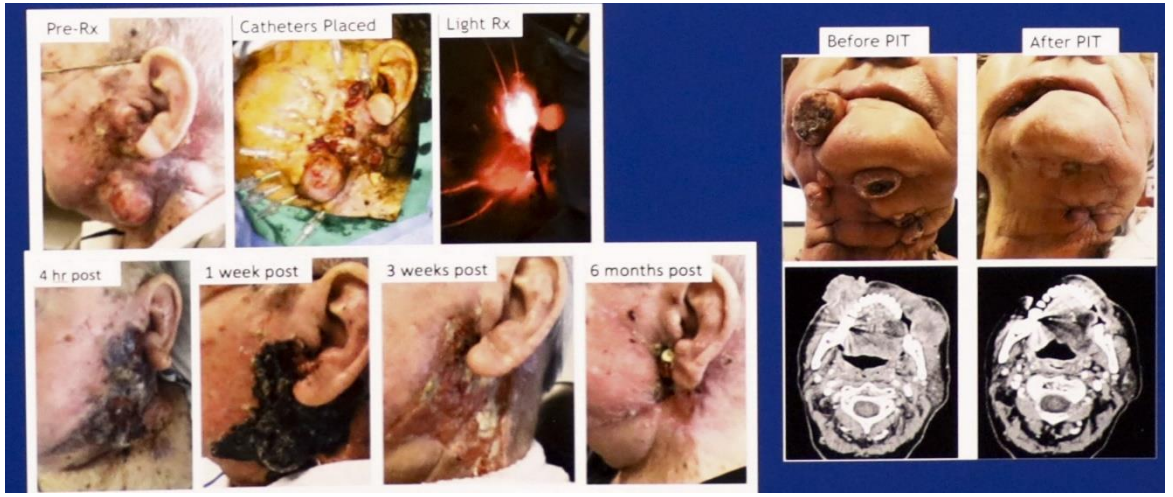
- PD-1^{+}CD8^{+} TILs increased after OBP-301 monotherapy in a responder with low PD-1^{+}CD8^{+} TILs at pre-treatment.
- T-bet^{hi}CD8^{+} TIL increased even after OBP-301 monotherapy.

Kojima T, et al. AACR 2019

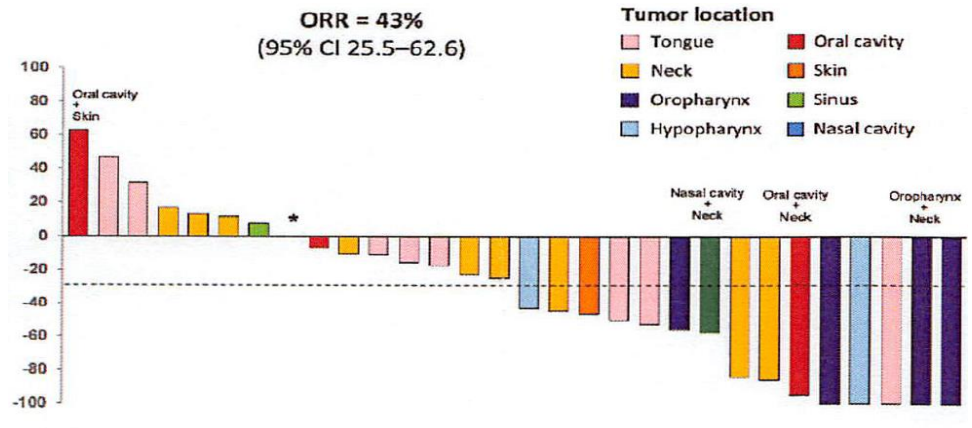
The combination of OBP-301 with pembrolizumab was well tolerated with the recommended dose for phase Ib part is $1x10^{12}$VP (cohort 3).
Infusion for liver mets is started

To turn cold tumor to hot: Near Infrared Photoimmunotherapy (PIT)

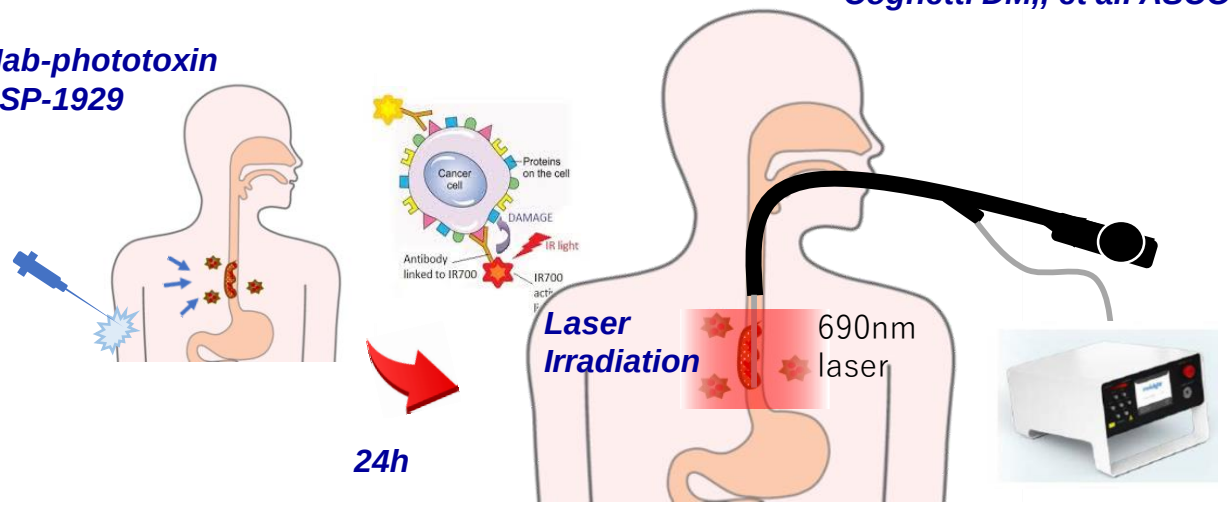




Cognetti DM,, et al. ASCO 2019



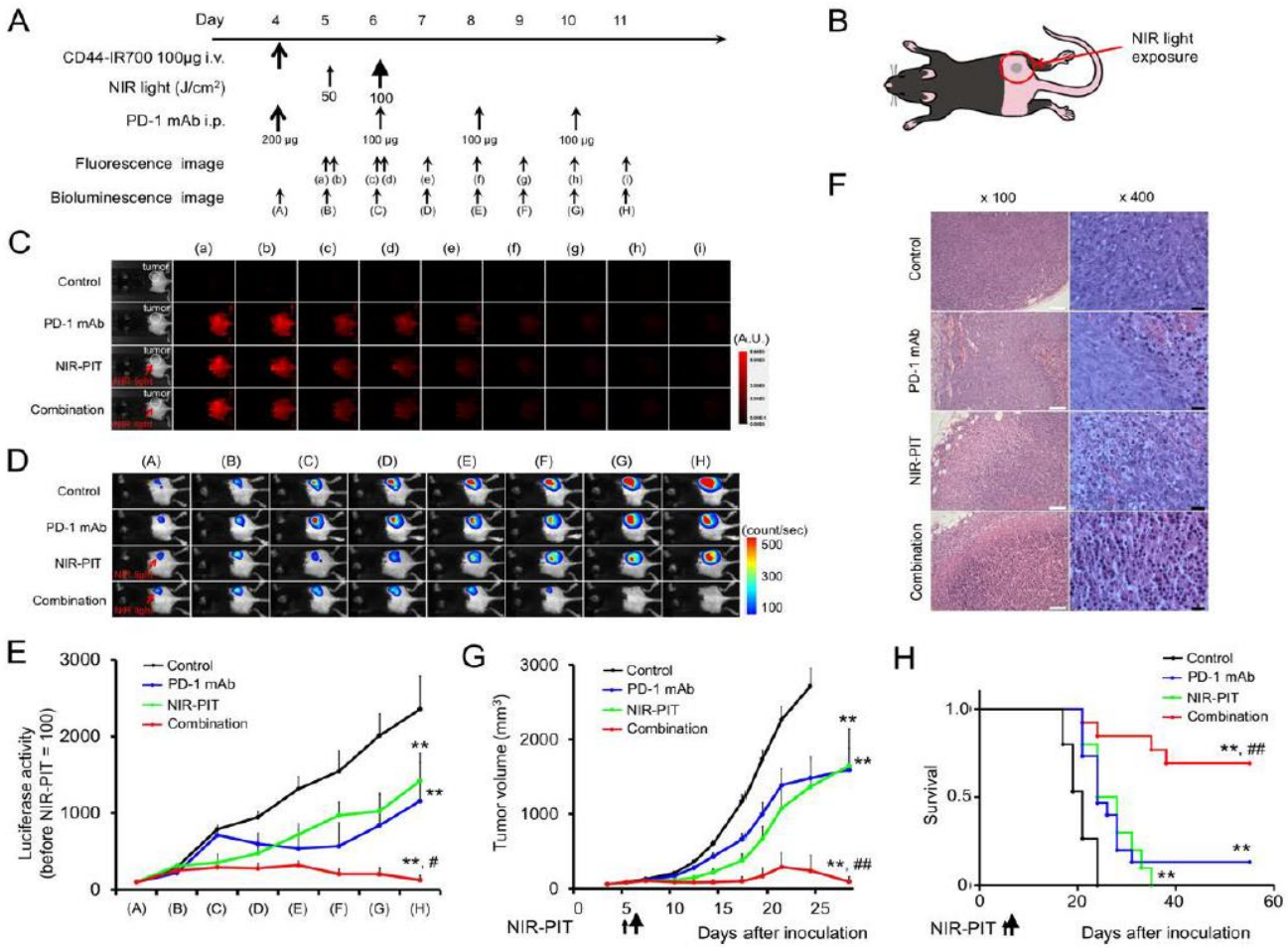
Mab-phototoxin
ASP-1929

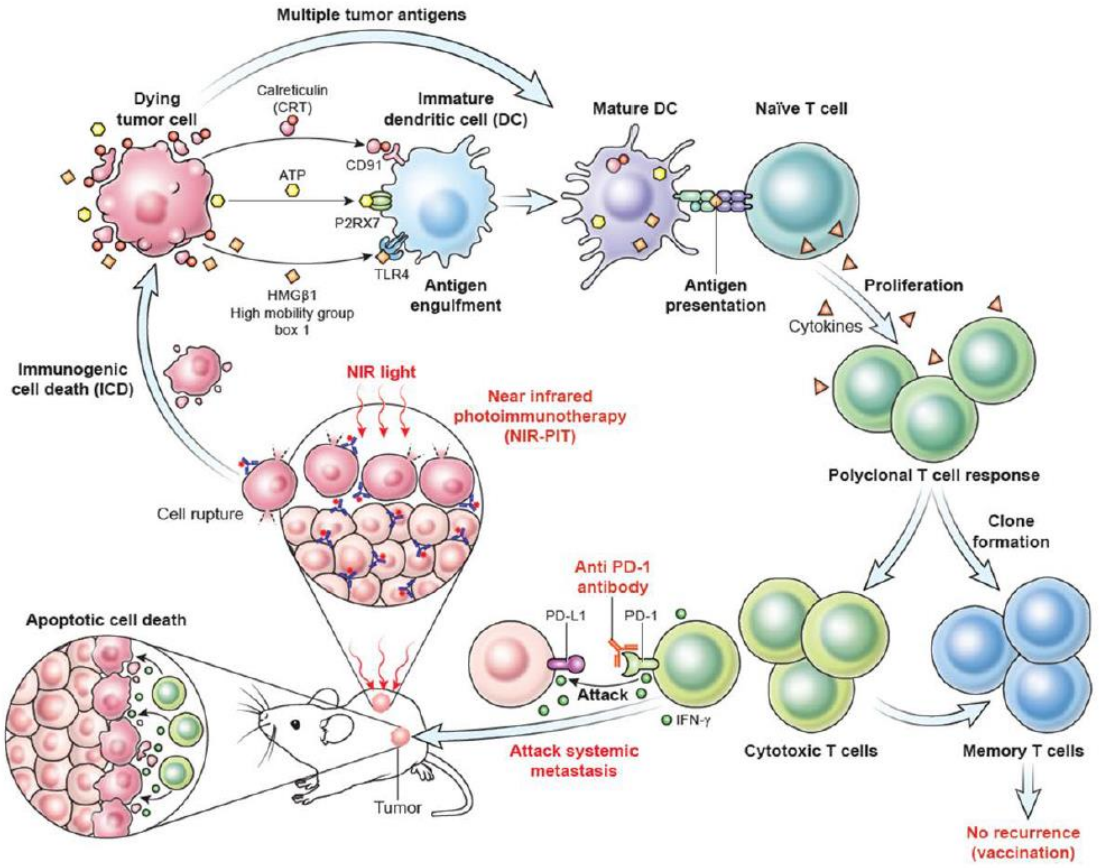


P2 a for recurrent H&N cancer
ORR43% (13% CR), mPFS5.2ms
P3 for recurrent H&N cancer is ongoing

P1 of NIR-PIT for esophageal cancer is ongoing (EPOC1709)

To turn cold tumor to hot: Near Infrared Photoimmunotherapy (PIT) Combination with Anti-PD1 for Gastric and Esophagel Cancer





Nagaya T,,Kobayashi H. Cancer Immunology Res. 2019

Addition of PD-1 blockade resulted in both enhanced pre-existing tumor antigen-specific T-cell responses and enhanced de novo T-cell responses induced by NIR-PIT.
P1b of NIR-PIT+A-PD1 for GC and EC will be started (GE-PIT, EPOC1901)

PI: K Shitara, Yano T
SC: A Kadota, D Kotani

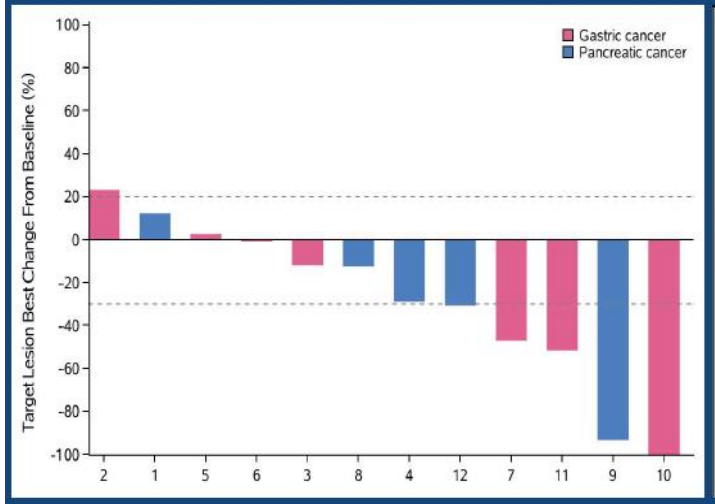
To turn cold tumor to hot:
Chimeric antigen receptor (CAR) T cell therapy

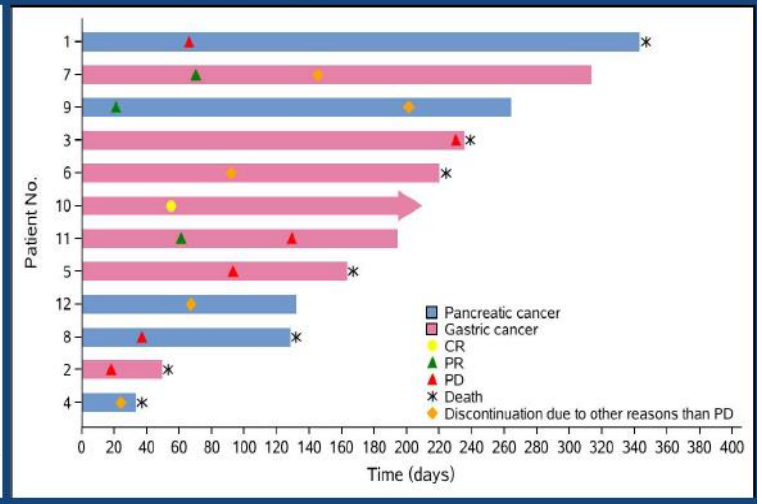
Claudin18.2-Specific CAR-T for gastric cancer

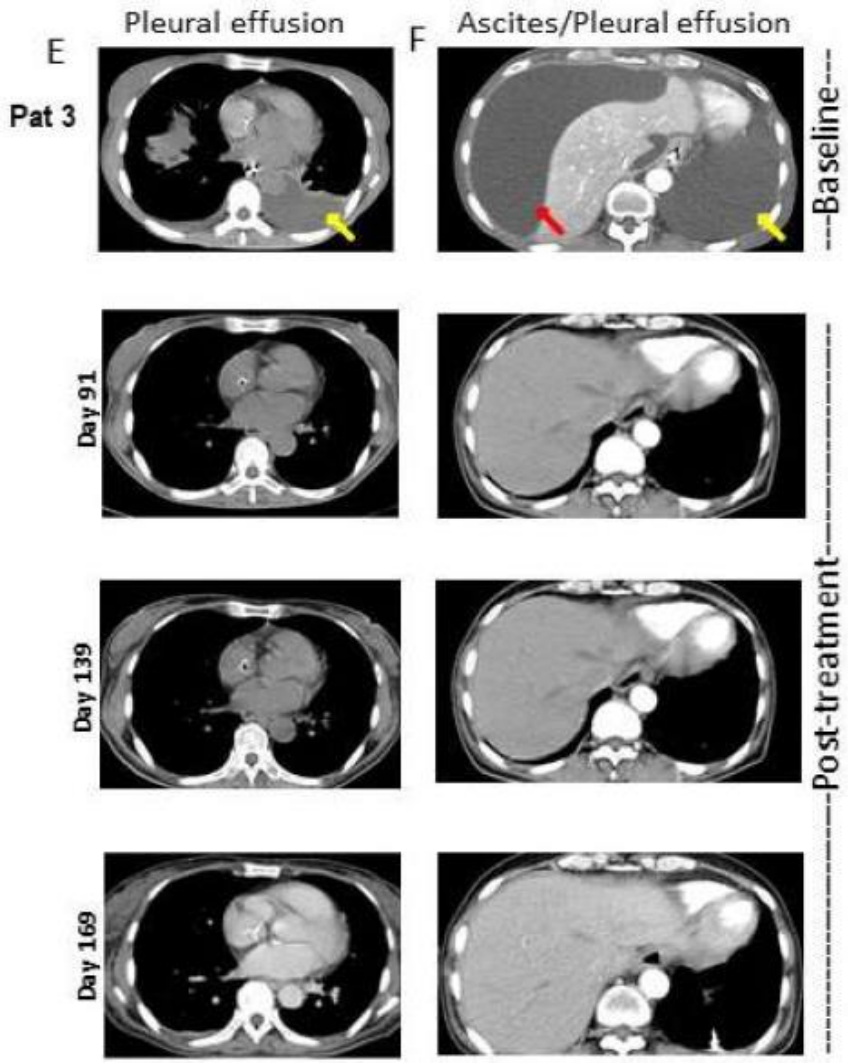
Jiang H, et al. JNCI 2018

Clinical Response

- Disease control rate (DCR) 75%: 1 CR, 3 PR, 5 SD
- Objective response rate (ORR) 33.3%
- mPFS of 136 days [95% CI (44, 237)], mOS of 242 days [95% CI (55, 349)]







Zhan X, et al. ASCO 2019

CAR-T therapy for solid tumor is under investigation

Check-Point Inhibitors in Gastric Cancer: KEYNOTE-061 trial and KEYNOTE-061 trial and beyond it

- **Still 3rd-line is optimal treatment line of anti-PD1 for GC (2nd-line for MSI-H)**
- **KN-061&062 opened the door for IO therapy for GC in earlier line**
  - **Lower AE or discontinuation rate may support non-inferiority**
- **Crossed OS curve necessitate optimal patients selection**
  - **MSI-H and/or CPS10 pts have greater benefit**
  - **Still we need better biomarker!**
- **Chemo combo did not show significant improvement of PFS or OS**
  - **Backbone chemotherapy matter?**
  - **Still we need better combinations!**

Thank you for your kind attention