VANDERBILT-INGRAM CANCER CENTER

Immune Checkpoint Inhibitors in Lung Cancer: Paving a New Avenue of Care

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Disclosures

- **Consulting:** Abbvie, Bristol Myers Squibb, EMD Serono, Incyte, Lilly, Merck, Pfizer, Roche-Genentech, Tessaro, Xcovery

- **Research funding:** Bristol Myers Squibb, Boehringer Ingelheim, Xcovery

Evolution of Therapy in Lung Cancer

- NSCLC was once considered a single disease, until distinct subtypes and characteristics were revealed[1-4]
- Characteristics of NSCLC subtypes are clinically relevant for treatment planning from the point of diagnosis[1]

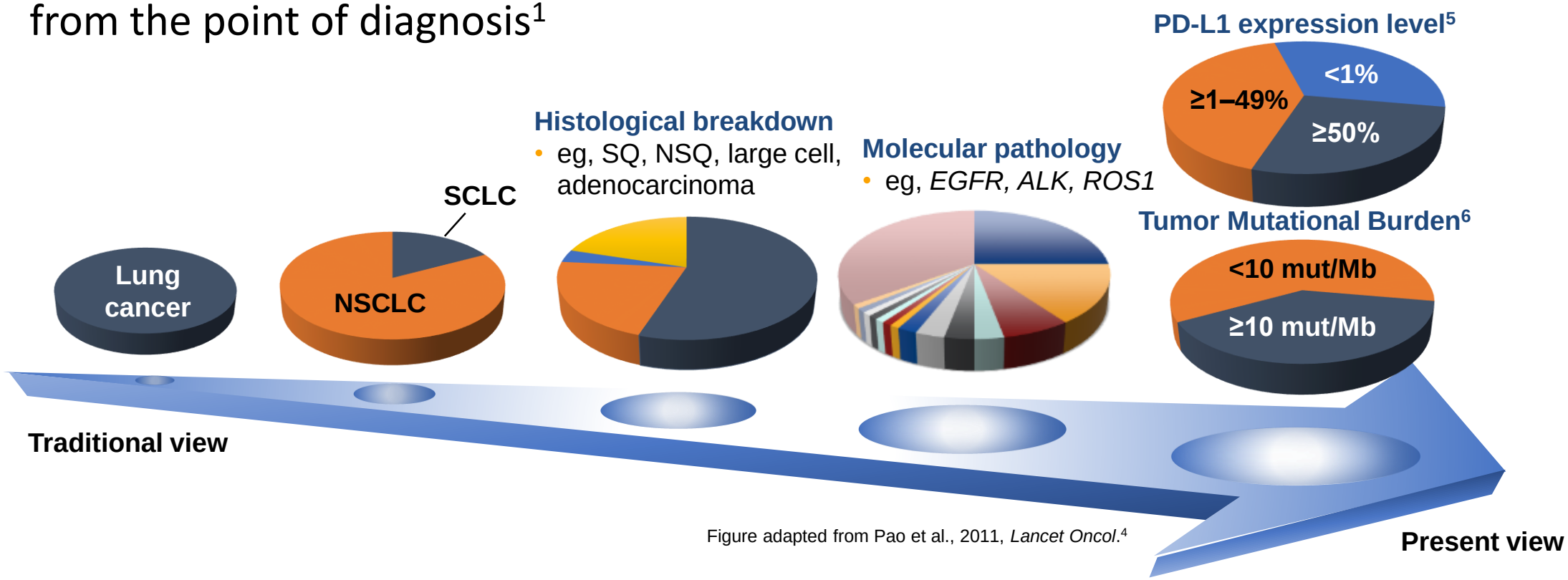
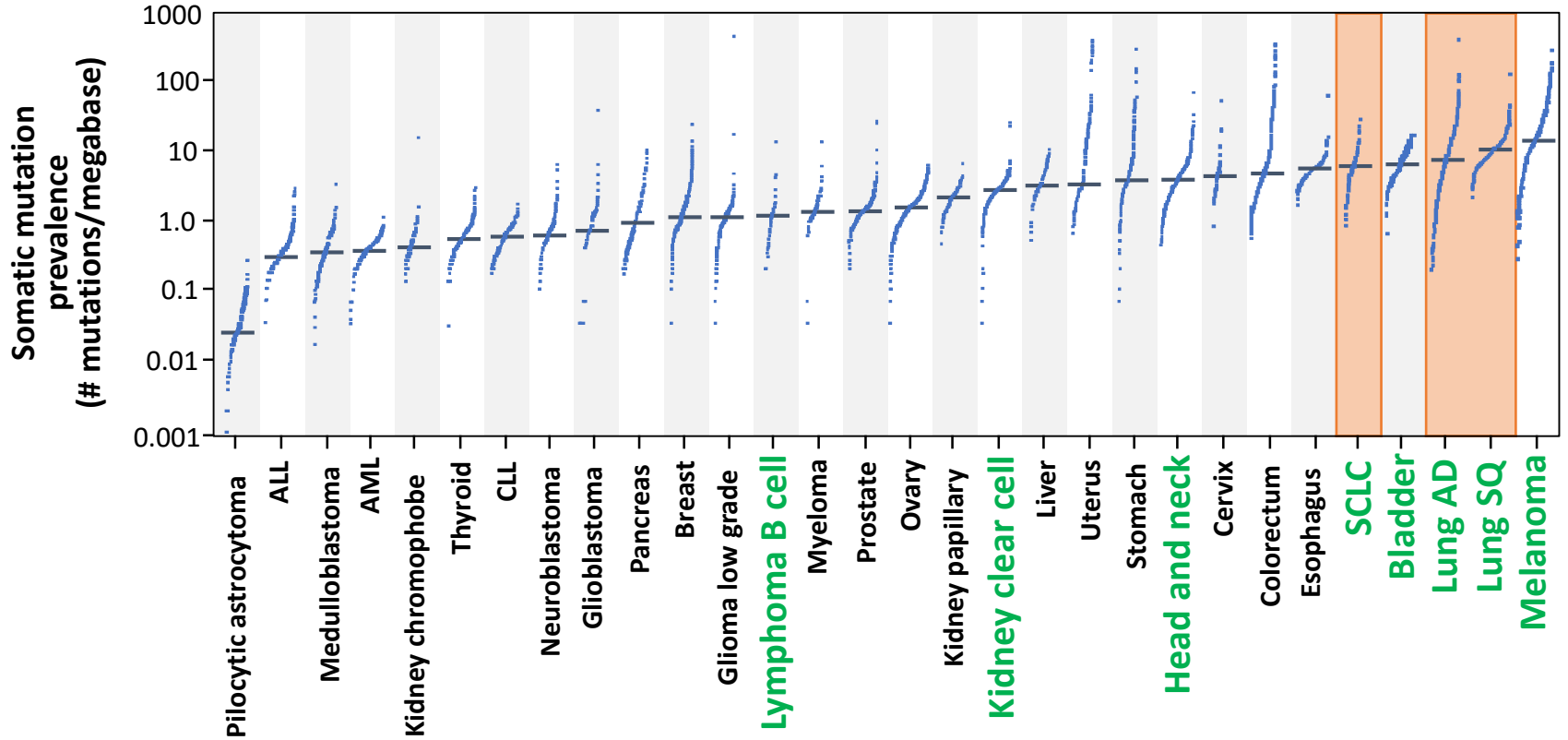


Figure adapted from Pao et al., 2011, *Lancet Oncol*.[4]

1. Cooper WA et al. *Pathology*. 2011;43(2):103-115. 2. Langer CJ et al. *J Clin Oncol*. 2010;28(36):5311-5320. 3. Galon J et al. *Immunity*. 2013;39(1):11-26. 4. Pao W Girard N. *Lancet Oncol*. 2011;12(2):175-180. 5. Krigsfeld G et al. Poster presentation at AACR 2017. Abstract CT143. 6. Hellmann MD et al. *N Engl J Med*. 2018; 378(22):2093-2104.

How Did We Get Here?

Many Cancers in which IO is approved have a high frequency of mutation



Lung cancers are associated with particularly high tumor mutation burdens (TMB)*

*Analyzed using an algorithm developed to extract mutational signatures from catalogues of somatic mutations in 7,042 primary cancers.

AD=adenocarcinoma; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CLL=chronic lymphocytic leukemia; SCLC=small cell lung cancer; SQ=squamous.

Alexandrov LB et al. *Nature* 2013;500(7463):415-421.

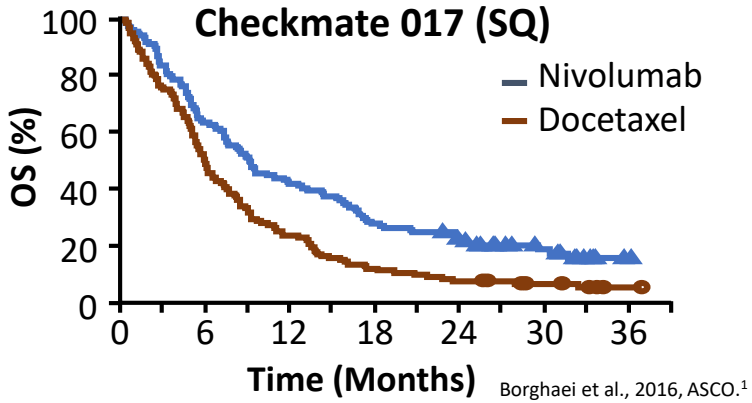
Alexandrov et al, 2013, *Nature*.

PD-L1 Inhibitors Improve OS in Second Line NSCLC

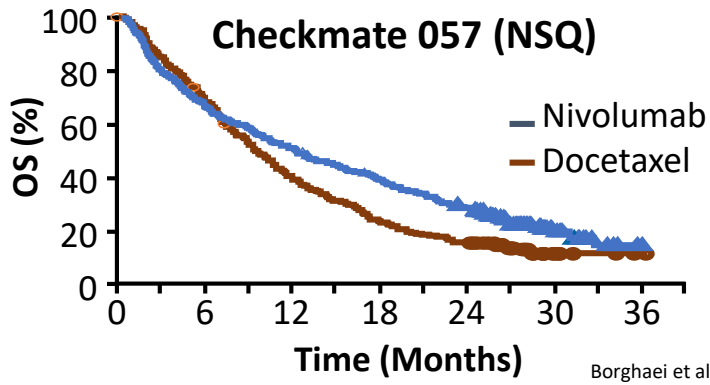
Checkmate 017/057[1] Median OS, months (95% CI)	CM017	CM057
Nivolumab	**9.2** (7.3–12.6)	**12.2** (9.7–15.1)
Docetaxel	**6.0** (5.1–7.3)	**9.5** (8.1–10.7)

KEYNOTE-010[2] Median OS, months (95% CI)	
Pembro 2 mg/kg	**10.5** (9.6–12.4)
Pembro 10 mg/kg	**13.4** (11.2–17.0)
Docetaxel	**8.6** (7.9–9.8)

OAK[3] Median OS, months (95% CI)	
Atezolizumab	**13.8** (11.8–15.7)
Docetaxel	**9.6** (8.6–11.2)



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



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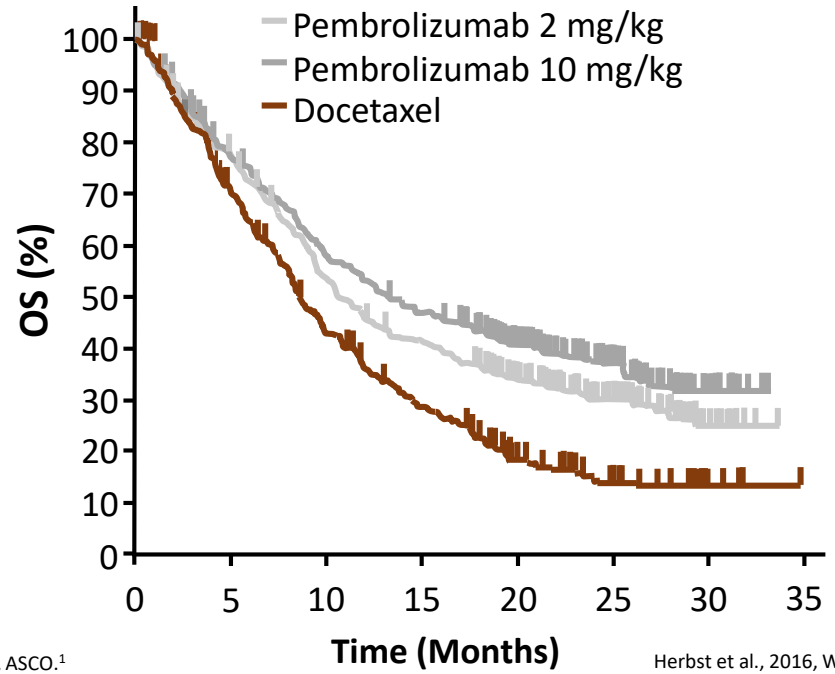
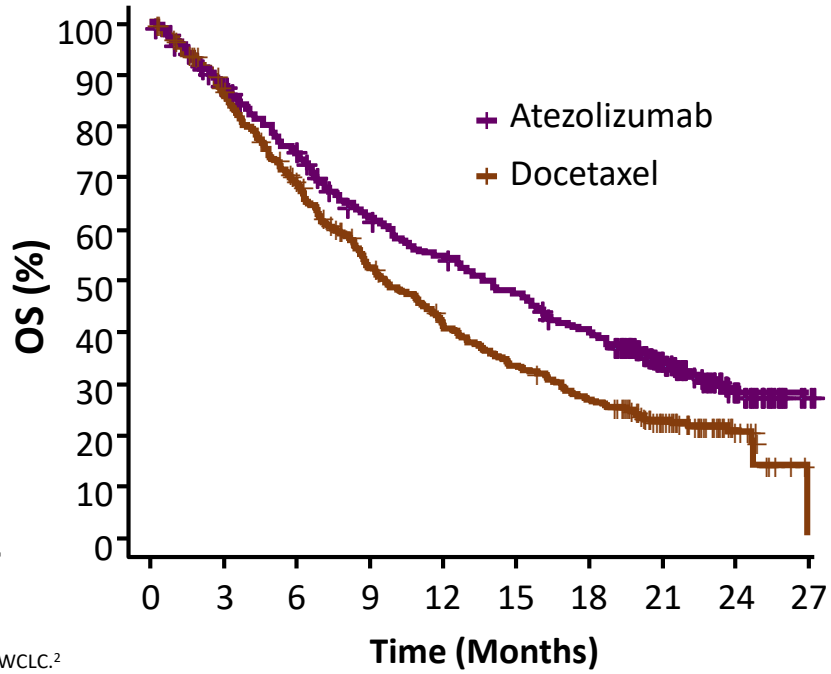


Herbst et al., 2016, WCLC.[2]



Cross-study comparisons are not intended.

CI=confidence interval; CM=Checkmate; NSQ=non-squamous; OS=overall survival; Pembro=pembrolizumab; SQ=squamous.

1. Borghaei H et al. Oral presentation at ASCO 2016. 9025. 2. Herbst RS et al. *Lancet*. 2016;387(10027):1540-1550. 3. Rittmeyer A et al. *Lancet.* 2017;389(10066):255-265.

But for the Majority of Patients They Do Not Work

Checkmate 017/057[1] Median OS, months (95% CI)	CM017	CM057
Nivolumab	**9.2** (7.3–12.6)	**12.2** (9.7–15.1)
Docetaxel	**6.0** (5.1–7.3)	**9.5** (8.1–10.7)

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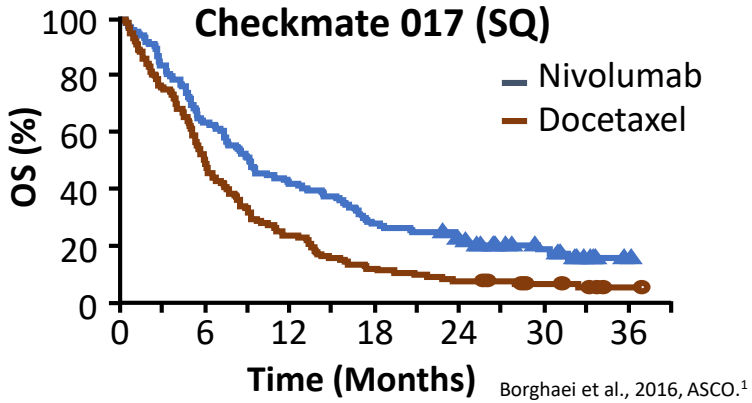

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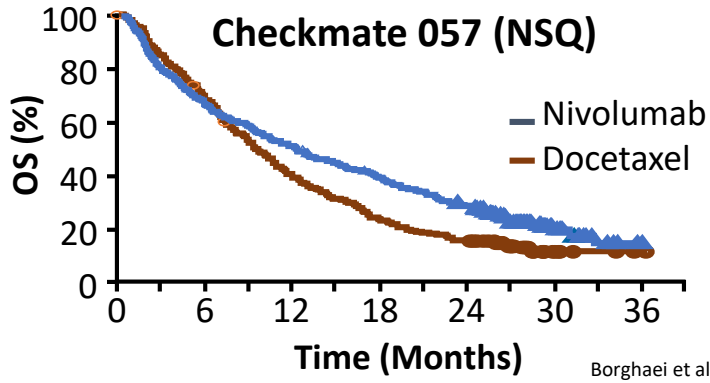

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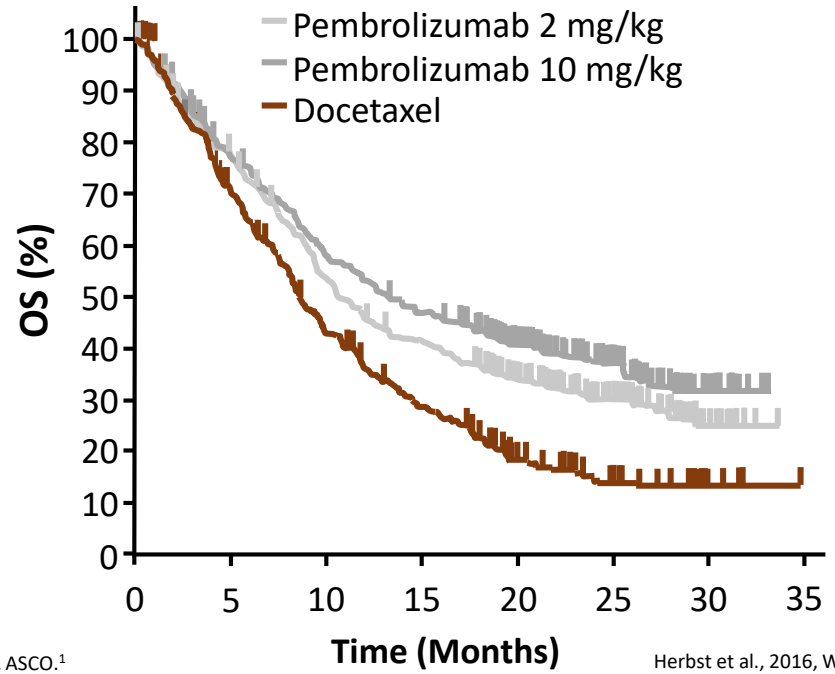

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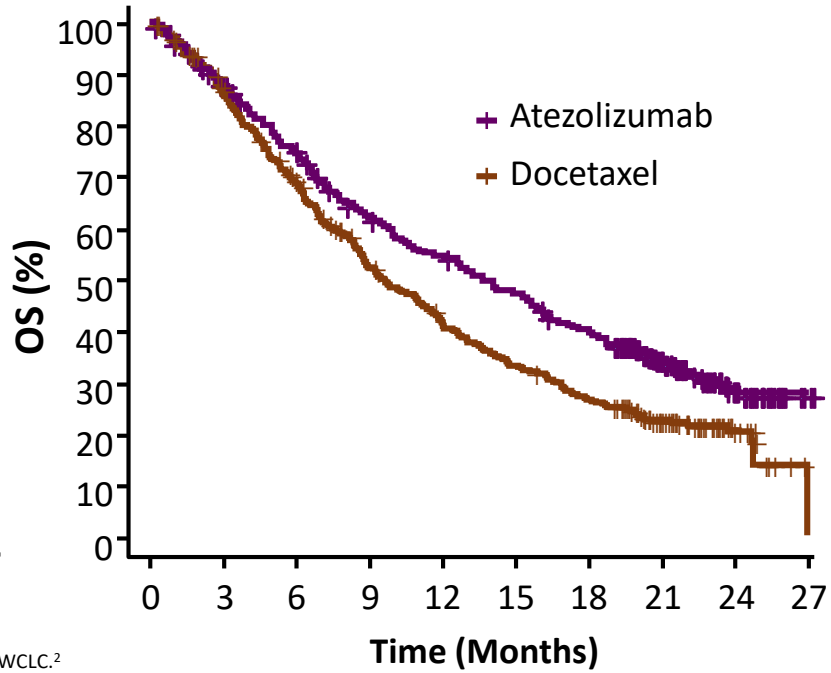

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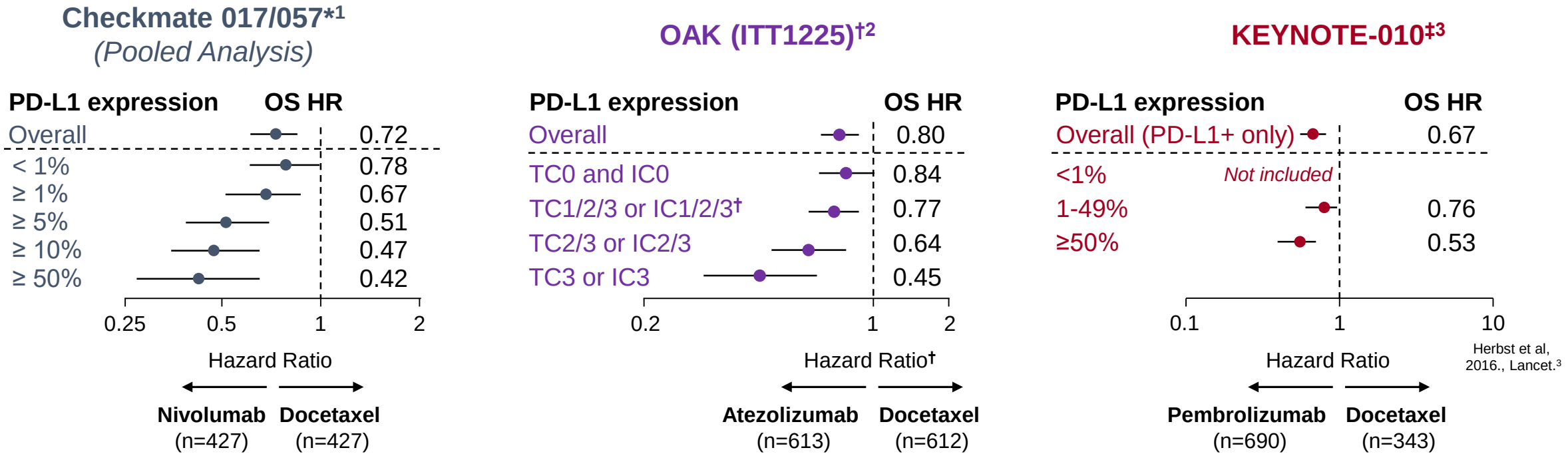
Increased Clinical Benefit of I-O Across PD-L1 Expression Levels in 2L NSCLC



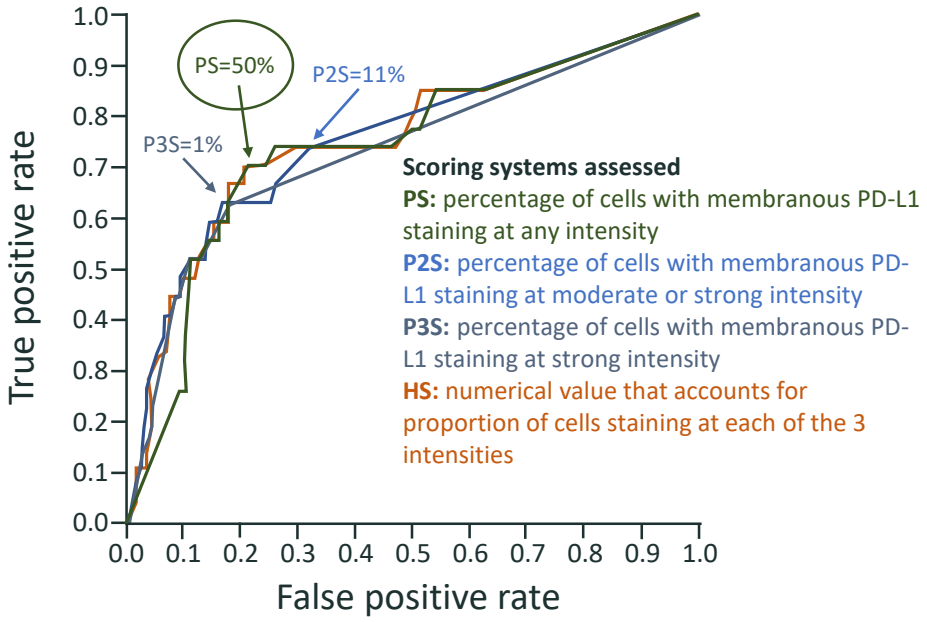
- OS benefit observed across the PD-L1 spectrum, including <1% PD-L1 expression[1]
- Enhanced benefit with increasing PD-L1 expression[1-3]

*Unstratified HR. These data are a pooled analysis of 2 separate trials with NSQ and SQ histologies. NSQ: N=582; SQ: N=272. †Unstratified HR for TC0 and IC0. Stratified HR for ITT and other PD-L1 subgroups. Overall, NSQ=74% and SQ=26%. NSQ and SQ histologies were pooled in this trial. ‡NSQ=70% and SQ=22% in patients who received pembrolizumab 2 mg/kg; NSQ=71% and SQ=23% in patients who received pembrolizumab 10 mg/kg; NSQ=70% and SQ=19% in patients who received docetaxel. NSQ and SQ histologies were pooled in this trial.

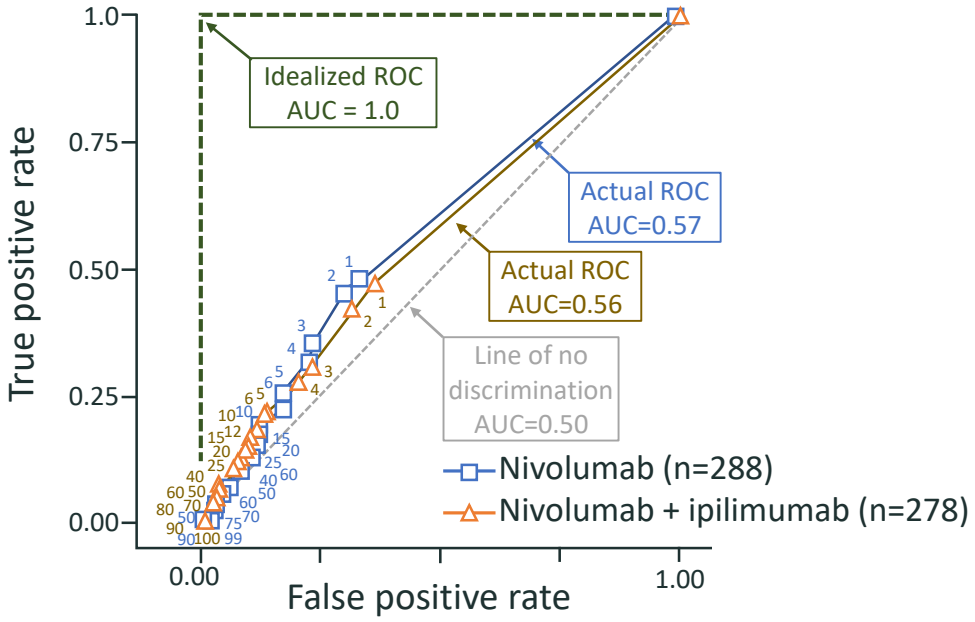
1. Horn L et al. *J Clin Oncol*. 2017;35:3924-3933. 2. Fehrenbacher L et al. *J Thorac Oncol*. 2018;13(8):1156-1170. 3. Herbst RS et al. *Lancet*. 2016;387(10027):1540-1550. 4. Merck KGaA [press release]. February 15, 2018.

Performance of PD-L1 is variable across cancer types

NSCLC[1]



Melanoma[2]

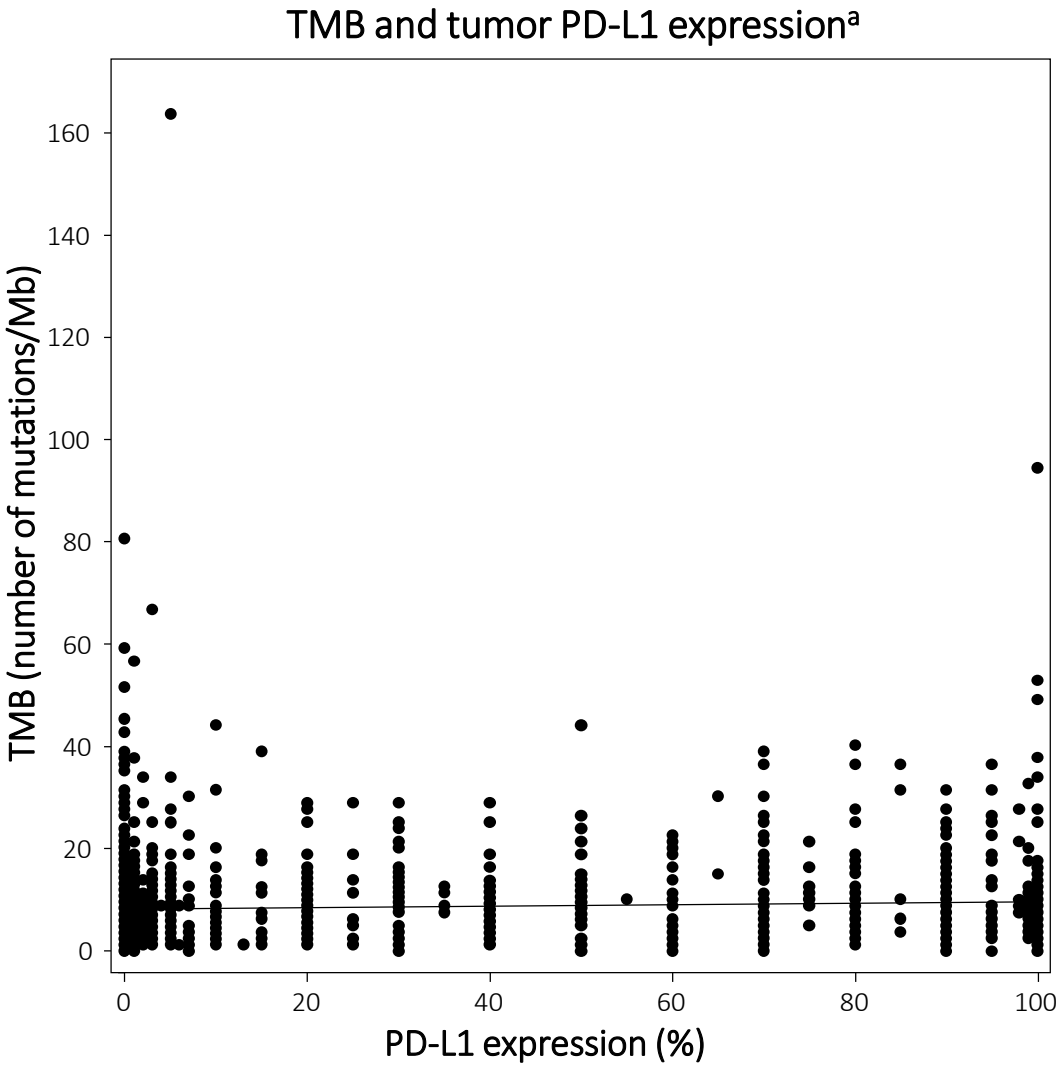


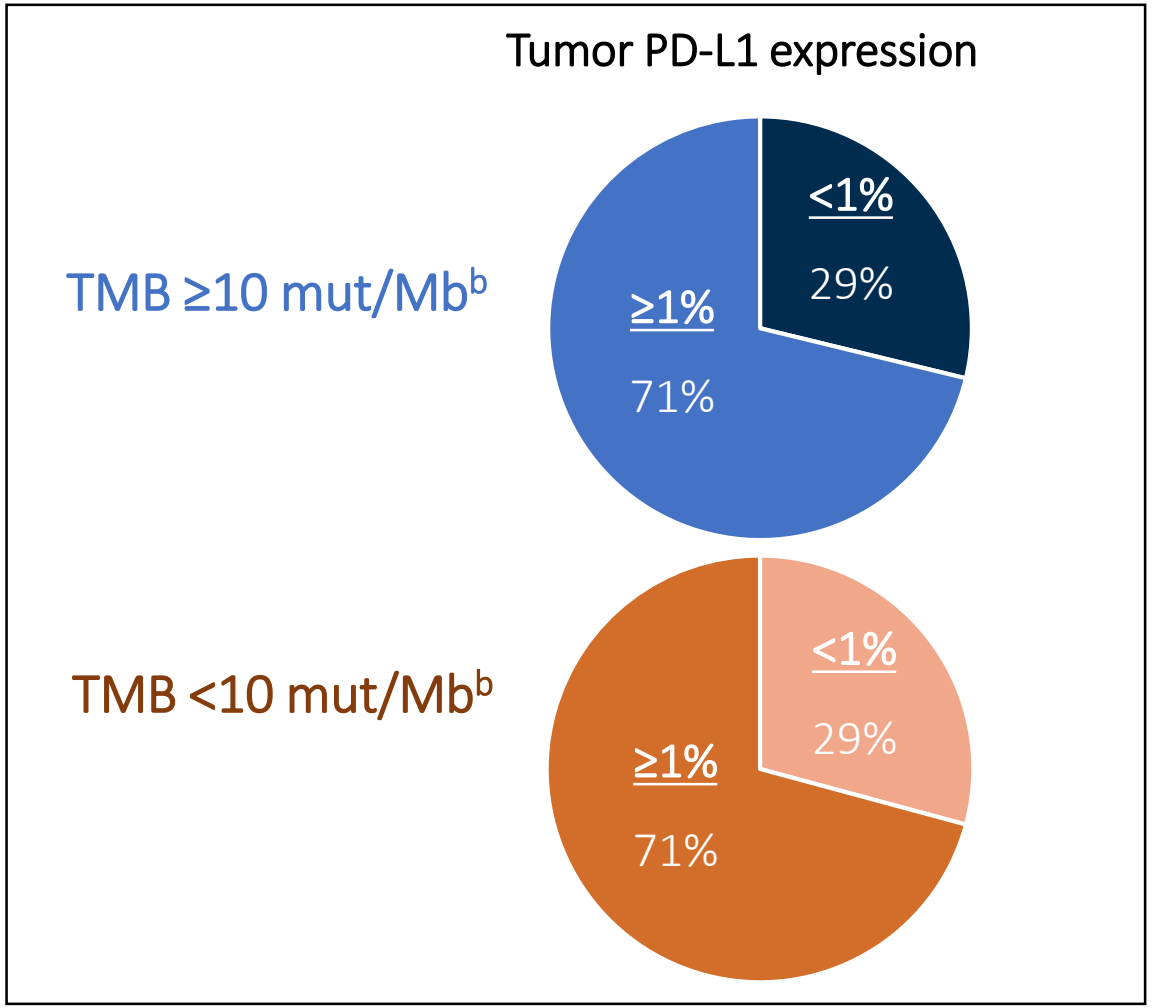
- ROC curves suggest insufficient performance of PD-L1 to guide patient selection across tumors
- PD-L1 does not allow for a binary classification: continuous, heterogenous, and dynamic
- Negative population can still derive benefit!

1. Garon EB, et al. N Engl J Med 2015;372(21):2018-2028. Supplementary information. Available at: https://www.nejm.org/doi/suppl/10.1056/NEJMoa1501824/suppl_file/nejmoa1501824_appendix.pdf
2. Wolchok JD, et al. N Engl J Med 2017;377(14):1345-1356. Supplementary information. Available at: https://www.nejm.org/doi/suppl/10.1056/NEJMoa1709684/suppl_file/nejmoa1709684_appendix.pdf

AUC, area under the curve; IO, immuno-oncology; NSCLC, non-small-cell lung cancer; PD-L1, programmed cell death ligand-1; ROC, receiver operating characteristic.

TMB and Tumor PD-L1 Expression Identify Distinct and Independent Populations of NSCLC





[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; [b]Among patients in the nivolumab +ipilimumab and chemotherapy arms; TMB ≥10 mut/Mb, n = 299; TMB <10 mut/Mb, n = 380

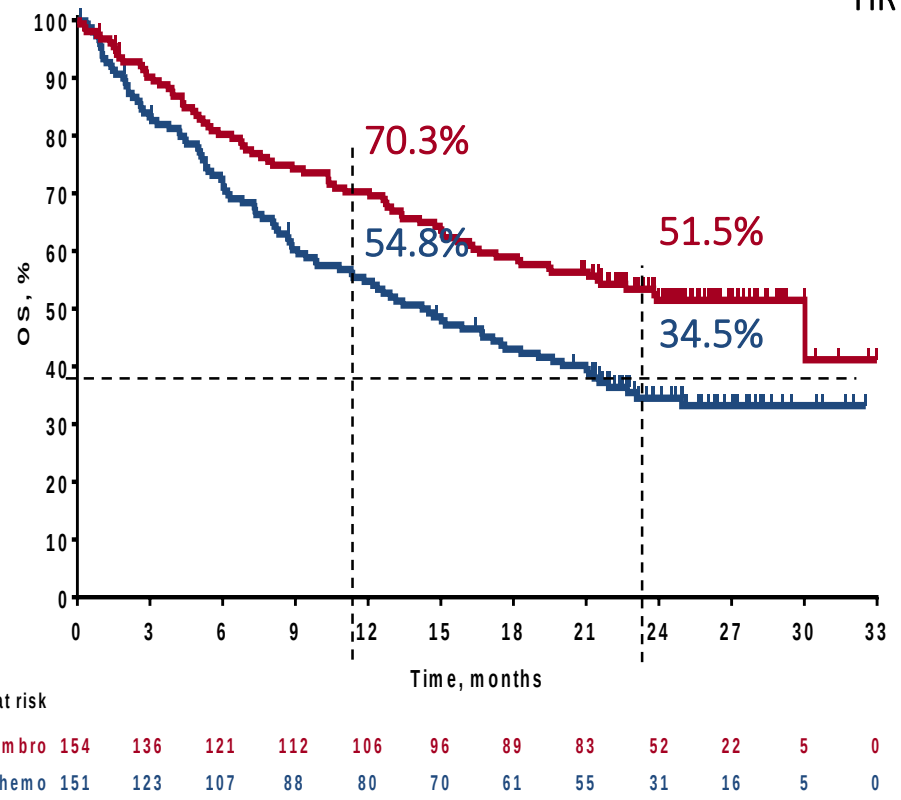
Paradigm Shift in First Line therapy for Advanced NSCLC
Pembrolizumab is Superior to Chemotherapy in Patients with TPS ≥ 50%

Key Eligibility Criteria

- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 TPS ≥50%
- No sensitizing *EGFR* or *ALK* alterations
- ECOG PS 0 or 1
- No untreated or unstable CNS metastases
- No history of pneumonitis that required systemic corticosteroids

Randomize (1:1)

- Pembrolizumab 200 mg Q3W for up to 35 cycles
- Platinum-Doublet Chemotherapy (4-6 cycles)

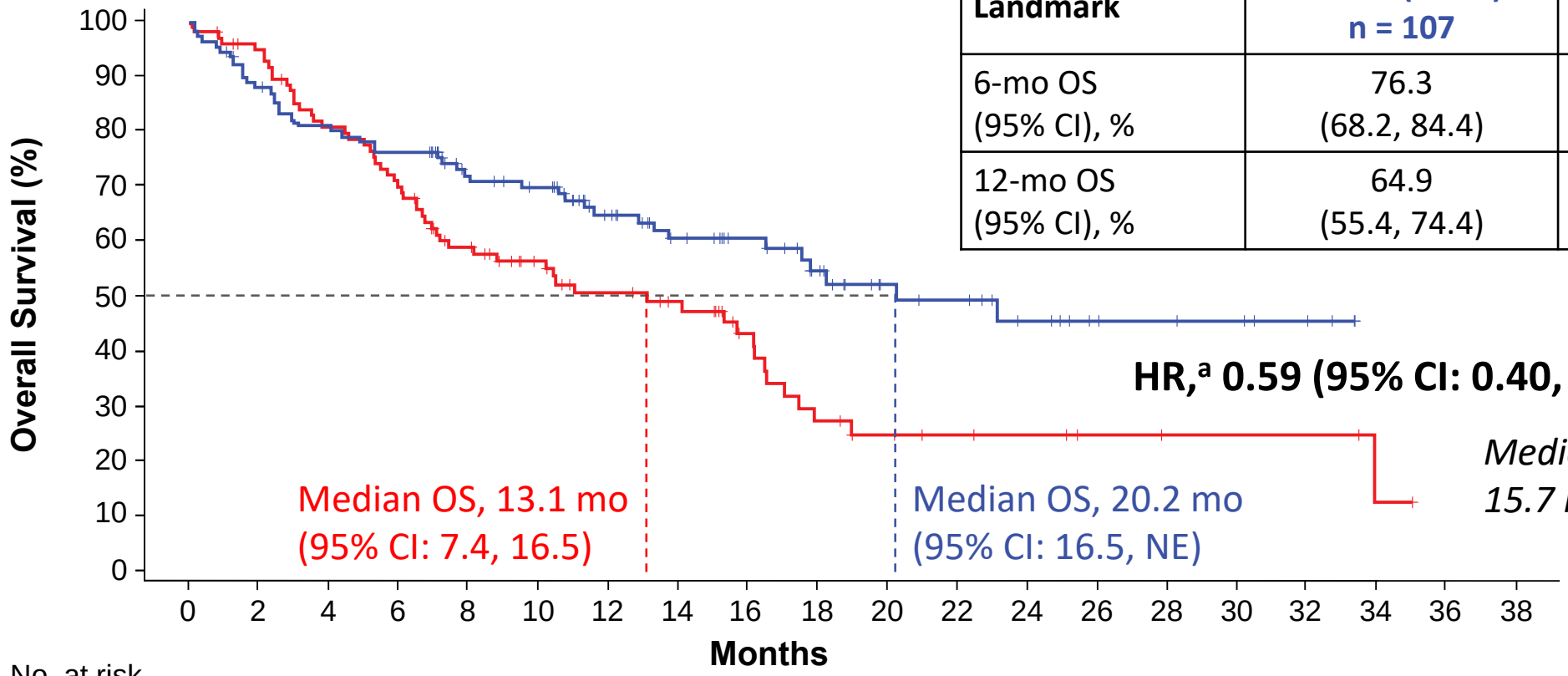


[a]Effective crossover rate from chemotherapy to anti-PD-L1 therapy, 62.3% (82 patients crossed over to pembrolizumab during the study and 12 received anti-PD-L1 therapy outside of crossover). [b]Nominal *P* value. NR, not reached.

Reck M et al. N Engl J Med 2016;375:1823–1833; Brahmer et al, WCLC 2017

Similar Efficacy with Atezolizumab
OS: TC3 or IC3 WT

Landmark	Arm A (atezo) n = 107	Arm B (chemo) n = 98
6-mo OS (95% CI), %	76.3 (68.2, 84.4)	70.1 (60.8, 79.4)
12-mo OS (95% CI), %	64.9 (55.4, 74.4)	50.6 (40.0, 61.3)



HR,[a] 0.59 (95% CI: 0.40, 0.89); *P* = 0.0106[b]

Median follow-up, 15.7 mo (range, 0-35)

No. at risk

Atezolizumab	107	94	85	80	66	61	48	40	34	25	18	16	11	7	6	5	2
Chemotherapy	98	89	75	65	50	40	33	28	19	12	9	7	6	4	3	3	3	1

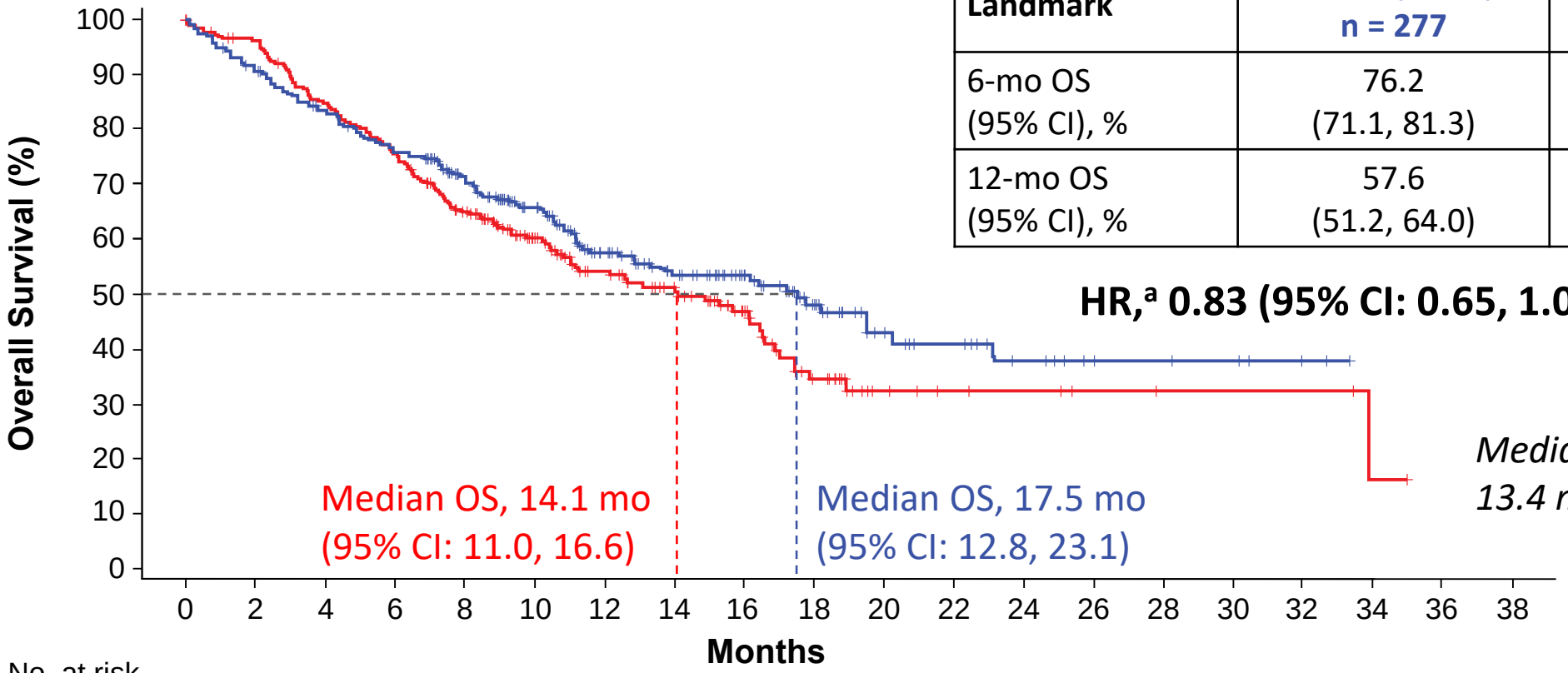
NE, not estimable. [a] Stratified. [b] Stratified log-rank.
Data cutoff: September 10, 2018.

Herbst et al., SITC 2019

Limited Benefit with in PD-L1 Low Expression
OS: TC1/2/3 or IC1/2/3 WT

Landmark	Arm A (atezo) n = 277	Arm B (chemo) n = 277
6-mo OS (95% CI), %	76.2 (71.1, 81.3)	75.7 (70.5, 80.9)
12-mo OS (95% CI), %	57.6 (51.2, 64.0)	54.3 (47.7, 60.8)

HR,[a] 0.83 (95% CI: 0.65, 1.07); *P* = 0.1481[b,c]



Median follow-up, 13.4 mo (range, 0-35)

No. at risk

Atezolizumab	277	252	226	204	170	134	93	74	58	37	22	17	11	7	6	5	2
Chemotherapy	277	254	223	199	153	108	79	63	43	24	10	7	6	4	3	3	3	1

[a] Stratified. [b] Stratified log-rank. [c] For descriptive purposes only.
Data cutoff: September 10, 2018.

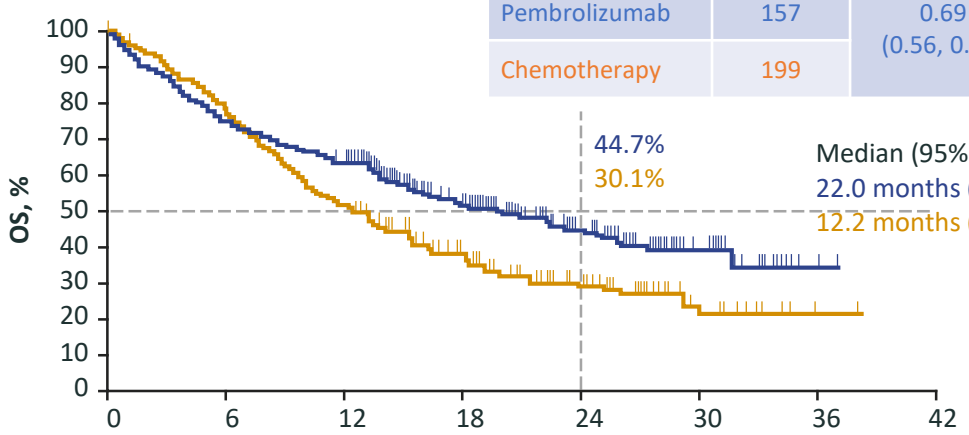
Herbst et al., SITC 2019

Pembrolizumab Not As Impressive in PD-L1 ≥ 1%: KEYNOTE-042

The PD-L1 ≥ 50% subgroup is the main driver of OS benefit in PD-L1-positive patients

OS: TPS ≥50%

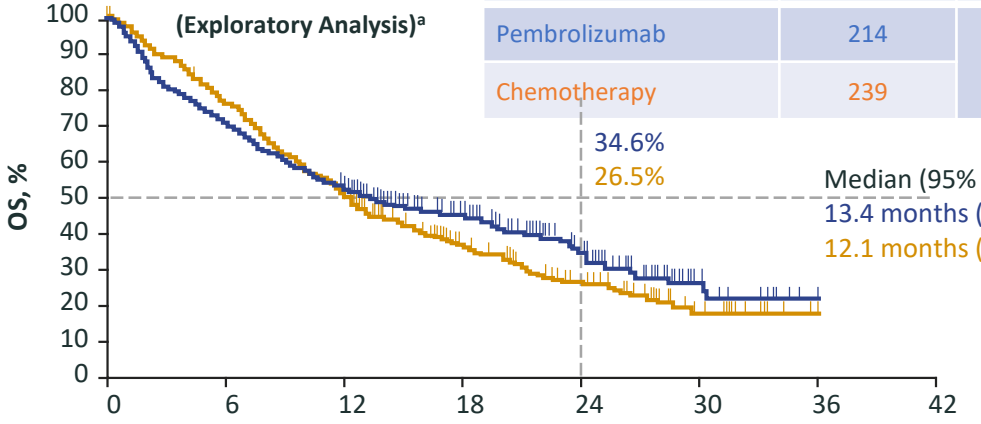
	Events	HR (95% CI)	*p-value*
Pembrolizumab	157	0.69 (0.56, 0.85)	0.0003
Chemotherapy	199		



OS: TPS ≥1-49%

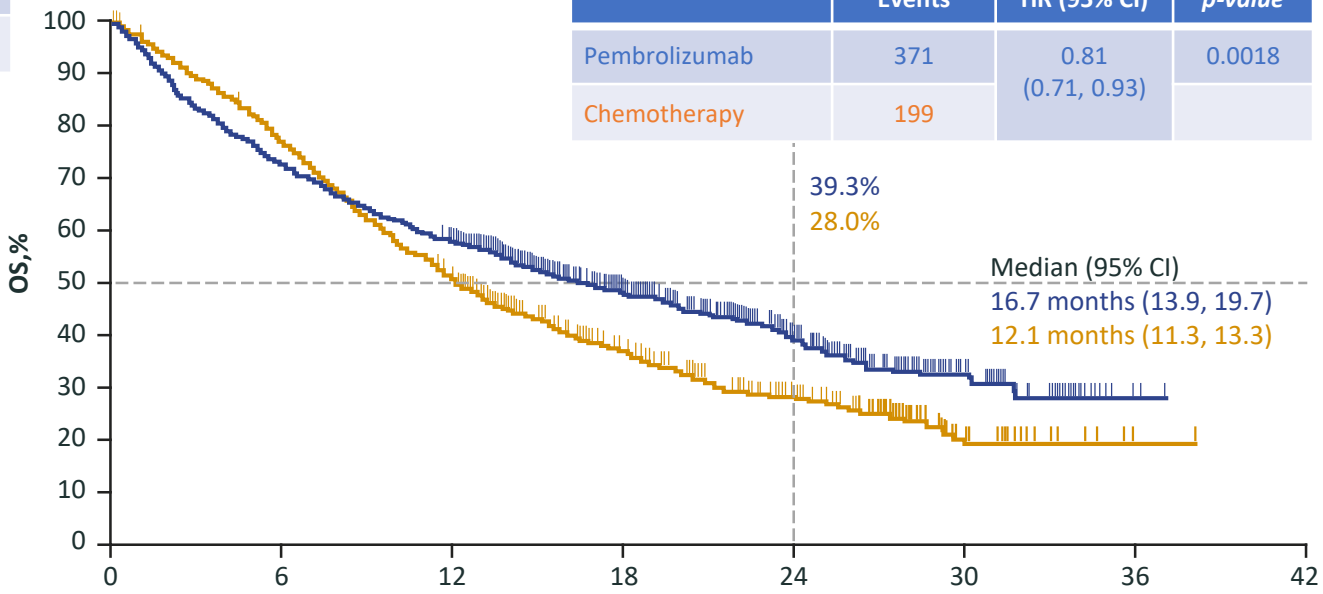
(Exploratory Analysis)[a]

	Events	HR (95% CI)
Pembrolizumab	214	0.92 (0.77, 1.11)
Chemotherapy	239	



Overall Survival: TPS ≥50%

	Events	HR (95% CI)	*p-value*
Pembrolizumab	371	0.81 (0.71, 0.93)	0.0018
Chemotherapy	199		

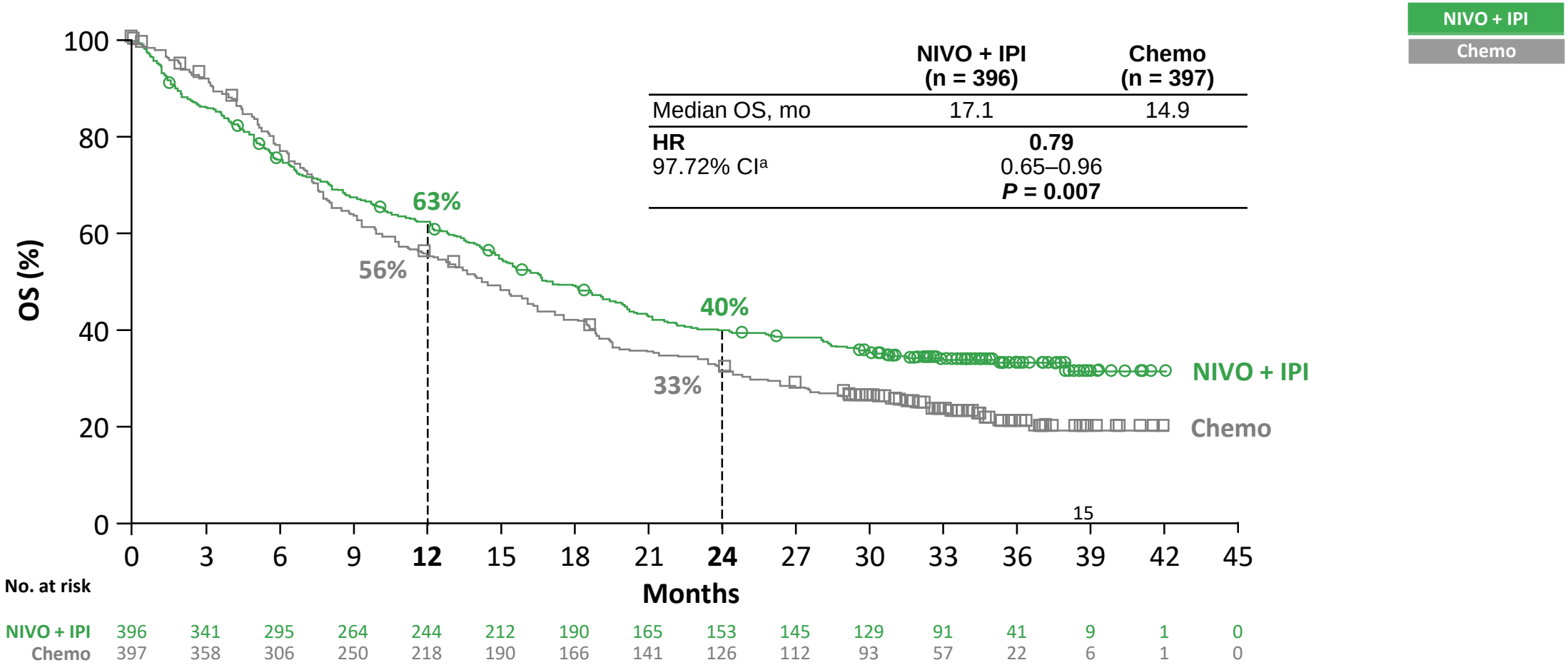


Primary endpoint OS by PD-L1 cut-offs ≥1% / ≥20% / ≥50%
Caveats: subsequent lines of treatment? Cross-over by 3% of patients from chemotherapy to immunotherapy (exposure to immunotherapy?)

CI, confidence interval; IO, immuno-oncology; HR, hazard ratio; KM, Kaplan Meier; OS, overall survival; PD-L1, programmed cell death ligand-1; TPS, tumor proportion score.

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

Benefit With NIVO + IPI in Patients With Tumor PD-L1 Expression ≥ 1%



	NIVO + IPI (n = 396)	Chemo (n = 397)
Median OS, mo	17.1	14.9
HR 97.72% CI[a]	**0.79** 0.65–0.96 ***P* = 0.007**	

Minimum follow-up for primary endpoint: 29.3 months.
NIVO + IPI dosage was NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W). Subsequent systemic therapy was received by 35% of patients in the NIVO + IPI arm and 54% of patients in the chemo arm; subsequent immunotherapy was received by 6% and 43%, respectively.
[a]95% CI, 0.67–0.94.

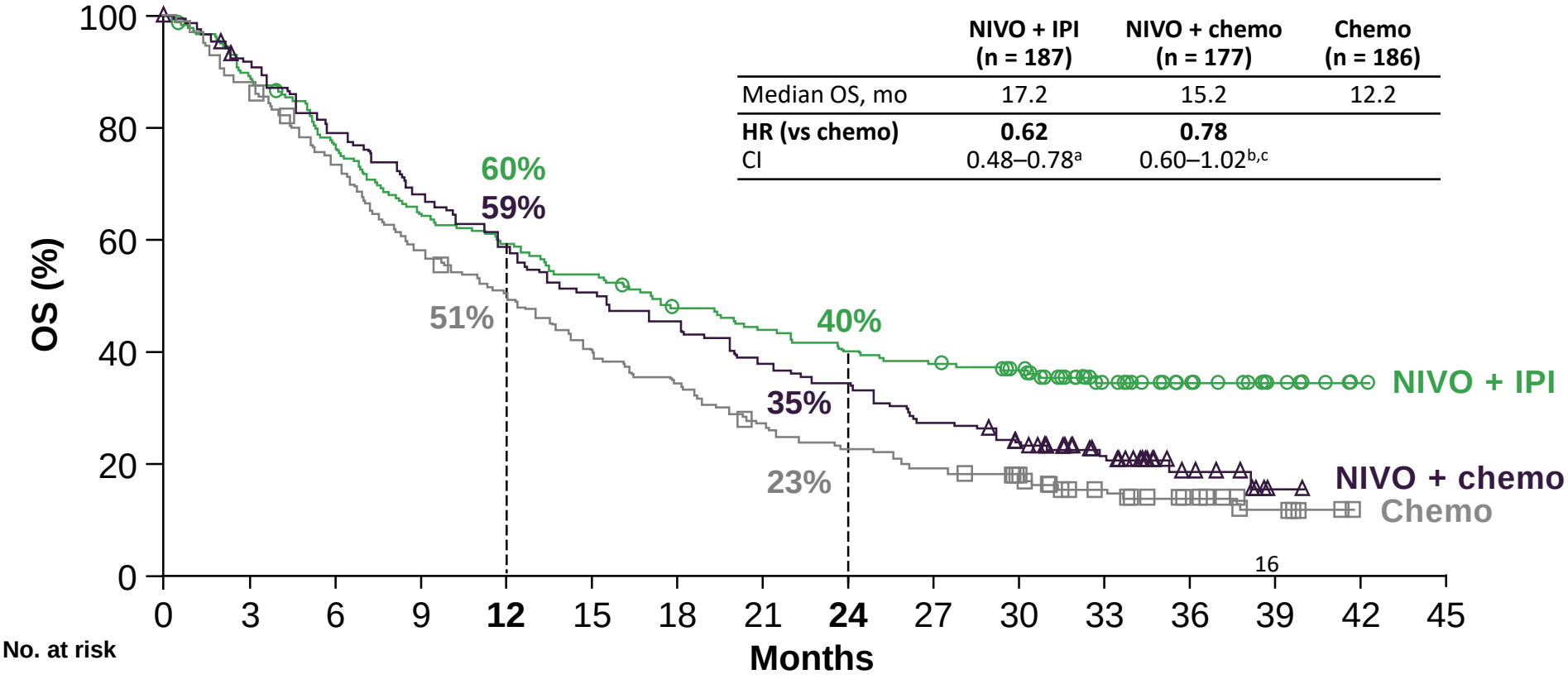
Peters et al., ESMO 2019

OS With NIVO + IPI and NIVO + Chemo vs Chemo in Patients With Tumor PD-L1 Expression < 1%

Part 1b

NIVO + IPI
Chemo
NIVO + chemo

	NIVO + IPI (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
Median OS, mo	17.2	15.2	12.2
HR (vs chemo)	**0.62**	**0.78**	
CI	0.48–0.78[a]	0.60–1.02[b,c]	



No. at risk

NIVO + IPI	187	165	142	120	110	100	87	80	73	69	59	34	19	8	2	0
NIVO + chemo	177	159	139	119	102	88	78	67	60	48	40	23	9	1	0	0
Chemo	186	164	135	107	92	74	62	49	41	35	29	19	12	5	0	0

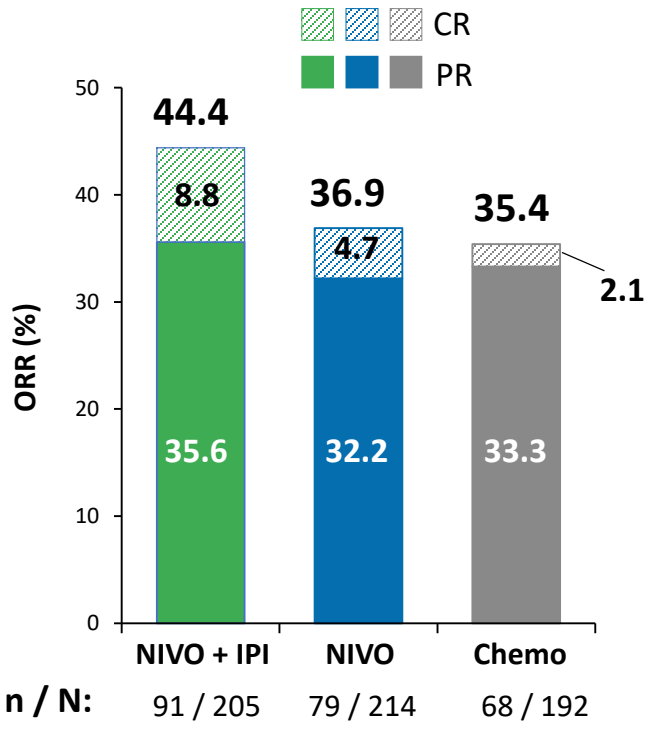
Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo. Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm, 41% of patients in the NIVO + chemo arm, and 53% of patients in the chemo arm; subsequent immunotherapy was received by 4%, 4%, and 36%, respectively.
[a]95% CI; [b]97.72% CI; [c]*P* = 0.0352.

Peters et al., ESMO 2019

Efficacy With NIVO + IPI and NIVO vs Chemo in Patients With Tumor PD-L1 Expression ≥ 50%

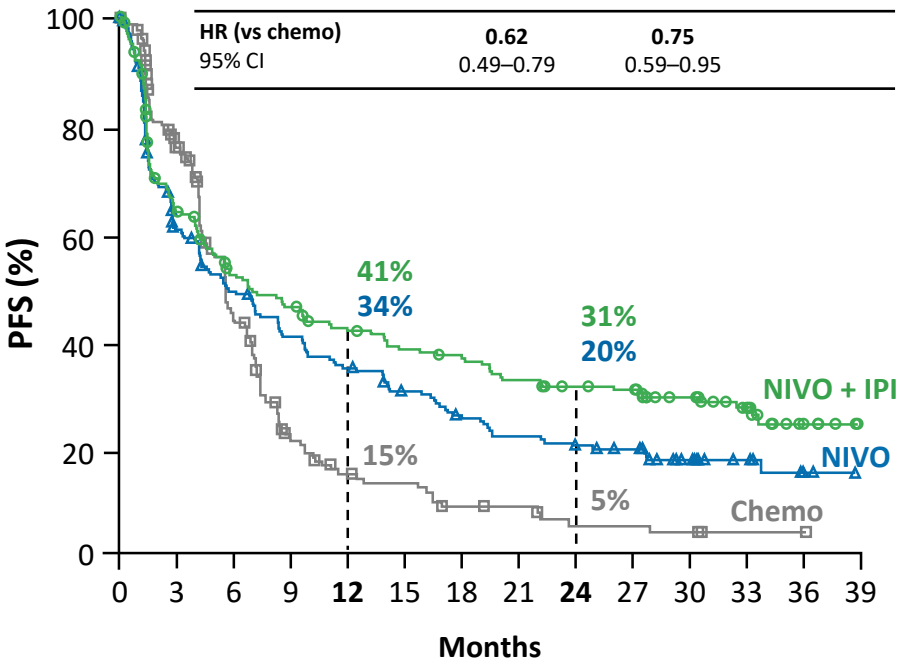
Part 1a
NIVO + IPI
Chemo
NIVO

ORR by BICR



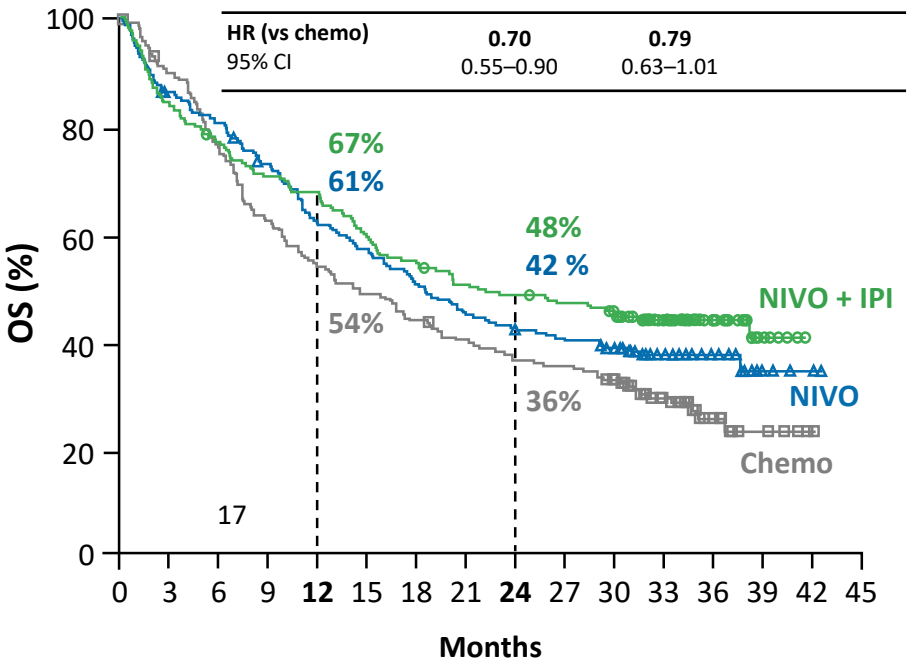
PFS by BICR

	NIVO + IPI (n = 205)	NIVO (n = 214)	Chemo (n = 192)
Median PFS, mo 95% CI	6.7 4.5–11.0	5.6 4.2–8.3	5.6 4.6–6.6
HR (vs chemo) 95% CI	**0.62** 0.49–0.79	**0.75** 0.59–0.95	



OS

	NIVO + IPI (n = 205)	NIVO (n = 214)	Chemo (n = 192)
Median OS, mo 95% CI	21.2 15.5–38.2	18.1 14.4–22.1	14.0 10.0–18.6
HR (vs chemo) 95% CI	**0.70** 0.55–0.90	**0.79** 0.63–1.01	



- Median DOR with NIVO + IPI, NIVO and chemo was 31.8, 17.5 and 5.8 months, respectively

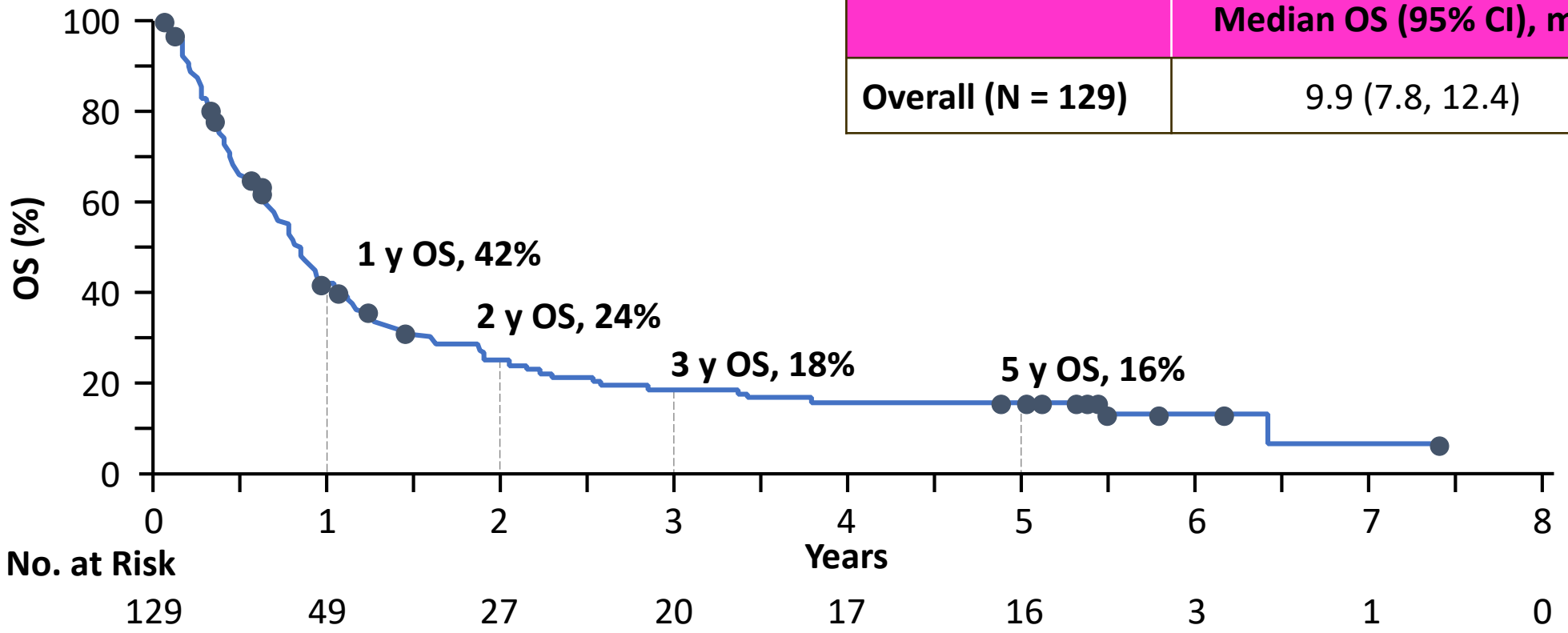
Dosages were NIVO (3 mg/kg Q2W) plus IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo.

Peters et al., ESMO 2019

Cohort of Long Term Survivors:
Checkmate 003: 5-Year Estimates of OS

Phase 1 trial of nivolumab in patients with advanced NSCLC of any histology after 1–5 lines of prior systemic therapy

	Median OS (95% CI), mos
Overall (N = 129)	9.9 (7.8, 12.4)



Brahmer et al., 2017, AACR.

There were 3 deaths between 3 and 5 years, all due to disease progression; 1 surviving patient was censored for OS prior to 5 years (OS: 58.2+ months).
CI=confidence interval; mos=months; No.=number; NSCLC=non-small cell lung cancer; OS=overall survival; y=years.

Brahmer JR et al. Oral presentation at AACR 2017. CT077.

Curing More Patients with chemo-RT → IO

- Patients with stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks
- Archived tissue was collected

All-comers population

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history
N=713

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

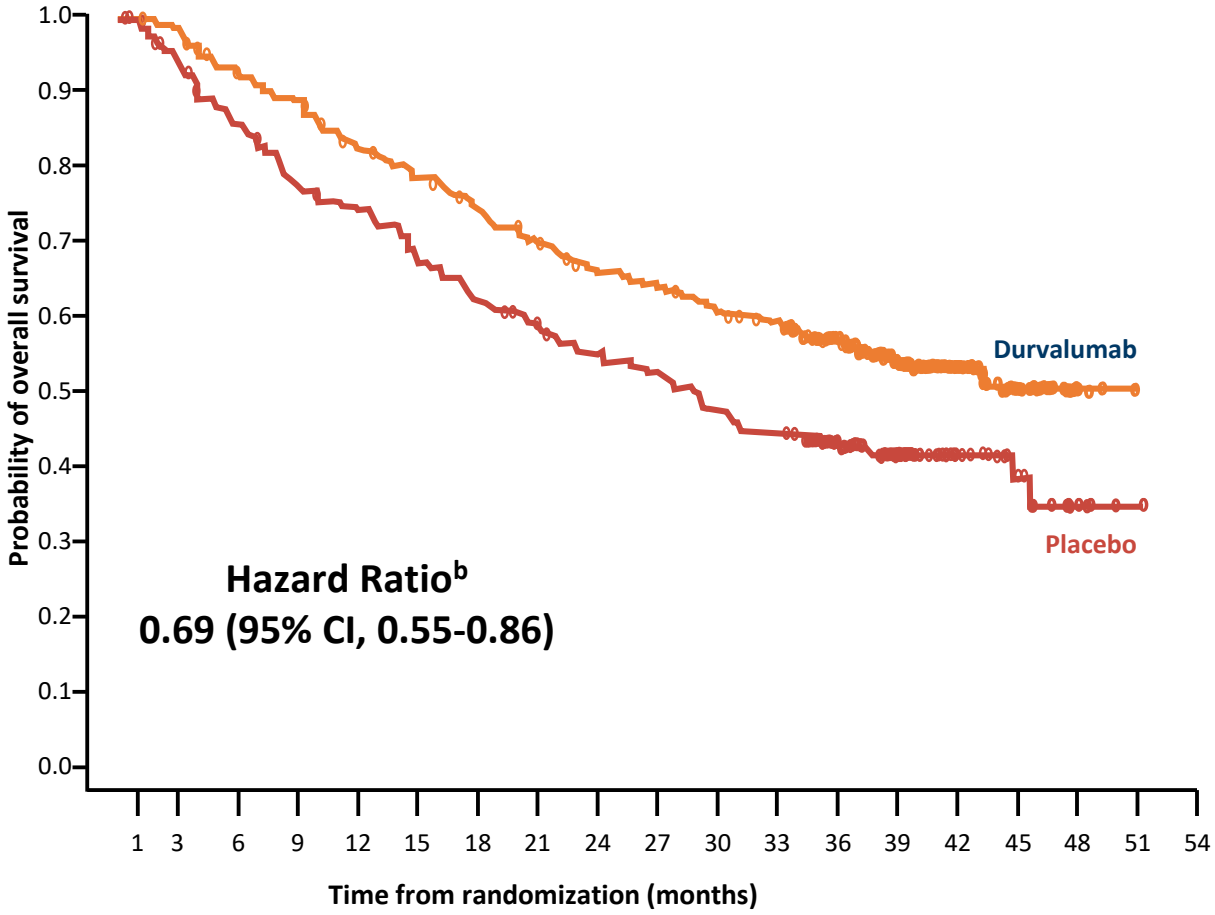
Placebo
10 mg/kg q2w for up to 12 months
N=237

Co-primary endpoints

- PFS by BICR using RECIST v1.1*
- OS

Key secondary endpoints

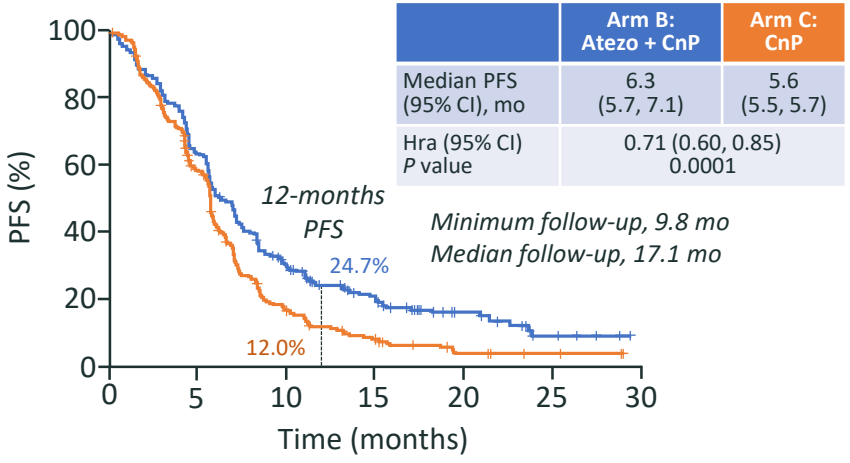
- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs



No. at risk																	
Durvalumab	476	464	431	415	385	364	343	319	298	289	274	263	205	132	73	33	7	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	79	49	25	13	5	1

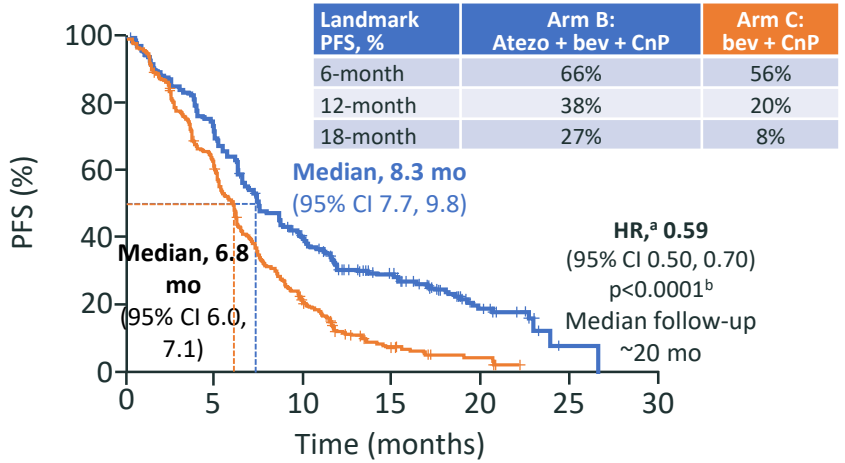
Combination IO and Chemotherapy in Unselected Advanced NSCLC Patients: Step Backwards or Forwards?

IMpower 131[1]



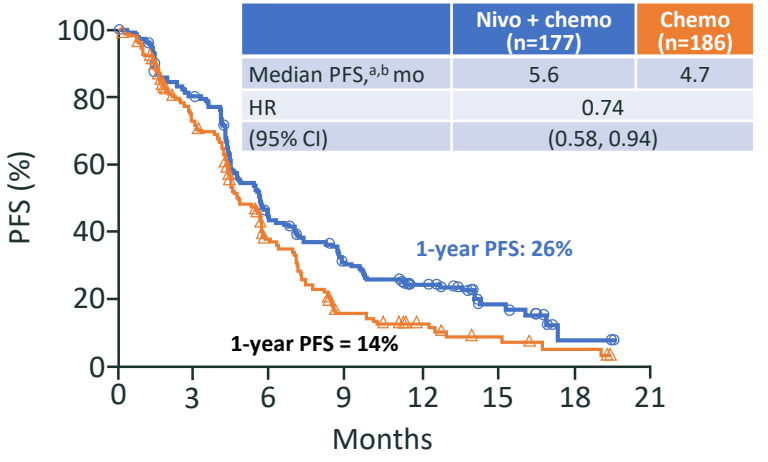
	Arm B: Atezo + CnP	Arm C: CnP
Median PFS (95% CI), mo	6.3 (5.7, 7.1)	5.6 (5.5, 5.7)
Hra (95% CI) *P* value	0.71 (0.60, 0.85) 0.0001	

Impower 150[2]



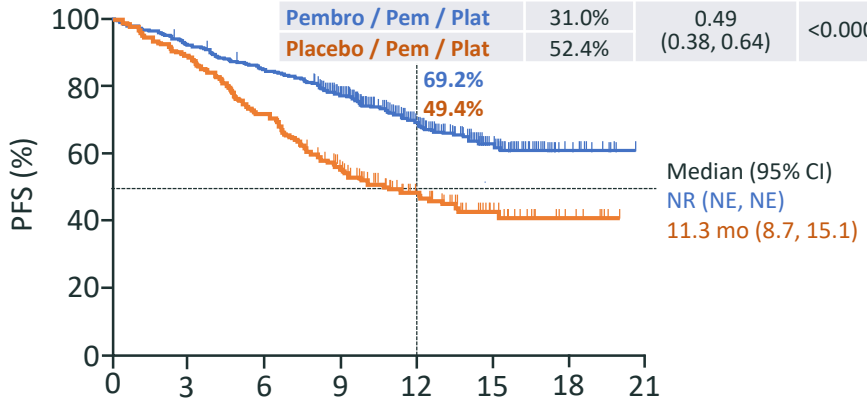
Landmark PFS, %	Arm B: Atezo + bev + CnP	Arm C: bev + CnP
6-month	66%	56%
12-month	38%	20%
18-month	27%	8%

CheckMate 227[3]



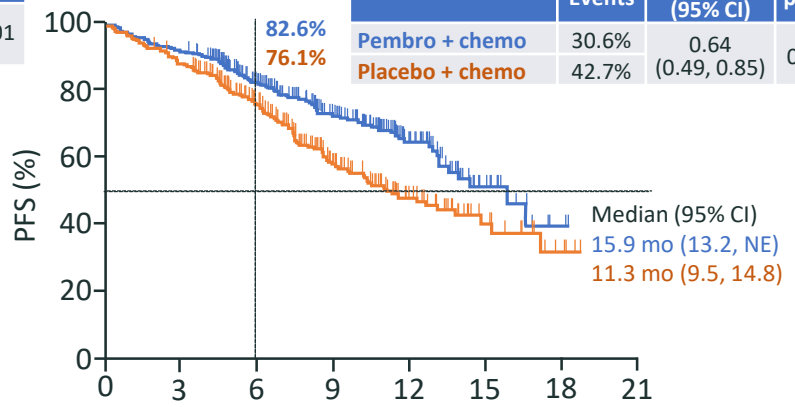
	Nivo + chemo (n=177)	Chemo (n=186)
Median PFS,[a,b] mo	5.6	4.7
HR	0.74	
(95% CI)	(0.58, 0.94)	

KEYNOTE-189[4]



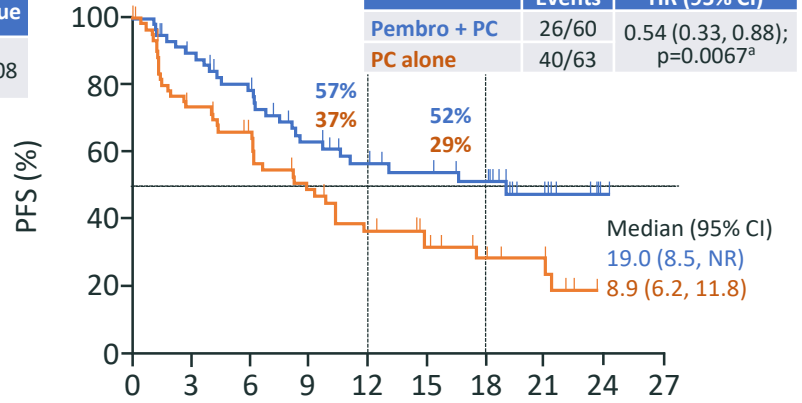
	Events	HR (95% CI)	p-value
Pembro / Pem / Plat	31.0%	0.49 (0.38, 0.64)	<0.00001
Placebo / Pem / Plat	52.4%		

KEYNOTE-407[5]



	Events	HR (95% CI)	p-value
Pembro + chemo	30.6%	0.64 (0.49, 0.85)	0.0008
Placebo + chemo	42.7%		

KEYNOTE-021[6]

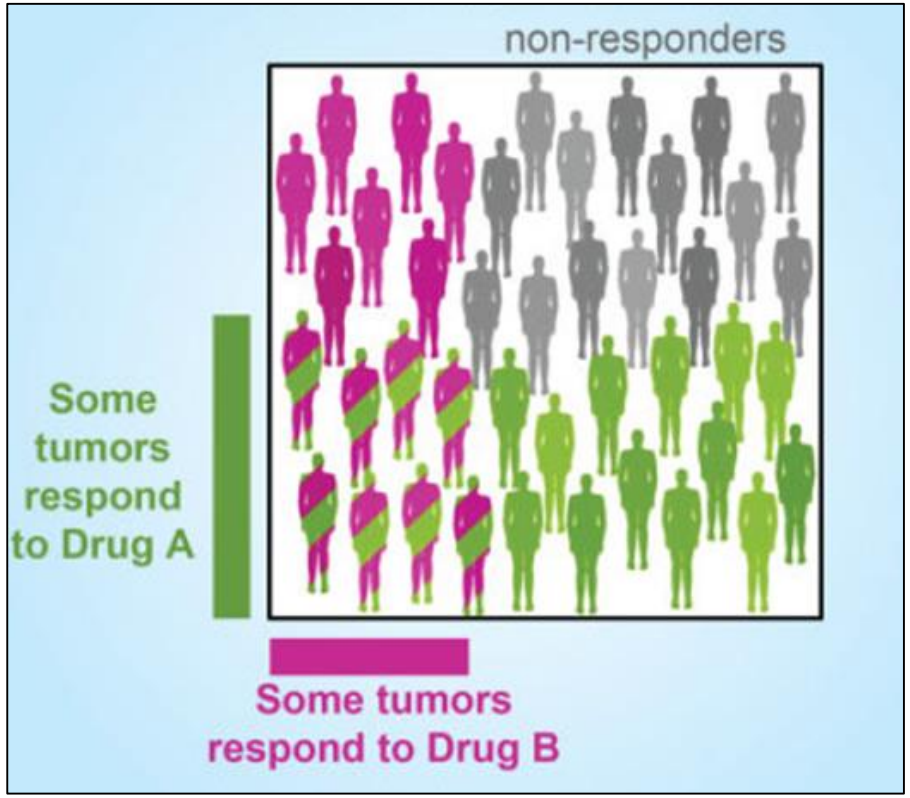


	Events	HR (95% CI)
Pembro + PC	26/60	0.54 (0.33, 0.88); p=0.0067[a]
PC alone	40/63	

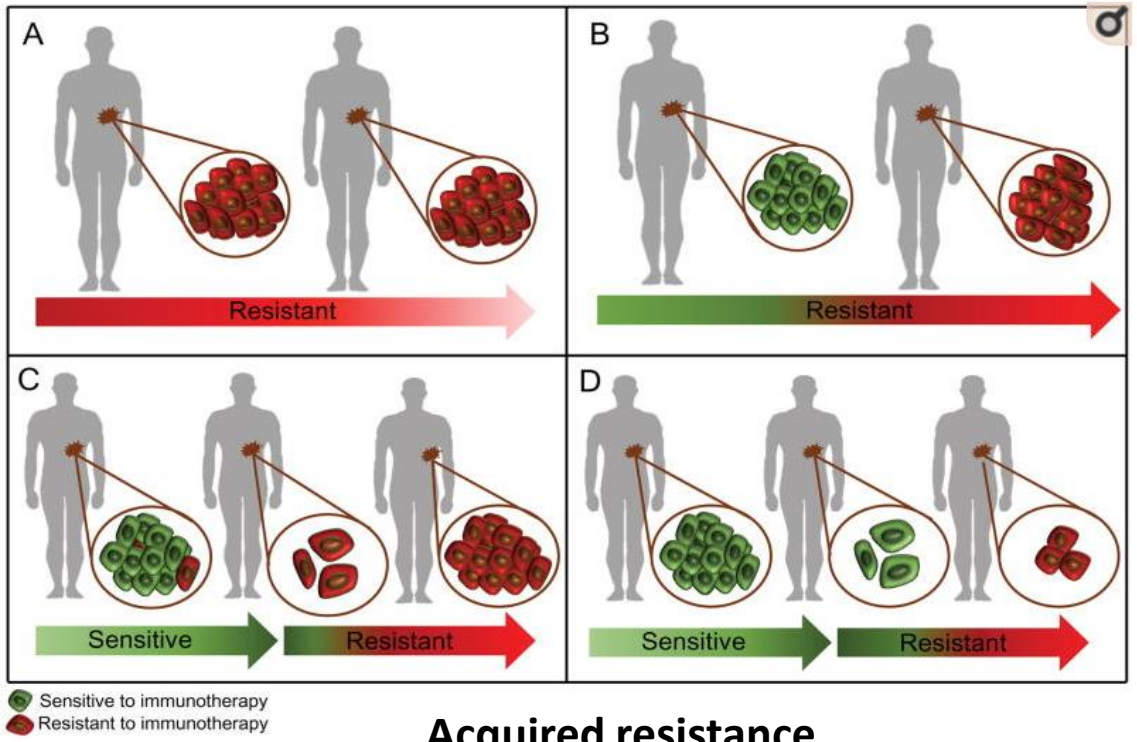
1. Jotte RM et al. J Clin Oncol 2018;36(suppl): Abstract LBA9000. 2. Socinski MA et al. J Clin Oncol 2018;36(suppl): Abstract 9002. 3. Borghaei H et al. J Clin Oncol 2018;36(suppl): Abstract 9001. 4. Gandhi L et al. N Engl J Med 2018;378(22):2078-2092. 5. Paz-Ares LG et al. J Clin Oncol 2018;36(suppl): Abstract 105. 6. Borghaei H et al. Annals Oncol 2017;28(suppl): Abstract LBA49. Atezo, atezolizumab; bev, bevacizumab; CI, confidence interval; chemo, chemotherapy; CnP, carboplatin + nab-paclitaxel; CP, carboplatin; HR, hazard ratio; IO, immuno-oncology; KM, Kaplan Meier; mo, months; NE, not evaluable; nivo, nivolumab;NR, not reached; pem, pemetrexed; pembro, pembrolizumab; PFS, progression-free survival; plat, platinum-based chemotherapy.

Where are We Going

Defining Response and Resistance To Immunotherapy? The Search for a Biomarker



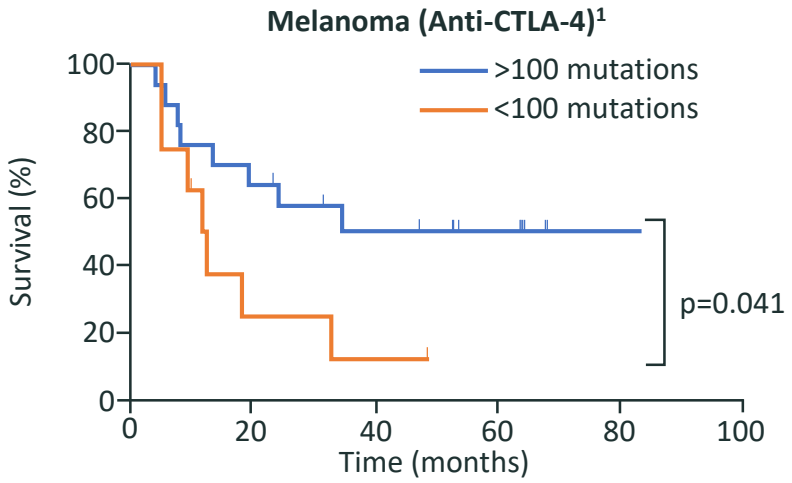
Primary resistance **Adaptive immune resistance**

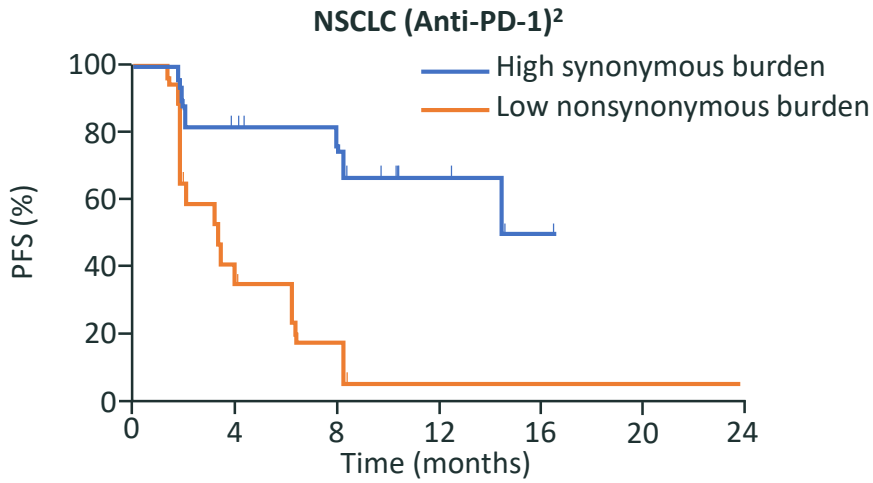


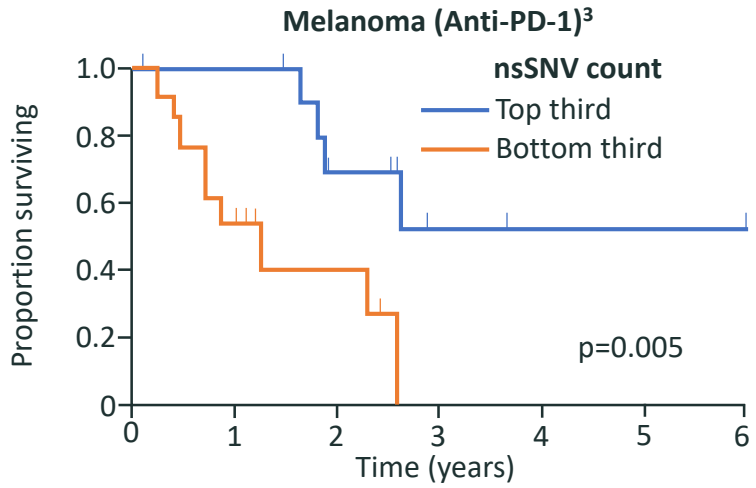
Acquired resistance

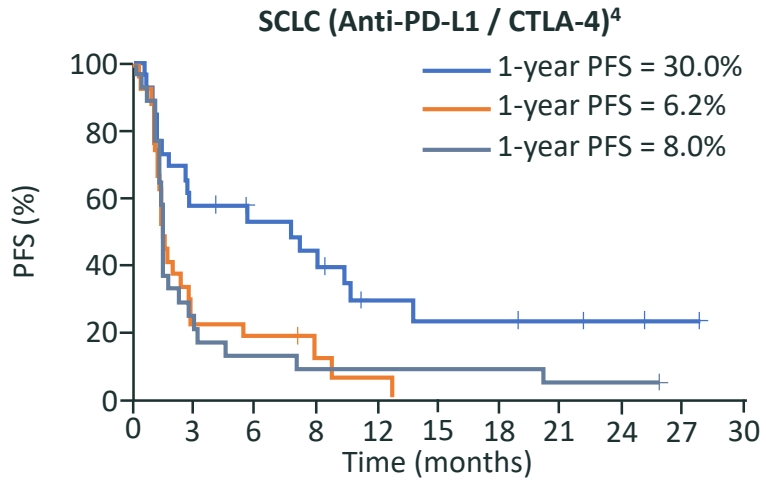
Palmer A., et al. *Cell* 2017 December 14; 171 (17) 1678-1691;
Sharm et al. Cell 168(4): 707-723 (2017)

Moving Towards a New Biomarker: TMB is a consistent biomarker across diseases using WES







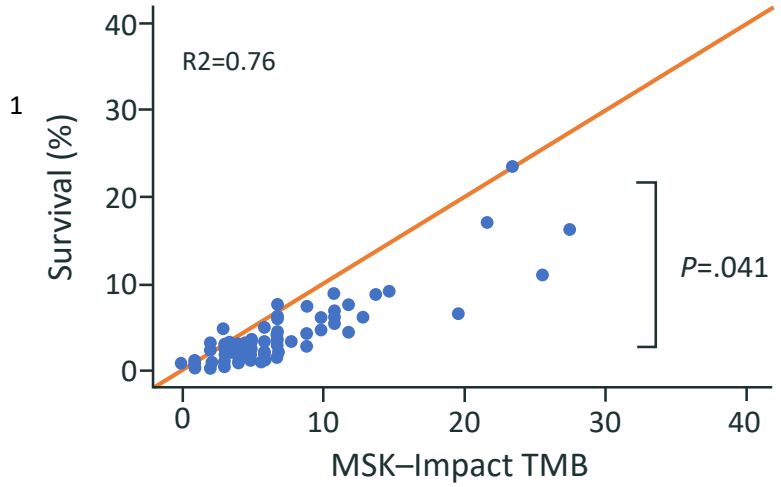


1. Snyder A, et al. N Engl J Med 2014;371(23):2189-2199. 2. Rizvi NA, et al. Science 2015;348(6230):124-128. 3. Hugo W, et al. Cell 2016;165(1):35–44. 4. Rizvi NA, et al. Presentation at WCLC 2017: Abs #OA 07.03a.

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; IO, immuno-oncology; NSCLC, non-small-cell lung cancer; nsSNV, non-synonymous single nucleotide variants; SCLC, small-cell lung cancer; TMB, tumor mutational burden; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; WES, whole exome sequencing.

Mutation burden: from WES to gene panels across diseases

1



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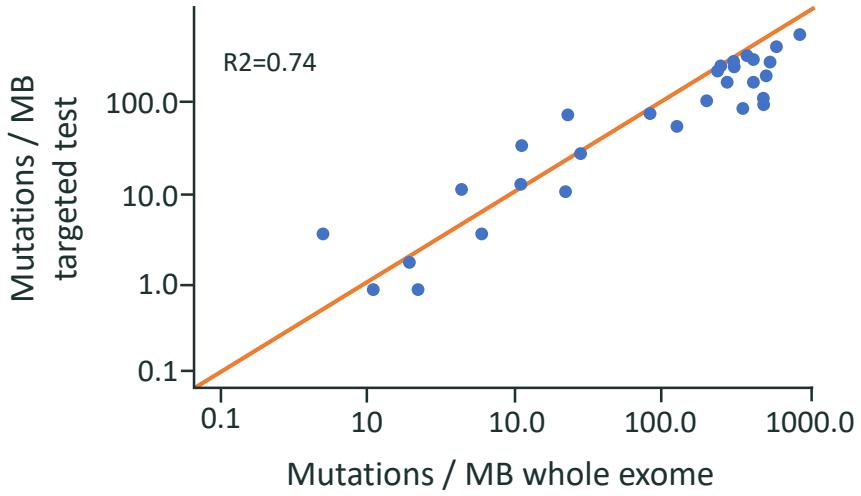
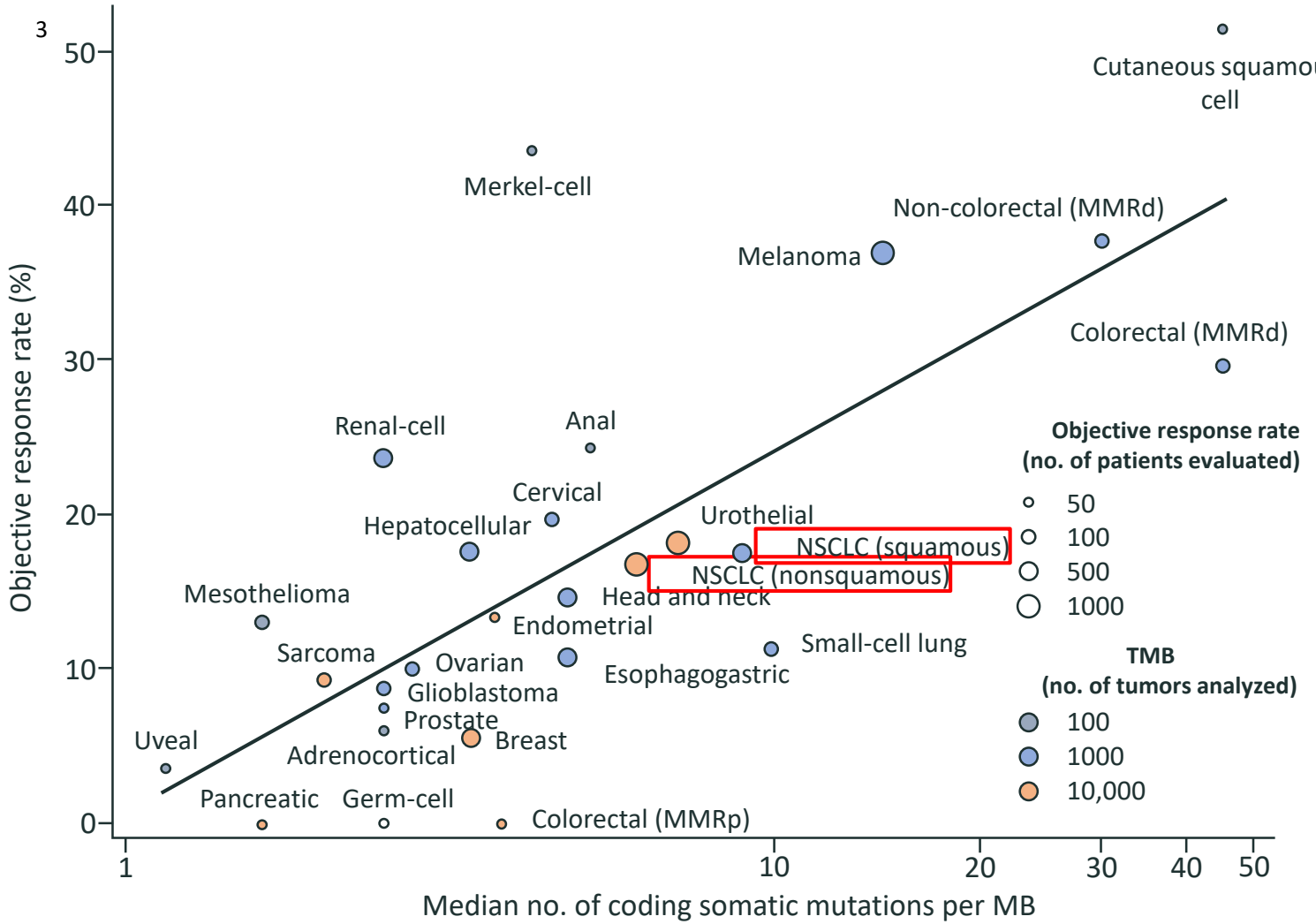


3

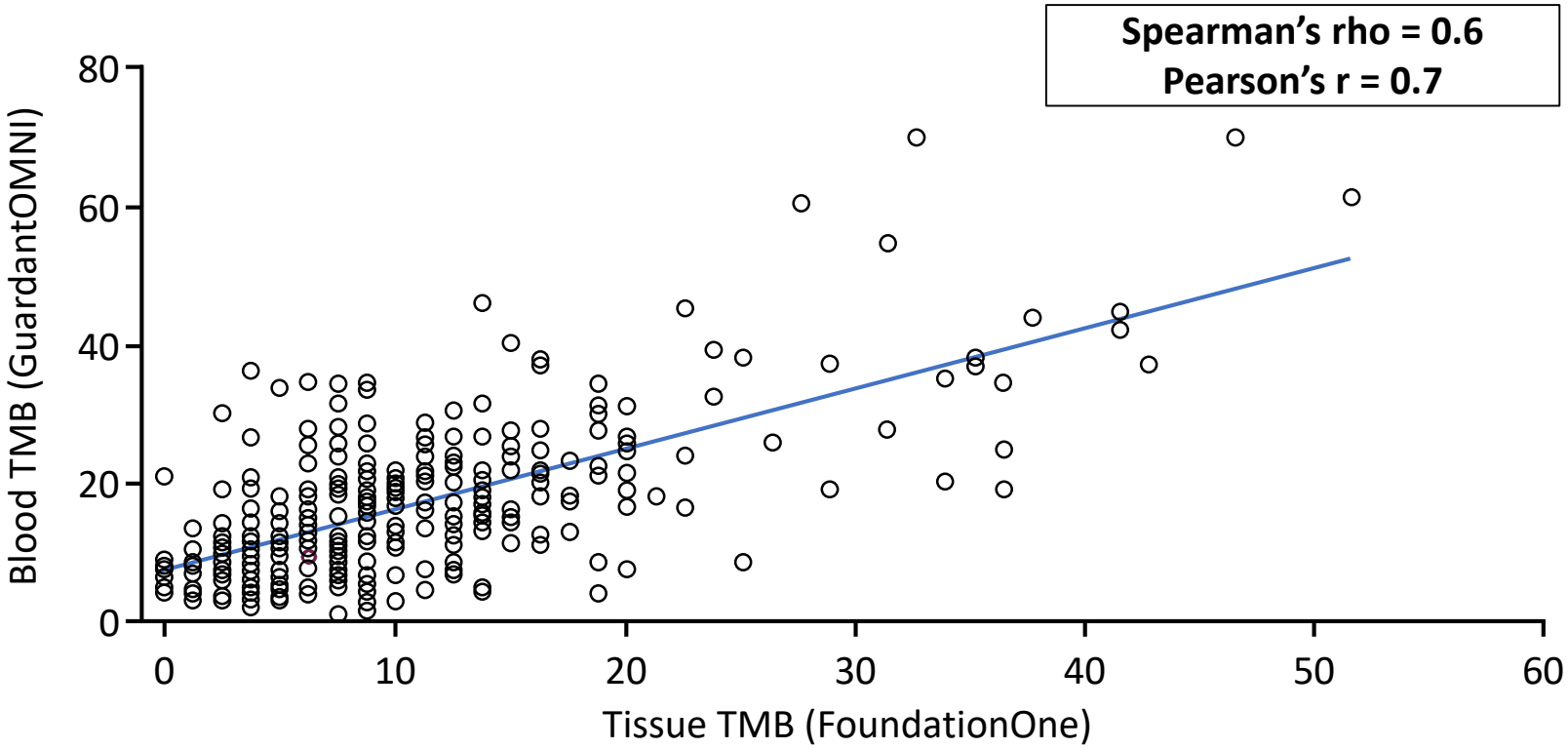


1. Zehir A, et al. Nat Med 2017;23(6):703–713. Supplementary information. Available at: https://media.nature.com/original/nature-assets/nm/journal/v23/n6/extref/nm.4333-S1.pdf . 2. Chalmers ZR, et al. Genome Med 2017;9(1):34. 3. Yarchoan M, et al. N Engl J Med 2017;377(25):2500-2501. IO, immuno-oncology; MB, megabase; MMRd, mismatch repair deficient; MMRp, mismatch repair proficient; NSCLC, non-small-cell lung cancer; TMB, tumor mutational burden; WES, whole exome sequencing.

Less Invasive Testing – Moving towards Blood?

Correlation of Tissue and Blood Tumor Mutational Burden (Mystic Trial)

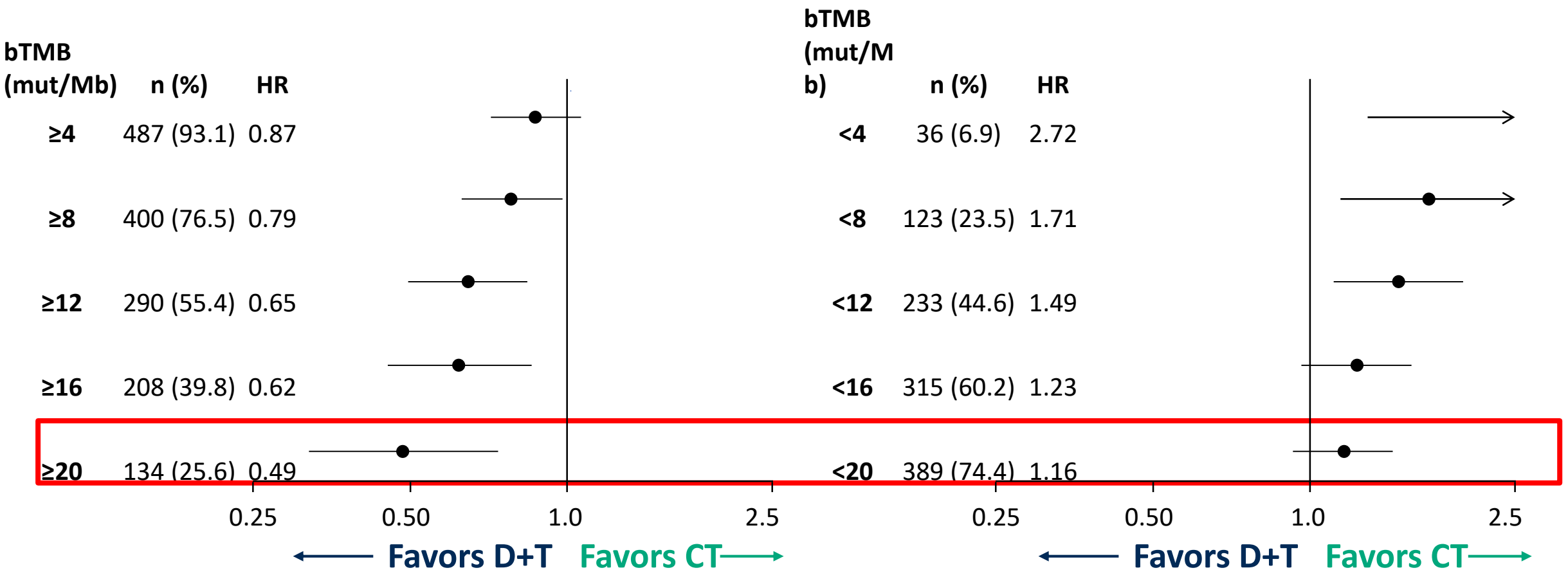
- In 352 (31.5% of ITT) matched patient specimens, tTMB values positively correlated with bTMB values



bTMB was evaluated with the GuardantOMNI sequencing platform (Guardant Health) comprised of a 500-gene panel (1.0 Mb DNA footprint [coding regions only])

Peters et al., AACR 2019

Overall Survival Based on Blood TMB Cut-offs: Durvalumab + Tremelimumab vs Chemotherapy



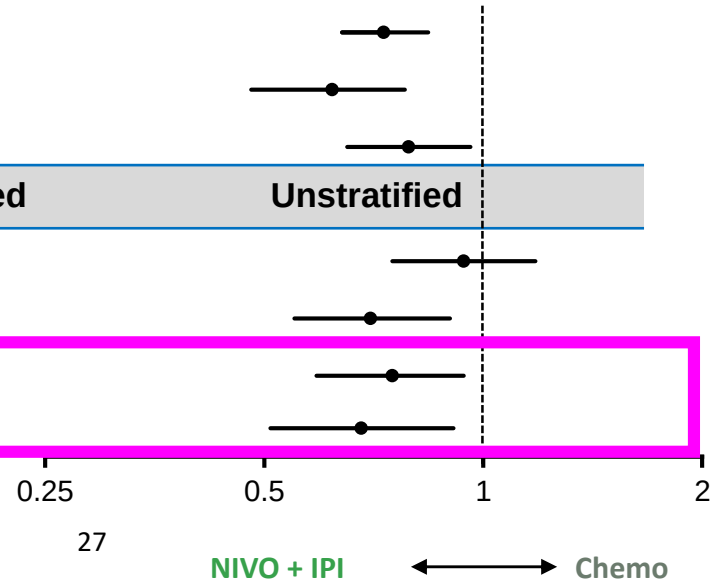
≥20 mut/Mb cut-off selected for further analysis based on the observed effect size for durvalumab + tremelimumab and the patient population deriving benefit

Symbol sizes in the figures do not correspond to patient sample sizes; data cut-off October 4, 2018

Peters et al., AACR 2019

OS for NIVO + IPI vs Chemo by Tumor PD-L1 Expression, TMB Status, and Combined Subgroups in All Randomized Patients

		Median OS, months NIVO + IPI n = 583	Chemo n = 583	HR	HR (95% CI)
Randomized groups				**Stratified**	**Stratified**
PD-L1	All randomized (N = 1166)	17.1	13.9	0.73	
	PD-L1 < 1% (n = 373)	17.2	12.2	0.62	
	PD-L1 ≥ 1% (n = 793)	17.1	14.9	0.79[a]	
Additional exploratory subgroups analyses[b,c]				**Unstratified**	**Unstratified**
PD-L1	1–49% (n = 396)	15.1	15.1	0.94	
	≥ 50% (n = 397)	21.2	14.0	0.70	
TMB[d] (mut/Mb)	low, < 10 (n = 380)	16.2	12.6	0.75	
	high, ≥ 10 (n = 299)	23.0	16.4	0.68	

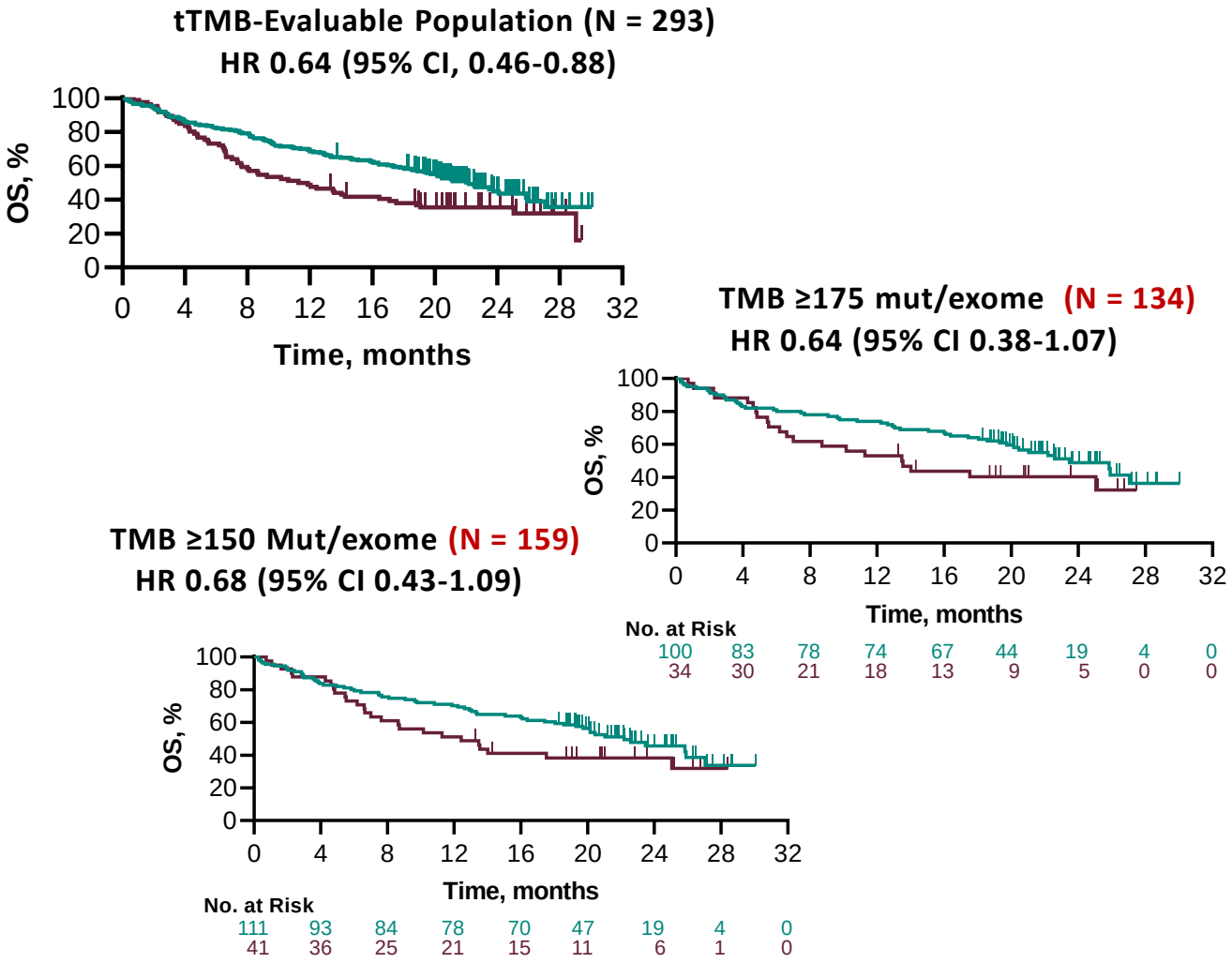


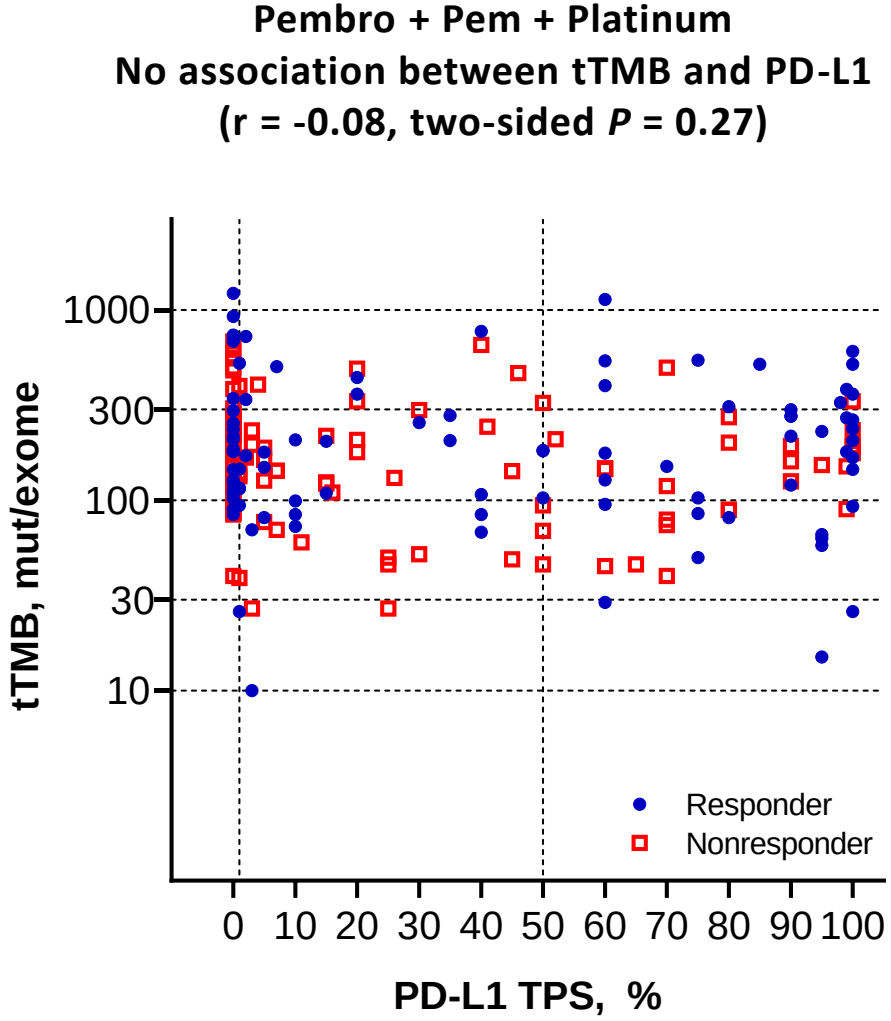
- No consistent correlation was observed between survival outcomes with NIVO + IPI vs chemo and PD-L1 or TMB alone or in combination

[a]Stratified HR (97.72% CI); [b]Patients were not stratified by TMB or PD-L1 ≥ or < 50% – subgroup analyses therefore may be impacted by imbalances and should be interpreted with caution; [c]Not controlled by randomization; [d]Unstratified HR for NIVO + IPI vs chemo in TMB-evaluable (n = 679) and non-evaluable (n = 487) patients was 0.74 (95% CI, 0.61–0.88) and 0.74 (95% CI, 0.60–0.92), respectively.

Peters et al., AACR 2019

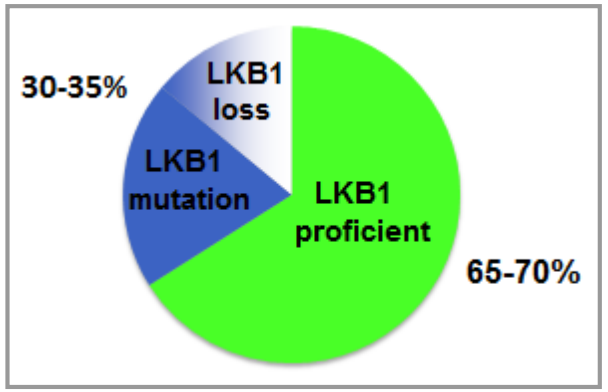
tTMB does not predict for clinical outcomes after chemo-IO
Analysis from Keynote 189 Patients

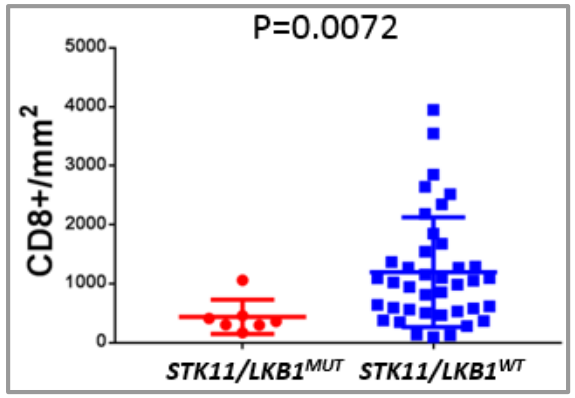


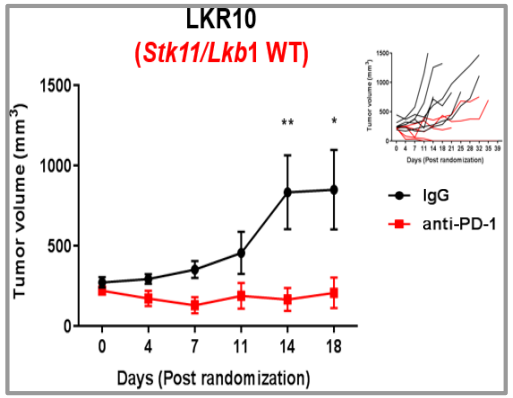


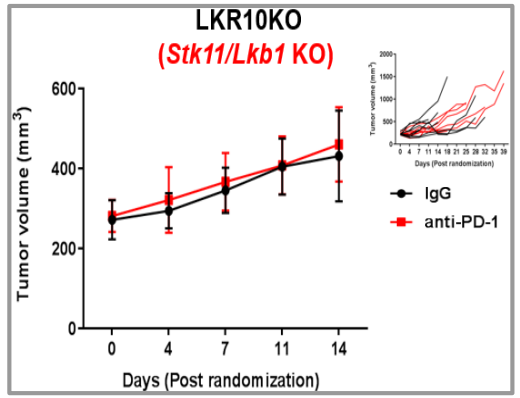
Garassion et al. WCLC 2019,

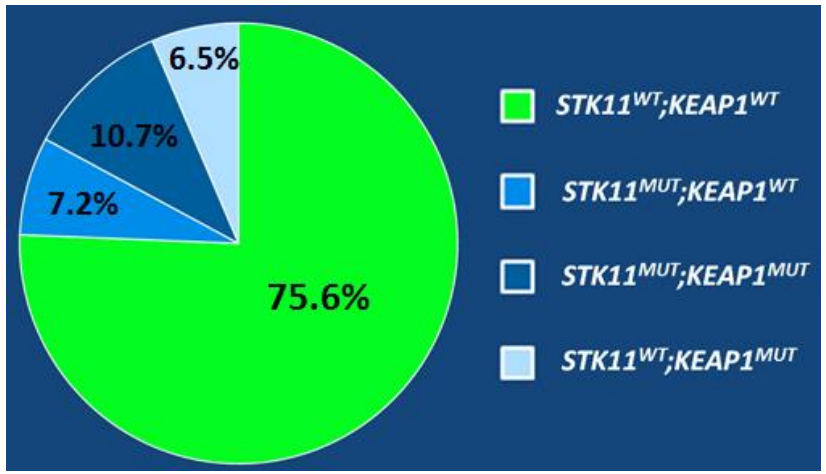
STK11/LKB1 genomic alterations are a mediator of the cold tumor immune microenvironment and a major driver of primary resistance to PD-1 axis blockade in non-squamous NSCLC

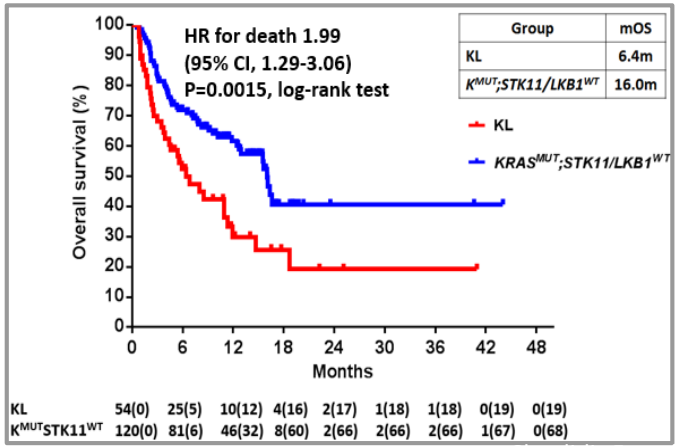












Ferdinandos Skoulidis et al., ASCO 2019

Patients and Study Design

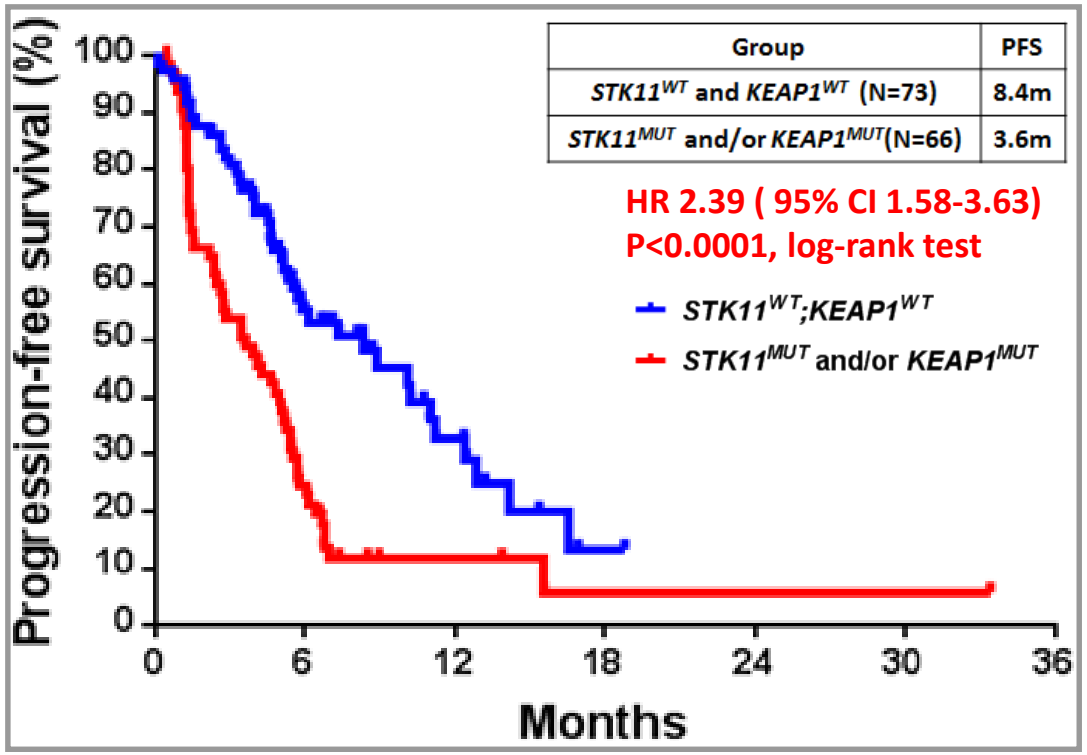
- Retrospective multi-center international study
- **Two distinct cohorts:**
  - Metastatic non-squamous NSCLC treated with 1st line PCP with available genomic profiling INCLUDING STK11
  - Metastatic STK11 and/or KEAP1-mutant non-squamous NSCLC treated with 1st line PC prior to regulatory approval of PCP (Cohort 2)
- Alive ≥ 14 days after C1D1
- All non-synonymous *STK11* and *KEAP1* mutations and bi-allelic deletions included
- Sensitizing *EGFR* mutations and *ALK* translocations excluded

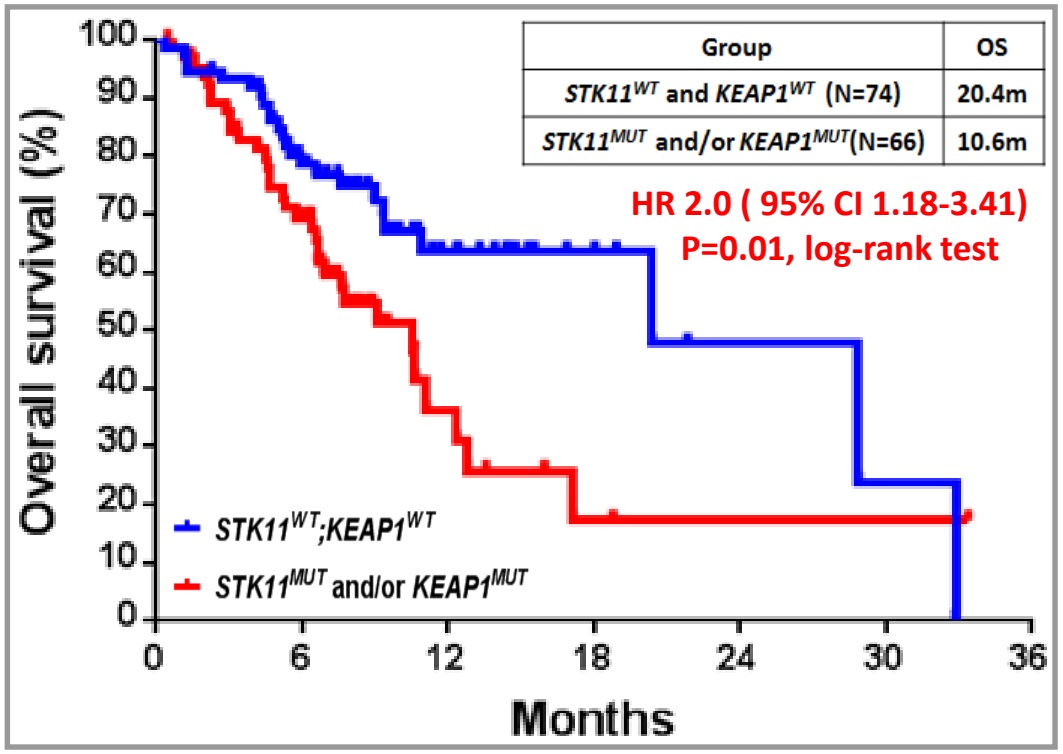
PCP = carboplatin, pemetrexed and pembrolizumab

	PCP (N=452)	PCP* (N=131)	PC (N=169)
STK11			
Mutant	117 (26%)	117	142
Wild-type	335 (74%)	14 (*KEAP1*^{MUT})	21 (*KEAP1*^{MUT})
NA	0	0	6 (*KEAP1*^{MUT})
ECOG PS			
0-1	379 (84%)	113 (86%)	132(78%)
2-3	59 (13%)	17 (13%)	30 (18%)
NA	56 (3%)	1 (1%)	7 (4%)
Brain mets			
No	286 (63%)	80 (61%)	111 (66%)
Yes	142 (31.5%)	47 (36%)	44 (26%)
NA	24 (5.5%)	4 (3%)	14 (8%)
Histology			
LUAD	421 (93%)	122 (93%)	154 (91%)
NSCLC-NOS	18 (4%)	4 (3%)	10 (6%)
Other	13 (3%)	5 (4%)	5 (3%)

Ferdinandos Skoulidis et al., ASCO 2019

Integration of *STK11/LKB1* and *KEAP1* onco-genotypes identifies a subgroup of non-squamous NSCLC with poor clinical outcomes with chemo-immunotherapy





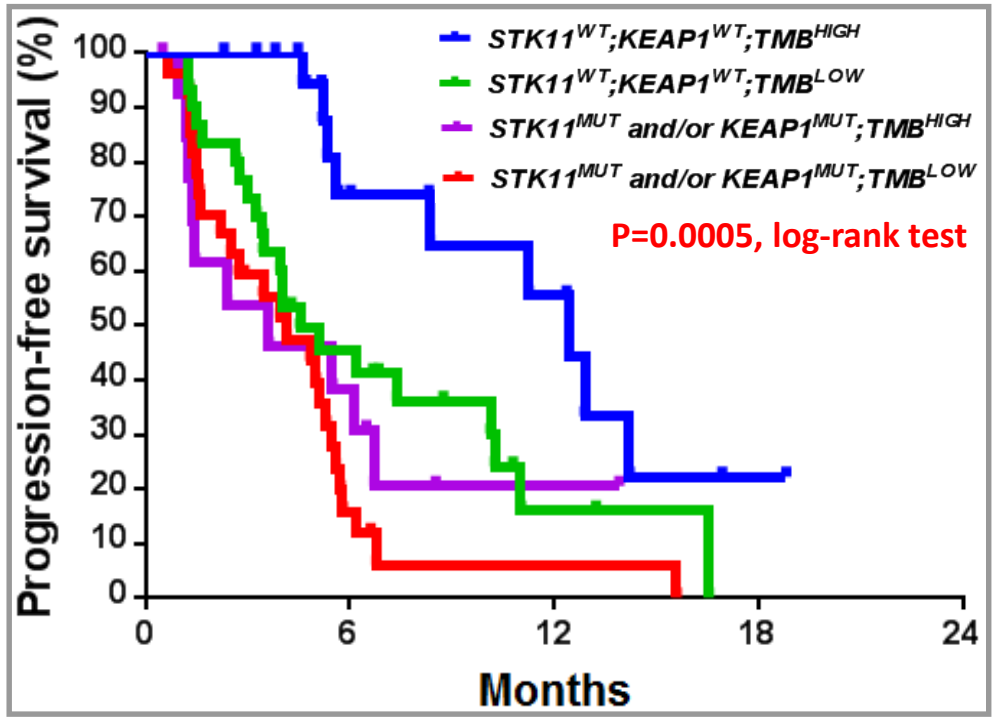
$STK11^{MUT}$ and/or $KEAP1^{MUT}$ PR/CR: 21.5%, SD: 38.5%, PD 40%

PCP = carboplatin, pemetrexed and pembrolizumab

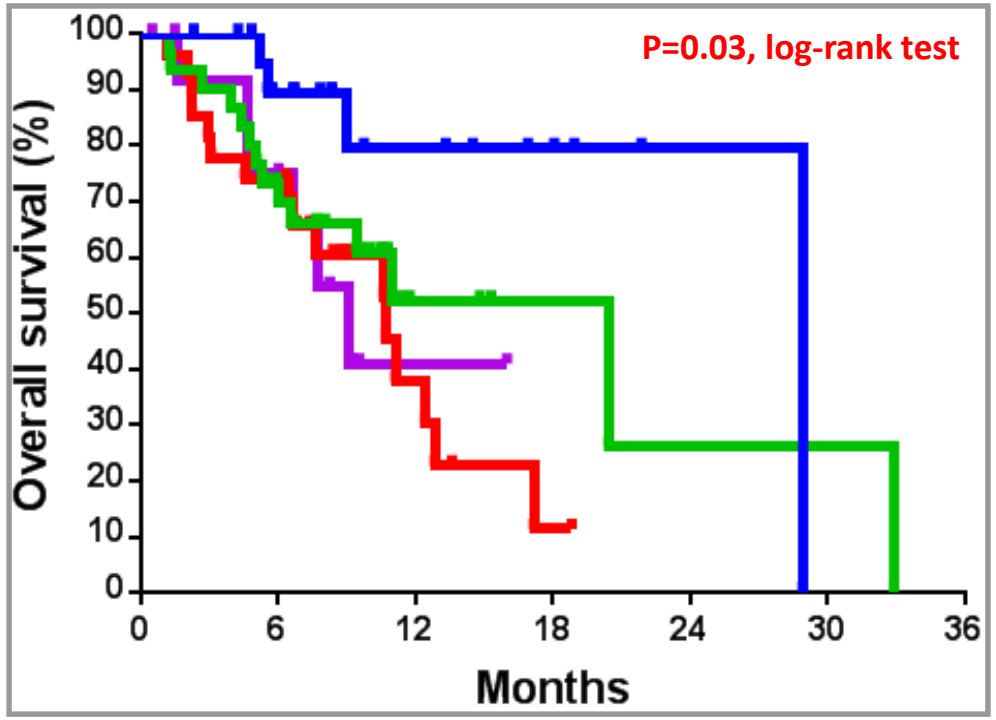
Ferdinandos Skoulidis et al., ASCO 2019

Integration of *STK11* and *KEAP1* genomic alterations with TMB

Group	PFS
$STK11^{WT}$;$KEAP1^{WT}$;TMB^{HIGH}	12.4m
$STK11^{WT}$;$KEAP1^{WT}$;TMB^{LOW}	4.5m
$STK11^{MUT}$ and/or $KEAP1^{MUT}$;TMB^{HIGH}	4.1m
$STK11^{MUT}$ and/or $KEAP1^{MUT}$;TMB^{LOW}	3.6m



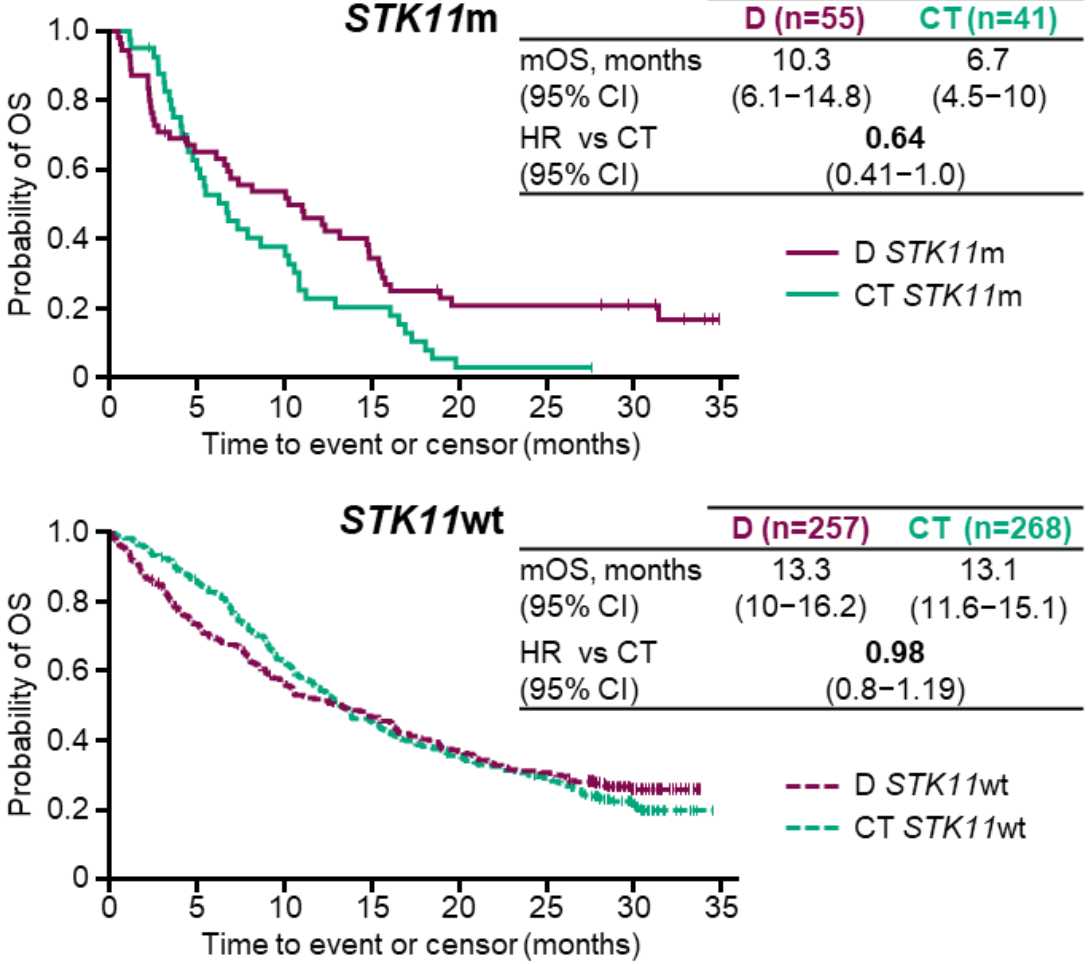
Group	OS
$STK11^{WT}$;$KEAP1^{WT}$;TMB^{HIGH}	28.9m
$STK11^{WT}$;$KEAP1^{WT}$;TMB^{LOW}	20.4m
$STK11^{MUT}$ and/or $KEAP1^{MUT}$;TMB^{HIGH}	10.7m
$STK11^{MUT}$ and/or $KEAP1^{MUT}$;TMB^{LOW}	9.1m



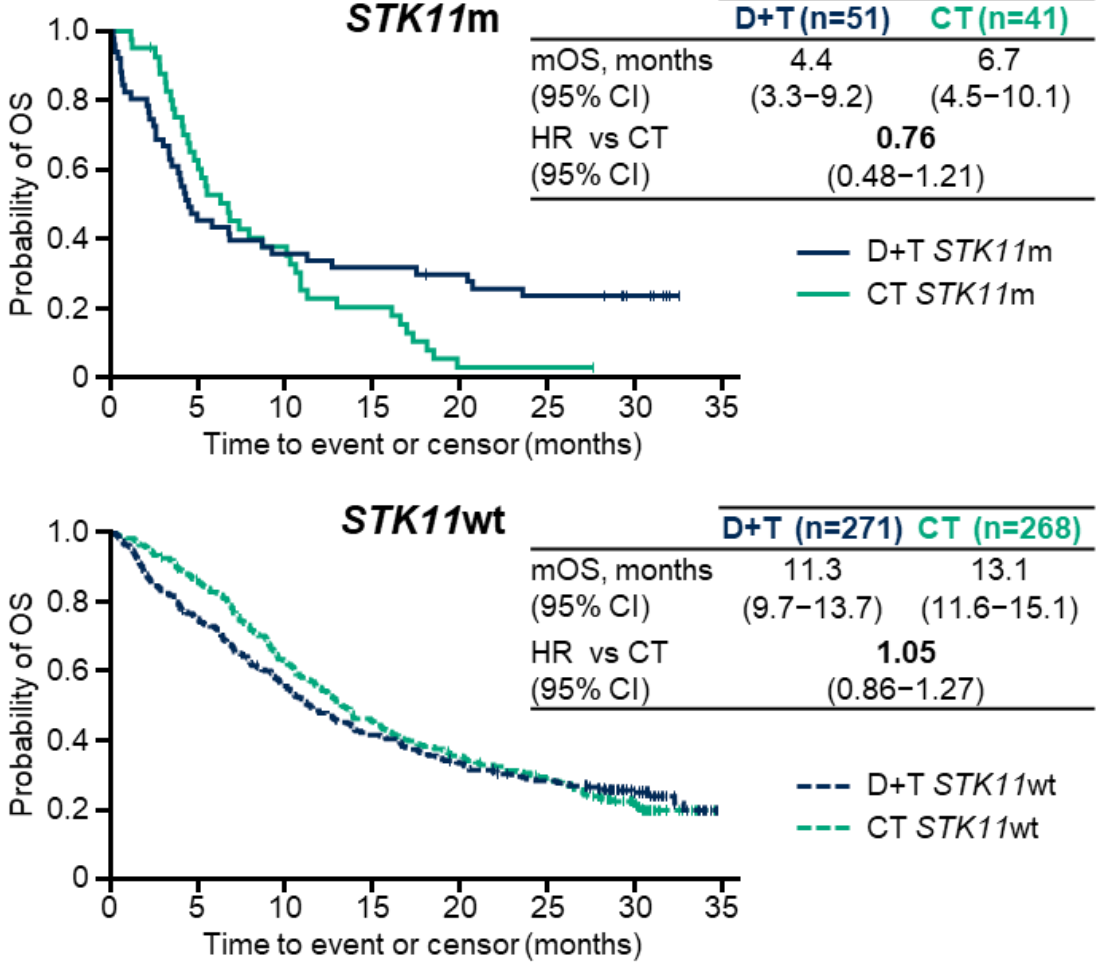
Ferdinandos Skoulidis et al., ASCO 2019

No clear predictive role for *STK11*m

Durvalumab vs chemotherapy



Durvalumab + tremelimumab vs chemotherapy

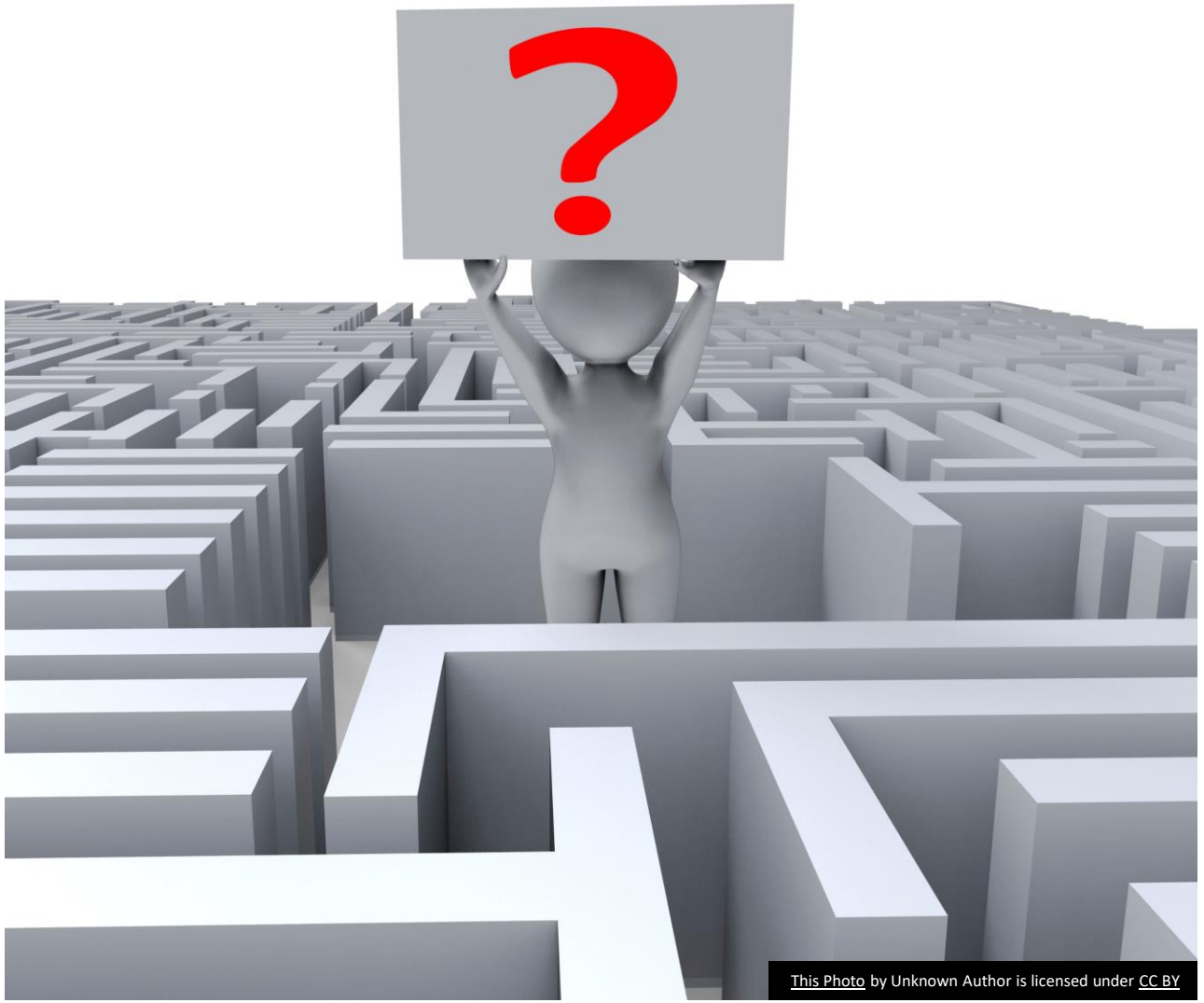


*Mutation-evaluable patients

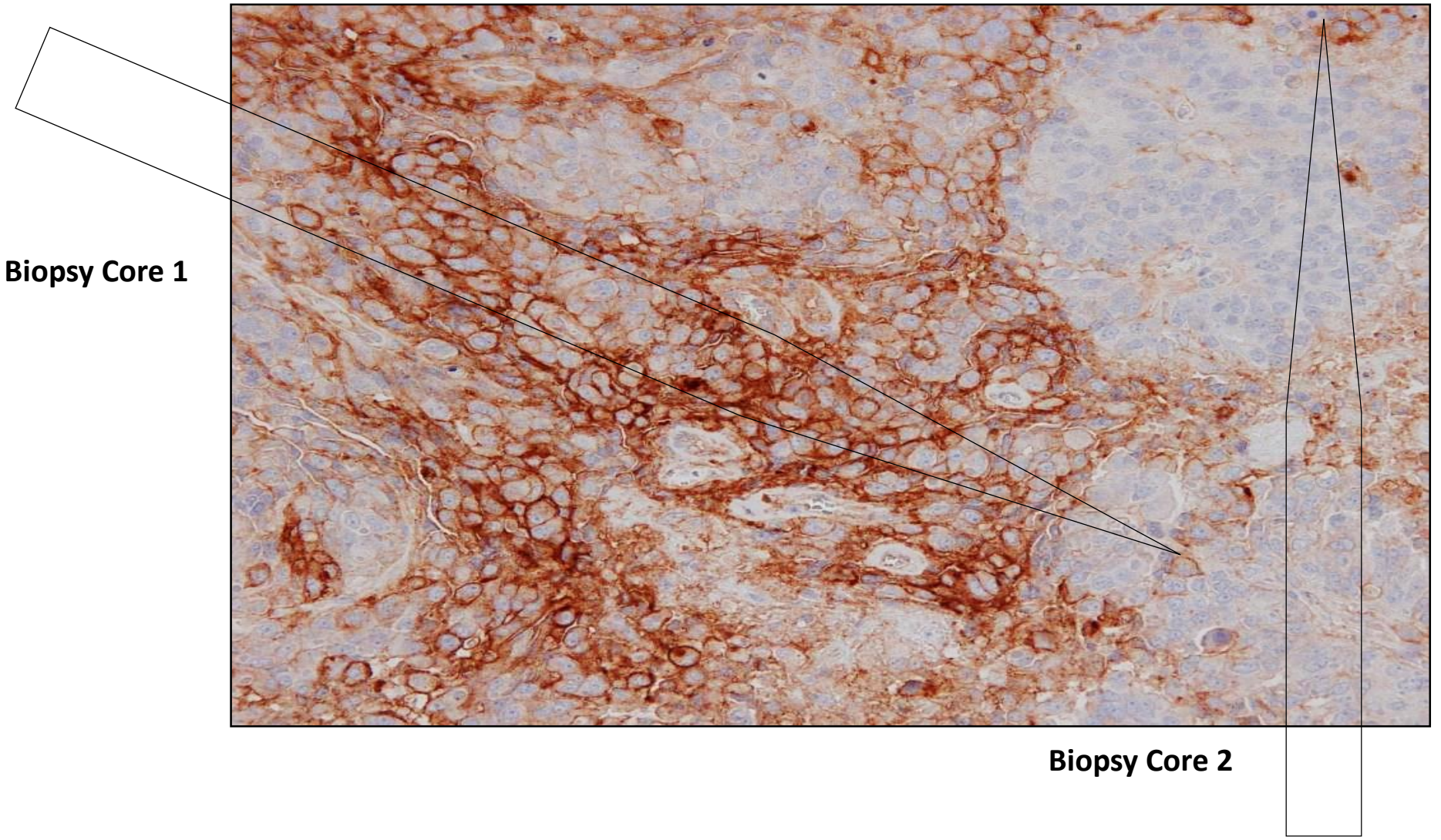
Rizvi et al., WCLC 2019

An Overwhelming Amount of Contradictory Data

Will A biomarker be identified?



The Problems: PD-L1 Immunohistochemistry: Expression Heterogeneity and Potential for Sampling Error



Courtesy: Ben Solomon via Michael Boyer

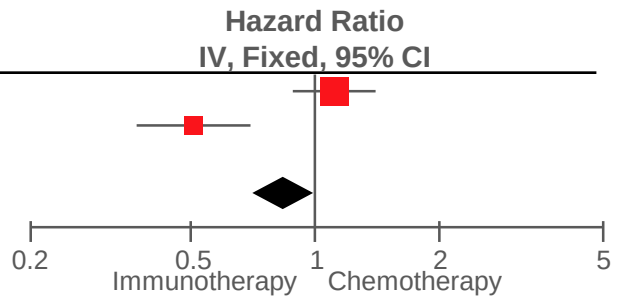
Back to the 2000s: Improved PFS in patients with smoking history

A

Study or Subgroup	log [Hazard Ratio]	SE	Immunotherapy Total	Chemotherapy Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CheckMate 026	0.1044	0.1137	238	237	65.2%	1.11 [0.89, 1.39]
Keytone 024	-0.6733	0.1558	149	132	34.8%	0.51 [0.38, 0.69]
Total (95% CI)			387	369	100.0%	0.85 [0.71, 1.01]

Heterogeneity Chi^2 = 16.26, df= 1 (P < 0.0001); I^2 = 94%

Test for overall effect Z = 1.81 (P = 0.07)

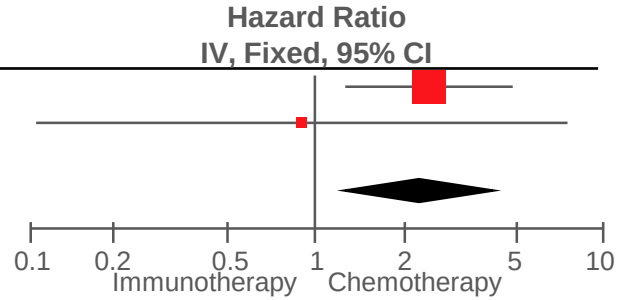


B

Study or Subgroup	log [Hazard Ratio]	SE	Total	Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CheckMate 026	0.9203	0.3329	30	29	91.3%	2.51 [1.31, 4.82]
Keytone 024	-0.1054	1.0801	5	19	8.7%	0.90 [0.11, 7.47]
Total (95% CI)			35	48	100.0%	2.30 [1.23, 4.28]

Heterogeneity Chi^2 = 0.82, df= 1 (P = 0.36); I^2 = 0%

Test for overall effect Z = 2.61 (P = 0.009)

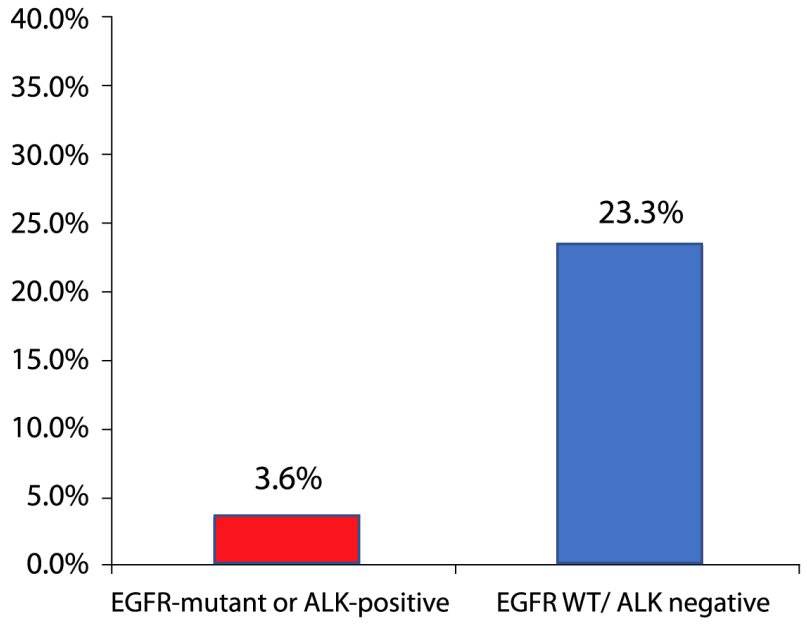


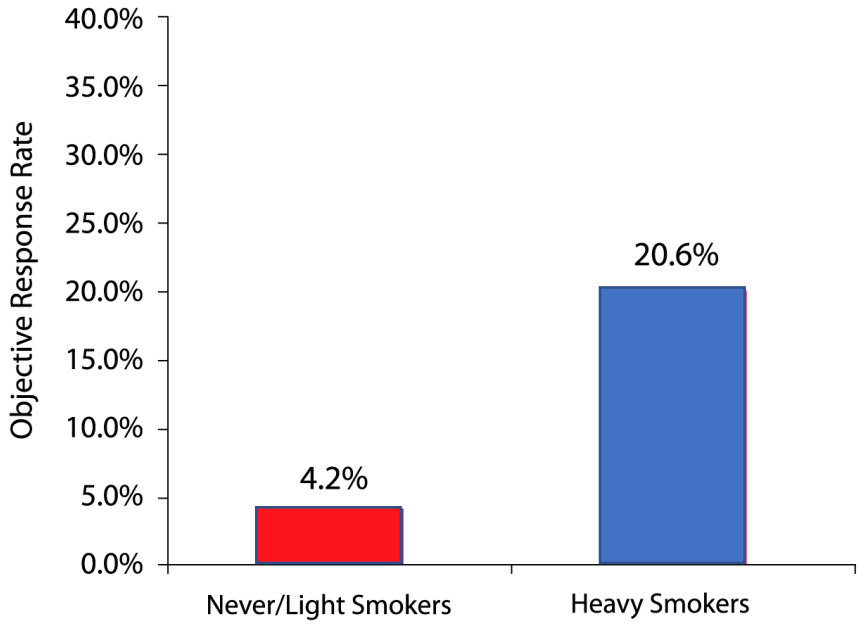
Forest plots of hazard ratios for progression-free survival in (**A**) ever-smokers and (**B**) never-smokers.

Kim et al., Oncotarget (2017) 93149

Back to the 2000s: Decreased Efficacy In Specific Molecular Cohorts?

PD-L1 Positive, n (%)	EGFR Mutant		ALK Positive		KRAS Mutant
	Pre-TKI (n = 62)	Post-TKI (n = 63)	Pre-Criz (n = 19)	Post-Criz (n = 12)	Pre-TKI (n = 56)
PD-L1 ≥ 50%	7 (11)	9 (14)	5 (26)	2 (17)	11 (17)
PD-L1 ≥ 5%	10 (16)	18 (29)	9 (47)	3 (25)	20 (31)

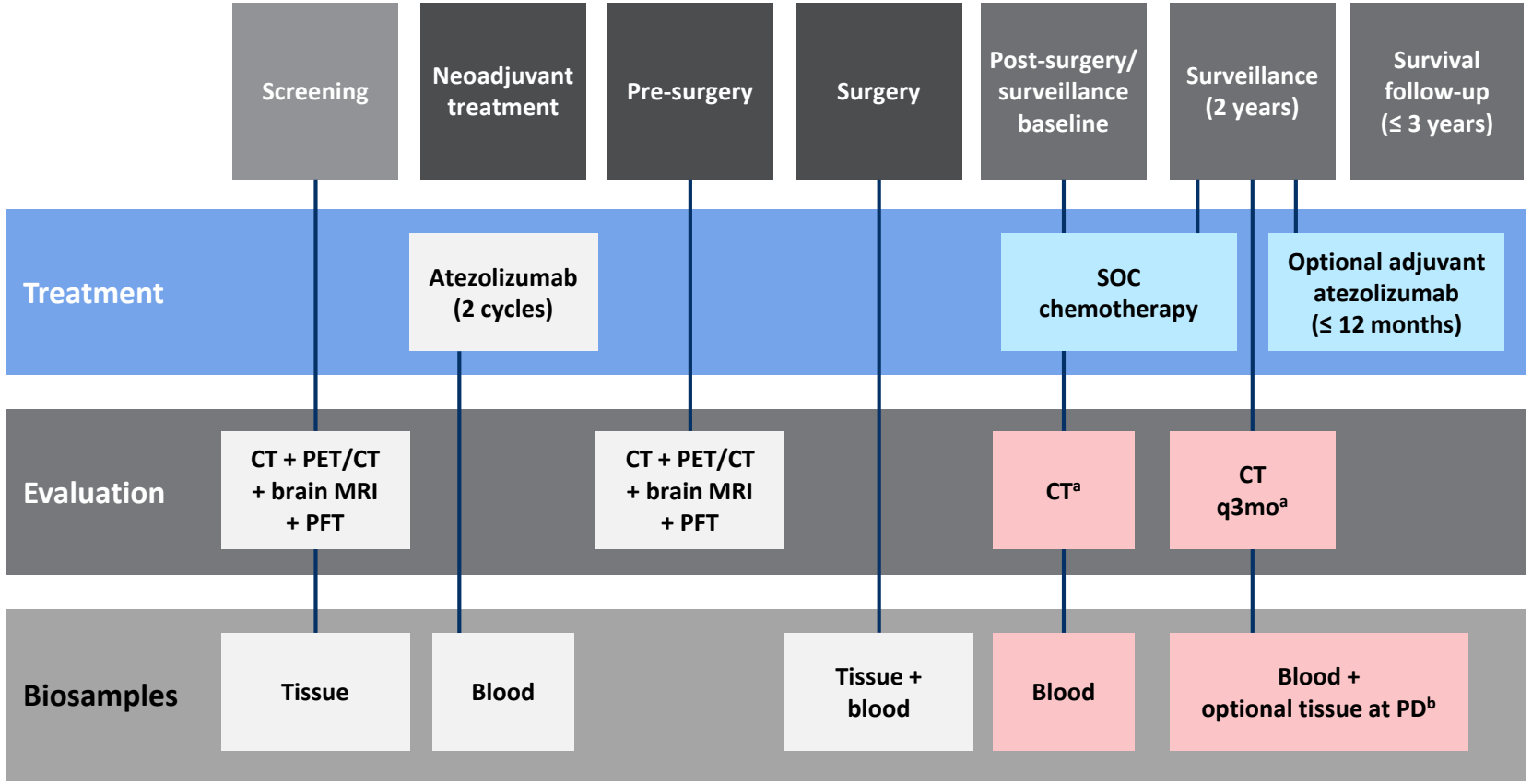




Gainor JF, et al. Clin Cancer Res. 2016;22:4585-4593.

Will Neoadjuvant Trials Help Our Understanding:

LCMC3 Study Design



Primary endpoint:

- MPR at surgical resection, defined as ≤ 10% viable tumor cells

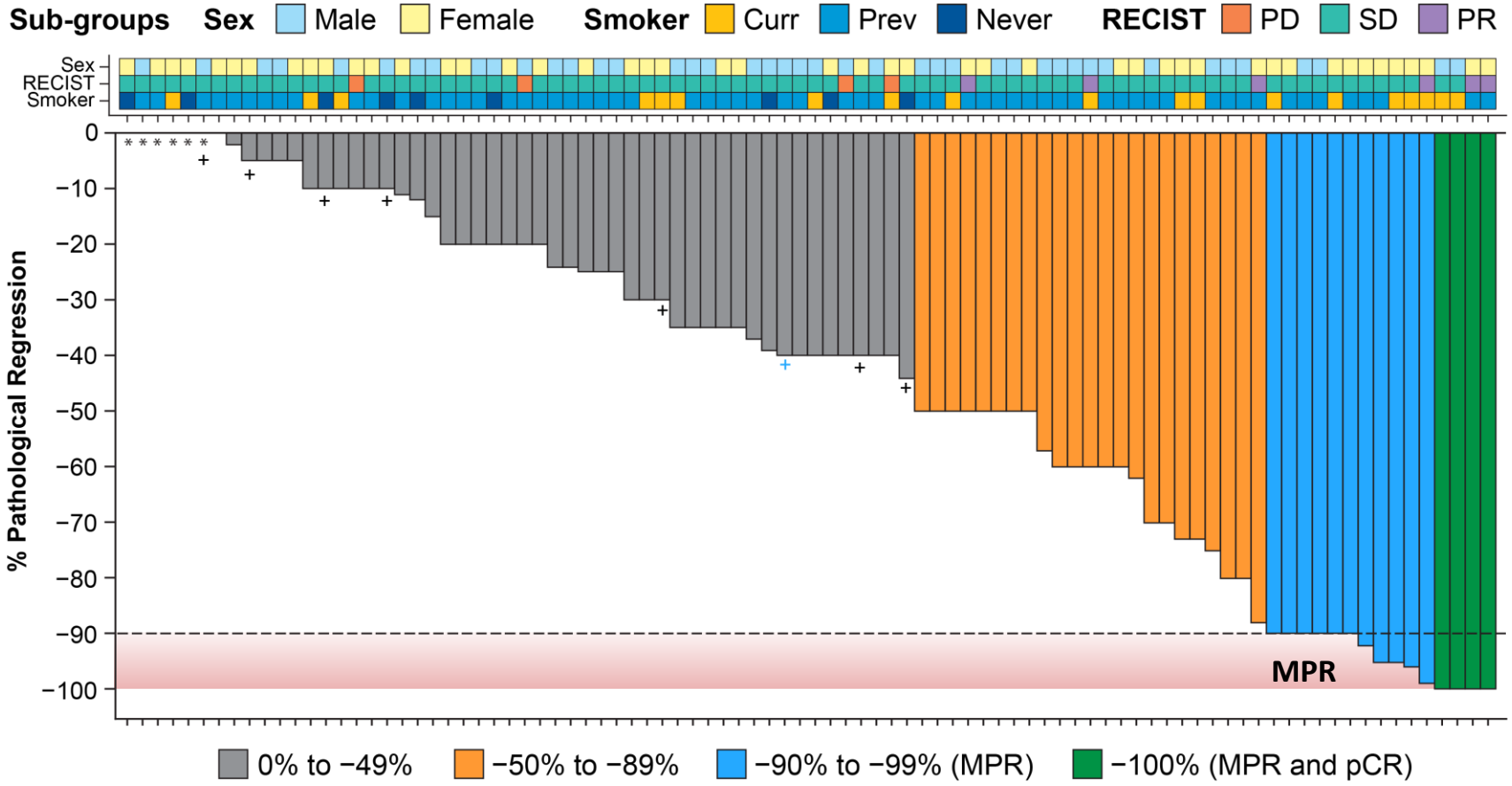
Secondary endpoints:

- Disease-free survival
- Response rate by RECIST 1.1
- OS
- Biomarkers
- Adverse events

MPR, major pathologic response, locally assessed; PFT, pulmonary function test; q3mo, every 3 months.
[a] Extended chest CT, including liver and adrenals. [b] At progression and/or recurrence. NCT02927301.

Presented by David J. Kwialkowski. ASCO 2019

Pathological Regression in Intended Surgery Population (n = 90)



Patients in intended surgery population (n = 90)

- PR: 6 (7%); SD: 80 (89%); PD: 4 (4%)
- 3 of 8 EGFR/ALK+ had 40% to 50% pathological regression

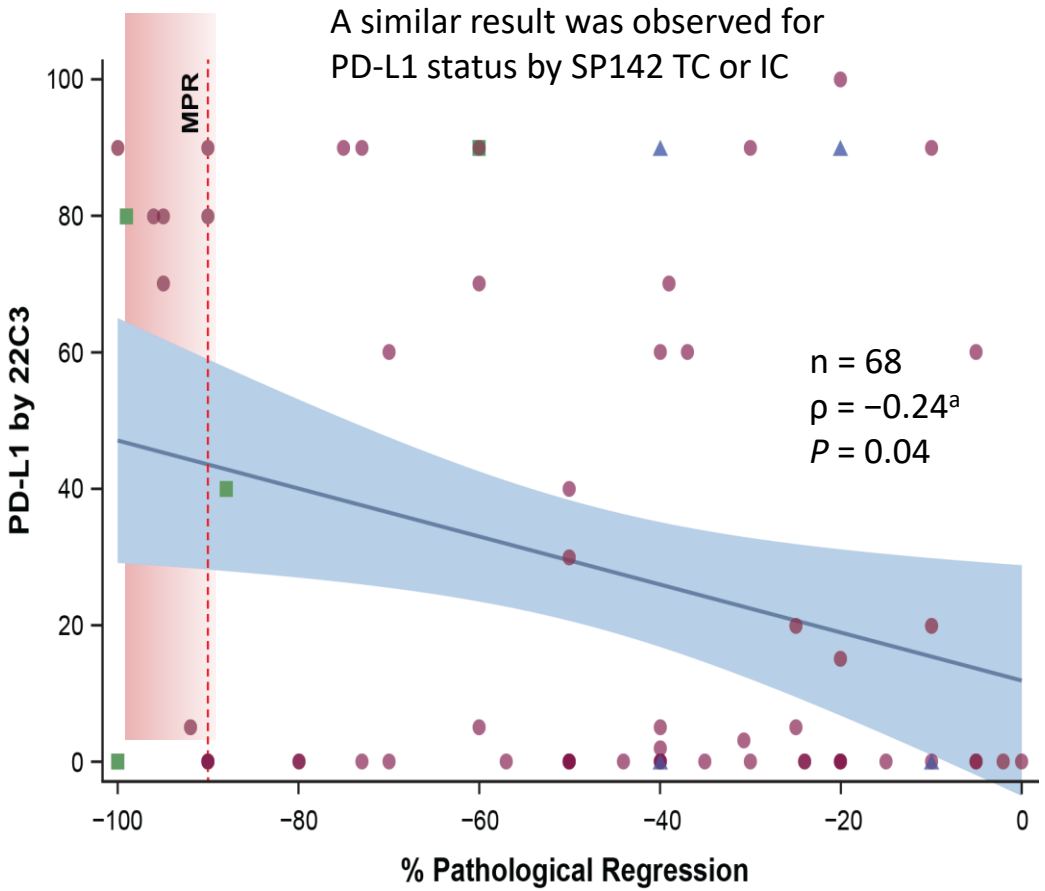
Primary efficacy population (n = 77)

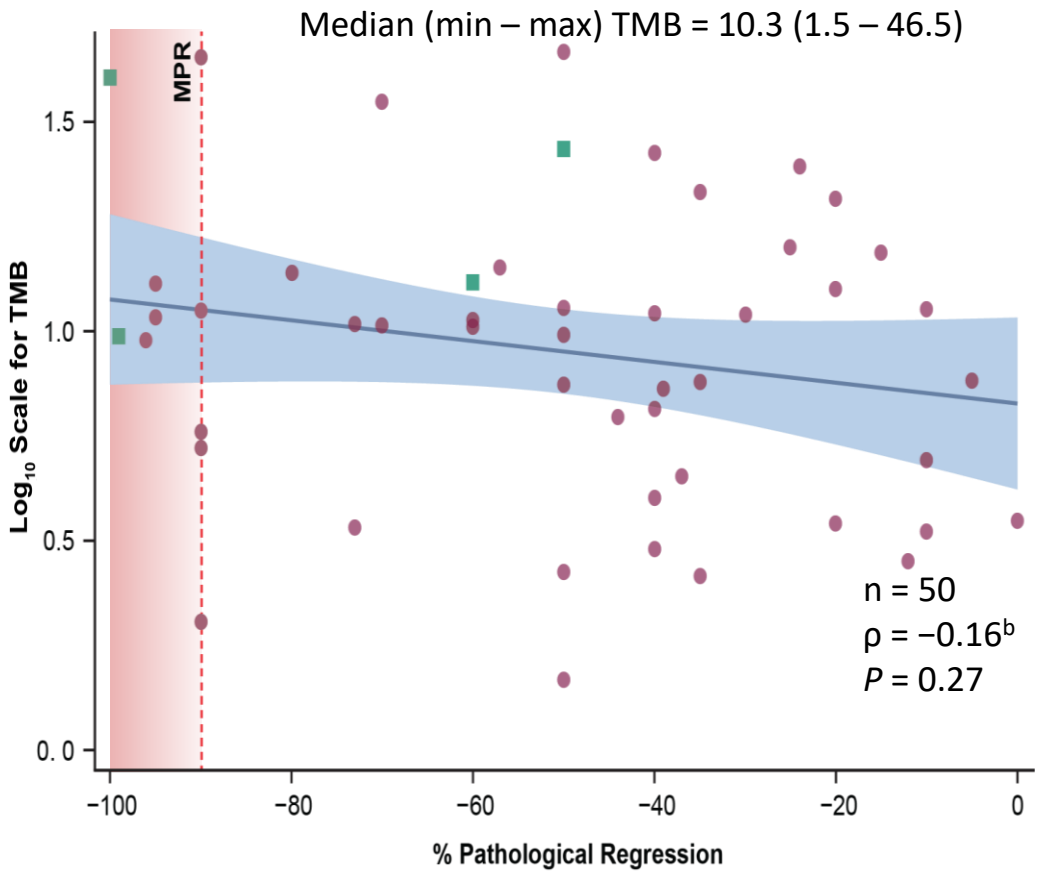
- MPR: 15 of 77 (19%; 95%CI: 11%, 30%)
- pCR: 4 of 77 (5%) patients
- 38 of 77 (49%) had ≥ 50% pathological regression

Pathologic regression defined as % viable tumor cells – 100%. pCR, pathologic complete response.
[a] 1 EGFR+ patient had aborted surgery. * Pathologic response could not be assessed. + EGFR+. ‡ ALK+.

Presented by David J. Kwialkowski. ASCO 2019

Pathological Regression and MPR Were Observed Irrespective of PD-L1 or TMB

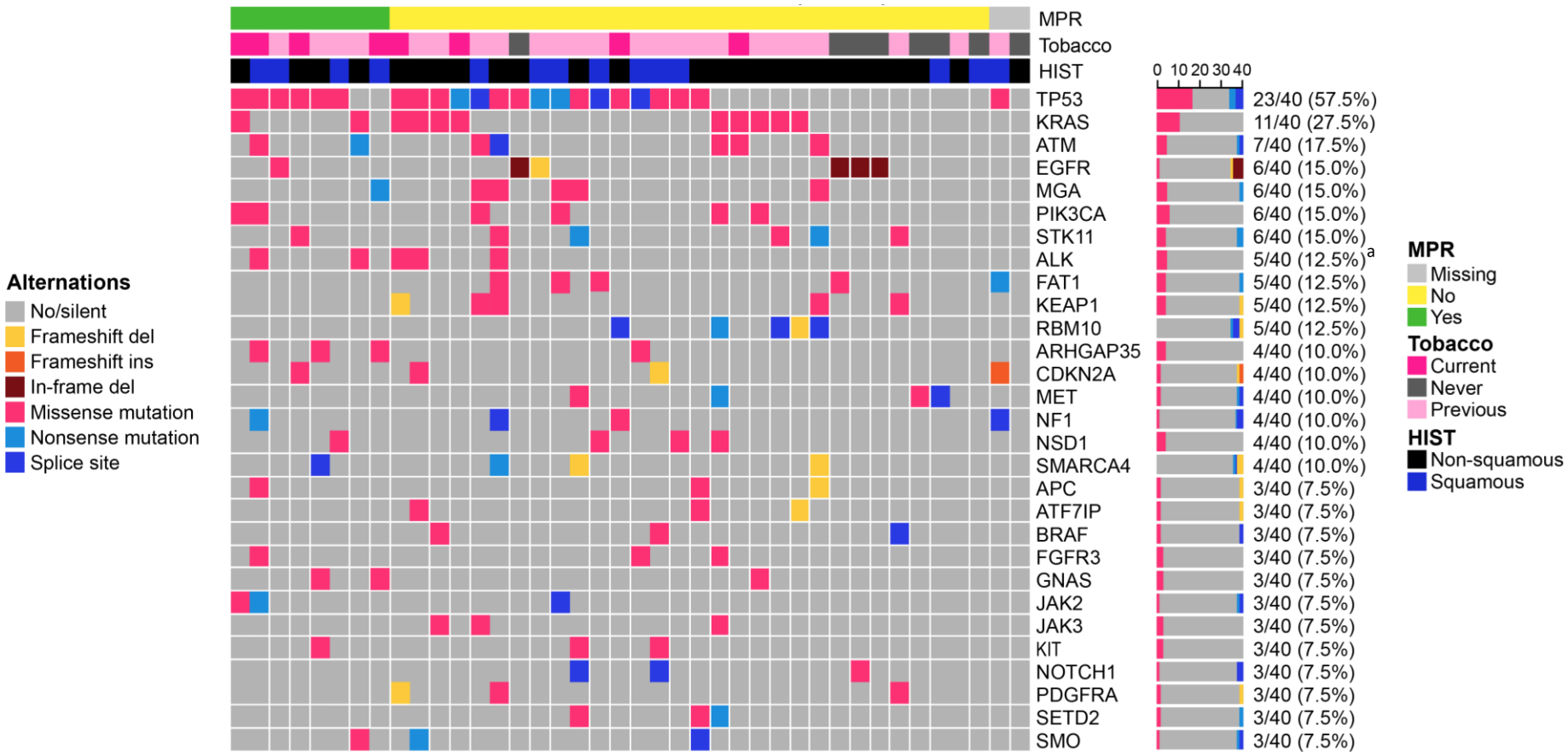




RECIST group ■ CR/PR ▲ PD ● SD

Analysis includes patients who had MPR assessment and PD-L1 IHC results at screening. The regression line is shown with shaded region indicating the confidence band for mean.
[a] Spearman correlation coefficient.PD-L1 testing performed by Chris Rivard and Fred Hirsch, University of Colorado, Denver.
Analysis includes patients who had MPR assessment and sufficient tissue for WES at screening or surgery.
[a] Wilcoxon test. [b] Spearman correlation coefficient. Data provided by Yan Tang, Brigham and Women's Hospital

No Significant Associations Between Gene Alterations and MPR

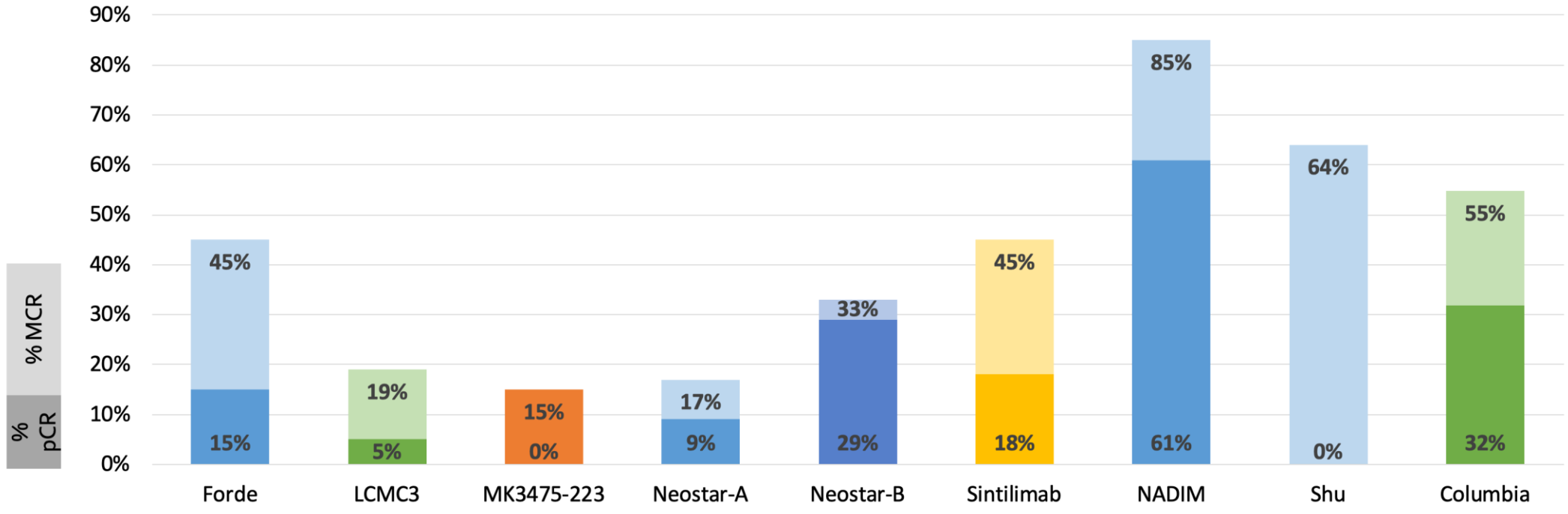


Exome sequence data are available for 40 patients at screening[b]

Genes mutated in ≥ 3 patients are displayed

[a] All *ALK* alterations were single-nucleotide variants. [b] Tissue availability as of September 5, 2018. Data provided by Yan Tang, Brigham and Women's Hospital.

Neo-adjuvant immuno(chemo)therapy studies



Neoadjuvant treatment	Nivolumab x2	Atezolizumab x2	Pembrolizumab x2	Nivolumab x3	Nivo + Ipilimumab x3	Sintilimab x2	Carbo – Pacli – Nivo x3	Carbo – Nab pacli – Nivo x2	Atezolizumab – Carbo – Nab pacli X4
Stage	IB - IIIA	I - IIIB	I - II	I - IIIA	I - IIIA	IB - IIIA	IIIA	IB - IIIA	IB - IIIA
Patient #	20	77	15	23	21	22	46	11	19
% surgery unattended	0%	11%	13%	11%	-	0%	11%	-	0%

Forde PM et al. N Engl J Med. 2018 May 24;378(21):1976-1986 – Kwiatkowski DJ, ASCO 2019, #8503 – Bar J, ASCO 2019, #8534 – Cascone T, ASCO 2019, #8504 – Ning LI, ASCO 2019, #8531 – Provencio M, ASCO 2019, #8509 – Shu, ASCO 2018, #8532 - Rizvi, IASLC targeted lung meeting, 2019

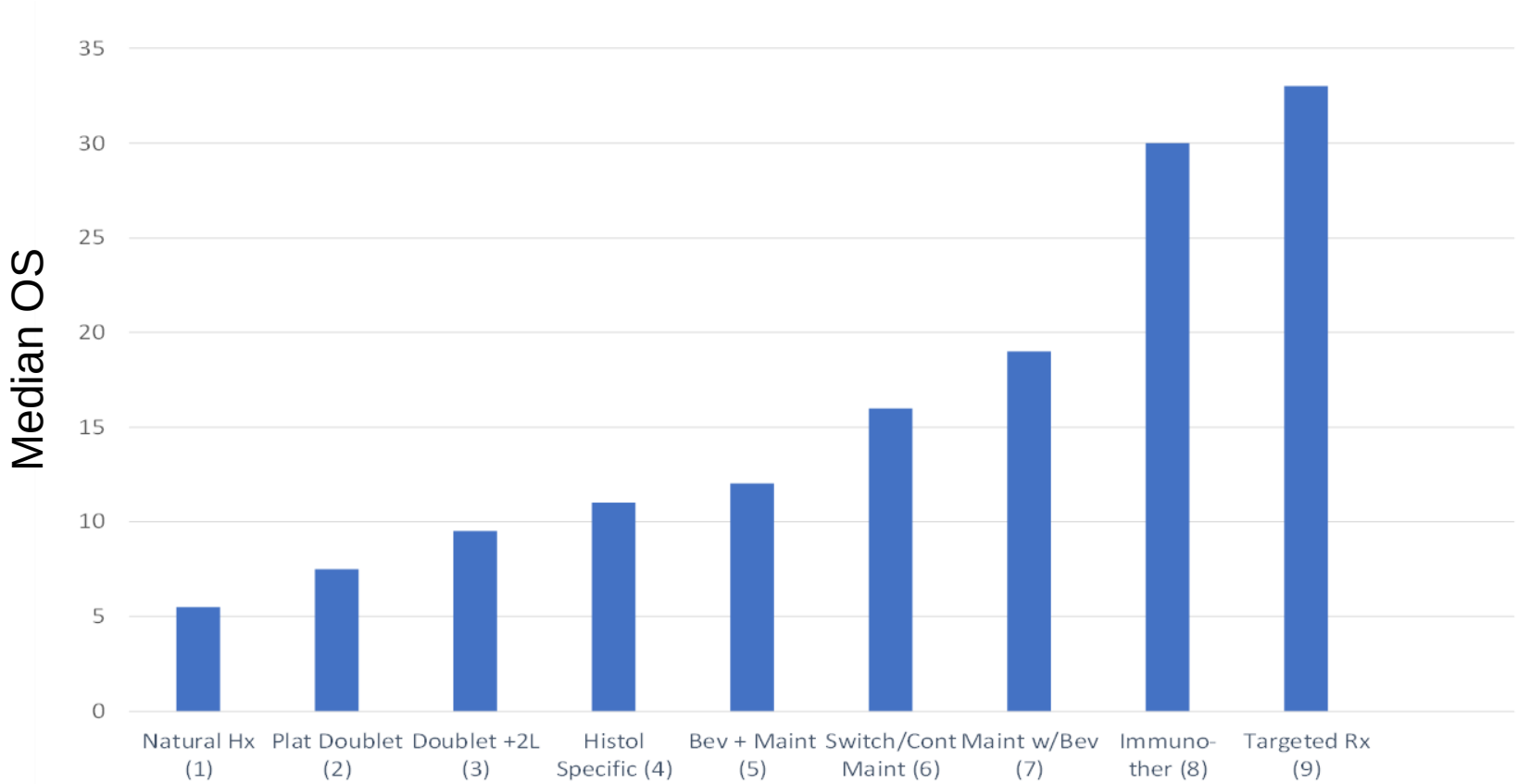
Slide courtesty Solange Peters

Conclusions

- Checkpoint Inhibitors have become first line standard of care as single agents or in combination with chemotherapy for a cohort of lung cancer patients
- PD-L1 can be used to select patients for single agent pembrolizumab
- Combination checkpoint inhibitor therapy lacks a good biomarker
- *STK11* and *KEAP1* genomic alterations are associated with poor clinical outcomes with chemotherapy and immunotherapy in non-squamous NSCLC.
- In the neoadjuvant setting checkpoint inhibitors can induce MPR which may correlate with survival
- PD-L1 and TMB don't appear to correlate with response in the neoadjuvant or advanced stage setting
- Ongoing phase III trials are comping checkpoint inhibition to chemotherapy or in combination with chemotherapy in patients with early stage lung cancer may help us answer some questions

Evolution of Ever-Improving Outcomes for Patients with Metastatic Lung Cancer

……..but Only if Patients Get the Best Treatments



Patients are now routinely able to live years, not just months, with *best available care*

Slide courtesy of Howard “Jack” West

谢谢