Checkpoint Inhibitors in Melanoma; Tumor-Infiltrating Lymphocytes (TILs) as Predictors of Response; Investigating the Immune State of the Tumor Microenvironment

David McDermott, MD
Beth Israel Deaconess Medical Center
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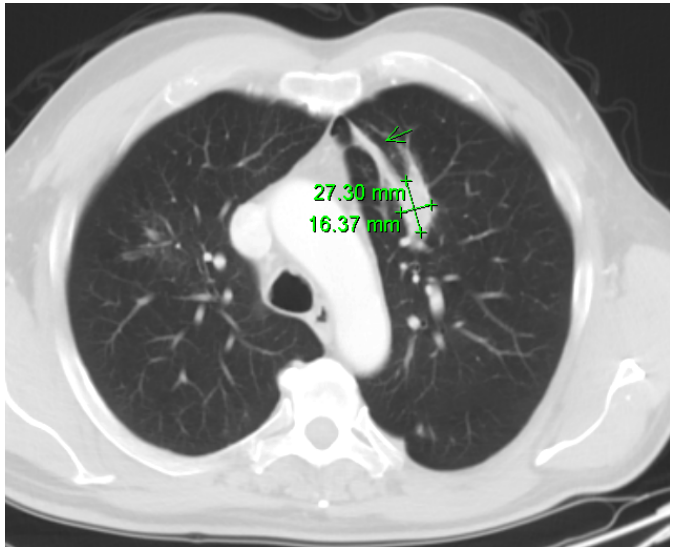
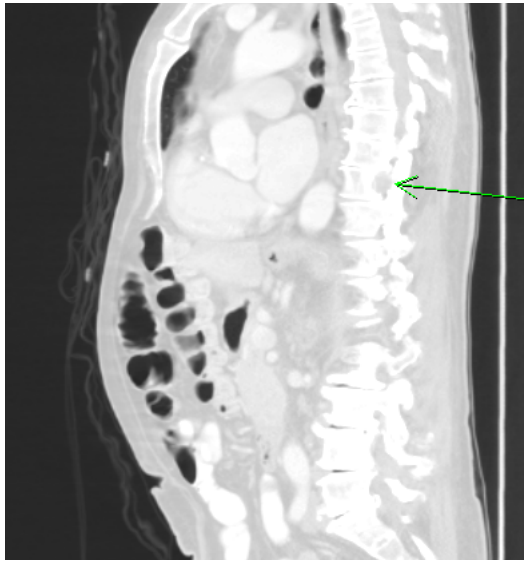
Case 1

- 62 year old male diagnosed with a thick primary melanoma (stage IIC) in 12/08
- Treated with surgery, no adjuvant therapy
- 6/09 - presents with numerous pulmonary nodules. Biopsy positive, BRAF+ melanoma
- 8/09 - HD IL-2 x 2 courses – partial response
- 4/11 – disease progression - lung and bone
- 6/11 – 4/12 - Rx nivolumab - pneumonitis

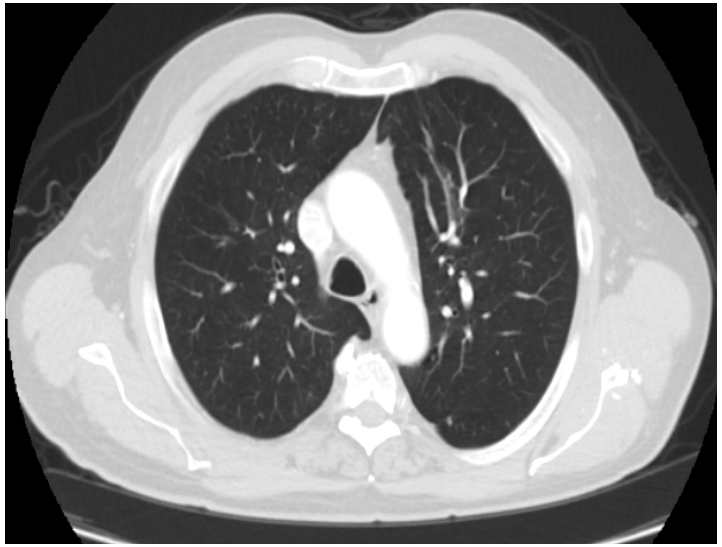
Case 1 – BRAF+ Melanoma – first-line PD-1 Blockade

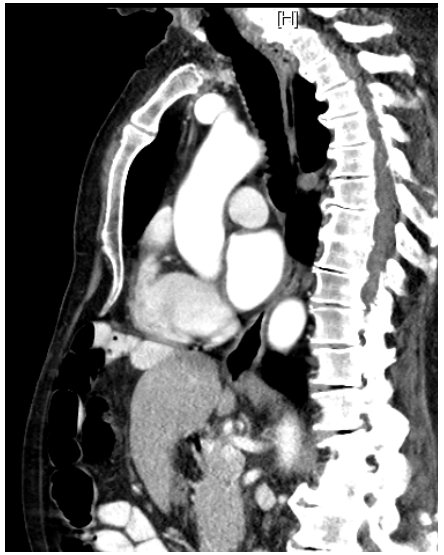
April 2011





March 2017





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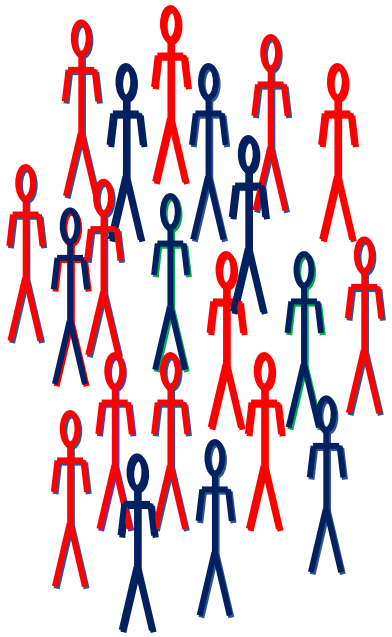
Disclosures

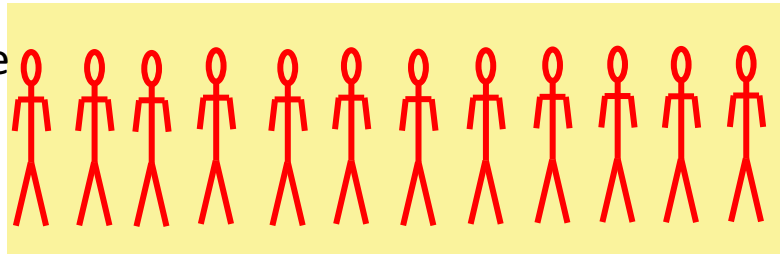
Consulting Agreements	Array BioPharma Inc, Bristol-Myers Squibb Company, Eisai Inc, Exelixis Inc, Genentech BioOncology, Merck, Novartis Pharmaceuticals Corporation, Pfizer Inc
Contracted Research	Prometheus Laboratories Inc.

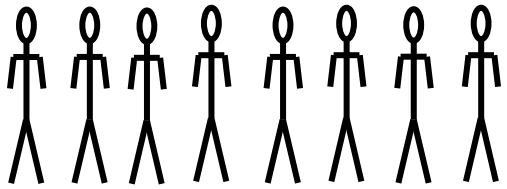
Optimizing Selection Strategy: Identifying immunotherapy responders



Blood or Tissue Assay

Immunotherapy responsive



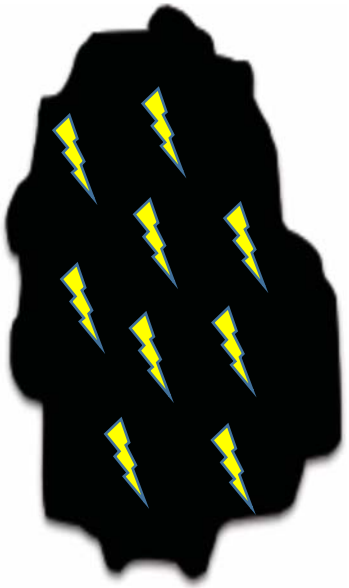


Immunotherapy non-responsive

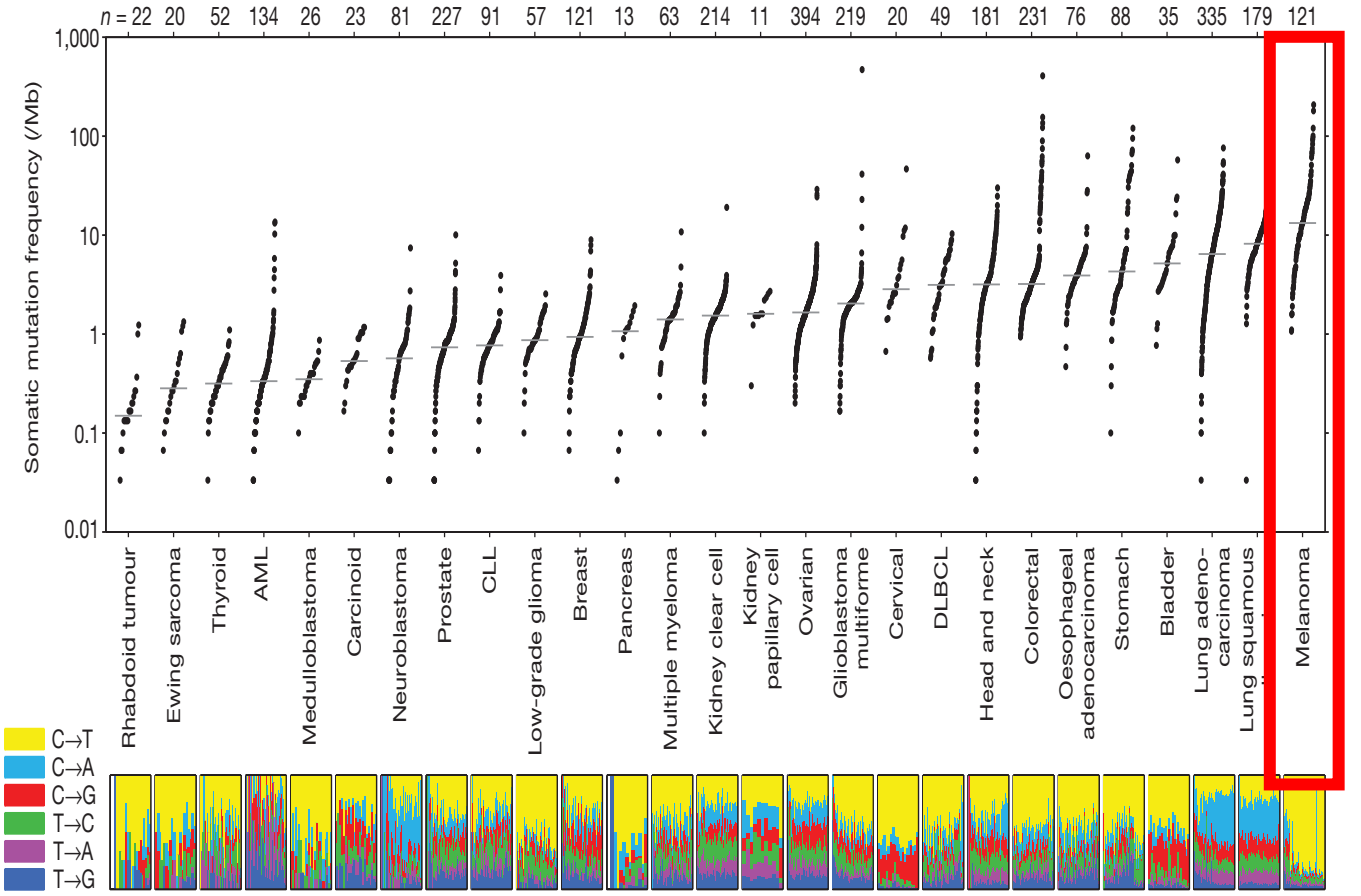
sitc

NIH NATIONAL CANCER INSTITUTE

Emerging Predictive Model of PD1 responsiveness

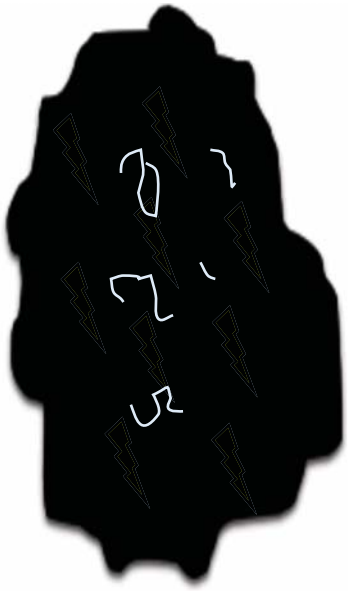


Mutational Load



Lawrence et al. Nature 2013

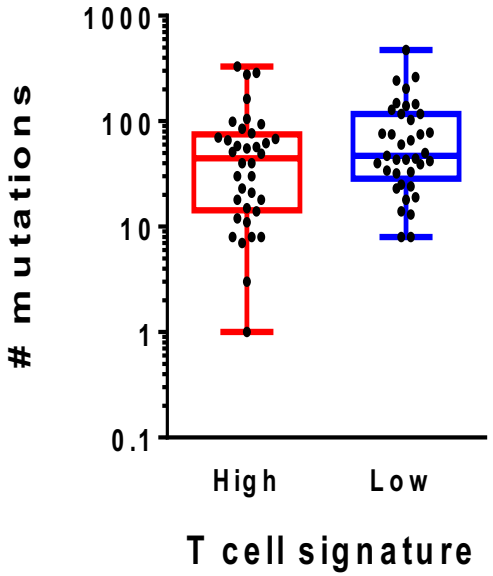
Emerging Predictive Model of PD1 responsiveness



Mutational Load

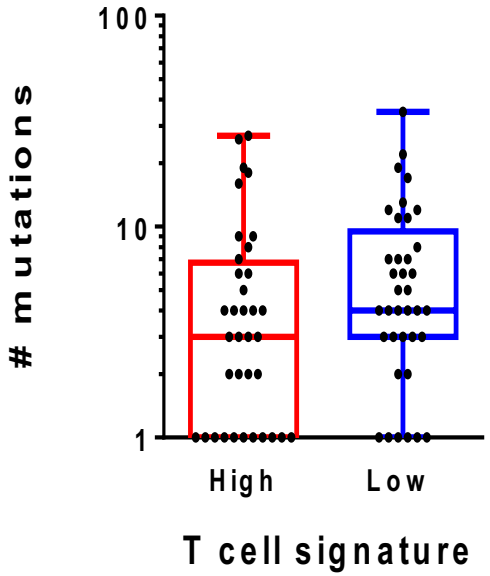
Neoantigen load

All neoantigens



p=0.36

Selected highly binding neoantigens



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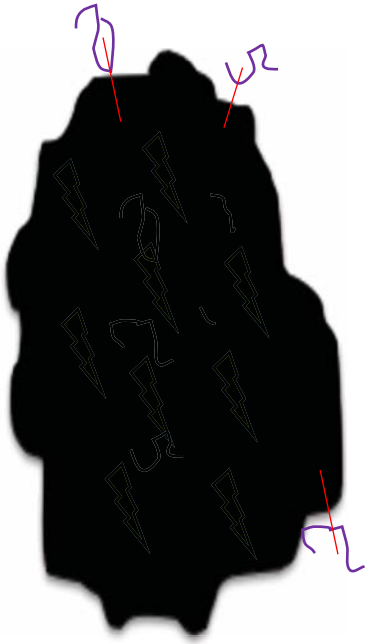
Gajewski et al. ASCO 2015

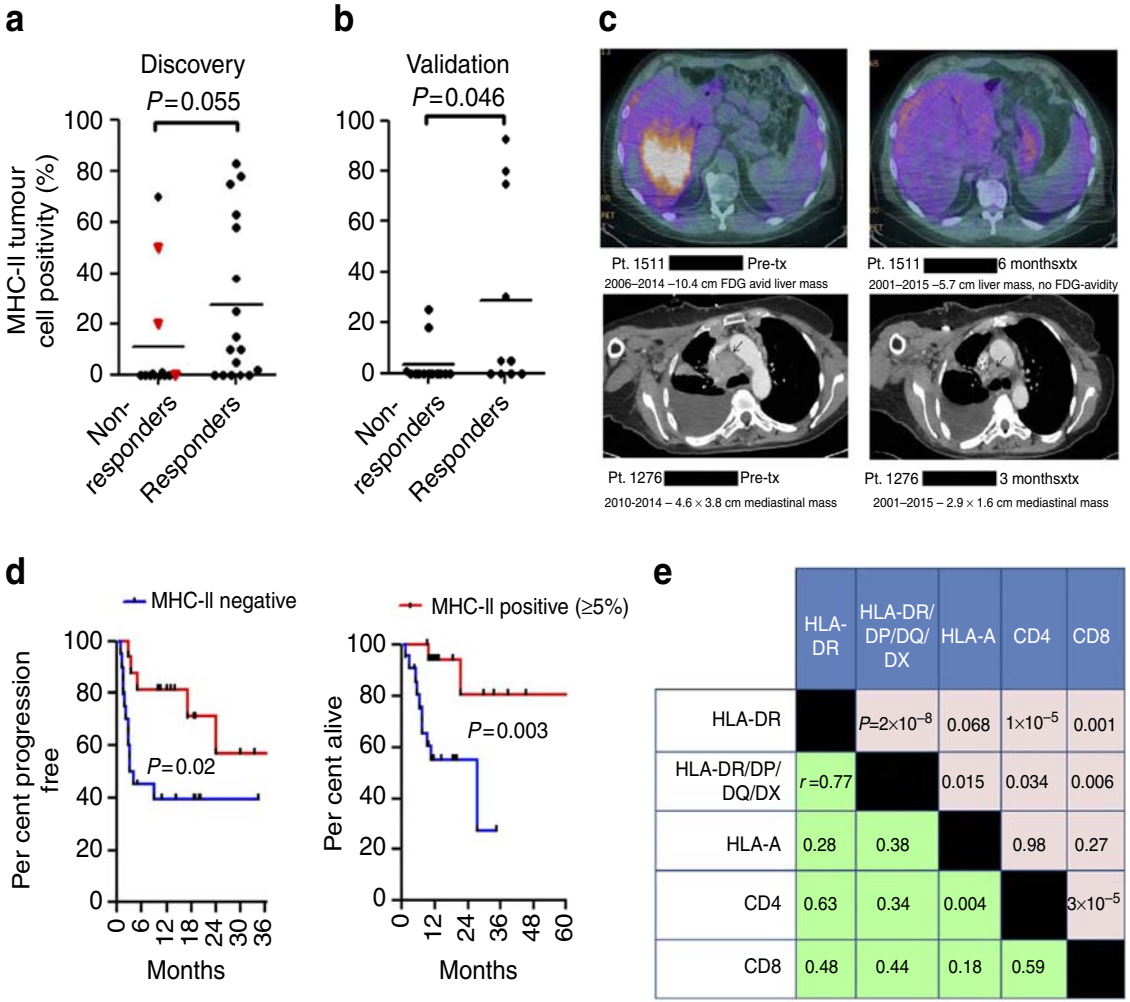
Emerging Predictive Model of PD1 responsiveness



Mutational Load

Neoantigen load

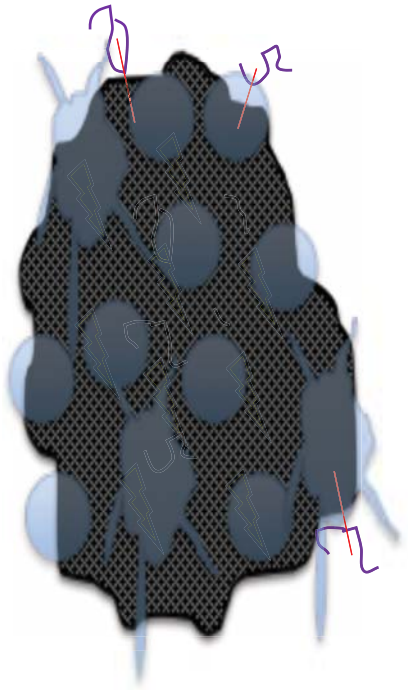
Antigen expression machinery



	HLA-DR	HLA-DR/DP/DQ/DX	HLA-A	CD4	CD8
HLA-DR		$P=2\times10^{-8}$	0.068	1×10^{-5}	0.001
HLA-DR/DP/DQ/DX	$r=0.77$		0.015	0.034	0.006
HLA-A	0.28	0.38		0.98	0.27
CD4	0.63	0.34	0.004		3×10^{-5}
CD8	0.48	0.44	0.18	0.59	

Johnson et al. Nature Commun. 2016

Emerging Predictive Model of PD1 responsiveness

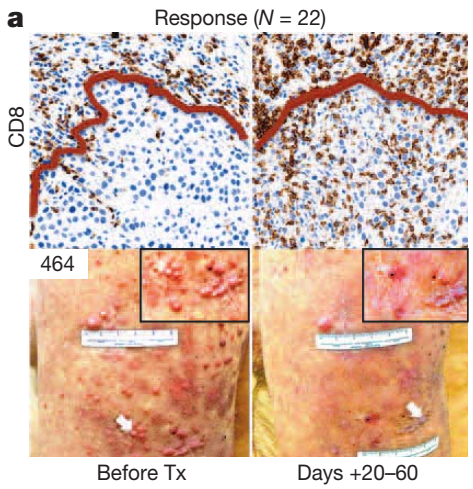


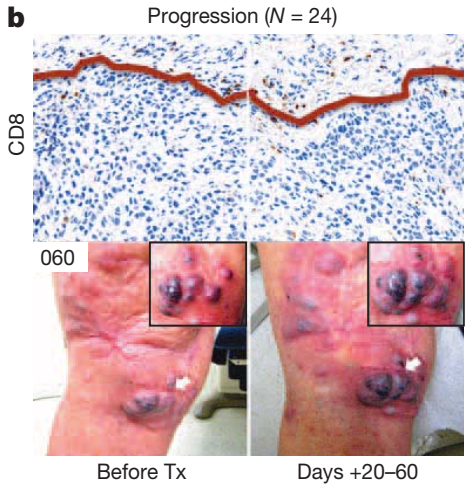
Mutational Load

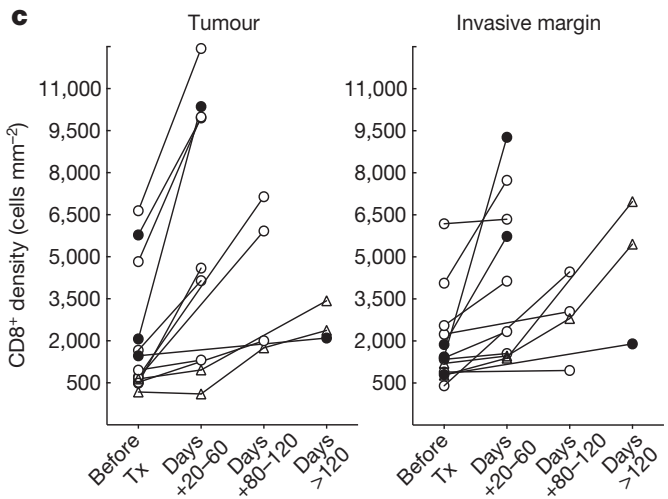
Neoantigen load

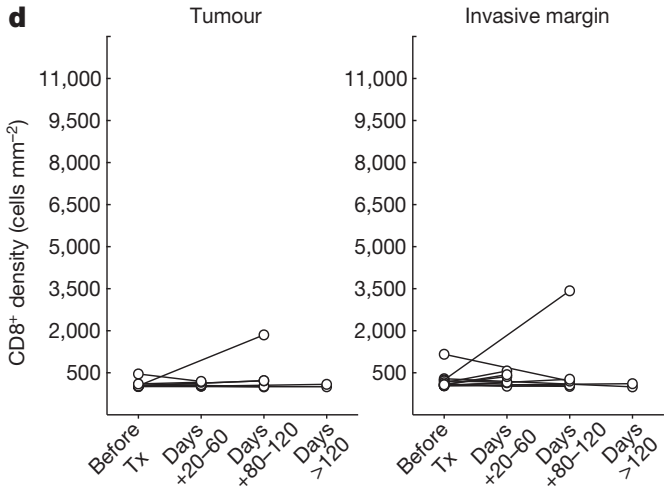
Antigen expression machinery

T-cell infiltration



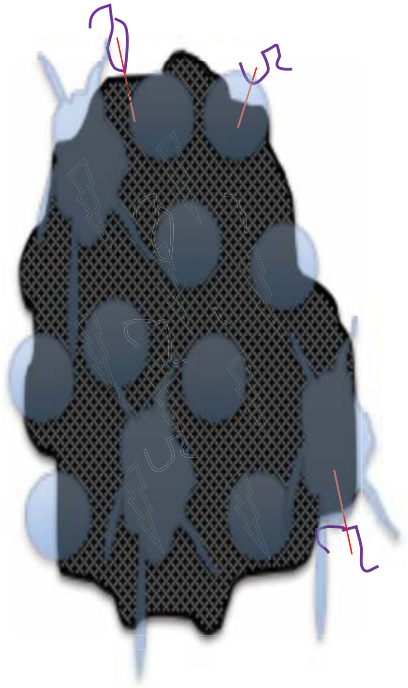






Tumeh et al. Nature 2015

Emerging Predictive Model of PD1 responsiveness

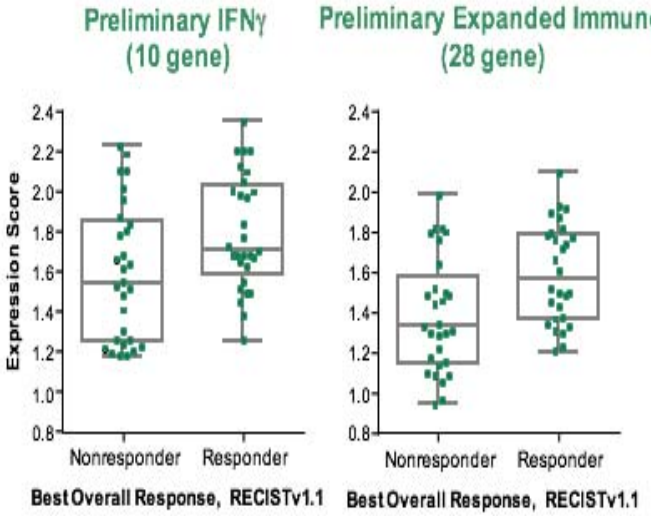


Mutational Load

Neoantigen load

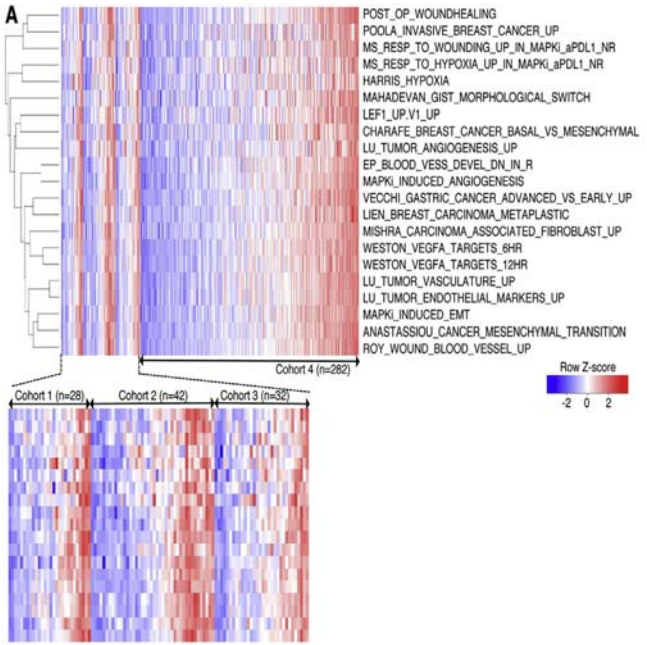
Antigen expression machinery

T-cell infiltration



Correlation With Response in the Validation Set[a]

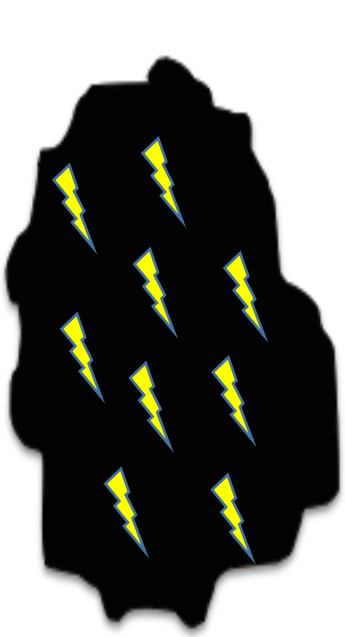
Signature	BOR by RECIST N = 51	PFS by RECIST N = 62	OS N = 62
Preliminary IFNγ	*P* = 0.047	*P* = 0.016	*P* = 0.090
Preliminary expanded immune	*P* = 0.027	*P* = 0.015	*P* = 0.105



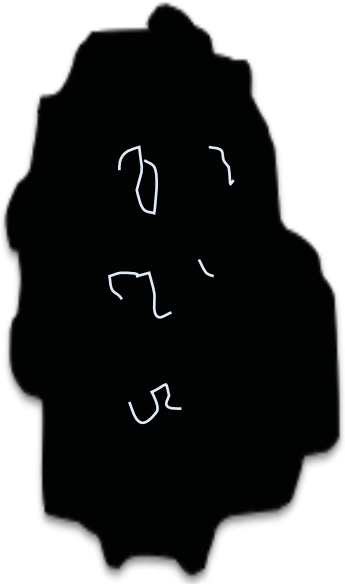
Hugo et al. Cell 2016

Ribas et al. ASCO 2015

Emerging Predictive Model of PD1 responsiveness

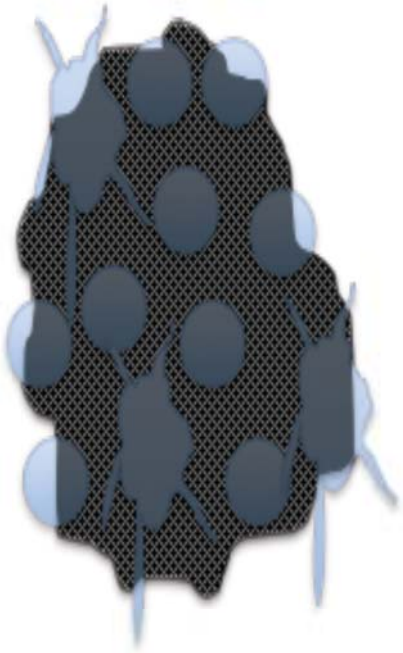


Mutational Load



Neoantigen load

Antigen expression machinery

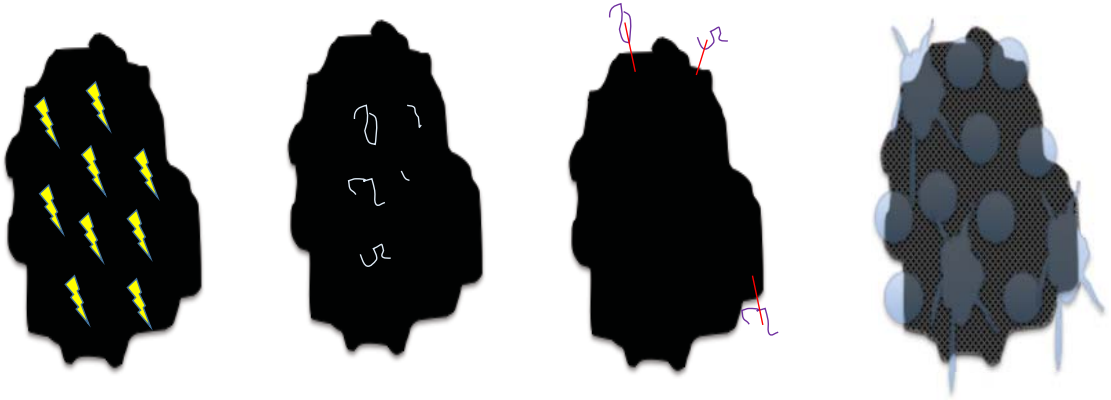


T-cell infiltration

Tissue/Tumor response is PDL1 expression

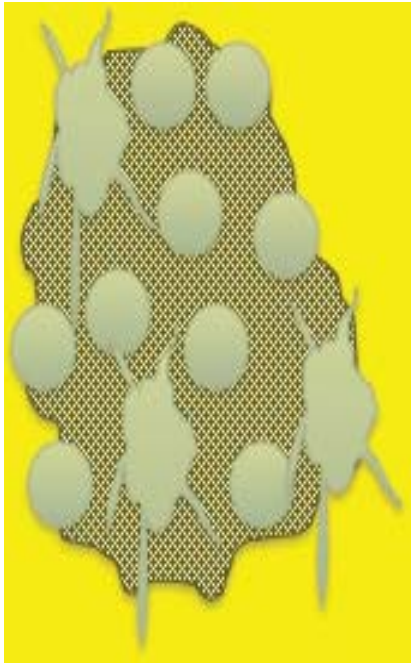
Neoantigen load

T-cell infiltration



Mutational Load

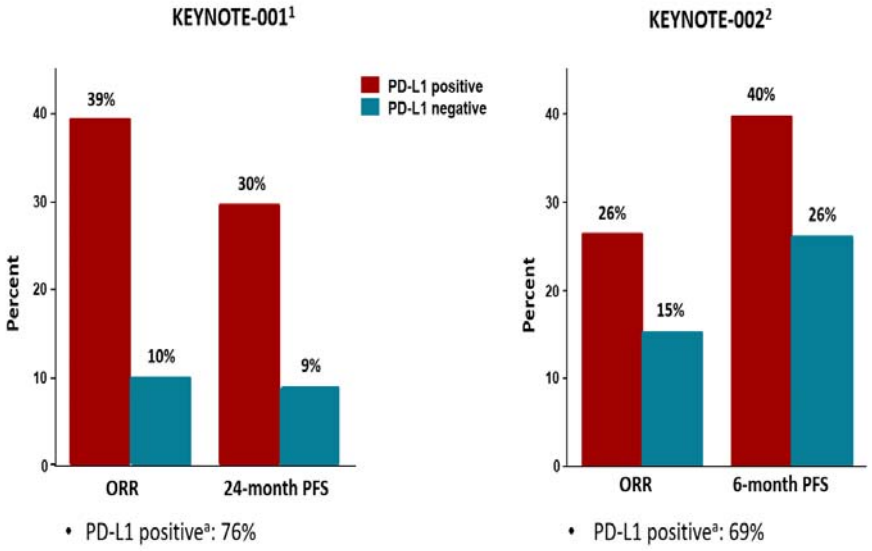
Antigen expression machinery



PD-L1 expression

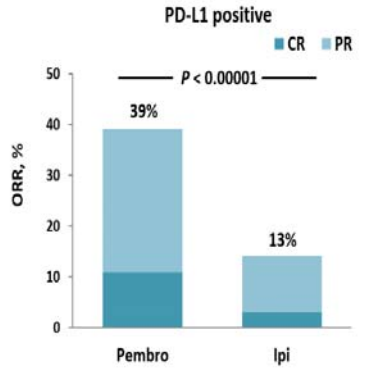
PDL1 expression is associated with better outcomes

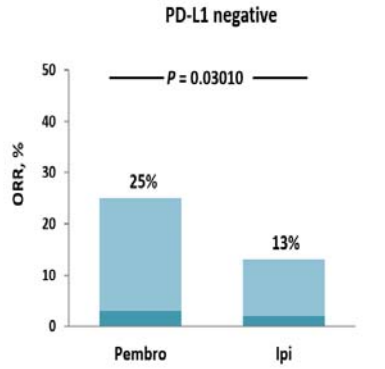
PD-L1 Expression Correlates with Improved Response



PD-L1 expression was assessed in pretreatment tumor biopsies by immunohistochemistry (IHC) using the 22C3 antibody (Merck); PD-L1 positivity was defined as PD-L1 expression in ≥1% of tumor and associated immune cells.
[a]Among patients with samples evaluable for PD-L1 expression.
1. Daud A, et al. Presented at: SMR 2015 Congress; November 18-21, 2015; San Francisco, CA.
2. Puzanov I, et al. Presented at: 2015 ASCO Annual Meeting: May 29-June 2, 2015; Chicago, IL.

Best Overall Response by PD-L1 Expression





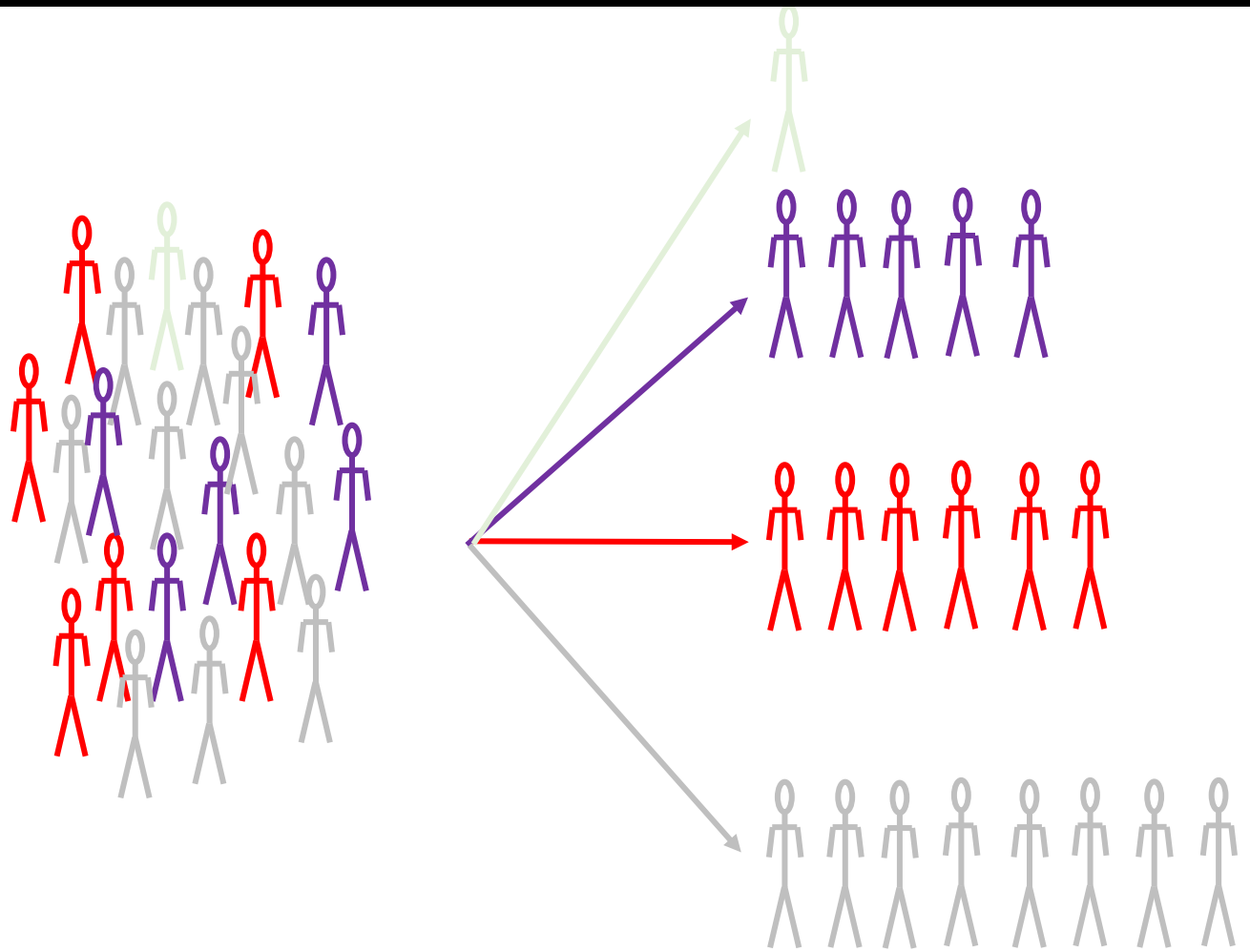
	PD-L1 positive	
	Pembro	Ipi
Median duration of response[a], days (range)	NR (42+ – 429+)	337 (41 – 412+)

	PD-L1 negative	
	Pembro	Ipi
Median duration of response[a], days (range)	NR (33+ – 418+)	NR (127+ – 295+)

[a]Based on patients with best overall response of confirmed complete or partial response.
Analysis cut-off date: March 3, 2015.

Carlino et al. AACR 2016

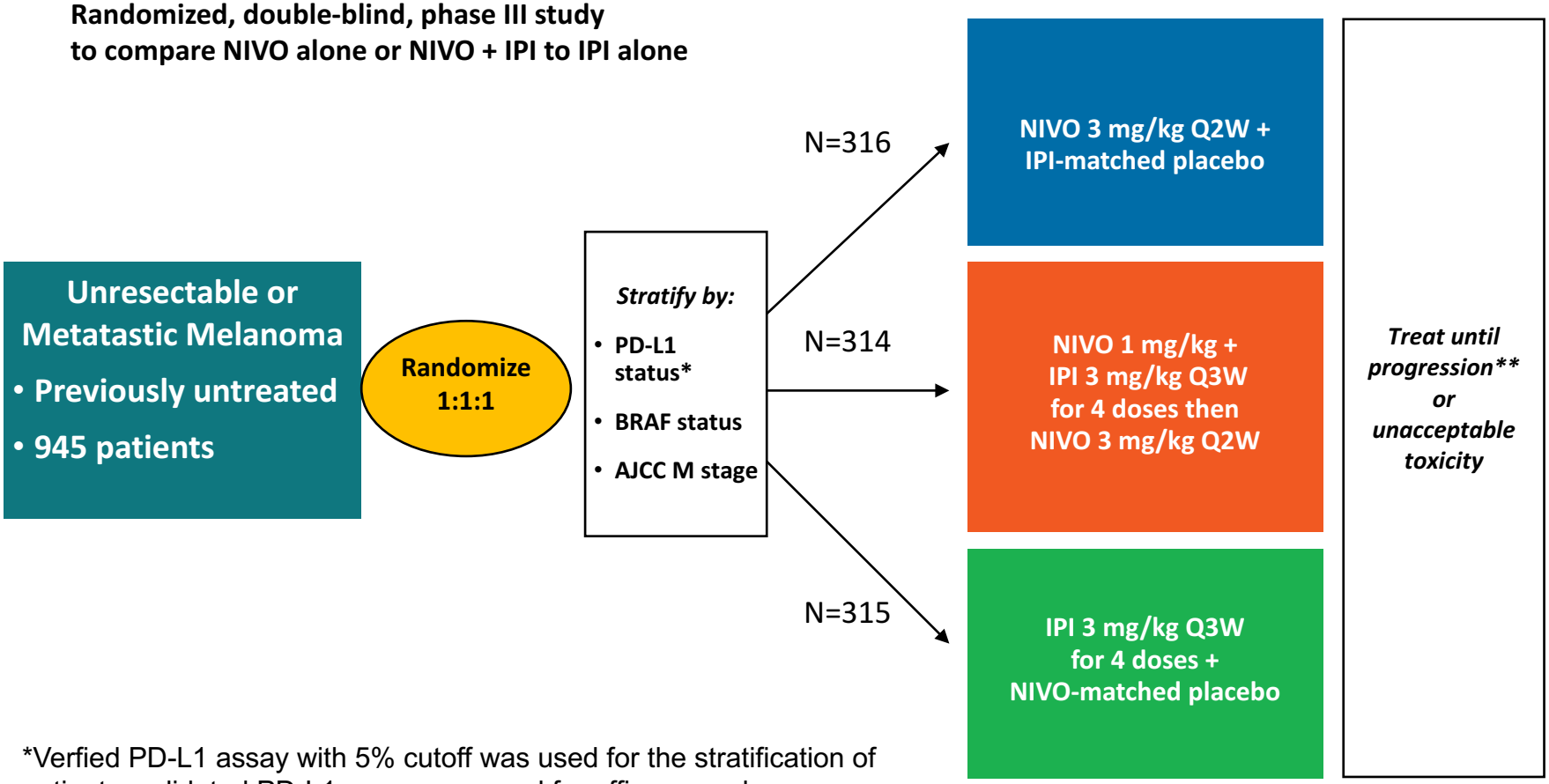
PDL1 Expression:
Helpful in choosing between IPI/NIVO vs anti-PD1?



Can we identify those patients who may be spared toxicity of combined immune checkpoint inhibitor therapy?

CheckMate 067 (CA209-067): Study Design

Randomized, double-blind, phase III study to compare NIVO alone or NIVO + IPI to IPI alone



*Verfied PD-L1 assay with 5% cutoff was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

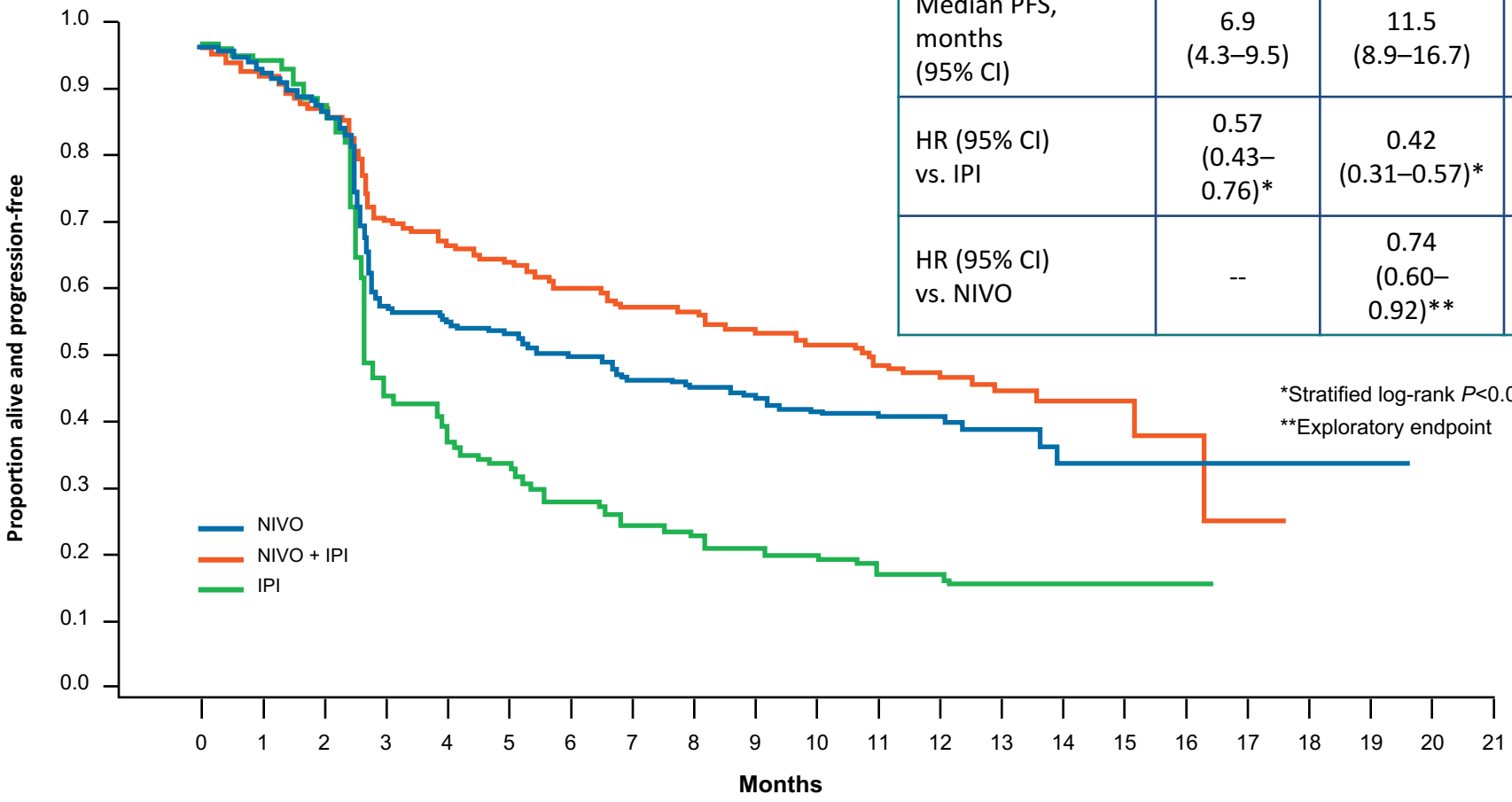
**Patients could have been treated beyond progression under protocol-defined circumstances.

Co-primary Endpoint: PFS (Intent-to-Treat)

	NIVO (N=316)	NIVO + IPI (N=314)	IPI (N=315)
Median PFS, months (95% CI)	6.9 (4.3–9.5)	11.5 (8.9–16.7)	2.9 (2.8–3.4)
HR (95% CI) vs. IPI	0.57 (0.43–0.76)*	0.42 (0.31–0.57)*	--
HR (95% CI) vs. NIVO	--	0.74 (0.60–0.92)**	--

*Stratified log-rank $P<0.00001$ vs. IPI

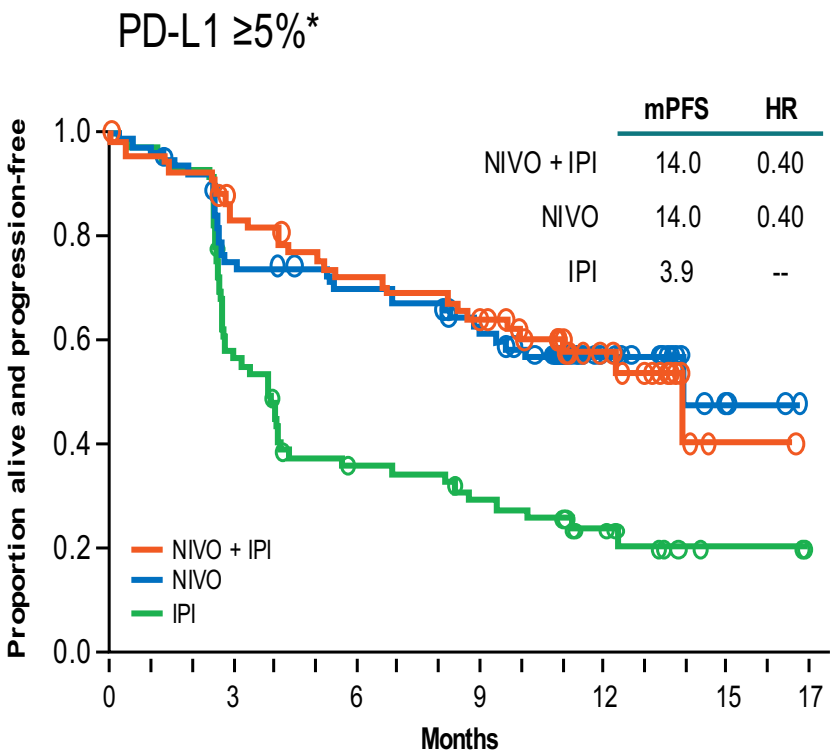
**Exploratory endpoint

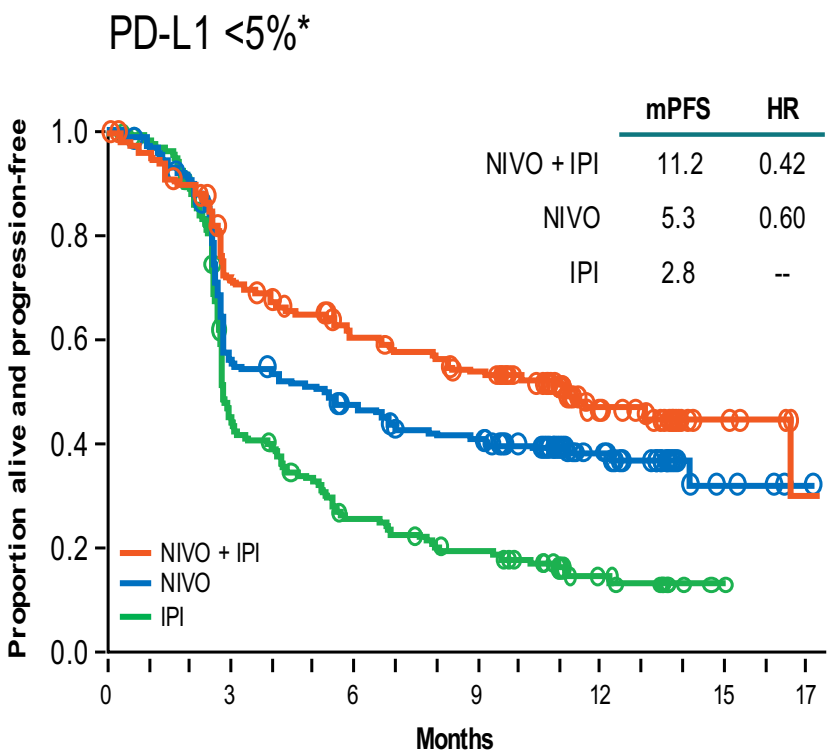


Number at Risk																						
NIVO	316	292	271	170	160	147	136	132	124	124	106	86	50	38	14	9	6	2	1	1	1	0
NIVO + IPI	314	293	275	208	191	173	164	163	151	151	137	116	65	54	18	11	7	2	1	0	0	0
IPI	315	285	265	118	95	77	68	63	54	54	47	42	24	17	7	4	3	0	0	0	0	0

PDL1 Expression: Helpful in choosing between IPI/NIVO vs anti-PD1?

PFS by PD-L1 Expression Level (5%)

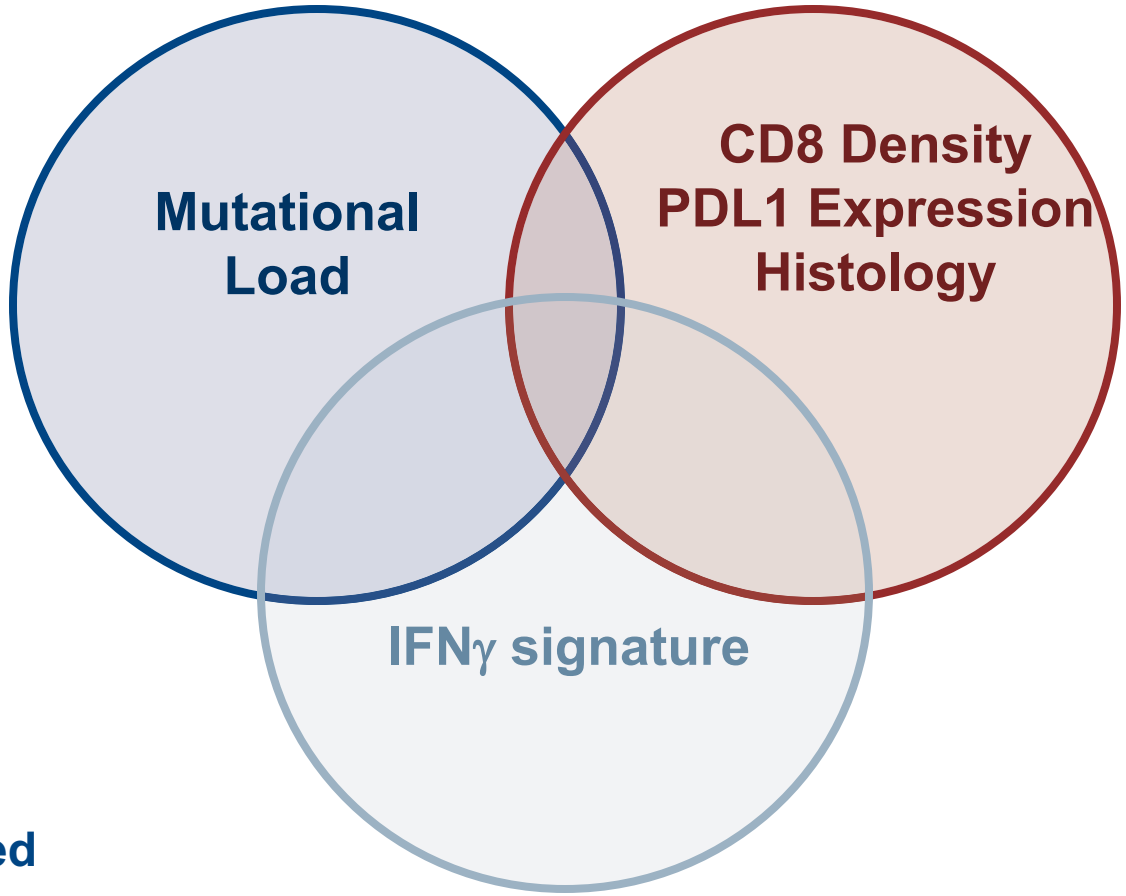




*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

Wolchok et al. ASCO 2015; Larkin et al. NEJM 2015

Biomarker Model

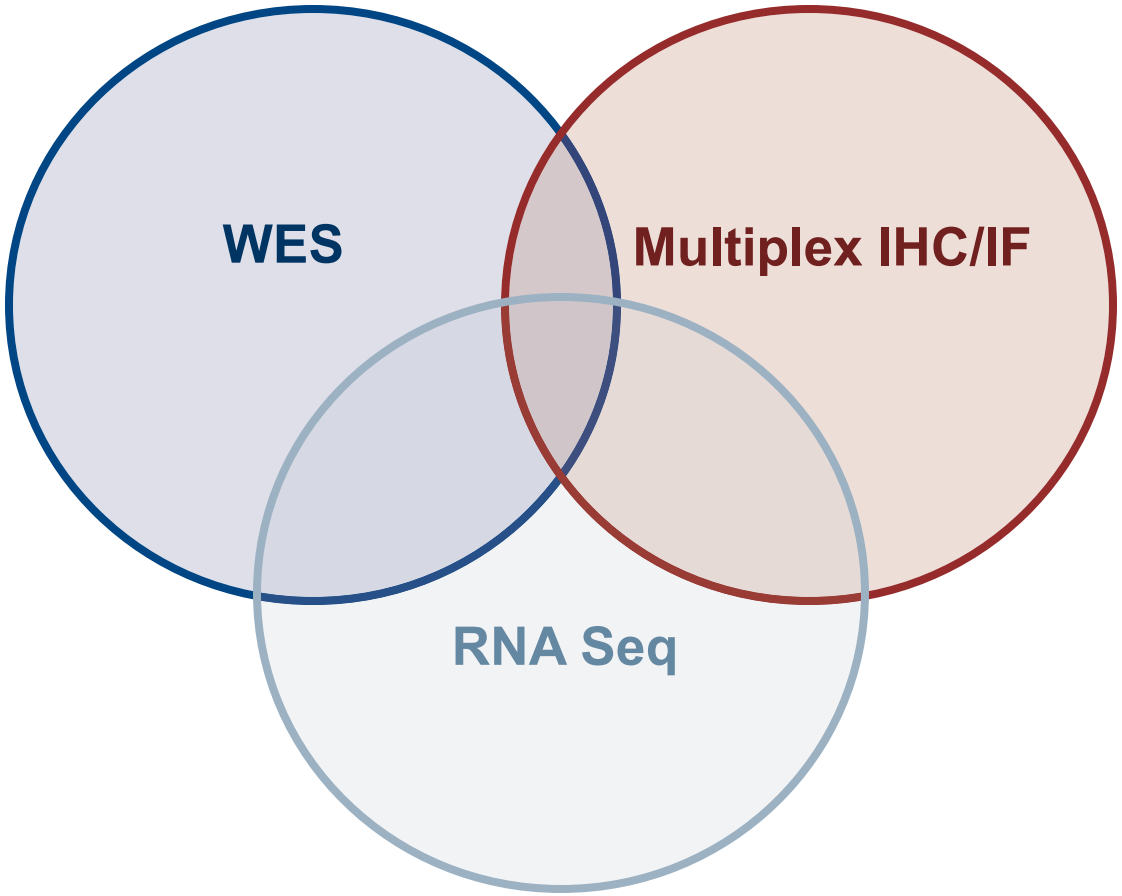


All inter-related

Some tumors may have a larger sweet spot

M Atkins with permission.

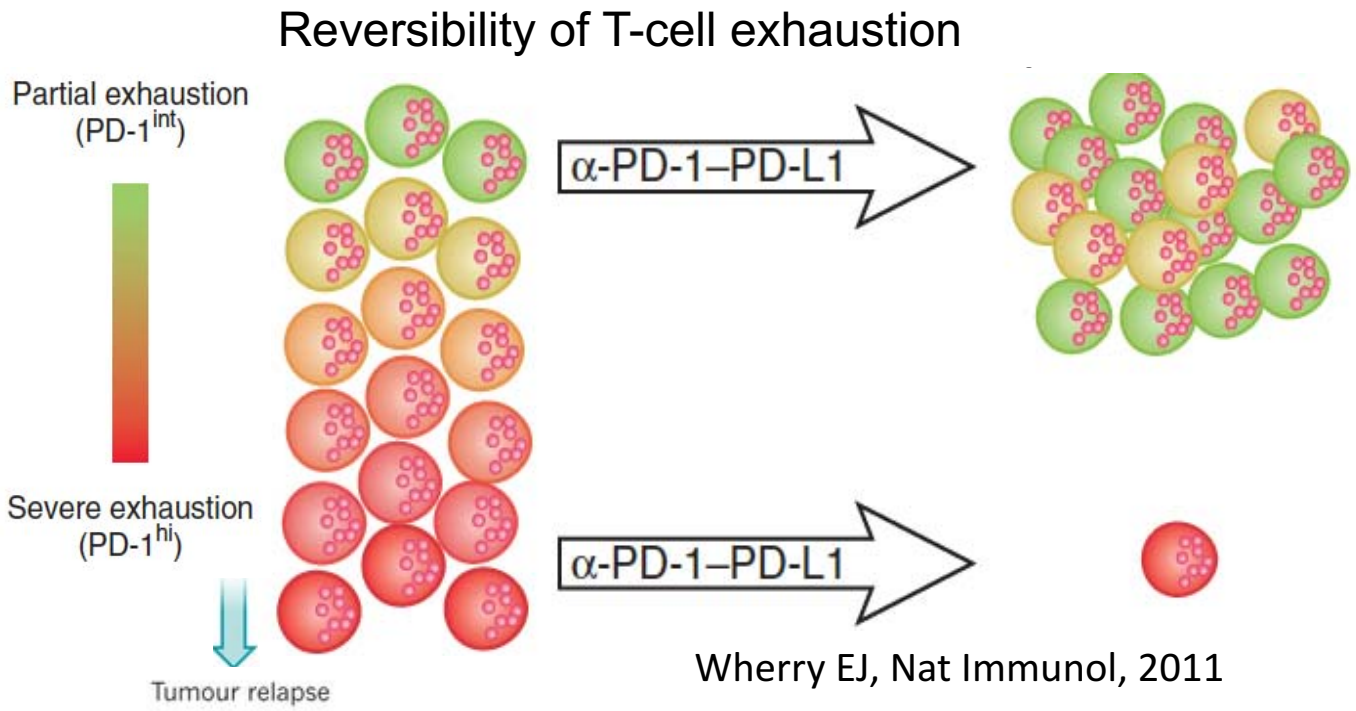
Biomarker Model



Needed Technologies

M Atkins with permission.

Problem: tumor complexity

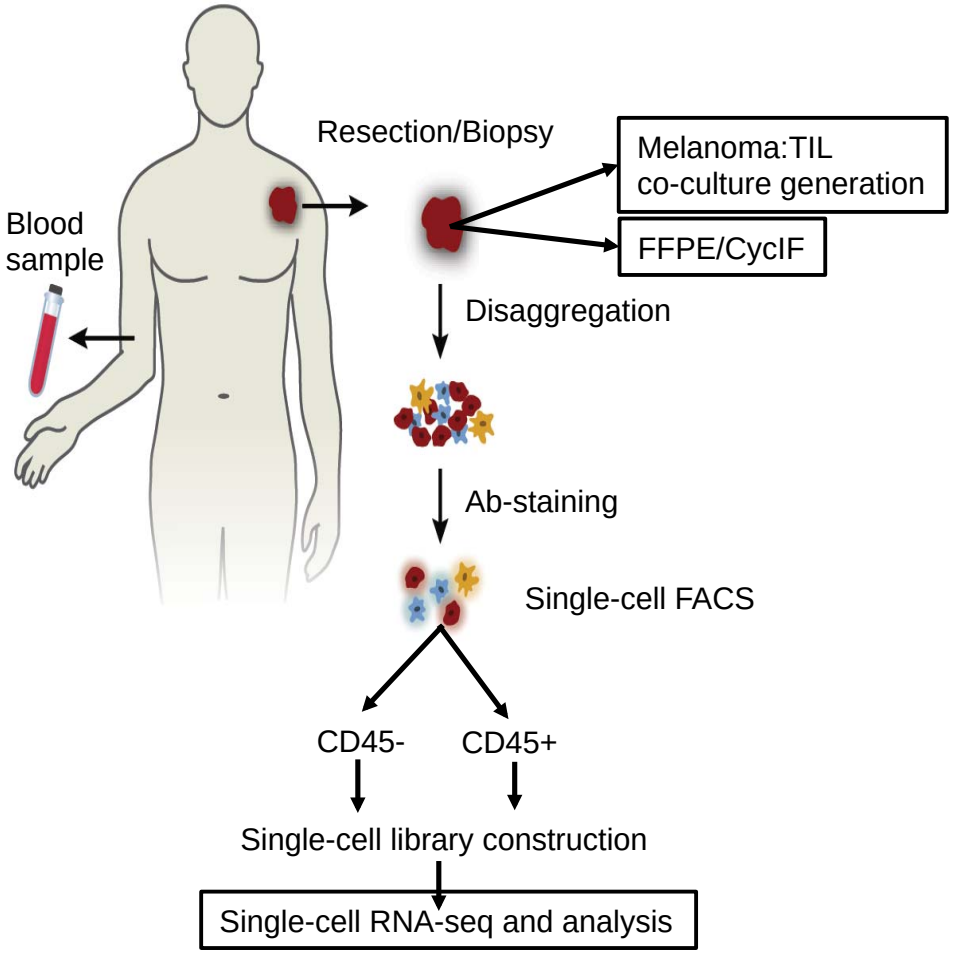


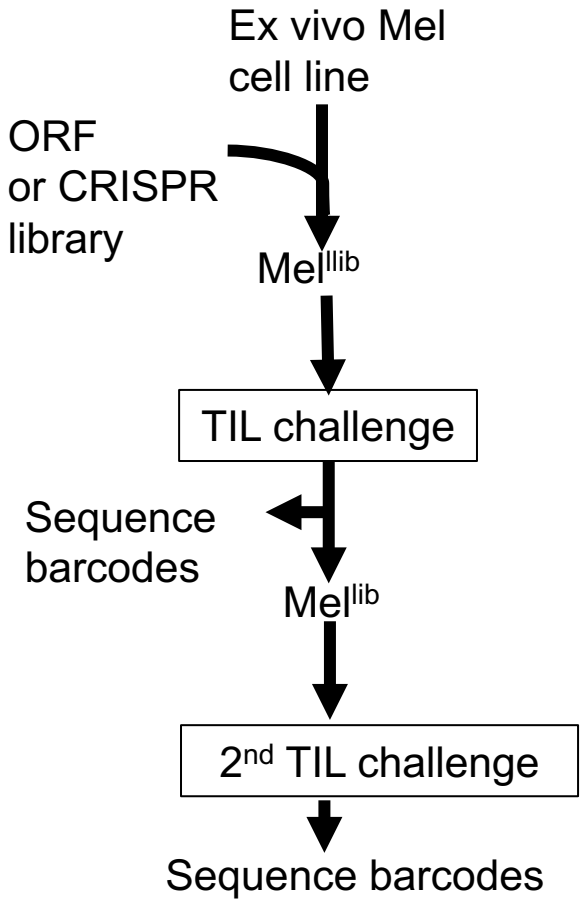
Wherry EJ, Nat Immunol, 2011

Challenges

1. Bulk tissue analysis unable to recapitulate inherent heterogeneity
2. Routine imaging (i.e. single-cell marker such as PD-L1) low throughput, low-plex, biased, subjective
3. Experiments difficult to implement in patient models

Genome-scale assessment of immune escape and IO-resistance mechanisms





Summary:
The state of predictive biomarker development

Analysis of the tumor:

- Total mutation burden
- Types of mutations (neoantigens)
- Capability of being recognized by the immune system

Analysis of immune cells in the tumor

- Presence or absence of cells
- Location of immune cells (periphery versus central)
- Types of immune cells (killers vs suppressors)
- Activity of the cells (gene expression analysis)

Response of the tumor against the immune cells

- PD-L1 expression
- Other “immune checkpoint” molecule expression

Analysis of blood…

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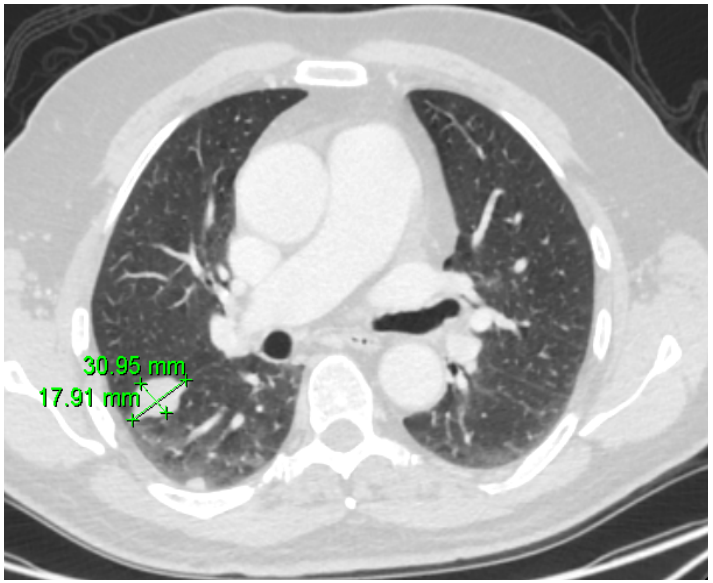
Case 2

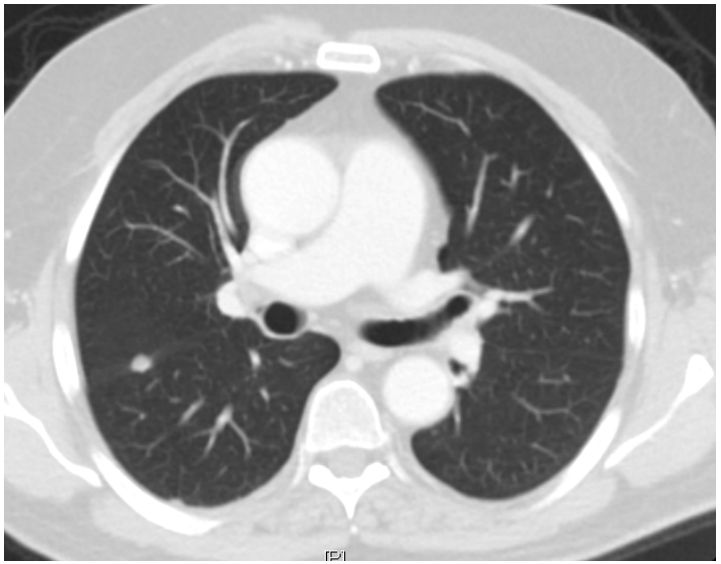
- 6/11 - 68 yo male – dx Melanoma Stage IIB
- 9/13 - presents with numerous pulmonary nodules. Biopsy positive, BRAF+ melanoma
- 12/13 – started ipi/nivo
- 1/14 – post C2, watery diarrhea, admit to BIDMC for two weeks, scope bx = colitis , rx IV steroids, infliximab
- 2/14 – CT torso – partial response
- 4/14 – off steroids

Case 2 – BRAF+ Melanoma – first-line PD-1/CTLA-4 Ab

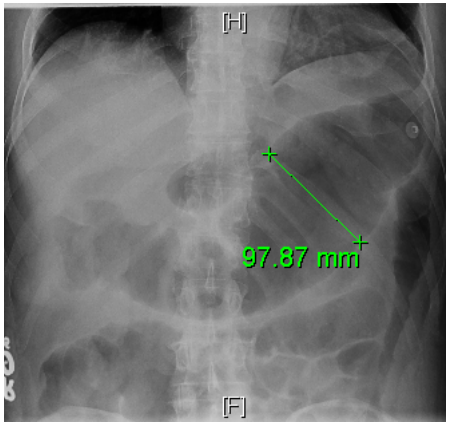
Dec 2013



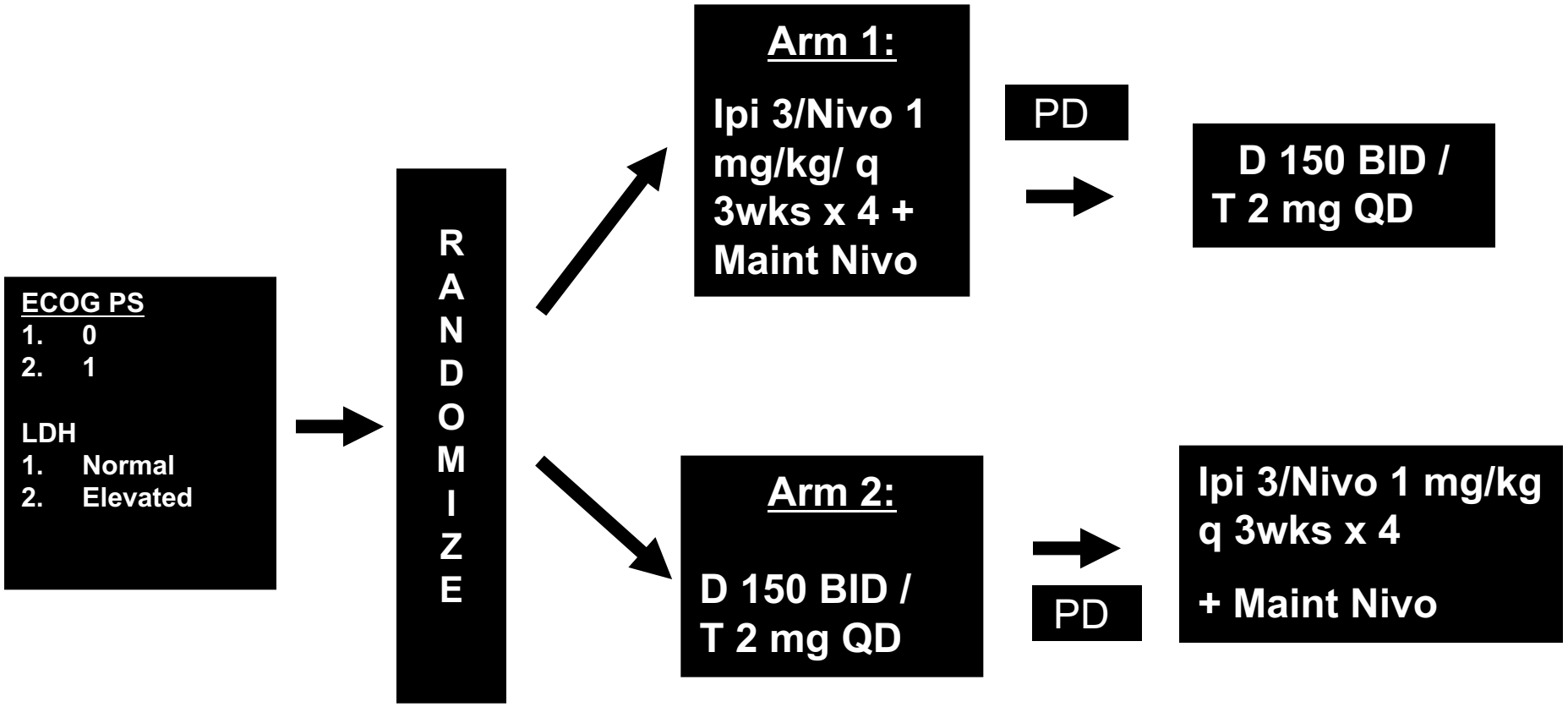
Jan 2017



Jan 2014



Sequence Comparison:
EA6134: Ipi/Nivo to D/T versus D/T to Ipi/Nivo



ECOG and SWOG protocol – Atkins, Chmielowski
Accruing

D – dabrafenib, T- trametinib