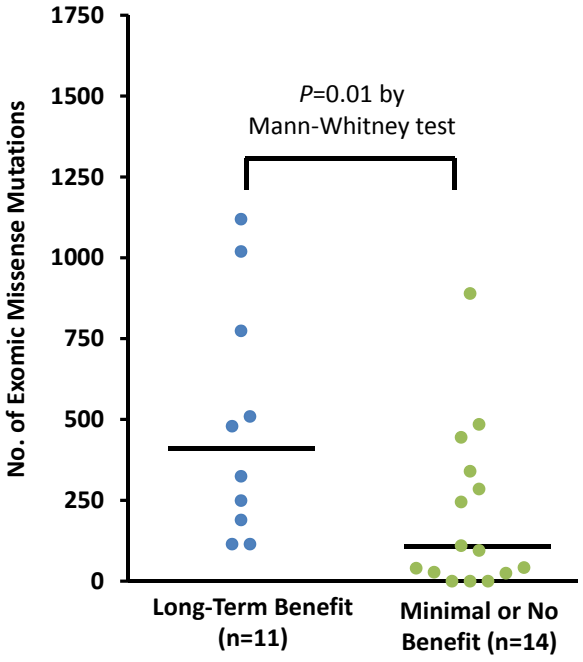
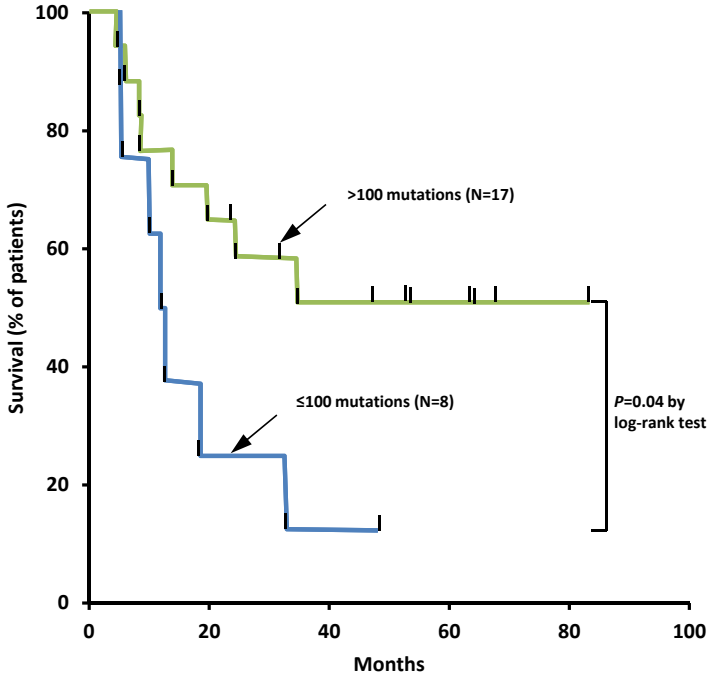
Can genetics be used to select patients for immune checkpoint blockade

Naiyer Rizvi, MD
Director of Thoracic Oncology
Director of Immuno-Oncology
Columbia University Medical Center
New York, New York

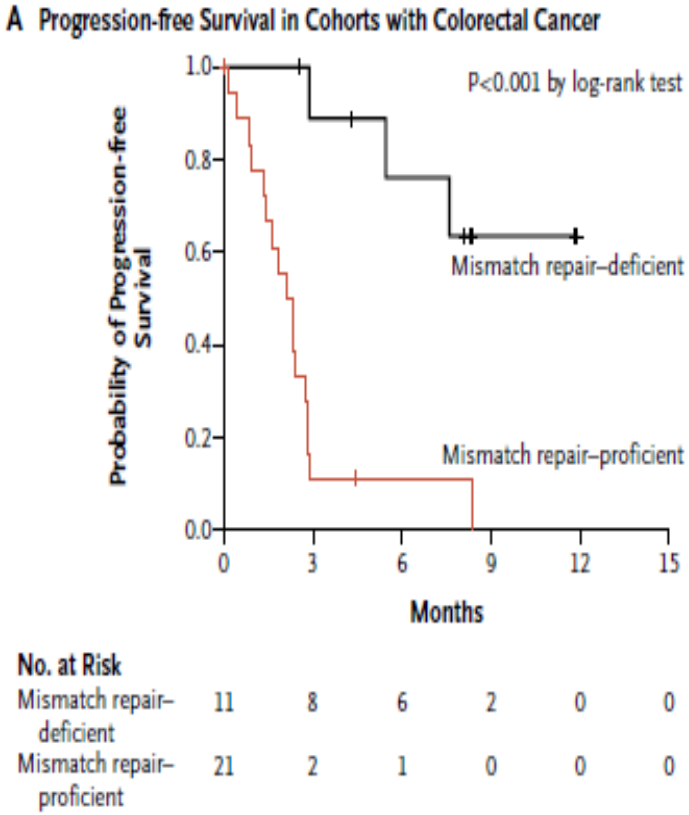
Mutational Load and Clinical Response to CTLA-4 Blockade in Melanoma





Snyder A, et al. *N Engl J Med.* 2014;371(23):2189-2199.

Mutational Burden, MSI, and Response to Anti-PD-1 Therapy



MSI+ 1782 mutations
MSI- 73 mutations

Le DT et al, NEJM

Is there a Genetic Basis for Response to PD-1 Blockade ?

Advanced NSCLC treated with pembrolizumab

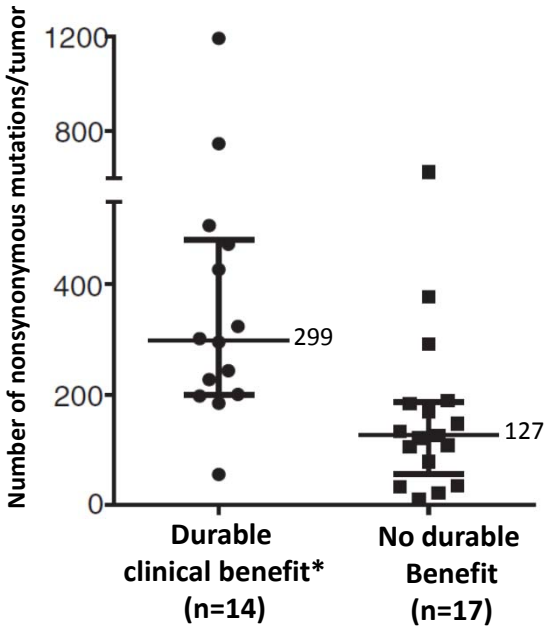
Significant range in number and type of mutations

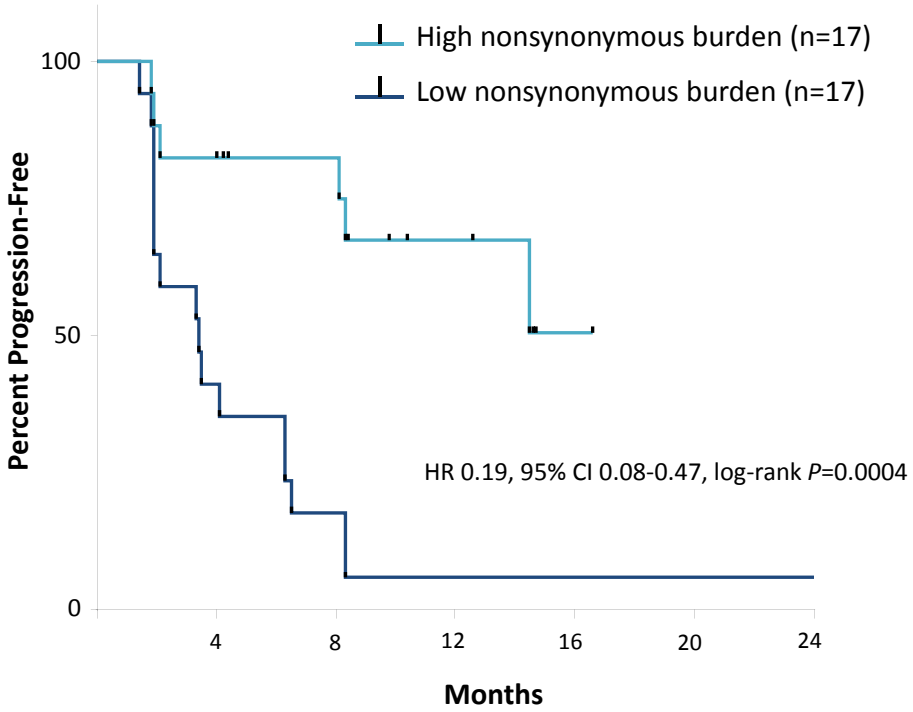
Mandatory Biopsy Within 60 Days of First Dose

Whole exome sequencing of tumor and germline DNA (n=34)

Correlation of non-synonymous mutation burden and durable response to pembrolizumab

Mutation Burden Determines Sensitivity to PD-1 Blockade in NSCLC





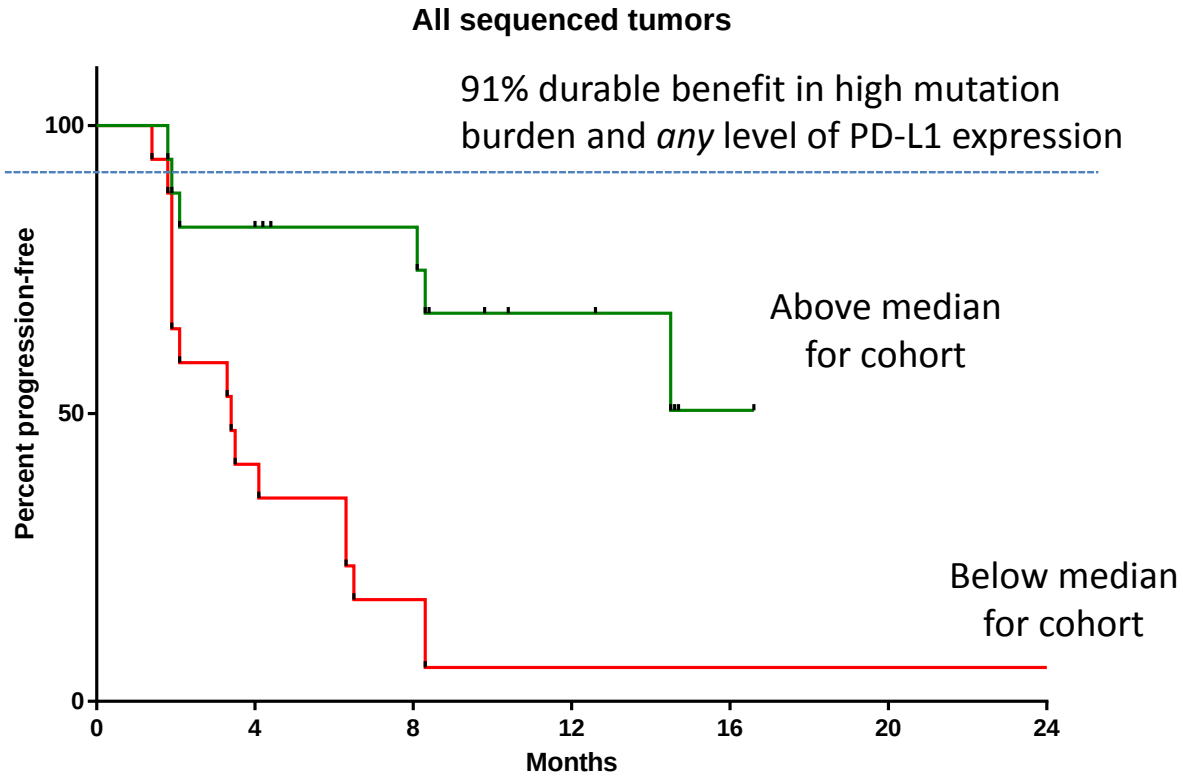
*Partial or stable response lasting >6 months.

Rizvi N, et al. *Science.* 2015;348(6230):124-128.

Mutation burden in PS 1-49%

PD-L1	PFS (mos)	Events	RR	DCB	Nonsyn.
1	18.8	0	PR	DCB	1192
40	8.3	1	SD	DCB	507
30	6.2	1	SD	NDB	368
40	14.8	1	PR	DCB	296
40	8.3	1	SD	DCB	185
1	6.5	1	SD	NDB	148
10	1.9	1	POD	NDB	134
33	1.4	1	POD	NDB	122
15	2.1	1	POD	NDB	106
5	3.5	1	SD	NDB	109
2	6.3	1	SD	NDB	79
2	1.9	1	POD	NDB	35
30	1.8	1	POD	NDB	34

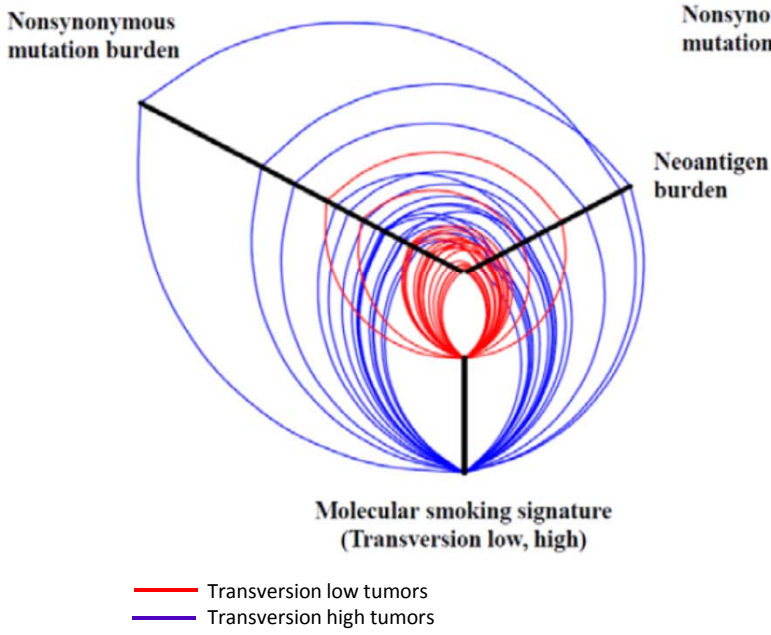
Highly significant correlation between non-synonymous mutation burden and durable benefit with pembrolizumab

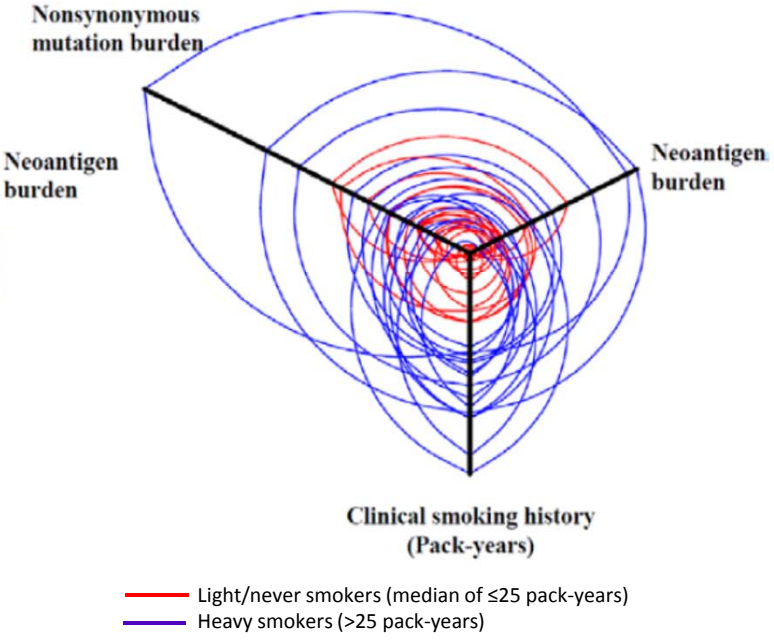


Correlation of Molecular Smoking Signature, Nonsynonymous Mutation Burden, and Neoantigen Burden in NSCLC

- Transversion low tumors have significantly lower mutation and neoantigen burden vs transversion high tumors (Mann Whitney *P*<0.0001 for both)
- Nonsynonymous mutation burden correlates with neoantigen burden (Spearman ρ 0.91, 95% CI 0.83-0.96, *P*<0.0001)

- Modest correlation is seen
  - Between pack-years and nonsynonymous mutation burden (Spearman ρ 0.31, 95% CI -0.05-0.59, *P*=0.08)
  - Between pack-years and neoantigen burden (Spearman ρ 0.35, 95% CI 0-0.62, *P*=0.04)

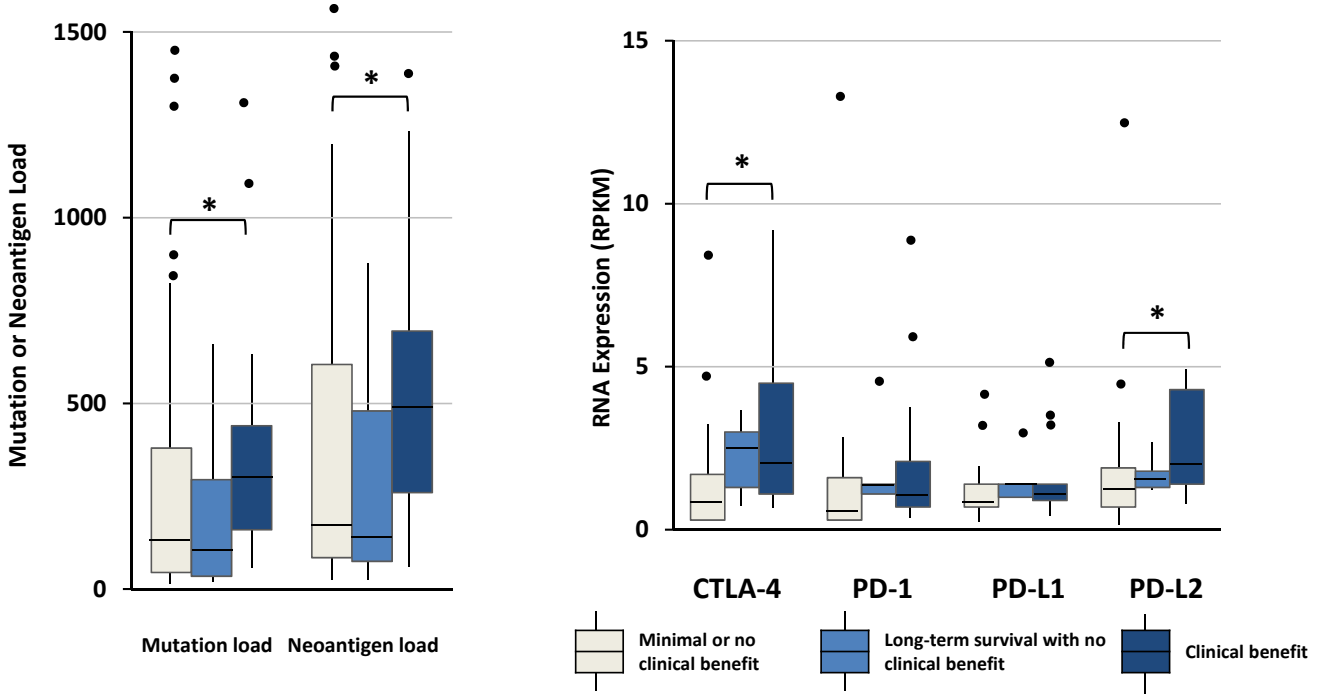




Rizvi N, et al. *Science.* 2015;348(6230):124-128.

Mutational Load and Neoantigen Are Significantly Associated With Clinical Benefit From Ipilimumab

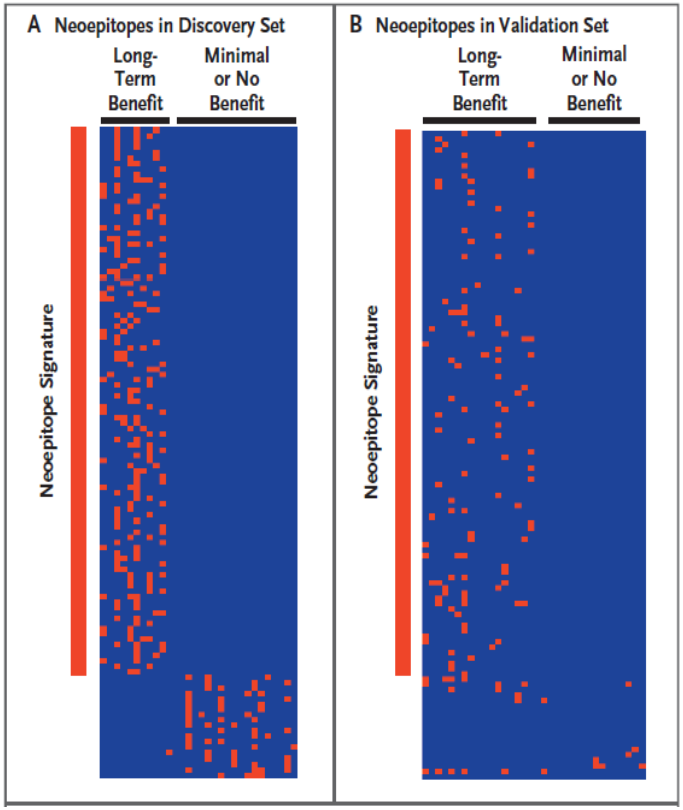
- Whole-exome sequencing performed on pretreatment tumor biopsies and matching germline tissue samples from 110 patients with metastatic melanoma treated with ipilimumab
  - Nonsynonymous mutational load and neoantigen load: significantly associated with clinical benefit (P=0.0076 and P=0.027)
  - CTLA-4 and PD-L2 expression: significantly elevated in clinical benefit vs no clinical benefit cohort (P=0.033 and P=0.041)
  - Granzyme A and perforin expression: significantly elevated in clinical benefit vs no clinical benefit cohort (P=0.042)



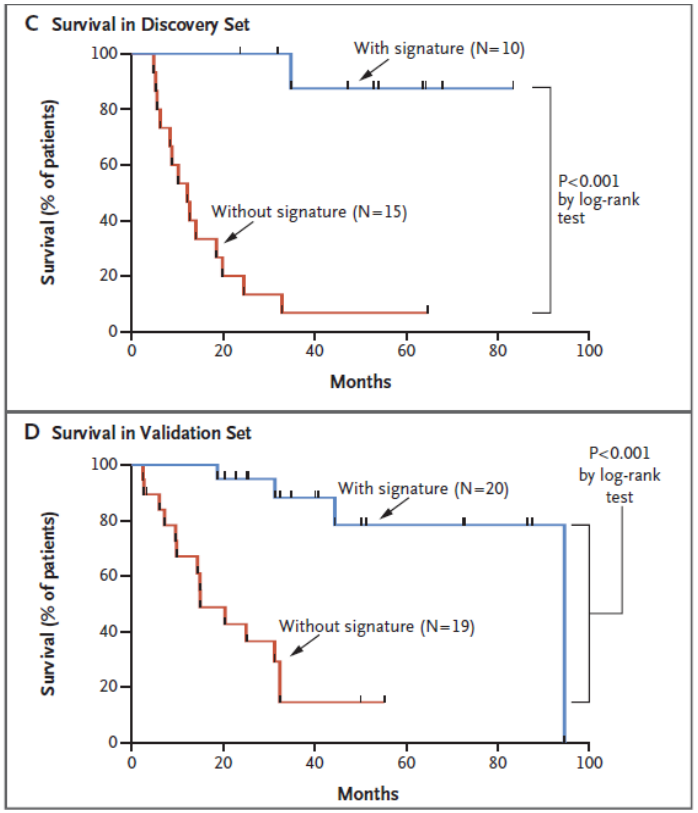
Asterisks indicate P<0.05 (Mann-Whitney). Van Allen EM, et al. *Science*. 2015 Sep 10; Epub ahead of print.

A Robust Neoantigen Signature Identifying Melanoma Patients That Respond to Anti-CTLA4 Therapy

Neoantigen signature

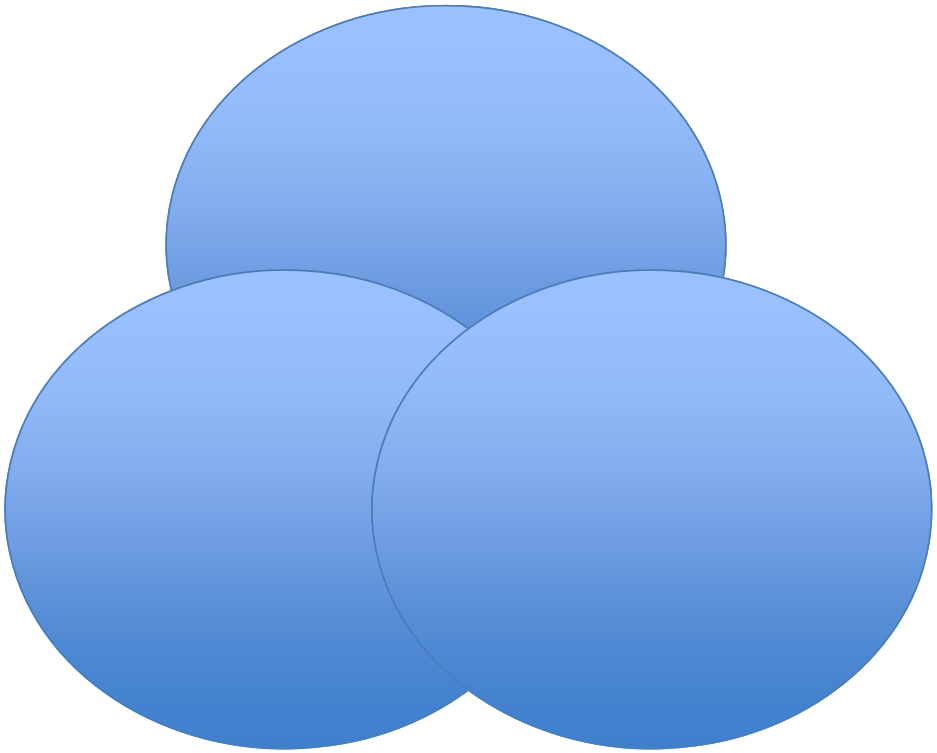


Survival following anti-CTLA4 Rx



Snyder et al. NEJM 2014

Immunotherapy strategy requires multiple lenses



Acknowledgements

MSKCC

Tim Chan
Matt Hellmann
Alex Snyder
Vlad Makarov
Will Lee
Jedd Wolchok
Taha Merghoub
Jianda Yuan
Phil Wong

NKI

Ton Schumacher
Pia Kvistborg

JHU

Janis Taube
Drew Pardoll

Future Biomarkers Panel Discussion

Moderator: Adrian Bot, MD, PhD – Kite Pharma, Inc.

Panelists:

- Lisa H. Butterfield, PhD – University of Pittsburgh
- Suzanne L. Topalian, MD – Johns Hopkins University
- Michael D. Kalos, PhD – Eli Lilly and Company
- Naiyer Rizvi, MD – Columbia University Medical Center