Carico mutazionale tumorale (TMB): considerazioni cliniche

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"NSCLC avanzato: quali novità nel 2018?" - II CONGRESSO NAZIONALE

Negrar (VR), 30.10.18

Outline

- Biomarker selection for immunotherapy in NSCLC: PD-L1
- The emerging role of tumor mutation burden (TMB) as opposed to PD-L1
- TMB in NSCLC
- Is “super-selection” possible?
- Unsolved issues with TMB

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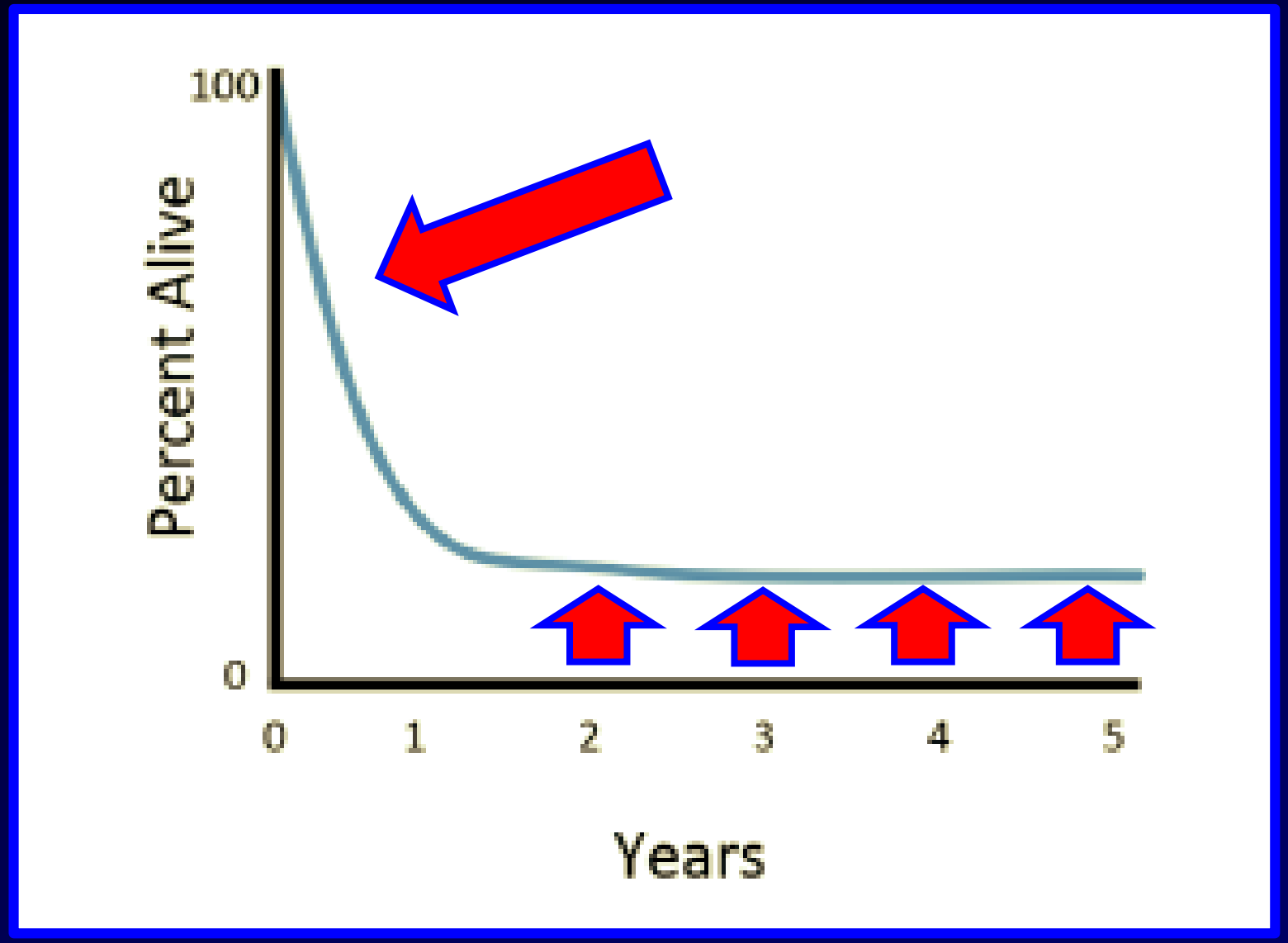
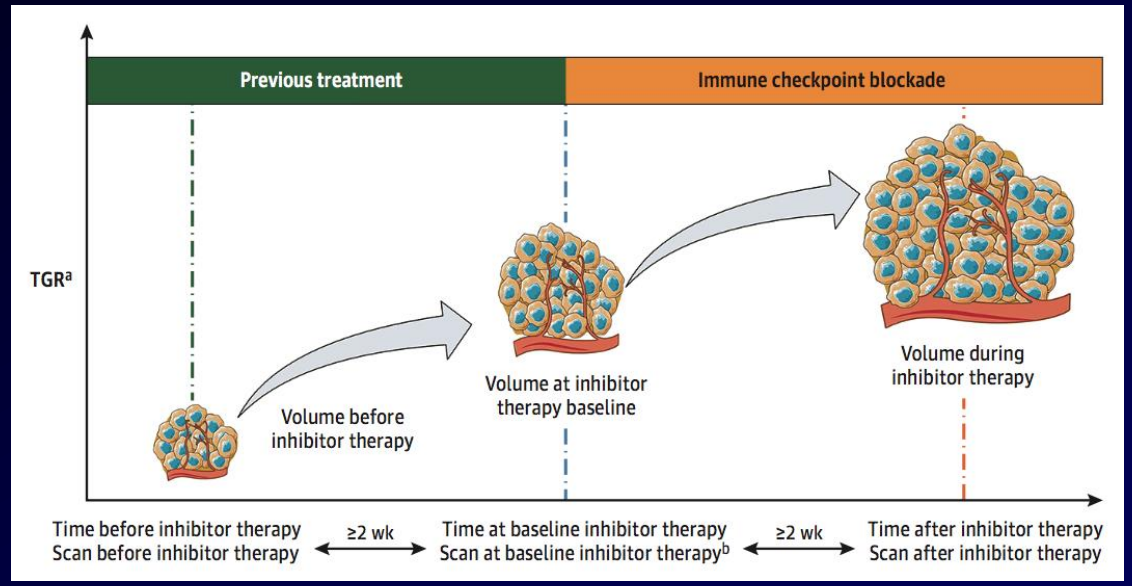
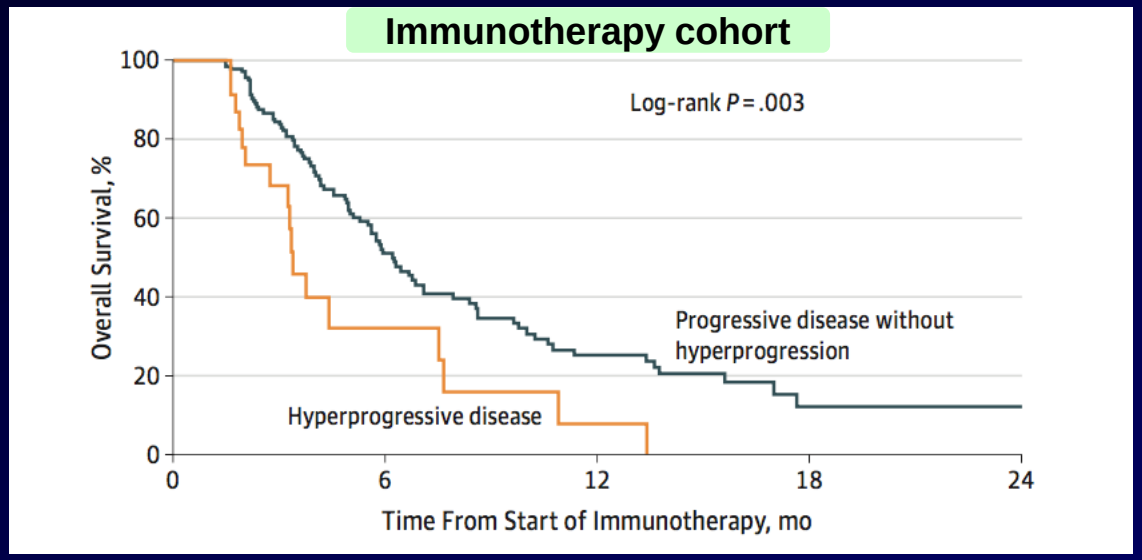
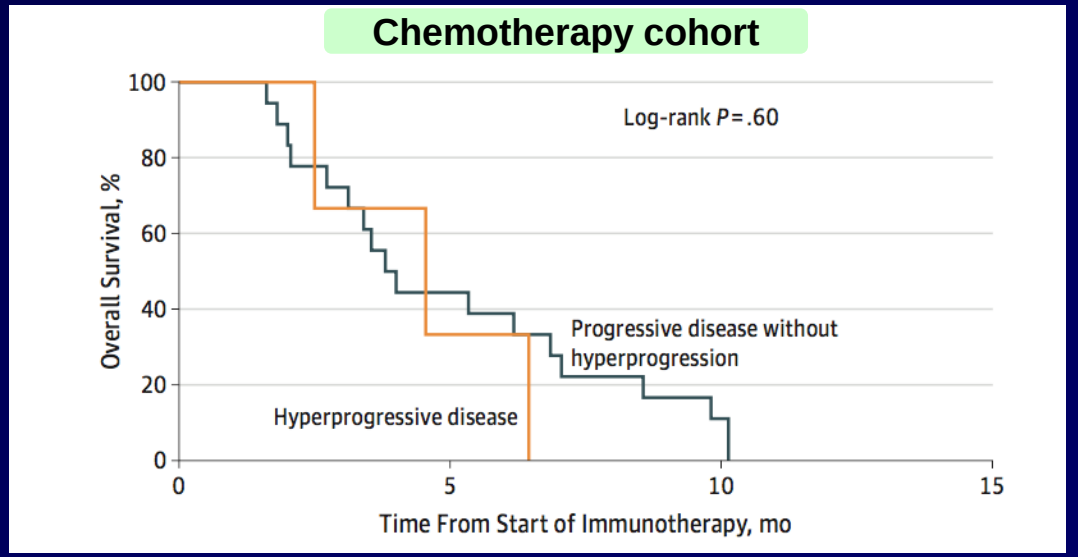
Immune checkpoint inhibitors (ICIs) targeting PD-(L)1 axis have transformed management of NSCLC



ICIs targeting PD-(L)1 and hyperprogressive disease



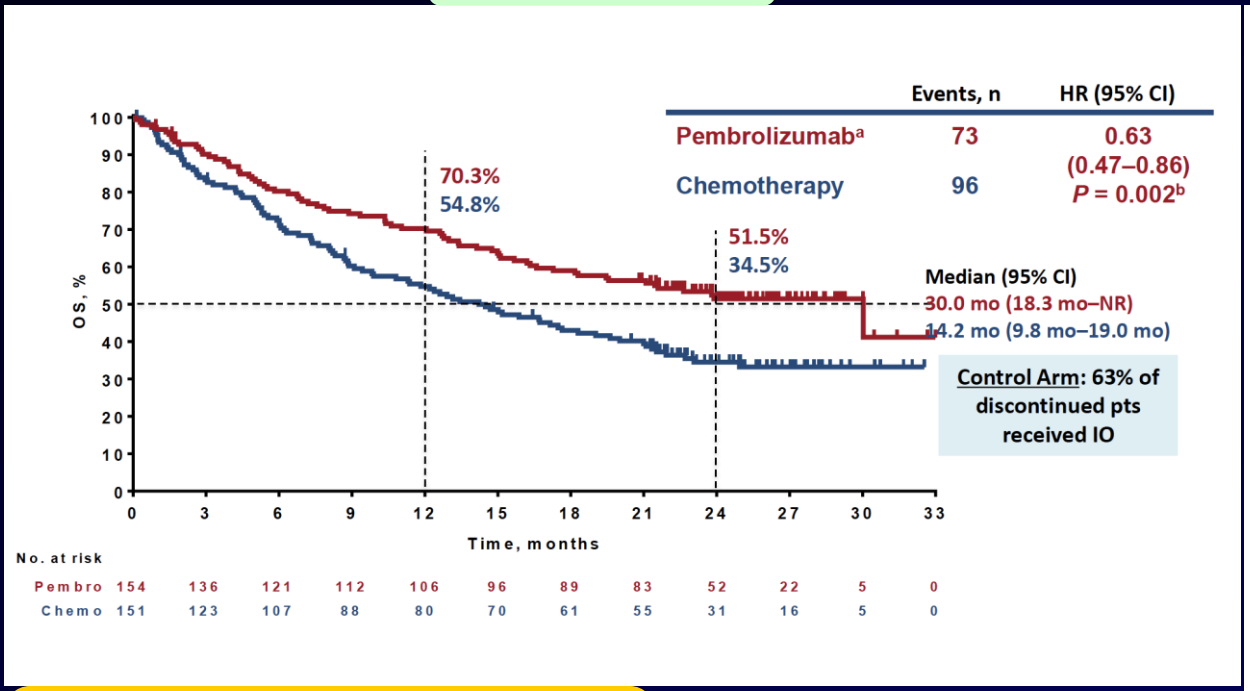




Ferrara et al., JAMA Oncol 2018

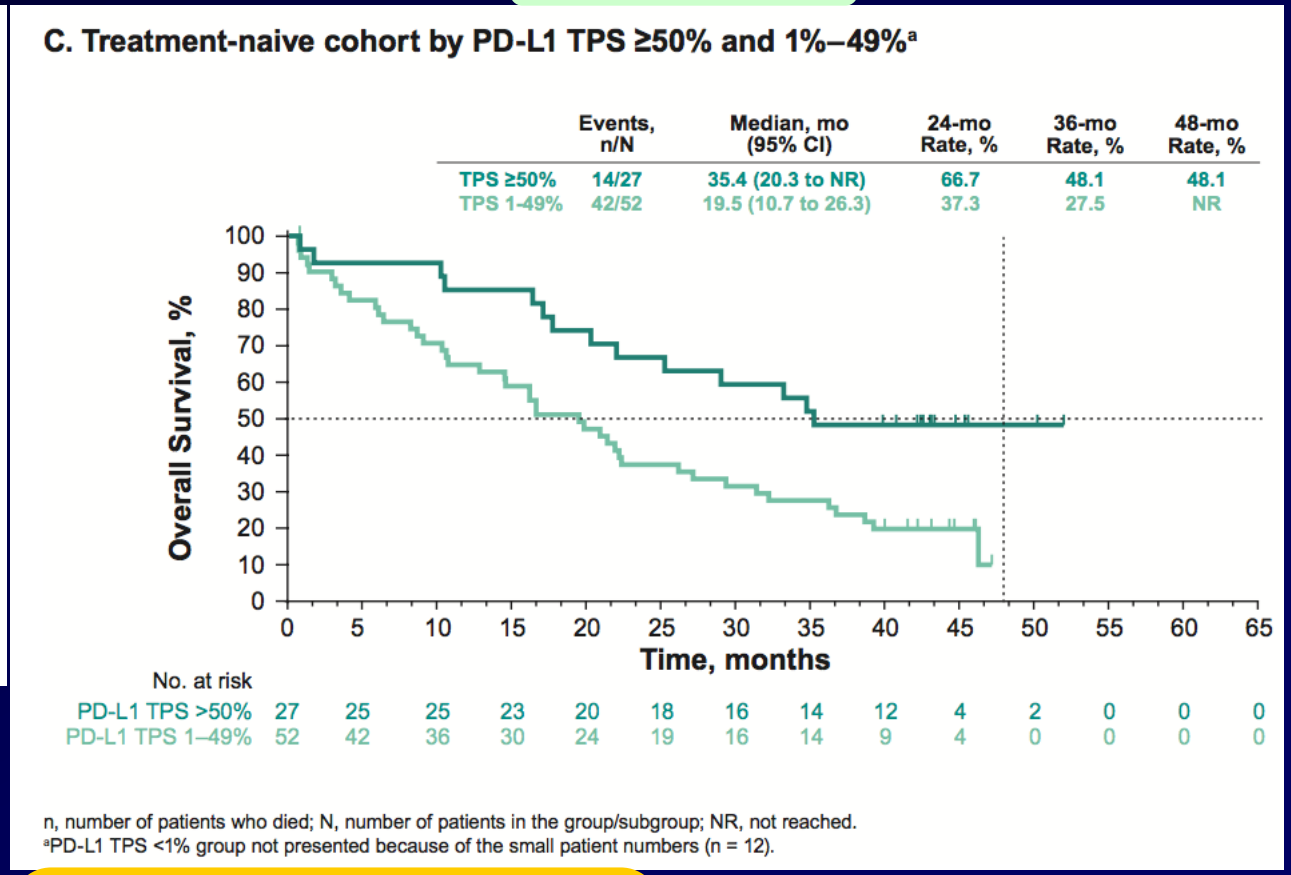
Pembrolizumab: large benefit in high-PD-L1 expressors (≥ 50%)

KEYNOTE-024[1]



Pembrolizumab:
Median OS 30.0 months
2-yr OS 51.5%

KEYNOTE-001[2]

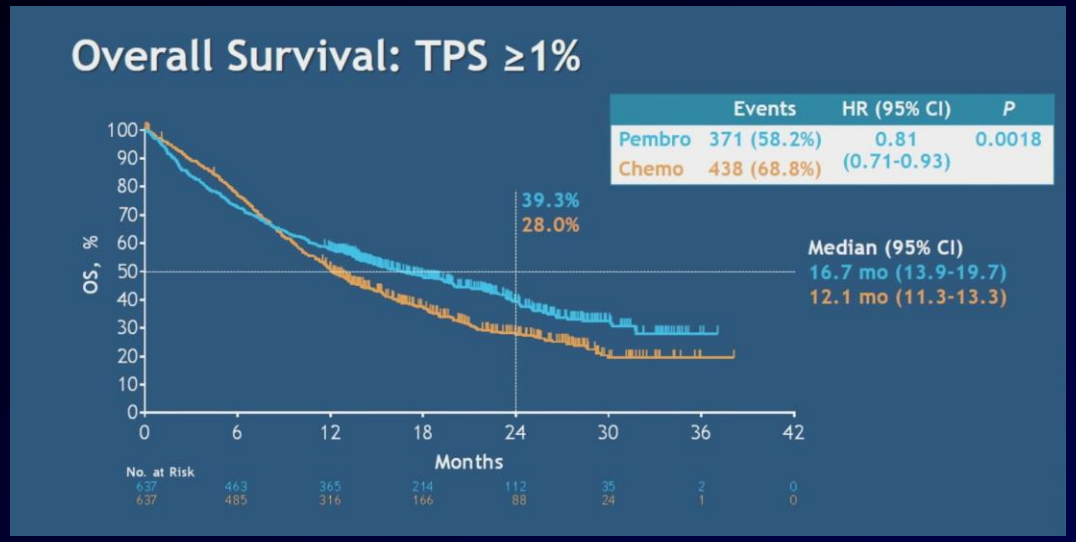


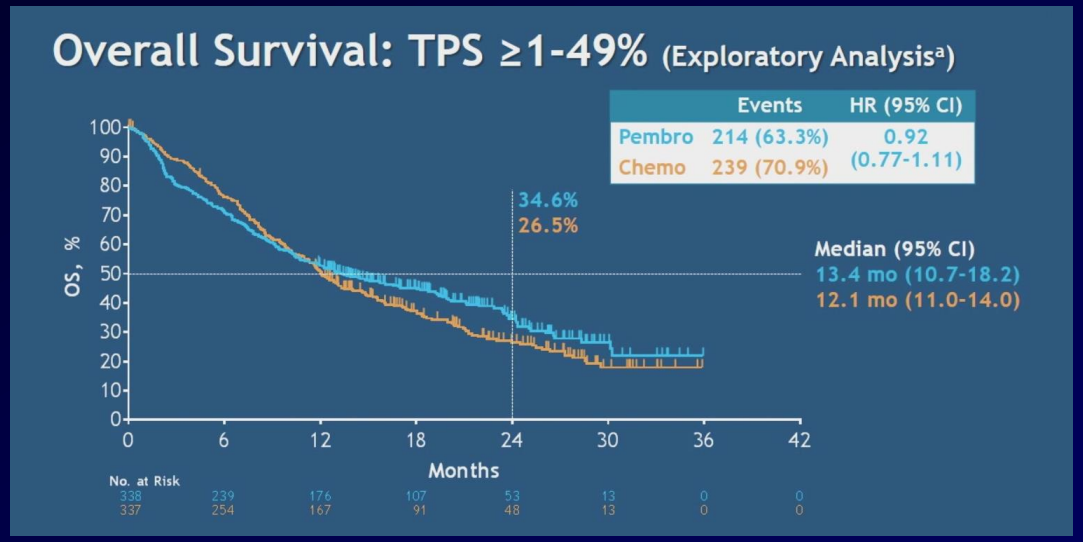
n, number of patients who died; N, number of patients in the group/subgroup; NR, not reached.
[a]PD-L1 TPS <1% group not presented because of the small patient numbers (n = 12).

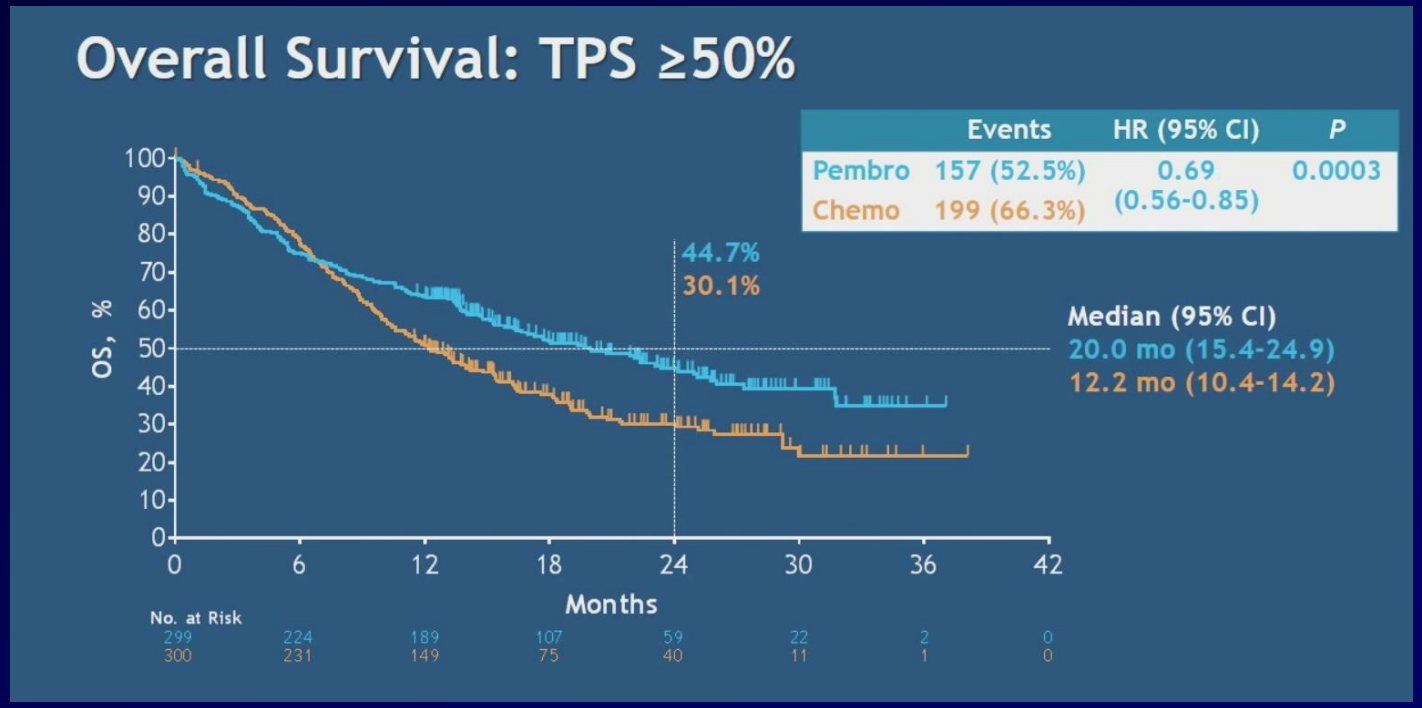
Pembrolizumab:
Median OS 35.4 months
2-yr OS 66.7%
3-yr OS 48.1%
4-yr OS 48.1%

[1]Brahmer et al., WCLC 2017
[2]Felip et al., ASCO 2018

Benefit in PD-L1+ is largely driven by high expressors

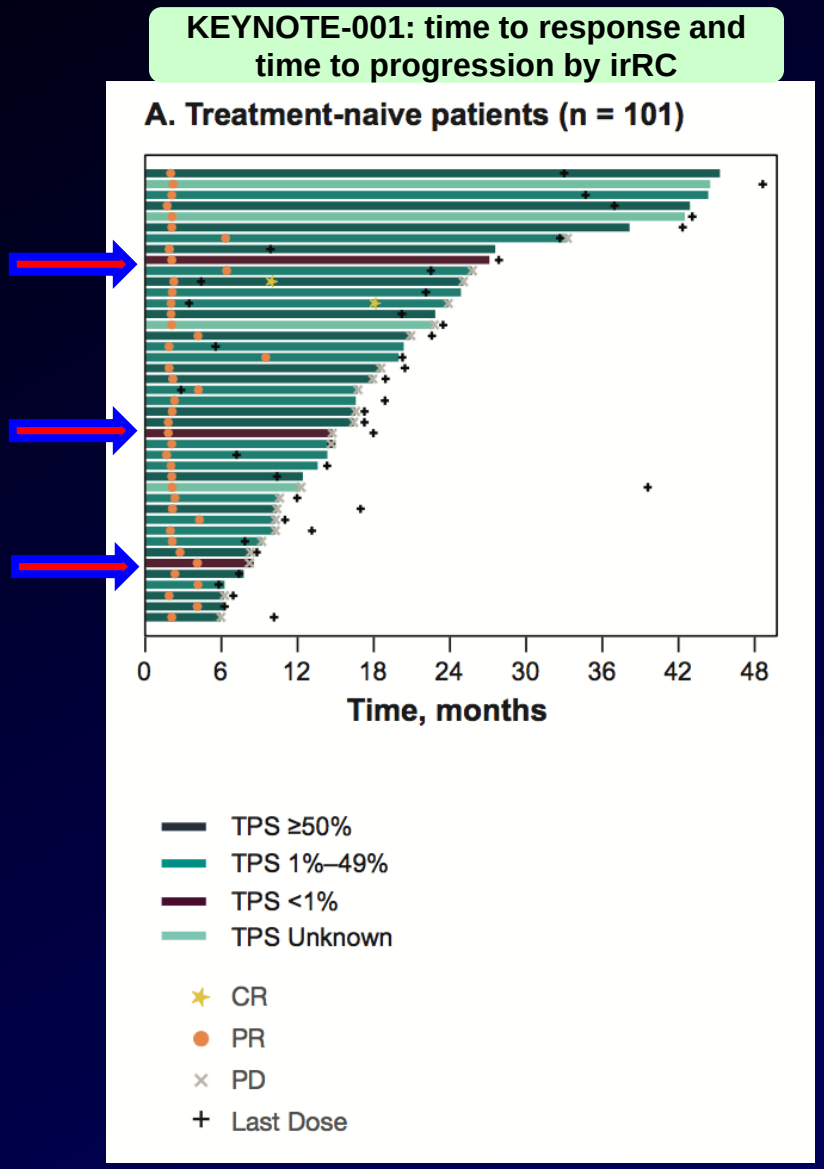






Lopes et al., ASCO 2018

PD-L1 <1% patients may respond to ICIs



Felip et al., ASCO 2018

PD-L1

- Dynamic marker (PD-L1 expression at a single time point may not reflect an evolving immune response in the blood or tumor microenviroment)
- Assessment on small biopsies may not exactly reflect tumor heterogeneity
- Imperfect biomarker (other biomarkers of response in PD-L1 neg patients? TMB? TILs)

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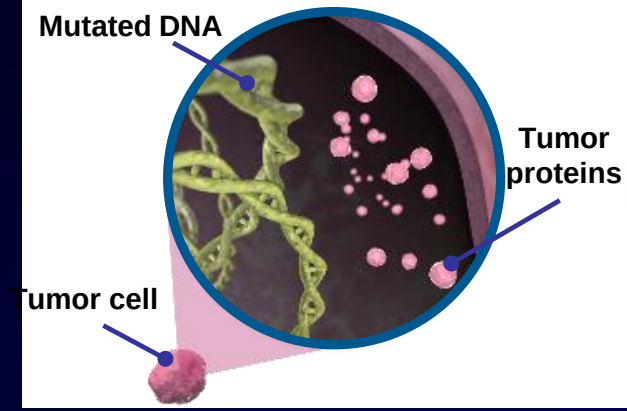
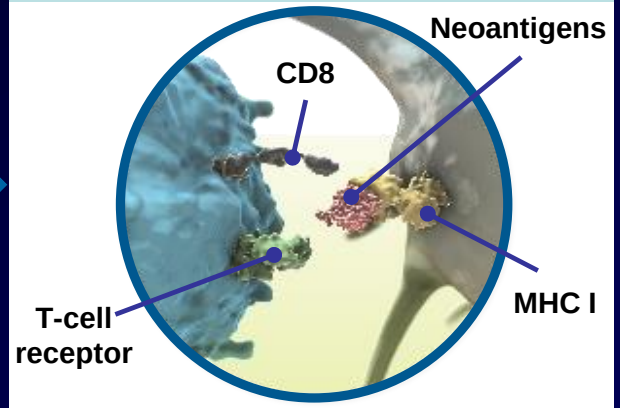
Tumors with high TMB are a rational target for ICIs

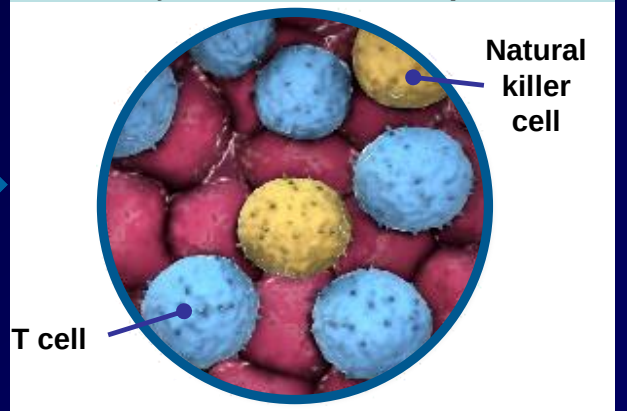
Tumor cells with high **TMB**…[1,2]



…may have high **neoantigen load**…[2]



…which can lead to high tumor immunogenicity and increased T-cell reactivity and **antitumor response**[2–6]



The high immunogenicity of tumors with high mutation burden makes them a rational target for treatment with I-O therapies[2]

CD8 = cluster of differentiation 8; DNA = deoxyribonucleic acid; I-O = immuno-oncology; MHC = major histocompatibility complex; TMB = tumor mutational burden.

[1]Stratton et al. Nature 2009
[2]Schumacher et al. Science 2015
[3]Chalmers et al. Genome Med 2017
[4]Chabanon et al. Clin Cancer Res 2017
[5]Kim et al. Ann Oncol 2016
[5]Giannakis et al. Cell Rep 2016

High TMB is predictive for response to ICIs in multiple tumor types

- **FoundationOne®: Retrospective analysis of 1638 patients who had TMB assessment using FoundationOne®[a1]**
- In 102 patients treated with single-agent anti–PD-1/PD-L1 therapy, high TMB (≥20 mut/Mb) correlated with significantly better outcomes compared with low to intermediate TMB (1–19 mut/Mb)[3]
  - CR/PR rate = 46% vs 14%; *P* = 0.0025
  - PFS = 10 months vs 2.2 months; *P* = 0.0005
  - OS = 11.1 months vs not reached; *P* = 0.0557

- **MSKCC cohort: ~1800 patients across 10 tumor types received commercial PD-(L)1 and/or CTLA-4 inhibitor therapy[2]**
- TMB was assessed using the MSK-IMPACT™ NGS gene panel[2]
- Data demonstrated improved survival/outcome, with greater mutations across all tumor types except glioma (**Figure**)[2]

MSKCC cohort: Hazard ratio–optimized cutoff (mut/Mb)[4]

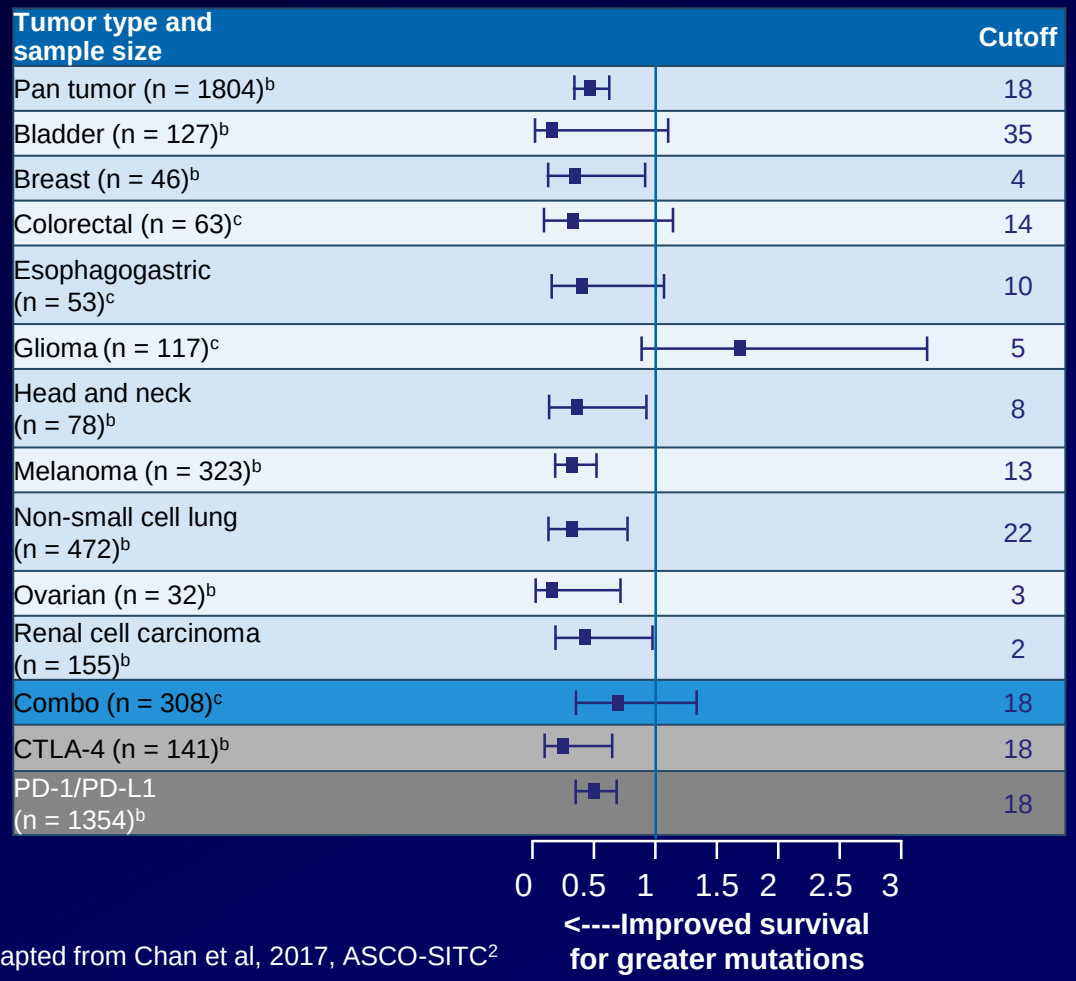
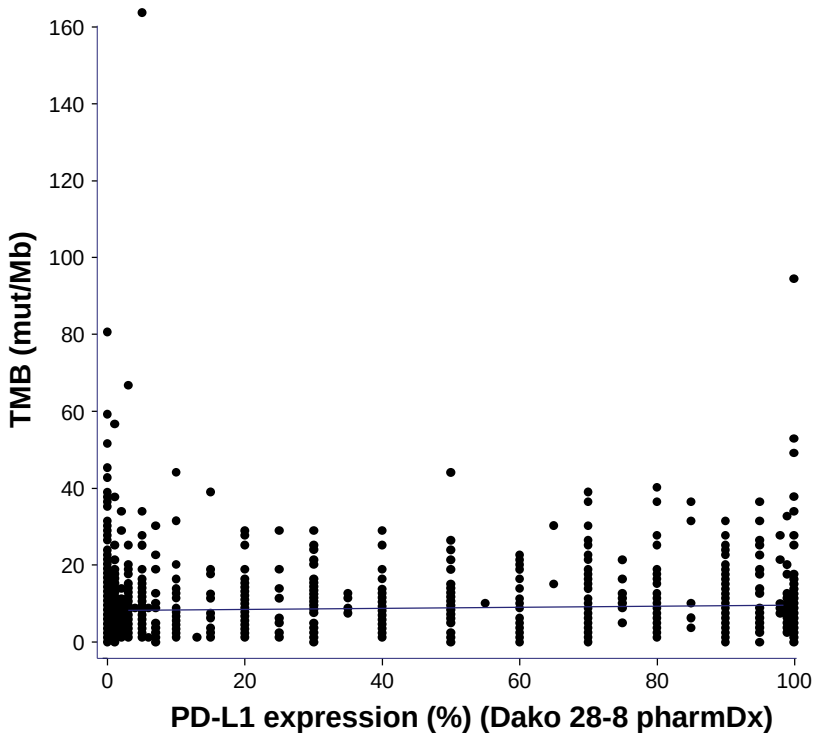


Figure adapted from Chan et al, 2017, ASCO-SITC[2]

[1]Goodman et al., Mol Cancer Ther 2017
[2]Chan et al., ASCO-SITC 2017

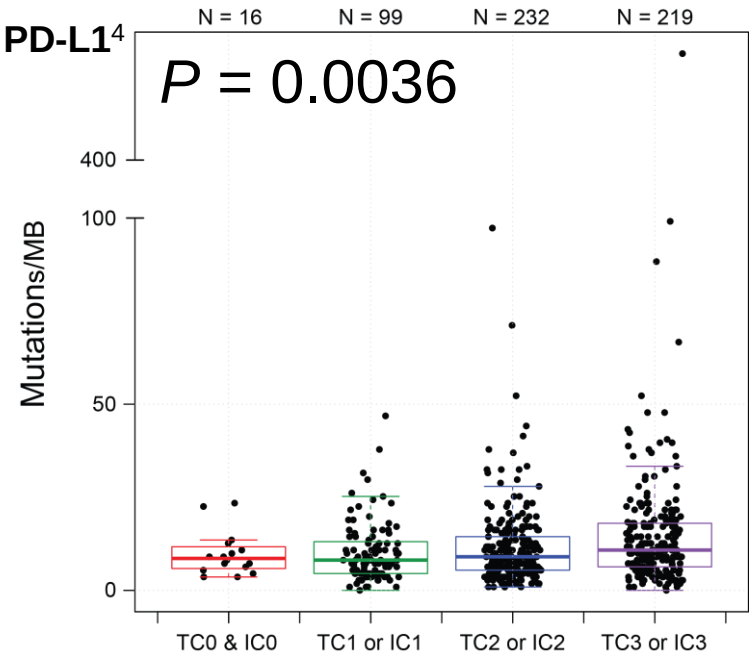
TMB and PD-L1 are different markers

CheckMate 227 (NSCLC)[3,a]



[a]Symbols (dots) in the scatterplot may represent multiple data points, especially for patients with <1% tumor PD-L1 expression. The black line shows the relationship between TMB and PD-L1 expression, as described by a linear regression model. Cutoff value for TMB expression was TMB ≥10 and TMB <10 mut/Mb.

TMB vs PD-L1[4]

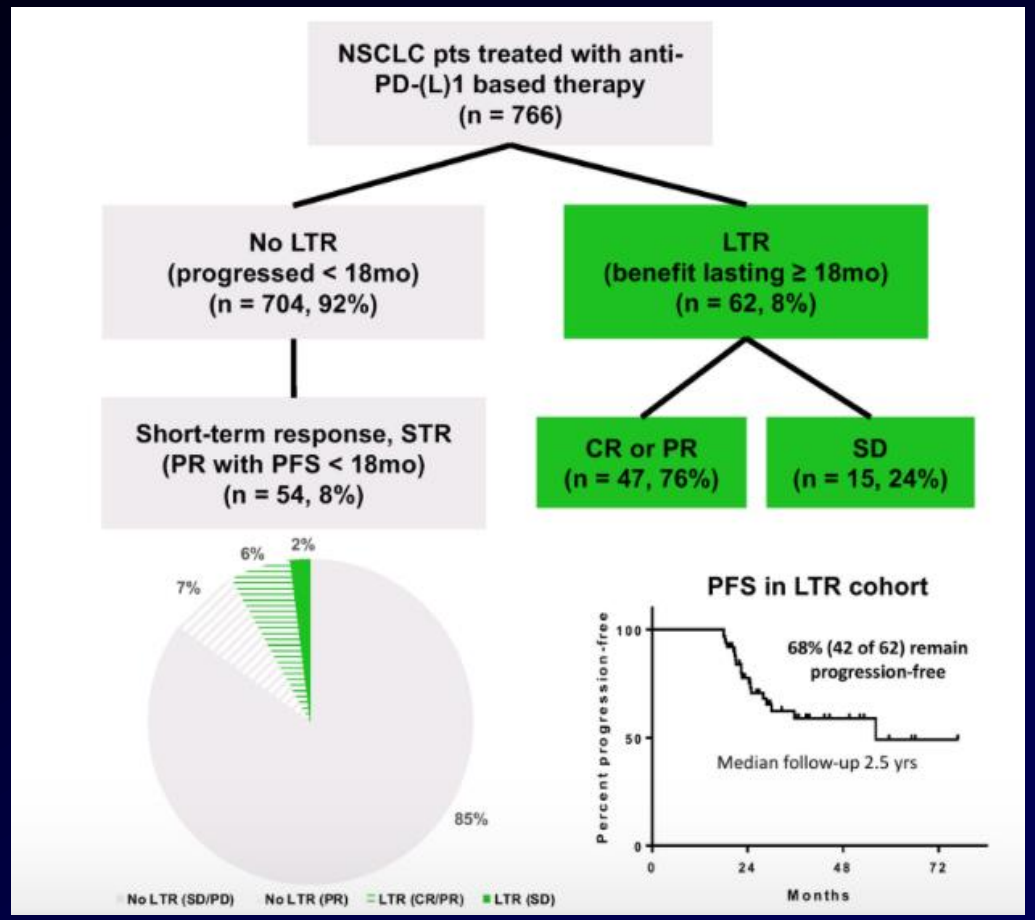


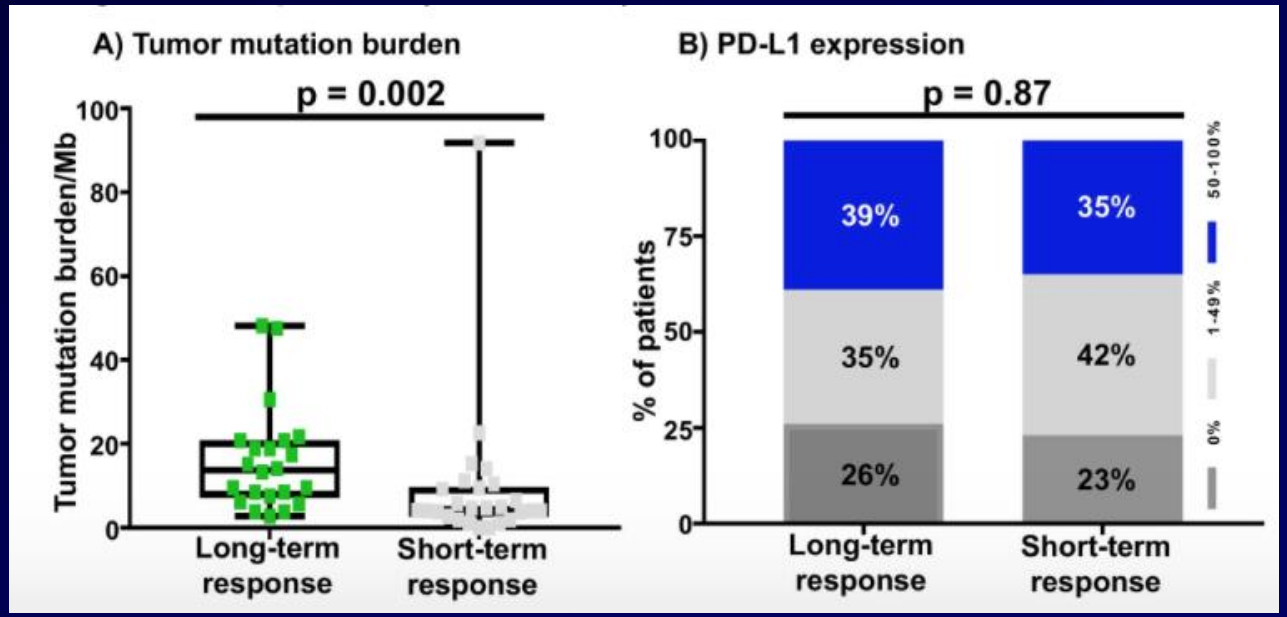
- Analyses from CheckMate 012, 026, and 227 show no association between TMB and PD-L1 expression[1–3]
- Data from the atezolizumab POPLAR, BIRCH, FIR (atezolizumab) studies also suggest that TMB and PD-L1 expression do not, or weakly, co-associate[4]

TMB was assessed by whole exome sequencing in CheckMate 026 and FoundationOne CDx™ in CheckMate 227.
Mut/Mb = mutations per megabase; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1; TMB = tumor mutational burden;

[1]Hellmann et al. Cancer Cell 2018
[2]Carbone et al. NEJM 2017
[3]Hellmann et al. NEJM 2018
[4]Kowantetz et al., WCLC 2016

TMB as molecular predictor of long-term benefit from anti-PD-(L)-1 therapy





Rizvi et al., ASCO 2018

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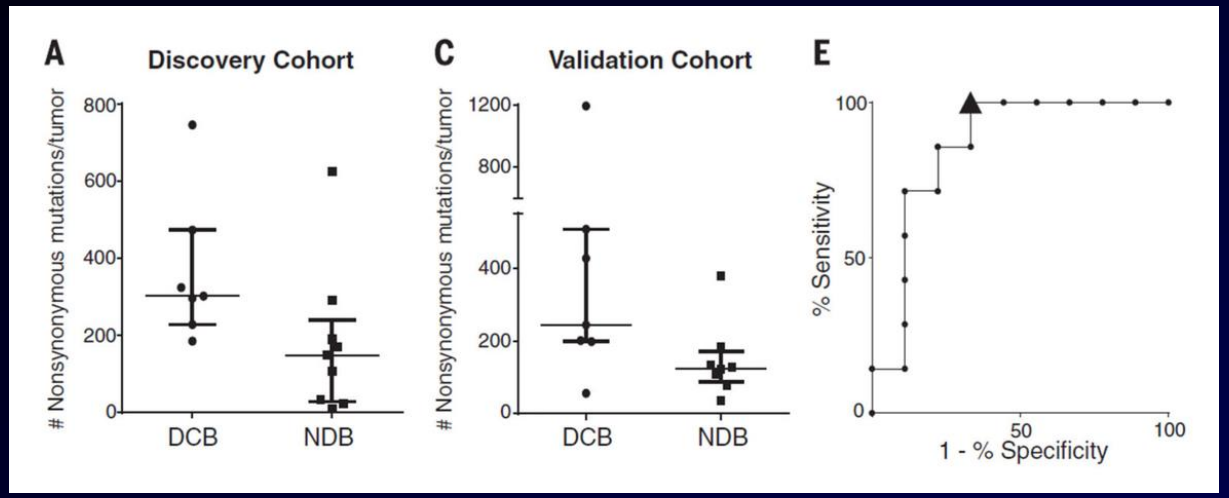
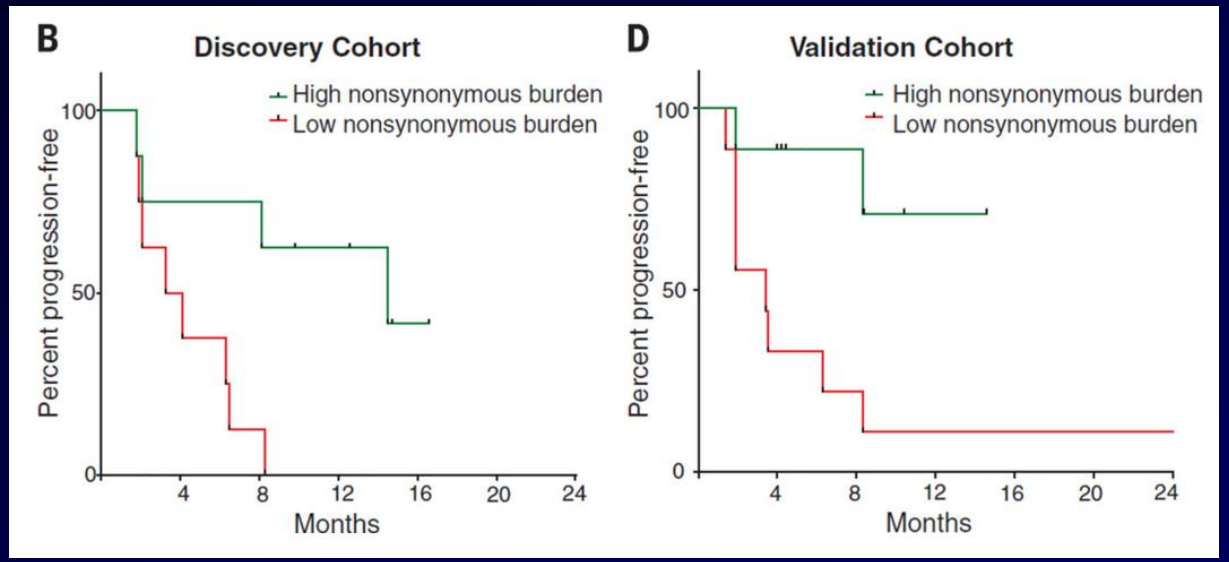
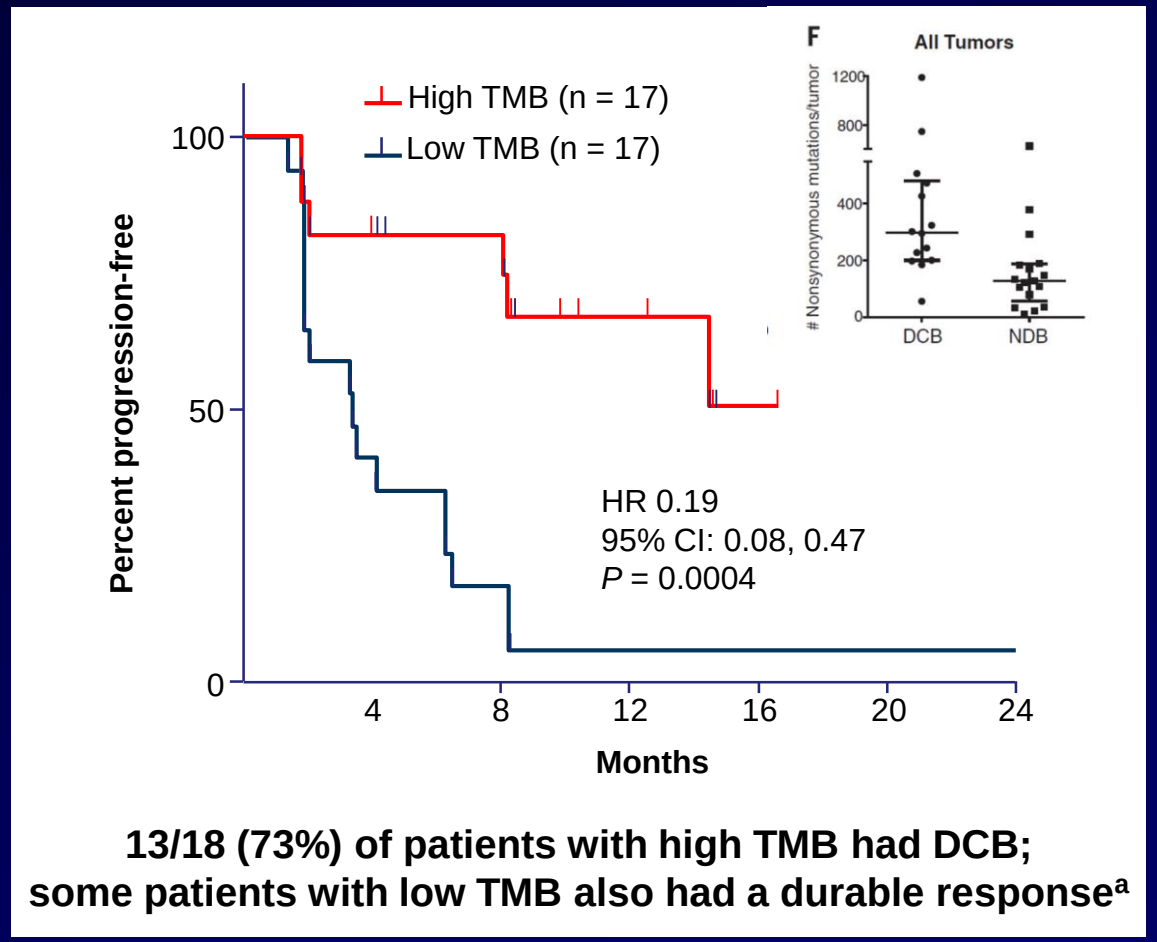
Pembrolizumab: clinical benefit by TMB







13/18 (73%) of patients with high TMB had DCB; some patients with low TMB also had a durable response[a]

TMB was assessed by whole exome sequencing (Illumina HiSeq 2000). High and low nonsynonymous TMB were defined as mutation burdens above and below the median (of 200), respectively. [a]DCB was defined as partial or stable response lasting >6 months; 5 of 18 tumors with ≥178 nonsynonymous mutations had NDB, and 1 of 18 tumors with 56 nonsynonymous mutations had DCB.

Rizvi et al., Science 2015

Atezolizumab: clinical benefit by TMB

	2L+ NSCLC unselected (n = 92)	
	TMB-evaluable population (n = 54 vs 38) [b,c]	High TMB (≥16.2 mut/Mb)
OS, HR[a] (95% CI)	0.65 (0.38, 1.12)	0.5 (0.15, 1.67)
PFS, HR[a] (95% CI)	0.98 (0.63, 1.53)	0.49 (0.19, 1.3)
ORR, atezolizumab/docetaxel	13%/15%	20%/8%

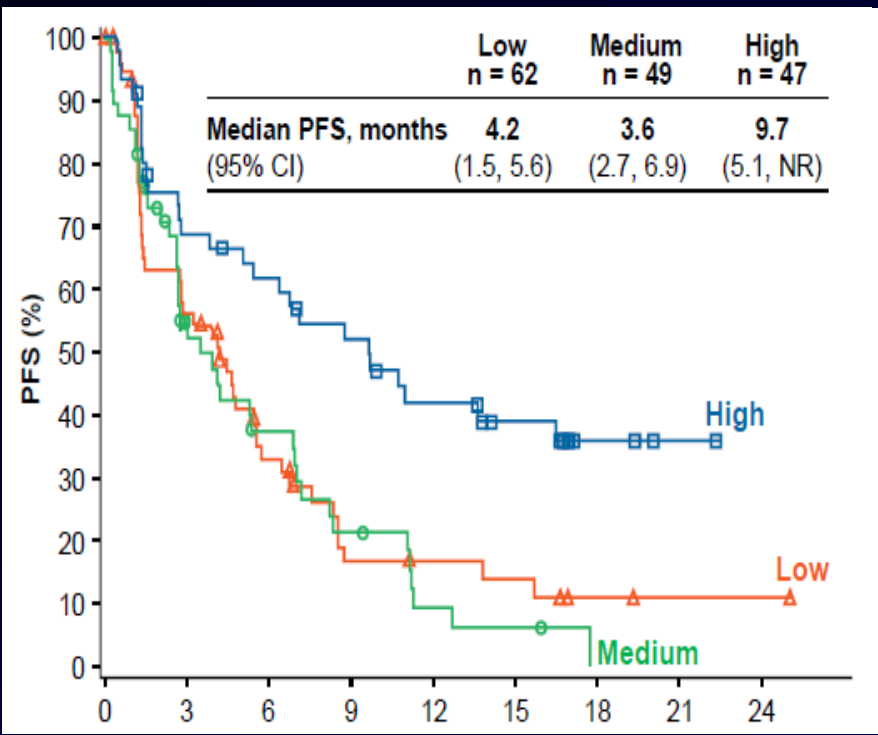
High TMB was associated with atezolizumab clinical benefit in all-comers with 2L+ NSCLC

[a]HR = efficacy-evaluable patients, atezolizumab vs docetaxel at/above cutoff. [b]Number of patients in docetaxel vs atezolizumab treatment arms. [c]Includes 3 patients who did not receive any study treatments.

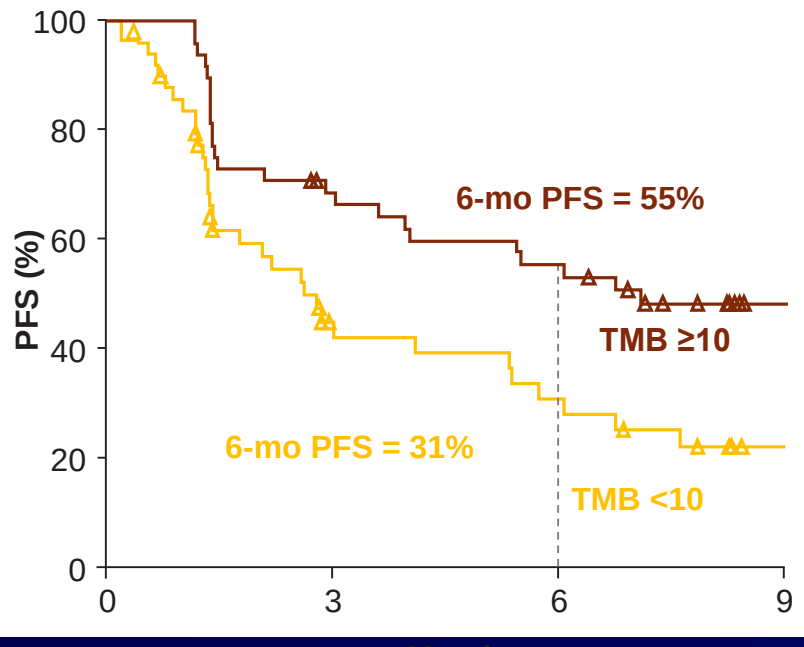
Table adapted from Kowanetz et al, WCLC 2016

Nivolumab ± ipilimumab: clinical benefit by TMB

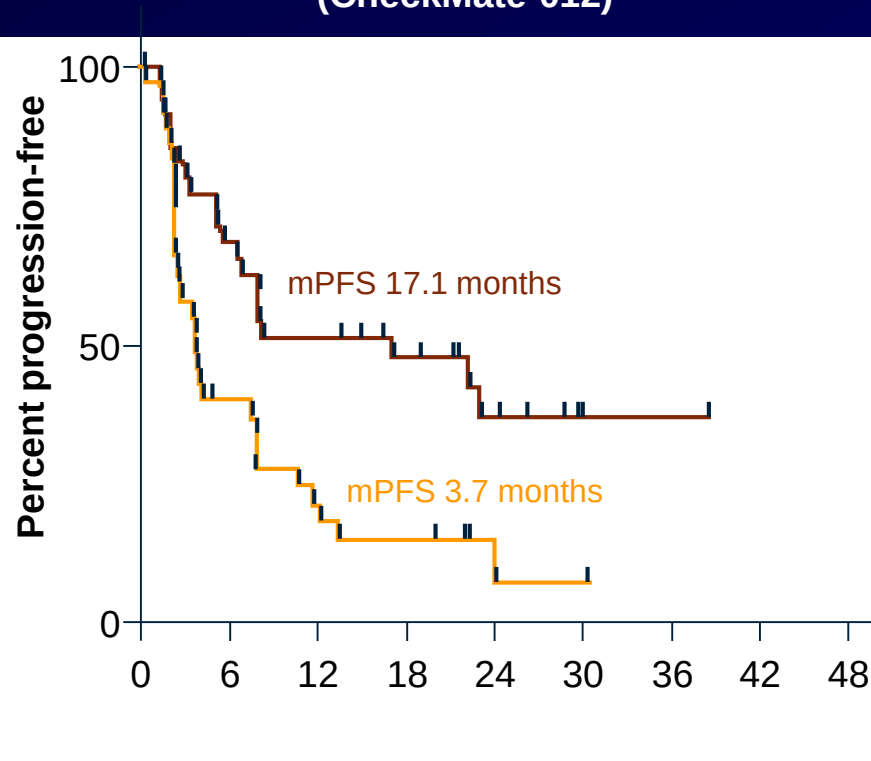
Nivolumab[1,a] (CheckMate-026)



Nivolumab + ipilimumab[2,b] (CheckMate-568)



Nivolumab + ipilimumab[3,a] (CheckMate-012)



[a]TMB was assessed by whole exome sequencing; TMB was divided into tertiles, with low TMB defined as 0 to <100 mutations, medium TMB as ≥100 to 242 mutations, and high TMB as ≥243 mutations. [b]High TMB defined as ≥10 mutations per megabase as assessed by FoundationOne CDx™. FoundationOne CDx™ uses next-generation sequencing to detect substitutions, insertions and deletions, and copy number alterations in 324 genes and select gene rearrangements.
I-O = immuno-oncology; mo = months; PFS = progression-free survival; TMB = tumor mutational burden.

[1]Carbone et al., NEJM 2016
[2]Ramalingam et al., AACR 2018
[3]Hellmann et all., Cancer Cell 2018

CheckMate-227: Nivo ± Ipi vs nivo + CT vs CT

Key eligibility criteria

- Stage IV or recurrent squamous or nonsquamous NSCLC
- No previous anticancer therapy
- Tumor must have been tested for PD-L1 expression during screening
- ECOG PS 0 or 1
- Measurable disease by RECIST criteria

Part 1a
N = 1189

PD-L1 expression ≥1%

- Nivolumab 3 mg/kg IV Q2W + ipilimumab 1 mg/kg Q6W (n = 396)
- Chemotherapy[a] (n = 397)
- Nivolumab 240 mg IV Q2W (n = 396)

PD-L1 expression <1%

N = 550
Part 1b

- Nivolumab 3 mg/kg IV Q2W + ipilimumab 1 mg/kg Q6W (n = 187)
- Chemotherapy[a] (n = 186)
- Nivolumab 360 mg IV Q3W + chemotherapy[a] (n = 177)

Patients for PD-L1 co-primary endpoint
- Nivolumab + ipilimumab
- Chemotherapy[a]

Patients for TMB co-primary endpoint
- Nivolumab + ipilimumab
- Chemotherapy[a]

Patients for PD-L1 <1% secondary endpoint
- Chemotherapy[a]
- Nivolumab + chemotherapy[a]

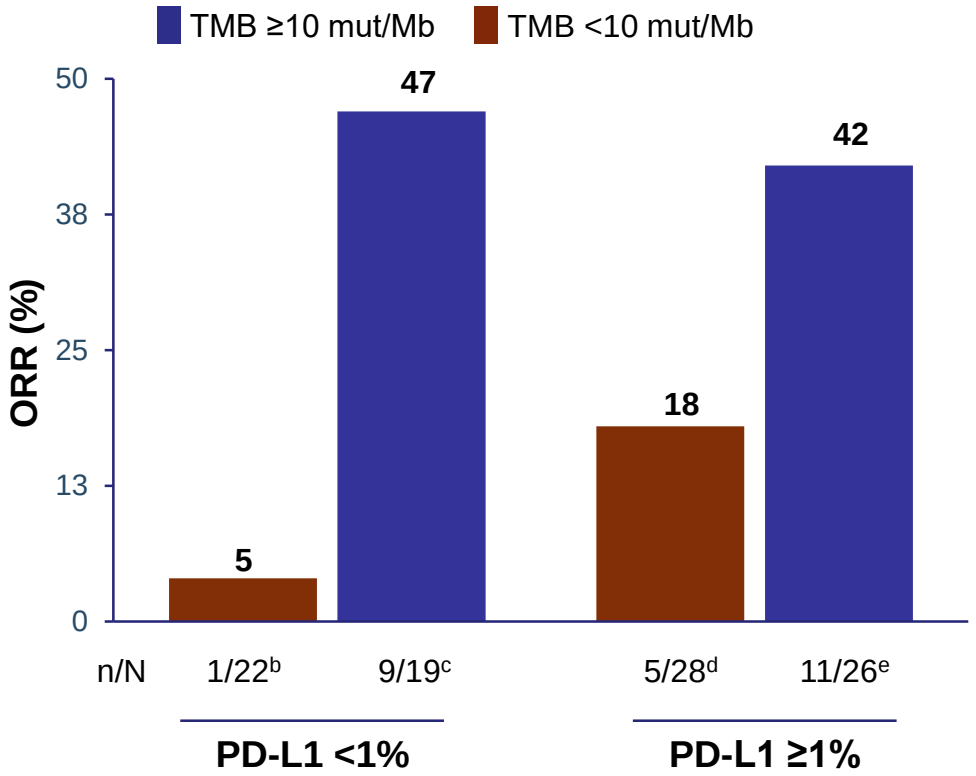
[a]**Nonsquamous:** pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy.
Squamous: gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤4 cycles.

FoundationOne CDx™ uses next-generation sequencing to detect substitutions, insertions and deletions, and copy number alterations in 324 genes and select gene rearrangements. 1L = first line; ECOG PS = Eastern Cooperative Oncology Group performance status; IV = intravenous; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1; Q2W = every 2 weeks; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST = Response Evaluation Criteria In Solid Tumors; TMB = tumor mutational burden.

Hellmann et al., NEJM 2018

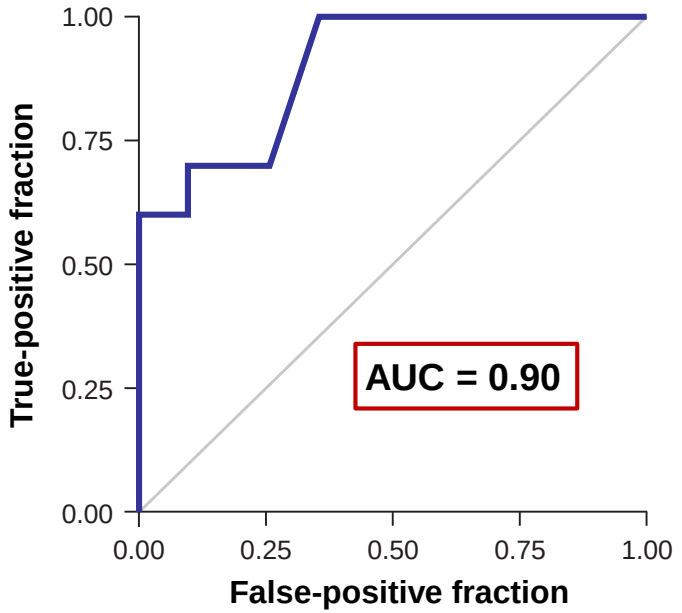
CheckMate-568: greater response to Nivo + Ipi in NSCLCs with high TMB irrespective of PD-L1 expression

Responses observed in TMB ≥10 mut/Mb irrespective of tumor PD-L1 expression[a]

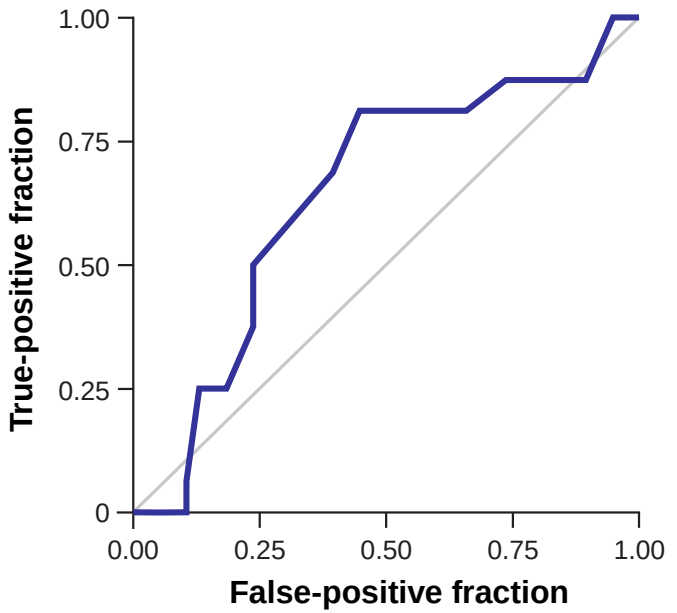


[a]ORR for all treated patients: 41% in PD-L1 ≥1% subgroup (n = 138) and 15% in PD-L1 <1% subgroup (n = 114). [b]CR = 0. [c]CR = 16%. [d]CR = 4%. [e]CR = 4%.

TMB in PD-L1 <1% patients (n = 41)



TMB in PD-L1 ≥1% patients (n = 54)



- TMB was an informative classifier of response with nivolumab + ipilimumab in patients with <1% tumor PD-L1 expression and ≥1% tumor PD-L1 expression

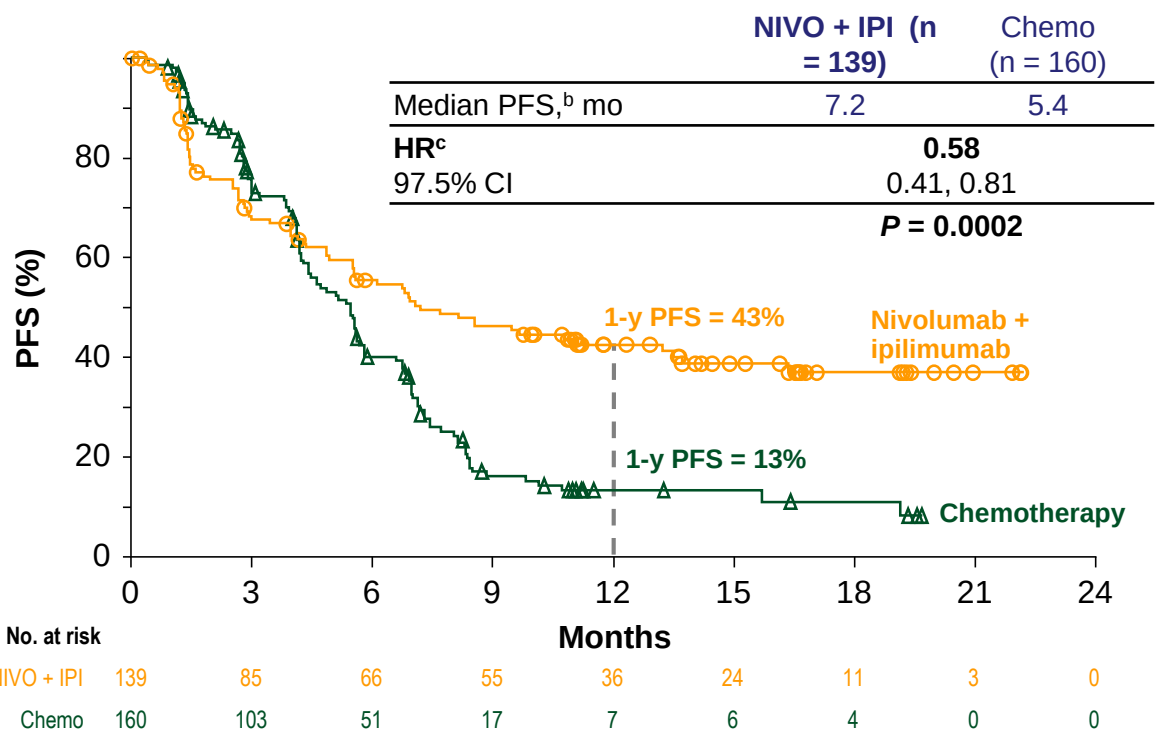
TMB assessed by FoundationOne CDx™ using next-generation sequencing to detect substitutions, insertions and deletions, and copy number alterations in 324 genes and select gene rearrangements. AUC = area under the curve; CR = complete response; mut/Mb = mutations per megabase; NSCLC = non-small cell lung cancer; ORR = objective response rate; PD-L1 = programmed death ligand 1; ROC = receiver operating characteristic; TMB = tumor mutational burden.

Ramalingam et al., AACR 2018

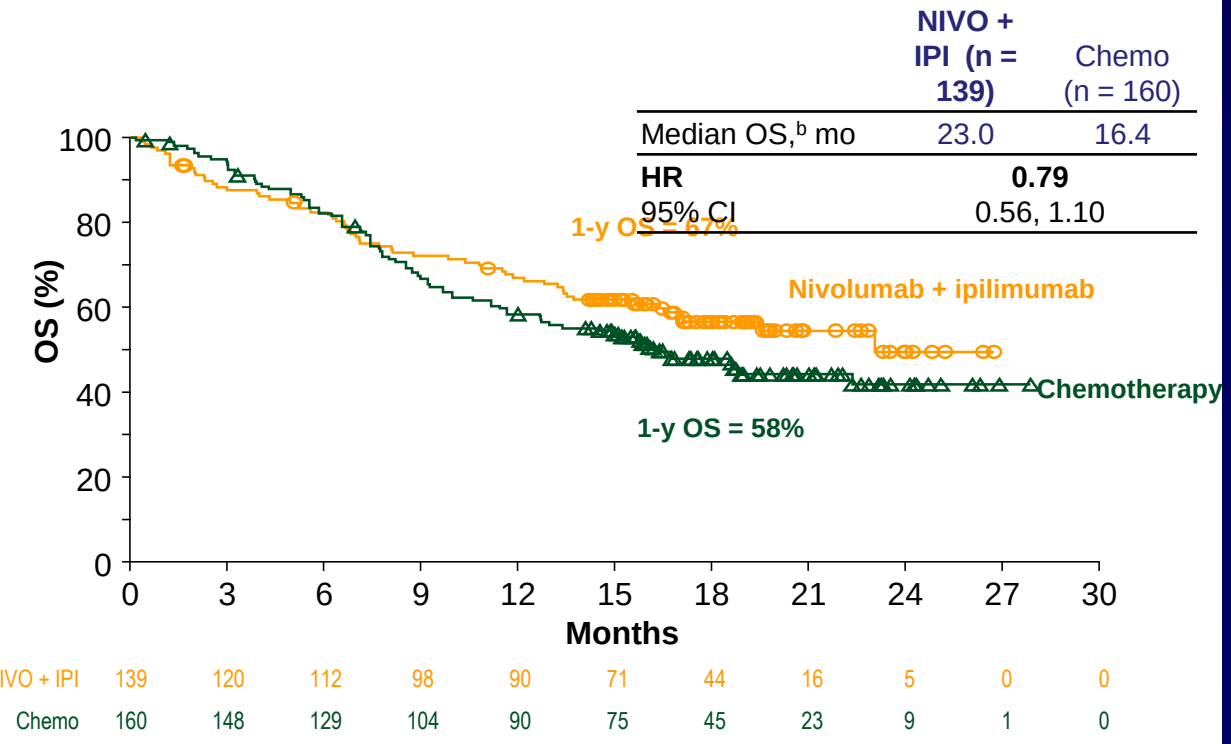
CheckMate-227: high TMB – PFS and preliminary OS

All randomized patients (N = 1739) → **TMB-evaluable patients (n = 1004)** → High TMB[b] Nivolumab + ipilimumab (n = 139) / **High TMB Chemotherapy (n = 160)**

PFS[a] with NIVO + IPI vs chemotherapy in patients with high TMB[b]



Preliminary OS[c] with NIVO + IPI vs chemotherapy in patients with high TMB[b]



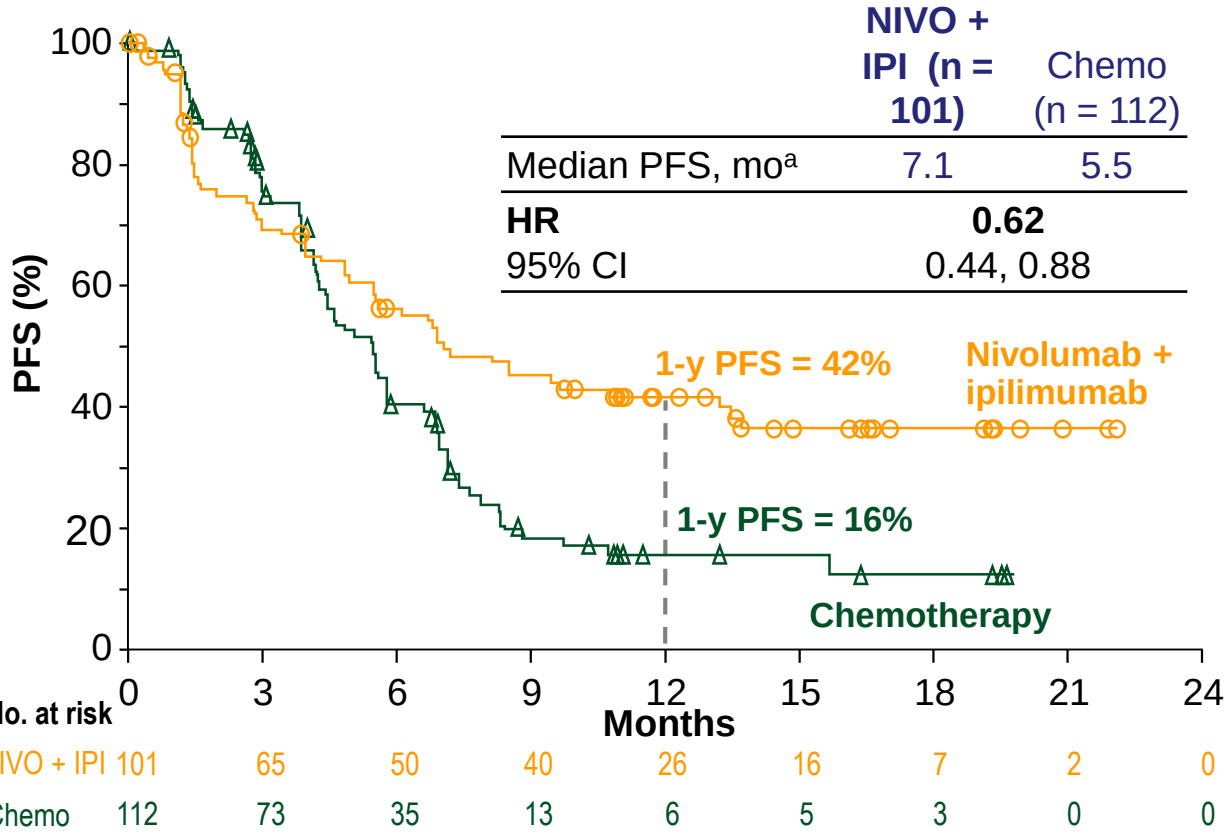
[a]Per blinded independent central review; median follow-up 13.6 months for NIVO + IPI and 13.2 months for chemotherapy. [b]High TMB defined as ≥10 mut/Mb. TMB was assessed by Foundation One CDx™. [c]In the first 1.5 months, 8 deaths occurred in the NIVO + IPI arm (4 due to disease progression; 1 never treated; 2 due to AEs unrelated to study drug; 1 due to AEs related to study drug), and 2 deaths occurred in the chemo arm (1 due to disease progression; 1 due to multiple brain infarctions related to carboplatin).

1L = first line; AE = adverse event; chemo = chemotherapy; CI = confidence interval; IPI = ipilimumab; mut/Mb = mutations per megabase; NIVO = nivolumab; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; TMB = tumor mutational burden

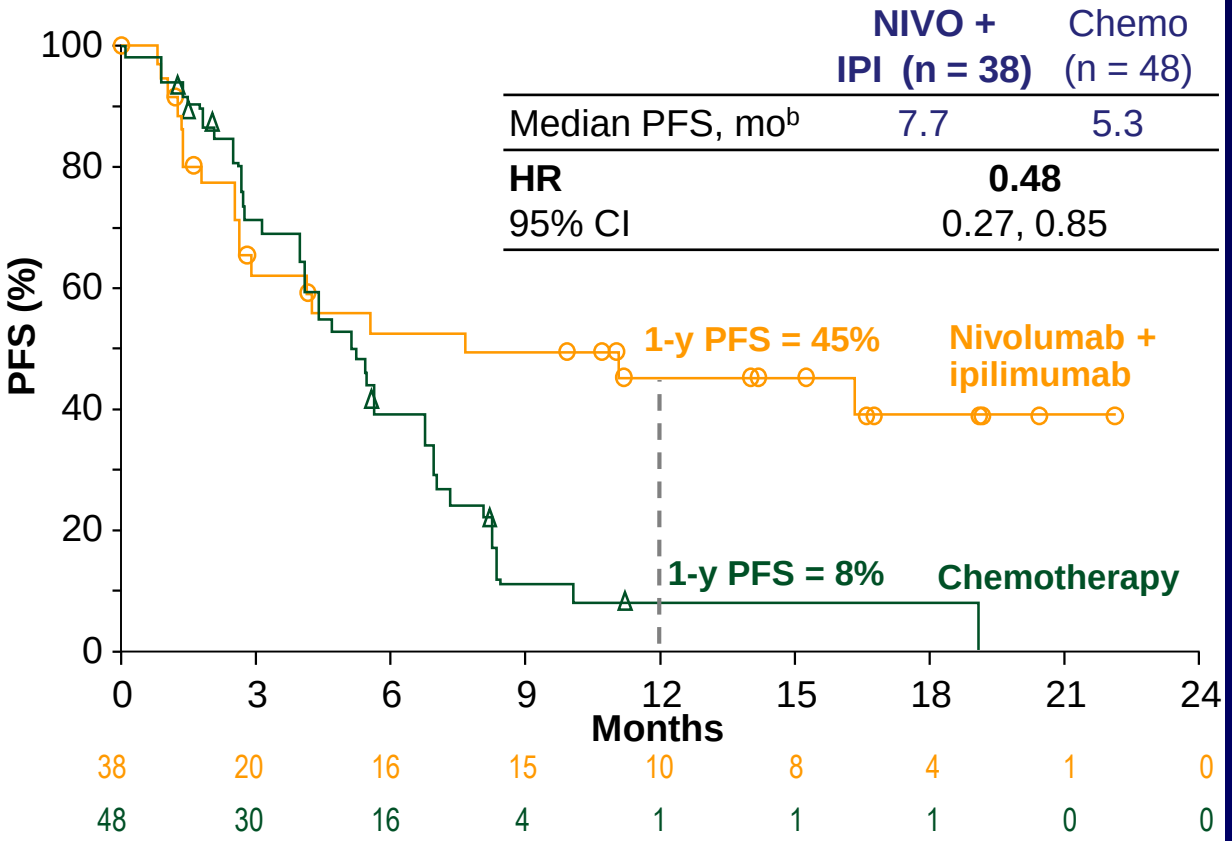
Hellmann et al., NEJM 2018

CheckMate-227: high TMB – PFS by PD-L1 expression

≥1% PD-L1 expression



<1% PD-L1 expression



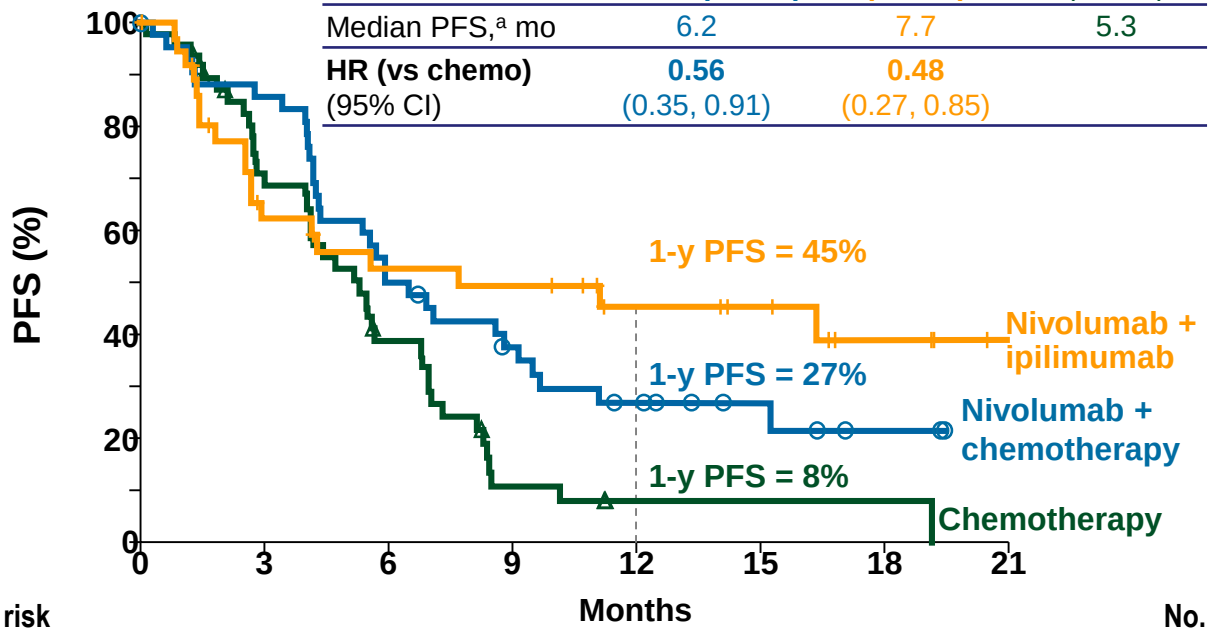
High TMB defined as ≥10 mut/Mb. [a]95% CI: NIVO + IPI (5.5, 13.5 mo), chemo (4.3, 6.6 mo). [b]95% CI: NIVO + IPI (2.7 mo, NR), chemo (4.0, 6.8 mo). FoundationOne CDx™ uses next-generation sequencing to detect substitutions, insertions and deletions, and copy number alterations in 324 genes and select gene rearrangements.
1L = first line; chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; NIVO = nivolumab; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1; PFS = progression-free survival; TMB = tumor mutational burden.

Hellmann et al., NEJM 2018

CheckMate-227: PFS by TMB in < 1% PD-L1 expression

TMB ≥10 mut/Mb and <1% Tumor PD-L1 expression

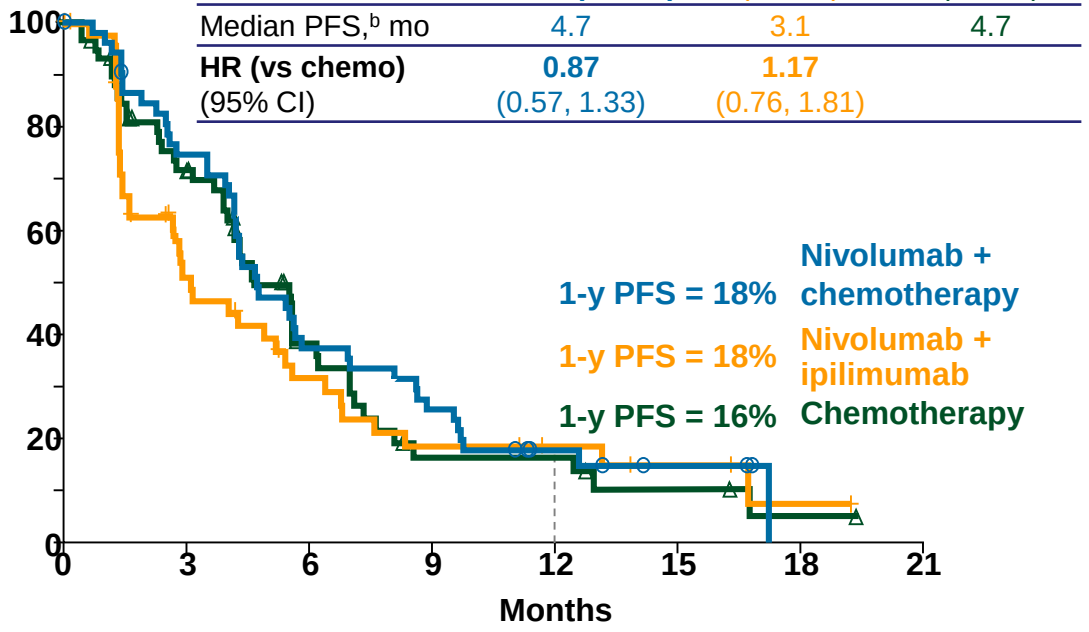
	NIVO + chemo (n = 43)	NIVO + IPI (n = 38)	Chemo (n = 48)
Median PFS,[a] mo	6.2	7.7	5.3
HR (vs chemo) (95% CI)	**0.56** (0.35, 0.91)	**0.48** (0.27, 0.85)	



No. at risk								
NIVO + chemo	43	36	21	14	9	5	2	0
NIVO + IPI	38	20	16	15	10	8	4	1
Chemo	48	30	16	4	1	1	1	0

TMB <10 mut/Mb and <1% Tumor PD-L1 expression

	NIVO + chemo (n = 54)	NIVO + ipi (n = 52)	Chemo (n = 59)
Median PFS,[b] mo	4.7	3.1	4.7
HR (vs chemo) (95% CI)	**0.87** (0.57, 1.33)	**1.17** (0.76, 1.81)	



No. at risk								
NIVO + chemo	54	38	19	13	6	3	0	0
NIVO + IPI	52	22	12	7	5	3	1	0
Chemo	59	39	16	6	6	3	1	0

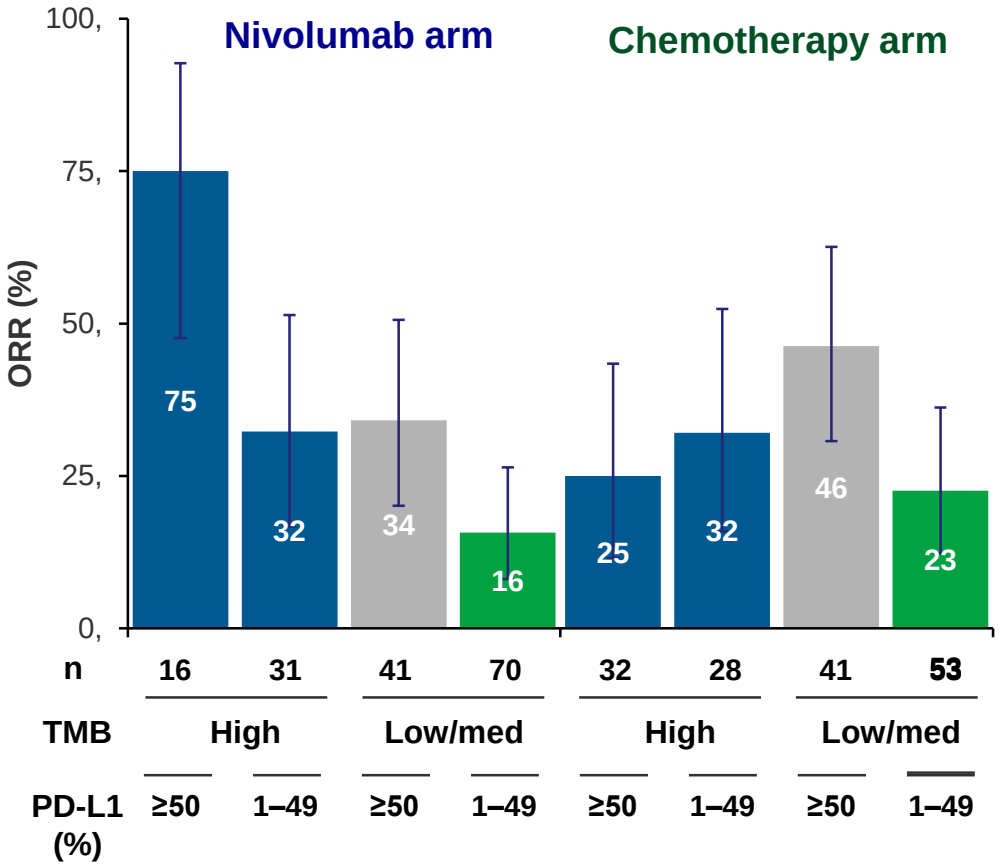
Exploratory analysis. [a]95% CI: NIVO + chemo (4.3, 9.1 mo), NIVO + IPI (2.7, NR mo), chemo (4.0, 6.8 mo). [b]95% CI: NIVO + chemo (4.2, 6.9 mo), NIVO + IPI (1.6, 5.4 mo), chemo (3.9, 6.2 mo). TMB assessed by FoundationOne CDx™ using next-generation sequencing to detect substitutions, insertions and deletions, and copy number alterations in 324 genes and select gene rearrangements.
1L = first line; chemo = chemotherapy; CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab; NR = not reached; mut/Mb = mutations per megabase; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1; PFS = progression-free survival; TMB = tumor mutational burden.

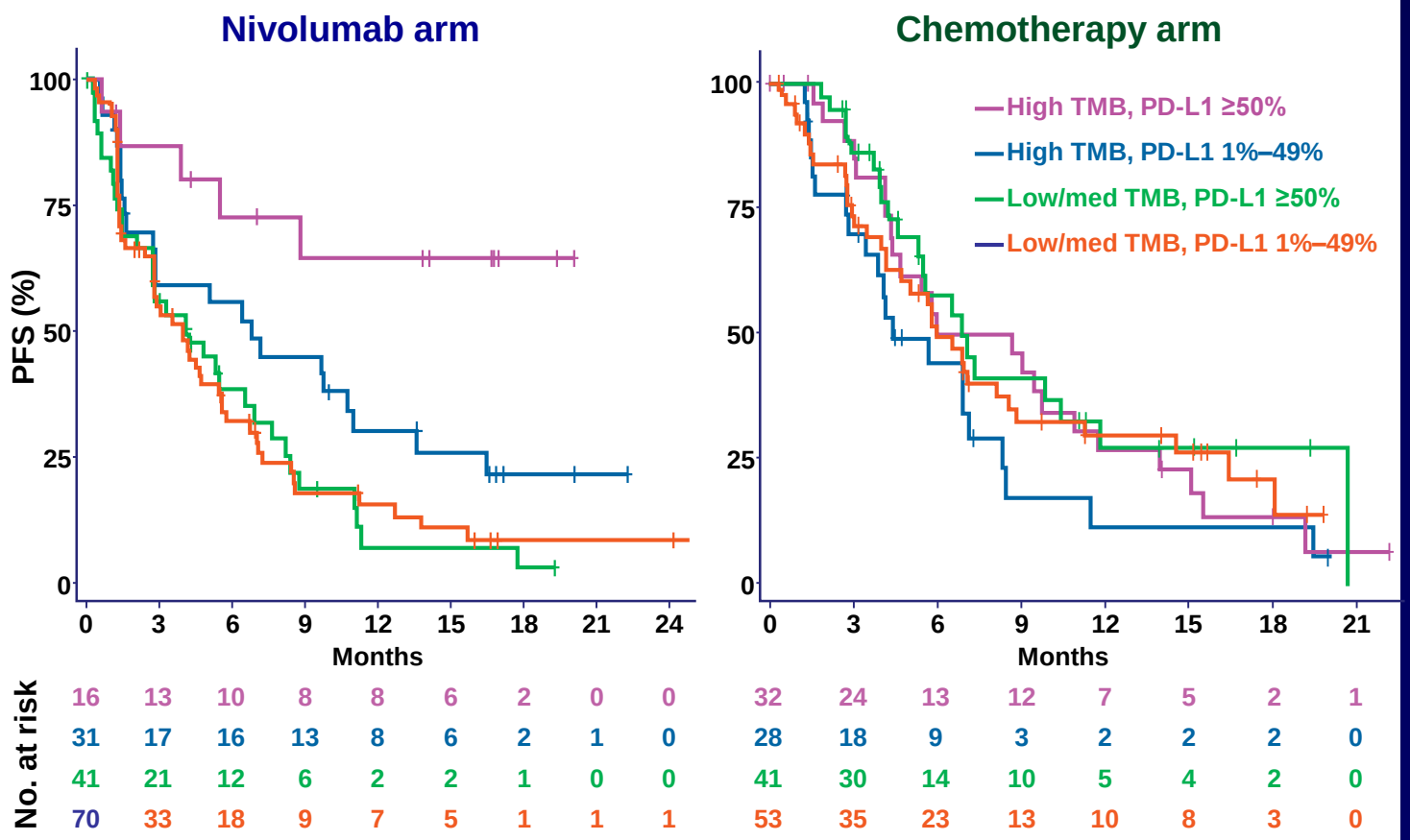
Borghaei et al., ASCO 2018

Outline

- Biomarker selection for immunotherapy in NSCLC: PD-L1
- The emerging role of tumor mutation burden (TMB) as opposed to PD-L1
- TMB in NSCLC
- Is “super-selection” possible?
- Unsolved issues with TMB

CheckMate-026: Nivo 1L NSCLC



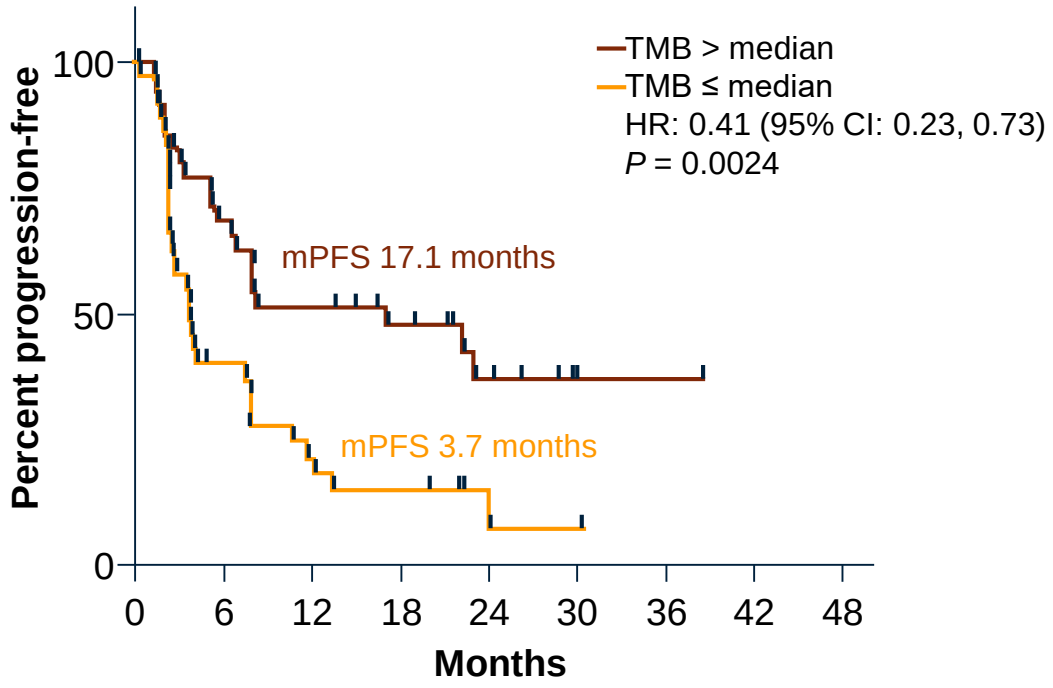


Patients with high TMB and tumor PD-L1 expression ≥50% showed a higher response rate and longer PFS than those with one of these factors (CheckMate 026), although the patient numbers are small in this high/high group

NSCLC = non-small cell lung cancer; ORR = objective response rate; PD-L1 = programmed death ligand 1; PFS = progression-free survival; TMB = tumor mutational burden. TMB assessed by whole exome sequencing and reported by tertile: 0 to <100 mutations (low), 100 to 242 mutations (med), and >243 mutations (high).

Peters et al. AACR 2017

CheckMate-012: Nivo + Ipi in 1L NSCLC



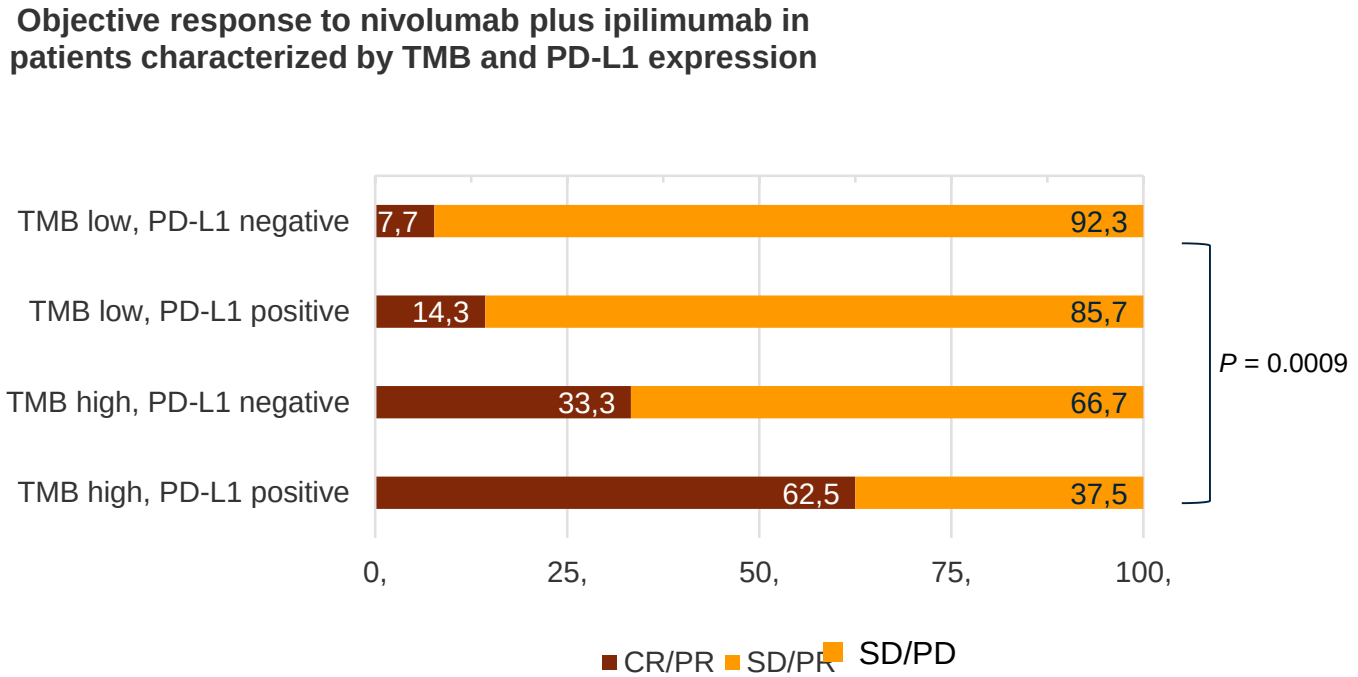


Figure adapted from Hellmann et al, 2018, *Cancer Cell.*

High TMB/PD-L1 + status improved objective response rate

TMB was assessed by whole exome sequencing. 1L = first line; CI = confidence interval; CR = complete response; HR = hazard ratio; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PR = partial response; TMB = tumor mutational burden.

Hellmann et al. Cancer Cell 2018

Outline

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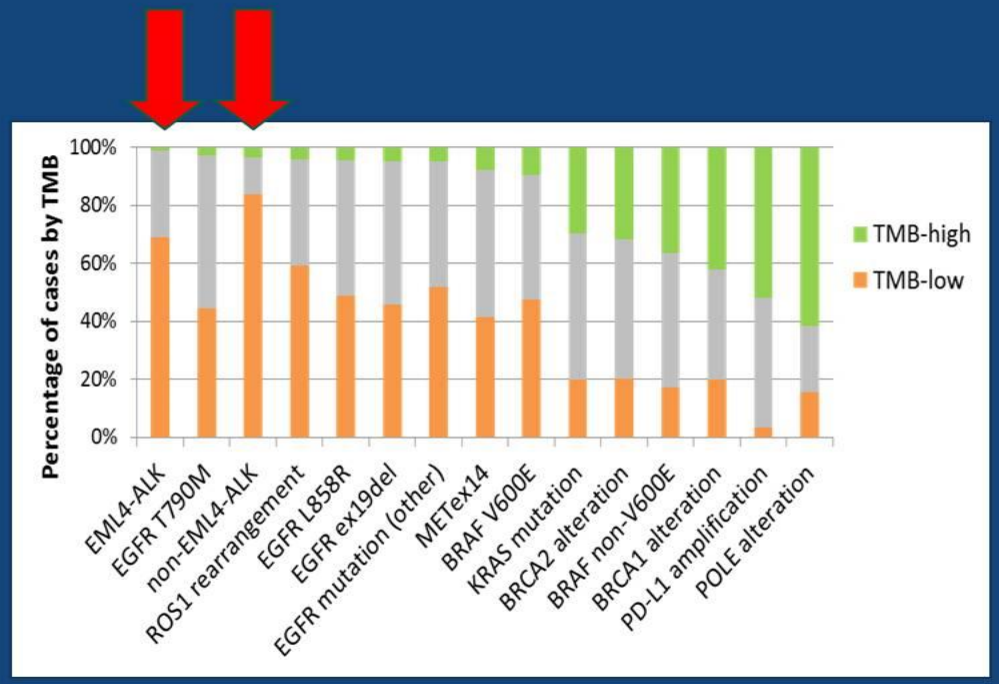
High *vs* low TMB: definitions

Study/reference	Technique	Definition of high TMB (method of determination)
Hellmann *et al.* 2018 (29)	WES	≥158 mutations (median)
Hellmann *et al.* 2018 (CheckMate 227) (26)	FoundationOne CDx	≥10 mutations/Mb (ROC)
Rizvi *et al.* 2018 (30)	MSK-IMPACT	≥7.4 mutations/Mb (median)
Kowanetz *et al.* 2017 (47)	FoundationOne	≥13.5 mutations/Mb (75th percentile; first-line treatment)
		≥17.1 mutations/Mb (75th percentile; second-line$^{\#}$ treatment)
Chalmers *et al.* 2017 (31)	FoundationOne CDx	≥20 mutations/Mb (?¶)
Carbone *et al.* 2017 (CheckMate 026) (27)	WES	≥243 mutations (?¶)
Rizvi *et al.* 2015 (25)	WES	≥209 mutations (median)

¶, no information was provided on how the cut-off value was determined; $^{\#}$, second-line treatment or later. WES, whole exome sequencing; MSK-IMPACT, Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets; ROC, receiver operating characteristics; TMB, tumor mutation burden; CDx, companion diagnostic test.

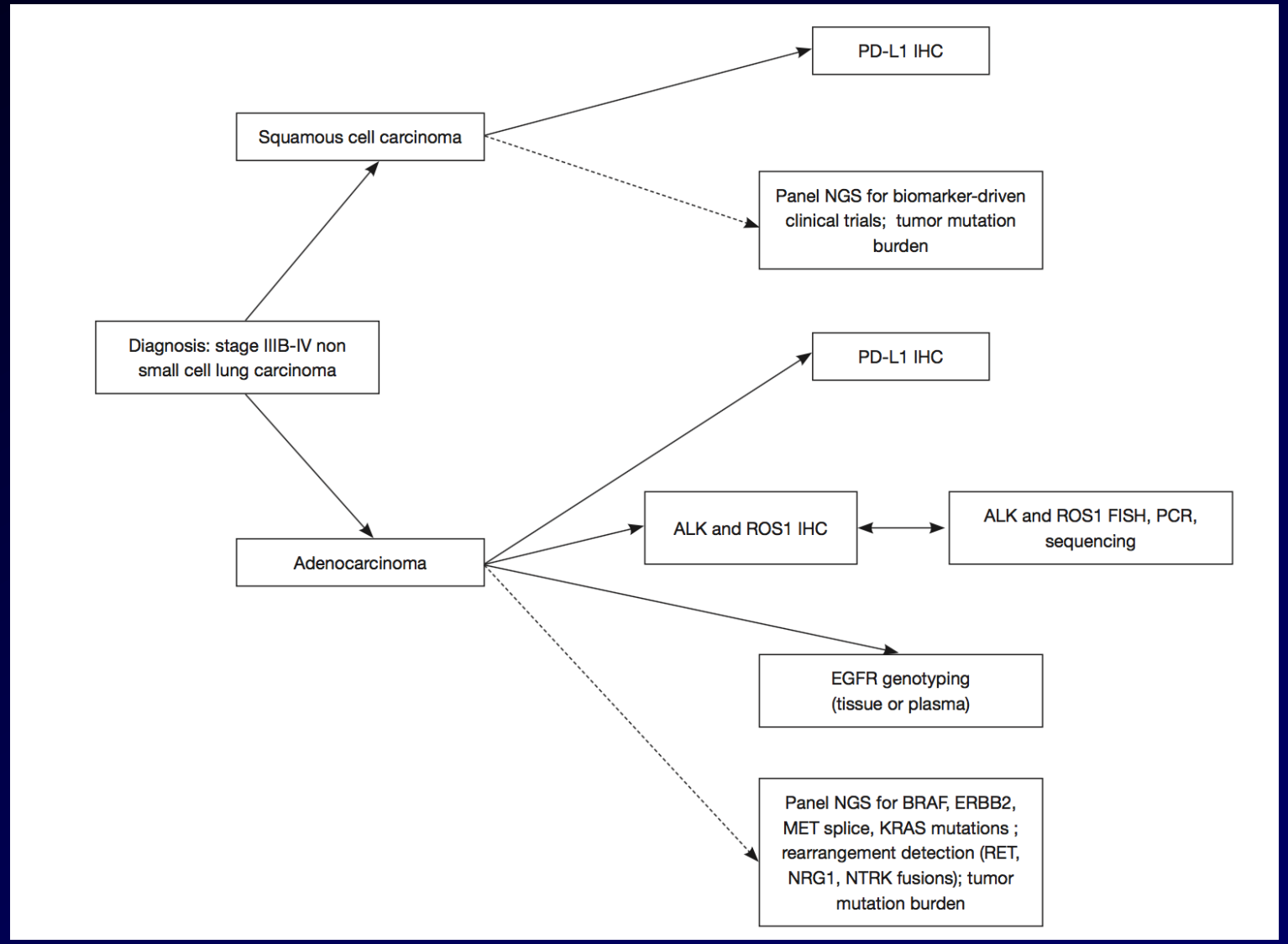
Heeke and Hofman, Transl lung Cancer Res 2018

TMB in NSCLC patients with selected mutations



Variant	Mean TMB	TMB-high		TMB-low	
		No. of cases	%	No. of cases	%
EGFR ex19del	4.5	36	5	354	46
EGFR L858R	4.6	22	4	242	49
EGFR T790M	4.4	8	3	132	44
EGFR mutation (other)	4.5	24	5	267	52
EML4-ALK	2.8	3	1	216	69
non-EML4-ALK	2.8	2	4	46	84
ROS1 rearrangement	3.9	5	4	71	59
MET ex14	6.2	22	8	118	41
BRAF V600E	6.8	20	10	99	48
BRAF non-V600E	9.7	104	36	49	17
KRAS mutation	10.3	934	30	622	20
BRCA1 alteration	19.2	62	42	29	20
BRCA2 alteration	13.8	77	32	49	20
POLE mutation	25.1	8	62	2	15
PD-L1 amplification	15.6	44	52	3	4

Sufficient amount of tissue must be available for molecular diagnostics



Sholl. Transl lung Cancer Res 2018

Data generation and analysis

- Plasma samples from the Phase II POPLAR study and the Phase III OAK st tested for bTMB, using this **394 gene-based NGS assay***
  - 211 of 273 samples from POPLAR, and 583 of 797 samples from OAK were bion the BEP for the study

2/3

bTMB Computational Methodology and Study

Blood collection, plasma isolation & cfDNA extraction

Sequencing

- All base substitutions with ≥0.5% allele frequency
- Remove germline polymorphisms & predicted driver mutations

bTMB

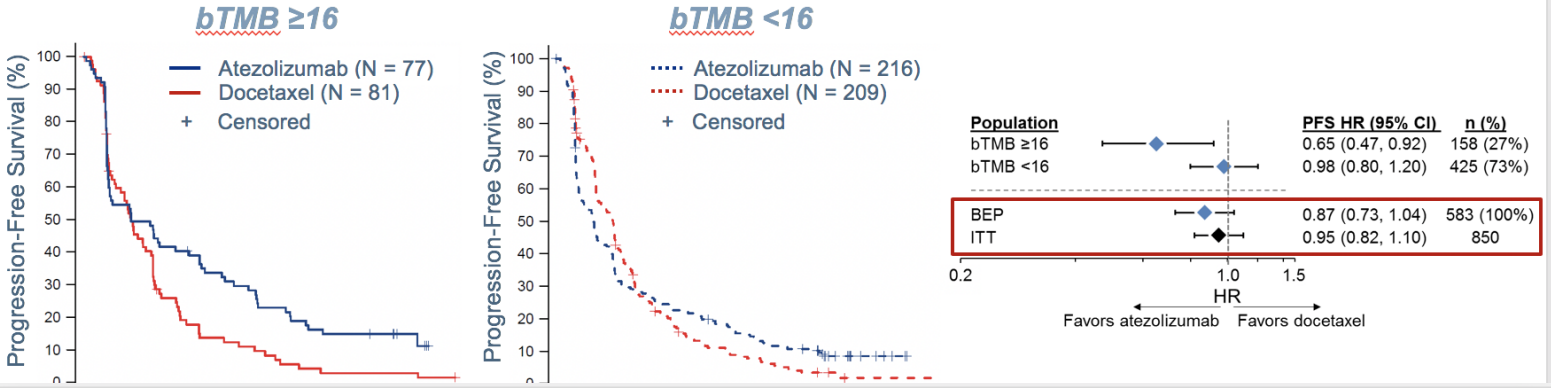
- The association between bTMB and atezolizumab efficacy was a of **bTMB ≥16** was **selected** based on POPLAR and **validated** in

***Please see poster presentation (Fabrizio DA, et al. #102P; Hall 8; Sept 11, 13:15-14:15)** for details of the bTMB analytical validation

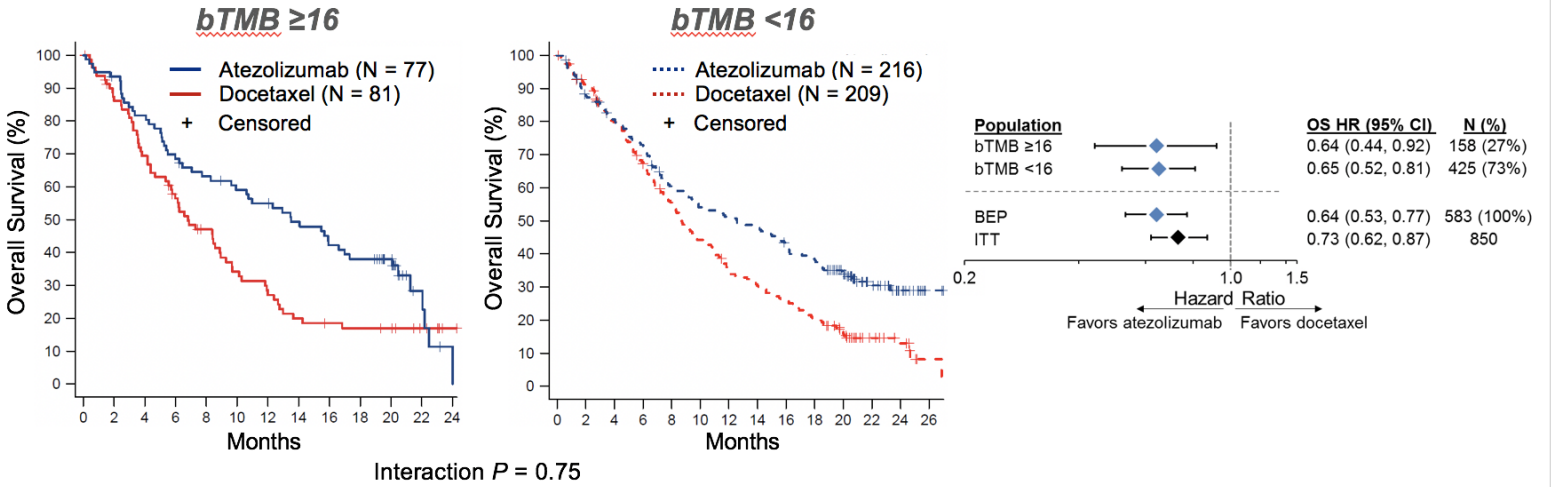
Gandara DR et al, Nature Me
Gandara DR, et al. bTMB in P

4 cfDNA, cell-free DNA; NGS, next-generation sequencing.

Atezolizumab PFS benefit in bTMB subgroups validated in the OAK study



Overall survival in bTMB subgroups in OAK



Interaction $P = 0.75$

- The OS benefit observed was consistent between the bTMB ≥16 population and the BEP
- This result may reflect the impact of subsequent therapies post-PD[1]
- Median OS for the bTMB ≥16 subgroup was 13.5 months in the atezolizumab arm and 6.8 months in the docetaxel arm

BEP, biomarker-evaluable population; HR, hazard ratio; ITT, intention-to-treat.
1. Gandara DR et al. ASCO 2017

Gandara DR et al, Nature Med Aug 2018
Gandara DR, et al. bTMB in POPLAR & OAK

MADRID 2017 ESMO congress

bTMB and PD-L1

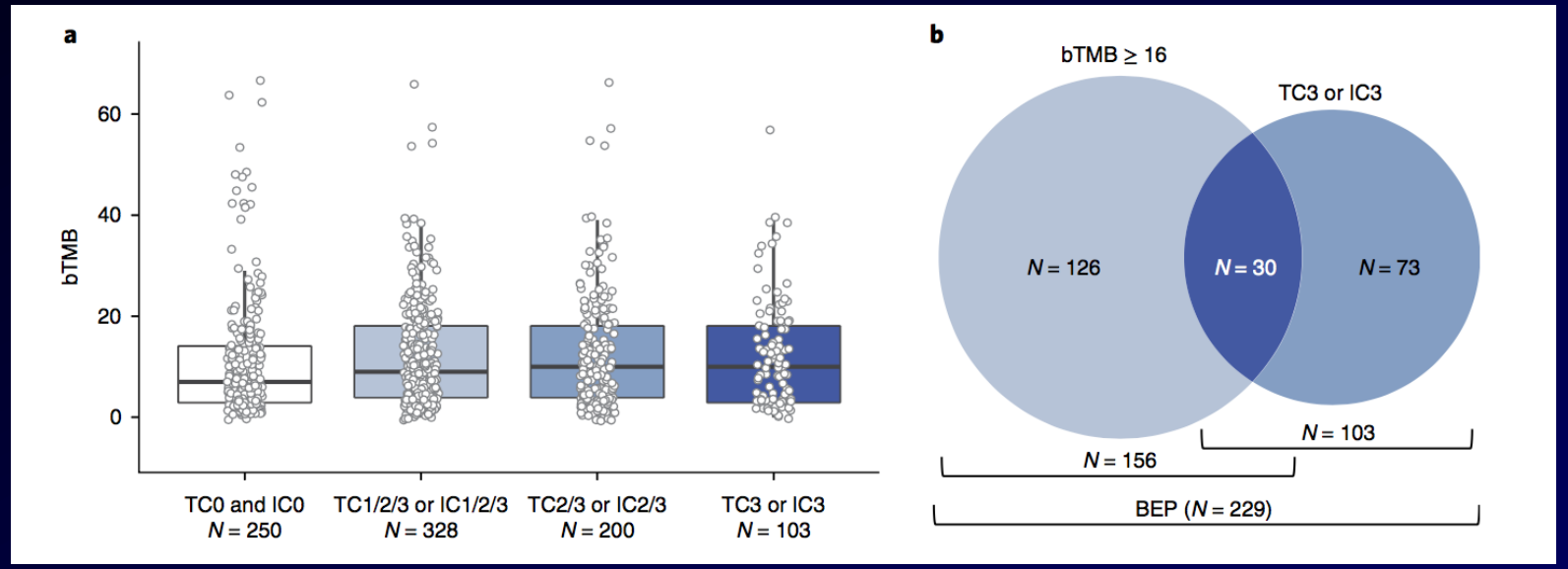


Table 1 | OS and PFS HRs in the OAK BEP with valid bTMB and PD-L1 IHC results

	N	PFS HR (95% CI)	OS HR (95% CI)
bTMB ≥ 16	156	0.64 (0.46–0.91)	0.64 (0.44–0.93)
TC3 or IC3	103	0.62 (0.41–0.93)	0.44 (0.27–0.71)
bTMB ≥ 16 and TC3 or IC3	30	0.38 (0.17–0.85)	0.23 (0.09–0.58)

N represents the number of patients in each subgroup. TC3 or IC3, ≥50% of tumor cells or ≥10% of tumor-infiltrating immune cells expressing PD-L1.

Gandara et al. Nat Med 2018

B-F1RST Study Design

Inclusion Criteria
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1
- Immunotherapy naive
- PD-L1 unselected
- Provision of blood[b]

Exclusion Criteria
- Sensitizing *EGFR* mutations or *ALK* rearrangements
- Active brain metastases requiring treatment

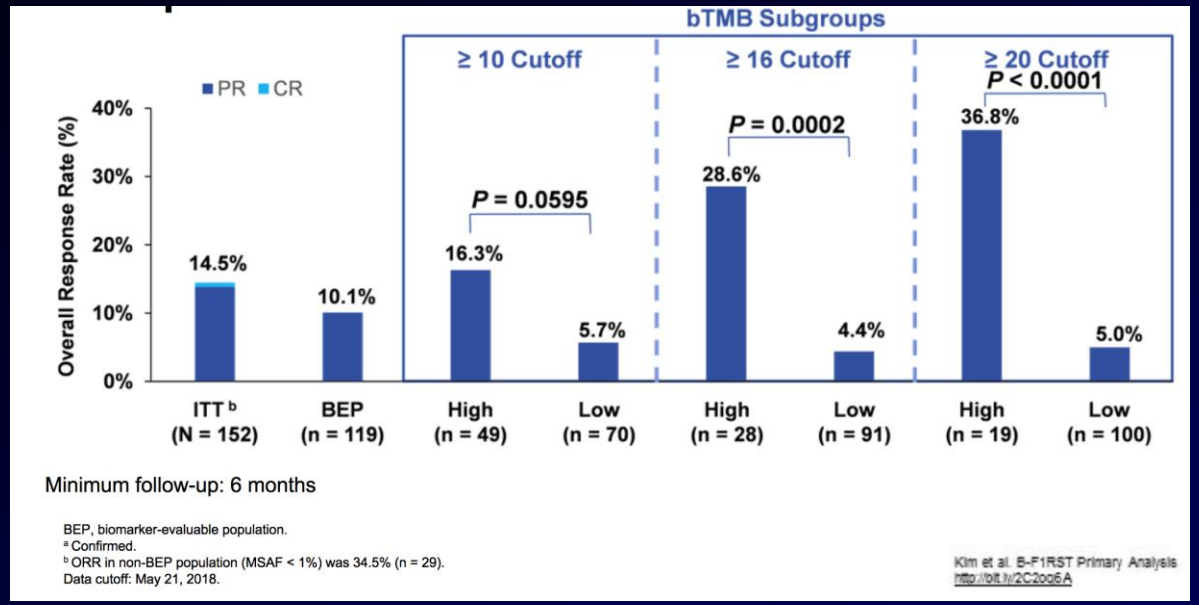
Interim Analysis:
- Prespecified interim analysis at 6 months after 50% of patients have been enrolled
- Prespecified bTMB biomarker cutoff of 16

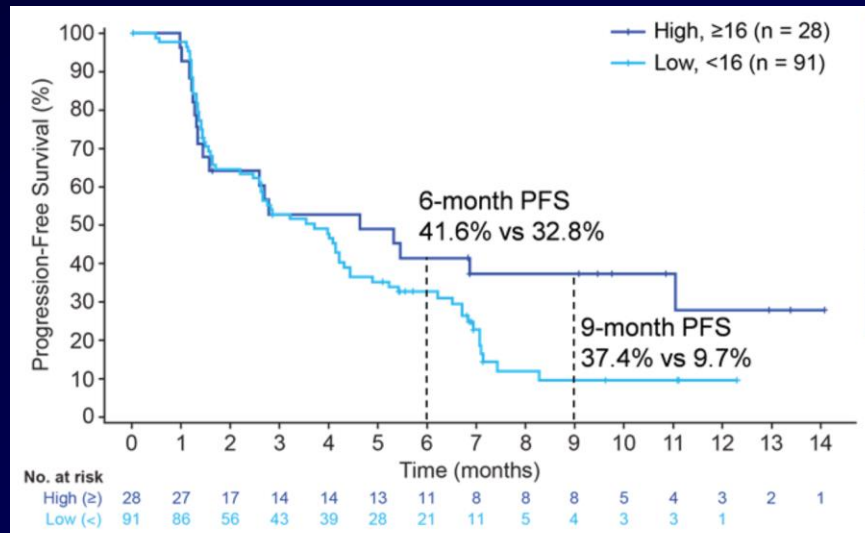
Co-Primary Endpoints:
- Evaluate the clinical efficacy of atezolizumab
  - Endpoint: INV-assessed ORR per RECIST v1.1
- Evaluate relationship between bTMB by NGS and PFS benefit
  - Endpoint: INV-assessed PFS per RECIST v1.1

Secondary Objectives:
- Safety and assessment of efficacy by INV-assessed DOR, OS

INV, investigator; NGS, next-generation sequencing.
[a] Staging criteria based on the IASLC Lung Cancer Staging Project proposed for the eighth edition of the AJCC NSCLC staging system; [b] Tissue biopsy was optional.

bF1RST: trial results





	bTMB High (n = 28)	bTMB Low (n = 91)
Median PFS	4.6 mo	3.7 mo
90% CI	1.6, 11.0	2.6, 4.3
HR	0.66	
90% CI	0.42, 1.02	
P value	0.12	

≈ 70% of events for PFS

Kim et al., ESMO 2018

Conclusions

- TMB is more predictive than PD-L1 in selecting patients candidate to ICIs
- TMB and PD-L1 could be used simultaneously to “superselect” patients candidate to ICIs
- Hurdles to the use of TMB as a biomarker in clinical proctice: different cutoffs used, need for prospective validation, different TMB assays requiring consistency across different platforms
- Availability of tumor tissue may limit the use of TMB in clinical practice
- Evaluation of TMB in circulating tumor DNA could overcome the challenges of obtaining sufficient tumor tissue

Thanks for your attention

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