PD-L1 as a Predictive Biomarker in Non-Small Cell Lung Cancer (NSCLC) and Beyond

Roy S. Herbst, MD, PhD

Ensign Professor of Medicine
Professor of Pharmacology
Chief of Medical Oncology
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April 3, 2017

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

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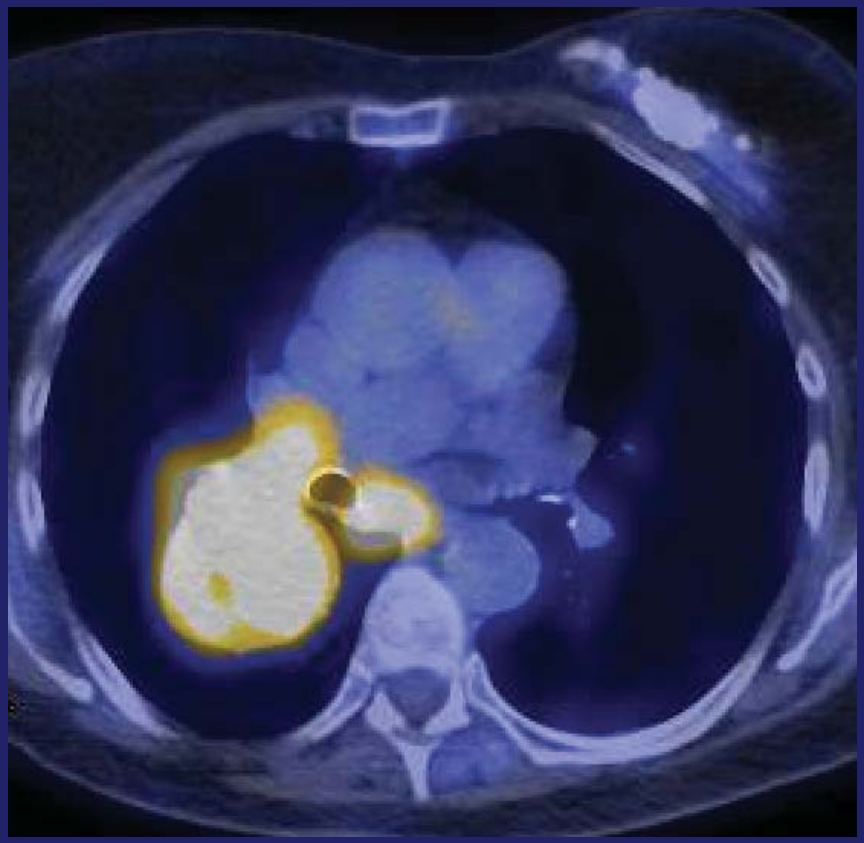
Case 1

- 72-year-old woman with 50 pack-year smoking history presents with cough and fatigue. Zubrod PS 1.
- Diagnosed with stage IV NSCLC-adenocarcinoma. RUL hilar mass with metastases to bone and lymph nodes.
- MRI of brain negative.
- *EGFR*-mut by PCR, *ALK* FISH, *ROS1* FISH testing is negative.
- PD-L1 testing by IHC with the 22C3 antibody. 80% PD-L1 expression is noted.



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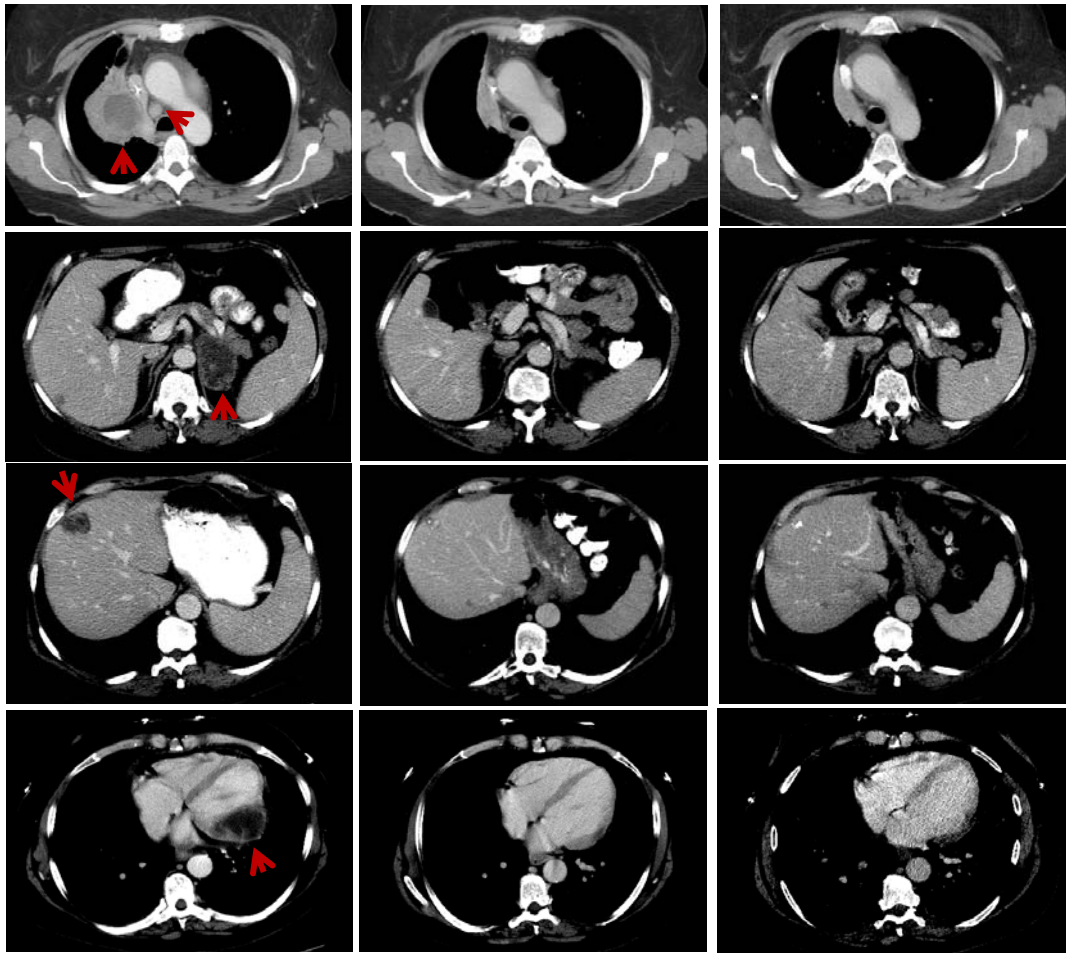
Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Kolltan Pharmaceuticals Inc, Lilly, Merck, Pfizer Inc
Contracted Research	Genentech BioOncology, Merck

Early Patient on Nivolumab June 2010



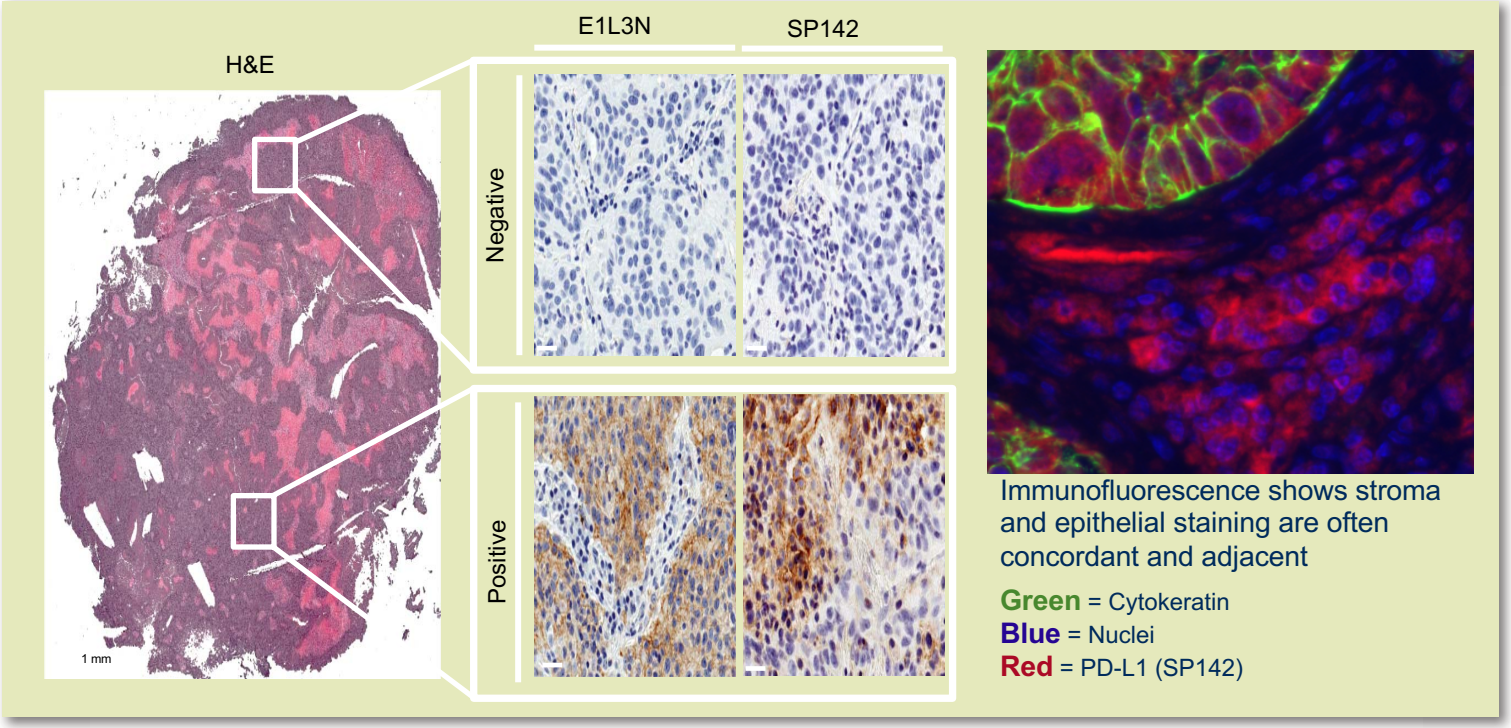
Pre- Nivolumab | 2 Years on Nivolumab | Last month, > 4 Years off Nivolumab

- 63 y/o ex-smoker (15 pack years, quit in 1983)
- Stage IV Squamous NSCLC dx in Jan. 2009; metastatic to hilum/ mediastinum, liver, adrenal, bone and later, myocardium
- 3 prior chemotherapy regimens
- Nivolumab initiated June 2010

Cure?

Is PD-L1 a Biomarker?

Issues with the PD-L1 Biomarker



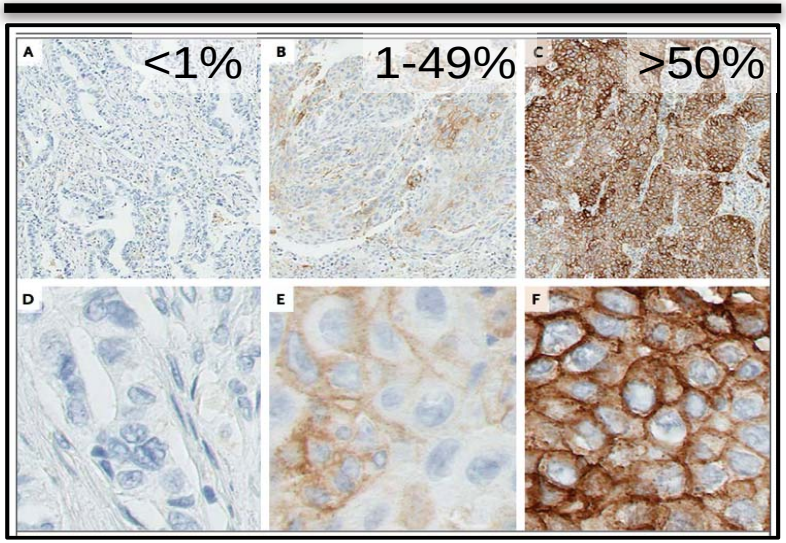
- Heterogeneity – multiple tumors and multiple passes within a tumor
- Interval between biopsy and treatment
- Primary versus metastatic disease
- Antibody and staining conditions

- Defining a positive result (cut-offs):
  - Cell type expressing PD-L1 (immune cell versus tumor or both)
  - Location of expression – cell surface versus intracellular versus stromal
  - Intensity, percent of cells 'positive'
  - Distribution - patchy versus diffuse, intratumoral versus peripheral

McLaughlin (Rimm) et al., *JAMA Oncology.* 2016 Jan 1;2(1):46-54

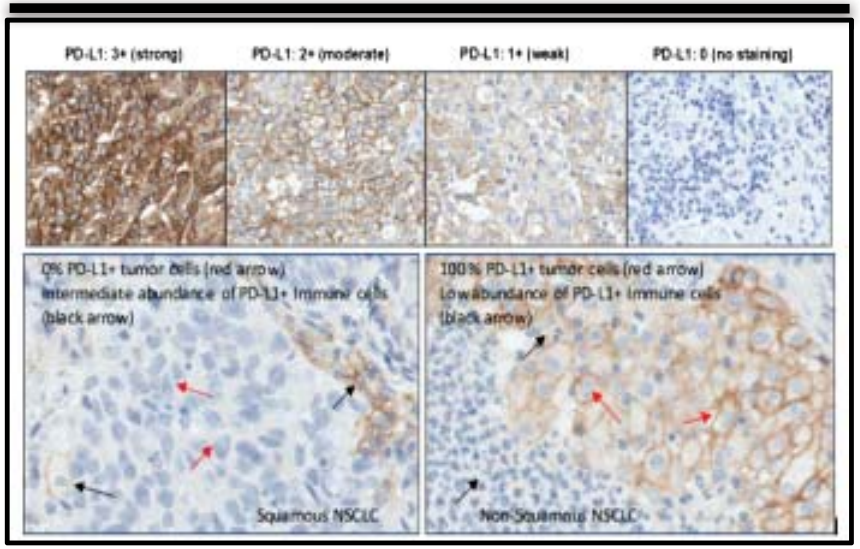
Multiple approved PD-L1 assays

Clone 22C3 (pembrolizumab, **companion**)



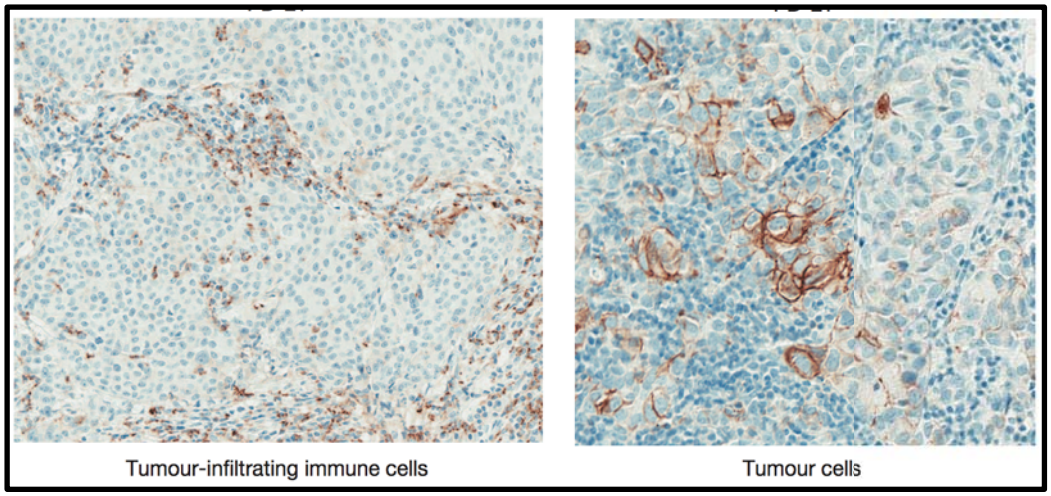
Garon et al., 2015, NEJM

Clone 28-8 (nivolumab, **complementary**)



Philips et al., 2015, AIMM

Clone SP142 (atezolizumab, **complementary**)

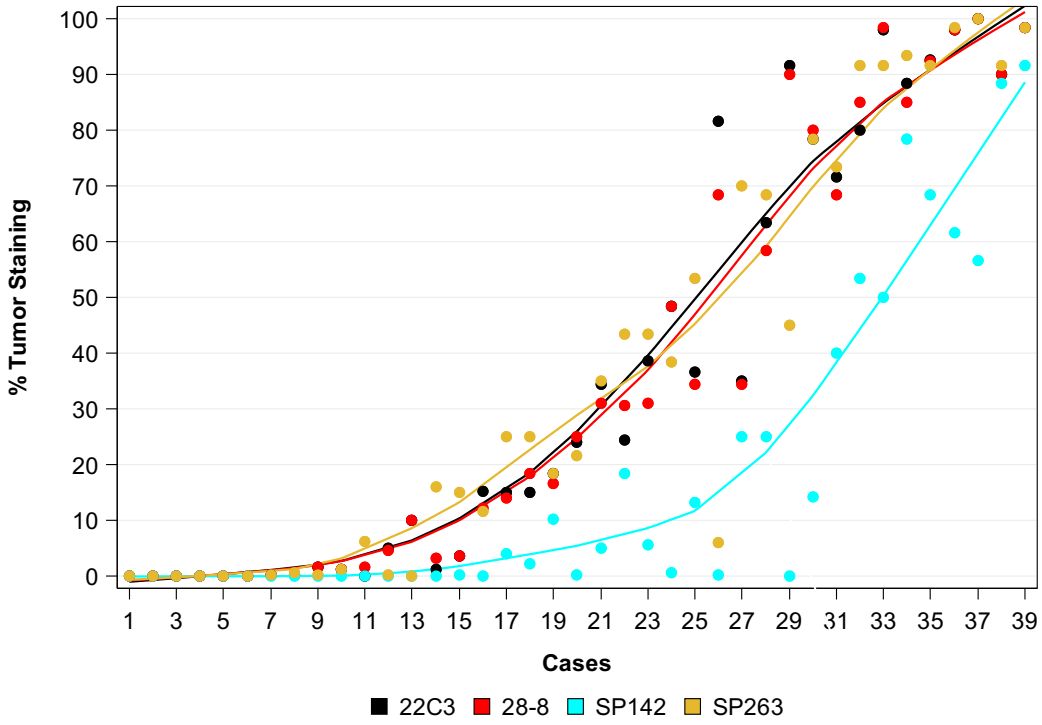


Powles et al., 2014, Nature

Analytical Evaluation Results: Mean Tumor Proportion Score (TPS) per case based on three readers

- Analytical comparison of % tumor cell staining (Tumor Proportion Score), by case, for each assay
- **Data points represent the mean score from three pathologists for each assay on each case**
- Superimposed lines / points indicate identical TPS values
- No clinical diagnostic cut-off applied
- **Conclusion:** 3 of 4 assays are analytically similar for tumor cell staining.

22C3 and 28-8
SP 263

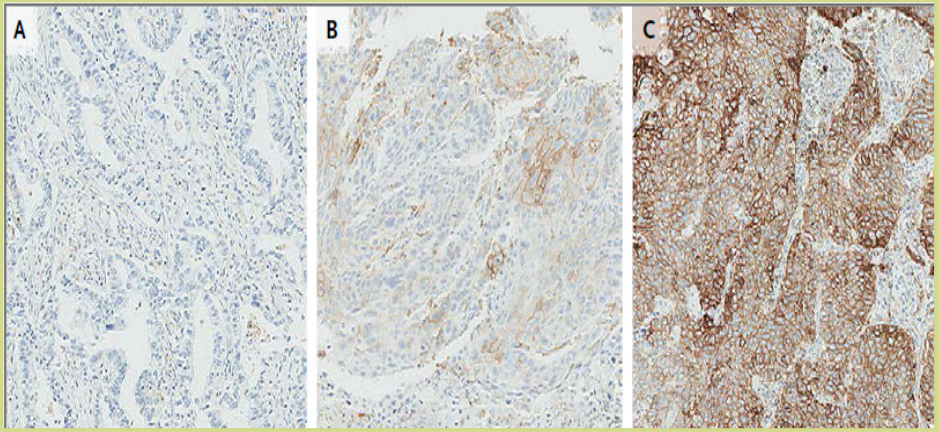


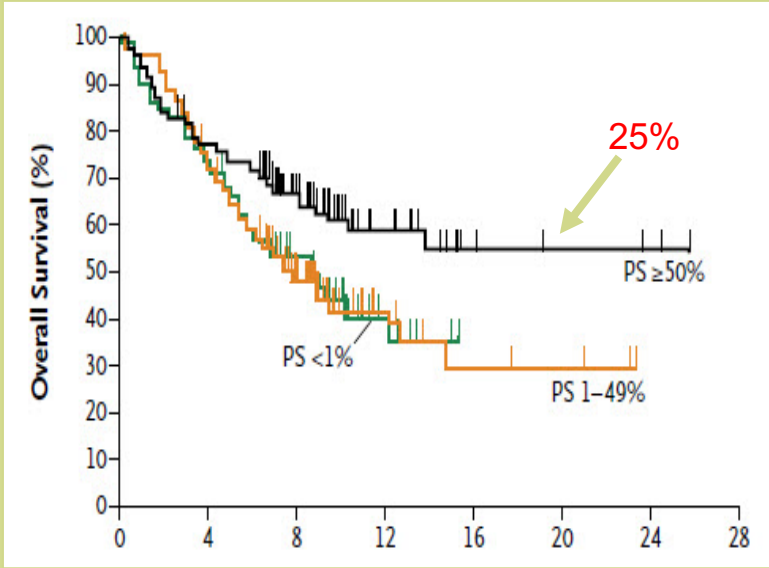
SP 142

Hirsch FR et al: AACR 2016

Pembrolizumab Biomarker Development

Pembrolizumab[1] 22C3 Ab





0

1-49%
low

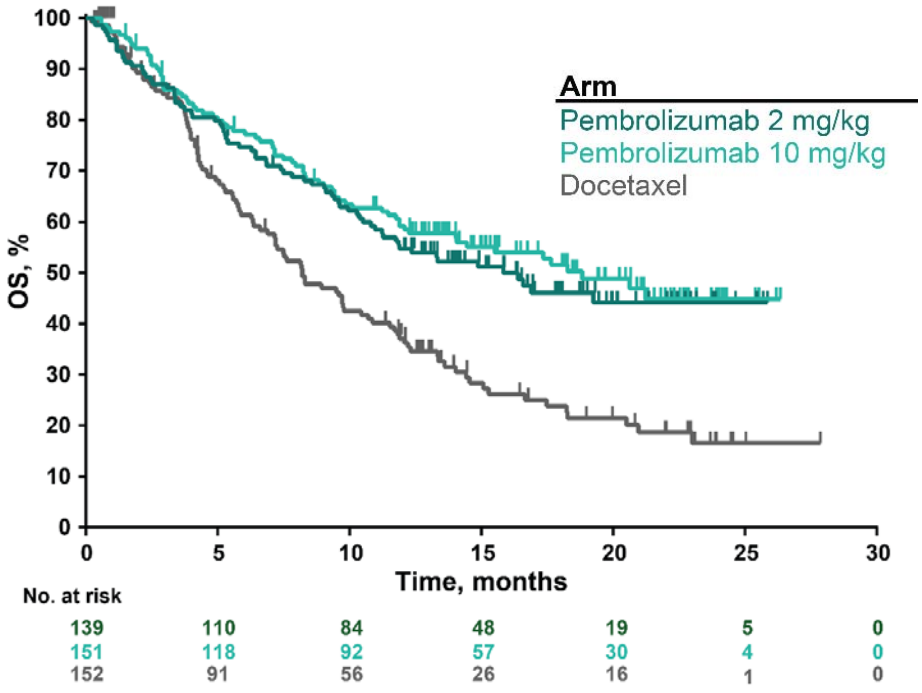
> 50%
high

[1] Garon EB et al. *N Engl J Med* 2015 372:2018-2028

KEYNOTE-010: Updated Analysis

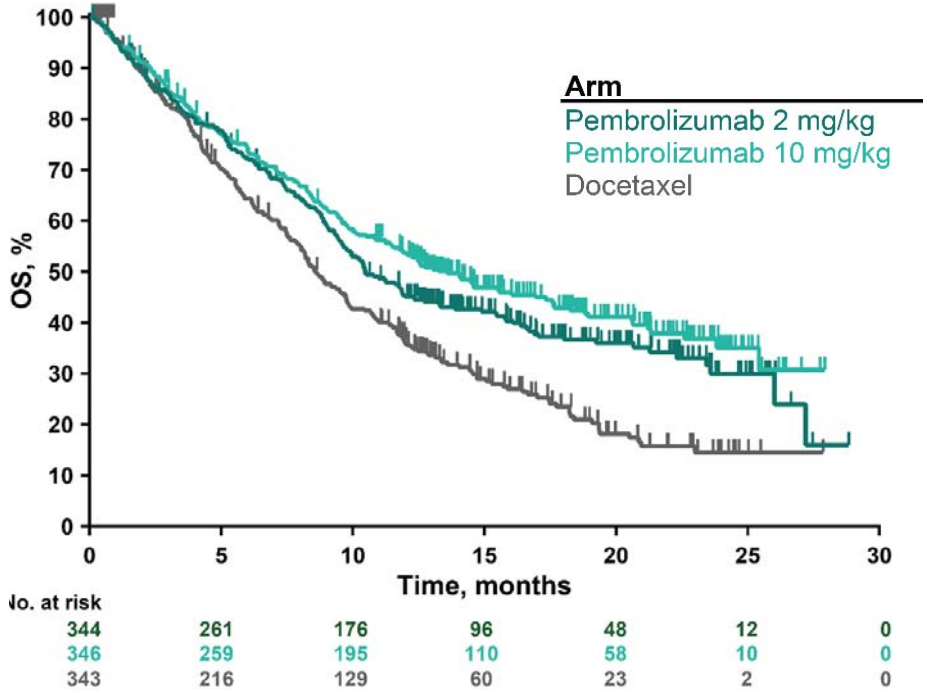
TPS ≥50%

Arm	Median, mo	18-mo Rate, %	HR (95% CI)	P[a]
Pembrolizumab 2 mg/kg	15.8	46	0.54 (0.39-0.73)	0.00004
Pembrolizumab 10 mg/kg	18.8	52	0.48 (0.35-0.66)	<0.00001
Docetaxel	8.2	24	—	—



TPS ≥1%

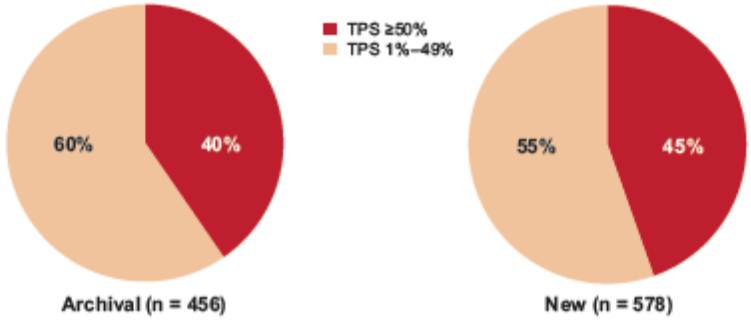
Arm	Median, mo	18-mo Rate, %	HR (95% CI)	P[a]
Pembrolizumab 2 mg/kg	10.5	37	0.72 (0.60-0.87)	0.0003
Pembrolizumab 10 mg/kg	13.6	43	0.60 (0.50-0.73)	<0.00001
Docetaxel	8.6	24	—	—



Herbst et al, Lancet 2015, updated ESMO 2016

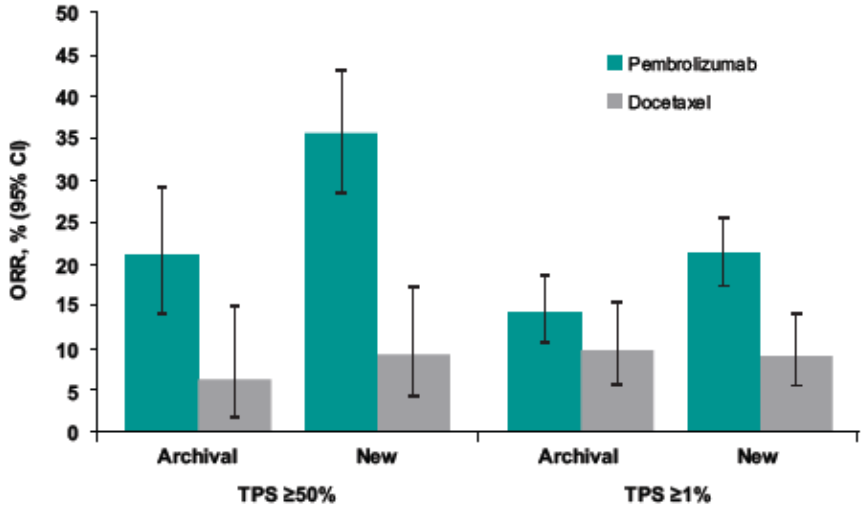
PD-L1 as a biomarker: Archival vs Fresh?

Figure 4. Prevalence of PD-L1 TPS ≥50% and TPS 1%-49% in archival and new tumor samples.



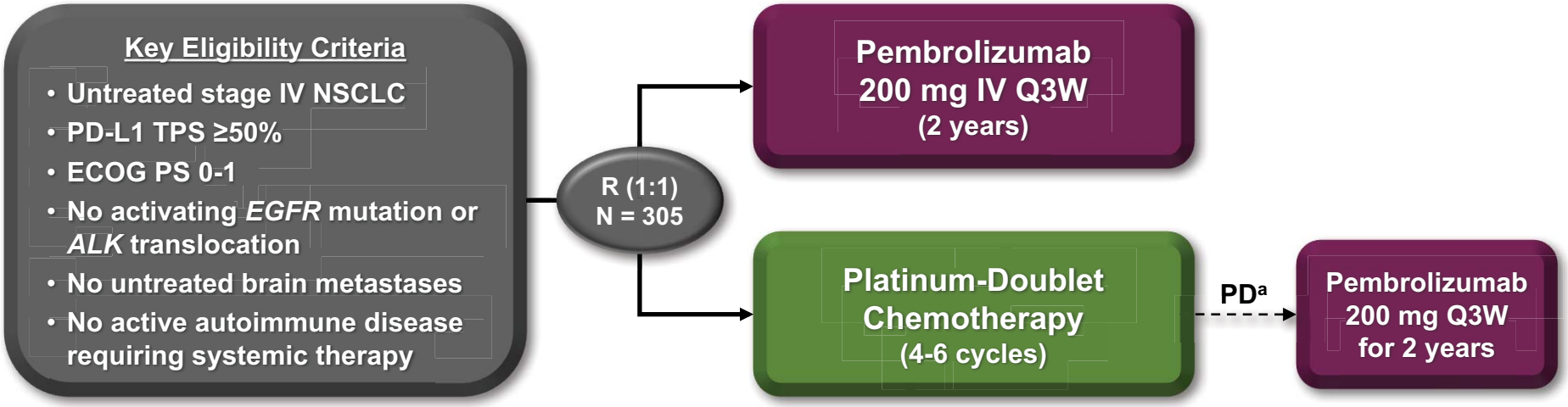
Archival tissue is reasonable to use for PD-L1 testing; fresh biopsy not routinely necessary

Figure 7. ORR for archival and new tumor samples by PD-L1 TPS.



Herbst, ASCO2016

KEYNOTE-024 Study Design (NCT02142738)



Key End Points

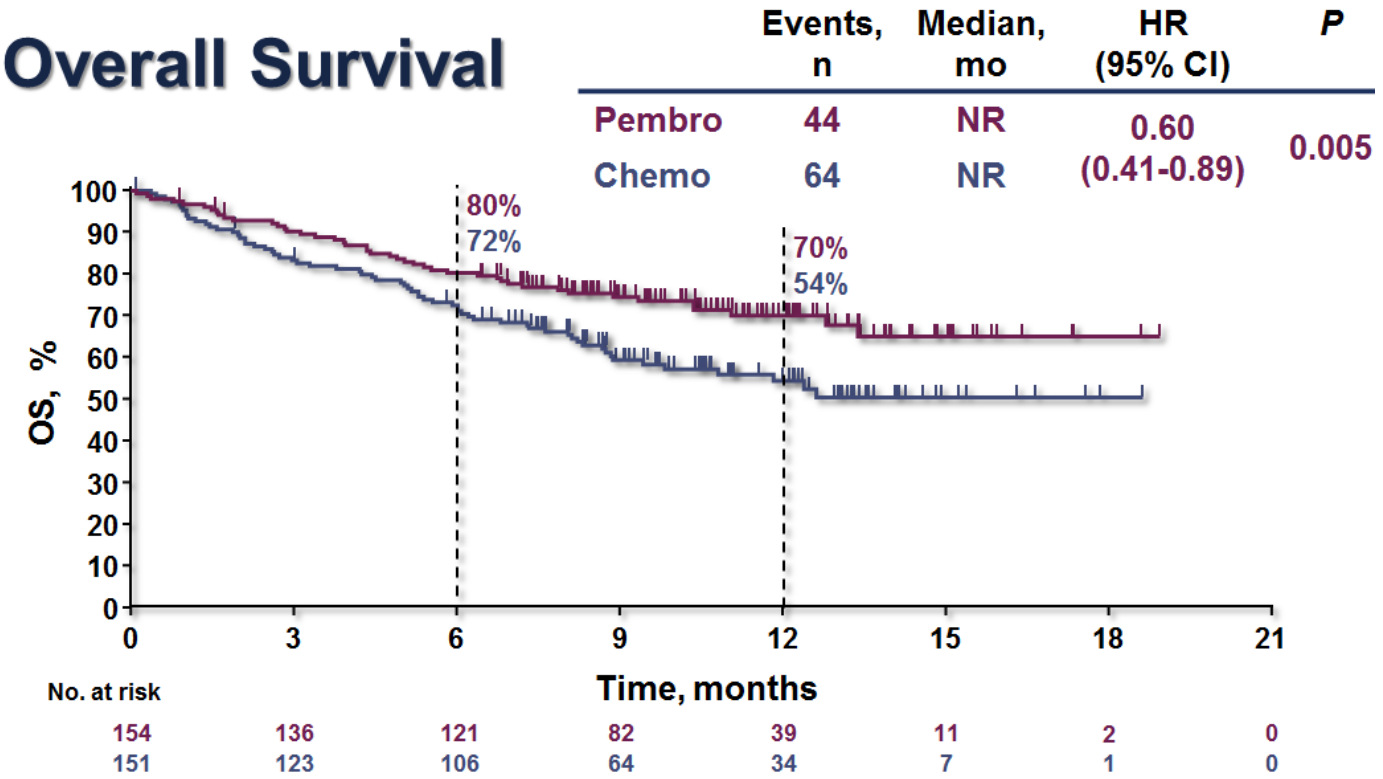
Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

Exploratory: DOR

[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

Survival data



- Clear survival benefit
  - Estimated rate of OS @ 12 months: 70% (Pembro) vs 54% (CT)
  - HR for death: **0.60**
  - cross-over **in 50% of the patients**

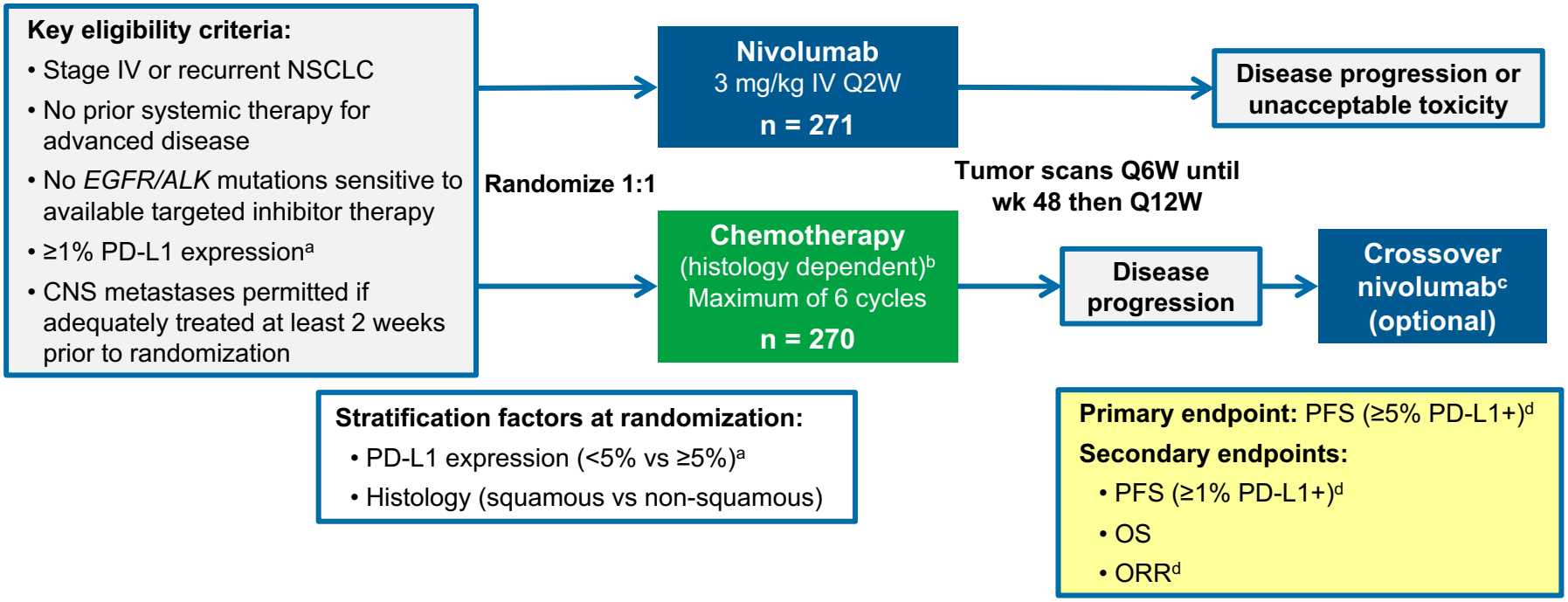
Biomarker Testing for PD-L1 Is Now Clearly Indicated in NSCLC

FDA APPROVAL

Immunotherapy for Front Line NSCLC

October 24, 2016!

Phase 3 CheckMate 026 Study Design: Nivolumab vs Chemotherapy in First-line NSCLC

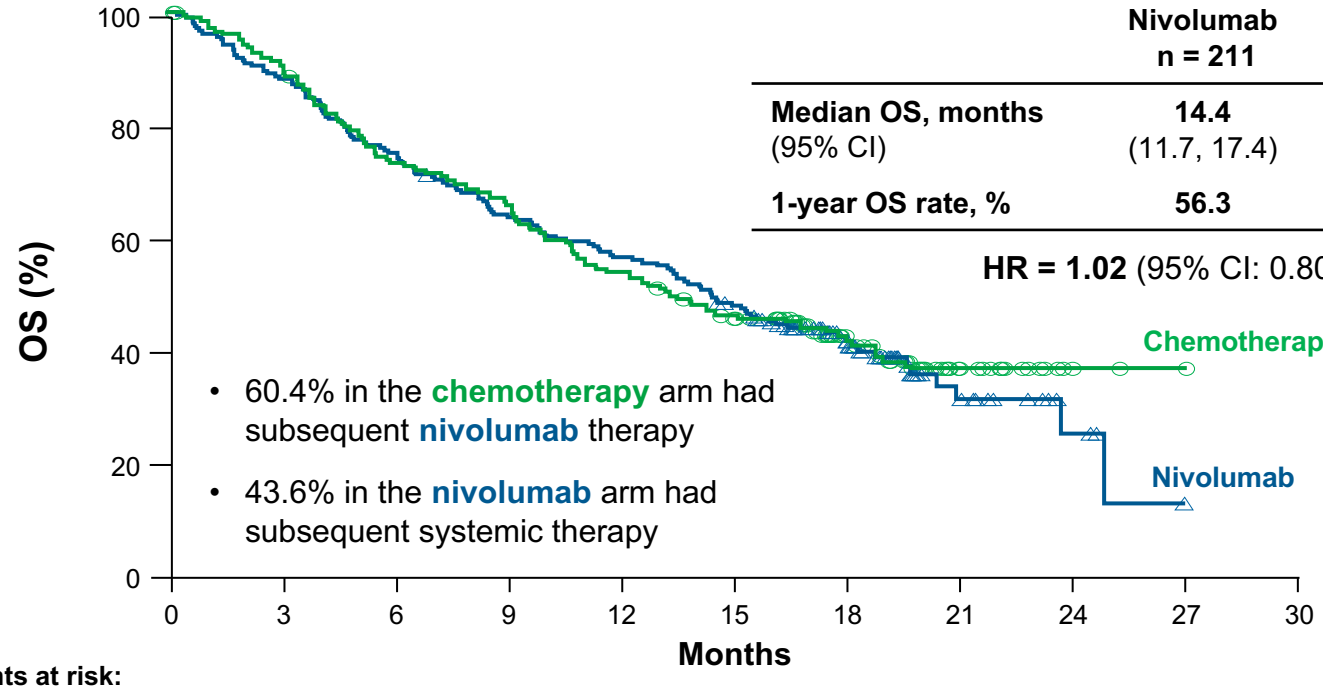


[a]28-8 validated; archival tumor samples obtained ≤6 months before enrollment were permitted; PD-L1 testing was centralized
[b]Squamous: gemcitabine 1250 mg/m^2 + cisplatin 75 mg/m^2; gemcitabine 1000 mg/m^2 + carboplatin AUC 5; paclitaxel 200 mg/m^2 + carboplatin AUC 6; Non-squamous: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2; pemetrexed 500 mg/m^2 + carboplatin AUC 6; option for pemetrexed maintenance therapy
[c]Permitted if crossover eligibility criteria met, including progression confirmed by independent radiology review
[d]Tumor response assessment for PFS and ORR per RECIST v1.1 as determined by independent central review

Socinski M et al. Proc ESMO 2016;Abstract LBA7_PR

OS (≥5% PD-L1+)

CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC



	Nivolumab n = 211	Chemotherapy n = 212
Median OS, months (95% CI)	**14.4** (11.7, 17.4)	**13.2** (10.7, 17.1)
1-year OS rate, %	**56.3**	**53.6**

HR = 1.02 (95% CI: 0.80, 1.30)

No. of patients at risk:											
Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1	0

All randomized patients (≥1% PD-L1+): HR = 1.07 (95% CI: 0.86, 1.33)

Socinski M et al. Proc ESMO 2016;Abstract LBA7_PR

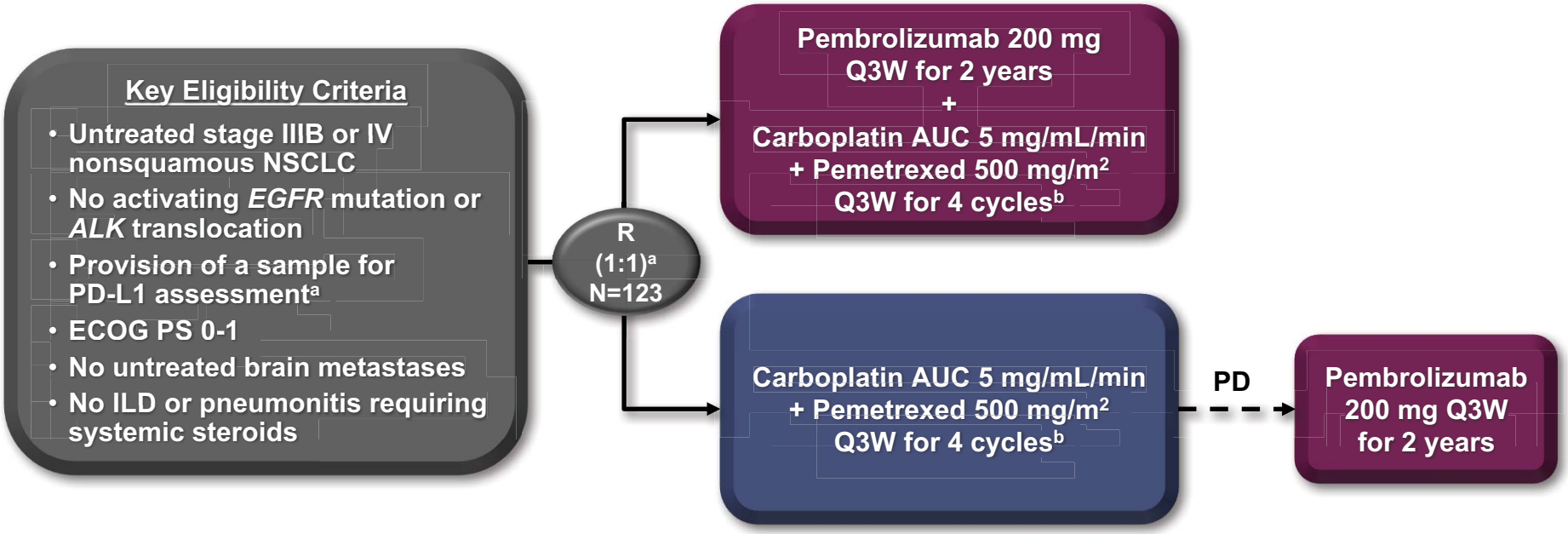
CM 026 vs. KN-024

	KN-024	CM 026
Tumor biopsy	After metastatic diagnosis	Within 6 months
PD-L1 cut off	50% (22C3 clone)	5% (28-8 clone)
Prevalence	30%	50%
Imaging interval	Q 9 weeks	Q 6 weeks for first 48 weeks
Primary endpoint	PFS (RECIST)	PFS (IRRC)
Never smokers (PD-1)	3%	11%
Squamous histology	19%	24%
Time from diagnosis to treatment	?	2 months
Prior radiation	? [1]	37.6 %

[1] Prior radiation therapy of > 30 Gy disallowed within 6 months of first dose of trial treatment

Socinski et al, ESMO 2016
Reck et al, ESMO 2016, NEJM 2016

KEYNOTE-021 Cohort G



End Points

Primary: ORR (RECIST v1.1 per blinded, independent central review)

Key secondary: PFS

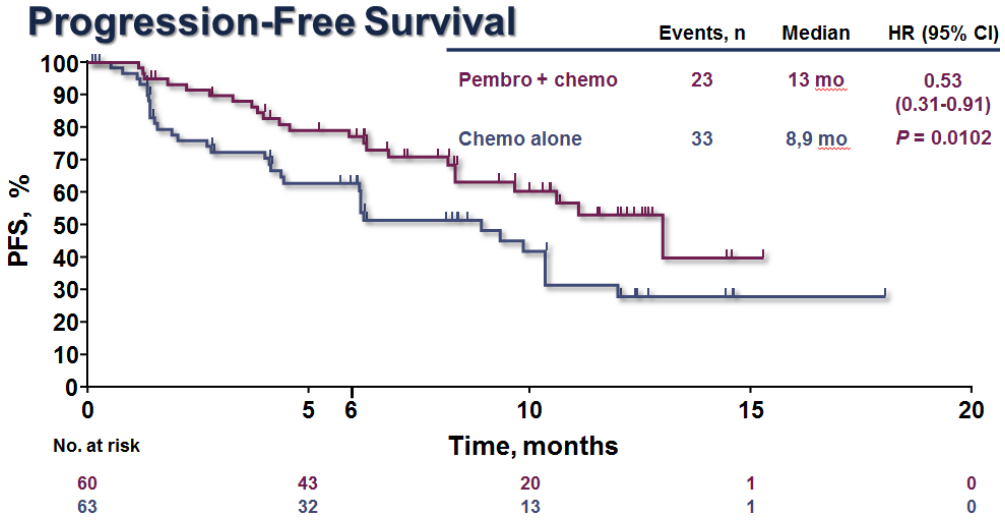
Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

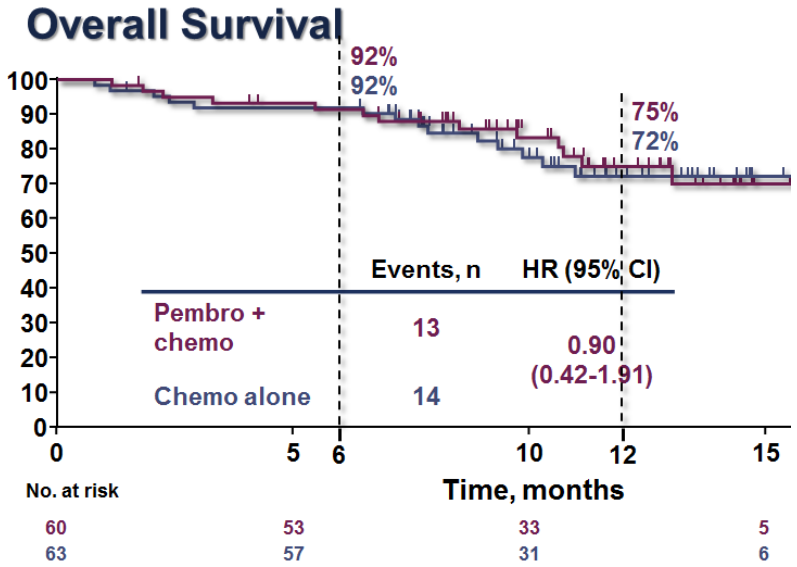
PD=progressive disease.

[a]Randomization was stratified by PD-L1 TPS <1% vs ≥1%.

[b]Indefinite maintenance therapy with pemetrexed 500 mg/m^2 Q3W permitted.

Survival data



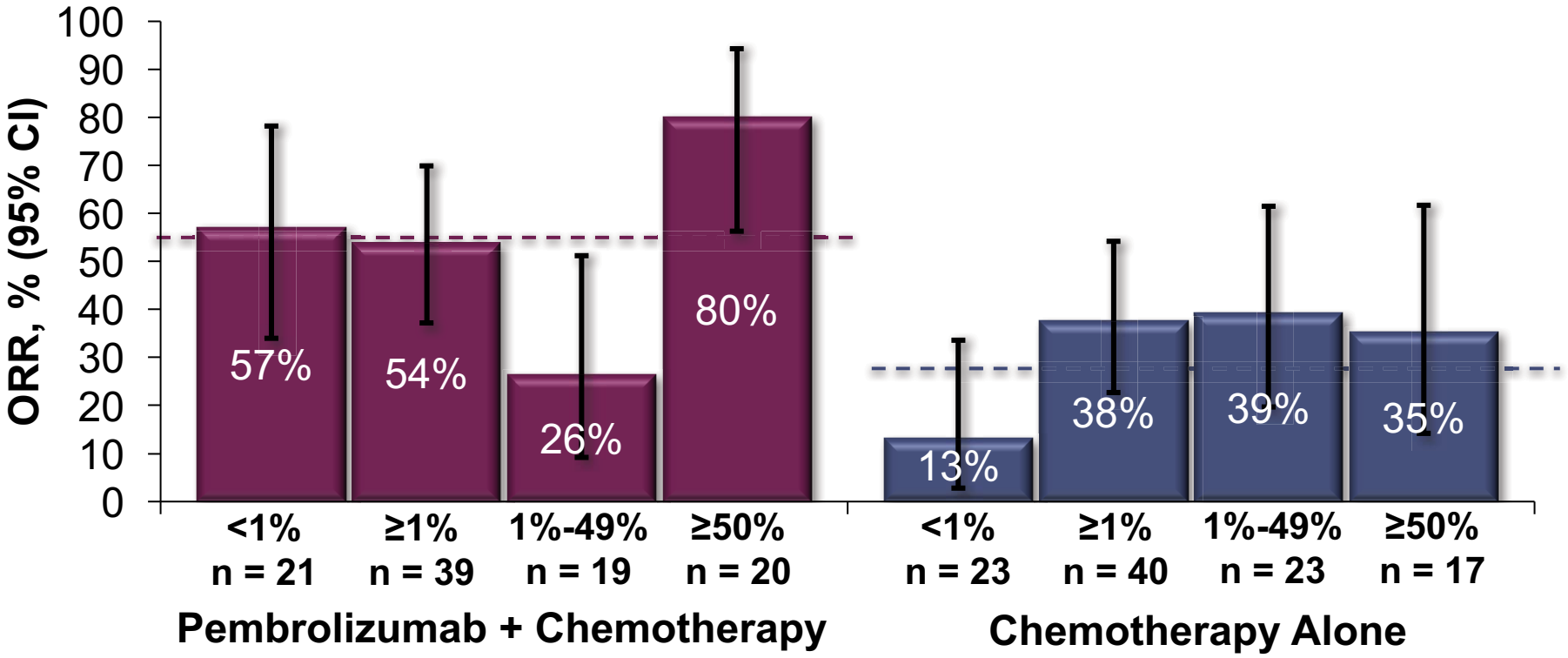


- Clear PFS benefit and no OS advantage
  - **Median PFS improved by 4.1 months**
  - PFS HR is 0.53
  - No difference for OS

Langer et al, Lancet Oncology 2016;17:1497

Objective Response Rate by PD-L1 Status

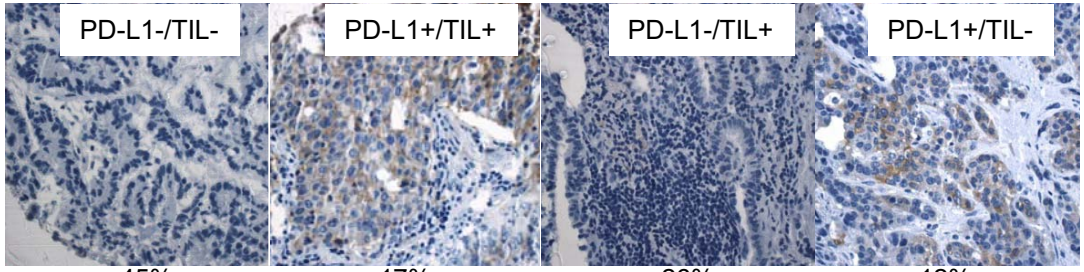
(RECIST v1.1 by Blinded, Independent Central Review)



Horizontal dotted lines represent the ORR in the total population.

Data cut-off: August 8, 2016.

Four Categories of Tumors
Based on Presence of PD-L1 and TILs



45% Type I | 17% Type II | 26% Type III | 12% Type IV

Proposed mechanisms associated with NSCLC resistance to anti-PD-1/B7-H1 therapy

Subgroup		Type	Tumor Distribution	Possible Resistance Mechanism(s)	Analysis
B7-H1	TIL				
-	-	I	45%	Poor priming of general T cell responses	Peripheral CD4+ and CD8+ T cell responses to autologous tumor cells
				Lack of inflammatory cell recruitment	Chemokine expression in biopsy or FFPE samples
+	+	II	17%	Incomplete PD-1/B7-H1 pathway blockade and activation of alternate immune suppressive pathways	CD80 expression on TILs, expression of alternate suppressive pathways in TME
-	+	III	26%	Alternate immune suppressive pathways	Expression of select molecules in pathways with roles in evasion of NSCLC immunity
+	-	IV	12%	Intrinsic induction of B7-H1 by oncogenes	Expression of molecules triggering aberrant signaling events

Velcheti (Rimm) et al. *Lab Invest*. 2014 Jan;94(1):107-16.; Chen L. Unpublished

450 samples analyzed

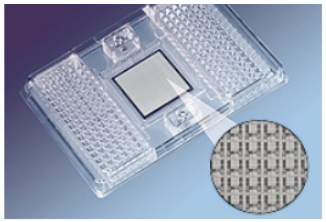
Understanding Anti-Cancer Immunity: Focus on Biomarkers

The Phase Ia trial is providing key information on the safety, tolerability and activity of MPDL3280A

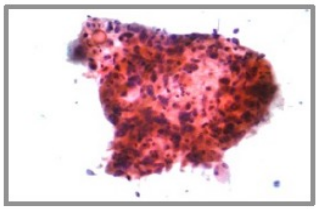
However, understanding the impact on immune biology is critical to determine who is expected to benefit from MPDL3280A

This information will help to guide future development of MPDL3280A, as well as other cancer immunotherapies, as monotherapy or combination therapy

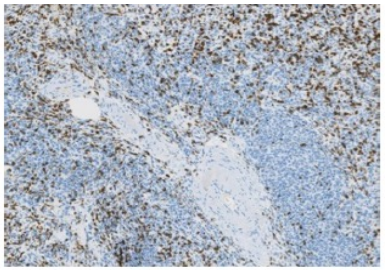
Gene Expression - iChip



High throughput and comprehensive evaluation of tumor and immune genes

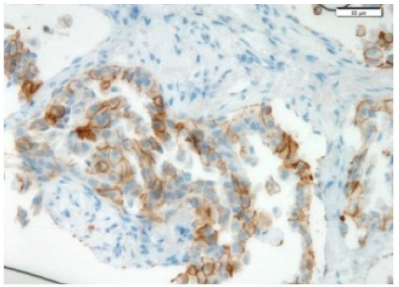


CD8 IHC



Spatial assessment of CD8 in response to treatment

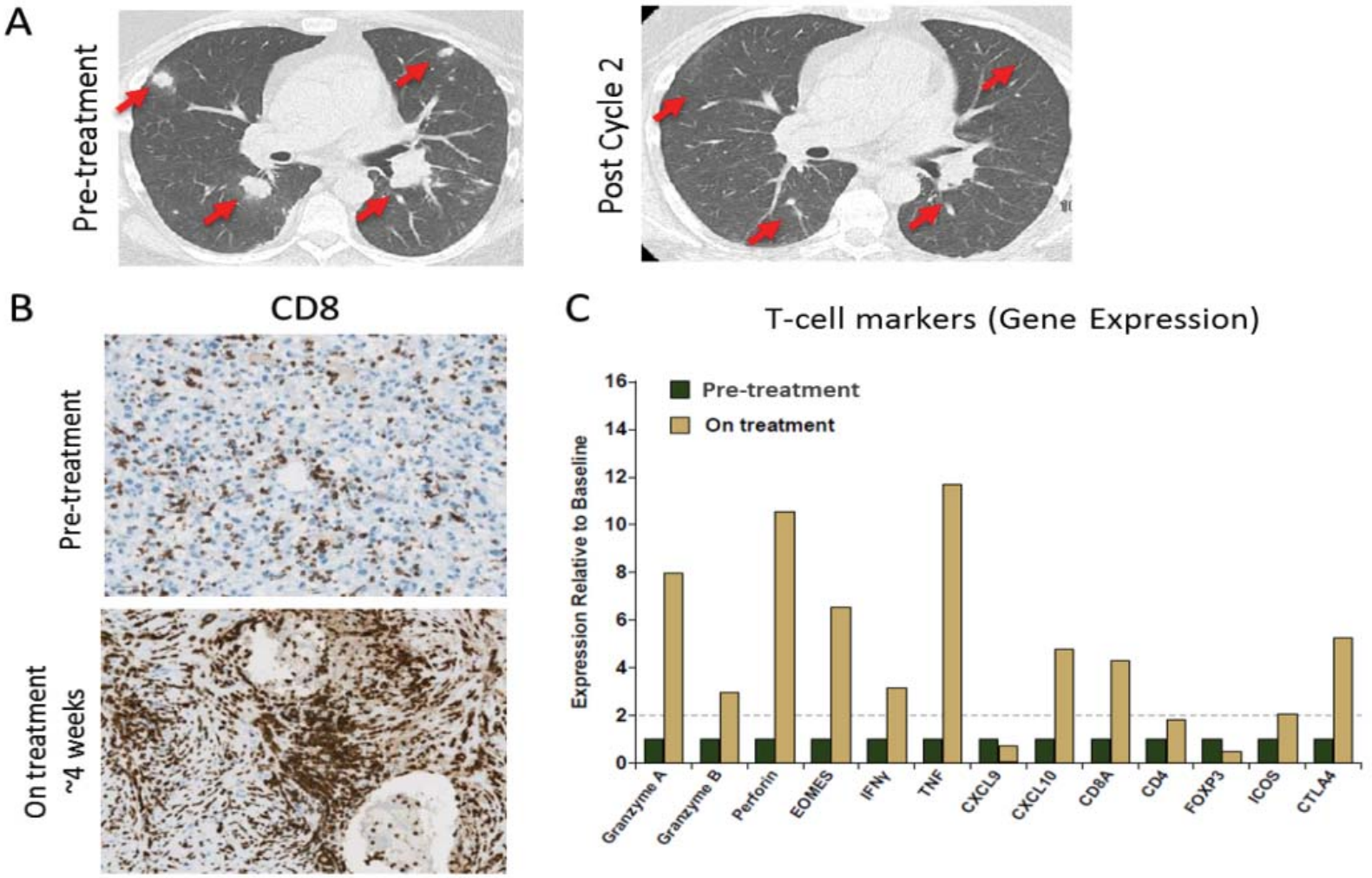
Target expression



Dx grade assays for assessment of target expression

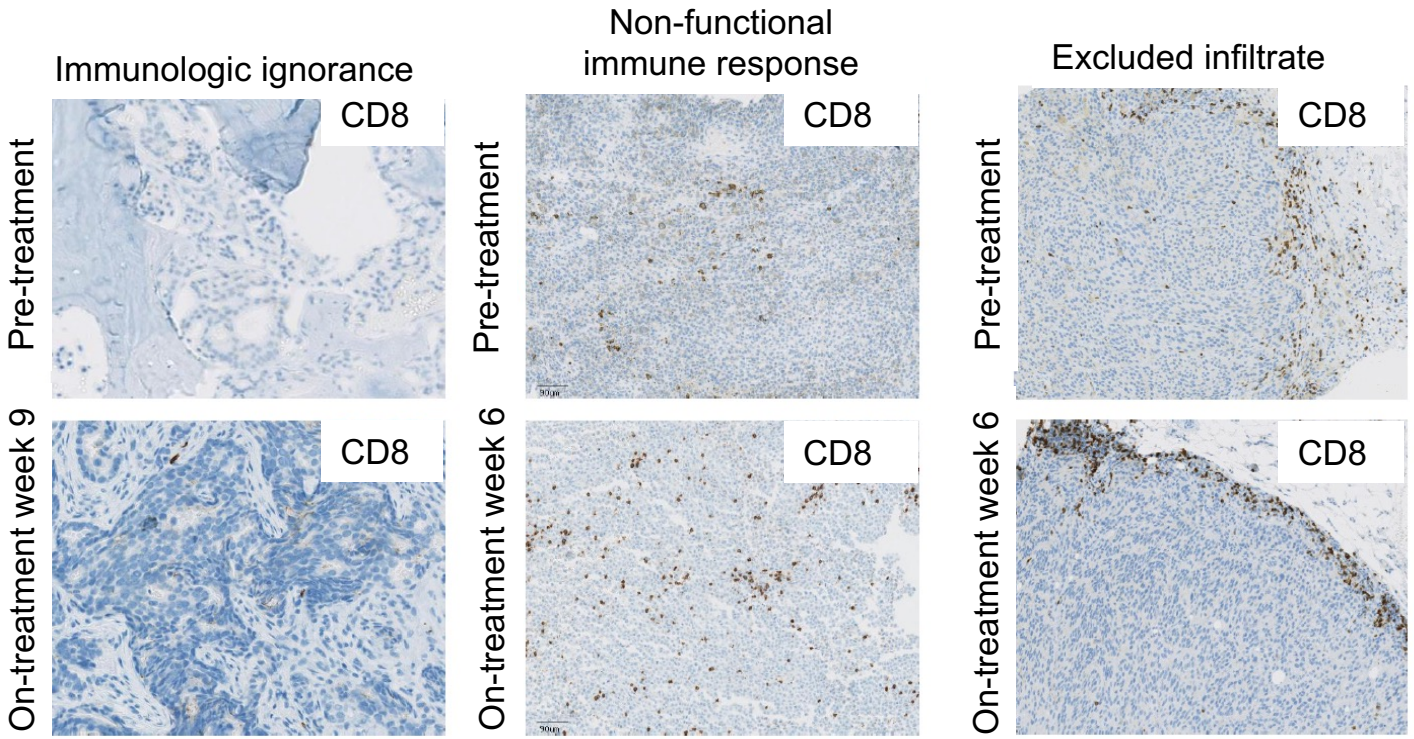
Biomarker Analyses for PD-L1 Treatment

Mechanistic studies using pre and post biopsies



Herbst RS et al. *Nature* 2014;515: 563-567;

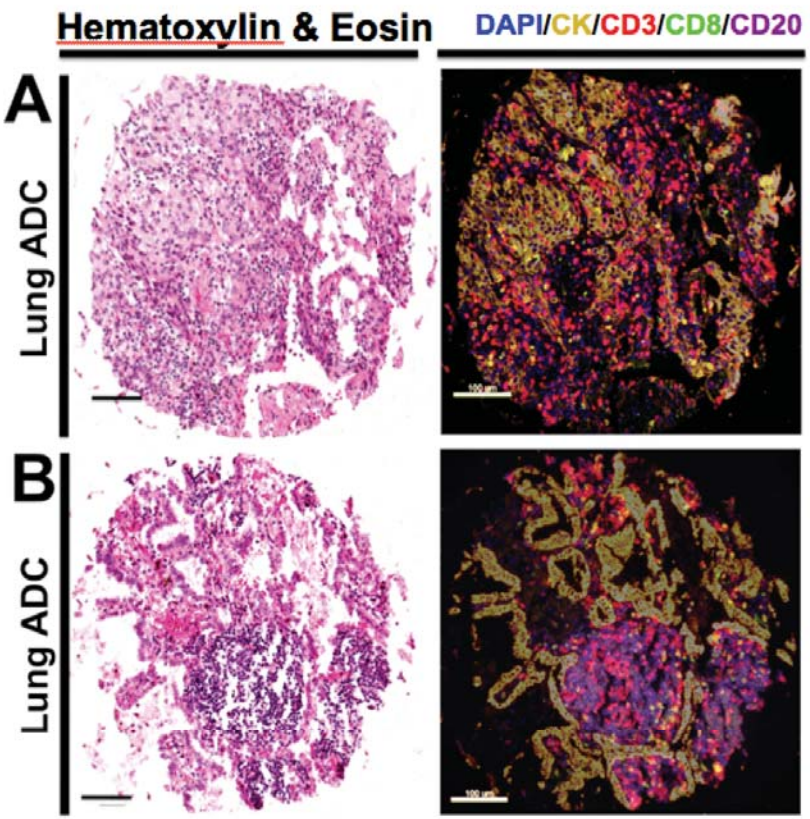
Biomarker Analyses
Defining the Profile of Non-responders

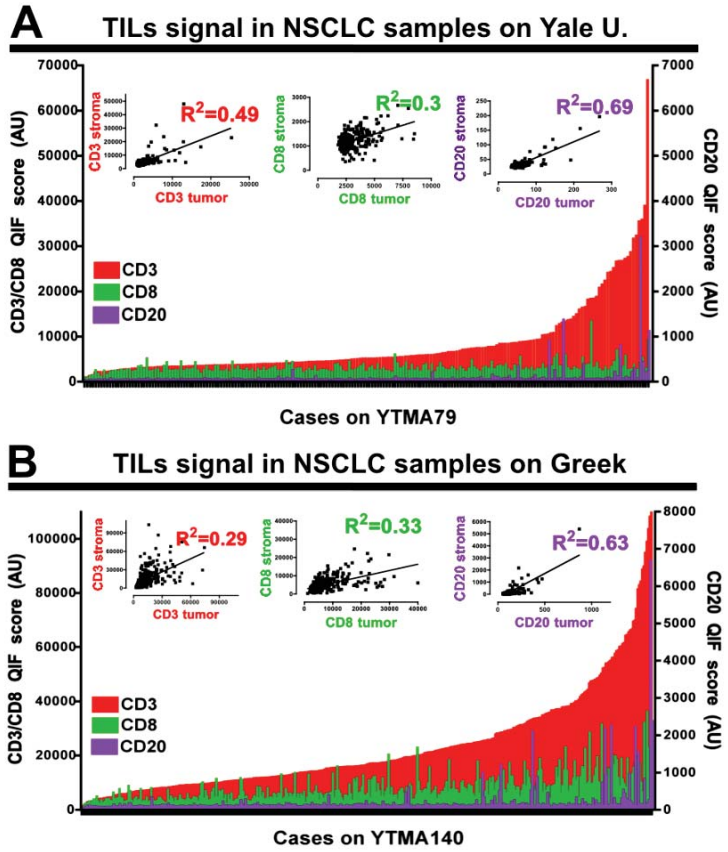


- Three distinct patterns of nonresponse were observed
- Most patients who progressed failed to show up-regulation of PD-L1 or evidence of activated T cells
- These results provide evidence for the “inflamed tumor” hypothesis

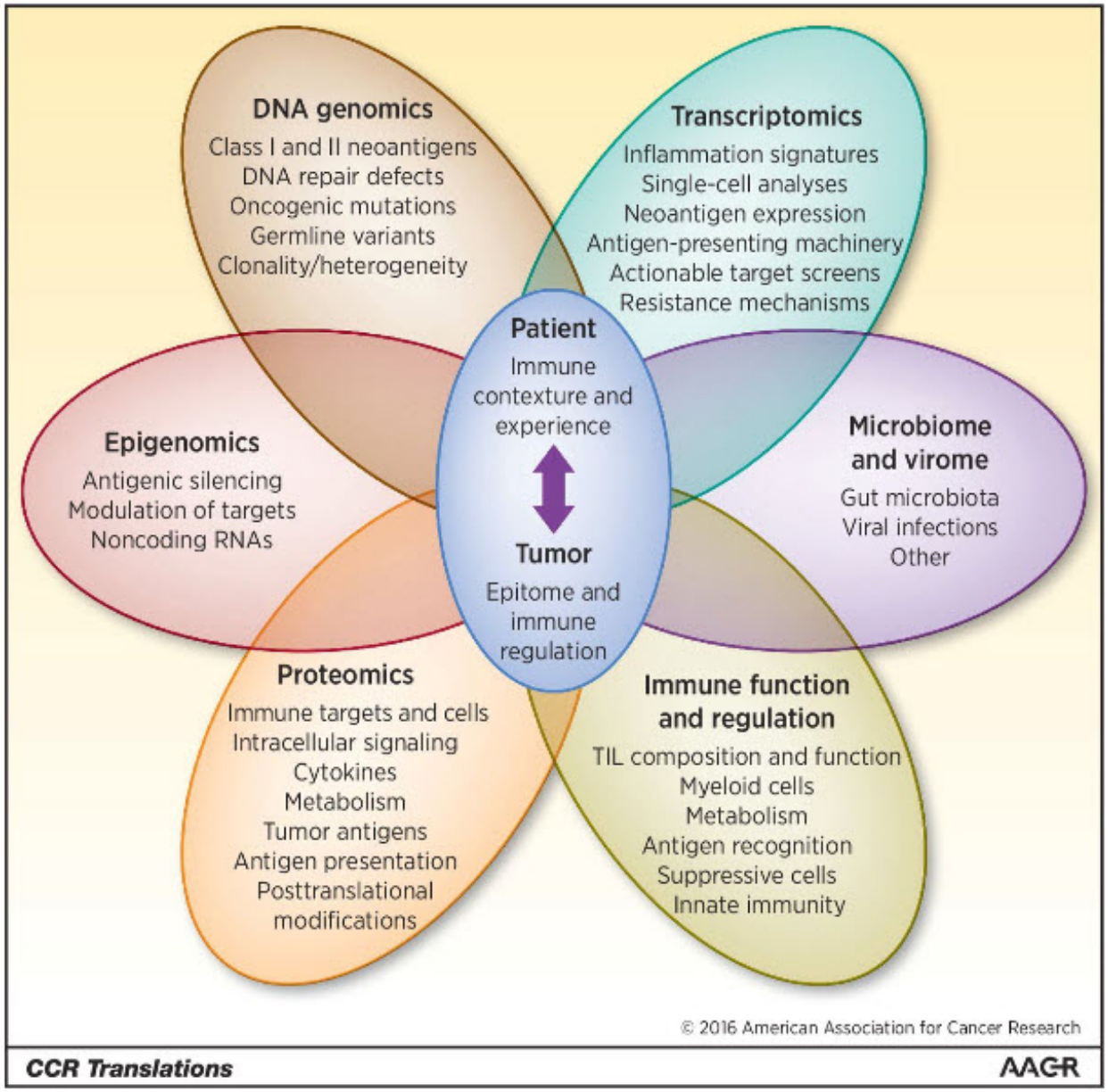
Herbst RS et al. *Nature* 2014;515: 563-567;

TIL subtype quantification in FFPE defines the "Inflamed" phenotype in NSCLC





Schalper et al, JNCI 2015;107(3)



Schalper and Herbst CCR 2016

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Roy S. Herbst, MD, PhD

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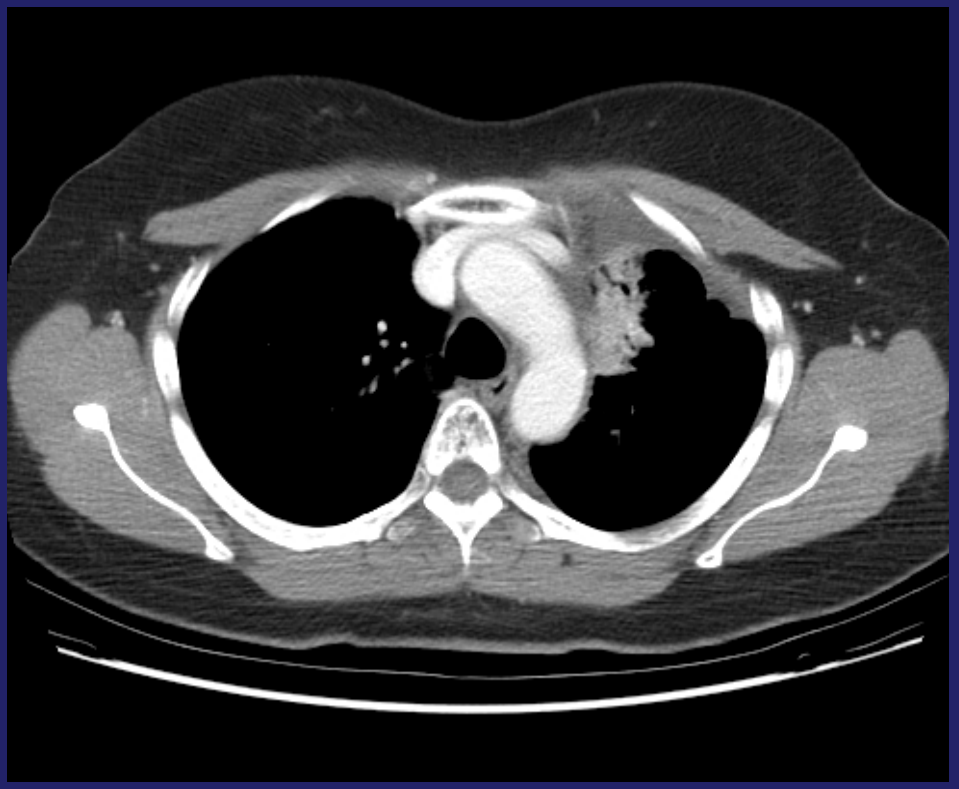
Case 2

- 69 year old man with chest discomfort & increasing SOB, weight loss and back pain
- 50 pack-year smoker
- CT chest: LUL primary (shown), mediastinal LNs, bone mets
- Bronchoscopy with EBUS of subcarinal node: positive for squamous lung cancer
- PD-L1 = 10%
- Zubrod PS is a 1.



Case 2

The patient enrolls into the clinical trial and is randomized to the anti-PD-L1 agent.

- **His restaging CT scan 6 weeks later shows some increase in size the indicator lesions (>20% RECIST) (no new lesions)**
- **He continues to have pain & has lost further weight.**
- **PS now=2 (PS was 1 at baseline)**