Immunotherapeutic Strategy:

Immune Checkpoint Blockade

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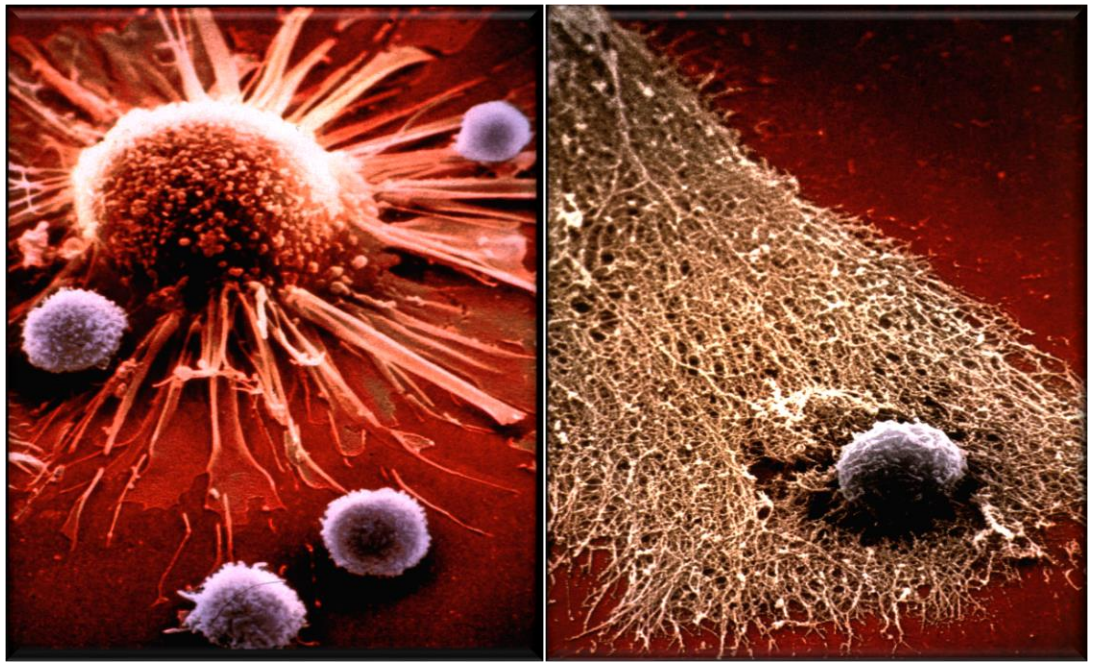
Disclosures

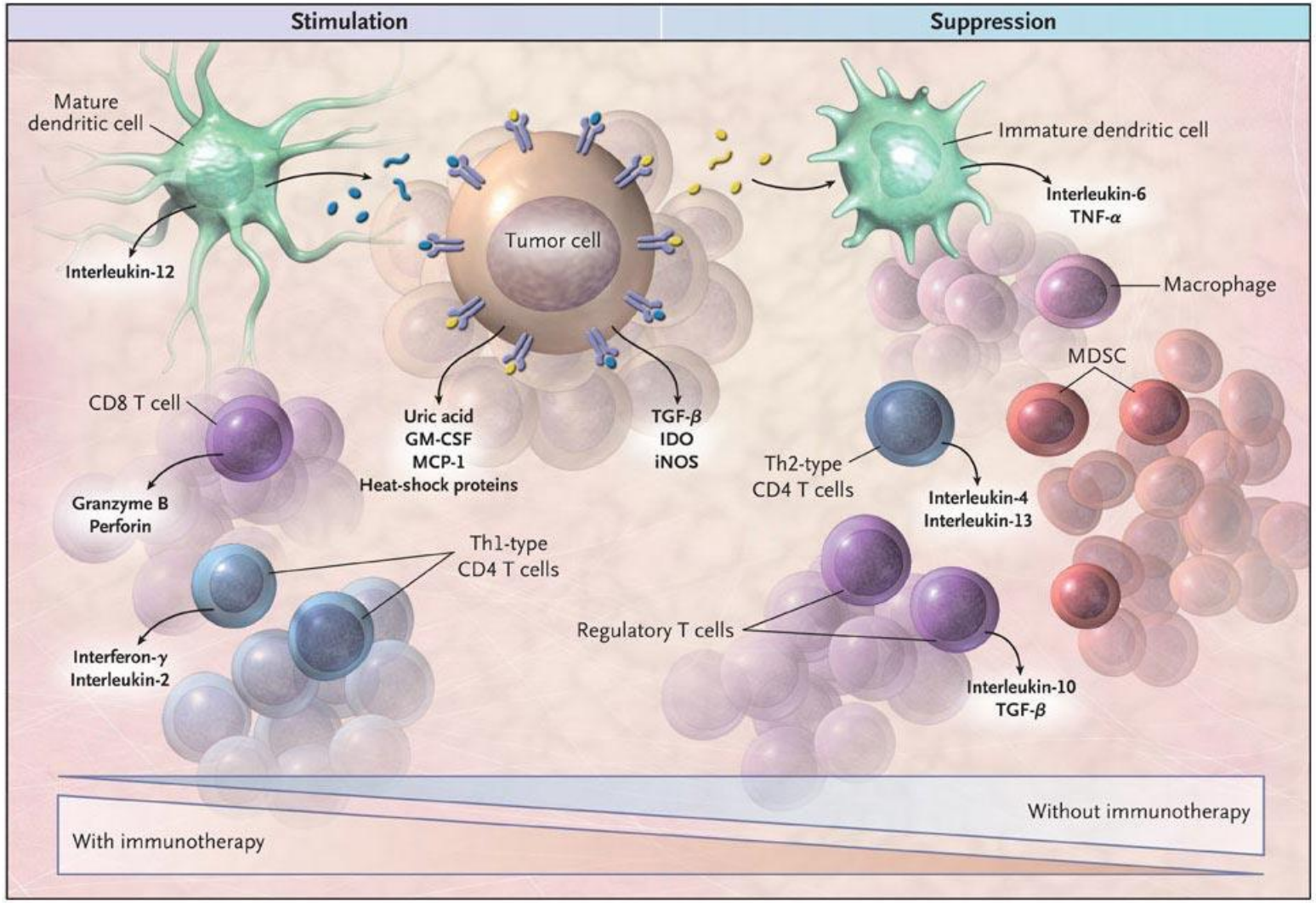
- **Consulting or Advisory Role:** Amgen, Apricity Health, AstraZeneca, Bayer, Bristol-Myers Squibb, Dava Oncology, Dendreon, Exelixis, and Janssen Oncology
- **Research Funding:** AstraZeneca, Bristol-Myers Squibb, and Janssen Oncology
- **Other (Joint Scientific Committee):** Janssen Oncology, Polaris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

Why Immunotherapy?

- **Immune system can eradicate tumor cells**
  - **Adaptability**
  - **Specificity**
  - **Memory**



Immune Tumor Microenvironment



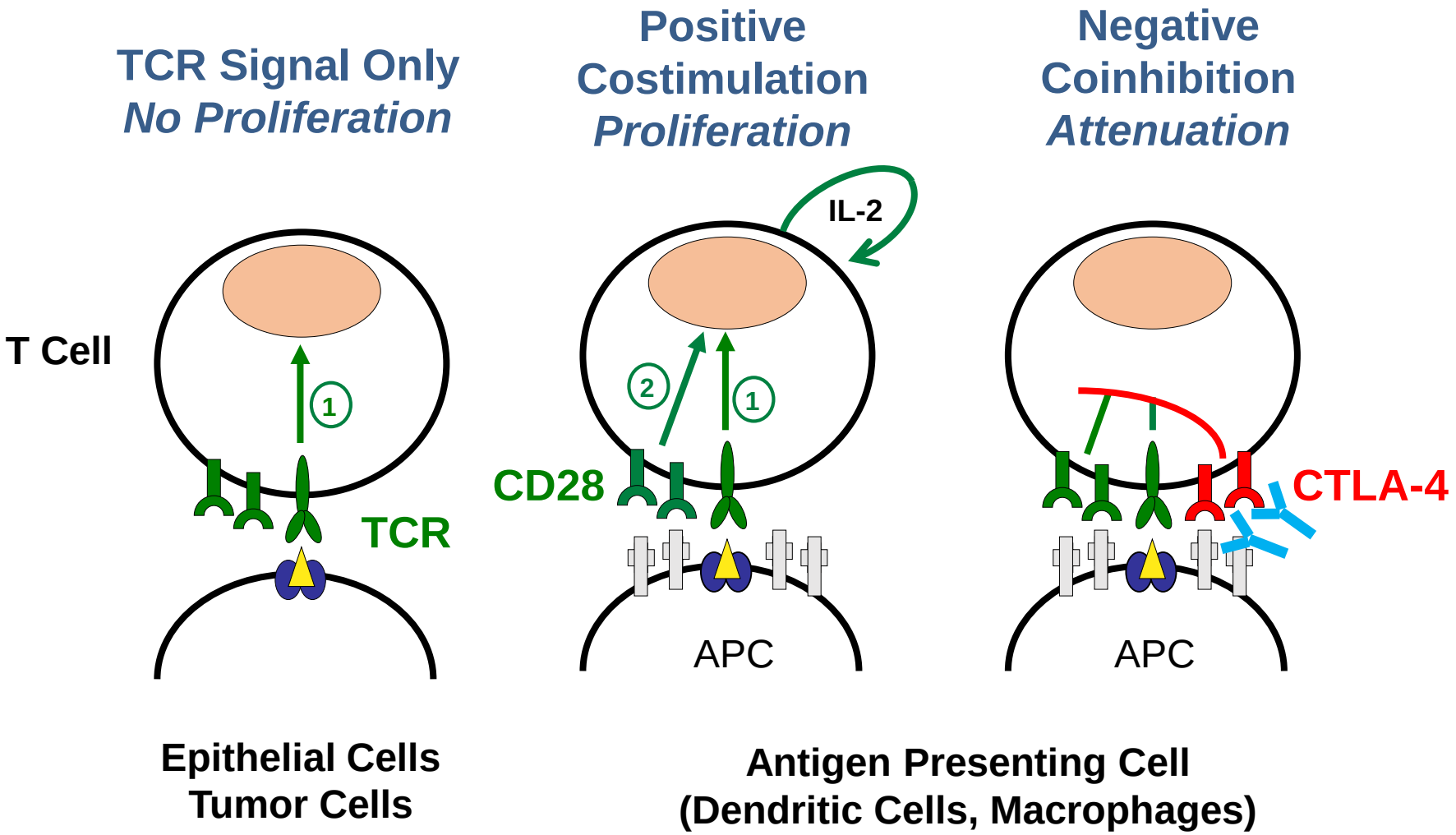
Finn ON et al, *New Engl J Med*, 2008.

Immunotherapies

Not all the same!

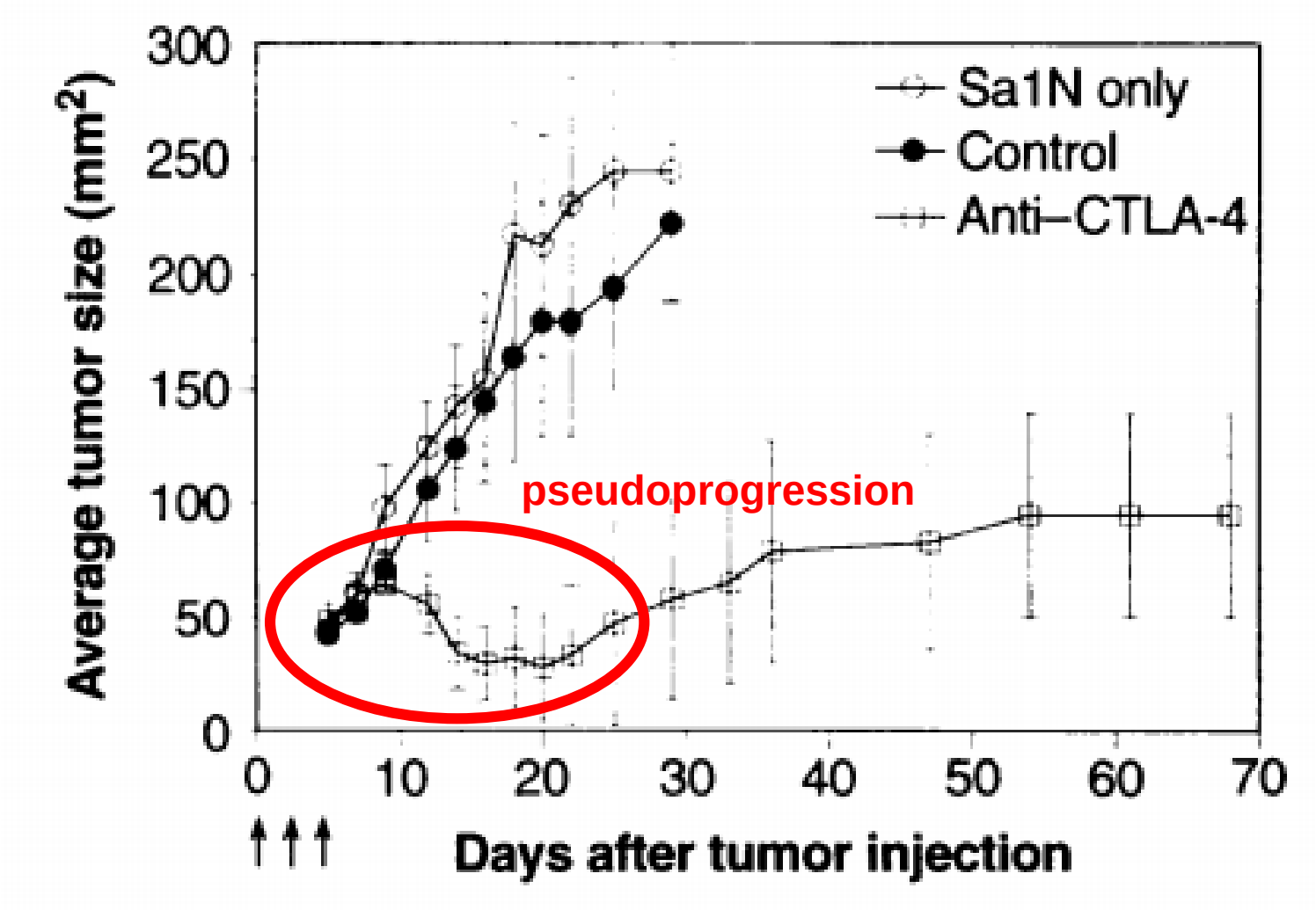
- **Vaccines**
  - **Directs immune system to focus on tumor antigen(s)**
- **Cellular therapies**
  - **CAR T cells target the tumor cells**
- **Immune checkpoint therapies**
  - **Increases T cell activation and function**

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



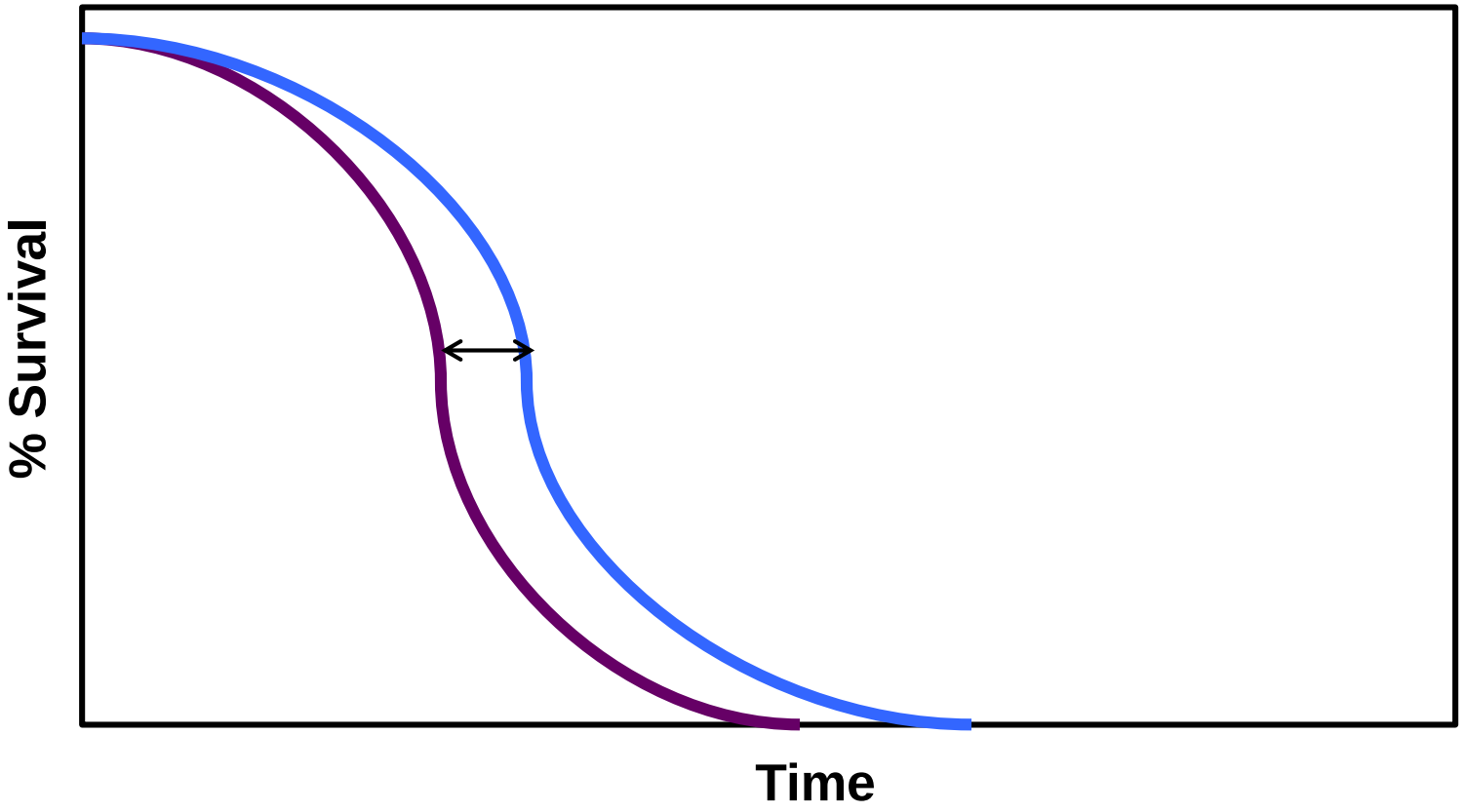
Courtesy of Jim Allison, PhD

Anti-CTLA-4 Reduces Tumor Growth Rate

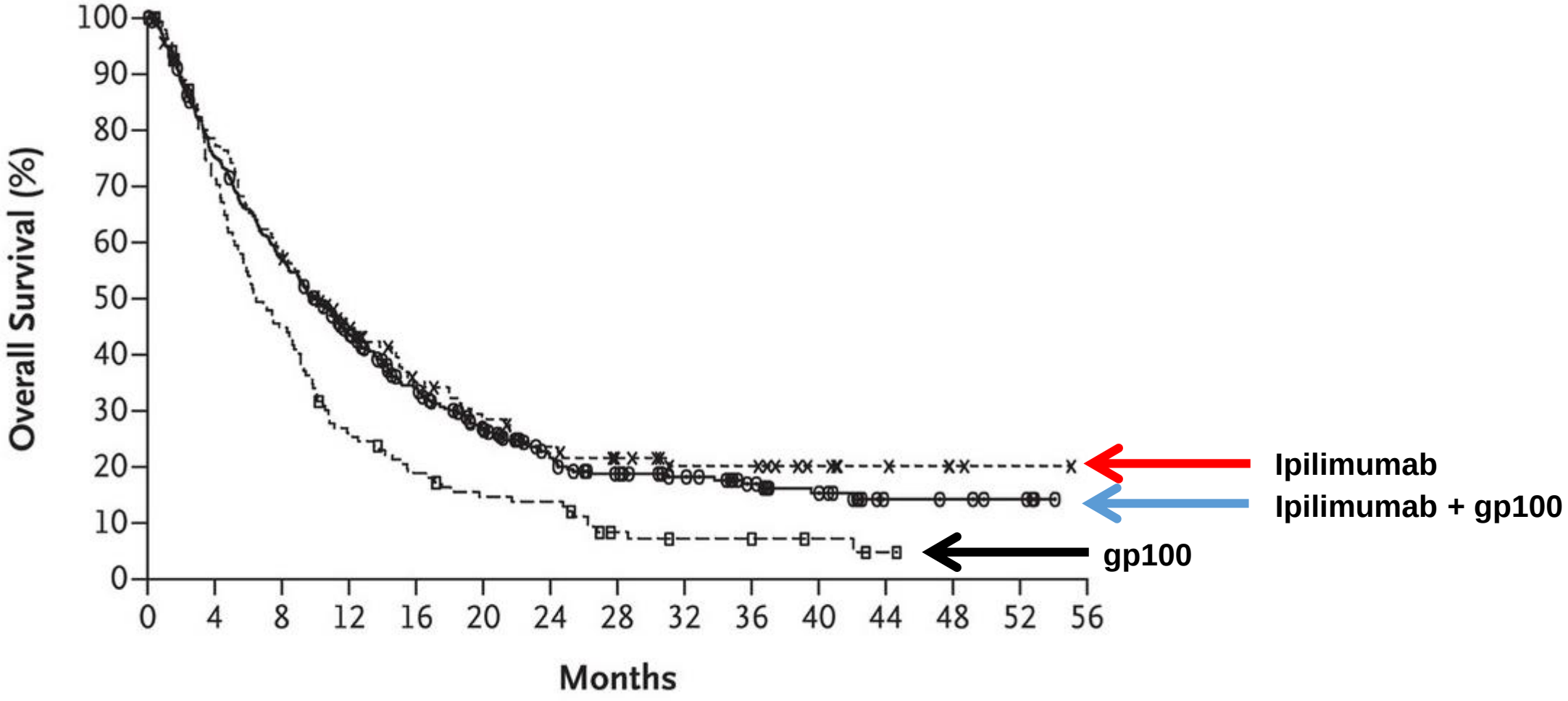


Leach DR et al, *Science*, 1996.

Improving Survival with a New Drug

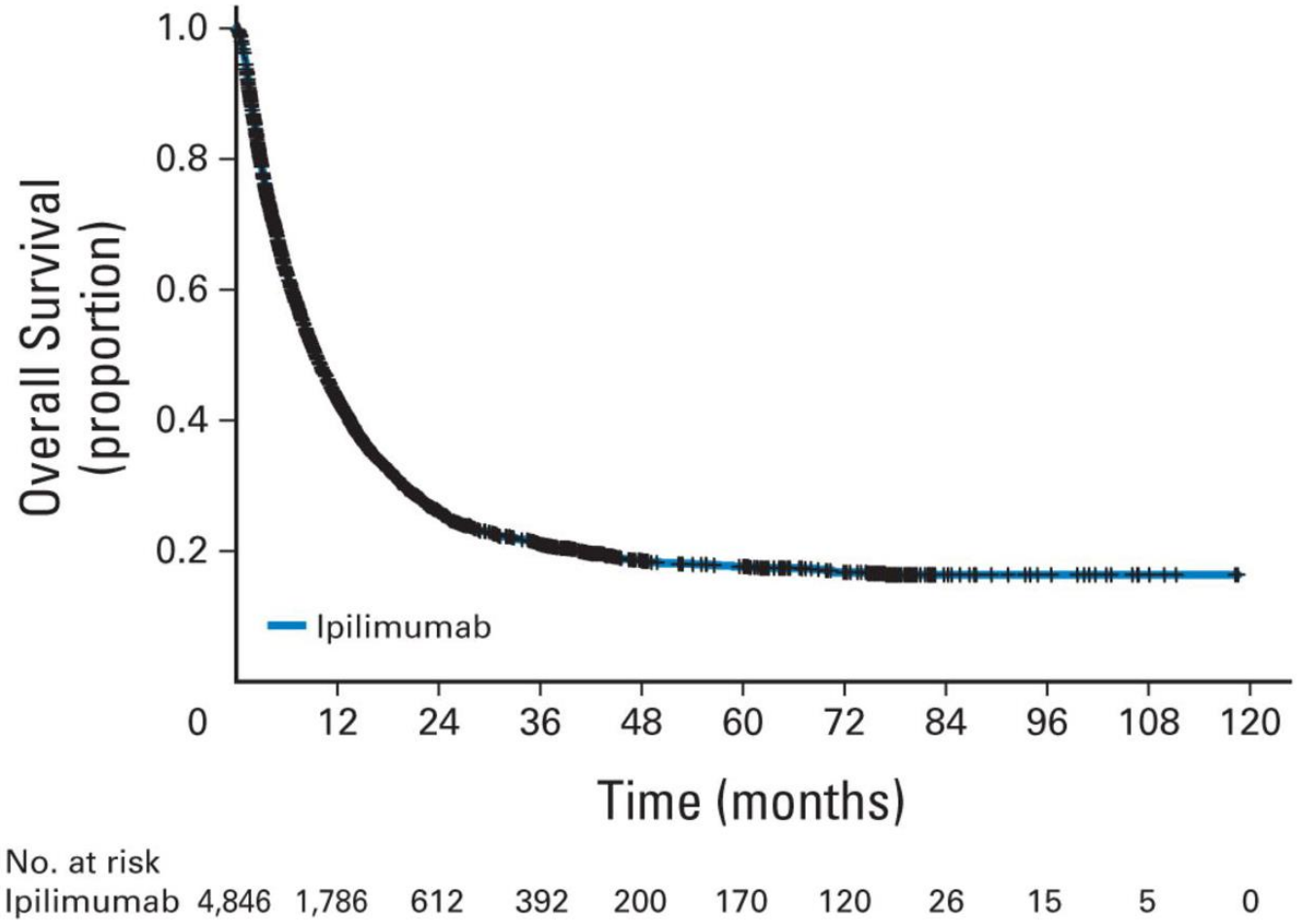


Anti-CTLA-4 (Ipilimumab) Improves Survival in Patients with Metastatic Melanoma



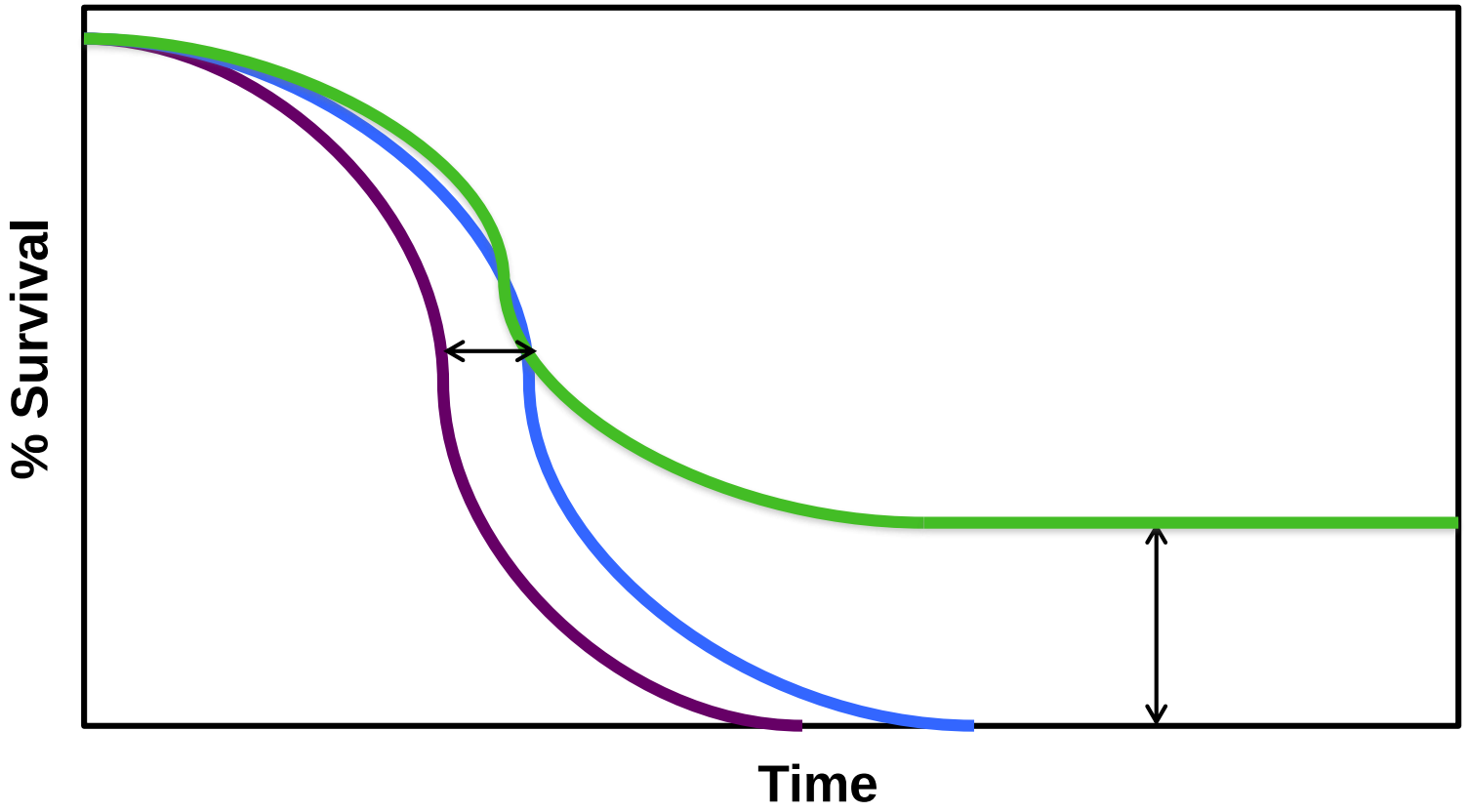
Hodi FS et al, *N Engl J Med,* 2010.

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



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

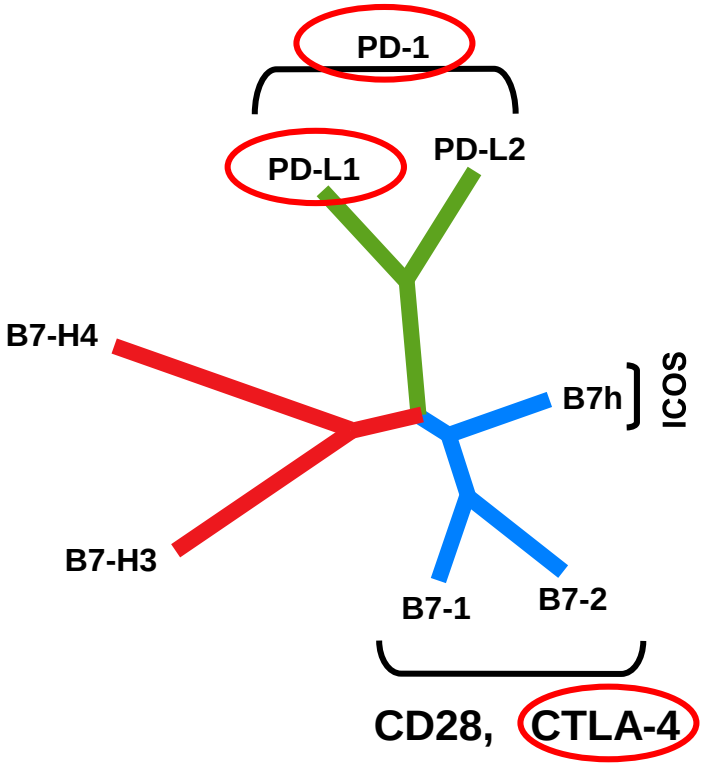
Improving Survival with Immune Checkpoint Therapy



2013: Breakthrough of the Year

December 20, 2013

FDA-Approved Immune Checkpoint Therapies



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

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

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

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

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)

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

Gastric/Gastroesophageal Adenocarcinoma
- Pembrolizumab (2017)

Cervical Carcinoma
- Pembrolizumab (2018)

Cutaneous Squamous Cell Carcinoma
- Cemiplimab (2018)

Breast Carcinoma
- Atezolizumab (2019)

Esophageal Carcinoma
- Pembrolizumab (2019)

Uterine Carcinoma
- Pembrolizumab (2019)

2018: Nobel Prize in Physiology or Medicine

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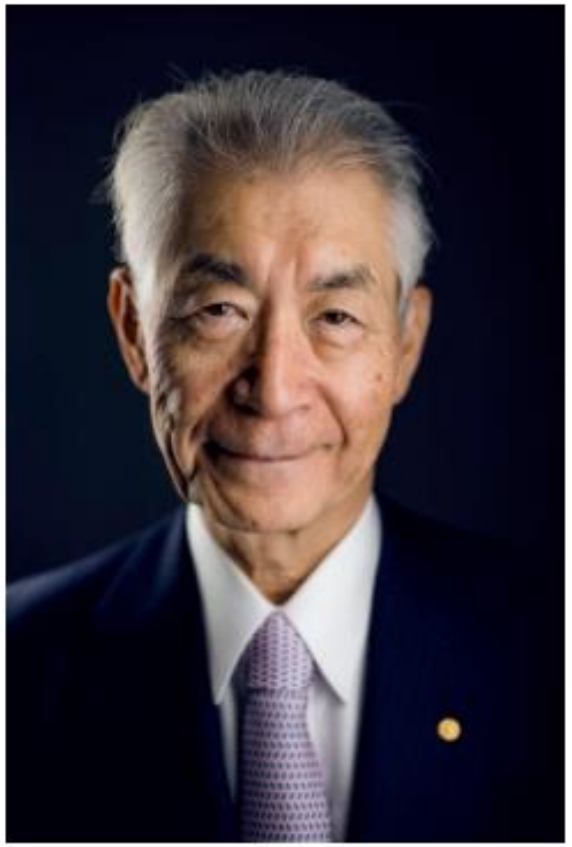
James P. Allison



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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”**
- **Understanding toxicities**

Moving Forward with Immune Checkpoint Therapies

- **Improving patient selection**
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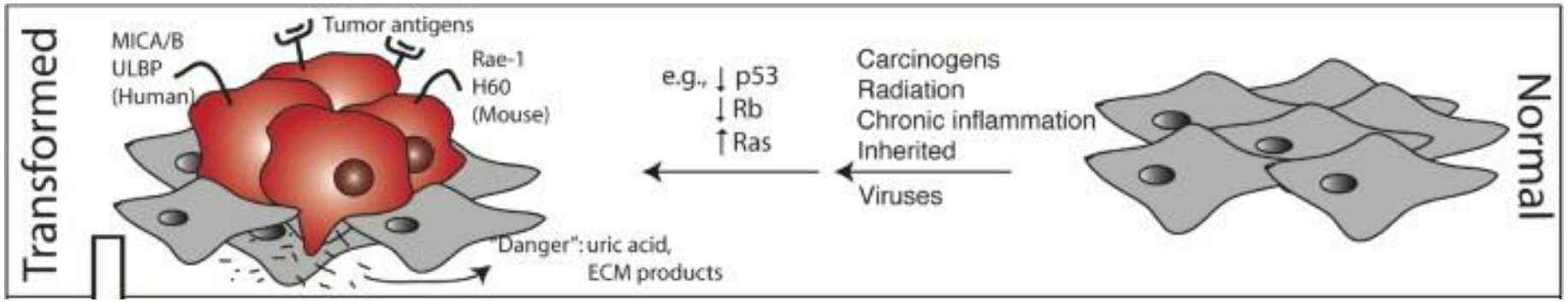
Ways to Improve Patient Selection

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

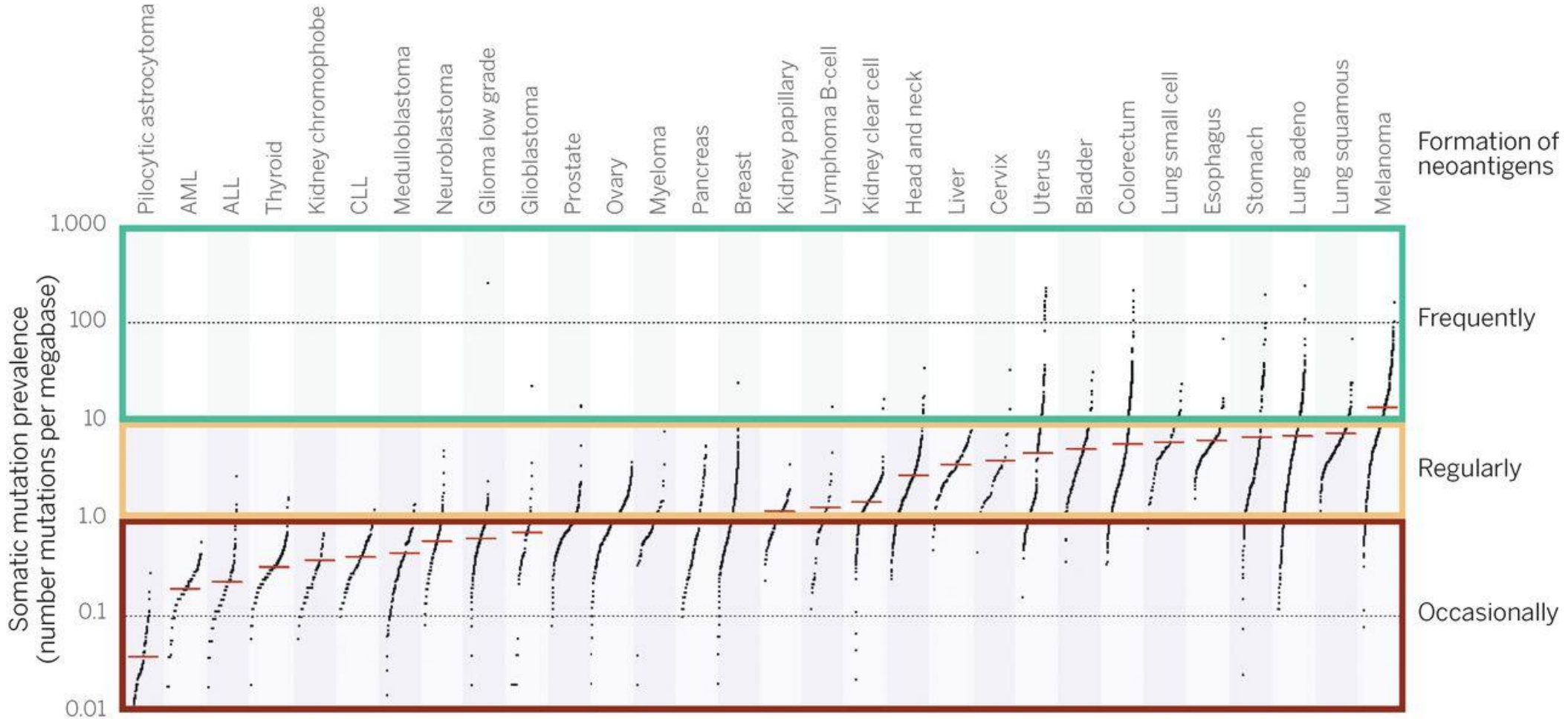
Tumor Neoantigens



The Immunobiology of Cancer Immunosurveillance and Immunoediting

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

Tumor Mutational Load and Frequency of Neoantigens



Schumacher TN and Schreiber RD, *Science*, 2015.

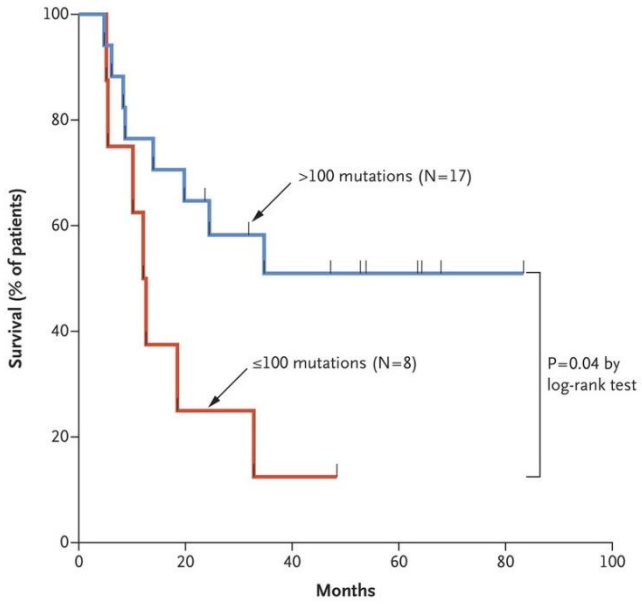
Neoantigens and Mutational Load Linked to Efficacy of Immune Checkpoint Therapies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

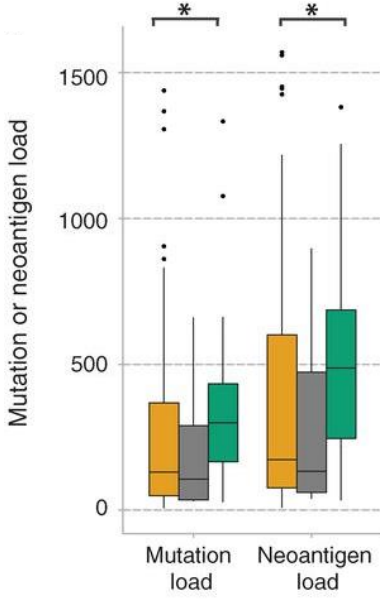
Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D., Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D., Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D., Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A., Kasthuri 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]†



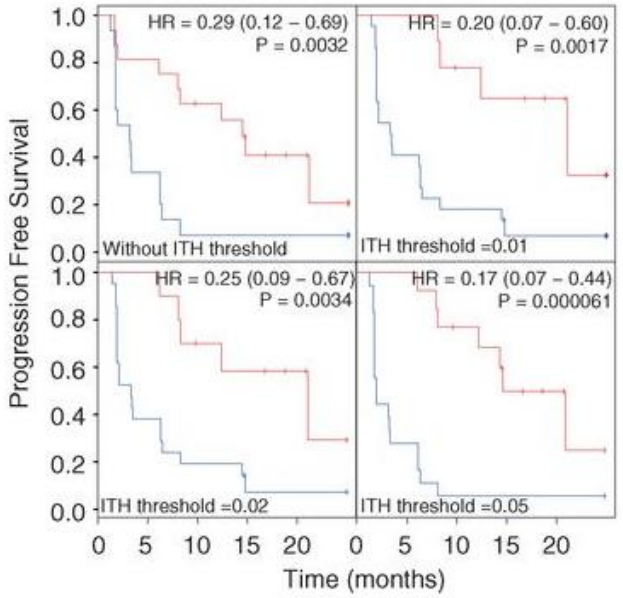
Science

REPORTS

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

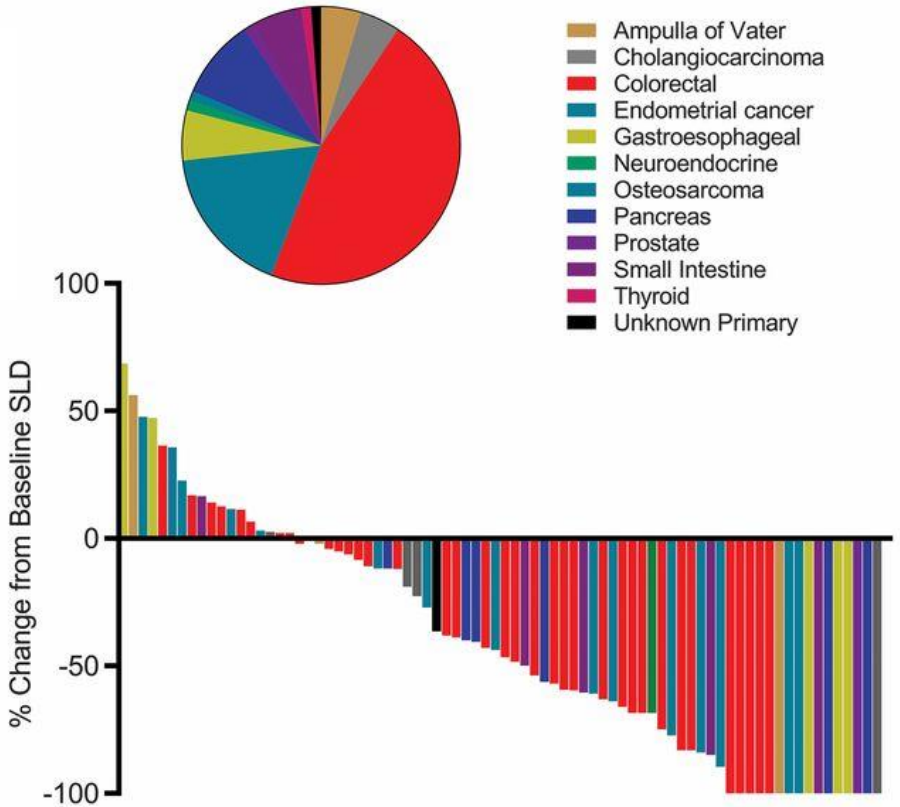
Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade

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]†



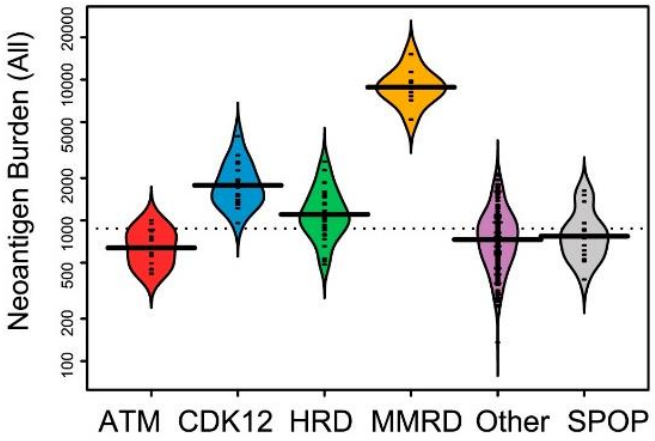
Genomic Defects that Increase Neoantigen Burden

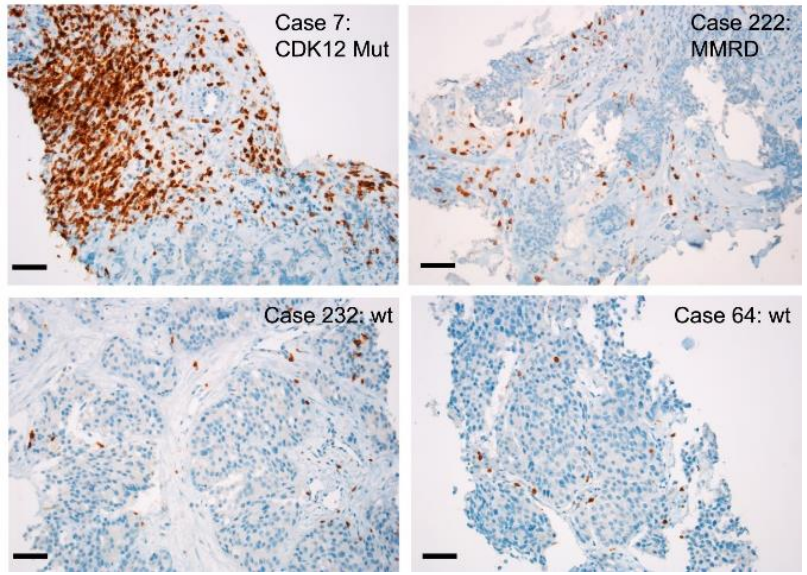
Mismatch Repair (MMR) Defects



Le DT et al. *Science,* 2017.

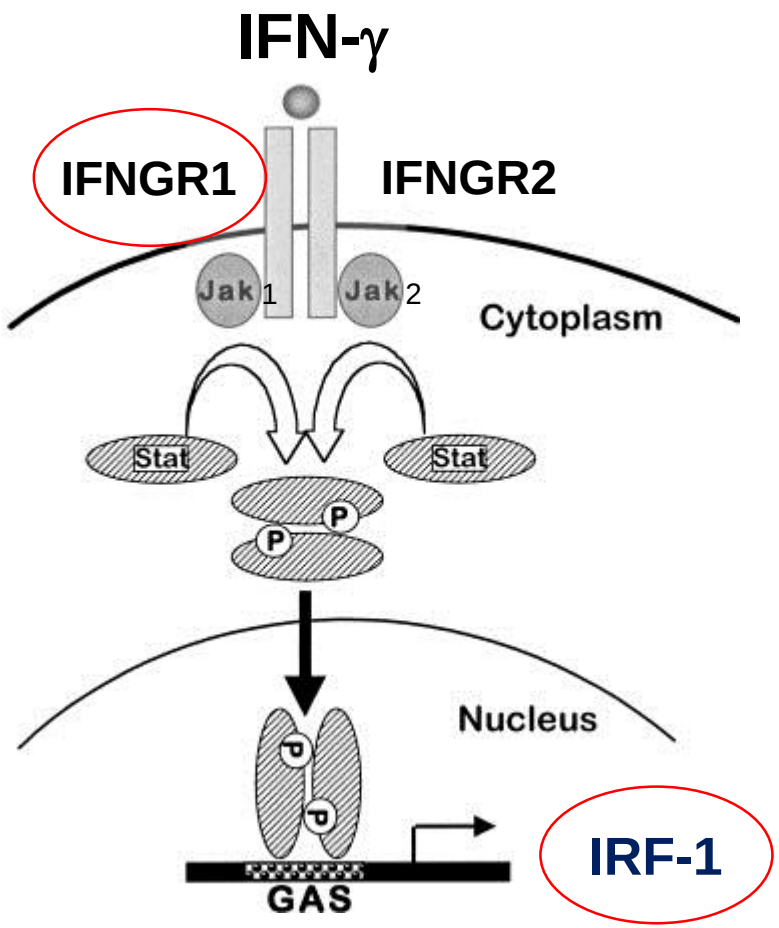
CDK12 Mutations



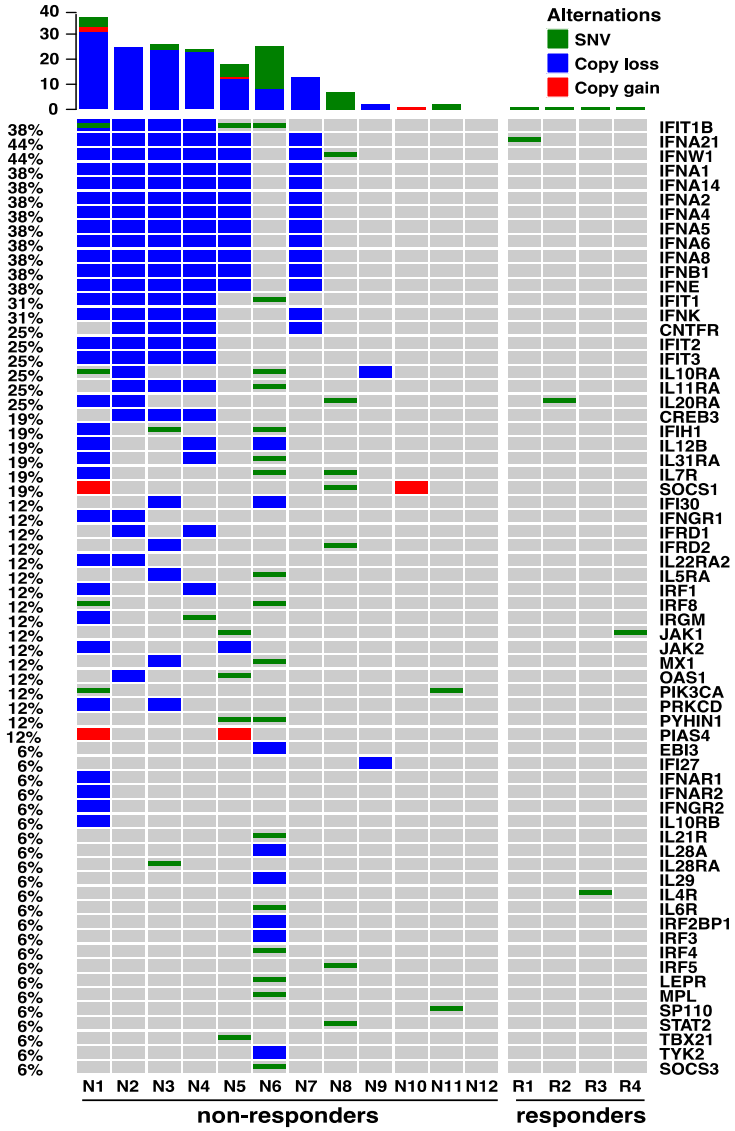


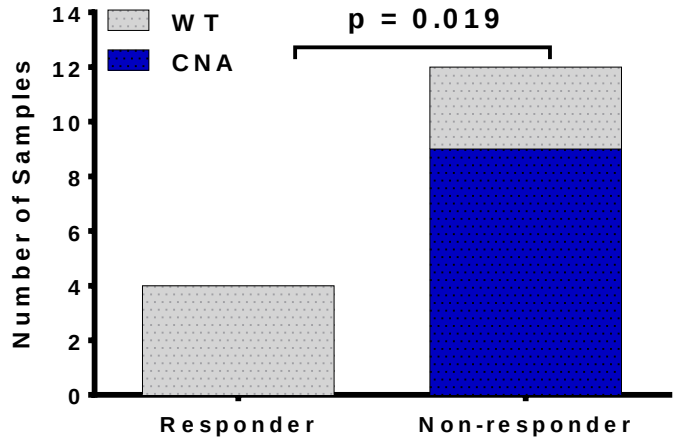
Wu YM et al. *Cell,* 2018.

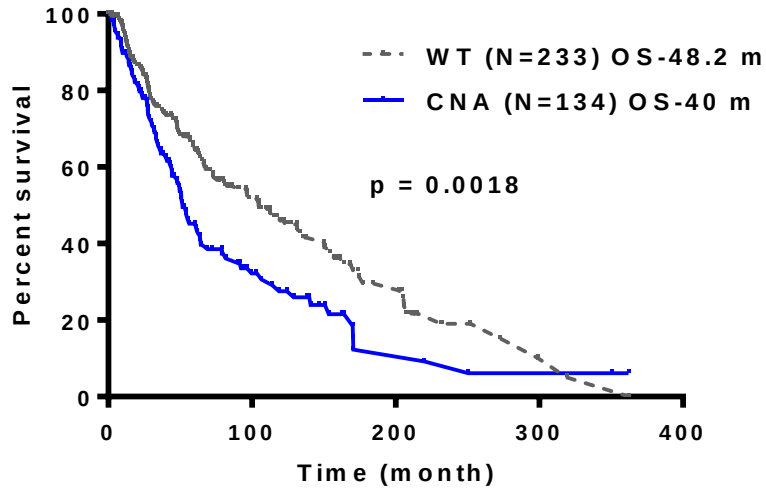
Defects in the IFN-γ Signaling Pathway Promote Resistance to Immune Checkpoint Therapies



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





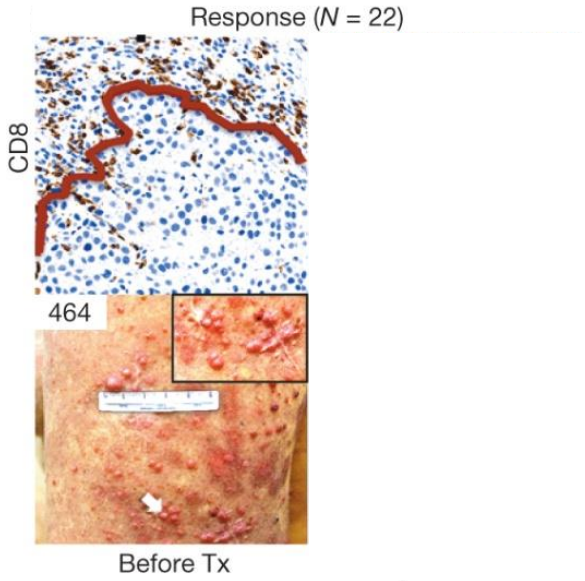


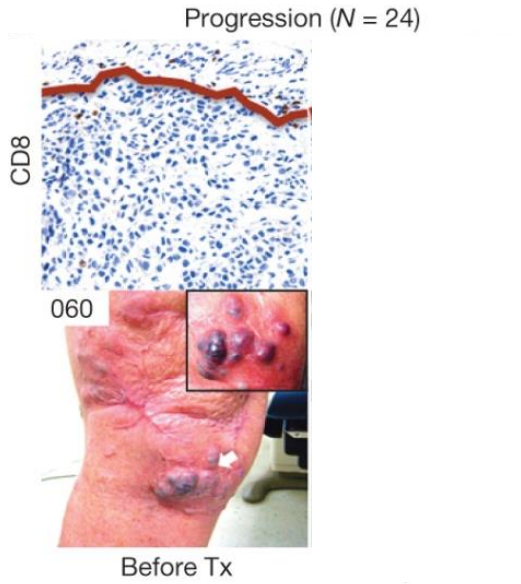
Gao JJ et al. *Cell*, 2016.

Moving Forward with Immune Checkpoint Therapies

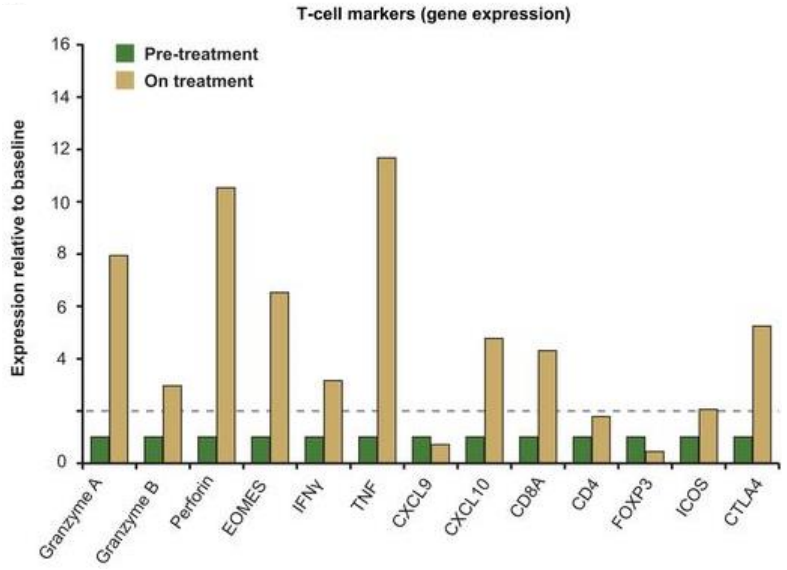
- Improving patient selection
- **Turning “cold” tumors “hot”**
- Understanding toxicities

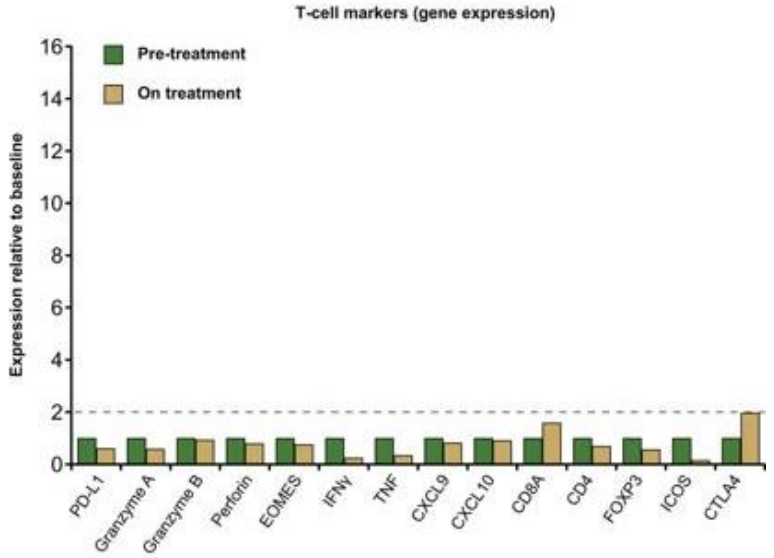
More CD8 T Cells Makes Anti-PD-1/PD-L1 Work Better





Tumeh PC et al. *Nature. 2*014.

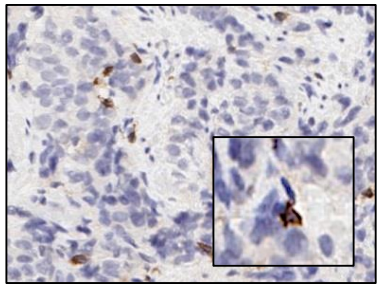




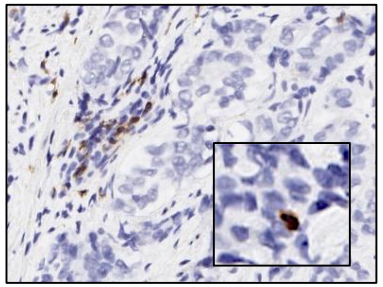
Herbst RS et al. *Nature. 2*014.

Few T Cells Within the Prostate Tumor Microenvironment

Primary

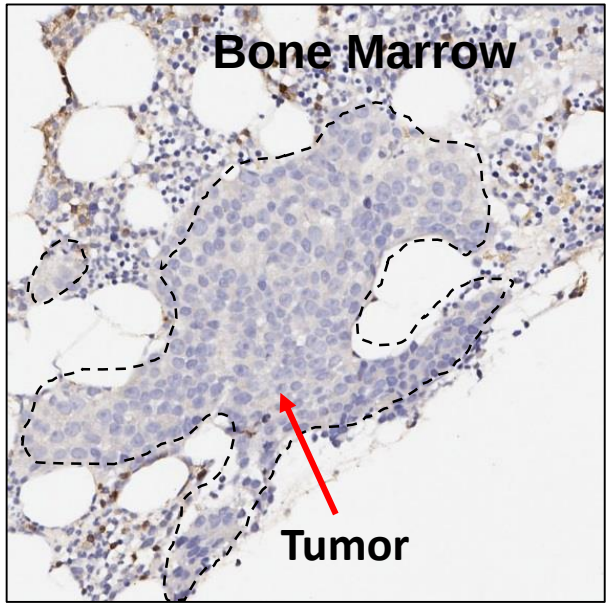


CD4

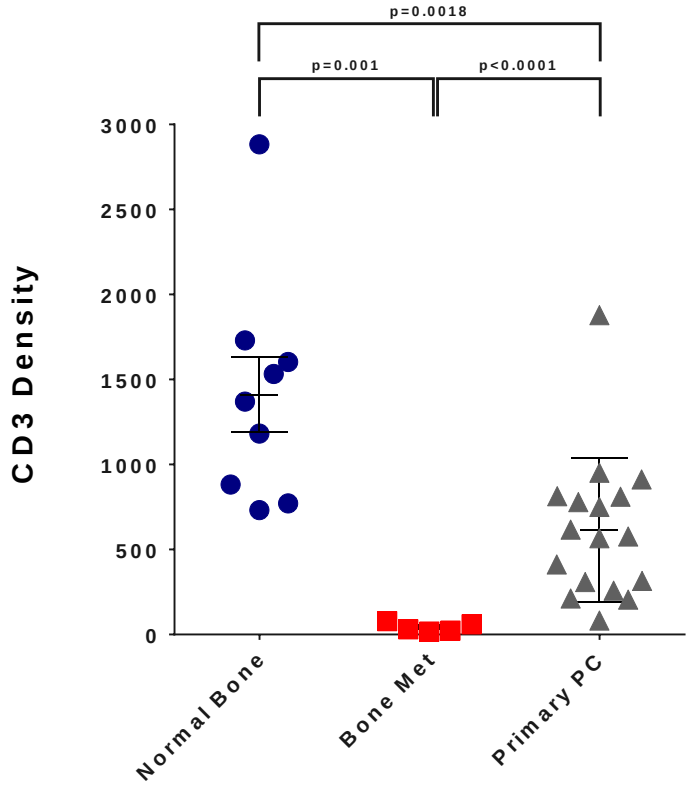


CD8

Bone Metastasis



CD3



Sumit K. Subudhi, Jorge Blando, Padmanee Sharma, James P. Allison

Original Article

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

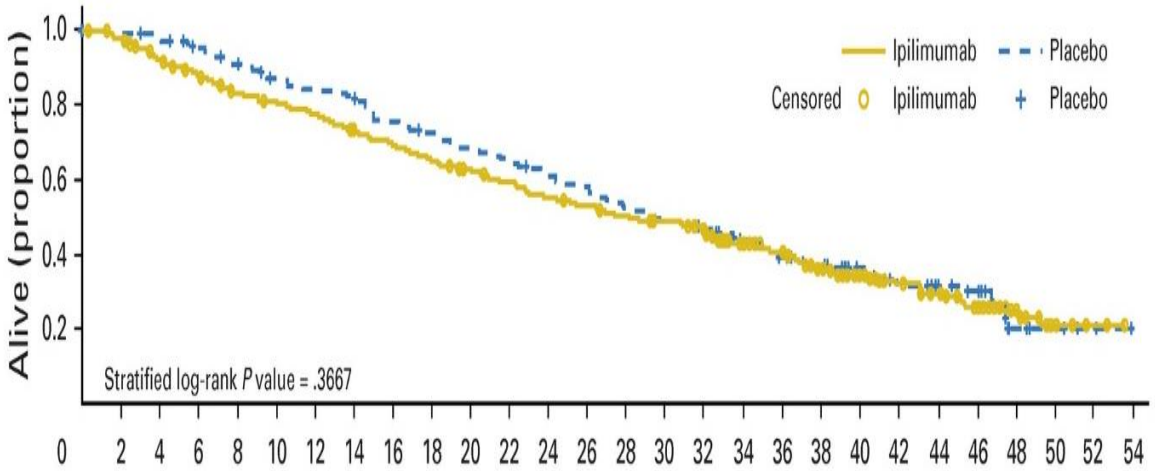
Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

N Engl J Med
Volume 366(26):2443-2454
June 28, 2012

0/17 prostate cancer patients with objective responses

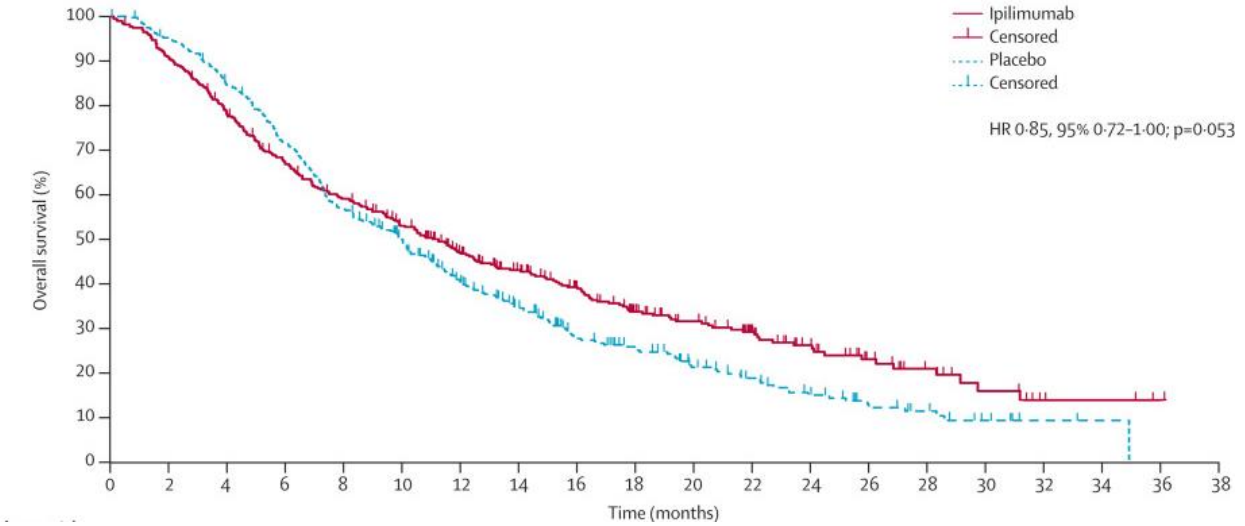
Ipilimumab Does Not Improve Overall Survival Metastatic Prostate Cancer

Pre-Chemotherapy



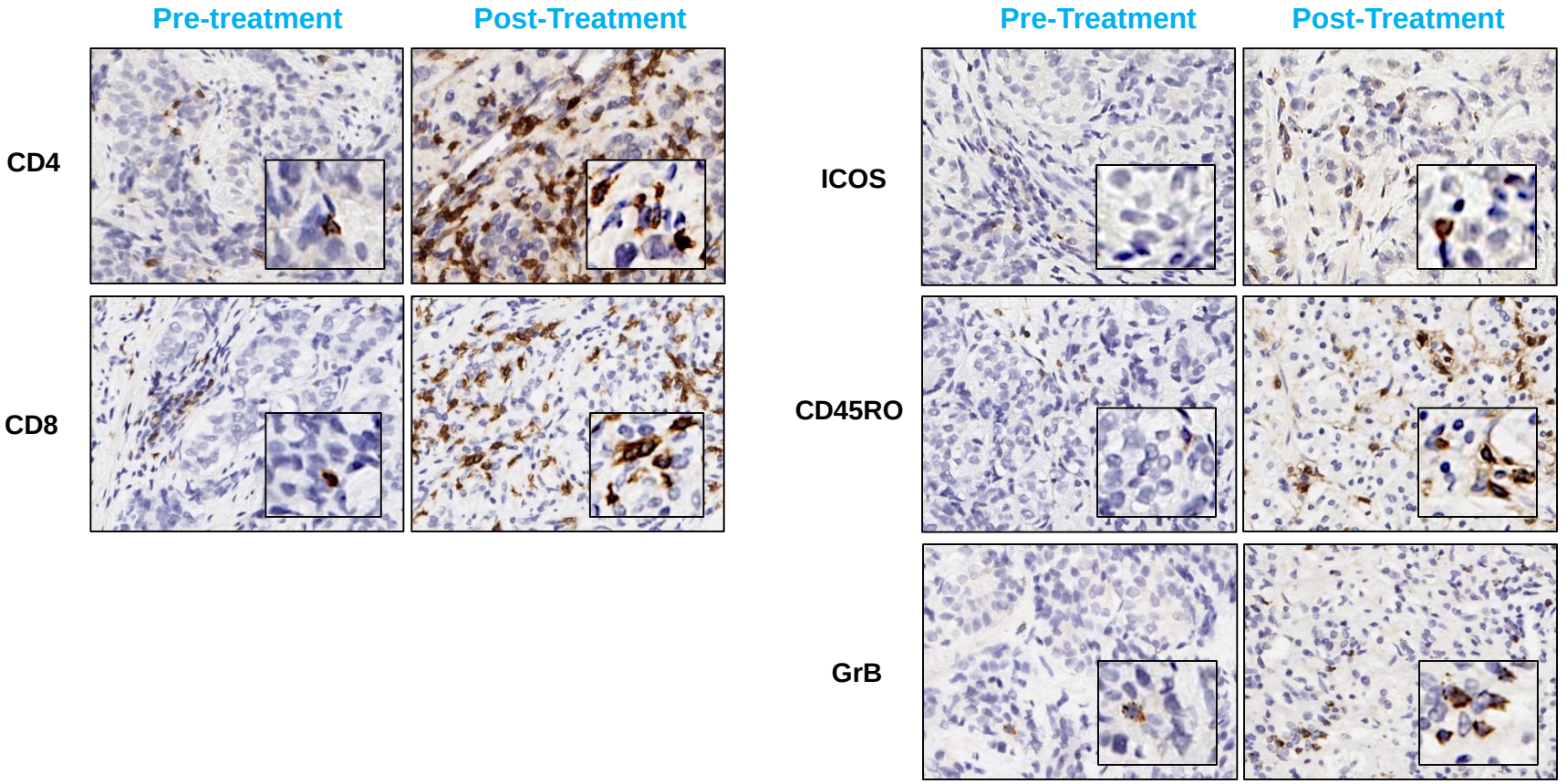
Beer, TM et al. *J Clin Oncol,* 2016.

Post-Chemotherapy



Kwon, ED et al. *Lancet Oncol.* 2014.

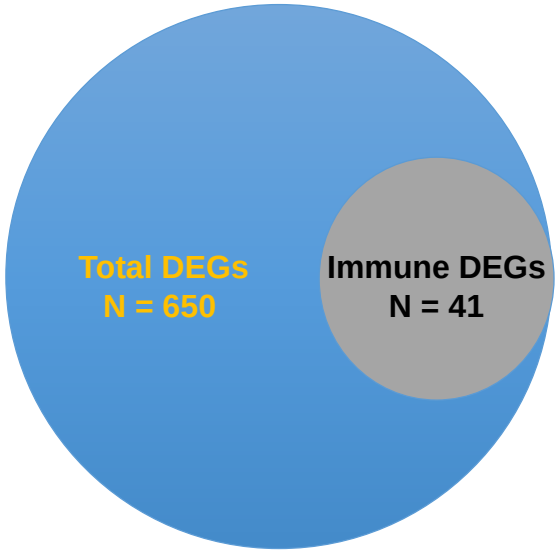
Ipilimumab Increases Immune Infiltration Within the Primary Prostate Tumor Microenvironment

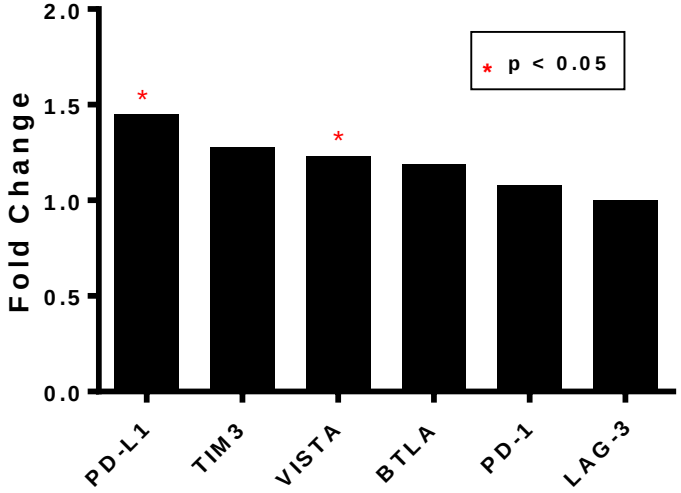


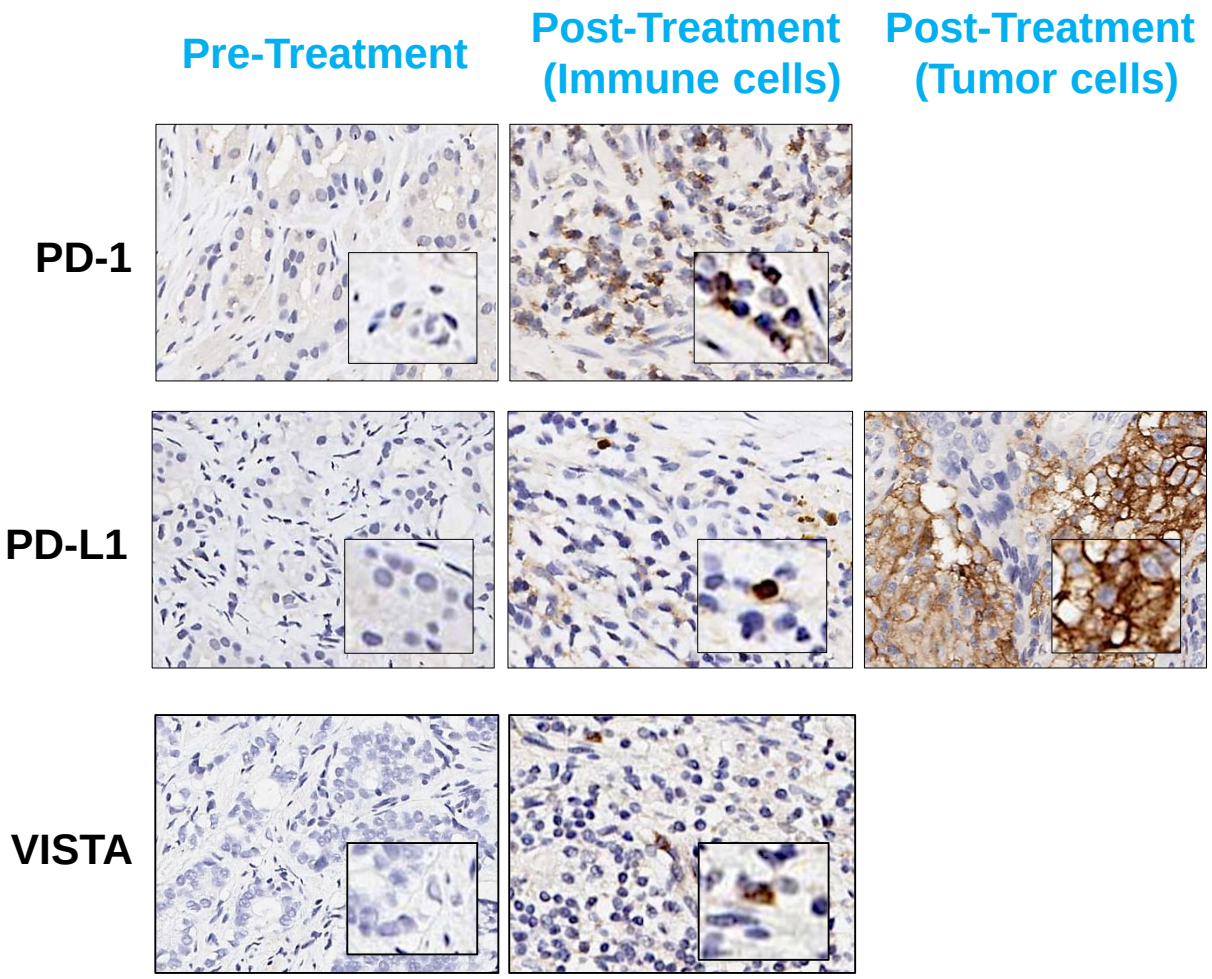
Gao JJ et al. *Nature Med*, 2017.

Increased Tumor-Infiltrating T Cells are Insufficient Due to Adaptive Resistance

Differentially-Expressed Genes (DEGs)



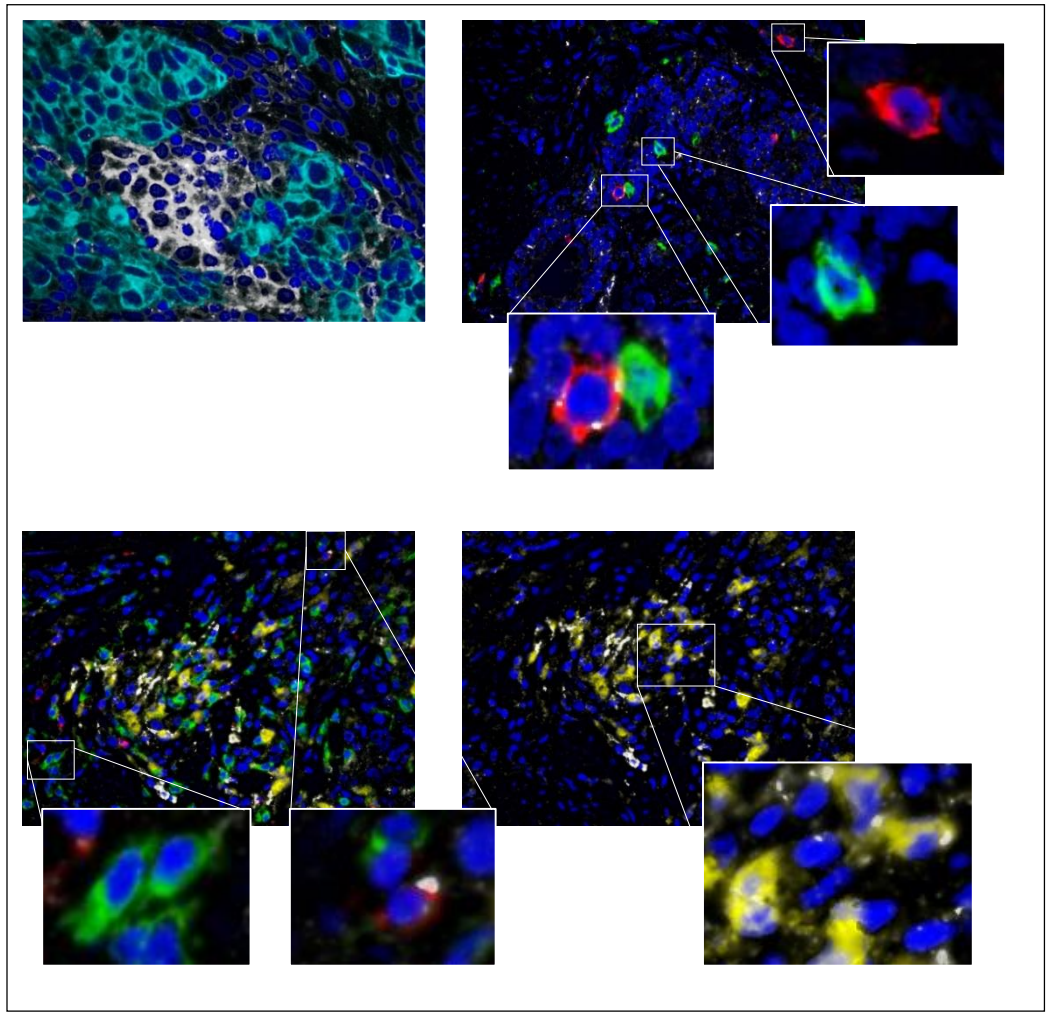


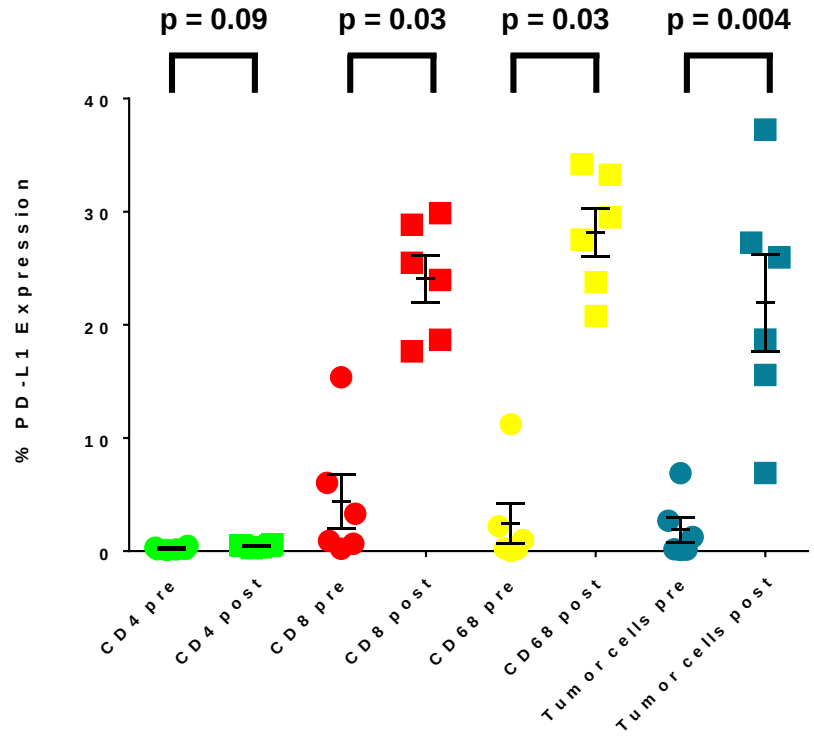


Gao JJ et al. *Nature Med*, 2017.

Ipilimumab Increases PD-L1 Expression on on CD8$^+$, CD68$^+$, and Tumor Cells

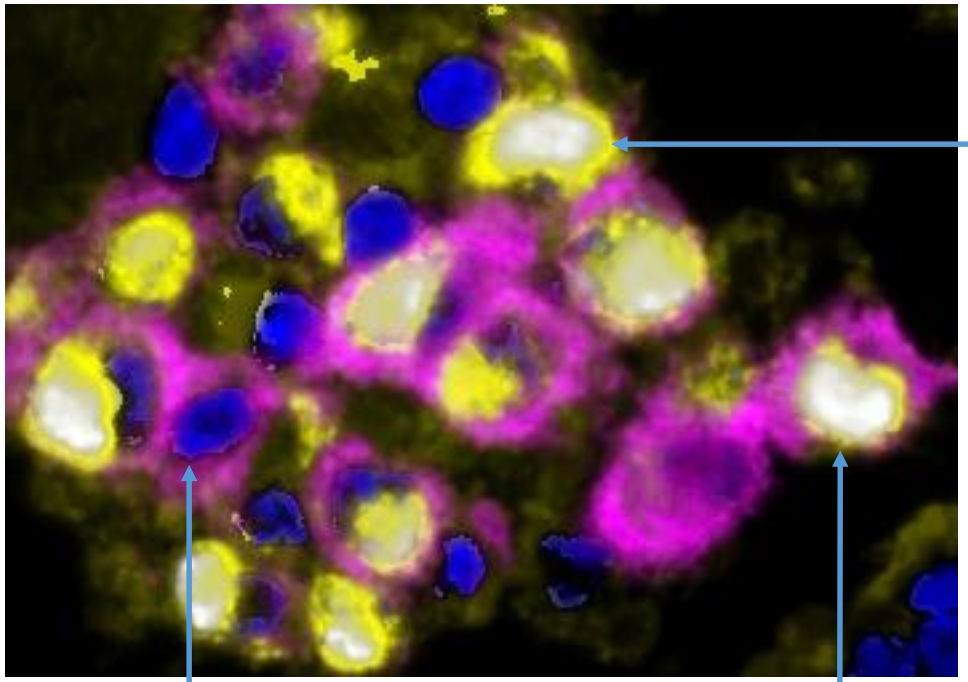
Nucleus
Tumor/Epithelial cells
PD-L1
CD4
CD8
CD68





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

VISTA and PD-L1 Expression on Macrophages

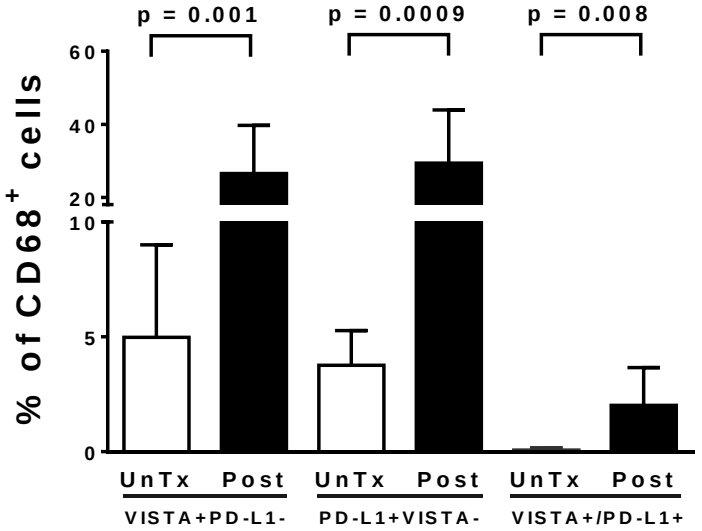


$CD68^+VISTA^+$ cells

CD68
VISTA
PD-L1
Nucleus

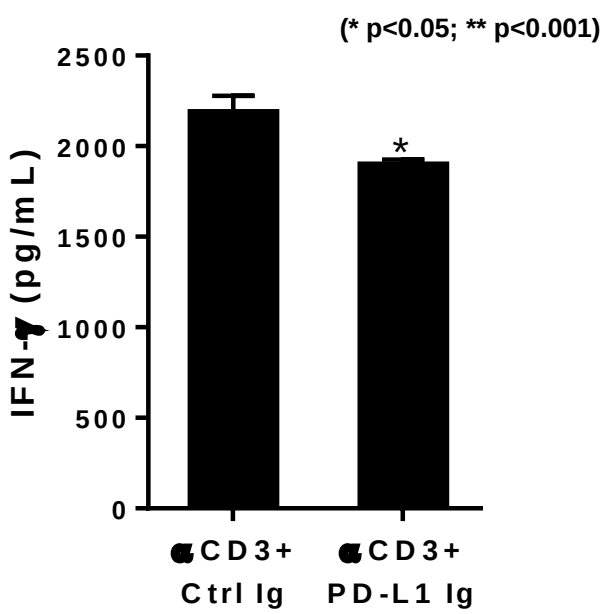
$CD68^+PD\text{-}L1^+$ cells

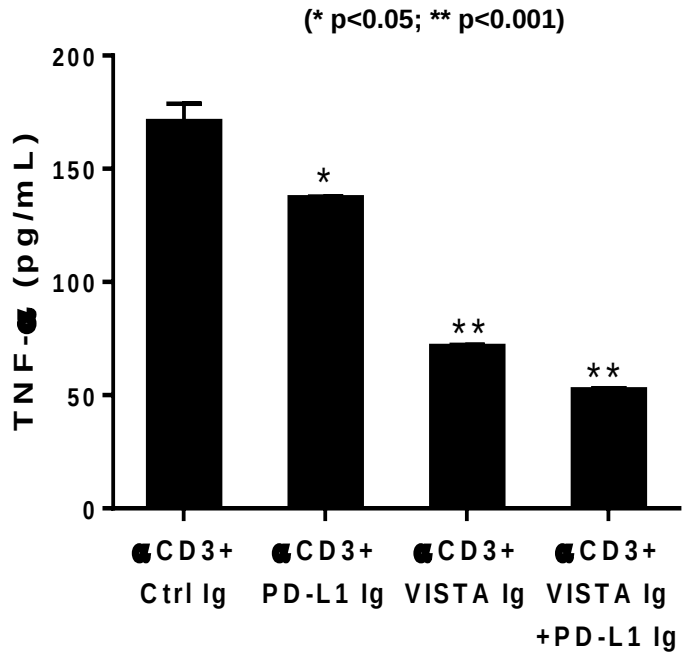
$CD68^+PD\text{-}L1^+VISTA^+$ cells



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

PD-L1 and VISTA Inhibit T Cell Cytokine Production

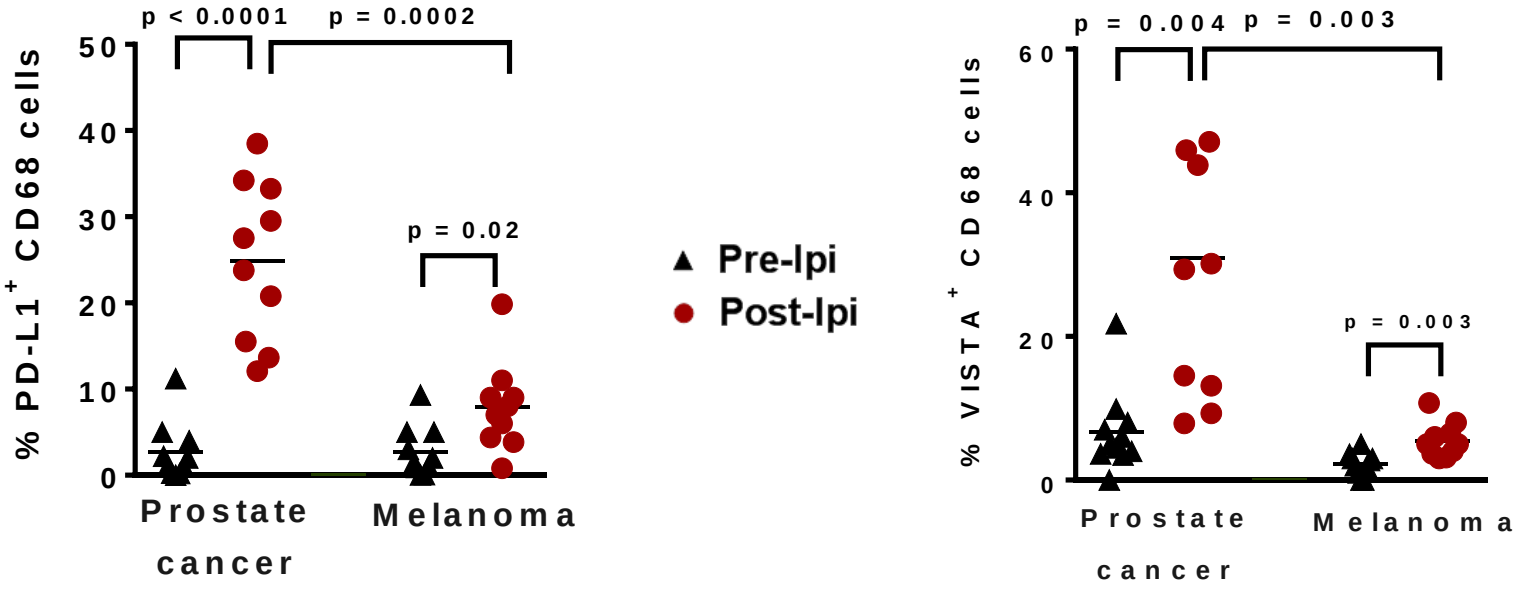




Gao JJ et al. *Nature Med*, 2017.

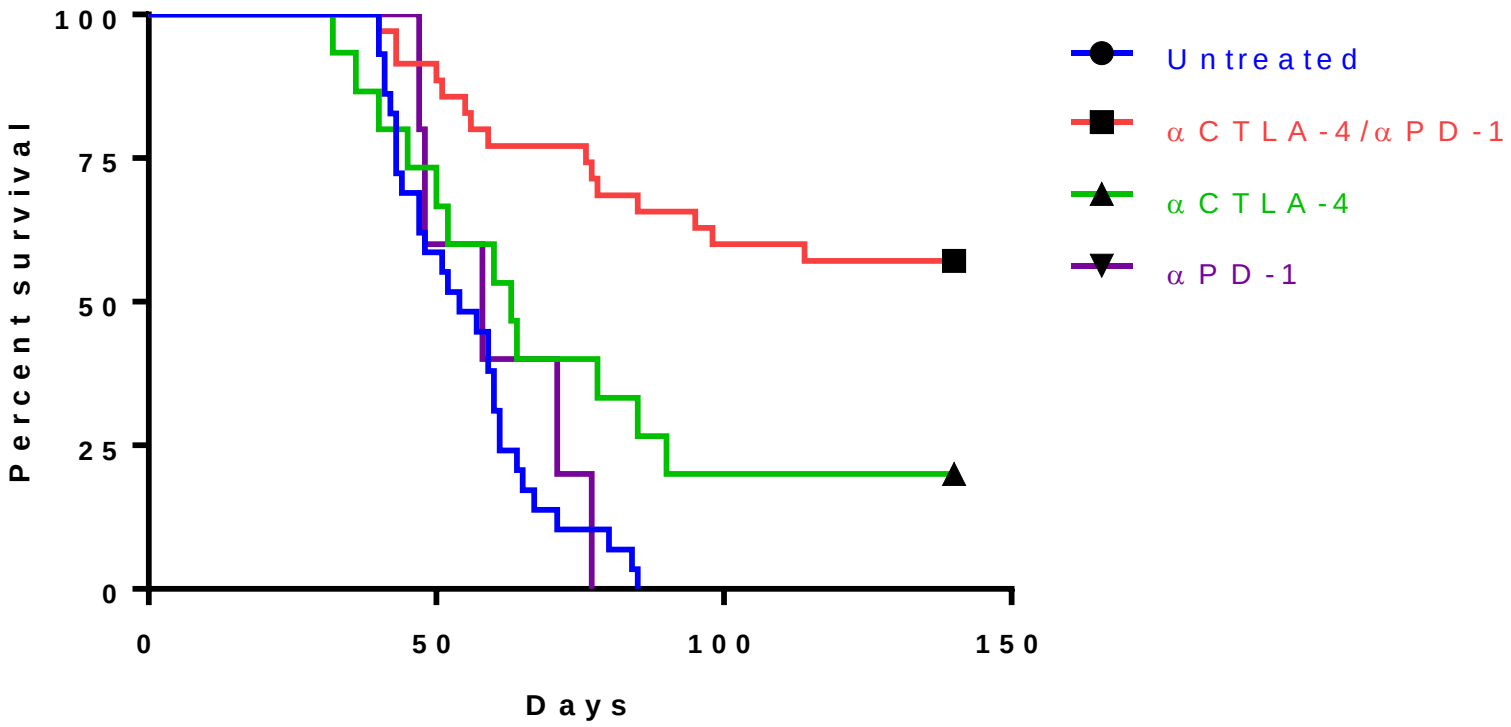
What's Different Between Prostate Cancer and Melanoma Following Treatment with Ipilimumab?

Immunosuppressive Macrophages



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

Initial Results From a Phase 2 Study of Nivolumab Plus Ipilimumab for the Treatment of Metastatic Castration-Resistant Prostate Cancer (CheckMate 650)

Padmanee Sharma,[1] Russell Pachynski,[2] Vivek Narayan,[3] Aude Fléchon,[4] Gwenaelle Gravis,[5] Matthew D. Galsky,[6] Hakim Mahammedi,[7] Akash Patnaik,[8] Sumit K. Subudhi,[1] Marika Ciprotti,[9] Burcin Simsek,[10] Abdel Saci,[10] Sarah Hu,[10] G. Celine Han,[10] Karim Fizazi[11]

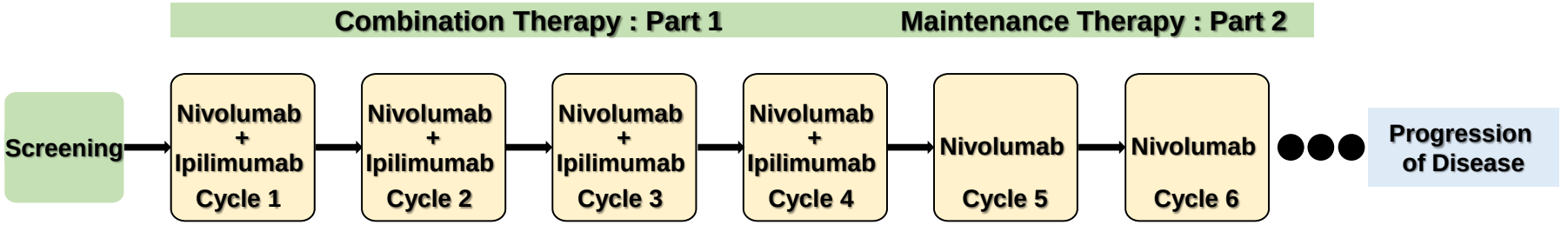
[1]MD Anderson Cancer Center, University of Texas, Houston, TX, USA; [2]Washington University School of Medicine, St. Louis, MO, USA; [3]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [4]Centre Léon Bérard, Lyon, France; [5]Institut Paoli-Calmettes, Marseille, France; [6]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [7]Centre Jean Perrin, Clermont-Ferrand, France; [8]The University of Chicago Medicine, Chicago, IL, USA; [9]Bristol-Myers Squibb, Uxbridge, UK; [10]Bristol-Myers Squibb, Princeton, NJ, USA; [11]Gustave Roussy, University of Paris Sud, Villejuif, France

PRESENTED AT: **2019 Genitourinary Cancers Symposium | #GU19**

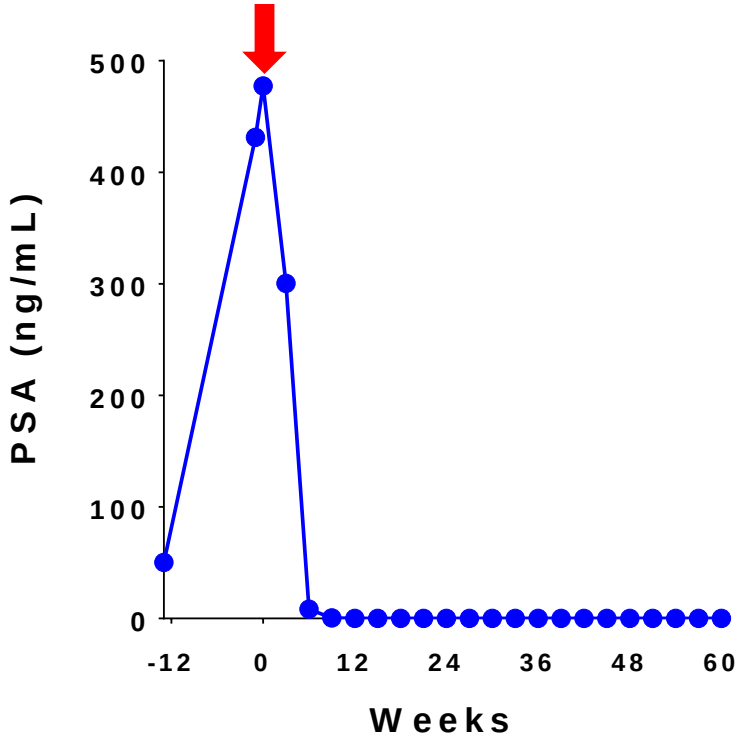
Presented by: Padmanee Sharma

Overcoming Adaptive Resistance: Anti-PD-1 + Anti-CTLA-4

Nivolumab + Ipilimumab in mCRPC (NCT02985957)



PI: Sharma; Co-PI: Subudhi



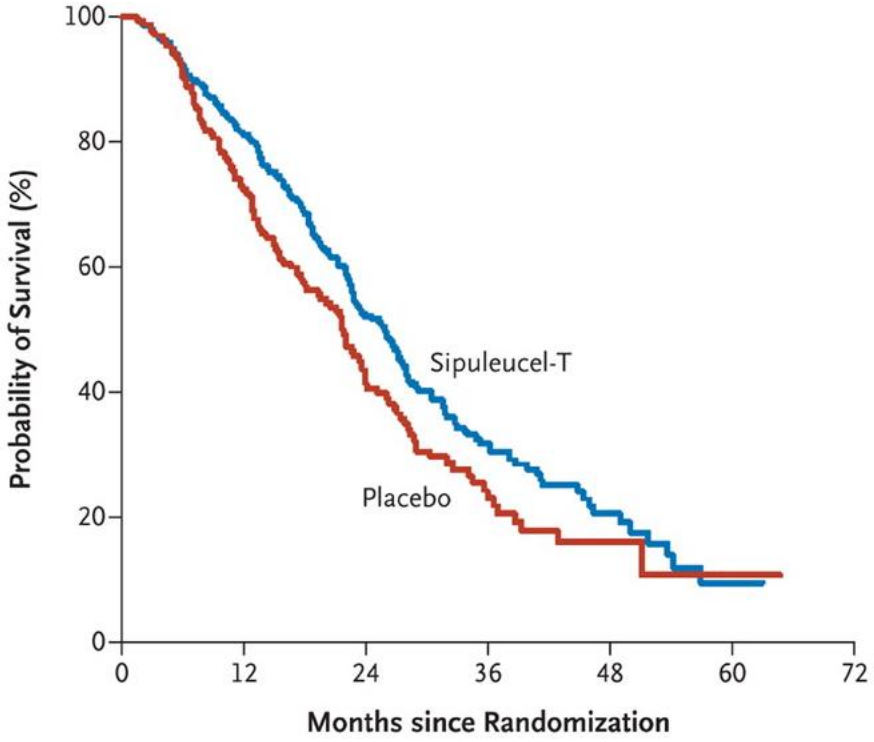
Tumor Mutational Burden (TMB) is Associated With Efficacy

Objective response, n (%)	Cohort 1		Cohort 2	
TMB	Low TMB (n = 11)	High TMB (n = 12)	Low TMB (n = 8)	High TMB (n = 6)
Complete or partial response	1 (9.1)[b]	6 (50.0)	0 (0)	3 (50.0)
Stable disease	5 (45.5)	5 (41.7)	1 (12.5)	2 (33.3)
Progressive disease/undetermined	5 (45.5)	1 (8.3)	7 (87.5)	1 (16.7)

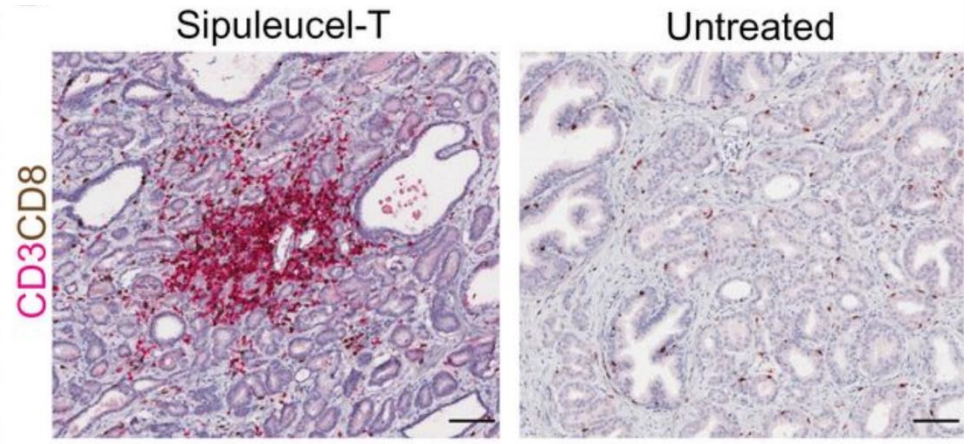
[a]TMB was derived from whole exome sequencing of tumor samples with whole blood DNA from the same patient as control. TMB was based on the total number of somatic missense mutations and high and low TMB in this analysis represents above and below the median in the study population (74.5 mutations per patient).
[b]This patient had an unconfirmed PR.

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

Sipuleucel-T (DC Vaccine)

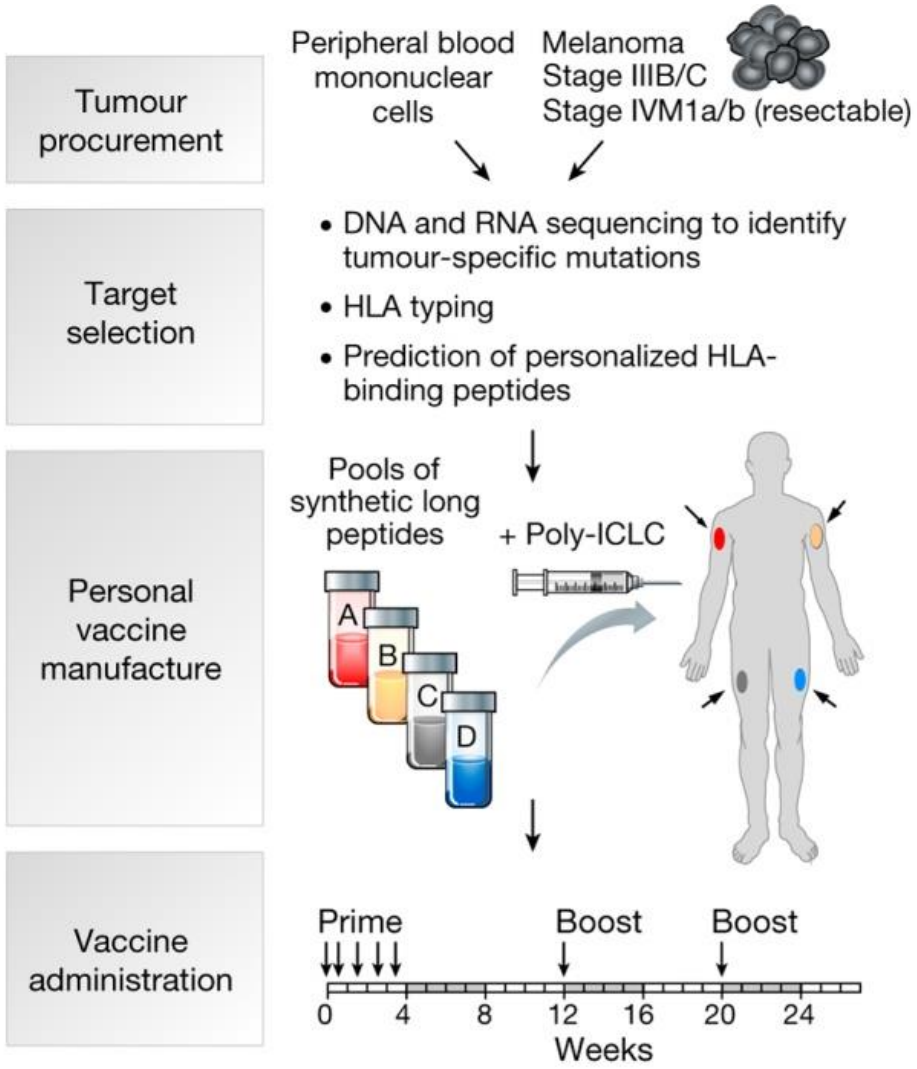


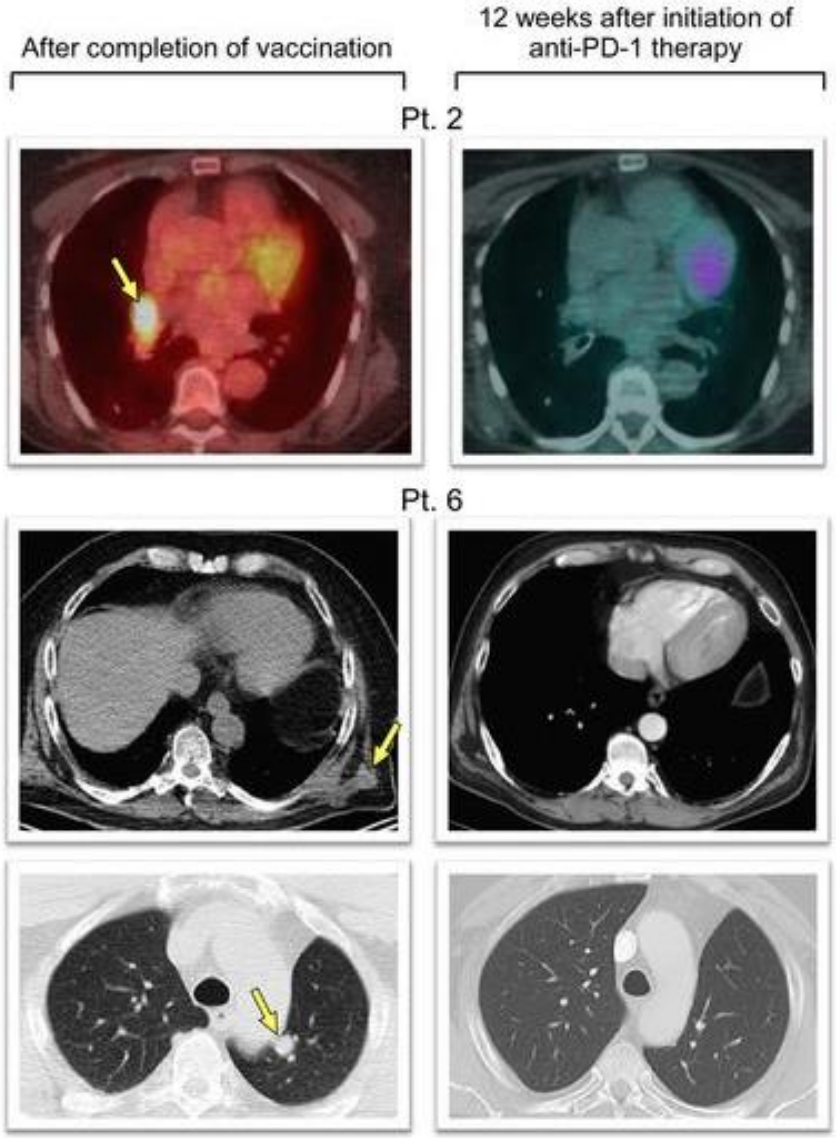
Kantoff, PW et al. *N Engl J Med* 2010.



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

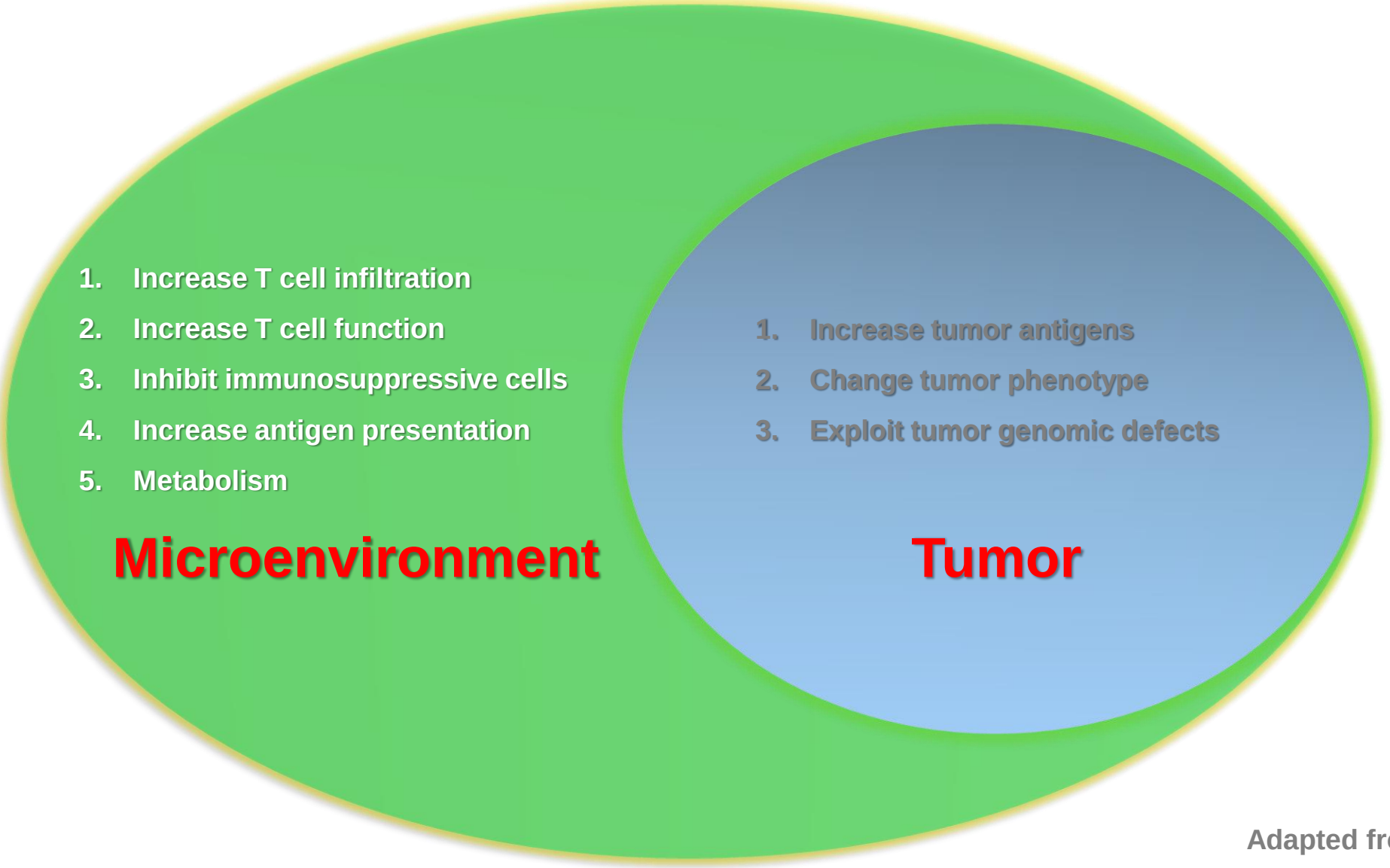
Personal Multi-Peptide Neoantigen Vaccine for Patients with High-Risk Melanoma





Ott PA et al. *Nature* 2017.

Making Immune Checkpoint Therapies More Effective



Targeting Strategies

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

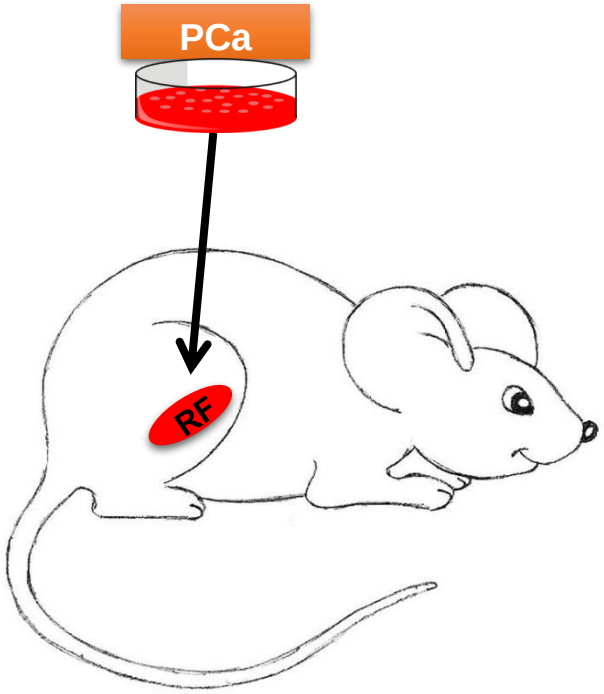
Adapted from Jianjun Gao

Prostate Cancer Bone Metastases are Associated with Poorer Survival

	Lymph Node Only	Bone Only	Bone + Lymph Node
% Men	6.4	42.9	29.8
Overall Survival (Months)	31.6	21.3	

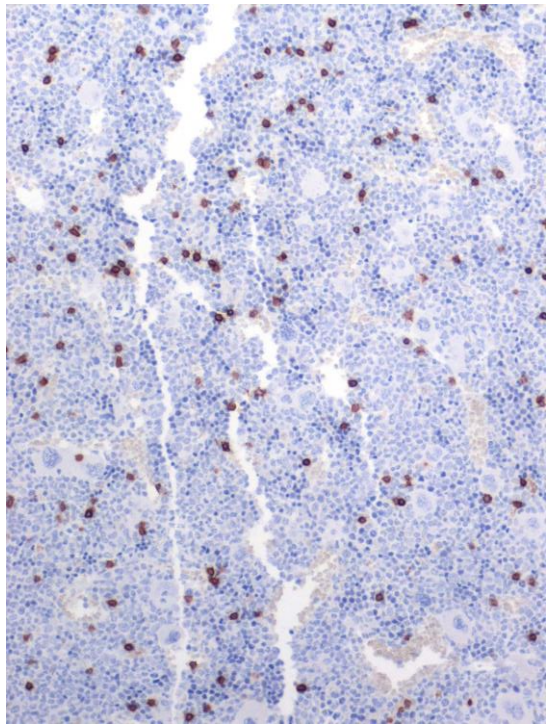
Halabi, S et al. *J Clin Oncol,* 2016.

CD3 T Cell Exclusion from the Mouse Bone Tumor Microenvironment

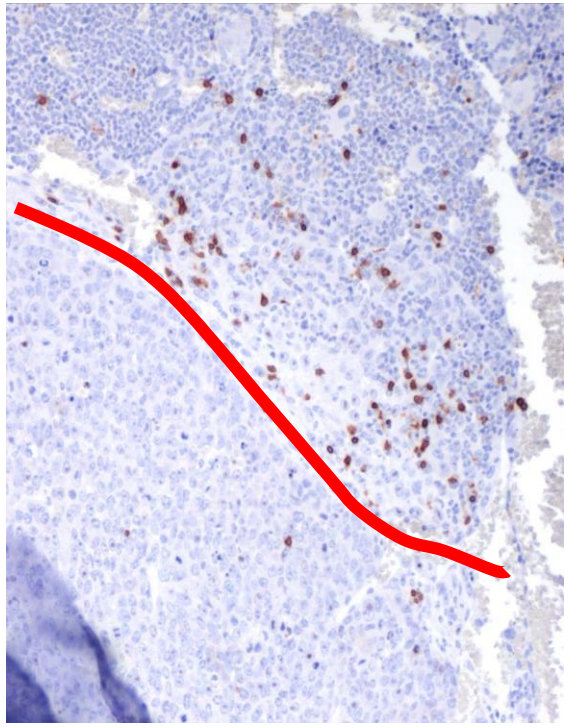


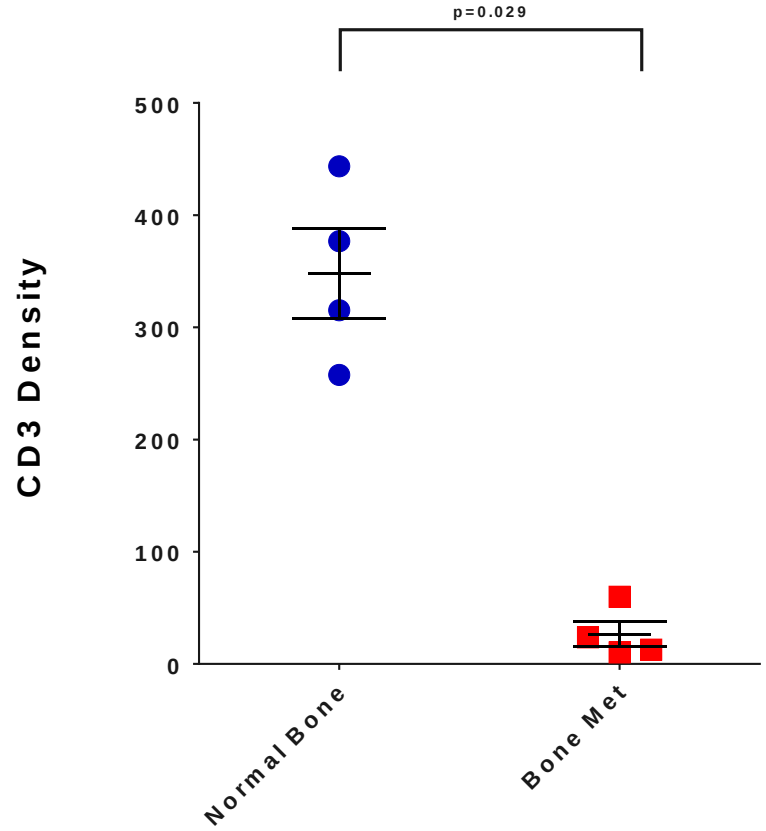
Immunocompetent Mouse

Left femur
No tumor



Right femur
Tumor

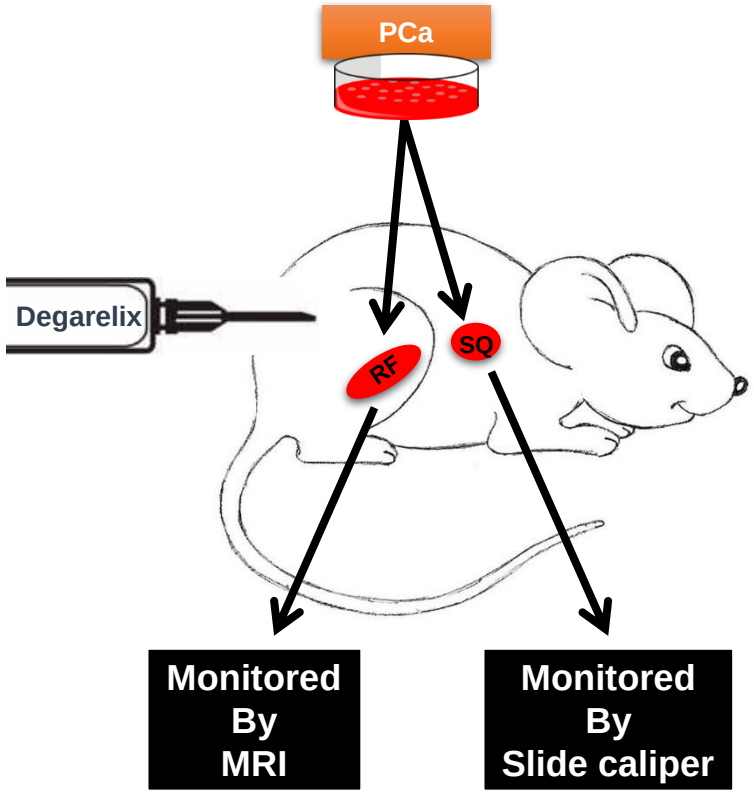




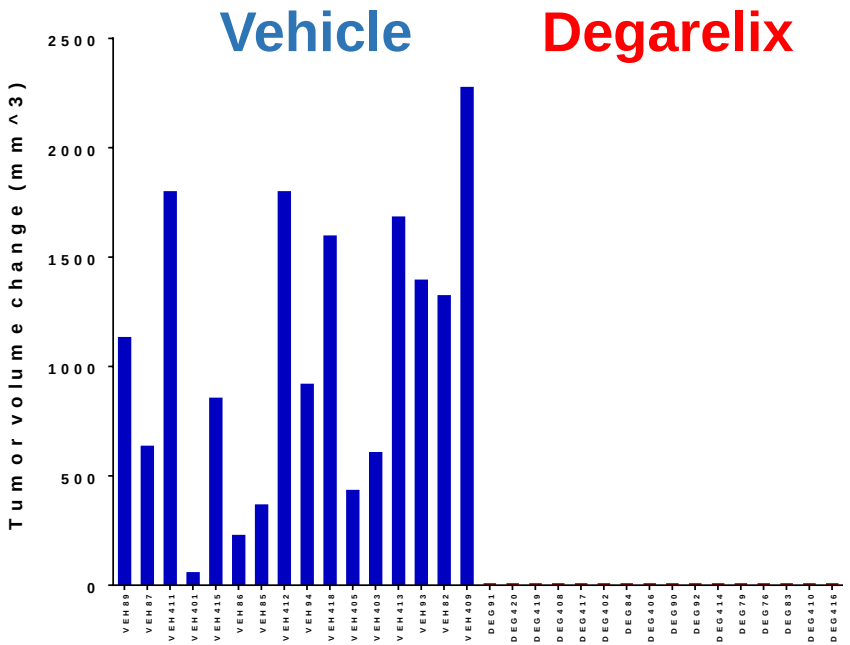
Subudhi SK, manuscript in preparation

Castration-Resistance Develops Faster in the Bone

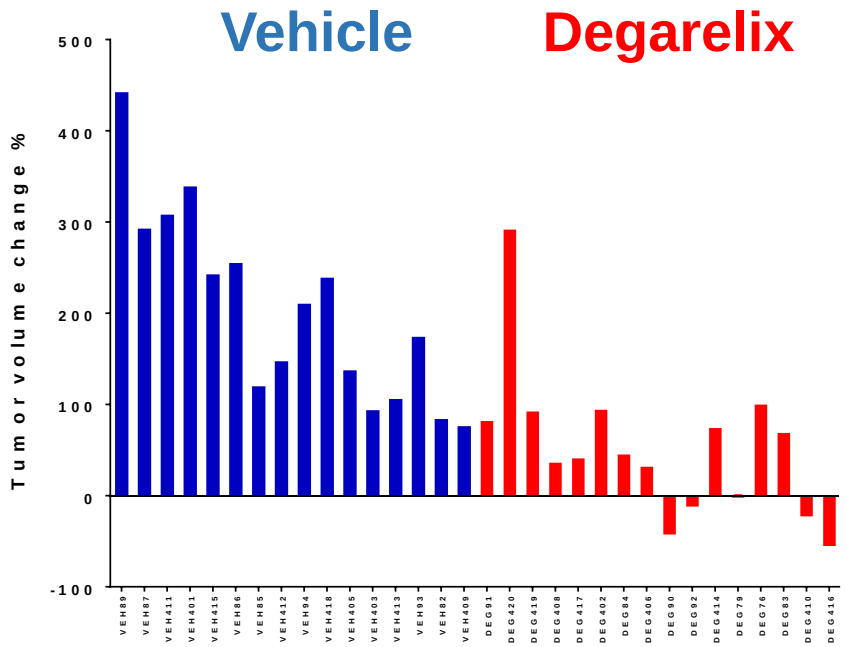
3-weeks Post-Treatment



Subcutaneous tumors

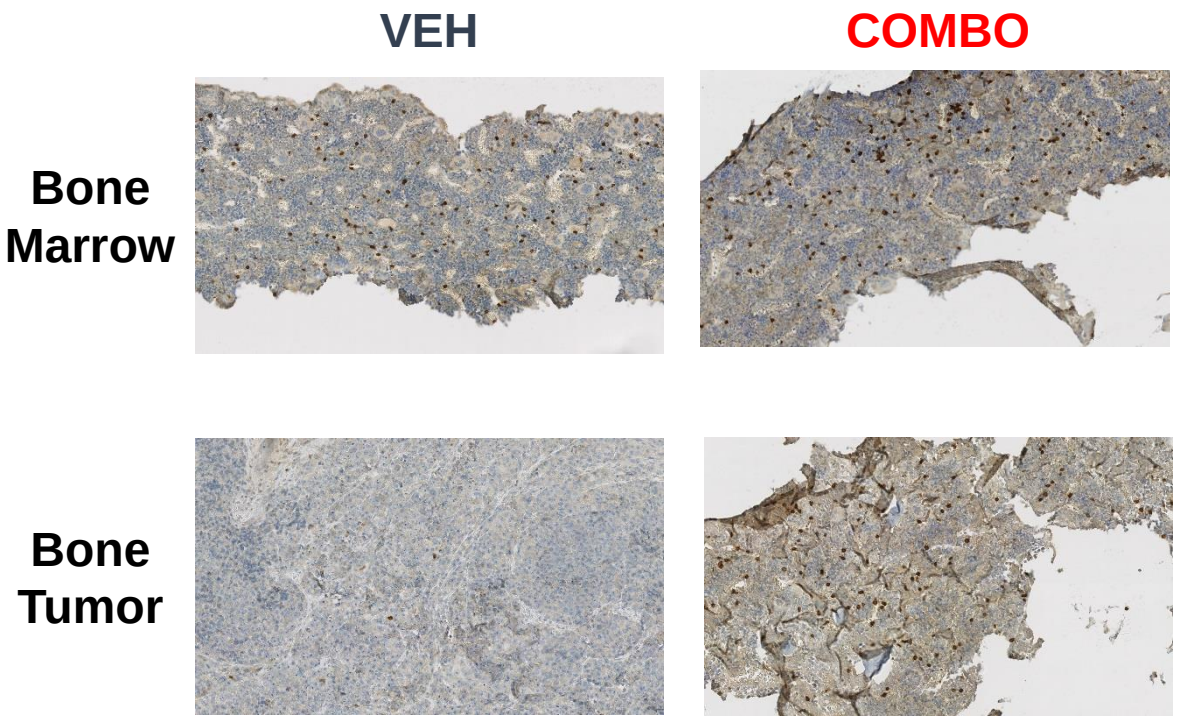


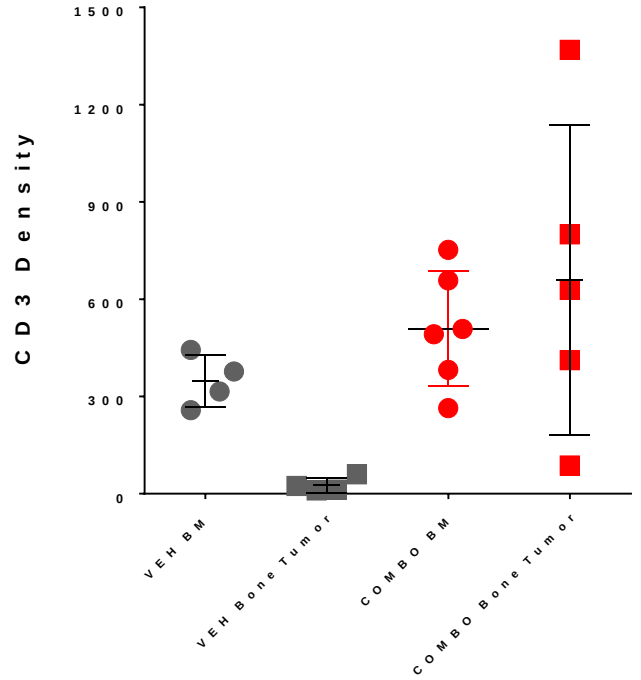
Intrafemoral tumors



Subudhi SK, manuscript in preparation

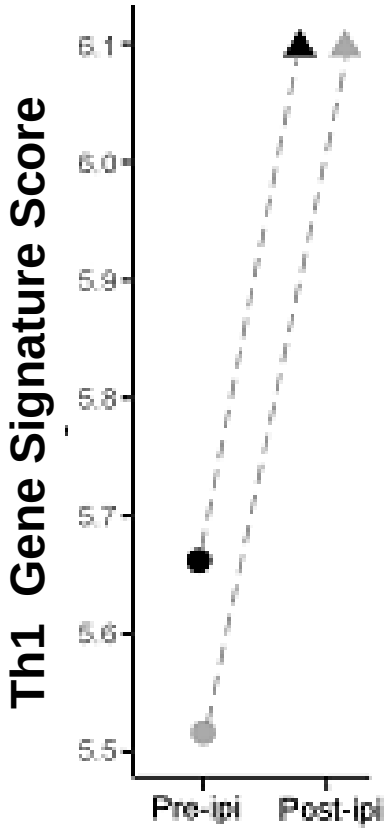
T Cell Exclusion is Overcome by Targeting CTLA-4 and PD-1



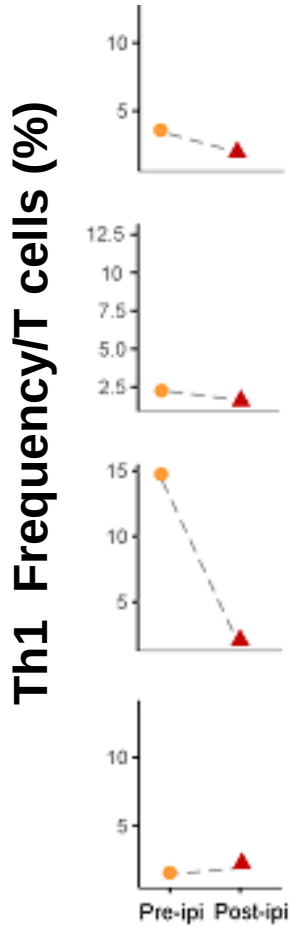


Anti-CTLA-4 Fails to Induce Th1 Responses in Human Prostate Cancer Bone Metastases

Primary Prostate Cancers
Th1



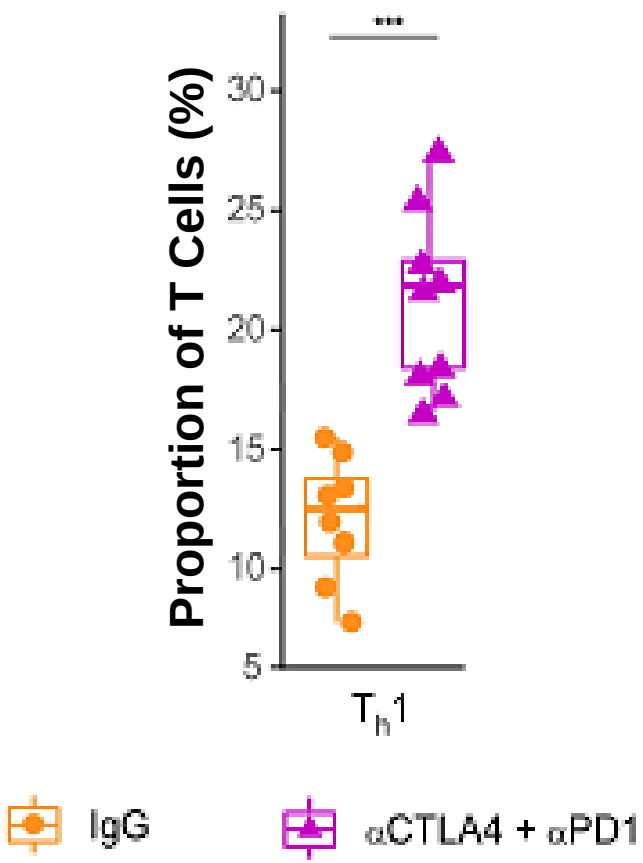
Prostate Bone Metastases
Th1



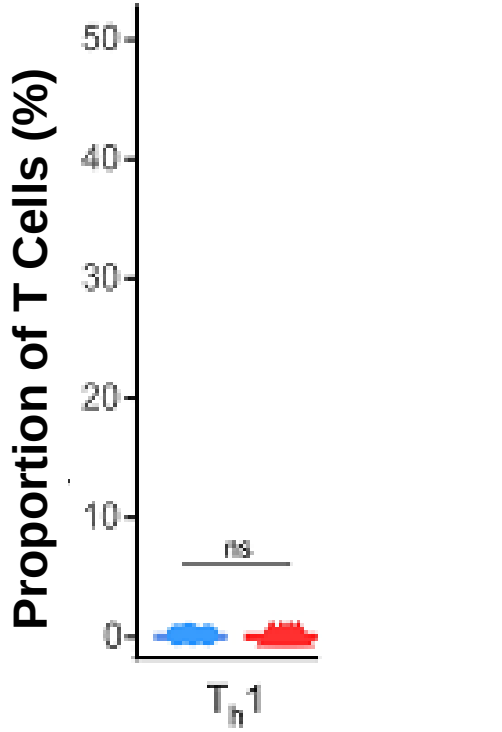
Jiao S, Subudhi SK et al. *Cell*, 2019.

Anti-CTLA-4 Fails to Induce Th1 Responses in Murine Prostate Bone Tumors

Subcutaneous Tumor



Bone Tumor

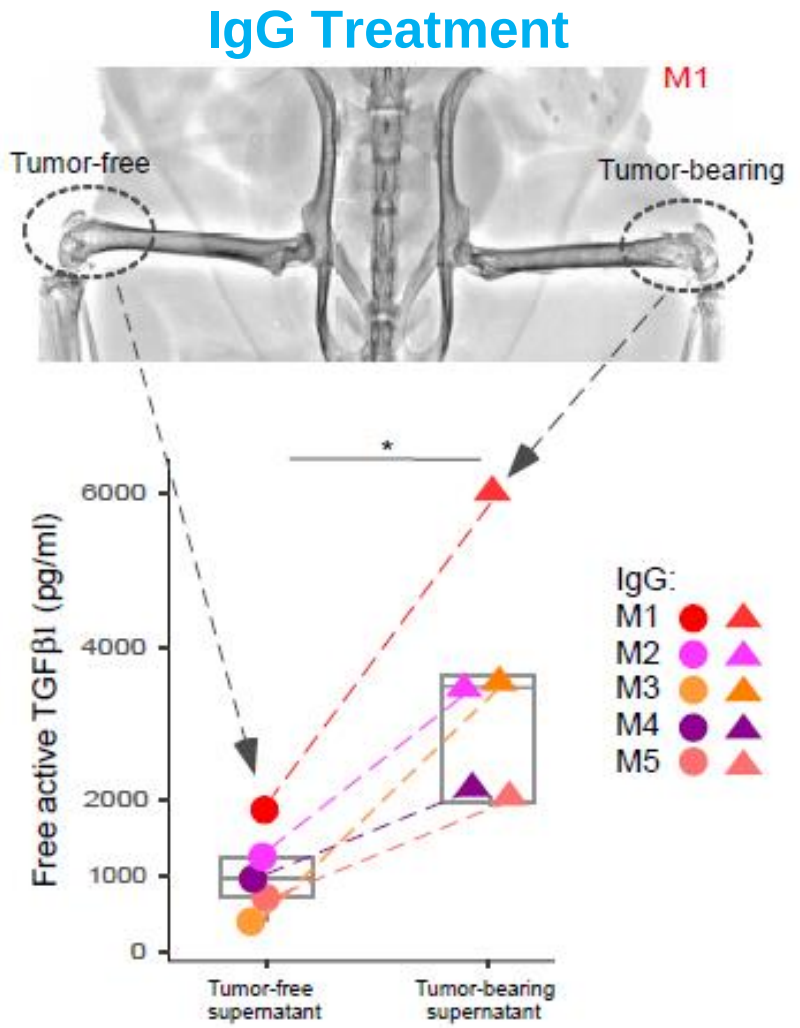


IgG αCTLA4 + αPD1

IgG αCTLA4 + αPD1

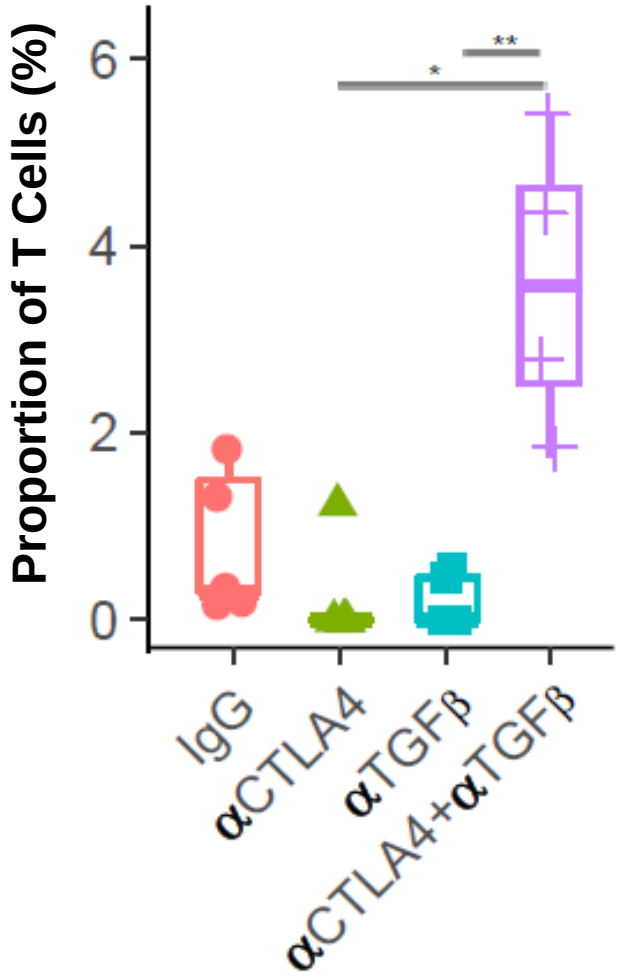
Jiao S, Subudhi SK et al. *Cell*, 2019.

Elevated TGF-β1 Levels in Murine Prostate Bone Tumors



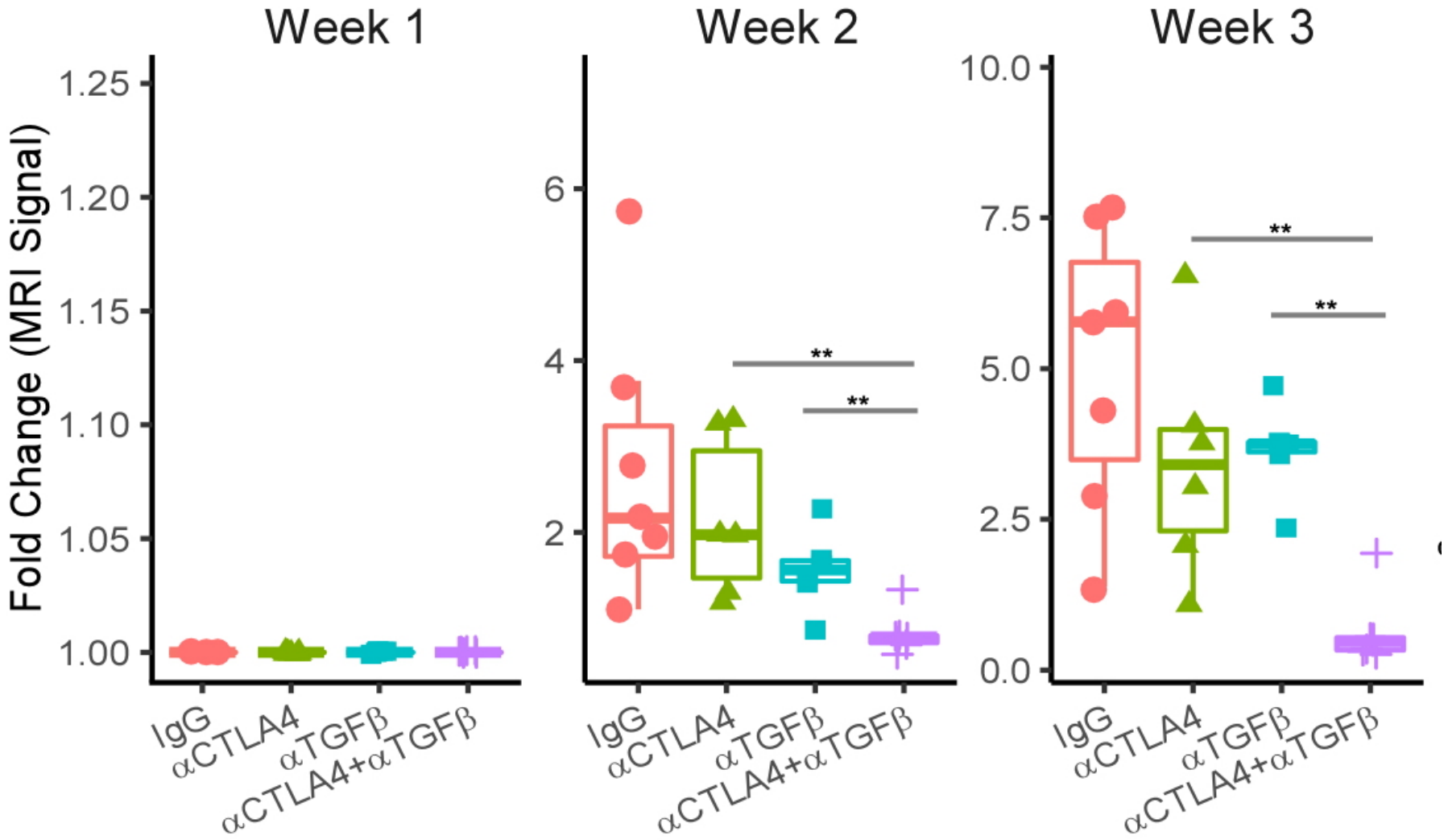
Jiao S, Subudhi SK et al. *Cell*, 2019.

Targeting CTLA-4 and TGF-β Promotes Th1 Responses



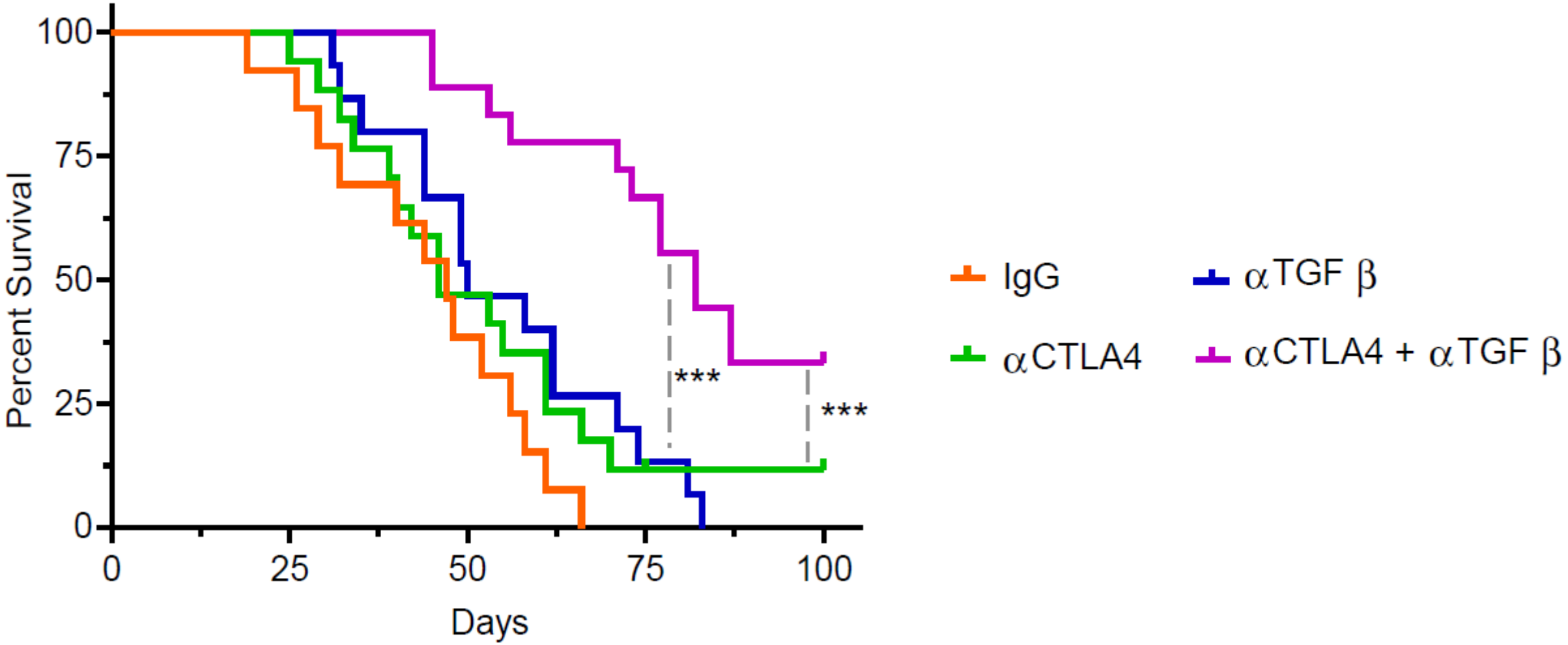
Jiao S, Subudhi SK et al. *Cell*, 2019.

Targeting CTLA-4 and TGF-β Reduces Bone Tumor Growth



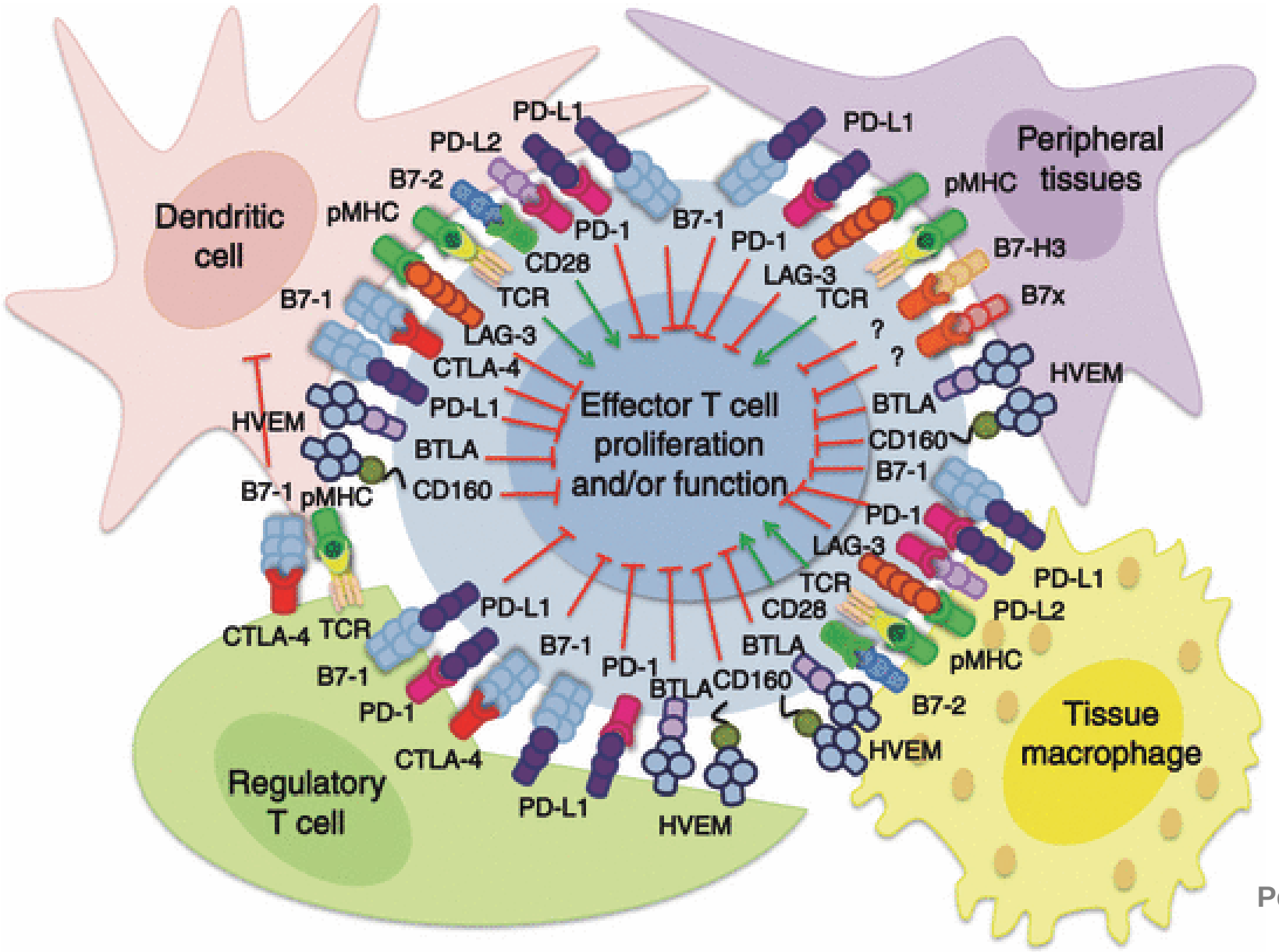
Jiao S, Subudhi SK et al. *Cell*, 2019.

Targeting CTLA-4 and TGF-β Improves Survival



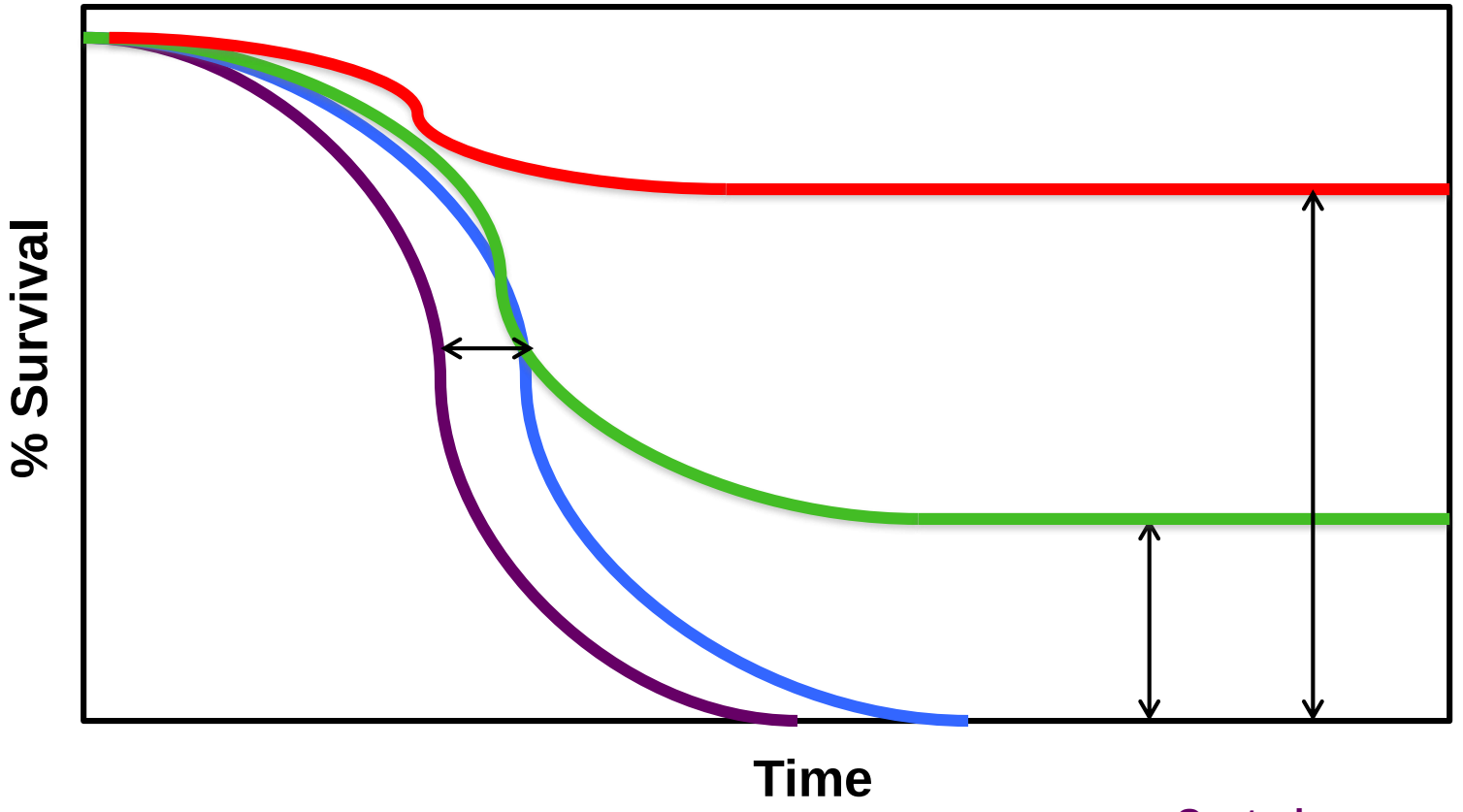
Jiao S, Subudhi SK et al. *Cell*, 2019.

Novel Immunotherapy Targets



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

Improving Survival with Combination Therapy

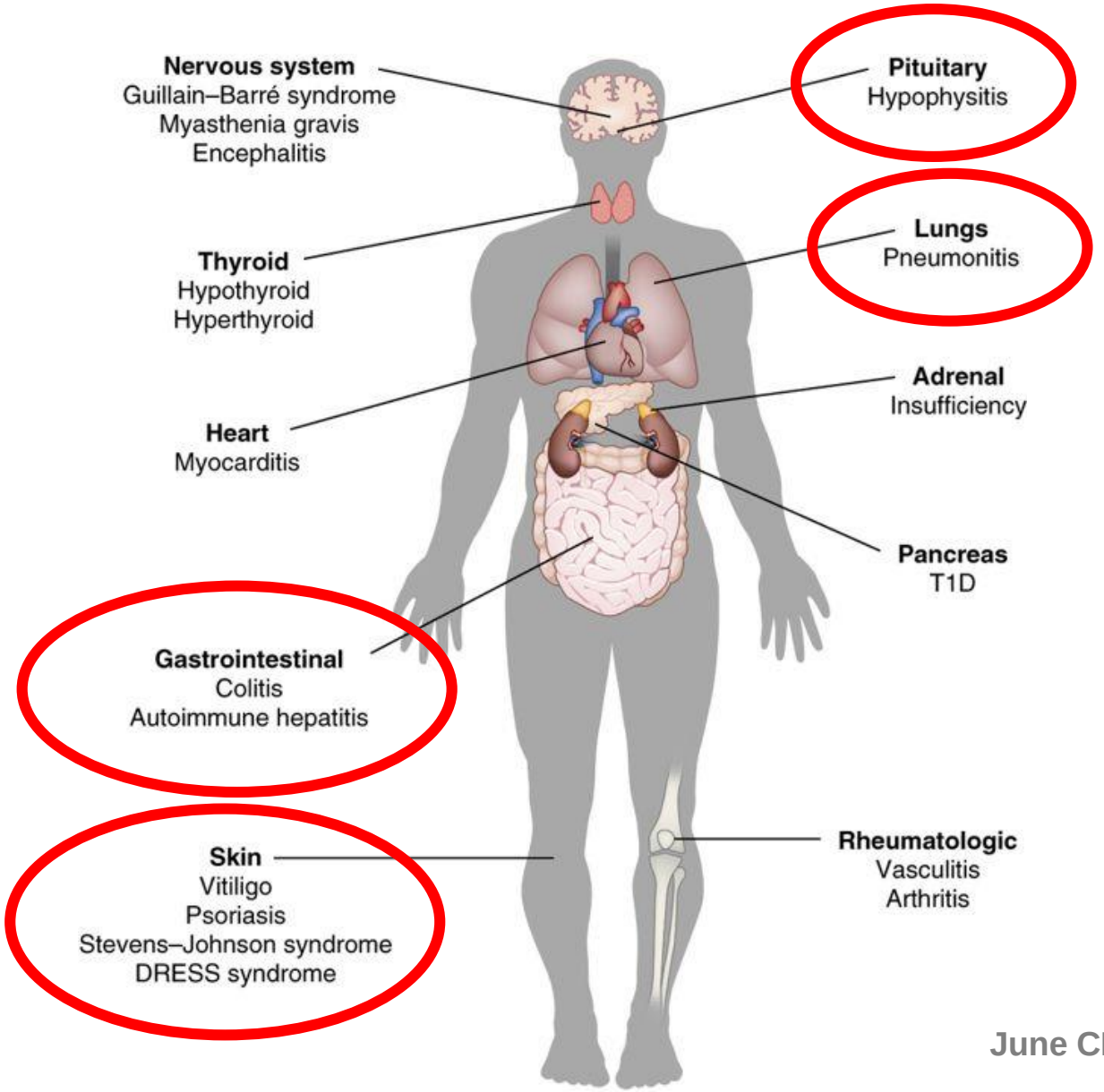


Sharma P and Allison JP, *Cell*, 2015.

Moving Forward with Immune Checkpoint Therapies

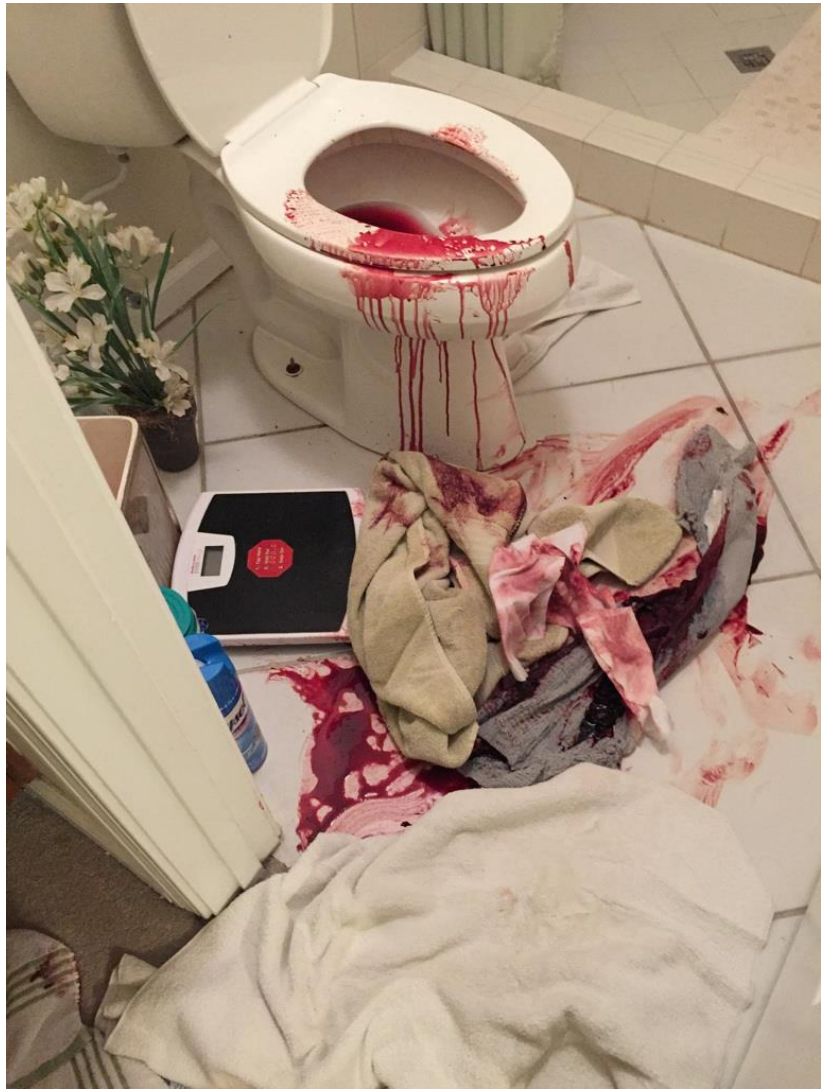
- Improving patient selection
- Turning “cold” tumors “hot”
- **Understanding toxicities**

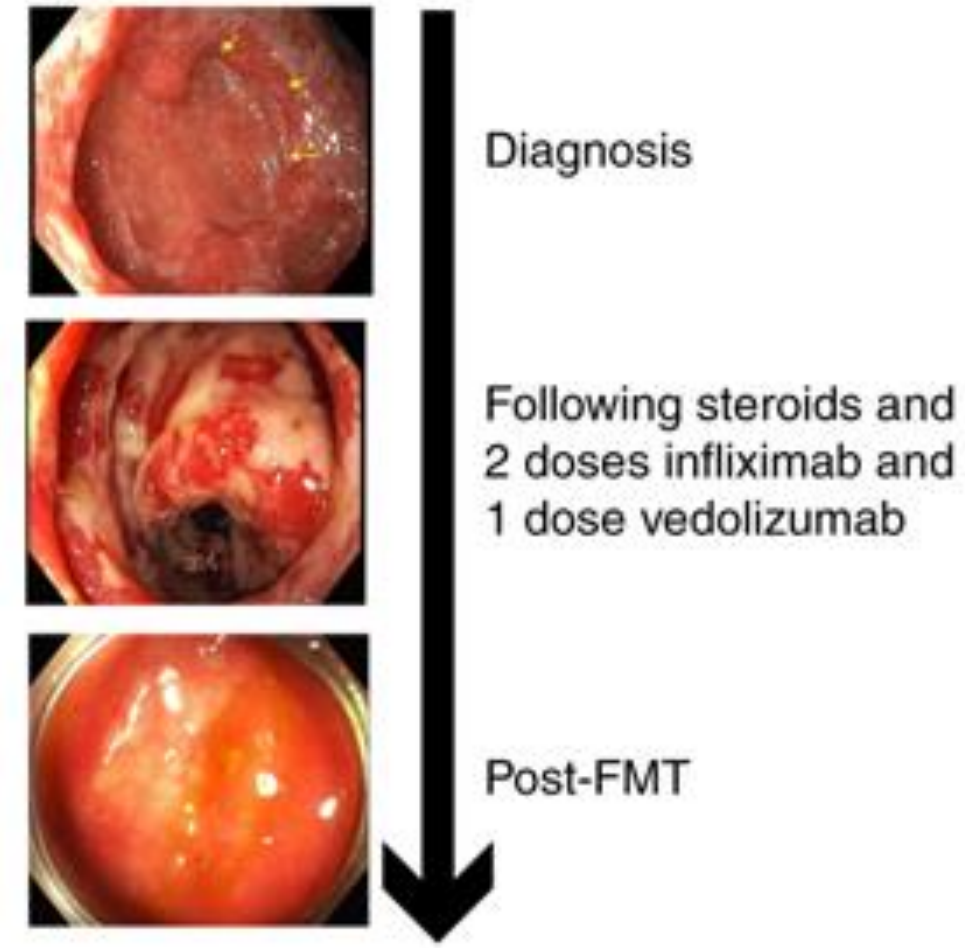
Organ-Specific Immune-Related Adverse Events (irAEs)



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

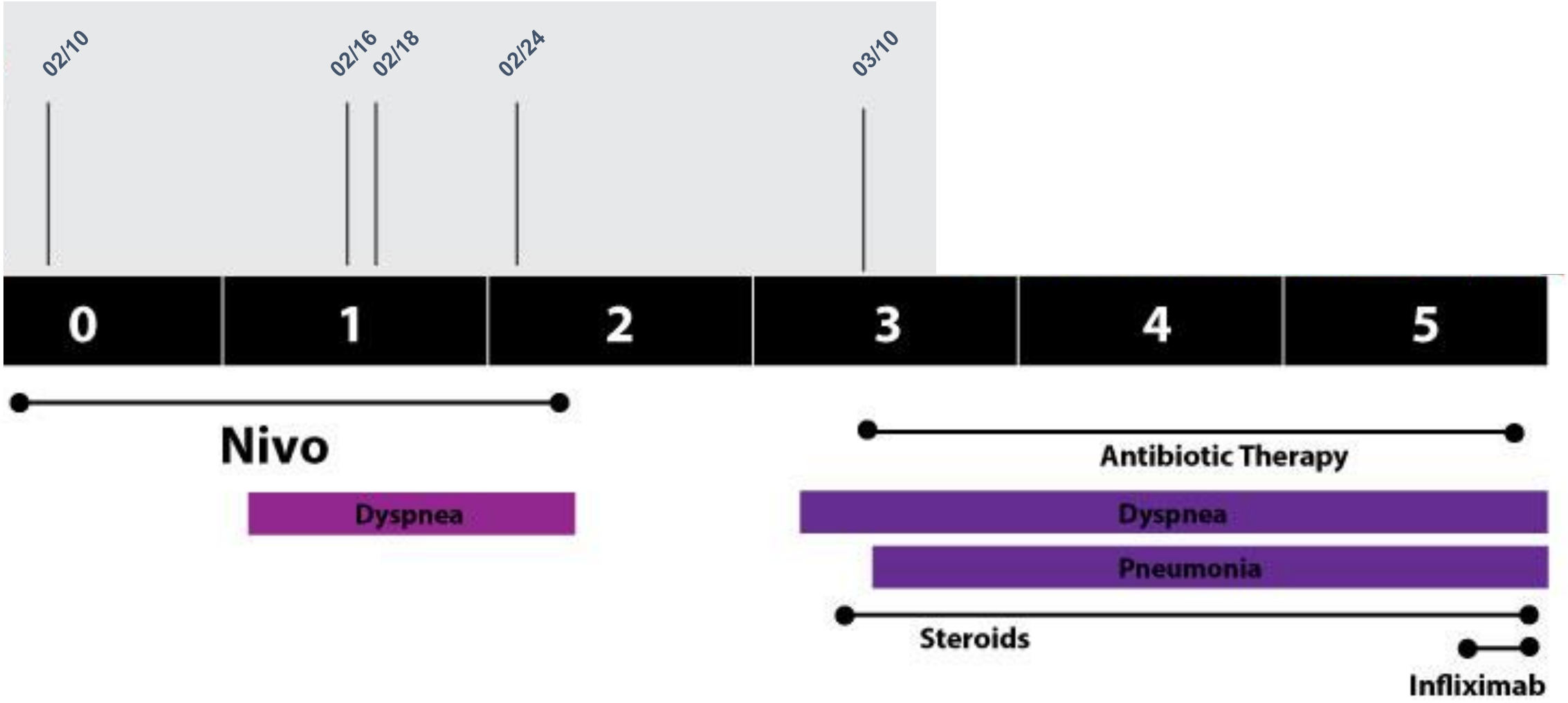
Immune-Related Colitis/Diarrhea





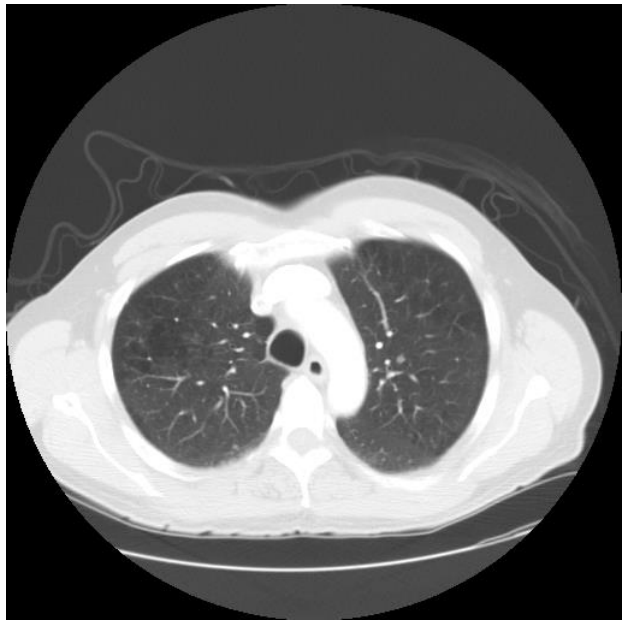
Wang Y et al, *Nat Med,* 2018.

Immune-Related Pneumonitis



Monday Morning Quarterback

02/05/2015



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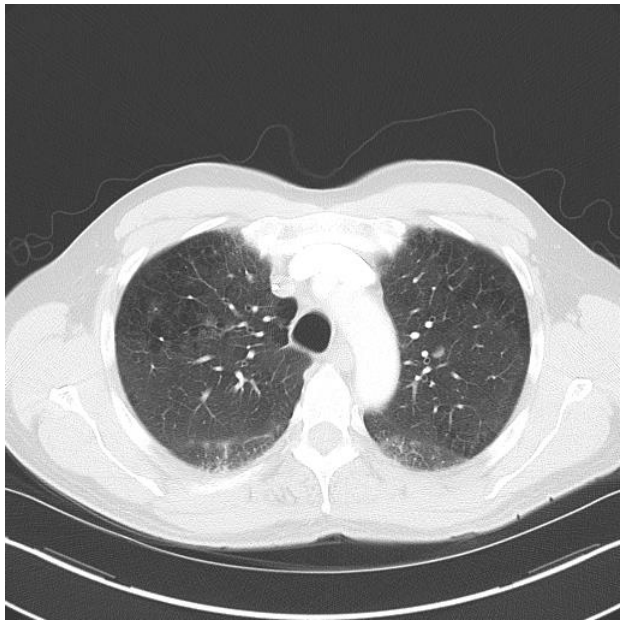

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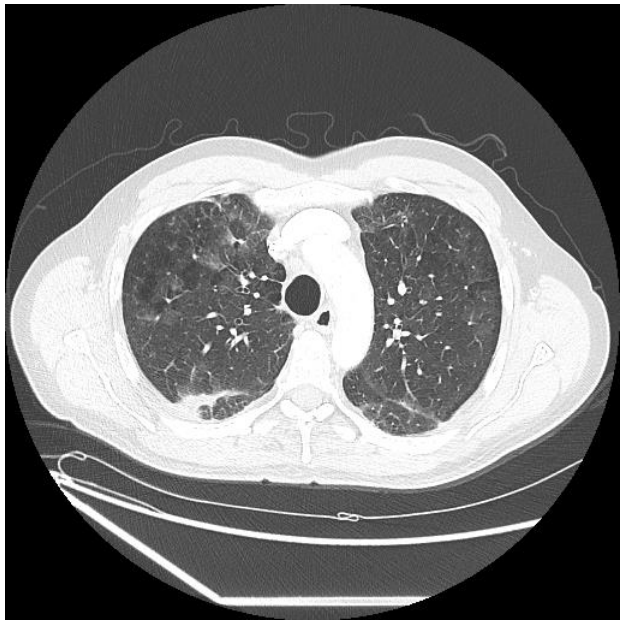
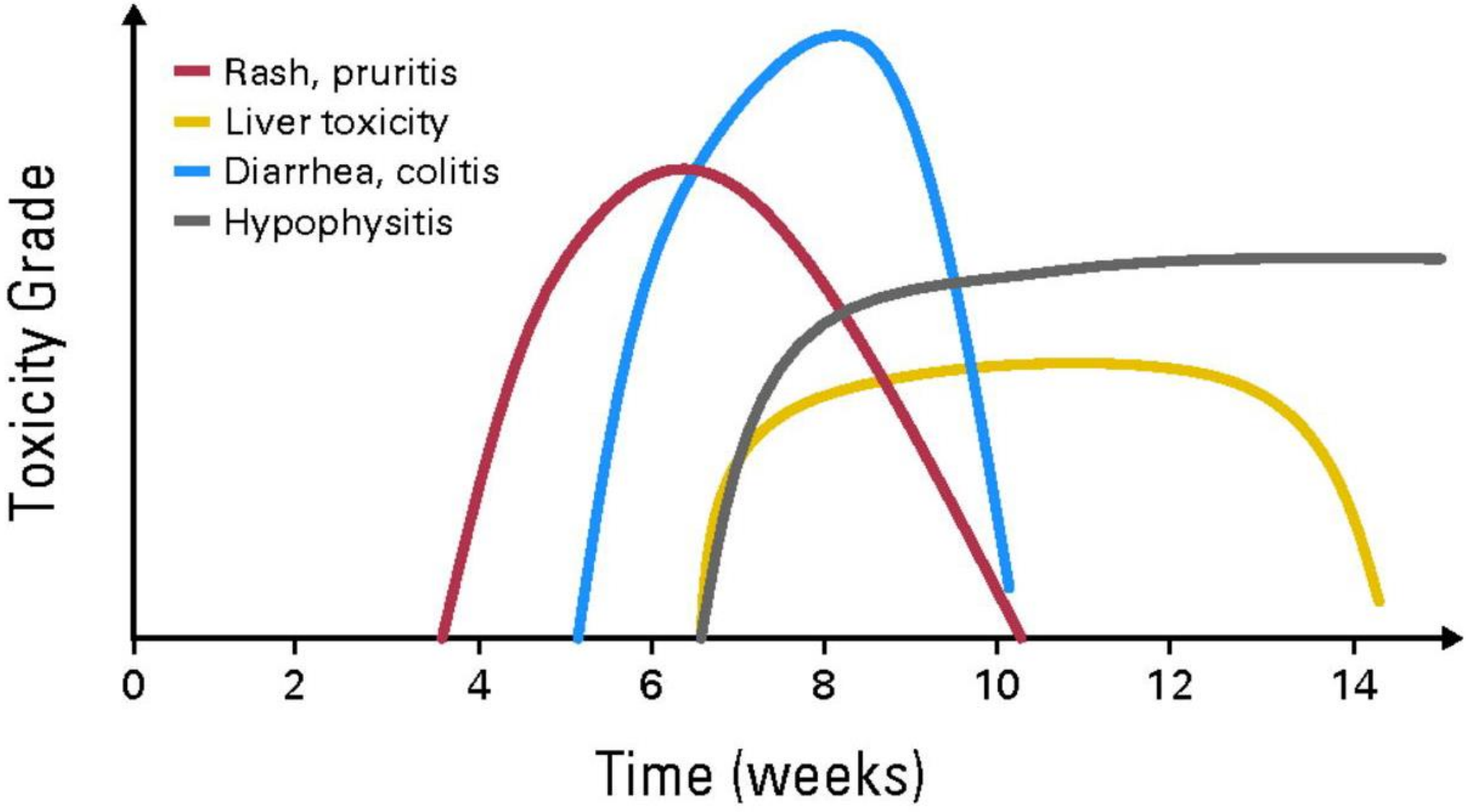


Safety Considerations

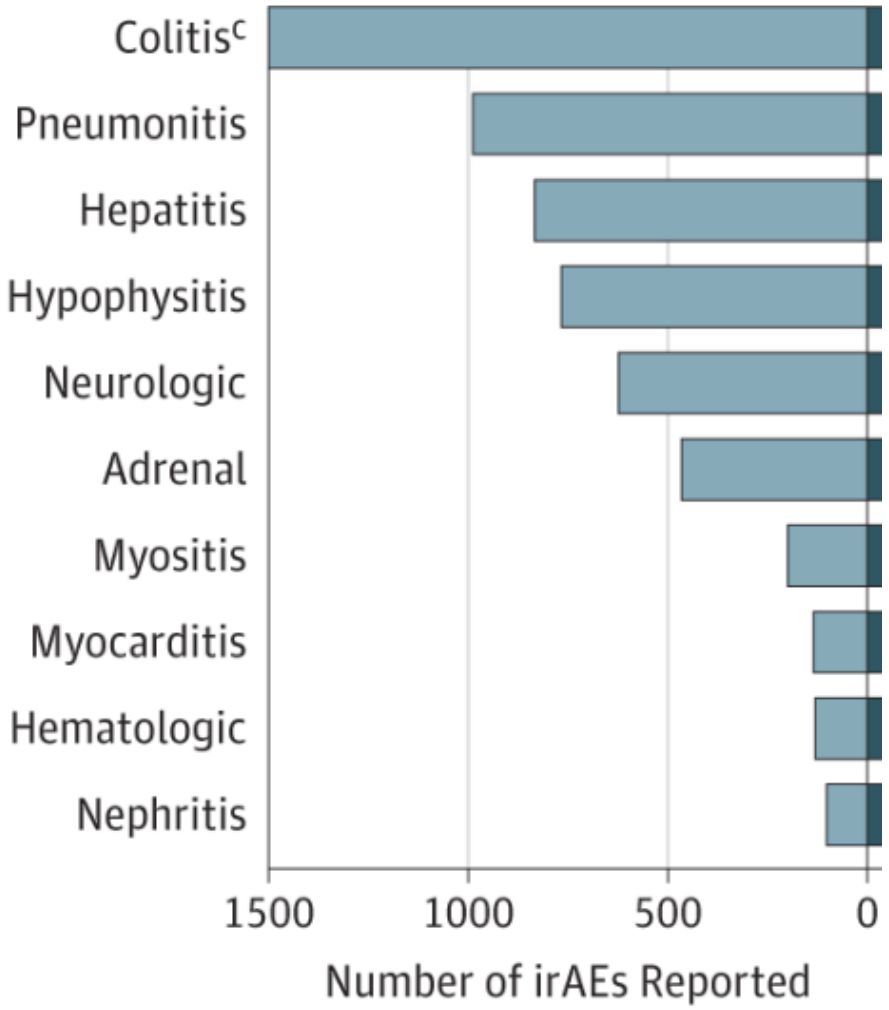
- **irAEs appear to be under-reported**
- **Early recognition/intervention with immunosuppressive/biological agents**
  - **Medical team**
  - **Patient/Family**
  - **Laboratory tests**
  - **Consult teams**

Kinetics of Appearance of irAEs



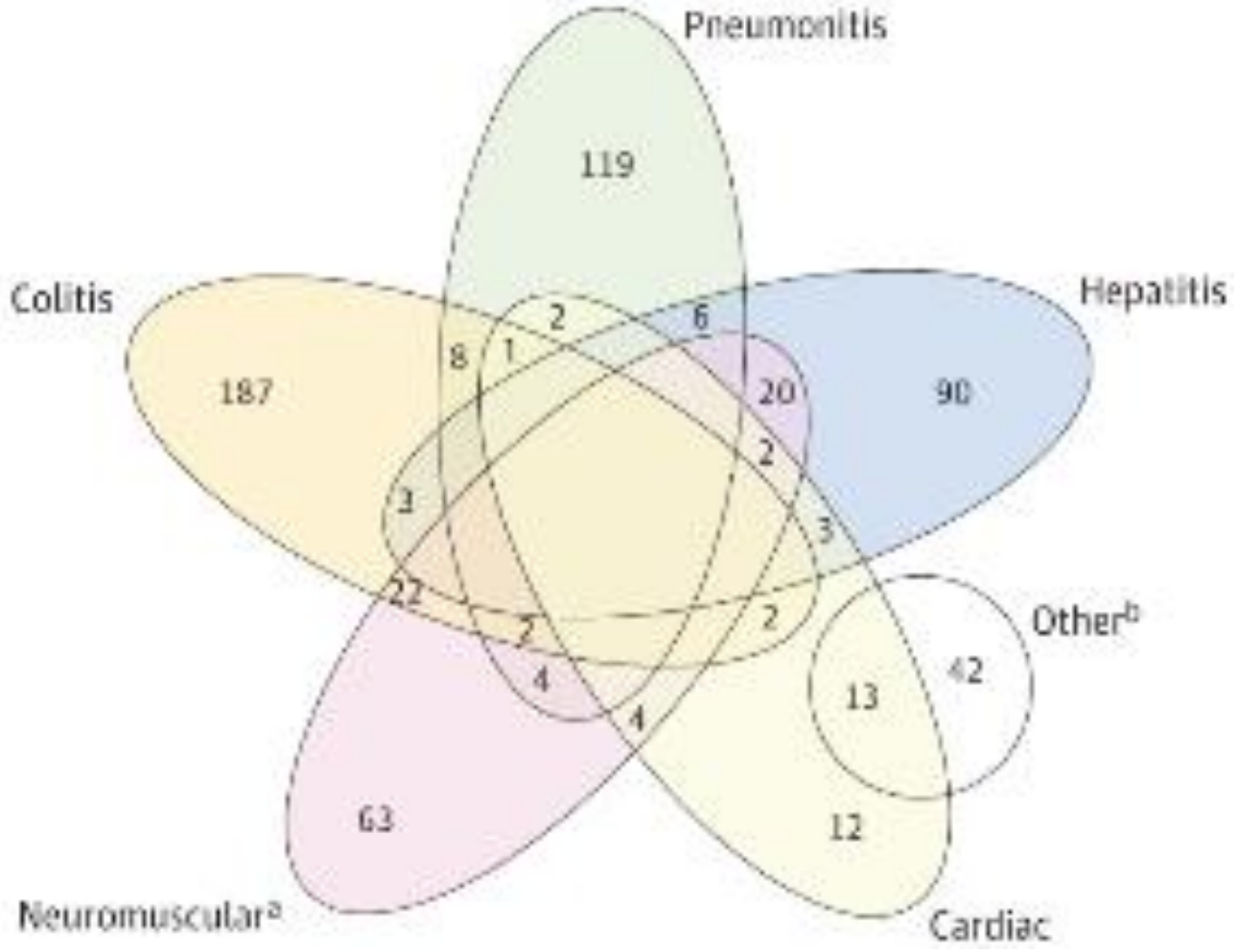
Weber JS et al, *J Clin Oncol*, 2012.

Cases and Fatality Rates for Different Types of irAEs



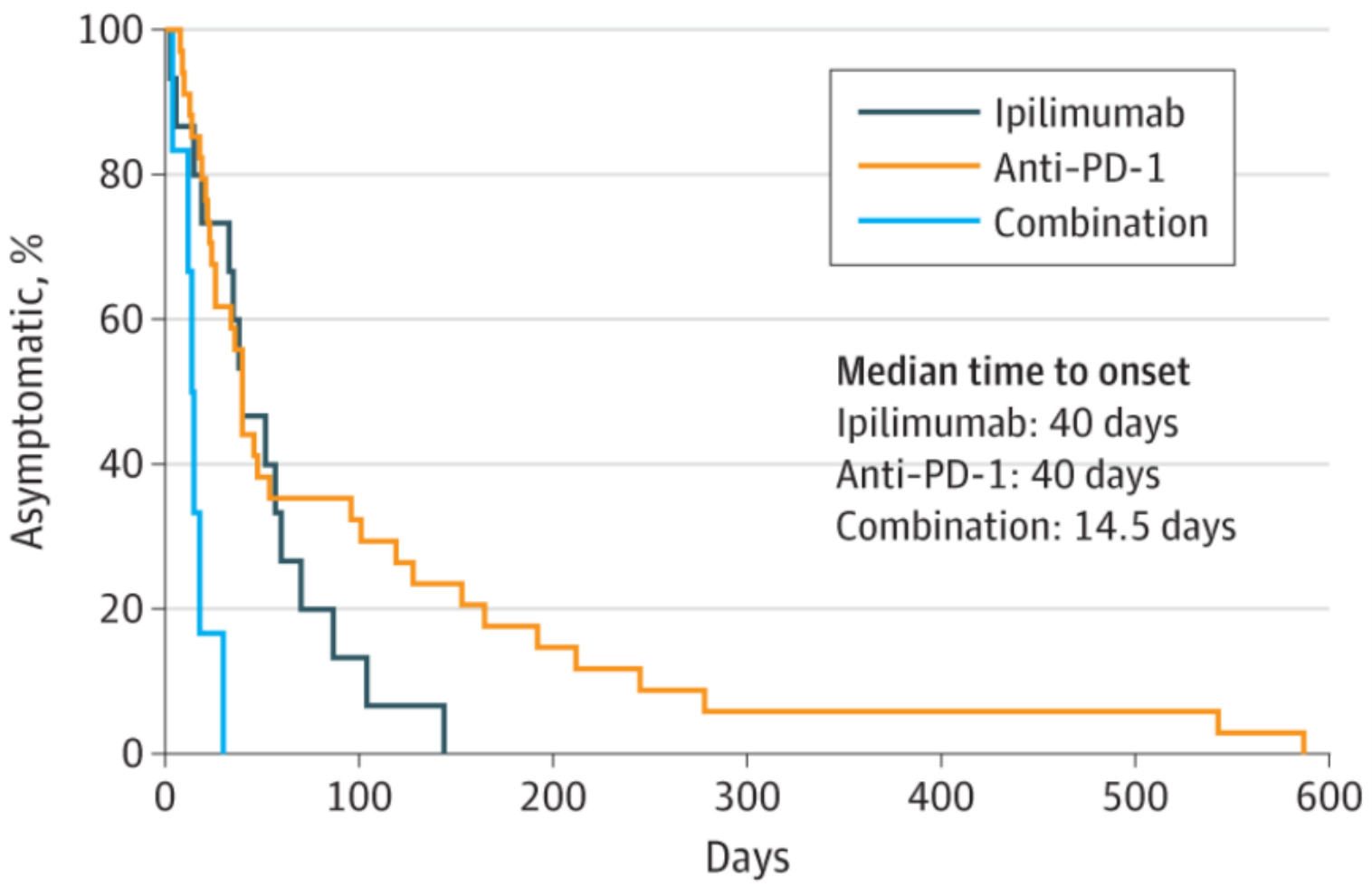
Wang DY et al, *JAMA Oncol*, 2018.

Co-Occurring Fatal irAEs



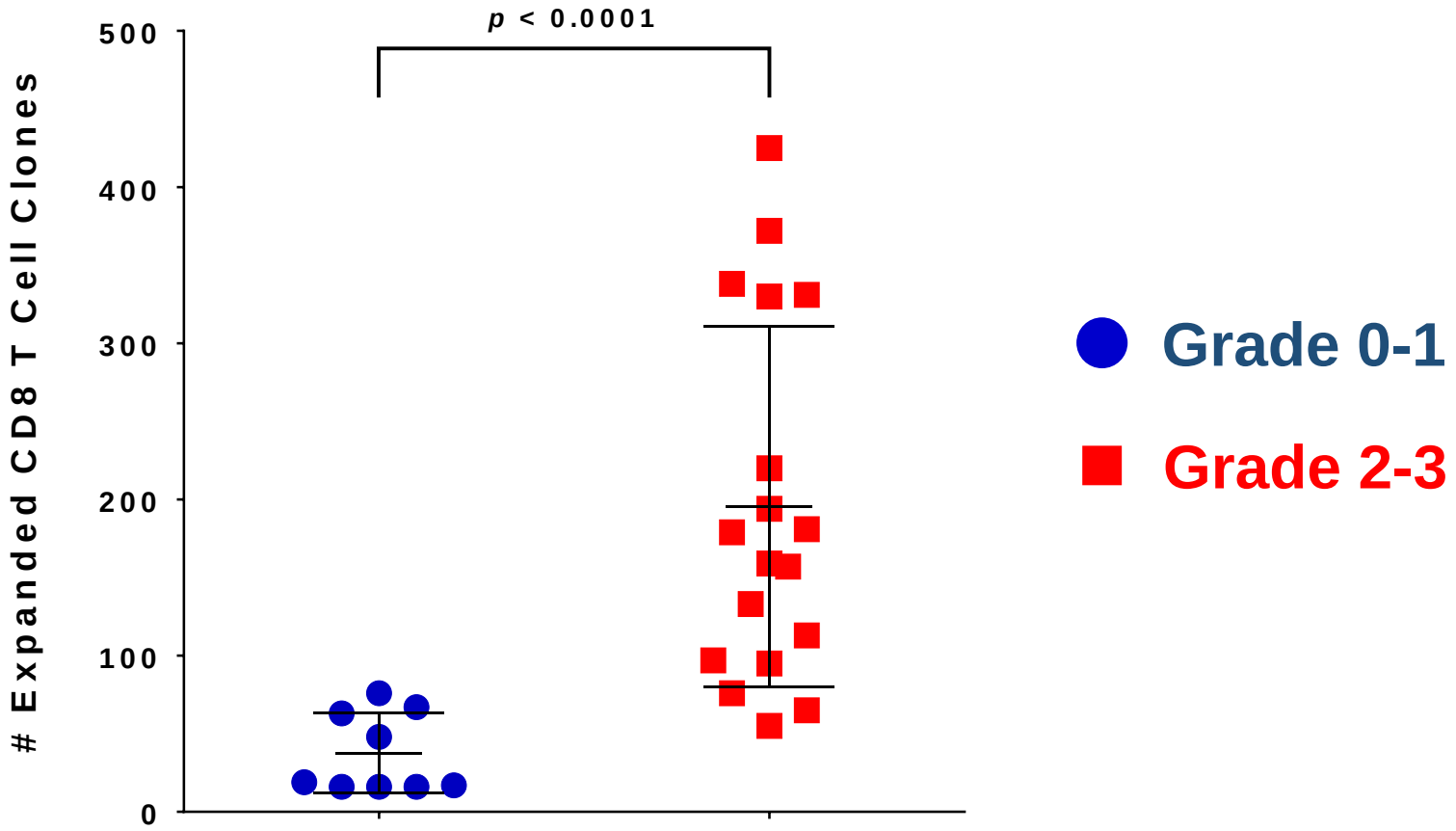
Wang DY et al, *JAMA Oncol*, 2018.

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
- Combinations can be used to turn “cold” tumors “hot”
- Toxicities can be fatal
- Better biomarkers are required to maximize efficacy and minimize toxicities