Cancer Immunotherapy Patient Forum

for the Treatment of Melanoma, Leukemia, Lymphoma, Lung and Genitourinary Cancers - November 7, 2015

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Society for Immunotherapy of Cancer

Melanoma Research Alliance

Global Resource for Advancing Cancer Education

Biomarkers and Patient Selection

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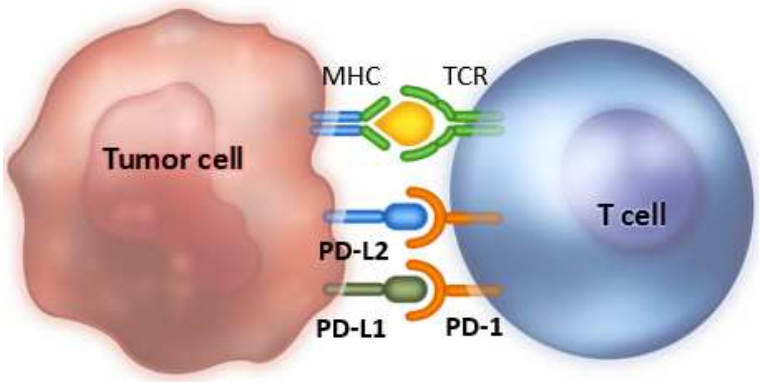
Overview

- PD-L1 expression on tumor cells is correlated with improved survival when treated with PD-1 checkpoint blockade except in the case of nivolumab in squamous cell lung cancer.
- PD-L1 expression tumor testing is required for treatment with pembrolizumab in non small cell lung cancer.
- PD-L1 expression may help guide combination immunotherapy in melanoma.
- PD-L1 expression is not correlated with benefit in Renal Cell Cancer
- Multiple questions remain regarding the use of PD-L1 staining as a biomarker.
  - Must know what antibody is used, and what cut off used to give a positive result.
- Mutational burden may also predict clinical benefit but is not ready for routine use due to cost and lack of confirmatory testing on large numbers of samples to correlate benefit.

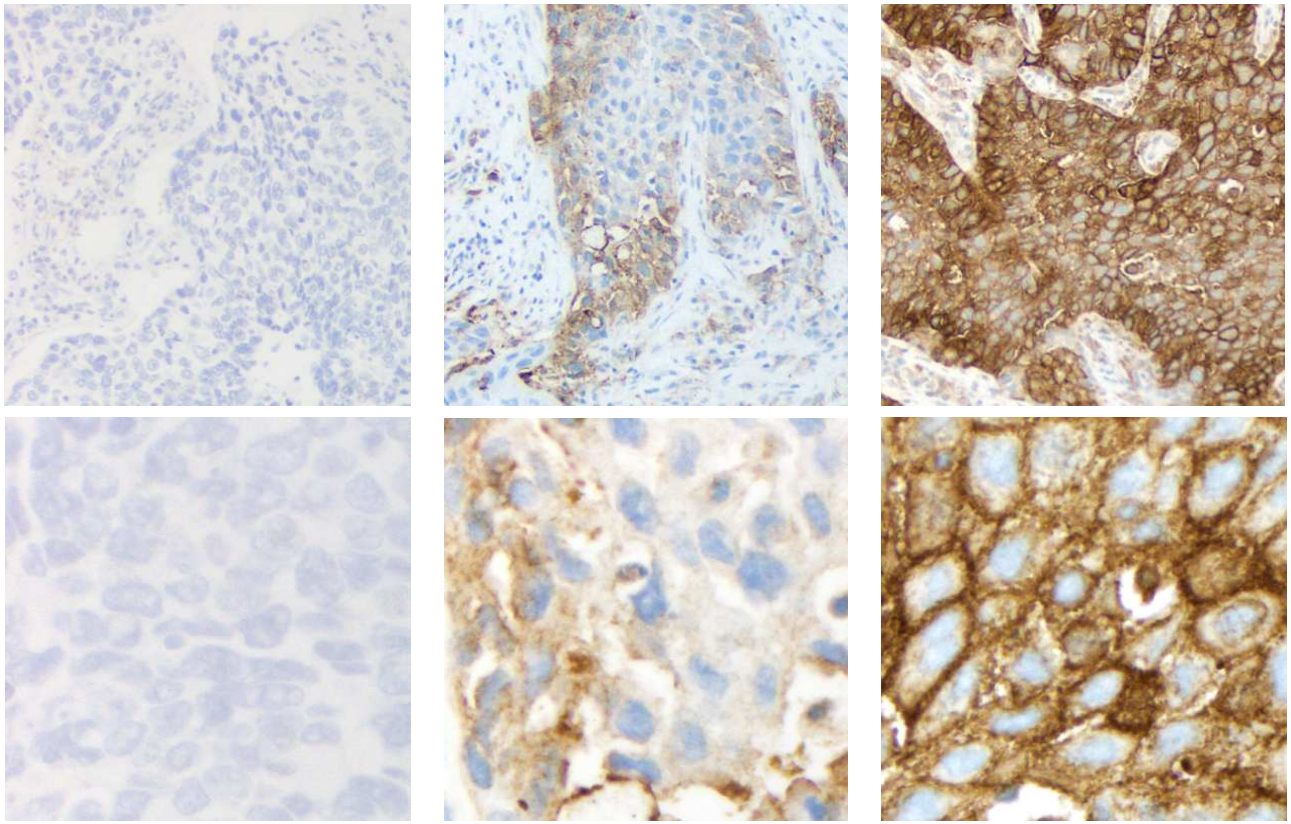
PD-L1 Testing

- This is a test that is run on a cancer biopsy in a pathology lab.
- The test stains for PD-L1 – the ligand (which is a protein) to the PD-1 receptor.



Examples of PD-L1 IHC Staining of Lung Cancer

PS <1% | **PS 1-49%** | **PS ≥50%**



5x magnification

40x magnification

Brown chromogen: PD-L1 staining.
Blue color: hematoxylin counterstain.

Garon E et al AACR 2015

Tumor PD-L1 expression

- PD-L1 can be expressed on tumor and various immune cells.
- PD-L1 staining can pick up membrane bound PD-L1 or cytoplasmic PD-L1.
- PD-L1 staining can be variable within a tumor i.e. typically concentrated at the tumor edge and can be patchy.
- PD-L1 expression can change over time i.e. is dynamic.
- PD-L1 expression is measured as a continuous variable not as a Positive or Negative. We artificially decide what means "positive" or "negative" based on studies that we will discuss.

Which PD-L1 Antibody Should We Use to Stain Your Cancer?

	Nivolumab	Pembrolizumab	Atezolizumab	MEDI4736
Antibody test	28-8	22C3	SP142	SP263
Cells measured	Tumor cell membrane	Tumor cell (and stroma)	Tumor and Immune cells	Tumor cells
Definition of positive	Depends on the trial - $\geq$ 5%	>50% expression – strongly positive	Depends on the trial	Depends on the trial - $\geq$ 25%

- What cut off is used to be labelled "positive"? 50%, 1%, 5%?

General Issues with PD-L1 Testing

- Bx type - Excisional versus core versus FNA
- **Addressing heterogeneity** – multiple tumors and multiple passes within a tumor can yield different results
- Interval between biopsy and treatment – effect of other therapies
- **Antibody** and staining conditions
- **Defining a positive result (cut-offs):**
  - Cell type expressing PD-L1 (immune cell versus tumor or both)
  - Presence or absence of T-cells near PD-L1 expression
  - Intensity
  - Distribution - patchy versus diffuse, intratumoral versus peripheral
  - percent of cells 'positive'

Mario Sznol, AACR 2014

PD-L1 Testing – Lung Cancer

- PD-L1 expression on tumor cells is correlated with improved survival when treated with PD-1 checkpoint blockade except in the case of nivolumab in squamous cell lung cancer.
- PD-L1 expression tumor testing is required for treatment with pembrolizumab in non small cell lung cancer.

Summary of Key PD-1/PD-L1 Blockade Clinical Data in Lung Cancer

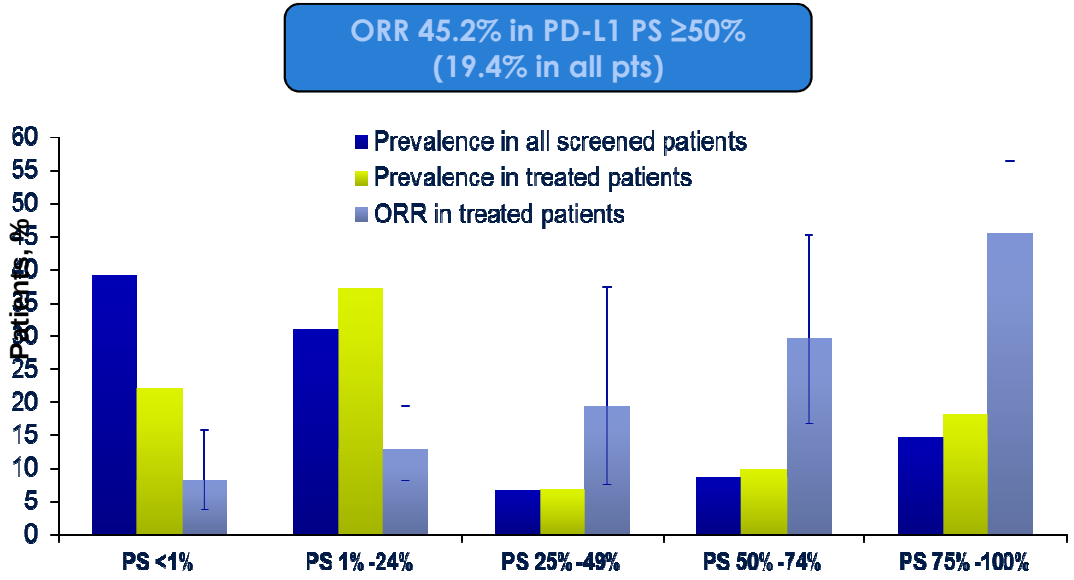
Agent	Nivolumab		Pembrolizumab		Atezolizumab	MEDI4736
Potential PD-L1+ definition	• TC ≥5%		• TC ≥50% (and 1% any stroma) – TEST FDA approved		• Lung: IC ≥10% or • TC >50%	• TC ≥25%
Trial/ Analysis	CheckMate 057[4]	CheckMate 017[5]	KEYNOTE-001 NSCLC ≥2L[2]	KEYNOTE-001 All NSCLC[3]	POPLAR[1]*	All NSCLC*
N	292	272	217	495	287	200
ORR, % (95% CI)	19 (15-24)	20 (14-28)	20 (15-26)† 18 (31-24)‡	19 (16-23)	15	16 (11.2-21.8)†
TTR, median	2.1 mo	2.2 mo	9 wk	NA	NA	NA
DOR, median	17.2 mo (nivo, n=56) 5.6 mo (DTX, n=36)	NR (nivo) 8.4 mo (DTX)	31 wk	NA	NR (atez) 7.8 mo (DTX)	NA 0.1+-54.4+ (range in wks)
PFS, median	2.3 mo (nivo) 4.2 mo (DTX)	3.5 mo (nivo) 2.8 mo (DTX	NA	3.7 mo	2.8 mo (atez) 3.4 mo (DTX)	NA
OS, median	12.2 mo (nivo) 9.4 mo (DTX)	9.2 mo (nivo) 6.0 mo (DTX)	NA	12.0 mo	9.5 mo (atez) 11.4 mo (DTX)	NR (PD-L1+) 8.9 mo (PD-L1–)
Any grade drug-related AEs	69%	58%	64%	71%	67%	50% (n=228)
Most frequent any grade drug-related AEs	Fatigue, nausea, decreased appetite	Fatigue, decrease appetite, asthenia, nausea	Fatigue, arthralgia, decreased appetite	Fatigue, pruritus, decreased appetite	Decreased appetite, dyspnea, nausea, anemia	Fatigue, decreased appetite, nausea

*Interim data. †Per RECIST v1.1. ‡irRC.

2L=second line; DTX=docetaxel; NA=not available; TTR=time to response.

1. Spira AI, et al. Presented at: ASCO. 2015 (abstr 8010). 2. Garon EB, et al. Presented at: ASCO. 2014 (abstr 8020). 3. Garon EB, et al. *N Engl J Med.* 2015;372:2018-2028. 4. Borgehi H et al N Engl J Med. Sept 2015 . 5. Brahmer J, et al. *N Engl J Med.* May 31, 2015 [Epub ahead of print].

KEYNOTE-001: Response by Level of PD-L1 Expression in Lung Cancer treated with Pembrolizumab



All screened patients, n (%)	323 (39.2)	255 (31.0)	55 (6.7)	71 (8.6)	120 (14.6)
All treated patients, n (%)	87 (22.0)	147 (37.2)	27 (6.8)	39 (9.9)	72 (18.2)
ORR in treated patients, n (%) [95% CI]	7 (8.1) [3.3-15.9]	19 (12.9) [8.0-19.4]	6 (19.4) [7.5-37.5]	13 (29.6) [16.8-45.2]	39 (45.4) [34.6-56.5]

Using the Merck antibody test for PD-L1 Expression

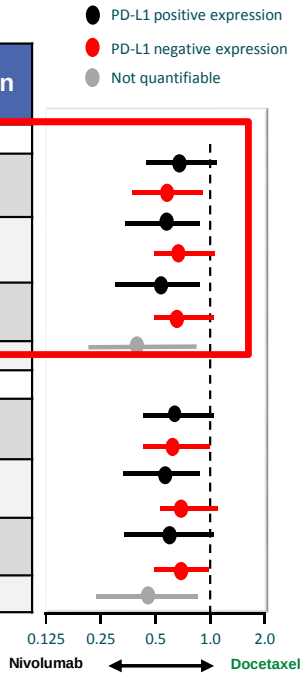
Garon EB, et al. *N Engl J Med*. 2015;372:2018-2028.

CheckMate 017: Survival by PD-L1 Expression in Squamous Lung Cancer

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

PD-L1 expression	Patients, n		Unstratified HR (95% CI)	Interaction *P*-value
	Nivolumab	Docetaxel		
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 (DAKO automated IHC assay)[15]



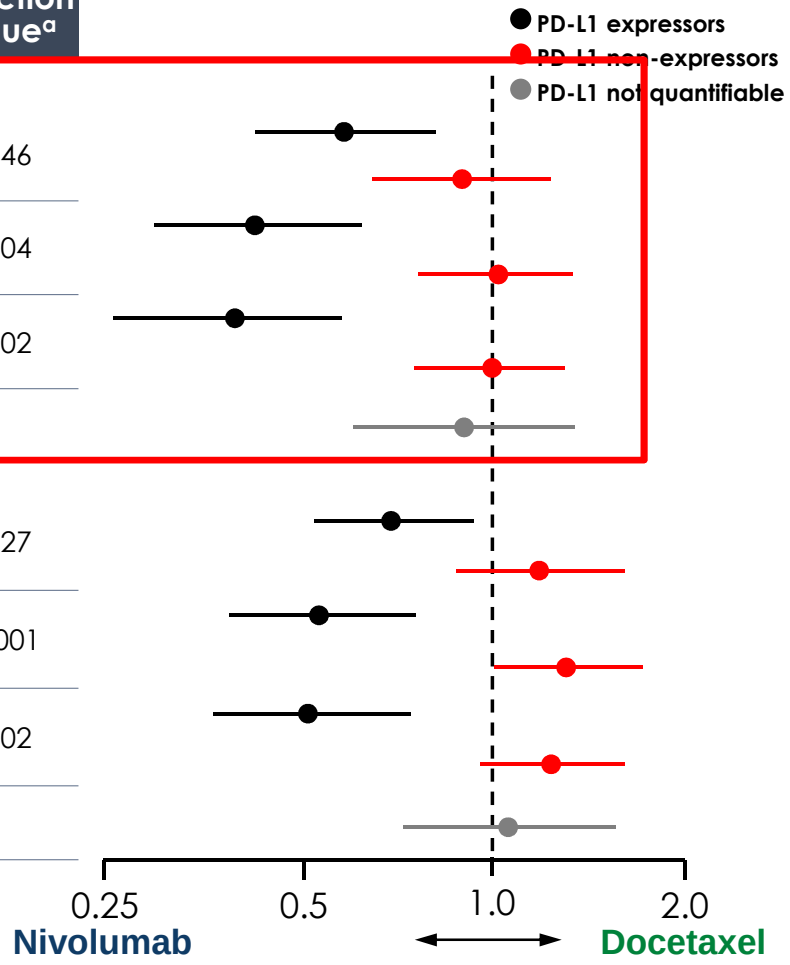
- In Squamous Lung Cancer, using the BMS antibody test for PD-L1, PD-L1 staining of the tumor did not predict a benefit from nivolumab.

Brahmer J, et al. *N Engl J Med*. May 31, 2015 [Epub ahead of print].

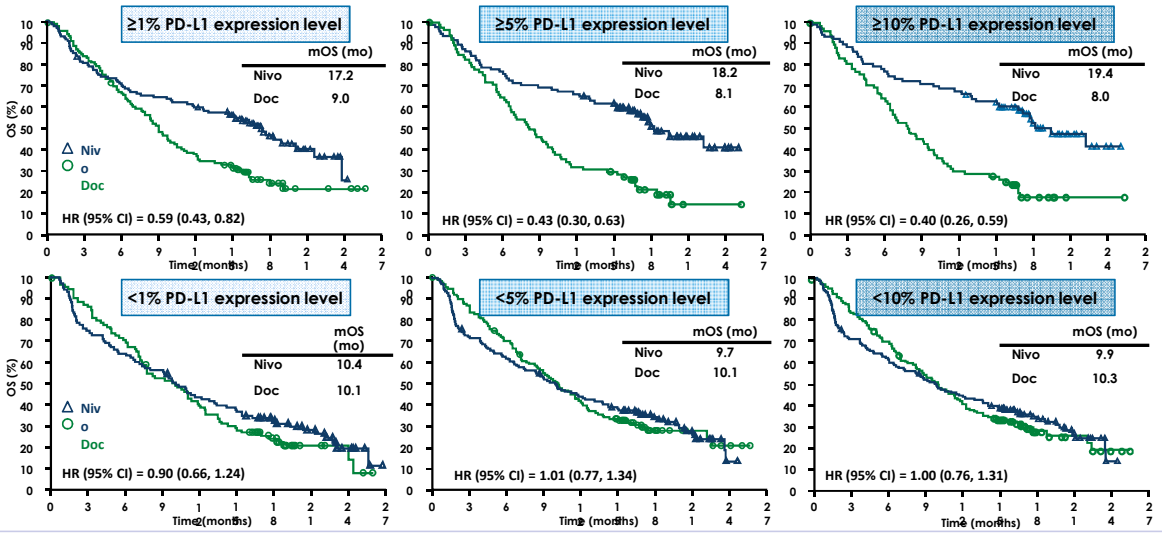
CheckMate 057: Survival by PD-L1 Expression in Non Squamous Lung Cancer

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.



CheckMate 057: OS by PD-L1 Expression in Nonsquamous Lung Cancer



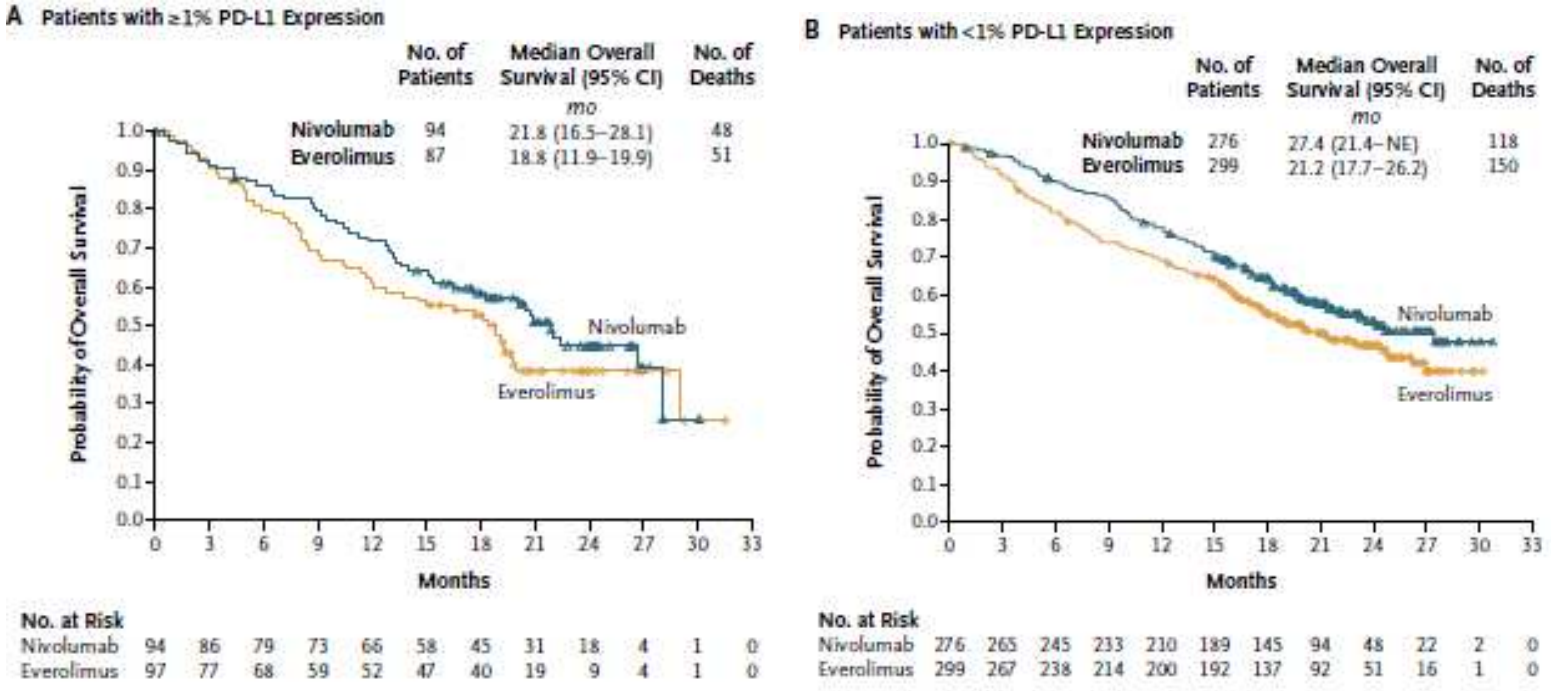
- In nonsquamous lung cancer, the test for PD-L1 expression on a tumor, did predict for improvement in survival when treated with nivolumab.
- If the tumor had PD-L1 staining of 1% or greater, the benefit was greater in those patients when treated with nivolumab.
- If the tumor did not have PD-L1 staining, then the patient benefit was similar if receiving nivolumab or docetaxel (taxotere).

Borghaei H et al NEJM 2015

PD-L1 Testing and Renal Cell Carcinoma

- PD-L1 expression is not associated with benefit with Nivolumab (anti-PD-1 therapy)

CheckMate 025: Nivolumab versus Everolimus in Renal Cell Cancer



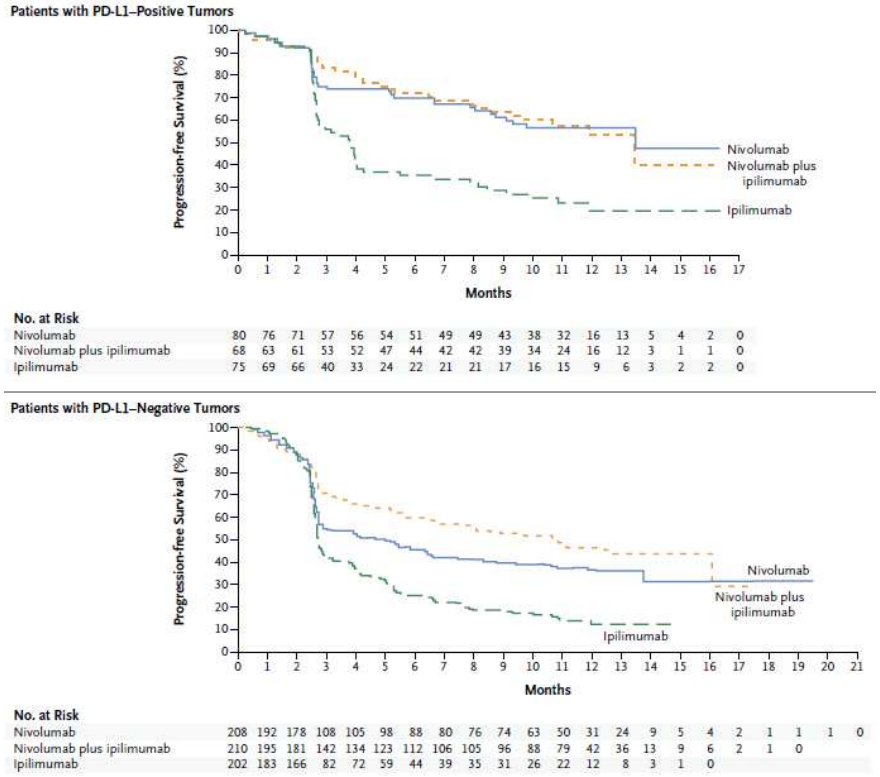
- Nivolumab improved survival in advanced Renal cell cancer compared to everolimus.
- No difference in benefit from nivolumab if the tumor was PD-L1 positive or negative.

Motzer RJ et al NEJM November 2015

PD-L1 Testing and Melanoma

- PD-L1 expression is much more common in Melanoma than in Lung Cancer
- PD-L1 expression may help guide combination immunotherapy in melanoma.

PD-L1 Expression in Melanoma Patients Treated with Ipilimumab and Nivolumab versus Nivolumab alone – CheckMate 067



- PD-L1 positive tumors – no difference in PFS between Nivo vs. combination
- PD-L1 negative tumors – improvement in PFS in combination vs. single agent Nivo
- PD-L1 positivity defined as ≥ 5% tumor cell staining

Larkin J et al NEJM 373:23-34 2015)

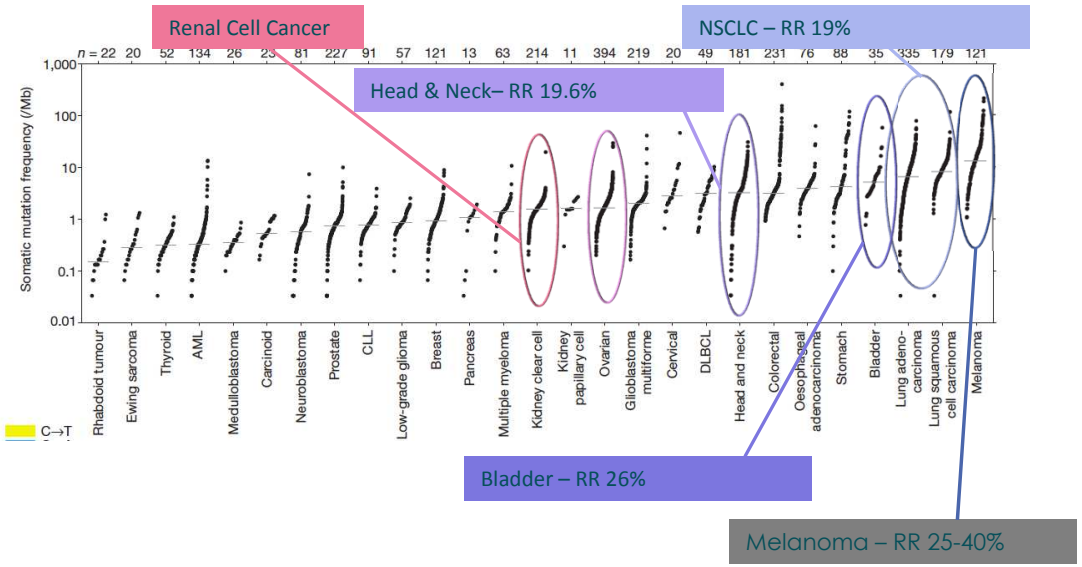
What do you need to know?

- Do you have enough tissue to do the test? i.e. can not use a fine needle aspirate
- If you have the PD-L1 test run, which antibody is being used and what is the definition of a positive result?
- Right now the only testing required to receive a PD-1 antibody is for patients with lung cancer whose doctor wants to prescribe pembrolizumab. In this case, the Merck antibody test must stain at least 50% of the tumor cells for PD-L1.
- PD-L1 staining may be helpful to predict the chance of benefit or help weigh the pros and cons of receiving PD-1 antibody treatment.
- There is NO test that will accurately predict whether the treatment will work in you.
- This is a rapidly changing field.

Tumor Mutation Burden

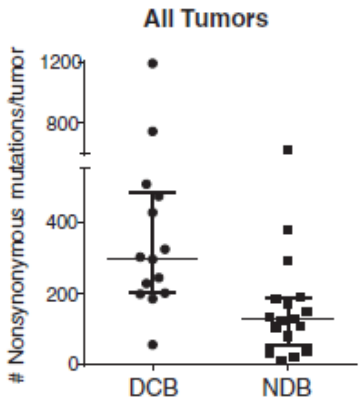
- These are mutations that make abnormal proteins that your immune system might be able to recognize as abnormal.
- There are not mutations that you can pass down to your children.
- This is very experimental.
- Do not go out and ask for your tumor whole exome to be sequenced.
- Please participate and consider allowing researchers to evaluate this in your tumor if you are considering going on immunotherapy.

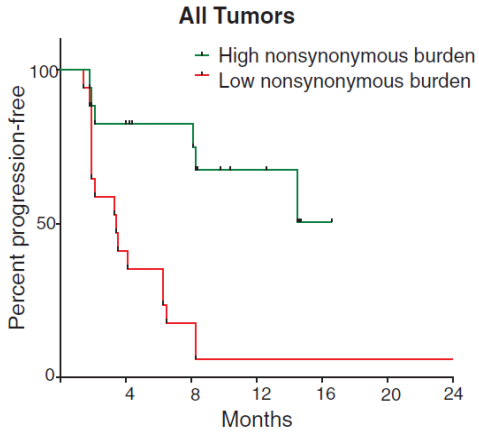
Can mutation burden help select for patients more likely to respond to immunotherapy ?



Adapted from Alexandrov et al., *Nature* 2013

Mutational Density as Predictor of Benefit to PD-1 Blockade (Pembrolizumab in Lung Cancer)

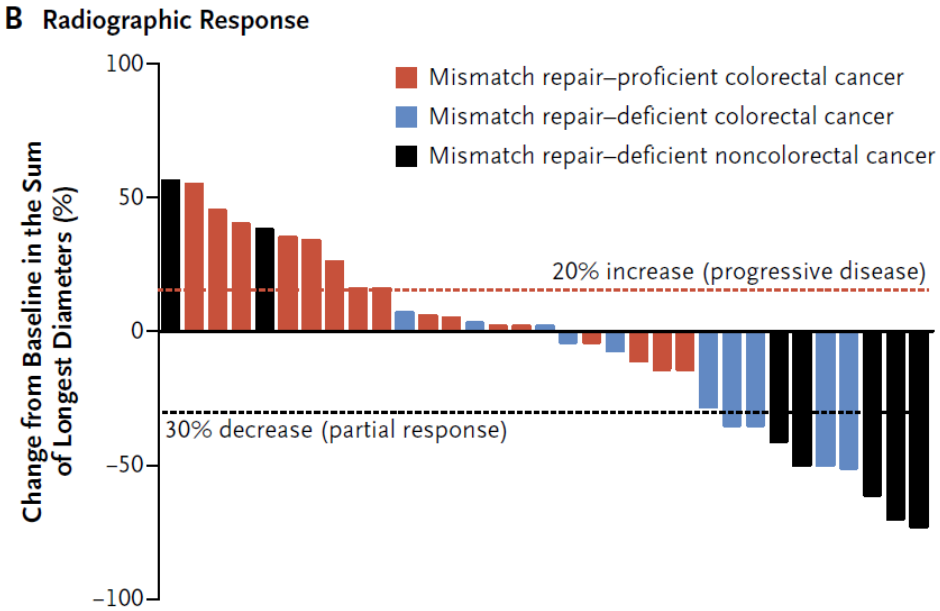




DCB – Durable clinical benefit (PR or SD lasting > 6 mo
NDB – No durable benefit

Rizvi NA, et al. *Science.* 2015;348:124-128.

Mismatch Repair Deficient Tumors (MSI high) and Response to Pembrolizumab



- Mismatch Repair Deficient Tumors aka Microsatellite instability are associated with high number of mutations in a given tumor.
- This data lends support to the notion that mutation burden is associated with clinical benefit with Pembrolizumab treatment.

Le DT et al .NEJM 2015; 372:2509-20

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