

# **Immunotherapeutic Strategy: Immune Checkpoint Blockade**

**Sumit K. Subudhi, MD, PhD**

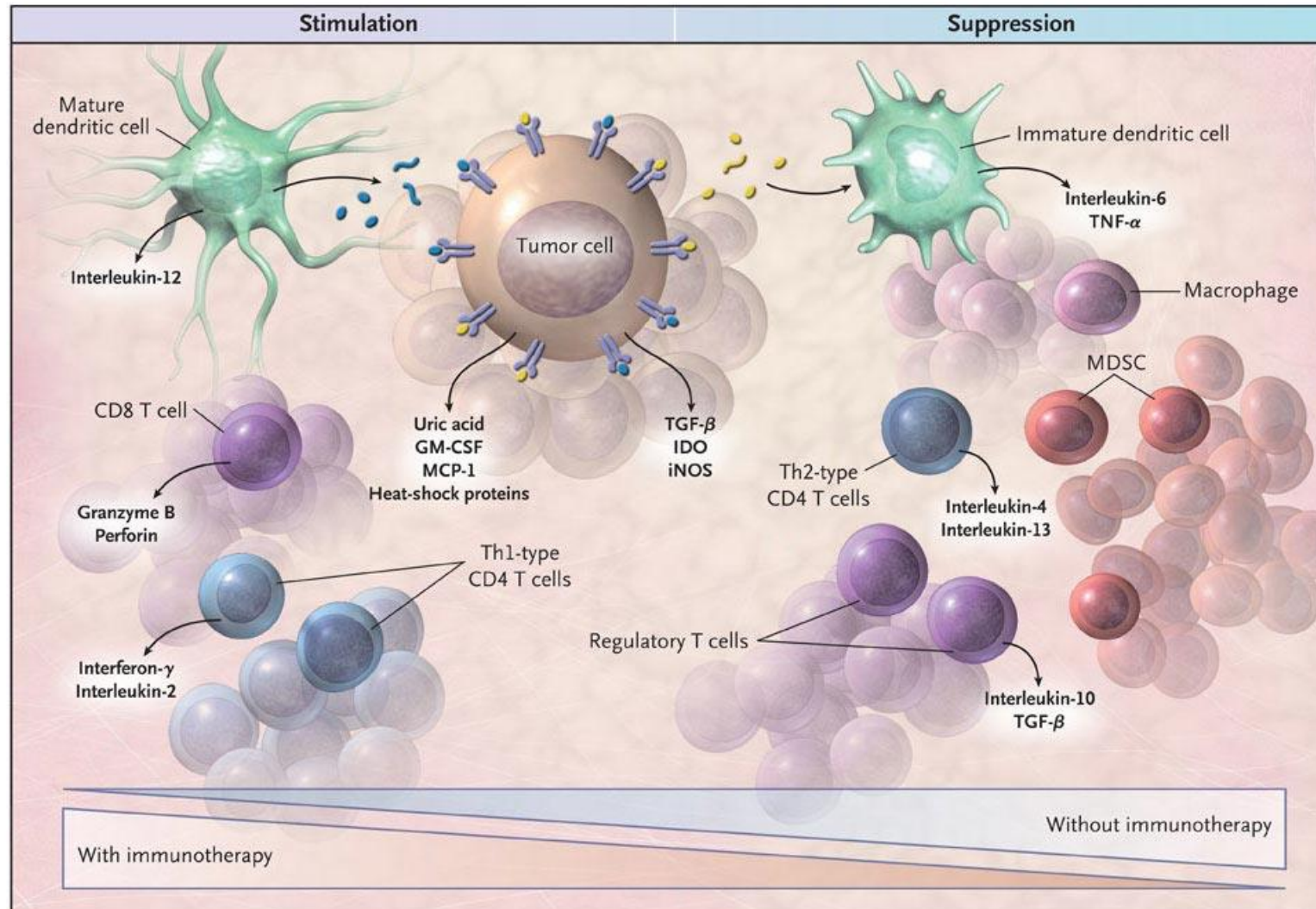
Associate Professor

Genitourinary Medical Oncology

# Disclosures

- **Consulting or Advisory Role:** Amgen, Apricity Health, AstraZeneca, Bayer, Bristol-Myers Squibb, Cancer Expert Now, Dava Oncology, Dendreon, Exelixis, Janssen Oncology, Javelin Oncology, Kahr Bio, and MD Education Limited
- **Research Funding:** AstraZeneca, Bristol-Myers Squibb, and Janssen Oncology
- **Other (Joint Scientific Committee):** Amgen, Janssen Oncology, and Polaris
- I **will** be discussing non-FDA approved indications during my presentation.

# Immune Tumor Microenvironment

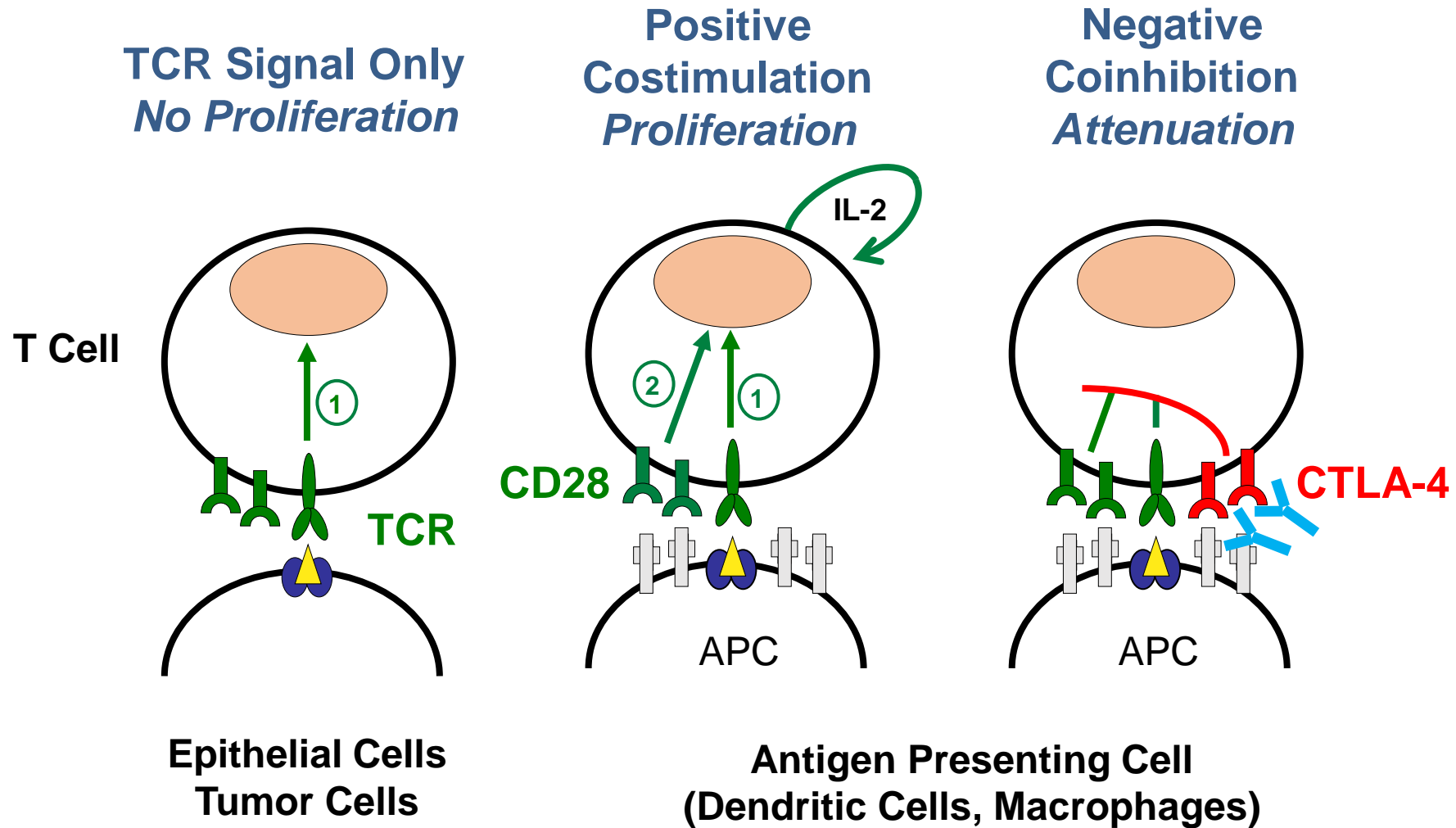


# Immunotherapies

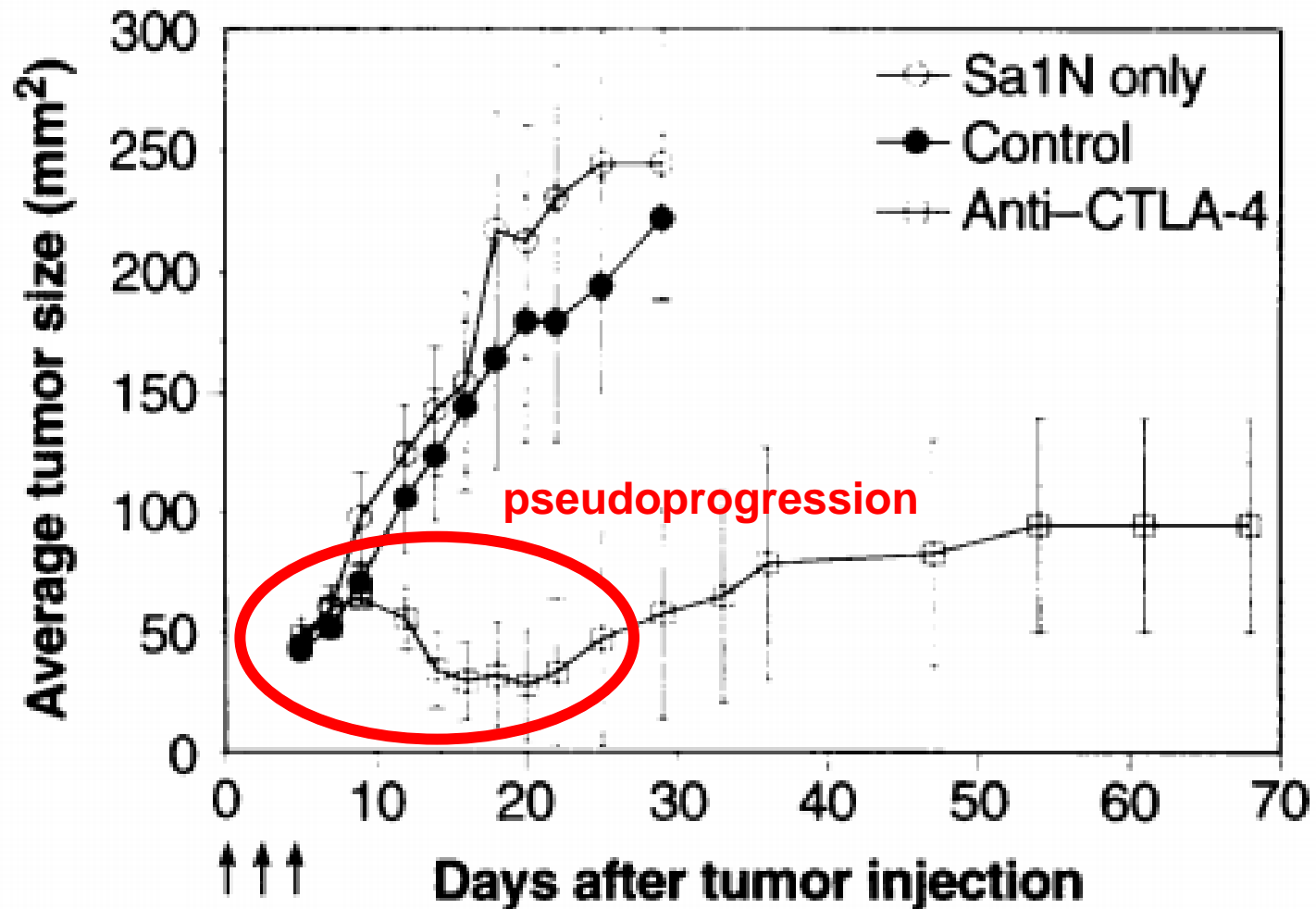
**Not all the same!**

- **Vaccines**
  - Directs immune system to focus on tumor antigen(s)
- **Cellular therapies**
  - CAR T cells target the tumor cells
- **Immune checkpoint therapies**
  - Increases T cell activation and function

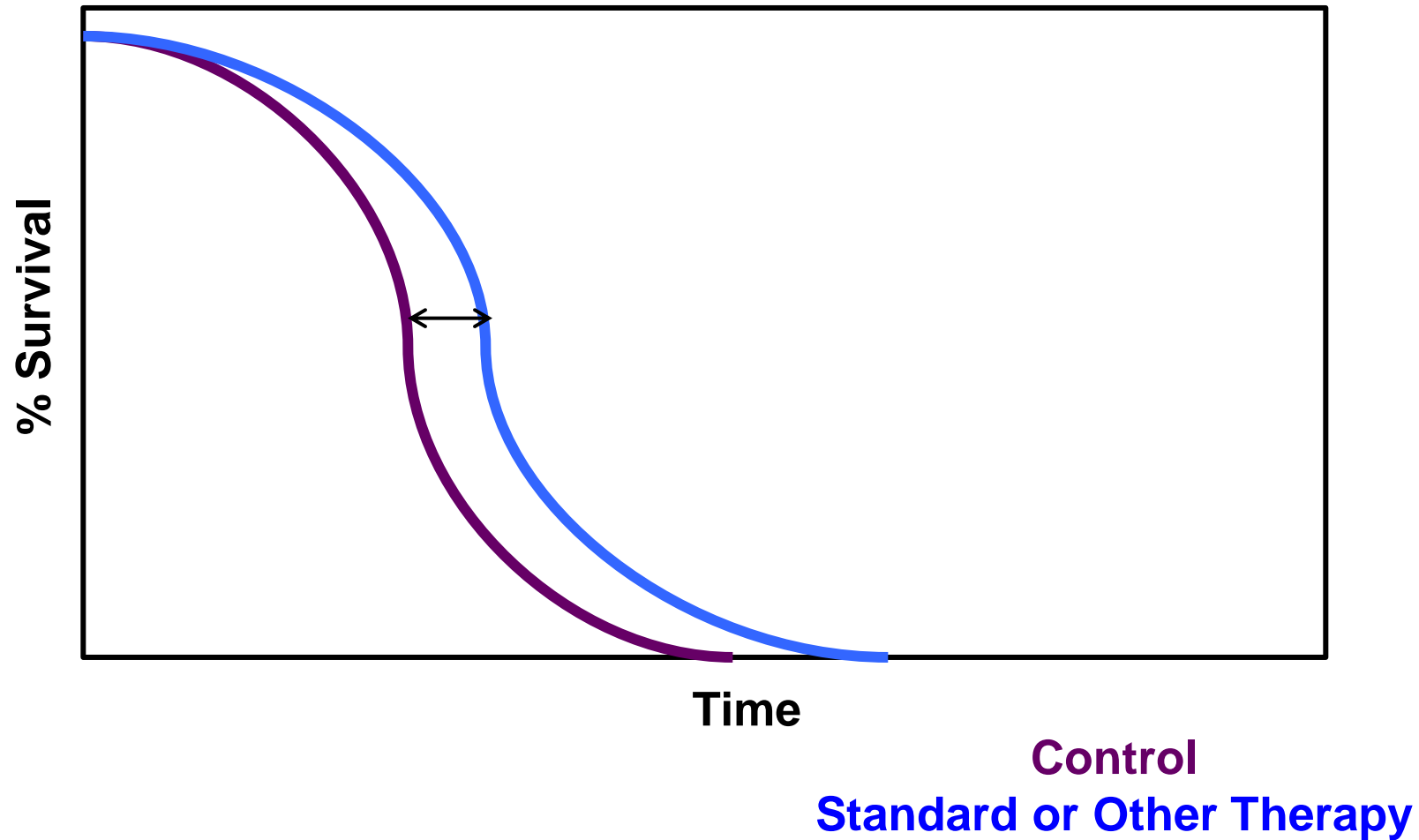
# New Understanding of T Cell Regulation: Positive/Negative Signals Govern Responses



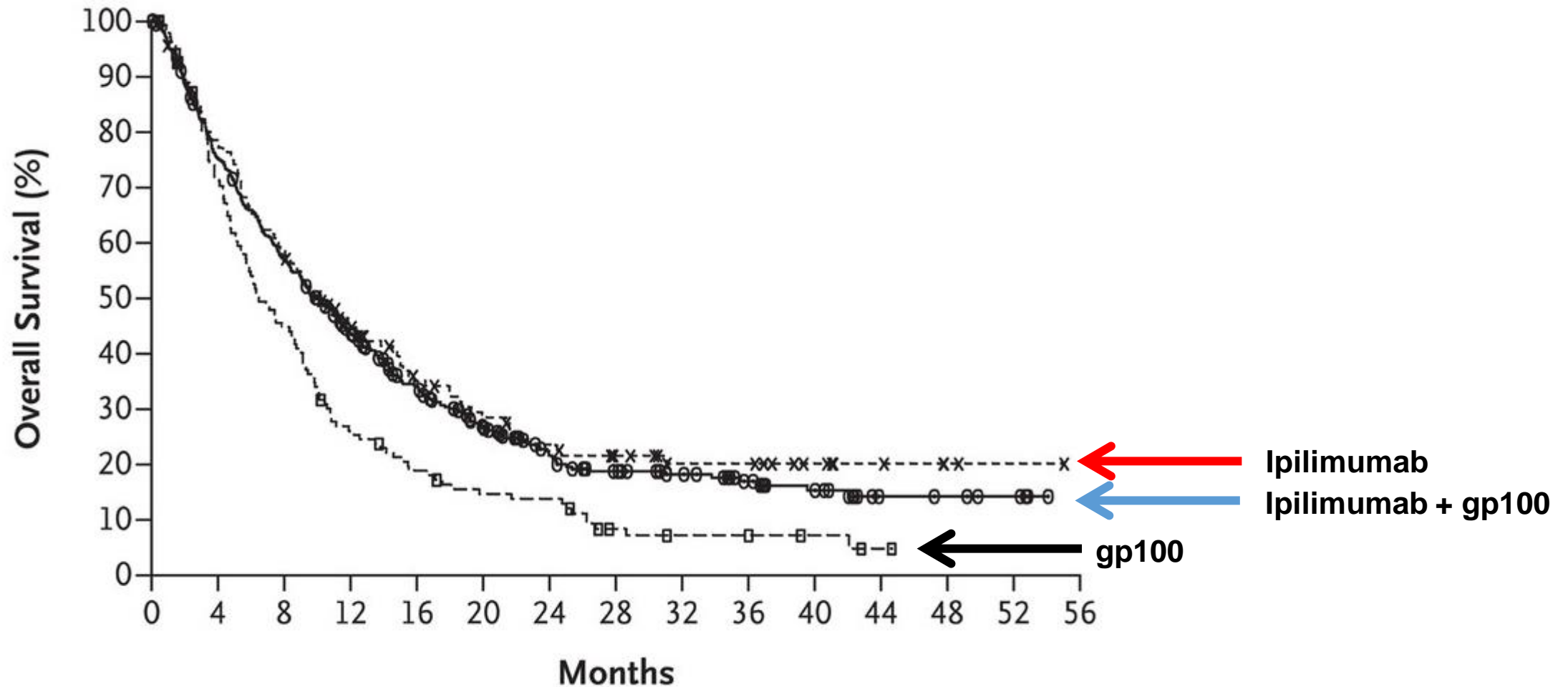
# Anti-CTLA-4 Reduces Tumor Growth Rate



# Improving Survival with a New Drug

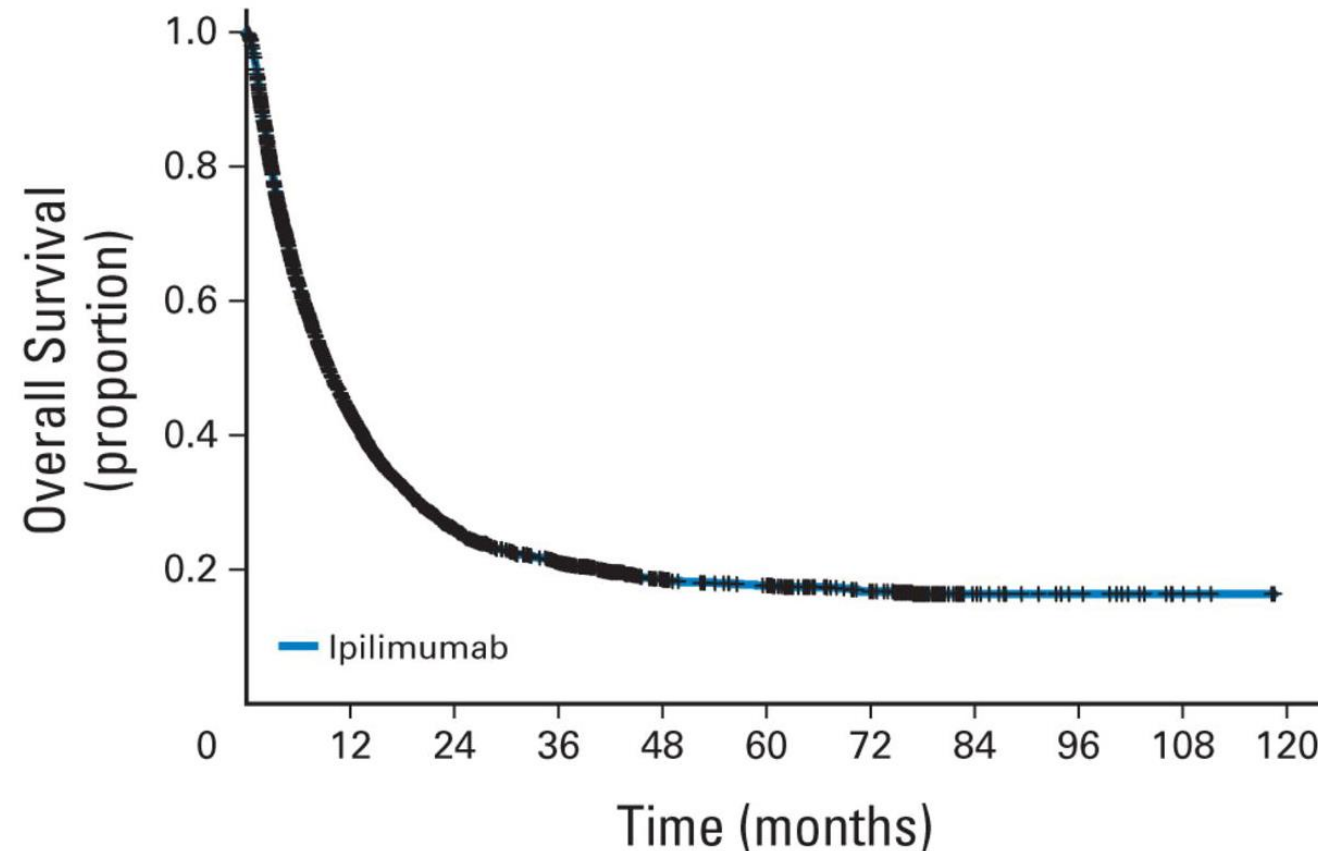


# Anti-CTLA-4 (Ipilimumab) Improves Survival in Patients with Metastatic Melanoma



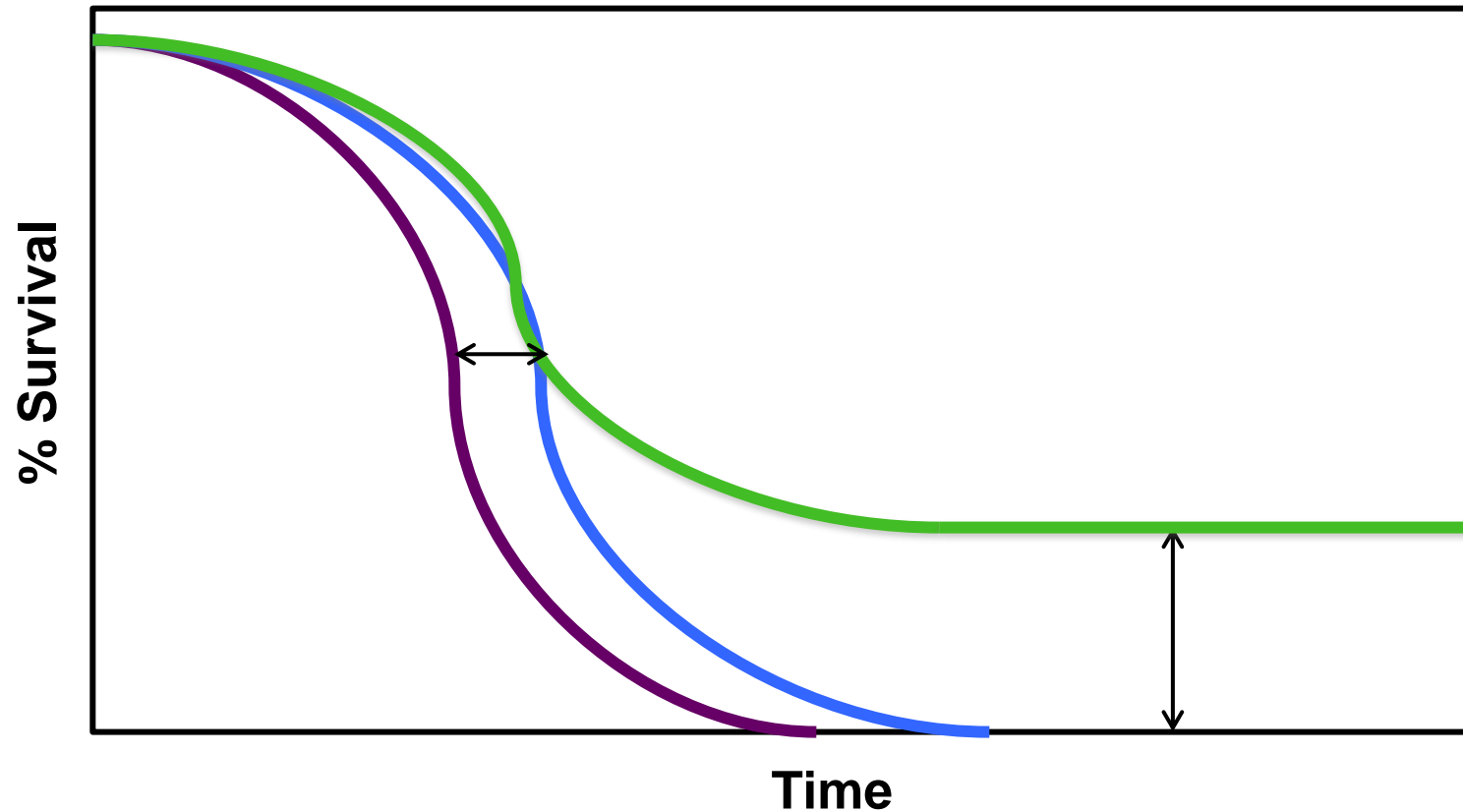


# Anti-CTLA-4 Induces Durable Anti-Tumor Responses in Patients with Metastatic Melanoma



No. at risk  
Ipilimumab 4,846 1,786 612 392 200 170 120 26 15 5 0

# Improving Survival with Immune Checkpoint Therapy

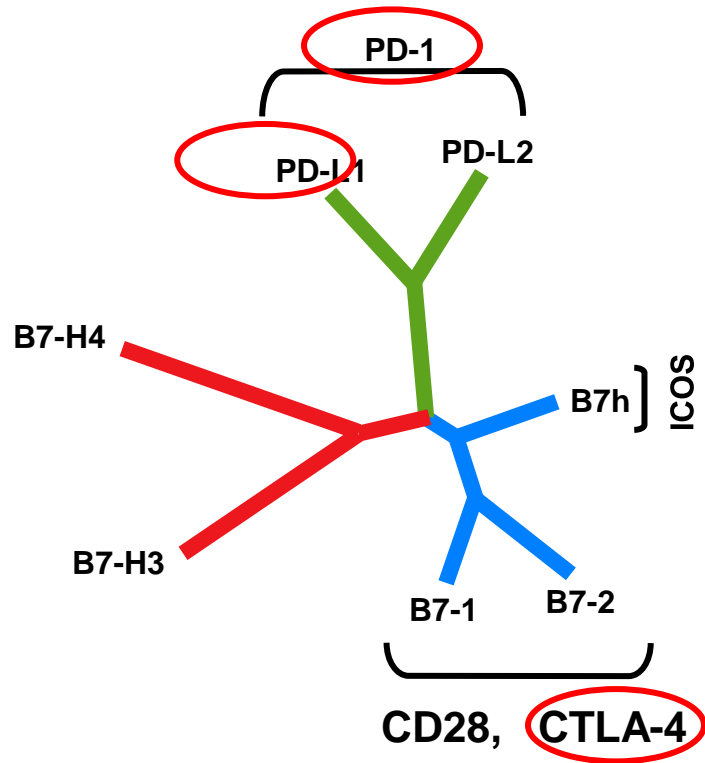


Control

Standard or Other Therapy

Immunotherapy (e.g. anti-CTLA-4)

# 2018: Nobel Prize in Physiology or Medicine

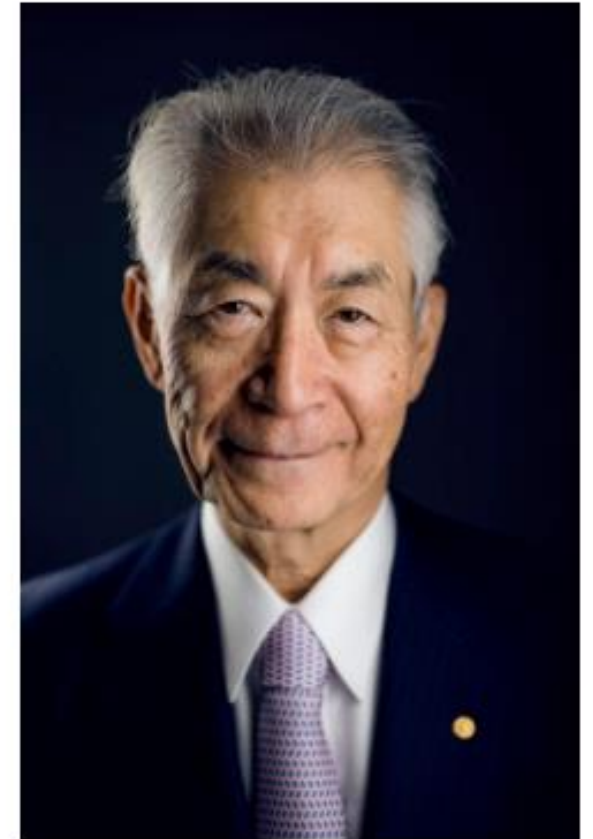


Zang X et al., *Proc Natl Acad Sci*, 2003



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James P. Allison



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Tasuku Honjo

# Differences Between Anti-CTLA-4 and Anti-PD-1

Anti-CTLA-4	Anti-PD-1

# **Challenges/Limitations of Immune Checkpoint Therapies**

- **Measuring disease burden / treatment response**
  - Immune-related response criteria (irRC)
- **Subset of patients benefit**
- **Toxicities**
  - Immune-related adverse events (irAEs)

# Delayed Responses with Ipilimumab

Screening



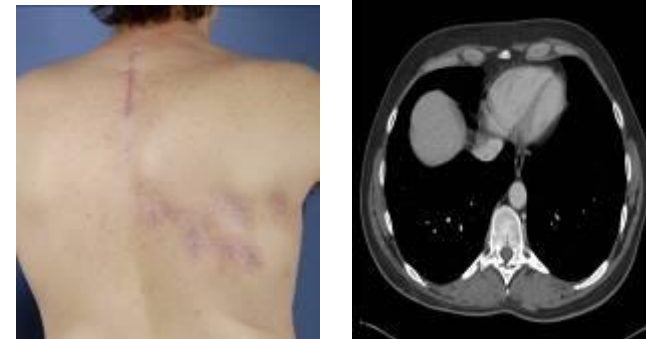
**Week 12**  
Initial increase in  
total tumour burden (mWHO PD)



**Week 16**  
Responding



**Week 72**  
Durable & ongoing response



Courtesy of K. Harmankaya

# **Moving Forward with Immune Checkpoint Therapies**

- **Improving patient selection**
- **Turning “cold” tumors “hot” / Resistance mechanisms**
- **Understanding toxicities**

# Moving Forward with Immune Checkpoint Therapies

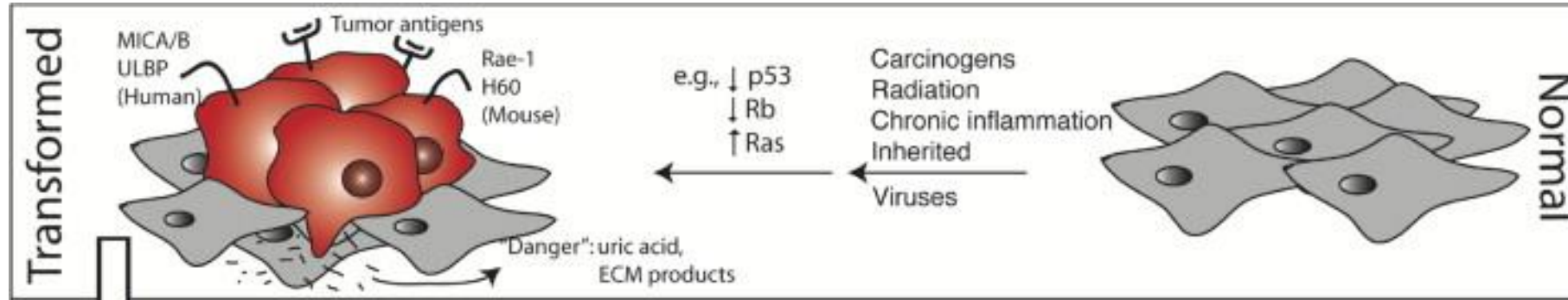
- Improving patient selection
- Turning “cold” tumors “hot” / Resistance mechanisms
- Understanding toxicities



# **Ways to Improve Patient Selection**

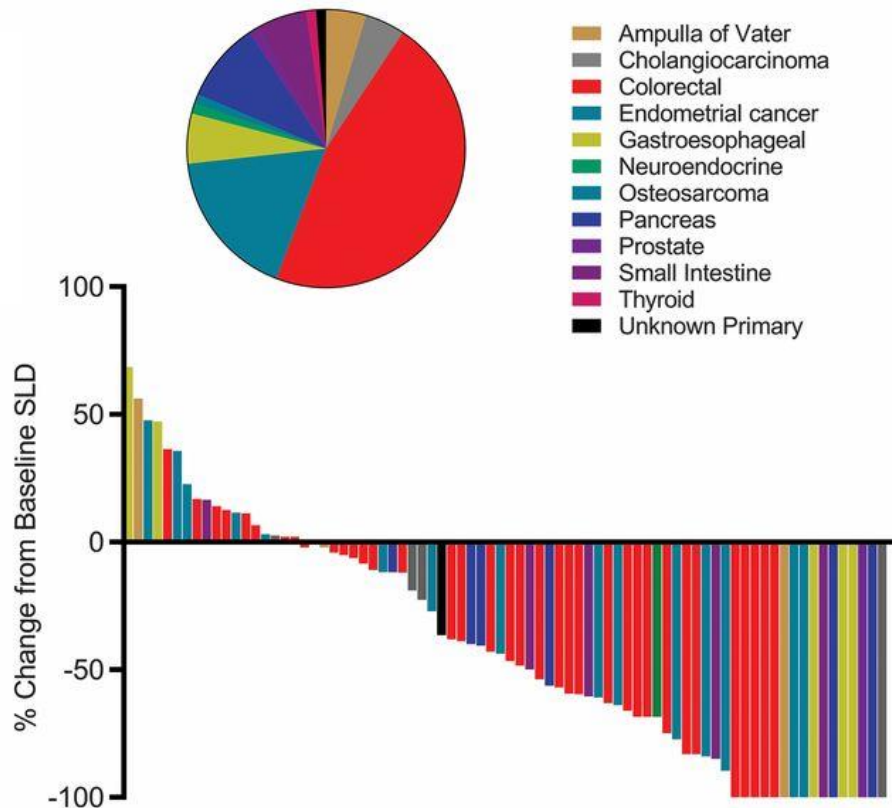
- **Identify patients who will more likely respond**
- **Exclude patients who will most likely not respond**

# Tumor Neoantigens



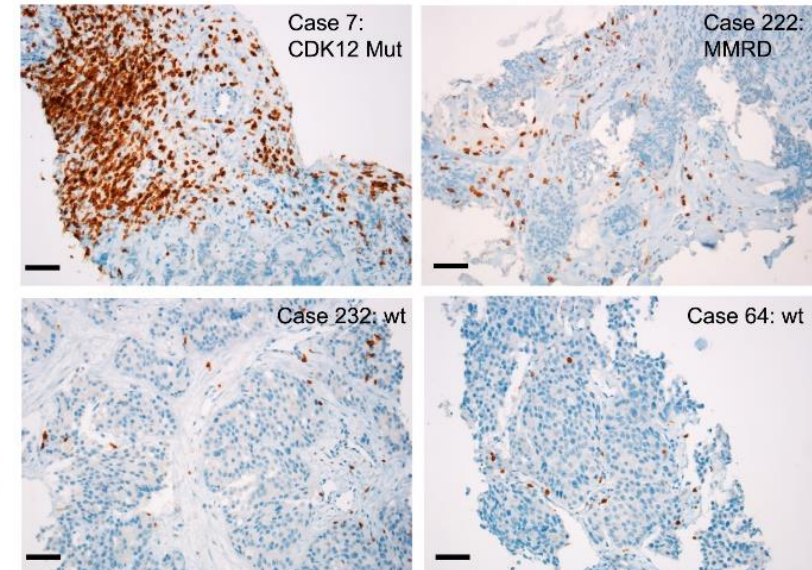
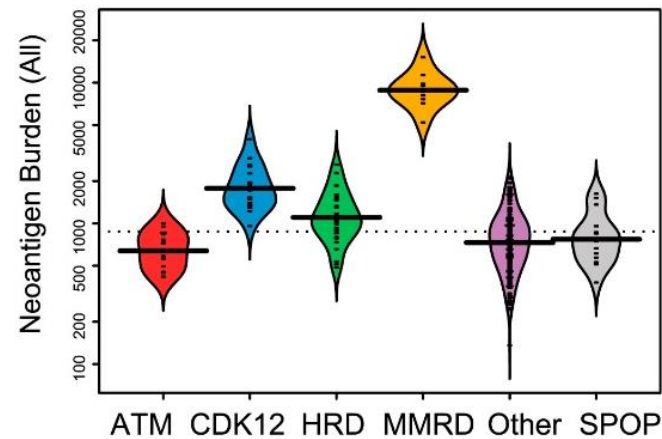
# Genomic Defects that Increase Neoantigen Burden

## Mismatch Repair (MMR) Defects



Le DT et al., *Science*, 2017

## CDK12 Mutations



Wu YM et al., *Cell*, 2018

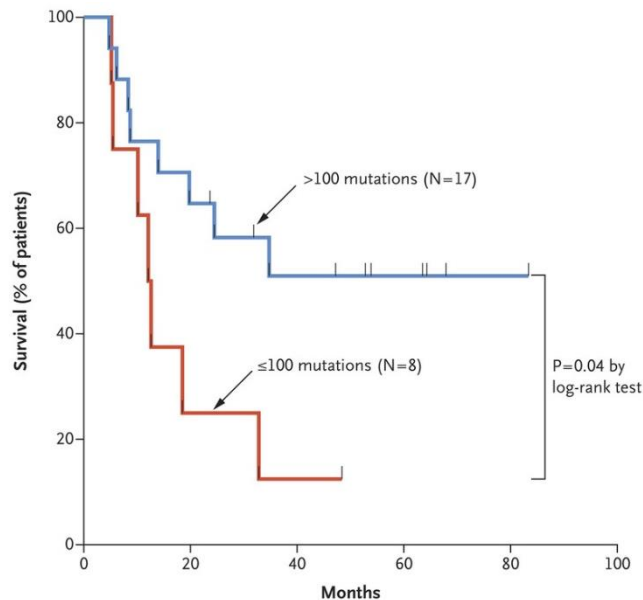
# Neoantigens and Mutational Load Linked to Efficacy of Immune Checkpoint Therapies

THE NEW ENGLAND JOURNAL of MEDICINE

## ORIGINAL ARTICLE

### Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

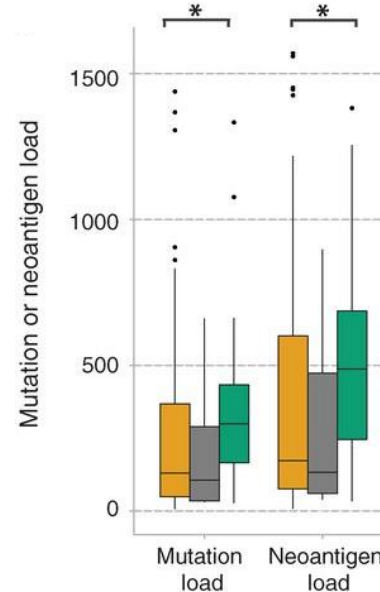
Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D., Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D., Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D., Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A., Kasthuri Kannan, Ph.D., Yanyun Li, M.D., Ph.D., Ceyhan Elipenahli, B.S., Cailian Liu, M.D., Christopher T. Harbison, Ph.D., Lisu Wang, M.D., Antoni Ribas, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and Timothy A. Chan, M.D., Ph.D.



## ONCOLOGY

### Genomic correlates of response to CTLA-4 blockade in metastatic melanoma

Eliezer M. Van Allen,<sup>1,2,3\*</sup> Diana Miao,<sup>1,2\*</sup> Bastian Schilling,<sup>4,5\*</sup> Sachet A. Shukla,<sup>1,2</sup> Christian Blank,<sup>6</sup> Lisa Zimmer,<sup>4,5</sup> Antje Sucker,<sup>4,5</sup> Uwe Hillen,<sup>4,5</sup> Marnix H. Geukes Foppen,<sup>6</sup> Simone M. Goldinger,<sup>7</sup> Jochen Utikal,<sup>5,8,9</sup> Jessica C. Hassel,<sup>10</sup> Benjamin Weide,<sup>11</sup> Katharina C. Kaehler,<sup>12</sup> Carmen Loquai,<sup>13</sup> Peter Mohr,<sup>14</sup> Ralf Gutzmer,<sup>15</sup> Reinhard Dummer,<sup>7</sup> Stacey Gabriel,<sup>2</sup> Catherine J. Wu,<sup>1,2</sup> Dirk Schadendorf,<sup>4,5,†</sup> Levi A. Garraway<sup>1,2,3,†</sup>



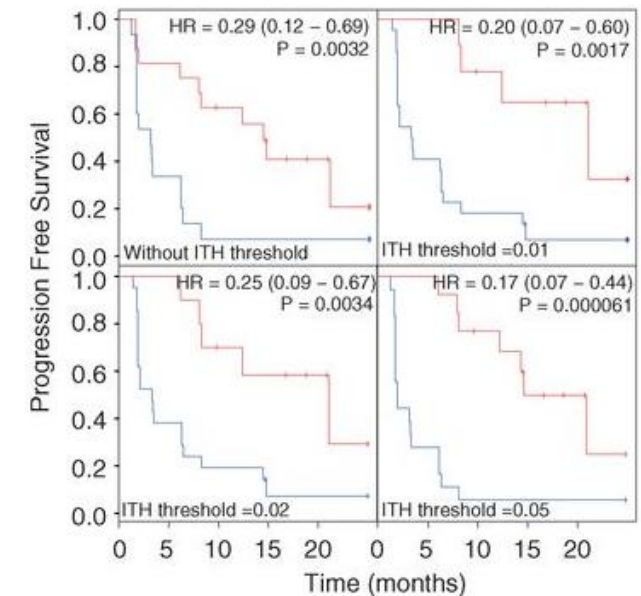
## Science

## REPORTS

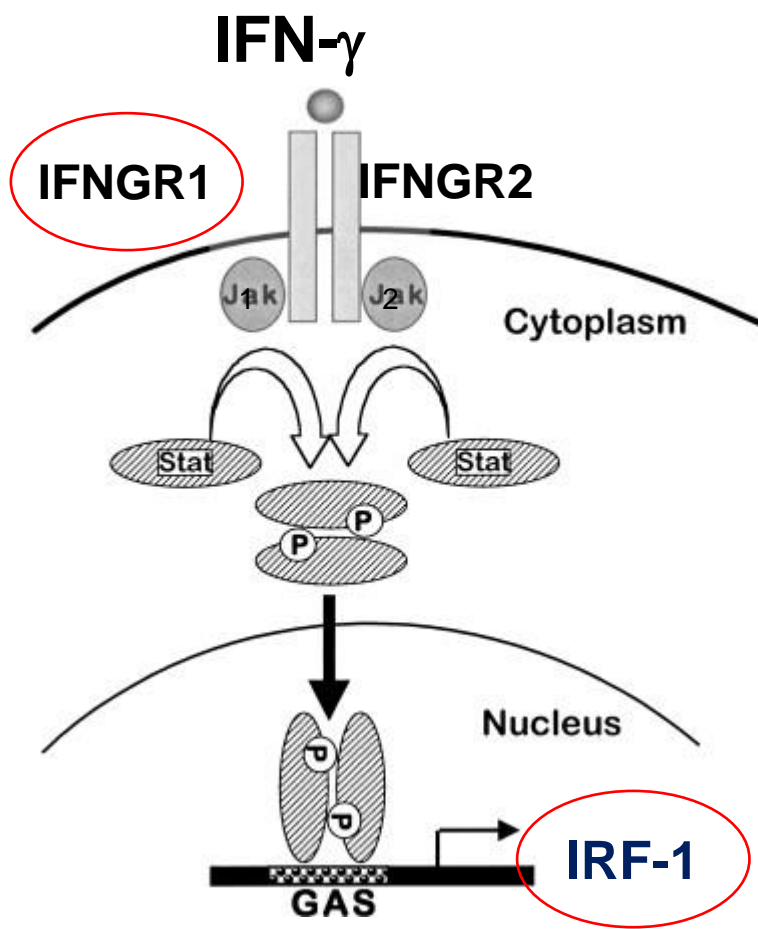
Cite as: N. McGranahan et al., *Science* 10.1126/science.aaf490 (2016).

### Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade

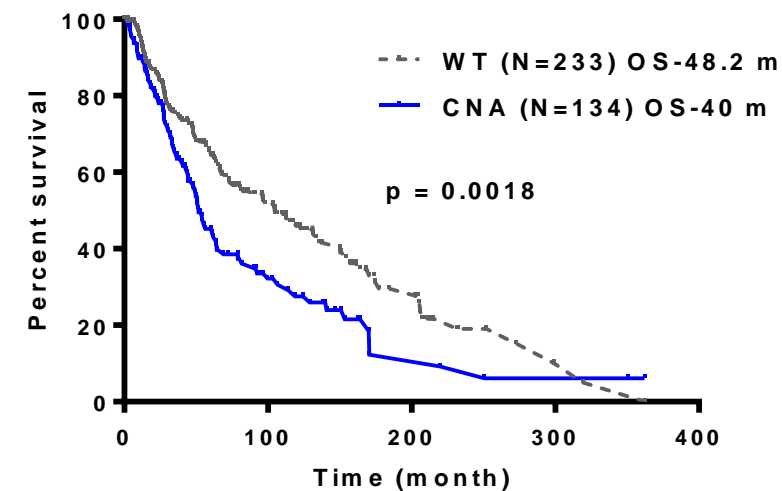
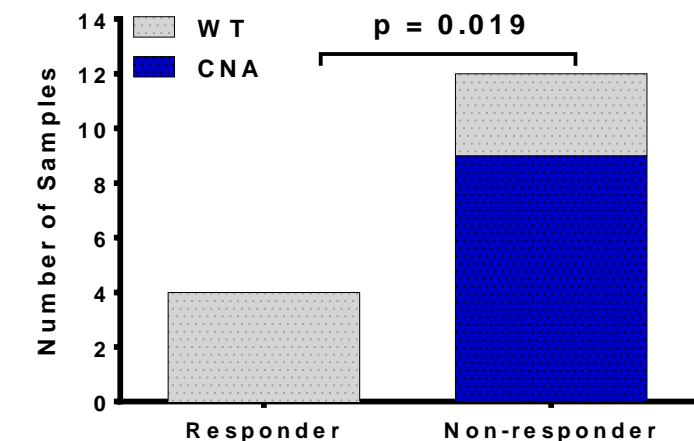
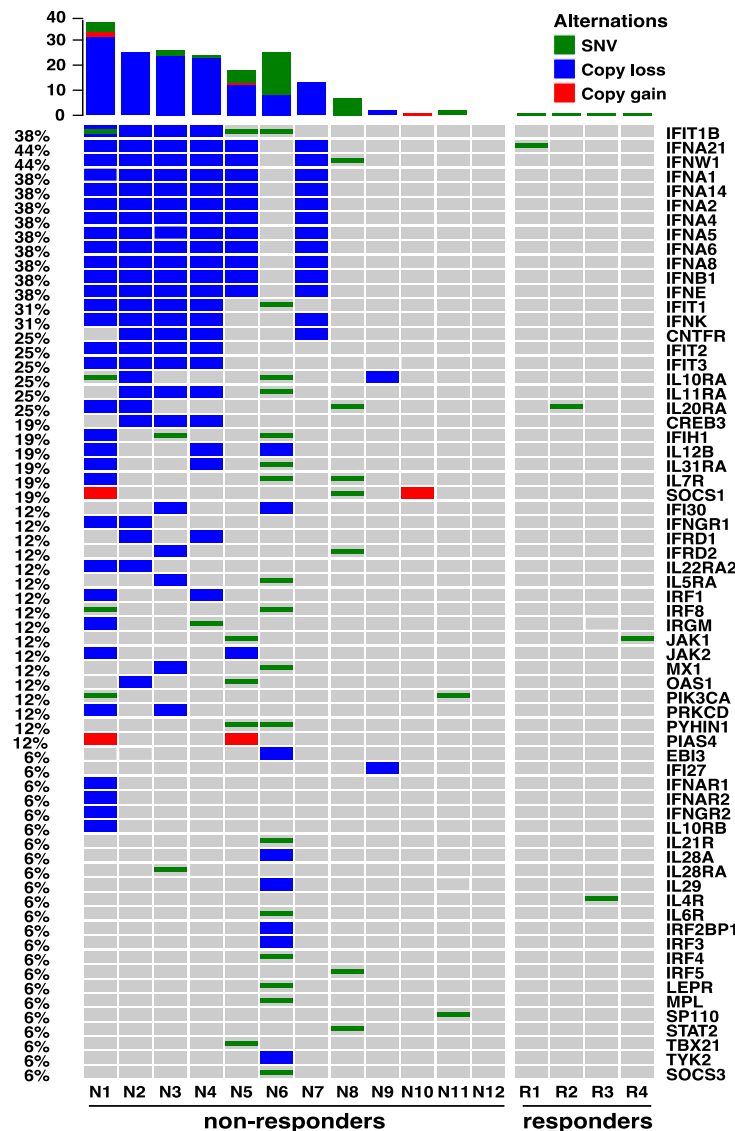
Nicholas McGranahan,<sup>1,2,3\*</sup> Andrew J. S. Furness,<sup>2,4\*</sup> Rachel Rosenthal,<sup>3\*</sup> Sofie Ramskov,<sup>2</sup> Rikke Lyngaa,<sup>2</sup> Sunil Kumar Saini,<sup>2</sup> Mariam Jamal-Hanjani,<sup>2</sup> Gareth A. Wilson,<sup>1,2</sup> Nicolai J. Birkbak,<sup>1,2</sup> Crispin T. Hiley,<sup>1,2</sup> Thomas B. K. Watkins,<sup>1,2</sup> Seema Shafi,<sup>2</sup> Nirupa Murugesu,<sup>2</sup> Richard Mitter,<sup>1</sup> Ayse U. Akarca,<sup>4,6</sup> Joseph Linares,<sup>4,6</sup> Teresa Marafioti,<sup>4,6</sup> Jake Y. Henry,<sup>2,4</sup> Eliezer M. Van Allen,<sup>7,8,9</sup> Diana Miao,<sup>7,8</sup> Bastian Schilling,<sup>10,11</sup> Dirk Schadendorf,<sup>10,11</sup> Levi A. Garraway,<sup>7,8,9</sup> Vladimir Makarov,<sup>12</sup> Nalayer A. Rizvi,<sup>12</sup> Alexandra Snyder,<sup>14,15</sup> Matthew D. Hellmann,<sup>14,15</sup> Taha Merghoub,<sup>14,16</sup> Jedd D. Wolchok,<sup>14,15,16</sup> Sachet A. Shukla,<sup>7,8</sup> Catherine J. Wu,<sup>7,8,17,18</sup> Karl S. Peggs,<sup>2,4</sup> Timothy A. Chan,<sup>12</sup> Sine R. Hadrup,<sup>2</sup> Sergio A. Quezada,<sup>2,4,†</sup> Charles Swanton<sup>1,2,†</sup>



# Defects in the IFN- $\gamma$ Signaling Pathway Promote Resistance to Immune Checkpoint Therapies



Modified from Kisseleva et al., *Gene*, 2002



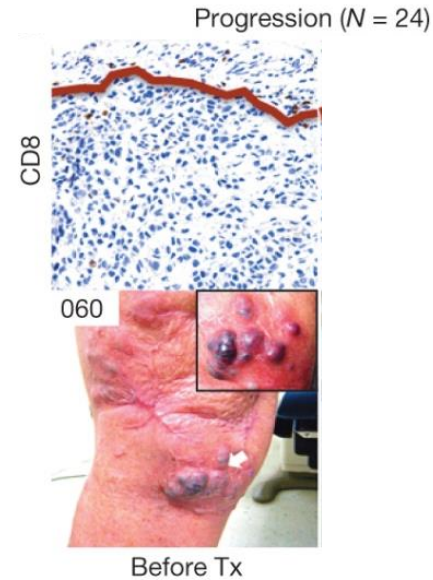
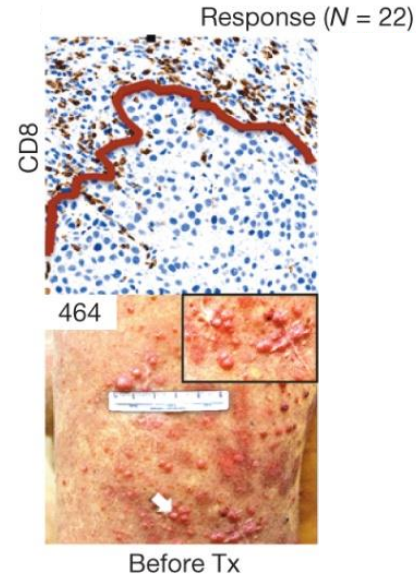
Gao J et al., *Cell*, 2016

# Moving Forward with Immune Checkpoint Therapies

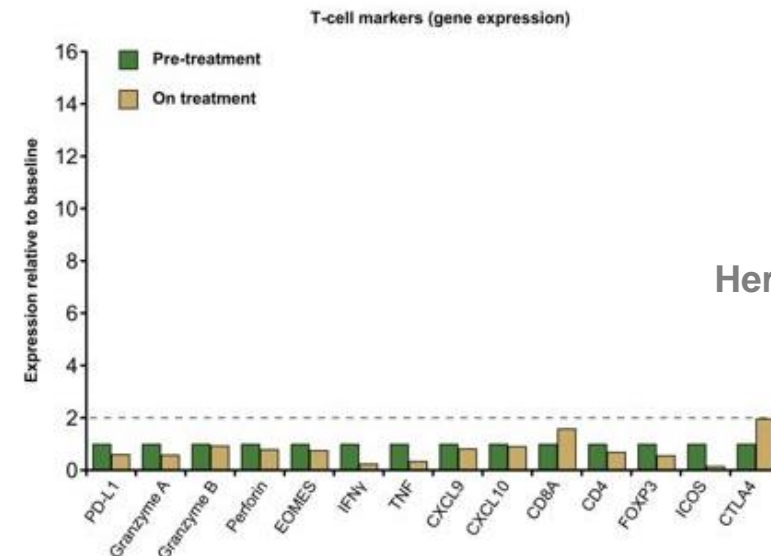
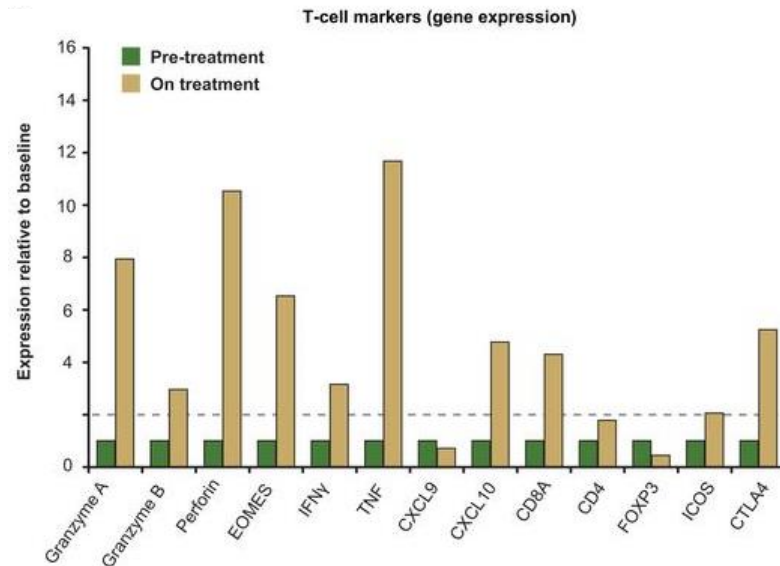
- Improving patient selection
- **Turning “cold” tumors “hot” / Resistance mechanisms**
- Understanding toxicities



# More CD8 T Cells Makes Anti-PD-1/PD-L1 Work Better

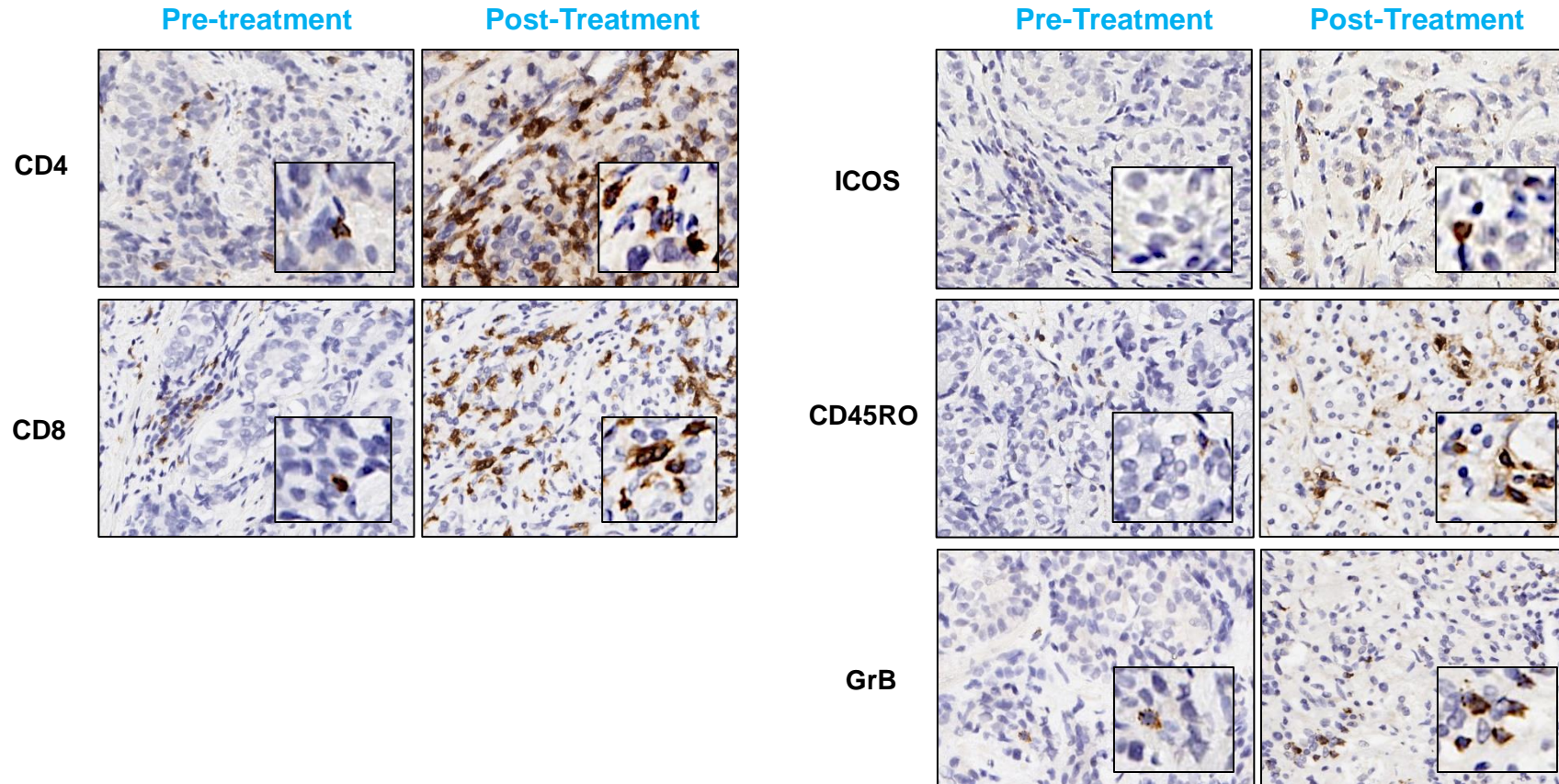


Tumeh PC et al., *Nature*, 2014



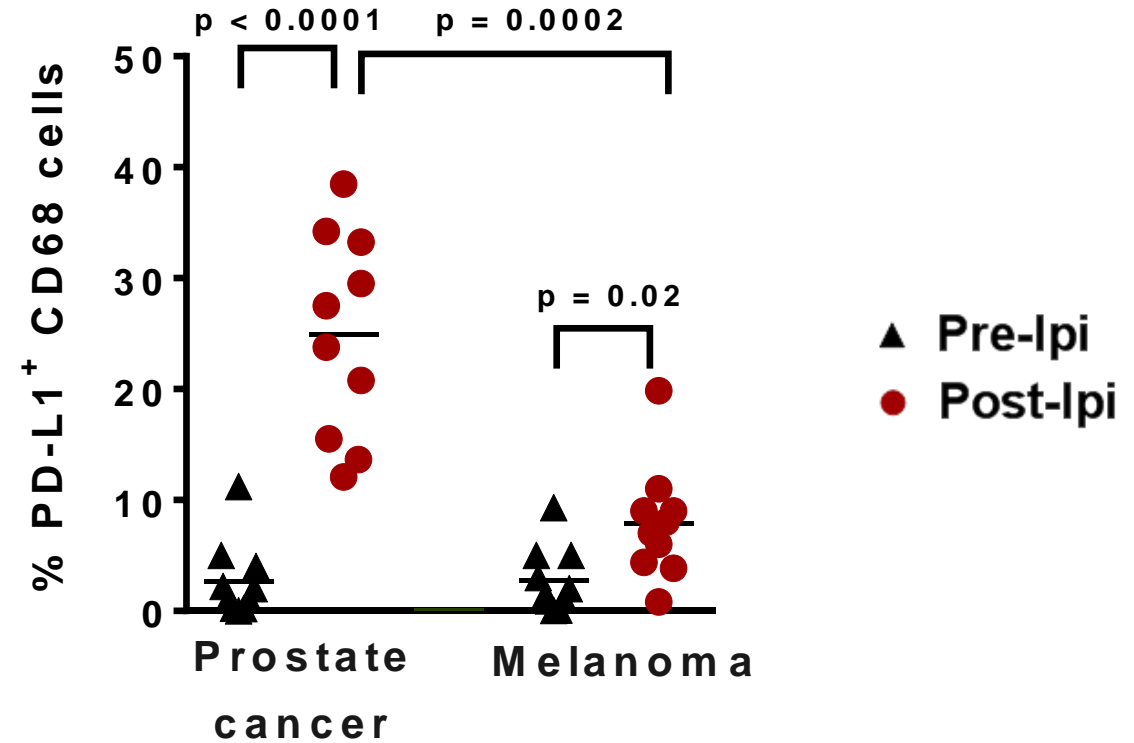
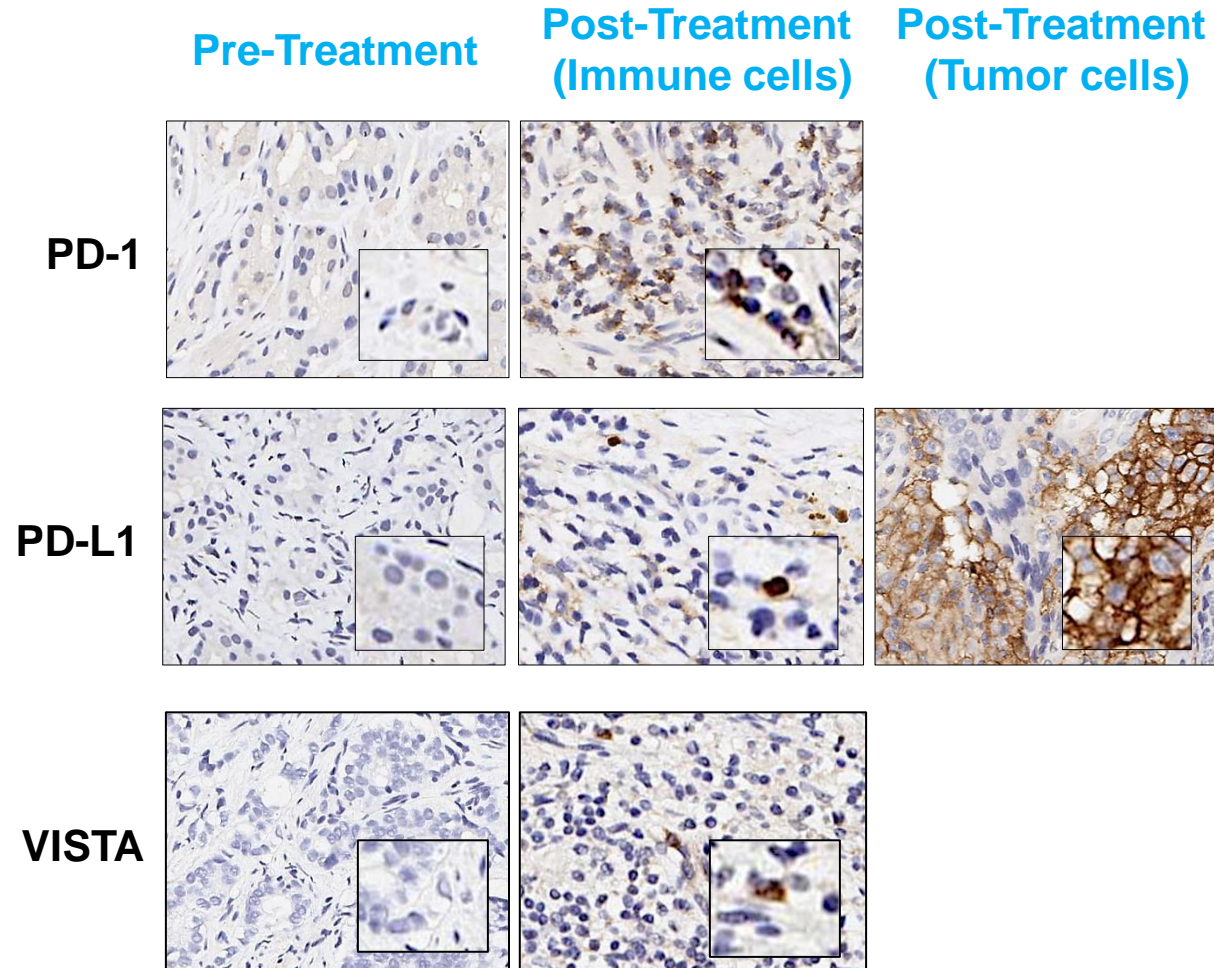
Herbst RS et al., *Nature*, 2014

# Ipilimumab Increases Immune Infiltration Within the Primary Prostate Tumor Microenvironment

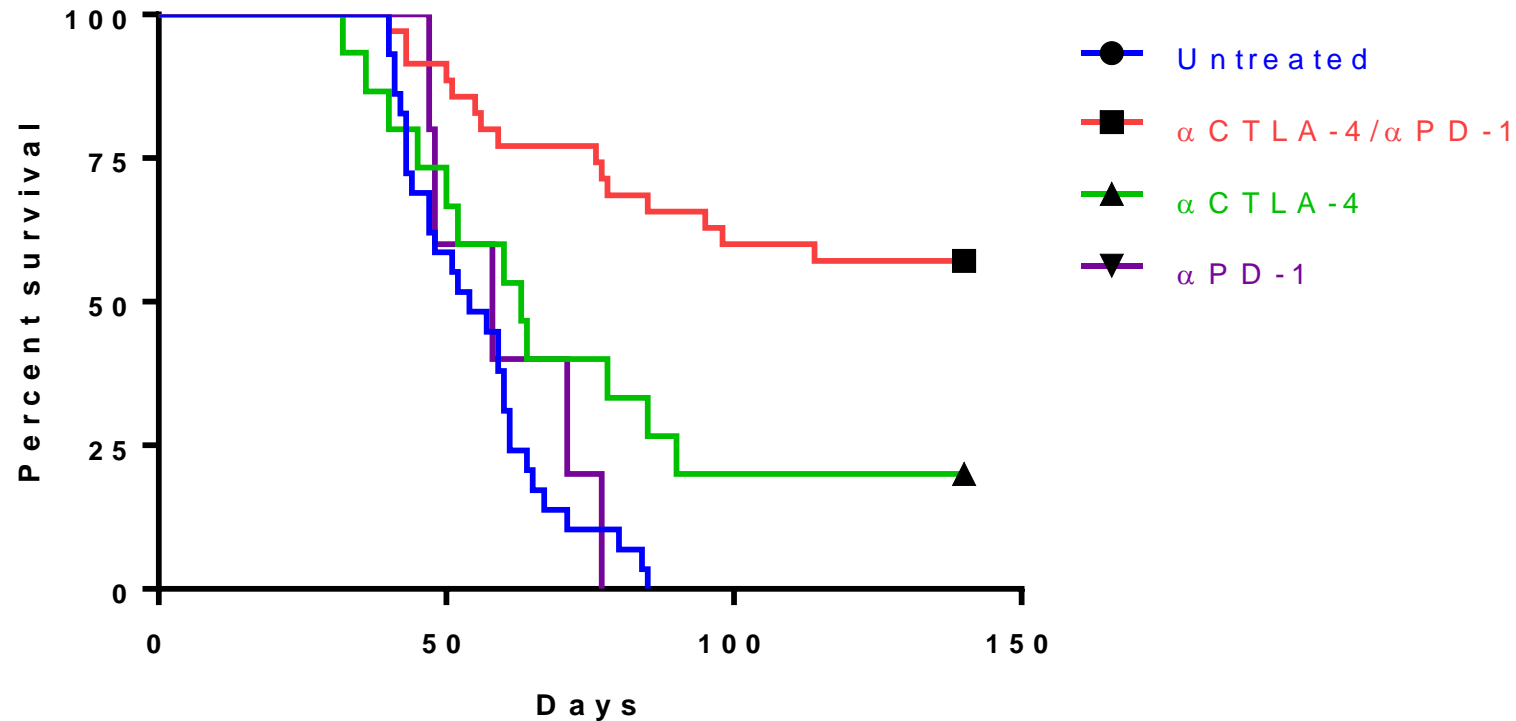




# Increased Tumor-Infiltrating T Cells are Insufficient Due to Adaptive Resistance (PD-L1 Upregulation)



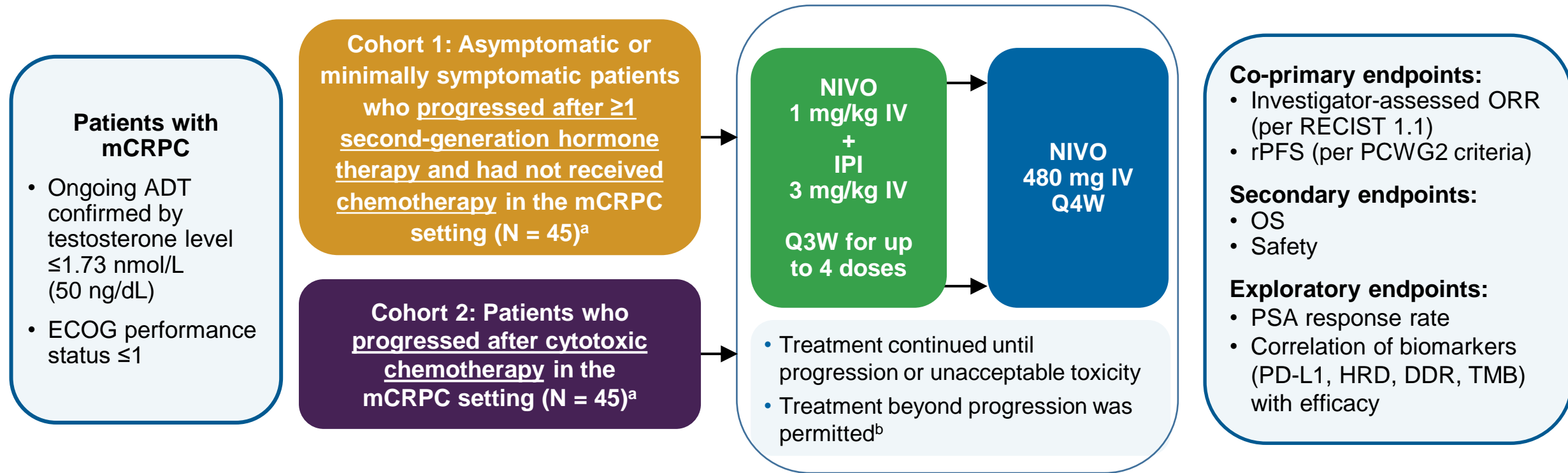
# CTLA-4 and PD-1/PD-L1 Targeting in a Mouse Model of Prostate Cancer



**Combination of “immune checkpoint targets”  
will improve efficacy**

# Study Design for CheckMate 650 in Prostate Cancer

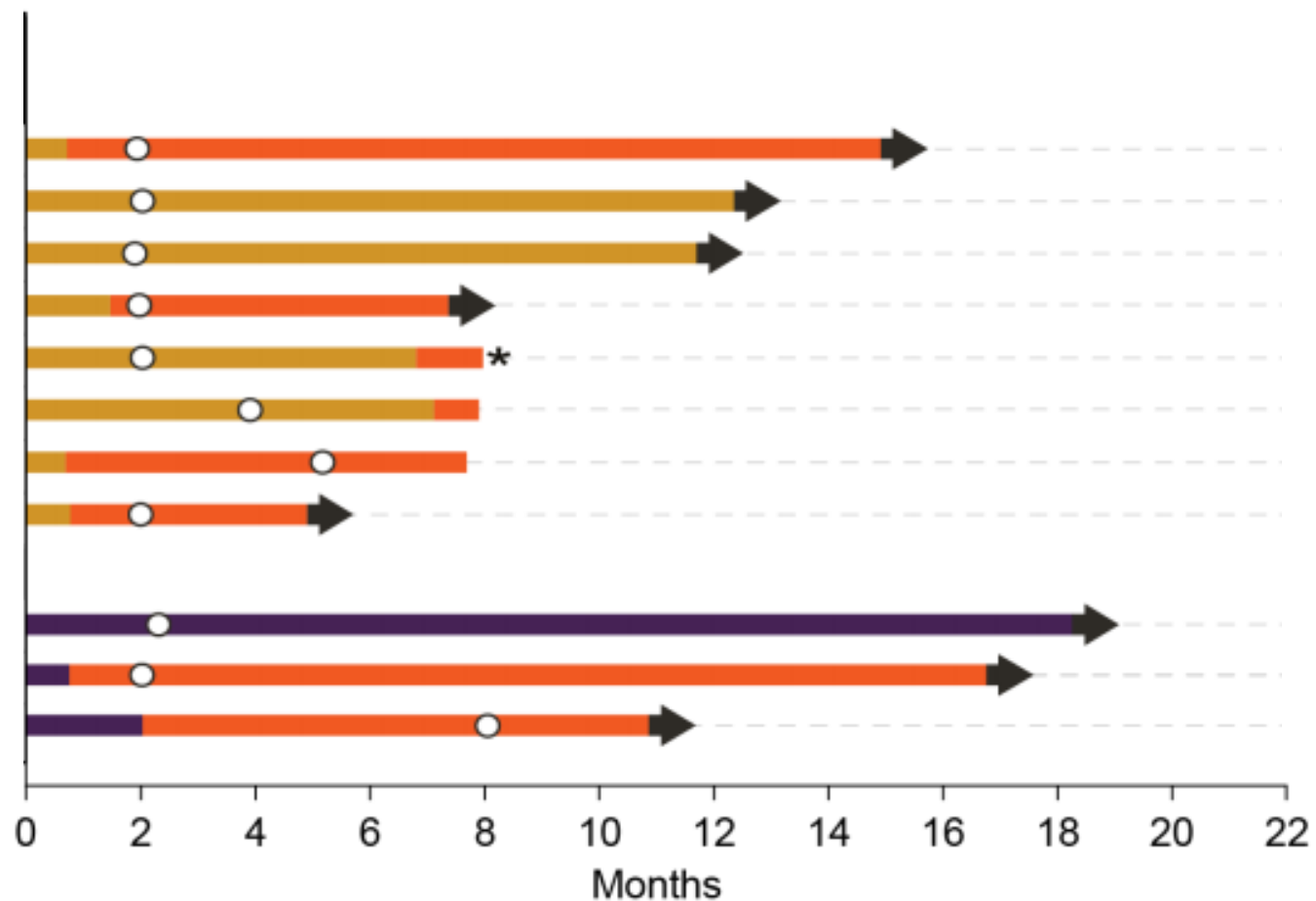
Open-label, multicenter, phase 2 study (NCT02985957)



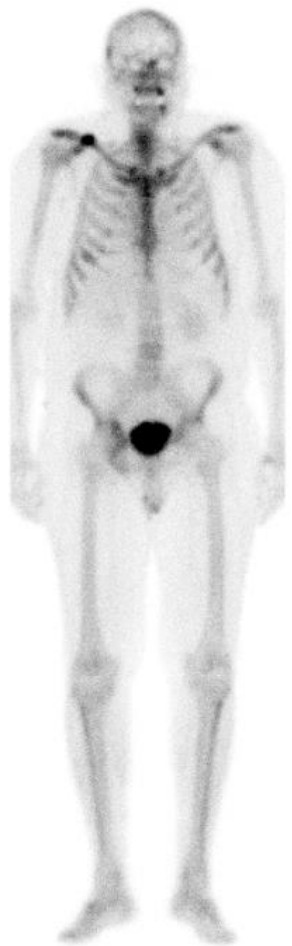
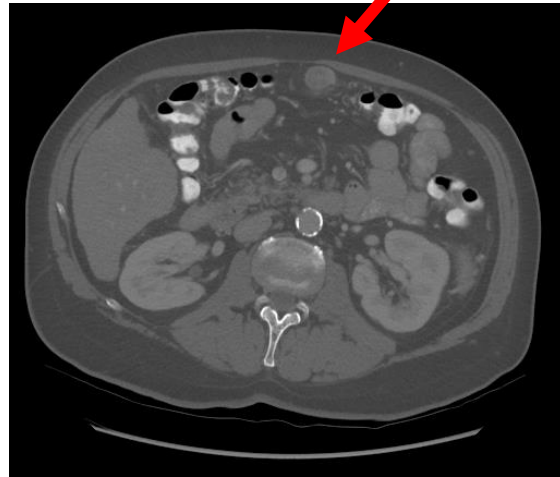
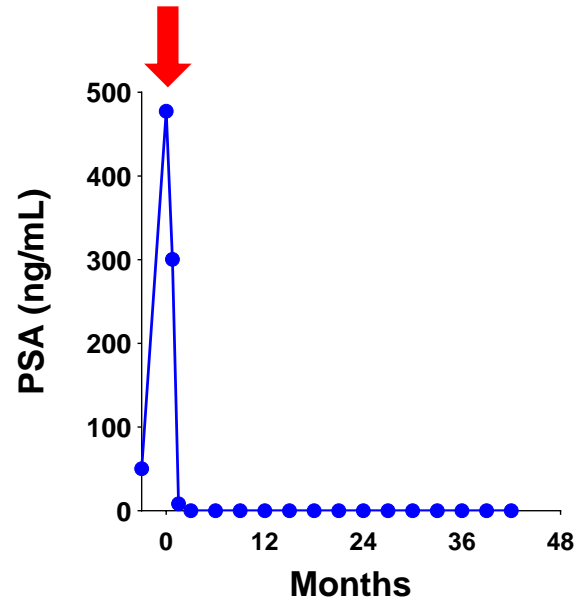
- Patients who had received  $\geq 1$  combination dose and who had toxicity that did not meet discontinuation criteria were permitted to begin NIVO maintenance before completion of all 4 combination doses

# Prolonged Responses

■ Cohort 1 } On treatment  
■ Cohort 2 }  
○ First response      ➡ Ongoing objective response      ■ Off treatment



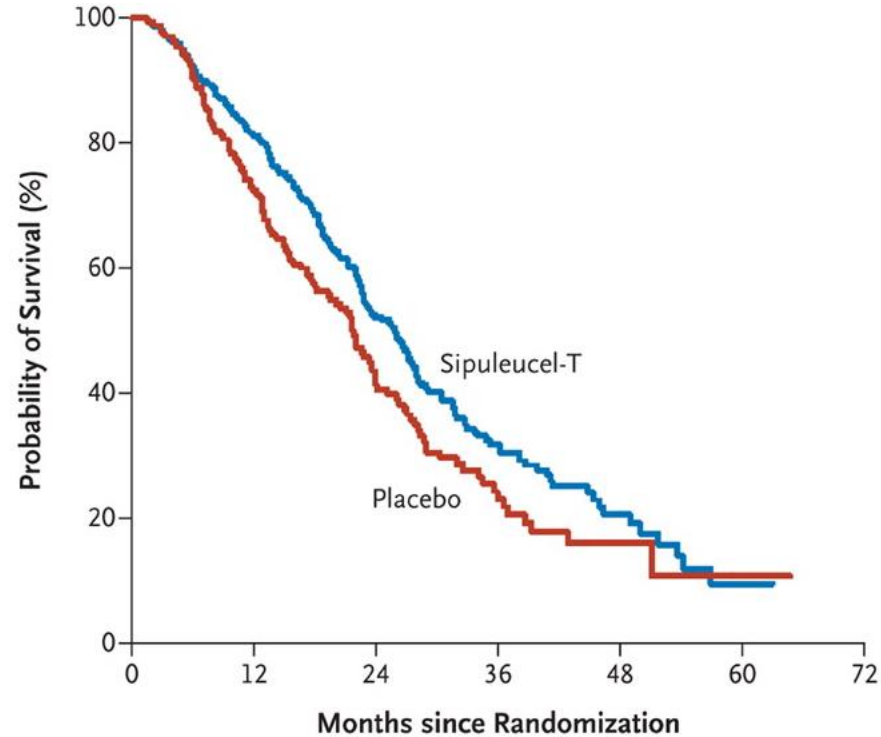
# Responder at MD Anderson



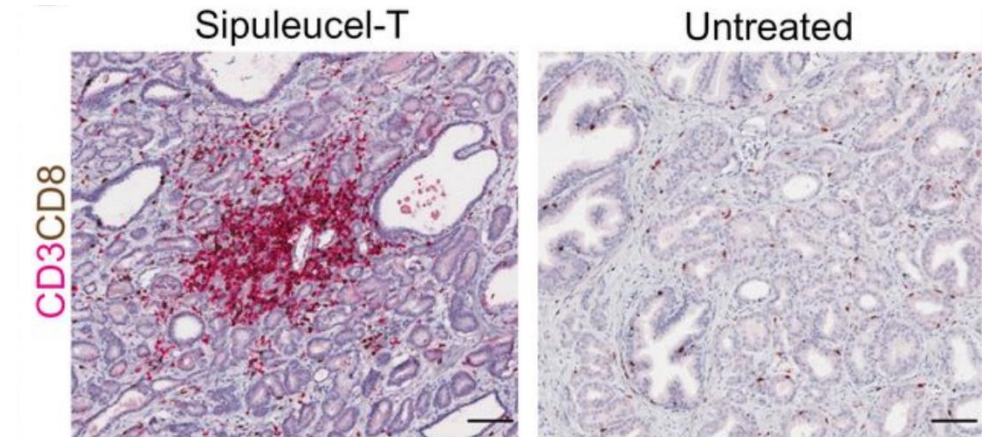


# Targeting a Conventional Prostate Cancer Antigen Induces T Cell Infiltration into the Tumor Microenvironment

## Sipuleucel-T (DC Vaccine)

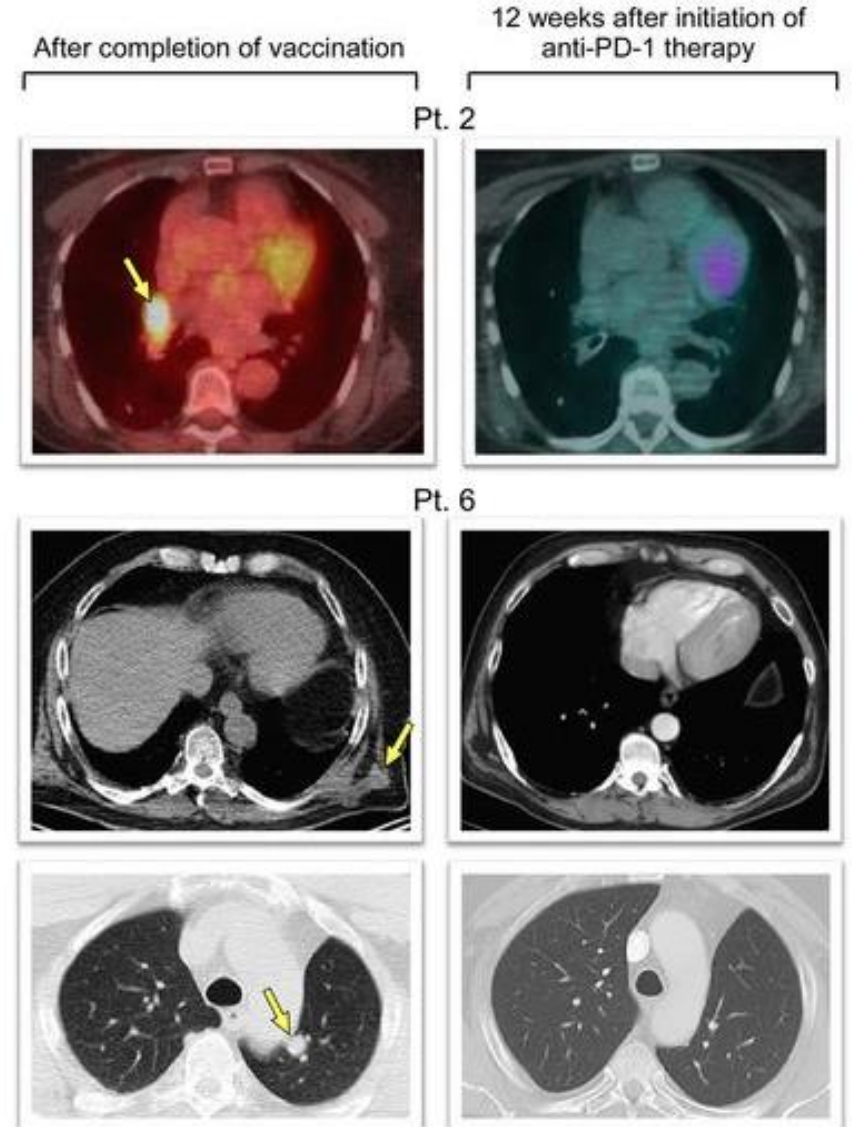
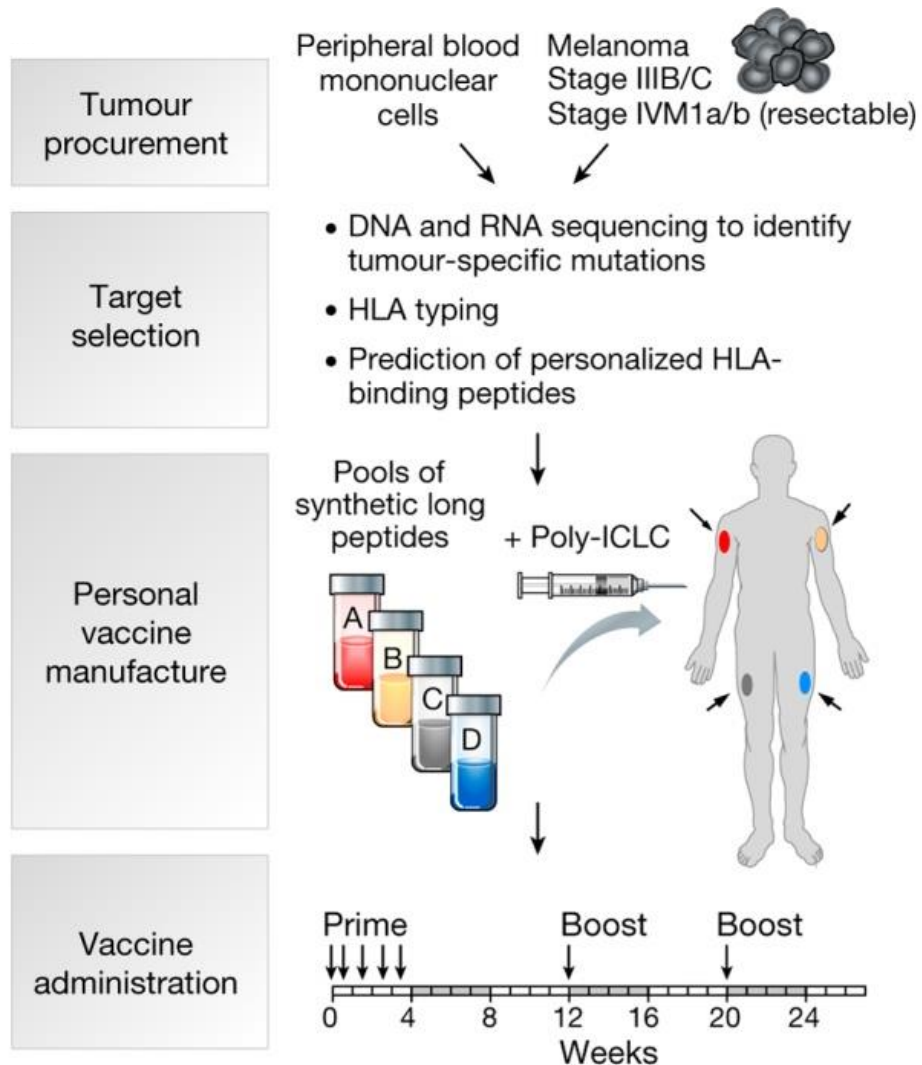


Kantoff PW et al., *N Engl J Med*, 2010

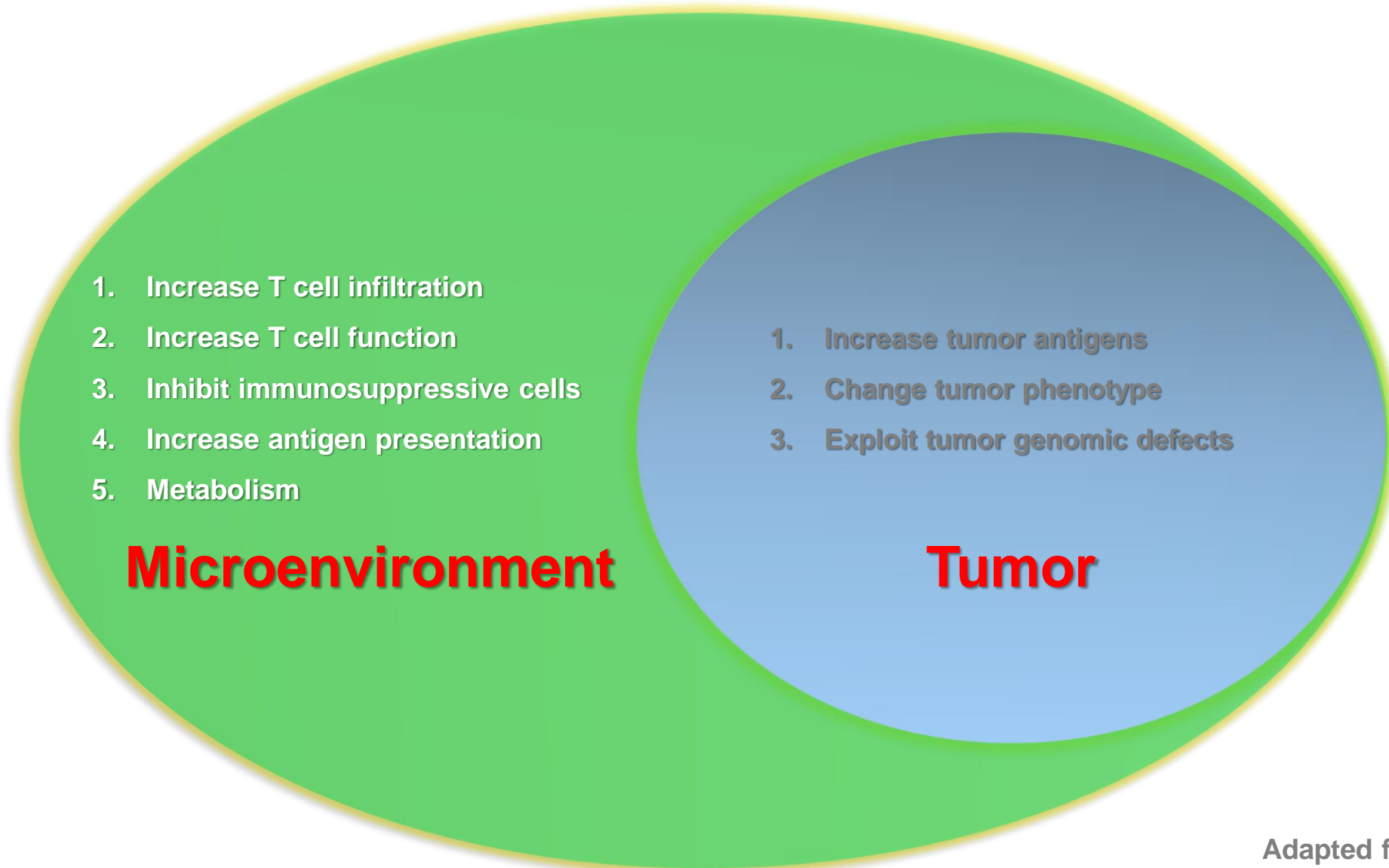


Fong L et al., *J Natl Cancer Inst*, 2014

# Personal Multi-Peptide Neoantigen Vaccine for Patients with High-Risk Melanoma



# Making Immune Checkpoint Therapies More Effective

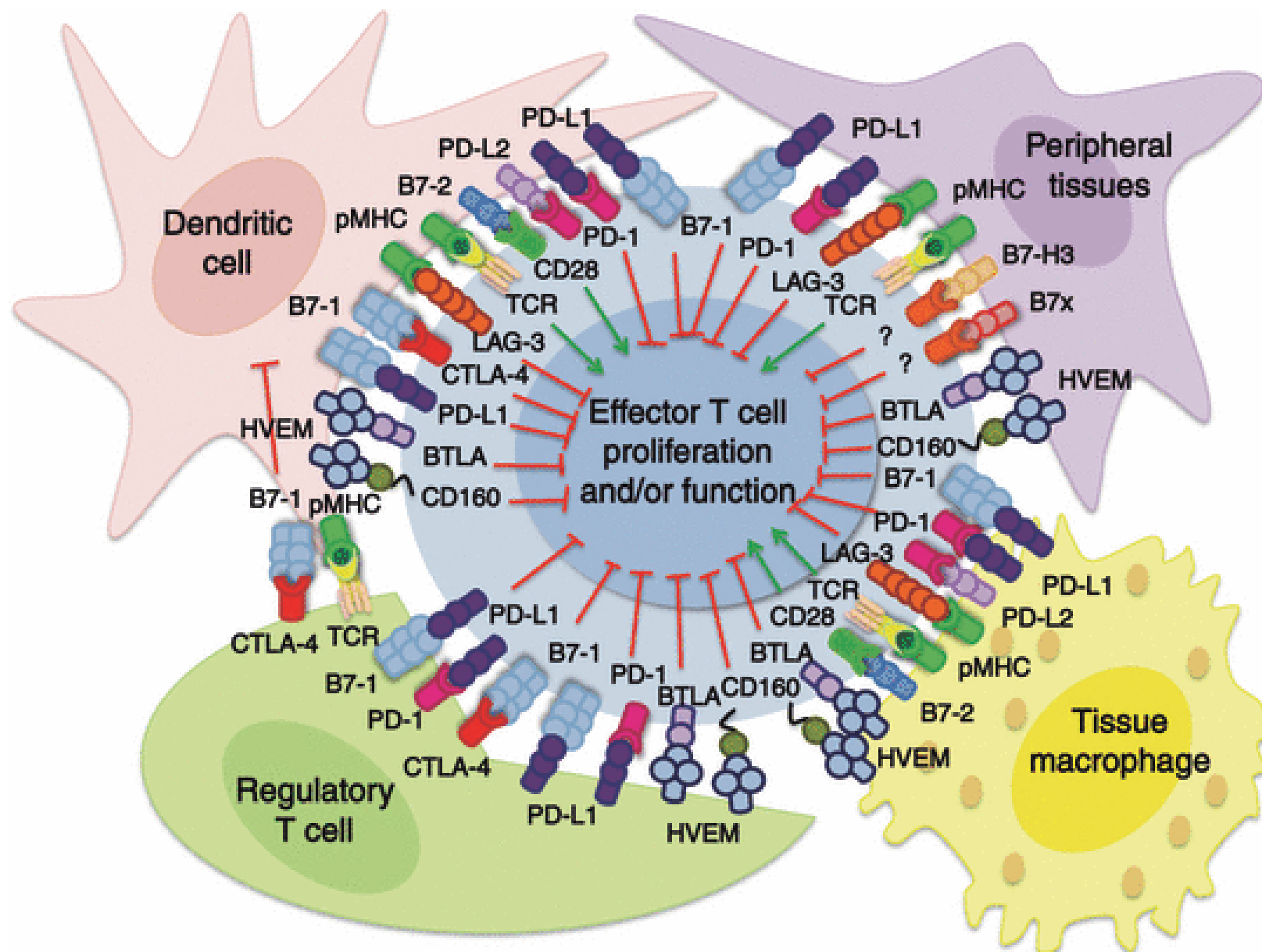


## Targeting Strategies

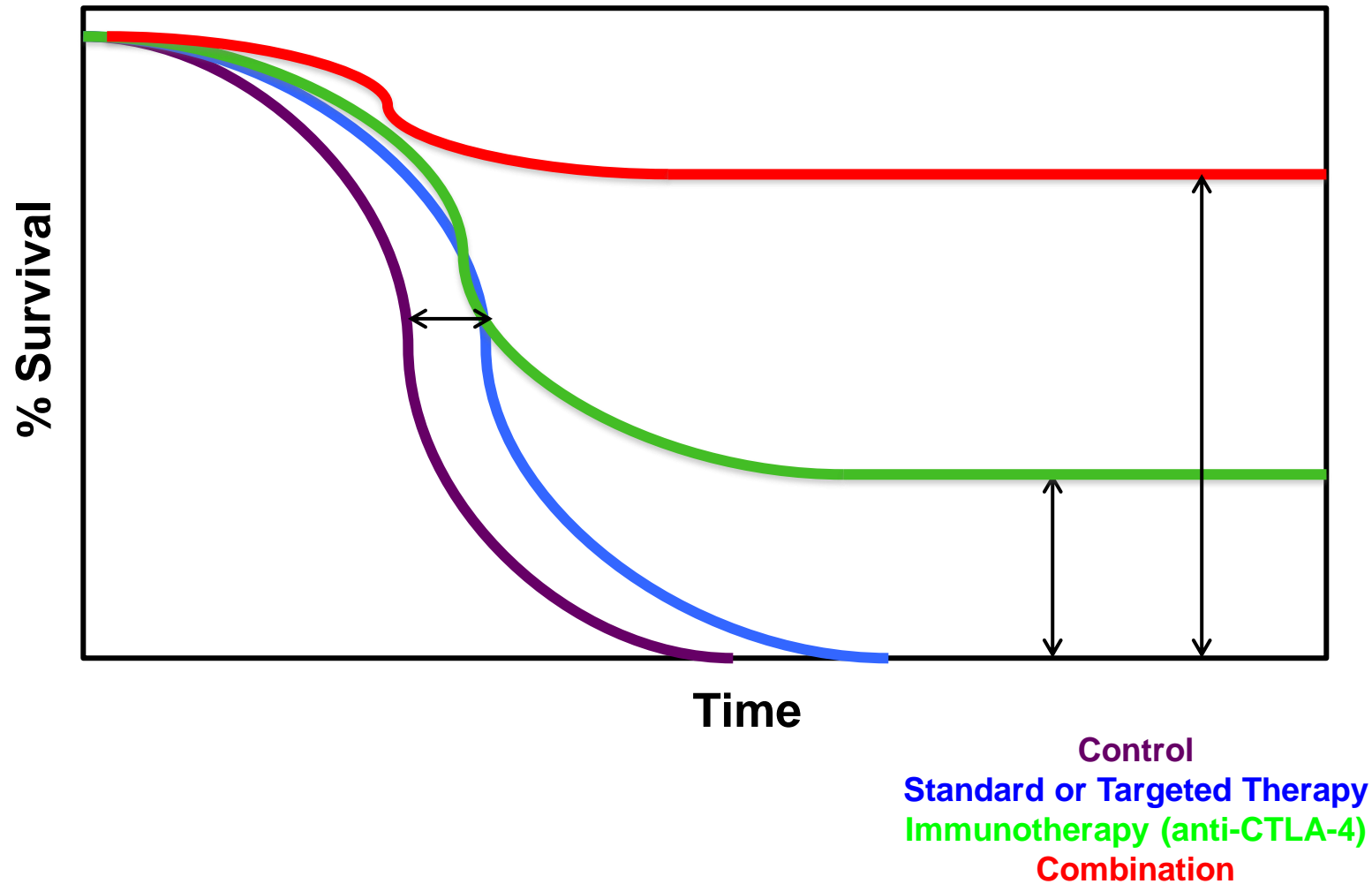
- Immune checkpoints
- Chemotherapy
- XRT
- Hormone therapy
- PARP inhibitors
- Vaccines
- Cytokines
- Epigenetic modulators
- Metabolites



# Novel Immunotherapy Targets



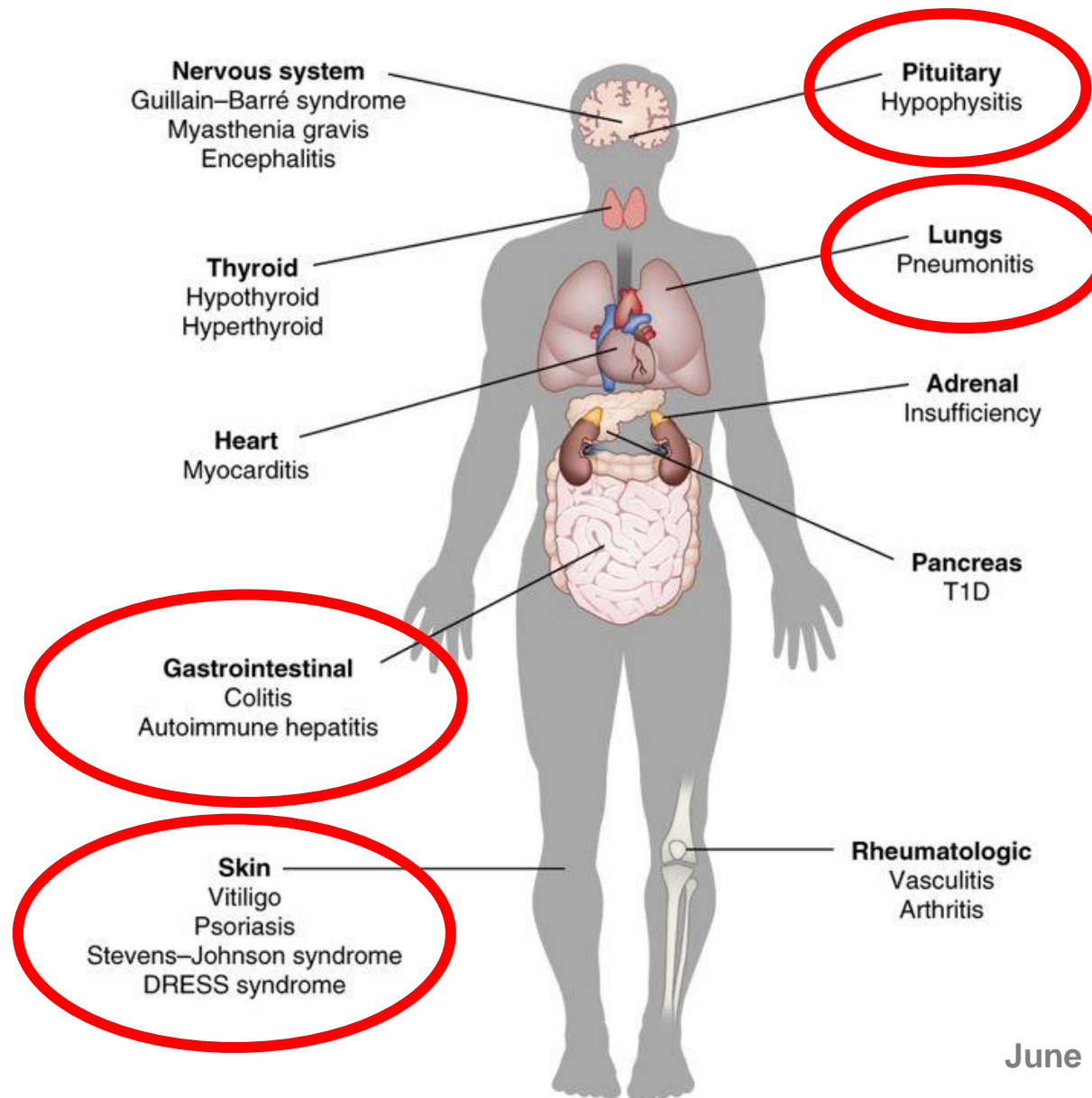
# Improving Survival with Combination Therapy



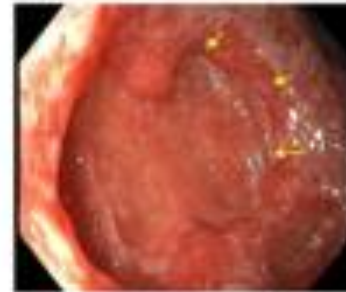
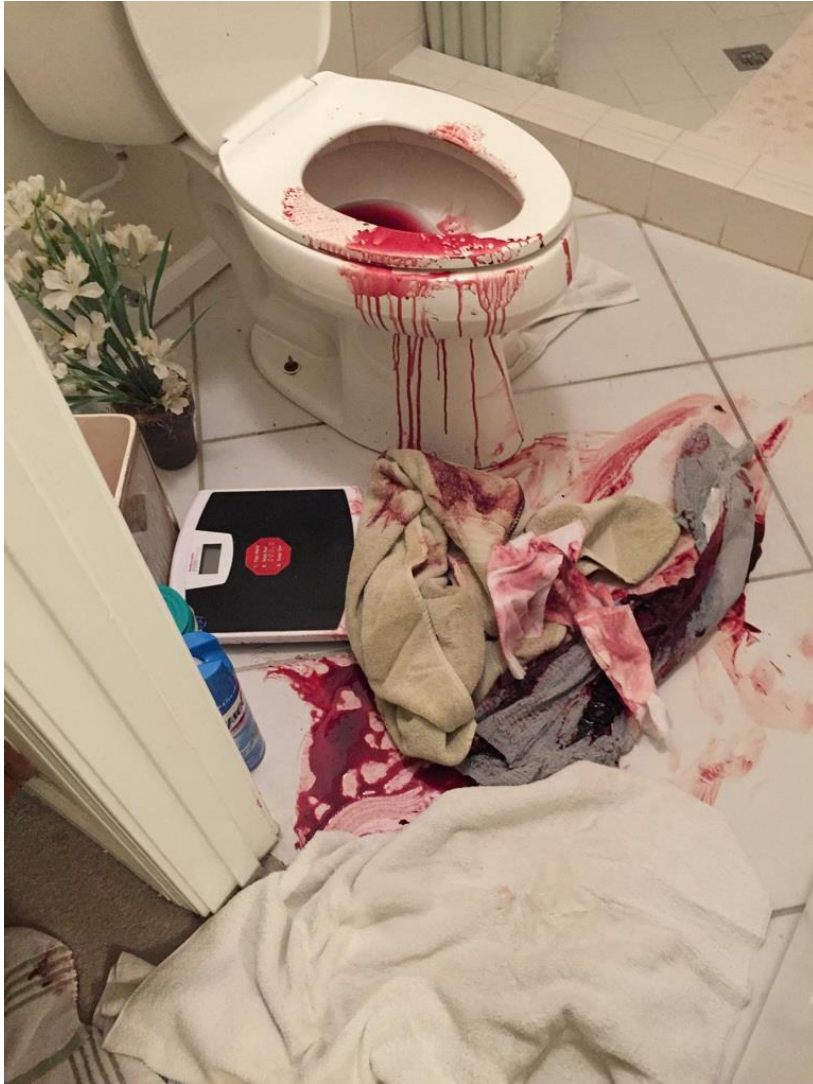
# Moving Forward with Immune Checkpoint Therapies

- Improving patient selection
- Turning “cold” tumors “hot”
- **Understanding toxicities**

# Organ-Specific Immune-Related Adverse Events (irAEs)



# Immune-Related Colitis/Diarrhea



Diagnosis



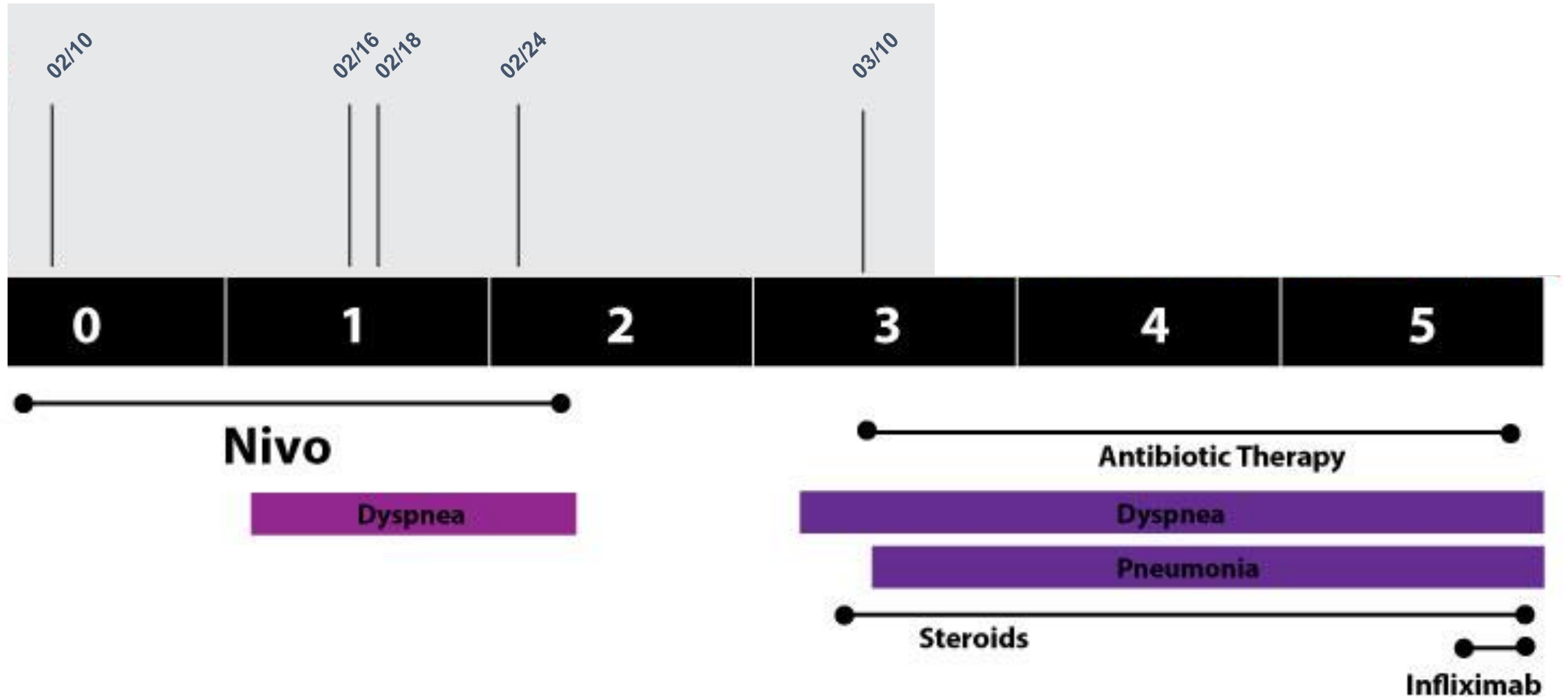
Following steroids and  
2 doses infliximab and  
1 dose vedolizumab



Post-FMT

Wang Y et al., *Nat Med*, 2018

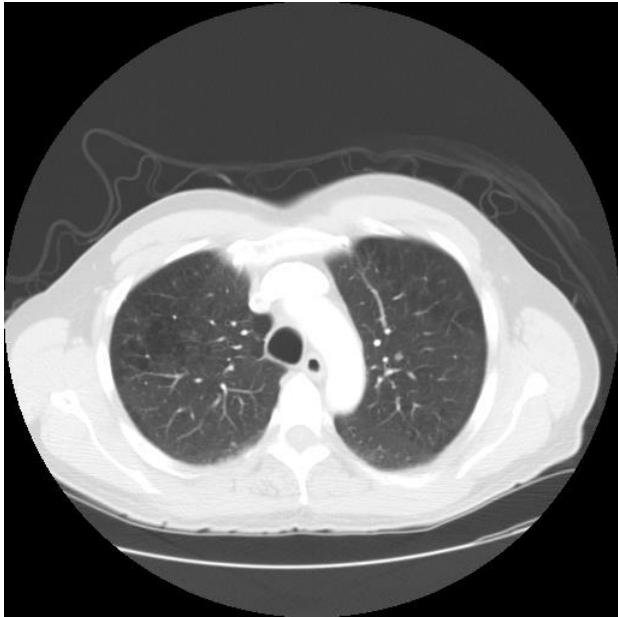
# Immune-Related Pneumonitis



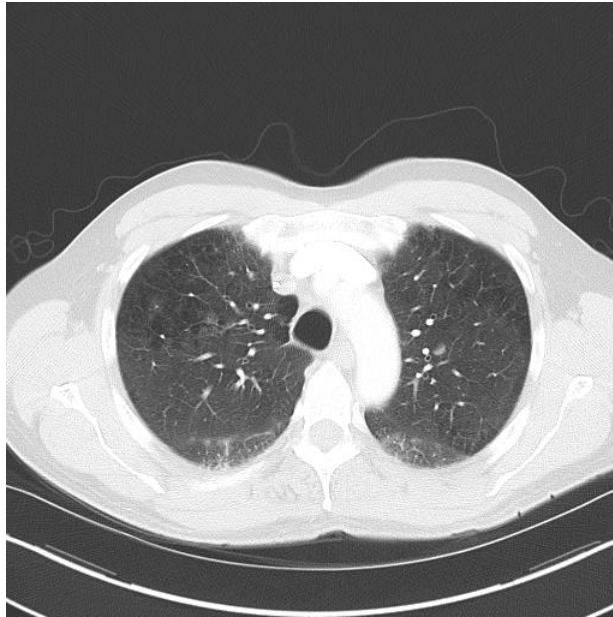


# Monday Morning Quarterback

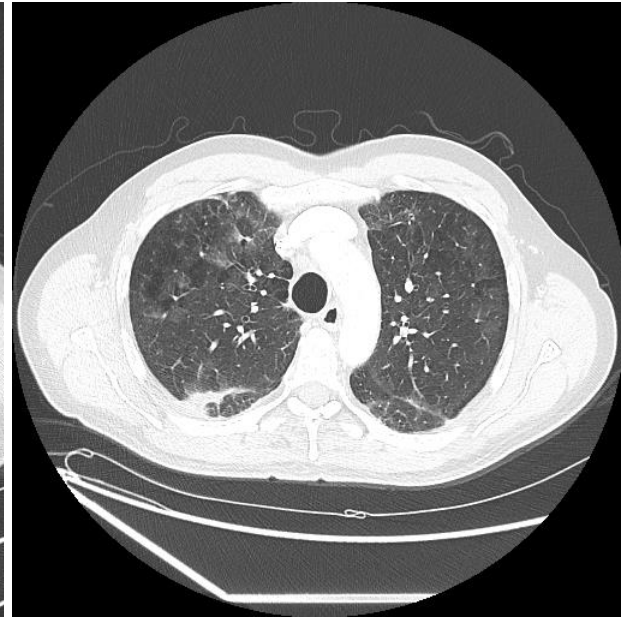
02/05/2015



02/18/2015



03/11/2015

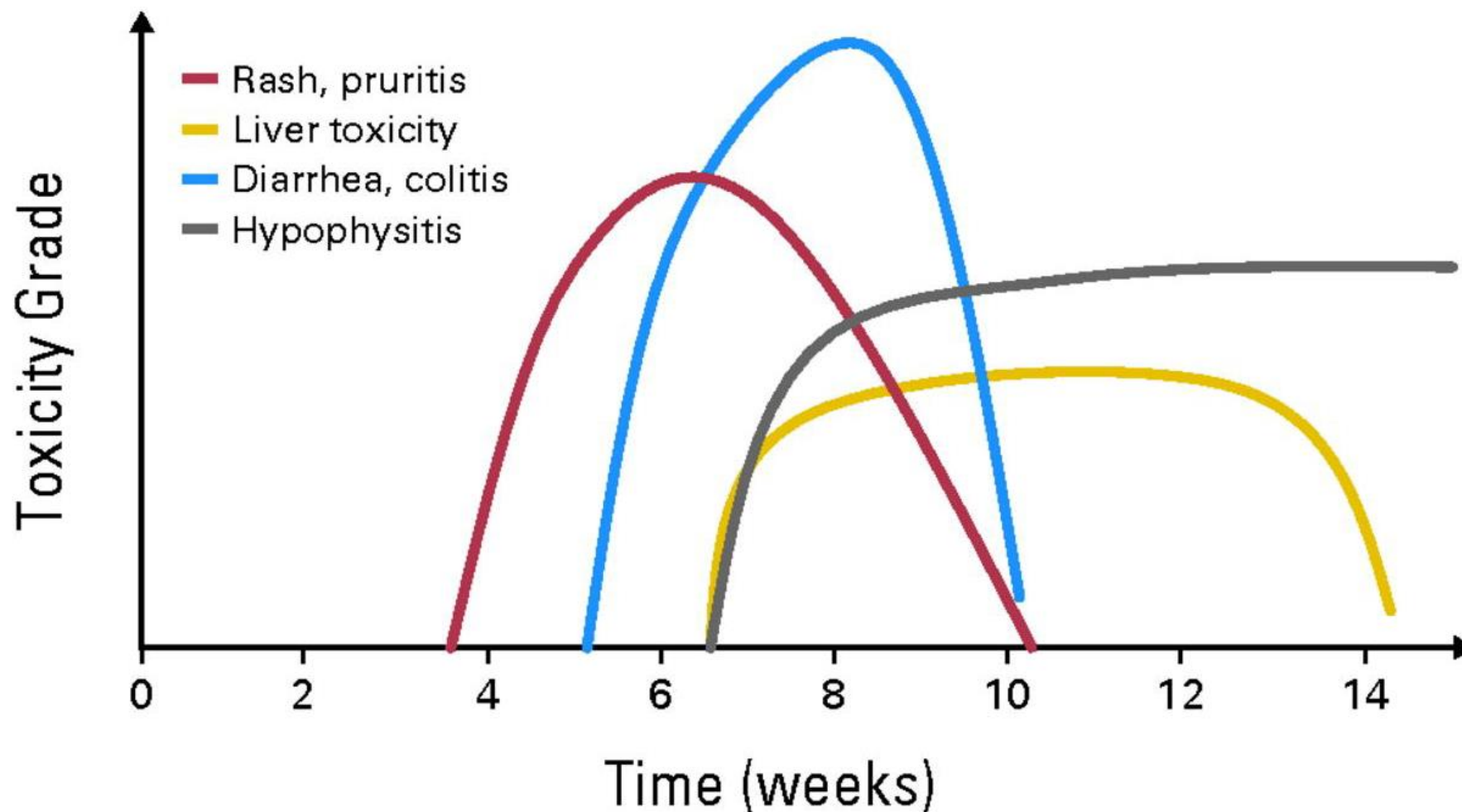


# **Safety Considerations**

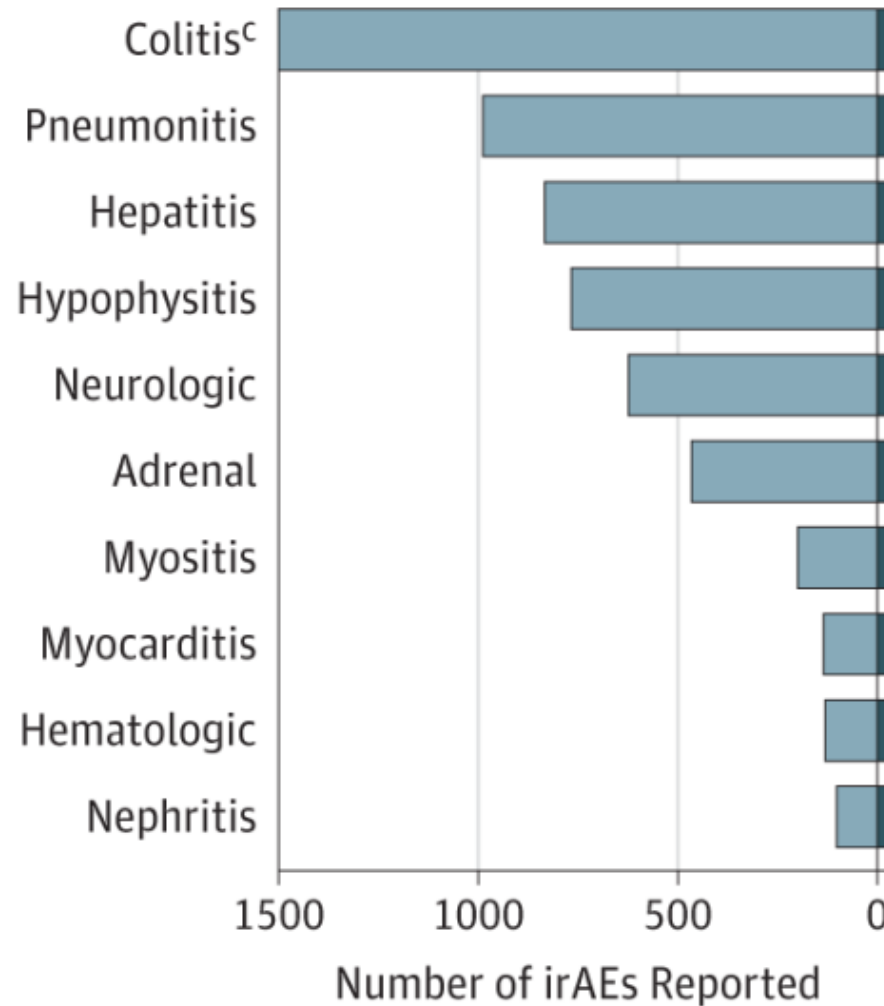
- **irAEs appear to be under-reported**
- **Early recognition/intervention with immunosuppressive/biological agents**
  - **Medical team**
  - **Patient/Family**
  - **Laboratory tests**
  - **Consult teams**



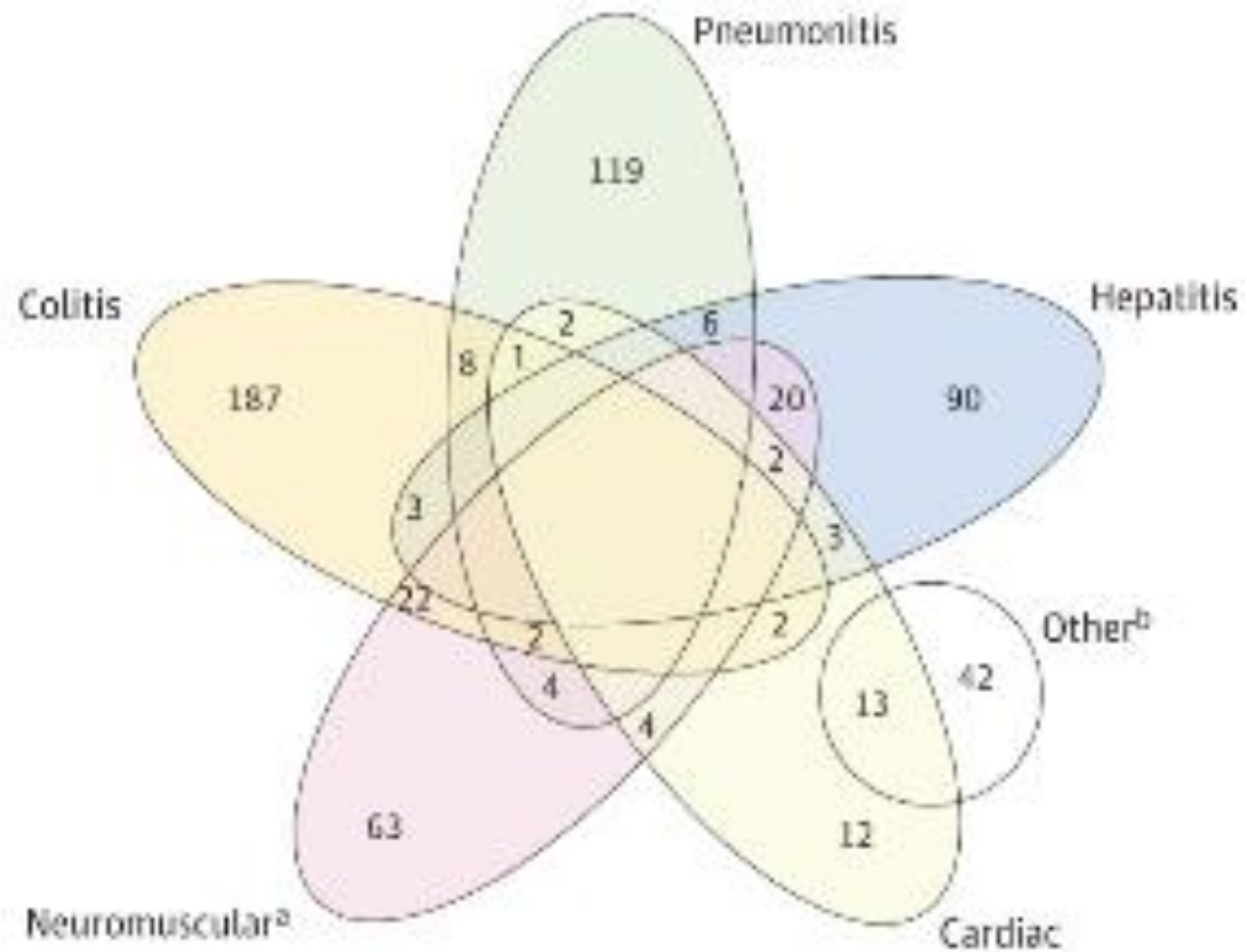
# Kinetics of Appearance of irAEs



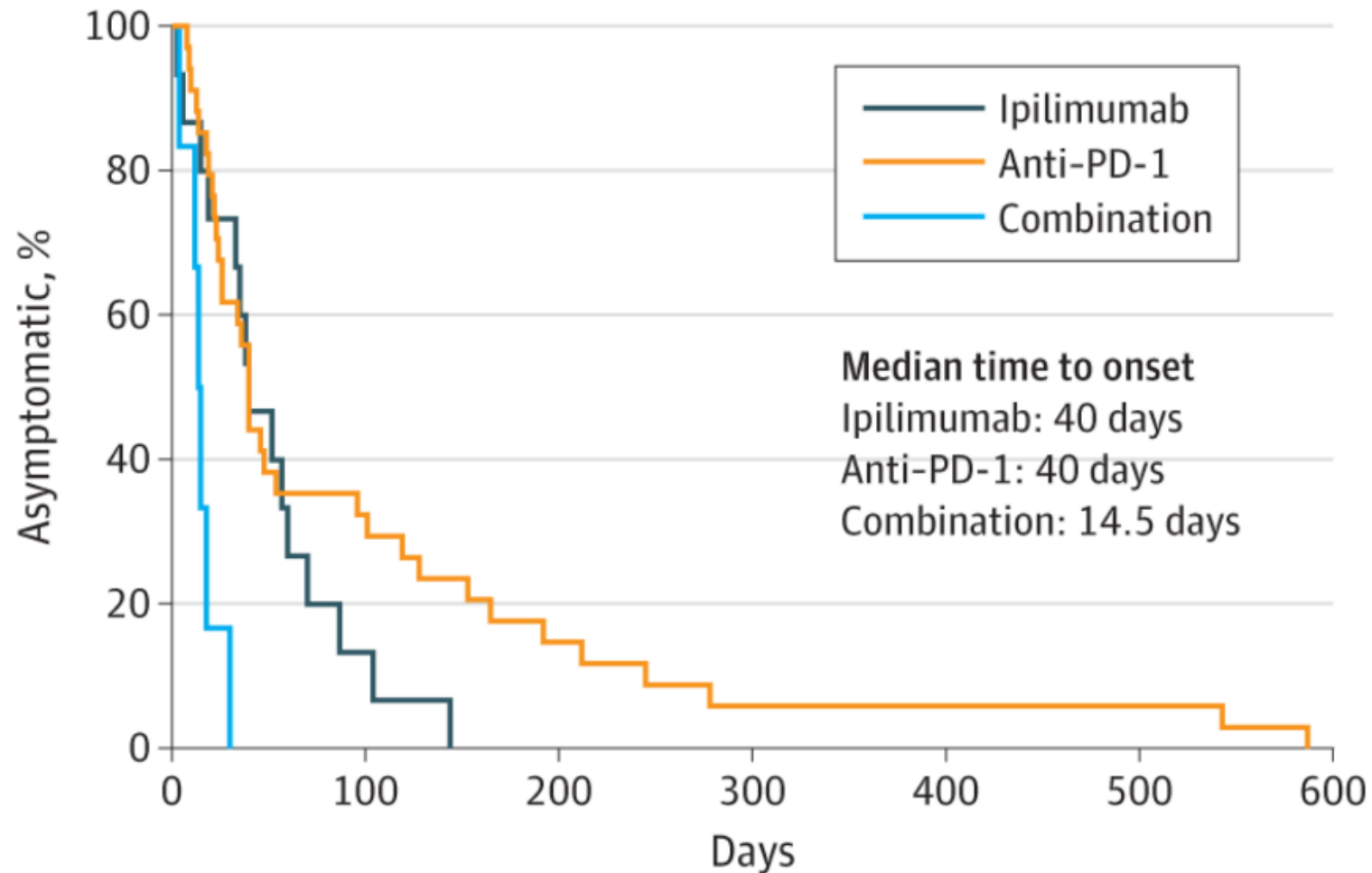
# Cases and Fatality Rates for Different Types of irAEs



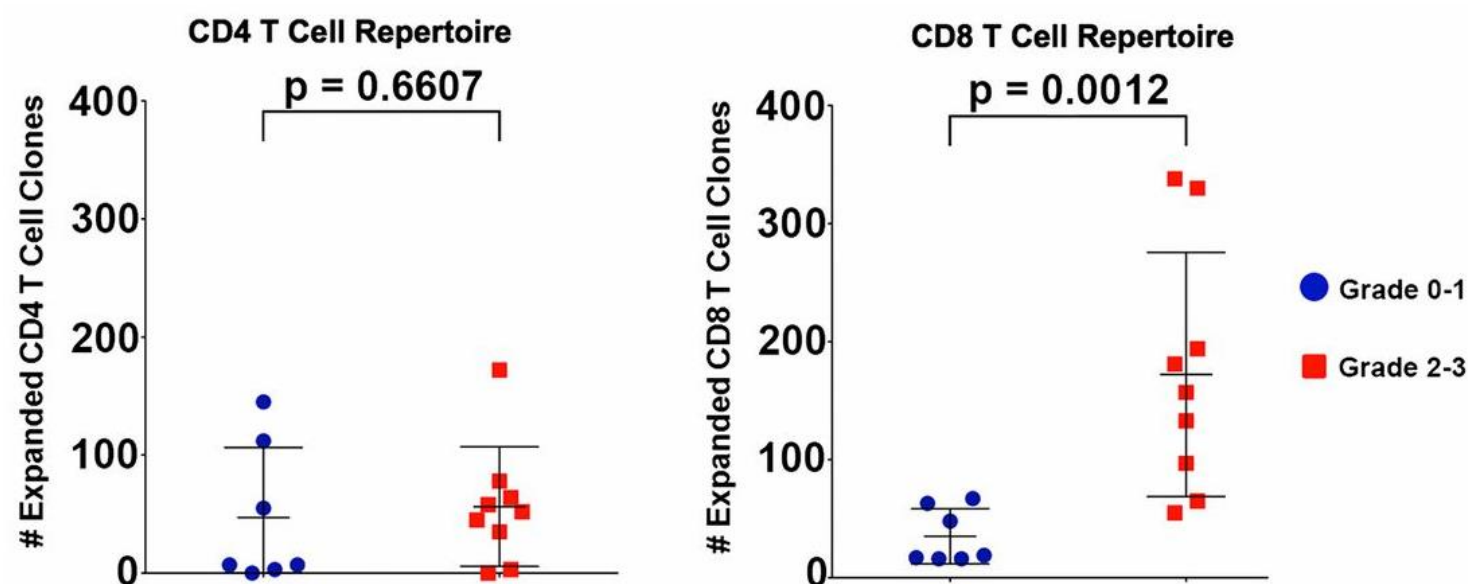
# Co-Occurring Fatal irAEs



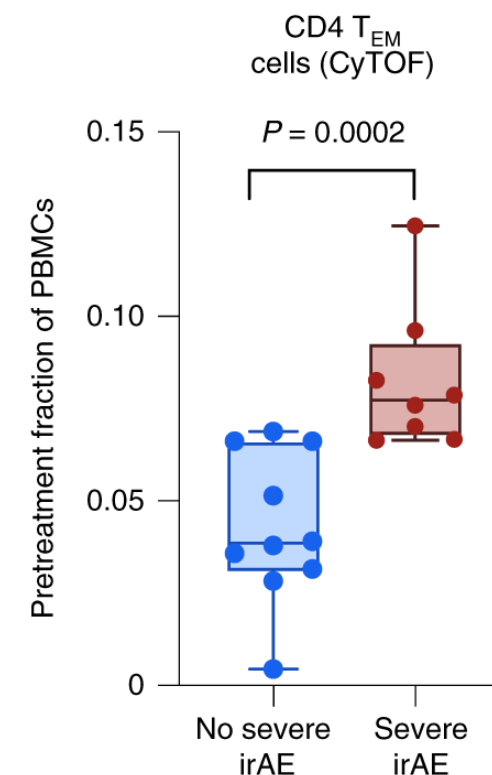
# Time to Symptom Onset for irAEs



# T Cell Subsets in Systemic Circulation Associated with irAEs



Subudhi SK et al., *Proc Natl Acad Sci U S A* , 2016



Lozano AX et al., *Nat Med*, 2022

# Management of irAEs

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

## Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

*Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network*

# **Conclusions for Immune Checkpoint Therapies**

- **Each target has a different mechanism of action**
- **Induce durable responses in a subset of patients**
- **Responses are associated with TMB in some malignancies**
- **Can be used to turn “cold” tumors “hot”**
- **Toxicities can be fatal**
- **Better biomarkers are required to maximize efficacy and minimize toxicities**