The impact of tumor genetics on host immune response

Matthew Hellmann, MD
Memorial Sloan Kettering Cancer Center

ESMO IMPAKT 2015 Breast Cancer Conference
May 8th, 2015

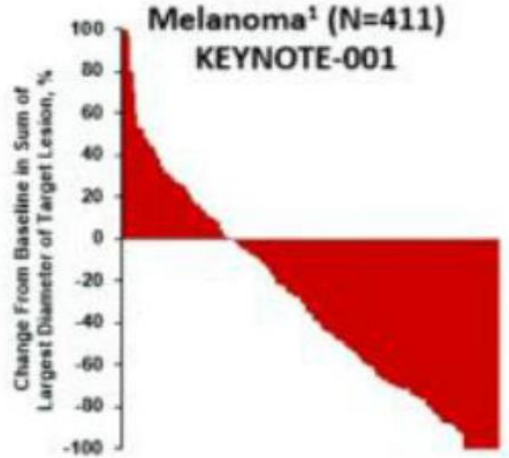
Memorial Sloan Kettering Cancer Center

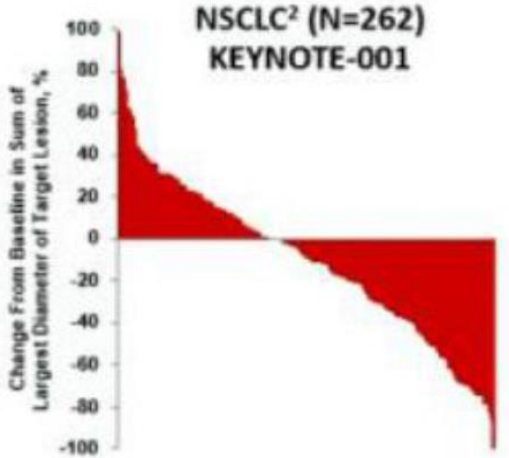
Background

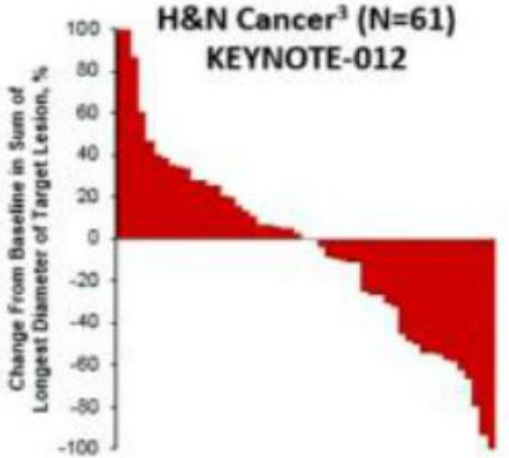
- T cell checkpoint inhibitors are revolutionizing treatment options for patients with cancers.

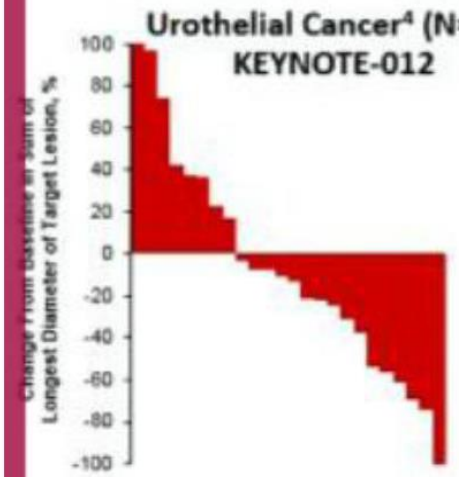
- The broad activity has validated the concept that the host immune system can be harnessed to treat a multitude of cancers.

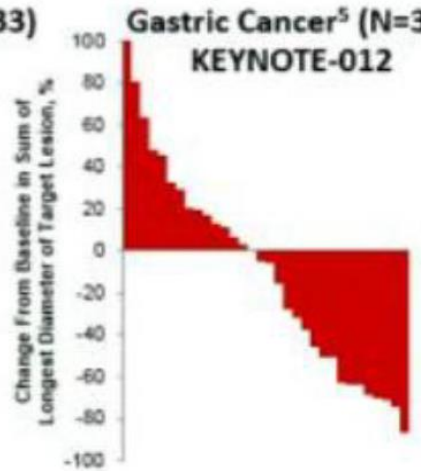
Pembrolizumab Antitumor Activity

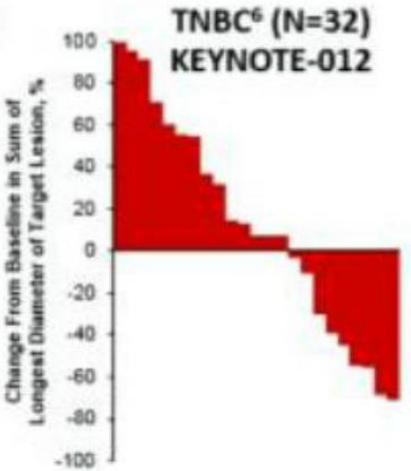


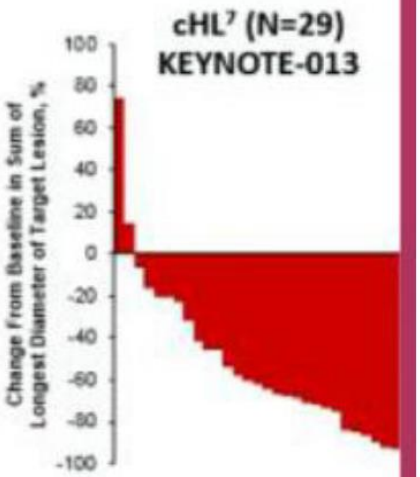








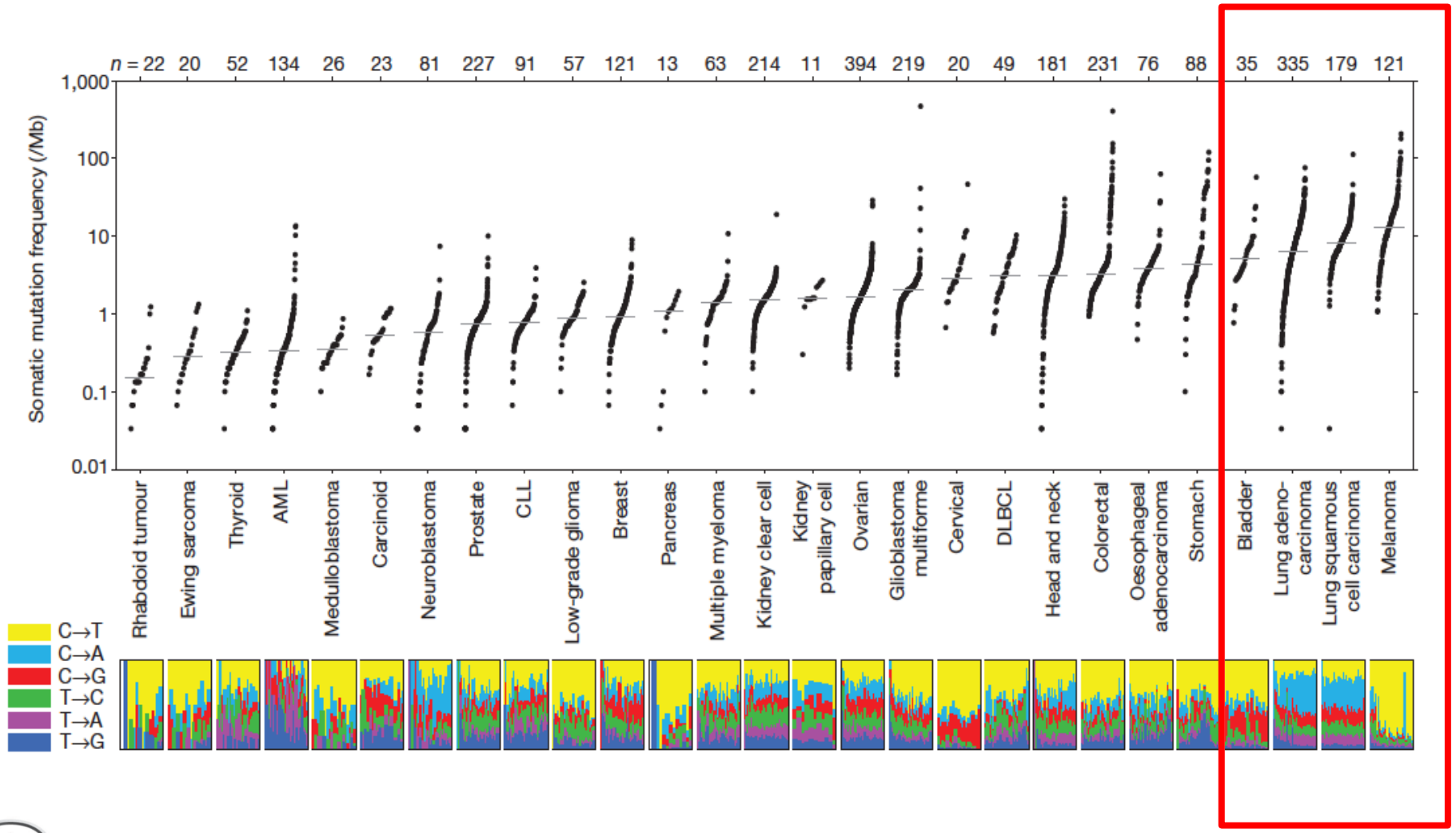




1. Daud A et al. Presented at SMR Annual Meeting 2014; Nov 13-16, 2014; Zurich, Switzerland; 2. Garon EB et al. Presented at ESMO 2014 Congress; Sep 26-30, 2014; Madrid, Spain; 3. Chow LQ et al. Presented at ESMO 2014 Congress; Sep 26-30, 2014; Madrid, Spain; 4. O'Donnell P et al. Presented at 2015 Genitourinary Cancers Symposium; Feb 26-28, 2015; Orlando, FL; 5. Muro K et al. Presented at 2015 Gastrointestinal Cancers Symposium; Jan 15-17, 2015; San Francisco, CA; 6. Nanda R et al.

Alley *et al*, AACR 2015

May genomics underlie differential response?

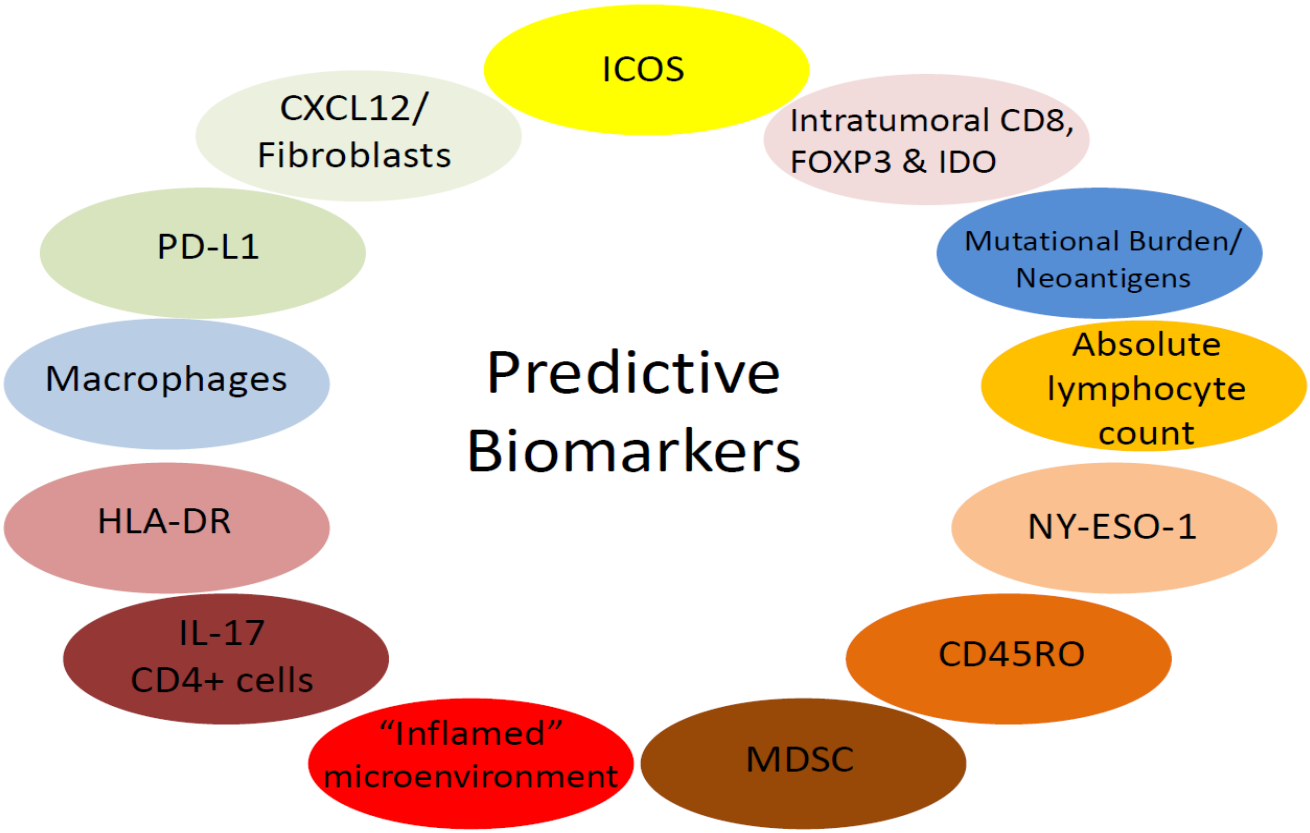


Lawrence *et al*, Nature 2013

Outline

- We recently described a strong correlation between the molecular landscape of tumors and response to T cell checkpoint blockade
  - Mutation burden
  - Neoantigens
  - Tetrapeptide signature and homology

Diversity of predictive markers



Feig et al PNAS 2013; Ku et al Cancer 2010; Menard et al Clin Cancer Res 2008; Weber et al JCO 2009; Hodi et al PNAS 2008; Hamid et al JCO 2009; Ng et al Cancer Immuno Res 2013; Tarhini et al PLoS One 2014; Kitano et al Cancer Immunol Res 2013; Spranger et al Sci Transl Med 2013; Kitano et al Cancer Immunol Res 2014; Ji RR et al, Cancer Immunol Immunother 2012; Yuan J et al, PNAS 2011; DiGiacom lo etal Cancer Immunol Immunother 2013; Queirolog et al, Cancer Invest 2013; Wolchok et al, Cancer Immun 2010

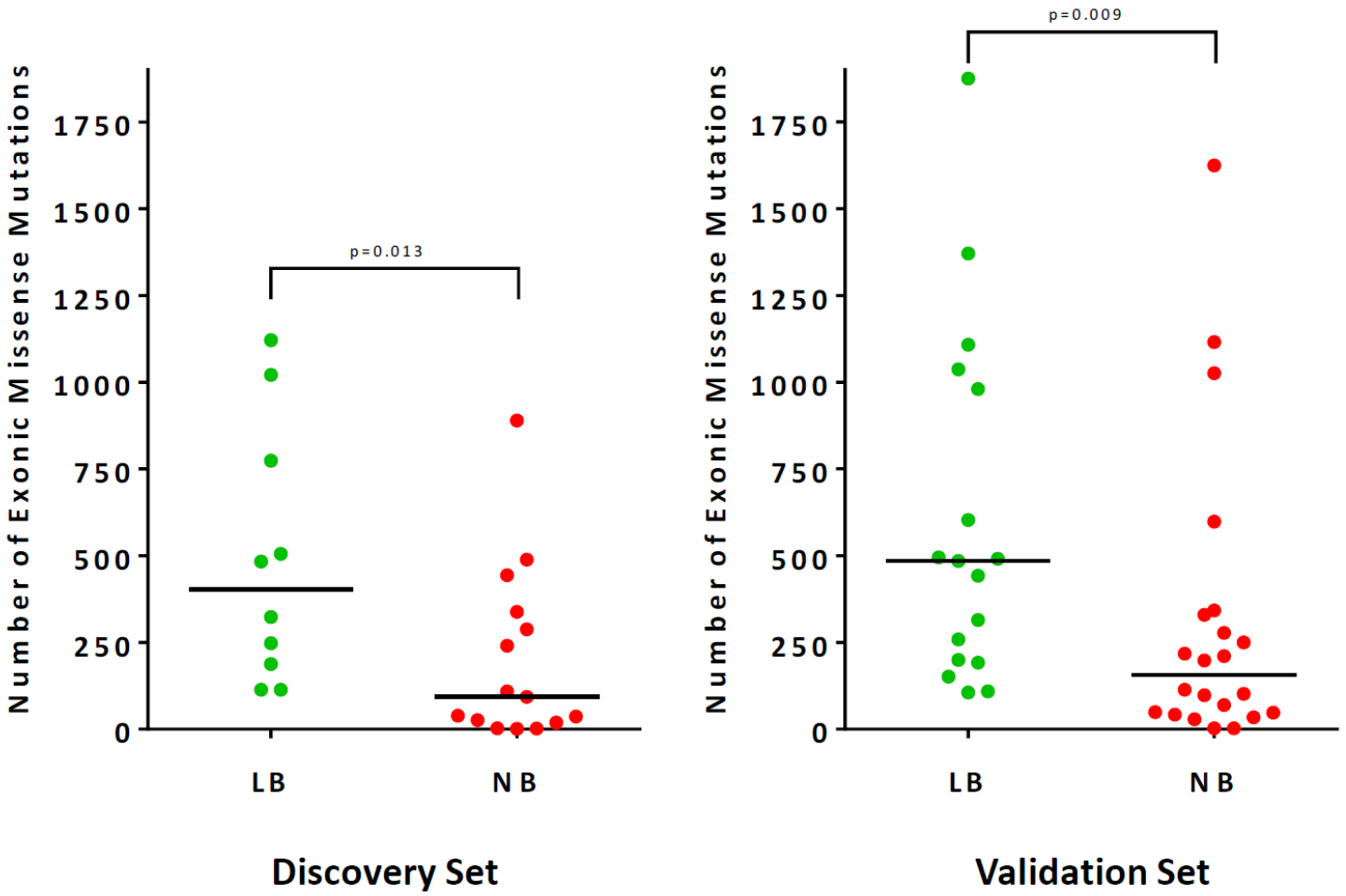
Slide courtesy of Alexandra Snyder

Melanoma and ipilimumab

	Discovery Set		Validation Set	
	Benefit	**No Benefit**	**Benefit**	**No Benefit**
Total	11	14	25	14
Age at start of treatment (median, range)	63 (39-70)	59.5 (48-79)	66 (33-90)	57 (18-74)
Disease origin (n, %)				
Acral	0 (0)	3 (21)	1 (4)	1 (7)
Uveal	0 (0)	0 (0)	1 (4)	0 (0)
Cutaneous	10 (82)	8 (57)	15 (60)	11 (79)
Unknown primary	1 (9)	3 (21)	3 (0.12)	0 (0)
Not available	0 (0)	0 (0)	5 (20)	2 (14)
BRAF or NRAS mutation (n, %)				
Absent	1 (9)	6 (43)	17 (68)	11 (79)
Present	10 (91)	8 (57)	8 (32)	3 (21)
Duration of response (median weeks, range)	59 (42-361)	14 (11-23)	130 (64-376)	11 (3-29)
Prior therapies (median number, range)*	1 (0-3)	1 (0-2)	0 (0-2)	0 (0-3)
Stage at Diagnosis (n, %)				
IIIC	0 (0)	0 (0)	3 (12)	0 (0)
M1a	0 (0)	1 (7)	4 (16)	1 (7)
M1b	5 (45)	1 (7)	2 (8)	3 (21)
M1c	6 (55)	12 (86)	16 (64)	10 (71)
Overall Survival (median years, range)	4.4 (2-6.9)	0.9 (0.4-2.7)	3.3 (1.6-7.2)	0.8 (0.2-2.1)

Snyder, Makarov, Merghoub, Yuan *et al*, NEJM 2014

Mutation burden significantly correlates with clinical benefit in melanoma



LB = Long-term clinical benefit lasting >6 months

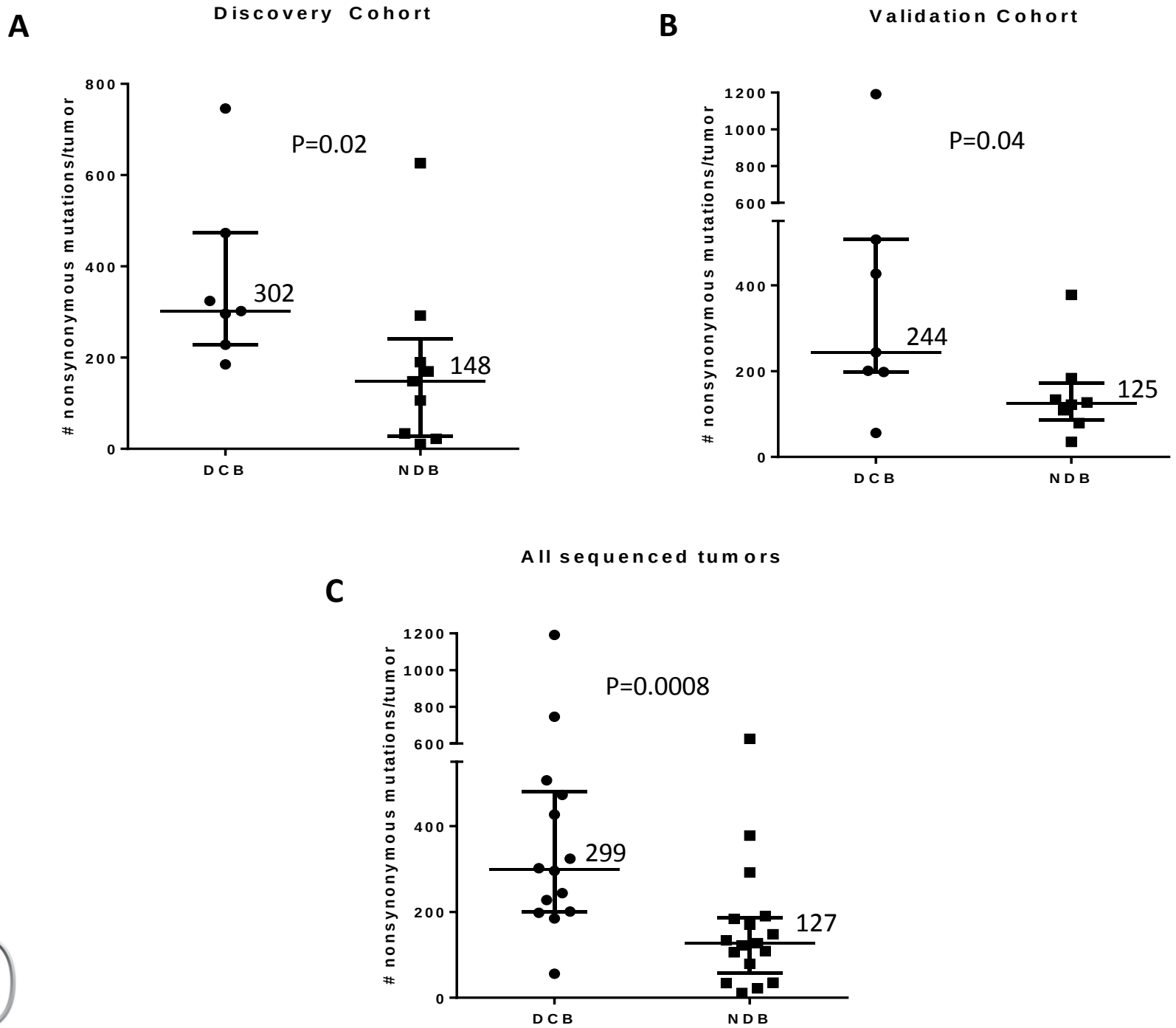
NB = No durable benefit

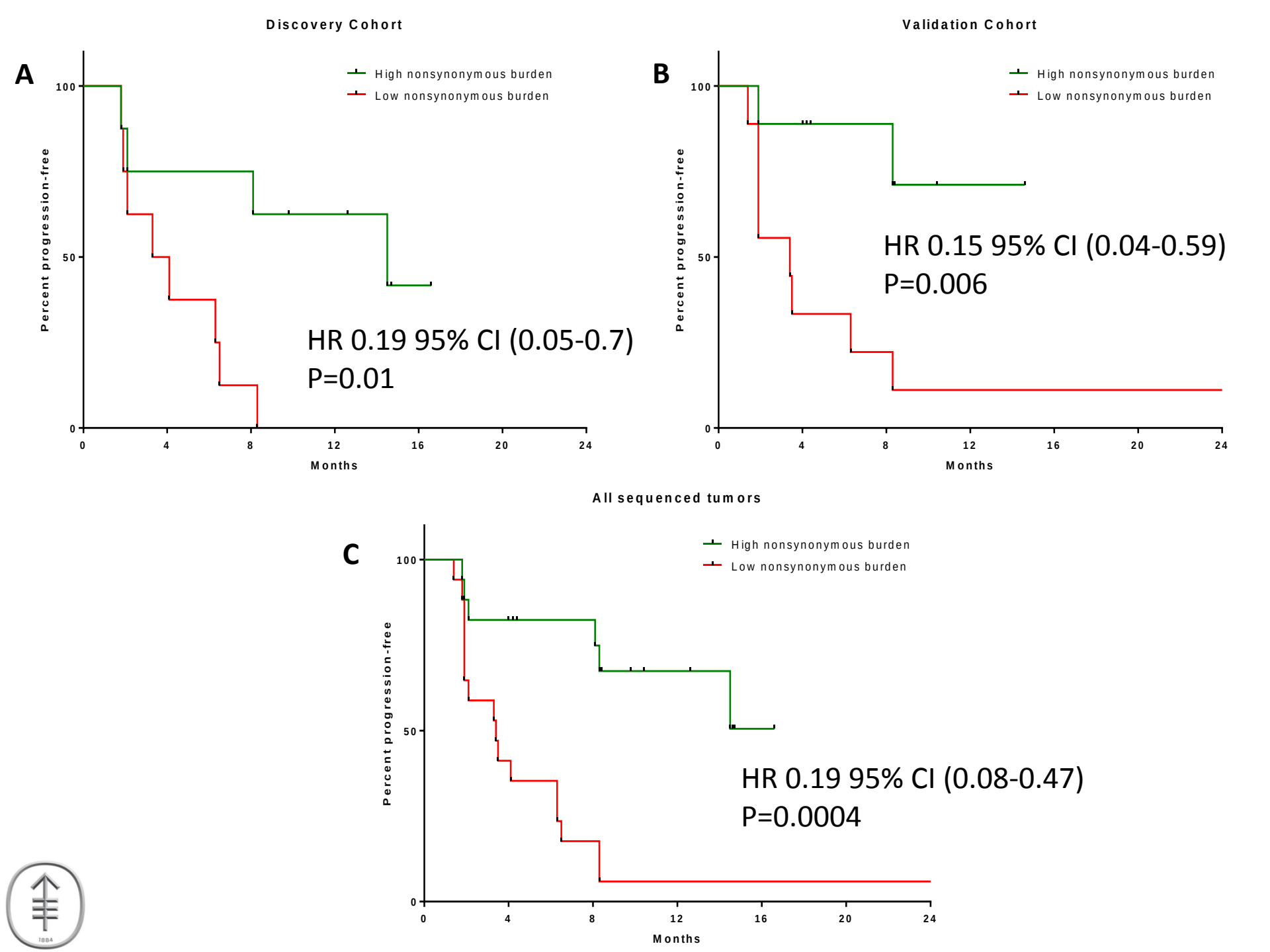
Snyder, Makarov, Merghoub, Yuan *et al*, NEJM 2014

NSCLC and pembrolizumab

	All patients	Discovery Cohort	Validation Cohort
n	34	16	18
Smoking status (n, %)			
Current	7 (21)	5 (31)	2 (11)
Former	21 (62)	10 (63)	11 (61)
Never	6 (17)	1 (6)	5 (28)
Histology (n, %)			
Adenocarcinoma	29 (85)	15 (94)	14 (78)
Squamous	4 (12)	1 (6)	3 (17)
NSCLC NOS	1 (3)	0 (0)	1 (6)
PD-L1 expression (n, %)			
Strong (≥50% membranous staining)	10 (29)	5 (31)	5 (28)
Weak (1-49%)	14 (41)	6 (38)	8 (44)
Negative (<1%)	6 (18)	3 (19)	3 (17)
Unknown	4 (12)	2 (12)	2 (11)
Confirmed objective response by irRC			
Partial response	12 (35)	5 (31)	7 (39)
Stable disease	9 (26)	5 (31)	5 (28)
Progressive disease	13 (39)	6 (38)	6 (33)
Durable clinical benefit (PR/SD) > 6 months			
Yes	14 (41)	7 (44)	7 (39)
No	17 (50)	9 (56)	8 (44)
Not yet reached 6 month follow up	3 (9)	0	3 (17)

Rizvi, Hellmann, Snyder *et al*, Science 2015


A
Discovery Cohort
nonsynonymous mutations/tumor
800
600
400
200
0
P=0.02
302
148
DCB
NDB
B
Validation Cohort
nonsynonymous mutations/tumor
1200
1000
800
600
400
200
0
P=0.04
244
125
DCB
NDB
All sequenced tumors
C
nonsynonymous mutations/tumor
1200
1000
800
600
400
200
0
P=0.0008
299
127
DCB
NDB


Discovery Cohort
A
High nonsynonymous burden
Low nonsynonymous burden
Percent progression-free
100
50
0
0
4
8
12
16
20
24
Months
HR 0.19 95% CI (0.05-0.7)
P=0.01
Validation Cohort
B
High nonsynonymous burden
Low nonsynonymous burden
Percent progression-free
100
50
0
0
4
8
12
16
20
24
Months
HR 0.15 95% CI (0.04-0.59)
P=0.006
All sequenced tumors
C
High nonsynonymous burden
Low nonsynonymous burden
Percent progression-free
100
50
0
0
4
8
12
16
20
24
Months
HR 0.19 95% CI (0.08-0.47)
P=0.0004

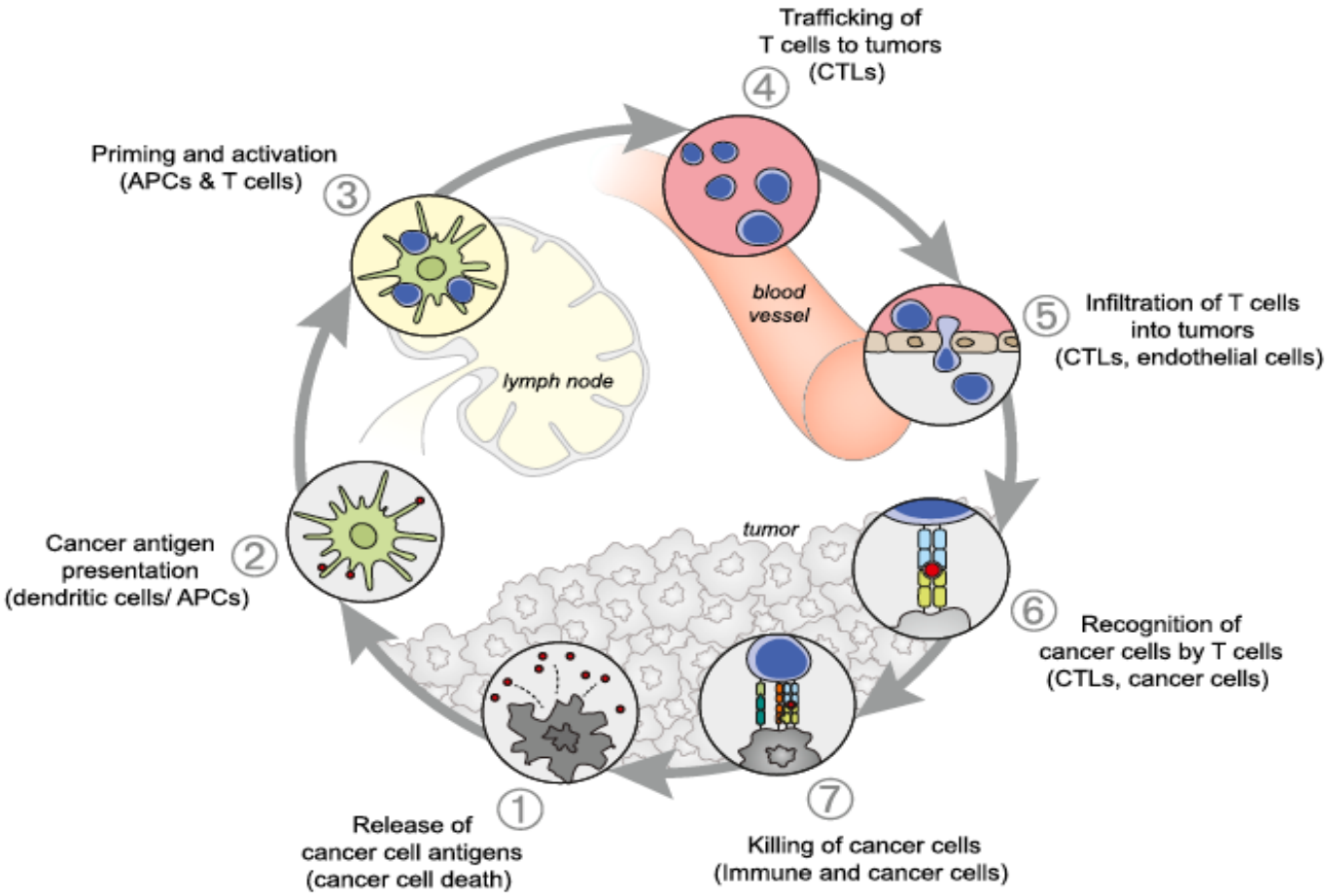
Mutation burden differentiates responders within group of PD-L1+ tumors

	High mutation burden	Low mutation burden
	PD-L1+ (n=11)	**PD-L1 + (n=10)**
Durable clinical benefit	91%	10%
No durable benefit	9%	90%

Neoantigens in cancer

- Somatic mutations in cancers can generate novel non-self peptides that, when presented on HLA, can be targets for tumor-specific T-cell response
- Uniquely expressed in tumor tissue
- Not subject to central tolerance

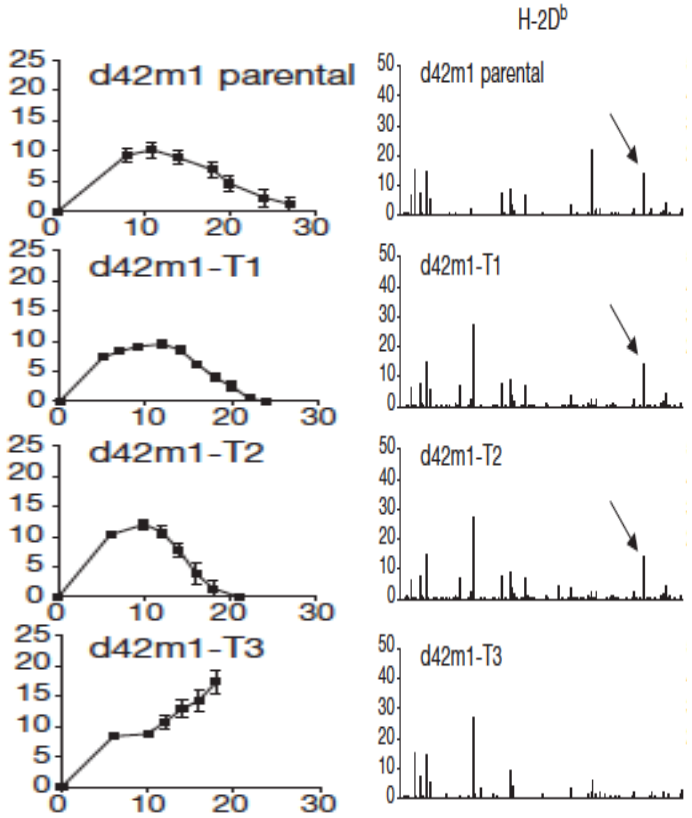
Neoantigens may underlie differential response in those with high mutation burden

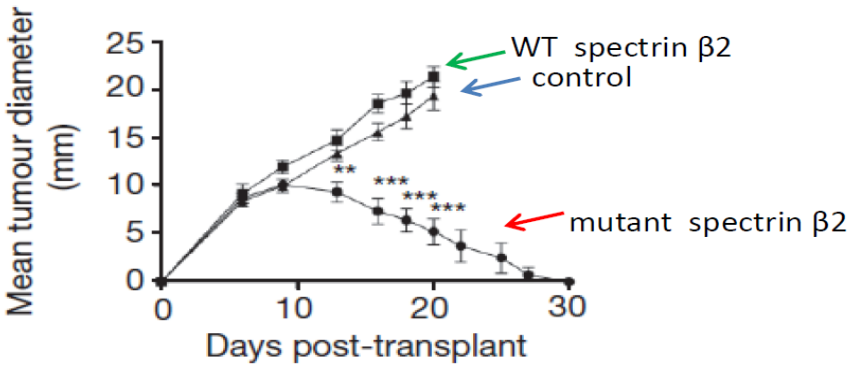


Chen and Mellman, Immunity 2013

Mutations, neoantigens, and immunogenicity

- Carcinogen-induced sarcomas harbor “rejection antigens” resulting from mutant spectrin-β2

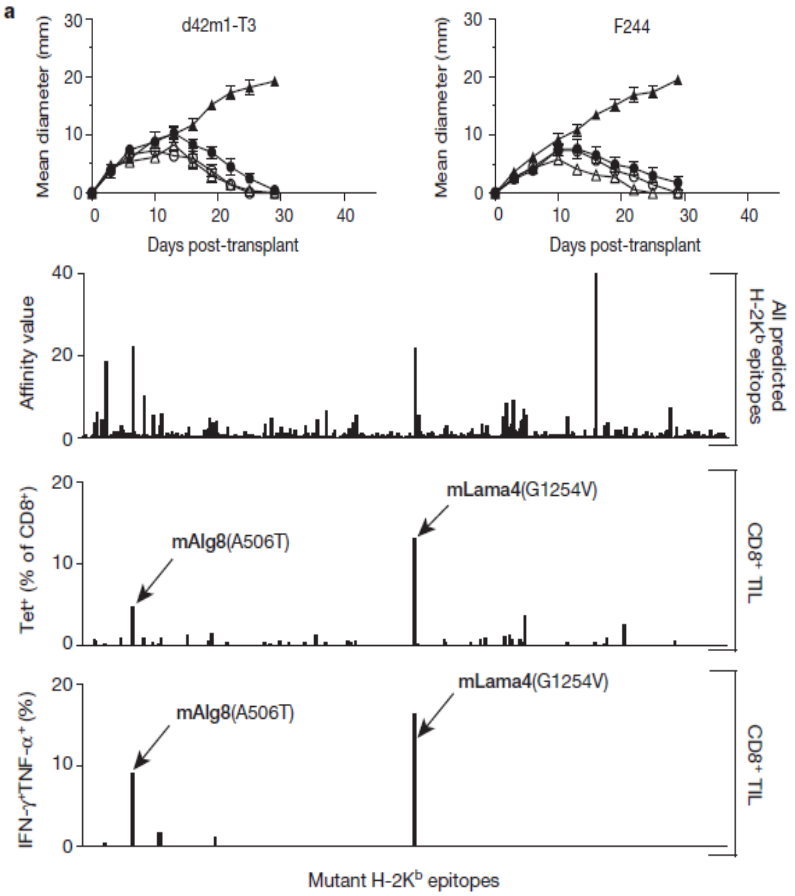


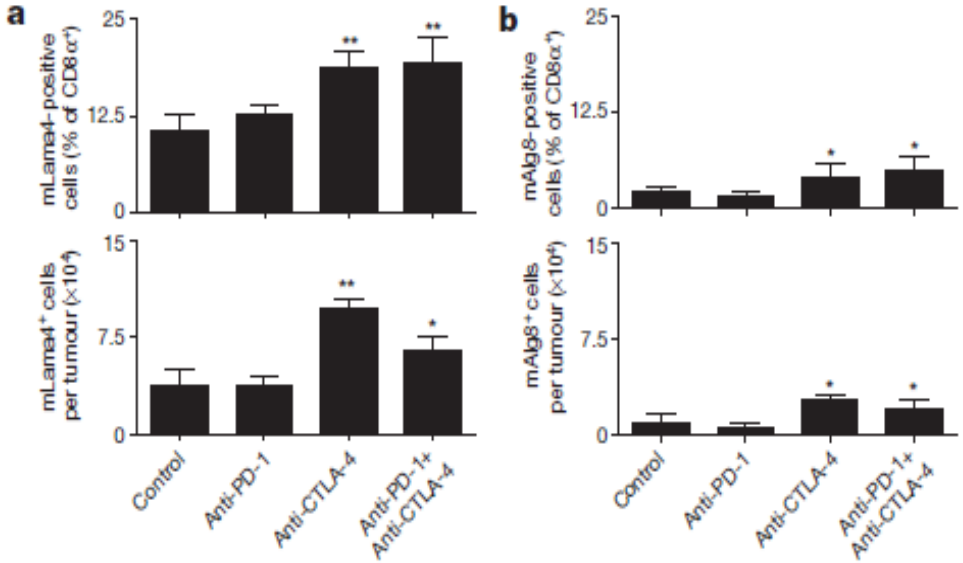


Matsushita *et al*, Nature 2012

Mutations, neoantigens, and immunogenicity

- T cell checkpoint blockade may enhance neoantigen-specific reactivity





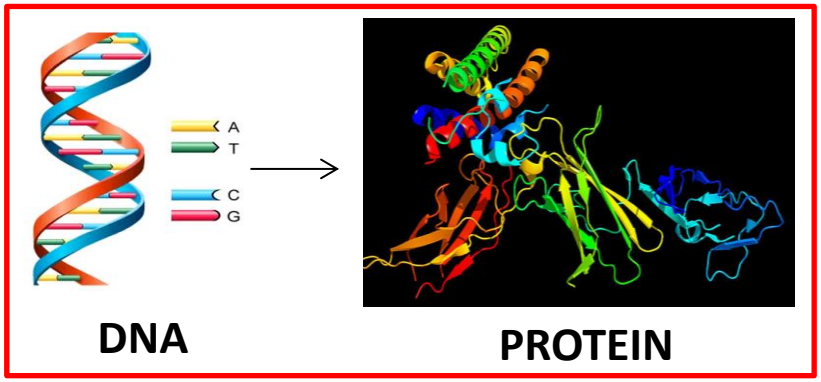
Gubins *et al*, Nature 2014

Neoantigens may underlie differential response in those with high mutation burden

Nucleotide sequence: …. AAT GCT AAA C**G** GGT TTC CAA AAA CGT CCC GGG TAT …..

Mutant 17mer peptide: ALLKMYCF**S**WGPSEFLL

Wild Type peptide: ALLKMYCF**V**WGPSEFLL



A*02:01	A*11:01	B*27:01	B*37:01	C*02:02	C*04:01

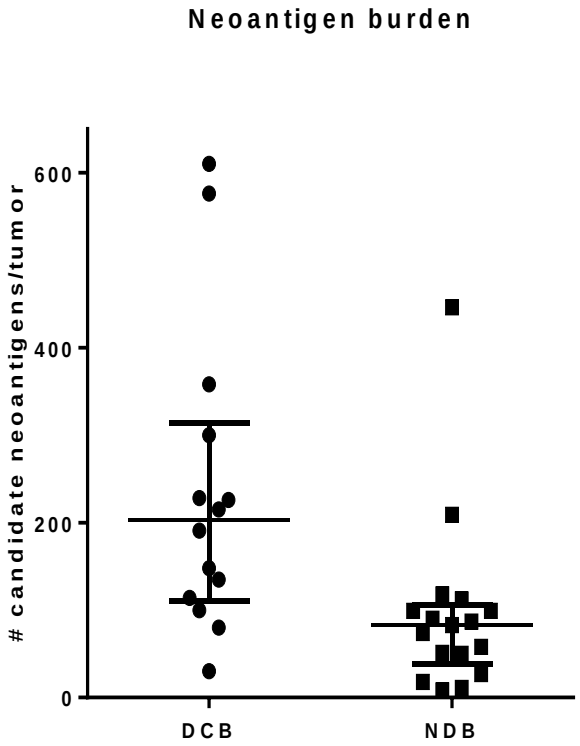
ALLKMYCFSWGPSEFLL

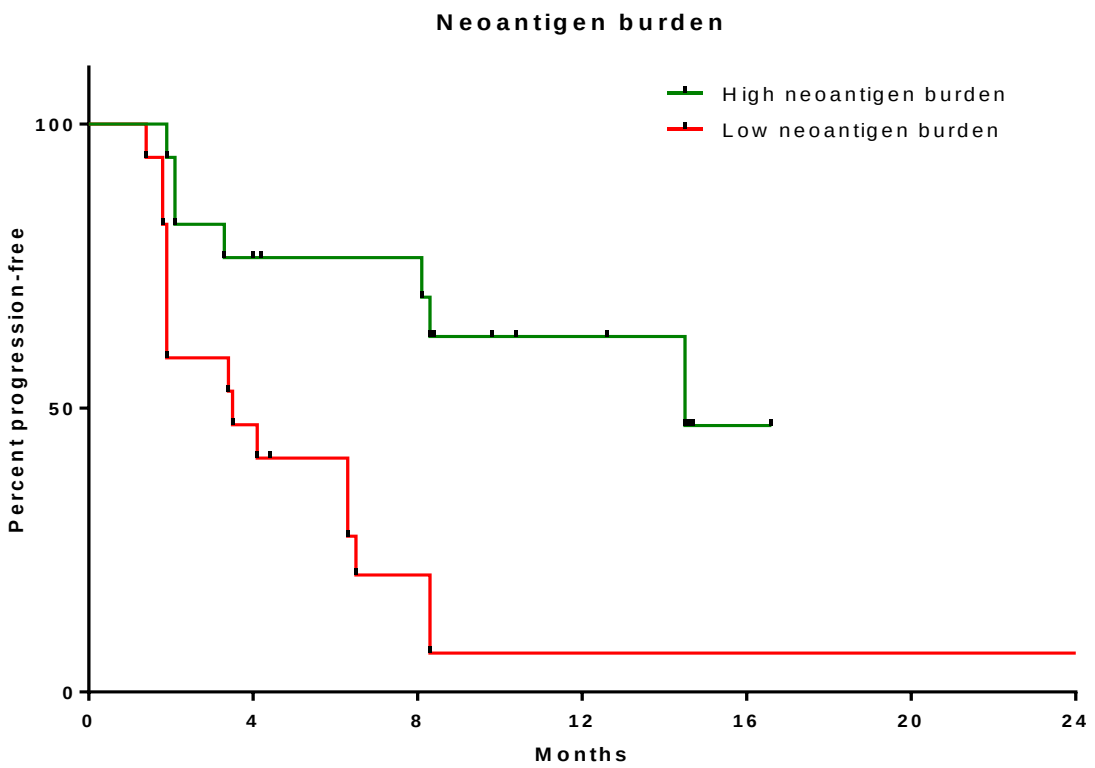
A**LLKMYCFSW**GPSEFLL

AL**LKMYCFSWG**PSEFLL

ALL**KMYCFSWGP**SEFLL

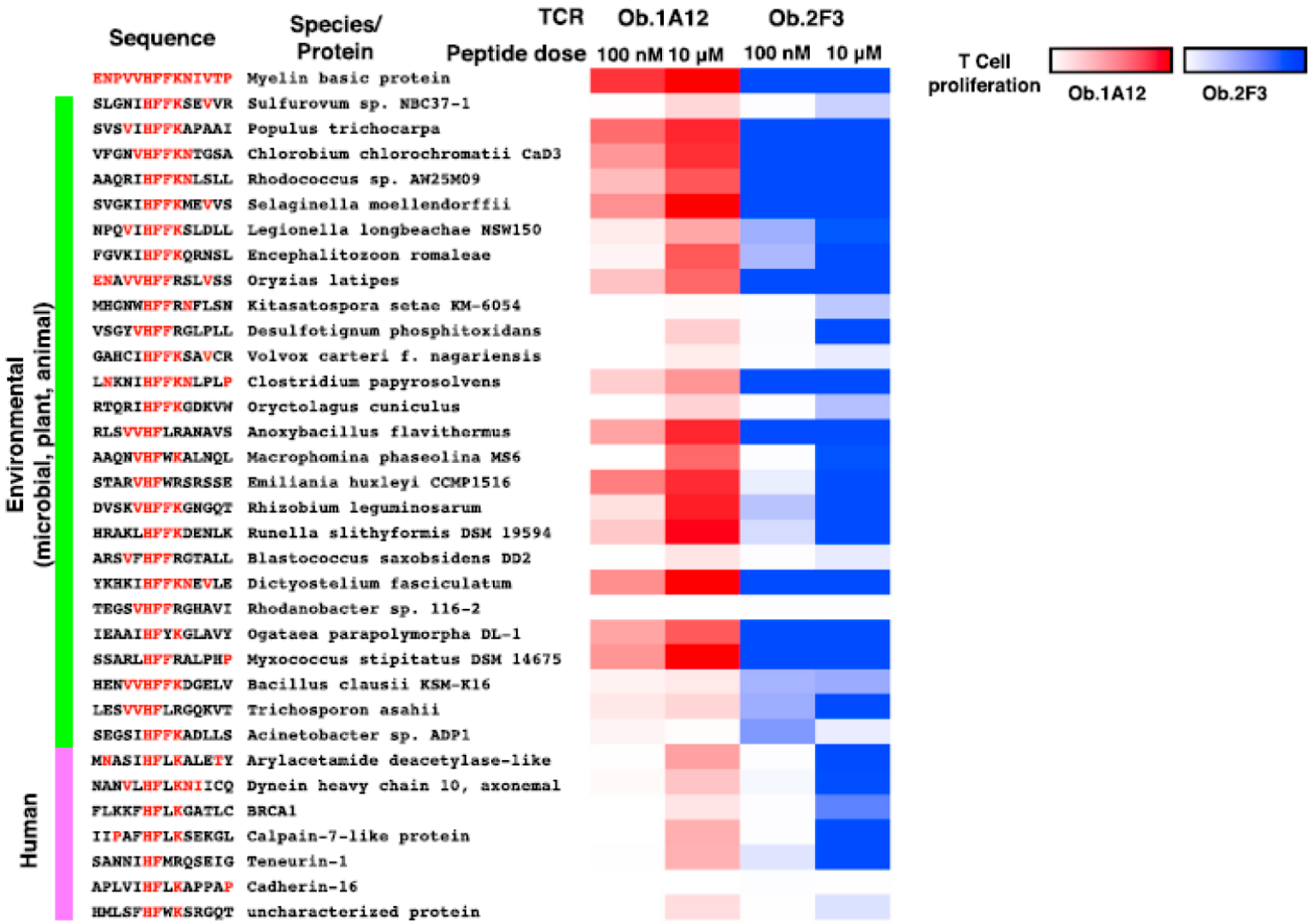
Neoantigen burden in patients with NSCLC treated with pembrolizumab





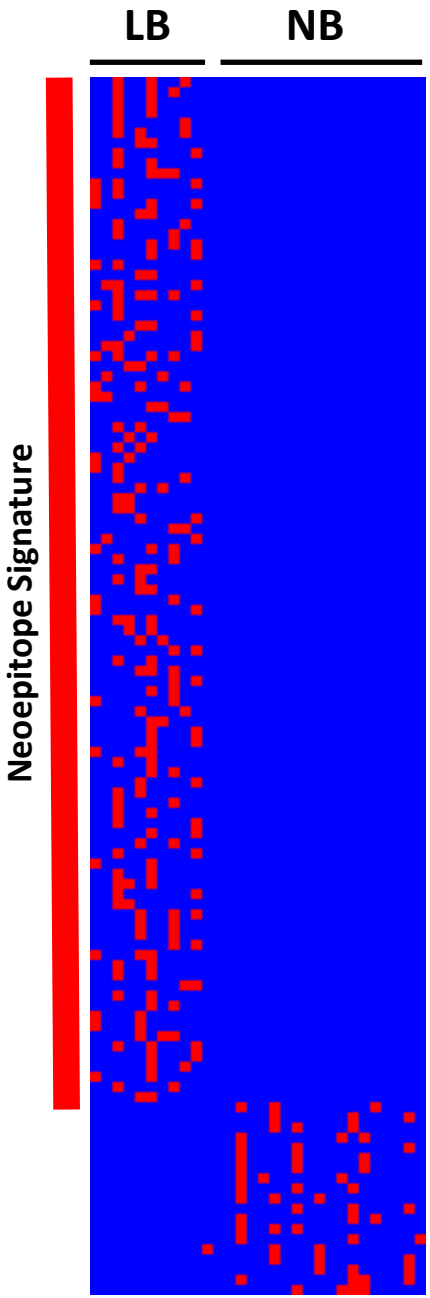
Rizvi, Hellmann, Snyder *et al*, Science 2015

Pattern of recurrent epitopes may drive T cell responses

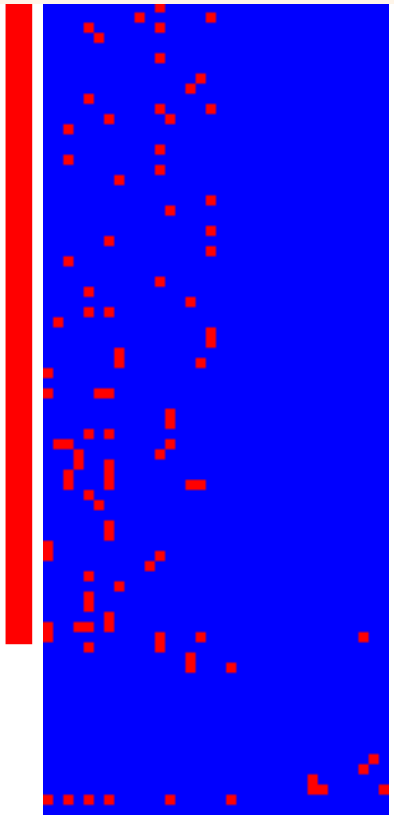


Birnbaum *et al*, Cell 2014

- LB, long-term clinical benefit lasting ≥6 months
- NB, no durable benefit

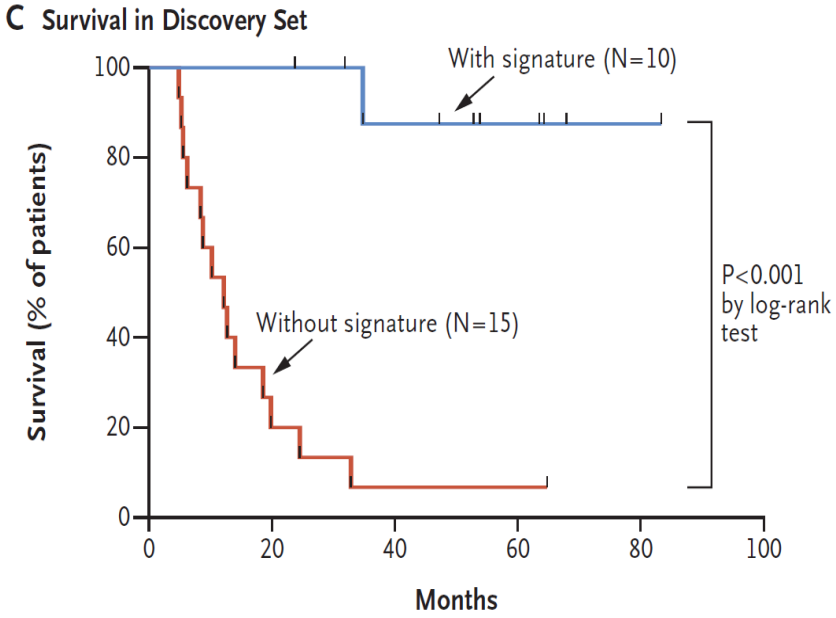


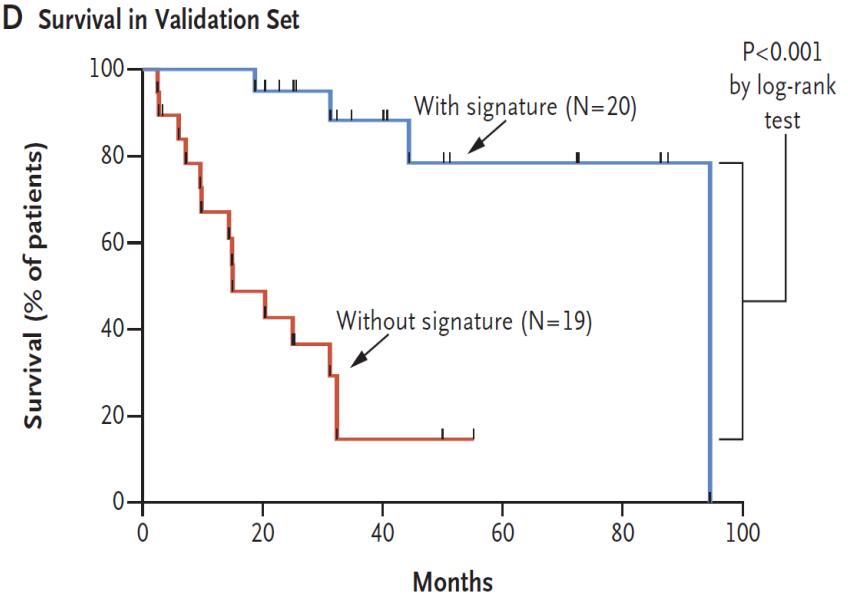
Patient No.	Nonmutant	Mutant
SD1494	YLLGSSALT	YLLESSALT
CR9306	VGSSADILY	VESSADILY
PR4092	YFPEESSAL	YSPEESSAL



Snyder, Makarov, Merghoub, Yuan *et al*, NEJM 2014

Neoantigen signature in melanoma and homology with infectious epitopes

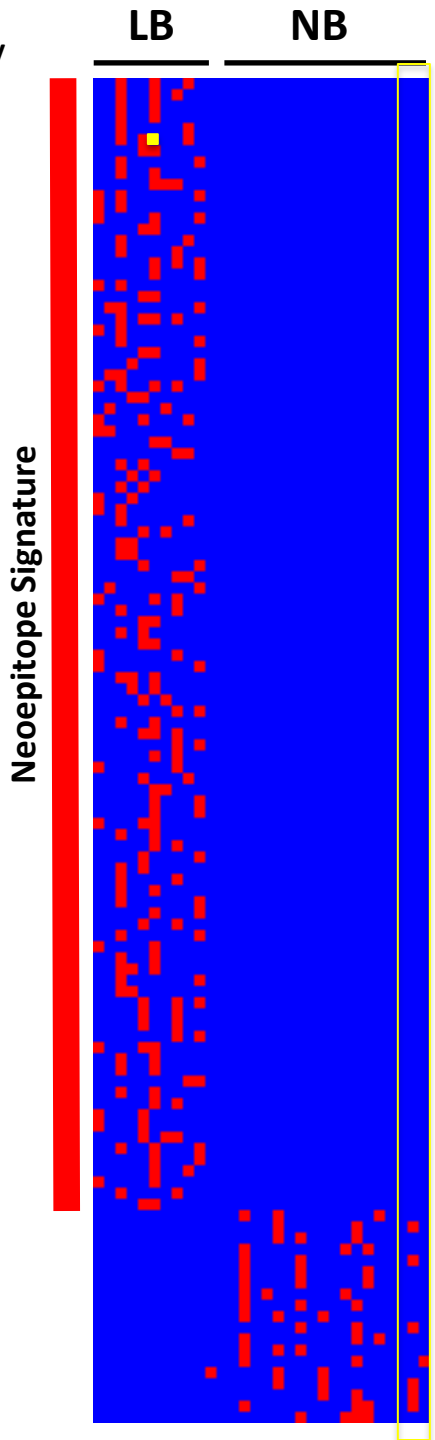




Pathogen	LB	NB
Adeno-associated virus-2		
Adenovirus		
Aspergillus fumigatus		
Bacillus anthracis		
BK polyomavirus		
Bordetella pertussis		

Snyder, Makarov, Merghoub, Yuan *et al*, NEJM 2014

A. Discovery Set

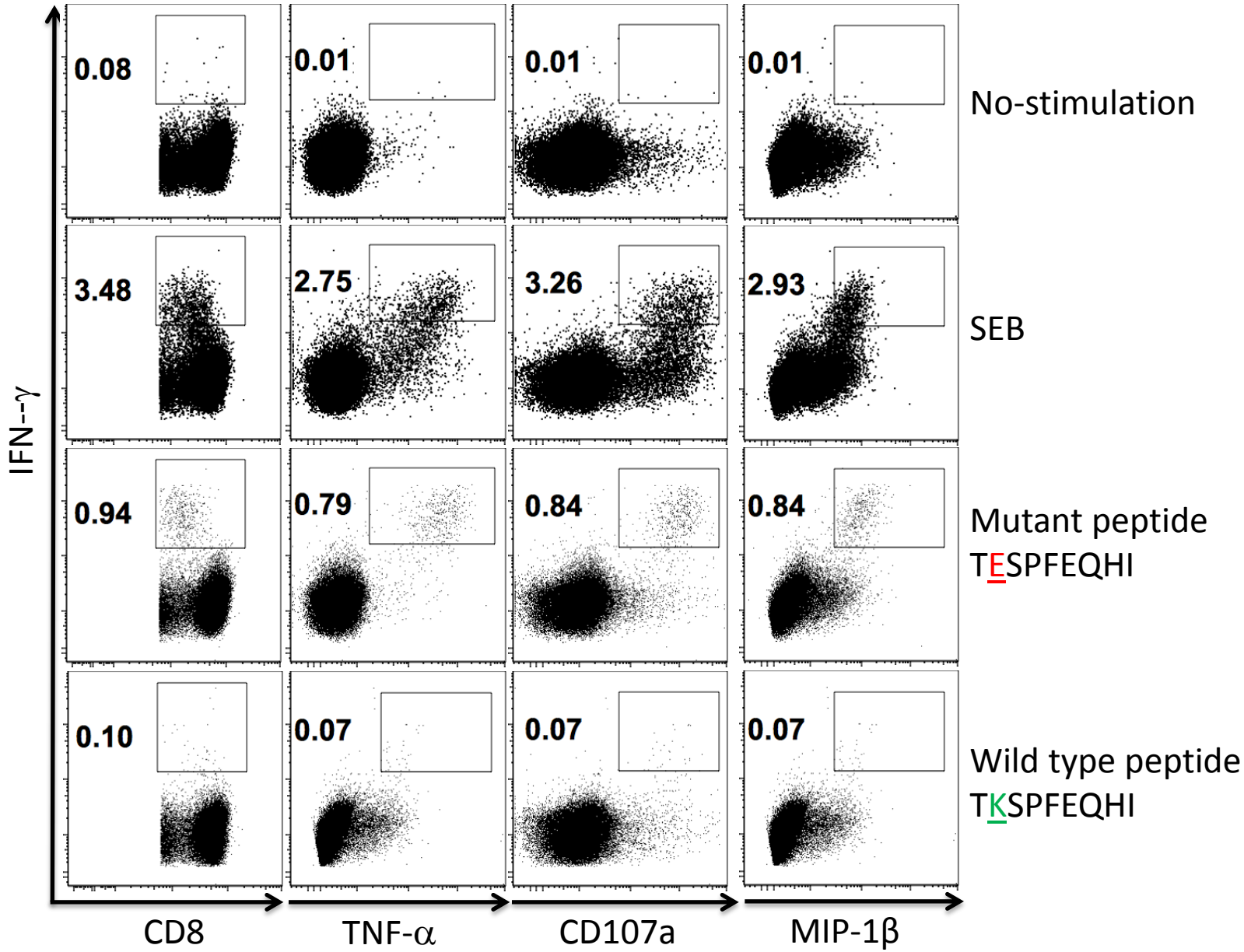


TESPFEQHI

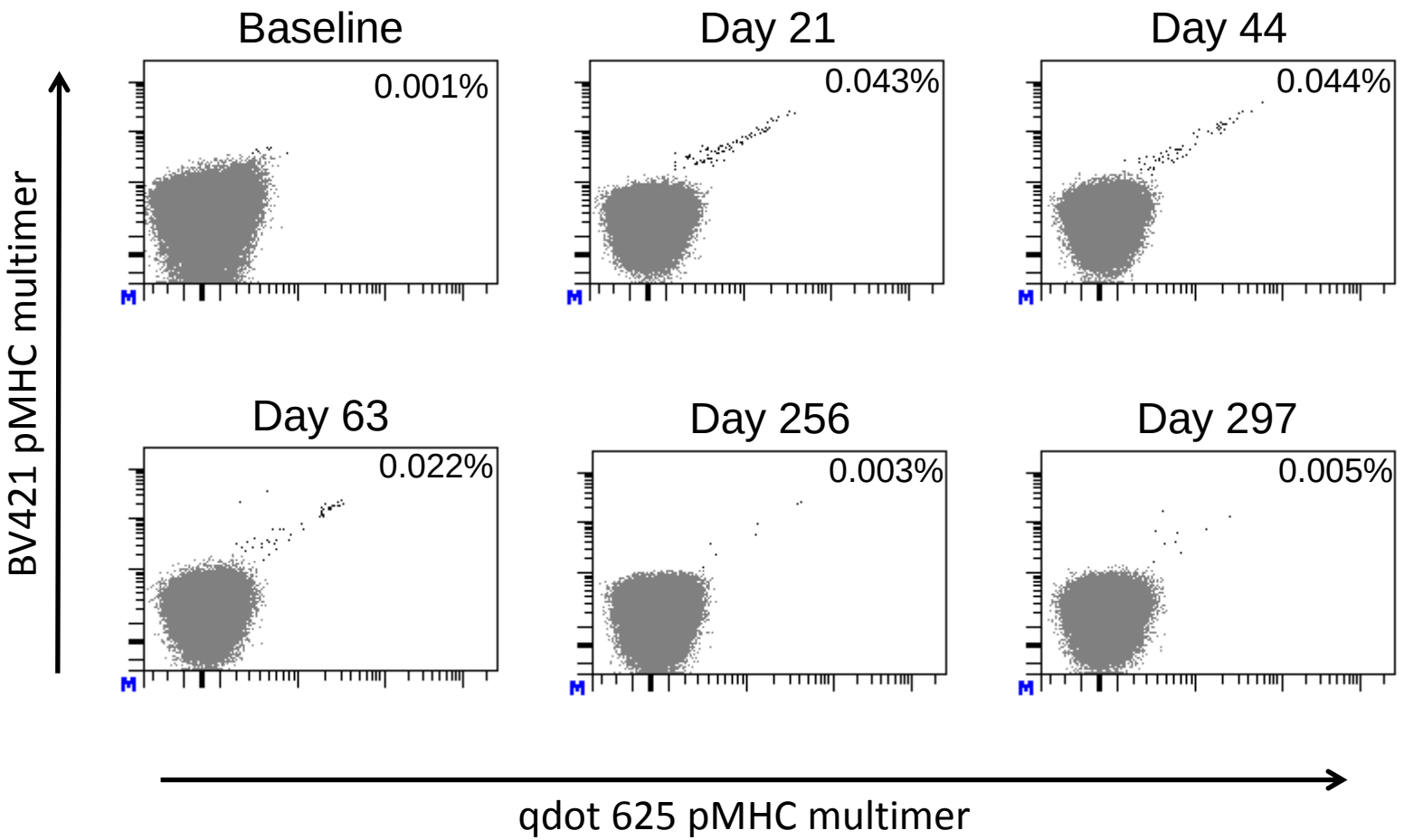
High mutation-burden non-responding tumors still lack critical neoantigens

Snyder, Makarov, Merghoub, Yuan *et al*, NEJM 2014

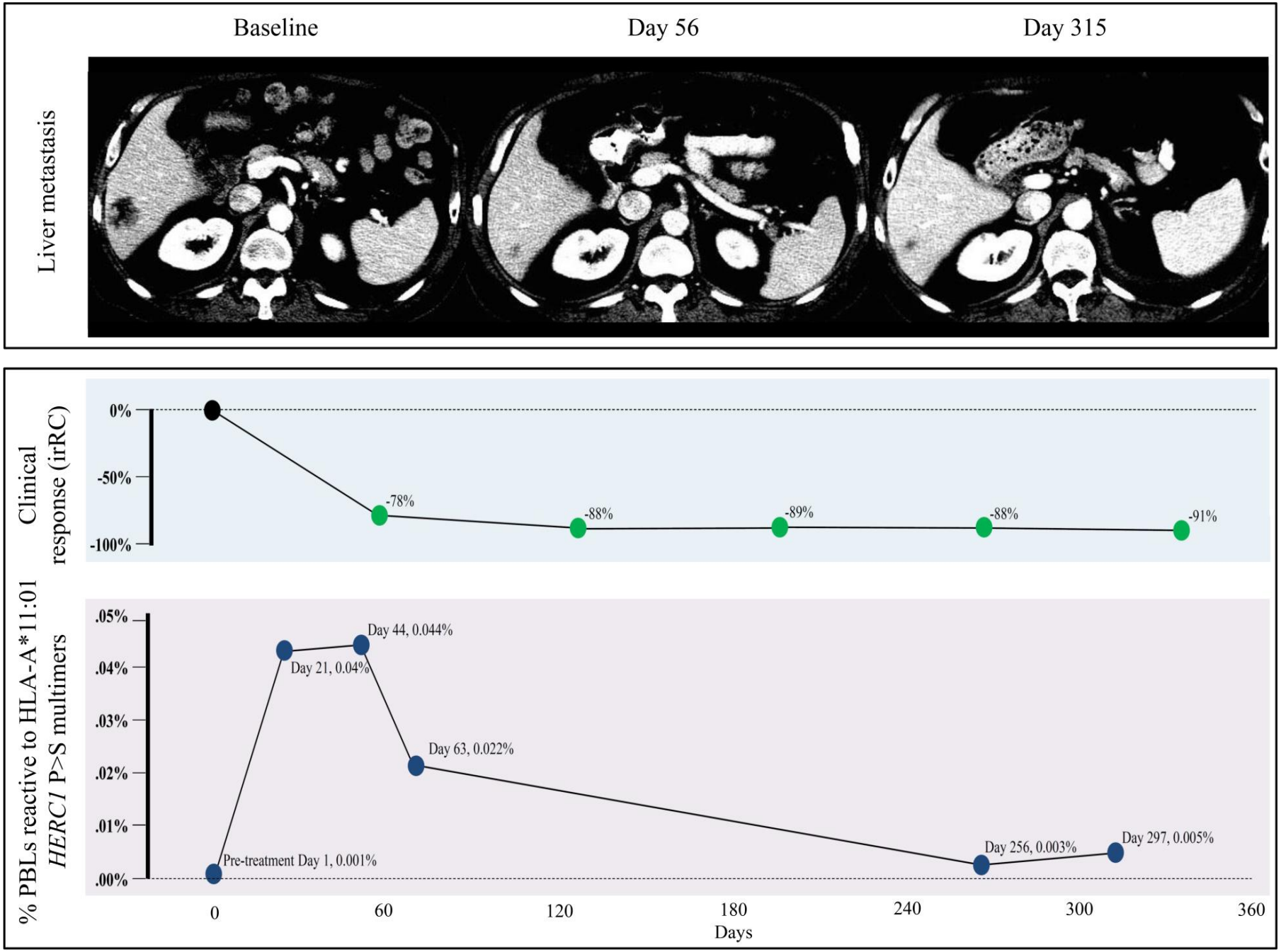
Validation of neoantigen-specificity



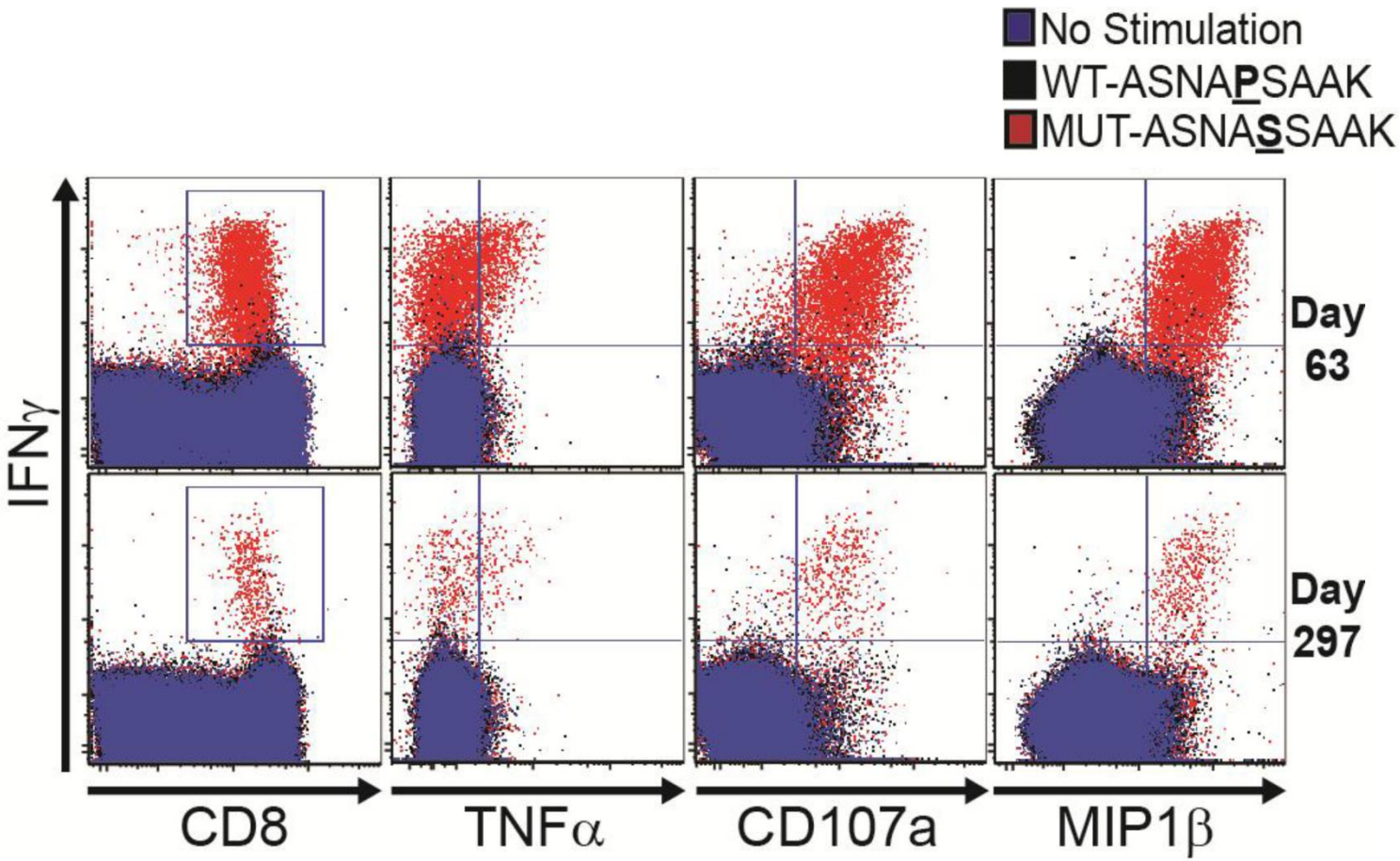
Neoantigen-specific T cells can be identified in peripheral blood and mirror clinical response to pembrolizumab



Pia Kvistborg, Ton Schumacher

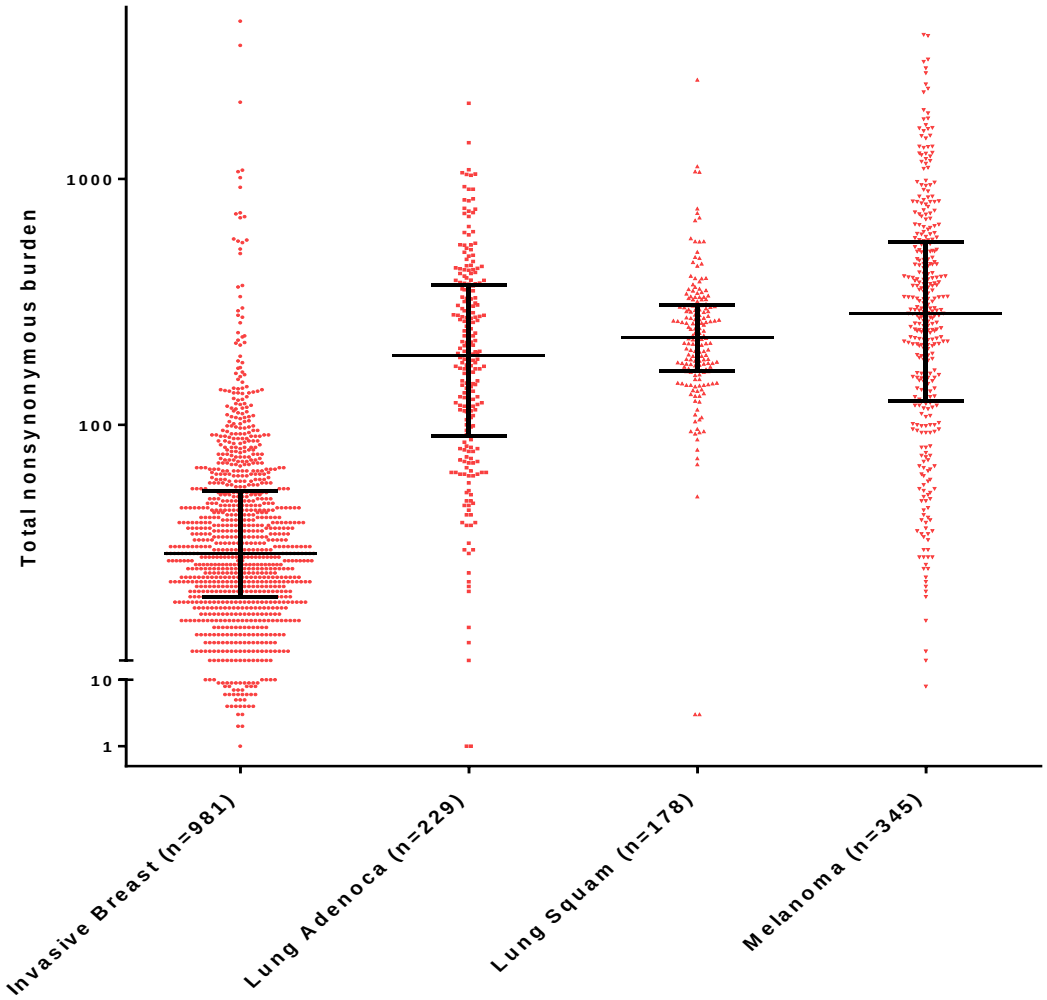


Rizvi, Hellmann, Snyder *et al*, Science 2015

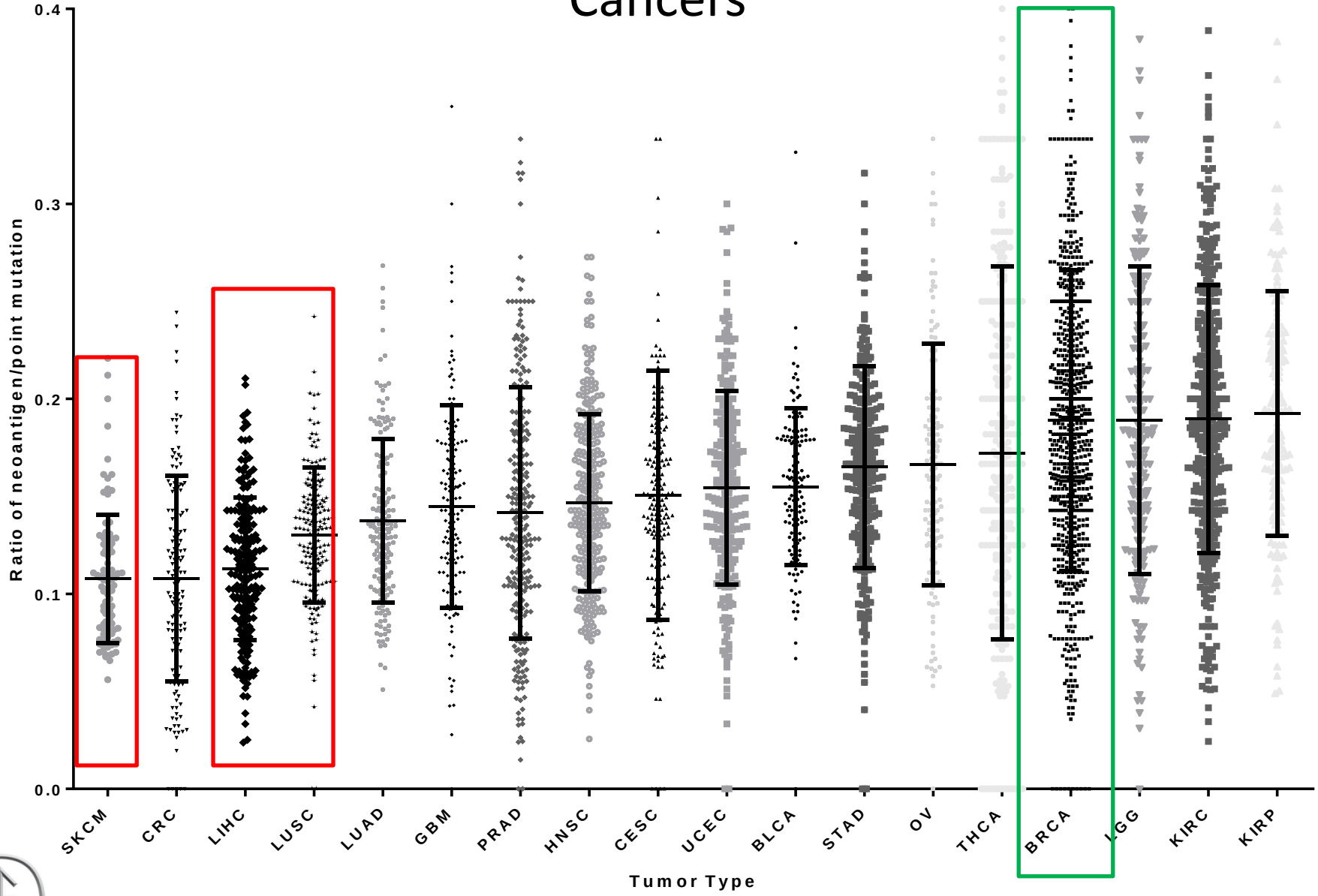


Rizvi, Hellmann, Snyder *et al*, Science 2015

Application in breast cancers?

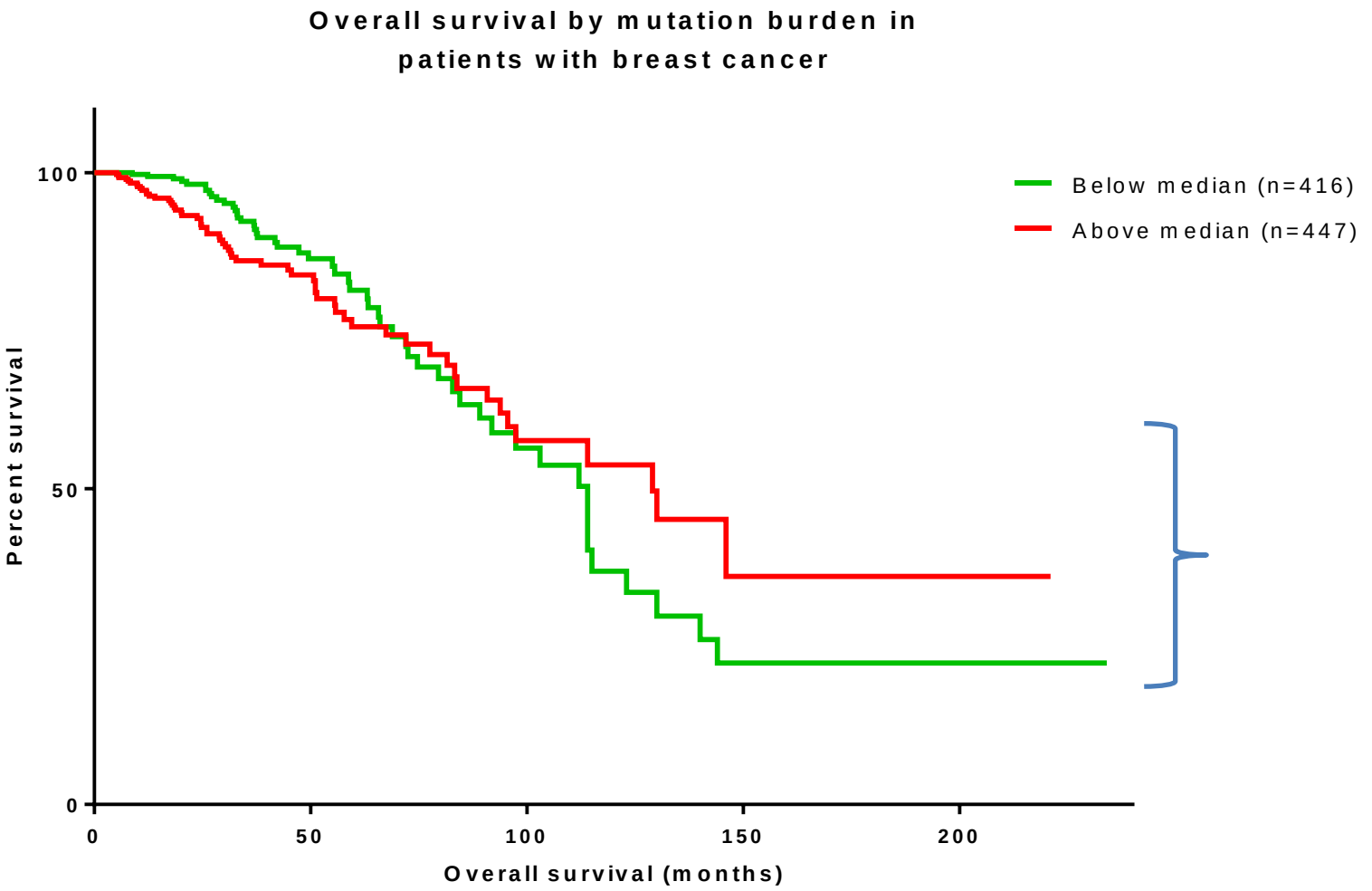


Ratio of Predicted Neoantigen:Mutation is High in Breast Cancers



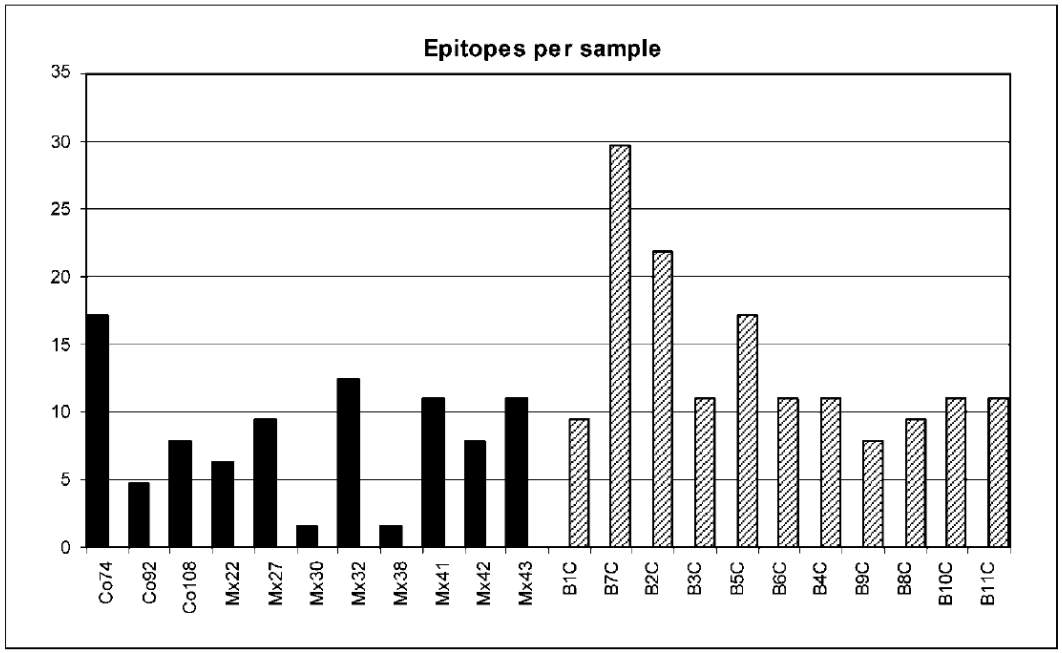
Reanalysis from Rooney et al Cell 2015

ENTIRELY speculative: Higher proportion of long-term survivors with elevated mutation burden



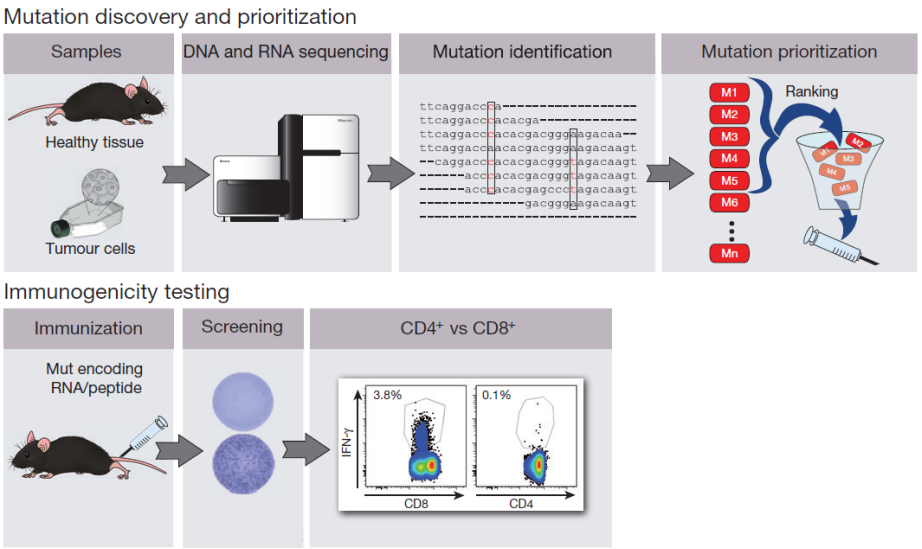
Initial *in silico* prediction of neoantigens derived from breast cancers

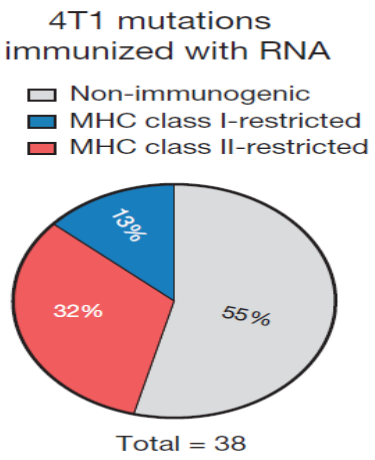
- *In silico* analysis of 1,152 putative neoantigens resulting from missense mutations in breast and colorectal cancers:
  - 7-10 unique HLA-A*0201 epitopes per tumor

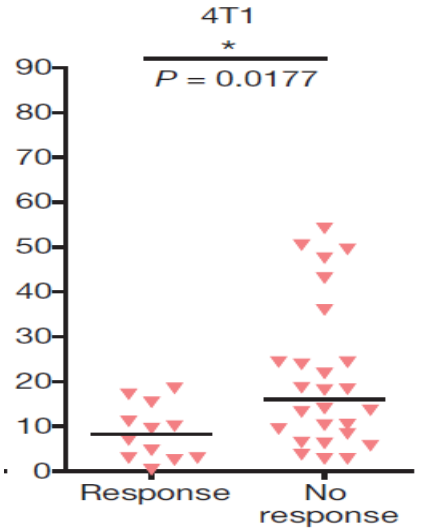


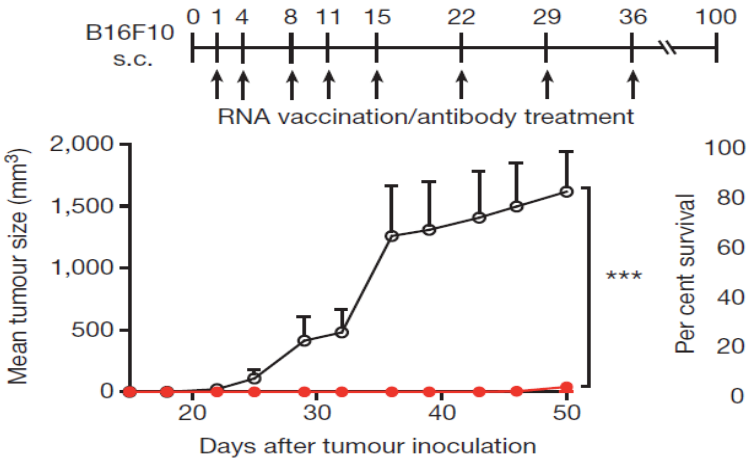
Segal et al, Cancer Res 2008

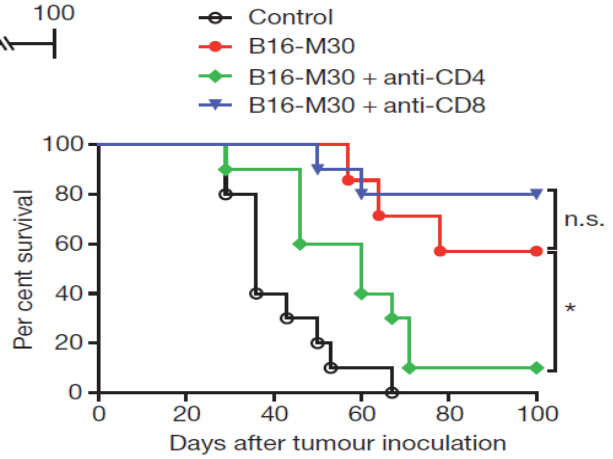
MHC class II neoantigens in 4T1 breast model











Kreiter et al, Nature 2015

Summary

- The genetics of melanoma and lung cancers substantially impact response to T cell checkpoint blockade
  - Mutation burden, specific neoantigens, and patterns of neoepitopes may be a prediction tool
- Exome data can be used to identify neoantigen-specific T cell responses
  - Neoantigen-specific T cells may mediate response to PD-1 blockade
- These principles appear to transcend tumor type and may be broadly applicable

Acknowledgements

MSKCC – Chan Lab
Tim Chan
Alex Snyder
Vlad Makarov
Will Lee
Jonathan Havel
Alexis Desrichard
Promita Bose
Logan Walsh

Columbia University
Naiyer Rizvi
Cam Bruggeman

MSKCC – Cbio
Martin Miller
Chris Sander

MSKCC – Wolchok Lab
Jedd Wolchok
Taha Merghoub
Billel Gasmi
Roberta Zappasodi
Michael Postow
Travis Hollman
Roberta Zappasodi
Margaret Callahan
Ceyhan Elipenahli
Cailian Liu
John Khoury
Yanyun Li

Immune Monitoring Facility
Phil Wong
Jianda Yuan
Teresa Rasalan

NKI – Schumacher Lab
Ton Schumacher
Pia Kvistborg

UCLA
Antoni Ribas
Jesse Zaretsky
Eddie Garon

BMS
Chris Harbison

Merck
Greg Lubiniecki

GEOFFREY BEENE Cancer Research Center @ Memorial Sloan-Kettering Cancer Center

THE STARR FOUNDATION

STAND UP TO CANCER™

CANCER RESEARCH INSTITUTE
The Leader in Immunotherapy

THE SOCIETY of MEMORIAL SLOAN KETTERING CANCER CENTER

Funding: Marsha Rivkin Center for Ovarian Cancer Research, NIH Clinical Scholars Biomedical Research Training Grant , Frederick Adler Fund, the National Institutes of Health, Stand Up to Cancer-Cancer Research Institute Immunotherapy Dream Team, Swim Across America, the Ludwig Trust, Melanoma Research Alliance, Hazen-Polsky Foundation and the STARR Cancer Consortium.

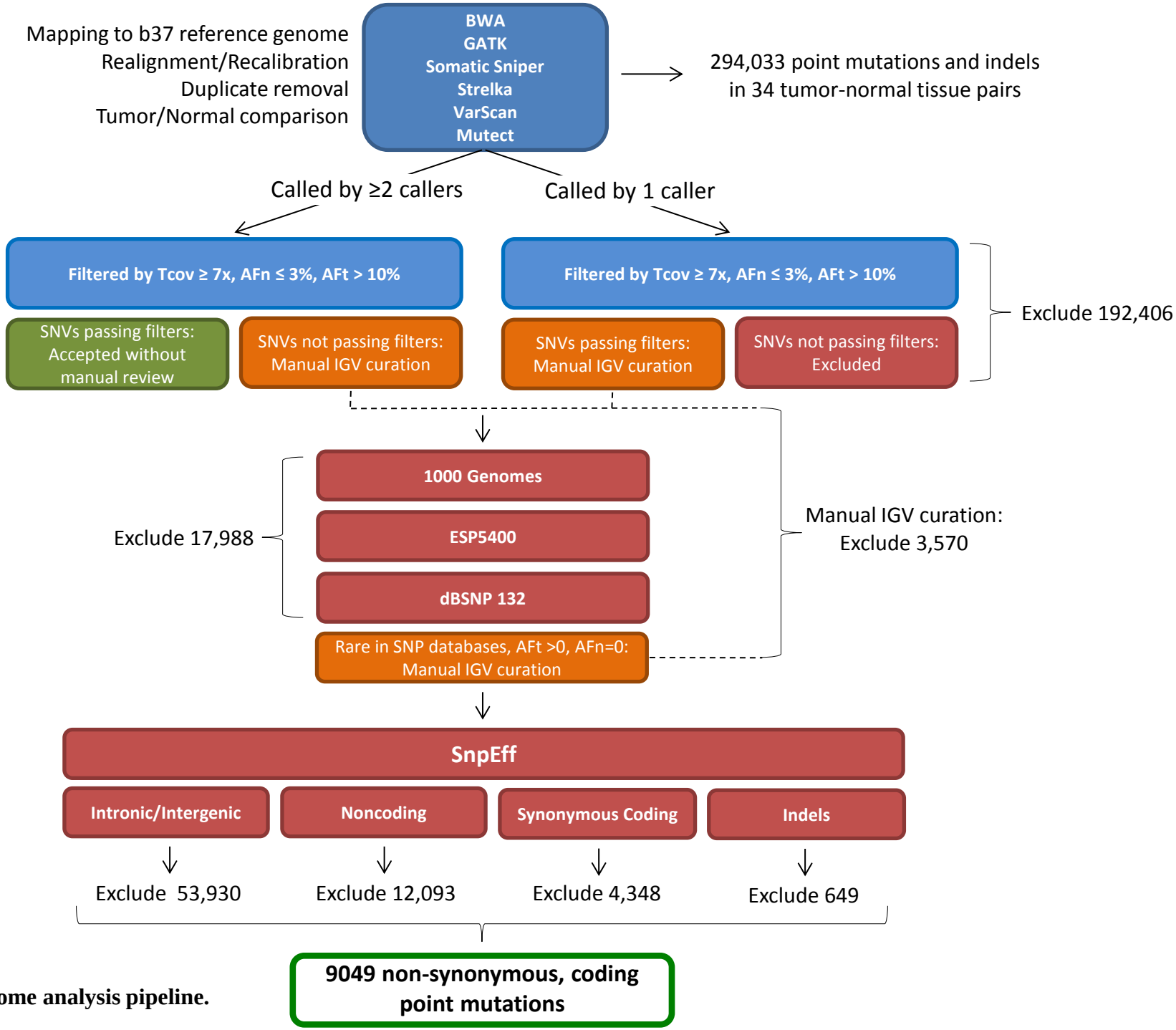
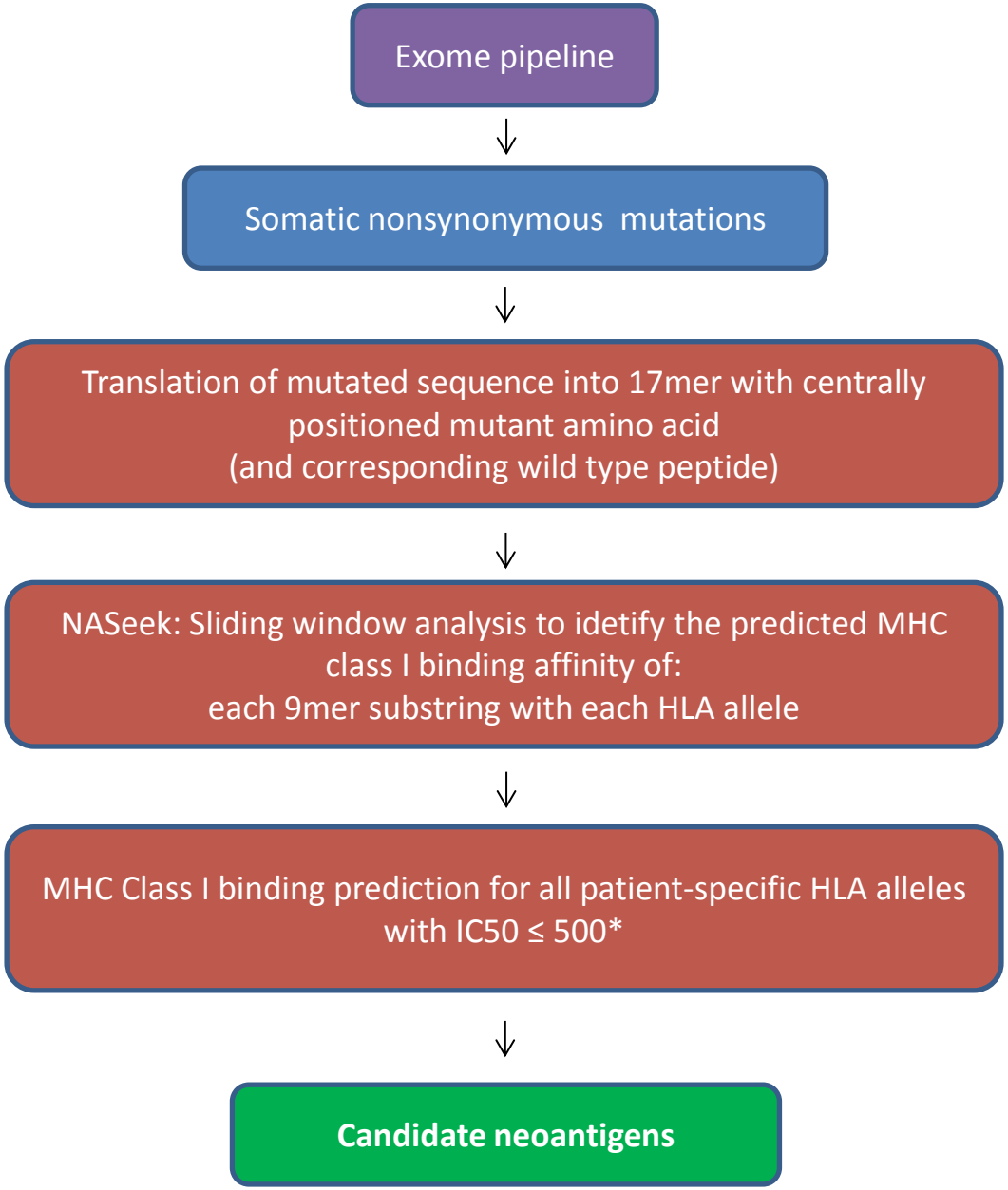


Figure S1. Exome analysis pipeline.


Exome pipeline
Somatic nonsynonymous mutations
Translation of mutated sequence into 17mer with centrally positioned mutant amino acid
(and corresponding wild type peptide)
NASeek: Sliding window analysis to idetify the predicted MHC class I binding affinity of:
each 9mer substring with each HLA allele
MHC Class I binding prediction for all patient-specific HLA alleles with IC50 ≤ 500*
Candidate neoantigens