Immunotherapeutic Strategy:
Immune Checkpoint Blockade

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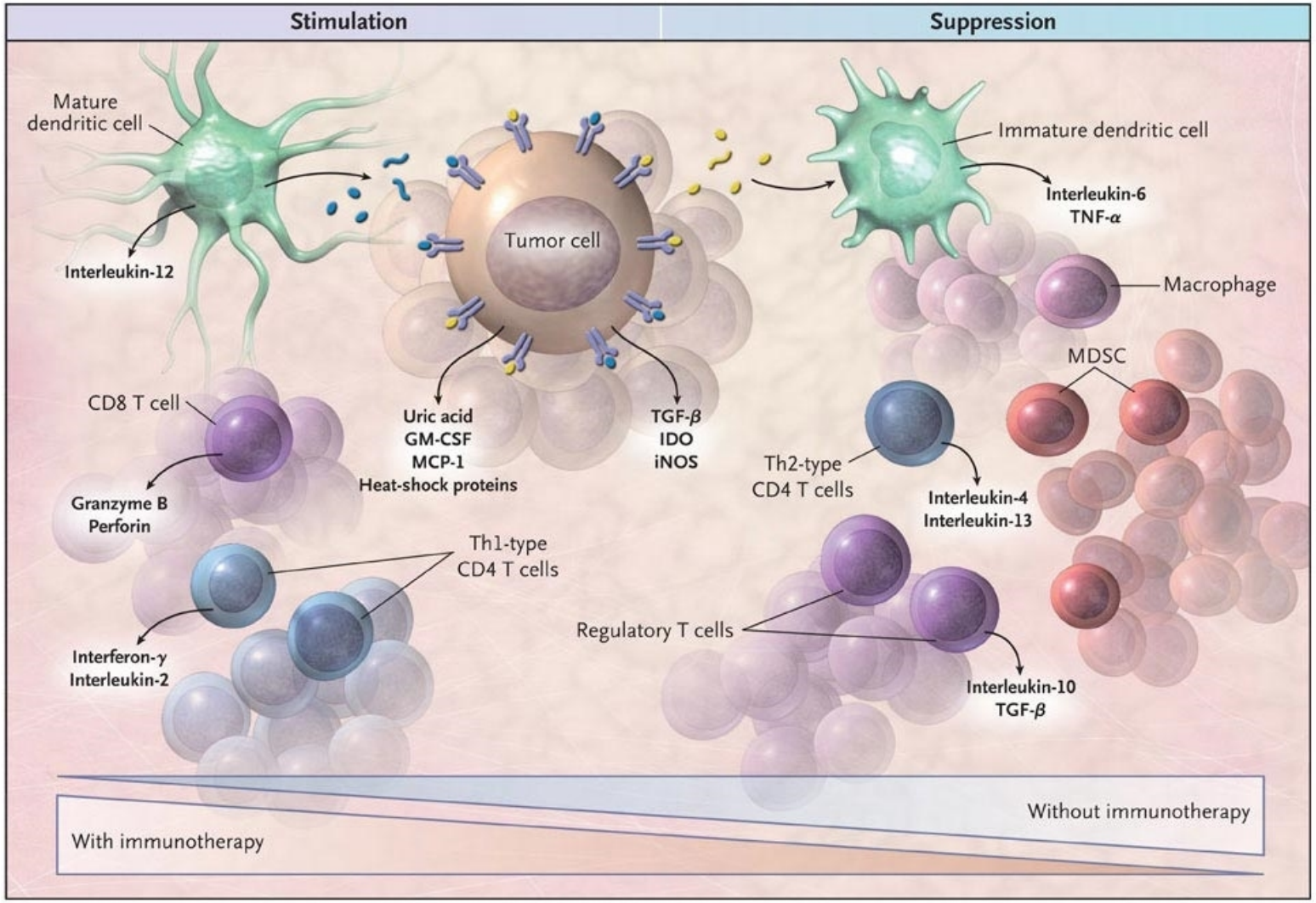
Disclosures

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

Immune Tumor Microenvironment



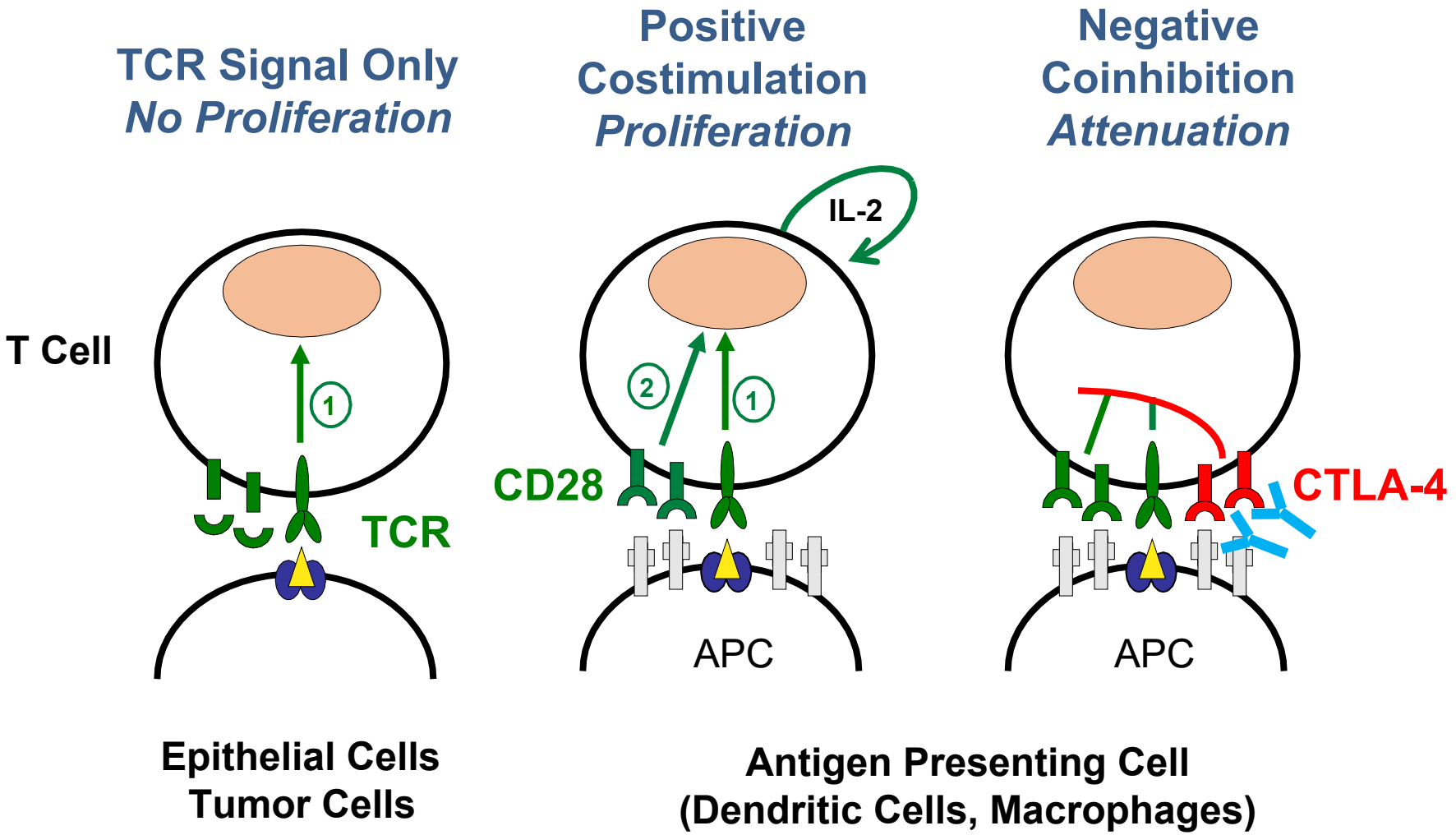
Finn ON et al., *New Engl J Med*, 2008.

Immunotherapies

Not all the same!

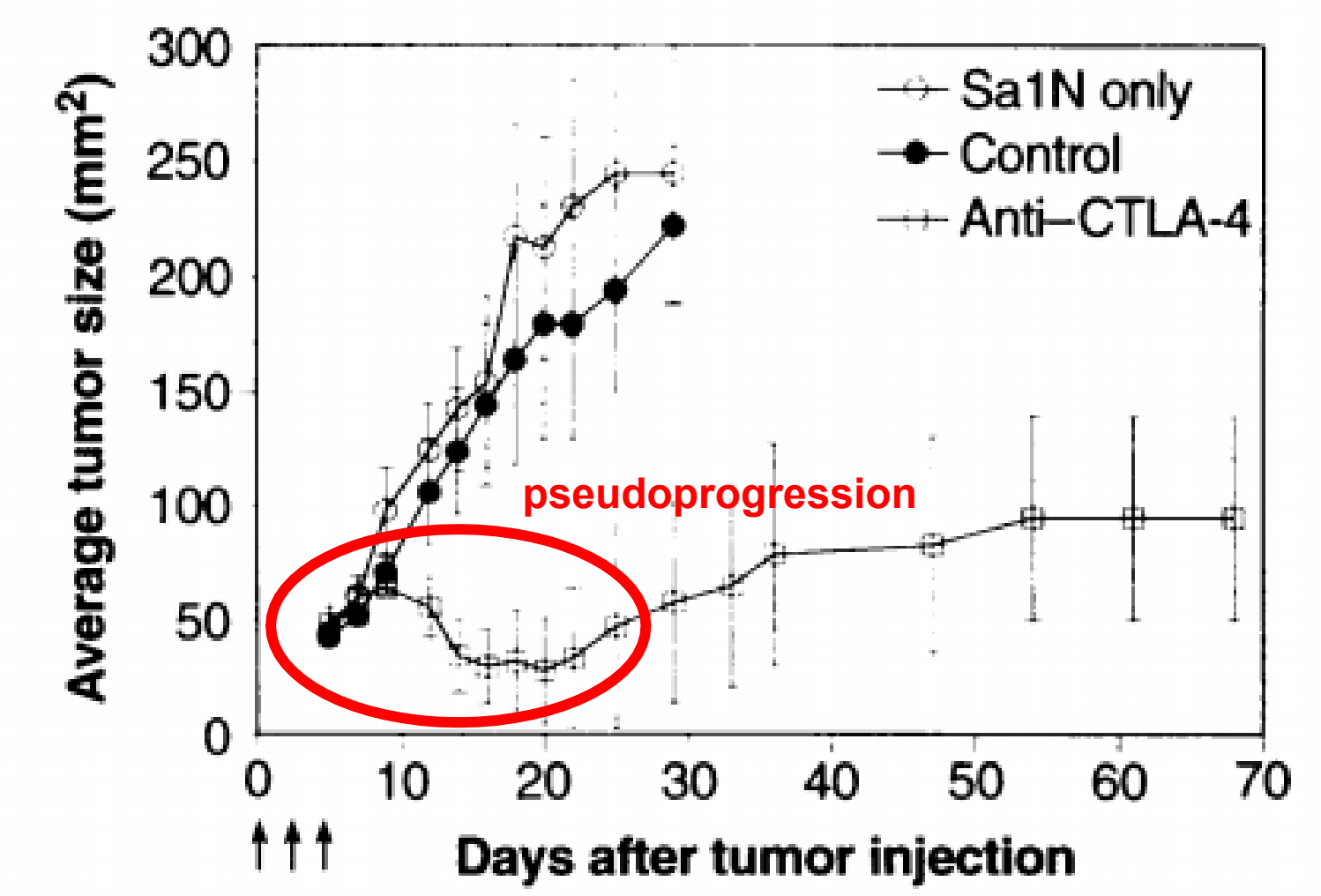
- **Vaccines**
  - Directs immune system to focus on tumor antigen(s)
- **Cellular therapies**
  - CAR T cells target the tumor cells
- **Immune checkpoint therapies**
  - Increases T cell activation and function

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



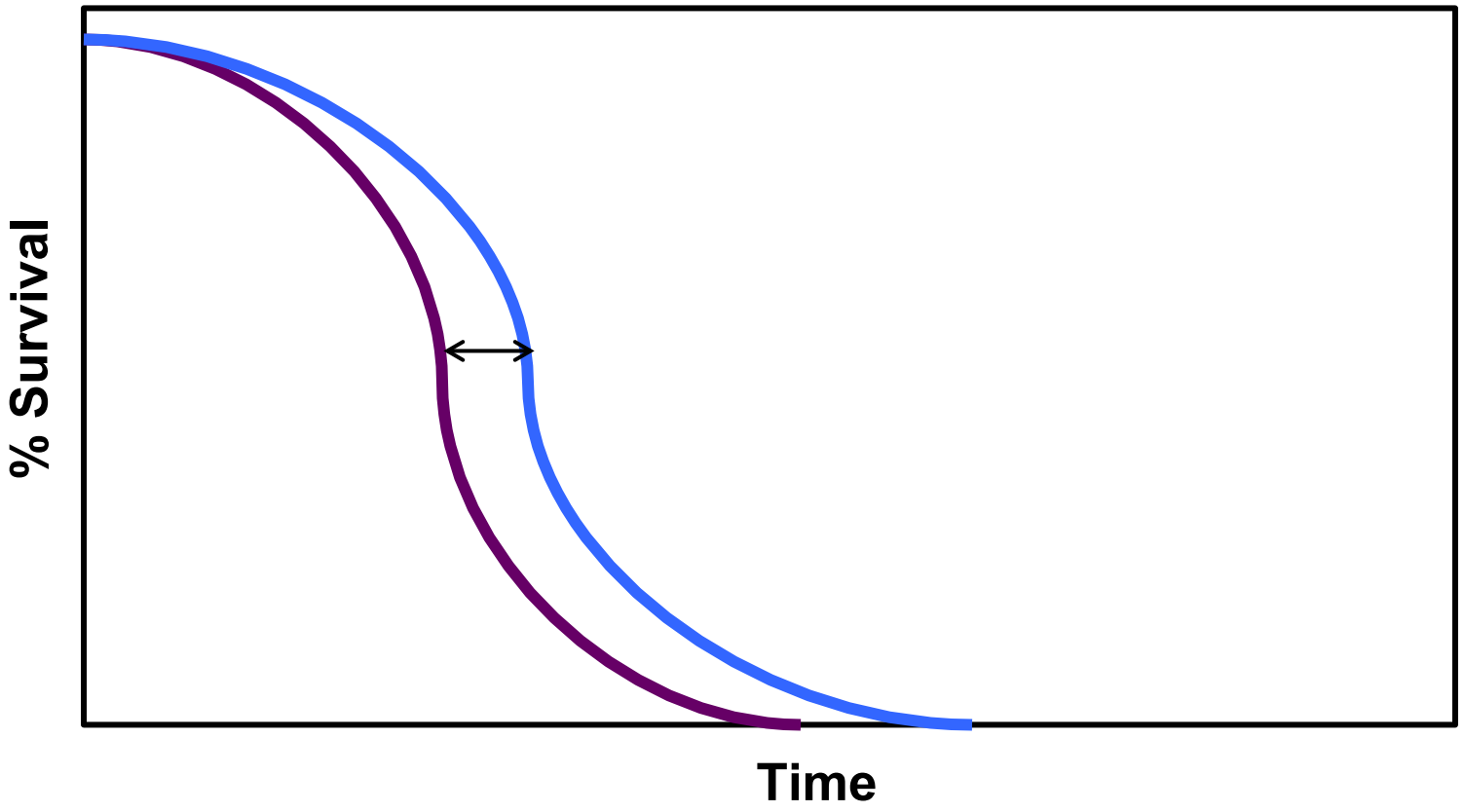
Courtesy of Jim Allison, PhD

Anti-CTLA-4 Reduces Tumor Growth Rate

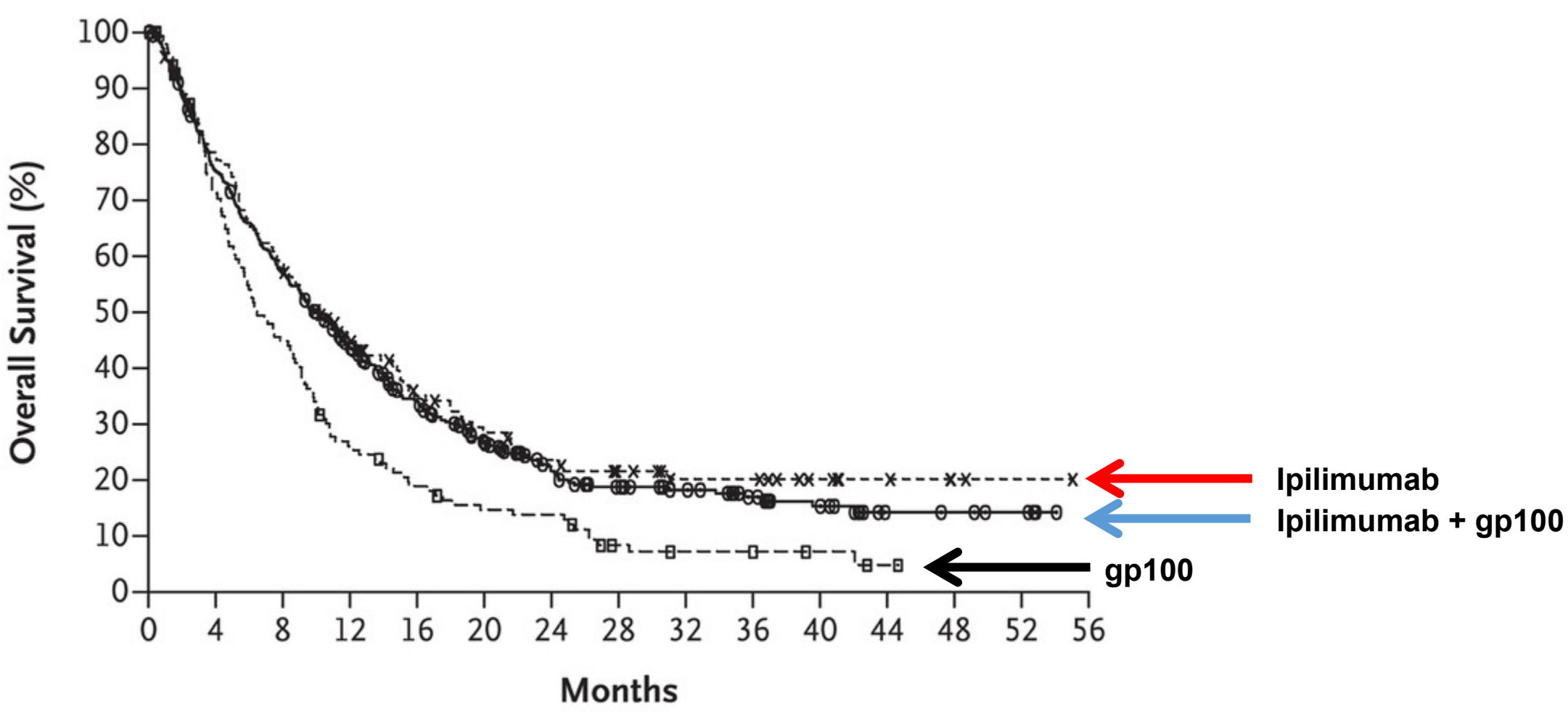


Leach DR et al., *Science*, 1996.

Improving Survival with a New Drug

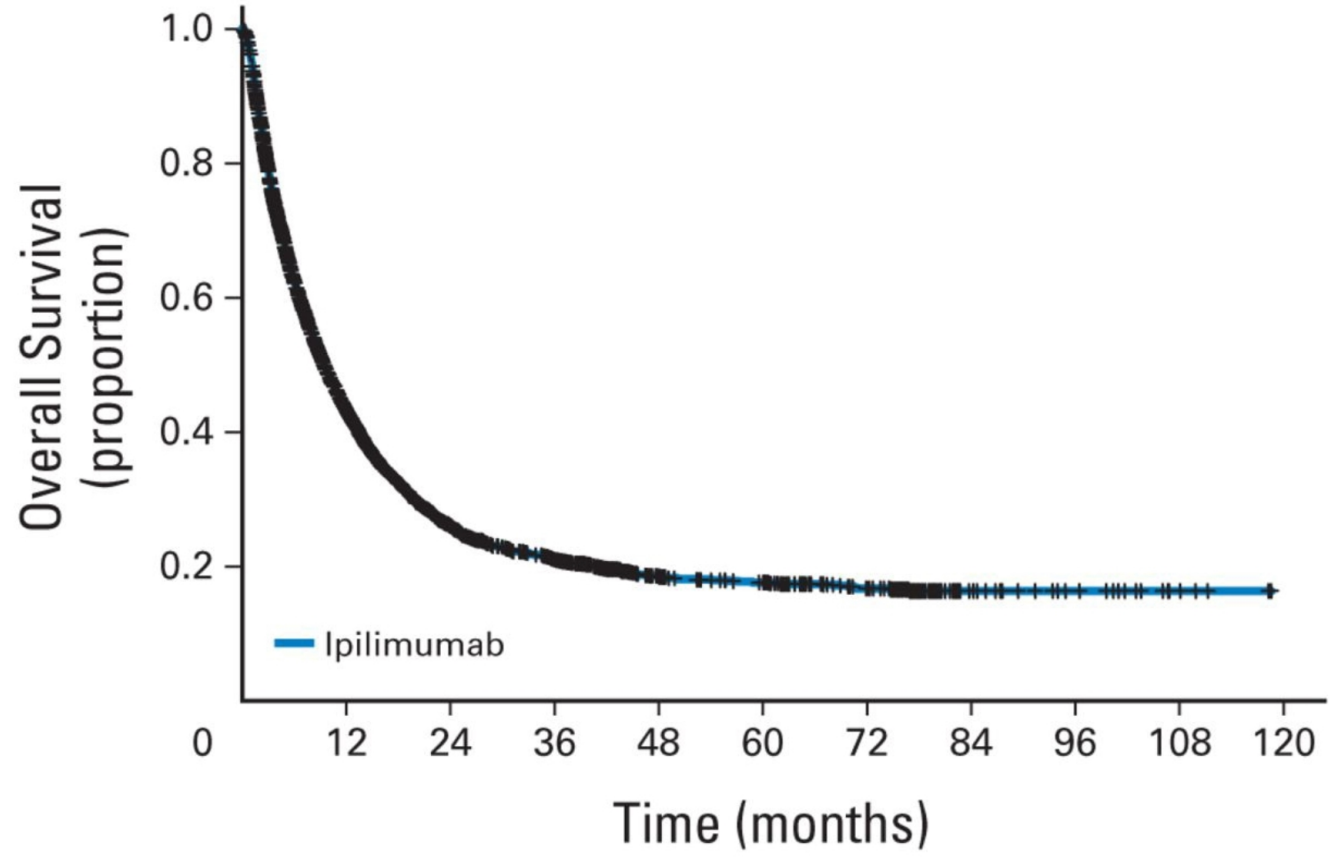


Anti-CTLA-4 (Ipilimumab) Improves Survival in Patients with Metastatic Melanoma



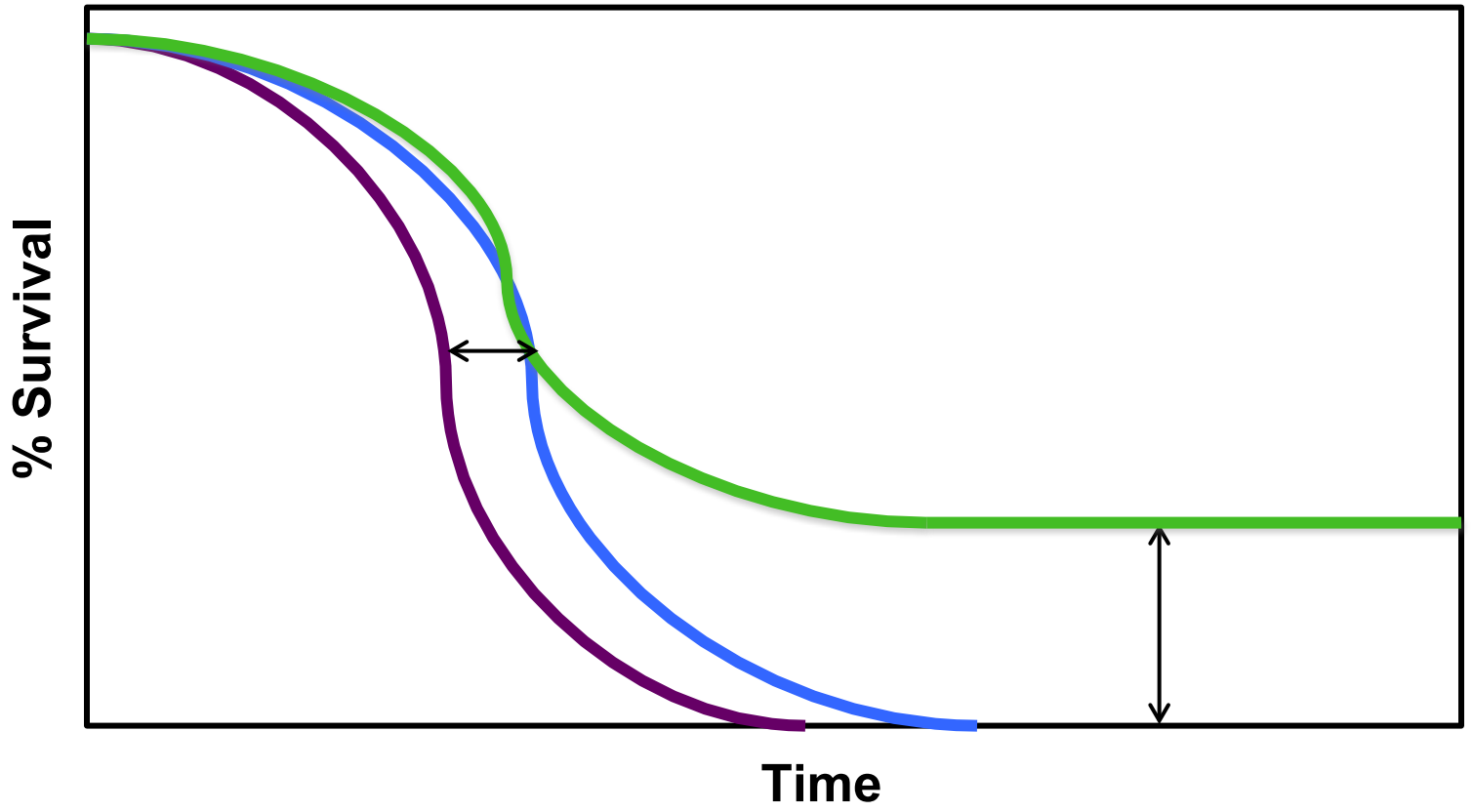
Hodi FS et al, *N Engl J Med,* 2010.

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



Schadendorf D et al, *J Clin Onc,* 2014.

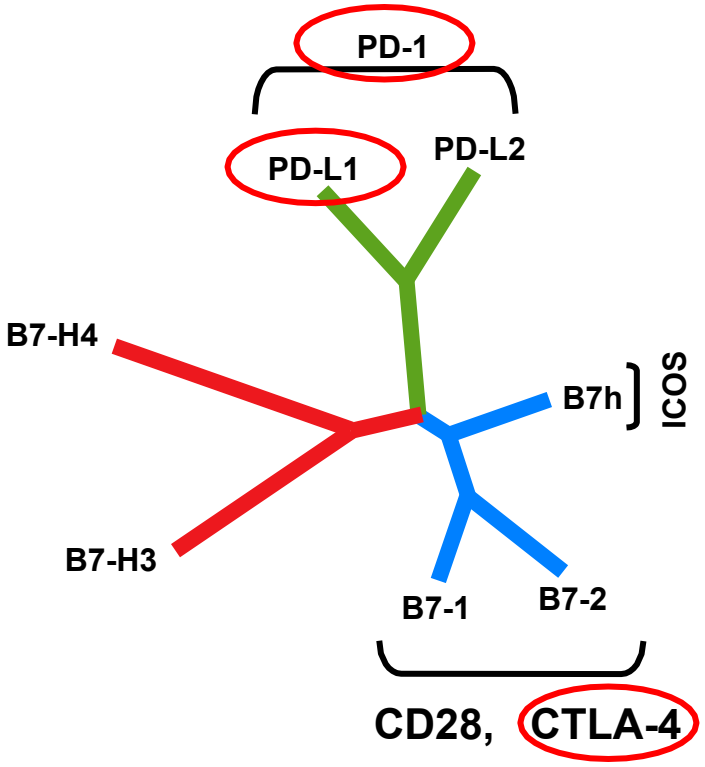
Improving Survival with Immune Checkpoint Therapy



2013: Breakthrough of the Year

December 20, 2013

FDA-Approved Immune Checkpoint Therapies



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

Melanoma
- Ipilimumab (2011)
- Nivolumab (2014)
- Ipilimumab + Nivolumab (2015)
- Pembrolizumab (2019)
- Atezolizumab (2020)

Lung Carcinoma
- Nivolumab (2015)
- Pembrolizumab (2015)
- Atezolizumab (2016)
- Durvalumab (2018)
- Ipilimumab + Nivolumab (2020)

Urothelial Carcinoma
- Atezolizumab (2016)
- Avelumab (2017)
- Durvalumab (2017)
- Nivolumab (2017)
- Pembrolizumab (2017)

Renal Cell Carcinoma
- Nivolumab (2015)
- Ipilimumab + Nivolumab (2018)
- Avelumab (2019)

Colorectal Carcinoma
- Nivolumab (2017)
- Pembrolizumab (2017)
- Ipilimumab + Nivolumab (2018)

Head and Neck Squamous Cell Carcinoma
- Nivolumab (2016)
- Pembrolizumab (2016)

Lymphoma
- Nivolumab (2016)
- Pembrolizumab (2017)

Hepatocellular Carcinoma
- Nivolumab (2017)
- Pembrolizumab (2018)
- Ipilimumab + Nivolumab (2020)

Merkel Cell Carcinoma
- Avelumab (2017)
- Pembrolizumab (2018)

Cutaneous Squamous Cell Carcinoma
- Cemiplimab (2018)
- Pembrolizumab (2020)

Esophageal Carcinoma
- Pembrolizumab (2019)
- Nivolumab (2020)

Gastric/Gastroesophageal Adenocarcinoma
- Pembrolizumab (2017)

Cervical Carcinoma
- Pembrolizumab (2018)

Breast Carcinoma
- Atezolizumab (2019)

Uterine Carcinoma
- Pembrolizumab (2019)

Mesothelioma
- Ipilimumab + Nivolumab (2020)

Basal Cell Carcinoma
- Cemiplimab (2020)

2018: Nobel Prize in Physiology or Medicine

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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

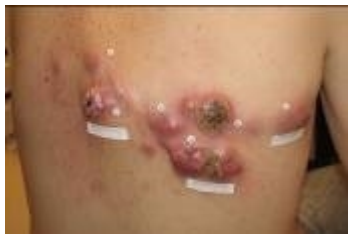
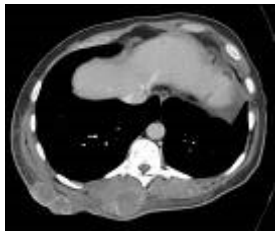
Courtesy of Jim Allison, PhD

Challenges/Limitations of Immune Checkpoint Therapies

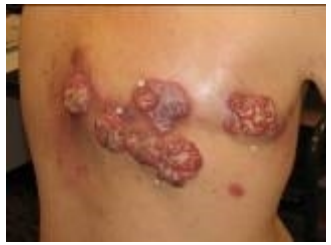
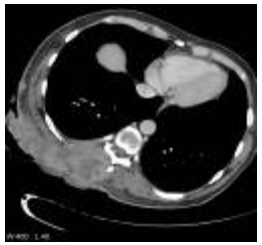
- Measuring disease burden / treatment response
  - Immune-related response criteria (irRC)
- Subset of patients benefit
- Toxicities
  - Immune-related adverse events (irAEs)

Delayed Responses with Ipilimumab

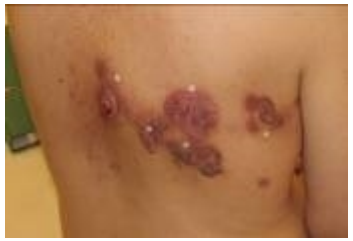
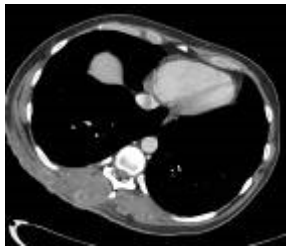
Screening

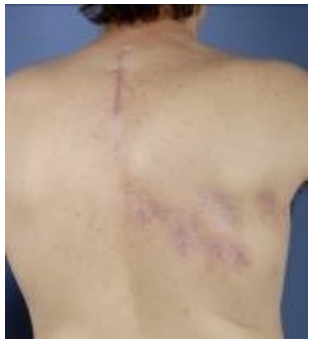
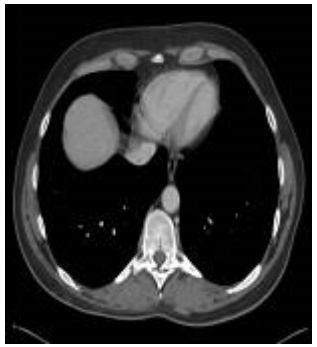
Week 12
Initial increase in
total tumour burden (mWHO PD)

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

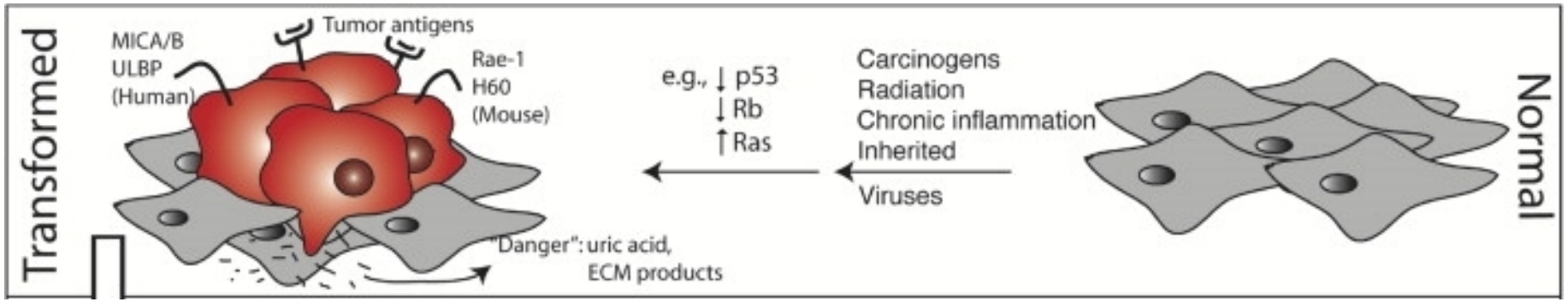
Moving Forward with Immune Checkpoint Therapies

- **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

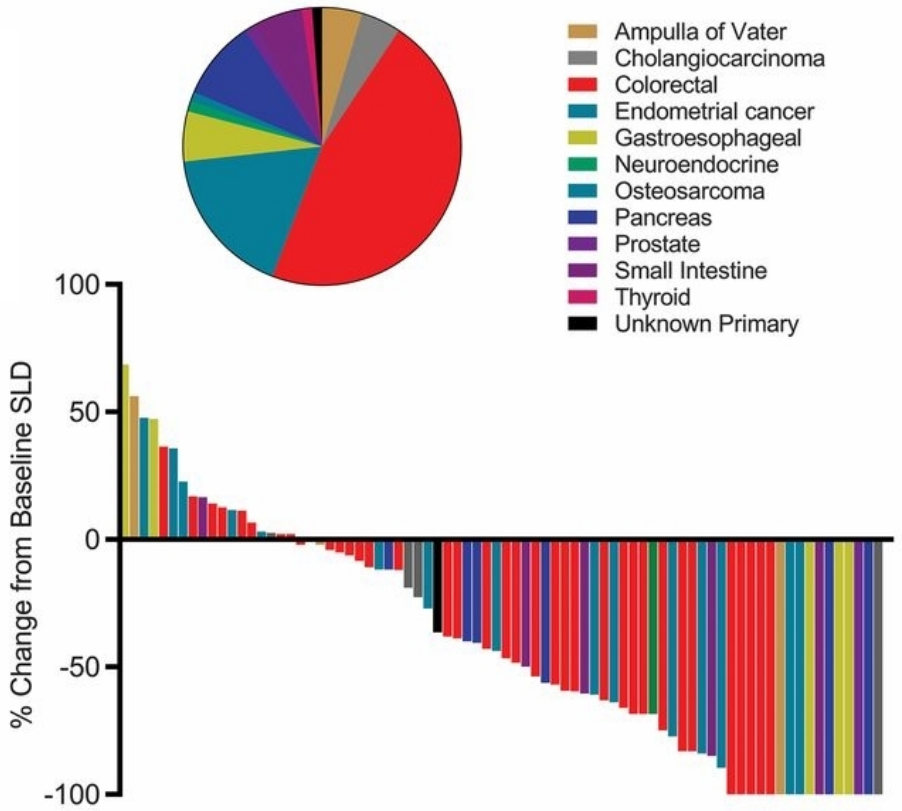


The Immunobiology of Cancer Immunosurveillance and Immunoediting

Gavin P. Dunn , Lloyd J. Old , Robert D. Schreiber
Immunity, Volume 21, Issue 2, 2004, 137 - 148

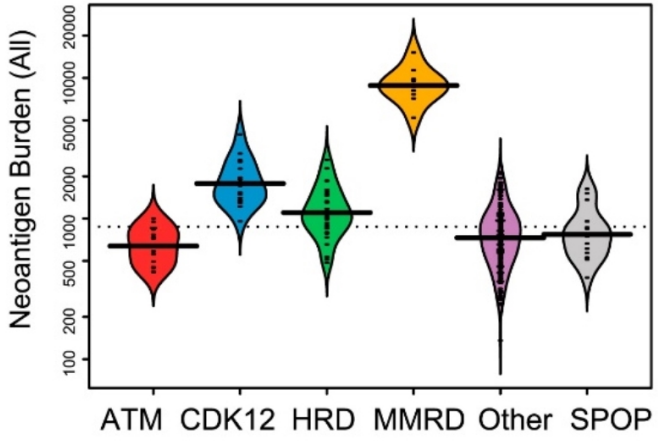
Genomic Defects that Increase Neoantigen Burden

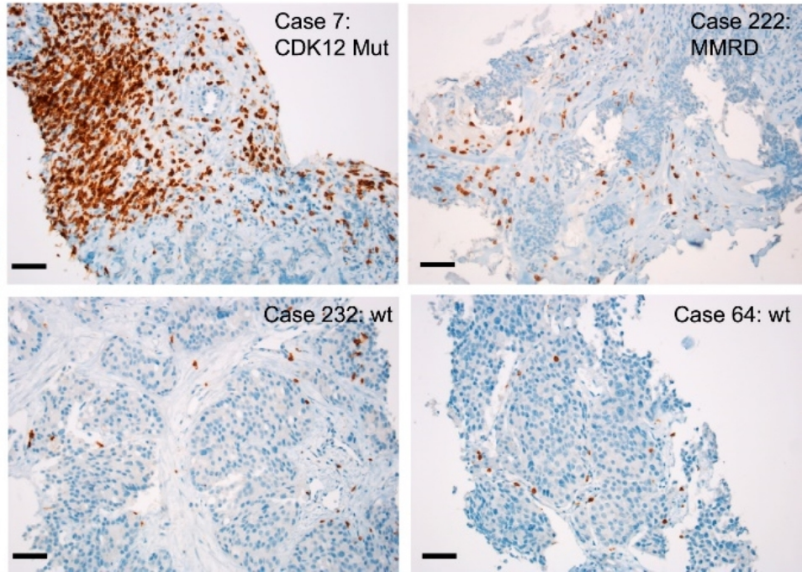
Mismatch Repair (MMR) Defects



Le DT et al., *Science,* 2017.

CDK12 Mutations





Wu YM et al., *Cell,* 2018.

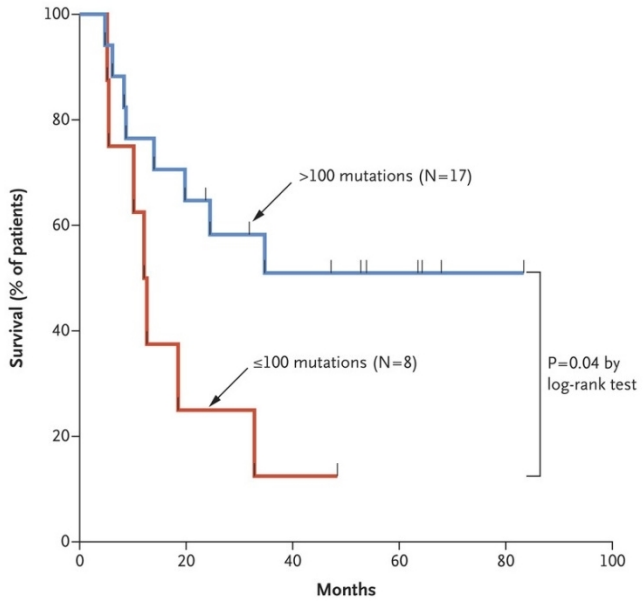
Neoantigens and Mutational Load Linked to Efficacy of Immune Checkpoint Therapies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

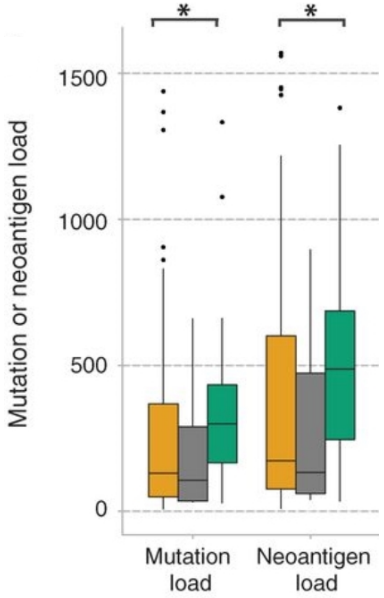
Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D., Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D., Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D., Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A., Kasthuri 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,[1,2,3*] Diana Miao,[1,2*] Bastian Schilling,[4,5*] Sachet A. Shukla,[1,2] Christian Blank,[6] Lisa Zimmer,[4,5] Antje Sucker,[4,5] Uwe Hillen,[4,5] Marnix H. Geukes Foppen,[6] Simone M. Goldinger,[7] Jochen Utikal,[5,8,9] Jessica C. Hassel,[10] Benjamin Weide,[11] Katharina C. Kaehler,[12] Carmen Loquai,[13] Peter Mohr,[14] Ralf Gutzmer,[15] Reinhard Dummer,[7] Stacey Gabriel,[2] Catherine J. Wu,[1,2] Dirk Schadendorf,[4,5†] Levi A. Garraway[1,2,3†]



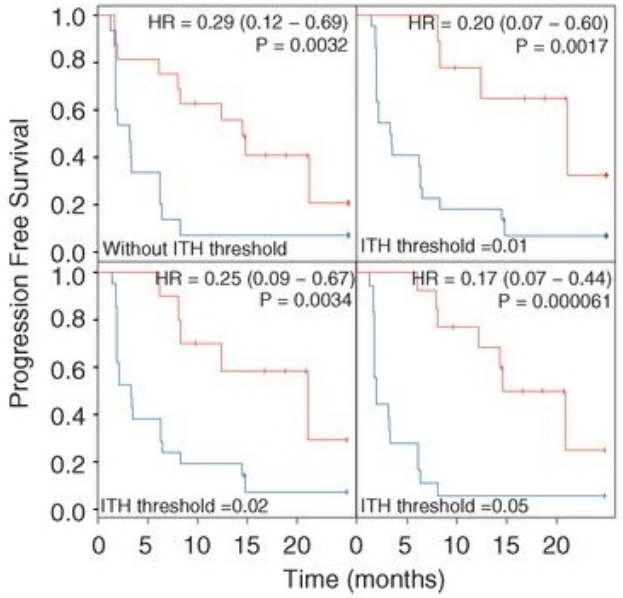
Science

REPORTS

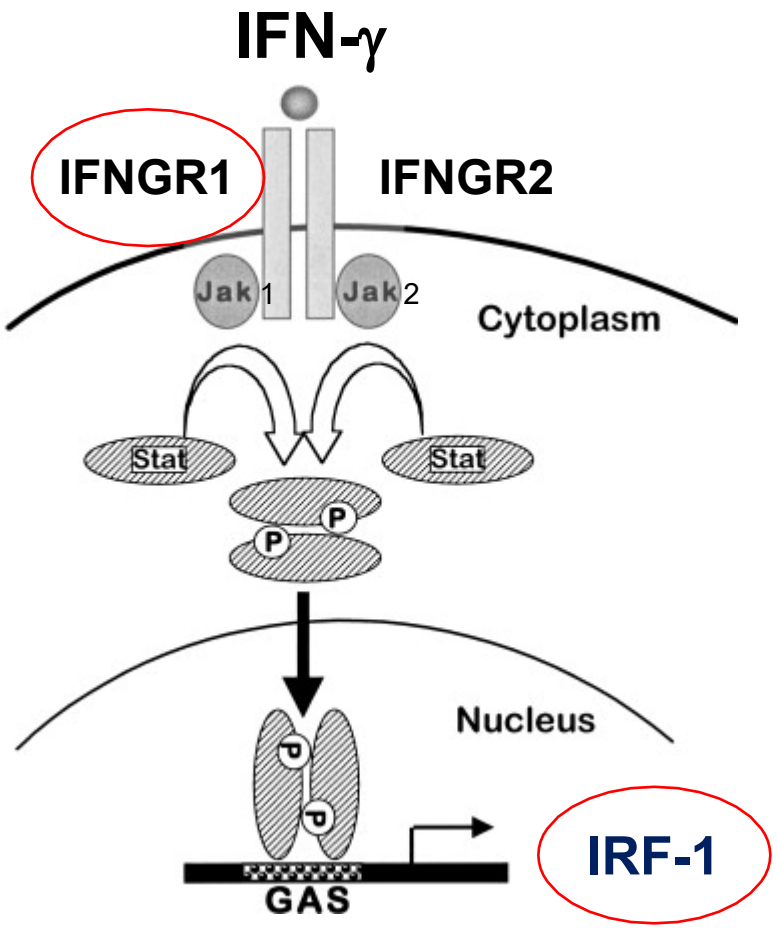
Cite as: N. McGranahan *et al.*, *Science* 10.1126/science.aaf490 (2016).

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

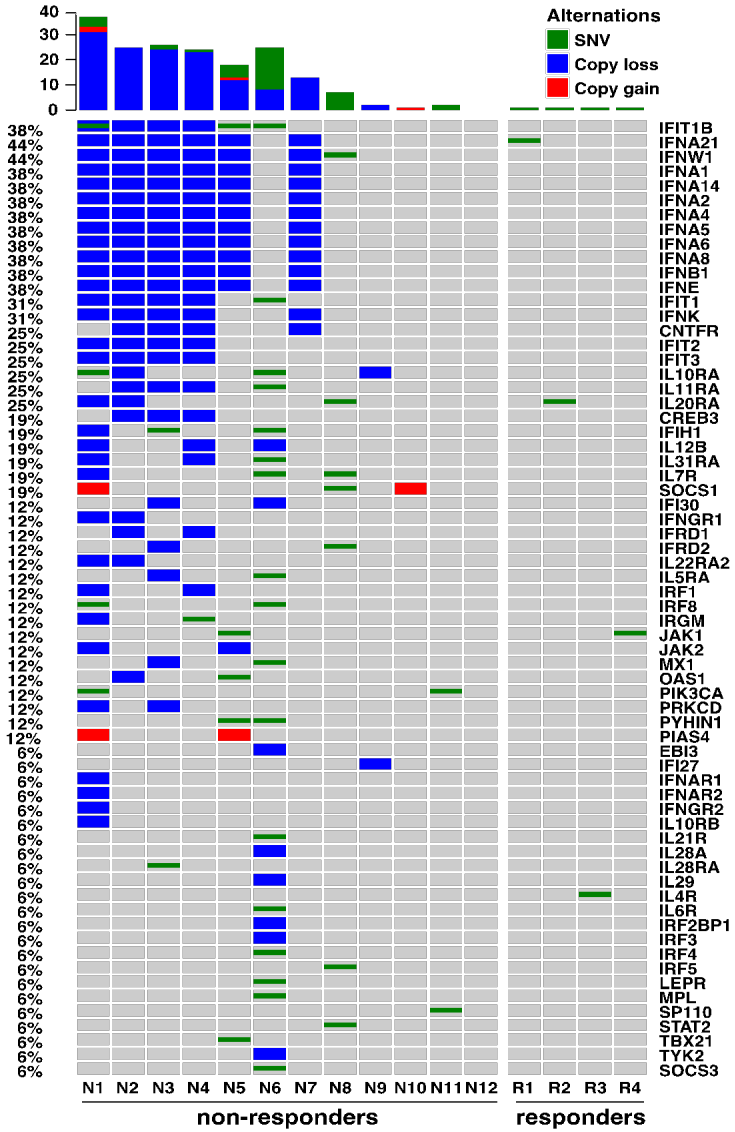
Nicholas McGranahan,[1,2,3*] Andrew J. S. Furness,[3,4*] Rachel Rosenthal,[3*] Sofie Ramskov,[5] Rikke Lyngaa,[5] Sunil Kumar Saini,[5] Mariam Jamal-Hanjani,[3] Gareth A. Wilson,[1,3] Nicolai J. Birkbak,[1,3] Crispin T. Hiley,[1,3] Thomas B. K. Watkins,[1,3] Seema Shafi,[3] Nirupa Murugaesu,[3] Richard Mitter,[1] Ayse U. Akarca,[4,6] Joseph Linares,[4,6] Teresa Marafioti,[4,6] Jake Y. Henry,[3,4] Eliezer M. Van Allen,[7,8,9] Diana Miao,[7,8] Bastian Schilling,[10,11] Dirk Schadendorf,[10,11] Levi A. Garraway,[7,8,9] Vladimir Makarov,[12] Naiyer A. Rizvi,[13] Alexandra Snyder,[14,15] Matthew D. Hellmann,[14,15] Taha Merghoub,[14,16] Jedd D. Wolchok,[14,15,16] Sachet A. Shukla,[7,8] Catherine J. Wu,[7,8,17,18] Karl S. Peggs,[3,4] Timothy A. Chan,[13] Sine R. Hadrup,[5] Sergio A. Quezada,[3,4†] Charles Swanton[1,3†]

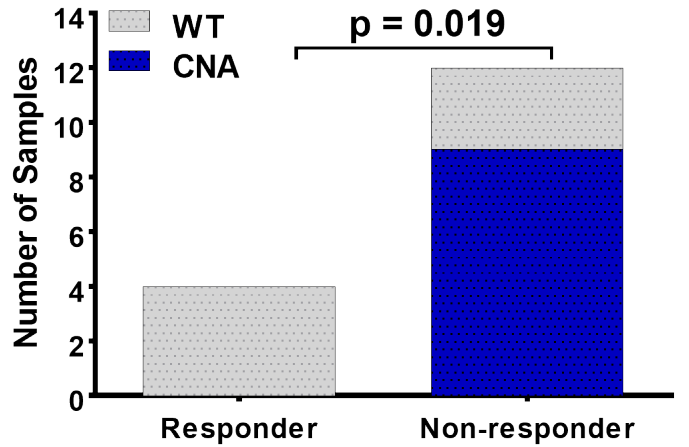


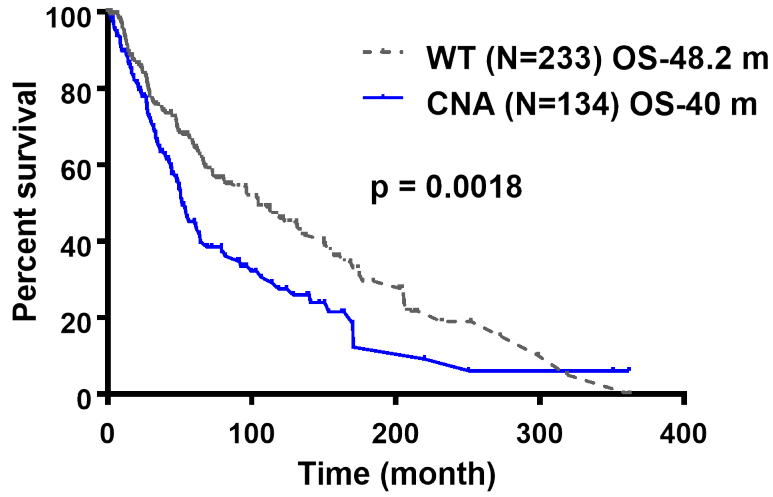
Defects in the IFN-γ Signaling Pathway Promote Resistance to Immune Checkpoint Therapies



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





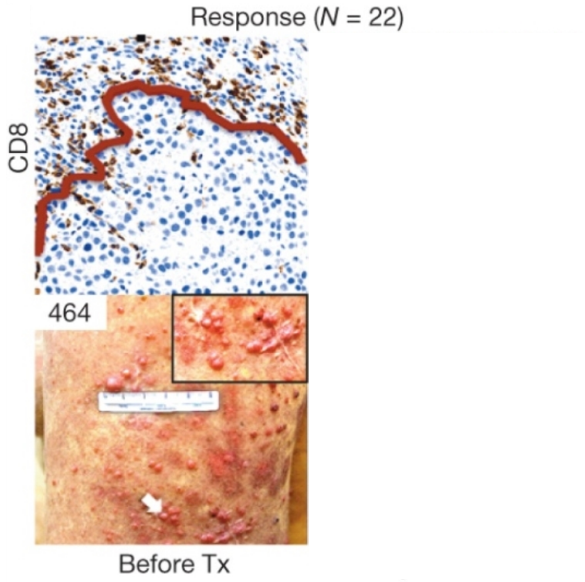


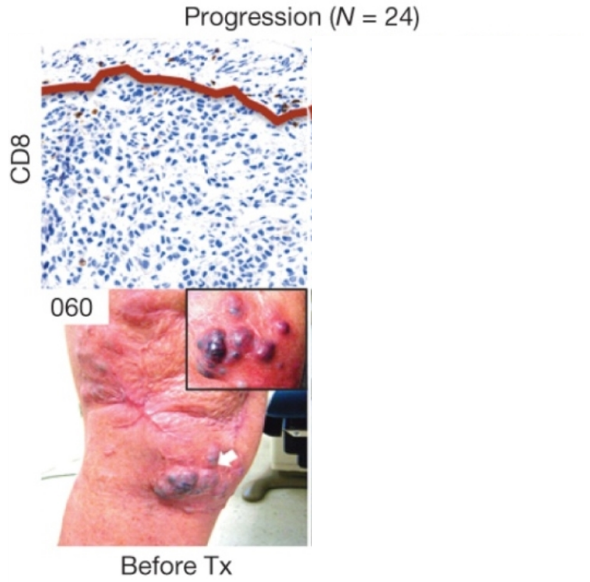
Gao JJ et al. *Cell*, 2016.

Moving Forward with Immune Checkpoint Therapies

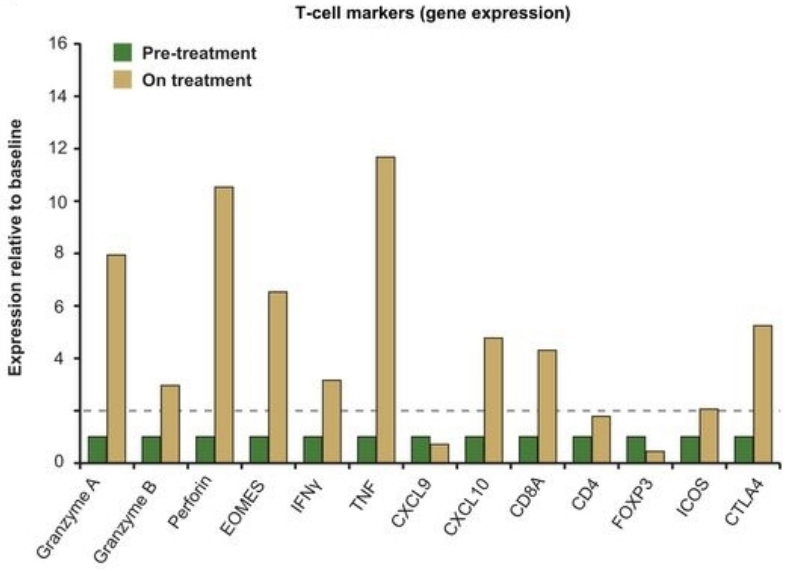
- Improving patient selection
- **Turning “cold” tumors “hot” / Resistance mechanisms**
- Understanding toxicities

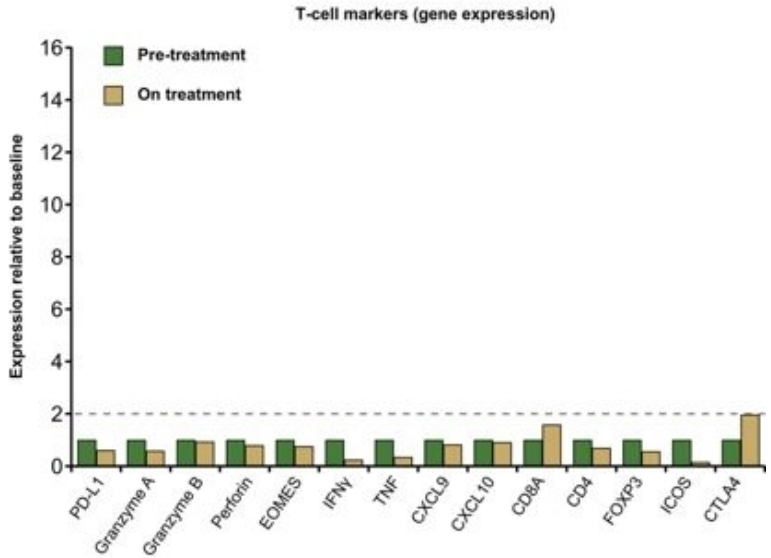
More CD8 T Cells Makes Anti-PD-1/PD-L1 Work Better





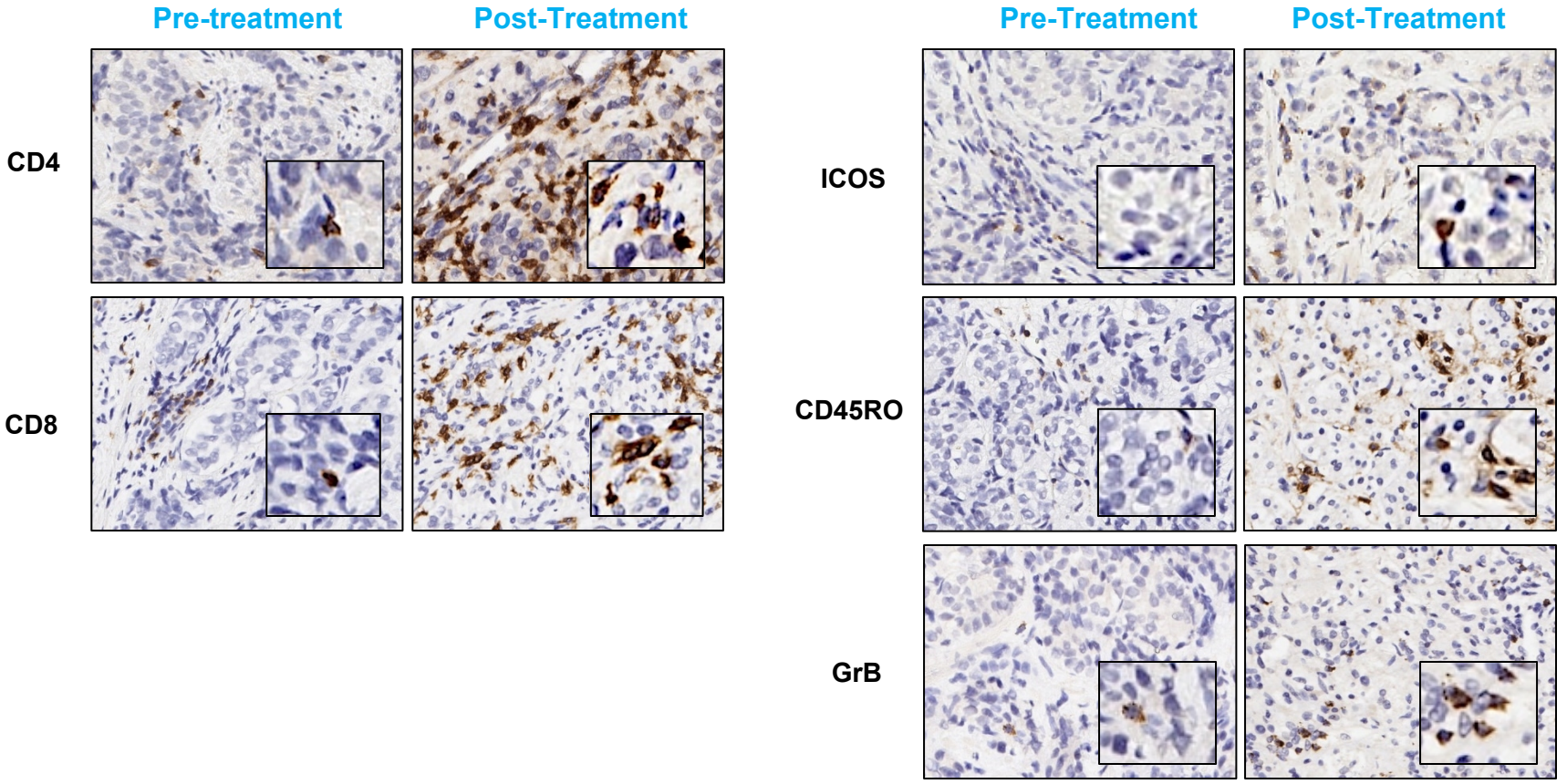
Tumeh PC et al. *Nature.* 2014.





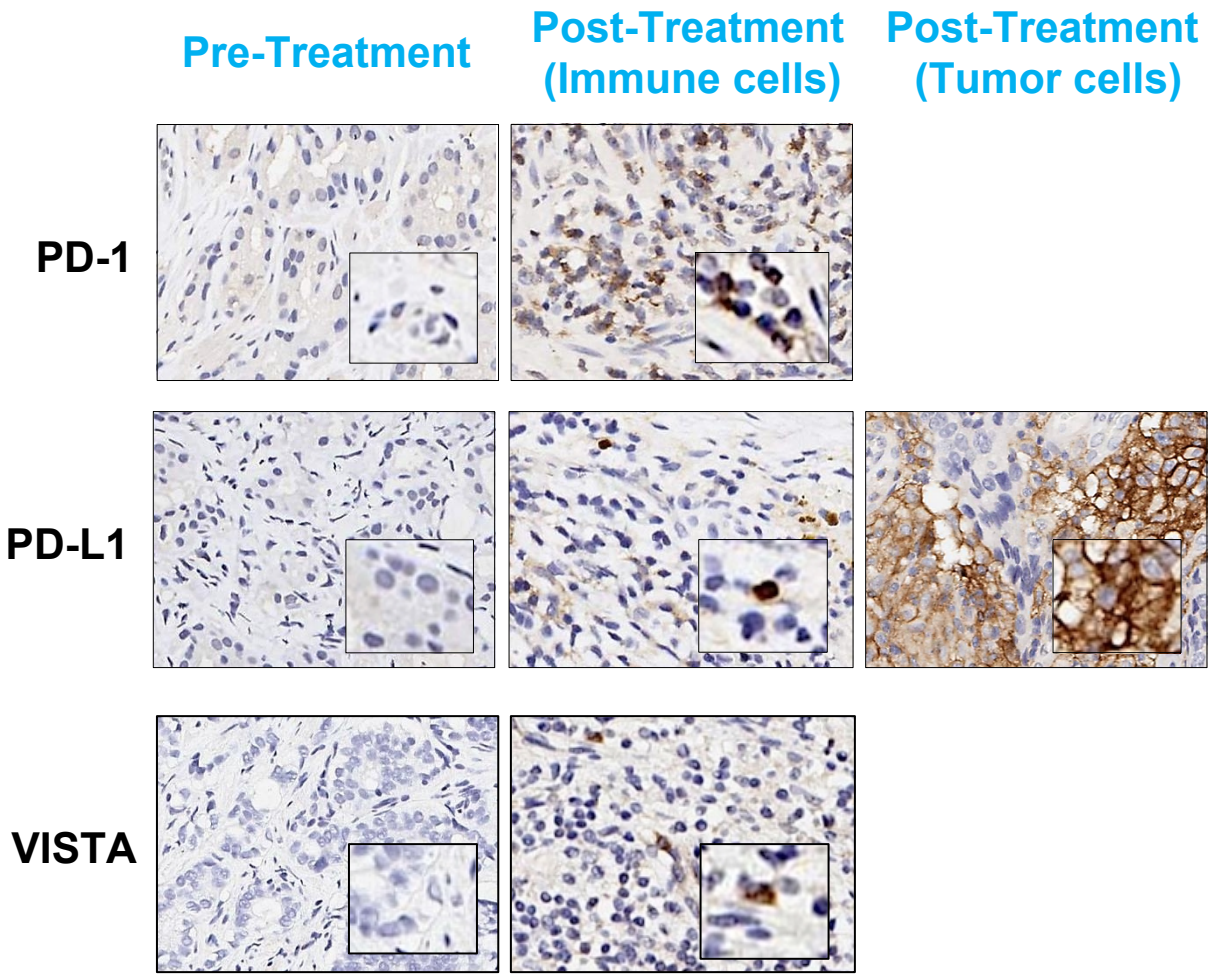
Herbst RS et al. *Nature.* 2014.

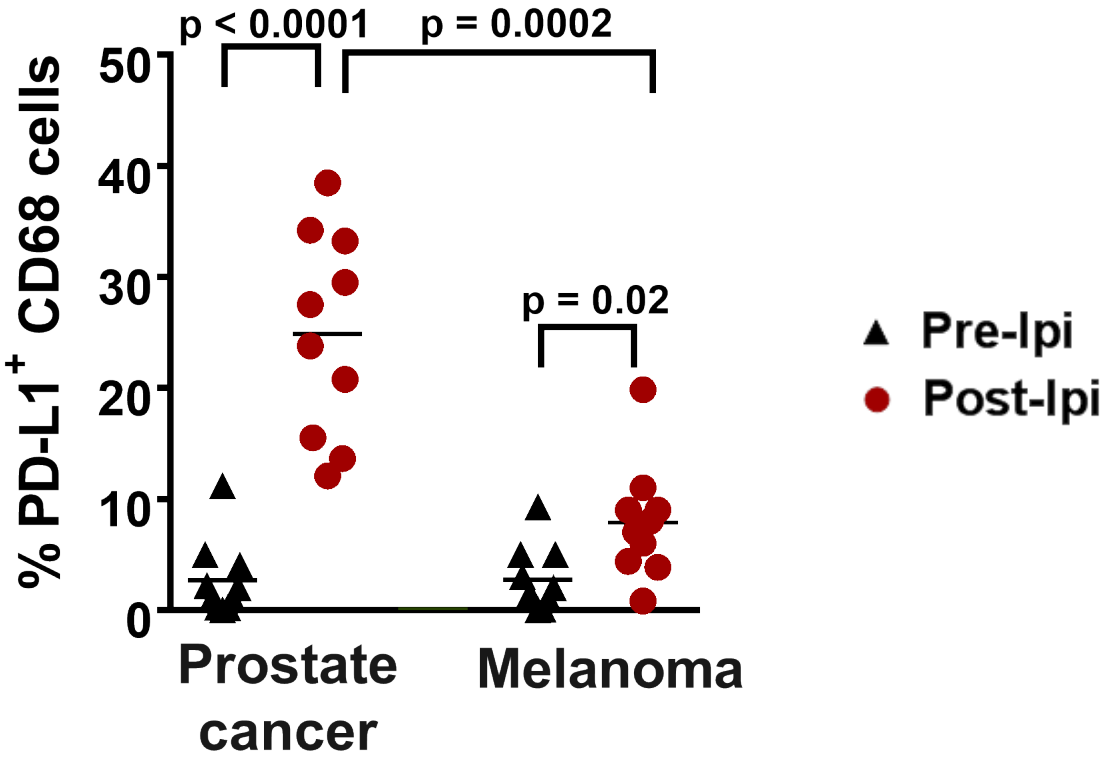
Ipilimumab Increases Immune Infiltration Within the Primary Prostate Tumor Microenvironment



Gao JJ et al. *Nature Med,* 2017.

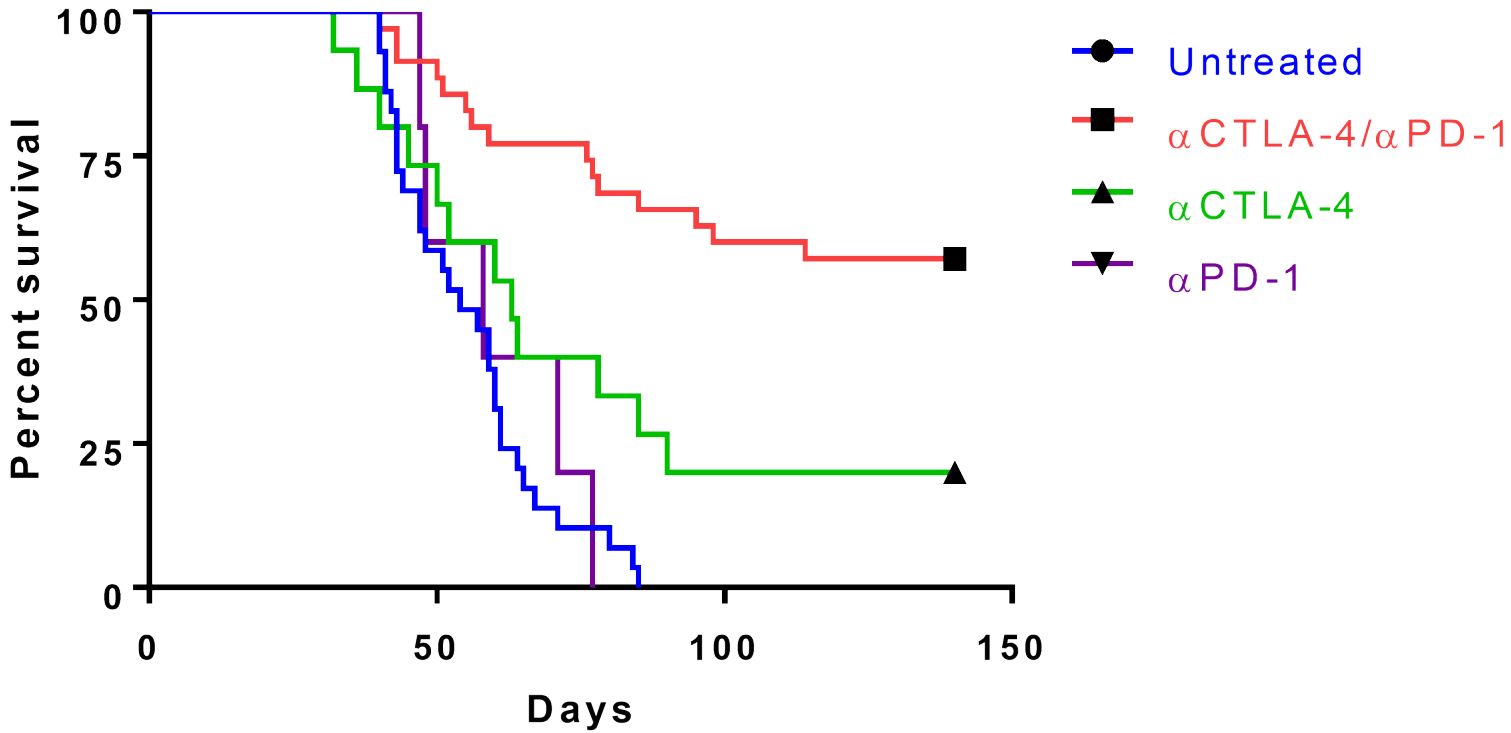
Increased Tumor-Infiltrating T Cells are Insufficient Due to Adaptive Resistance (PD-L1 Upregulation)





Gao JJ et al. *Nature Med*, 2017.

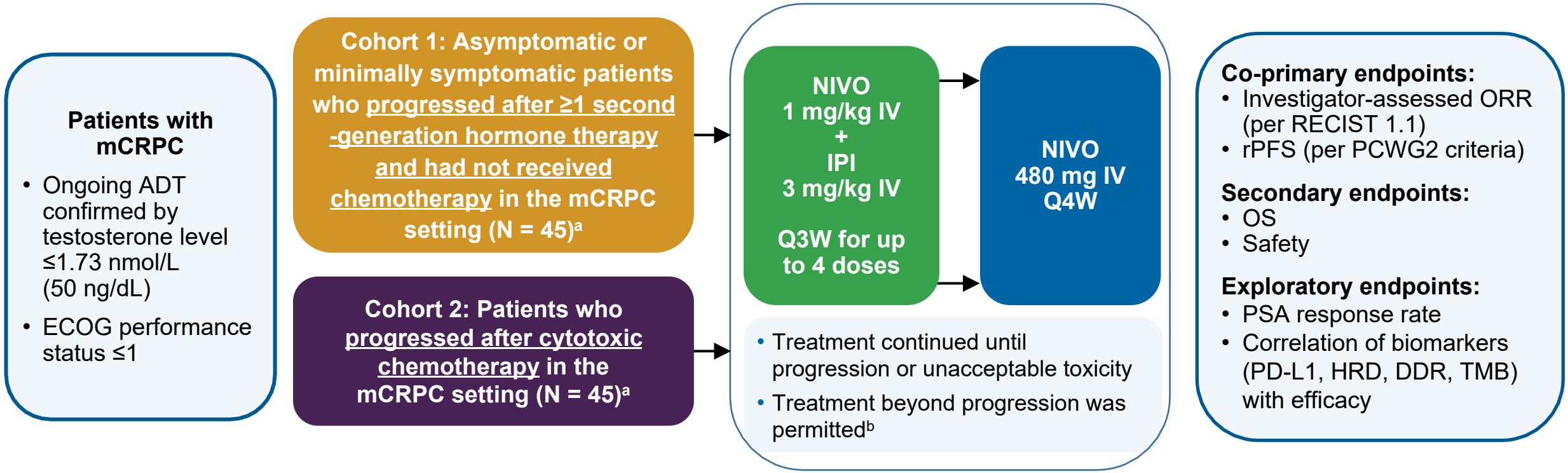
CTLA-4 and PD-1/PD-L1 Targeting in a Mouse Model of Prostate Cancer



Combination of "immune checkpoint targets" will improve efficacy

Study Design for CheckMate 650 in Prostate Cancer

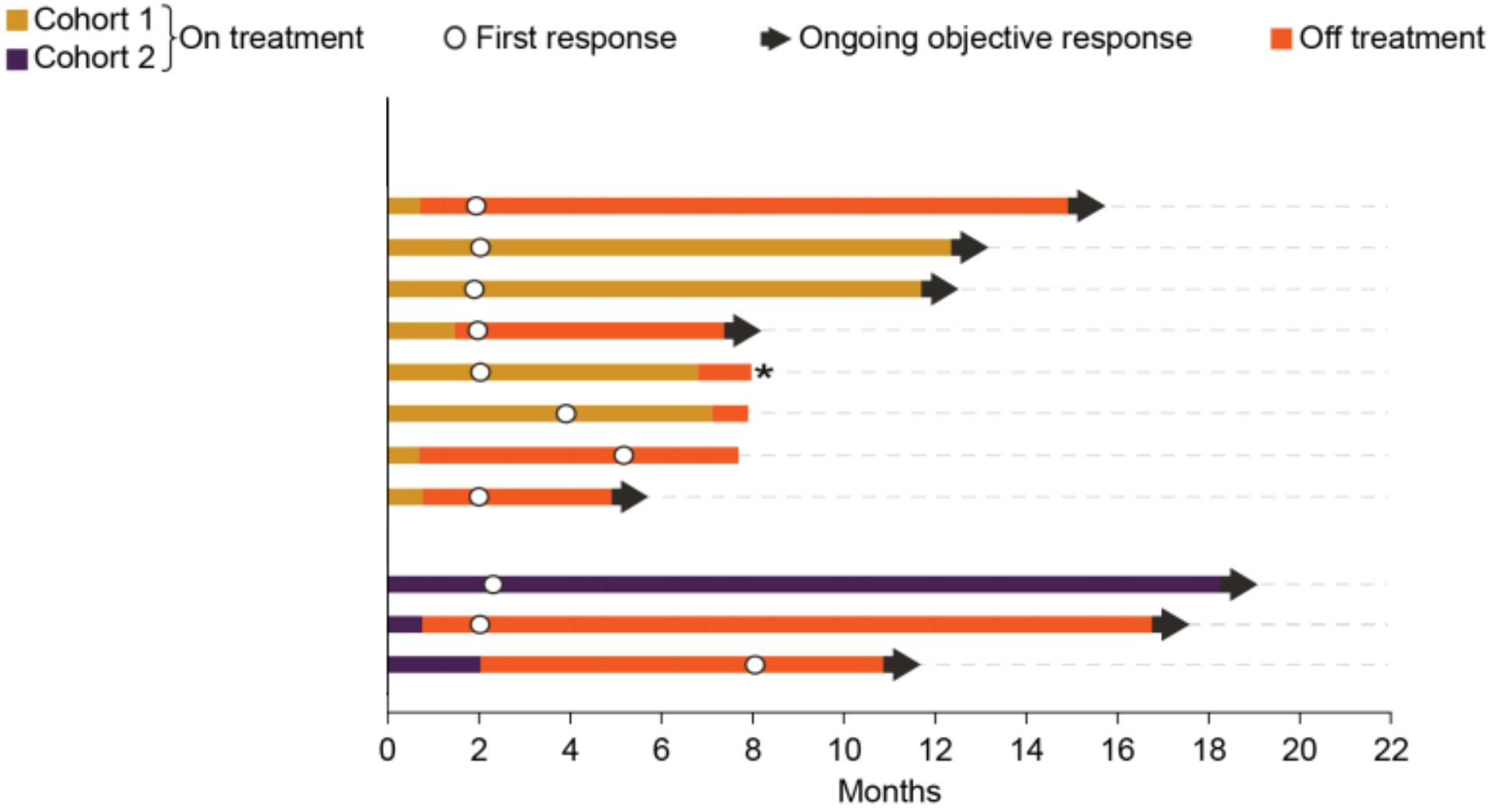
Open-label, multicenter, phase 2 study (NCT02985957)



- Patients who had received ≥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

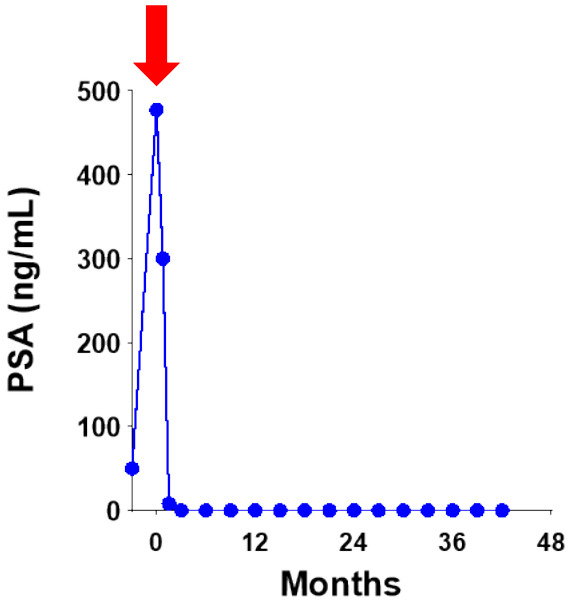
Sharma P et al., *Cancer Cell,* 2020.

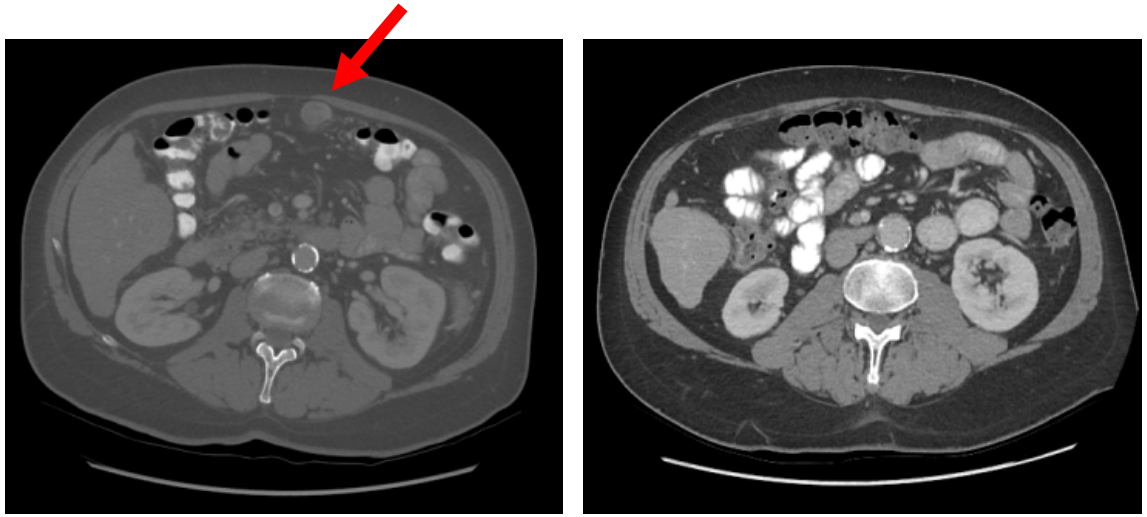
Prolonged Responses

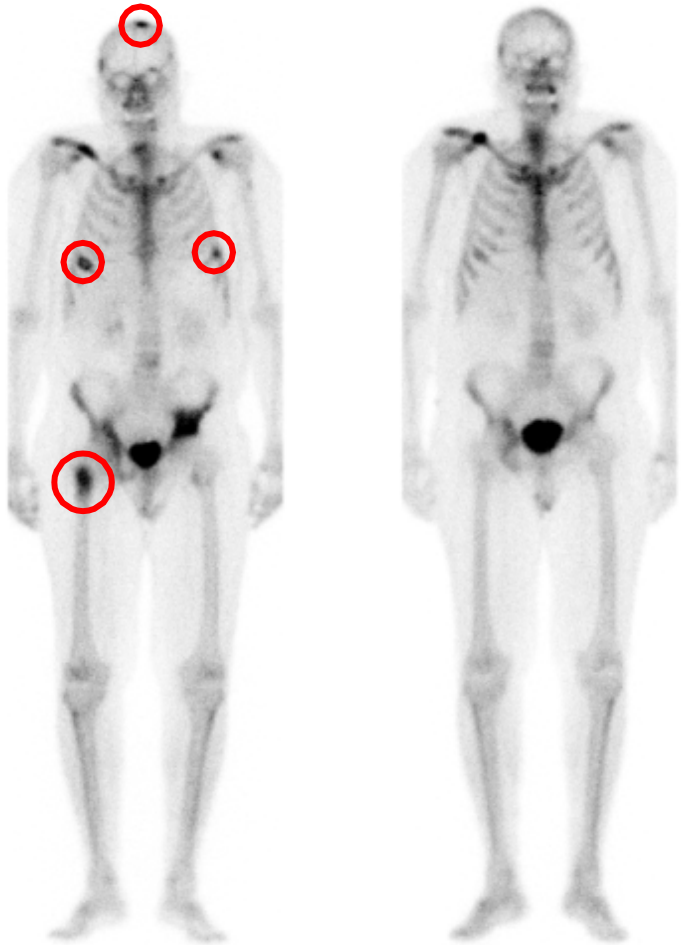


Sharma P et al., *Cancer Cell,* 2020.

Responder at MD Anderson

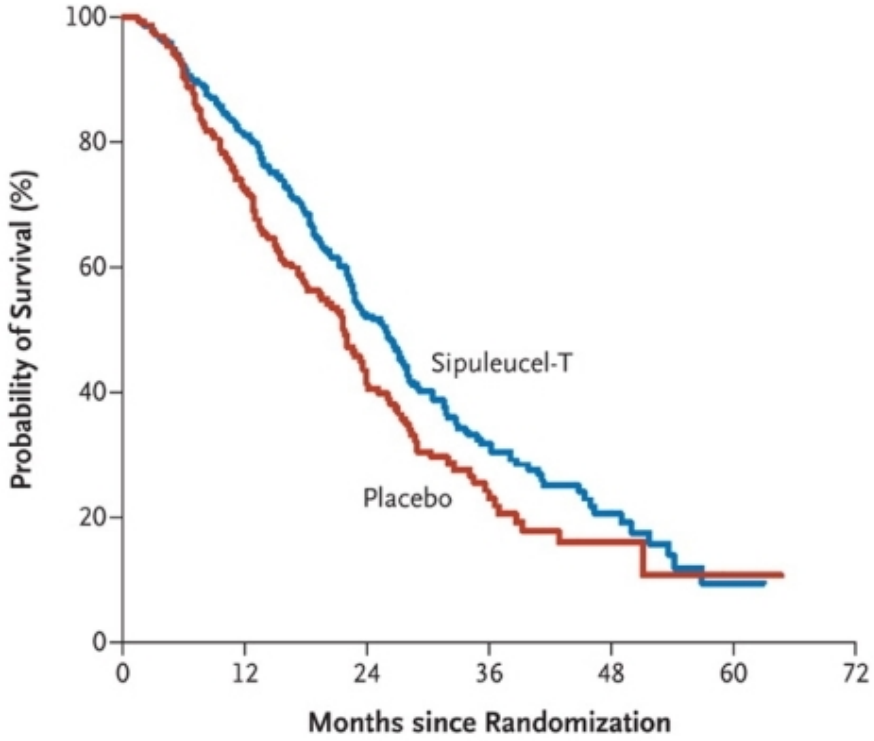




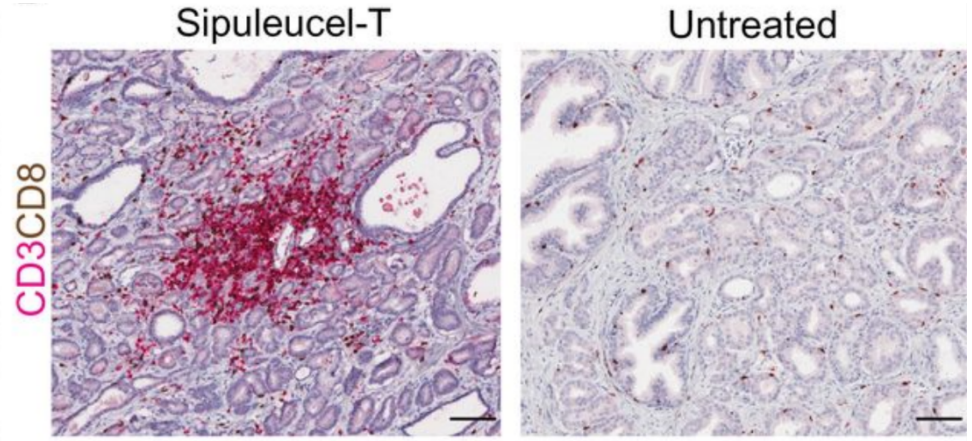


Targeting a Conventional Prostate Cancer Antigen Induces T Cell Infiltration into the Tumor Microenvironment

Sipuleucel-T (DC Vaccine)

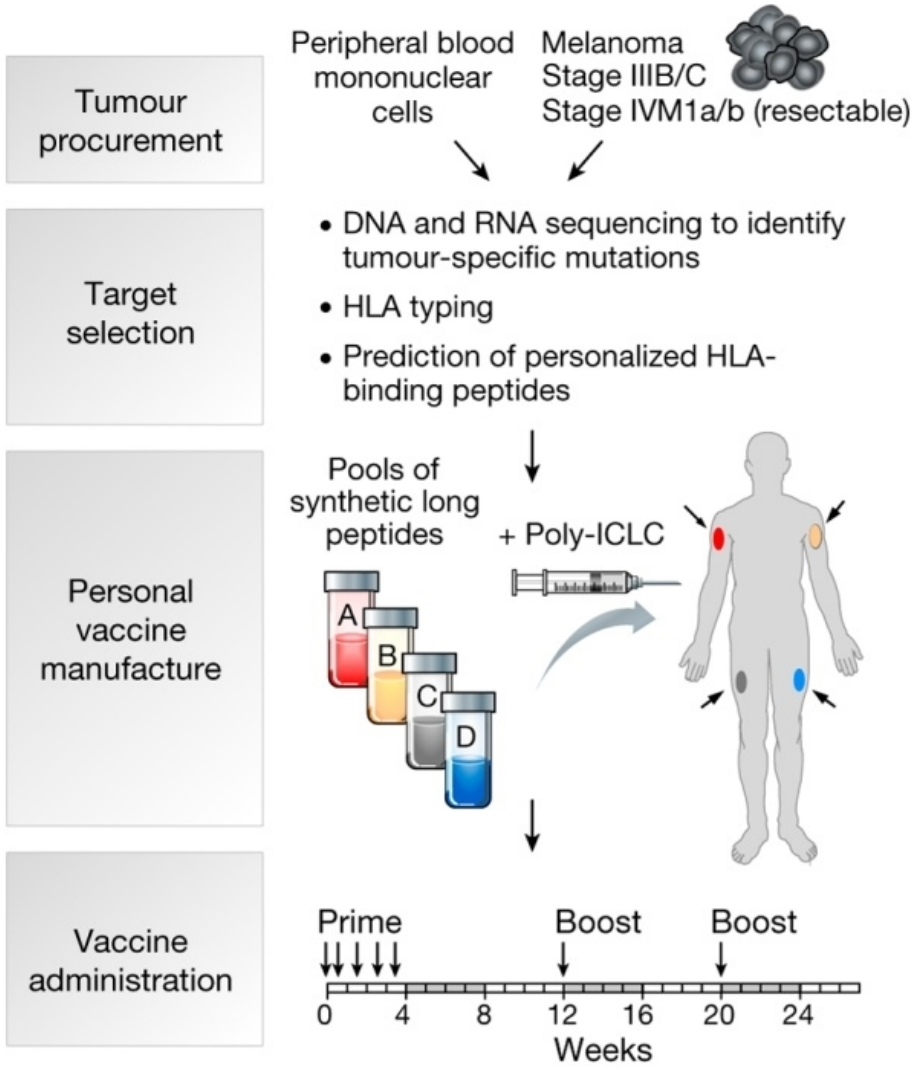


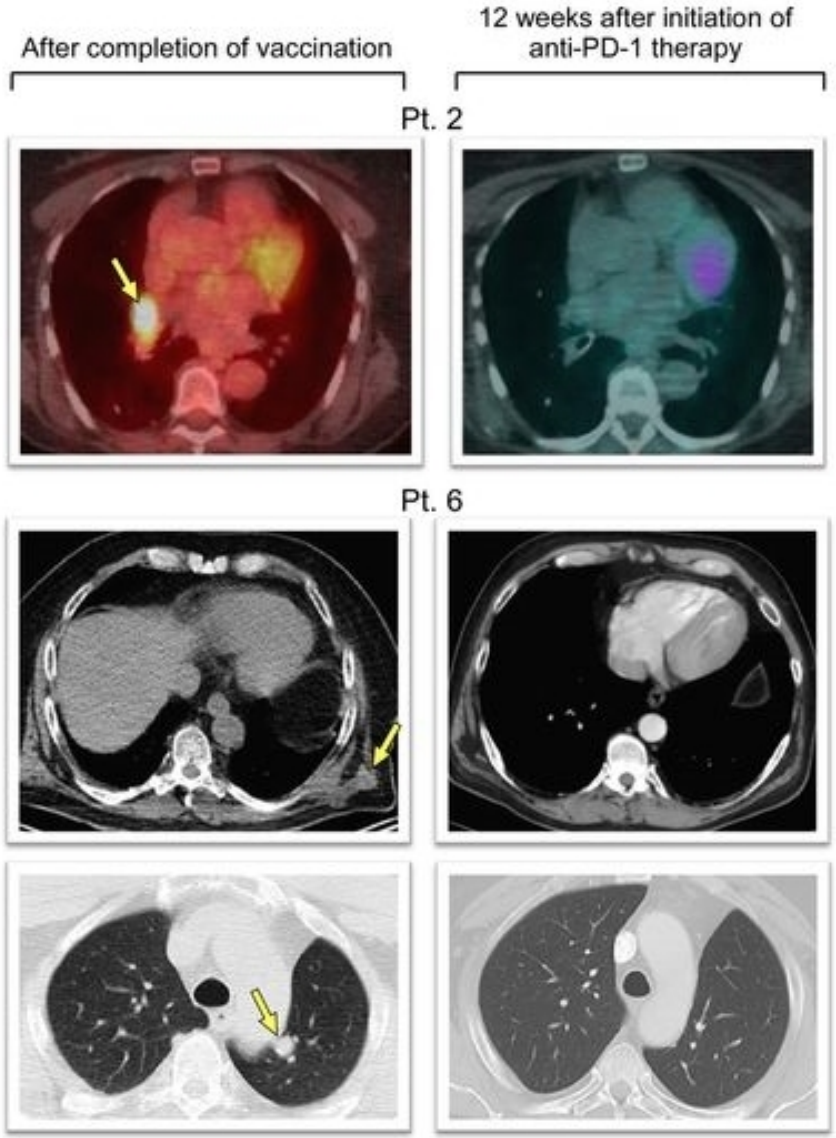
Kantoff, PW et al., *N Engl J Med,* 2010.



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

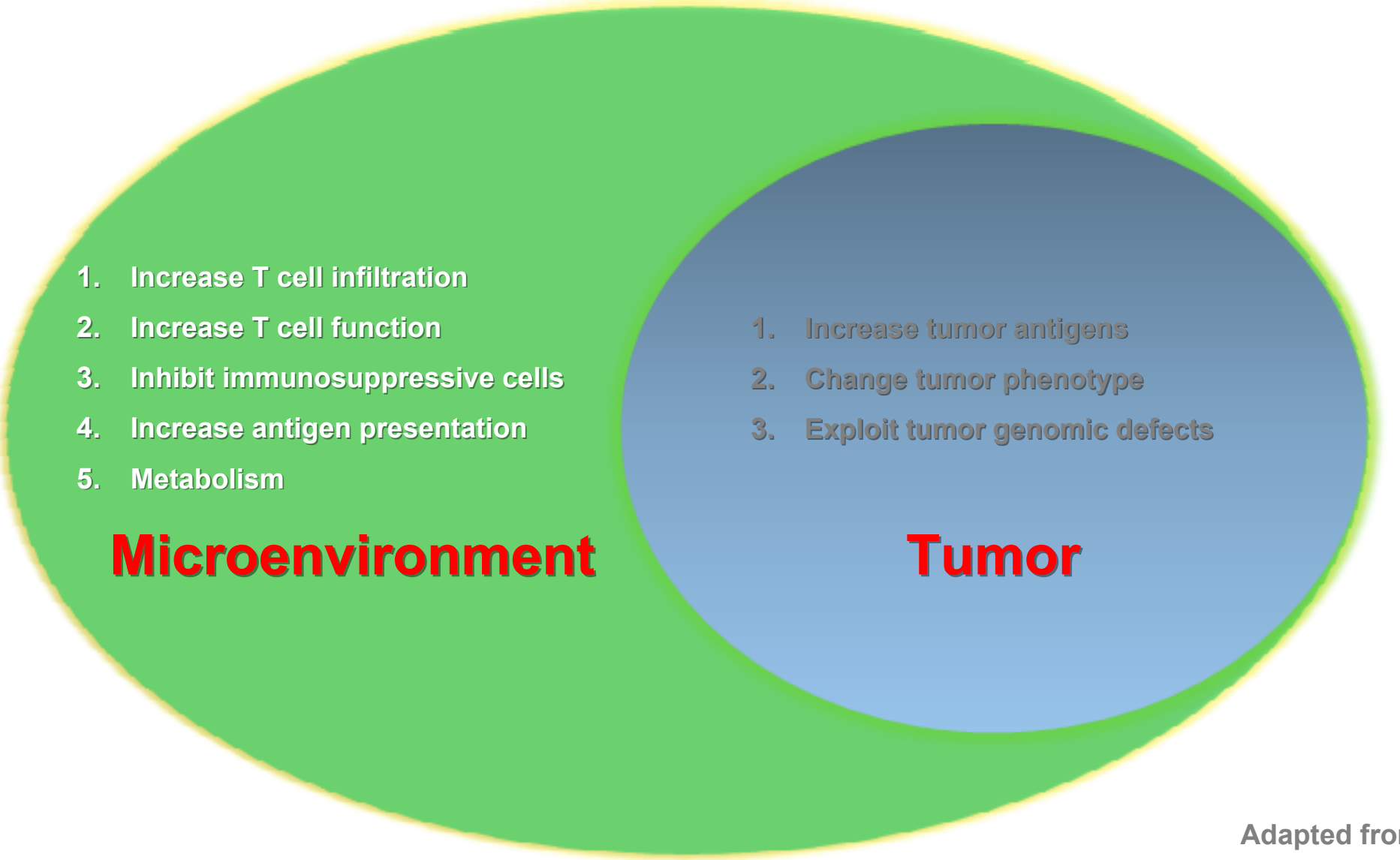
Personal Multi-Peptide Neoantigen Vaccine for Patients with High-Risk Melanoma





Ott PA et al., *Nature,* 2017.

Making Immune Checkpoint Therapies More Effective

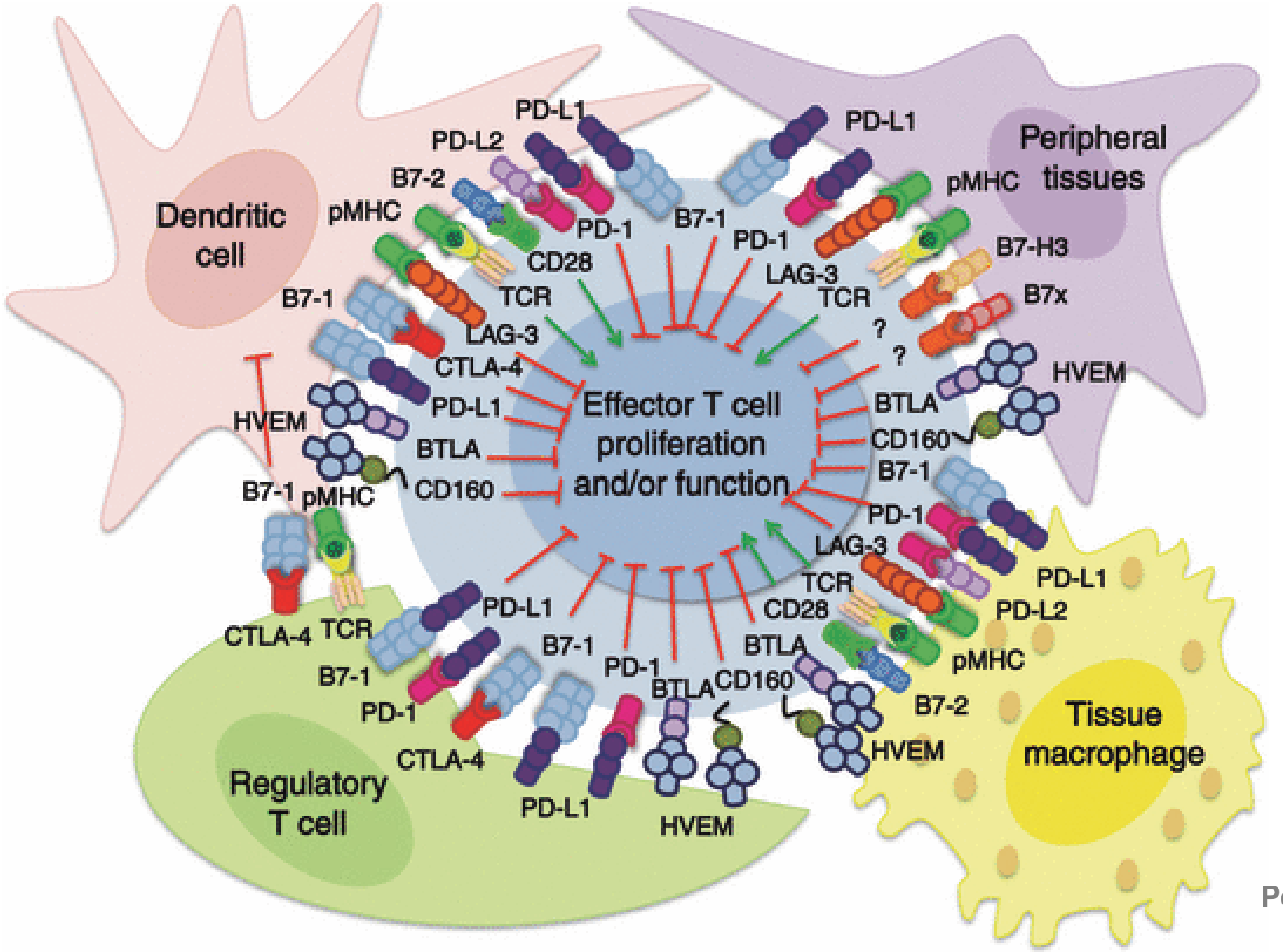


Targeting Strategies

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

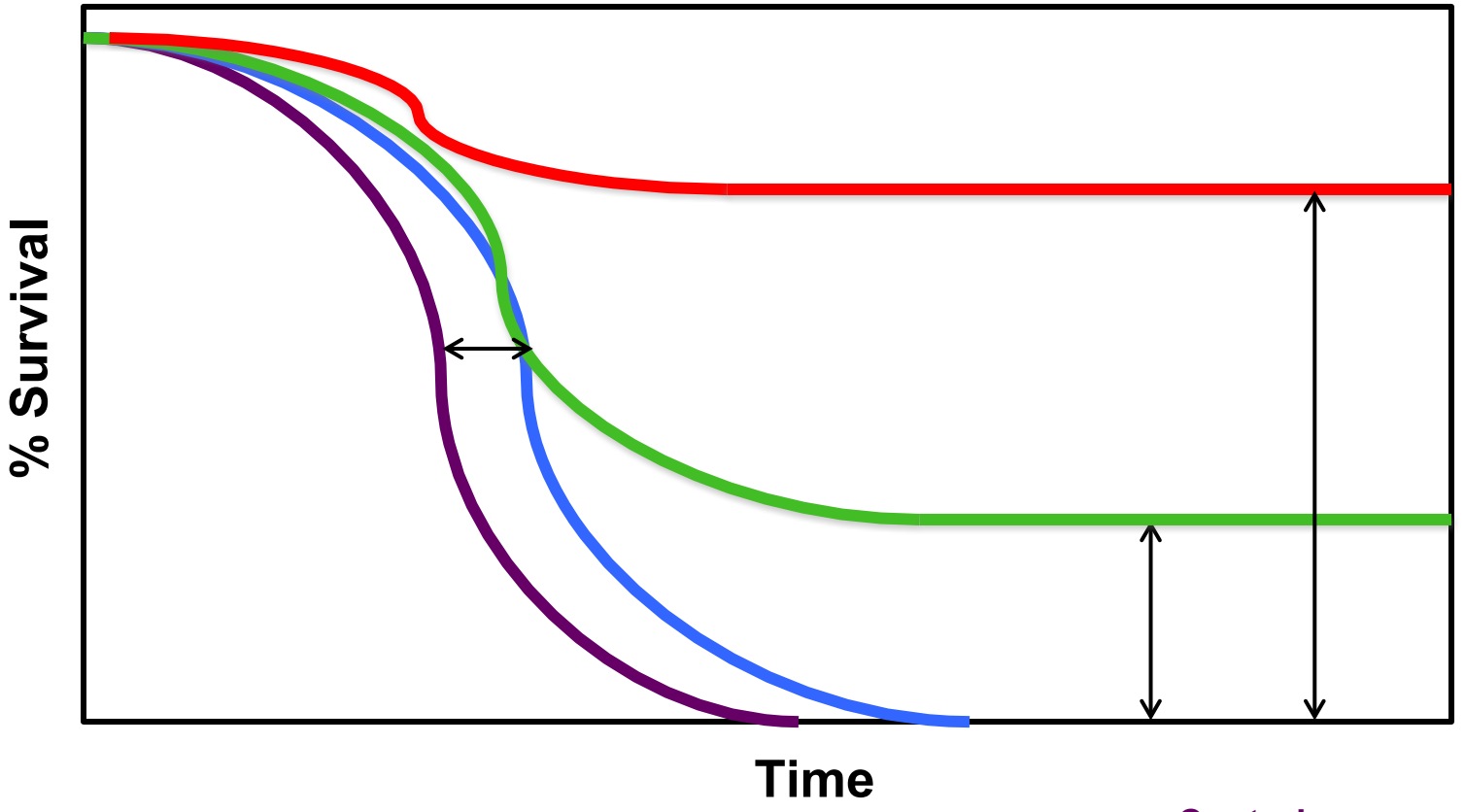
Adapted from Jianjun Gao

Novel Immunotherapy Targets



Pentcheva-Hoang T et al. *Immunol Rev*, 2009.

Improving Survival with Combination Therapy

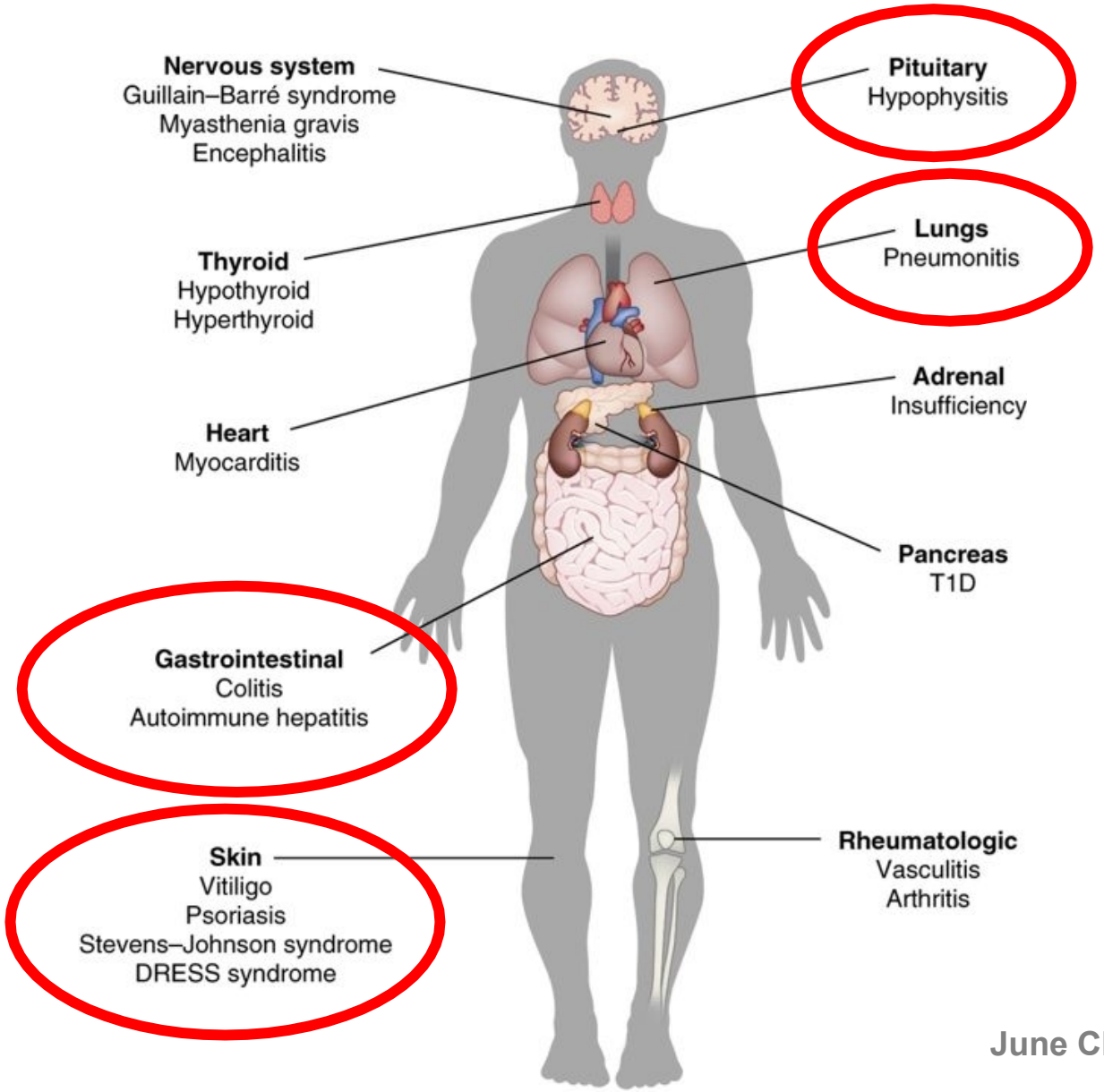


Sharma P and Allison JP, *Cell,* 2015.

Moving Forward with Immune Checkpoint Therapies

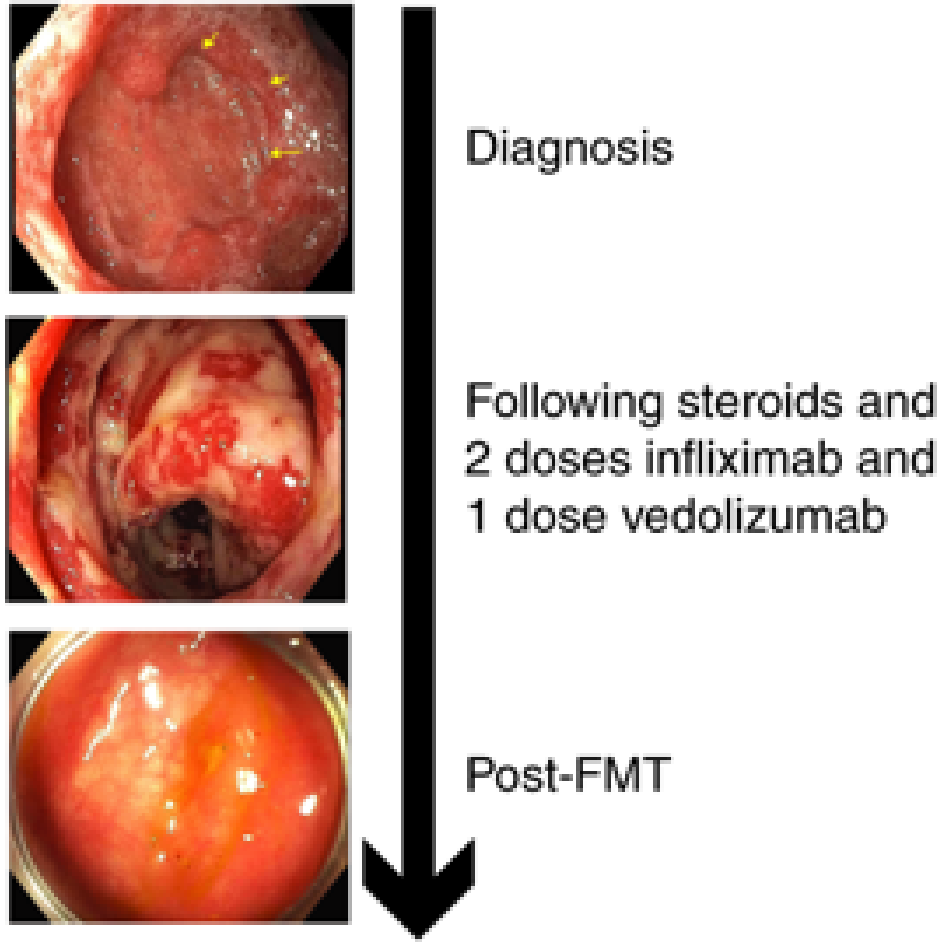
- Improving patient selection
- Turning “cold” tumors “hot”
- **Understanding toxicities**

Organ-Specific Immune-Related Adverse Events (irAEs)



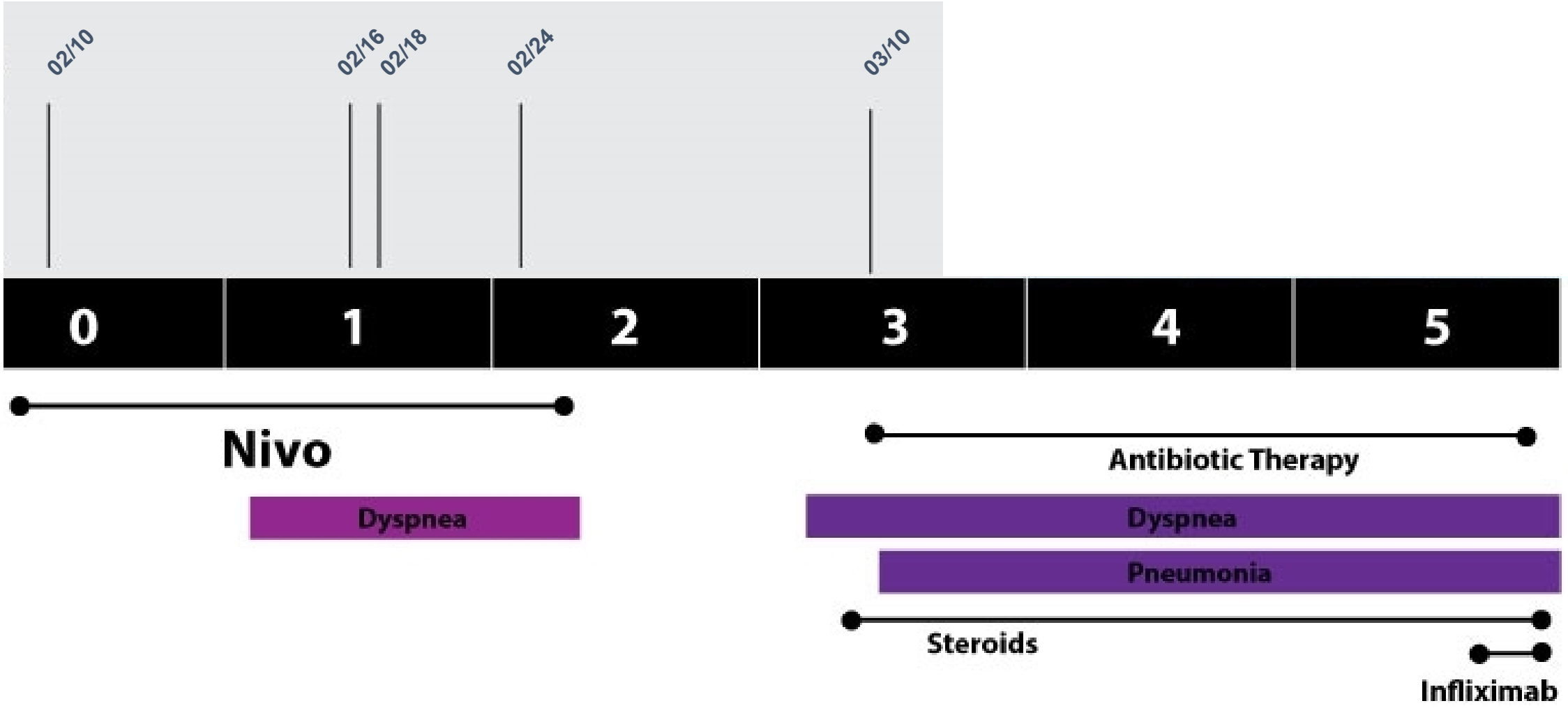
June CH et al, *Nat Med,* 2017.

Immune-Related Colitis/Diarrhea



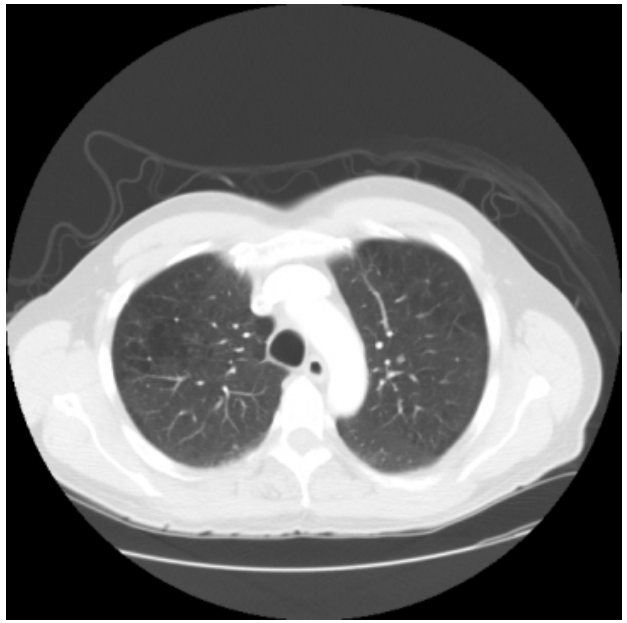
Wang Y et al., *Nat Med,* 2018.

Immune-Related Pneumonitis



Monday Morning Quarterback

02/05/2015



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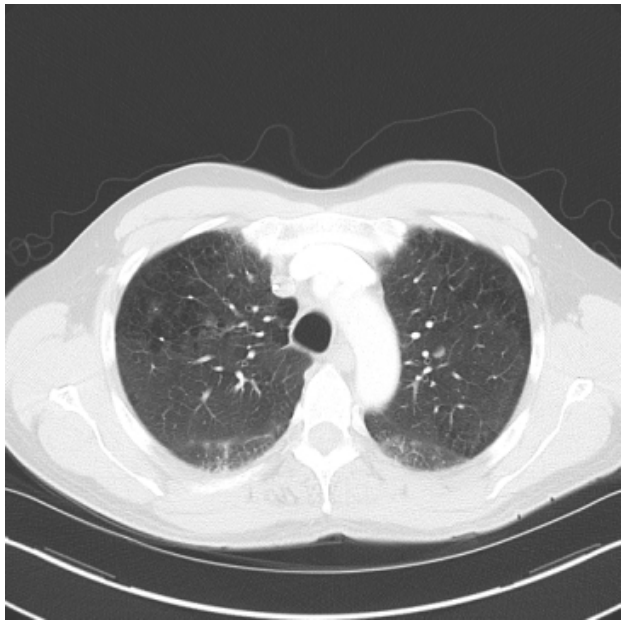

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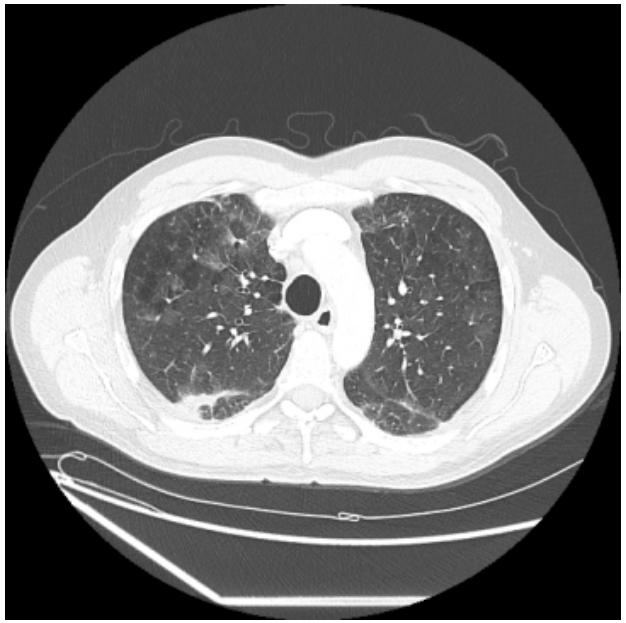
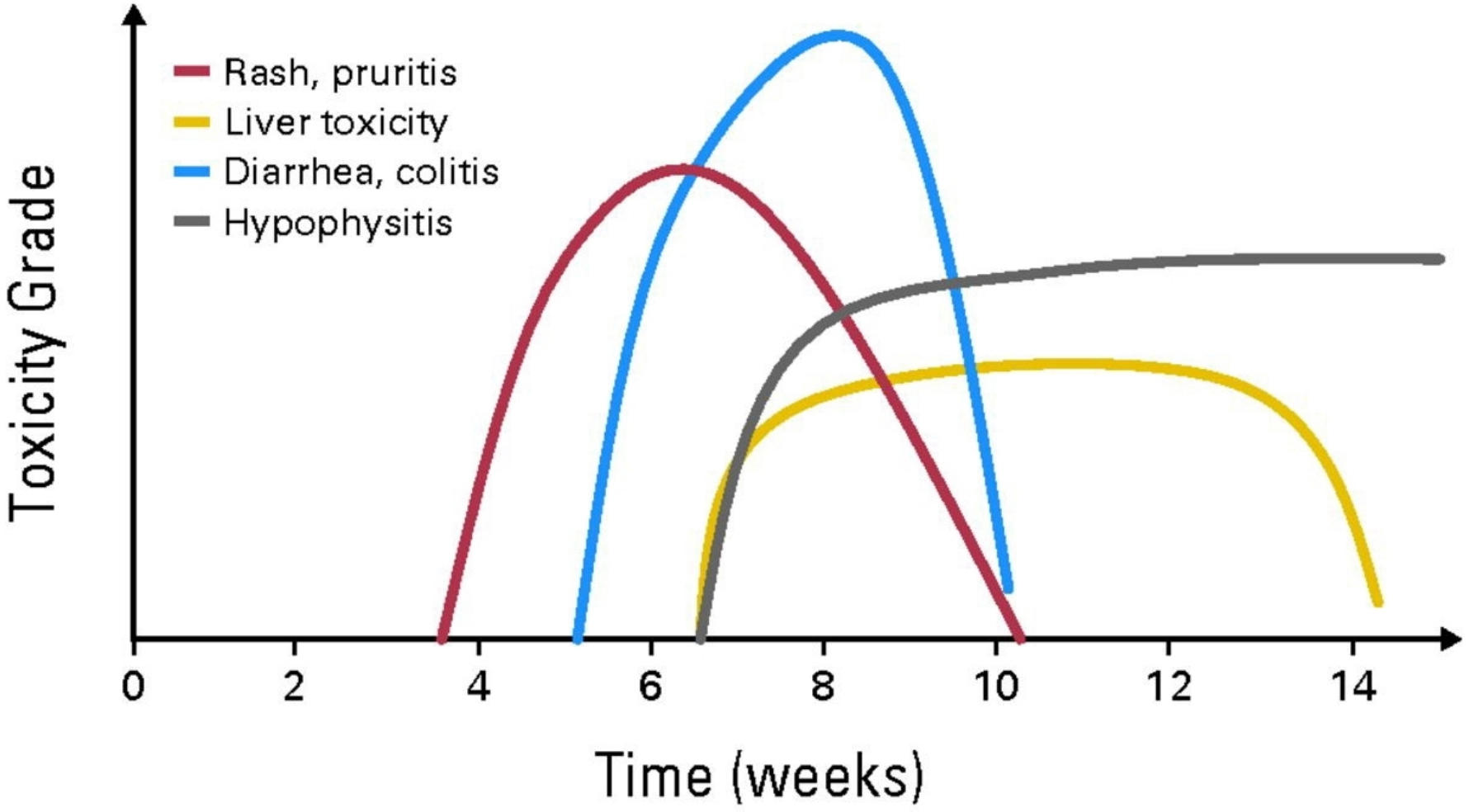


Safety Considerations

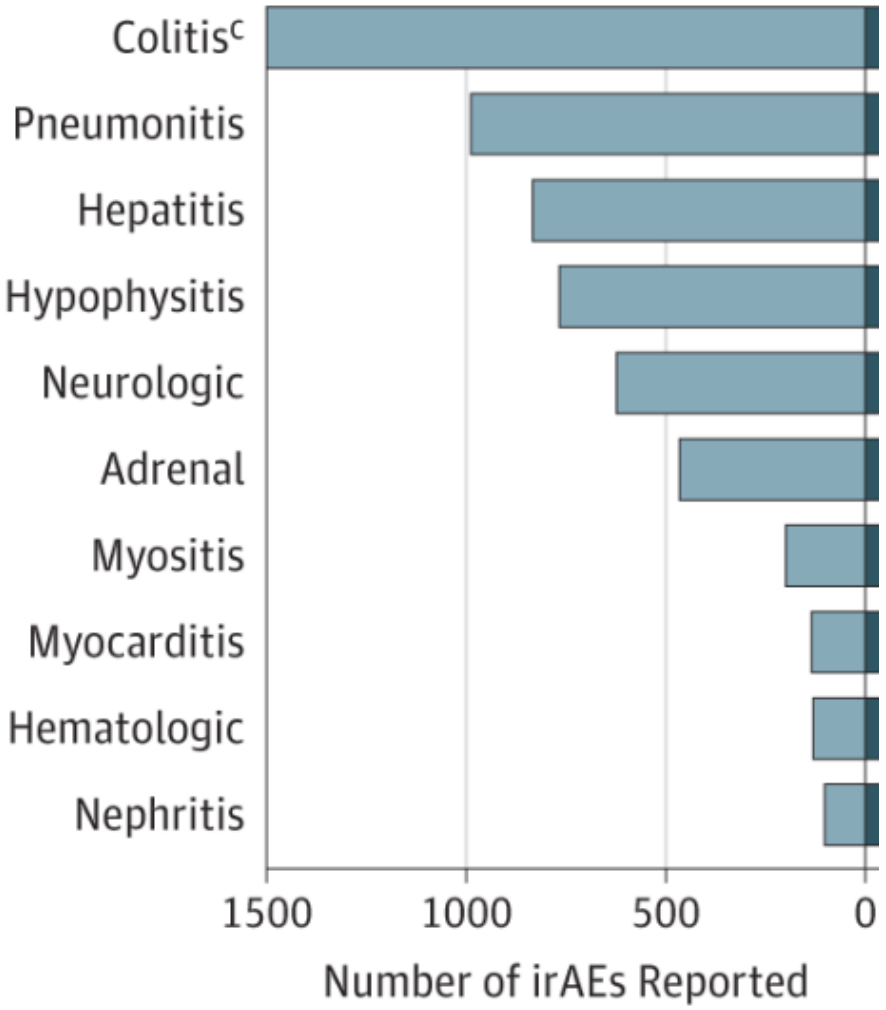
- irAEs appear to be under-reported
- Early recognition/intervention with immunosuppressive/biological agents
  - Medical team
  - Patient/Family
  - Laboratory tests
  - Consult teams

Kinetics of Appearance of irAEs



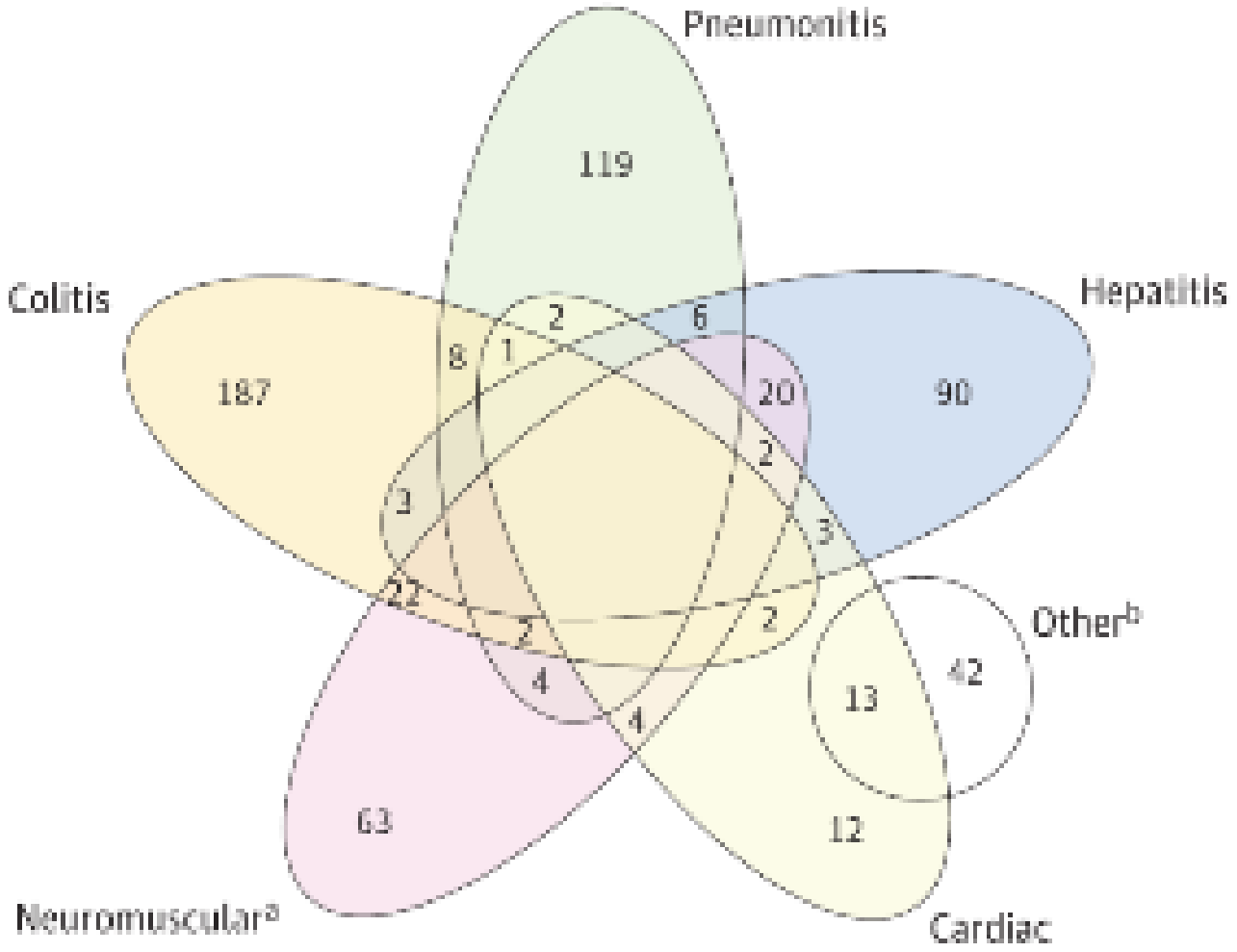
Weber JS et al., *J Clin Oncol,* 2012.

Cases and Fatality Rates for Different Types of irAEs



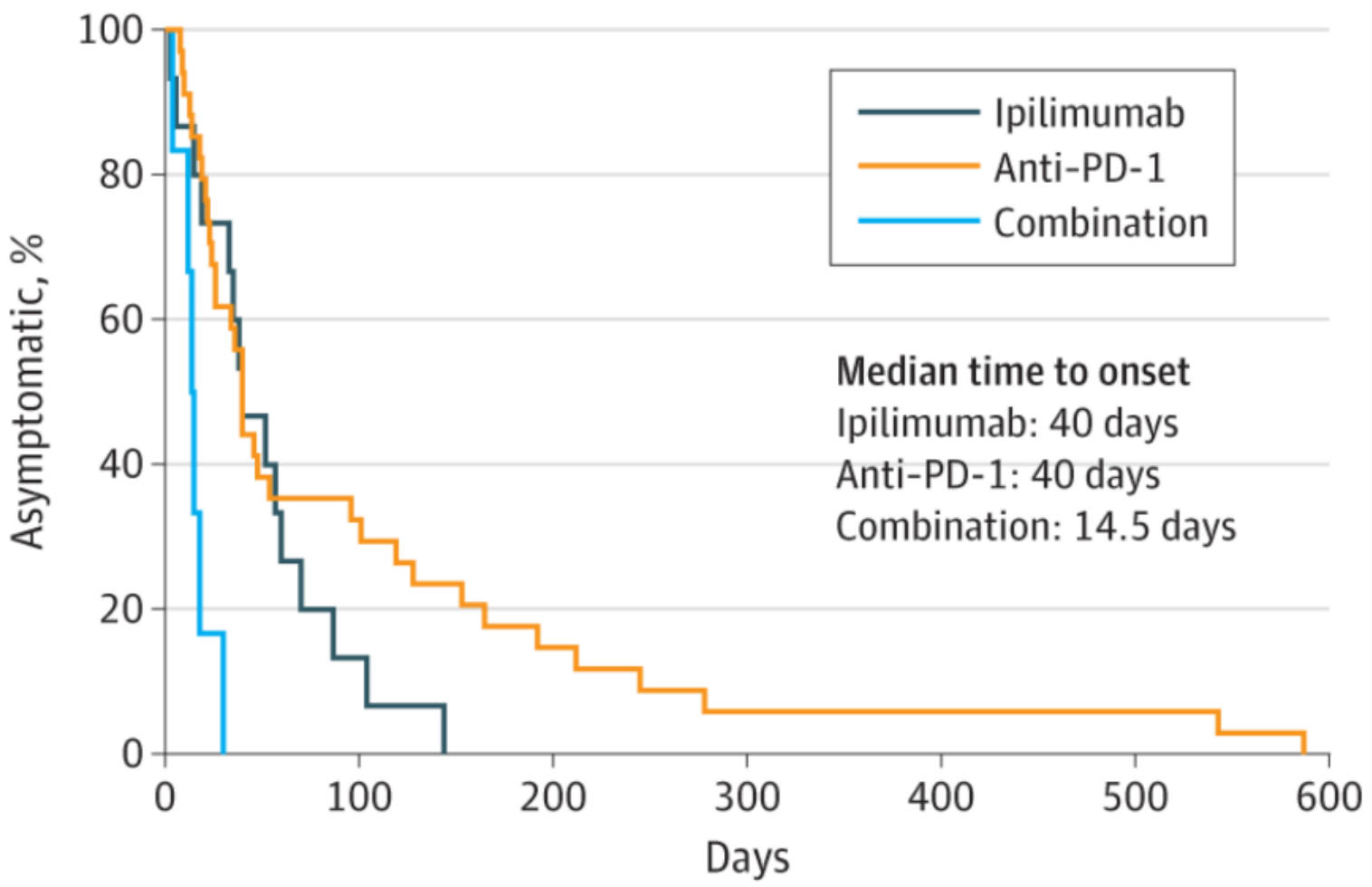
Wang DY et al., *JAMA Oncol,* 2018.

Co-Occurring Fatal irAEs



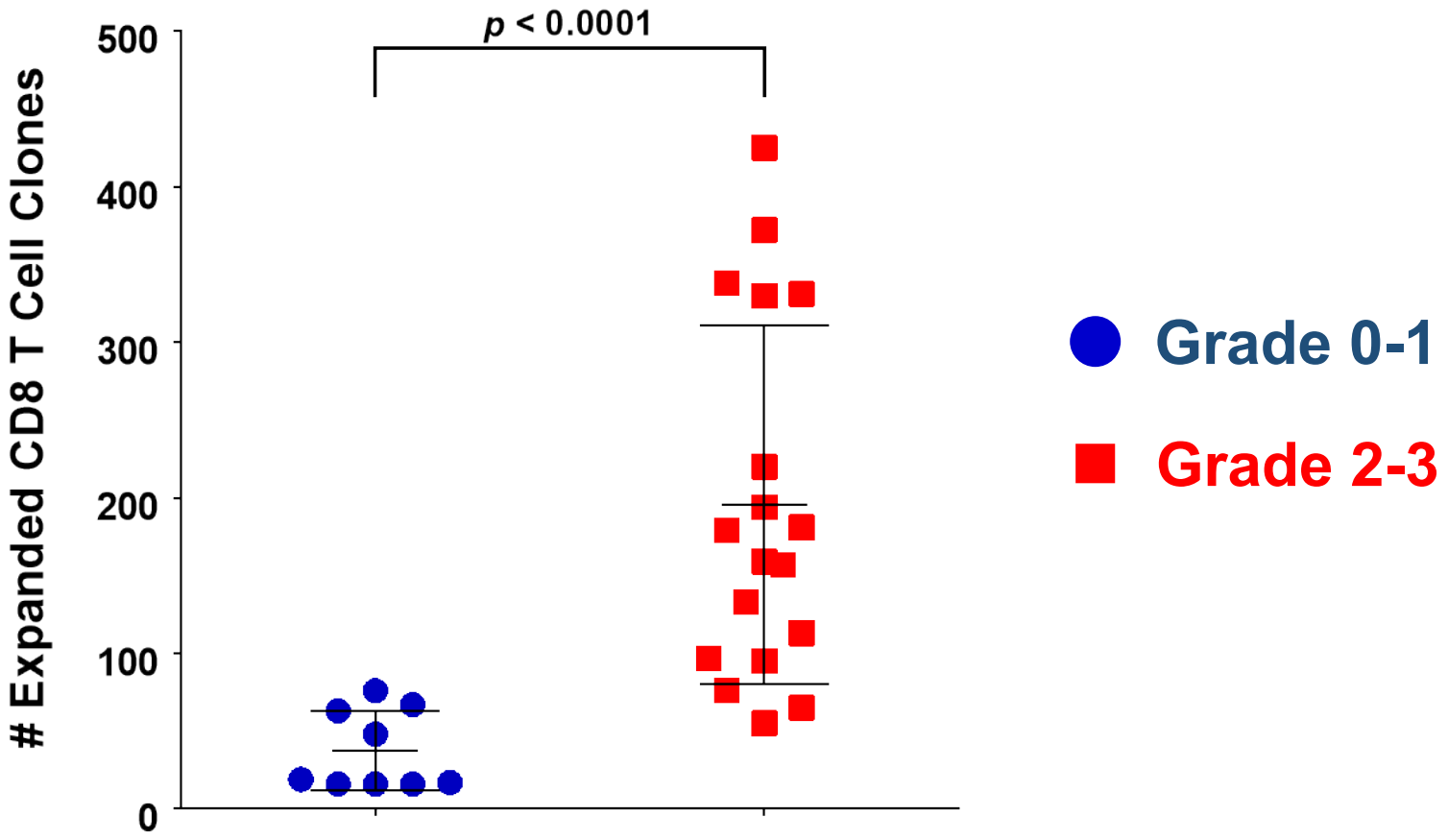
Wang DY et al., *JAMA Oncol,* 2018.

Time to Symptom Onset for irAEs



Wang DY et al., *JAMA Oncol,* 2018.

Systemic CD8 Clonal Expansion Precedes Grade 2-3 irAEs



Subudhi SK et al., *PNAS*, 2016.

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