Predictive Markers for Response to Immunotherapy in NSCLC

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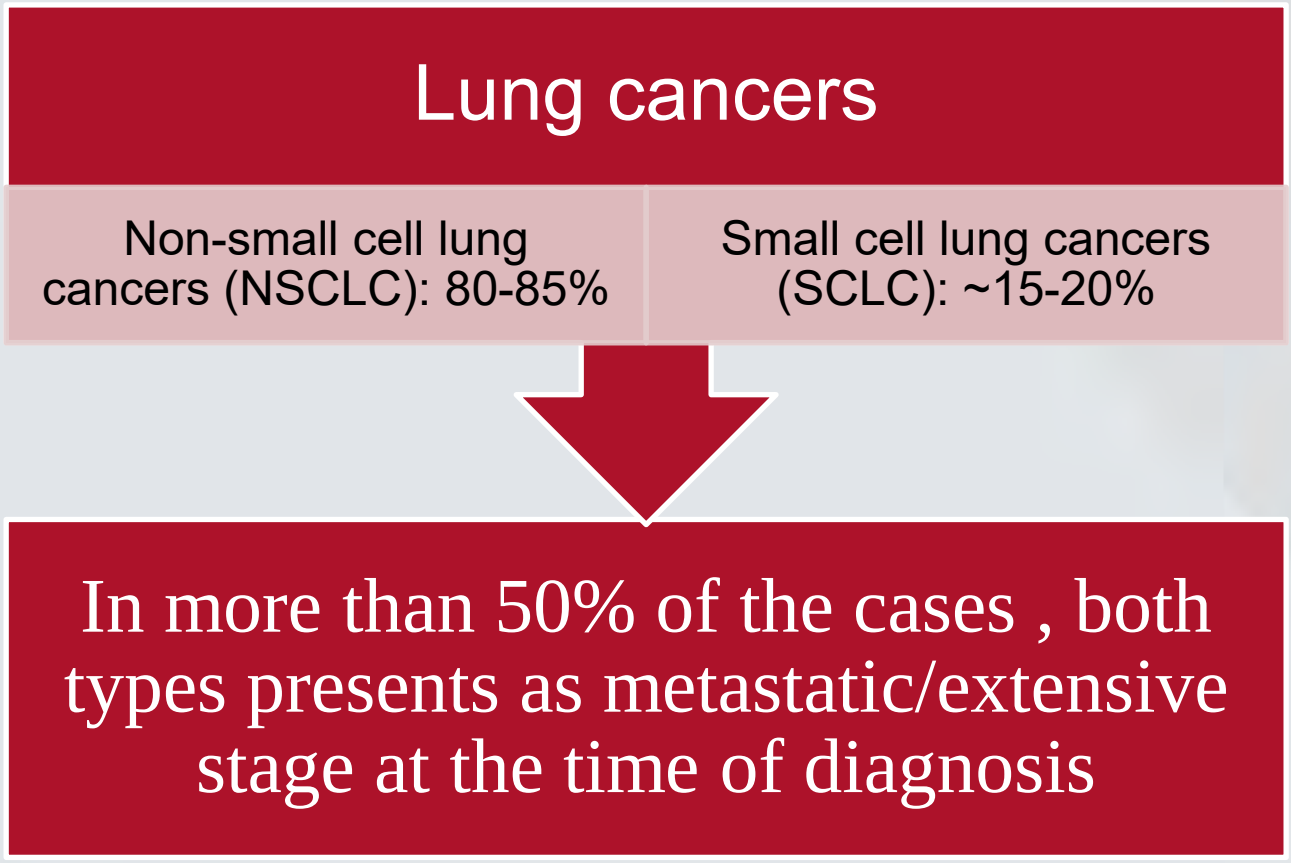
Types of Lung Cancer



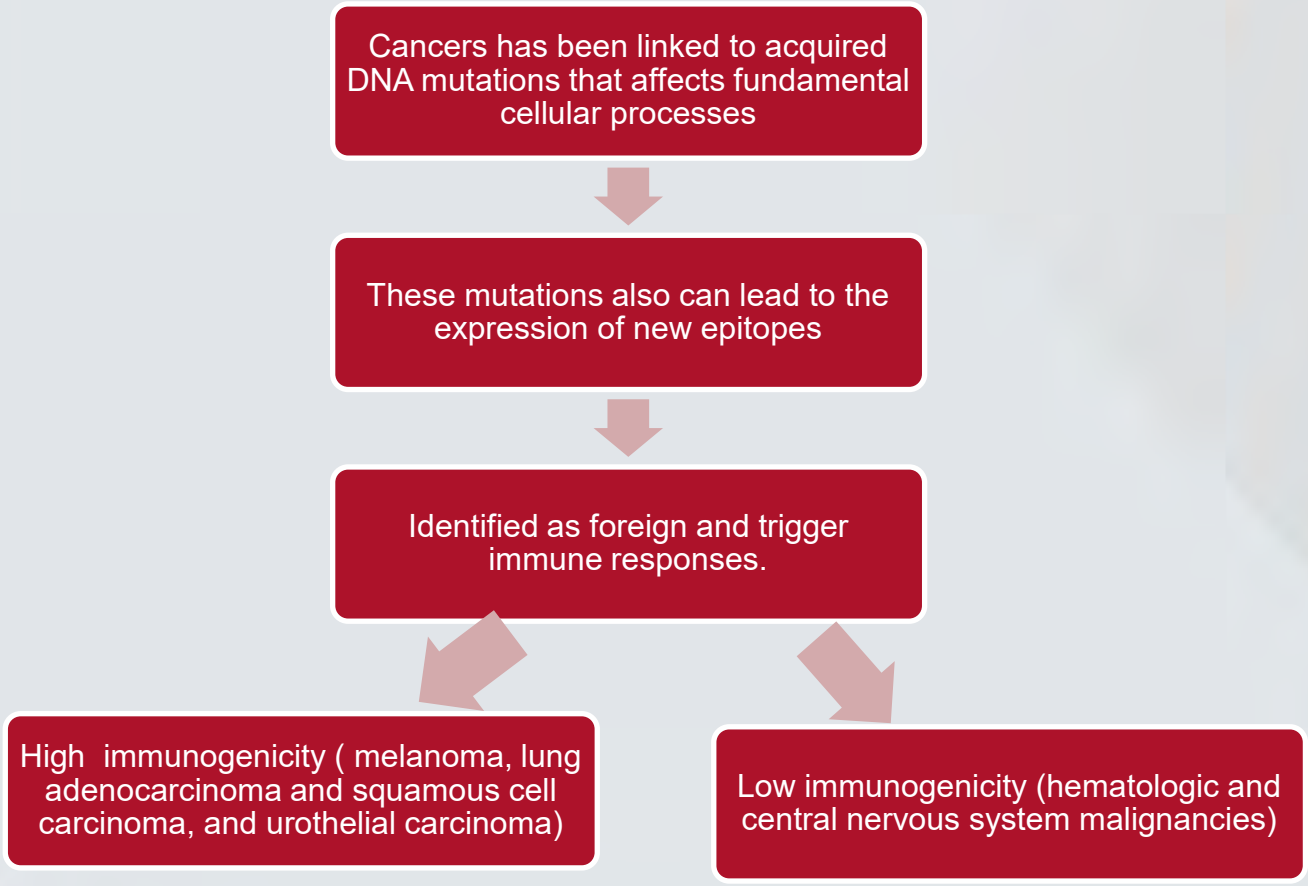
Seminars in oncology, S0093-7754(22)00024-0.

Treatment options

- NSCLC: Chemotherapy , immunotherapy, targeted therapy
- Small cell lung cancer: Chemotherapy (+/- immunotherapy)

NCCN guidelines 2022

Basics of immunotherapy



DeVita H, et al. Cancer Principles & Practice of Oncology 11th edition. Chapter 17

Tumor infiltrating lymphocytes (TILs)

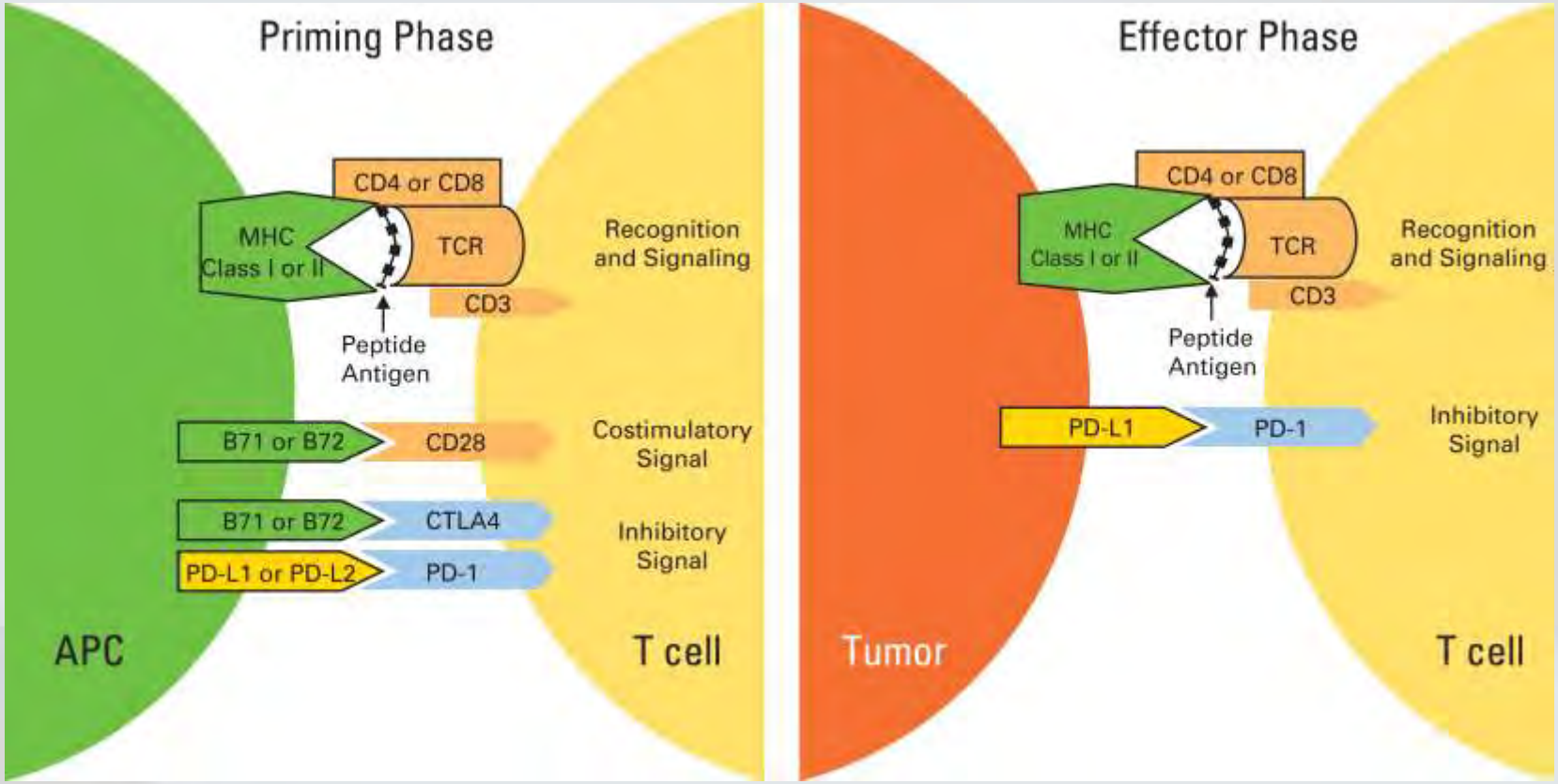


Image from ASCO- SEP 2022- Chapter 4 – Figure 4-2

Immune checkpoint inhibitors (ICIs)

Anti-PD1

- Pembrolizumab
  first approval 2014
- Nivolumab
  First approval 2014
- Cemiplimab
  First approval 2018

Anti-PD-L1

- Atezolizumab
  First approval 2016
- Avelumab
  First approval 2017
- Durvalumab
  First approval 2017

Anti-CTLA4

- Ipilimumab
  - First approval 2011

ICIs in lung cancer

- ICIs **can** elicit durable antitumor responses in NSCLC

- However, only a few patients benefit from a durable response to ICIs, and nearly 50% of them develop early progression

Blons H, et al. J Thorac Dis. 2019 Jan;11(Suppl 1):S25-S36.

Miura, et al. *Cancers* vol. 10,8 245. 27 Jul. 2018,

Predictors to response

1-Biomarkers

2-Oncogenic mutations

3-Environmental factors

PD-L1

- Cluster of differentiation 274 (CD274)
- Testing:
  - **Immunohistochemistry assays:**
    PD-L1 IHC 22C3 and PD-L1 IHC 28-8 are approved by FDA
- **Combined positive score (CPS):**

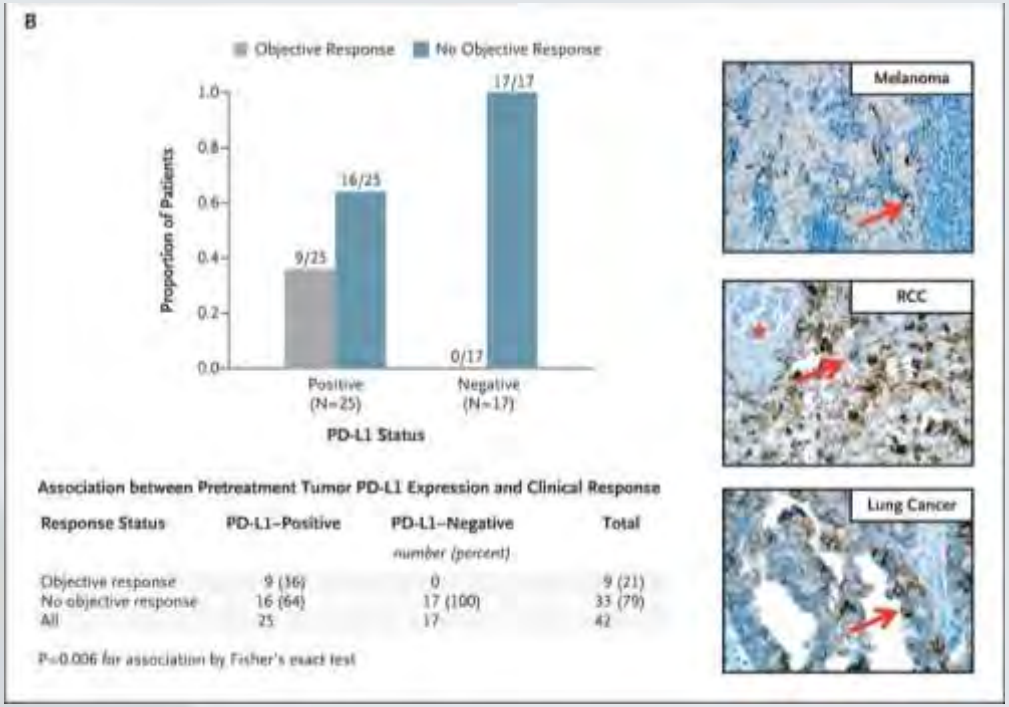
$$CPS = \left(\frac{PD\text{-}L1\ Staining\ Cells\ [TC.\ \ lymphocytes\ and\ macrophages]}{Total\ Number\ of\ Viable\ TC}\right) \times 100$$

- **Tumor proportion score (TPS)**

$$TPS = \left(\frac{PD\text{-}L1\ Staining\ TC}{Total\ Number\ of\ Viable\ TC}\right) \times 100$$

PD-L1 and Nivolumab

- Phase I, Evaluated nivolumab in different cancers.
- They used PD-L1 of 5% as a cutoff value between PD-L1 positive and negative tumors



Association between Pretreatment Tumor PD-L1 Expression and Clinical Response

Response Status	PD-L1–Positive	PD-L1–Negative	Total
		number (percent)	
Objective response	9 (36)	0	9 (21)
No objective response	16 (64)	17 (100)	33 (79)
All	25	17	42

P=0.006 for association by Fisher's exact test

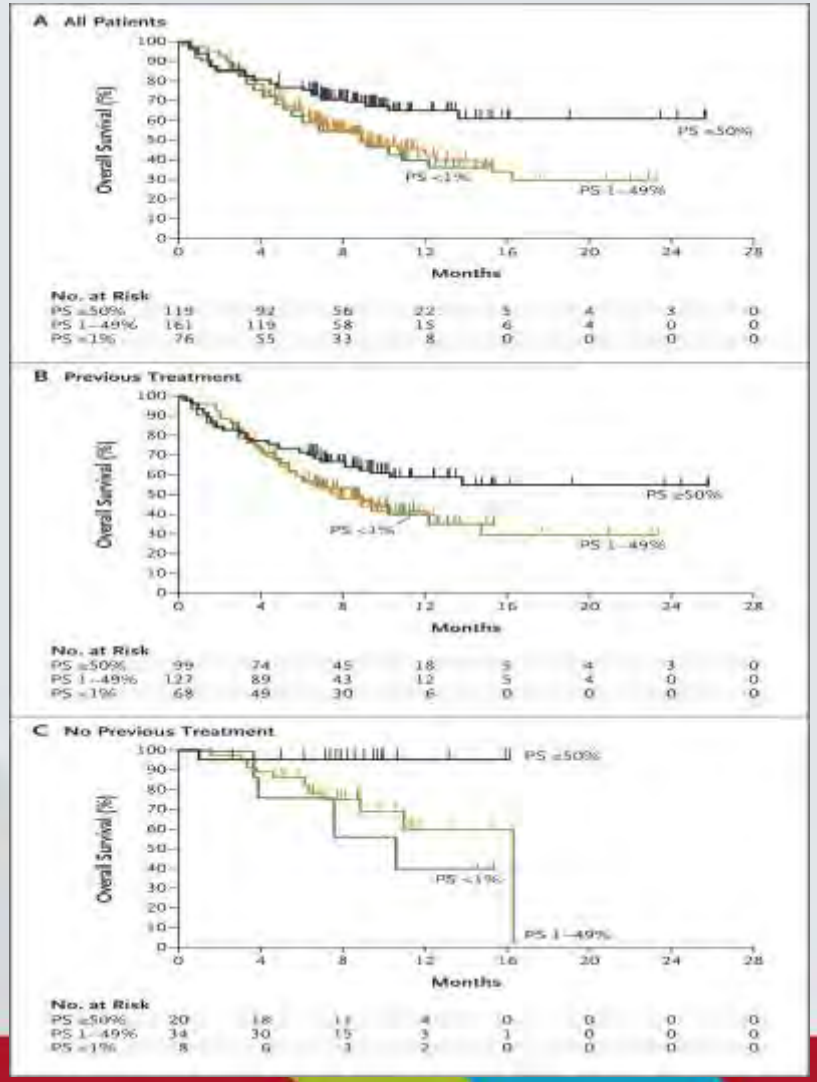
Nivolumab produced OR in ~ 1 in 4-5 patients with NSCLC, melanoma or RCC.

Preliminary data suggest a relationship between PD-L1 expression on tumor cells and OR

N Engl J Med 2012; 366:2443-2454

KEYNOTE-001

- Phase I, evaluated safety and efficacy of pembrolizumab in advanced NSCLC (untreated and previously treated).



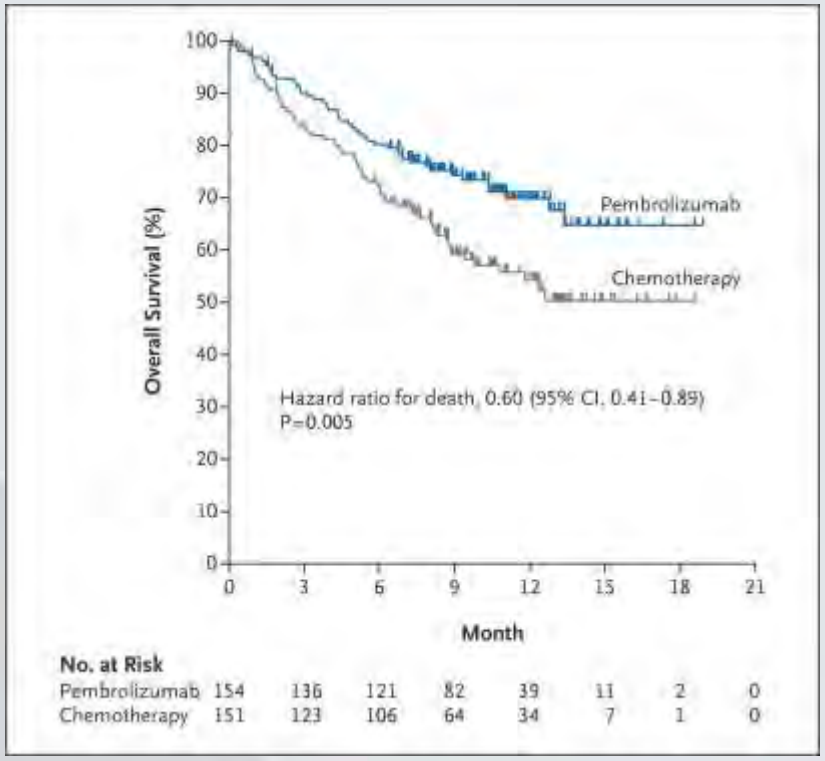
Pembrolizumab showed antitumor activity in patients with advanced non–small-cell lung cancer.

PD-L1 expression in at least 50% of tumor cells correlated with improved efficacy of pembrolizumab

N Engl J Med 2015; 372:2018-2028

KEYNOTE-024

- Phase III, untreated advanced NSCLC → Pembro vs platinum based chemotherapy <u>in patients with PD-L1 50% or more , no sensitizing EGFR or ALK mutations</u>



In patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab was associated with significantly longer PFS + OS , and with fewer adverse events than was platinum-based chemotherapy

N Engl J Med 2016; 375:1823-1833

CheckMate 057

- Phase III→ Nivolumab vs Docetaxel as 2nd line in advanced Nonsquamous NSCLC regardless of PD-L1 expression

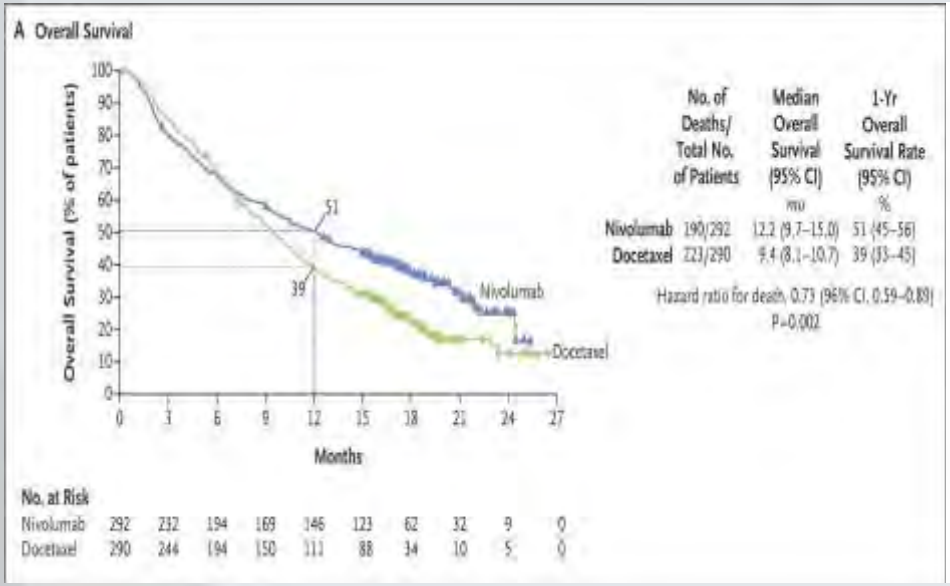


Table S6. Predictive Relationship of PD-L1 Expression Level for Efficacy of Nivolumab.

Efficacy endpoint	PD-L1 Expression Level[a] 1%	5%	10%
Overall survival[b]			
Treatment by PD-L1 expression interaction P-value	0.06	<0.001	<0.001
Progression-free survival[b]			
Treatment by PD-L1expression interaction P-value	0.02	<0.001	<0.001
Objective response rate[c,d]			
Treatment by PD-L1 expression interaction P-value	0.002	0.002	0.002

N Engl J Med 2015; 373:1627-1639

CheckMate 057

Nivolumab had better OS as 2nd line in advanced nonsquamous NSCLC in PD-L1 positive tumor

OS benefit was observed in all PD-L1 expressing groups. However there was a trend toward a greater response rate as the PD-L1 expression level increased.

In PD-L1 negative OS was similar between nivolumab and docetaxel but toxicity profile favoring nivolumab

N Engl J Med 2015; 373:1627-1639

CheckMate 017

- Phase III→ nivolumab vs docetaxel in previously treated SCC

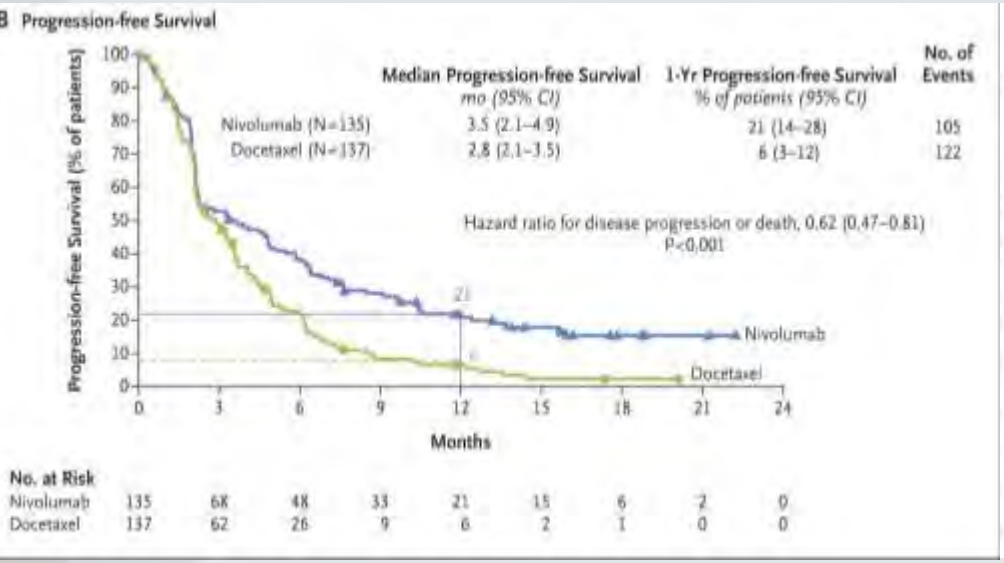


Table S6. Predictive Relationship of PD-L1 Expression Level for Efficacy of Nivolumab.

Efficacy endpoint	PD-L1 expression level* 1%	5%	10%
Overall survival[b]			
Treatment by PD-L1 expression interaction P-value	0.5556	0.4747	0.4092
Progression-free survival[b]			
Treatment by PD-L1 expression interaction P-value	0.6982	0.1591	0.3473
Objective response rate[c,d]			
Treatment by PD-L1 expression interaction P-value	0.0364	0.2908	0.6411

N Engl J Med 2015; 373:123-135

CheckMate 017

OS was better in nivolumab arm regardless of PD-L1 expression.

Across the prespecified expression levels (1%, 5%, and 10%), PD-L1 expression was neither prognostic nor predictive of any of the efficacy end points

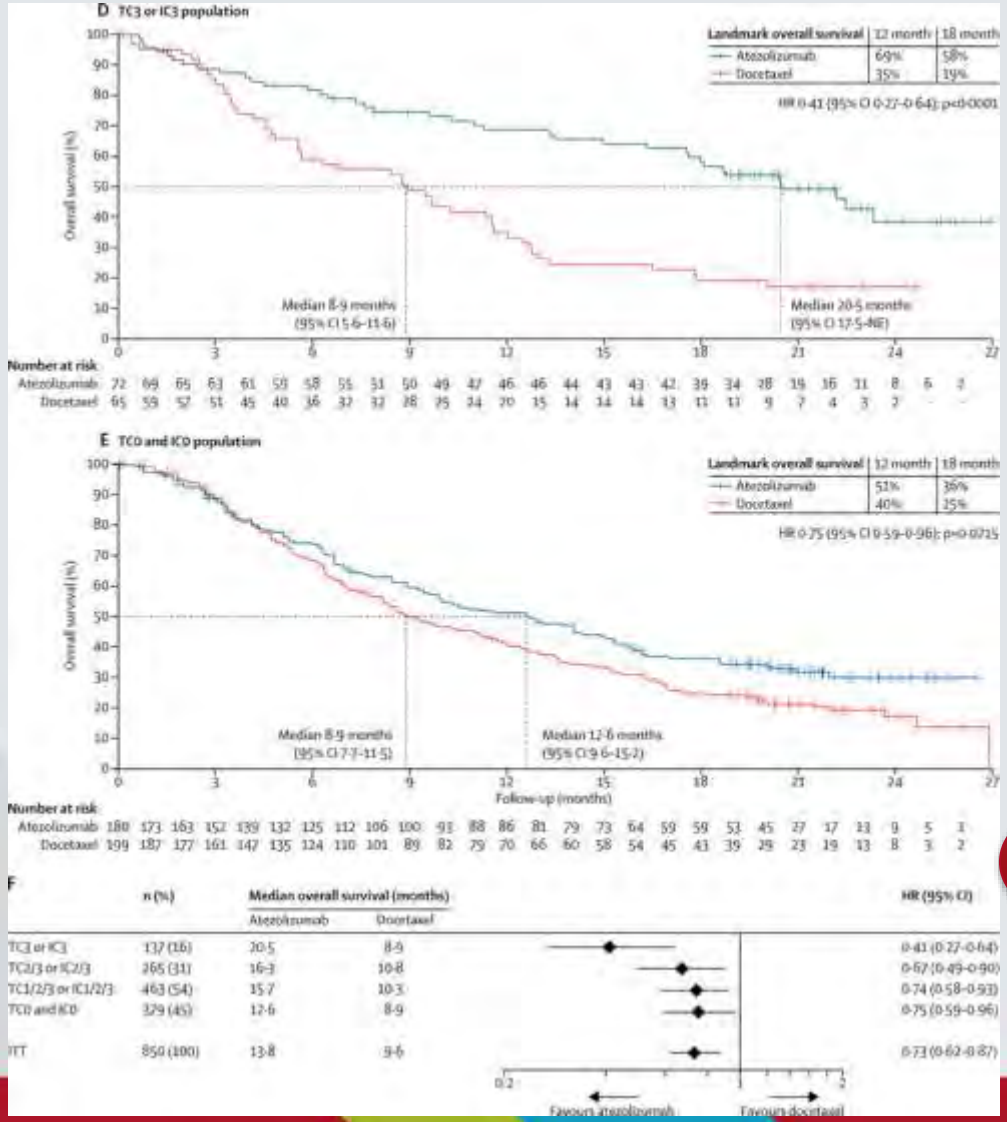
Limitations:

- PD-L1 expression was assessed in archival tumor tissue (Not time of treatment)
- Only 83% of the patients had quantifiable sample

N Engl J Med 2015; 373:123-135

OAK trial

Phase III → atezolizumab vs docetaxel in previously treated NSCLC



OS benefit favoring atezolizumab regardless of PD-L1 expression.

Lancet. 2017 Jan 21; 389(10066): 255–265.

Why these different results?

- Heterogeneous intra-tumor distribution of PD-L1/ Dynamic changes in PD-L1
- PD-L1 expression can be discordant between primary tumors and metastases
- Differential methods of PD-L1 detection, and cut-off values of PD-L1-positive tumor cells

Cancer letters vol. 414 (2018): 166-173.

PD-L1 , Conclusion

- It is a good marker but not great!
- It is the main marker recommended by NCCN panel members to determine eligibility for immunotherapy in NSCLC.

Tumor mutational burden (TMB)

- It is the number of non-synonymous somatic point mutations based on exome sequencing.
- Measured by WES , or NGS
- It is expressed as a number of mutations per mega base (Mb).

TMB and immunogenicity

High-TMB (H-TMB) tumors have more mutations

↓

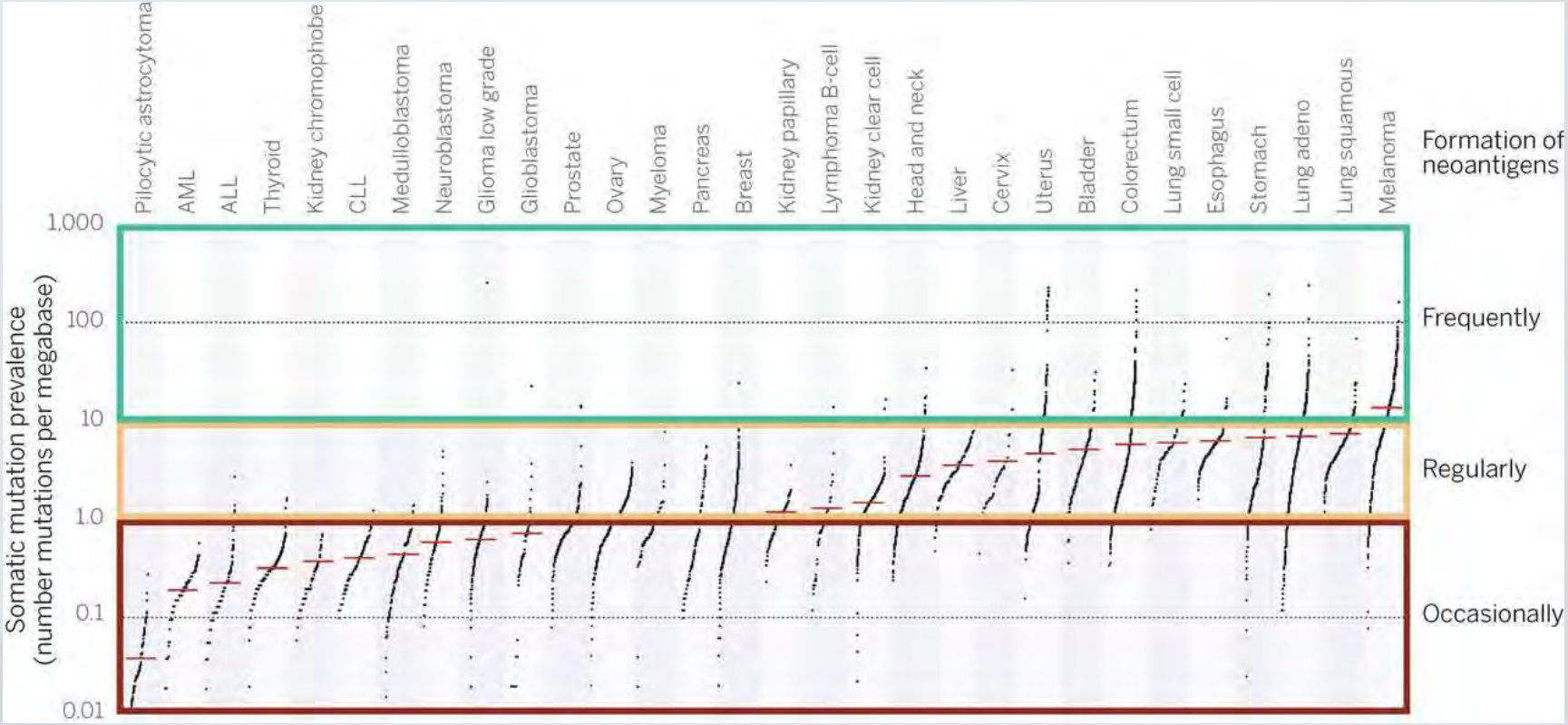
Expected to have more neoantigens

↓

Better chance to induce immunogenicity)

Oncotarget. 2015 Oct 27;6(33):34221-

TMB value

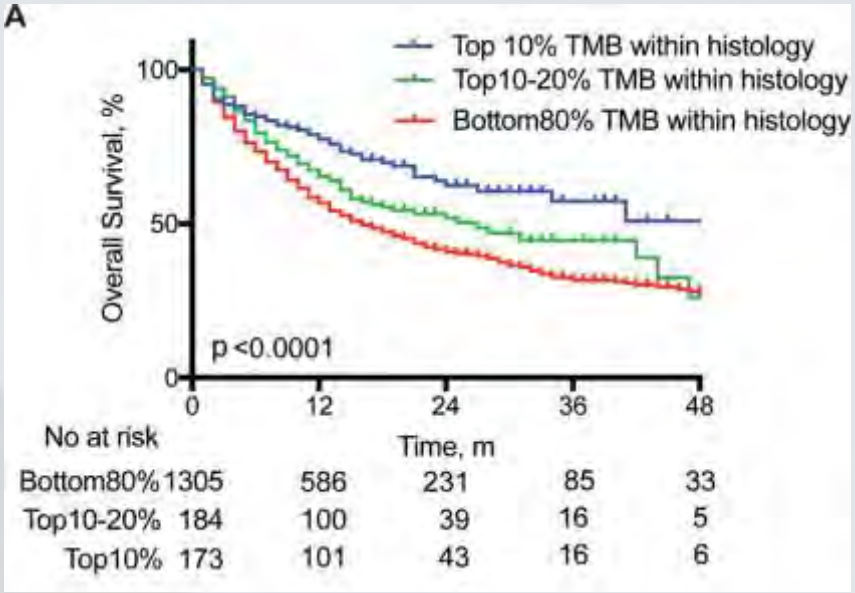


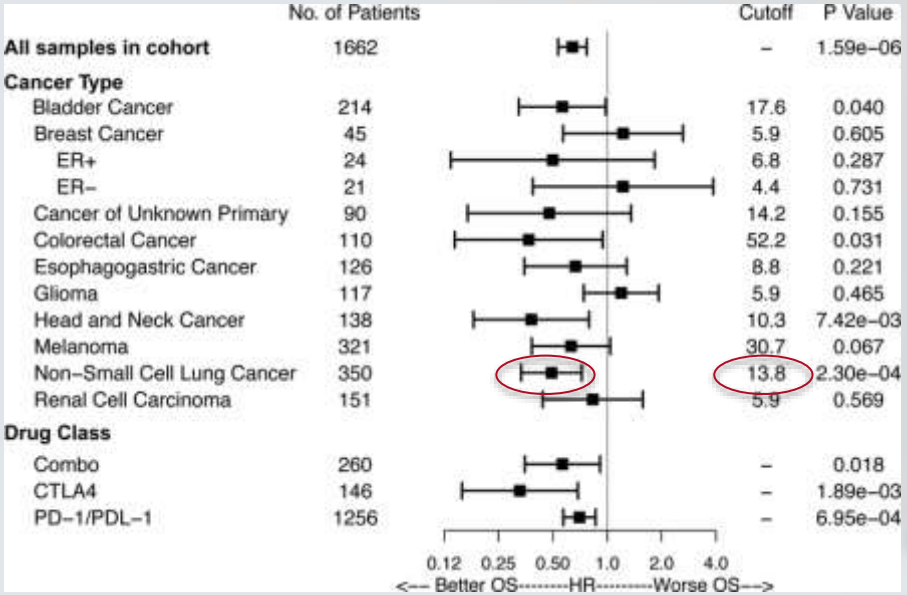
A TMB score of ≥ 10 mut/Mb has been proposed as a threshold with a high likelihood of neoantigen formation, and therefore defining TMB-H status

Nature. 2013 Aug 22;500(7463):415-21

TMB and ICI response

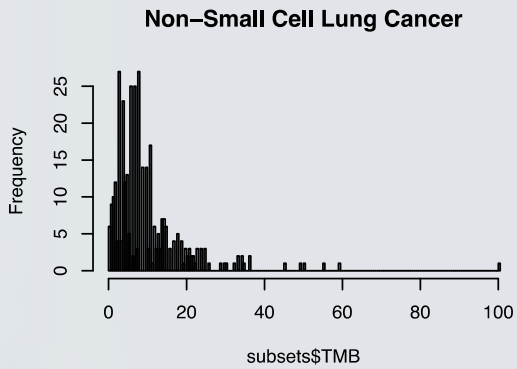
- A reterospective study at MSKCC looked at patients with different types of cancers who received at least one dose of ICIs.

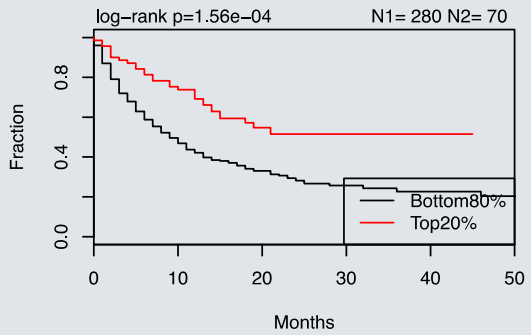




Nat Genet. 2019 Feb;51(2):202-206.

Retrospective data from MSKCC





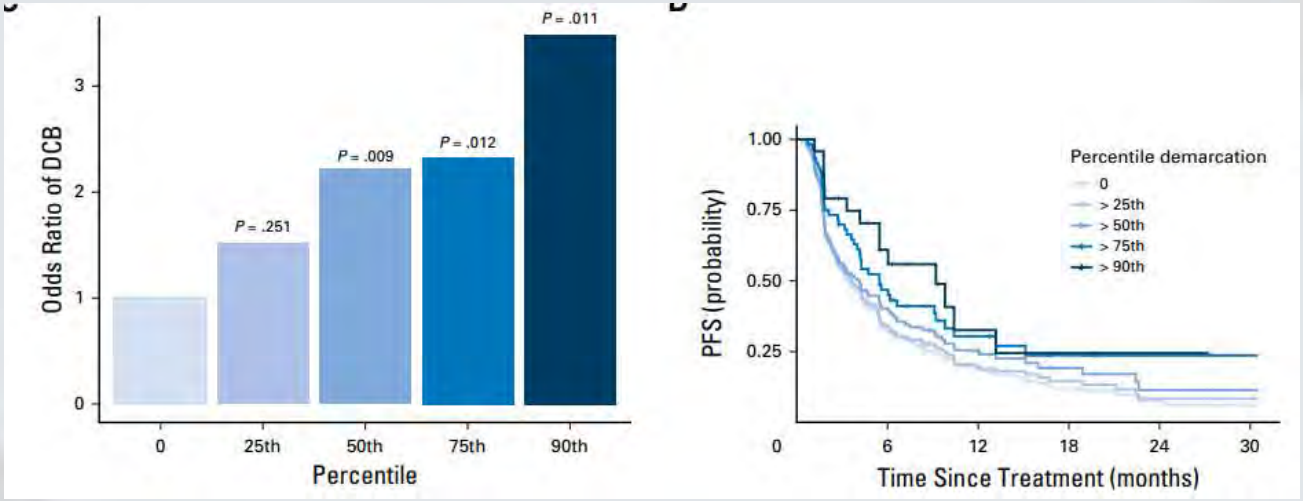
For most cancer histologies→ higher TMB = improved survival

The TMB cutpoints associated with improved survival varied markedly between cancer types.

Nat Genet. 2019 Feb;51(2):202-206.

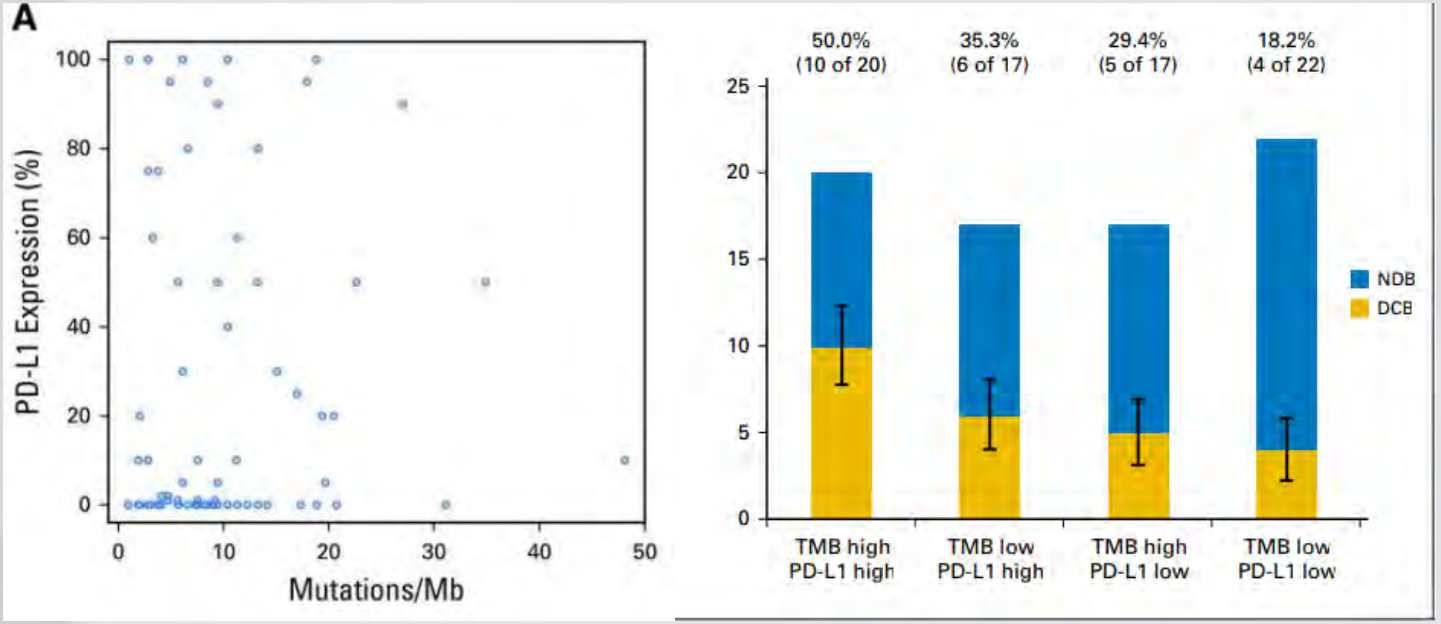
TMB and lung cancer

- Another MSKCC retrospective study evaluated TMB utilization in lung cancer
  - Look at TMB impact on durable clinical benefit (DCB) , defined as PR/SD for at least 6 months
  - Dose TMB correlates with PD-L1?



J Clin Oncol. 2018 Mar 1;36(7):633-641

TMB relation to PD-L1 in lung cancer



-TMB did not correlate with PD-L1 expression.

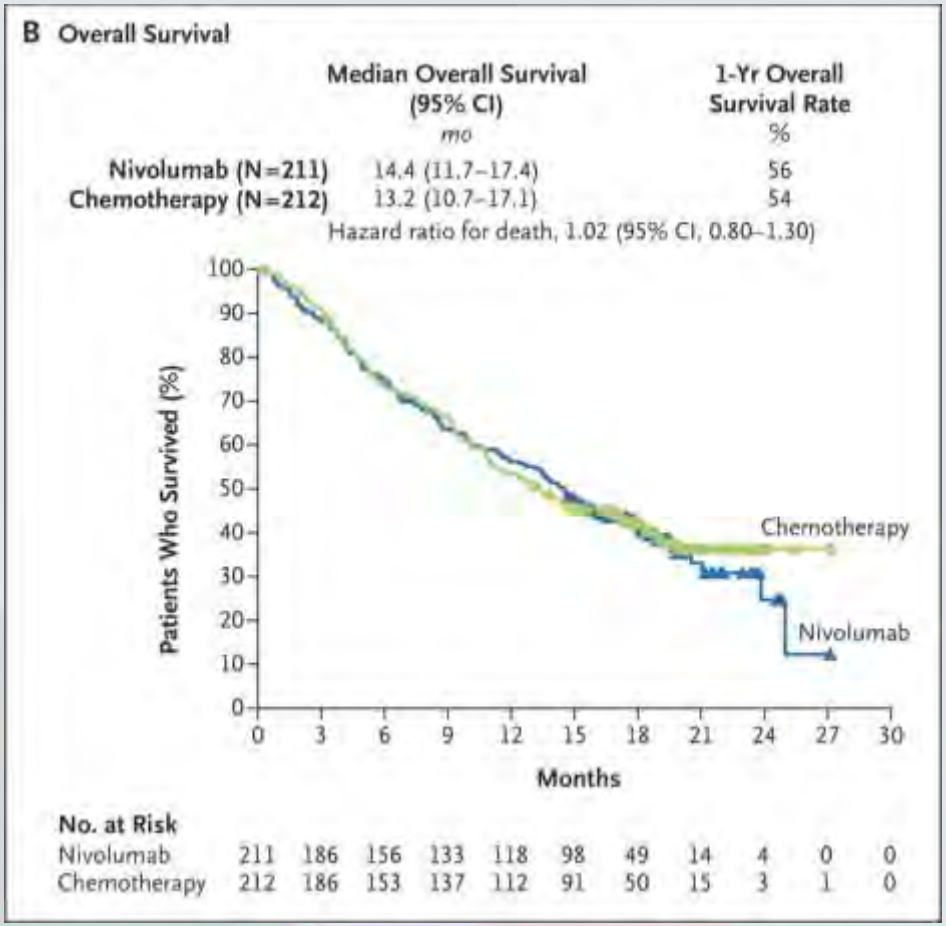
-Both variables had similar predictive capacity.

-The incorporation of both TMB and PD-L1 expression into multivariable predictive models should result in greater predictive power.

J Clin Oncol. 2018 Mar 1;36(7):633-641

CheckMate 026

- Phase III → Nivolumab vs platinum based chemotherapy as first-line in NSCLC with a PD-L1 expression level 1% or more (5% or more was primary efficacy analysis population).

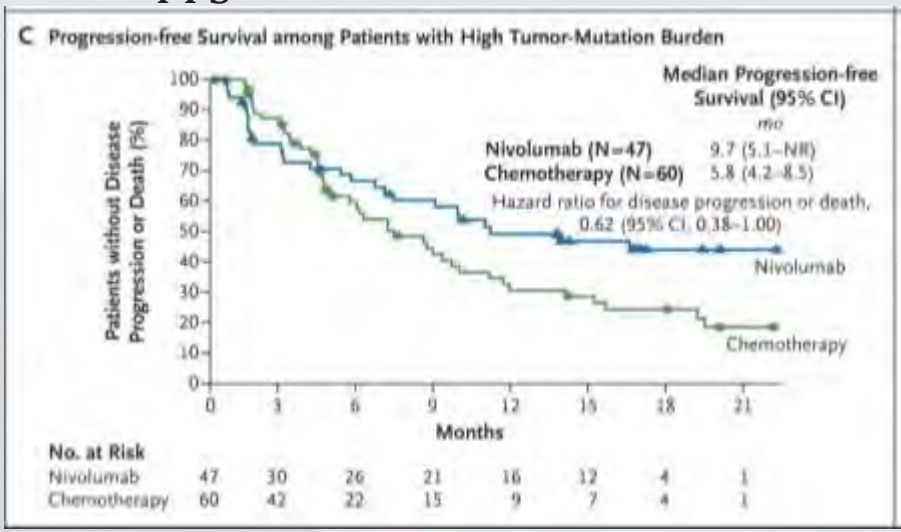


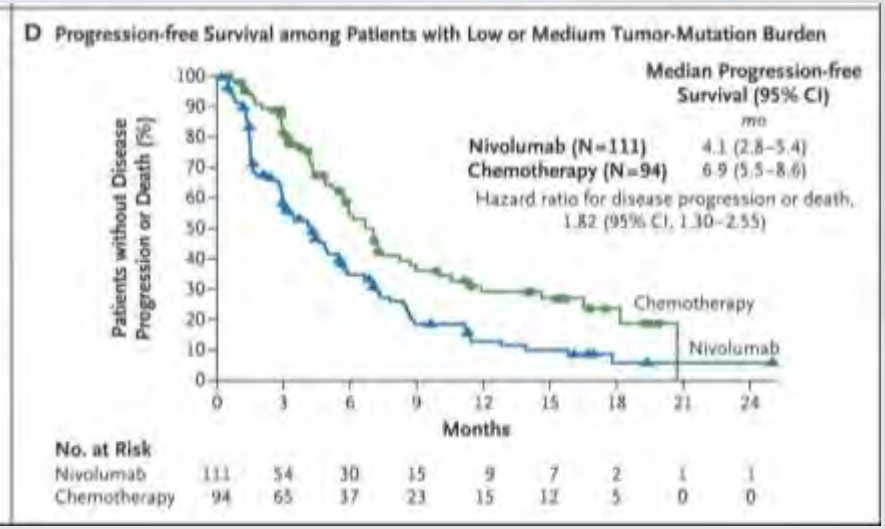
Similar OS and PFS in the study population. Better safety with IO

N Engl J Med 2017; 376:2415-2426

CheckMate 026

- In subgroup analysis PFS was longer in high TMB group (>243 mutations per exome or 8 mutations/Mb)
- OS did not differ → was attributed to treatment crossover.
- No overlap was found between PD-L1 expression and TMB
- However patients with both PD-L1 >50% and TML high experienced longer PFS



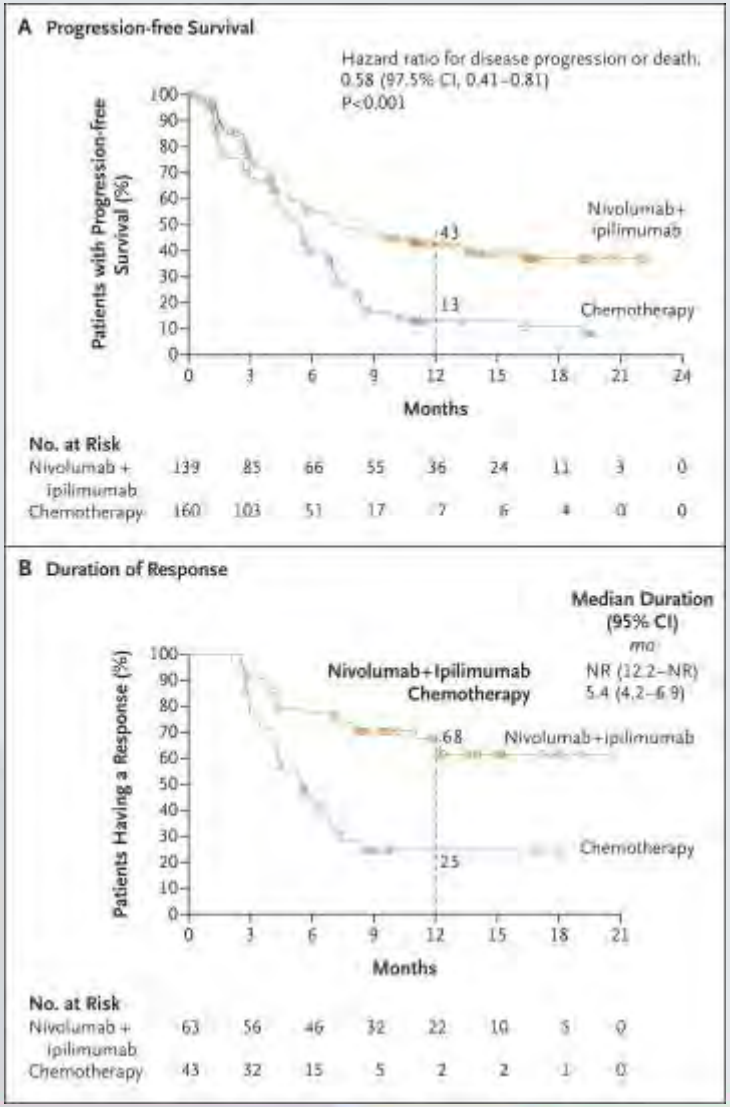


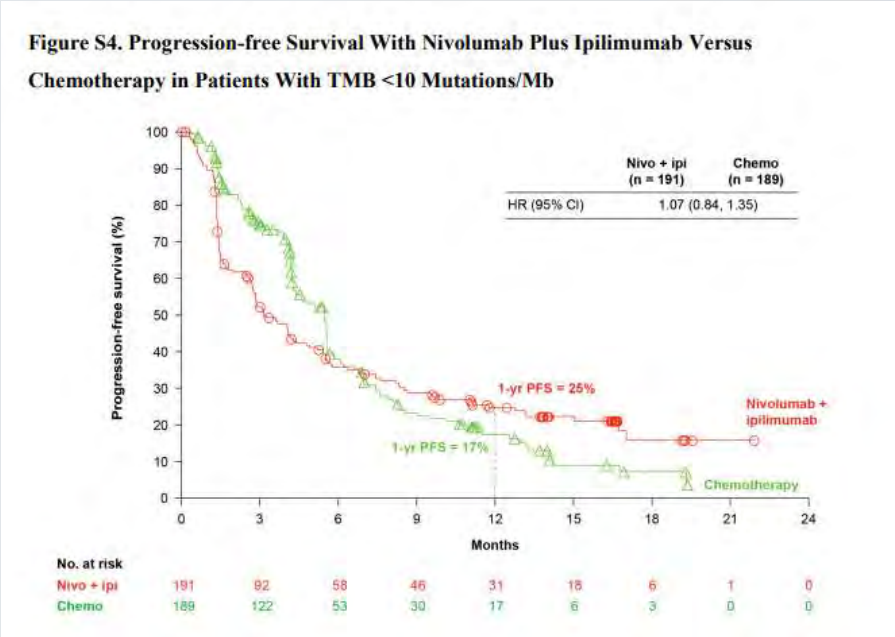
CheckMate 227

- Phase III , evaluated Nivolumab plus ipilimumab vs chemotherapy as first-line treatment in advanced NSCLC
  - Looked at PD-L1 differences
  - Looked at H-TMB effect

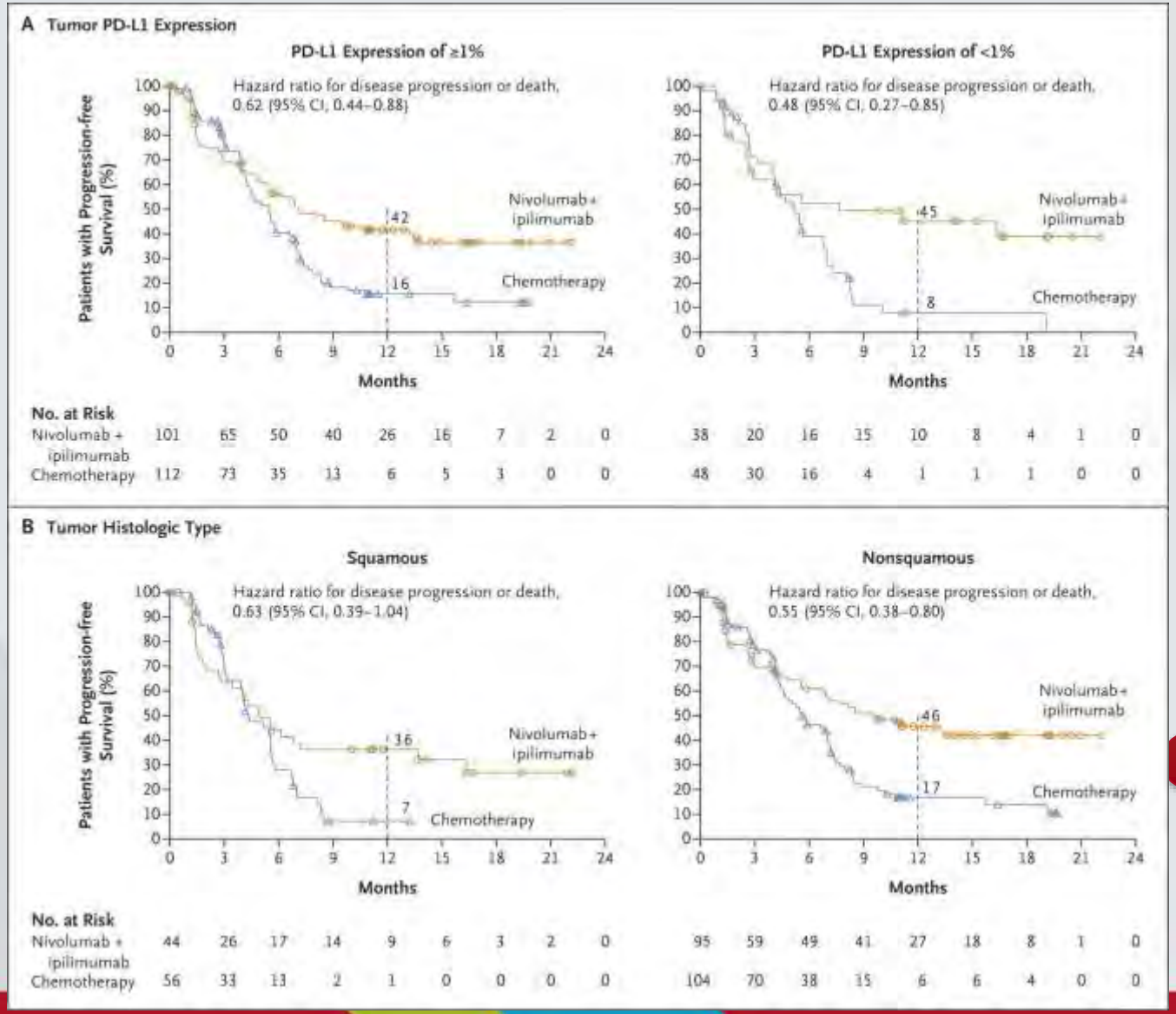
N Engl J Med 2018; 378:2093-2104

CheckMate 227 -TMB





CheckMate 227

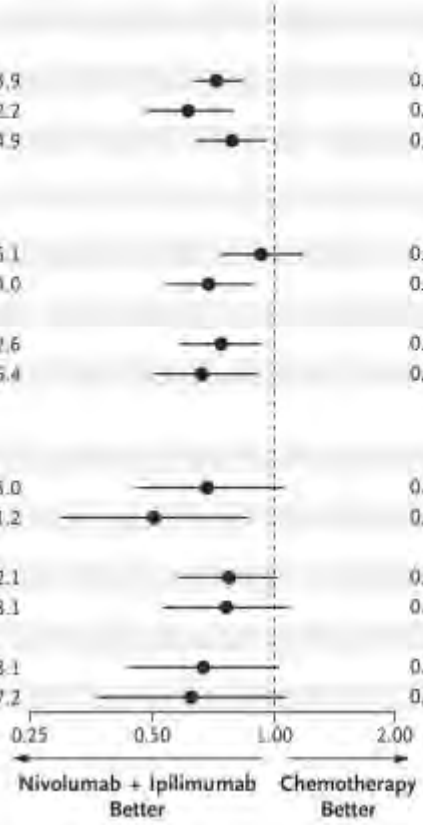


In H-TMB NSCLC, there was better PFS for ipi/nivo **irrespective of PD-L1 expression level.**

N Engl J Med 2018; 378:2093-2104

Updated CheckMate 227

Subgroup	No. of Patients	Median Overall Survival: Nivolumab + Ipilimumab (N=583)	Median Overall Survival: Chemotherapy (N=583)	Unstratified Hazard Ratio for Death (95% CI)
		months		
Randomized Groups				
PD-L1				
All randomized	1166	17.1	13.9	0.73 (0.64–0.84)
<1%	373	17.2	12.2	0.62 (0.49–0.79)
≥1%	793	17.1	14.9	0.79 (0.65–0.96)
Additional Exploratory Subgroup Analyses				
PD-L1				
1–49%	396	15.1	15.1	0.94 (0.75–1.18)
≥50%	397	21.2	14.0	0.70 (0.55–0.90)
Tumor mutational burden				
Low, <10 mut/Mb	380	16.2	12.6	0.75 (0.59–0.94)
High, ≥10 mut/Mb	299	23.0	16.4	0.68 (0.51–0.91)
PD-L1 and tumor mutational burden (mut/Mb) combined				
PD-L1 <1%				
Tumor mutational burden <10	111	15.5	13.0	0.69 (0.46–1.05)
Tumor mutational burden ≥10	86	20.4	11.2	0.51 (0.30–0.87)
PD-L1 ≥1%				
Tumor mutational burden <10	269	16.2	12.1	0.78 (0.59–1.02)
Tumor mutational burden ≥10	213	24.4	18.1	0.77 (0.54–1.09)
PD-L1 ≥50%				
Tumor mutational burden <10	125	18.1	8.1	0.67 (0.44–1.03)
Tumor mutational burden ≥10	111	NR	17.2	0.63 (0.37–1.07)



N Engl J Med 2019; 381:2020-2031

TMB effect on atezolizumab

- Data evaluated multiple studies of atezolizumab in different cancers including OAK study in NSCLC.
- ~18% of patients had high TMB (16 Mut/Mb or more).
- TMB was associated with efficacy across tumor types and lines of therapy.
  - ORR 29.7% vs 13.5% (high TMB vs low TMB)
  - DoR 29 m vs 13.8 m

High tTMB (≥16 mut/Mb) was associated with improved atezo response and DoR across cancers including NSCLC.

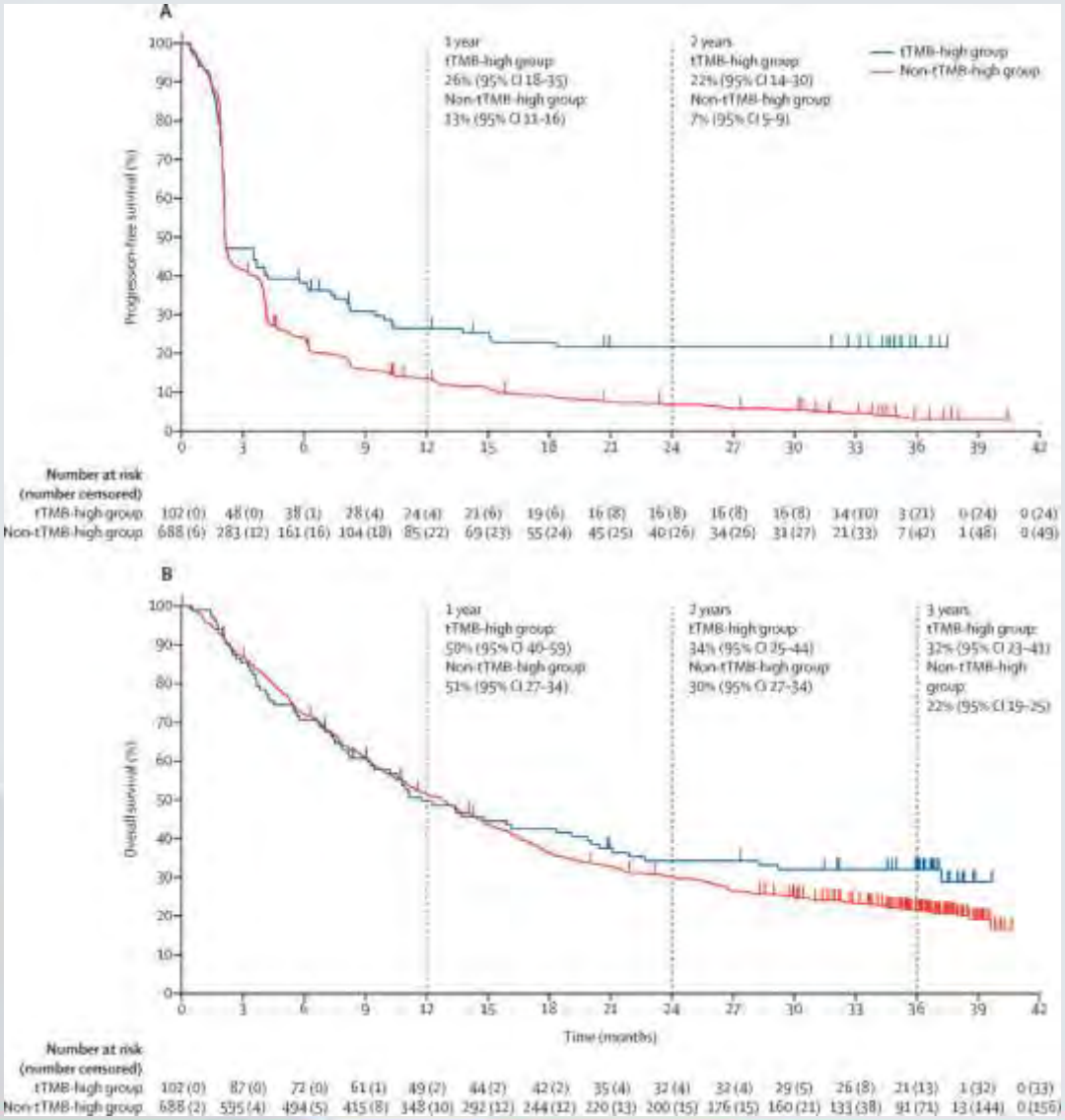
J Clin Oncol 2018;36:abstr 12000.

KEYNOTE-158

- Pembrolizumab in previously treated solid tumors (They did not include NSCLC, they had some SCLC and mesothelioma).
- They looked at TMB and defined high TMB as 10 mut/mb
- Total of 1066 patients were treated → 805 (76%) were evaluable for TMB→ 105 had tTMB-high status.
- ORR 29% vs 6% (H-TMB vs L-TMB)

Lancet Oncol . 2020 Oct;21(10):1353-1365

KEYNOTE-158



FDA approved pembrolizumab adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors

Conclusion

- TMB is good marker but not ideal!
  - Technical problems with measuring → no agreement on cut off value for H-TMB , lack of standardization of TMB measurements across labs
- No association between TMB and PD-L1.
  - BUT PD-L1 is more useful → quicker, less tissue needed, data demonstrate relative reproducibility across platforms and individuals.
- NCCN dose not recommend using it in NSCLC

Mismatch repair (MMR) deficiency

- Lynch syndrome vs sporadic cases (mainly GI and gyn onc)
- MMR deficiency causes replication errors to accumulate→ leading to microsatellite instable (MSI) phenotype and high TMB.
- The MSI phenotype is a predictive marker of response to ICIs in various cancer types and can easily be assessed by standard routine methods.

Cancer Discov. 2017 Aug;7(8):818-831

Mismatch repair (MMR) deficiency

- MMR testing is not common in lung cancer→
  - Data from the AACR GENIE database → 2.1%, 1.09%, 1.65% and 1.87% of lung tumors have mutations in the MMR genes *MSH2*, *MLH1*, *PMS2* and *MSH6* respectively

Cancer Discov. 2017 Aug;7(8):818-831

Conclusion

- Valuable in other cancers, not common in lung cancer

Oncogenic mutations

- *Not all mutations induce neoantigens!!*
- *It is known that EGFR* mutated or *ALK* rearranged tumors do not respond well to ICIs
- Most ICIs trials have excluded EGFR, ALK and ROS1 positive tumors

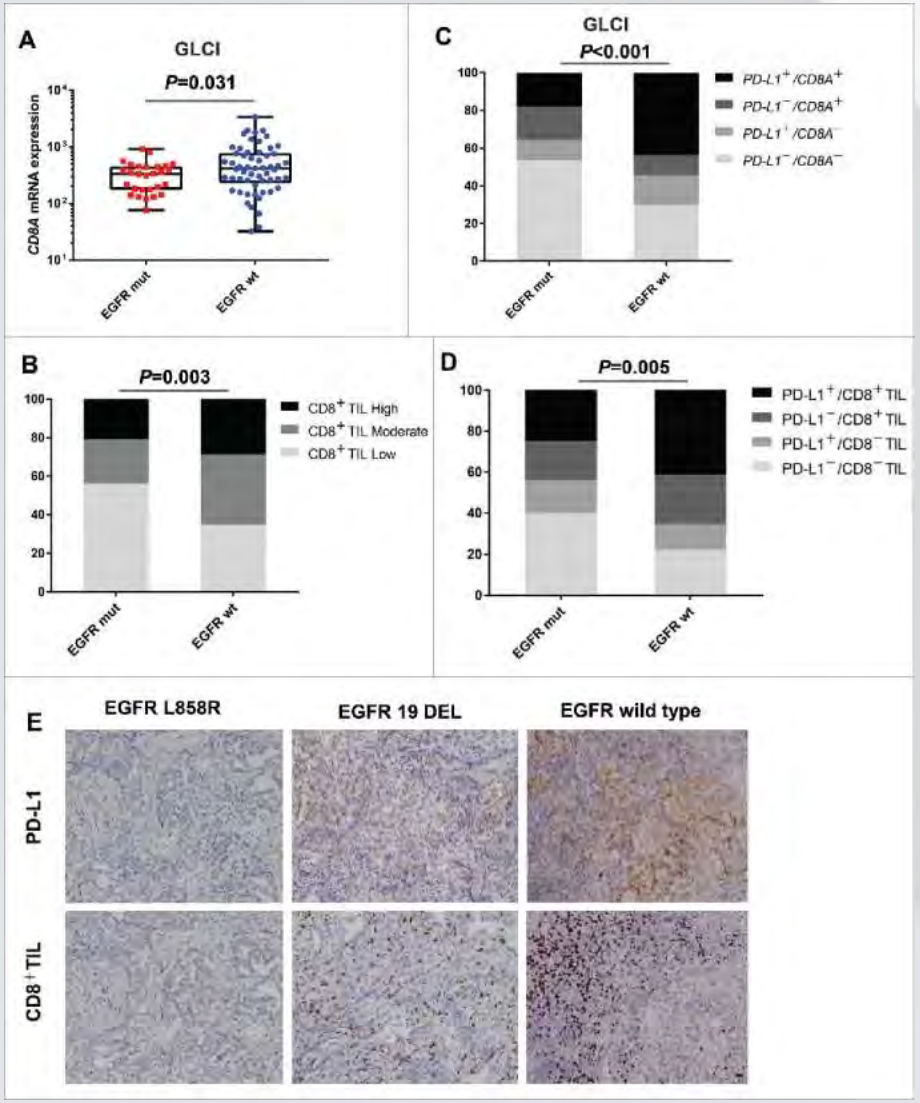
Oncoimmunology vol. 6,11 e1356145

J Thorac Dis. 2019 Jan;11(Suppl 1):S25-S36.

The Cancer Genome Atlas (TCGA)

- *EGFR* mutation showed a lack of T-cell infiltration and shrinking proportion of PD-L1^{+}/CD8^{+} TIL.
- This was correlated with uninflamed tumor microenvironment

However, High PD-L1 is not rare in some oncogenic mutations such as EGFR and ALK



Oncoimmunology. 2017 Jul 26;6(11):e1356145

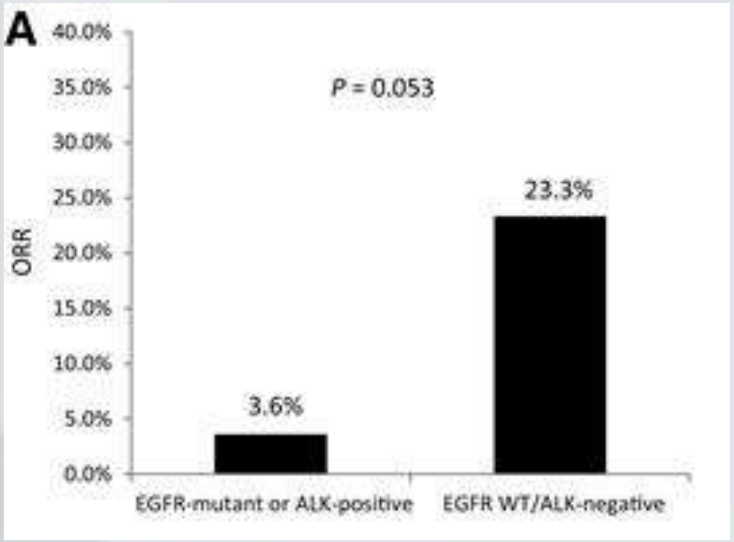
Retrospective data

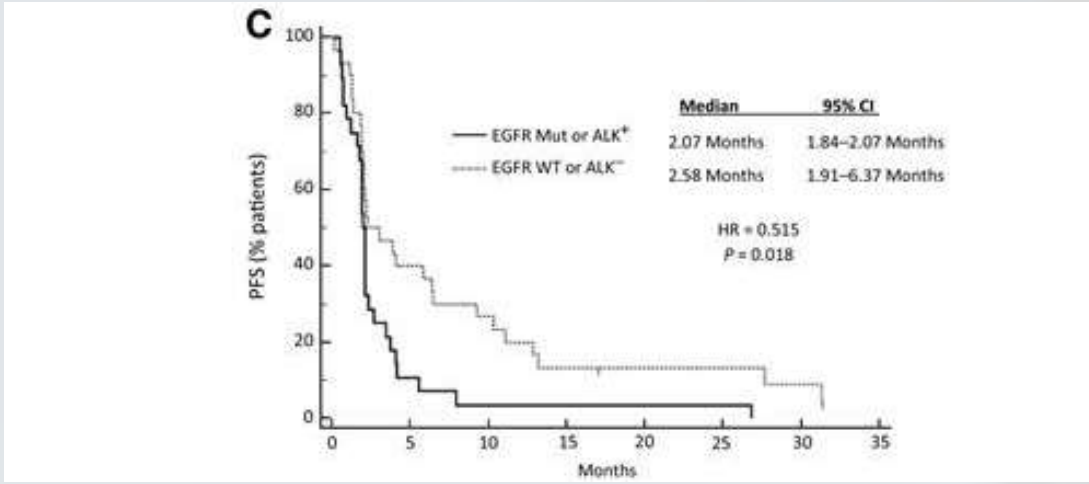
- 58 patients with NSCLC treated at Massachusetts General Hospital with immunotherapy and looked at EGFR/ALK mutation.
- They looked at PD-L1 expression and $CD8^+$ TILs, ORR.

	EGFR-Mutant			ALK-Rearranged		
	Pre-TKI (*N*=62)	Post-TKI (*N*=63)	*P* Value[a]	Pre-Criz (*N*=19)	Post-Criz (*N*=12)	*P* Value[a]
PD-L1 Positive						
PD-L1+ (≥50%)	7 (11%)	9 (14%)	0.727	5 (26%)	2 (17%)	1.000
PD-L1+ (≥5%)	10 (16%)	18 (29%)	0.119	9 (47%)	3 (25%)	0.500
CD8+ TILs (Immunohistochemistry; IHC)[b]						
0	17 (35%)	18 (42%)	0.847	2 (15%)	4 (44%)	
1+	29 (60%)	20 (47%)		8 (62%)	5 (56%)	
2+	2 (4.2%)	5 (12%)		3 (23%)	0 (0%)	
3+	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
CD8+ TILs (Image-Based)[c] per mm^2						
Median (Range)	185.1 (6.1–1161.9)	140.2 (4.3–1029.3)	0.527	178.9 (30.1–477.4)	69.2 (17.9–523.6)	
Concurrent PD-L1 Expression & CD8+ TILs (IHC)						
PD-L1+ (≥ 50%) & High CD8+ TILs (grade 2–3)	1/48 (2.1%)	1/43 (2.3%)	1.000	0/13 (0%)	0/9 (0%)	
PD-L1+ (≥ 5%) & High CD8+ TILs (grade 2–3)	1/48 (2.1%)	5/43 (11.6%)	0.219	0/13 (0%)	0/9 (0%)	

Clin Cancer Res (2016) 22 (18): 4585–4593

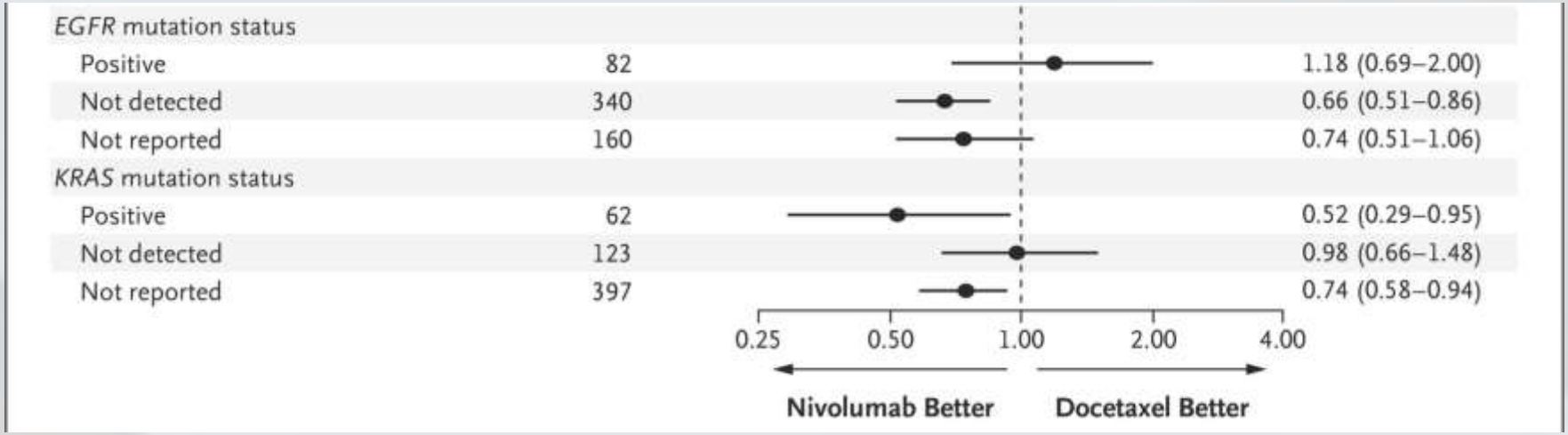
Retrospective data (Mutations and response to ICI)





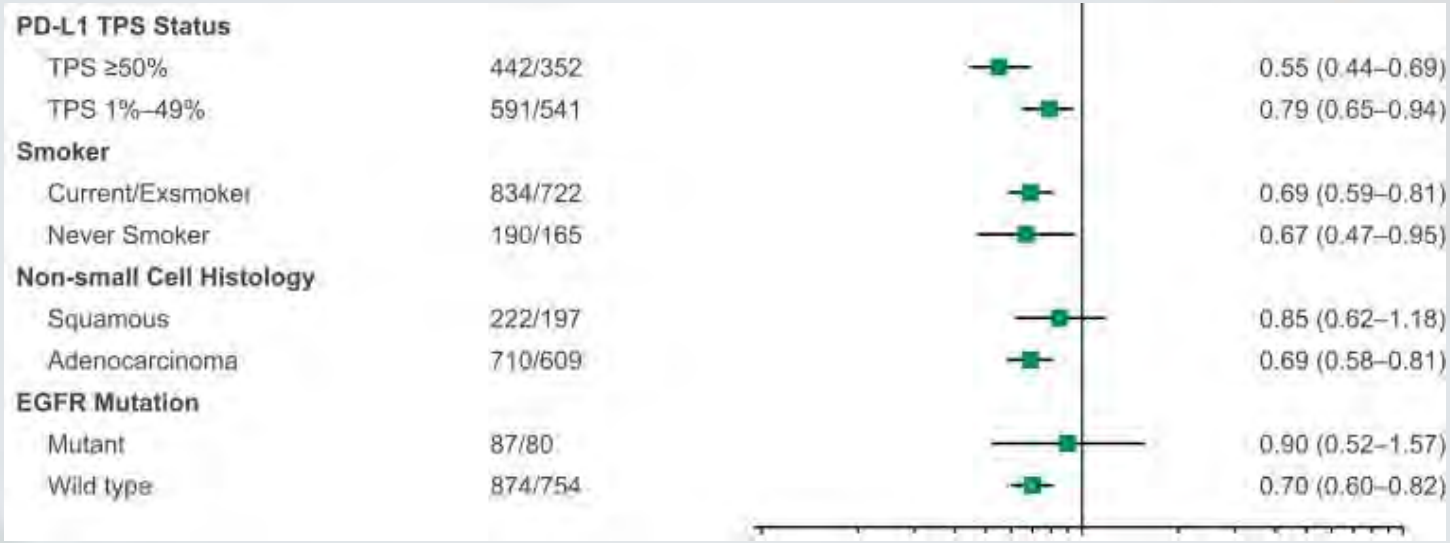
CheckMate 057

- Nivolumab vs docetaxel as 2nd line allowed EGFR patients to be enrolled



KEYNOTE 010

- Pembrolizumab vs docetaxel in second line→ Allowed EGFR to be enrolled.



IMpower150 trial → THE EXCEPTION!

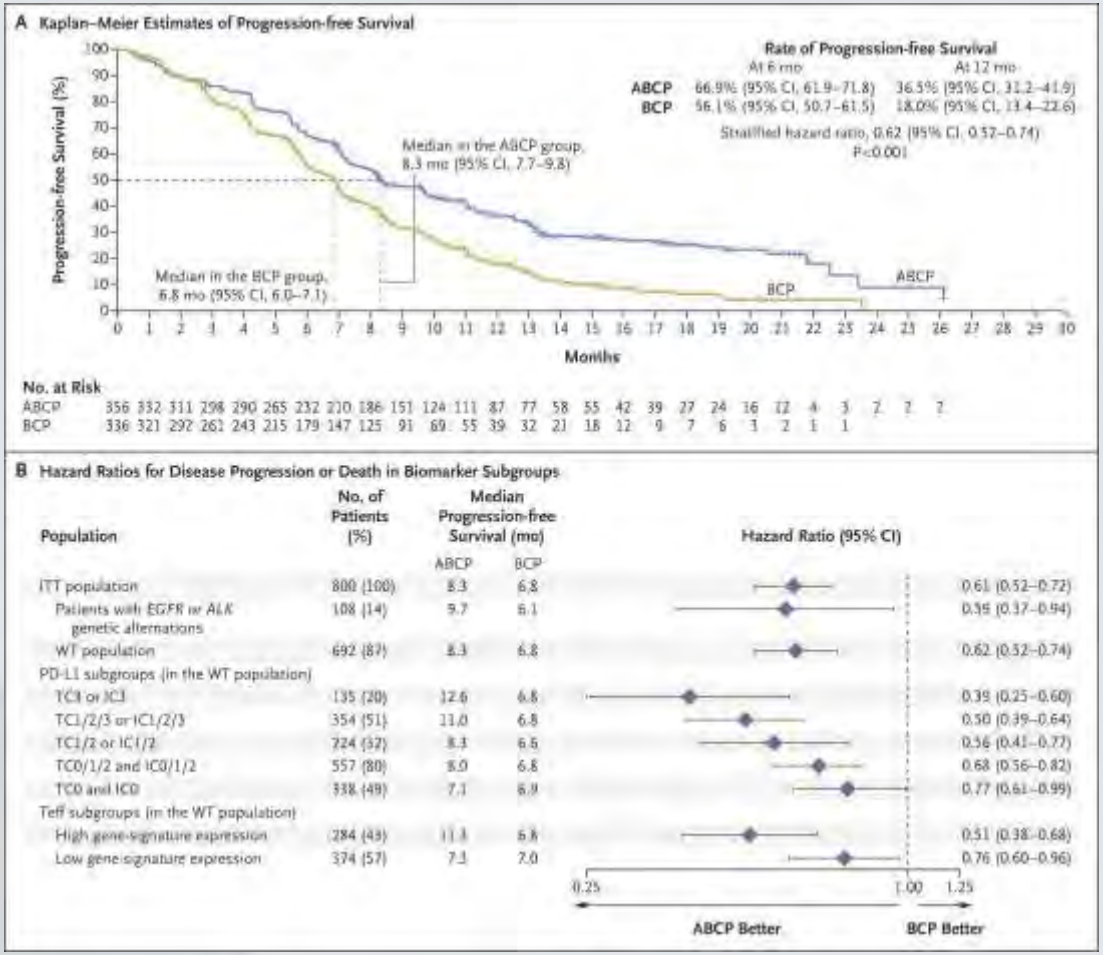
- Phase III, advanced nonsquamous NSCLC as first line:
  - Atezolizumab plus carboplatin plus paclitaxel (ACP)
  - Bevacizumab plus carboplatin plus paclitaxel (BCP)
  - Atezolizumab plus BCP (ABCP)

Table 1. Baseline Characteristics of All Enrolled Patients (Intention-to-Treat Population).*

Characteristic	ABCP Group (N = 400)	BCP Group (N = 400)
Median age (range) — yr	63 (31–89)	63 (31–90)
Age group — no. (%)		
<65 yr	215 (53.8)	226 (56.5)
65–74 yr	149 (37.2)	132 (33.0)
75–84 yr	33 (8.2)	39 (9.8)
≥85 yr	3 (0.8)	3 (0.8)
Male sex — no. (%)	240 (60.0)	239 (59.8)
Liver metastases absent at enrollment — no. (%)	347 (86.8)	343 (85.8)
Race or ethnic group — no. (%)†		
White	322 (80.5)	335 (83.8)
Asian	56 (14.0)	46 (11.5)
Black	3 (0.8)	12 (3.0)
American Indian or Alaska Native	3 (0.8)	1 (0.2)
Multiple	3 (0.8)	0
Unknown	13 (3.2)	6 (1.5)
ECOG performance-status score — no./total no. (%)‡		
0	159/397 (40.1)	179/397 (45.1)
1	238/397 (59.9)	218/397 (54.9)
History of tobacco use — no. (%)		
Never	82 (20.5)	77 (19.2)
Current	90 (22.5)	92 (23.0)
Previous	228 (57.0)	231 (57.8)
Nonsquamous histologic subtype — no. (%)		
Adenocarcinoma	378 (94.5)	377 (94.2)
Other§	19 (4.8)	17 (4.2)
Unknown or not assessed	3 (0.8)	6 (1.5)
EGFR mutation status — no. (%)¶		
Positive	35 (8.8)	45 (11.3)
Negative	352 (88.0)	345 (86.3)
EML4-ALK rearrangement status — no. (%)‖		
Positive	13 (3.2)	21 (5.2)
Negative	383 (95.8)	375 (93.8)
KRAS mutation status — no. (%)**		
Positive	47 (11.8)	38 (9.5)
Negative	59 (14.8)	77 (19.2)

N Engl J Med 2018; 378:2288-2301

IMpower150 trial



The addition of atezolizumab to bevacizumab plus chemotherapy significantly improved progression-free survival and overall survival among patients with metastatic nonsquamous NSCLC, regardless of PD-L1 expression and *EGFR* or *ALK* genetic alteration status

N Engl J Med 2018; 378:2288-2301

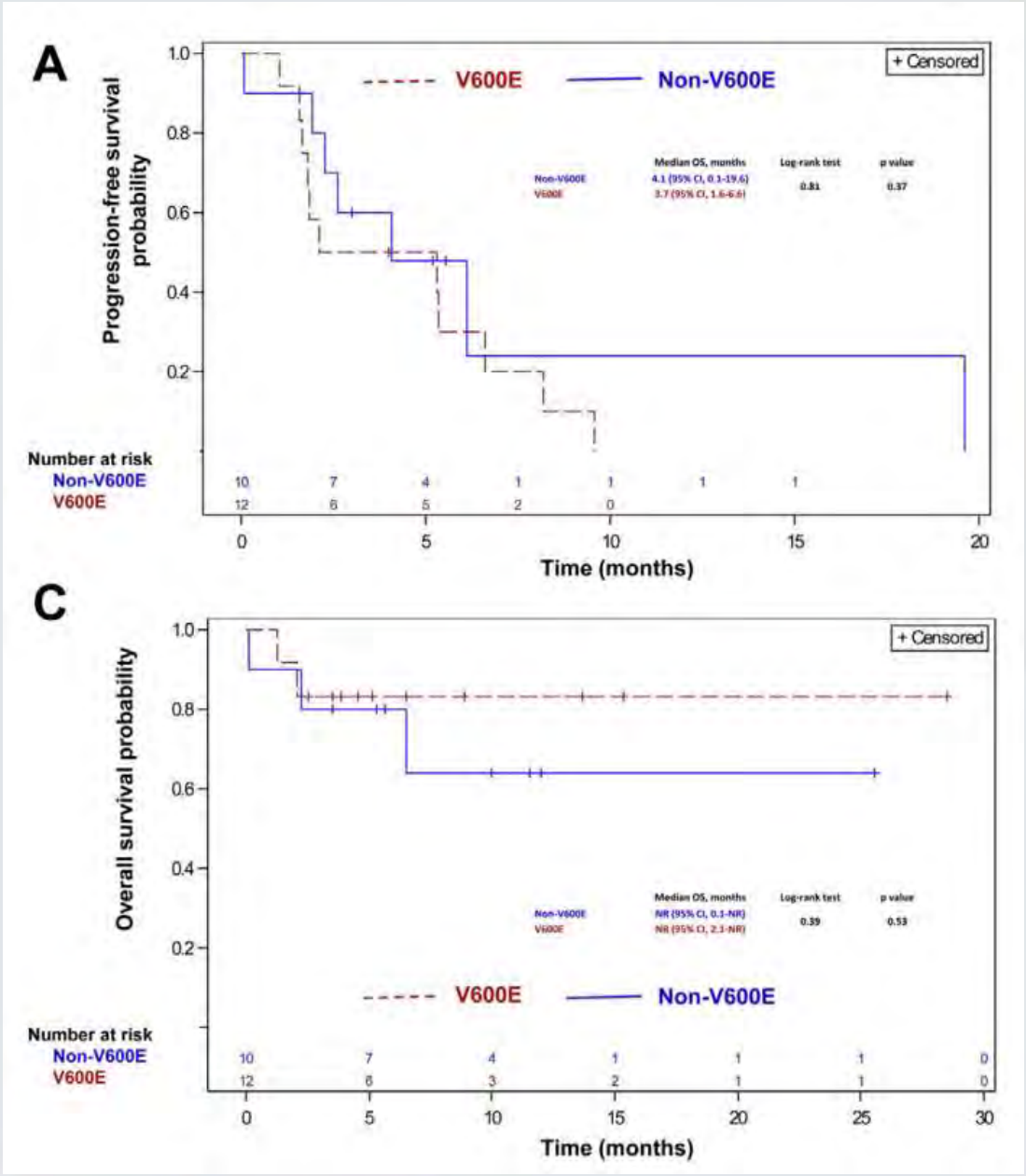
BRAF

- A retrospective data of 39 patients with *BRAF* mutant NSCLC (21 had V600E mutation and 18 had non-V600E)
  - Looked at PD-L1 expression and TMB
  - Response to ICIs

	BRAF V600E (n = 21), n	*BRAF* V600E, % of Tumors Assessed	*BRAF* Non-V600E (n = 18)[a], n	*BRAF* Non-V600E, % of Tumors Assessed	*p* Value	ICPi (n = 22), n	ICPi, % of Tumors Assessed	No ICPi (n = 17), n	No ICPi, % of Tumors Assessed	*p* Value	Total (N = 39), n
PD-L1 TPS (%), assessed	19		10			19		10			29
Negative (<1%)	5	26	4	40	0.051	4	21	5	50	0.056	9
Intermediate (1-49%)	6	32	1	10		4	21	3	30		7
High (≥50%)	8	42	5	50		11	58	2	20		13
NA	2		8			3		7			10
TMB (muts/Mb), assessed	8		3			6		5			11
Low (≤5)	4	50	0	0	0.08	2	33.3	2	40	0.34	4
Intermediate (6-19)	2	25	3	100		2	33.3	3	60		5
High (≥20)	2	25	0	0		2	33.3	0			2
NA	13		15			16		12			28
TMB (muts/Mb), median (range)	5 (1-42)		11 (7-14)		0.82	9 (1-42)		6 (1-14)		0.26	7 (1-42)

J Thorac Oncol. 2018 Aug;13(8):1128-1137

BRAF


A
Progression-free survival probability
1.0
0.8
0.6
0.4
0.2
V600E
Non-V600E
+ Censored
Median OS, months
Log-rank test
p value
Non-V600E
4.1 (95% CI, 0.1-19.6)
0.81
0.37
V600E
3.7 (95% CI, 1.6-6.6)
Number at risk
Non-V600E
10 7 4 1 1 1 1
V600E
12 6 5 2 0
0 5 10 15 20
Time (months)
C
Overall survival probability
1.0
0.8
0.6
0.4
0.2
+ Censored
Median OS, months
Log-rank test
p value
Non-V600E
NR (95% CI, 0.1-NR)
0.39
0.53
V600E
NR (95% CI, 2.1-NR)
V600E
Non-V600E
Number at risk
Non-V600E
10 7 4 1 1 1 0
V600E
12 6 3 2 1 1 0
0 5 10 15 20 25 30
Time (months)

KRAS/TP53

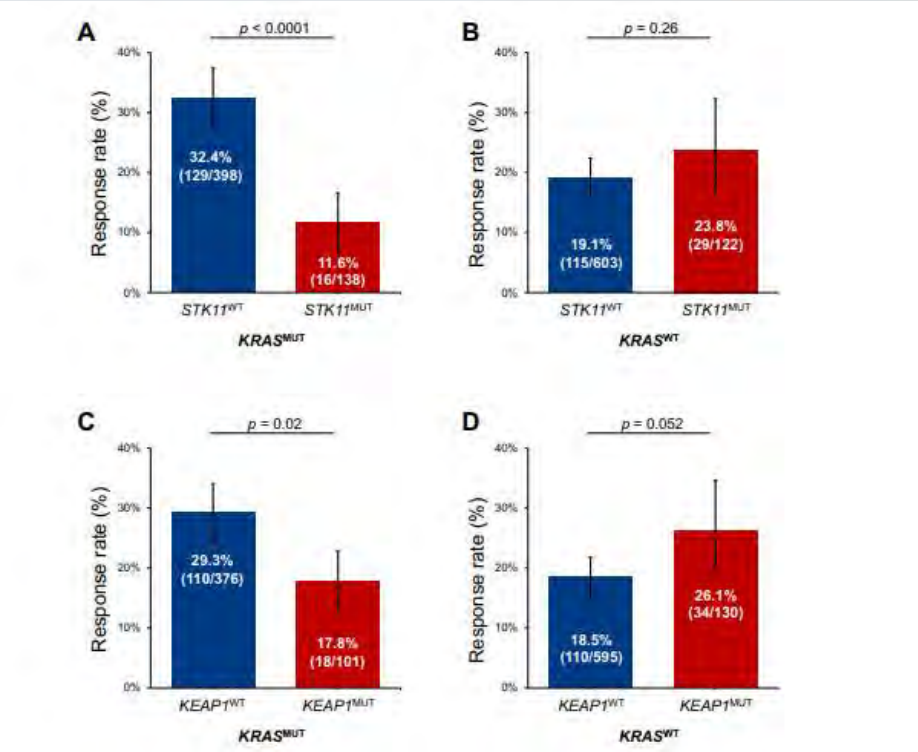
- Some studies suggested that *KRAS-TP53* co-mutation can have predictive value to response to immunotherapy (and high TMB). However, these data were not consistent through studies.

- It is believed that *KRAS* or TP53 had no predictive value to be used in clinical practice

Clin Cancer Res. 2017 Jun 15;23(12):3012-3024
J Clin Oncol. 2018 Mar 1;36(7):633-641

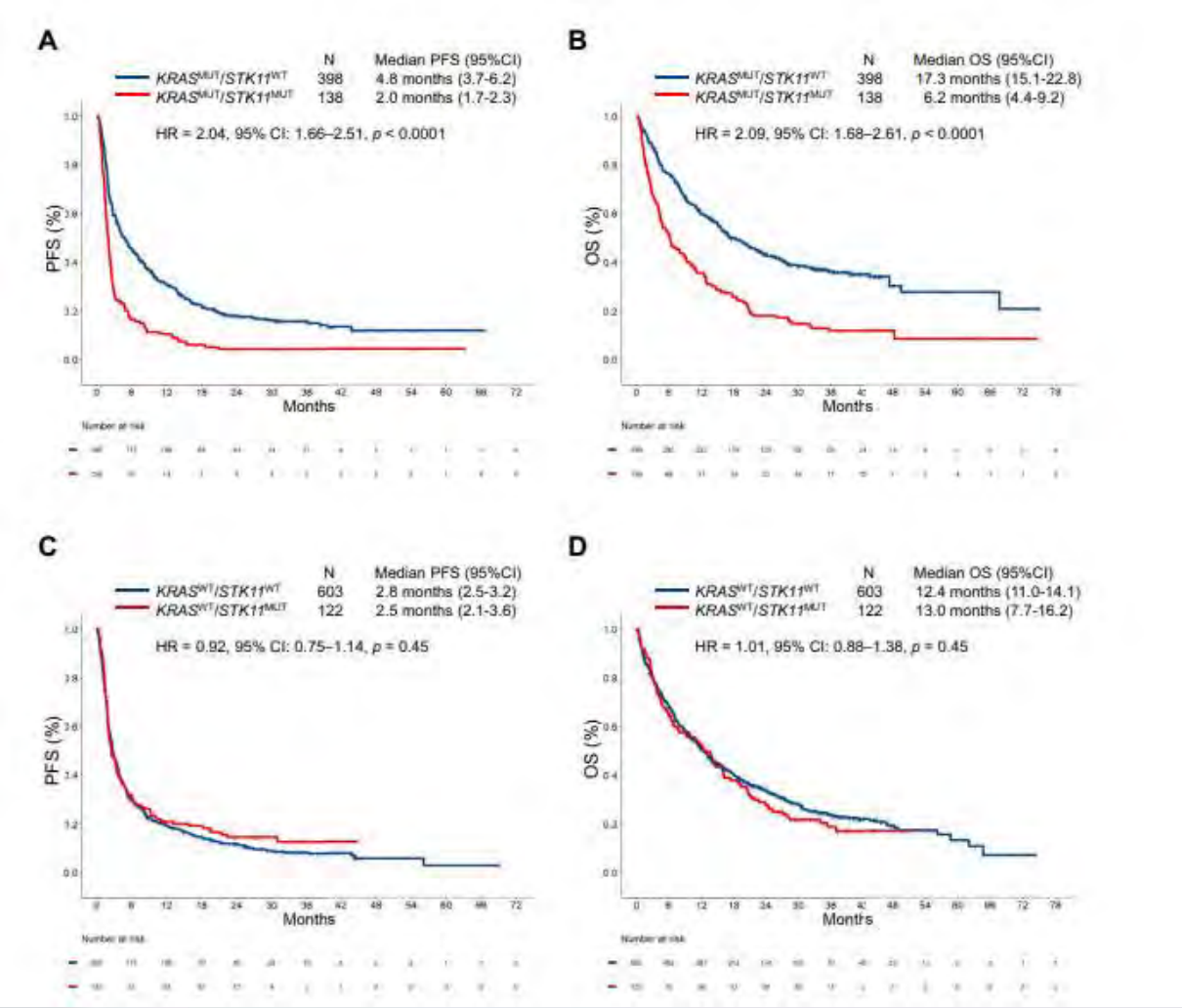
STK11/*KEAP1*

- *STK11* /KEAP1 were associated with worse immunotherapy outcomes in KRAS mutant lung cancers.



J Thorac Oncol. 2022 Mar;17(3):399-410

STK11/*KEAP1*



J Thorac Oncol. 2022 Mar;17(3):399-410

Conclusion

- In presence of oncogenic mutation, targetable therapy is preferred even if PD-L1 is high.
- EGFR, ALK, STK11/KEAP1 with KRAS has poor response.
- Need more investigations in future line or combined with targetable therapy.

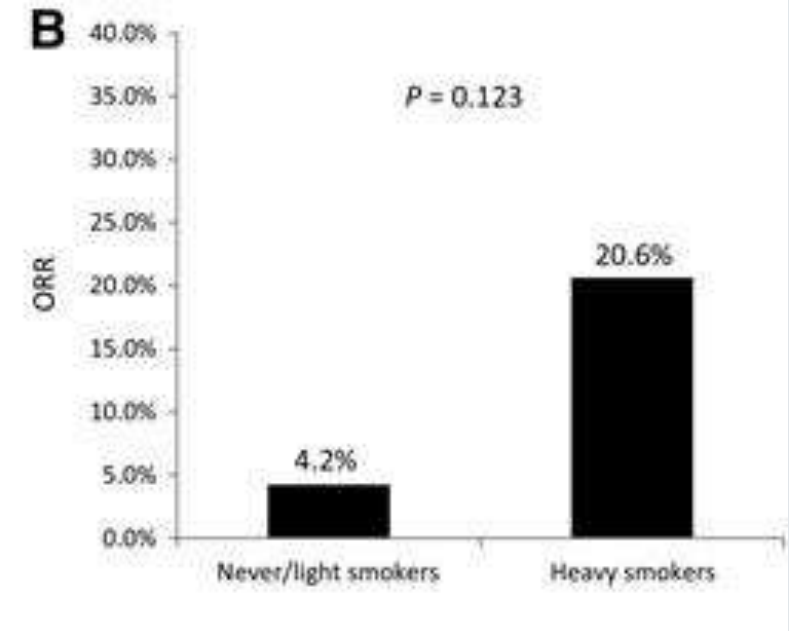
Smoking

- Somatic mutation load in NSCLC is related to tobacco exposure→ Higher TMB

J Thorac Dis. 2019 Jan; 11(Suppl 1): S25–S36.

Retrospective data

- 58 patients with NSCLC treated at Massachusetts General Hospital with immunotherapy and looked at EGFR/ALK mutation.
  - In subgroup analysis they looked at smoking as predictive factor



Clin Cancer Res (2016) 22 (18): 4585–4593

Summary

- PD-L1
  - Currently the only validated marker in first line for NSCLC.
  - Immunotherapy is recommended in first line for patients with an *EGFR* or *ALK* wild type, PD-L1 >50% tumors
- TMB, MMR has value in other cancers . So far limited in NSCLC
- CtDNA could be new marker?

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