Tumor mutation burden as a biomarker for Immuno-oncology

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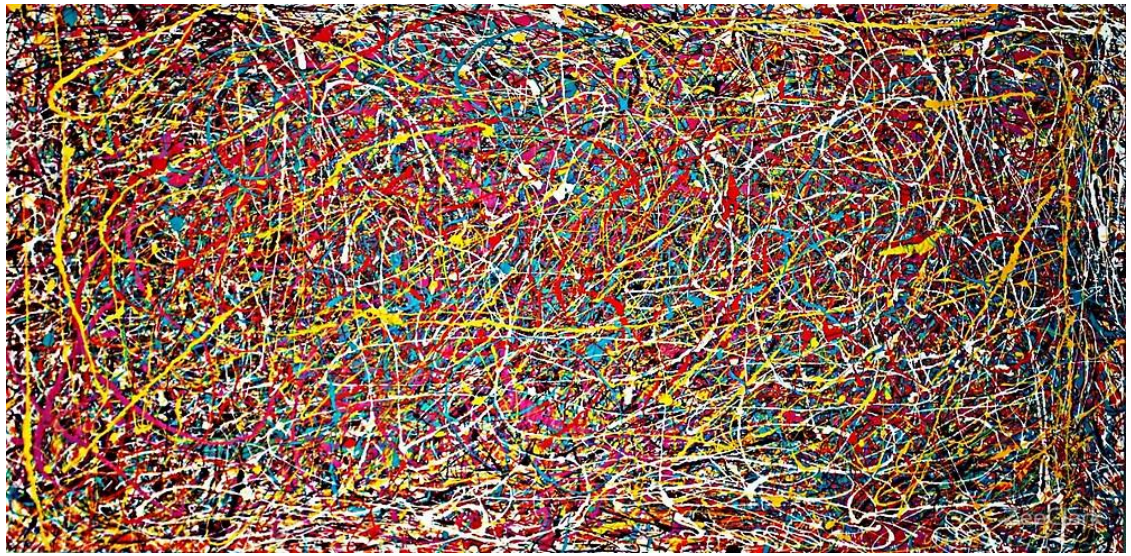
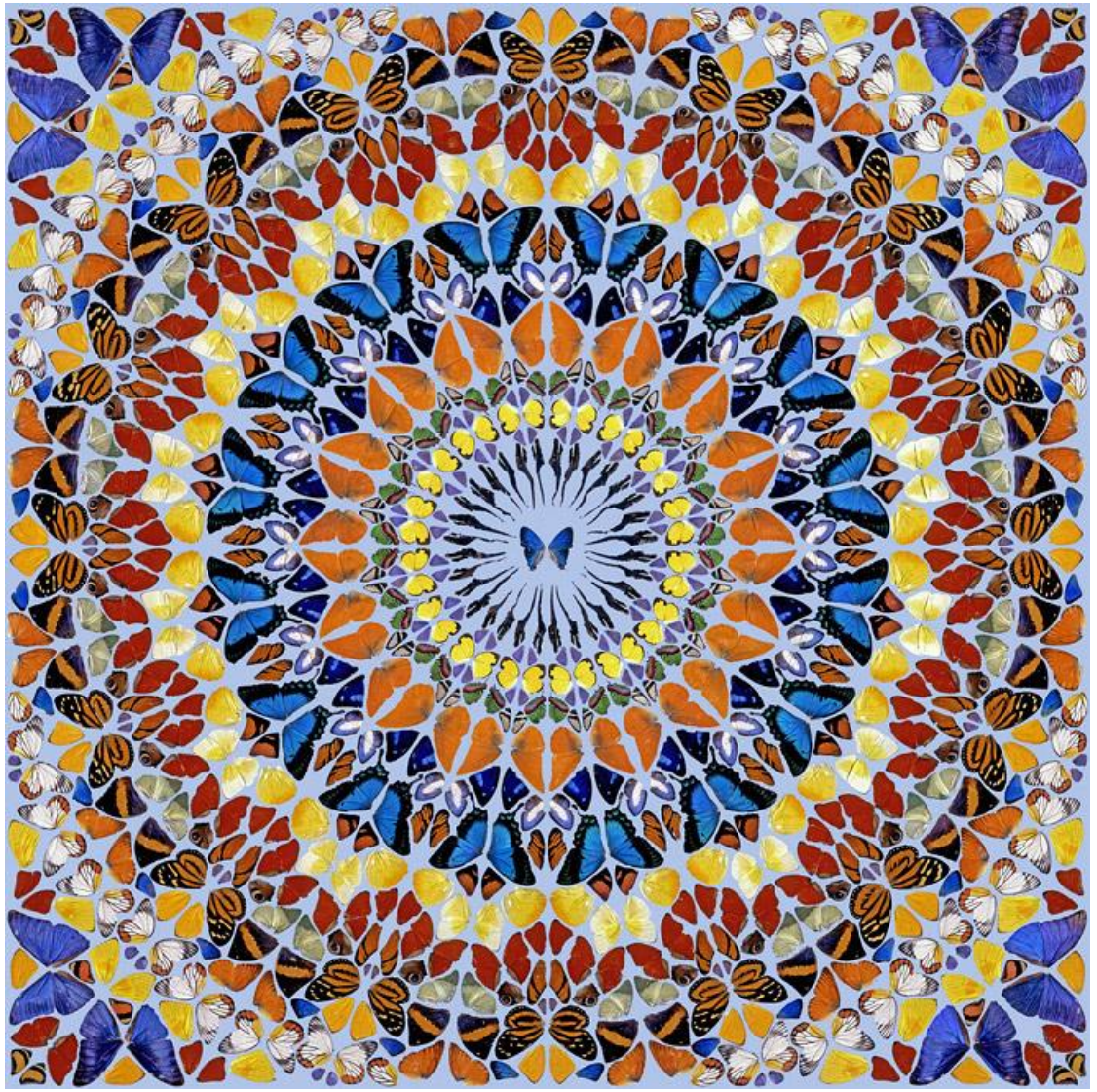
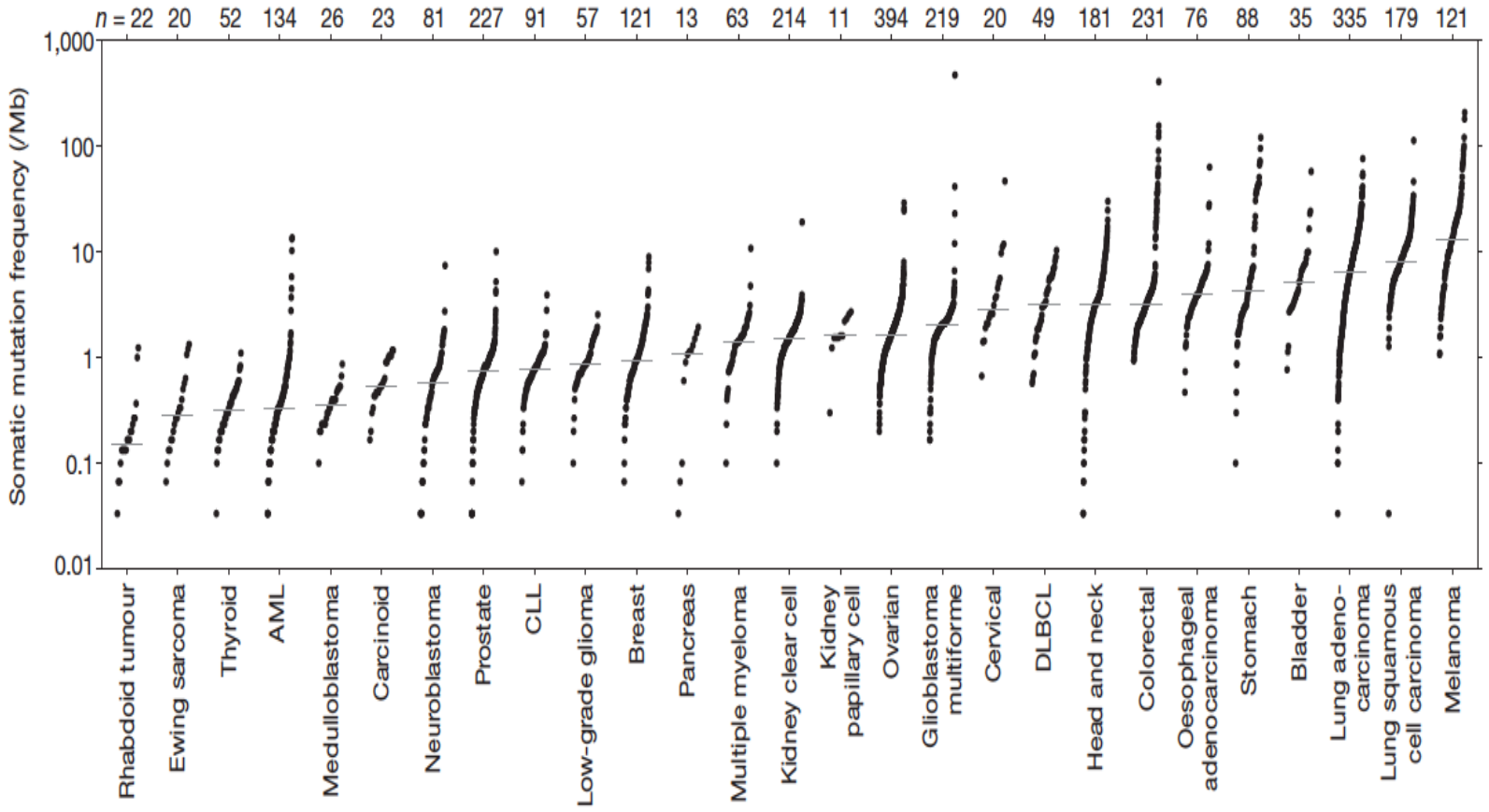




Introduction

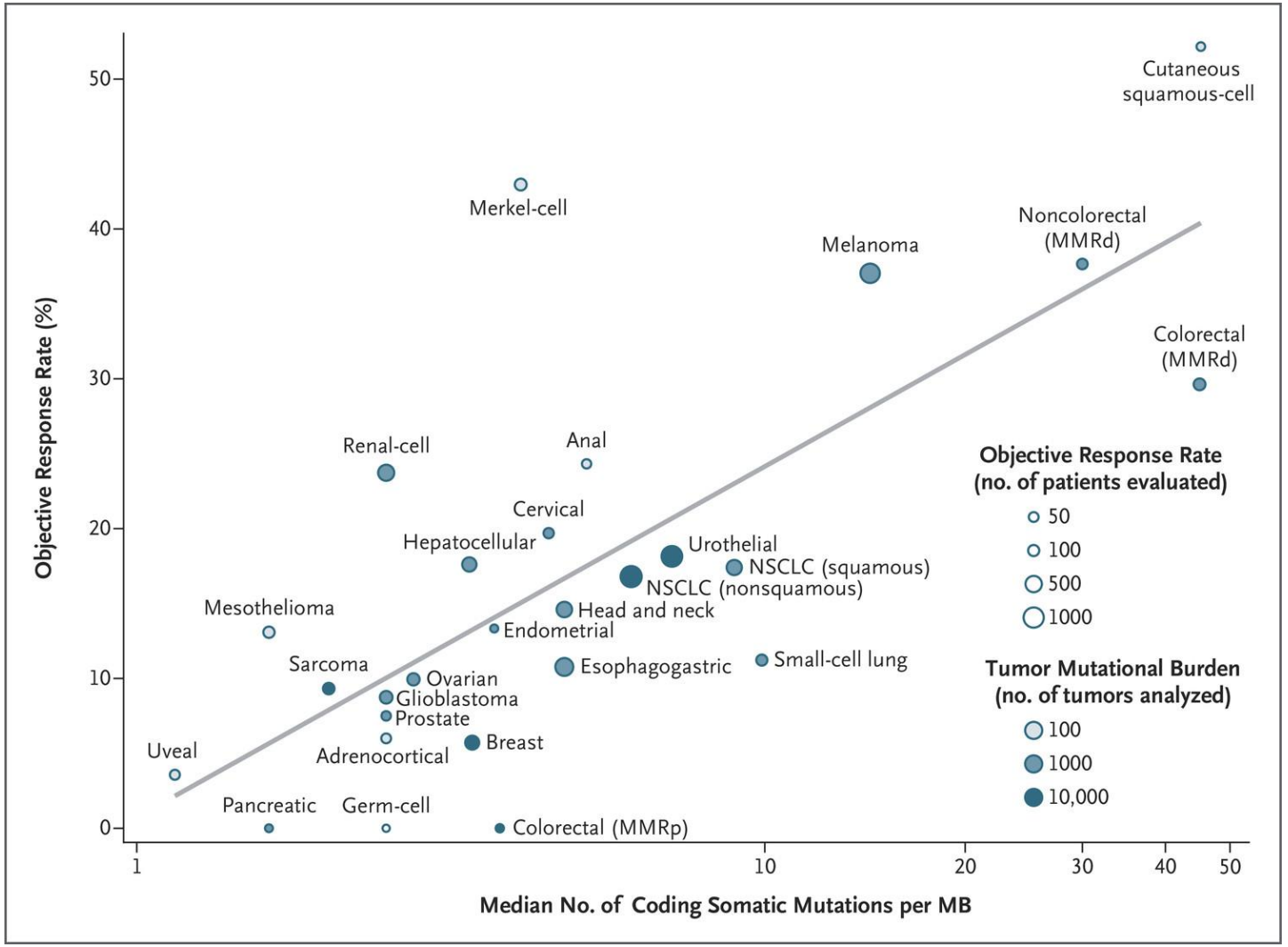
- Why is tumor mutation burden a biomarker
- What mutations do we measure
- How do we measure TMB
- What is the TMB threshold
- Do we need PD-L1?
- Does TMB threshold apply to all immune checkpoint blockers
- Can this TMB threshold be applied pan cancer

TMB as a biomarker – extrapolating TCGA data



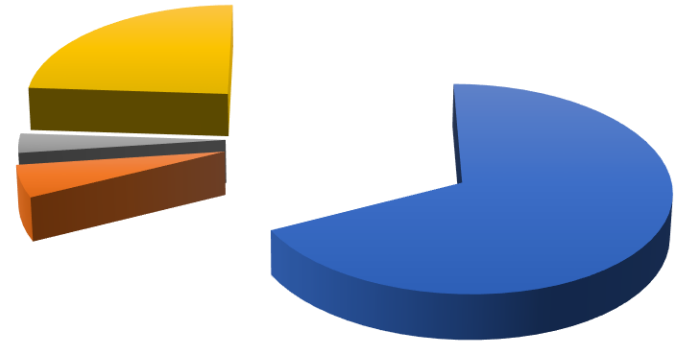
Alexandrov et al, *Nature* 2013

Correlation between TMB and IO response

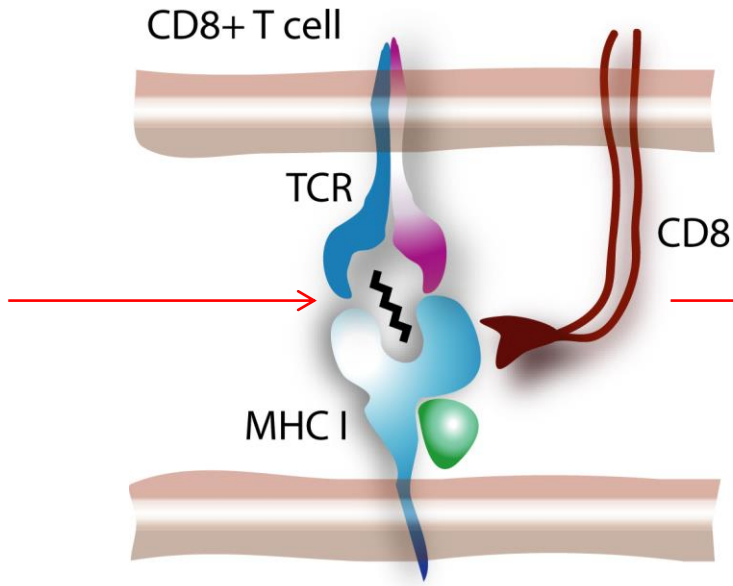


Yarchoan et al, NEJM 2017

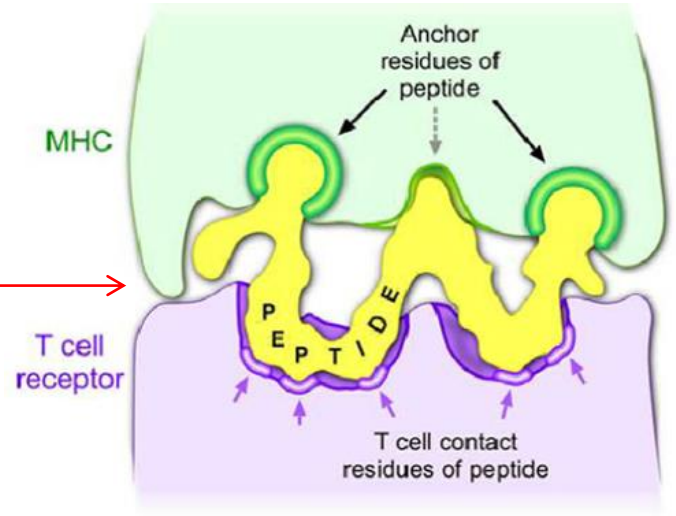
TMB is a surrogate for (predicted) neoantigens



Missense (65%) Nonsense (5%)
Indels (3%) Silent (21%)

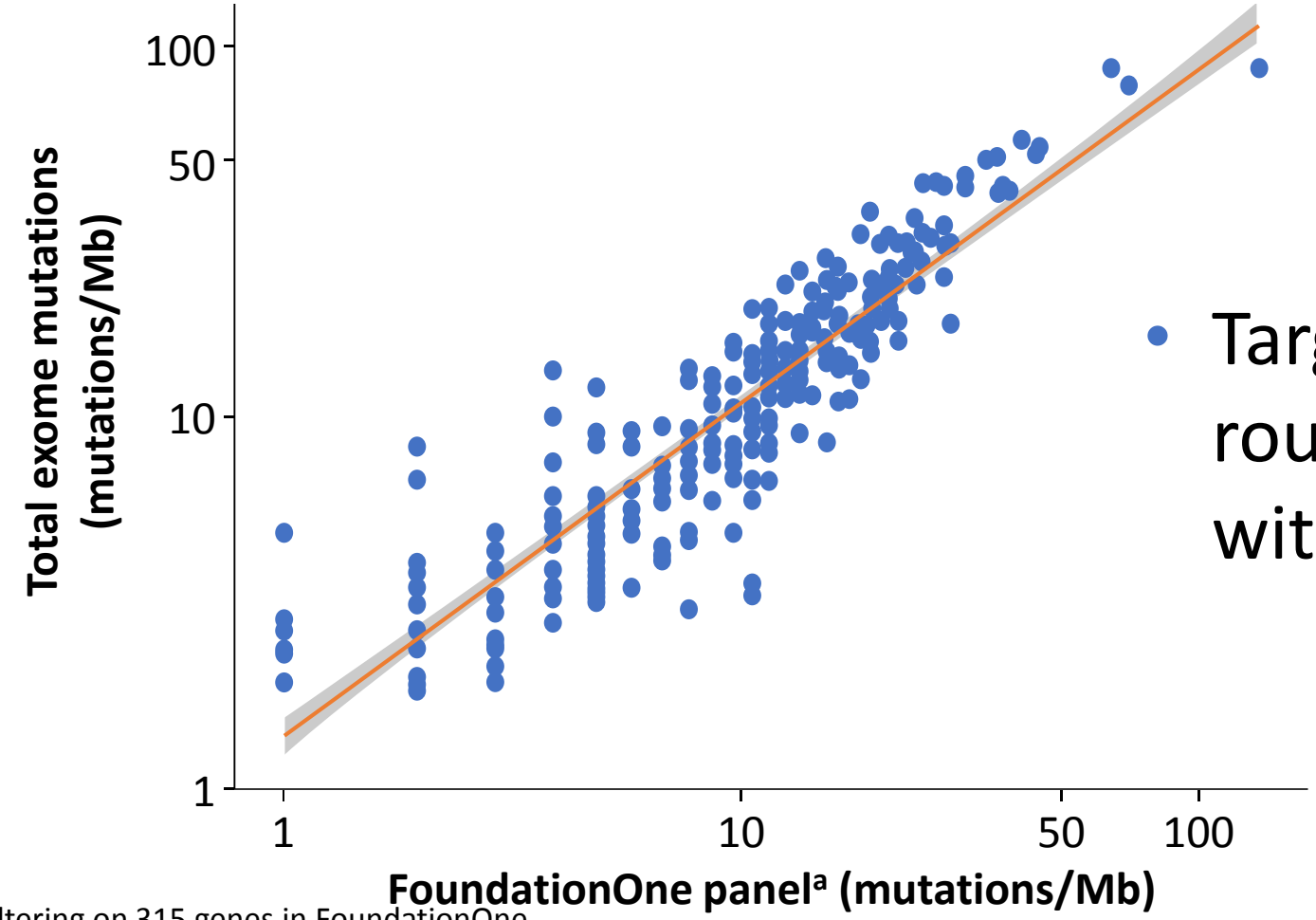


Courtesy of Ton Schumacher



Fritsch EF, et al. Cancer Immunol Res. 2014

Total Exome Mutations vs Genes in FoundationOne Panel[a] CheckMate 026 TMB Analysis[1]



- Targeted panels in routine use correlate with WES

[a] Based on in silico analysis filtering on 315 genes in FoundationOne comprehensive genomic profile (Foundation Medicine, Inc, Cambridge, MA, USA).[2]

1. Carbone DP, et al. N Engl J Med. 2017;376:2415-26.
2. Frampton GM, et al. Nat Biotechnol. 2013;31:1023-31.

What mutations do we measure ? Comparing platforms

Parameter	WES	FM NGS (F1CDx)	MSKCC NGS (MSK-IMPACT)
# of genes	~ 22,000 gene coding regions	324 cancer-related genes	468 cancer-related genes
Types of mutations captured	# of somatic, missense mutations in the sequenced tumor genome	# of somatic, coding mutations (synonymous and non-synonymous), short indels per MB of tumor genome	# of somatic, missense mutations per MB of tumor genome
Germline mutations	Subtracted using patient-matched blood samples	Estimated via bioinformatics algorithms and subtracted	Subtracted using patient-matched blood samples
Capture region (tumor DNA)	~30 MB	0.8 MB	1.22 MB
Validation	Reference	In silico, phase 2 and phase 3 IO trials	In silico, phase 2 IO trials
TAT	4-6 weeks	2 weeks	2-3 weeks

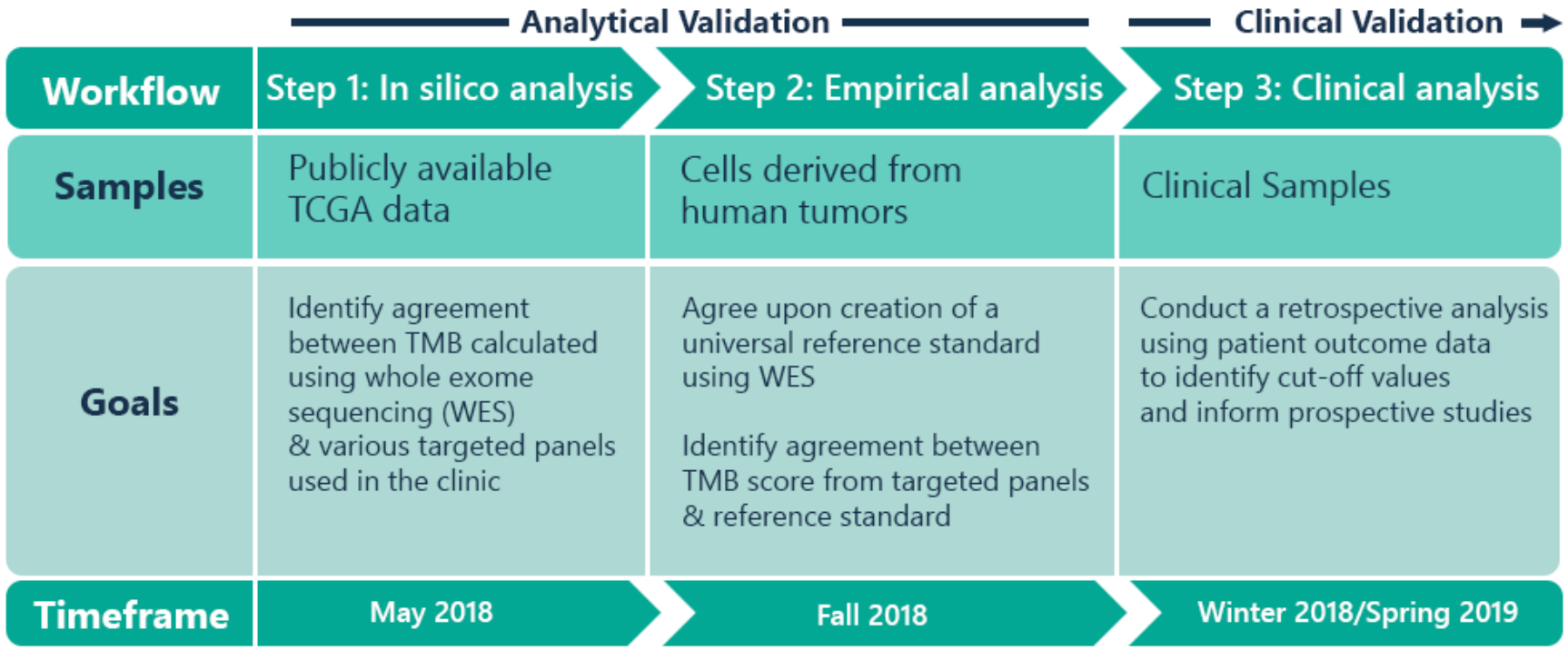
Friends of Cancer Research: TMB Harmonization Effort

Friends of Cancer Research has convened a multi-stakeholder working group to align on and publish universal best practices for defining TMB, analytic validation, and alignment against reference standards.

Participants:

- Seven test developers
- Six pharma companies
- FDA
- NCI
- Academia

TMB Workflow



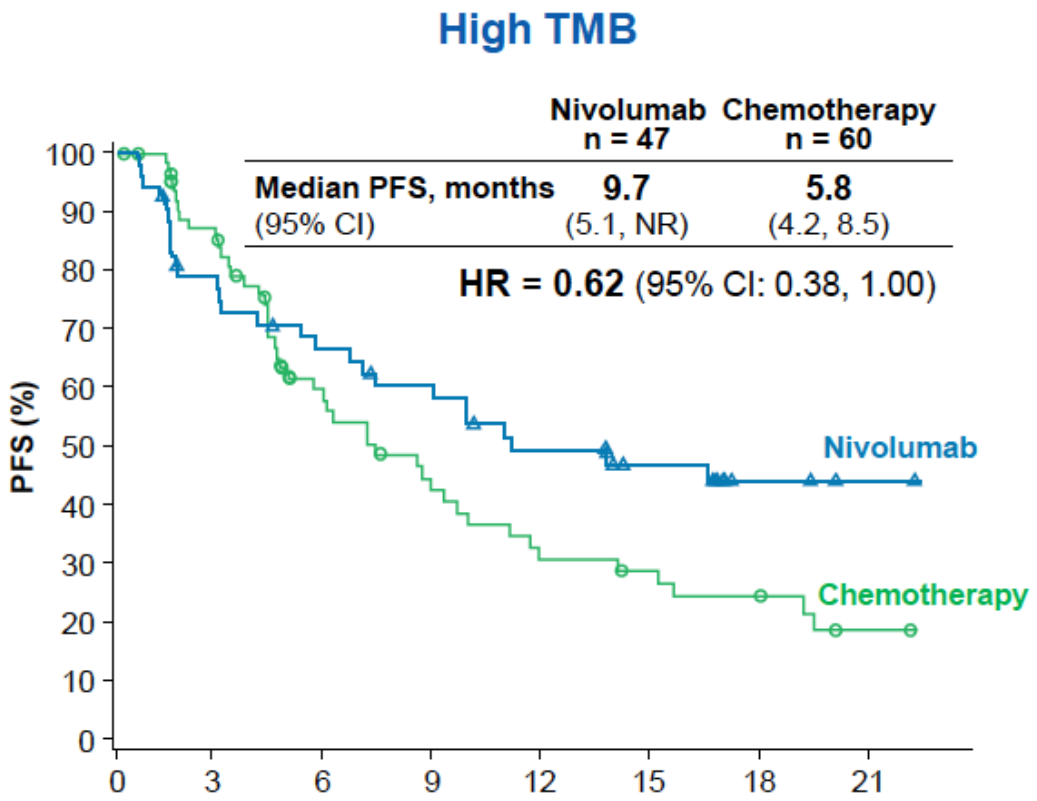
https://www.focr.org/tmb

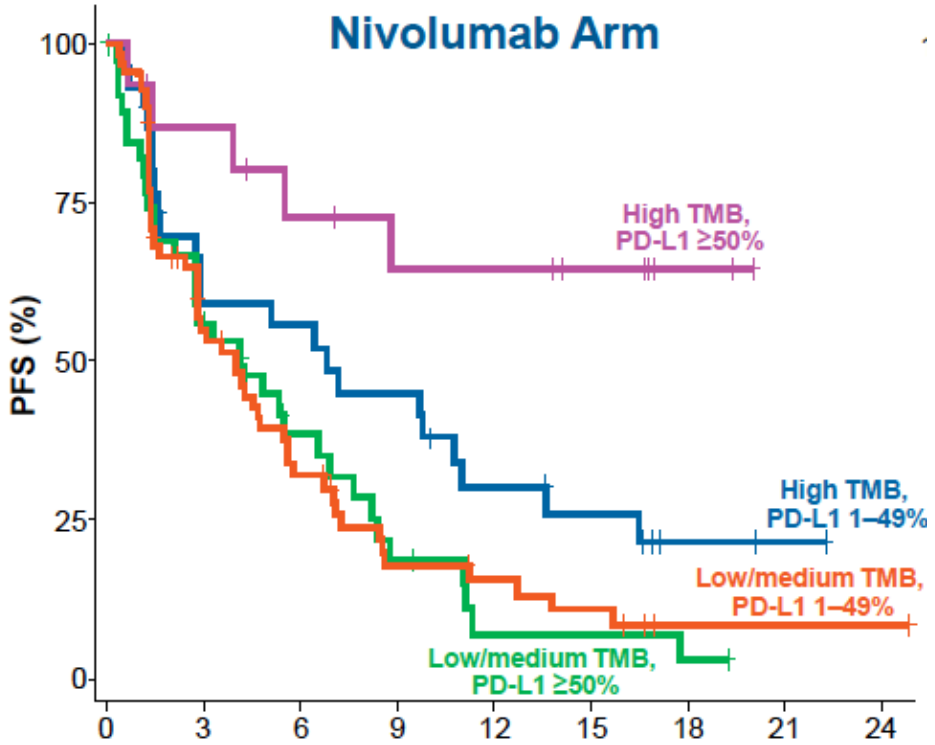
What is the TMB threshold ? Phase 2 data

Cancer	Trial and treatment	Method	Threshold Defined	RR	PFS	OS	Ref.
NSCLC	KN 001 Phase 1/2 Pembrolizumab	WES	200 mutations (median)	63% vs. 0% 73% vs. 13%	14.5 vs. 3.7 mo. NR vs. 3.4 mo.		(Rizvi et al., 2015)
NSCLC	POPLAR Randomized Ph. 2 Atezolizumab	FM NGS	Atezolizumab vs. docetaxel in $\geq$ 9.9 Mut/Mb	20% vs. 4%	7.3 vs. 2.8 mo.	16.2 vs. 8.3 mo.	(Kowanetz et al., 2016)
NSCLC	MSKCC: various immunotherapies	MSKCC NGS	7.4 mut/MB (Median)		38.6 vs. 25%		(H. Rizvi et al., 2018)
NSCLC	CM 568 Nivolumab/ipilimumab	FM NGS	10 mut/Mb	44% vs. 12%	7.1 vs. 2.6 mo.		(Ramalingam et al., 2018)
Urothelial	CM 275 Phase 2 Nivolumab	WES	≥170 vs. <85 mutations	31.9% vs. 10.9%	3 vs. 2 mo.	11.63 vs. 5.72 mo.	(Galsky et al., 2017)
Urothelial	IMvigor210 Phase 2 Atezolizumab	FM NGS	16 mut/Mb (Upper quartile)			OS advantage	(Balar et al., 2017)
HNSCC	KN 012 and KN 055 Pembrolizumab	WES	175 mutations		0.64	0.98	Seiwert et al, 2018

Parameter	WES	FM NGS (F1CDx)	MSKCC NGS (MSK-IMPACT)
Validation in phase 2	200 missense mutations	10 mut/MB	7.4 mut/MB

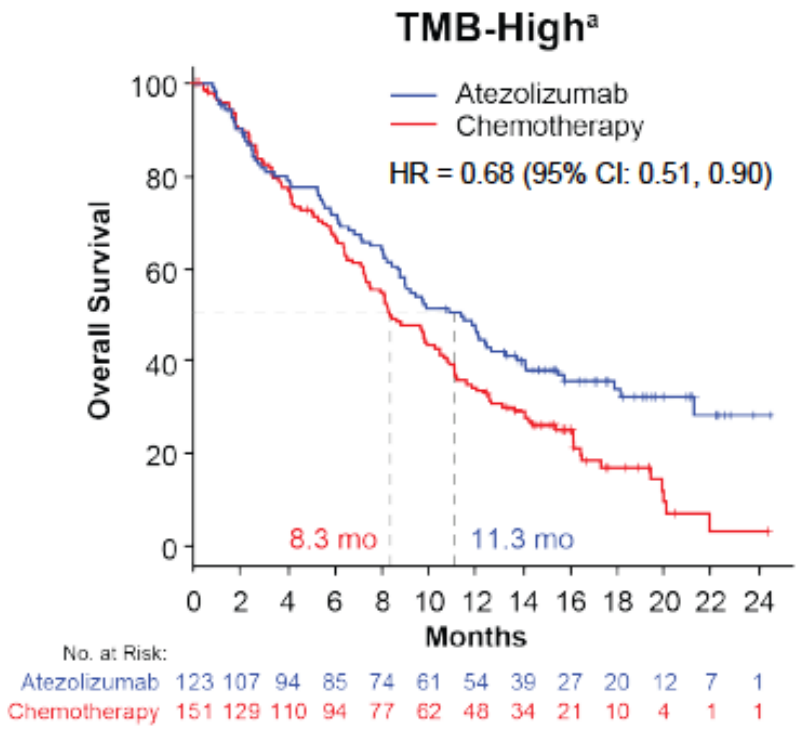
Checkmate 026: Phase 3 NSCLC

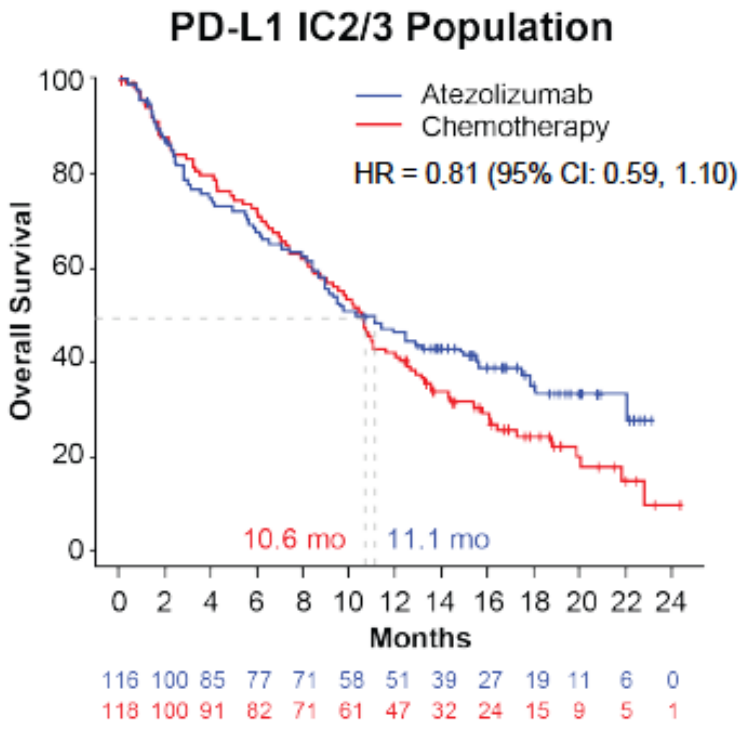


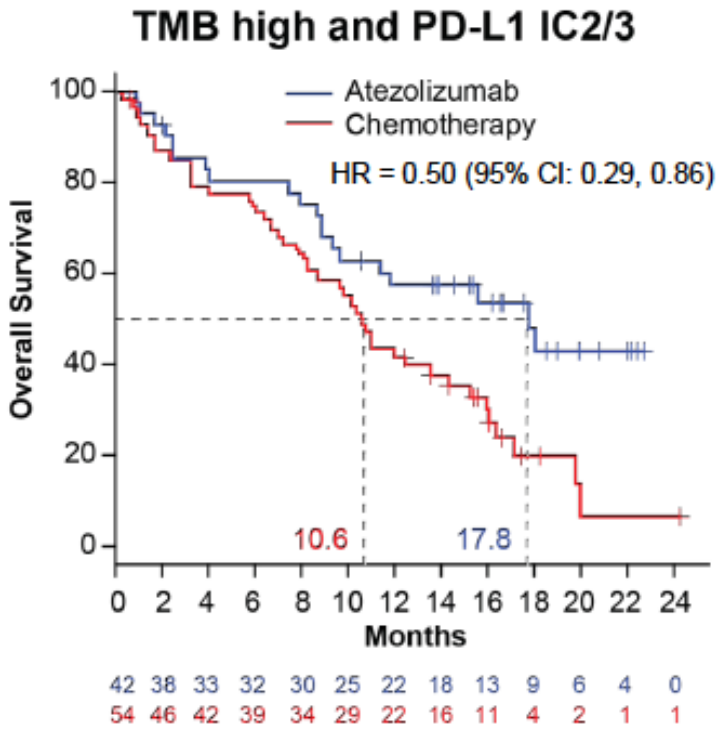


Peters et al, AACR 2017
Carbone et al, NEJM 2017

IMvigor 211 (urothelial cancer phase 3)

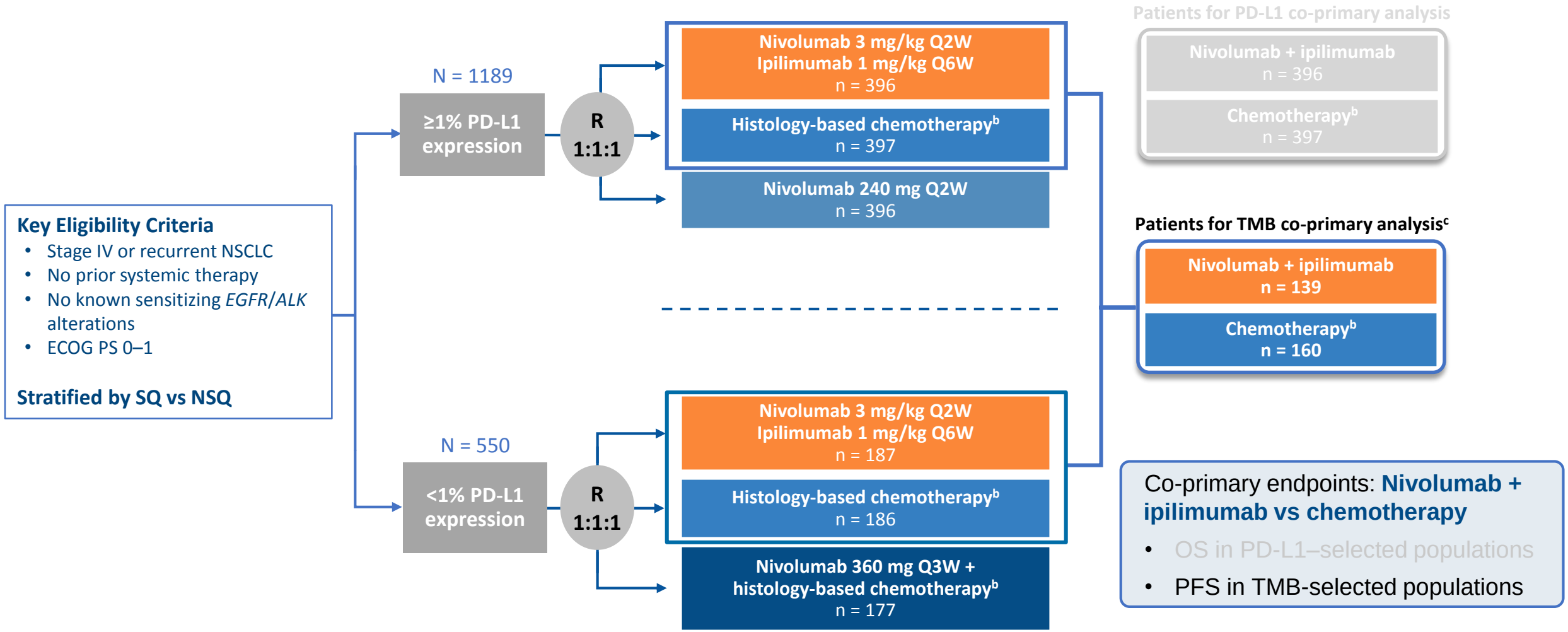






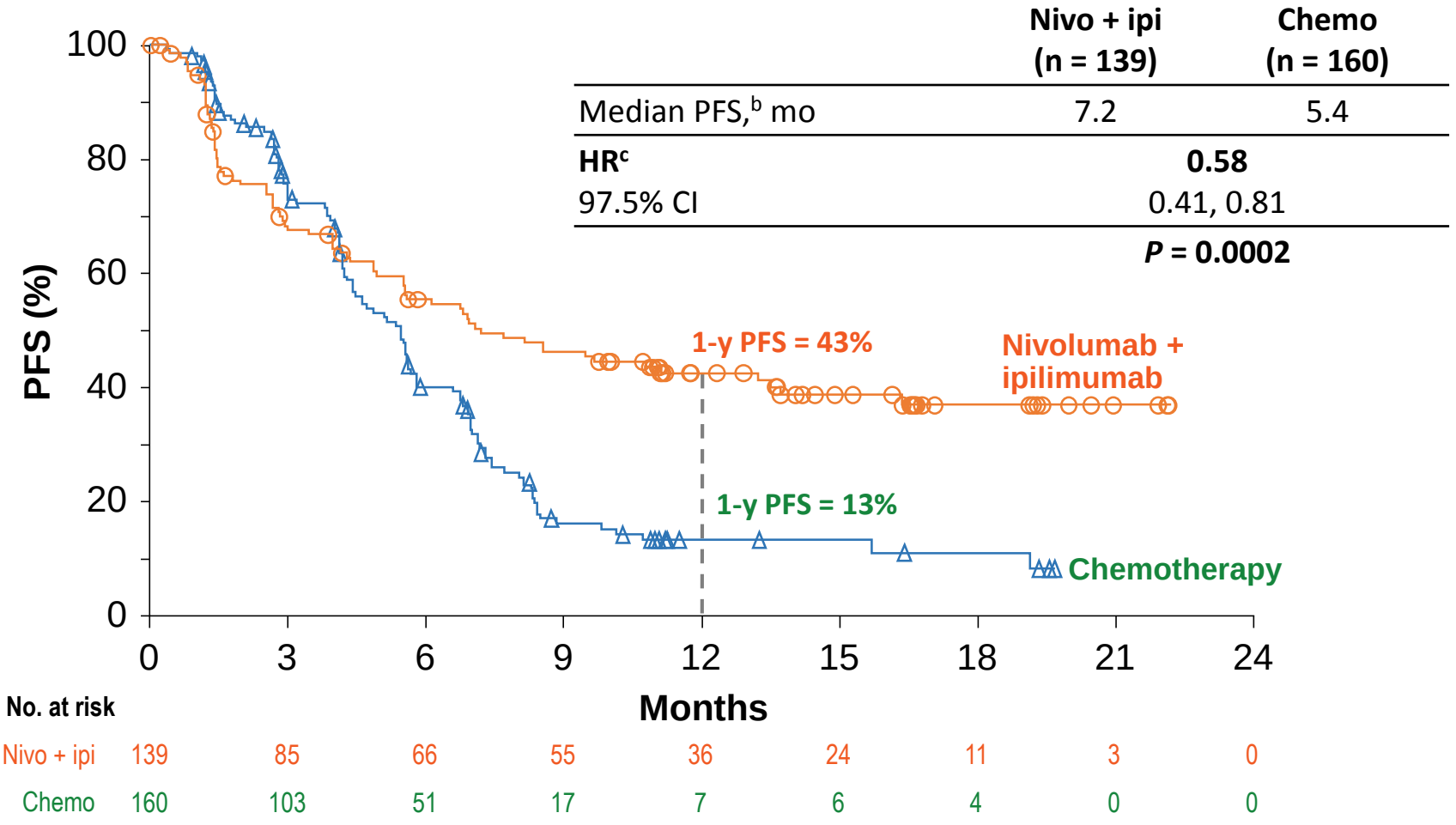
Powles et al, Lancet 2018

CheckMate 227: Phase 3 NSCLC



Database lock: January 24, 2018; minimum follow-up: 11.2 months

Co-primary Endpoint: PFS With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)[a]

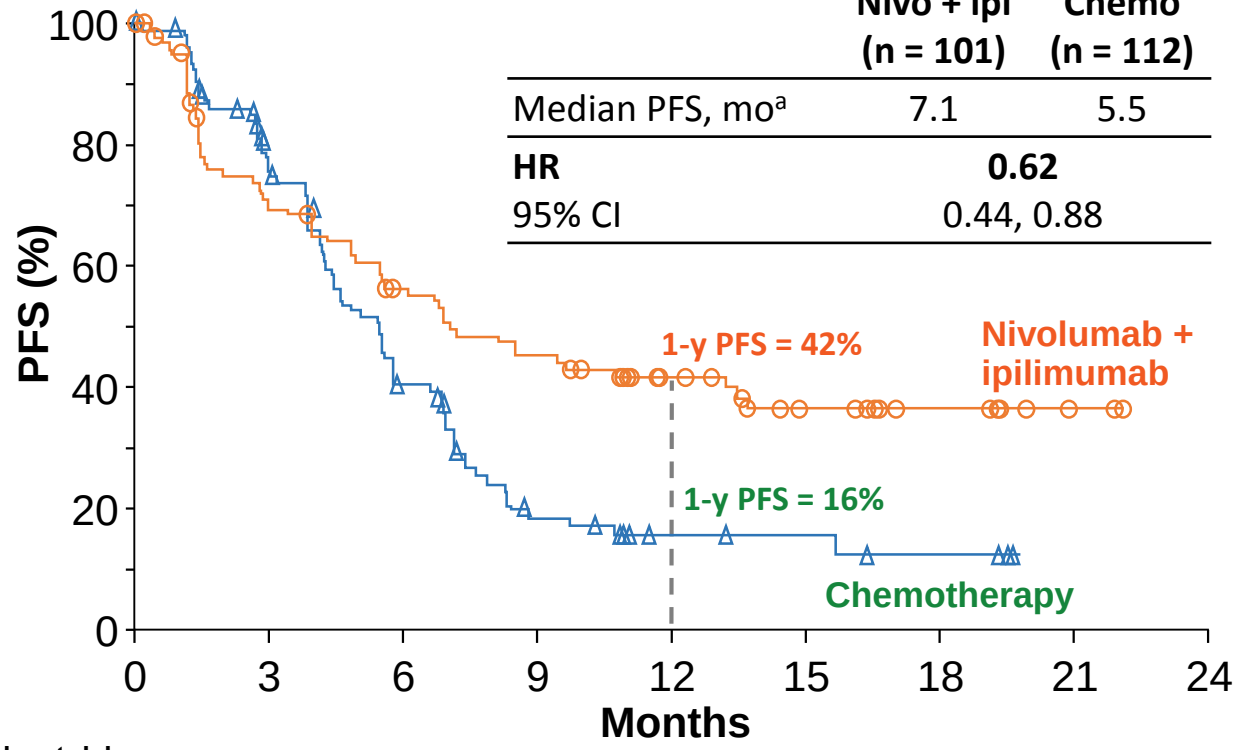


- In patients with TMB <10 mut/Mb treated with nivo + ipi vs chemo, the HR was 1.07 (95% CI: 0.84, 1.35)[d]

Hellmann et al, NEJM 2018

PFS in Patients With High TMB (≥10 mut/Mb) by Tumor PD-L1 Expression

≥1% PD-L1 expression

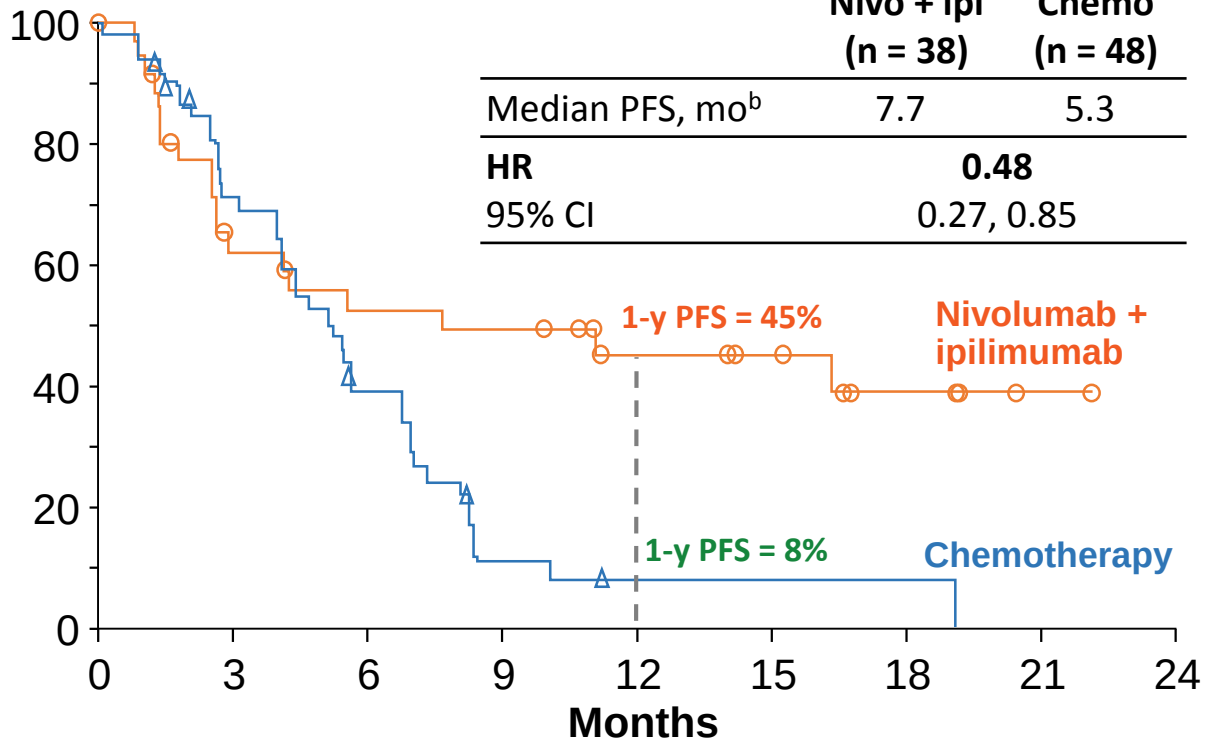


	Nivo + ipi (n = 101)	Chemo (n = 112)
Median PFS, mo[a]	7.1	5.5
HR	**0.62**	
95% CI	0.44, 0.88	

No. at risk

Nivo + ipi	101	65	50	40	26	16	7	2	0
Chemo	112	73	35	13	6	5	3	0	0

<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	

Nivo + ipi	38	20	16	15	10	8	4	1	0
Chemo	48	30	16	4	1	1	1	0	0

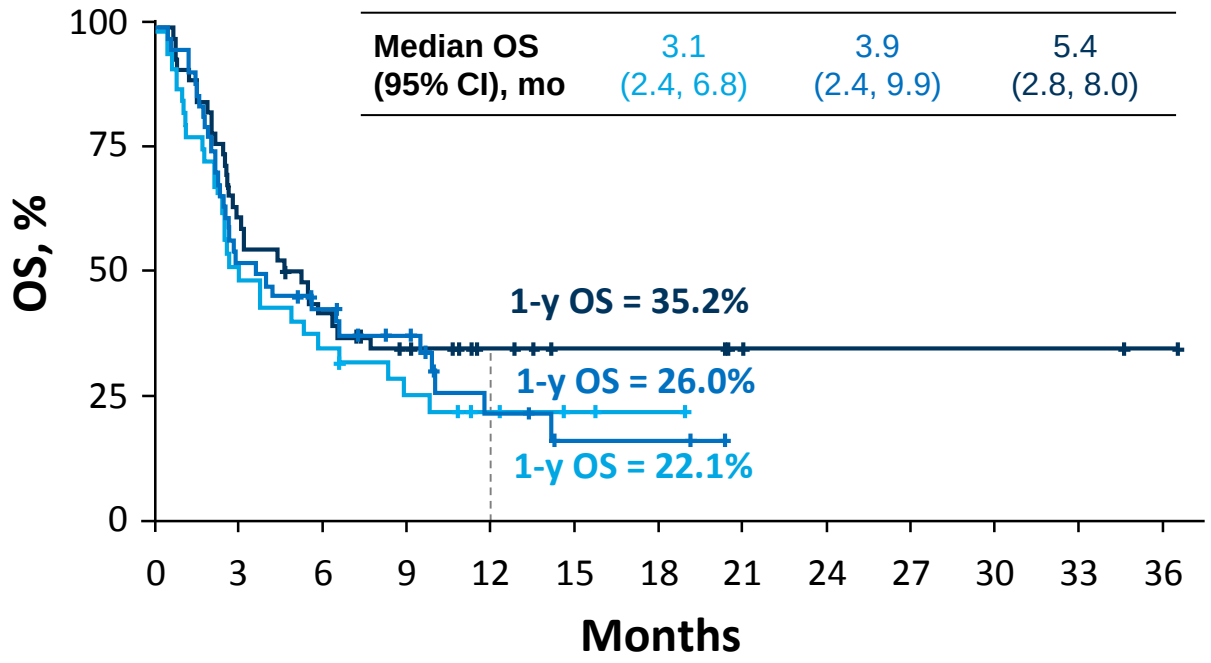
Hellmann et al, NEJM 2018

[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)

OS by TMB Subgroup: CM 032 SCLC Phase 2

Nivolumab

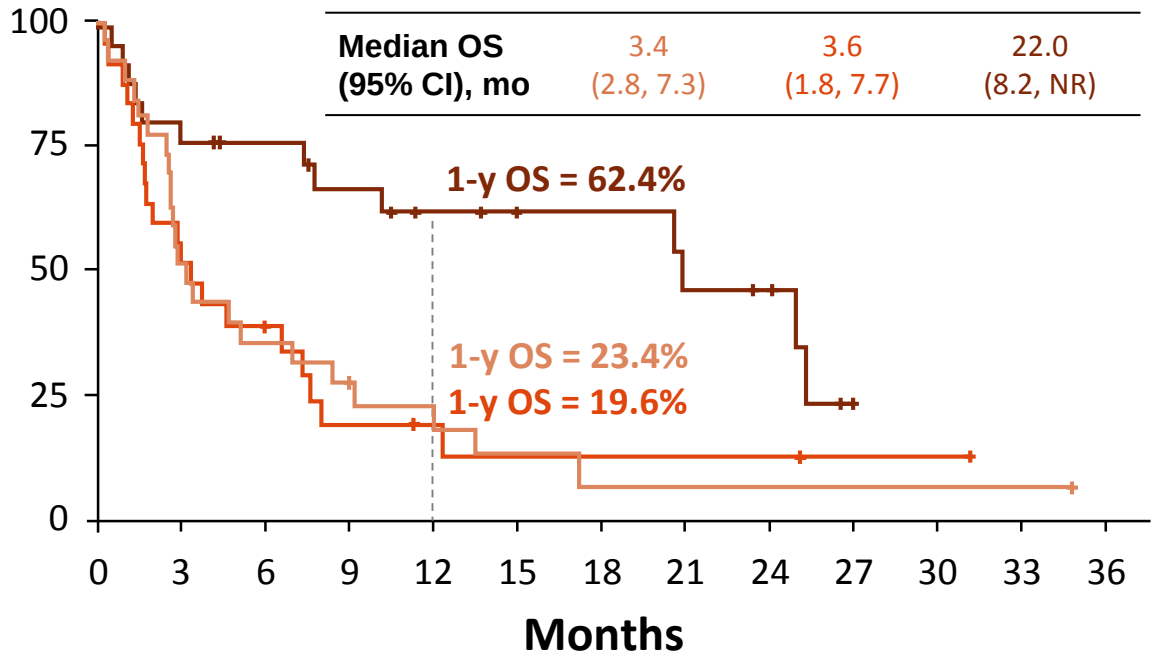
	Low TMB	Med TMB	High TMB
Median OS (95% CI), mo	3.1 (2.4, 6.8)	3.9 (2.4, 9.9)	5.4 (2.8, 8.0)



No. at risk													
Low	42	19	13	9	4	3	1	0	0	0	0	0	0
Medium	44	23	17	12	6	2	2	1	0	0	0	0	0
High	47	29	20	14	8	5	5	5	2	2	2	2	2

Nivolumab + ipilimumab

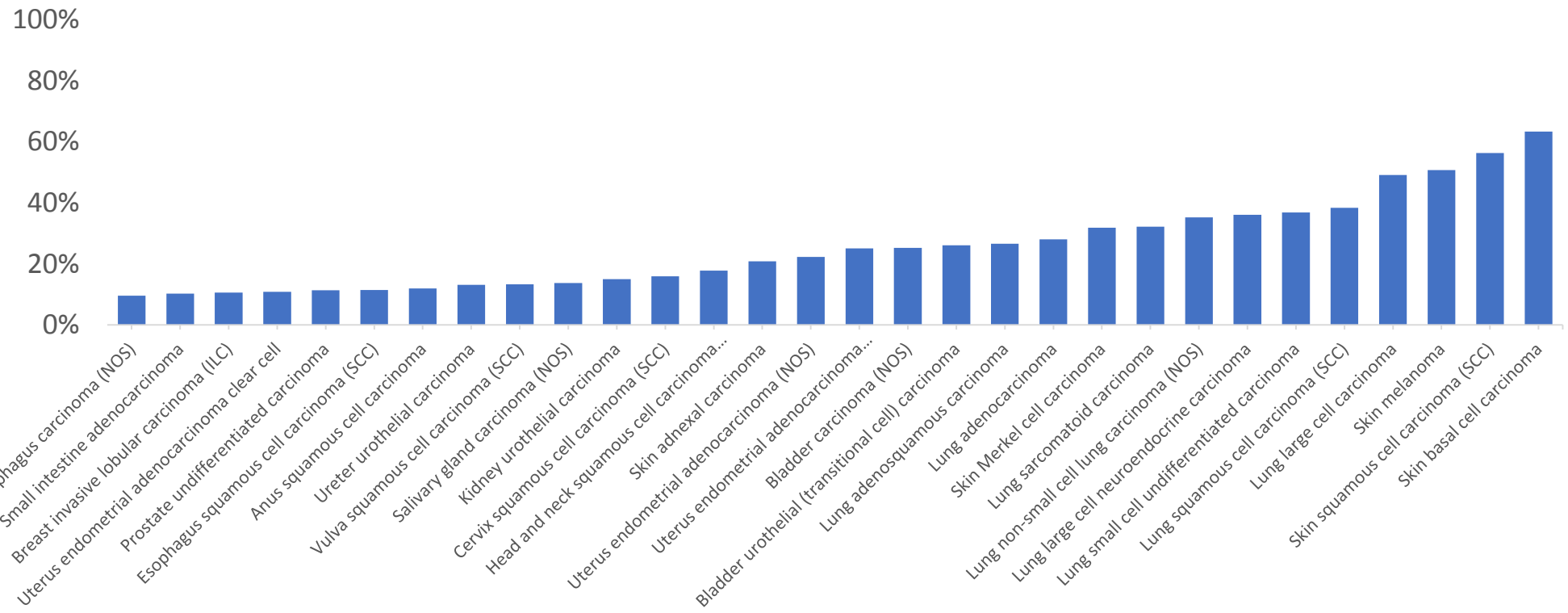
	Low TMB	Med TMB	High TMB
Median OS (95% CI), mo	3.4 (2.8, 7.3)	3.6 (1.8, 7.7)	22.0 (8.2, NR)



27	15	9	7	5	2	2	1	1	1	1	1	1
25	15	9	4	3	2	2	2	2	1	1	0	0
26	20	17	14	10	9	8	8	6	2	0	0	0

Hellmann et al Cancer Cell 2018

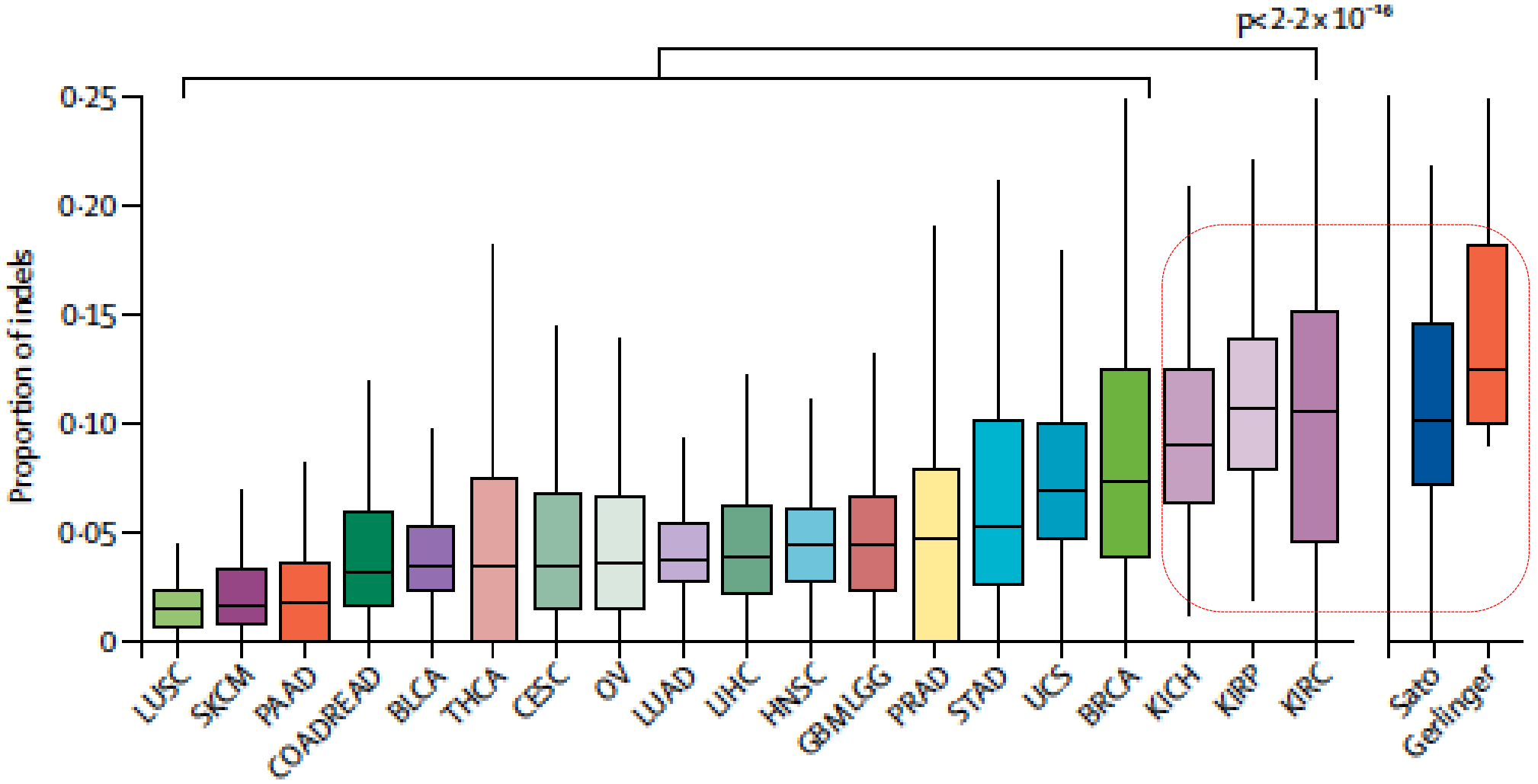
Impact of TMB pan-cancer:
Percent of Solid Tumors with TMB ≥10 mut/Mb



Analysis of top 30 solid tumor types selected from 104,814 total cases sorted by percent of cases with TMB ≥10 mut/Mb according to the Foundation Medicine database. TMB is defined as the number of somatic synonymous and non-synonymous base substitutions and indels divided by the region over which it was counted. Only cancer types with at least 100 total cases are reported. The average across all solid tumor types was 13.3%.

Courtesy of Vincent Miller and David Fabrizio, Foundation Medicine

Frameshift Indels Generate Highly Immunogenic Tumor Neoantigens



Turajlic et al, Lancet Oncology 2017

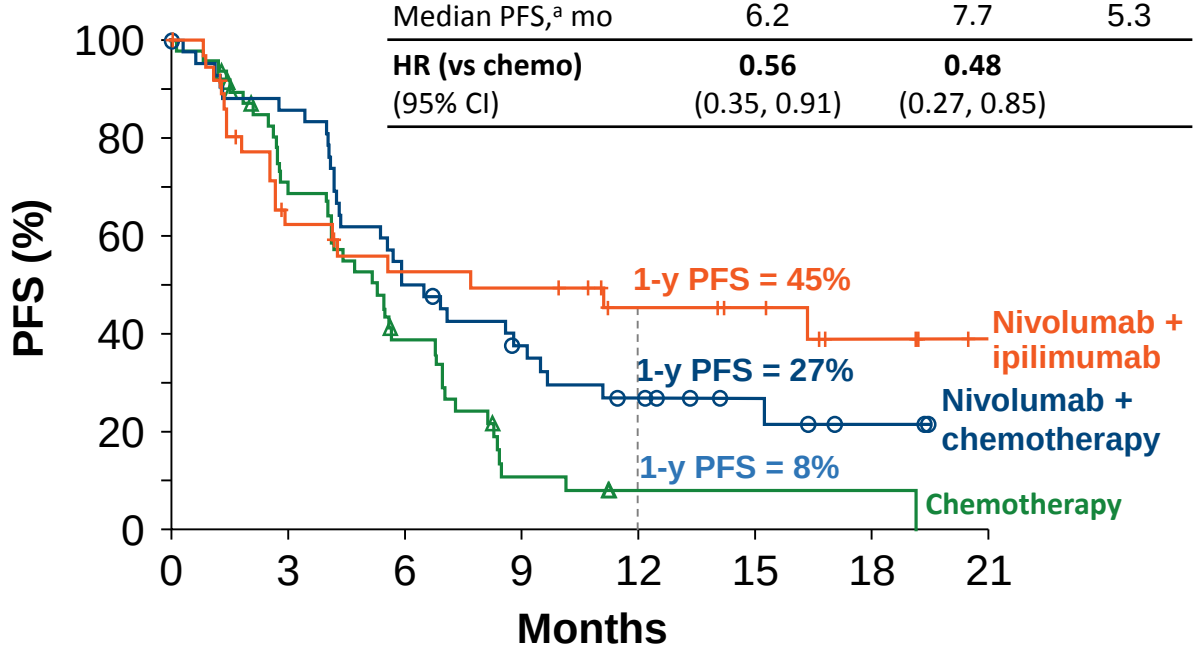
Is TMB relevant to chemotherapy combinations?

Trial	Histology	Agent	PD-L1 Status	ORR	OS
KEYNOTE-189	Nonsquamous	Pemetrexed/carboplatin ± Pembrolizumab (200 mg flat dosing q 3 wk)	Any PD-L1 status	47.6% vs. 18.9%	NR vs. 11.3 (HR=0.49)
KEYNOTE-407	Squamous	Paclitaxel or nab-paclitaxel and carboplatin ± Pembrolizumab	Any PD-L1 status	58.4% vs. 35%	15.9 vs. 11.3 (HR=0.64)
Impower 130 Phase III	Nonsquamous	nab-paclitaxel and carboplatin ± Atezolizumab	Any PD-L1 status	pending	"Positive"
Impower 131 Phase III	Squamous	Paclitaxel or nab-paclitaxel and carboplatin ± Atezolizumab	Any PD-L1 status	49% vs. 41%	23.6 vs. 14.1 (HR=0.56)
Impower 132	Nonsquamous	Pemetrexed and carboplatin or cisplatin ± Atezolizumab	Any PD-L1 status	Pending	Pending
Impower 150	Nonsquamous	Paclitaxel/carboplatin with or without bevacizumab ± Atezolizumab	Any PD-L1 status	64% vs. 48%	19.2 vs. 14.7 (HR=0.78)

PFS: Nivolumab + Chemotherapy and Nivolumab + Ipilimumab By TMB

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

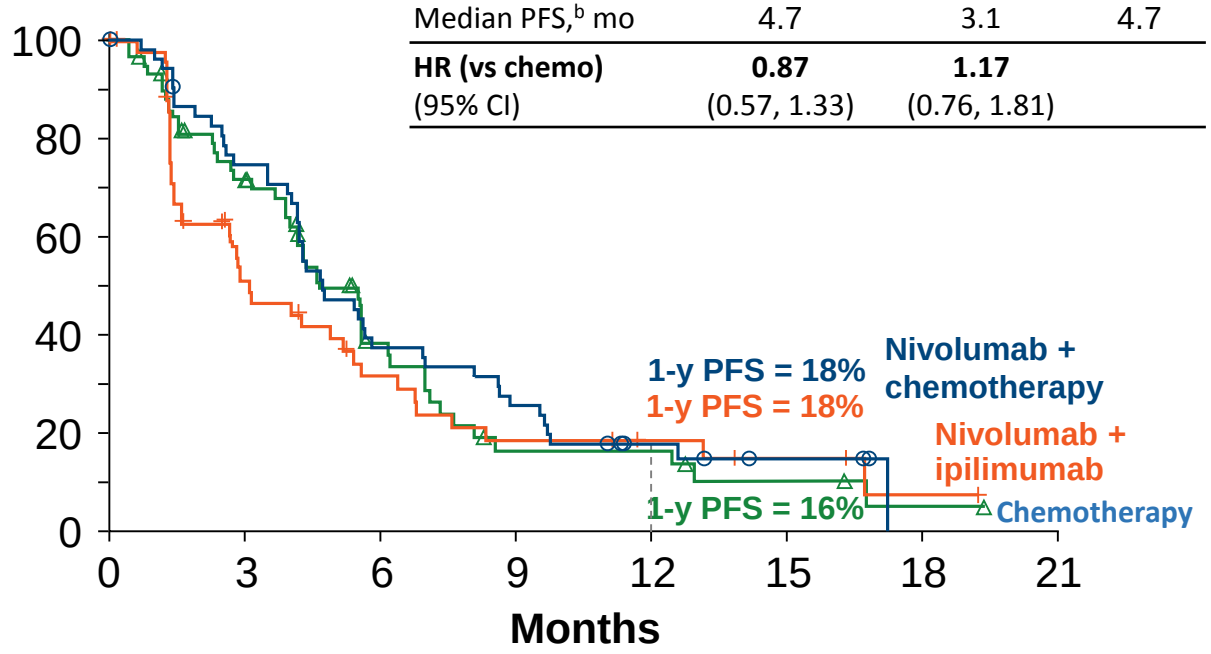
	Nivo + chemo (n = 43)	Nivo + ipi (n = 38)	Chemo (n = 48)
Median PFS,[a] mo	6.2	7.7	5.3
HR (vs chemo)	**0.56**	**0.48**	
(95% CI)	(0.35, 0.91)	(0.27, 0.85)	



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)	**0.87**	**1.17**	
(95% CI)	(0.57, 1.33)	(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

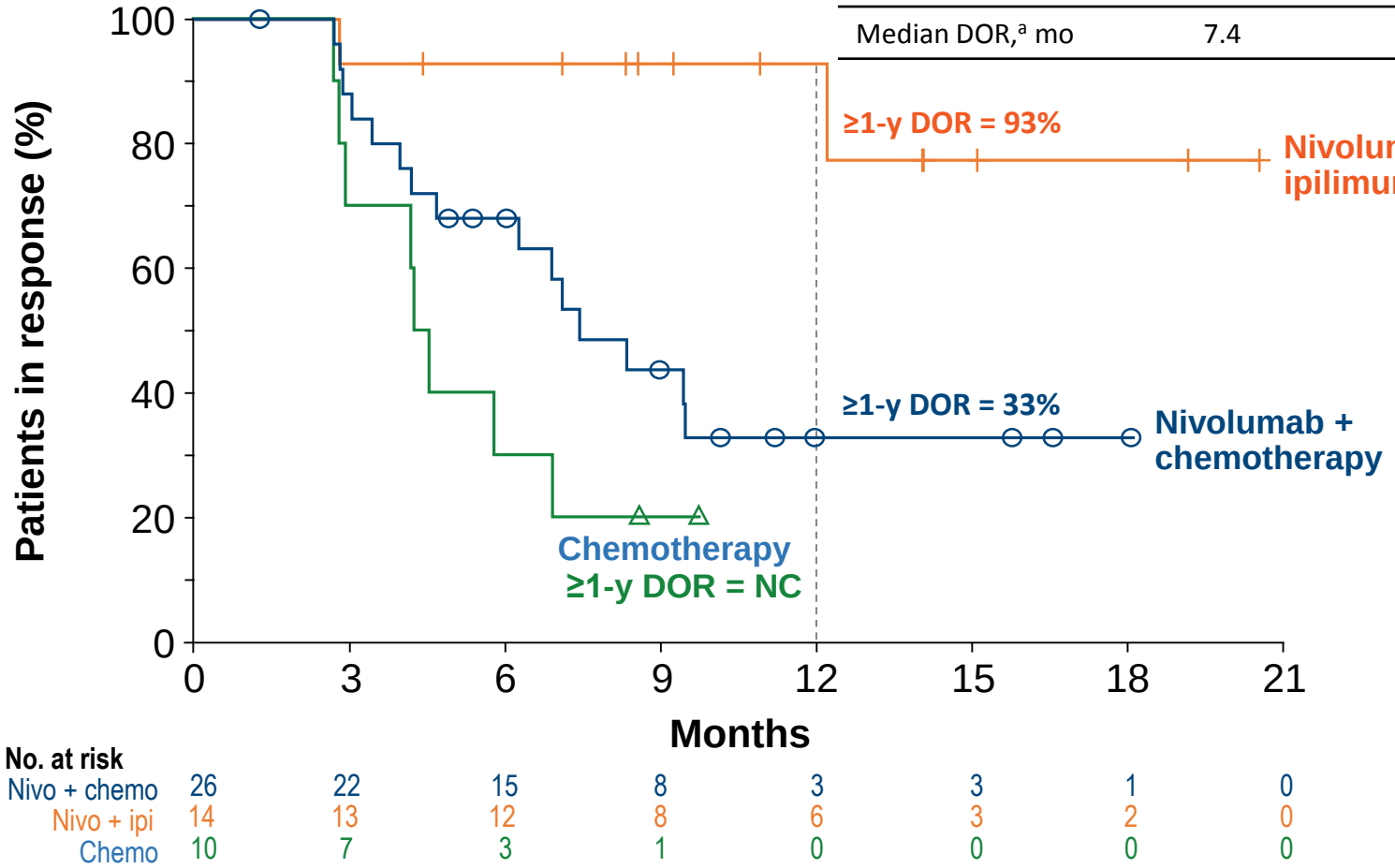
Exploratory analysis

[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)

Borghaei, ASCO 2018

DOR: Nivolumab + Chemotherapy and Nivolumab + Ipilimumab in Patients With TMB ≥10 mut/Mb and <1% Tumor PD-L1 Expression

	Nivo + chemo (n = 26)	Nivo + ipi (n = 14)	Chemo (n = 10)
Median DOR,[a] mo	7.4	NR	4.4



- ORR was 60.5% with nivo + chemo, 36.8% with nivo + ipi, and 20.8% with chemo

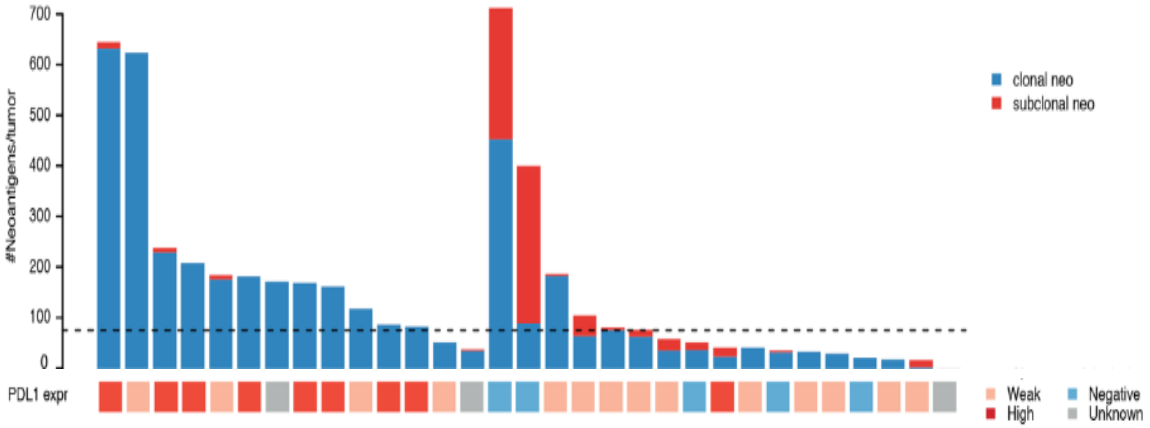
Exploratory analysis

[a]95% CI: nivo + chemo (4.6, NR mo), nivo + ipi (12.2, NR mo), chemo (2.7, 6.9 mo)

Borghaei, ASCO 2018

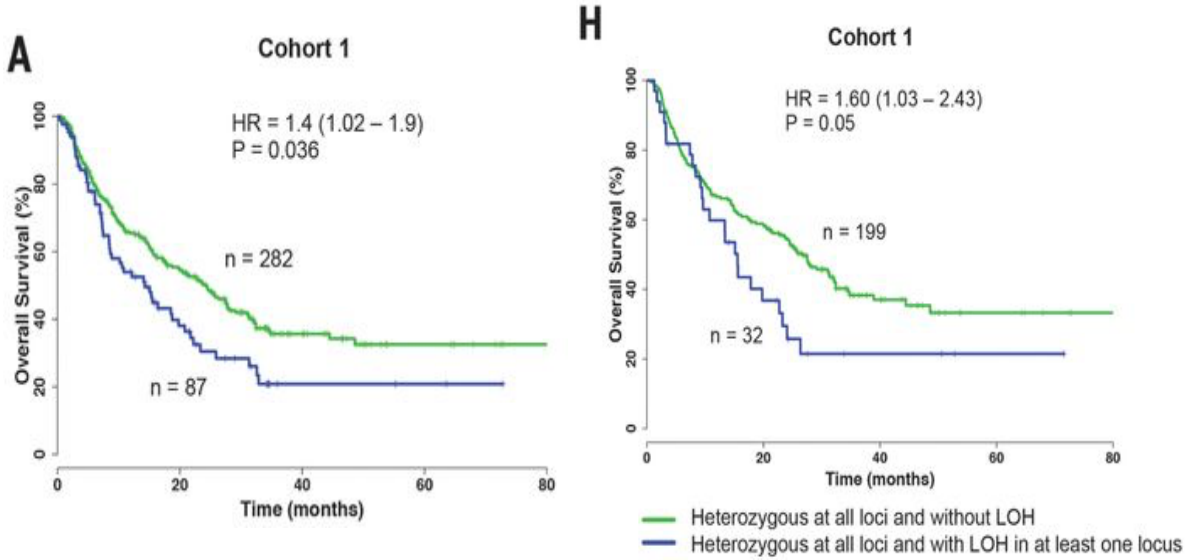
Genetic reasons why not all patients respond to immune checkpoint blockade

Tumor heterogeneity



McGranahan et al, Science 2016

HLA Class I zygosity and LOH



Chowell D, et al. Science. 2017

Conclusions

- TMB a valuable biomarker
- Effective as a a patient selection tool in phase 3 trials
- Targeted NGS panels correlate with exome data
- BUT
  - Threshold may vary by tumor type
  - Needs to be analyzed in concert with PD-L1 – may not be required in PD-1/CTLA-4
  - Platform validation and TAT
  - Will be more complex – unique mutations, heterozygosity, LOH…