

# Immunotherapy in Non-Small Cell Lung Cancer

Renato G. Martins

Stephen H. Petersdorf Endowed Chair in Cancer Care  
Associate Medical Director, Solid Tumor Adult Oncology,  
Seattle Cancer Care Alliance  
Professor, University of Washington



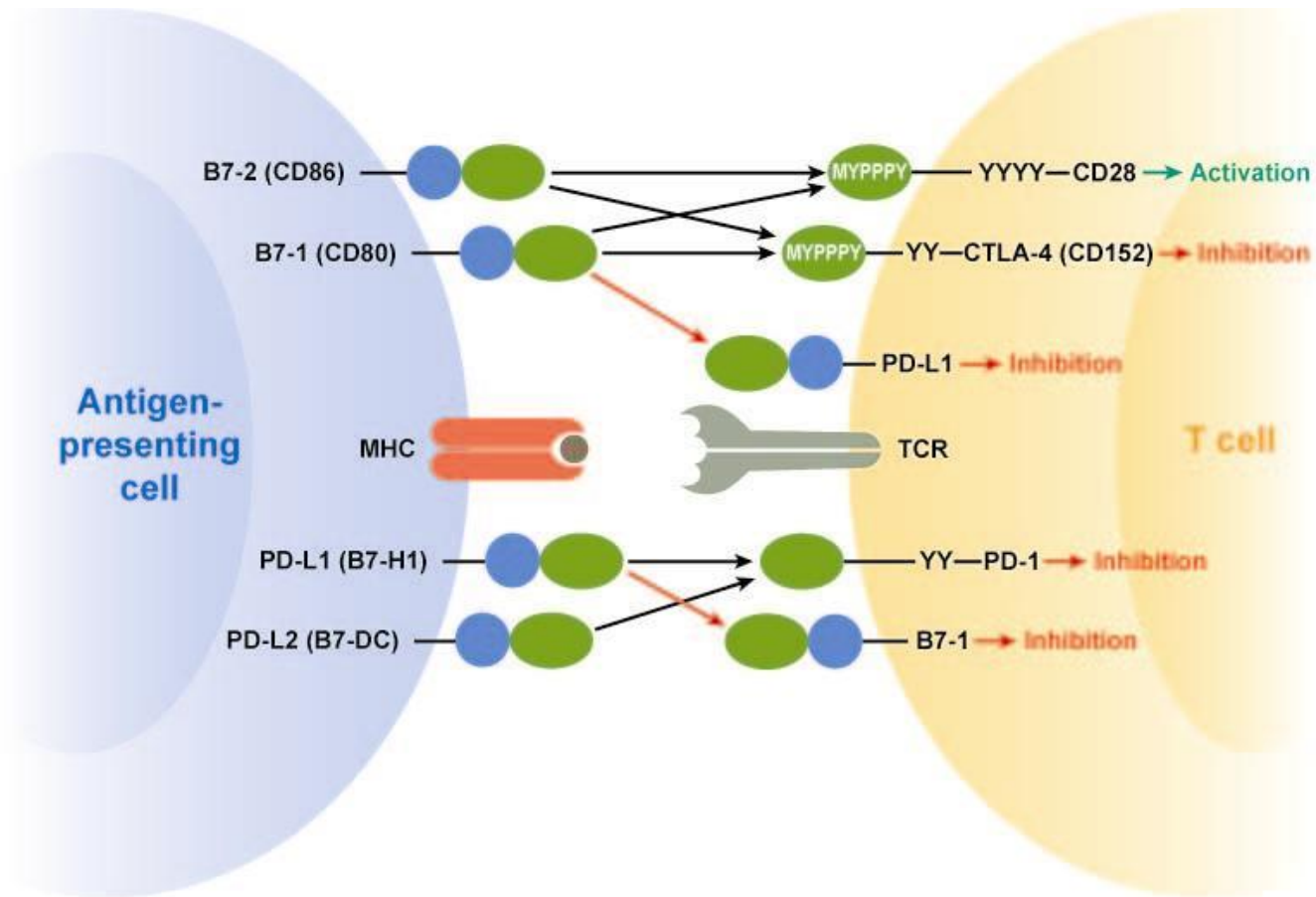
# Conflict of Interests

- None

\*I will discuss non-FDA approved treatments

# NSCLC in 2015

- Five groups of patient have a much better prognosis of advanced NSCLC:
  1. Activating EGFR mutation
  2. ALK translocation
  3. ROS-1 translocation
  4. Prolonged disease control on maintenance pemetrexed (almost  $\frac{1}{4}$  patients who start maintenance pemetrexed will get more than 10 cycles)
  5. Prolonged response to immunotherapy



**AR** Keir ME, et al. 2008.  
Annu. Rev. Immunol. 26:677–704

Original Article

# **Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer**

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthi, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.

N Engl J Med  
Volume 366(26):2455-2465  
June 28, 2012



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**Table 1. Adverse Events of Special Interest in 207 Patients Receiving Anti-PD-L1 Antibody.\***

Event	Anti-PD-L1, 0.3 mg/kg (N=3)		Anti-PD-L1, 1 mg/kg (N=37)		Anti-PD-L1, 3 mg/kg (N=42)		Anti-PD-L1, 10 mg/kg (N=125)		Anti-PD-L1, Total (N=207)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	<i>number of patients (percent)</i>									
Any adverse event of special interest†	1 (33)	0	18 (49)	2 (5)	14 (33)	2 (5)	48 (38)	6 (5)	81 (39)	10 (5)
Skin or subcutaneous disorder										
Any rash	0	0	5 (14)	0	1 (2)	0	8 (6)	0	14 (7)	0
Pruritus	0	0	6 (16)	0	3 (7)	0	3 (2)	0	12 (6)	0
Vitiligo	0	0	3 (8)	0	1 (2)	0	1 (1)	0	5 (2)	0
Pruritic rash	0	0	1 (3)	0	1 (2)	0	2 (2)	0	4 (2)	0
Macular rash	0	0	2 (5)	0	1 (2)	0	0	0	3 (1)	0
Erythema	0	0	2 (5)	0	0	0	0	0	2 (1)	0
Erythematous rash	0	0	0	0	1 (2)	0	1 (1)	0	2 (1)	0
Gastrointestinal disorder										
Diarrhea	1 (33)	0	4 (11)	0	6 (14)	0	8 (6)	0	19 (9)	0
Procedural complication										
Infusion-related reaction	0	0	0	0	2 (5)	0	19 (15)	1 (1)	21 (10)	1 (<1)
Endocrine disorder										
Hypothyroidism	0	0	0	0	1 (2)	0	5 (4)	0	6 (3)	0
Adrenal insufficiency	0	0	0	0	1 (2)	1 (2)	1 (1)	0	2 (1)	1 (<1)
Autoimmune thyroiditis	0	0	2 (5)	0	0	0	0	0	2 (1)	0
Eye disorder										
Dry eye	0	0	0	0	2 (5)	0	0	0	2 (1)	0
Immune-system disorder										
Hypersensitivity	0	0	1 (3)	0	0	0	2 (2)	0	3 (1)	0
Laboratory investigation										
Increased alanine aminotransferase	0	0	1 (3)	0	0	0	1 (1)	0	2 (1)	0

\* Listed events were reported in at least 1% of the patients. The following events that were categorized as adverse events of special interest occurred in one patient each: sarcoidosis, diabetes mellitus, and myasthenia gravis (in patients receiving the 10-mg dose) and endophthalmitis (in patients receiving the 3-mg dose).

† The numbers reported within a column may not add up to the total number reported because patients who had more than one adverse event were counted for each event but were counted only once for "any adverse events of special interest."

# Toxicity: Case

- 70 yo male with adenocarcinoma of lung with L858R diagnosed 8/210. No history of diabetes
- Prior therapies : dacomitinib; carboplatin+pemetrexed→pem maintenance; weekly paclitaxel
- Started on PD-L1 antibody on 10/2013
- 15 weeks latter presented with glucose of 512mg/dl
- Started on metformin and 10 days latter presented with diabetic ketoacidosis

**Table 1—Patients' characteristics at the time of presentation with DKA**

	Patient 1	Patient 2
BMI, kg/m <sup>2</sup>	23.2	15.1
Plasma glucose, mmol/L	22.83	41.77
Anion gap (3–11)	18	22
Bicarbonate (22–32 mEq/L)	15	7
Arterial pH	Unavailable	7.09
A1C [4–6% (20–42 mmol/mol)]	9.8 (84)	9.4 (79)
Thyroid-stimulating hormone (0.4–5.0 µIU/mL)	0.944	34.19
Total triiodothyronine (73–178 ng/dL)	126	26
Free triiodothyronine (2.3–3.9 pg/mL)	—	1.7
Total thyroxine (4.8–10.8 µg/dL)	13.2	—
Free thyroxine (0.6–1.2 ng/dL)	—	0.3
Thyroid peroxidase antibody (0.0–8.9 IU/mL)	—	83.3
C-peptide (1.0–7.1 ng/mL)	0.3	<0.1
GAD65 antibody	0 (≤0.02 nmol/L)*	465 (<142 WHO units)
Insulin autoantibody	0 (0.0–0.02 nmol/L)*	0.02 (<0.05 index)
IA2 autoantibody	—	11 (<21 WHO units)
ZnT8 autoantibody	—	0.00 (<0.033 index)
IA2β/phogrin	—	0.001 (<0.0015 index)
HLA+	—	DR3-DQ2/DR4-DQ8
Islet-specific T cell <sup>^</sup>	—	7 positive protein bands

Normal ranges given in parentheses where appropriate. WHO, World Health Organization.

\*Measured only at the clinical laboratory. +Genotyping at the HLA class II locus (IDDM1) was performed using the direct sequencing of separately amplified exons 2 of DRB1, DQA1, and DQB1. <sup>^</sup>Cellular immunoblotting was performed on blood mononuclear cells to test for the presence of islet-specific T cells, as described previously (5). Control subjects without diabetes respond to 0–3 blots, whereas patients with autoimmune diabetes respond to 4–18 blots (5).



**Table 2. Clinical Activity of Anti-PD-L1 Antibody in the Efficacy Population.\***

Tumor Type and Dose	No. of Patients	Objective Response†		Duration of Response‡	Stable Disease ≥24 Weeks		Rate of Progression-free Survival at 24 Weeks§
		no. of patients	% (95% CI)		no. of patients	% (95% CI)	
Melanoma							
0.3 mg/kg	1	0	0 (0–98)	NA	0	0 (0–98)	NA
1 mg/kg	18	1	6 (0–27)	6.9	6	33 (13–59)	39 (16–61)
3 mg/kg	17	5¶	29 (10–56)	23.5+, 22.9+, 16.2+, 4.1+, 3.5	3	18 (4–43)	47 (21–72)
10 mg/kg	16	3	19 (4–46)	20.8+, 16.6, 2.8	5	31 (11–59)	44 (19–68)
All doses	52	9	17 (8–30)		14	27 (16–41)	42 (28–56)
Non–small-cell lung cancer							
All patients, 1 mg/kg	11	0	0 (0–29)	NA	0	0 (0–29)	NA
All patients, 3 mg/kg	13	1	8 (0–36)	2.3+	1	8 (0–36)	34 (7–60)
Squamous subtype	4	0	0 (0–60)	NA	1	25 (0–81)	50 (1–99)
Nonsquamous subtype	9	1	11 (0–48)	ND	0	0 (0–34)	25 (0–55)
All patients, 10 mg/kg	25	4	16 (5–36)	16.6+, 12.6+, 9.8, 3.5	5	20 (7–41)	46 (25–67)
Squamous subtype	8	1	13 (0–53)	ND	2	25 (3–65)	47 (10–83)
Nonsquamous subtype	17	3	18 (4–43)	ND	3	18 (4–43)	46 (20–72)
All patients, all doses	49	5	10 (3–22)		6	12 (5–25)	31 (17–45)
Squamous subtype	13	1	8 (0–36)	ND	3	23 (5–54)	43 (15–71)
Nonsquamous subtype	36	4	11 (3–26)	ND	3	8 (2–23)	26 (10–42)
Ovarian cancer	1	0	0 (0–98)	NA	0	0 (0–98)	NA
3 mg/kg	1	0	0 (0–98)	NA	0	0 (0–98)	NA
10 mg/kg	16	1	6 (0–30)	1.3+	3	19 (4–46)	25 (4–46)
All doses	17	1	6 (0–29)		3	18 (4–43)	22 (2–43)
Renal-cell cancer, 10 mg/kg	17	2	12 (2–36)	17, 4	7	41 (18–67)	53 (29–77)

\* The efficacy population included 160 patients in whom a response could be evaluated and who initiated treatment by August 1, 2011. These patients had measurable disease at a baseline tumor assessment and at least one of the following: an assessment of tumor burden during the study, clinical progression, or death. NA denotes not applicable, and ND not determined.

† Objective response rates (including both complete response and partial response) are based on confirmed responses only, with 95% confidence intervals calculated with the use of the Clopper–Pearson method.

‡ The duration of response is the time from the first response to the time of documented disease progression, death, censoring of data (denoted by a plus sign), or last tumor assessment.

§ The rate of progression-free survival was the proportion of patients who did not have disease progression and were alive at 24 weeks, as calculated by the Kaplan–Meier method. The Greenwood method was used to calculate confidence intervals.

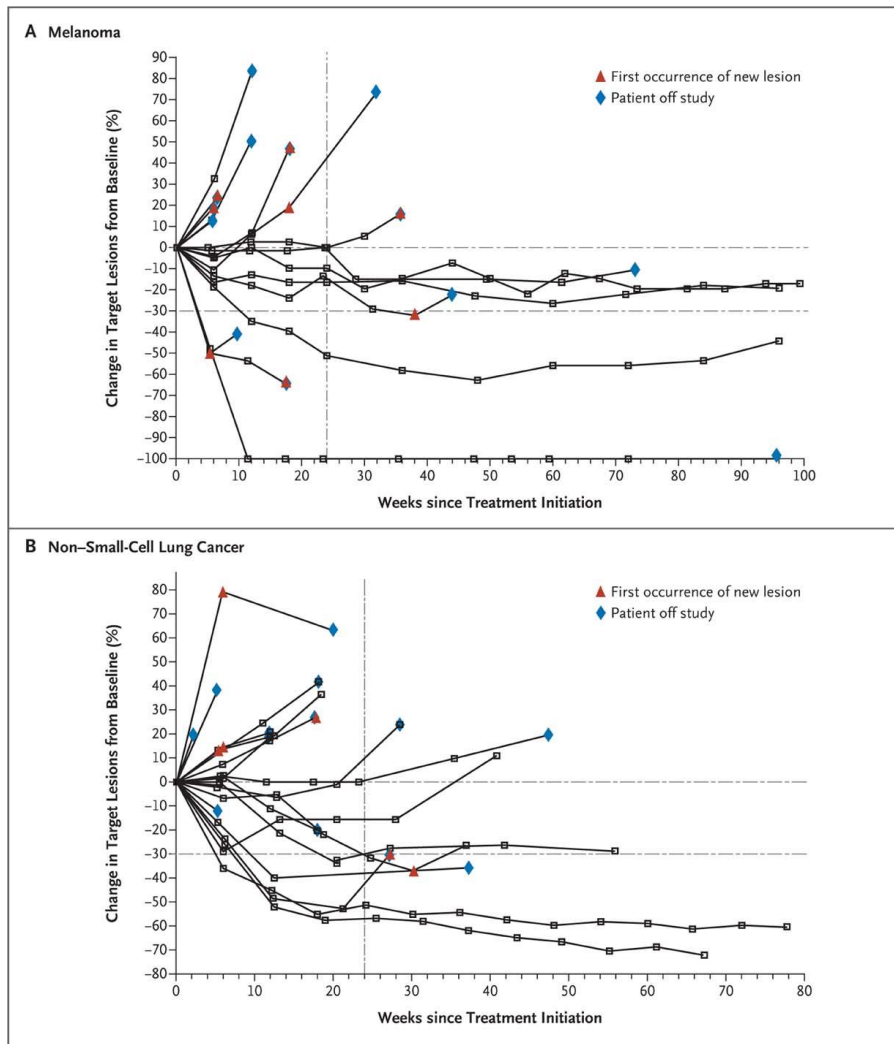
¶ Two of these patients had a complete response.

|| One of these patients had a complete response.

**Brahmer JR et al. N Engl J Med 2012;366:2455-2465**



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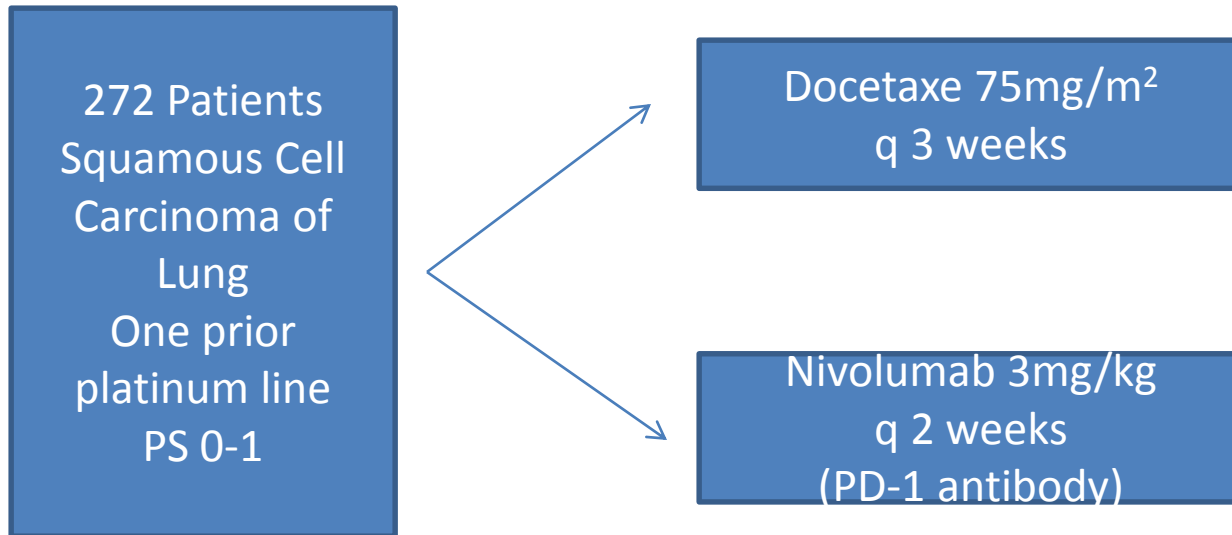
**Brahmer JR et al. N Engl J Med 2012;366:2455-2465**

# Safety

## CheckMate-063

- Phase II single arm trial
- At least 2 lines of prior therapy including platinum based
- 117 patients included
- RR:15% with 59% of those lasting for 6 months or longer
- Serious adverse events: 59%
- Most common SAEs: dyspnea; pneumonia; COPD exacerbation; pneumonitis; hypercalcemia; pleural effusion; hemoptysis; and pain
- Treatment was discontinued in 27% of patient because of adverse events

# CheckMate-017



PD-L1 status not used for inclusion  
Primary endpoint: Overall Survival

# Results

- Former/current smoker: 92%
- No CNS metastases: 94%
- ORR: 20% (N) and 9% (D)
- Median follow-up: 11 months
- Median duration of response of nivolumab: not reached
- PFS at 1 year: 21% (N) and 6% (D)

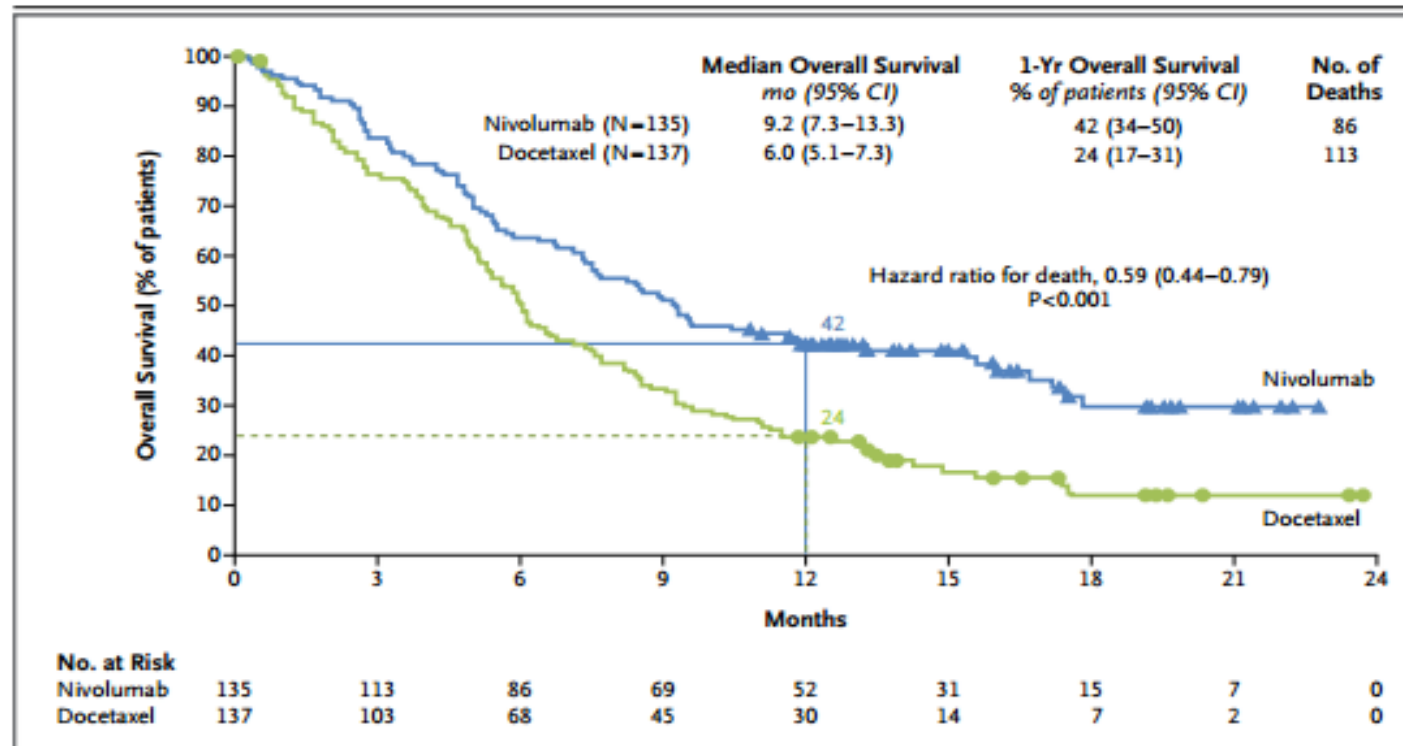
# Safety

**Table 3. Treatment-Related Adverse Events Reported in at Least 5% of Patients.\***

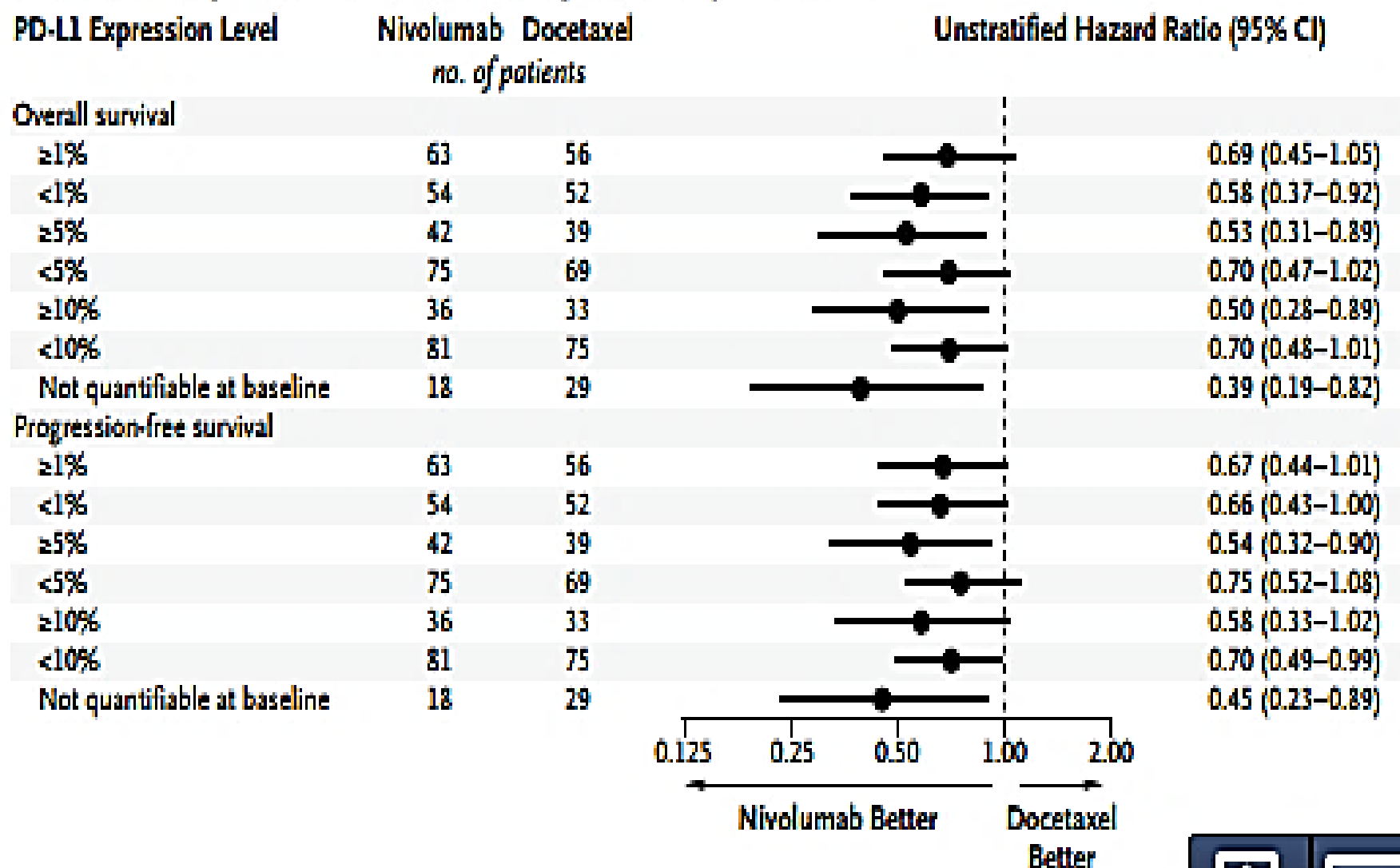
Event	Nivolumab (N = 131)		Docetaxel (N = 129)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	<i>number of patients with an event (percent)</i>			
Any event	76 (58)	9 (7)	111 (86)	71 (55)
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	0	0	0
Rash	5 (4)	0	8 (6)	2 (2)
Mucosal inflammation	3 (2)	0	12 (9)	0
Myalgia	2 (2)	0	13 (10)	0
Anemia	2 (2)	0	28 (22)	4 (3)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)
Febrile neutropenia	0	0	14 (11)	13 (10)
Alopecia	0	0	29 (22)	1 (1)

# Results

- Median survival improvement: 3.2 months (9.2 months vs 6 months)

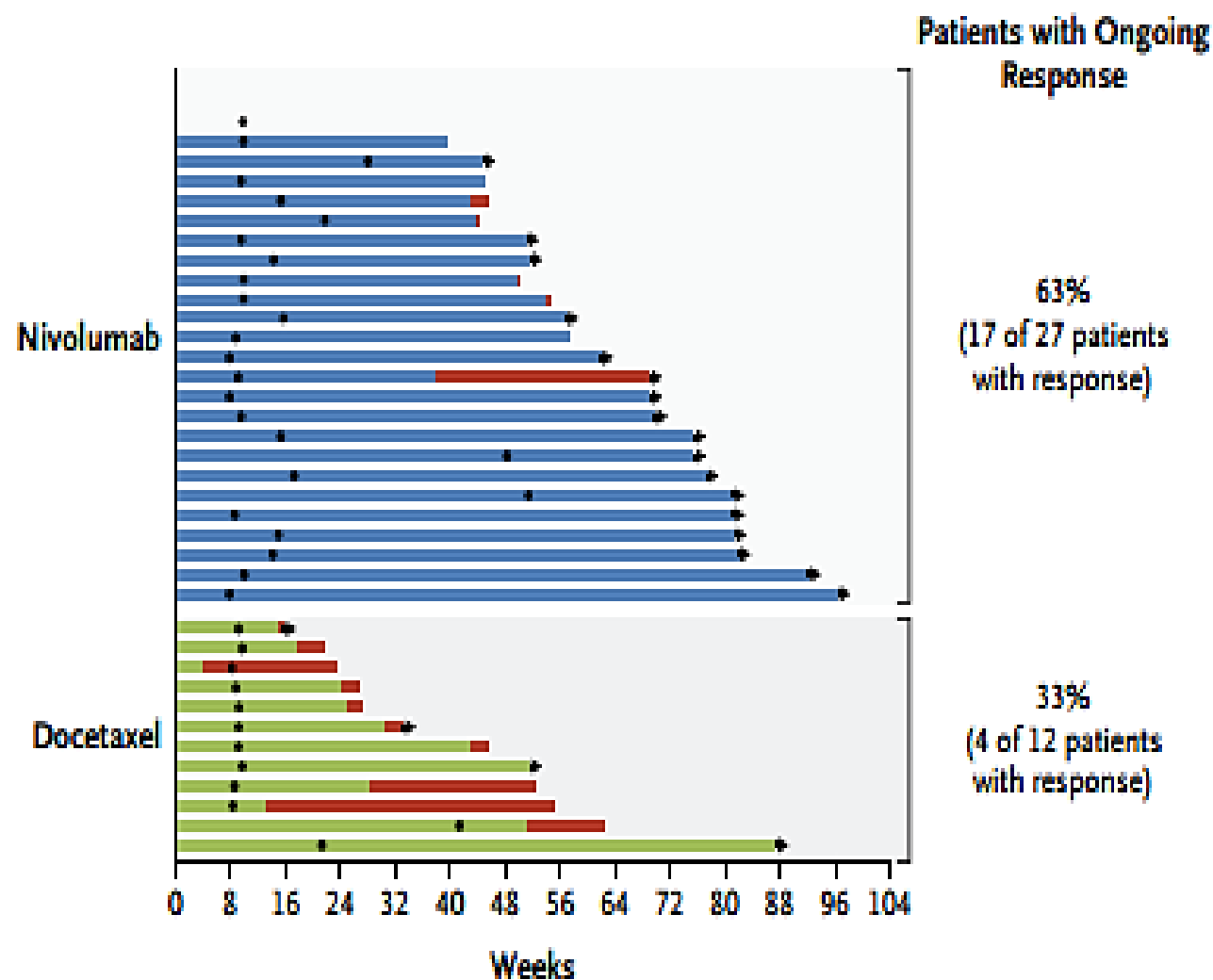


### C Overall and Progression-free Survival According to PD-L1 Expression Level





## A Duration of Response



# CheckMate 057

- Randomized phase III of nivolumab vs docetaxel in previously treated advanced “non-squamous” NSCLC
- One prior platinum doublet (maintenance allowed)
- No PD-L1 expression required but tissue submission was a requirement
- Nivolumab 3mg/kg Q2weeks vs docetaxel 75mg/m<sup>2</sup> Q3weeks
- Primary endpoint: Overall survival

# Results

- Interim analysis with 93% of the events of the final analysis declared the superiority of nivolumab
- PD-L1 expression:

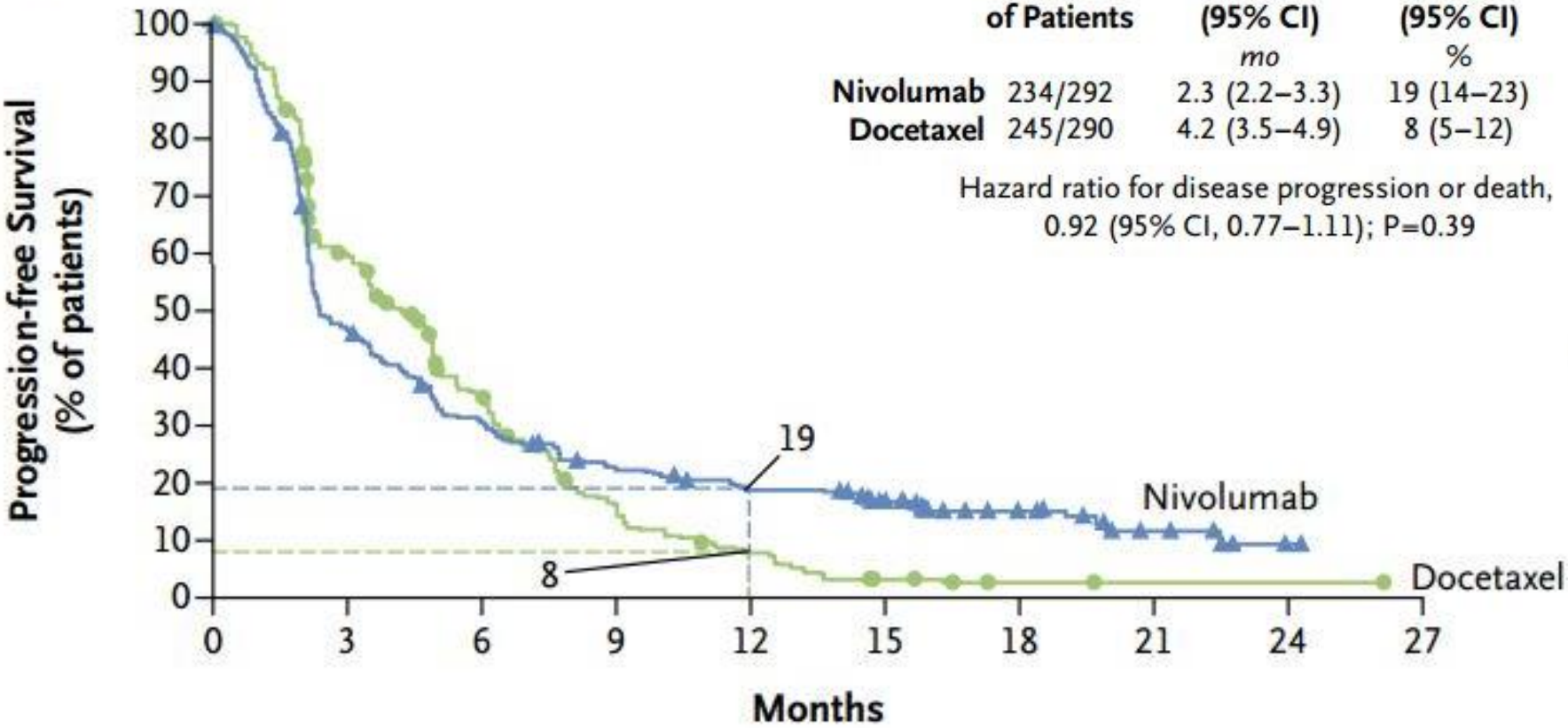
	Nivolumab	Docetaxel
≥1%	53%	55%
≥5%	41%	38%
≥10%	37%	35%

- 22% did not have enough tissue for evaluation

# Results

- Median survival:  
12.2 months Nivolumab  
9.4 months Docetaxel  $p=0.0015$ ; HR 0.73
- 1 year survival:  
51% Nivolumab  
39% Docetaxel
- Two subsets did not benefit in the subgroup analysis:  
EGFR mut (+) and never smokers
- ORR: 19% (N) and 12% (D)  $p=0.02$
- Median duration of response:  
17.2 months (N) and 5.6 months (D)

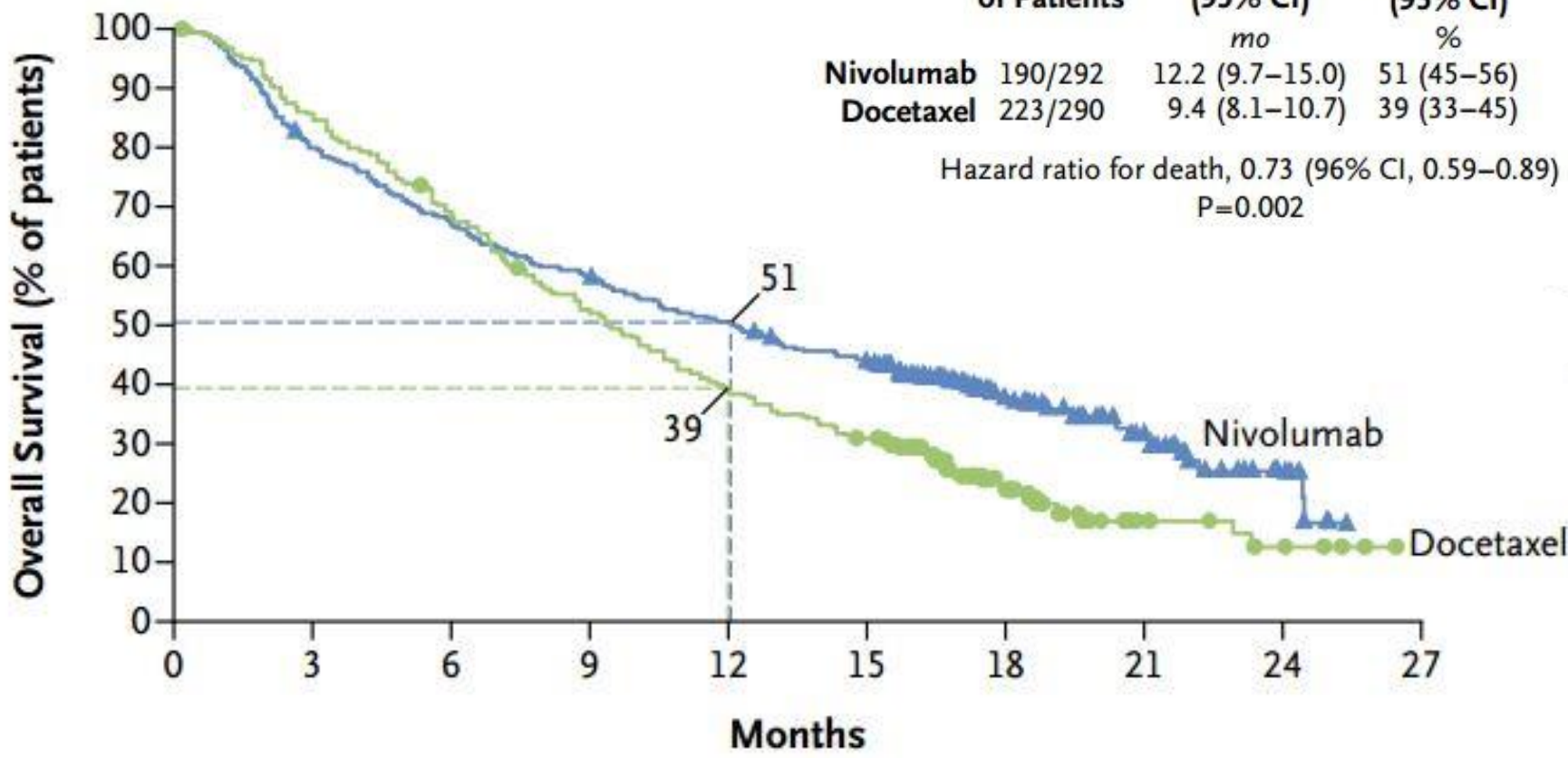
# **C Progression-free Survival**



## **No. at Risk**

Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

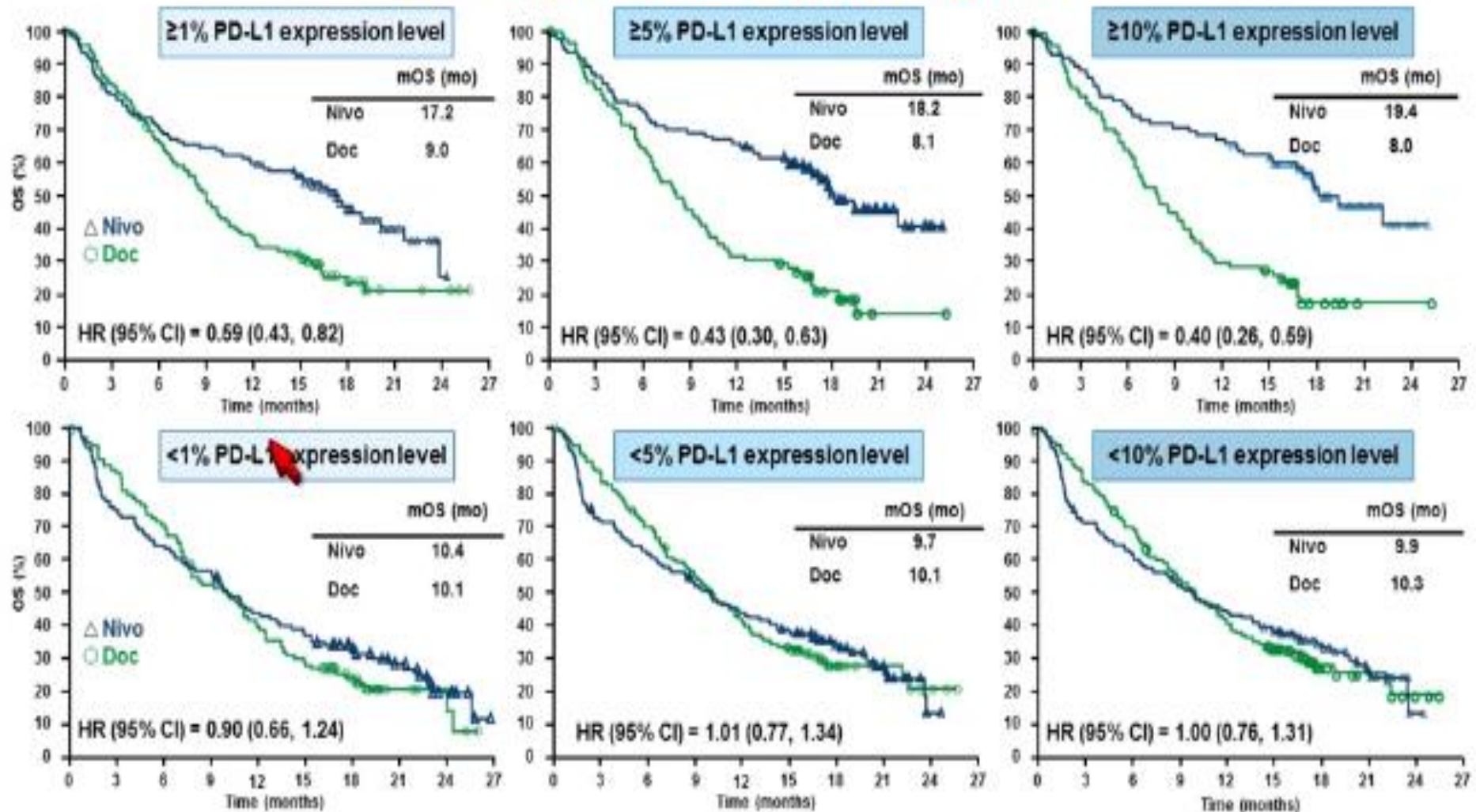
# A Overall Survival



## No. at Risk

Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

# OS by PD-L1 Expression



# Toxicity

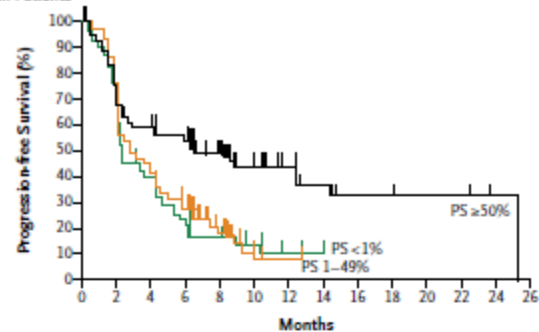
- Treatment related SAEs: 7% (N) and 20% (D)
- Treatment AEs leading to discontinuation: 5% (N) and 15% (D)
- Immune toxicity of nivolumab (%G3-4):  
hypothyroidism 7%(0); diarrhea 8 %(1); AST 3% (0); ALT 3% (<1); pulmonary 3% (1); rash 9% (<1)



# Pembrolizumab in NSCLC

- 495 patients with advanced NSCLC
- 182 patients in the training group and 313 in the validation group
- ORR 19.4% and median duration of response was 12.5 months
- Tumors were divided into those with more or less of the cells positive for PD-L1 expression (in cancer cells)

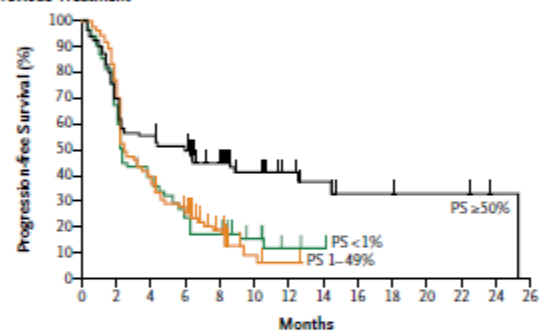
### A All Patients



#### No. at Risk

PS ≥50%	119	86	66	60	38	20	13	8	4	3	3	3	1	0
PS 1-49%	161	122	70	45	21	4	1	0	0	0	0	0	0	0
PS <1%	76	52	29	17	11	6	2	0	0	0	0	0	0	0

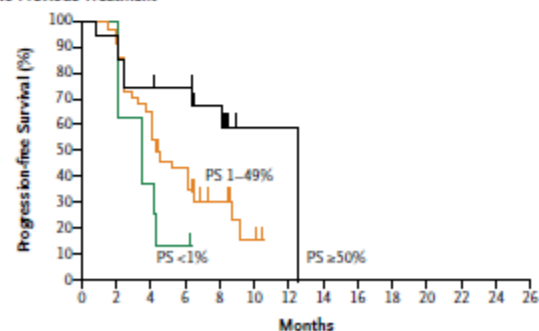
### B Previous Treatment



#### No. at Risk

PS ≥50%	99	67	53	47	30	19	12	8	4	3	3	3	1	0
PS 1-49%	127	93	48	31	15	3	1	0	0	0	0	0	0	0
PS <1%	68	44	26	16	11	6	2	0	0	0	0	0	0	0

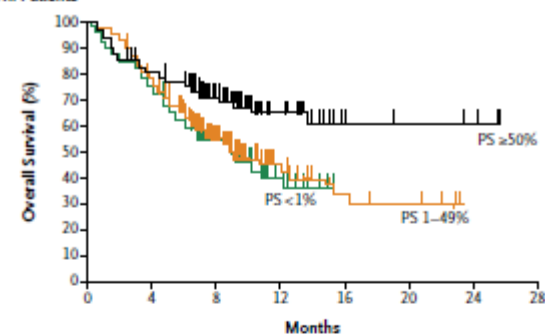
### C No Previous Treatment



#### No. at Risk

PS ≥50%	20	19	13	13	8	1	1	0	0	0	0	0	0	0
PS 1-49%	34	29	22	14	6	1	0	0	0	0	0	0	0	0
PS <1%	8	8	3	1	0	0	0	0	0	0	0	0	0	0

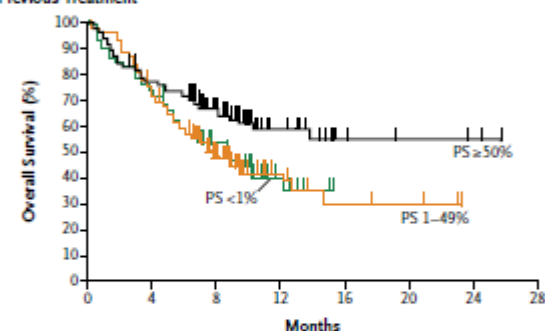
### A All Patients



#### No. at Risk

PS ≥50%	119	92	56	22	5	4	3	0
PS 1-49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

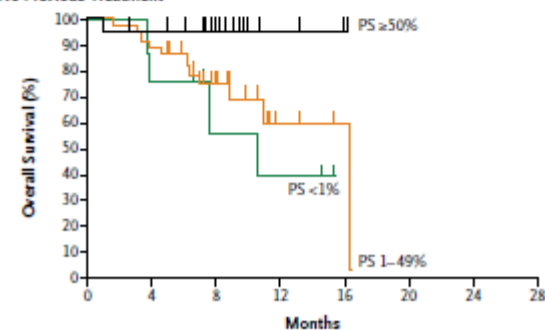
### B Previous Treatment



#### No. at Risk

PS ≥50%	99	74	45	18	5	4	3	0
PS 1-49%	127	89	43	12	5	4	0	0
PS <1%	68	49	30	6	0	0	0	0

### C No Previous Treatment

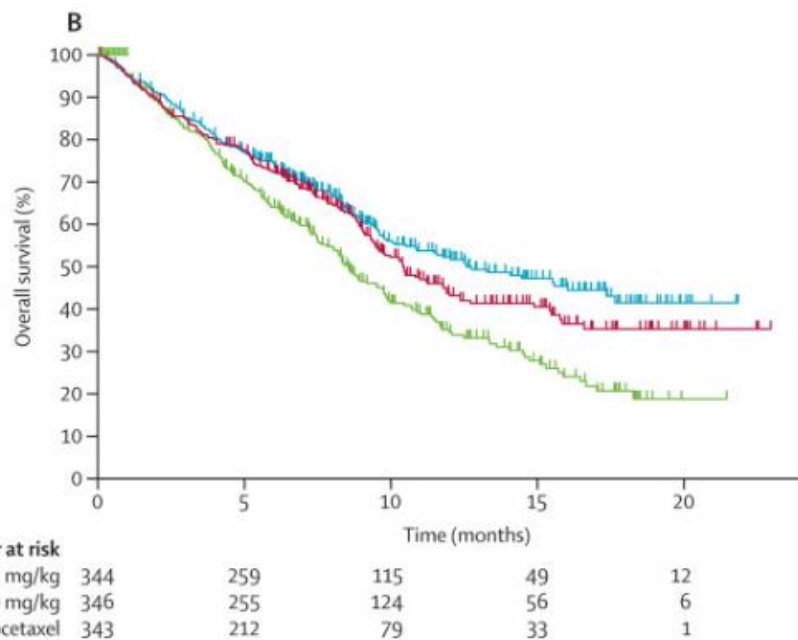


#### No. at Risk

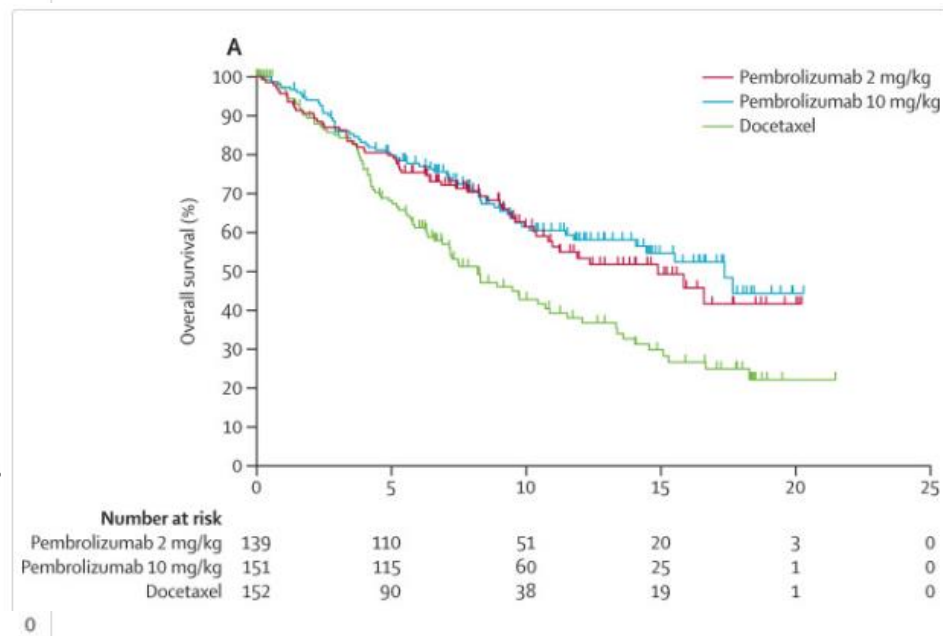
PS ≥50%	20	18	11	4	0	0	0	0
PS 1-49%	34	30	15	3	1	0	0	0
PS <1%	8	6	3	2	0	0	0	0

# Pembrolizumab

- Randomized phase 2/3
- Pembrolizumab 2mg/kg; Pembrolizumab 10mg/kg; docetaxel 75mg/m<sup>2</sup>
- Tumors had to have at least 1% PD-L1 expression and progression after 2 or more cycles of platinum-doublet
- 2222 patients had tumor evaluated and 66% had 1% expression on tumor cells and 28% had at least 50% expression
- 1034 patients were randomized



Pembro 2mg/kg: 10.4 months  
 Pembro 10mg/kg: 12.7 months  
 Docetaxel: 8.5 months



Pembro 2mg/kg: 14.9 months  
 Pembro 10mg/kg: 17.3 months  
 Docetaxel: 8.2 months

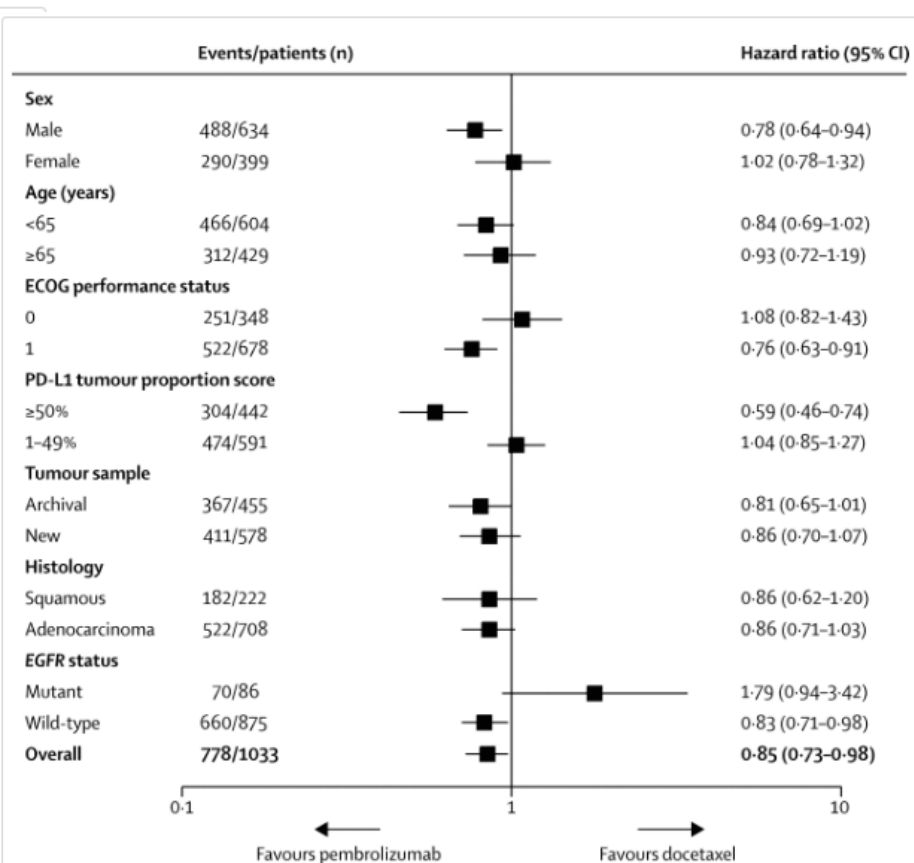
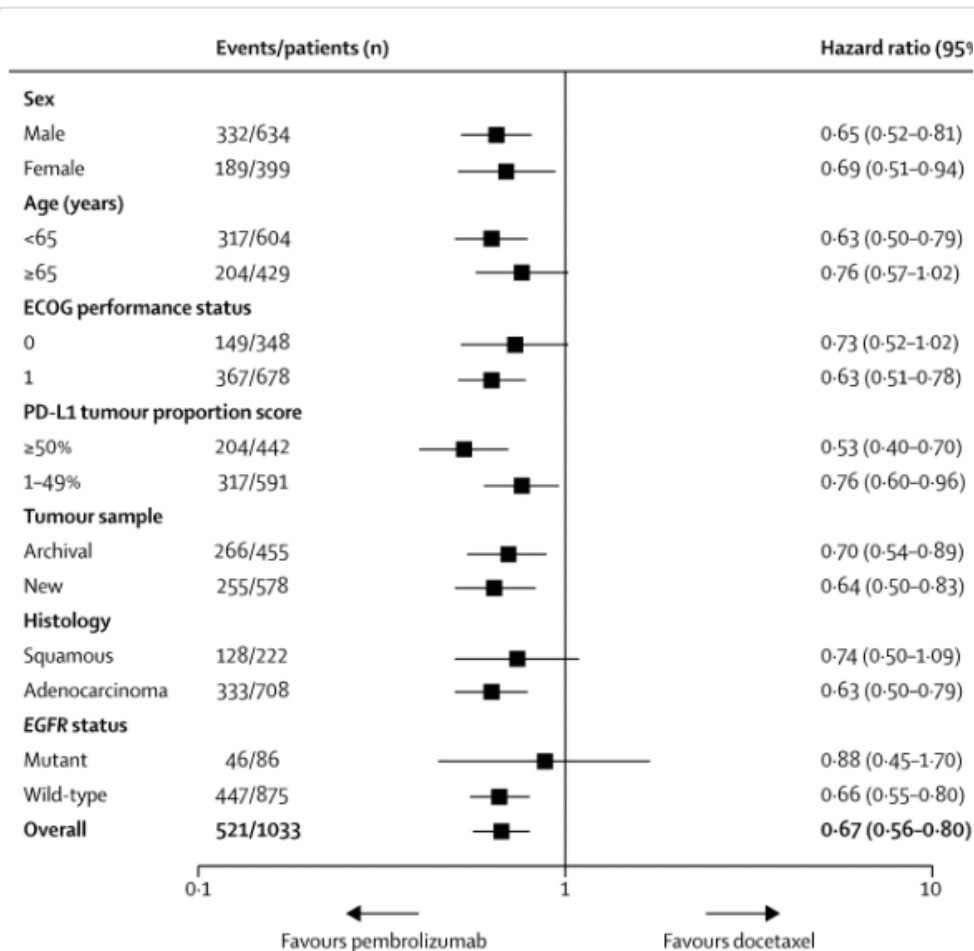


Figure 5.  
Subgroup analysis of progression-free survival

No statistical difference between  
pembrolizumab and docetaxel

# Who Benefits?

## Is there a Biomarker?

- Patients with tumor with (-) expression of PD-L1 have lower response.
- Smokers may have higher response rate
- Patients with SCCa have higher benefit or larger gain vs current available therapies

# PD-L1 expression as a predictor of response

- CheckMate 057<sup>1</sup>: 108/287 (37%) treated with nivolumab had <1% tumor cells expressing PD-L1
- Keynote-001<sup>2</sup>: 12/91 (13%) patients had tumor or stroma with <1% PD-L1 expression
- POPLAR<sup>3</sup>: 51/144 (35%) patients had tumor or infiltrating immune cells graded as 0

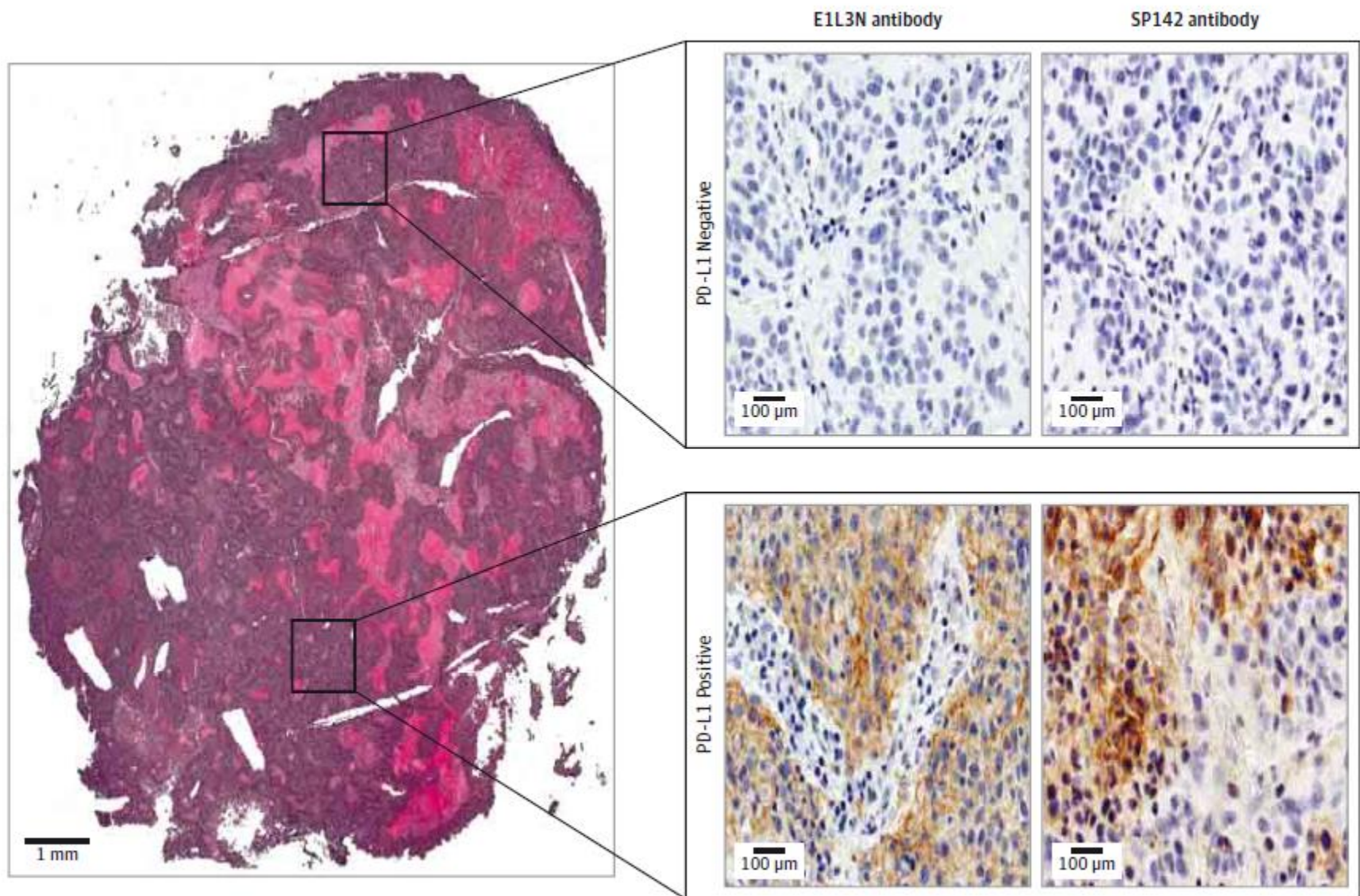
1. J Clin Oncol 33,2015(suppl; abstr LBA 109)
2. J Clin Oncol 33;2015 (suppl;abstr 8026)
3. J Clin Oncol 33,2015 (suppl;abstr 8010)

# PD-L1 expression as a predictor of response

	# Negative tumors	# Responded among (-) tumors	RR (%)
CheckMate 057 <sup>1</sup>	108	10	9%
Keynote-001 <sup>2</sup>	12	1	8%
POPLAR <sup>3</sup>	51	4	8%
Combined	171	15	8.7% (95% CI 5-14%)

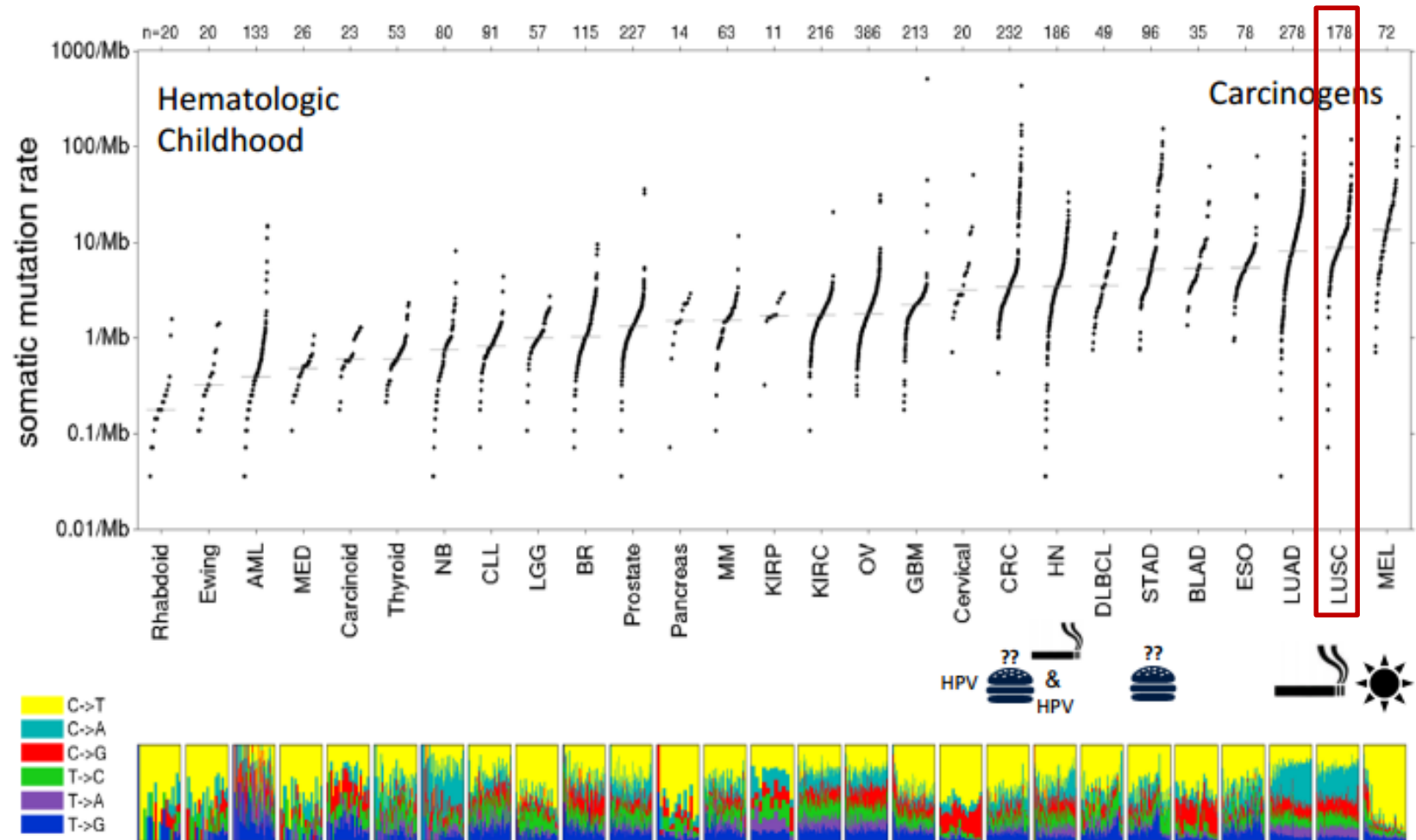
1. J Clin Oncol 33,2015(suppl; abstr LBA 109)
2. J Clin Oncol 33;2015 (suppl;abstr 8026)
3. J Clin Oncol 33,2015 (suppl;abstr 8010)





McLaughlin JM, et al. JAMA Oncol 2016;2:46-54.

# mutation rates across cancer



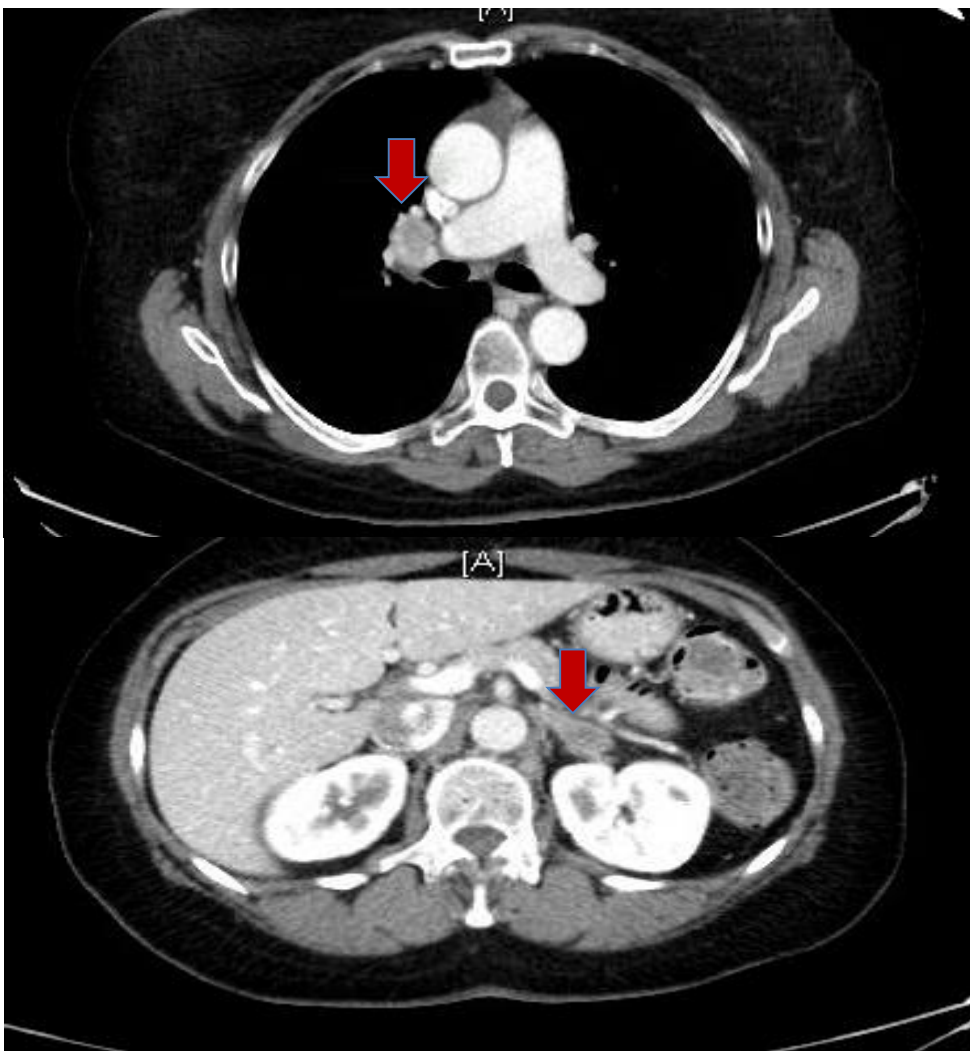
# Case

- 55yo presented outside of our system with stage IV (cervical LN)
- Smoker up to her diagnosis of 20pack/year
- Pathology: Poorly differentiated NSCLC CK7 and p63 (+) TTF-1 (-) (3-25-2011)
- Treated with combination of docetaxel+cisplatin+XRT (70Gy)

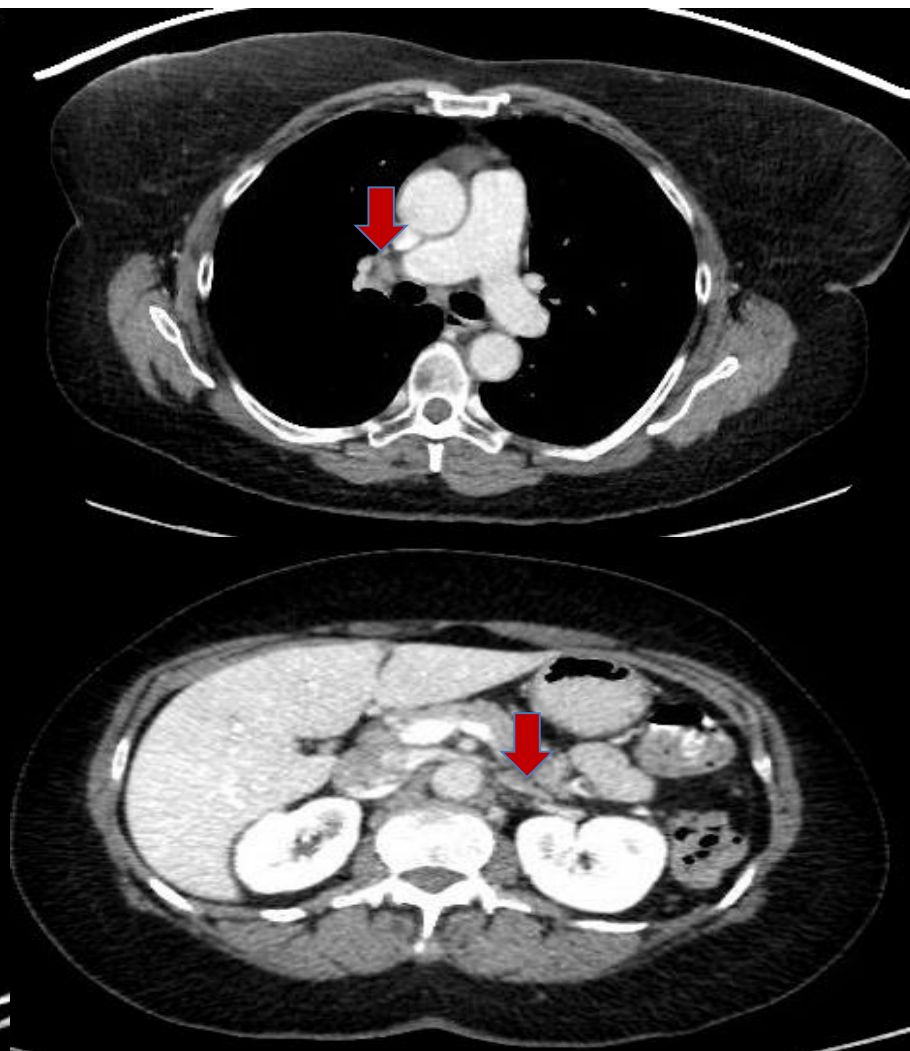
# Case

- Trial of vaccine for 6 months until she had evidence progression
- Performance status 1
- Enrolled on a phase I clinical trial of a anti-PD-L1 antibody
- First dose 3-20-2012

2-29-2012



4-29-2015



# Combination Immunotherapy



# CheckMate 012

- Nivolumab and ipilimumab in combination in patients with advanced NSCLC **in first line**
- Investigators struggled to find a tolerable dose and end up investigating 2 arms: Nivo3Q2W+Ipi1Q12W (n=38/19%  $\geq$  50% PD-L1) and Nivo3Q2W+Ipi1Q6W (n=39/23%  $\geq$  50% PD-L1)
- Toxicity grade 3-4 treatment related AEs (%): N3IpiQ12 (37%); N3IpiQ6 (33%)
- AEs leading to treatment discontinuation (%): N3IpiQ12 (5%); N3IpiQ6 (8%); Nivo alone arm (n=52) (10%)
- Most common grade 3-4: GI, pulmonary, renal, skin endocrine

# CheckMate 012

- Efficacy confirmed RR (%): Nivo3Ipi1Q12 (47%); Nivo3Ipi1Q6 (39%)
- Responses long lasting as expected in immunotherapy responses
- Higher RRs were observed in every cohort of PD-L1 expression
- They observed 4/8 responses in tumors with EGFR mutation but 3 were former smokers and 3 had PD-L1 expression  $\geq 50\%$
- Nivo 3mg/kg Q2W plus ipilimumab 1mg/kg Q6W will be evaluated further, including a randomized phase III trial (CheckMate 227)



# First Line Therapy

## KEYNOTE-024

# KEYNOTE-024

- Randomized trial of first line pembrolizumab vs platinum doublet chemotherapy in tumors expressing PD-L1  $\geq 50\%$
- 305 patients randomized
- Primary objective was progression-free survival and patients randomized to chemotherapy had the option of crossing over pembrolizumab
- Data Monitoring Committee recommended trial to be stopped because primary endpoint of PFS **and** secondary endpoint of OS were both superior

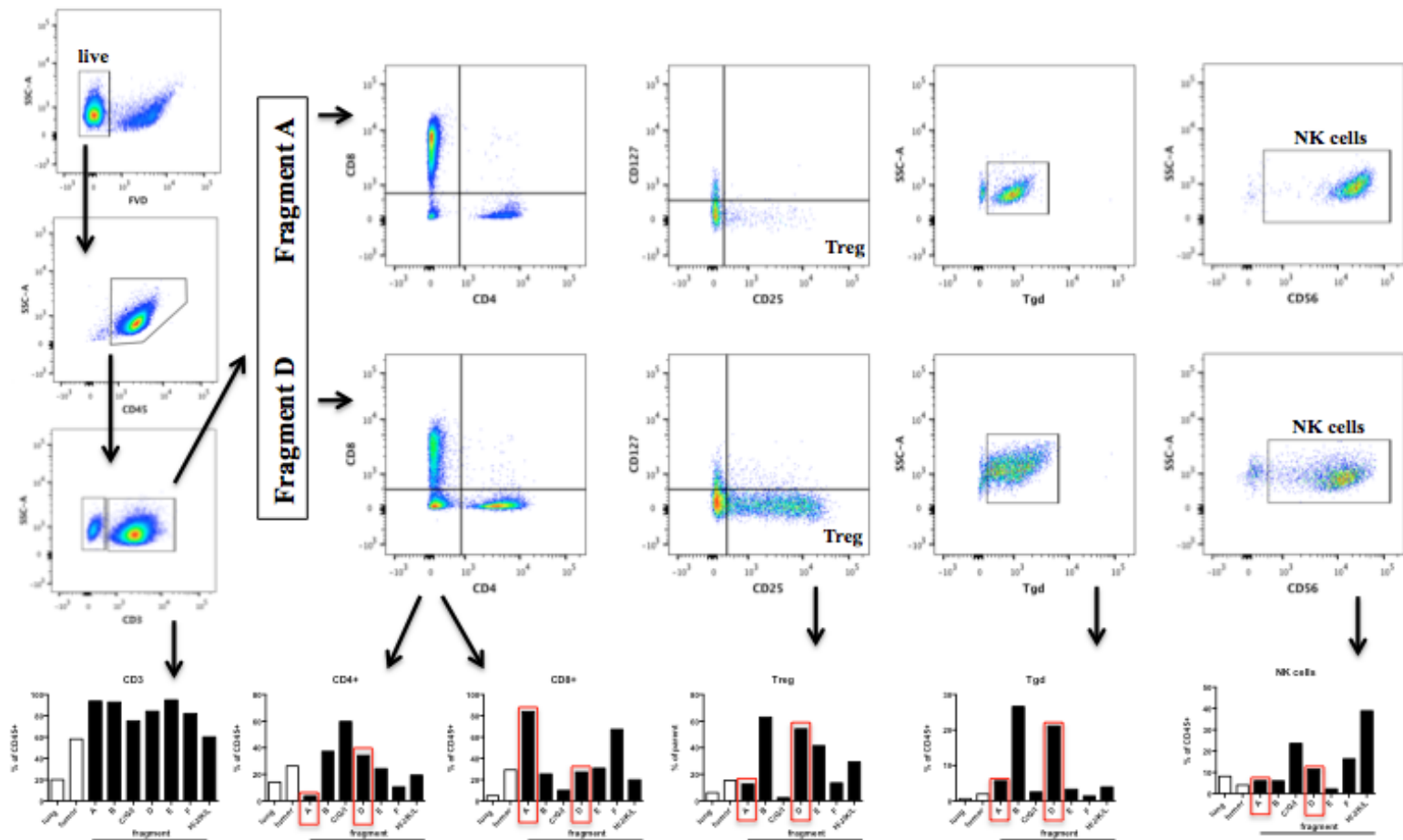
# Major Practice Change

- Now 4 populations who should not receive chemotherapy as initial therapy for advanced NSCLC: EGFRmut (+); ALK (+); ROS-1 (+); PD-L1  $\geq 50\%$
- These 4 groups compromise 40-50% of all patients diagnosed with advanced NSCLC
- PD-L1 testing should be incorporated in the initial evaluation of advanced NSCLC

# The TIL Program

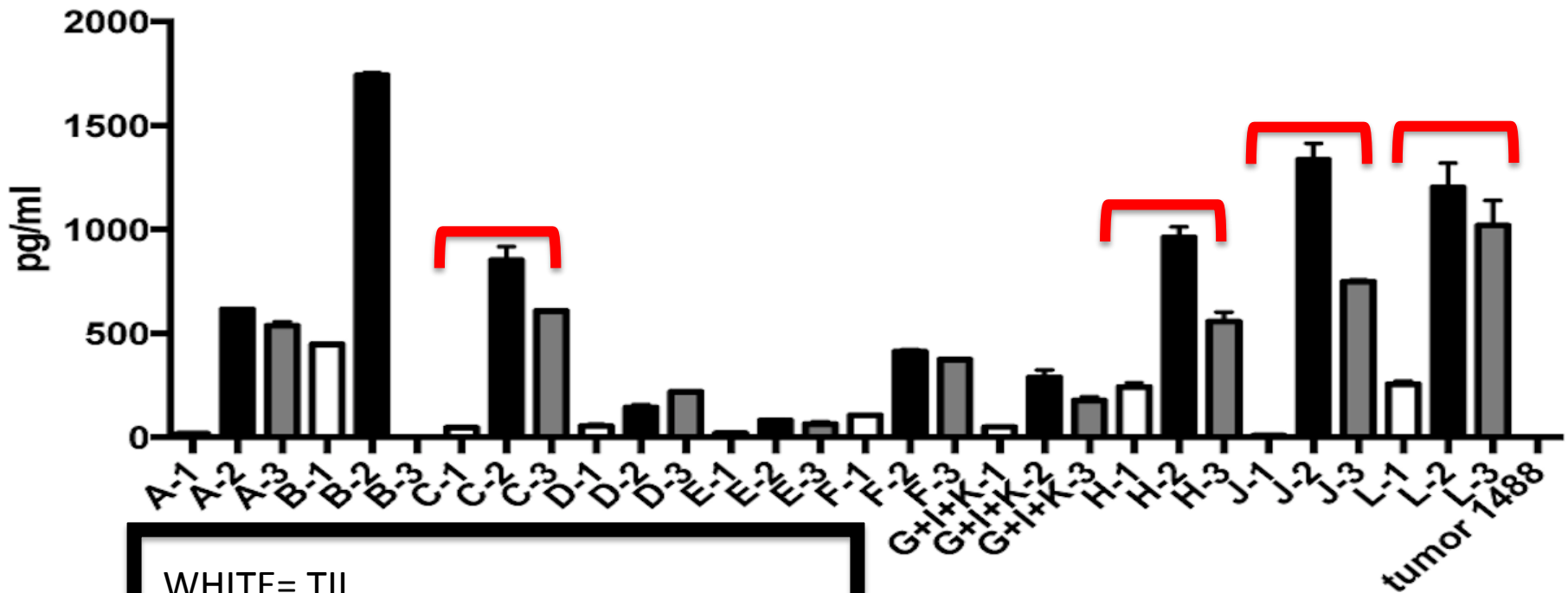
# TIL in Lung Cancer

- 27 NSCLC specimens: 96% success rate in generating adequate TIL numbers



# TIL in Non-Small Cell Lung Cancer

- Of 7 TIL cases co-cultured with autologous tumor, 4 with tumor reactivity



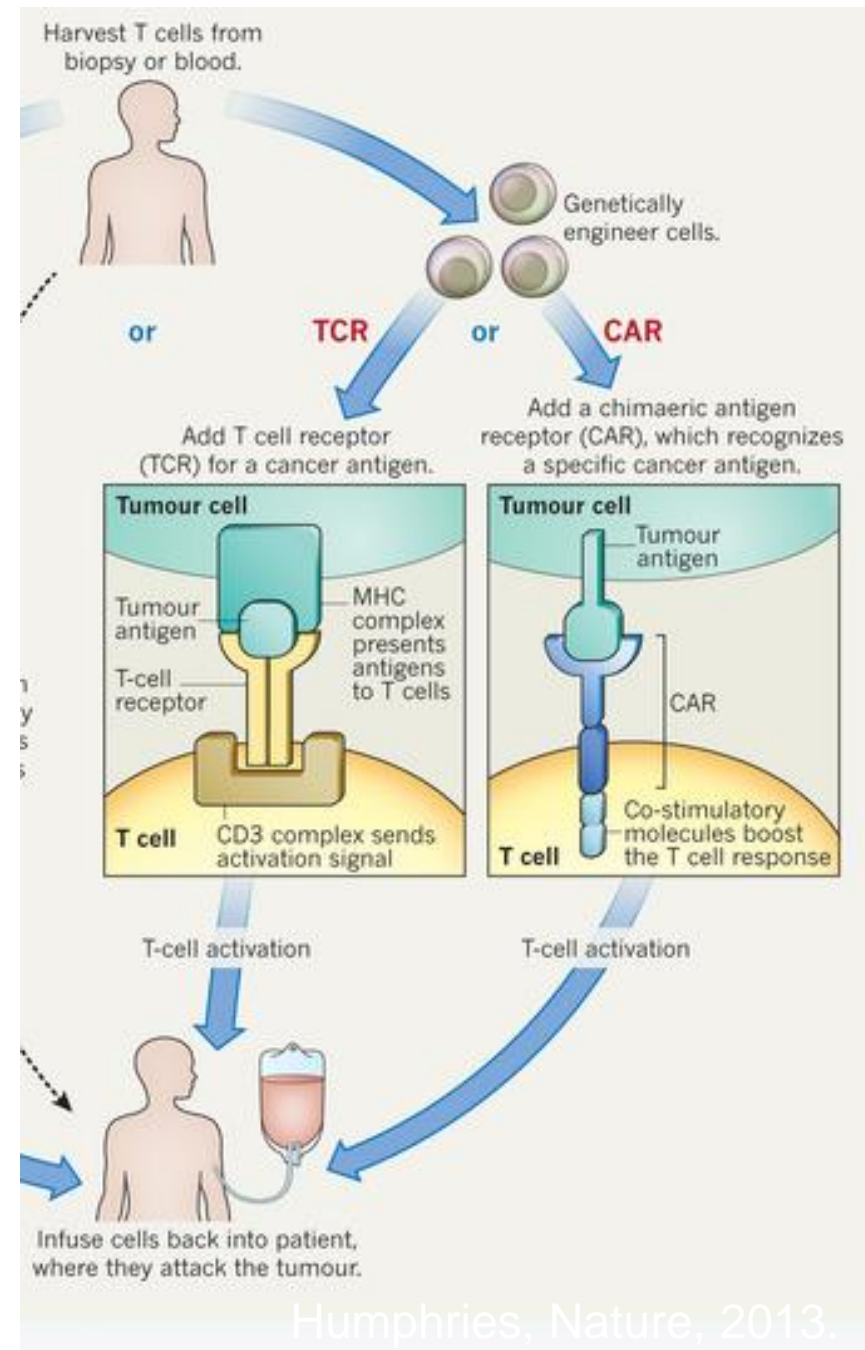
WHITE= TIL

BLACK= TIL + tumor

GRAY= TIL + tumor+ Class I blocking Ab

# CARs vs. TCRs

- CARs
  - Target surface molecules
  - No HLA restriction
  - Chimeric construct, murine anti-human sequences → can be attacked by patient's immune system
- TCRs
  - Can target all cellular proteins
    - Susceptible to MHC downregulation
  - HLA restricted
  - Human construct → Does not get targeted by patient's immune system



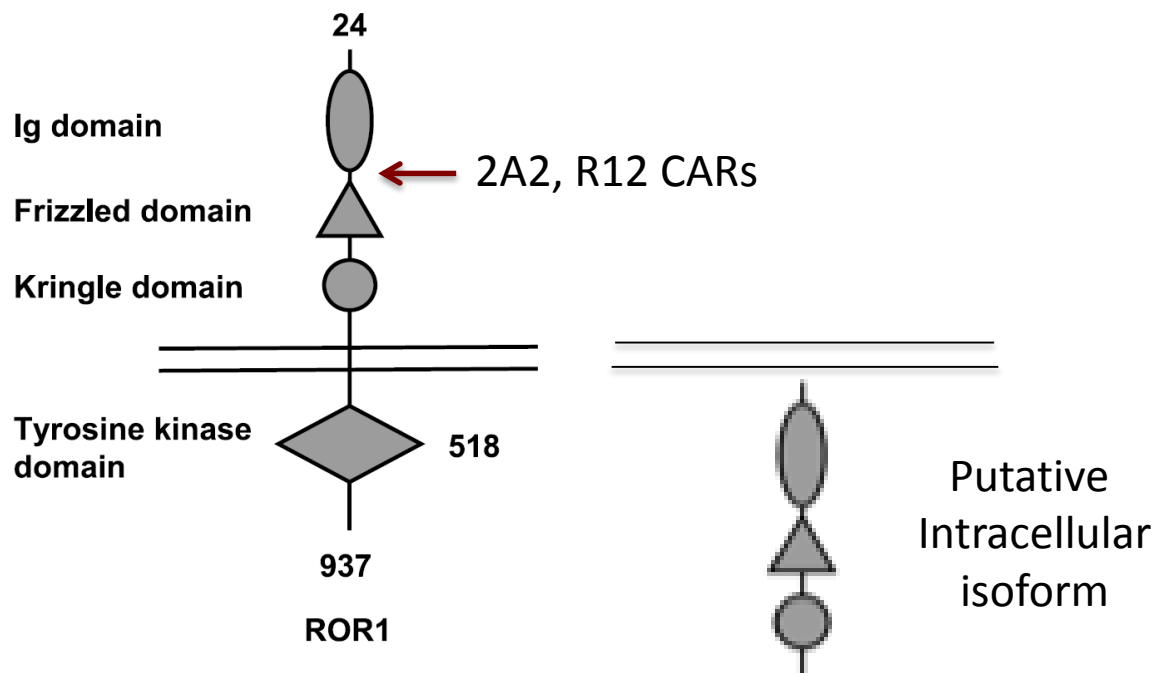
# WT-1 Directed T Cells

- WT-1 frequently expressed in mesothelioma
- Discordant data regarding frequency in lung cancer
- Trial includes advanced mesothelioma; advanced NSCLC and a small sample of stage IIIA NSCLC to be treated in the neoadjuvant setting
- Two patients treated



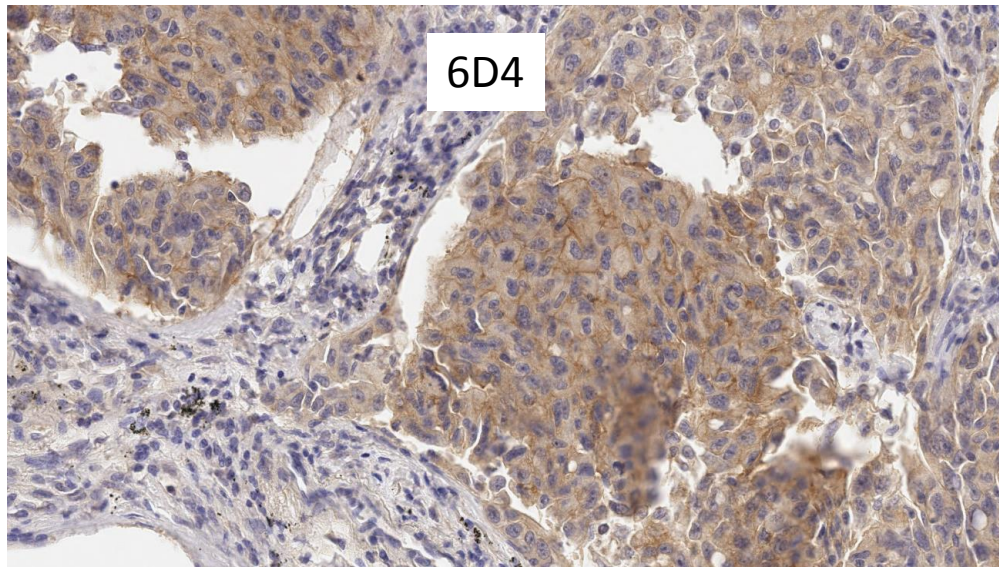
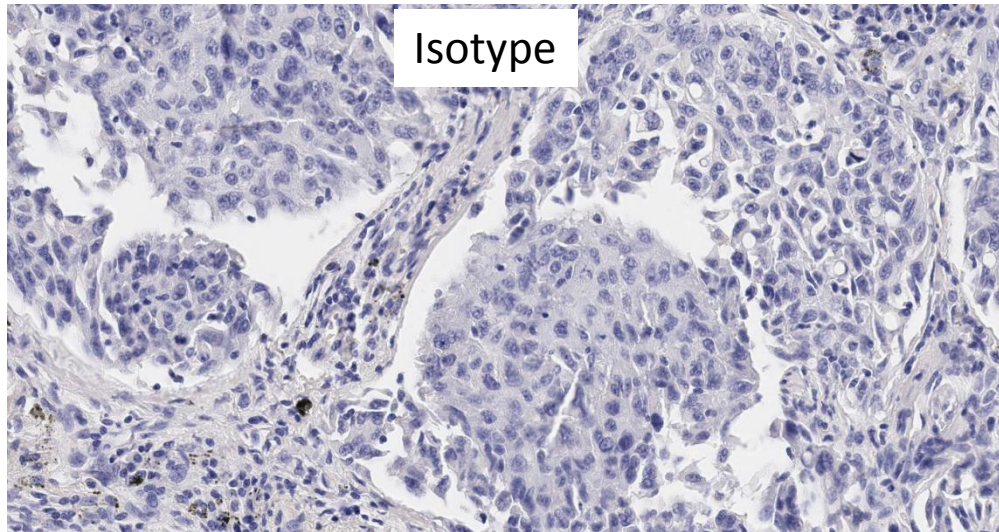
# ROR1 CAR T (Riddell Lab)

(receptor tyrosine kinase-like orphan receptor)

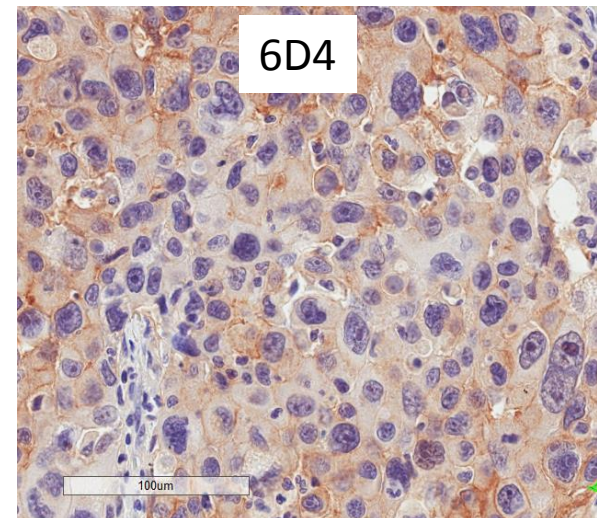
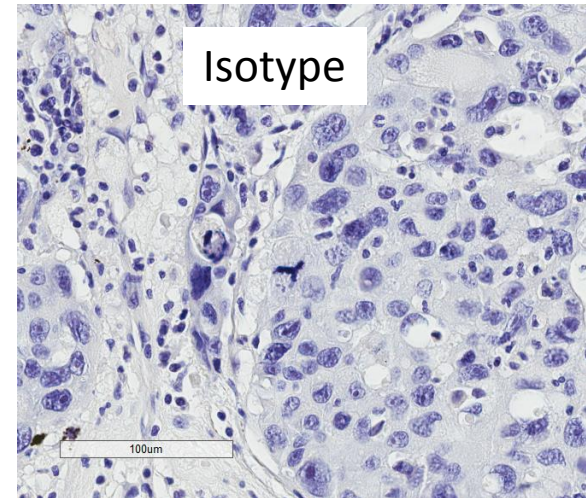


- Full length isoform expressed in embryonic development, low levels of RNA in adult tissues
- Normal tissues with some RNA expression include pre B cells, adipocytes, pancreas (low)
- Highly expressed in all chronic lymphocytic leukemia, mantle cell lymphoma
- Expressed in many solid tumors (RNA) and cell lines (flow cytometry)  
(NSCLC, breast cancer, ovarian cancer, prostate, melanoma, and others)

Lung adenocarcinoma D7 Lung TMA 20X

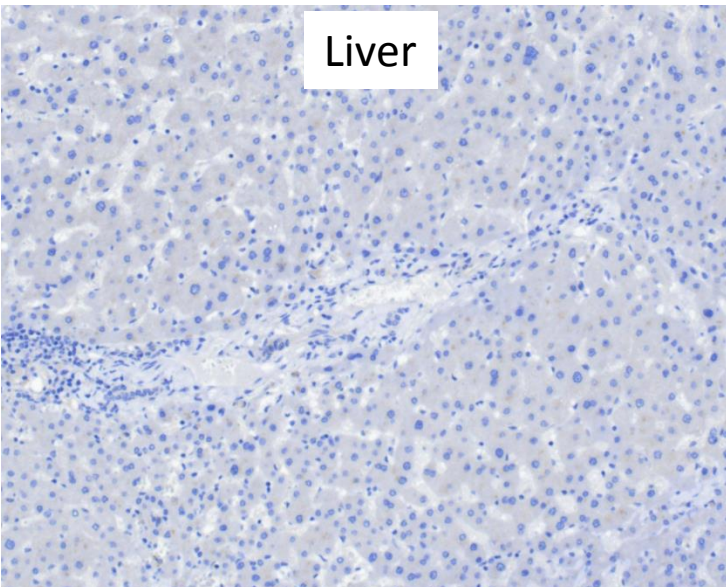
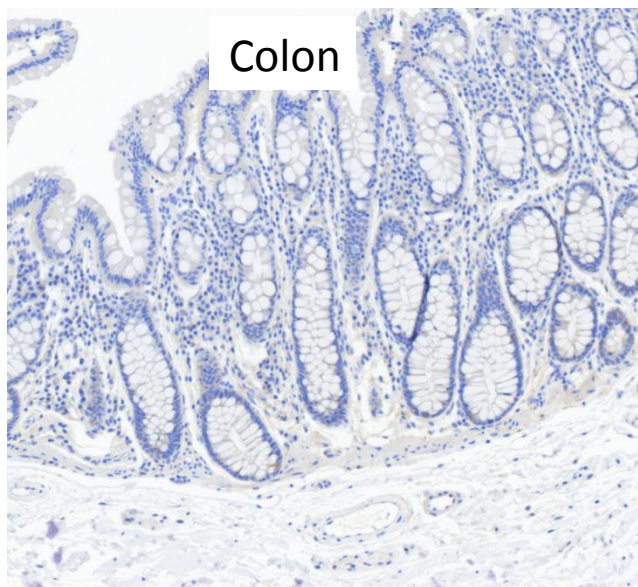
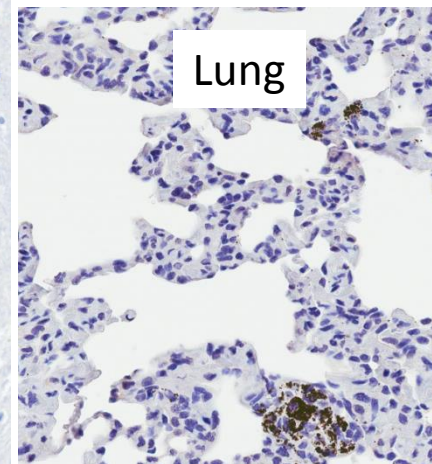
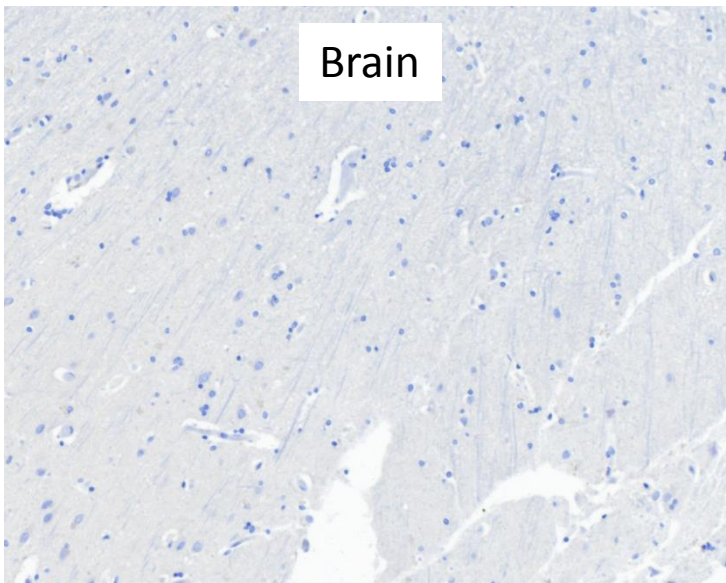
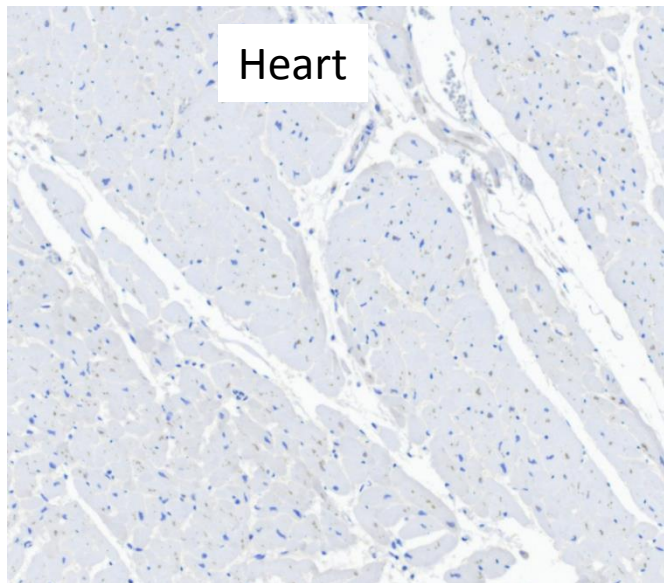


Squamous cell carcinoma





## Vital Normal Tissues Are Negative – Representative Stains of FDA 999 Normal Tissue Panel With 6D4



# Back to Checkpoint Inhibitors

## So What Do We Know?

- Response seems to be irrespective of number of prior therapies
- Tumors with multiple somatic mutations appear to be more immunogenic
- Serious immune toxicities may appear months into treatment

# Future Directions

- Better biomarker
- Combination therapies
- Management of toxicities particularly those developing late in patients with a good response



Thank you!

