Patients should be selected based on predictive biomarkers

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GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ADVANCED COURSE ON LUNG CANCER IN IMMUNOTHERAPY

ZURICH SWITZERLAND
3-4 JULY 2019

Save the date!

DISCLOSURES

Consulting, advisory role or lectures: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche

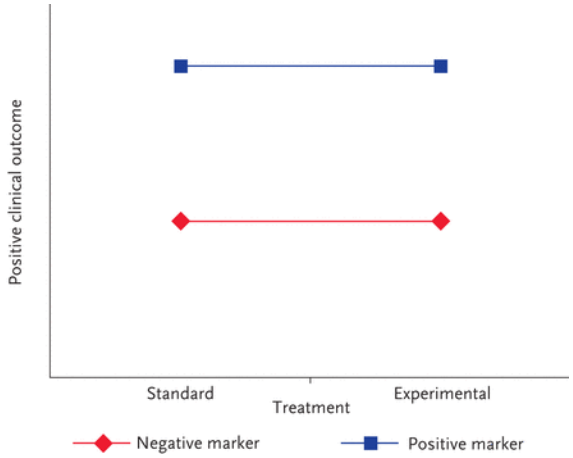
Honoraria: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche

Clinical trials research: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmun, Sanofi-Aventis, Taiho Pharma, Novocure, Daiichi Sankyo

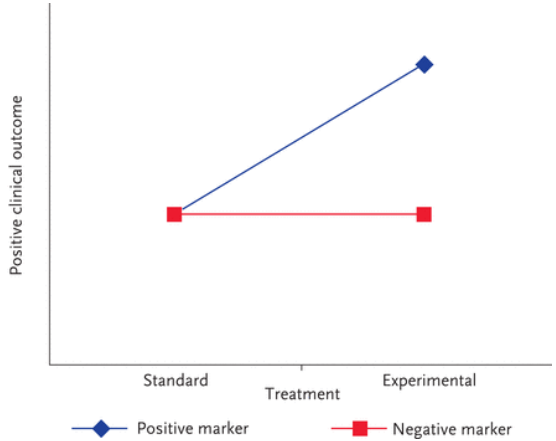
Travel, Accommodations, Expenses: AstraZeneca, Roche, Novartis, prIME Oncology, Pfizer

Prognostic vs. predictive markers

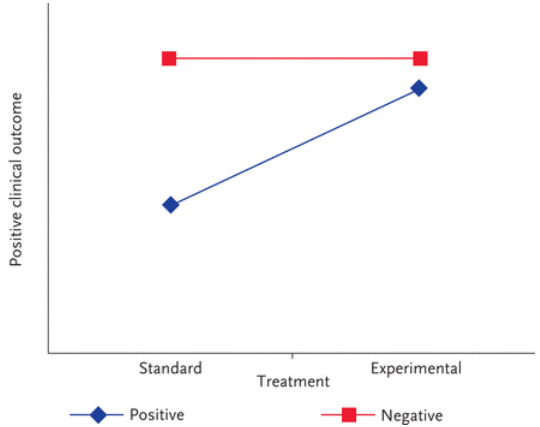
Prognostic



Predictive



Prognostic + Predictive



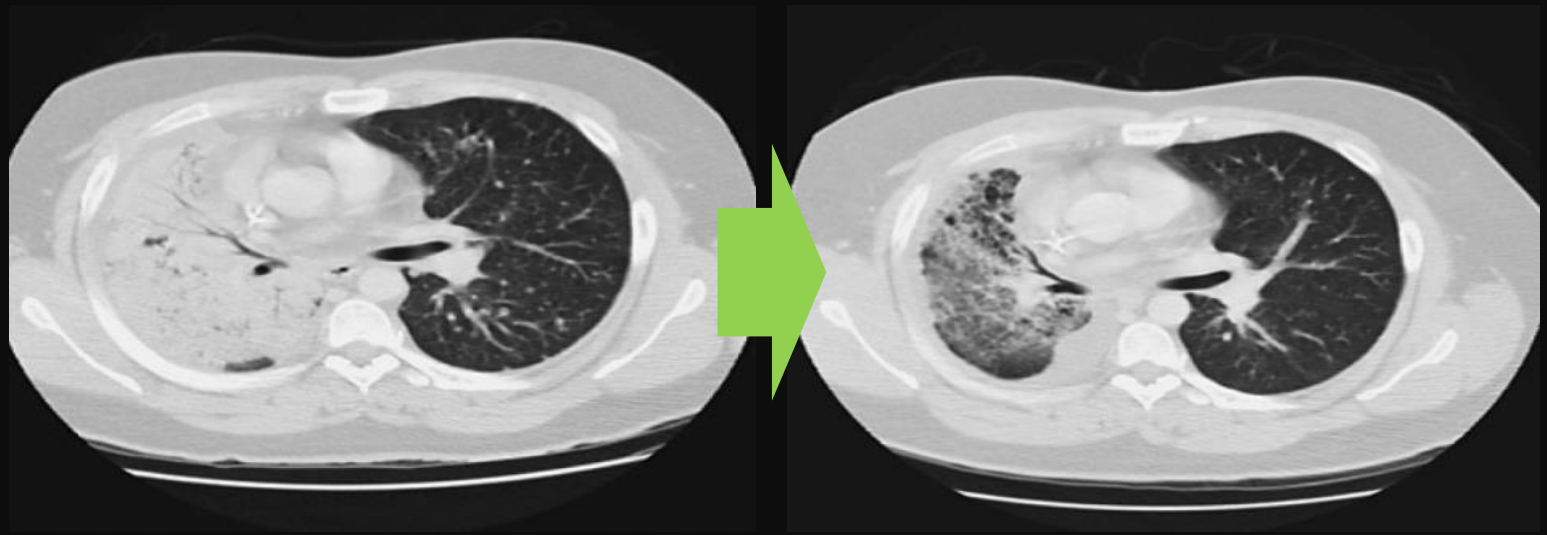
Paesmans, Breathe 2012

2004

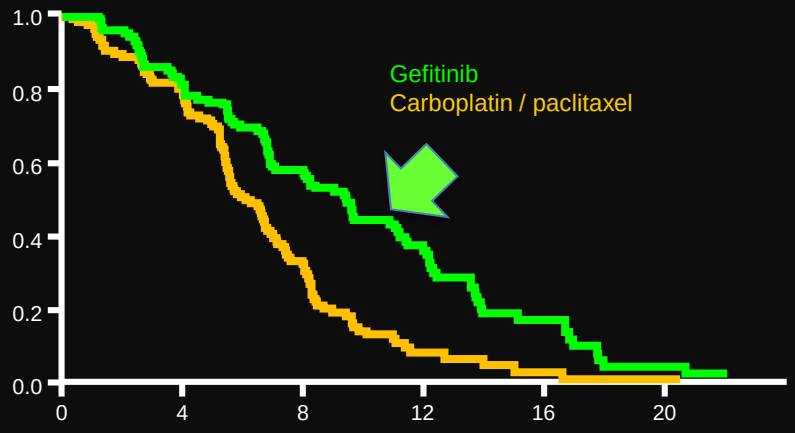
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

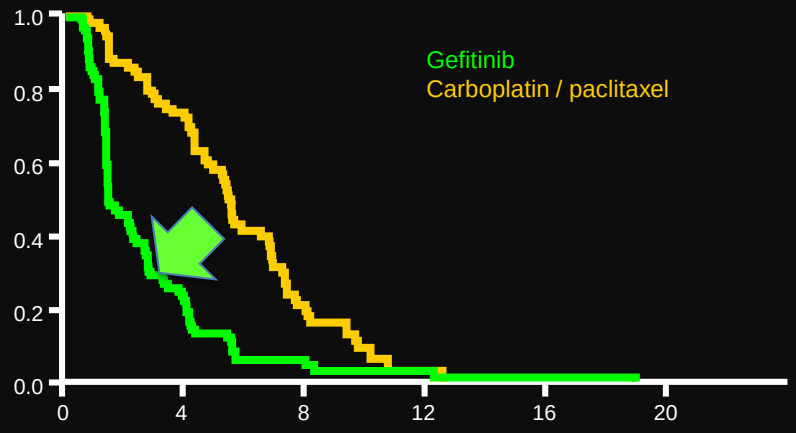
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib



EGFR+



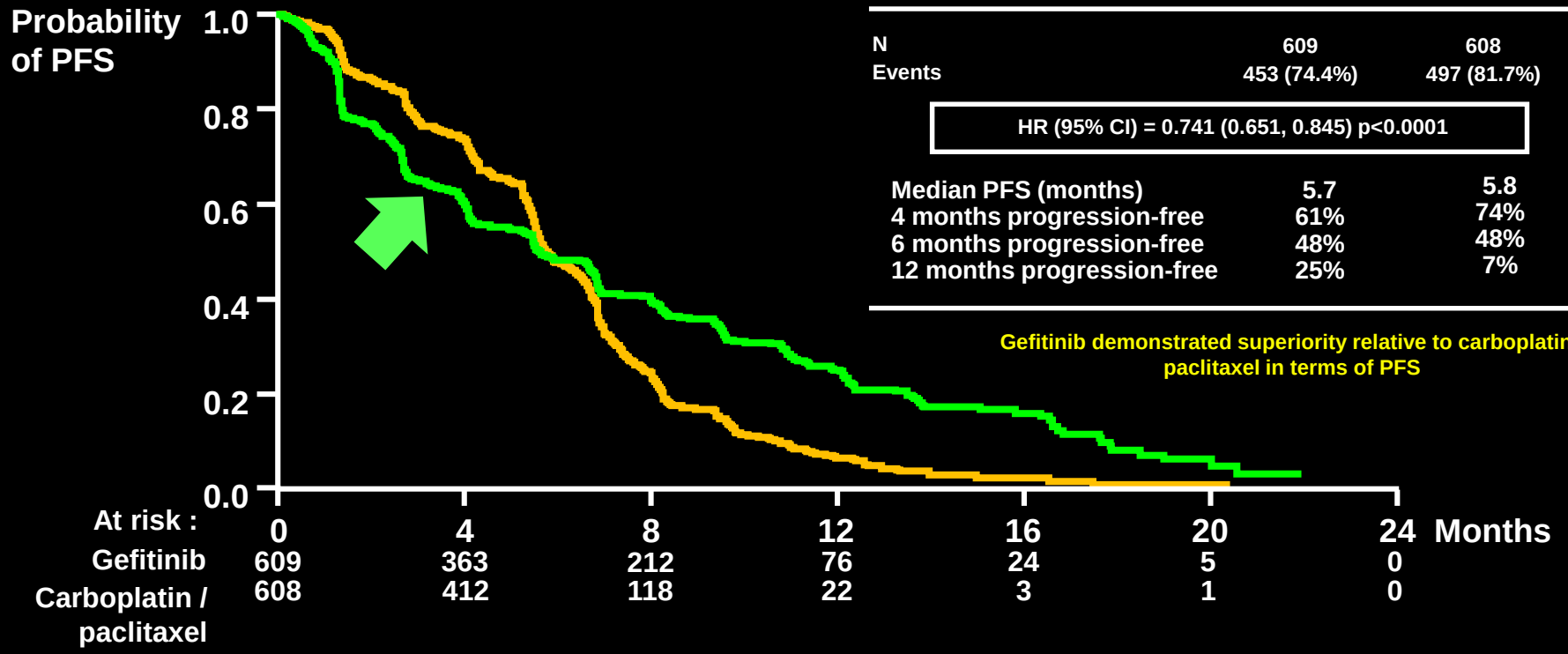
EGFR-



2008 (IPASS Trial; T.Mok et al, NEJM)

Treatment by subgroup interaction test, p<0.0001

Progression-free survival



	Gefitinib	Carboplatin / paclitaxel
N	609	608
Events	453 (74.4%)	497 (81.7%)

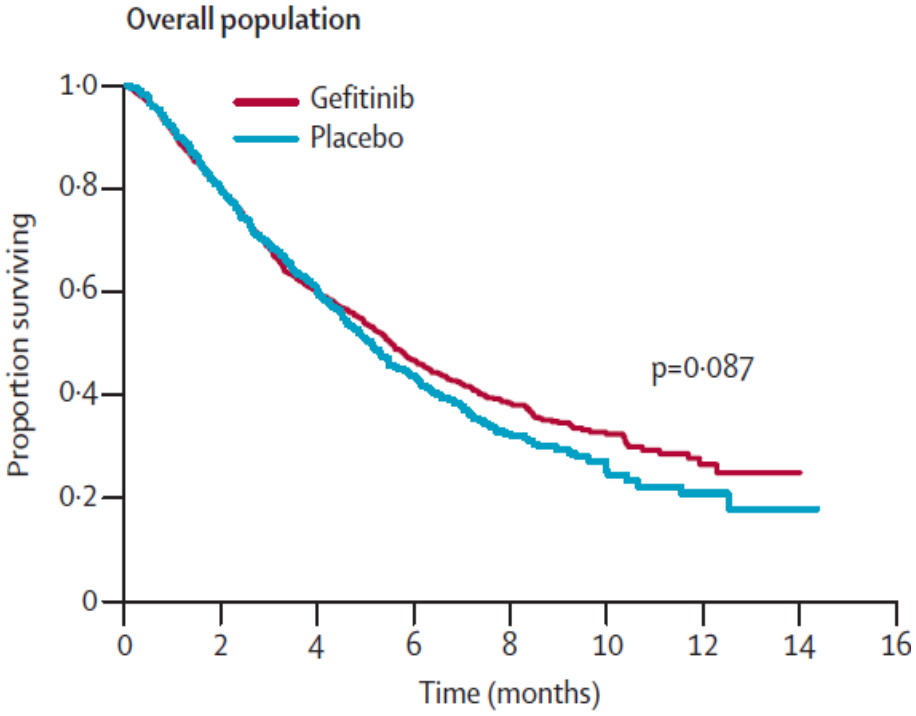
HR (95% CI) = 0.741 (0.651, 0.845) p<0.0001

Median PFS (months)	5.7	5.8
4 months progression-free	61%	74%
6 months progression-free	48%	48%
12 months progression-free	25%	7%

Gefitinib demonstrated superiority relative to carboplatin / paclitaxel in terms of PFS

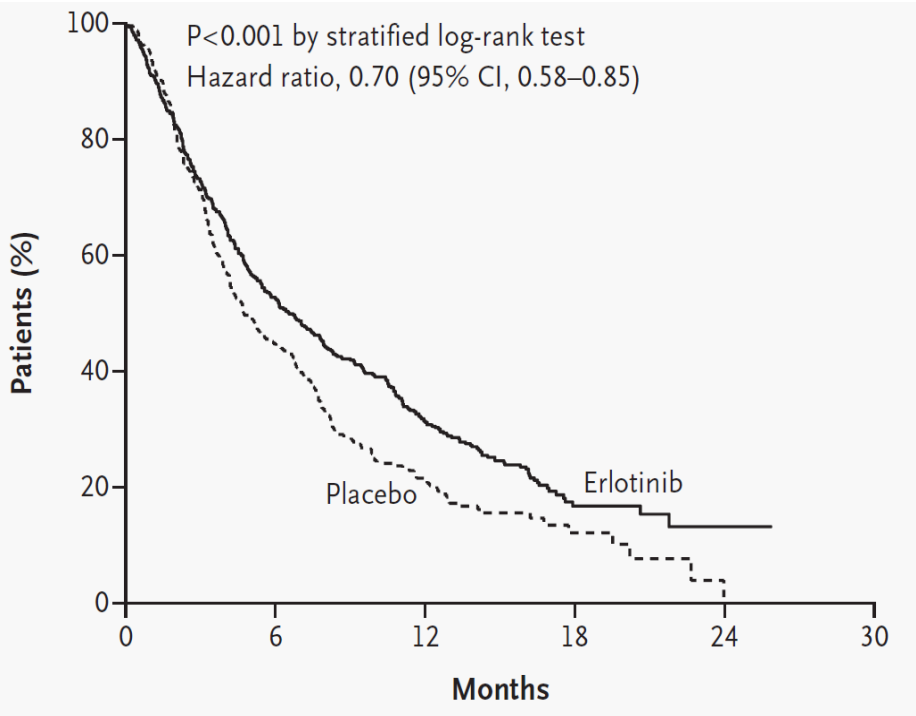
Mok et al 2008

ISEL Trial



Nick Thatcher et al, lancet 2005

BR.21 Trial



Frances A. Shepherd et al, NEJM 2005

Why we need biomarkers?

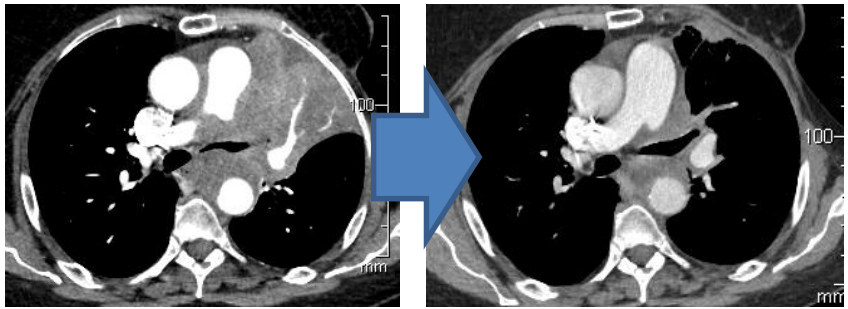
BENEFIT

PROVIDE DRUGS ONLY TO PATIENTS WHO COULD BENEFIT FROM THEM

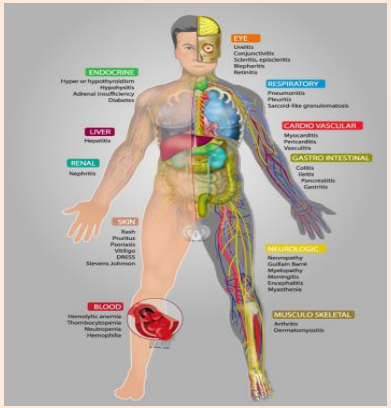
RISK

AVOID TO EXPOSE PATIENTS TO TOXICITY WHEN THERE ARE NO CHANCES OF EFFICACY

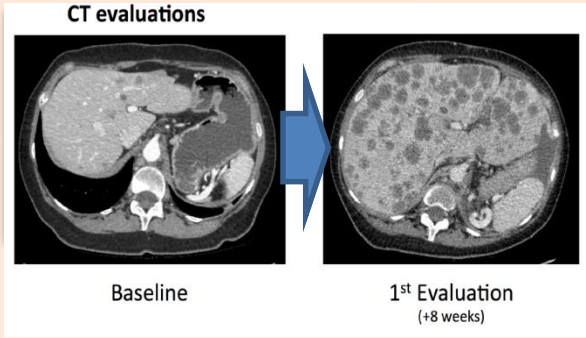
Efficacy with IO (PDL1 80%)



Toxicity

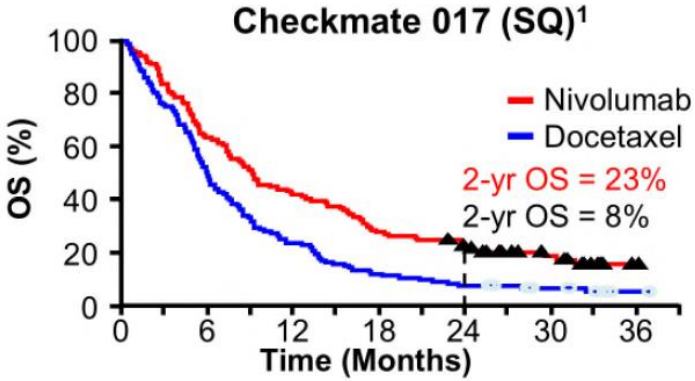


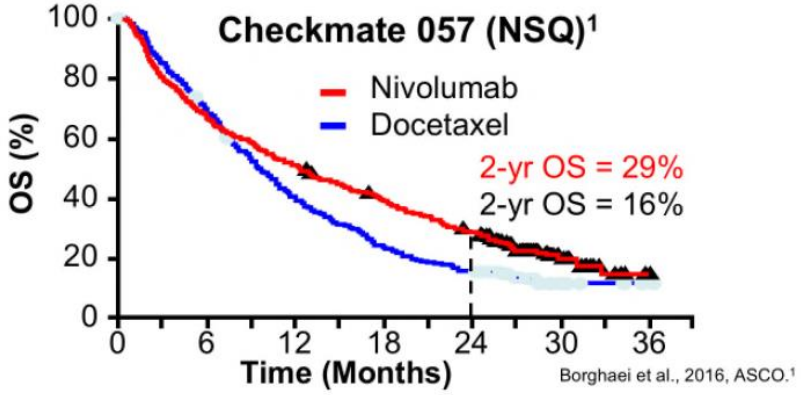
Hyperprogressive disease



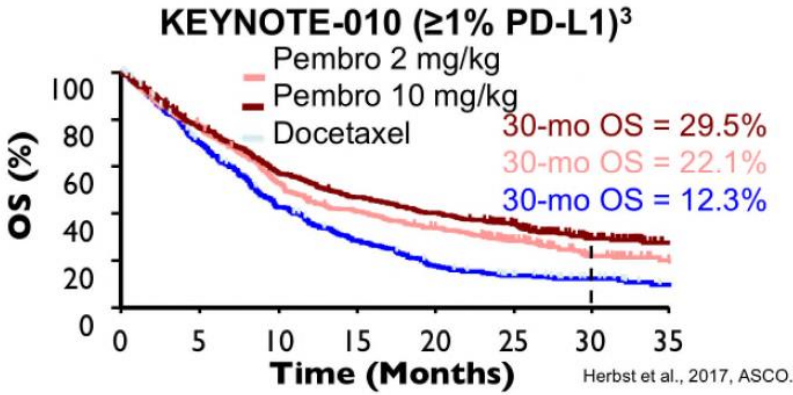
Cabañero, Arch Bronconeumol 2018, Champiat, Ann Oncol 2016, Ferrara JAMA Oncol 2018

A consistent but limited benefice in OS 2nd line

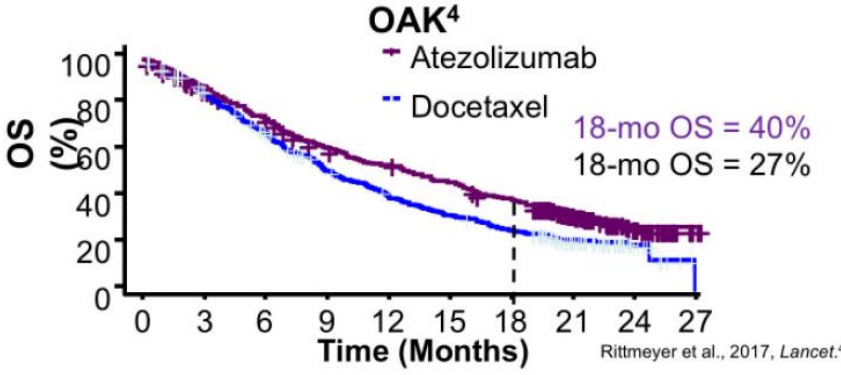




Borghaei et al., 2016, ASCO.[1]

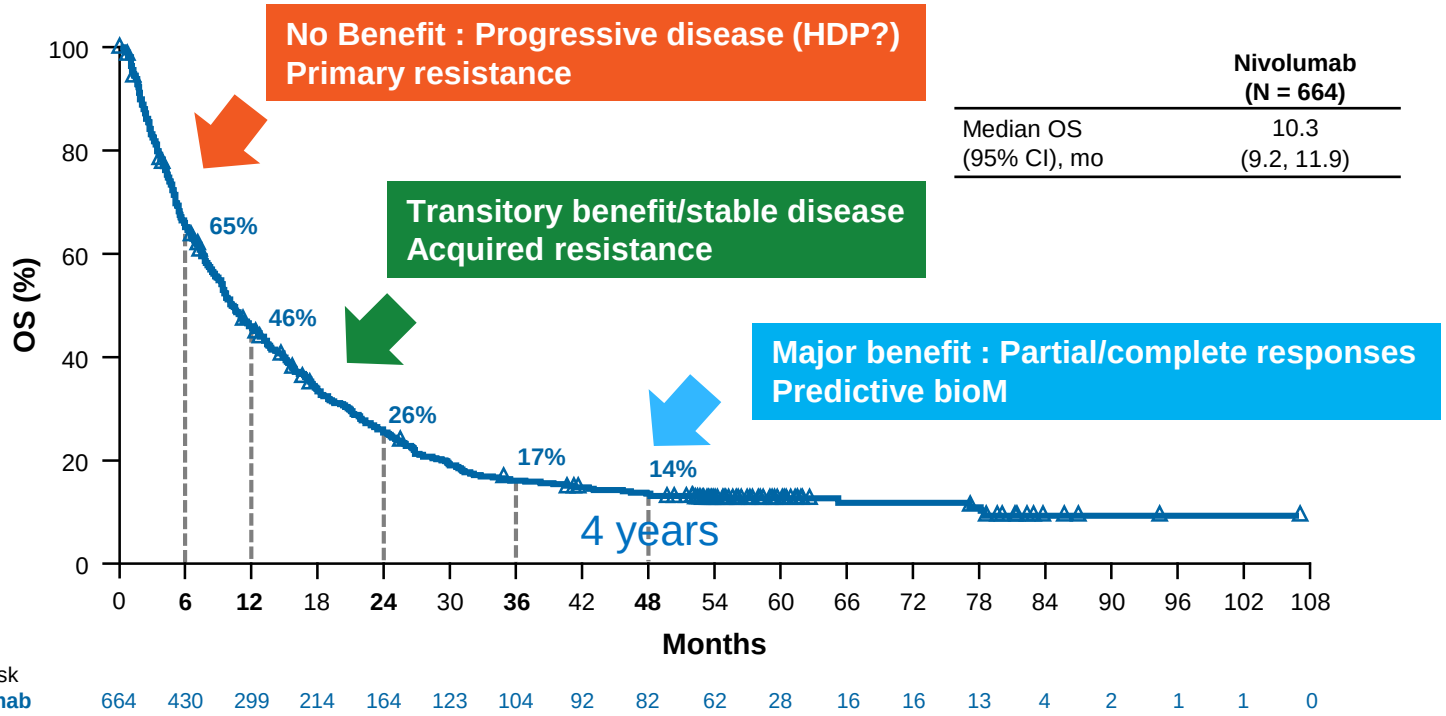


Herbst et al., 2017, ASCO.[3]



Rittmeyer et al., 2017, *Lancet*.[4]

UNSELECTED PATIENTS
OS in all nivolumab-treated patients (CM 003, 063, 017 and 057 studies)



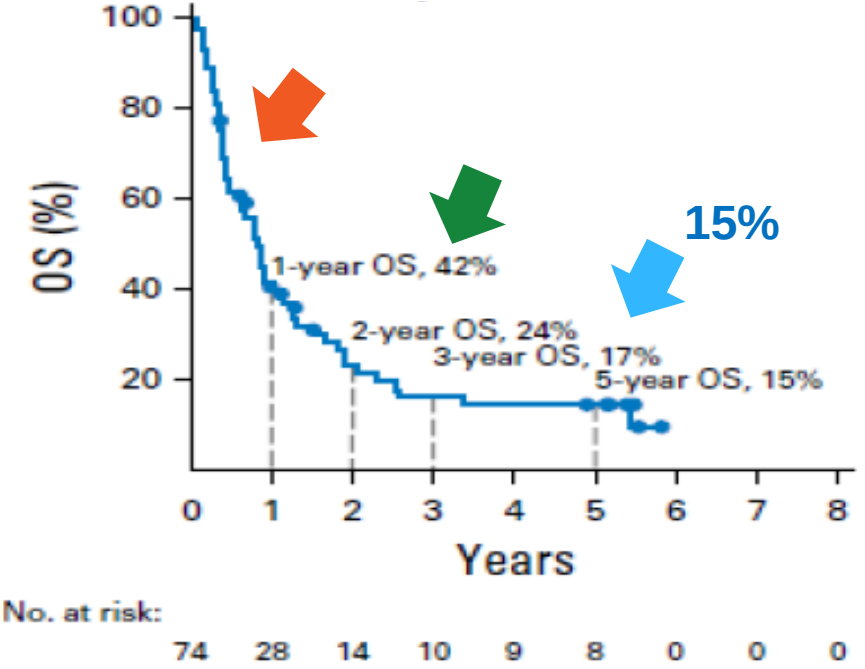
	Nivolumab (N = 664)
Median OS (95% CI), mo	10.3 (9.2, 11.9)

Julie Brahmer et al, AACR 2019

5-Year Estimates of OS
CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC

Squamous (n=54)

Nonsquamous (n=74)

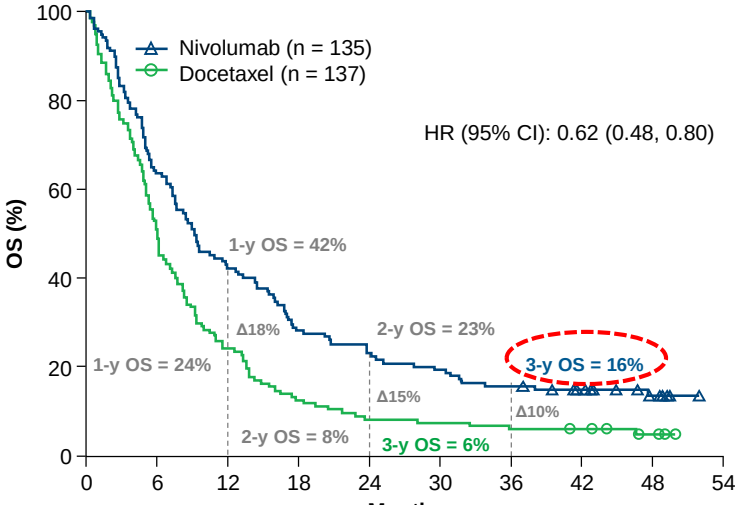


Julie Brahmer et al, AACR 2016

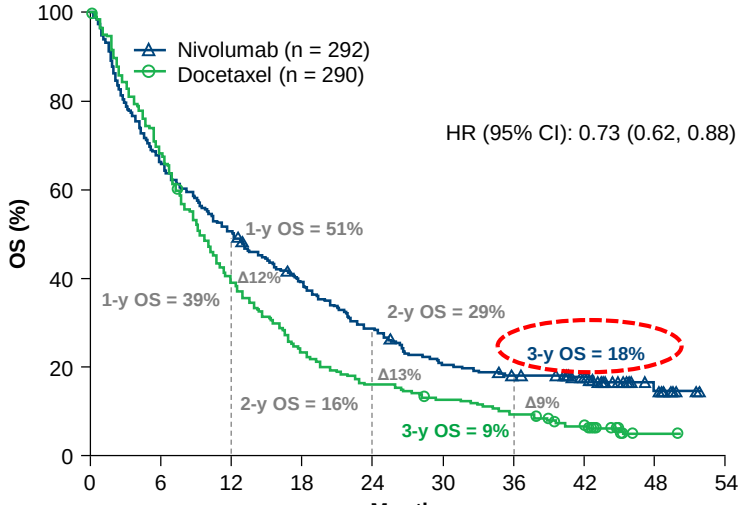
Long Term Survival

OS (3 Years' Minimum Follow-up)

CheckMate 017 (SQ NSCLC)



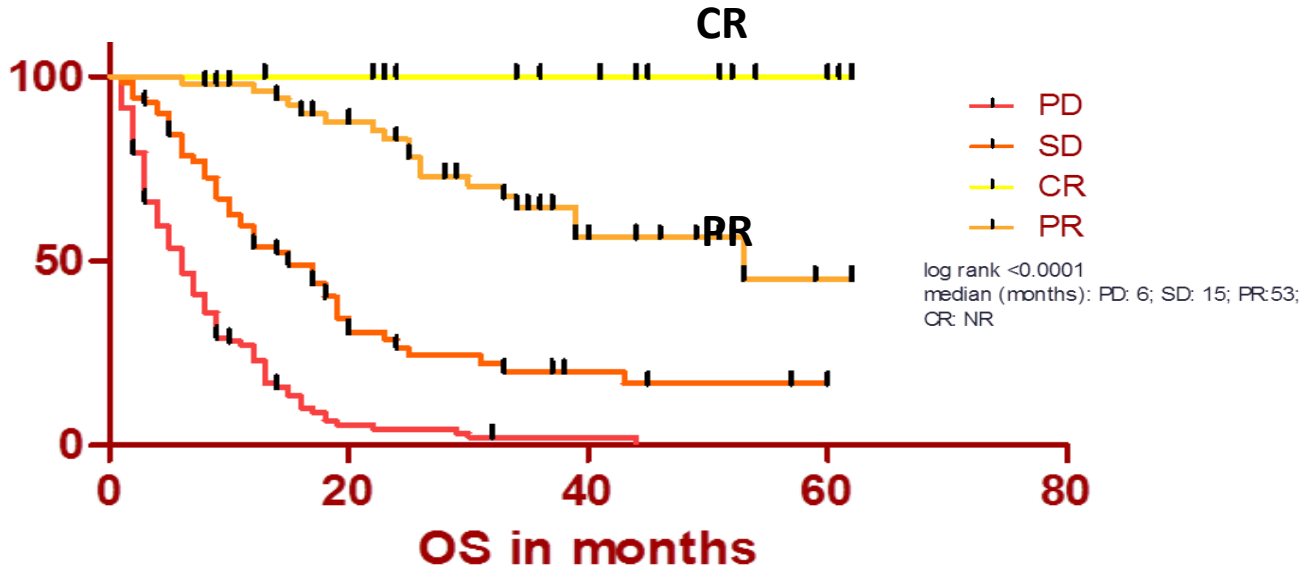
CheckMate 057 (non-SQ NSCLC)



Enriqueta Felip et al, ESMO 2017

NEED TO ENRICHE PATIENTS WITH HIGH ORR

ANTI-PD(L)1 SURVIVAL BASED ON RESPONSE TYPE



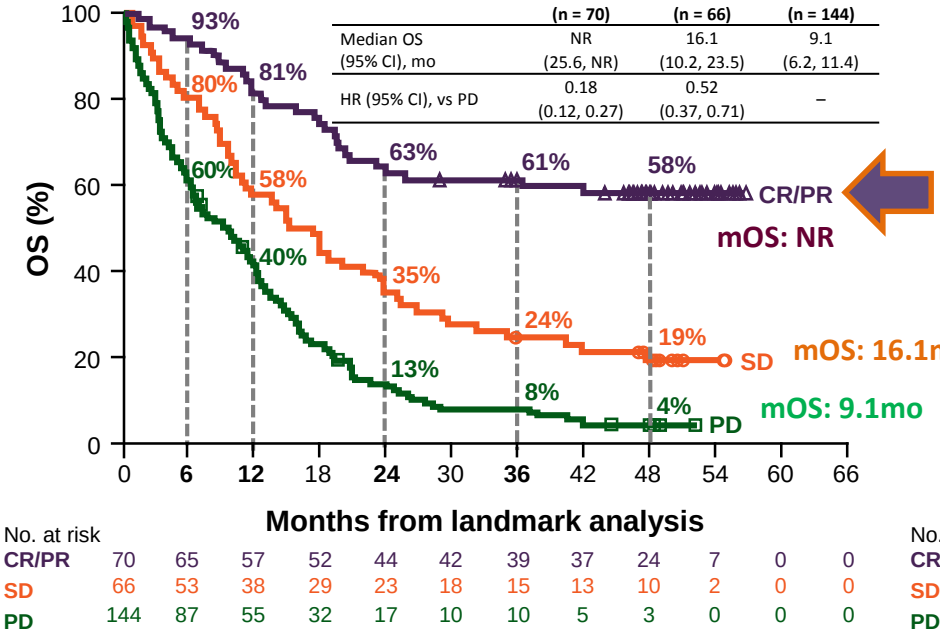
Data from patients treated with an anti–PD-(L)1 monotherapy in a phase I trial at Gustave Roussy were retrospectively analyzed over a period of 5 years.

Impact on practice for PR/SD patients ?

Gauci M-L, et al. Clin Cancer Res 2019;25:946–56.

Landmark analysis of OS by response category status at 6 months (CM 017 and 057)[a]

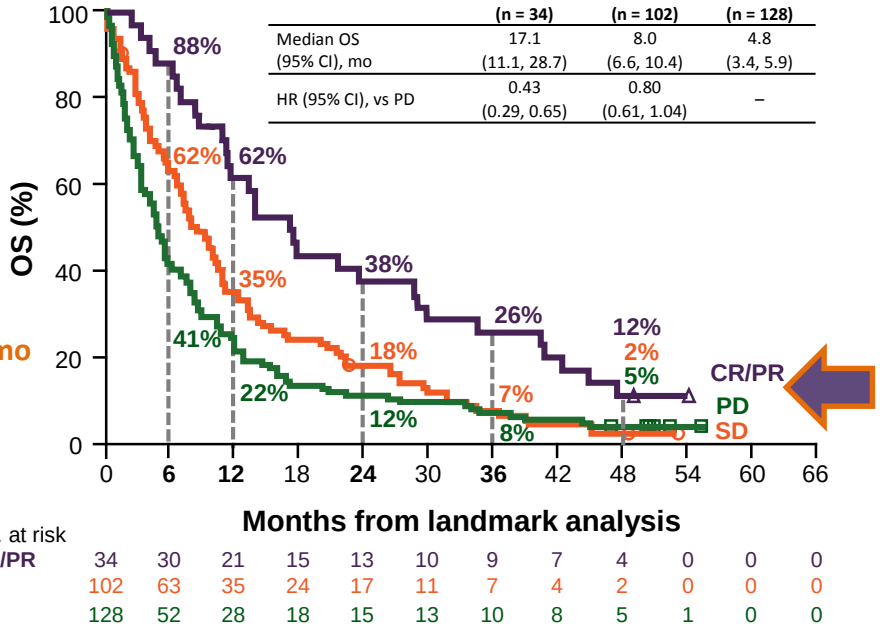
Nivolumab



	CR/PR (n = 70)	SD (n = 66)	PD (n = 144)
Median OS (95% CI), mo	NR (25.6, NR)	16.1 (10.2, 23.5)	9.1 (6.2, 11.4)
HR (95% CI), vs PD	0.18 (0.12, 0.27)	0.52 (0.37, 0.71)	–

No. at risk												
CR/PR	70	65	57	52	44	42	39	37	24	7	0	0
SD	66	53	38	29	23	18	15	13	10	2	0	0
PD	144	87	55	32	17	10	10	5	3	0	0	0

Docetaxel



	CR/PR (n = 34)	SD (n = 102)	PD (n = 128)
Median OS (95% CI), mo	17.1 (11.1, 28.7)	8.0 (6.6, 10.4)	4.8 (3.4, 5.9)
HR (95% CI), vs PD	0.43 (0.29, 0.65)	0.80 (0.61, 1.04)	–

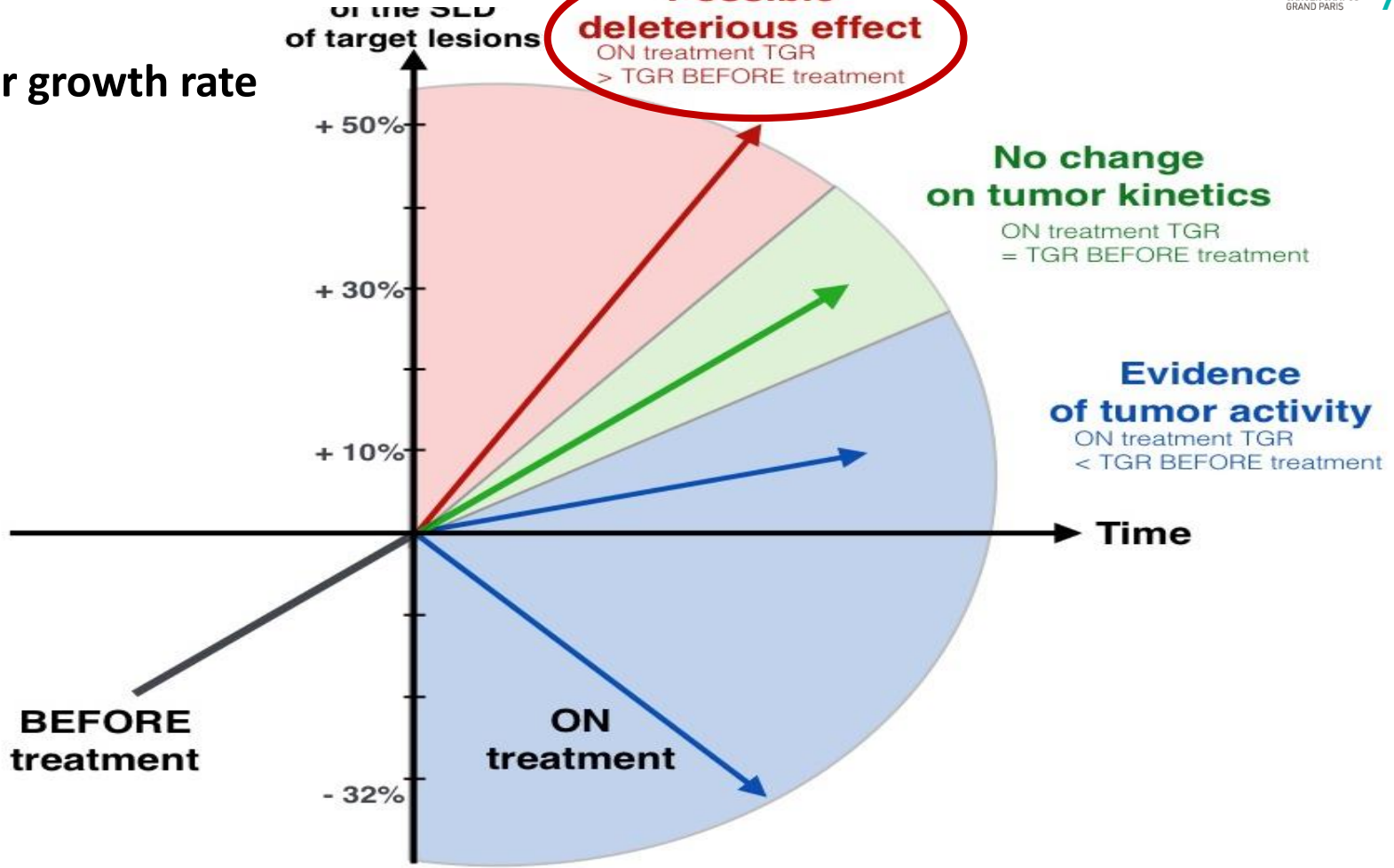
No. at risk												
CR/PR	34	30	21	15	13	10	9	7	4	0	0	0
SD	102	63	35	24	17	11	7	4	2	0	0	0
PD	128	52	28	18	15	13	10	8	5	1	0	0

[a]In all randomized patients from CheckMate 017 and 057 studies alive at the 6-month landmark; 65.6% and 61.8% patients in the nivolumab and docetaxel treatment arms, respectively, were included in this analysis.

Julie Brahmer et al , AACR 2019

NEED TO AVOID PD OR HPD

TGR:Tumour growth rate



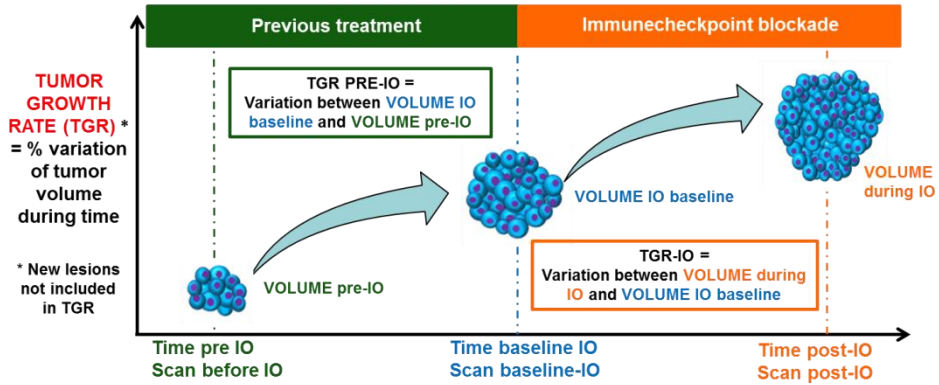
HPD in NSCLC

JAMA Oncology | Original Investigation

Hyperprogressive Disease in Patients With Advanced Non–Small Cell Lung Cancer Treated With PD-1/PD-L1 Inhibitors or With Single-Agent Chemotherapy

Roberto Ferrara, MD; Laura Mezquita, MD, PhD; Matthieu Texier, MSc; Jihene Lahmar, MD; Clarisse Audigier-Valette, MD; Laurent Tessonnier, MD; Julien Mazieres, MD, PhD; Gerard Zalcman, MD, PhD; Solenn Brosseau, MD; Sylvestre Le Moulec, MD; Laura Leroy, MD; Boris Duchemann, MD; Corentin Lefebvre, MD; Remi Veillon, MD; Virginie Westeel, MD, PhD; Serge Koscielny, MSc; Stephane Champiat, MD; Charles Ferté, MD, PhD; David Planchard, MD, PhD; Jordi Remon, MD; Marie-Eve Boucher, MD; Anas Gazzah, MD; Julien Adam, MD, PhD; Emilio Bria, MD; Giampaolo Tortora, MD, PhD; Jean-Charles Soria, MD, PhD; Benjamin Besse, MD, PhD; Caroline Caramella, MD

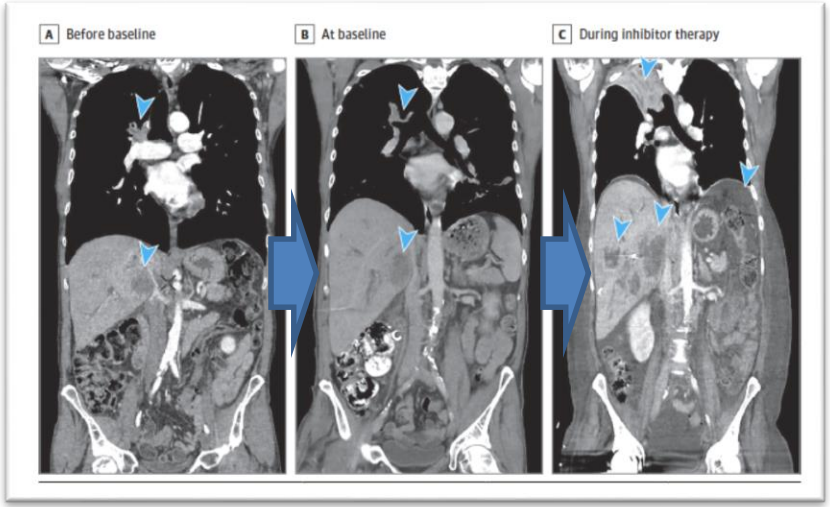
13.8% of the patients



HPD = (TGR IO – TGR PRE IO) > 50% + PD RECIST AT 1st CT SCAN

- **N = 406 advanced NSCLC patients, ICIs**
- n= 59 patients in chemo cohort

- **Only 5.1% in chemo cohort**



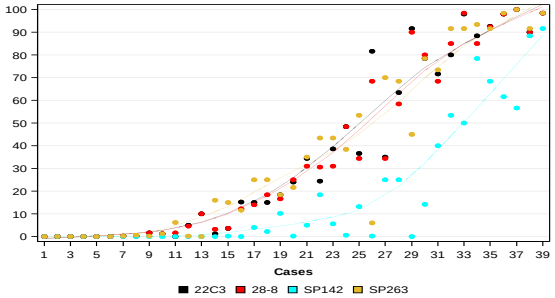
Ferrara , JAMA Oncol 2018

PD-L1 a good bioM ?

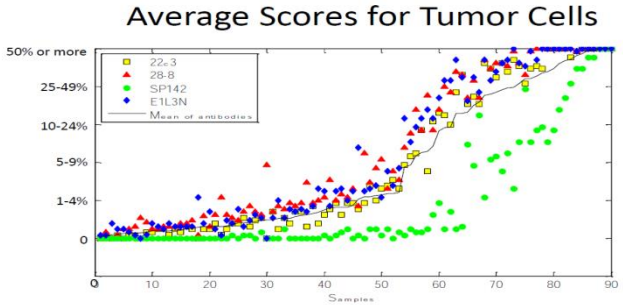
Comparison of PD-L1 assays in NSCLC

Immunotherapy (IO)	Nivolumab	Pembrolizumab	Durvalumab	Avelumab	Atezolizumab
Detection antibody	28-8	22C3	SP263	73-10	SP142
IHC platform	Dako	Dako	Ventana	Dako	Ventana
Cell types scored for NSCLC	TC	TC	TC	TC	TC & IC
Cut-off definitions for positivity (complementary vs companion)	>5%	First line: PD-L1+ ≥50% Late lines: PD-L1+ ≥1%	>25%	None	None

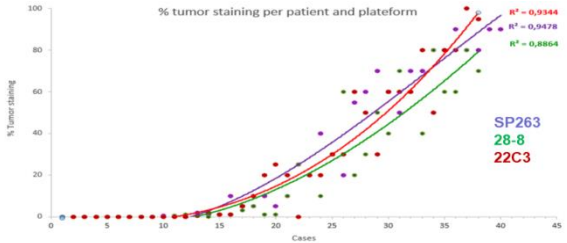
Blueprint phase 1[1]



NCCN study[2]



French study[3]



AstraZeneca study[4]

Figure 3. Overall Percentage Agreement (values >90% are shown in bold)

A. Ventana SP263 versus Dako 22C3

Ventana SP263 (% staining) \ Dako 22C3 (% staining)	1	5	10	20	30	40	50	60	70	80	90	100
10	89.25%	**90.67%**	88.44%	84.58%	78.09%	74.85%	72.21%	68.76%	66.33%	62.88%	57.20%	52.94%
20	81.54%	88.24%	**92.49%**	**93.10%**	**90.26%**	87.42%	84.79%	81.34%	78.90%	75.46%	69.78%	65.52%
25	76.88%	83.98%	89.45%	**92.90%**	**94.12%**	**91.68%**	89.45%	86.41%	83.98%	80.53%	74.85%	70.59%
30	74.65%	81.74%	87.22%	**91.48%**	**95.54%**	**93.91%**	**92.09%**	89.05%	86.61%	83.16%	77.48%	73.23%
40	72.41%	79.51%	84.99%	**90.06%**	**95.33%**	**94.12%**	**93.10%**	**90.87%**	88.84%	85.40%	79.72%	75.46%
50	69.57%	77.08%	82.96%	88.03%	**93.31%**	**93.31%**	**93.51%**	**92.49%**	**90.87%**	87.83%	82.56%	78.30%
60	67.75%	75.25%	81.14%	86.61%	**92.29%**	**93.91%**	**94.52%**	**93.51%**	**92.70%**	89.66%	84.38%	80.12%
70	63.89%	71.40%	77.28%	83.16%	89.25%	**91.68%**	**93.10%**	**94.52%**	**94.52%**	**91.89%**	87.42%	83.57%
80	59.03%	66.53%	72.41%	78.70%	84.79%	87.63%	89.05%	**92.49%**	**94.12%**	**94.73%**	**91.89%**	88.44%
90	55.98%	63.49%	69.37%	75.66%	82.15%	84.99%	87.22%	**90.67%**	**92.29%**	**94.12%**	**93.31%**	**91.48%**
100	51.32%	58.82%	64.71%	70.99%	77.48%	80.73%	82.96%	86.41%	88.44%	**91.89%**	**93.91%**	**94.93%**

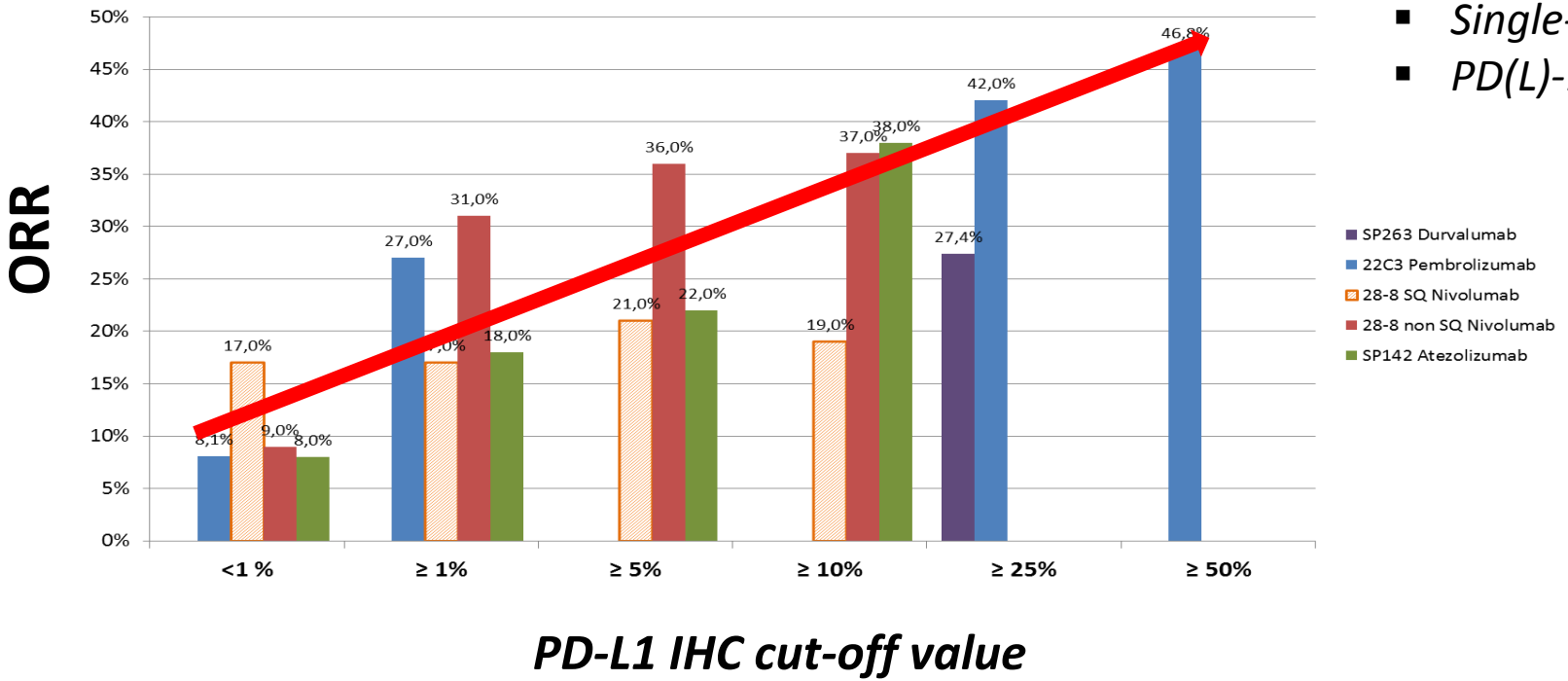
- ✓ **Comparables: 22C3, 28-8 and SP263**
- ✓ **Weaker: SP142**
  lower sensitivity

Courtesy of Julien Adam

1. Hirsch FR, et al. J Thorac Oncol. 2017;12(2):208-222. 2. Rimm D et al. JAMA Oncol. 2017;3(8):1051-1058 3. Adam J et al. Oral presentation at IASLC WCLC 2016. PL04.04a. 4. Ratcliffe MJ et al. Clin Cancer Res. 2017;23(14):3585-3591.

High PD-1 expression associated with higher responses and outcomes

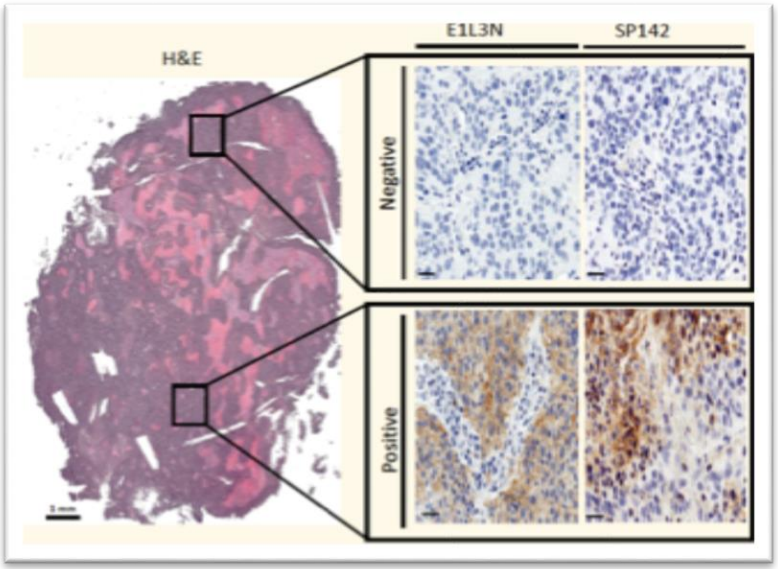
- *NSCLC*
- *Single-agent*
- *PD(L)-1 inh*



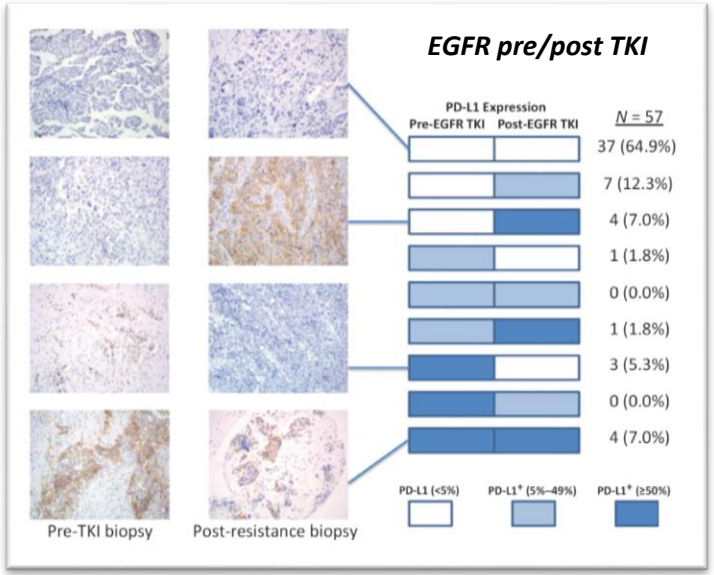
Garon, NEJM 2015; Brahmer, NEJM 2015; Borghaei, NEJM 2015; Spira ASCO 2015; Besse ECC 2015; Higgs, ECC 2015

Limitations for PD-L1

.. is heterogeneous



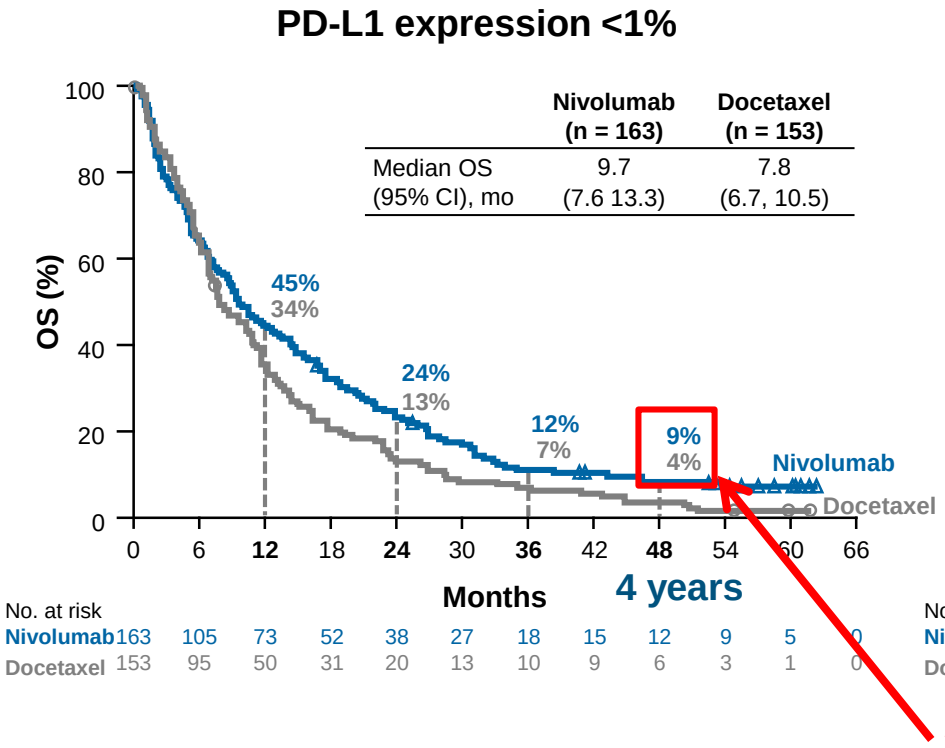
… is dynamic

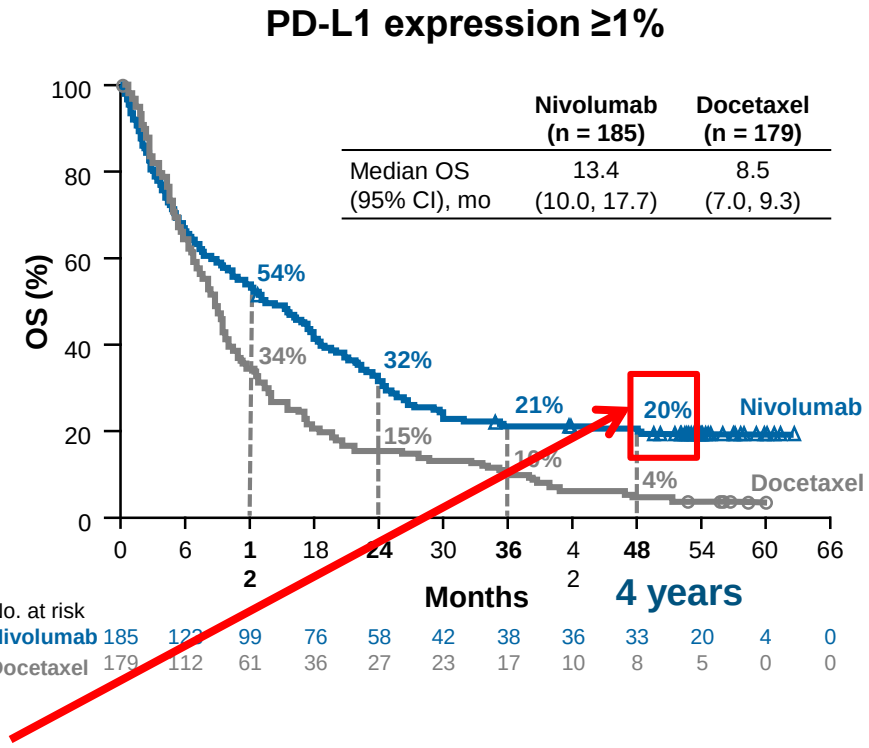


McLaughlin et al, JAMA Oncol 2016; Gainor et al, CCR 2016

OS with nivolumab versus docetaxel by tumor PD-L1 expression in CM017 and 057

Should we exclude <1% tumours from anti-PD(L1) therapy ?





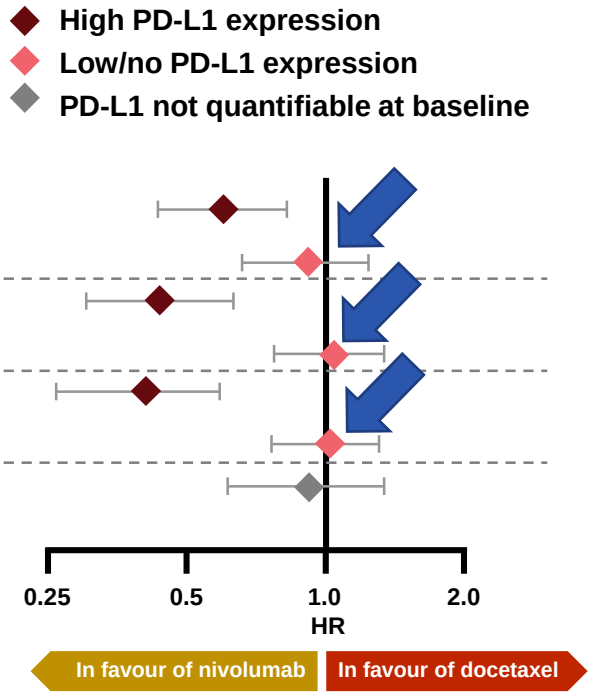
PD-L1 can predict long term survival

Patients with non-squamous histology and low/no PD-L1 expression did not derive benefit

CheckMate 057

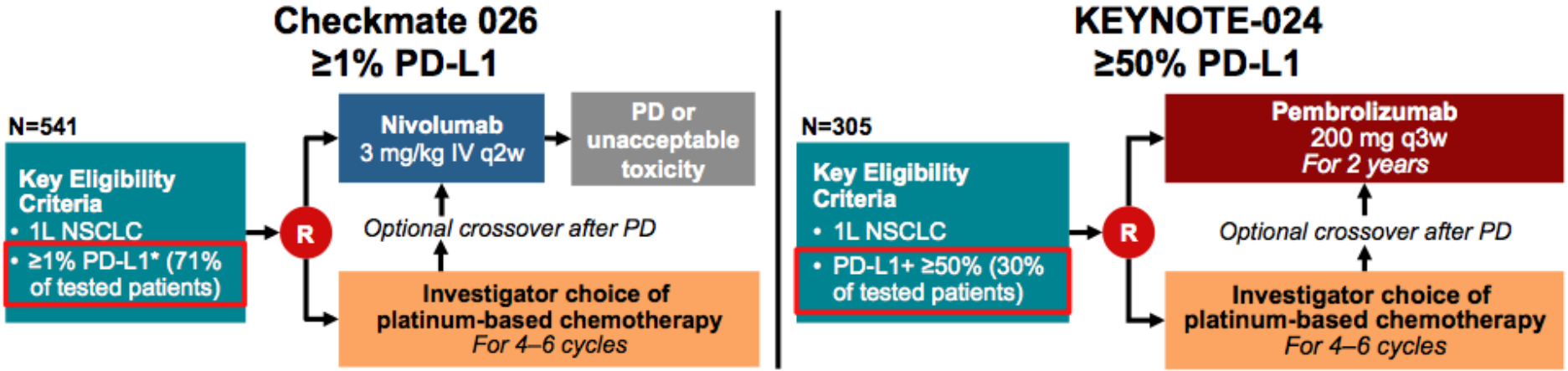
PD-L1 expression level
Overall survival

	Patients, n		Unstratified HR	Interaction p value
	Nivolumab	Docetaxel		
≥1%	123	123	0.59	0.06
<1%	108	101	0.90	
≥5%	95	86	0.43	<0.001
<5%	136	138	1.01	
≥10%	86	79	0.40	<0.001
<10%	145	145	1.00	
Not quantifiable at baseline	61	66	0.91	



PD-L1 expression measured retrospectively on TCs using Dako 28-8 IHC assay in prospectively collected, pretreatment (archival or recent) tumour specimens
Borghaei, et al. N Engl J Med 2015

Two „similar“ trials..

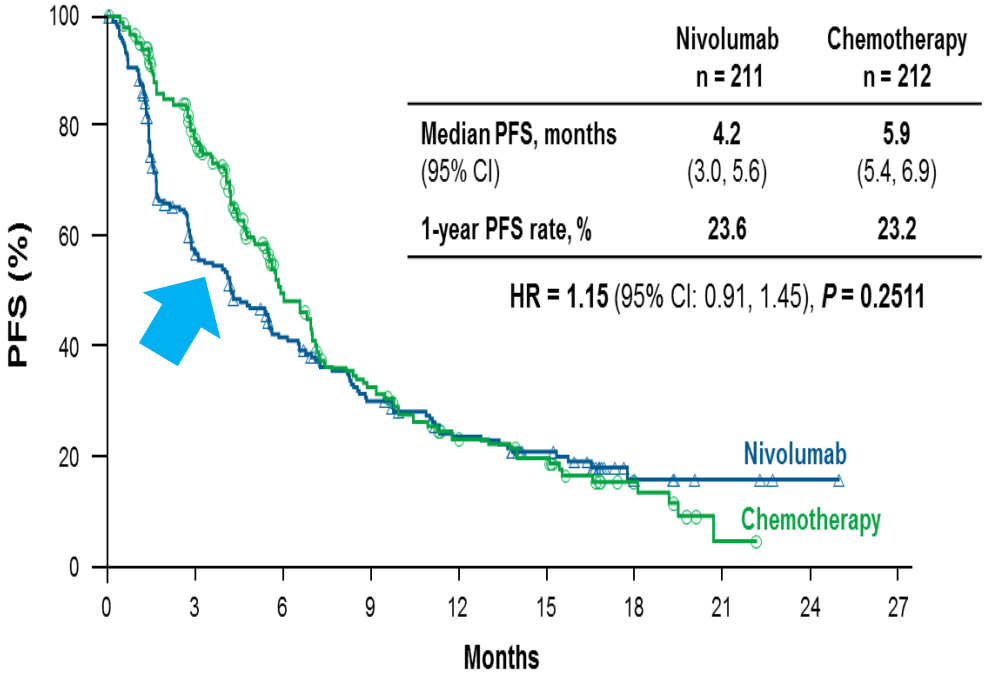


...but completely different outcomes!

Carbone D et al, NEJM 2017; 376 (25): 2415-2426; Reck M et al, NEJM 2016; 375 (19): 1823-1833

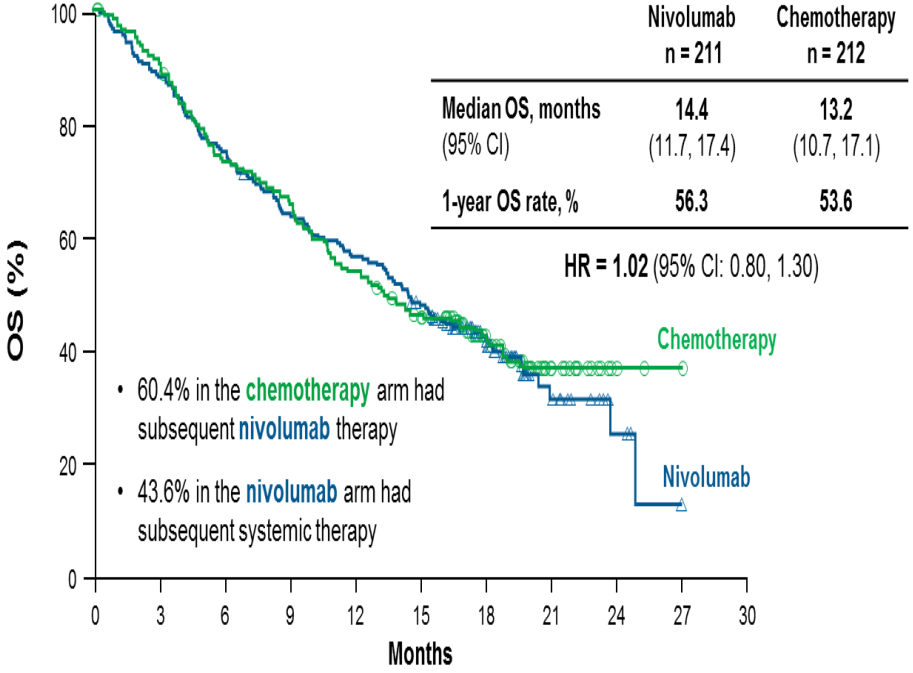
OS (≥5% PD-L1+)

CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC



	Nivolumab n = 211	Chemotherapy n = 212
Median PFS, months (95% CI)	4.2 (3.0, 5.6)	5.9 (5.4, 6.9)
1-year PFS rate, %	23.6	23.2

HR = 1.15 (95% CI: 0.91, 1.45), ***P* = 0.2511**

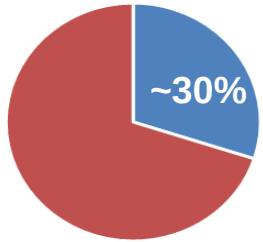


	Nivolumab n = 211	Chemotherapy n = 212
Median OS, months (95% CI)	14.4 (11.7, 17.4)	13.2 (10.7, 17.1)
1-year OS rate, %	56.3	53.6

HR = 1.02 (95% CI: 0.80, 1.30)

Carbone DP, et al. *N Engl J Med*. 2017;376(25):2415-2426

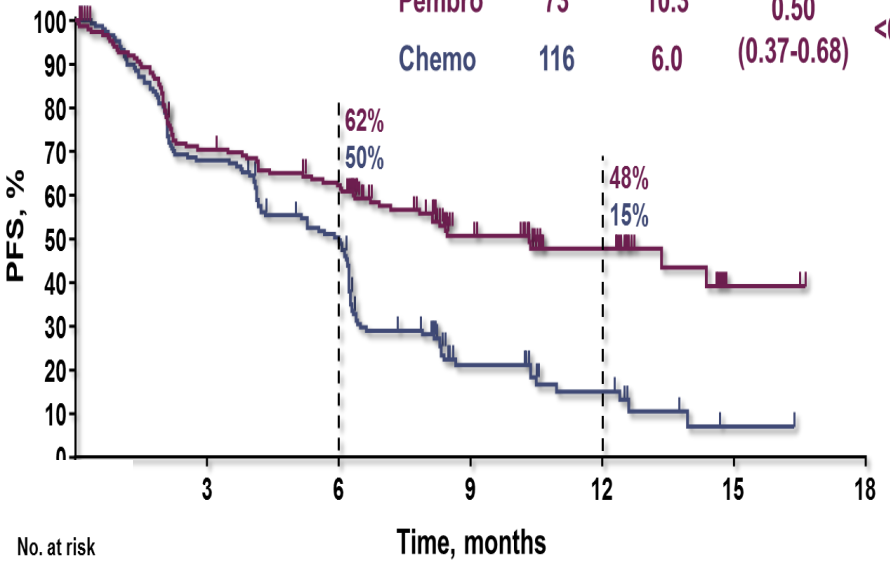
KN-024: Patients with advanced NSCLC and PD-L1 expression ≥50%



PD-L1 ≥50%
EGFR/ALK WT

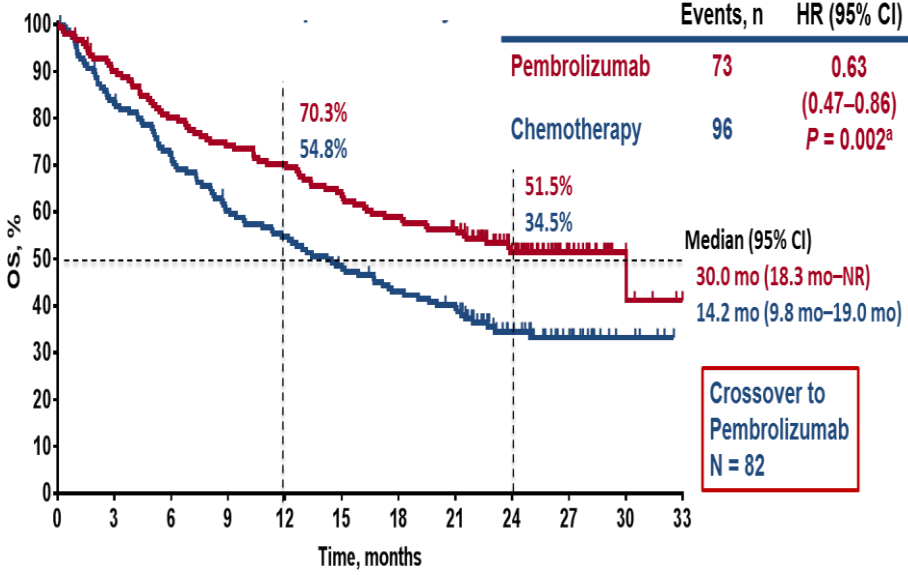
PFS

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	73	10.3	0.50 (0.37-0.68)	<0.001
Chemo	116	6.0		



OS

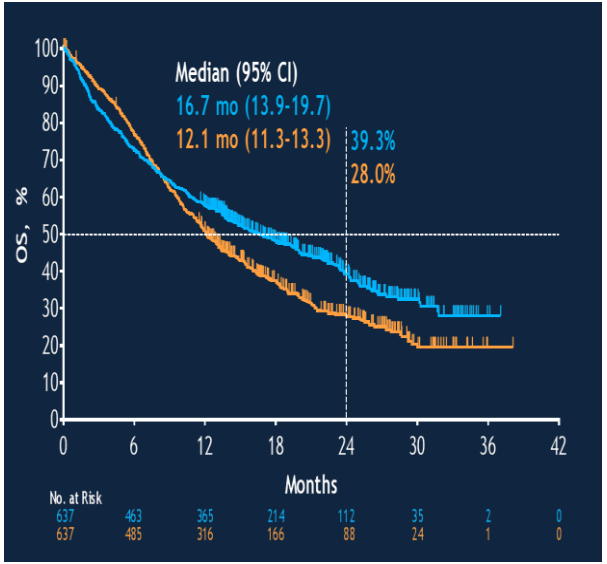
	Events, n	HR (95% CI)
Pembrolizumab	73	0.63 (0.47–0.86)
Chemotherapy	96	*P* = 0.002[a]



Reck M, et al. *N Engl J Med.* 2016;375(19):1823-1833.

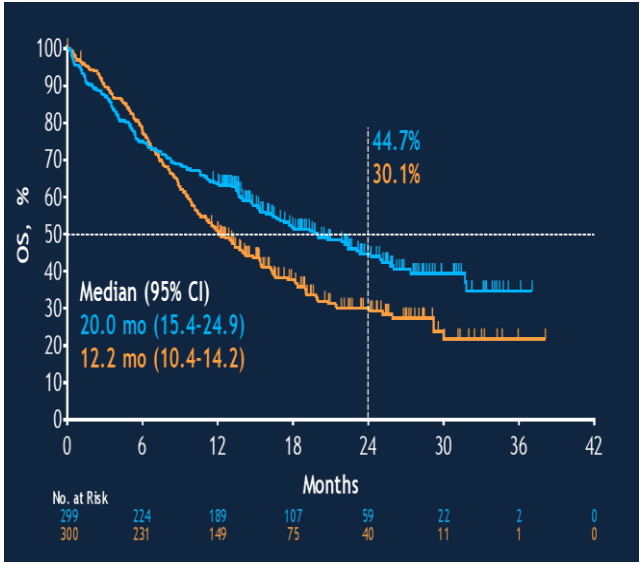
Overall Survival

TPS ≥1%



	Events	HR (95% CI)	*P*
Pembro	371 (58.2%)	0.81 (0.71-0.93)	0.0018
Chemo	438 (68.8%)		

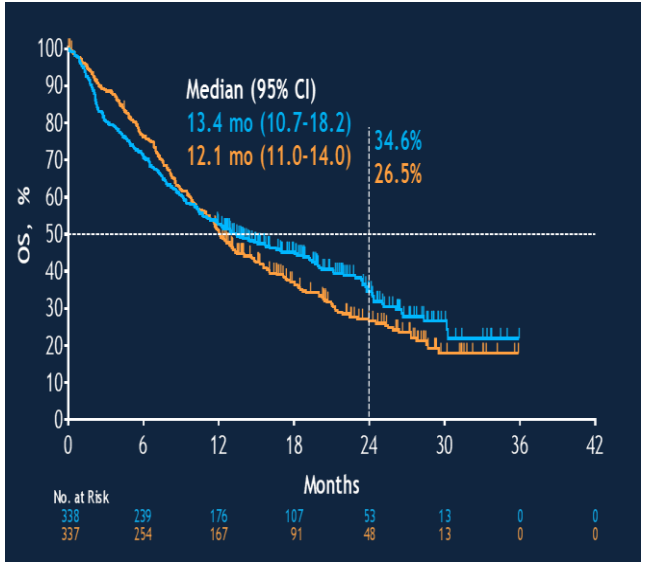
≥50%



	Events	HR (95% CI)	*P*
Pembro	157 (52.5%)	0.69 (0.56-0.85)	0.0003
Chemo	199 (66.3%)		

≥1-49%

(Exploratory analysis)



	Events	HR (95% CI)
Pembro	214 (63.3%)	0.92 (0.77-1.11)
Chemo	239 (70.9%)	

The PD-L1 ≥50% Subgroup Is the Main Driver of OS Benefit in PD-L1-Pos Cases

Small but important early death rate with Pembro

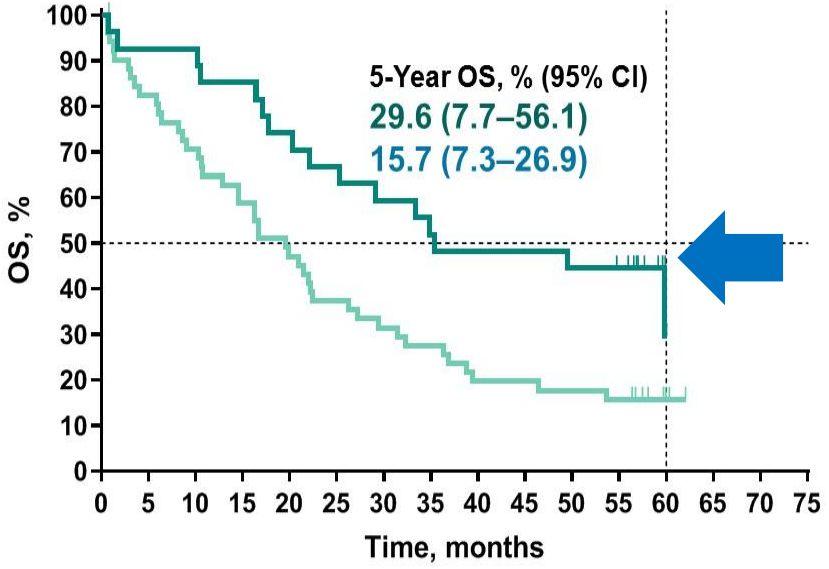
Lopes G, et al. *J Clin Oncol*. 2018;36(suppl): Abstract LBA4.

5-years long-term OS for patients withs advances NSCLC treated with pembrolizumab

KN-001

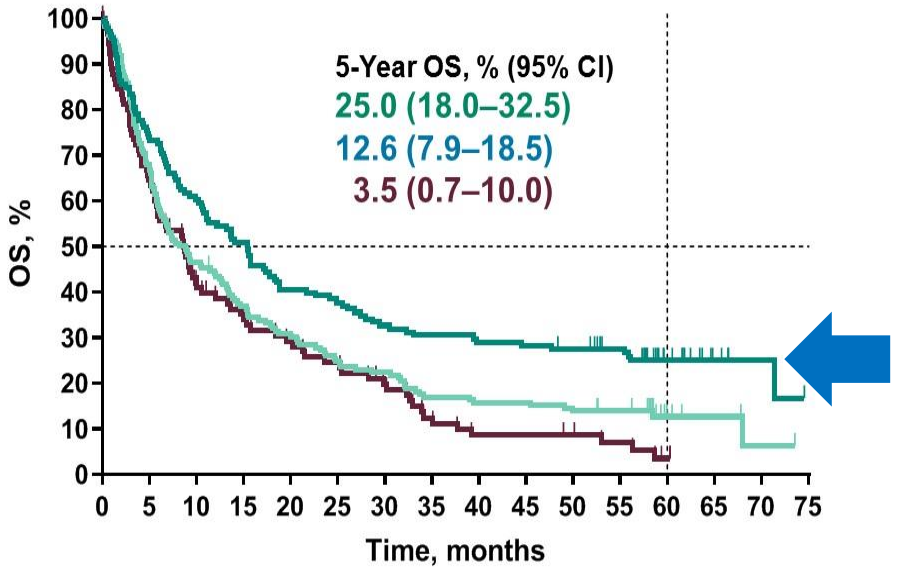
Treatment-Naive Patients

PD-L1 TPS	Events, n/N	Median (95% CI) OS, mo
TPS ≥50%	17/27	35.4 (20.3–63.5)
TPS 1%–49%	43/52	19.5 (10.7–26.3)



Previously Treated Patients

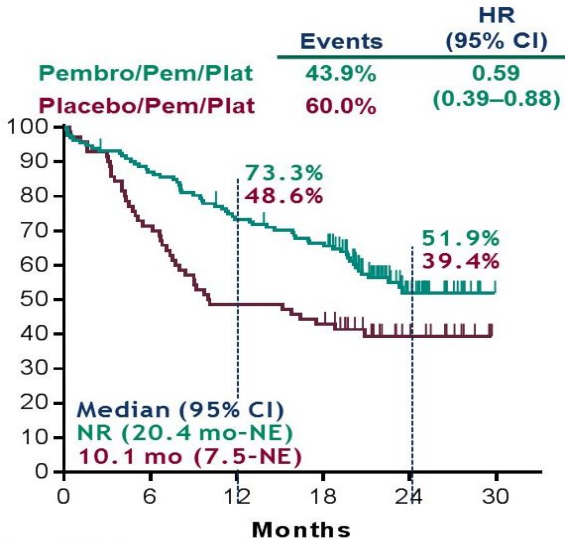
PD-L1 TPS	Events, n/N	Median (95% CI) OS, mo
TPS ≥50%	104/138	15.4 (10.6–18.8)
TPS 1%–49%	146/168	8.5 (6.0–12.6)
TPS <1%	83/90	8.6 (5.5–10.6)



Pembro alone remains a reasonable choice for PD-L1≥50% patients

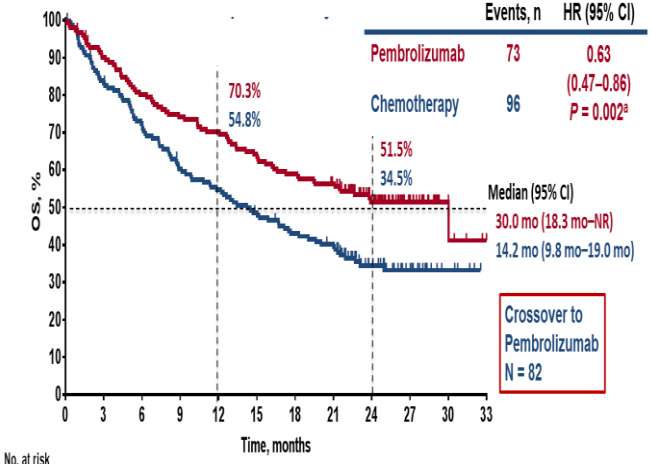
GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

KN-189
(up-date OS ASCO 19)



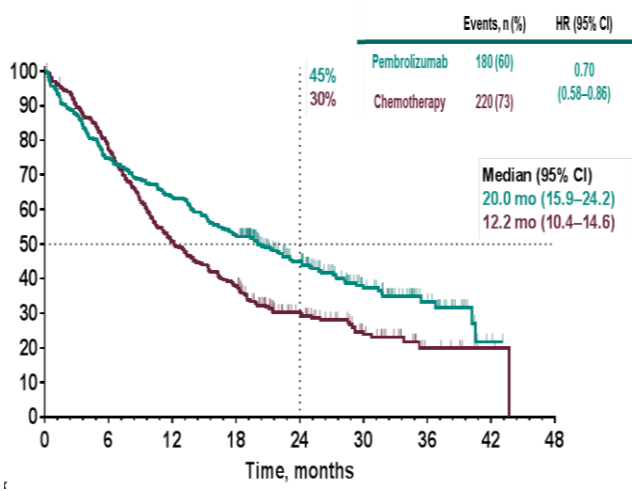
HR:0.59

KN-024
(up-date OS)



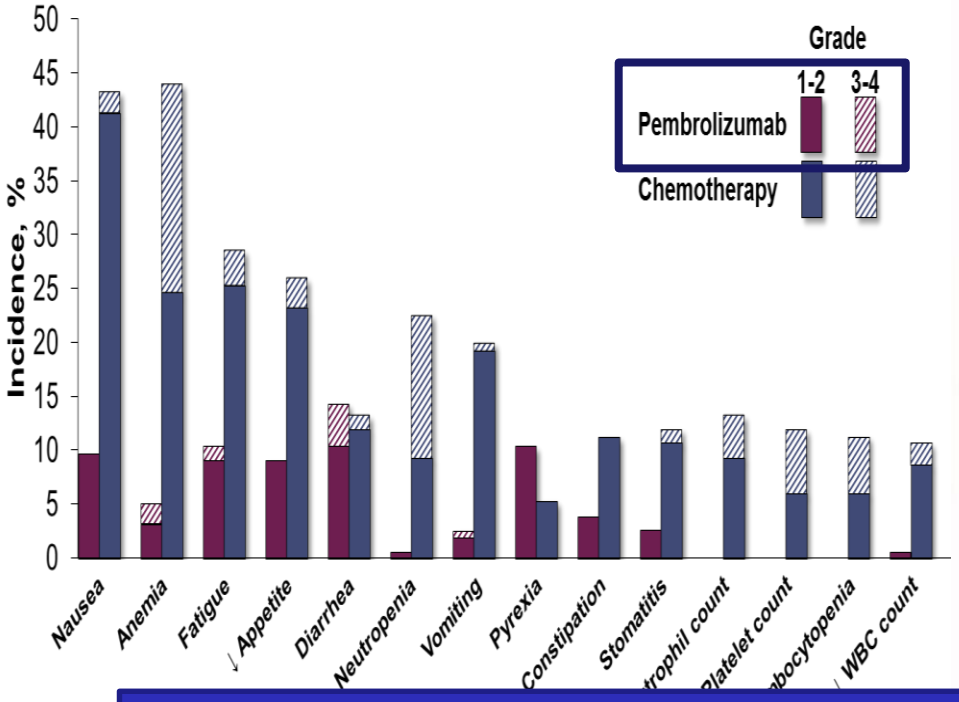
HR:0.63

KN-042
(up-date OS ELCC)

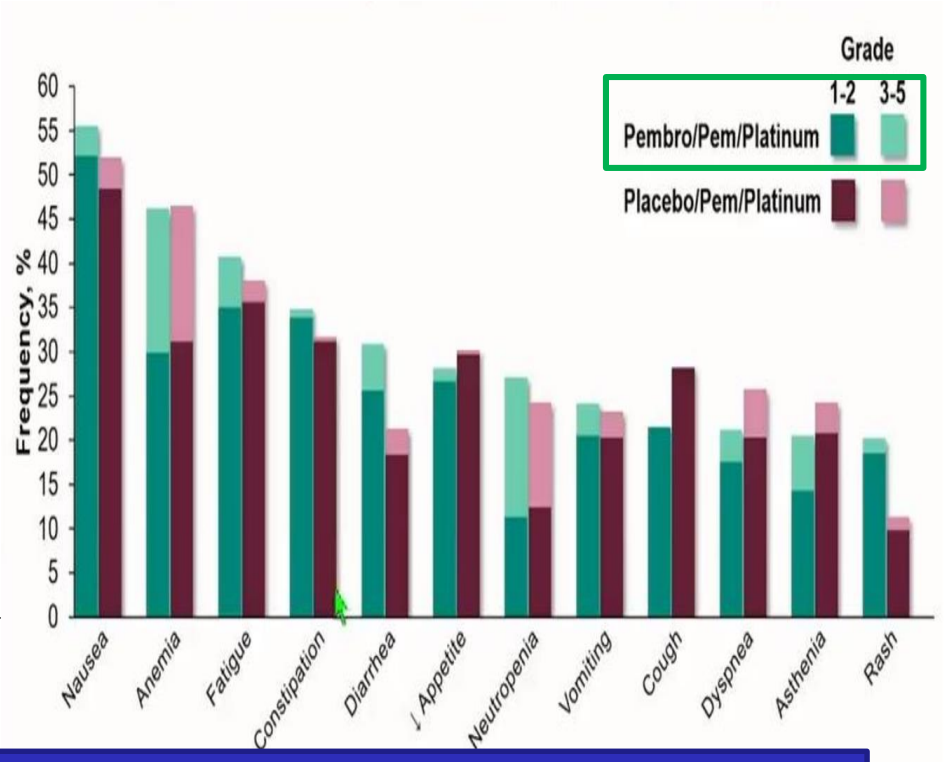


HR:0.71

KN-024, chemo toxicities….

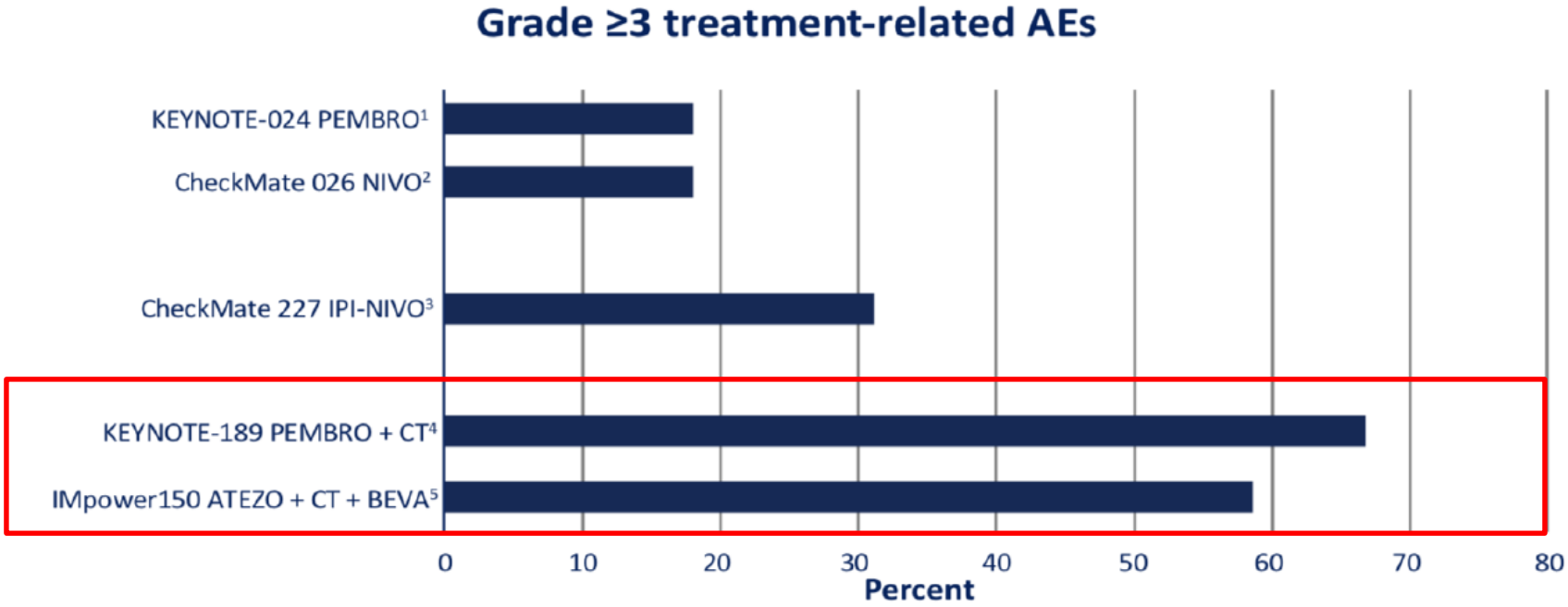


KN-189: chemoT toxicities….



PD-L1 IHC can be used to determine chemotherapy sparing

CT adds toxicity in combination with IO



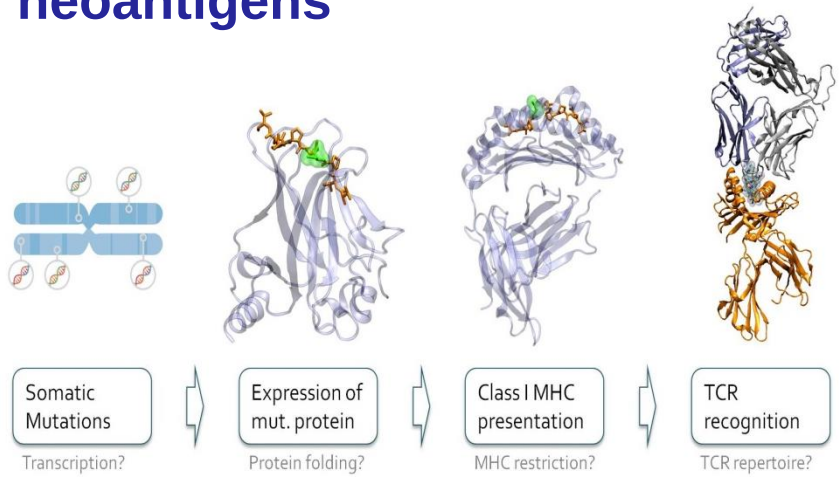
Reck NEJM 16, Carbone NEJM 17, Hellmann NEJM 18, Gandhi NEJM 18,Socinski NEJM 18

PD-L1 IHC determines who should have chemotherapy or not

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

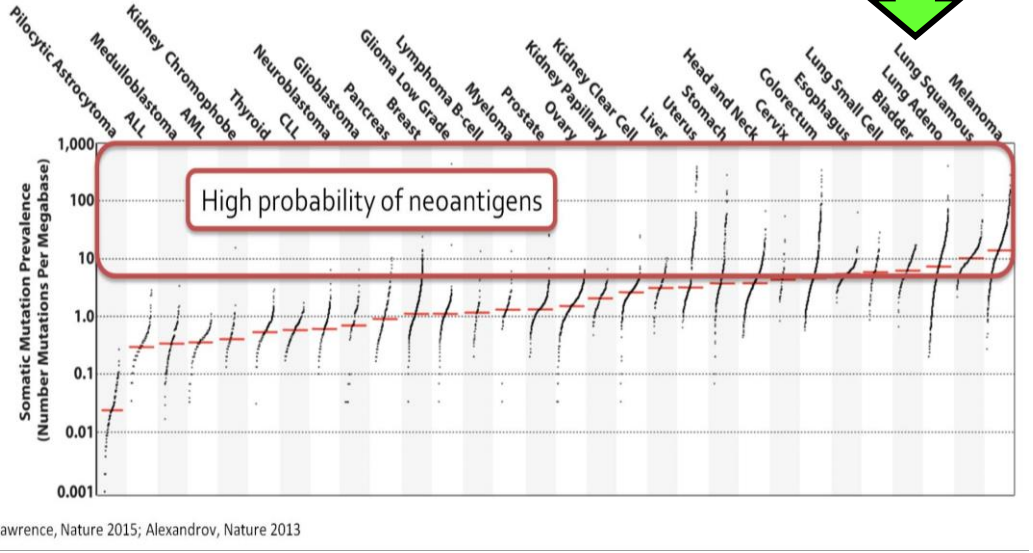
TMB ?

A minority of mutation produce neoantigens



Accumulation of mutation increasing its likelihood to be recognized

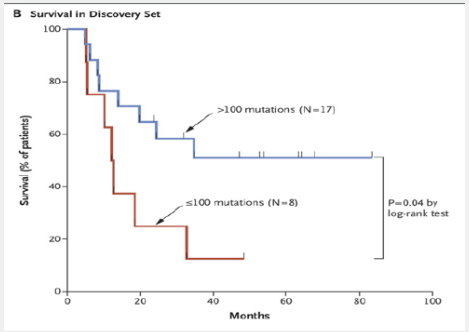
NSCLC



Lawrence, Nature 2015; Alexandrov, Nature 2013

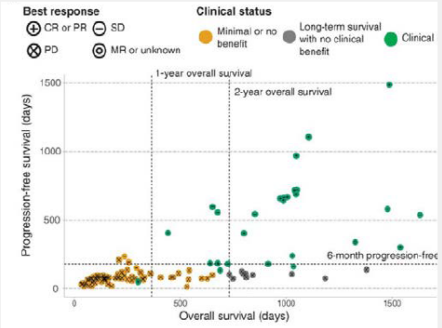
TMB correlates with tumor response in several tumor types

High TMB Melanoma



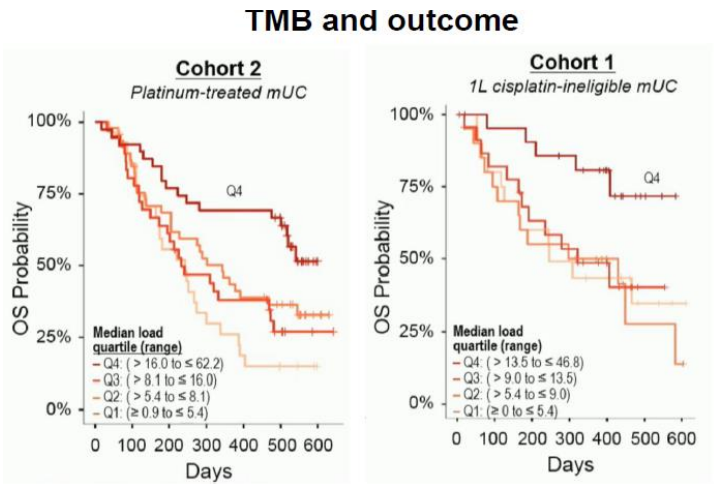
Snyder et al., NEJM, 2014

High TMB Melanoma

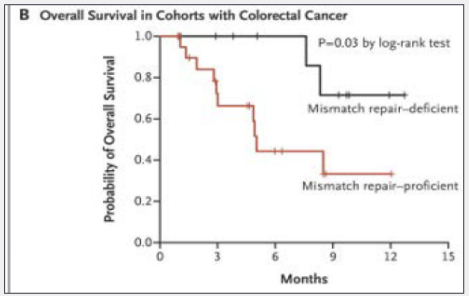


Van Allen *et al.*, Science, 2015

Urothelial cancer

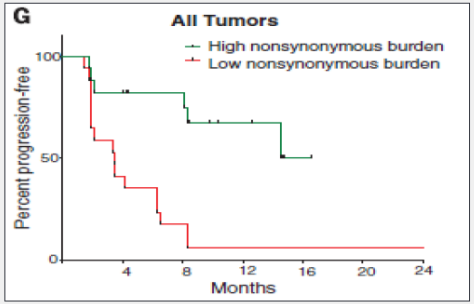


MSI-High Colorectal Cancer



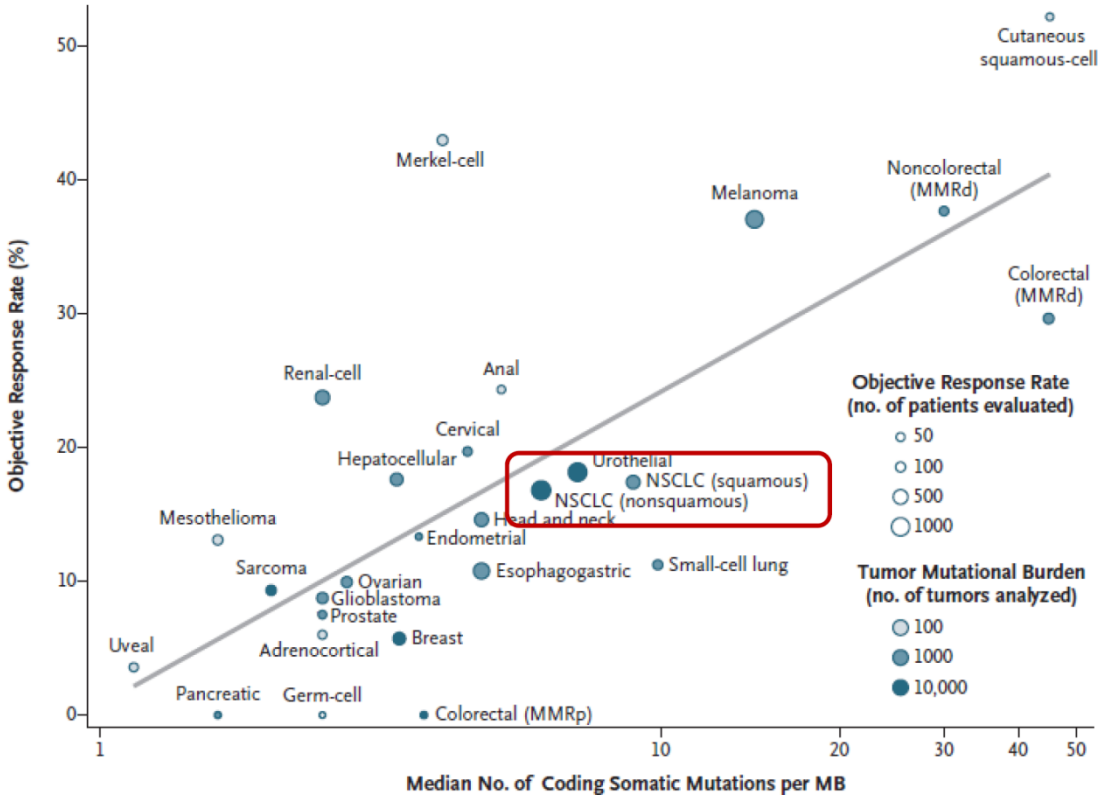
Le et al., NEJM, 2015

High TMB NSCLC



Rizvi *et al.*, Science, 2015

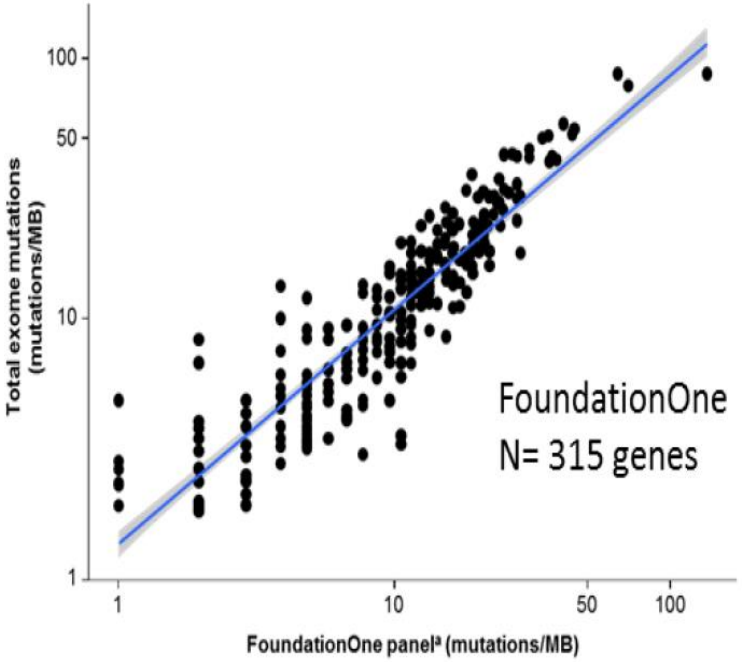
Evidence for correlation of response to TMB across tumour types

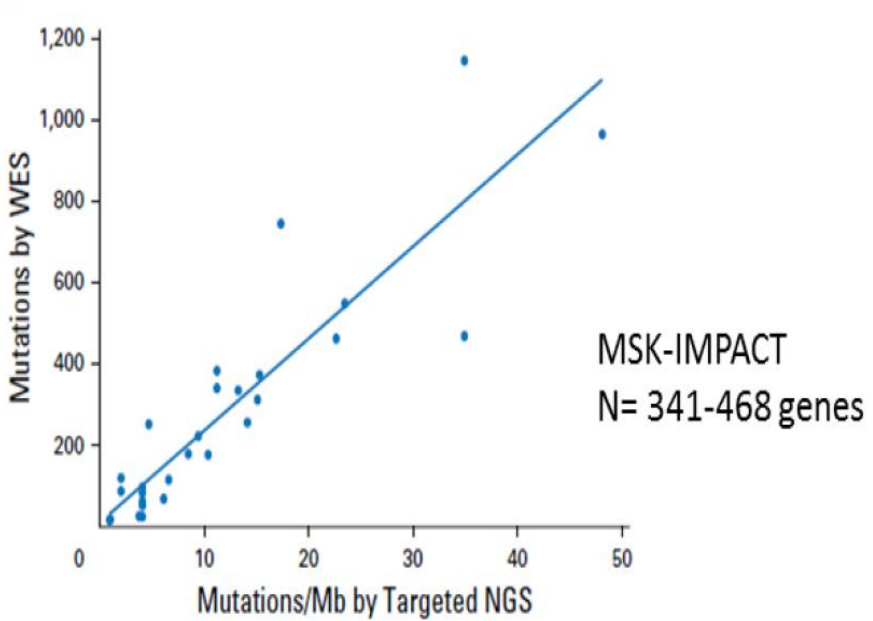


Correlation coefficient = 0.74, meaning that 55% of the differences in the ORR across cancer types may be explained by variations of TMB

Yarchoan et al, NEJM 2017

Correlation of WES and targeted sequencing panels in NSCLC

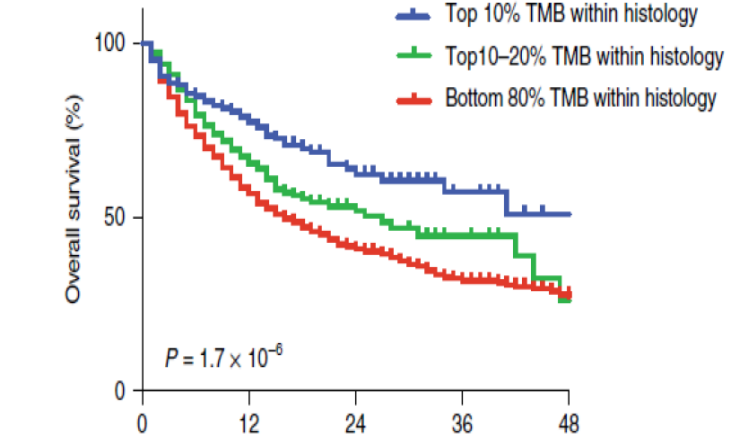




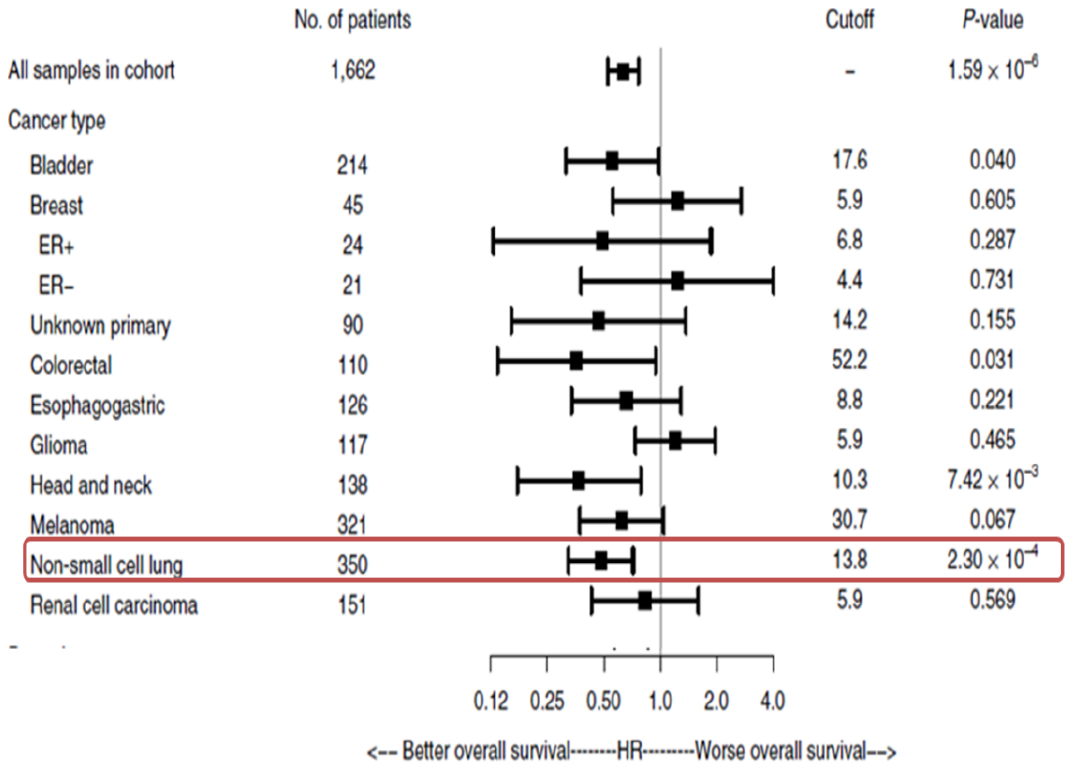
Peters , AACR 2017; Rizvi, JCO 2018

TMB is predictive of OS benefit across tumour types

Clinical and genomic (MSK-IMPACT) data of 1,622 advances pts treated with ICI

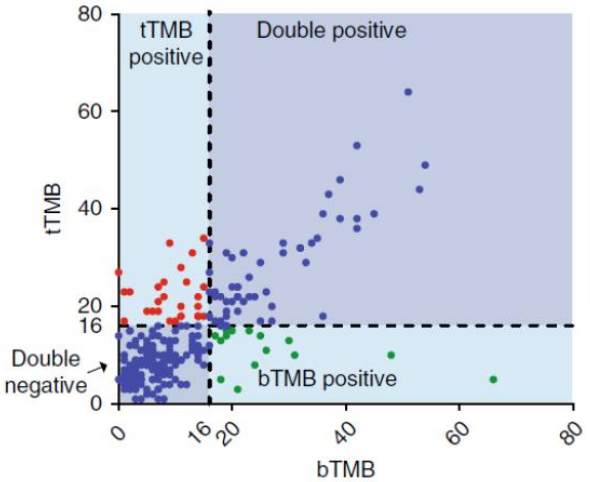


No. at risk					
Bottom 80%	1,305	586	231	85	33
Top10–20%	184	100	39	16	5
Top10%	173	101	43	16	6



Samstein, Nat Gen 2019

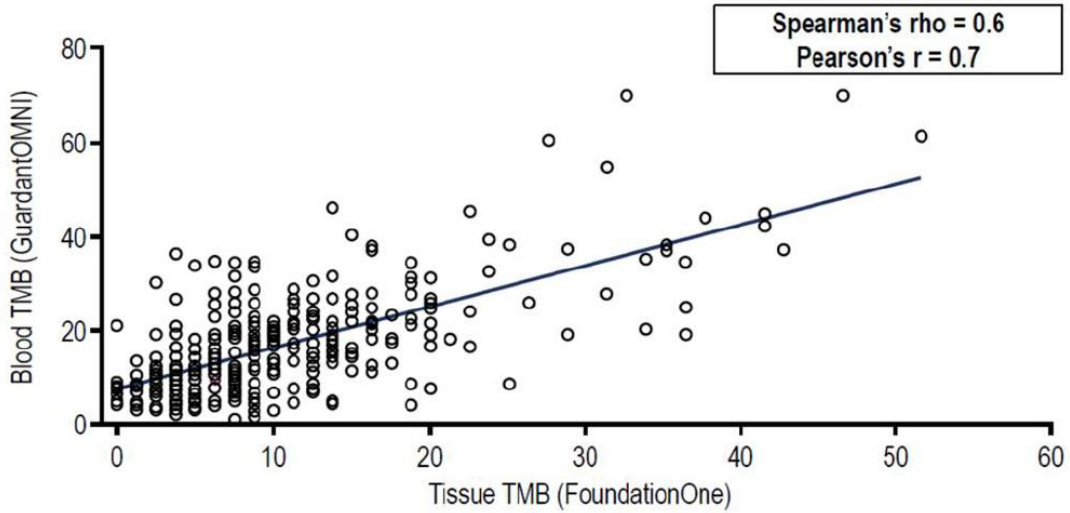
Correlation of Tissue and Blood Tumor Mutational Burden



Spearman rank correlation = 0.64 (95% CI: 0.56–071)

Metric	Performance
PPA	64% (95% CI: 54–74%)
NPA	88% (95% CI: 83–92%)

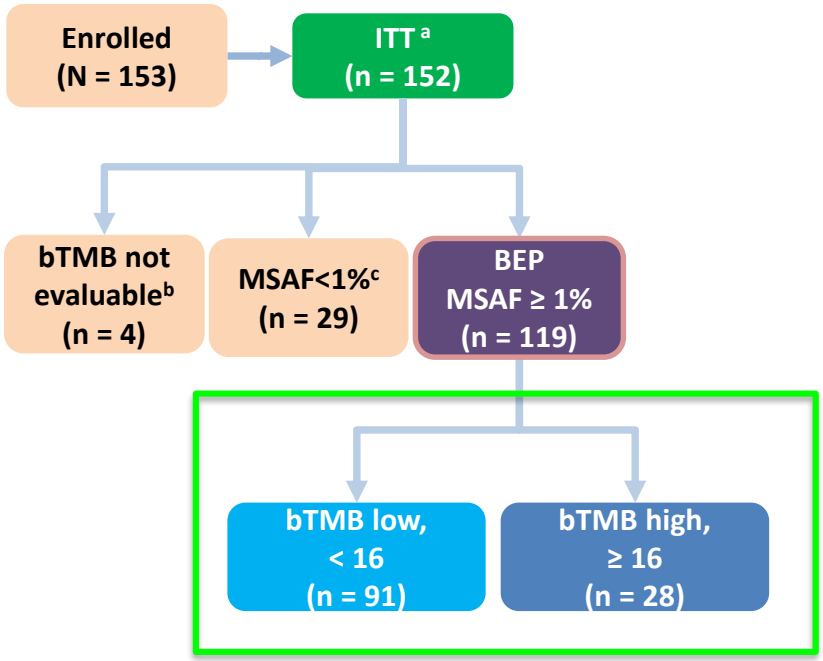
- In 352 (31.5% of ITT) matched patient specimens, tTMB values positively correlated with bTMB values

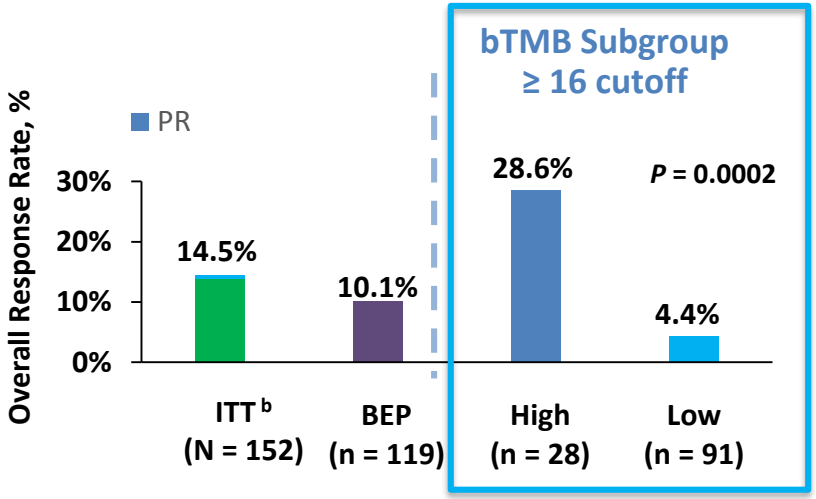


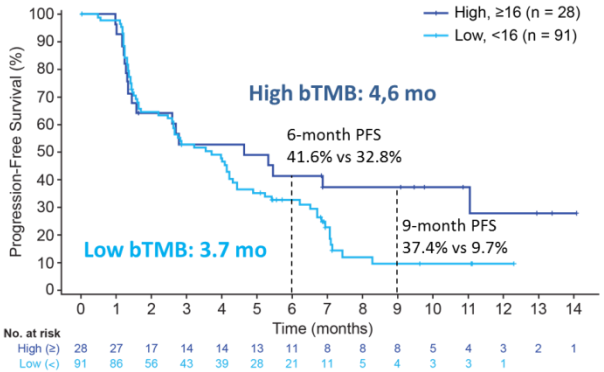
In 352 matched patient specimens,
tTMB values positively correlated with bTMB values

Gandara D et al, Nat Med 2018; Peters S et al, AACR 2019

B-F1RST



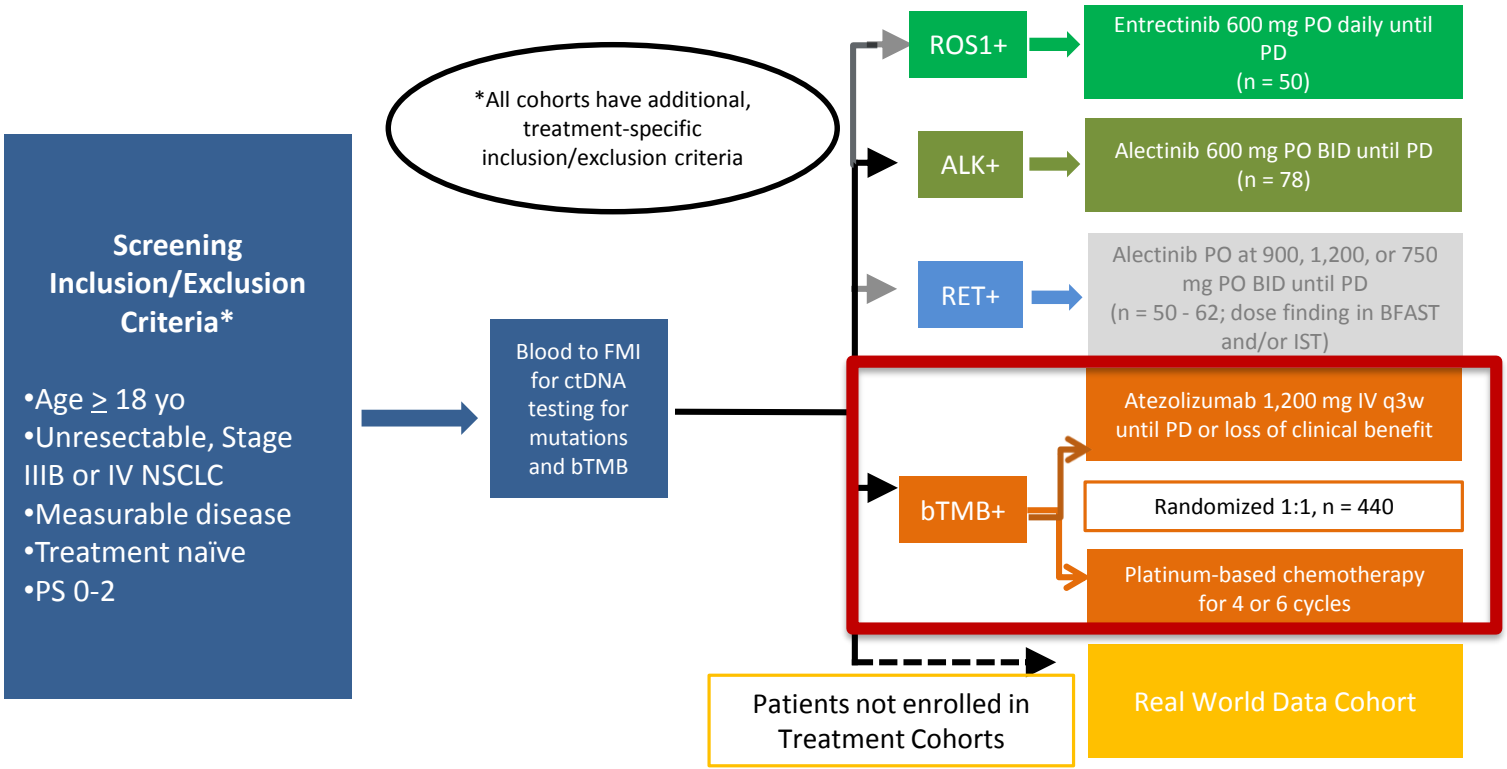




- [a] Excludes one patient who was never treated.
- [b] Assay QC failures.
- [c] The MSAF < 1% population was considered as non-biomarker evaluable (non-BEP).

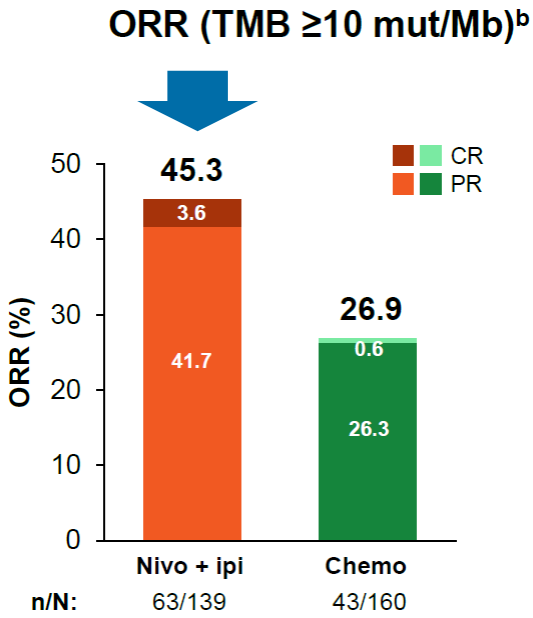
Kim ESMO 2018

BFAST: Trial Schema

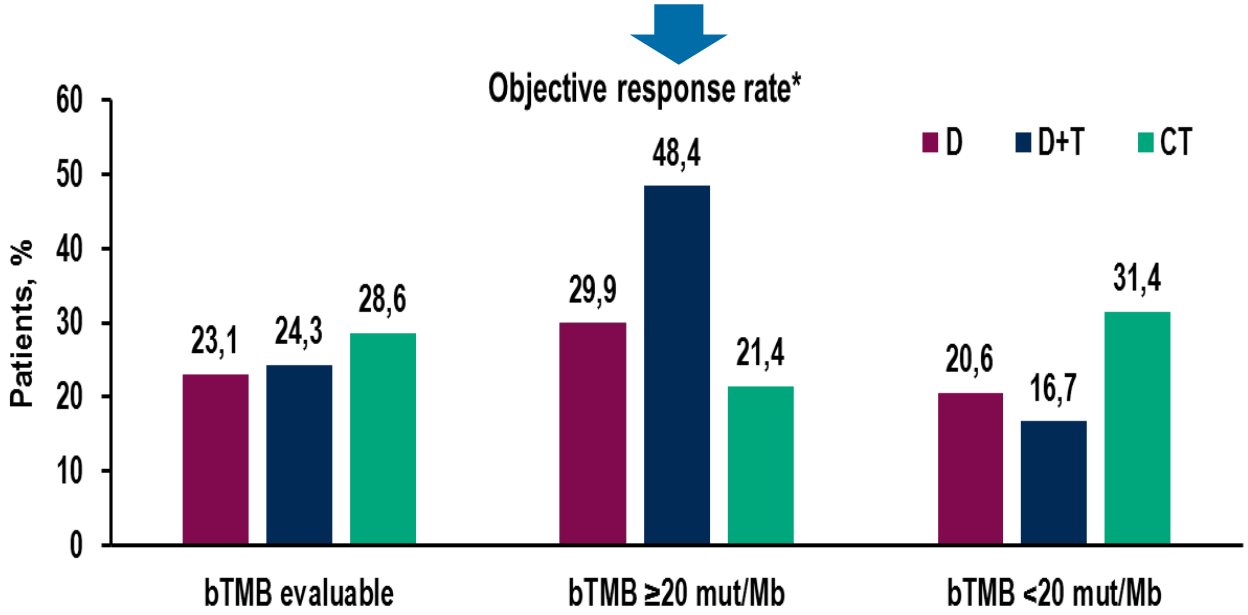


Correlation of TMB and ORR

Nivo + Ipilimumab (CM-227)



Durva+Tremelimumab (MYSTIC)



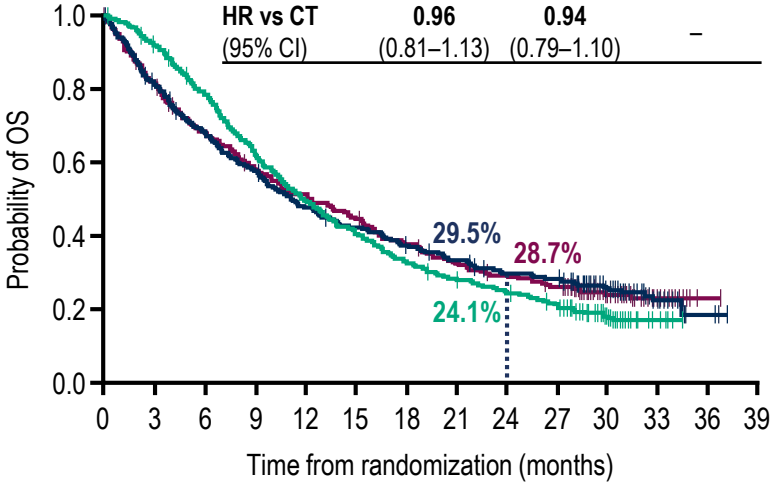
Matthew D. Hellmann et al, AACR 2018

Peters.S and al, AACR 2019

Overall Survival in ITT and Blood TMB Evaluable Populations
(MYSTIC Trial)

ITT population

	D (n=374)	D+T (n=372)	CT (n=372)
mOS, months	**12.3**	**11.2**	**11.8**
(95% CI)	(10.1–14.9)	(9.5–12.9)	(10.5–13.3)
HR vs CT	**0.96**	**0.94**	–
(95% CI)	(0.81–1.13)	(0.79–1.10)	

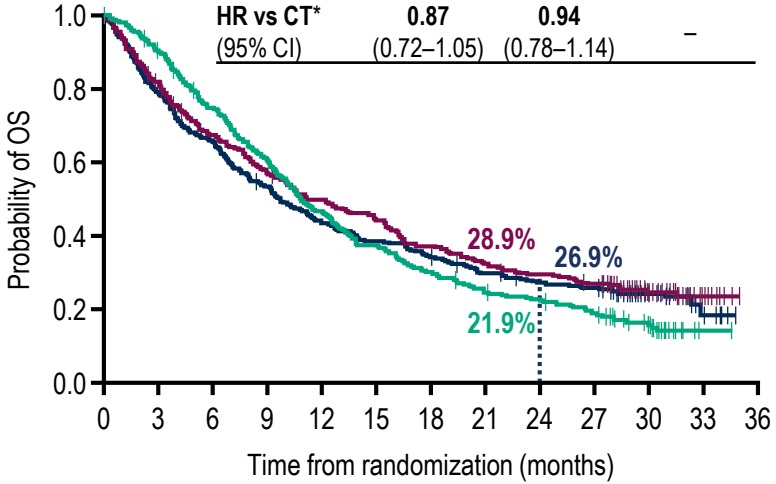


No. at risk

D	374	303	249	212	185	161	136	115	103	92	41	14	1	0
D+T	372	303	253	212	175	154	136	119	104	98	55	16	3	0
CT	372	336	287	227	180	148	118	100	85	71	37	6	0	0

bTMB evaluable population

	D (n=286)	D+T (n=268)	CT (n=255)
mOS, months	**11.1**	**9.7**	**10.8**
(95% CI)	(9.3–14.9)	(8.0–11.6)	(9.5–12.5)
HR vs CT*	**0.87**	**0.94**	–
(95% CI)	(0.72–1.05)	(0.78–1.14)	



286	231	187	158	137	121	102	88	80	72	31	9	0
268	211	176	141	115	102	90	77	68	64	32	6	0
255	227	186	151	116	93	74	61	53	45	23	1	0

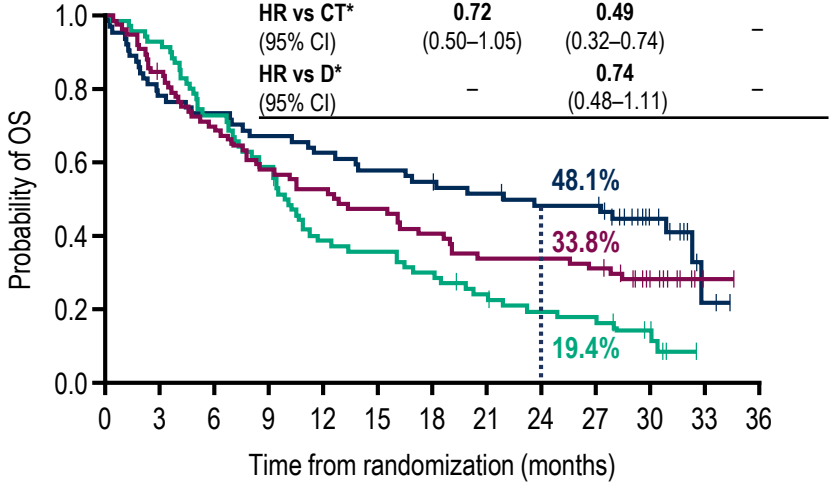
*Unadjusted; data cut-off October 4, 2018

Peters.S and al, AACR 2019

OS in Patients With Blood TMB ≥20 and <20 mut/Mb (MYSTIC Trial)

bTMB ≥20 mut/Mb

	D (n=77)	D+T (n=64)	CT (n=70)
mOS, months (95% CI)	**12.6** (7.8–18.6)	**21.9** (11.4–32.8)	**10.0** (8.1–11.7)
HR vs CT* (95% CI)	**0.72** (0.50–1.05)	**0.49** (0.32–0.74)	–
HR vs D* (95% CI)	–	**0.74** (0.48–1.11)	–

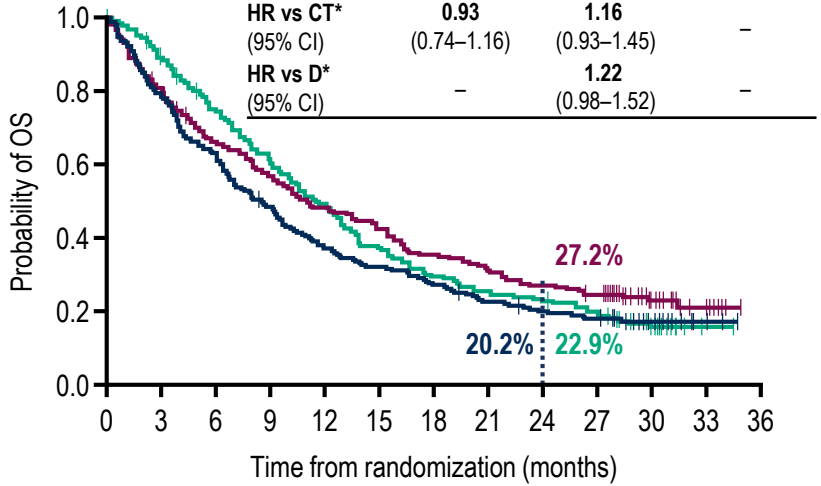


No. at risk

D	77	64	53	44	39	35	30	25	25	23	10	1	0
D+T	64	50	47	43	40	37	35	32	29	29	14	2	0
CT	70	65	51	41	27	25	21	16	12	11	6	0	0

bTMB <20 mut/Mb

	D (n=209)	D+T (n=204)	CT (n=185)
mOS, months (95% CI)	**11.0** (8.9–14.9)	**8.5** (6.7–9.8)	**11.6** (9.6–13.1)
HR vs CT* (95% CI)	**0.93** (0.74–1.16)	**1.16** (0.93–1.45)	–
HR vs D* (95% CI)	–	**1.22** (0.98–1.52)	–



209	167	134	114	98	86	72	63	55	49	21	8	0
204	161	129	98	75	65	55	45	39	35	18	4	0
185	162	135	110	89	68	53	45	41	34	17	1	0

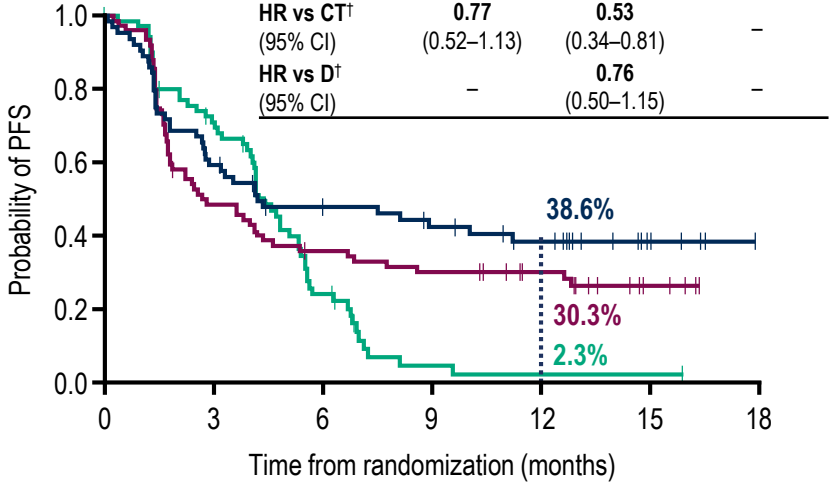
*Unadjusted; data cut-off October 4, 2018

Peters.S and al, AACR 2019

PFS in Patients With Blood TMB ≥20 and <20 mut/Mb (MYSTIC Trial)

bTMB ≥20 mut/Mb

	D (n=77)	D+T (n=64)	CT (n=70)
mPFS,* months (95% CI)	**2.7** (1.8–4.4)	**4.2** (2.8–NR)	**4.4** (4.1–5.4)
HR vs CT† (95% CI)	**0.77** (0.52–1.13)	**0.53** (0.34–0.81)	–
HR vs D† (95% CI)	–	**0.76** (0.50–1.15)	–

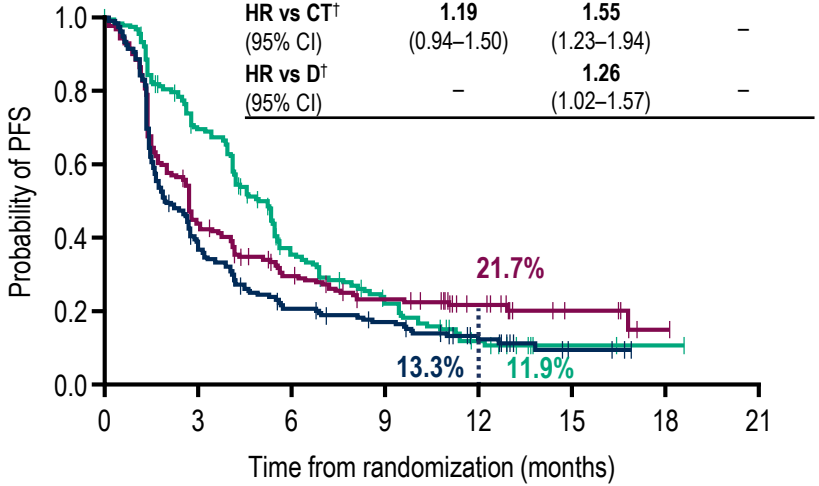


No. at risk

D	77	35	25	21	16	4	0
D+T	64	38	28	23	18	5	0
CT	70	47	14	2	1	1	0

bTMB <20 mut/Mb

	D (n=209)	D+T (n=204)	CT (n=185)
mPFS,* months (95% CI)	**2.8** (2.2–3.1)	**2.0** (1.7–2.8)	**5.0** (4.2–5.5)
HR vs CT† (95% CI)	**1.19** (0.94–1.50)	**1.55** (1.23–1.94)	–
HR vs D† (95% CI)	–	**1.26** (1.02–1.57)	–

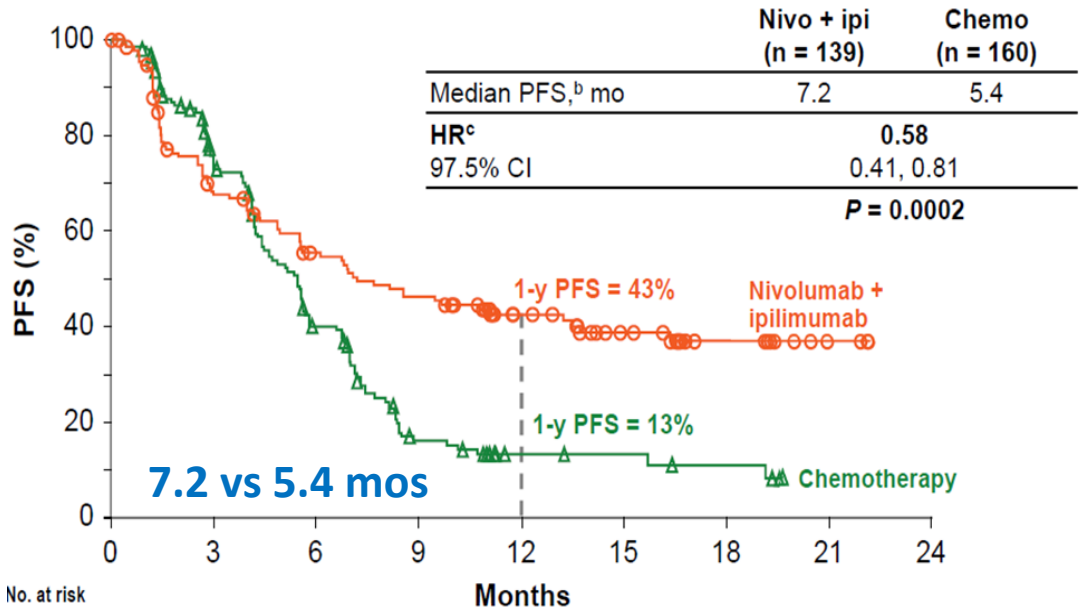


209	86	53	38	20	6	1	0
204	77	37	28	14	3	0	0
185	116	52	30	10	2	1	0

*Blinded independent central review per RECIST v1.1; †Unadjusted; data cut-off June 1, 2017
mPFS, median progression-free survival; NR, not reported; RECIST, Response Evaluation Criteria for Solid Tumors.

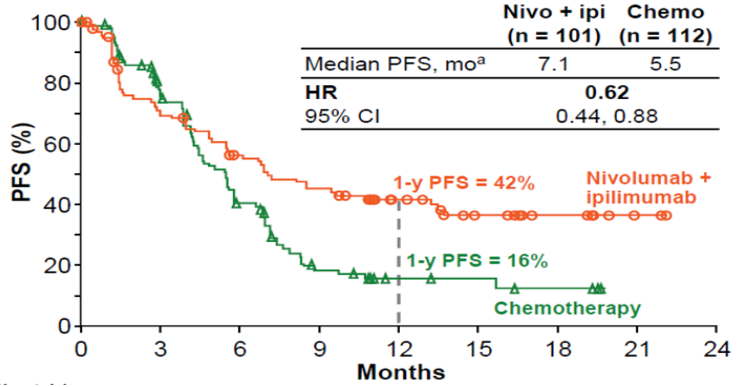
Peters.S and al, AACR 2019

Co-primary endpoint (CM227): PFS with nivolumab+Ipilimumab vs chemotherapy with high TMB (≥10 mut/Mb)



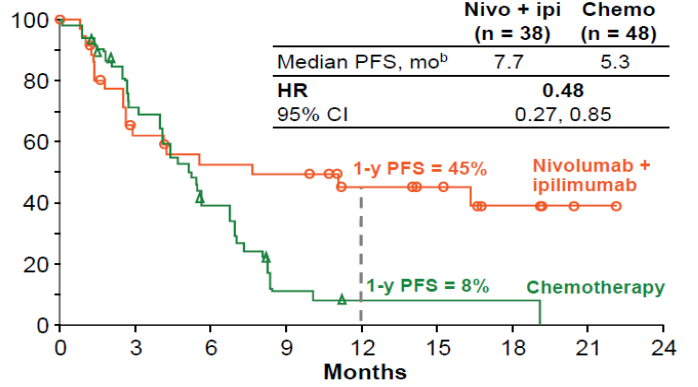
	Nivo + ipi (n = 139)	Chemo (n = 160)
Median PFS,[b] mo	7.2	5.4
HR[c]	**0.58**	
97.5% CI	0.41, 0.81	
	***P* = 0.0002**	

≥1% PD-L1 expression



	Nivo + ipi (n = 101)	Chemo (n = 112)
Median PFS, mo[a]	7.1	5.5
HR	**0.62**	
95% CI	0.44, 0.88	

<1% PD-L1 expression



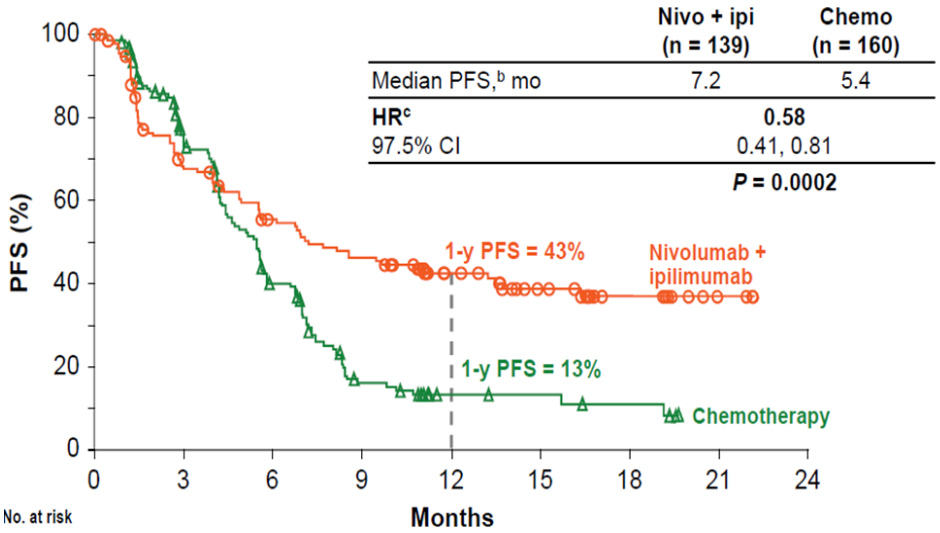
	Nivo + ipi (n = 38)	Chemo (n = 48)
Median PFS, mo[b]	7.7	5.3
HR	**0.48**	
95% CI	0.27, 0.85	

Hellmann MD, et al. *N Engl J Med.* 2018;378(22):293-2104.

IO combo TMB (≥10 mut/Mb) or IO-ChemoT ?

CM227

TMB (≥10 mut/Mb)

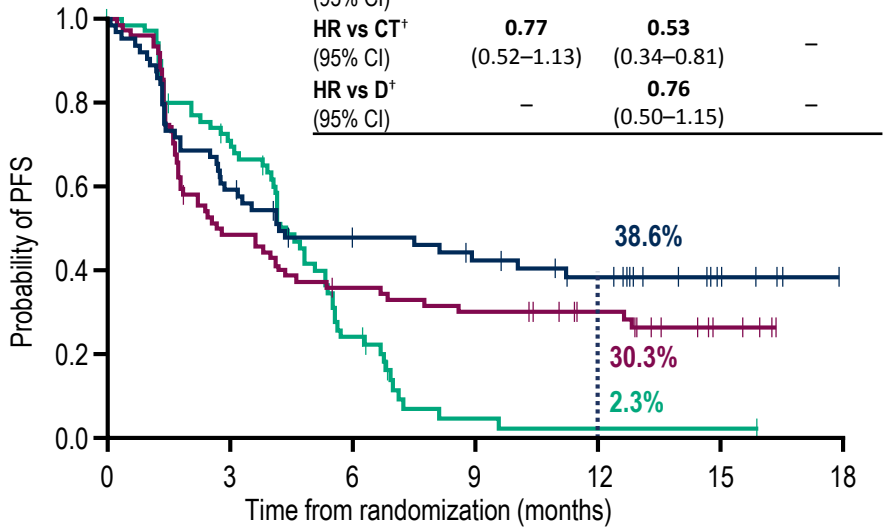


	Nivo + ipi (n = 139)	Chemo (n = 160)
Median PFS,[b] mo	7.2	5.4
HR[c]	0.58	
97.5% CI	0.41, 0.81	
	P = 0.0002	

MYSITC

bTMB ≥20 mut/Mb

	D (n=77)	D+T (n=64)	CT (n=70)
mPFS,* months (95% CI)	2.7 (1.8–4.4)	4.2 (2.8–NR)	4.4 (4.1–5.4)
HR vs CT† (95% CI)	0.77 (0.52–1.13)	0.53 (0.34–0.81)	–
HR vs D† (95% CI)	–	0.76 (0.50–1.15)	–

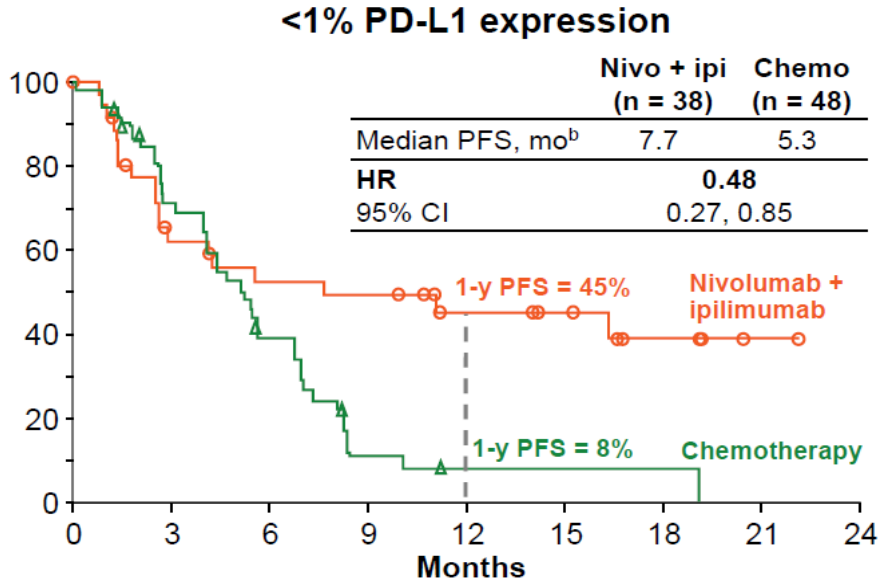


Hellmann MD, et al. *N Engl J Med.* 2018;378(22):293-2104.

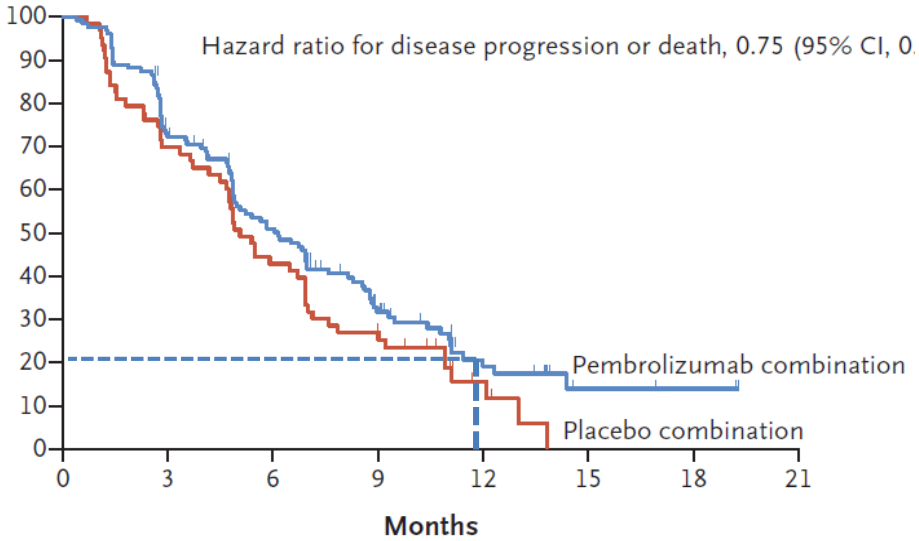
Peters.S and al, AACR 2019

IO combo TMB (≥10 mut/Mb) or IO-ChemoT ?

CM227



KN-189
(PD-L1 low, TMB?)

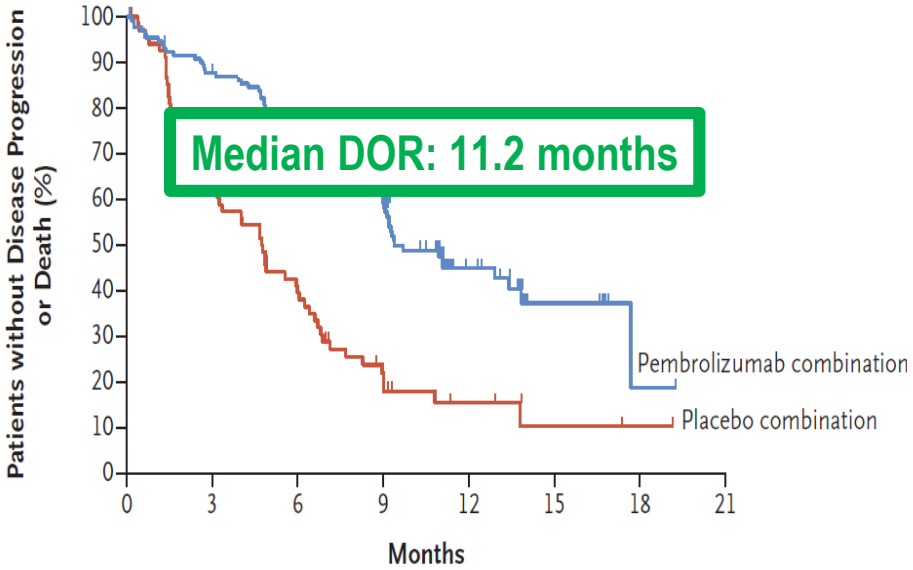


Would consider use of nivolumab plus ipilimumab, particularly in pts PD-L1–negative with high TMB, durable outcomes may exceed chemotherapy plus pembrolizumab (1-year PFS: 45%...vs ≈ 20%)

Hellmann MD, et al. *N Engl J Med*. 2018;378(22):293-2104.

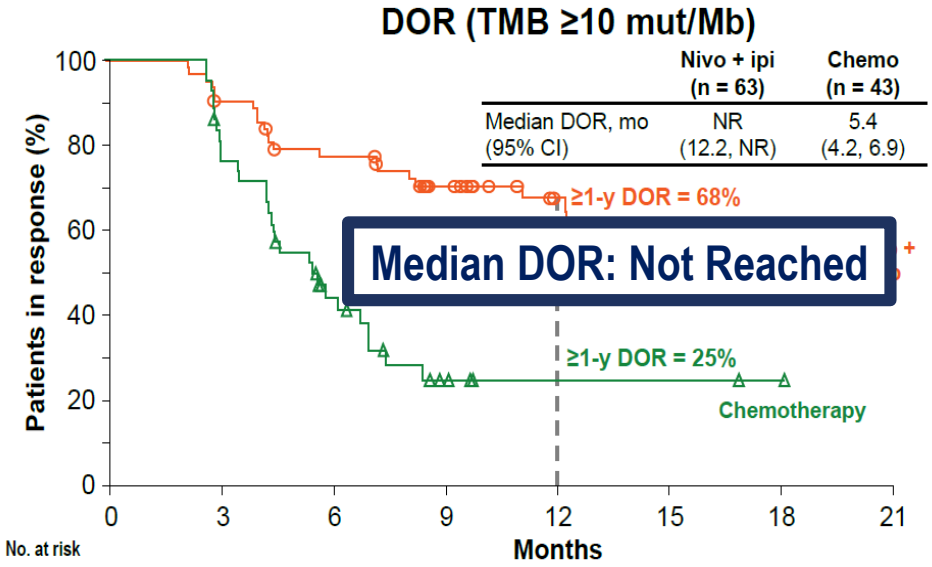
NSCLC ANTI-PD1 COMBINATIONS FOR IO NAIVE PATIENT

+CHEMO IN PDL1^{HIGH}



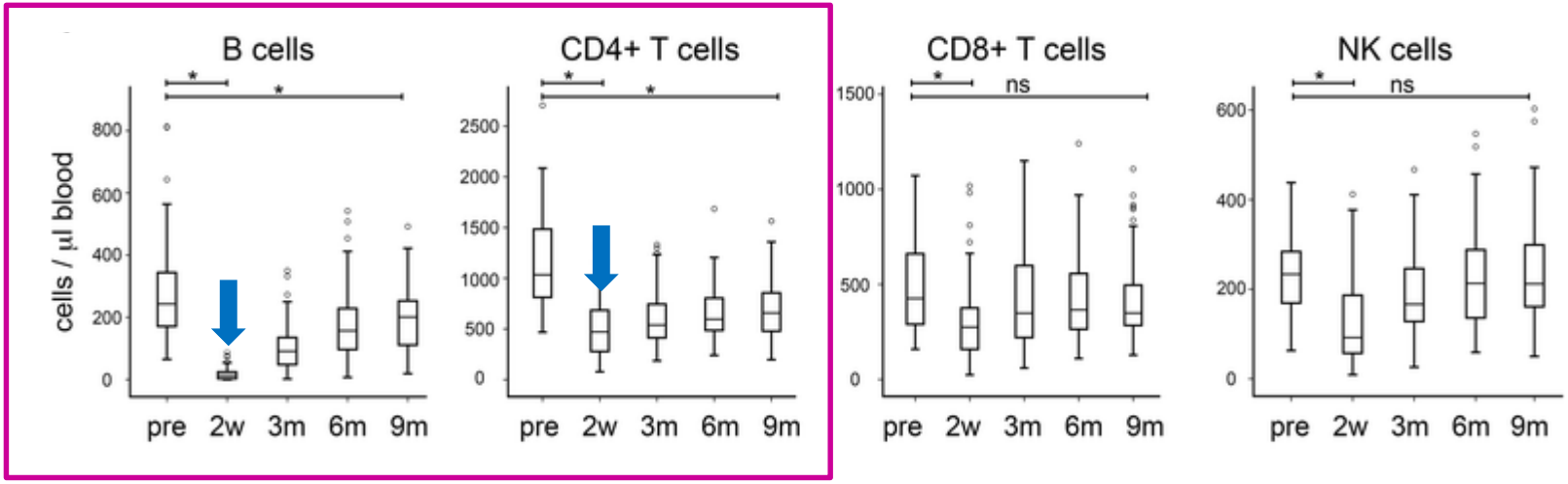
Gandhi L., et al. (2018). N. Engl. J. Med. *378*, 2078–2092.

+ANTI-CTLA-4 IN TMB^{HIGH}



Hellmann M.D., et al. (2018). N. Engl. J. Med. *378*, 2093–2104.

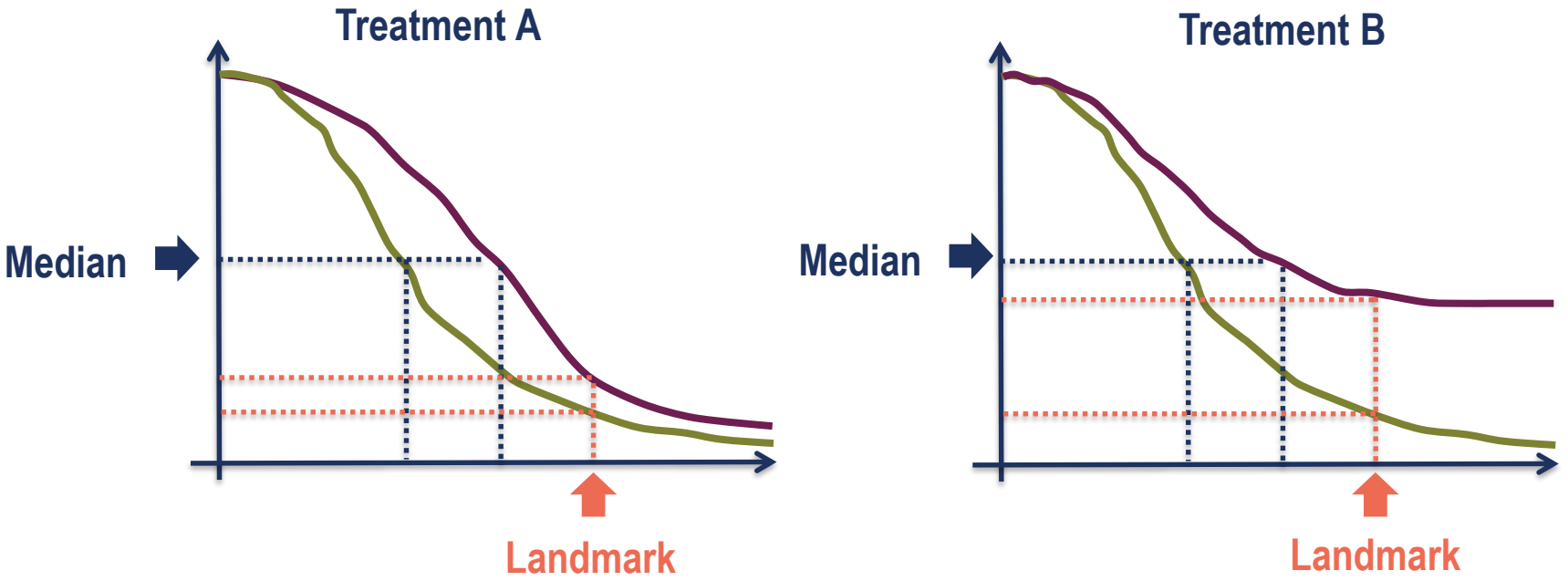
Impact of chemo on lymphocytes



Lymphocyte depletion and repopulation after chemotherapy for primary breast cancer

Verma R, et al.Breast Cancer Res 2016;18:10.

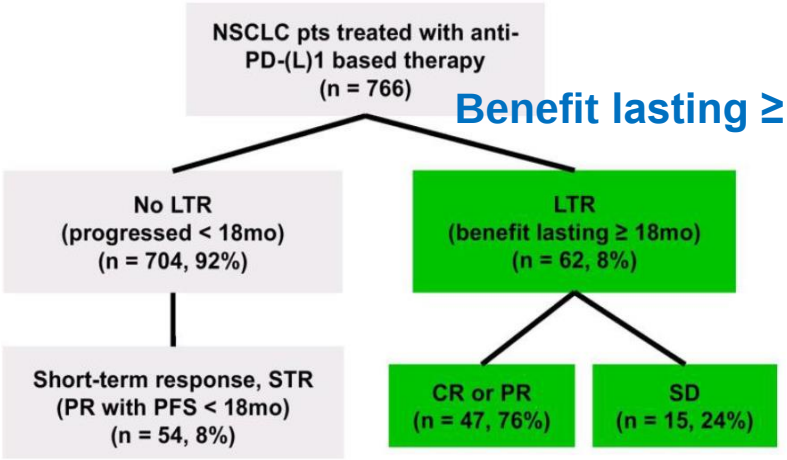
SURVIVAL PITFALLS



We need Follow Up+++
Duration of Response as a surrogate Endpoint for OS benefits

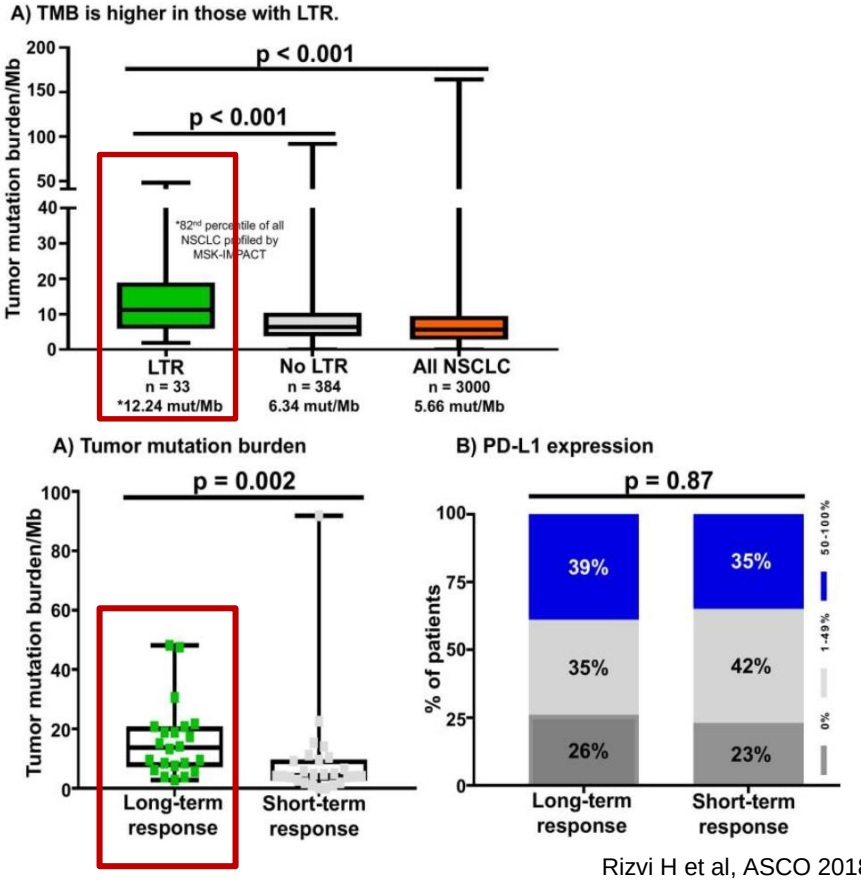
A.Marabelle, Gustave Roussy 2019

TMB but not PD-L1 expression is predictive of response duration and of long term benefit from anti-PD(L)-1 therapy



TMB assessed with MSK-IMPACT

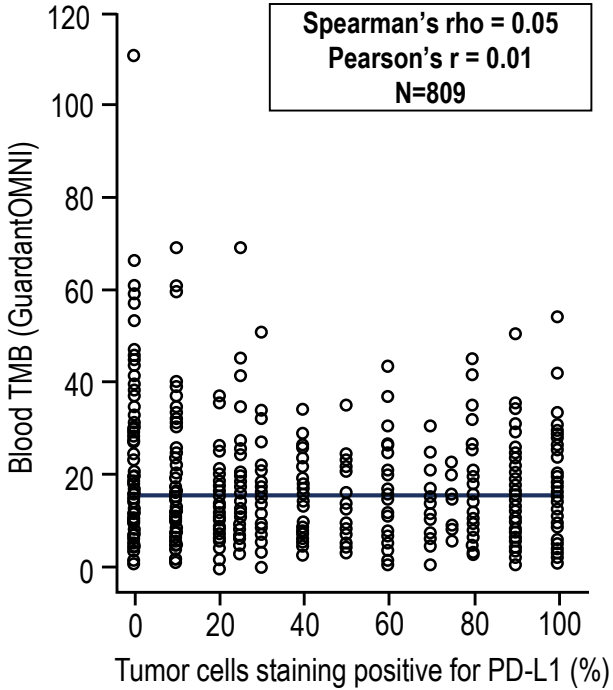
76% (CR or PR) **24%(SD)**

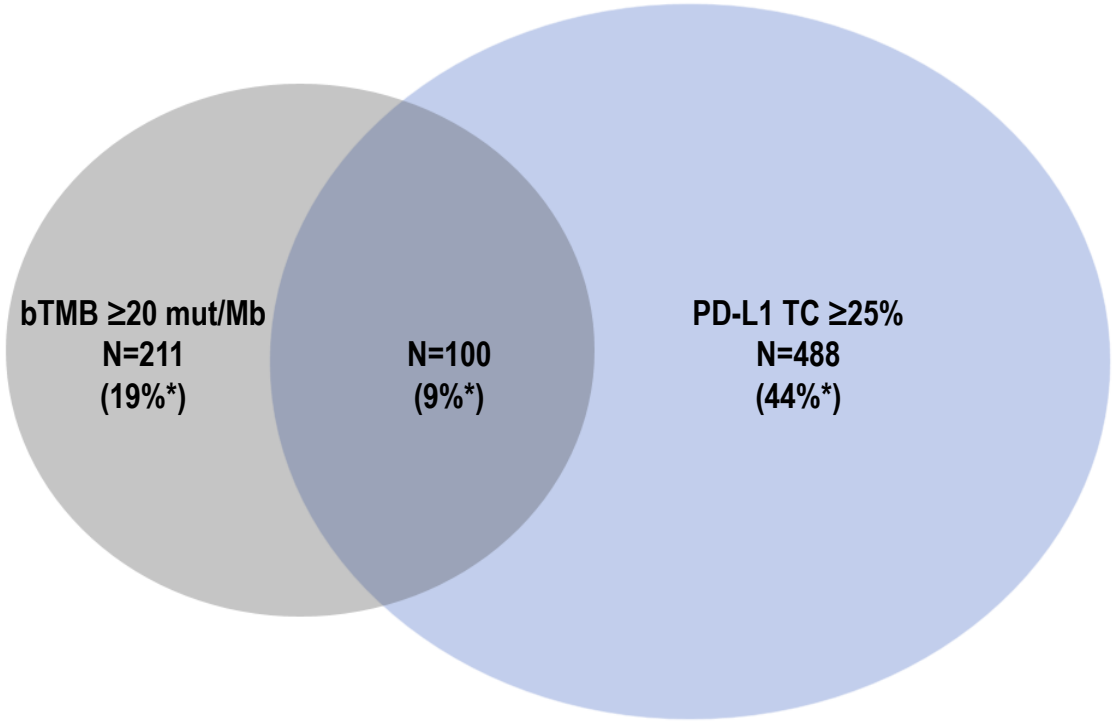


Rizvi H et al, ASCO 2018

PD-L1 and Blood TMB are Independent Biomarkers (MYSTIC Trial)

- bTMB values did not correlate with PD-L1 expression levels

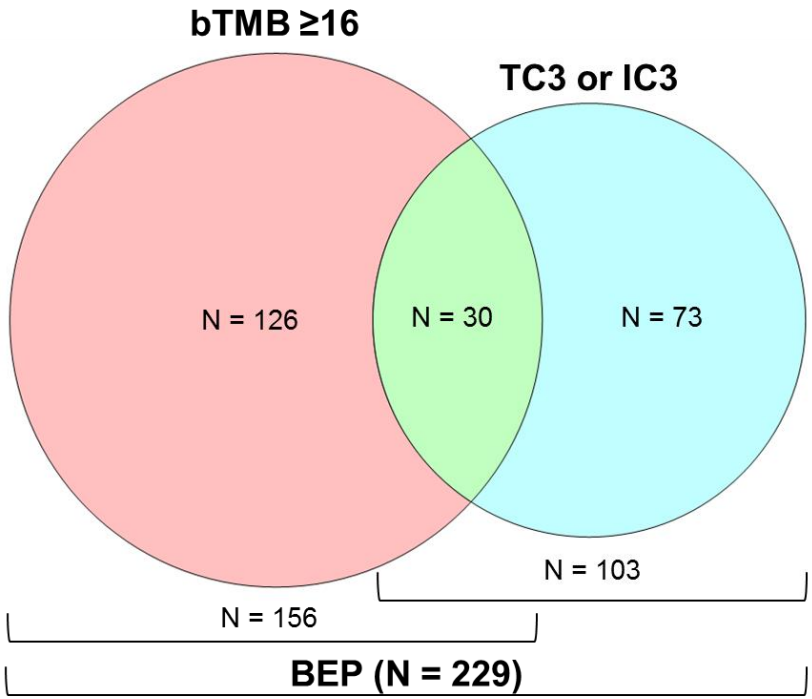




*Percentages are calculated from the ITT (n=1118)
Reference line in correlation plot is from linear regression

Peters.S and al, AACR 2019

LIMITED OVERLAP BETWEEN bTMB ≥16 AND PD-L1 EXPRESSION[a] (OAK BEP)



- Non-significant overlap between the bTMB ≥16 and TC3 or IC3 subgroups (Fisher exact test, *P* = 0.62)
  - **19.2%** of tumors with bTMB ≥16 were also TC3 or IC3
  - **29.1%** of tumors with TC3 or IC3 also had bTMB ≥16

	PFS HR (95% CI)	OS HR (95% CI)
bTMB ≥16	0.64 (0.46, 0.91)	0.64 (0.44, 0.93)
TC3 or IC3	0.62 (0.41, 0.93)	0.44 (0.27, 0.71)
bTMB ≥16 and TC3 or IC3	0.38 (0.17, 0.85)	0.23 (0.09, 0.58)

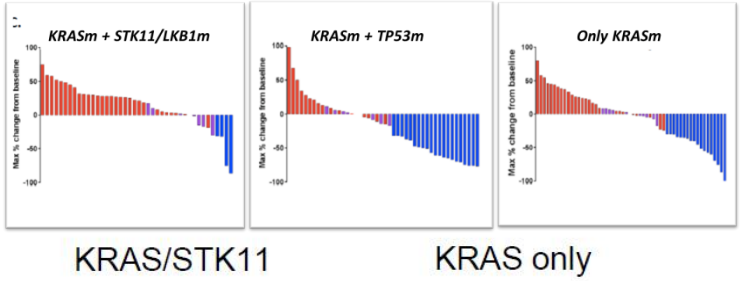
[a] PD-L1 expression was evaluated by immunohistochemistry (IHC) using the VENTANA SP142 assay;
TC3 or IC3, ≥50% of TC or ≥10% of IC express PD-L1.
BEP, biomarker-evaluable population; IC, tumor-infiltrating immune cell; TC, tumor cell.

PD-L1 IHC determines who should have chemotherapy or not

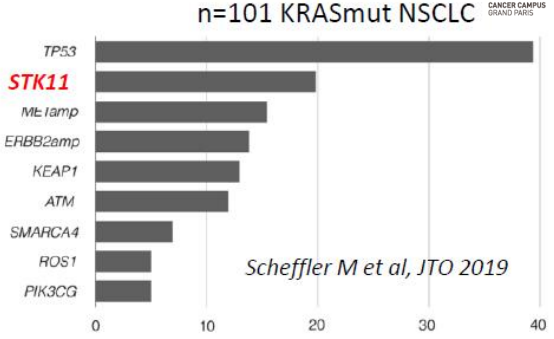
TMB determines who should have IO-IO combination

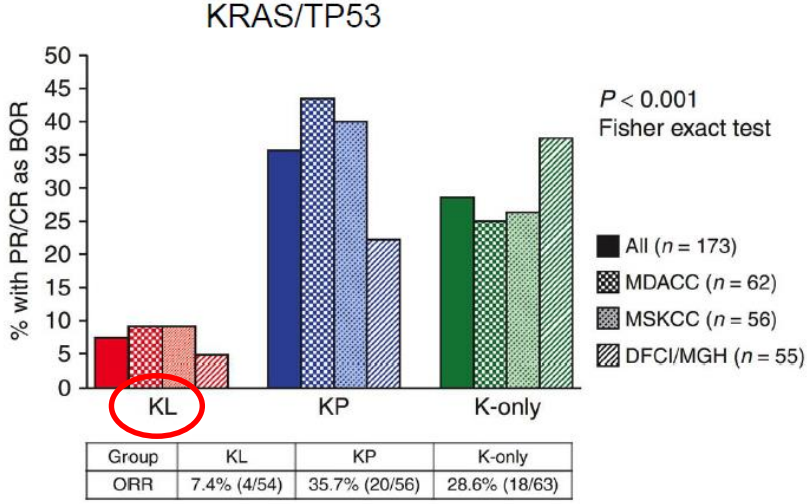
Other IO BioM ?

STK11/LKB1 mutations drive resistance to PD-1 inhibitors in KRAS mutant NSCLC

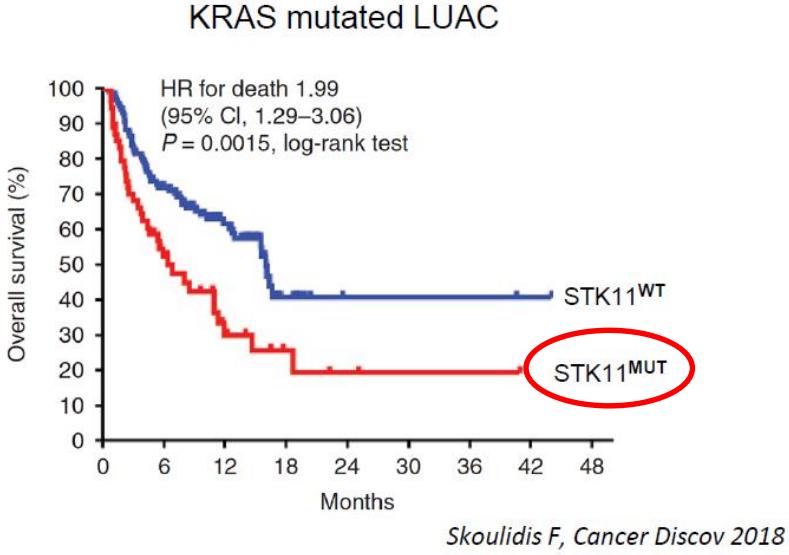


- i.e. Loss of LKB1 can drive production of G-CSF, CXCL7, and IL-6 by the tumor, which promotes neutrophil recruitment, which can block anti-tumoral cytotoxic T cells
- i.e. Loss of p53 can modulate the immune microenvironment by regulating NF-kB signaling. This results in increased cytokine production by tumor cells and recruitment and activation of immune cells, such as macrophages





Group	KL	KP	K-only
ORR	7.4% (4/54)	35.7% (20/56)	28.6% (18/63)



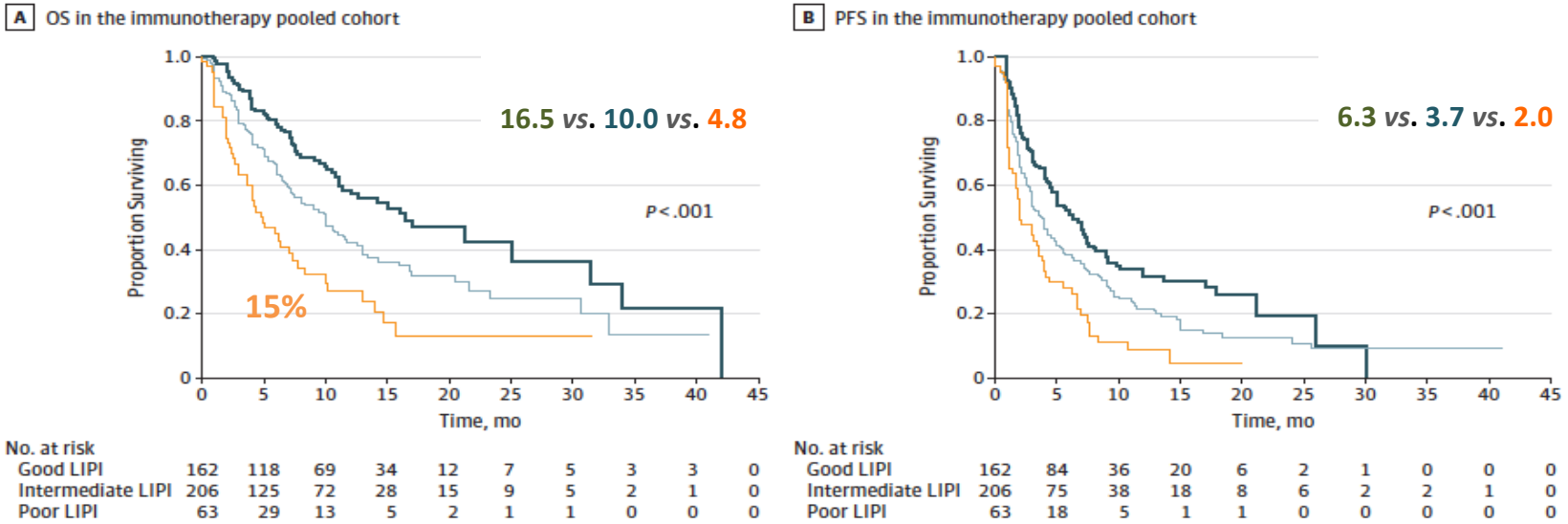
LIPI: Lung Immune Prognostic Index

Neutrophil recruitment can block anti-tumoral cytotoxic T cells

Lung Immune Prognostic Index		
No factor	dNLR ≤3 and LDH≤ULN	**Good**
1 factor	dNLR>3 or LDH>ULN	**Intermediate**
2 factors	dNLR>3 and LDH>ULN	**Poor**

dNLR >3 *[neutrophils/(leucocytes-neutrophils]*

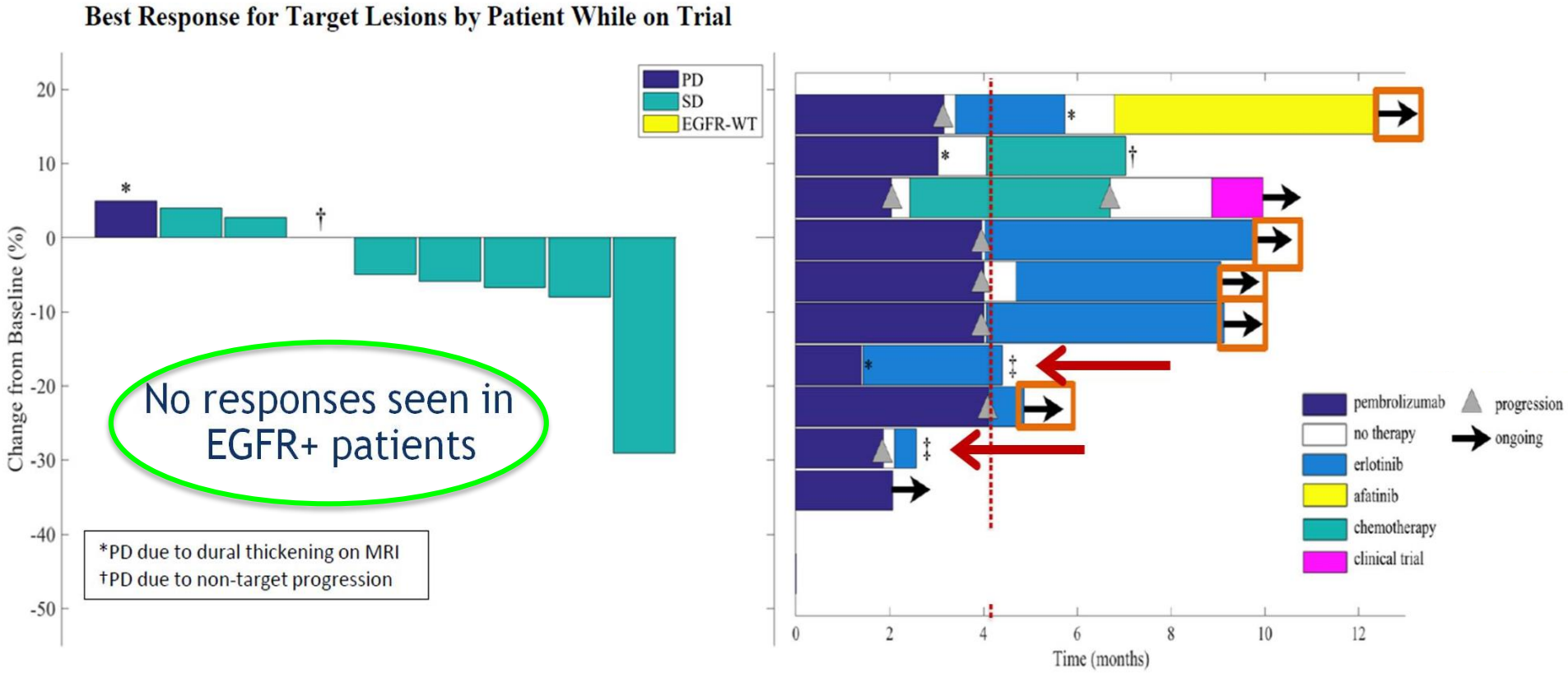
- ***N=466 advanced NSCLC patients*** *treated with PD(L)1 inh*
- ***8 European centers***



Predictive for IO ! (not for chemotherapy)

Mezquita, JAMA Oncol 2018

Phase II Study of Pembrolizumab in EGFR-Mutant, PD-L1+, TKI Naïve Patients

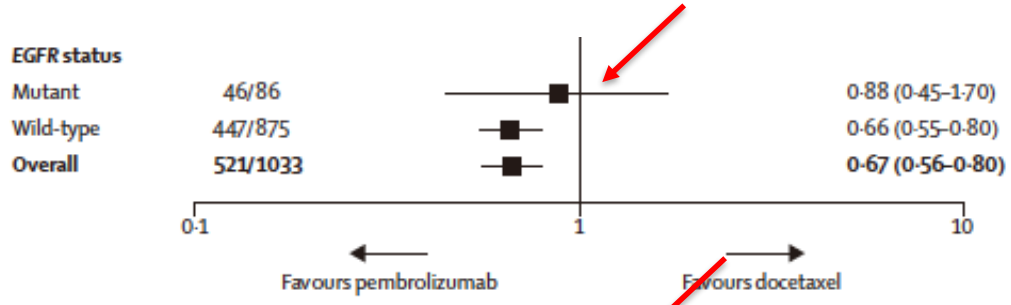


Lisberg et al, JTO 2018

Hazard ratios of OS by EGFR mutational status in 3 Phase III trials comparing ICI with docetaxel

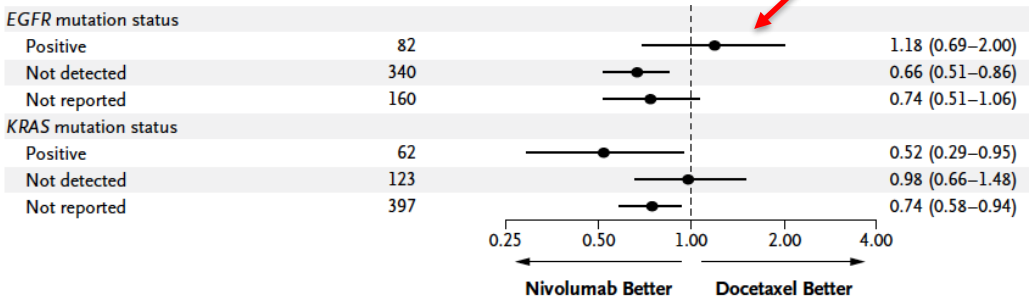
KEYNOTE-010

Pembrolizumab



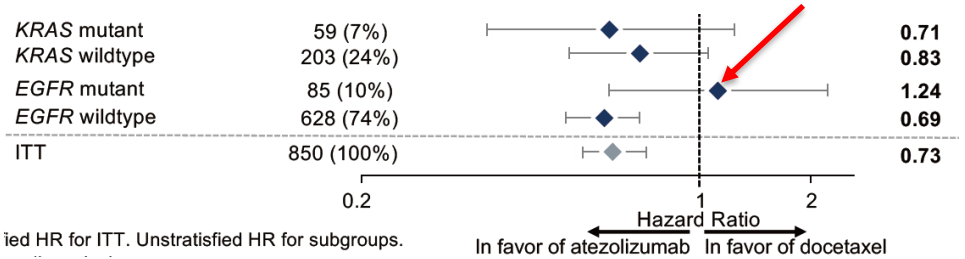
CheckMate 057

Nivolumab



Oak

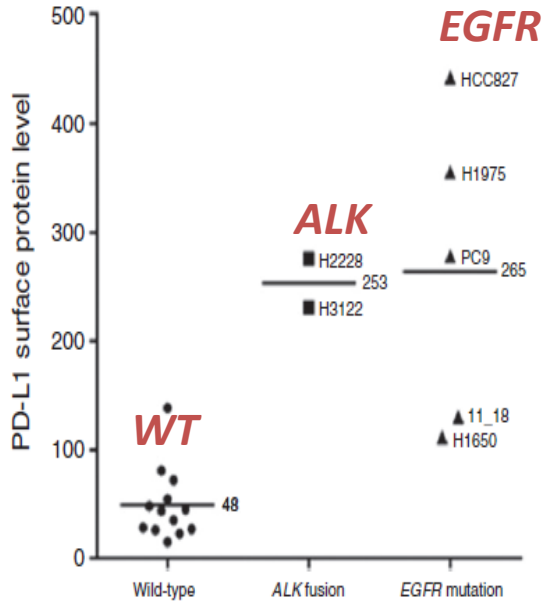
Atezolizumab



ied HR for ITT. Unstratisfied HR for subgroups.

DRIVER +: *PD-L1, IMMUNE TME*

Constitutive PD-L1 expression



Ota et al CCR 2015

Immunotarget, ≥1% PD-L1 expression

Driver	N	PD-L1 + (%)
KRAS	95	66.4%
EGFR	**49**	**63.2%**
BRAF	11	70.0%
MET	20	75.5%
HER2	15	53.3%
ALK	**11**	**63.3%**
RET	8	75.0%
ROS1	5	100%

Maziéres, ASCO 2018

These subgroups have not routinely benefited from immunotherapy

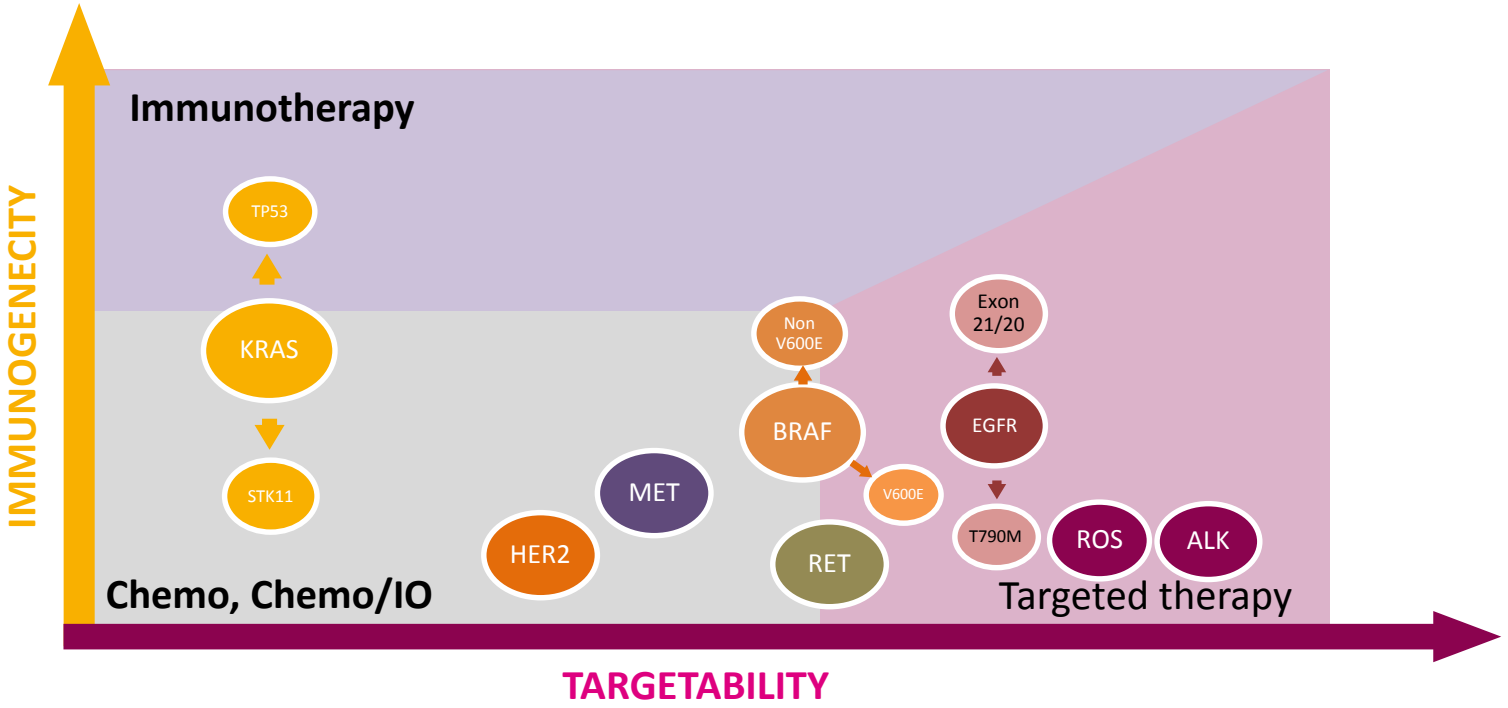
Immunotarget Cohort

Low benefit of immunotherapy in case of molecular alteration...need for specific studies

Driver	n	RR	PFS	OS	Impact (+/X) on PFS of				Comments
					PDL1	Smoking	Nb line	Subtype	
Total		19%	2.8	13.3					Outcome consistent with registration trials for ICI
KRAS	271	26%	3.2	13.5	+	X	X	X	Clear benefit across all subgroups
EGFR	125	12%	2.1	10	+	X	X	X	Could be considered in PDL1 + after TKIs exhaustion
BRAF	43	24%	3.1	13.6	X	+	X	NA	Could be considered in smokers
MET	36	16%	3.4	18.4	NA	X	NA	X	Could be considered after conventionnal treatment
HER2	29	7%	2.5	20.3	NA	+	X	NA	
ALK	23	0	2.5	17	X	X	X	NA	Poor outcome. New biomarker needed.
RET	16	6%	2.1	21.3					
ROS1	7	17%	-	-					

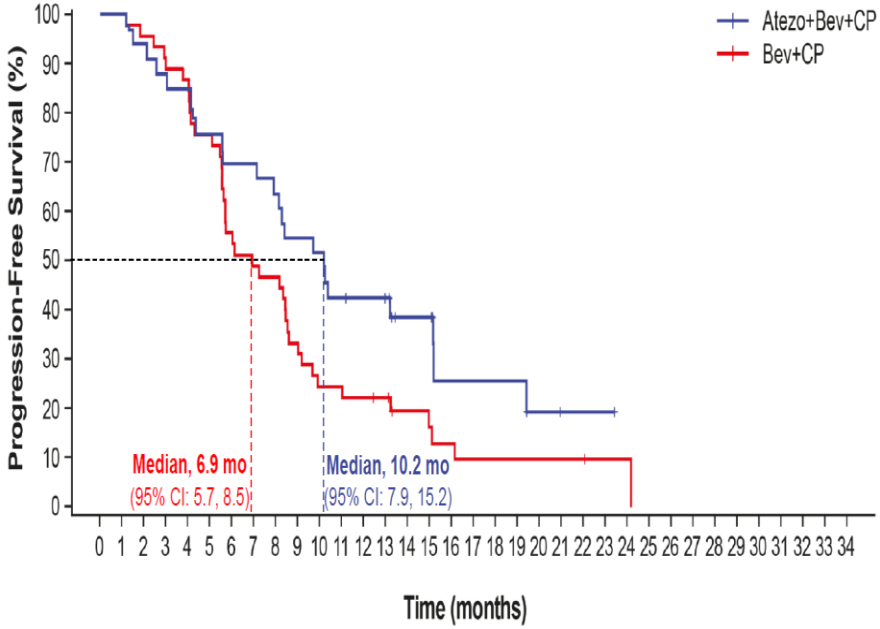
Julien MAZIERES et al, ASCO 18

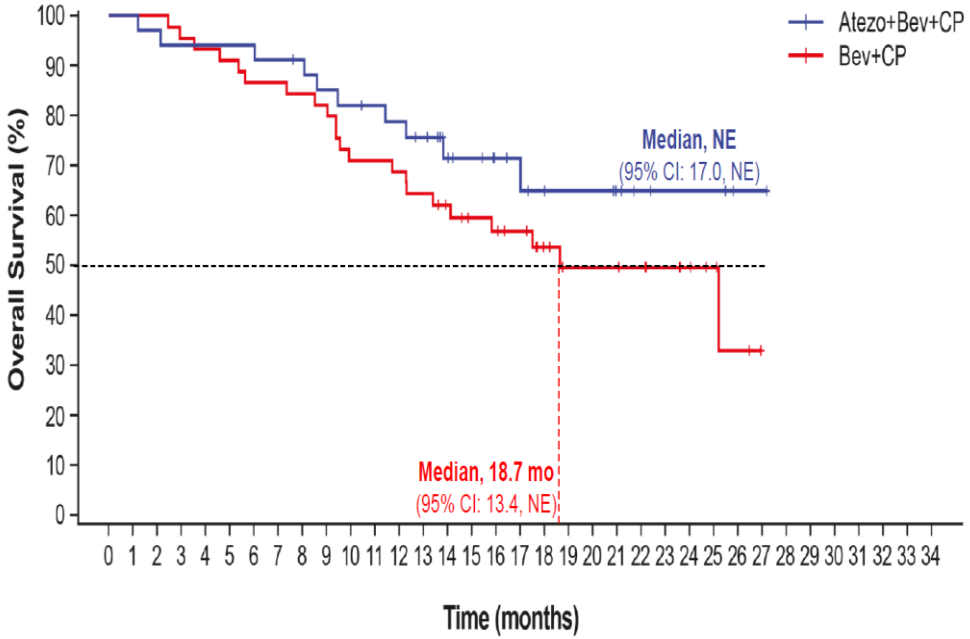
The best place for IO



Courtesy of Prof. Mazières, ELCC 2019

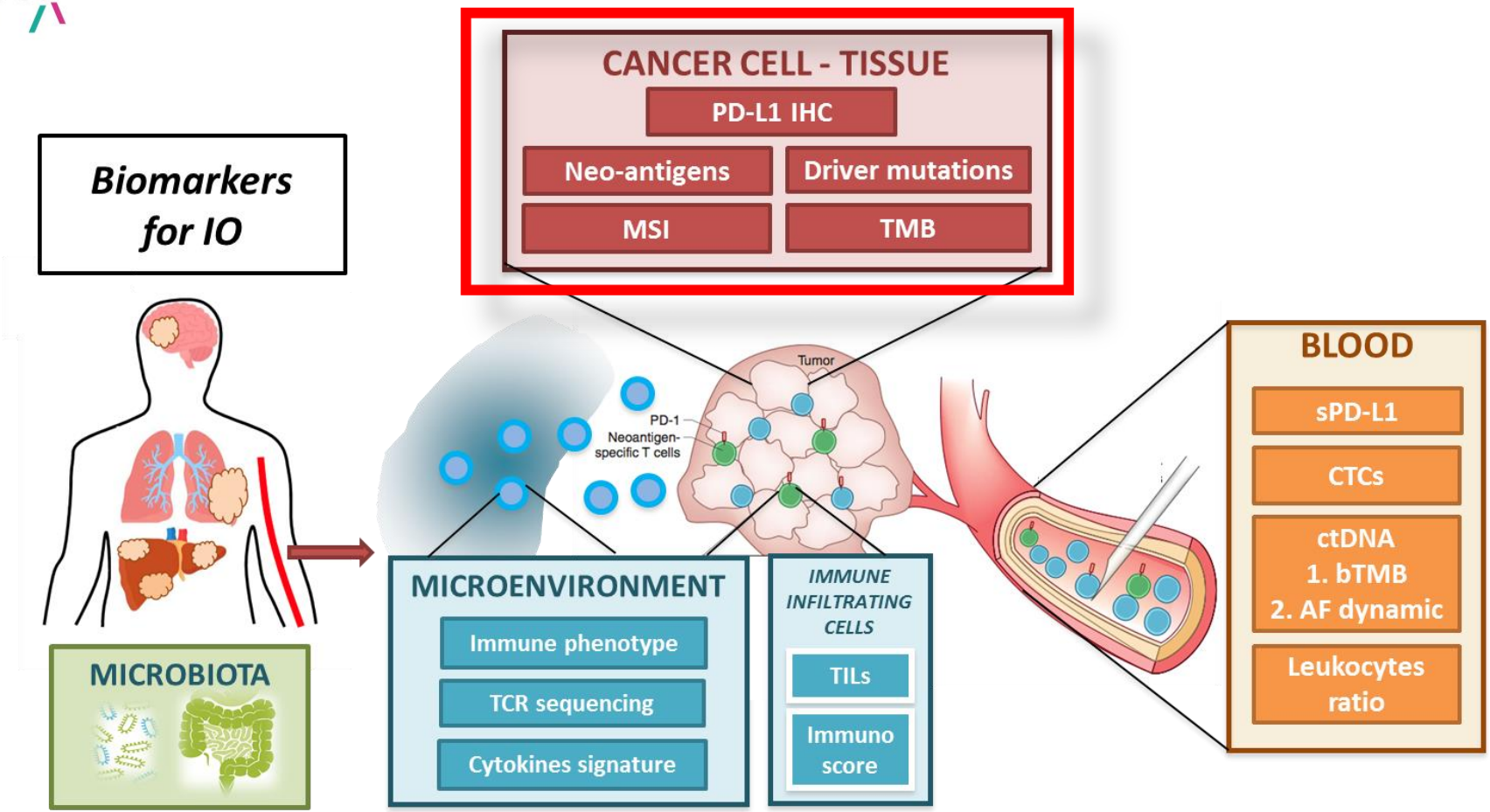
Carbo+Pacli+Atezolizumab, potentiel new option in EGFR-mutant post TKIs (Impower 150)





Reck, M et al; lancet resp 2019

So IO alone or combo…need to take in account many factors

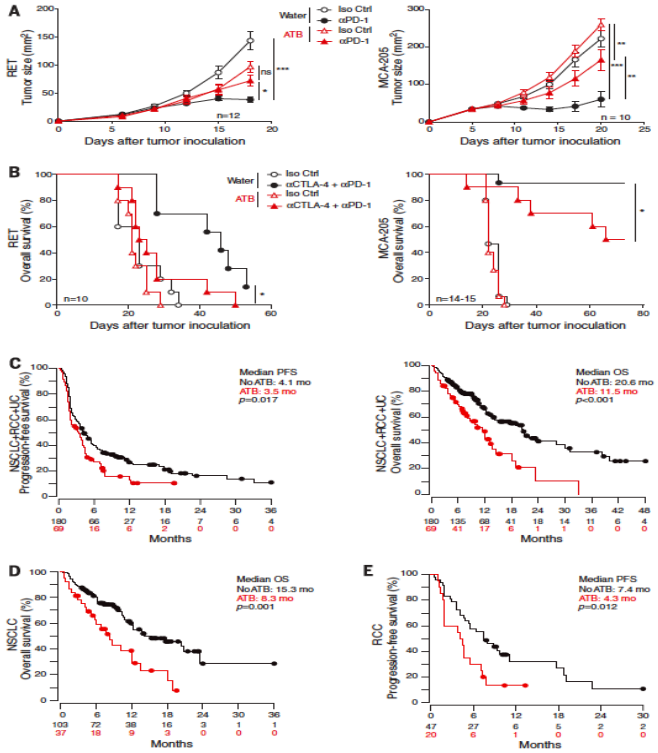


IHC: immunohistochemistry; MSI: microsatellite instability;
TMB: tumor mutational buden; TILS: Tumor Infiltrating Lymphocytes; AF: Allelic Fraction

Adapted from Schumacher T, Nature 2016 and Sacher J Thorac Oncol. 2017

From forgotten to superorganism

Strong evidences that bacteria in the gut may influence responses to cancer immunotherapy



CANCER IMMUNOTHERAPY

91 Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors
B. Routy et al.

97 Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients
V. Gopalakrishnan et al.

104 The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients
V. Matson et al.

► PERSPECTIVE P. 32

Science Volume 359(6371):91-97-104-32 January 5, 2018

Precision medicine using microbiota

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

1.Cancer Screening

Microbiota specific medical history:
- Weight, Diet, Smoking
- ATB 30 days before
- PPI, Metformin
- Apendectomy

Diagnostic kit:
Cancer signature

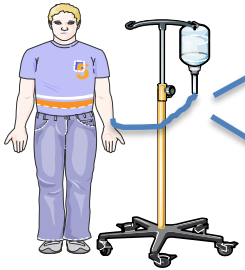
No

Continue healthy microbiota lifestyle

Yes

Perform adequate testing:
CT scan
Mammography
PSA, CEA, LDH

2. Cancer Diagnosis

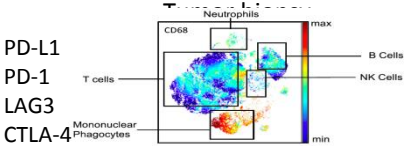


Diagnostic Kit

3. Investigations

Immune atlas on

PD-L1
PD-1
LAG3
CTLA-4
TIM-3



Favorable feces

Unfavorable feces

Immune adverse effect feces

4. Immunotherapy + oncomicrobiotherapy

Selection of ICB monotherapy vs combination

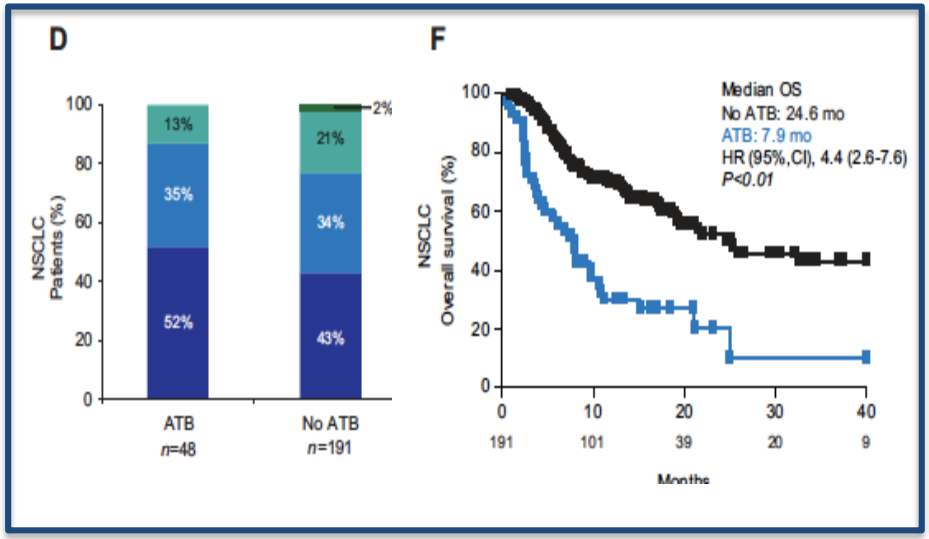
Proceed to immunotherapy alone

IO combo

- Specific antibiotics
- Diet
- Fecal transplant from healthy volunteer vs patients in complete response
- Oncomicrobiotics: Consortium of bacteria
- Metabolites

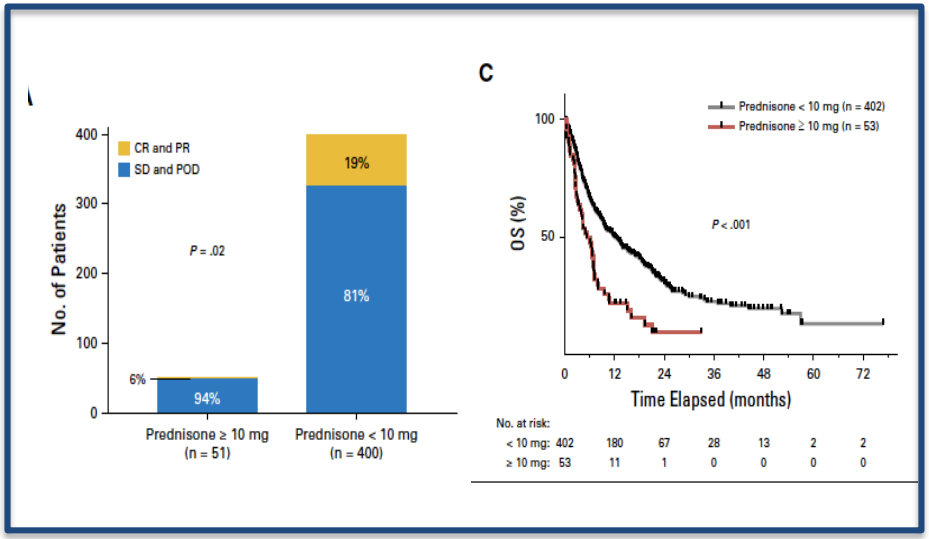
Concomitant medications at baseline to IO

Antibiotics



Derosa, Annals of Oncol 2018

Steroids



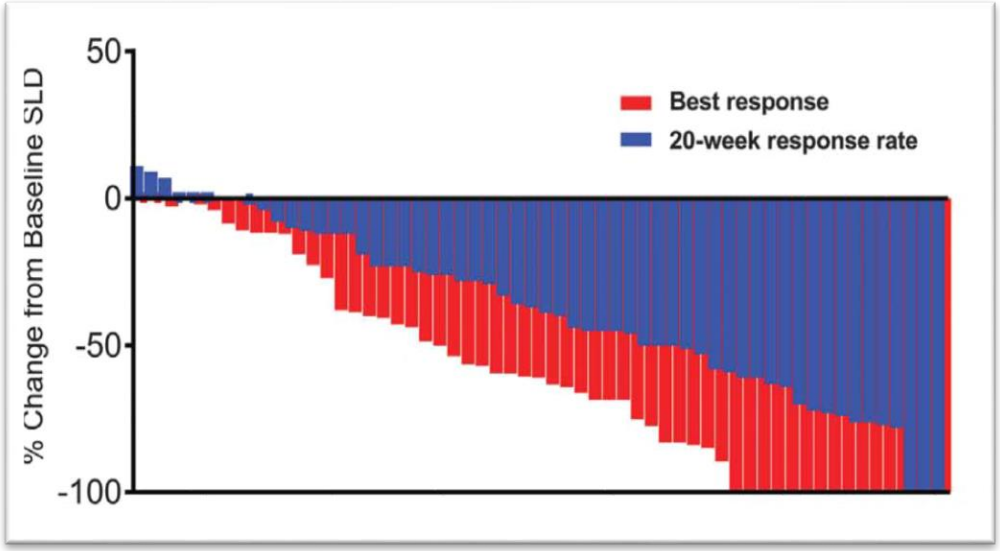
Arbour & Mezquita, J Clin Oncol 2018

Retrospective cohorts & probably comorbidities associated

Mismatch repair deficiency

Science

Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade



- **N=86 MMRD patients**
- 12 different solid tumors (no lung)
- **Pembrolizumab ≥ 2nd line**
  - ✓ ORR 53% (21% CR)
- **Median OS NR**
  - ✓ 1y-OS 76%; 2y-OS 64%

U.S. Department of Health and Human Services
FDA U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

23 May 2017

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

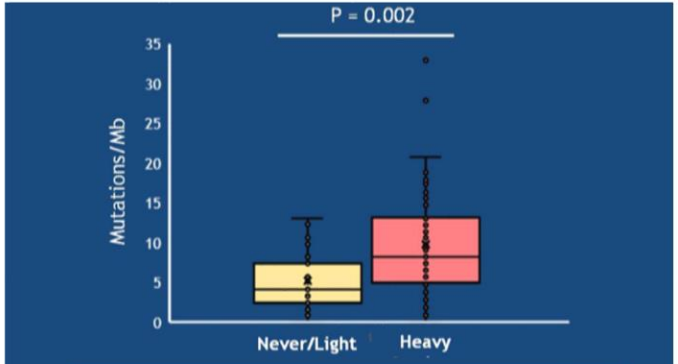
Listen to the FDA D.I.S.C.O. podcast about this approval (/Drugs/InformationOnDrugs/ApprovedDrugs/ucm558268.htm)

On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This is the FDA's first tissue/site-agnostic approval.

Le et al Science 2017

4 US centers, n=78 *(23 non-smokers)*



Tumor Mutation Burden (Mut/Mb)	Never/Light Smokers* N=23	Heavy Smokers N=55	P value
Median	4.1	8.2	0.002
Range	0-12.3	0-33	

N=1)

*Median TMB was similar (4.1) between never and light smokers.

Gainor ASCO 2018

PD-L1 IHC
Is still the king

- **Growing evidence that TMB is predictive of immunotherapy efficacy in NSCLC**
- **Relevant challenges:**
  - methodology standardization
  - Definition of high/low TMB
  - Turn-around time
  - Clinical validation
  - Reimbursement/cost

-Several new biomarkers under development: mircobiom, genomic markers, epigenetic markers

-still a lot of work to be done

Biomarker selection for 1st line

TMB high

PD-L1 high

Pembrolizumab
Nivolumab+Ipilimumab
Durvalumab+Tremelimumab

PD-L1 Low

Nivolumab+Ipilimumab
Durvalumab+Tremelimumab

TMB Low

PD-L1 high

Pembrolizumab
Chemotherapy

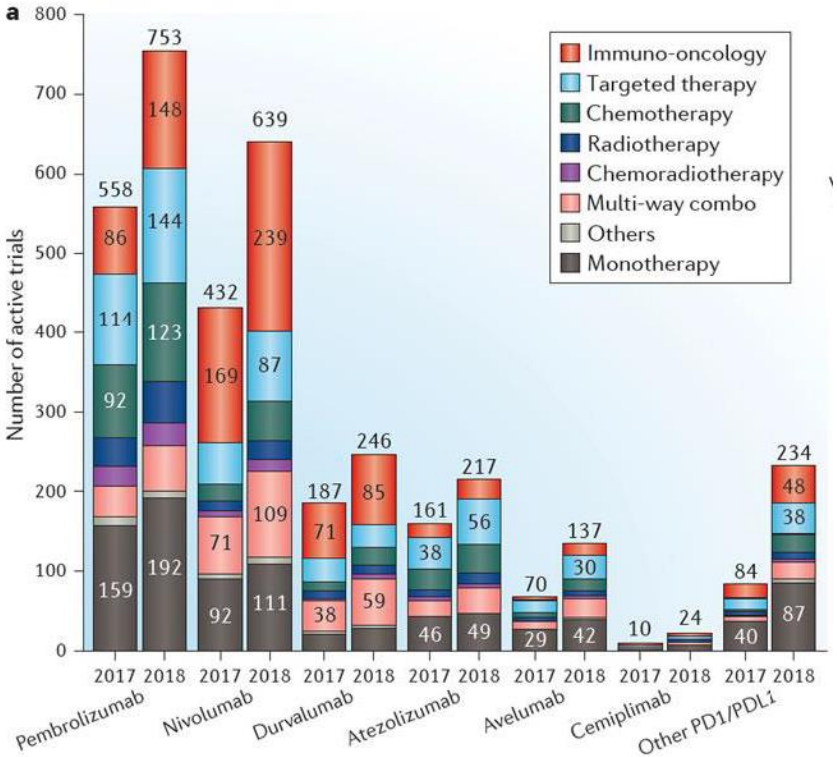
PD-L1 Low

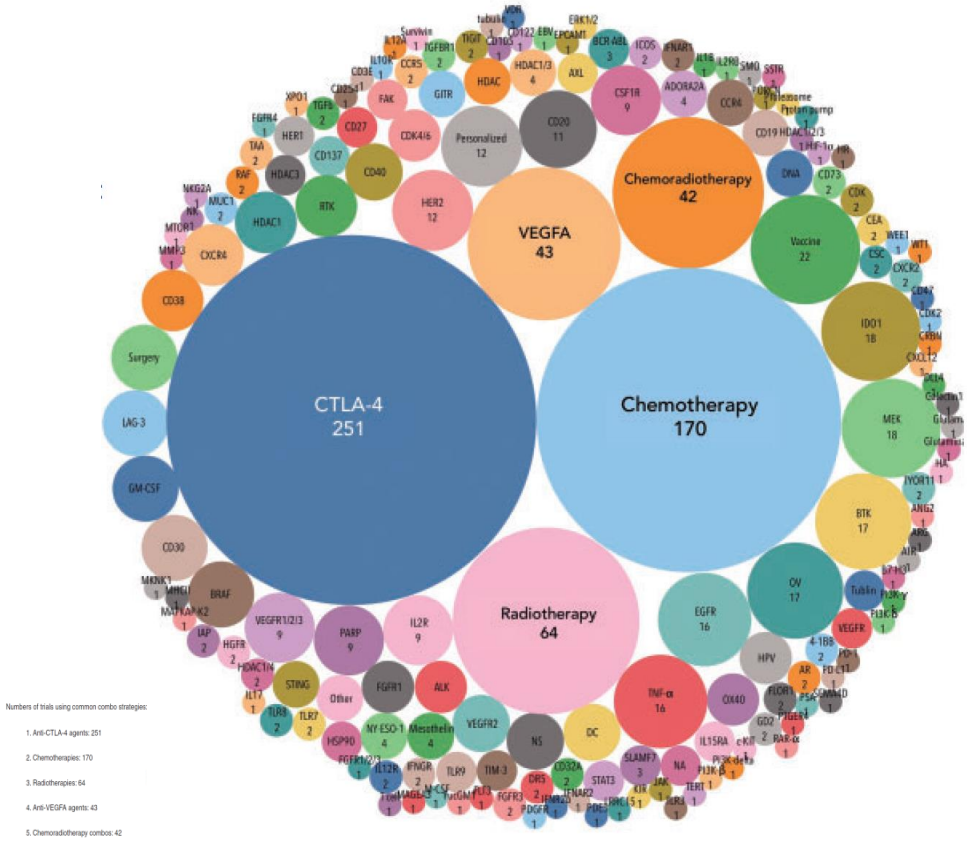
Chemotherapy

IO+chemotherapy

Need TMB data

IO combo tomorrow…
we need bioM !!!





J. Tang, A. Shalabi V. M. Hubbard-Lucey , annams of onco 2018

THANK YOU !

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