Practical assessment of PD-L1 status and integration of PD-L1 assays into clinical practice

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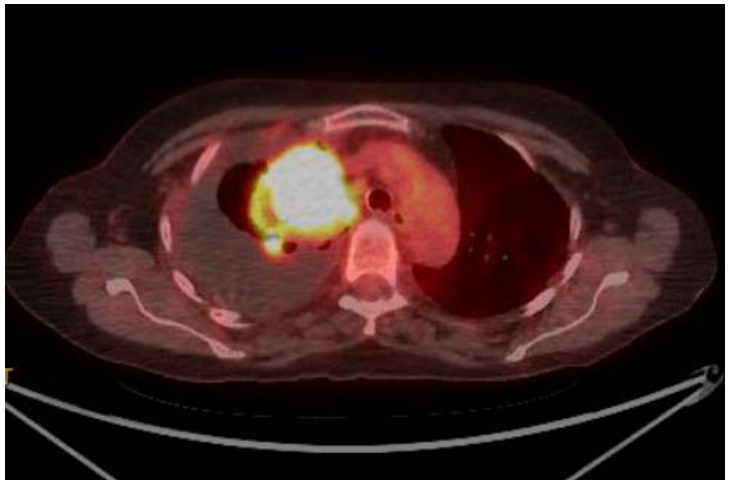
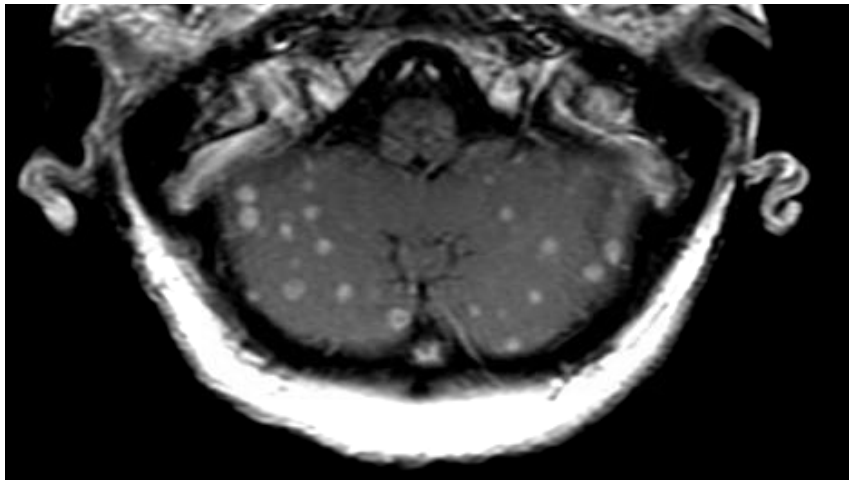
Case presentation

- 70F with 10 pack-year smoking history (quit 1972) presents with pleuritic chest pain after a vacation
- CXR and CT shows large RUL mass and pleural effusion
- Cytology positive for adenocarcinoma, insufficient for molecular testing
- Staging shows bone mets and numerous brain mets
- A repeat biopsy is obtained by EBUS for molecular testing and she is urgently started on carboplatin and pemetrexed to cover systemic and CNS disease





Case presentation

- Molecular testing demonstrates KRAS G12C, and a MET R988C variant of uncertain significance
- PD-L1 testing with the 22C3 antibody is 5% positive
- Her tumor restaging at 2 months demonstrates stable large lung mass, increased lytic bone progression, and progression of CNS lesions. She feels unwell.
- She undergoes whole brain radiotherapy (WBRT)

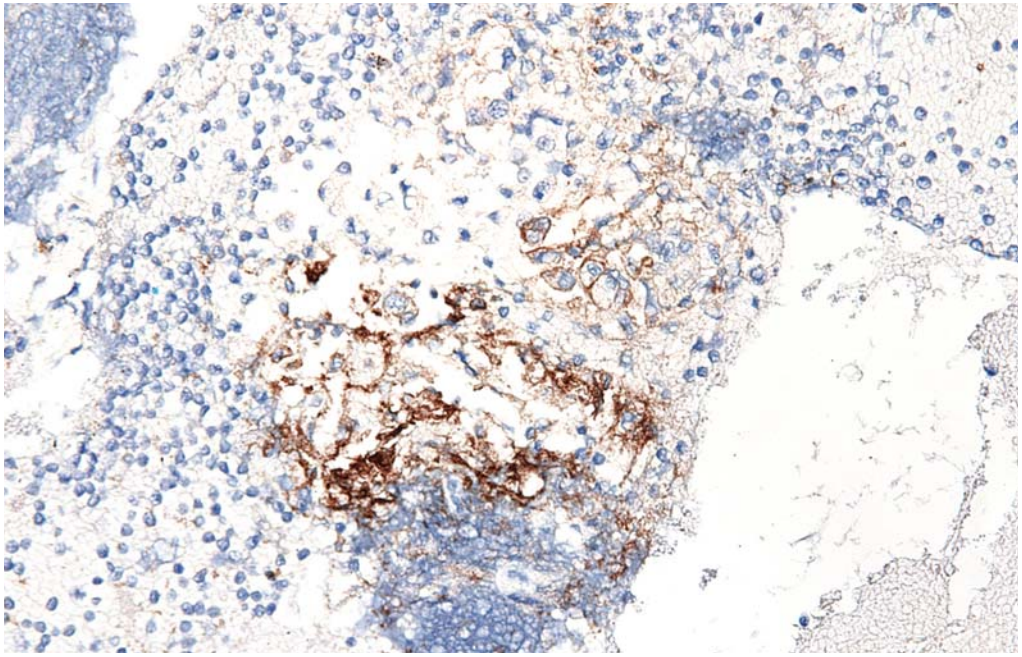
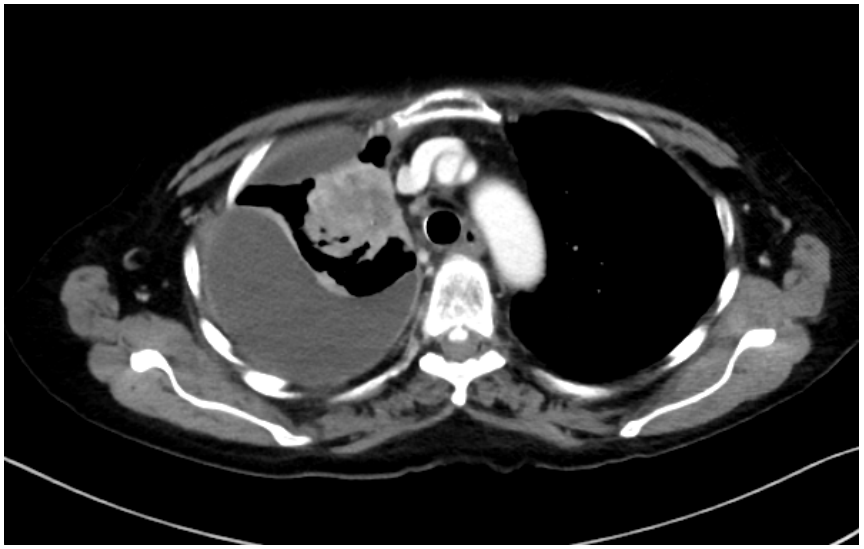
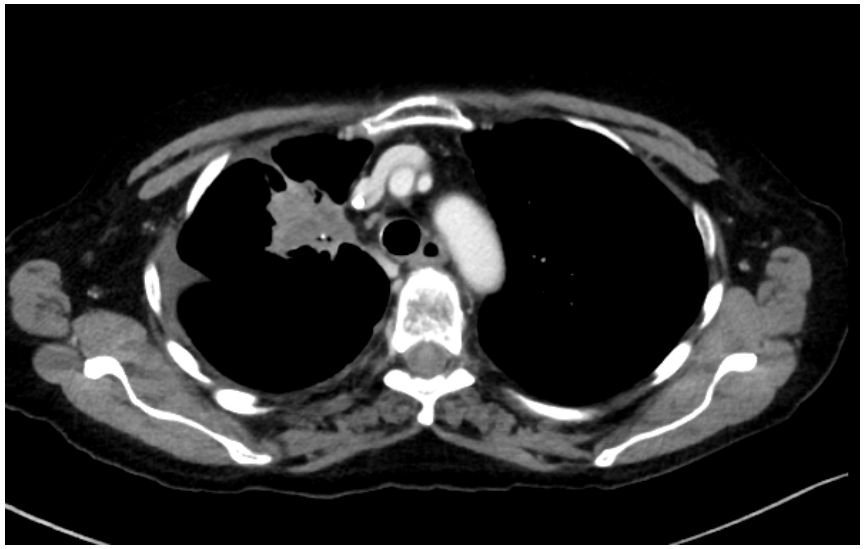


Image courtesy of
G. Berry (Stanford)

Case presentation

- She is started on pembrolizumab 1 week after completion of WBRT
- She starts to feel better within a few weeks, and restaging after 3 months demonstrates regression of the lung mass, spontaneous resolution of the effusion, sclerosis of the bony metastases, and stability of the brain lesions





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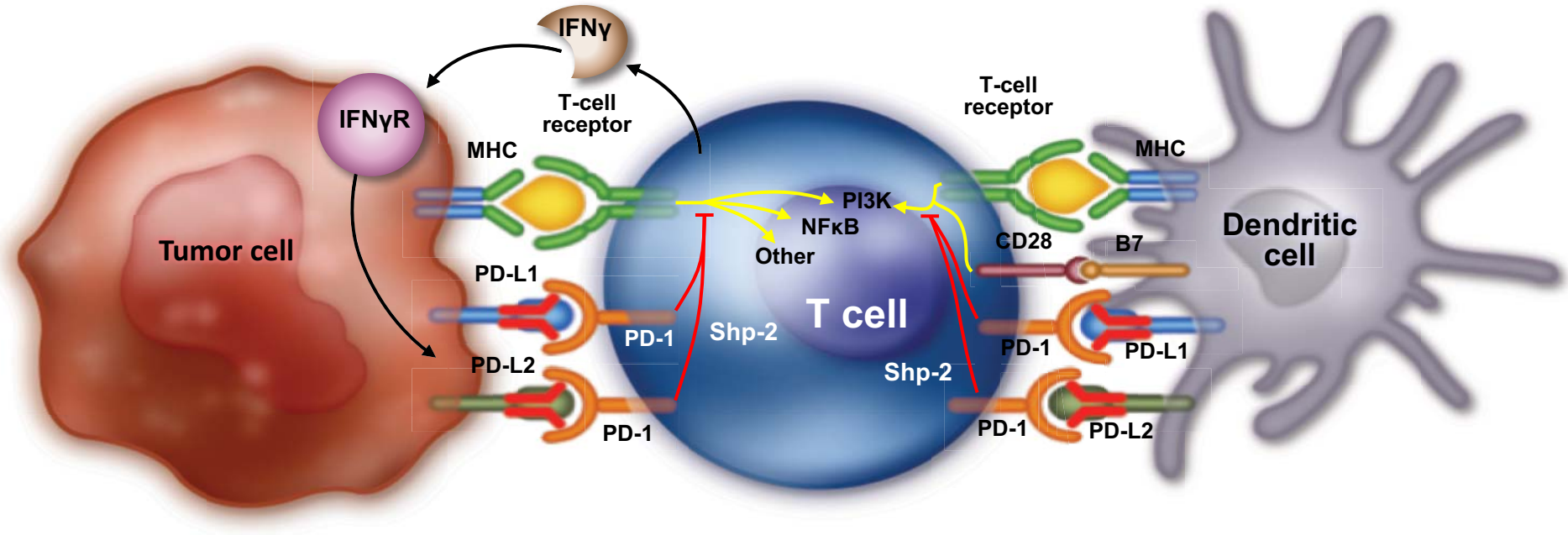
Disclosures

Consulting Agreements	Ariad Pharmaceuticals Inc, ARMO BioSciences, Boehringer Ingelheim Pharmaceuticals Inc, CARET/Physician Resource Management, Clovis Oncology, Nektar
Contracted Research	Ariad Pharmaceuticals Inc, ArQule Inc, Boehringer Ingelheim Pharmaceuticals Inc, Exelixis Inc, Genentech BioOncology, Merck, Nektar, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc

Anti-PD-1/PD-L1 Antibodies: Mechanism of Action

- PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function
- 3 Approved Drugs:
- Nivolumab/pembrolizumab bind PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function
- Atezolizumab binds PD-L1 receptors

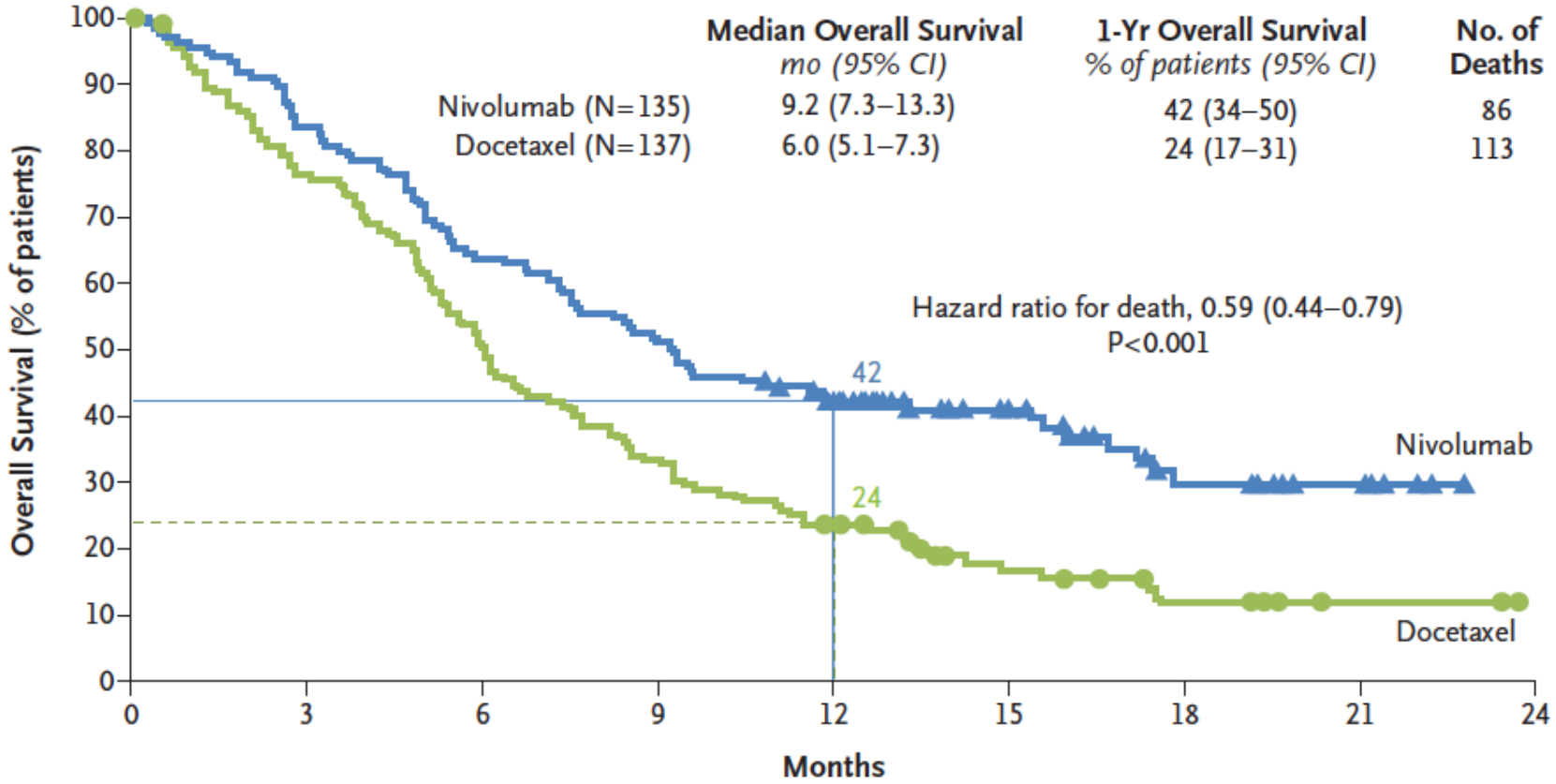


Nivolumab/Pembrolizumab: PD-1 Receptor Blocking Ab
Atezolizumab: PD-L1 Receptor Blocking Ab

PD-1/PD-L1 Inhibitors in NSCLC

Checkpoint inhibitor	Antibody type	Stage	PD-L1 test
Nivolumab (BMS-936558)	IgG4	Approved 2nd line CheckMate 057/017	28-8 "complementary"
Pembrolizumab (MK-3475)	IgG4 (humanized)	1st line – PD-L1 >50% 2nd line – PD-L1 >1% Keynote 010/024	22C3 "companion"
Anti-PD-L1			
Atezolizumab (MPDL3280A)	IgG1 (engineered)	Approved 2nd line OAK,BIRCH, Impower	SP142 "complementary"
Durvalumab (MEDI-4736)	IgG1	Phase III (ATLANTIC, PACIFIC, BR31, ARCTIC, MYSTIC, LUNG-MAP)	SP263
Avelumab (MSB0010718C)	IgG	Phase III (JAVELIN)	

Nivolumab vs Docetaxel in Squamous NSCLC (CheckMate 017)



Brahmer. *N Engl J Med* 2015.

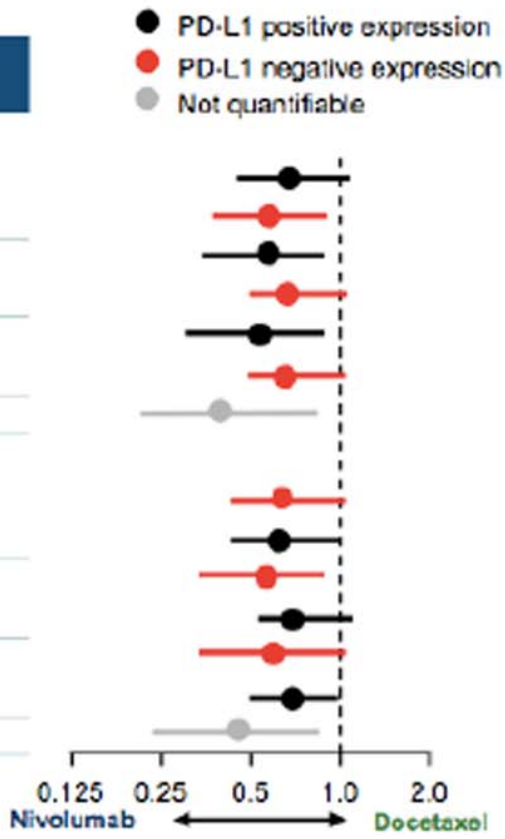
Nivolumab vs Docetaxel in Squamous NSCLC (CheckMate 017)

OS and PFS by PD-L1 Expression

- Survival benefit with nivolumab was independent of PD-L1 expression level

PD-L1 expression	Patients, n Nivolumab	Docetaxel	Unstratified HR (95% CI)	Interaction *P*-value
OS				
≥1%	63	56	0.69 (0.45, 1.05)	0.56
<1%	54	52	0.58 (0.37, 0.92)	
≥5%	42	39	0.53 (0.31, 0.89)	0.47
<5%	75	69	0.70 (0.47, 1.02)	
≥10%	36	33	0.50 (0.28, 0.89)	0.41
<10%	81	75	0.70 (0.48, 1.01)	
Not quantifiable	18	29	0.39 (0.19, 0.82)	
PFS				
≥1%	63	56	0.67 (0.44, 1.01)	0.70
<1%	54	52	0.66 (0.43, 1.00)	
≥5%	42	39	0.54 (0.32, 0.90)	0.16
<5%	75	69	0.75 (0.52, 1.08)	
≥10%	36	33	0.58 (0.33, 1.02)	0.35
<10%	81	75	0.70 (0.49, 0.99)	
Not quantifiable	18	29	0.45 (0.23, 0.89)	

- PD-L1 expression was measured in pre-treatment tumor biopsies

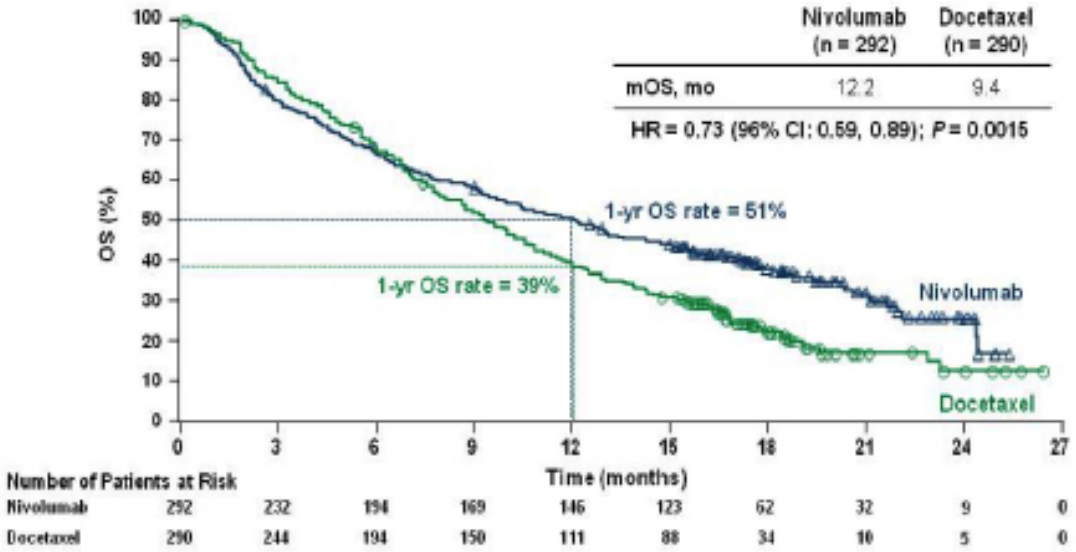


28-8 IHC

Brahmer. *N Engl J Med* 2015.

Nivolumab vs Docetaxel in Non-Squamous NSCLC (CheckMate 057)

- **Phase III, 582 patients randomized**
- **Nivolumab 3 mg/kg Q2W vs docetaxel 75 mg/m^2 Q3**
- **Primary endpoint OS**
- **Trial stopped early by DSMC, met its primary endpoints at interim analysis**



	Nivolumab (n=292)	Docetaxel (n=290)
ORR	19%	12%
P-value	0.0246	
Median DOR, mos	17.2	5.6

- 71 (24%) patients on nivolumab were treated beyond RECIST v1.1-defined progression
- Non-conventional benefit was observed in 16 patients (not included in best overall response)

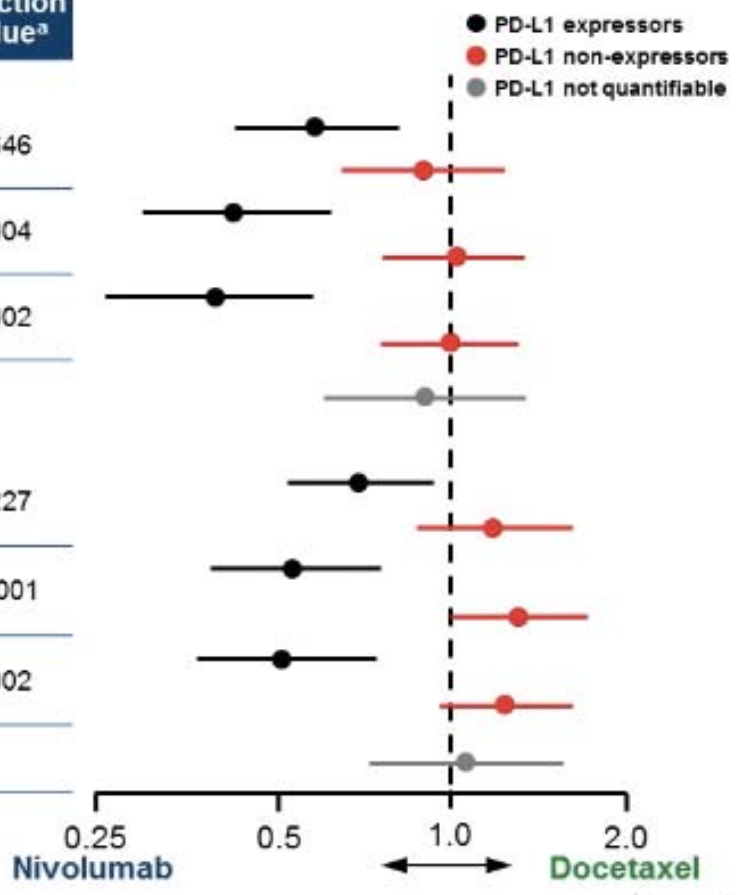
Borghaei. *N Engl J Med* 2015.

Nivolumab vs Docetaxel in Non-Squamous NSCLC (CheckMate 057)

OS and PFS Hazard Ratios by Baseline PD-L1 Expression

PD-L1expression level	Nivolumab n	Docetaxel n	Unstratified HR (95% CI)	Interaction *P*-value[a]
OS				
≥1%	123	123	0.59 (0.43, 0.82)	0.0646
<1%	108	101	0.90 (0.66, 1.24)	
≥5%	95	86	0.43 (0.30, 0.63)	0.0004
<5%	136	138	1.01 (0.77, 1.34)	
≥10%	86	79	0.40 (0.26, 0.59)	0.0002
<10%	145	145	1.00 (0.76, 1.31)	
Not quantifiable at baseline	61	66	0.91 (0.61, 1.35)	
PFS				
≥1%	123	123	0.70 (0.53, 0.94)	0.0227
<1%	108	101	1.19 (0.88, 1.61)	
≥5%	95	86	0.54 (0.39, 0.76)	<0.0001
<5%	136	138	1.31 (1.01, 1.71)	
≥10%	86	79	0.52 (0.37, 0.75)	0.0002
<10%	145	145	1.24 (0.96, 1.61)	
Not quantifiable at baseline	61	66	1.06 (0.73, 1.56)	

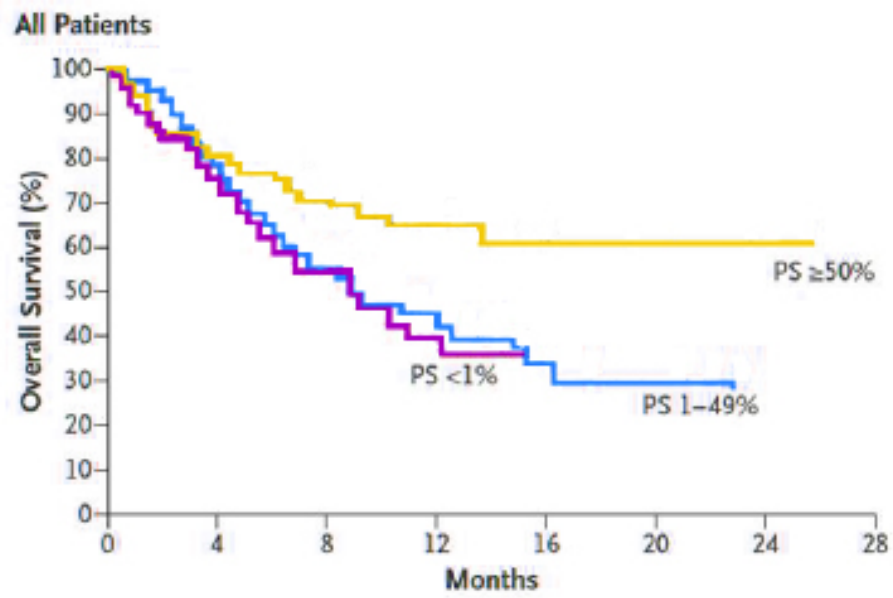
[a] Interaction p-value from Cox proportional hazard model with treatment, PD-L1 expression and treatment by PD-L1 expression interaction.

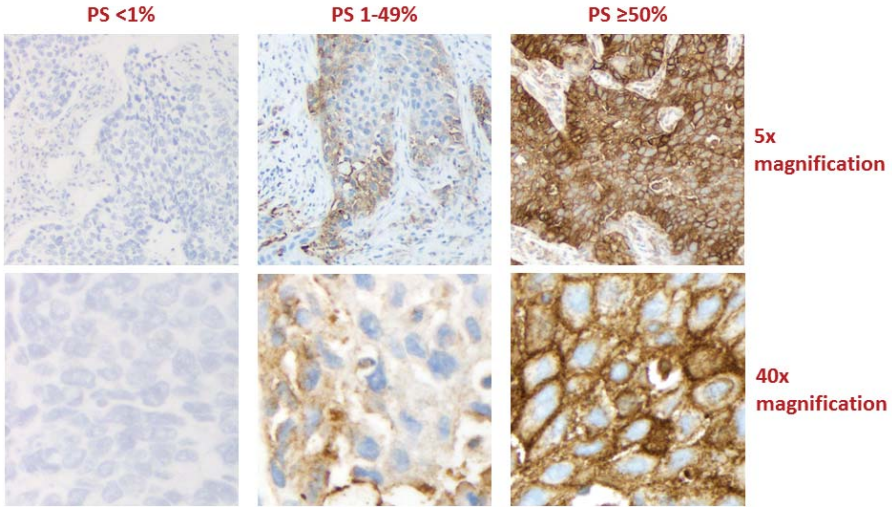


28-8 IHC

Borghaei. *N Engl J Med* 2015.

Pembrolizumab in NSCLC (Keynote 001)





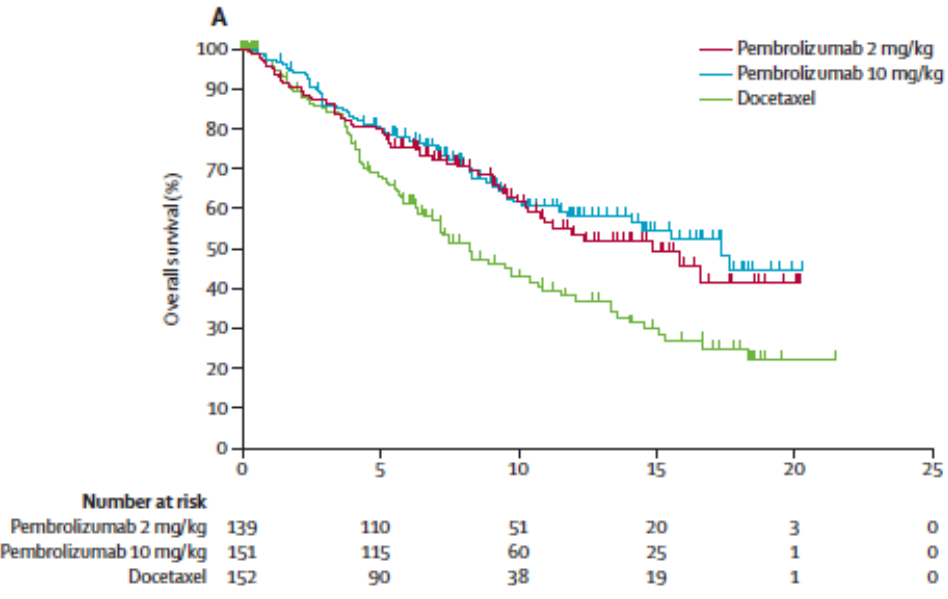
Brown chromogen:PD-L1 staining with 22C3 antibody
Blue color: hematoxylin counterstain

22C3 IHC

Garon. *N Engl J Med* 2015.

KEYNOTE-010: Pembrolizumab vs docetaxel

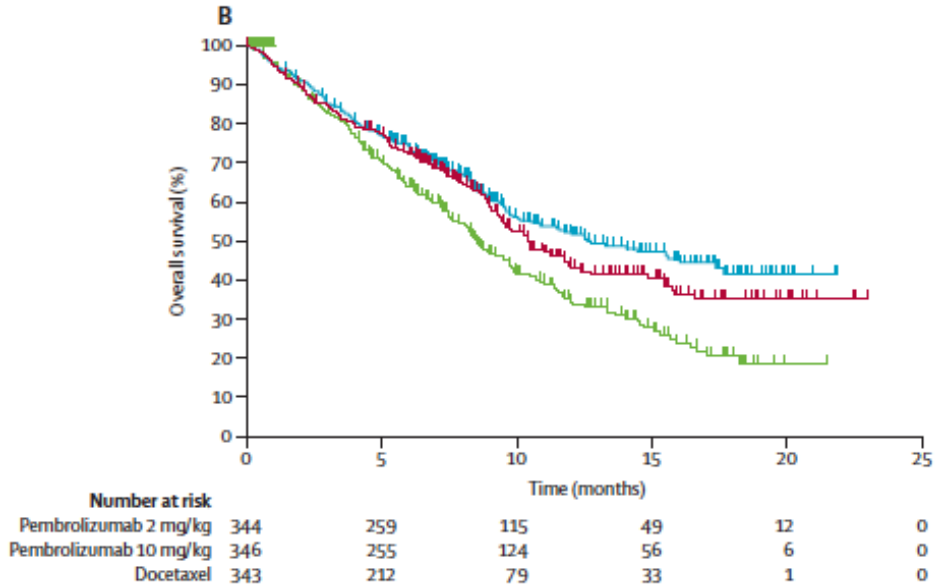
22C3 ≥50%



Pembro 2 mg/kg vs. docetaxel HR 0.54
(14.9 mo vs. 8.2 mo; 95% CI 0.38–0.77; *p* = 0.0002)

Pembro 10 mg/kg vs. docetaxel HR 0.50
(17.3 mo vs. 8.2 mo; 0.36–0.70; *p*<0.0001).

22C3 ≥1%

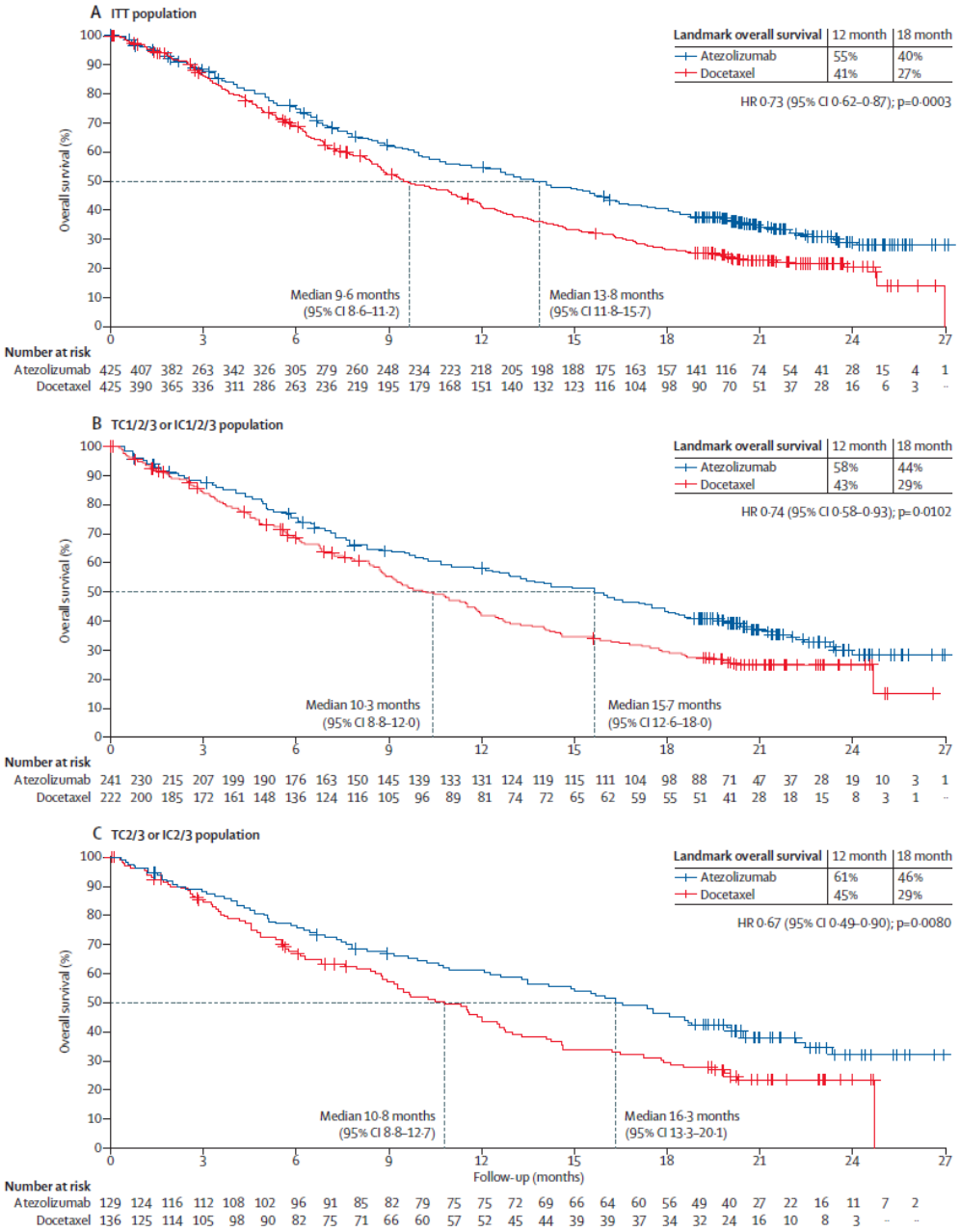


Pembro 2 mg/kg vs. docetaxel HR 0.71
(10.4 mo vs. 8.5 mo; 95% CI 0.58–0.88; *p* = 0.0008)

Pembro 10 mg/kg vs. docetaxel HR 0.61
(12.7 mo vs.8.5 mo; 0.49–0.75; *p*<0.0001)

Herbst et al. *Lancet* 2015.

Atezolizumab vs docetaxel in NSCLC (OAK)



SP142 TC/IC ≥0

SP142 TC/IC ≥1

SP142 TC/IC ≥2

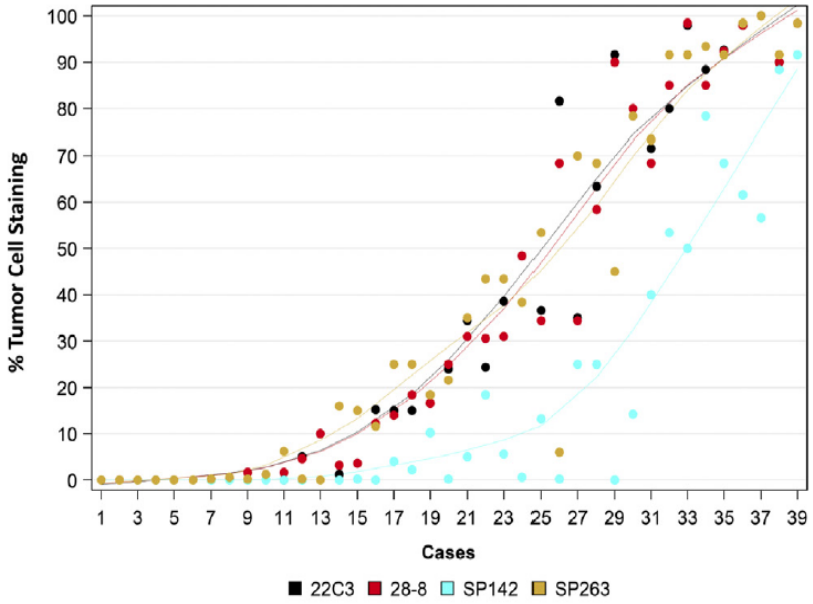
Rittmeyer. *Lancet* 2017.

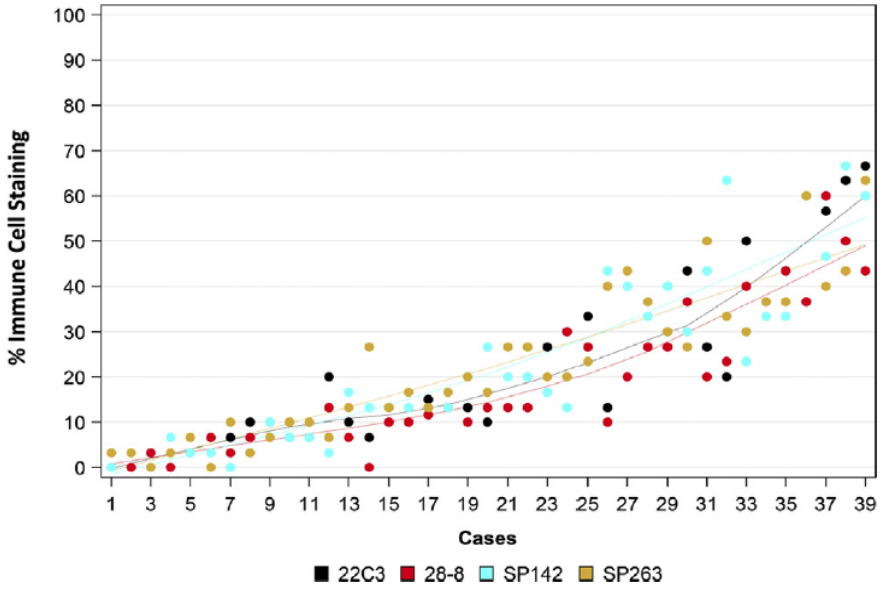
Biomarkers: PD-L1 (IHC) as a Biomarker in Lung Cancer for Anti-PD-(L)1 Therapy

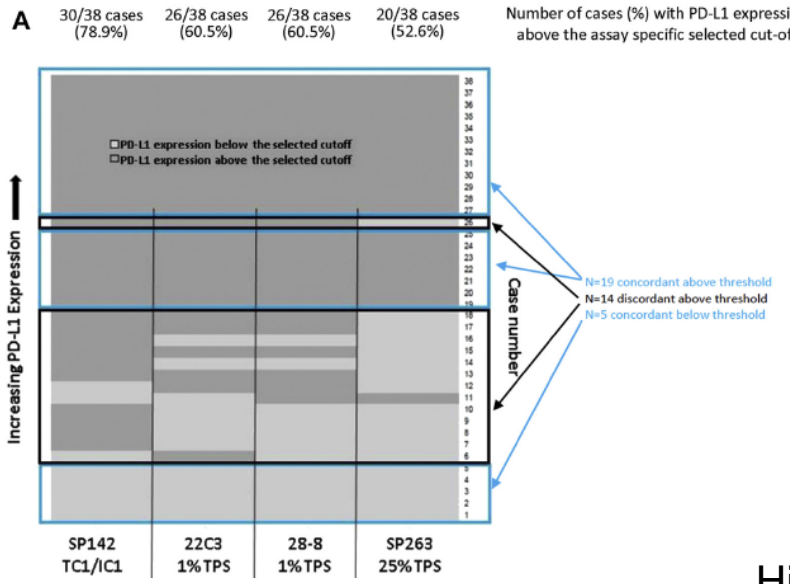
Drug	Nivolumab[1,2]		Pembrolizumab[3]		Atezolizumab[4]	Durvalumab[5]
Assay	Rabbit mAb 28-8 automated IHC		Murine mAb 22C3 IHC		Rabbit mAb SP142 automated IHC	Rabbit mAb SP263 automated IHC
Cells scored	Tumor cell membrane		Tumor cell (and stroma)		Infiltrating immune cells	Tumor cell membrane
Tissue	FFPE		FFPE		FFPE	FFPE
Cut-point	1-50%	1-50%	1-50%	1-50%	TC1 or IC1	NR

1. Gettinger SN et al. *J Clin Oncol* 2015;33(suppl): Abstract 8025. 2. Gettinger SN et al. *J Clin Oncol* 2015 Apr 20
3. Garon EB et al. *N Engl J Med* 2015;372(21):2018-2028. 4. Horn L et al. *J Clin Oncol* 2015;33(suppl): Abstract 8029.
5. Rebelatto MC et al. *J Clin Oncol* 2015;33(suppl): Abstract 8033.

BLUEPRINT: Comparison of different PD-L1 assays

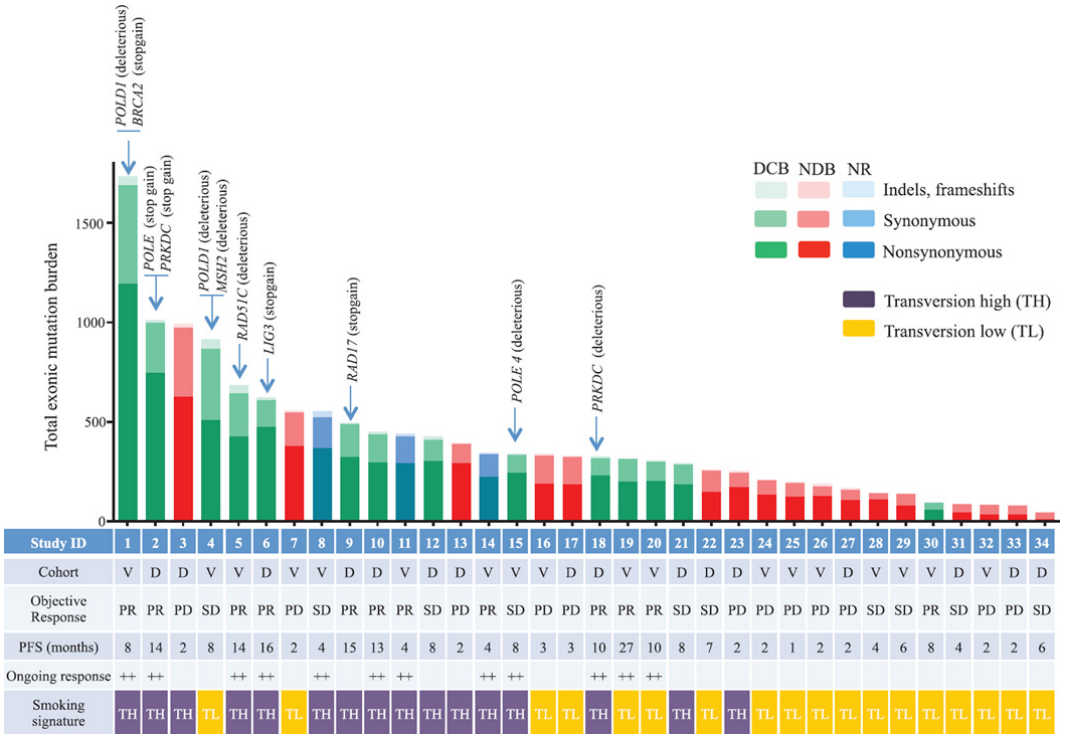




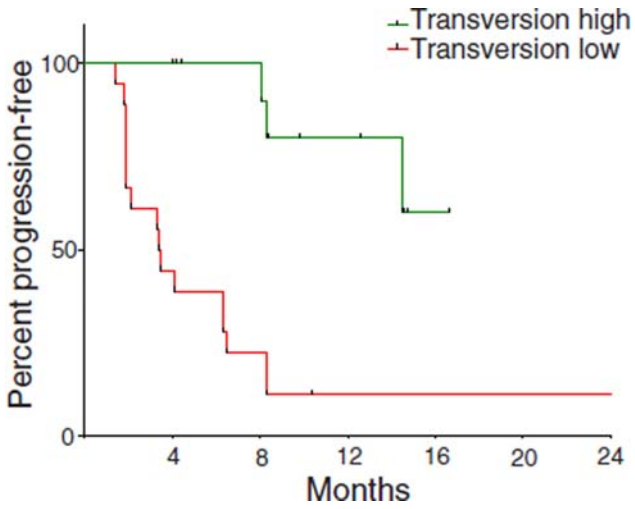


Hirsch J. *Thoracic Oncol* 2017.

Tumor mutational load - another predictor of response to immunotherapy?



Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
Cohort	V	D	D	V	V	D	V	V	D	D	V	D	D	V	V	V	D	D	V	V	D	D	D	V	V	V	D	V	V	V	D	V	D	D
Objective Response	PR	PR	PD	SD	PR	PR	PD	SD	PR	PR	PR	SD	PD	PR	SD	PD	PD	PR	PR	PR	SD	SD	PD	PD	PD	PD	PD	SD	SD	PR	SD	PD	PD	SD
PFS (months)	8	14	2	8	14	16	2	4	15	13	4	8	2	4	8	3	3	10	27	10	8	7	2	2	1	2	2	4	6	8	4	2	2	6
Ongoing response	++	++			++	++		++		++	++			++	++			++	++	++														
Smoking signature	TH	TH	TH	TL	TH	TH	TL	TH	TH	TH	TH	TH	TH	TH	TH	TL	TL	TH	TL	TL	TH	TL	TH	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL



Hellmann Science 2015

PD-L1 testing in NSCLC - Conclusions

- Many PD-L1 IHC tests exist – all require paraffin tissue
- Assays generally correlate with each other
- Genomic testing (tumor mutational burden) is an emerging second predictor of response
- For now, testing with the 22C3 antibody is the most compelling single assay (to allow access to first line pembrolizumab).
- Testing in the second line setting with any assay is also reasonable (to estimate probability of response).