What's Next for Cancer Immunotherapy?

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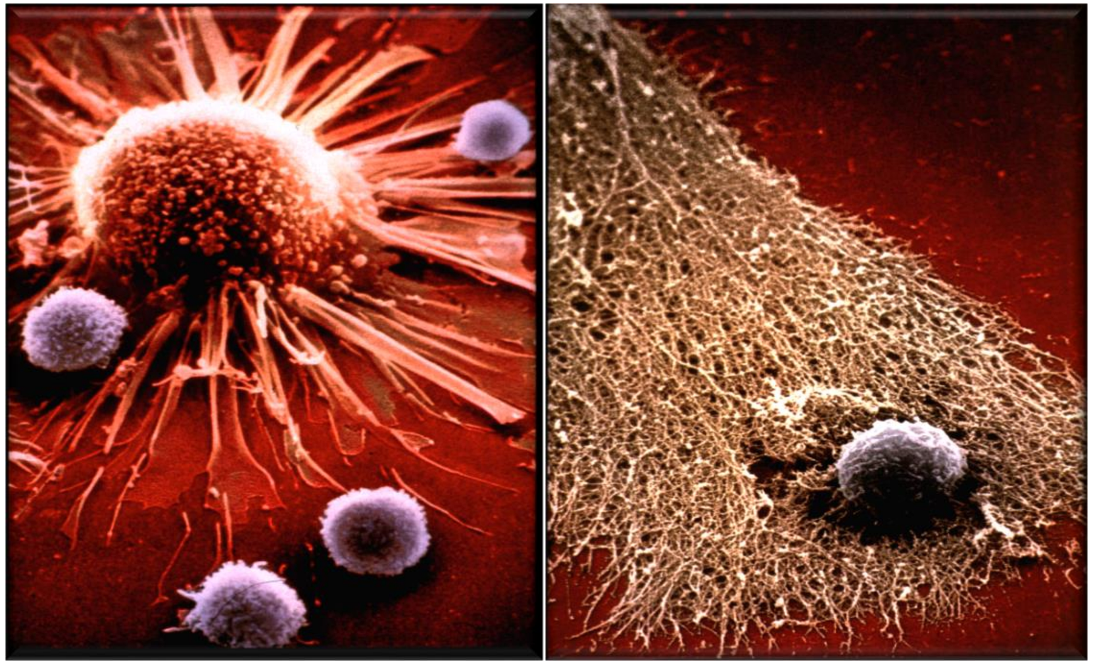
Disclosures

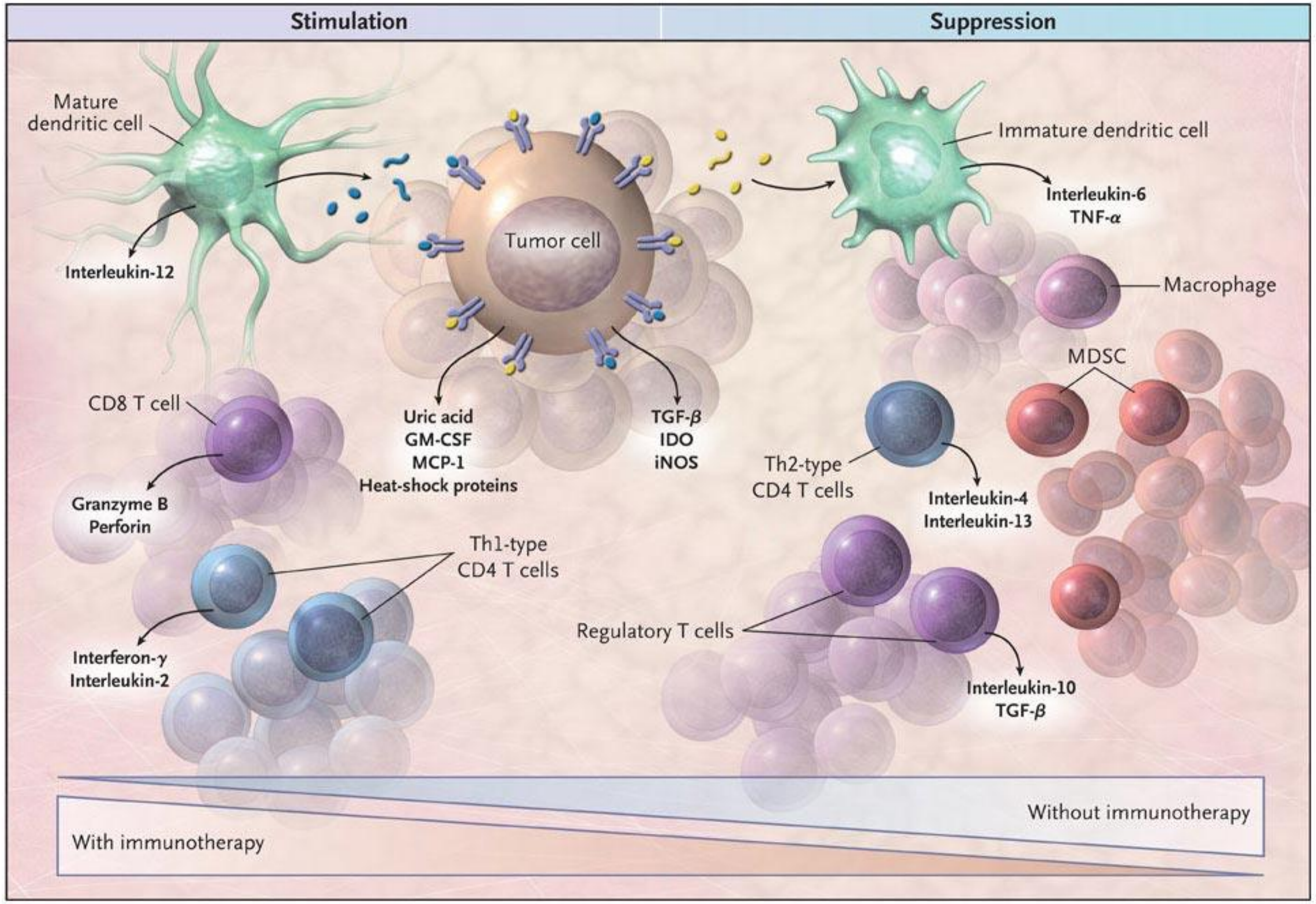
- **Consulting or Advisory Role:** Apricity Health, Compugen, Dendreon, Janssen and Polaris
- **Other (Joint Scientific Committee):** Janssen, Polaris
- I **will** be discussing non-FDA approved indications during my presentation.

Why Immunotherapy?

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



Tumor Microenvironment



Finn O. N Engl J Med 2008;358:2704-2715

Immunotherapies

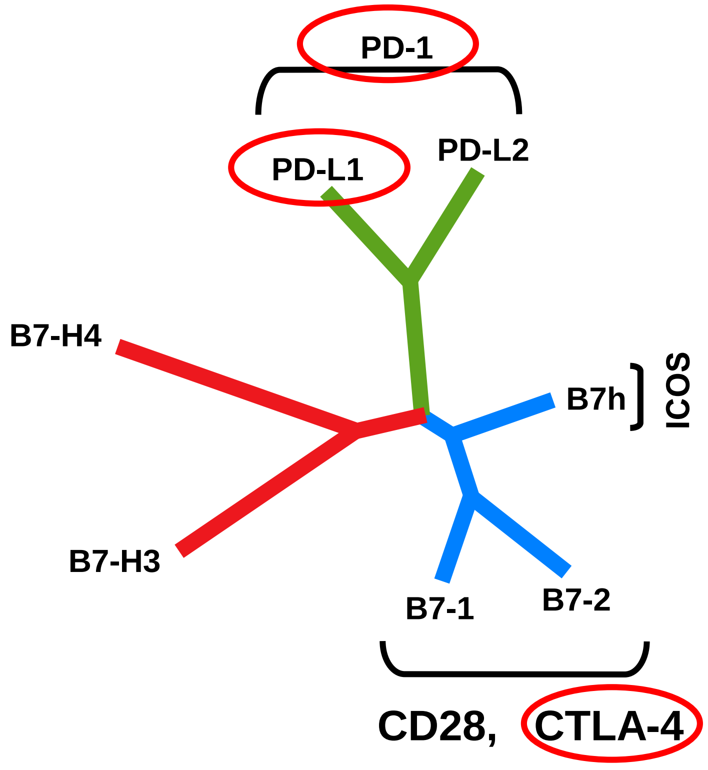
Not all the same!

- **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**

2013: Breakthrough of the Year

December 20, 2013

FDA-Approved Immune Checkpoint Therapies



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

Lung Carcinoma
- Nivolumab
- Pembrolizumab
- Atezolizumab
- Ipilimumab + Nivolumab
- Durvalumab

Urothelial Carcinoma
- Atezolizumab
- Nivolumab
- Durvalumab
- Pembrolizumab
- Avelumab

Melanoma
- Ipilimumab
- Pembrolizumab
- Nivolumab
- Ipilimumab + Nivolumab

Colorectal Carcinoma
- Nivolumab
- Pembrolizumab
- Ipilimumab + Nivolumab

Head and Neck Squamous Cell Carcinoma
- Pembrolizumab
- Nivolumab
- Ipilimumab + Nivolumab

Hodgkin's Lymphoma
- Nivolumab
- Pembrolizumab

Renal Cell Carcinoma
- Nivolumab
- Ipilimumab + Nivolumab

Cervical Carcinoma
- Pembrolizumab

Cutaneous Squamous Cell Carcinoma
- Cemiplimab

Gastric/Gastroesophageal Adenocarcinoma
- Pembrolizumab

Hepatocellular Carcinoma
- Nivolumab

Merkel Cell Carcinoma
- Avelumab

Primary Mediastinal Large B-Cell Lymphoma
- Pembrolizumab

Challenges/Limitations

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

Delayed Responses with Ipilimumab

Screening

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

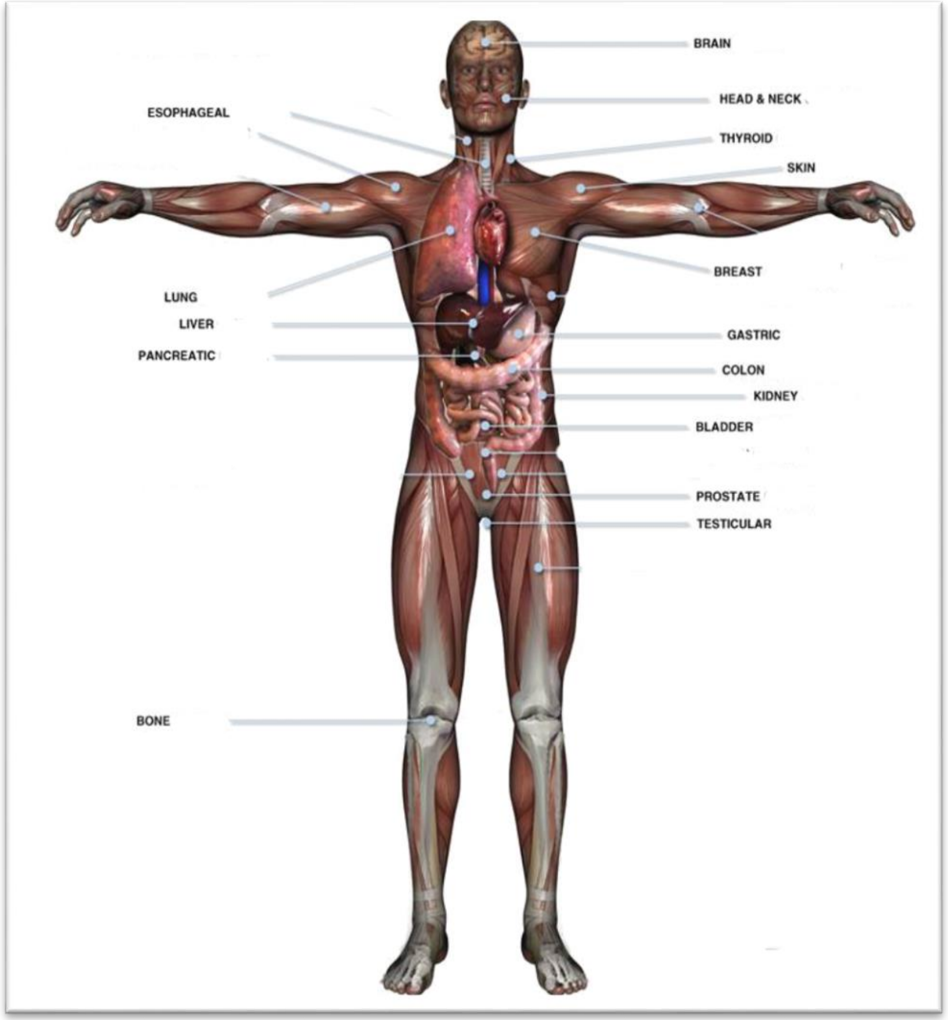
Week 16
Responding

Week 72
Durable & ongoing response

Courtesy of K. Harmankaya

Immune-Related Adverse Events (irAEs)

- **Dermatitis**
- **Colitis**
- **Hypophysitis**
- **Thyroiditis**
- **Pneumonitis**
- **Hepatitis**



Colitis/Diarrhea

Moving Forward with Immune Checkpoint Therapies

- Turning “cold” tumors “hot”

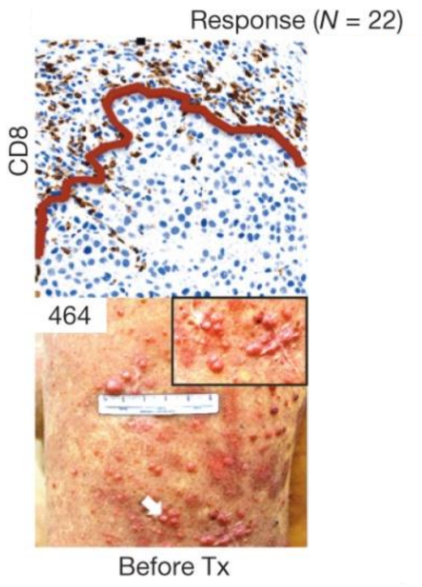
- Improving patient selection

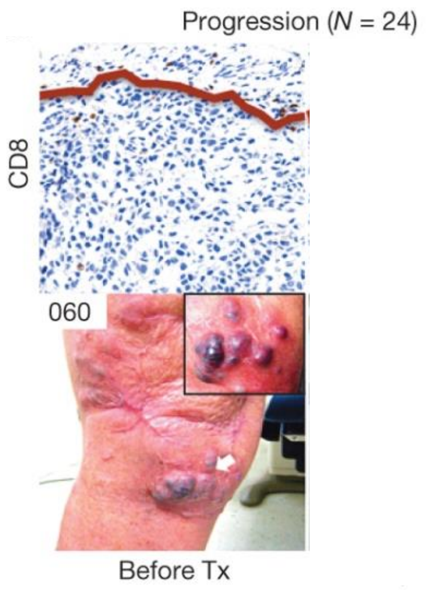
Moving Forward with Immune Checkpoint Therapies

- **Turning “cold” tumors “hot”**

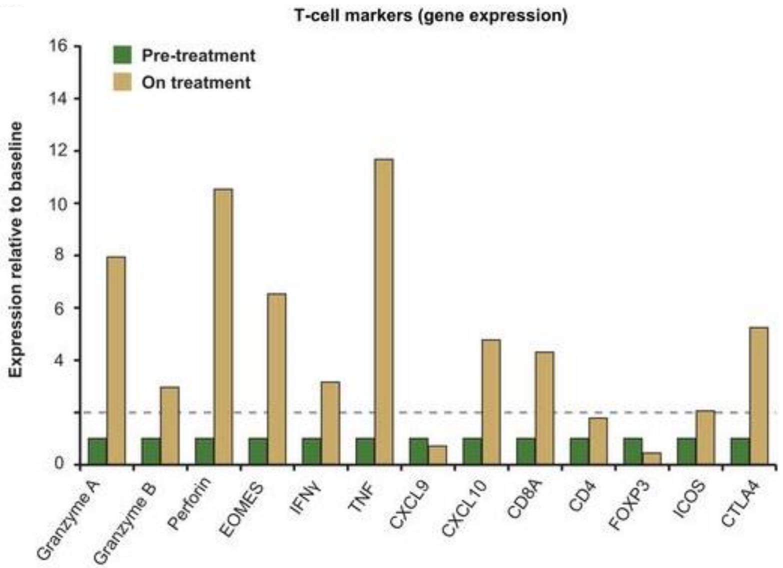
- **Improving patient selection**

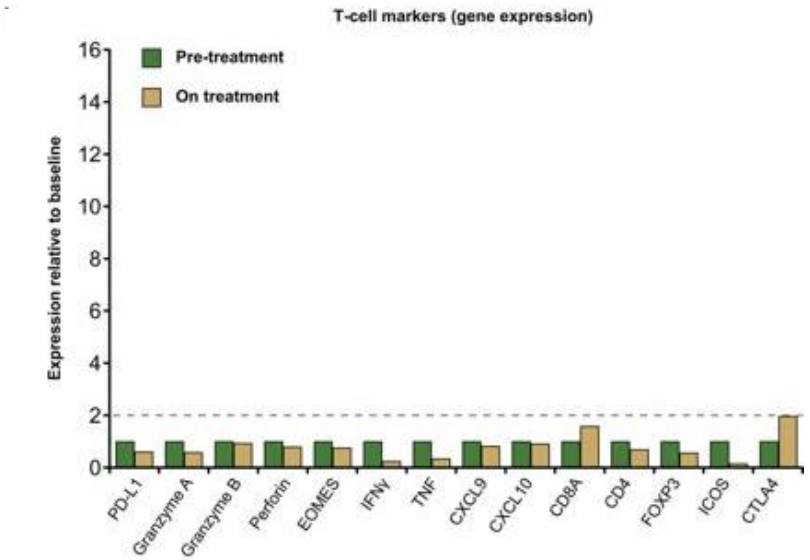
More CD8 T Cells Makes Anti-PD-1/PD-L1 Work Better





Tumeh PC et al. *Nature.* 2014.

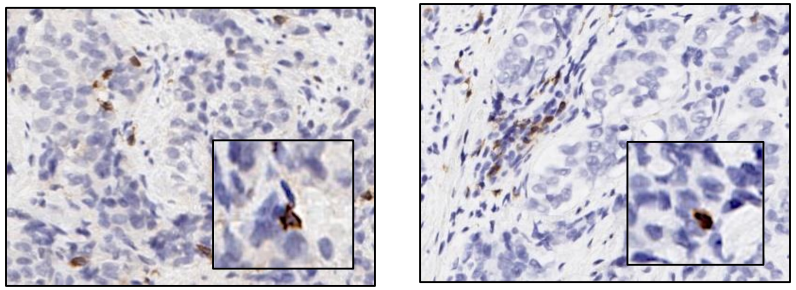




Herbst RS et al. *Nature.* 2014.

Few T Cells Within the Prostate Tumor Microenvironment

Primary



CD4 CD8

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

Original Article

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

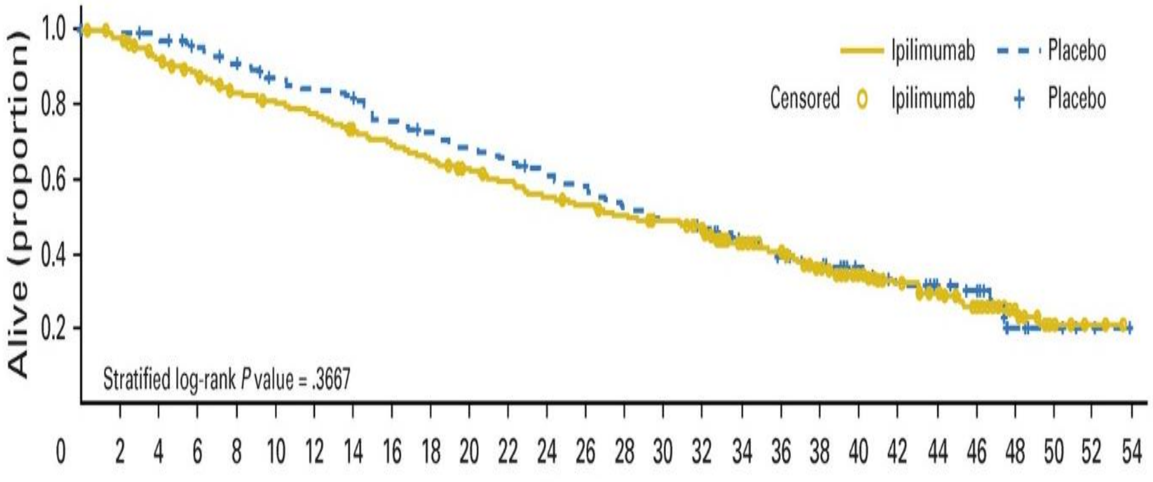
Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott 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

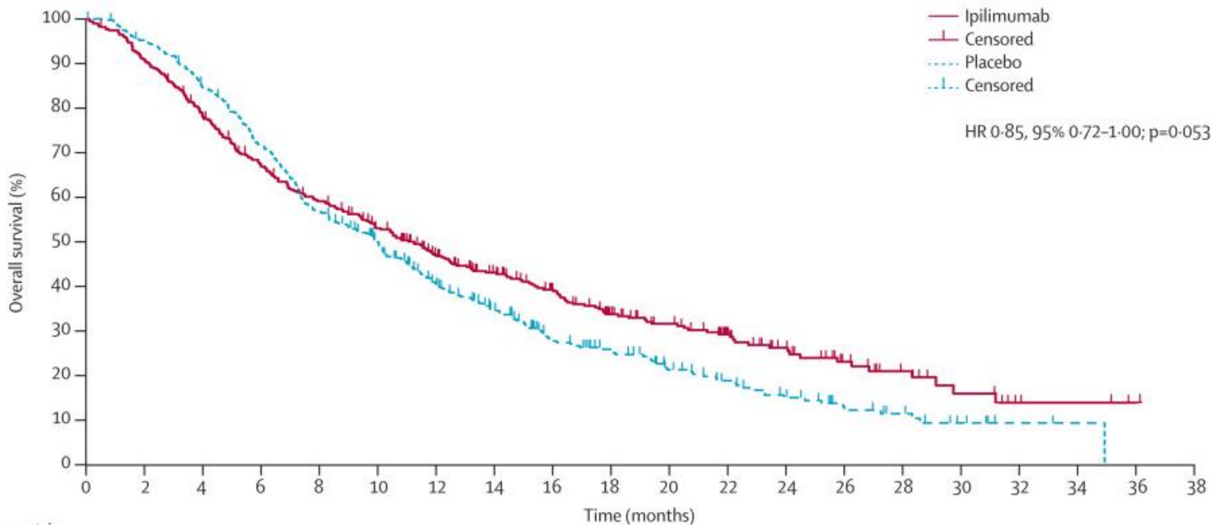
Ipilimumab Does Not Improve Overall Survival Metastatic Prostate Cancer

Pre-Chemotherapy



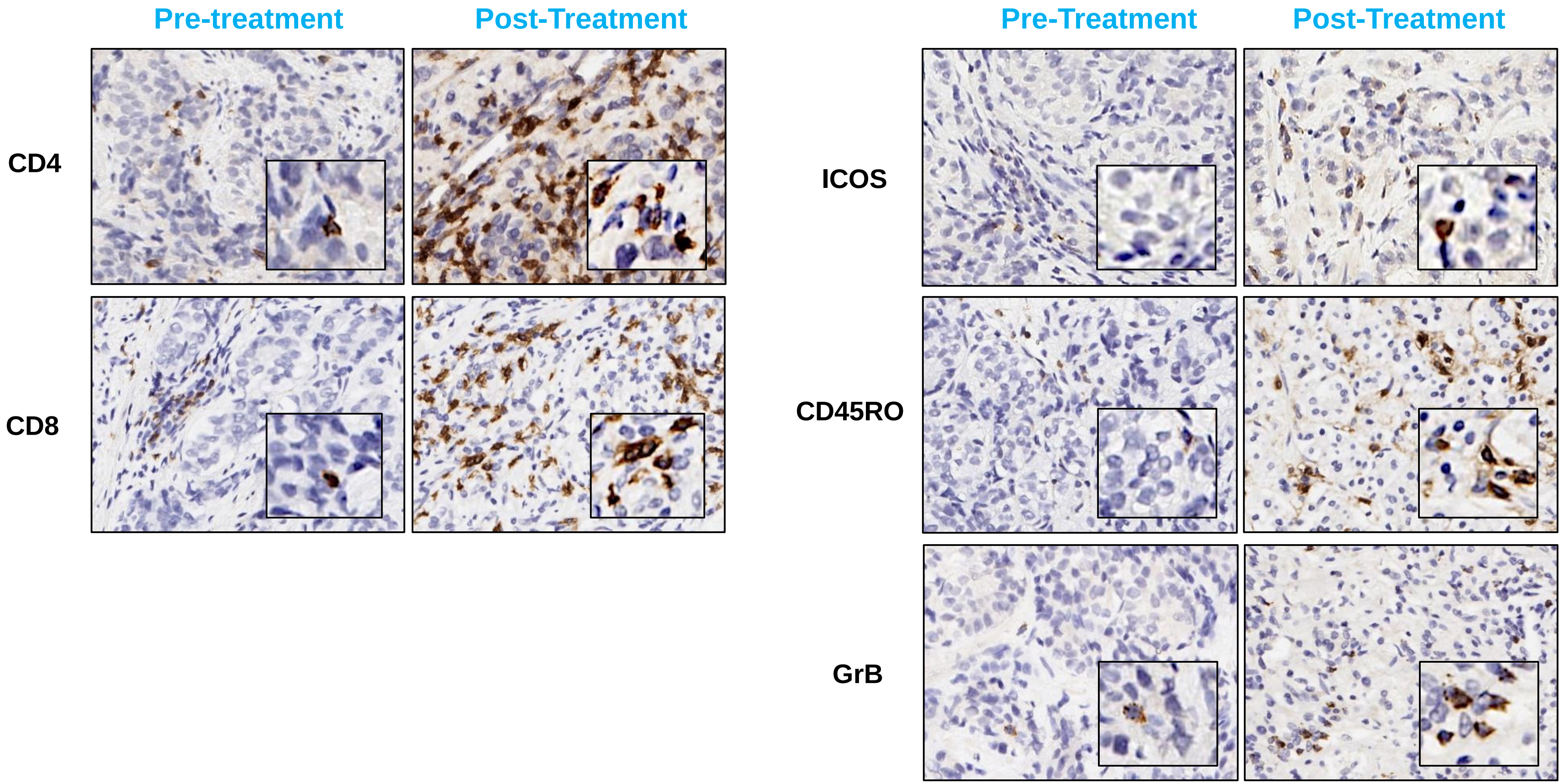
Beer, TM et al. *J Clin Oncol,* 2016.

Post-Chemotherapy



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

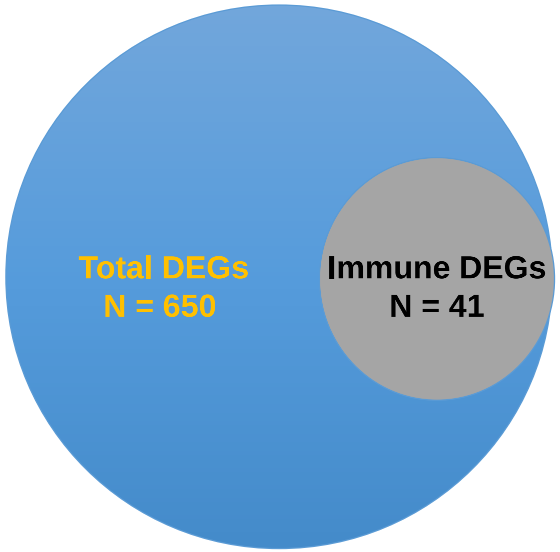
Ipilimumab Increases Immune Infiltration Within the Primary Prostate Tumor Microenvironment

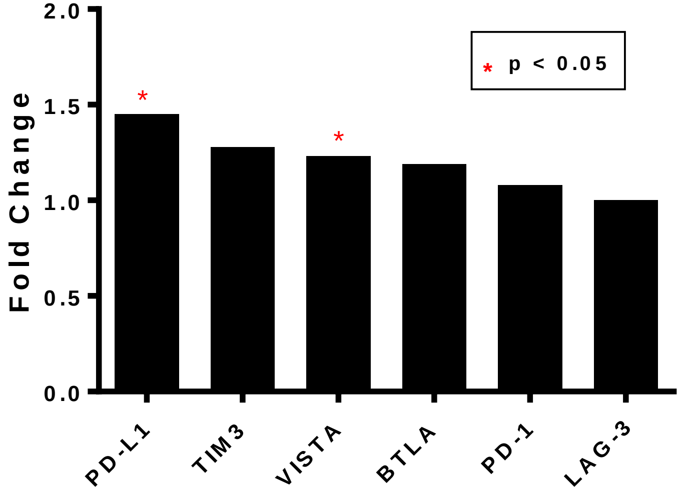


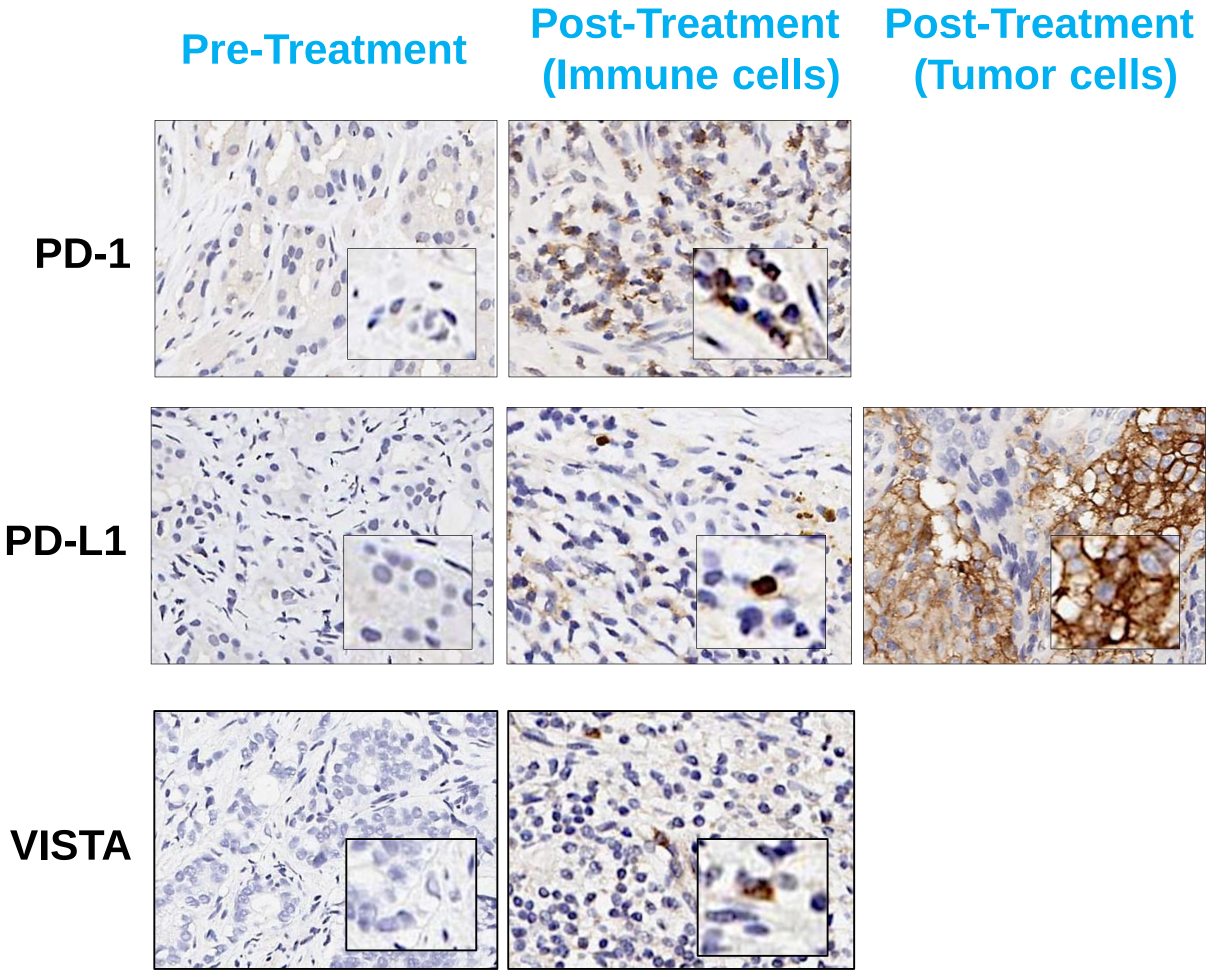
Gao JJ et al. *Nature Med,* 2017.

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

Differentially-Expressed Genes (DEGs)

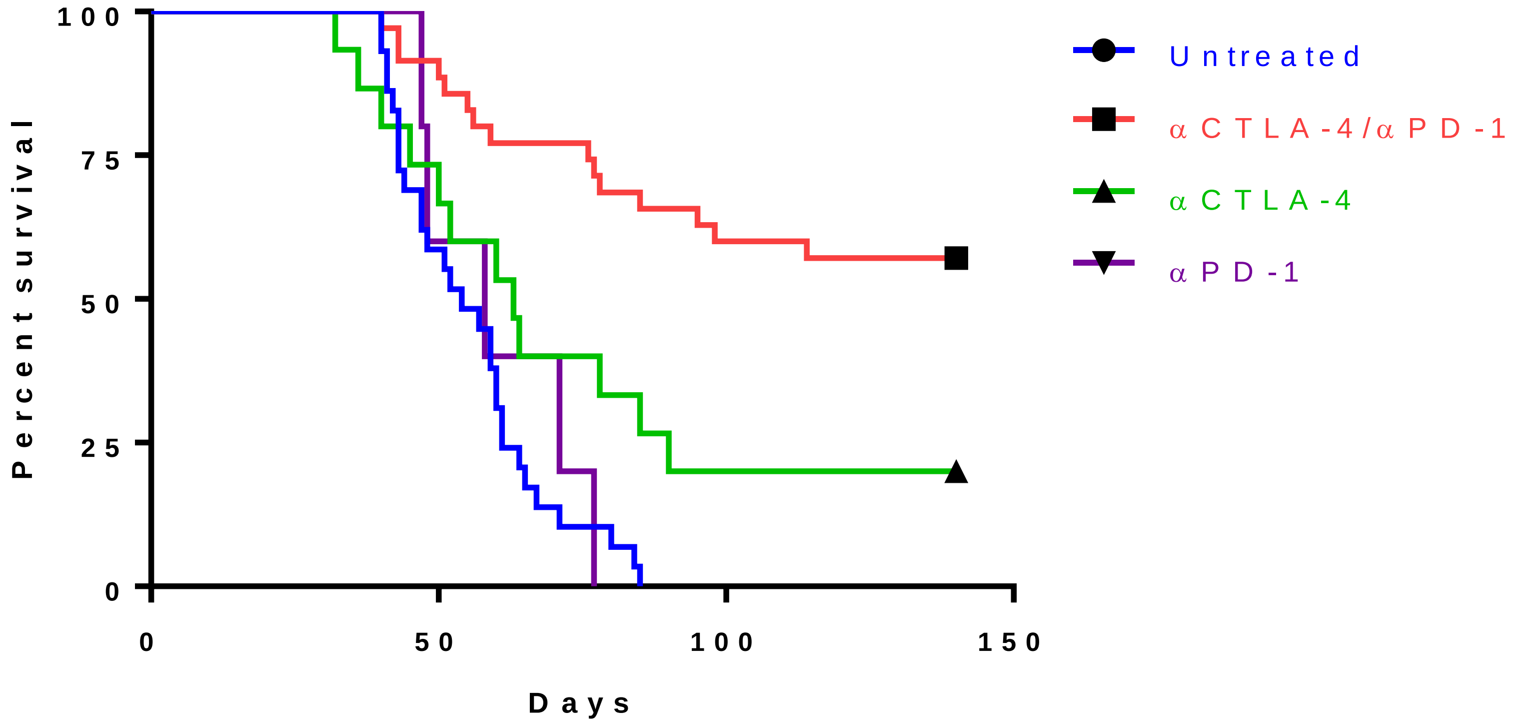






Gao JJ et al. *Nature Med,* 2017.

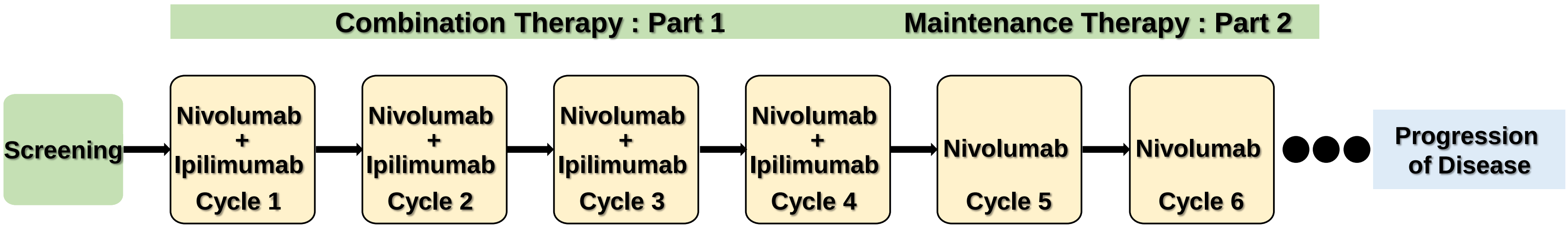
CTLA-4 and PD-1/PD-L1 Targeting in a Mouse Model of Prostate Cancer



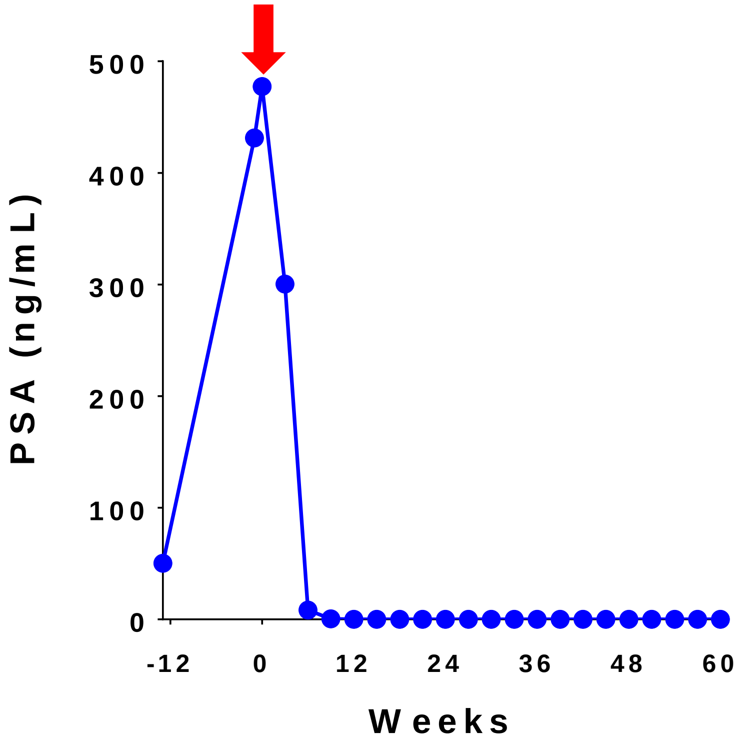
Combination of "immune checkpoint targets" will improve efficacy

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

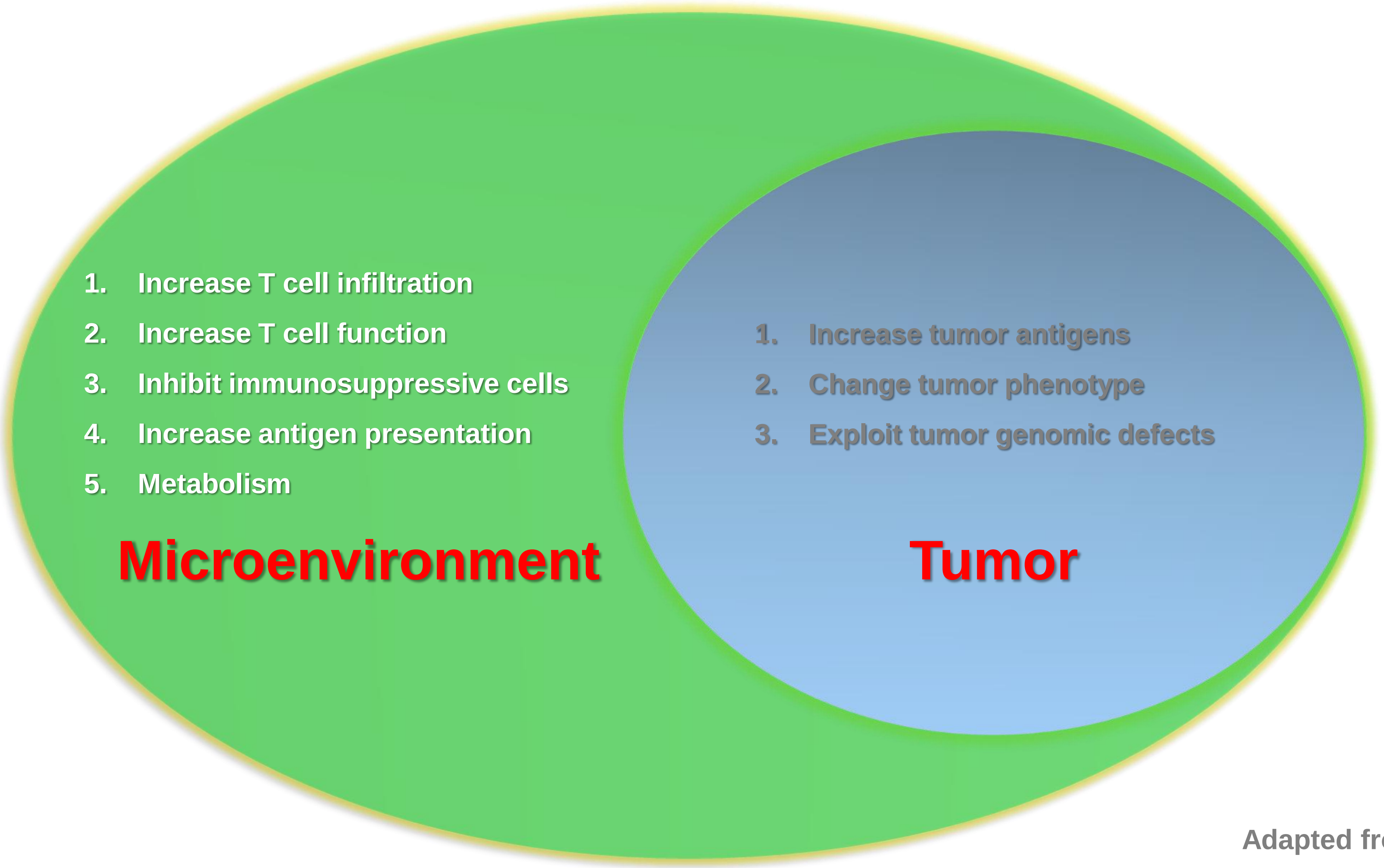
Nivolumab + Ipilimumab in mCRPC (NCT02985957)



PI: Sharma; Co-PI: Subudhi



Making Immune Checkpoint Therapies More Effective



Targeting Strategies

- Immune checkpoints
- Chemotherapy
- XRT
- Vaccines
- Cytokines
- Epigenetic modulators
- Metabolites

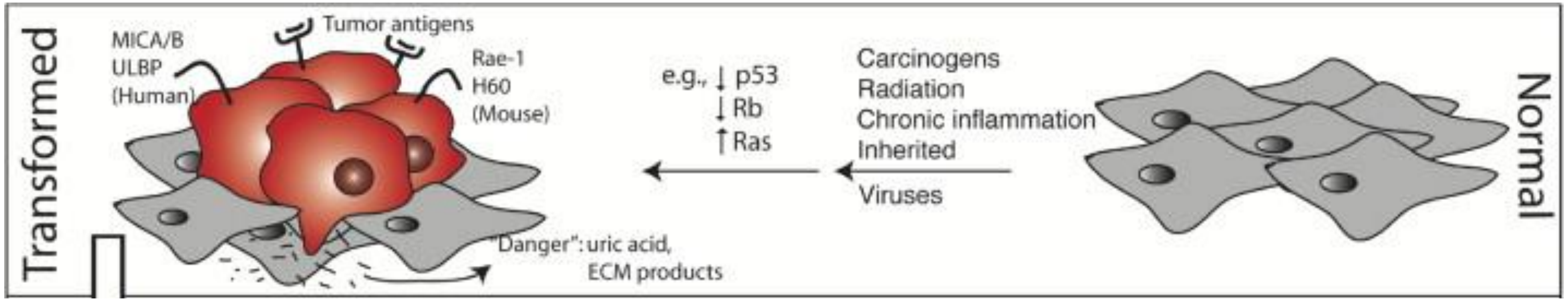
Adapted from Jianjun Gao

Moving Forward with Immune Checkpoint Therapies

- Turning “cold” tumors “hot”

- **Improving patient selection**

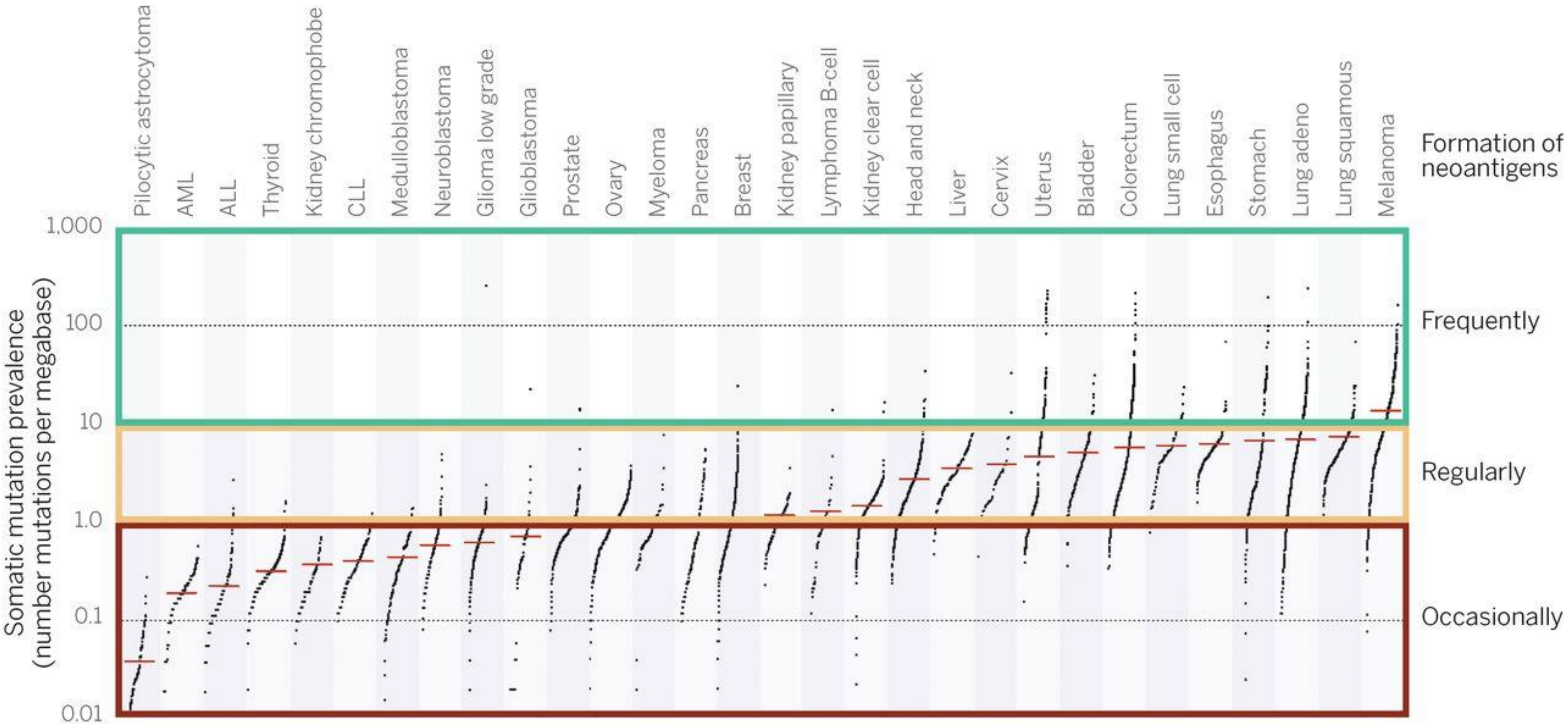
Tumor Neoantigens



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.

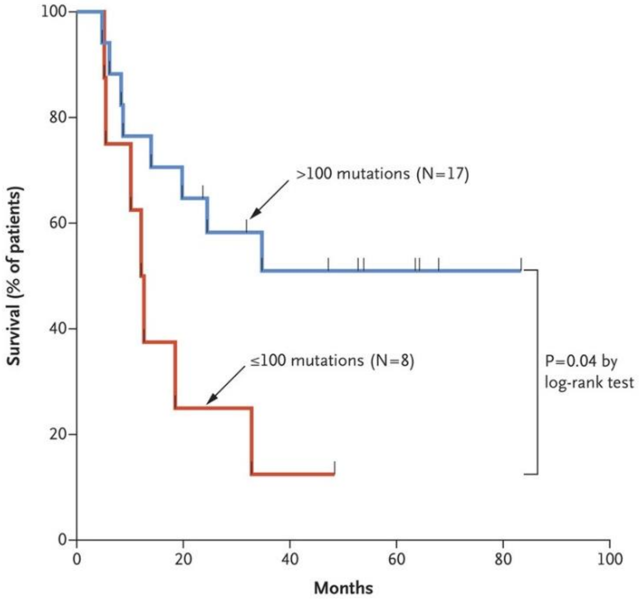
Neoantigens and Mutational Load Linked to Efficacy of Immune Checkpoint Therapies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

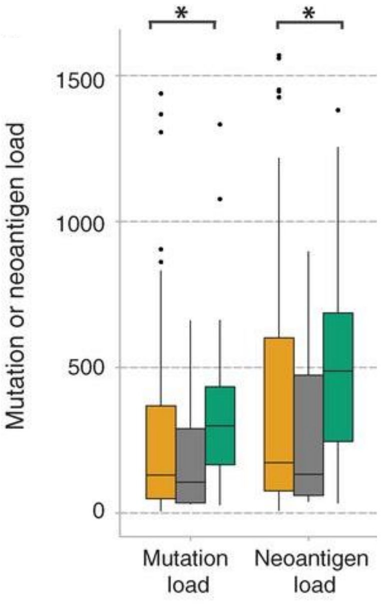
Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D., Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D., Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D., Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A., Kasthuri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



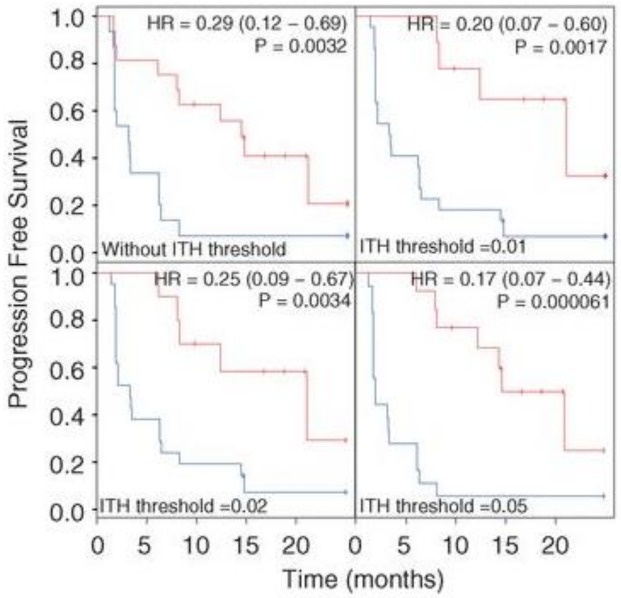
Science

REPORTS

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

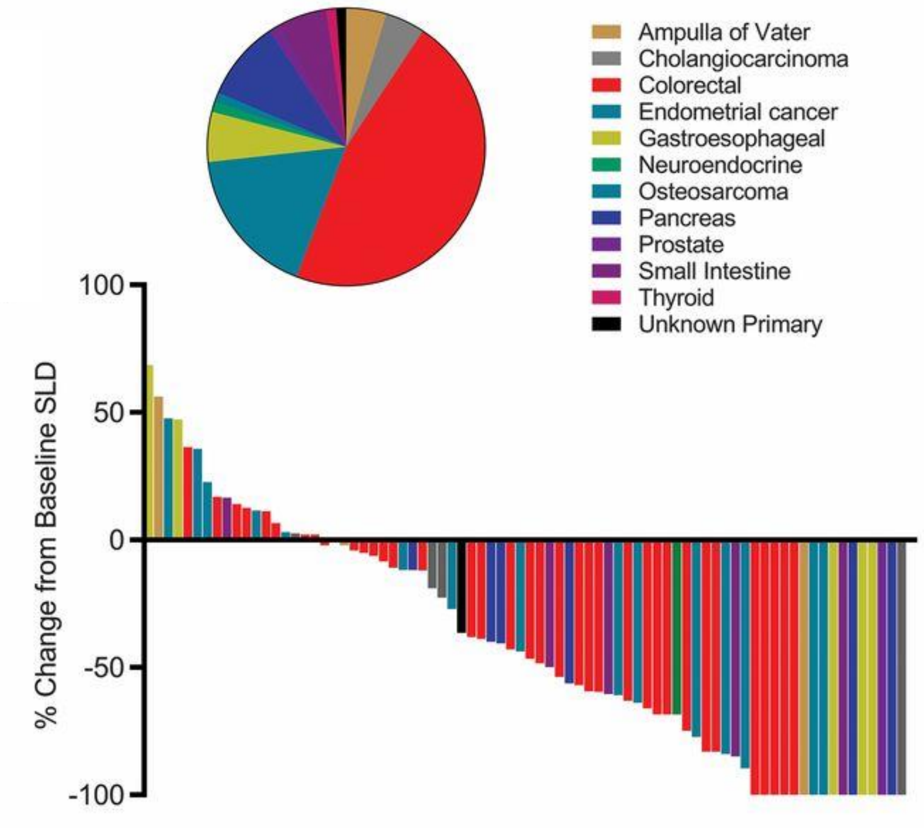
Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade

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†]



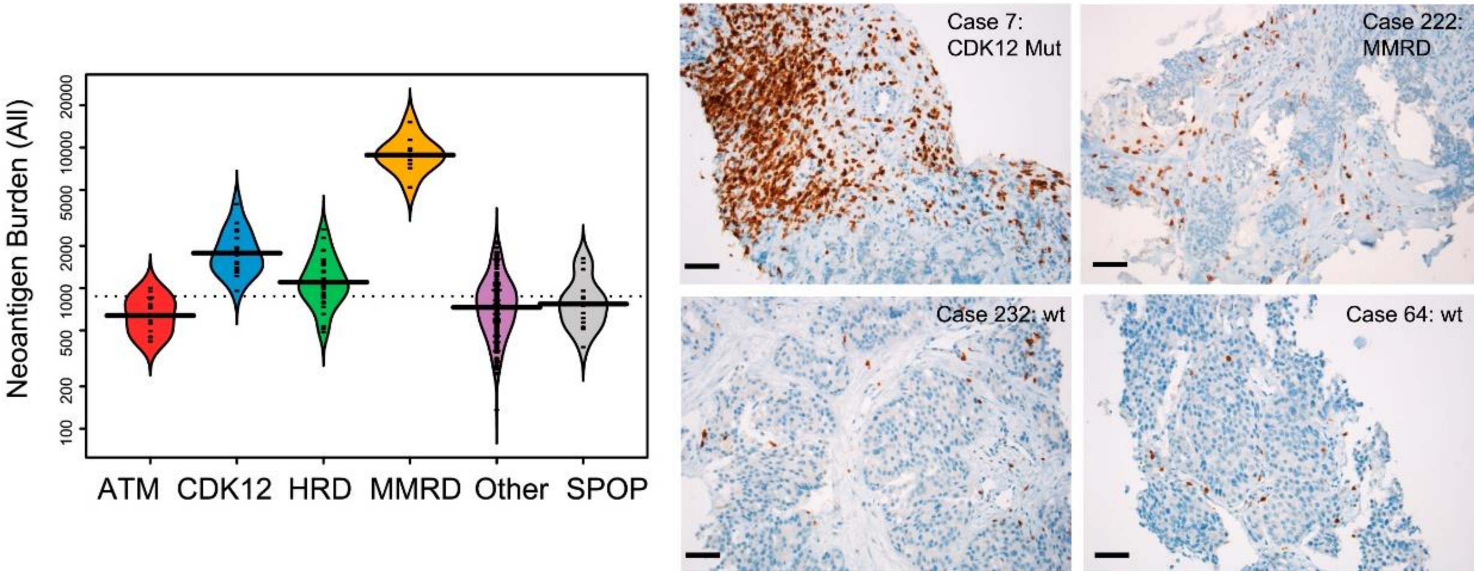
Genomic Defects that Increase Neoantigen Burden

Mismatch Repair (MMR) Defects



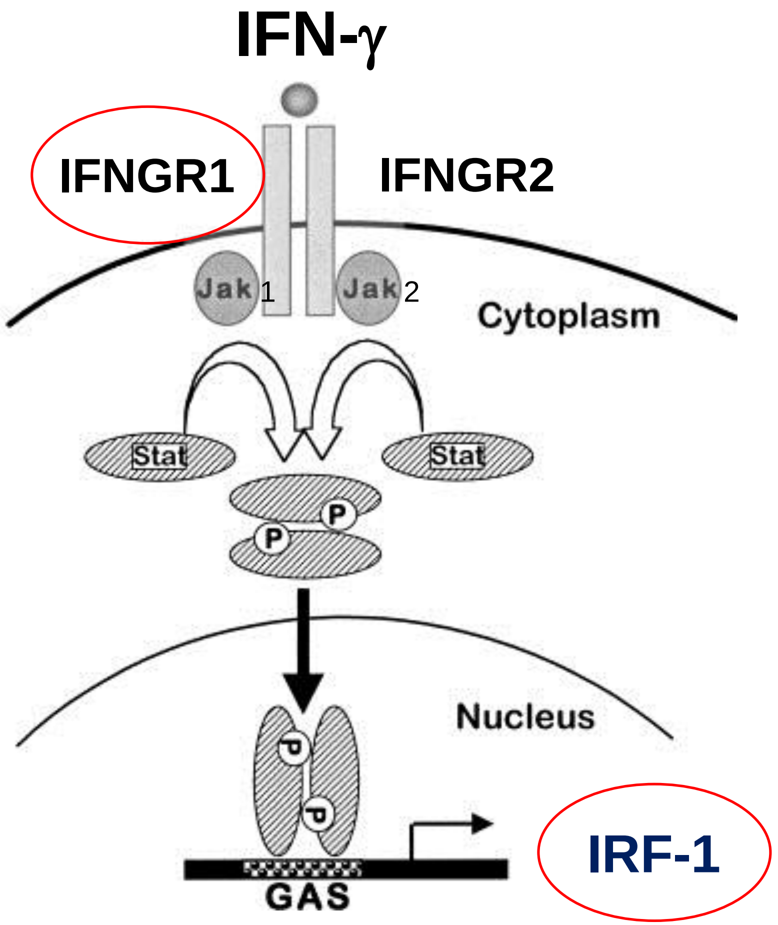
Le DT et al. *Science*, 2017.

CDK12 Mutations

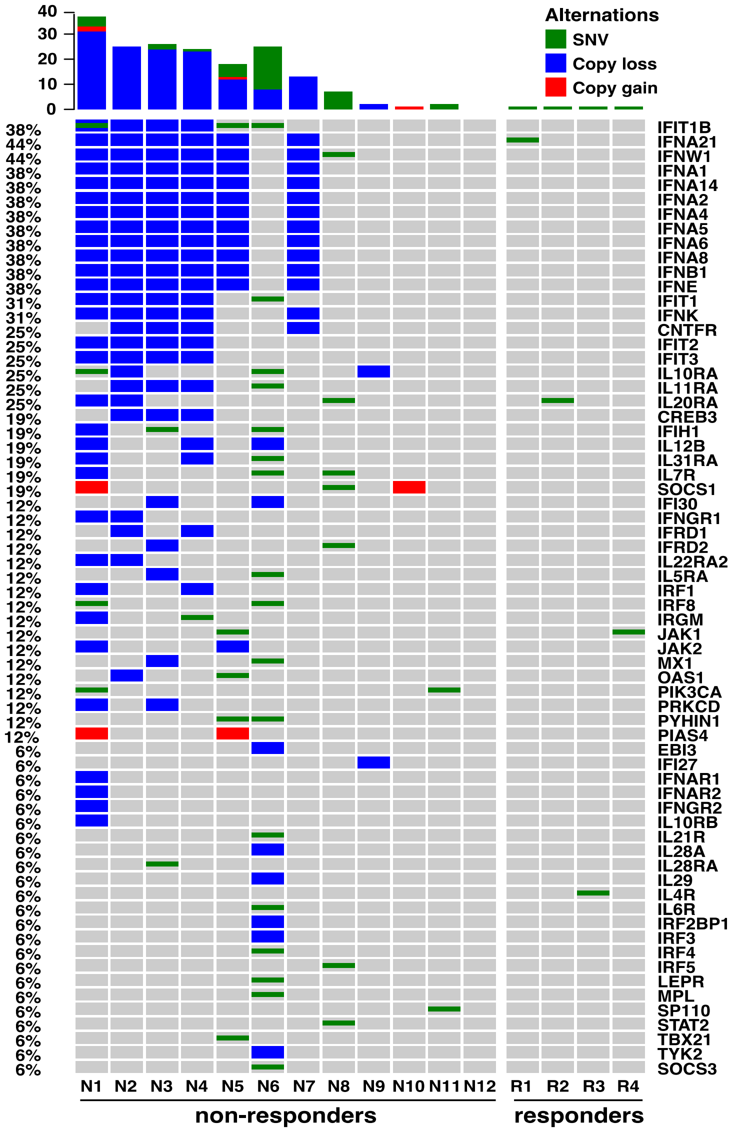


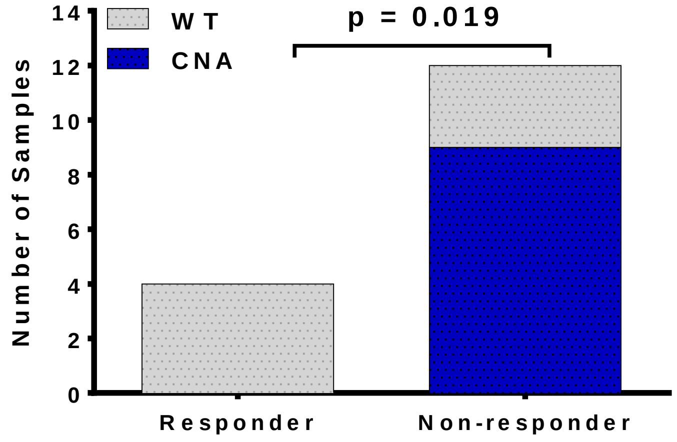
Wu YM et al. *Cell*, 2018.

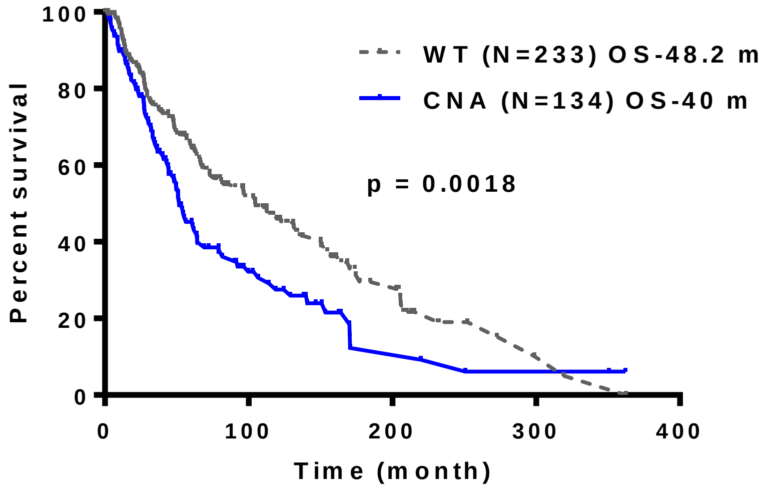
Defects in the IFN-γ Signaling Pathway Promote Resistance to Immune Checkpoint Therapies



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







Gao JJ et al. *Cell*, 2016.

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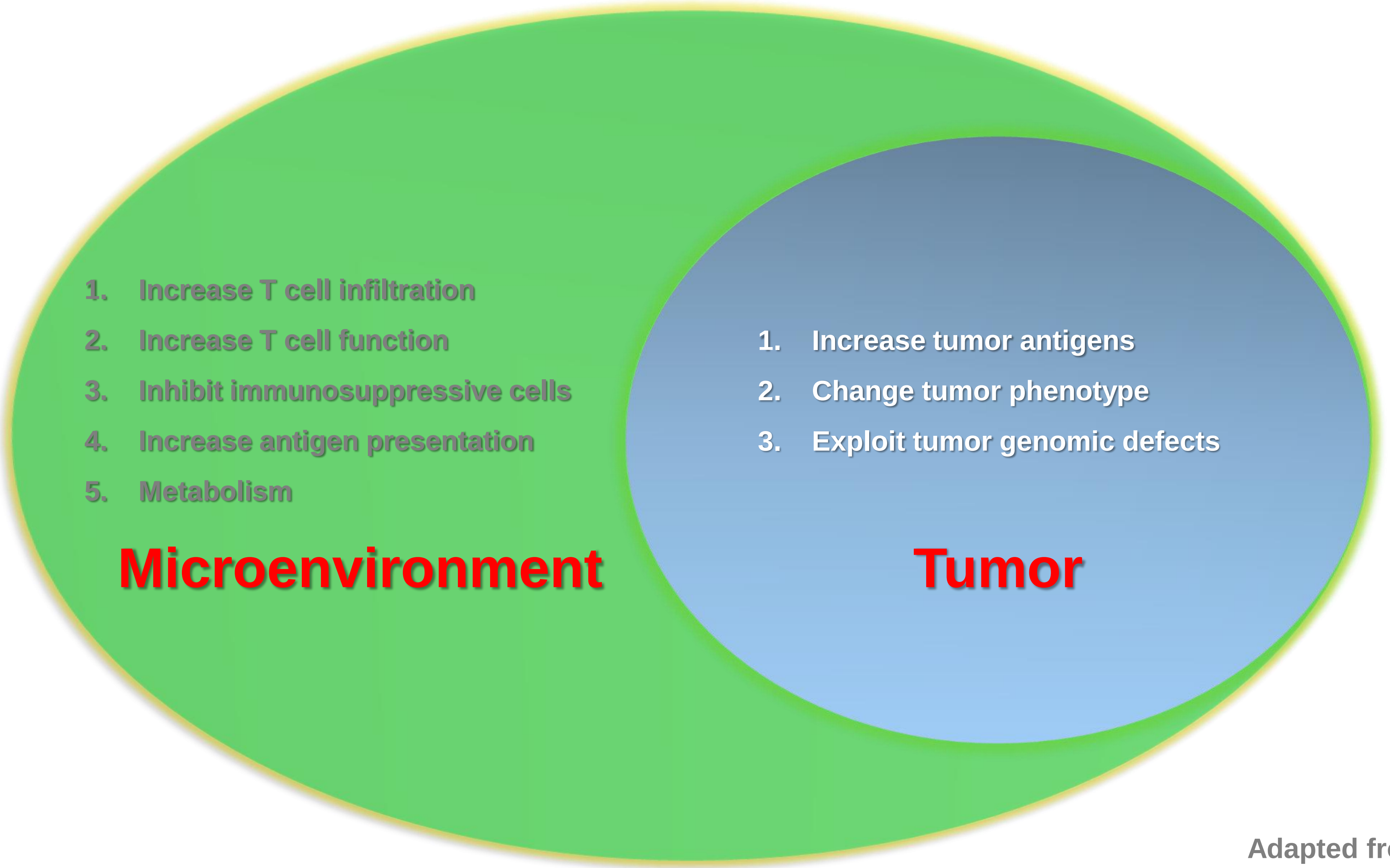

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Adapted from Jianjun Gao

Moving Forward with Immune Checkpoint Therapies

- Turning “cold” tumors “hot”
  - More active $CD8^+$ T cells
  - Less immunosuppressive cells

- Improving patient selection
  - Genomics to identify those patients most likely to benefit

Novel Immunotherapy Targets