

# ***Innovative Clinical Trial Design for Immune Monitoring***

**Society for Immunotherapy of Cancer (SITC)**

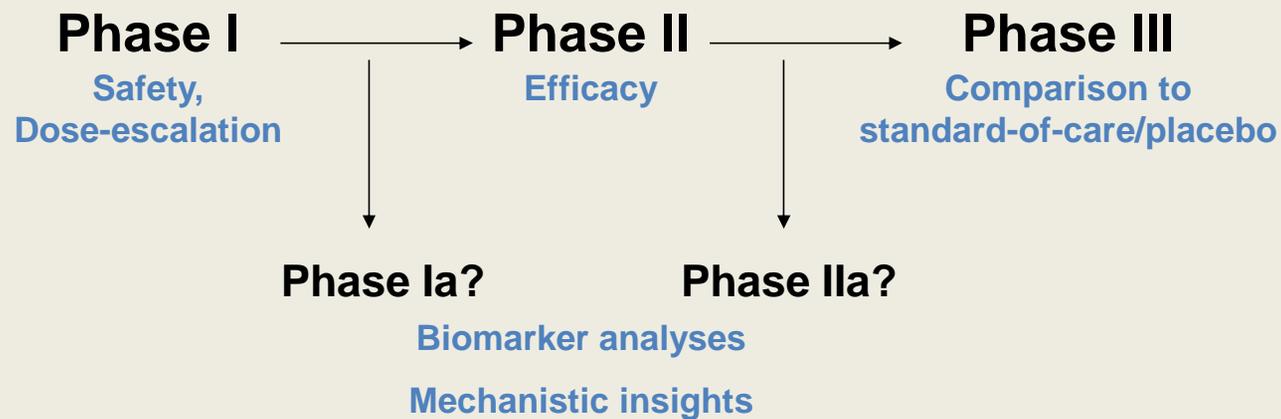
**Primer on Tumor Immunology and Cancer Immunotherapy™**

**November 5, 2015**

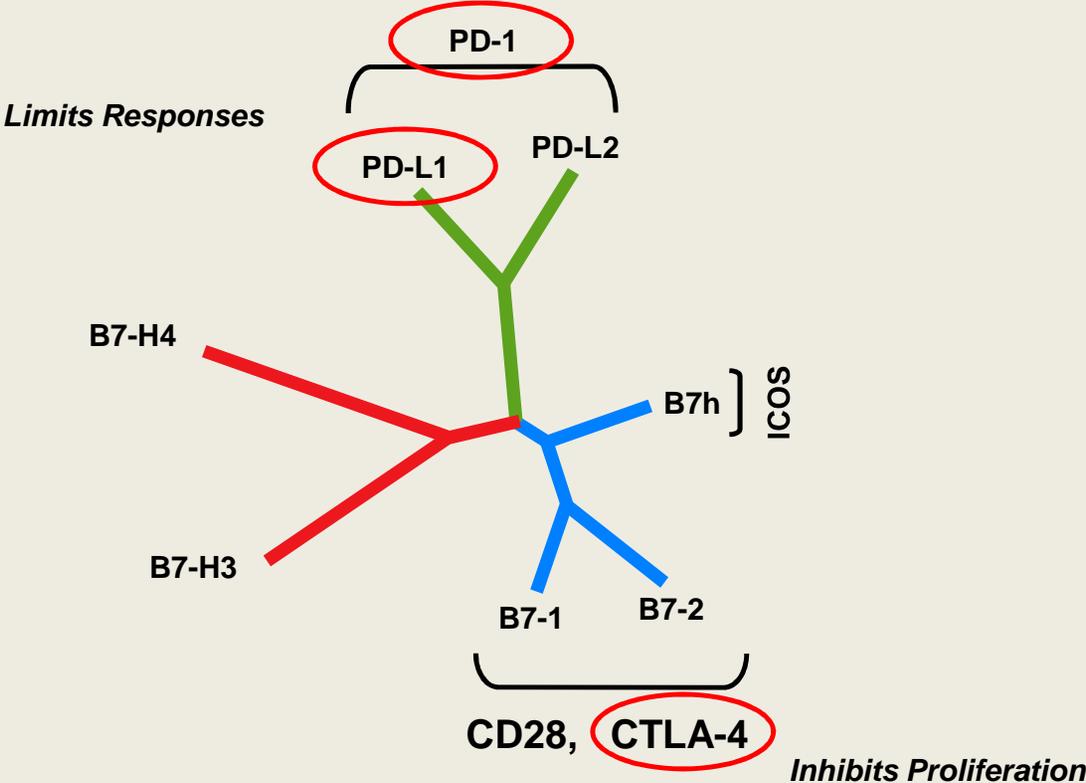
**Sumit K. Subudhi, MD, PhD**

**Assistant Professor, Genitourinary Medical Oncology**

# Re-thinking clinical trial design to obtain appropriate samples for biomarker studies



# Targeting immune checkpoints



# Challenges/Limitations

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

# Delayed immune responses with ipilimumab

Screening



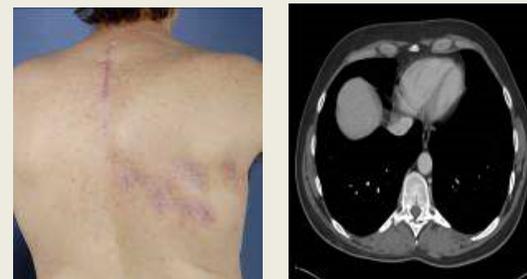
Week 12  
Initial increase in  
total tumour burden (mWHO PD)



Week 16  
Responding



Week 72  
Durable & ongoing response



Courtesy of K. Harmankaya

# Clinical states model of prostate cancer

Non-castrate

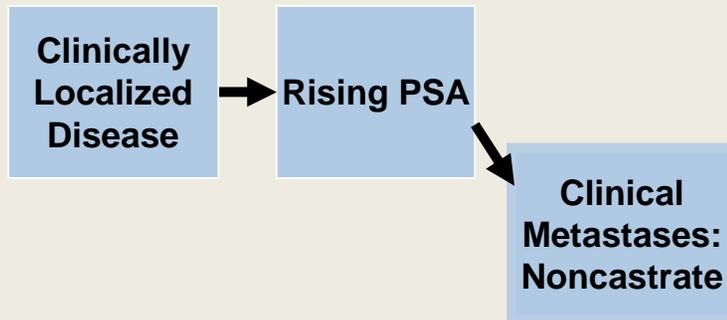
Castration-resistant

Modified from Scher and Heller. *Urology* 2000.

# Clinical states model of prostate cancer

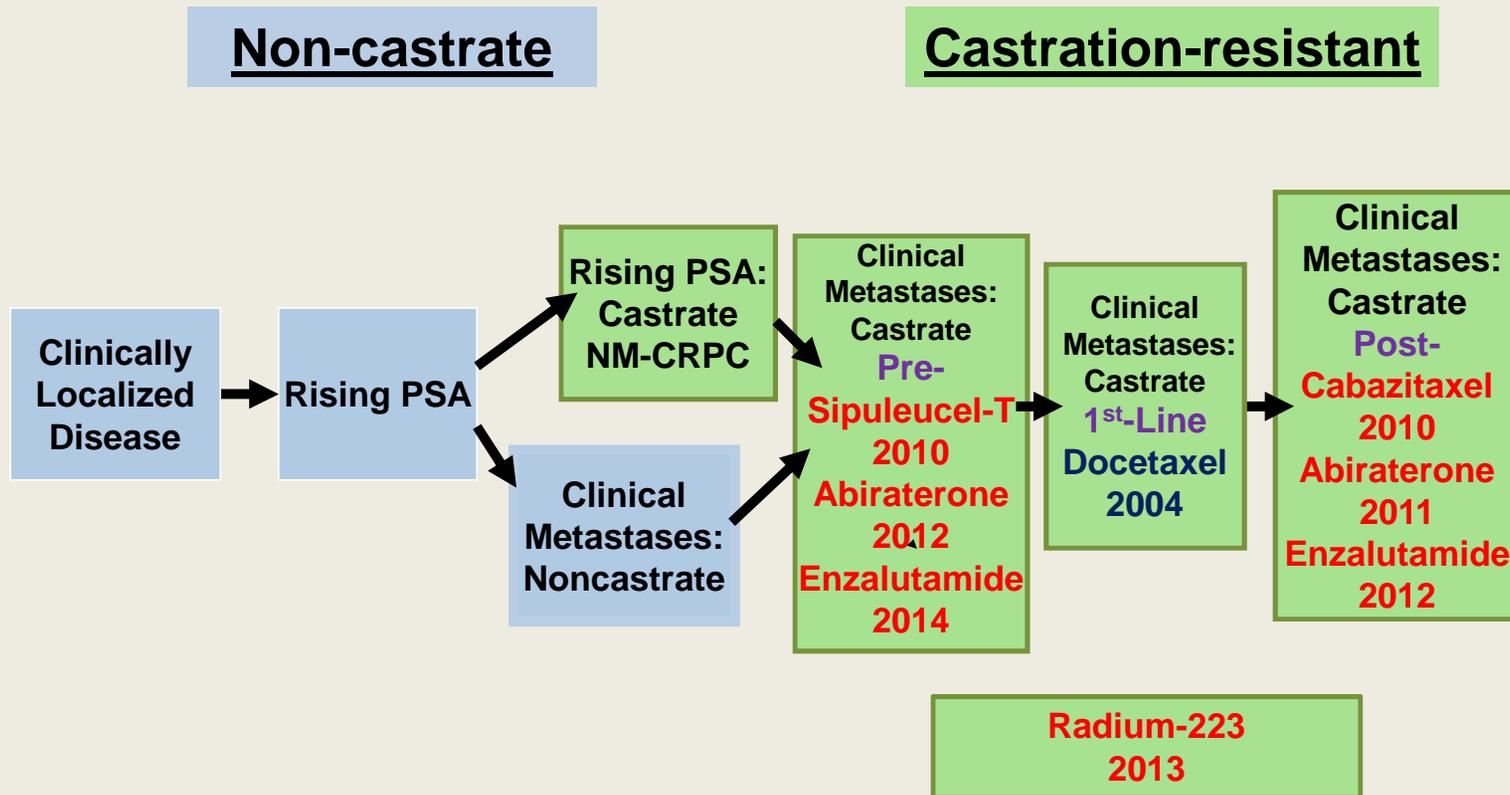
Non-castrate

Castration-resistant



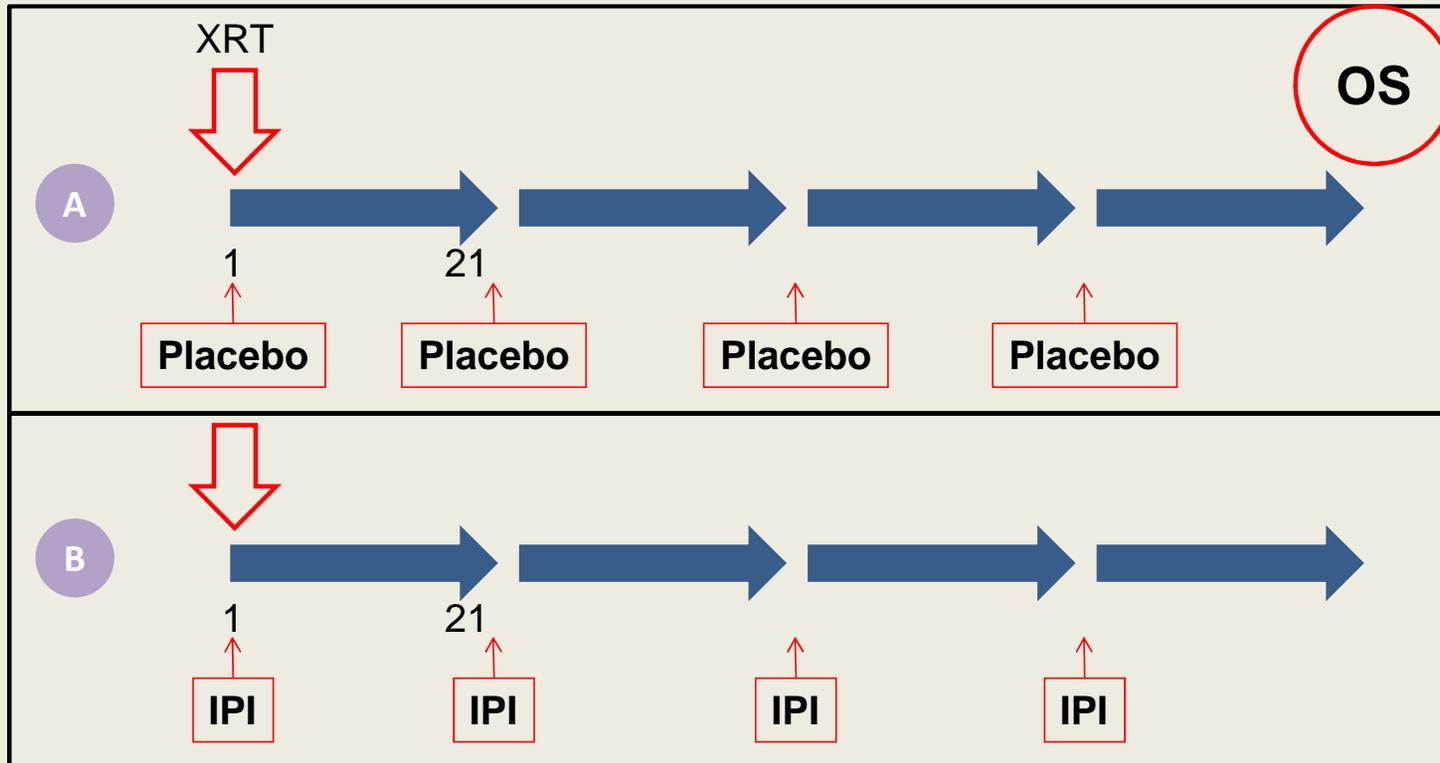
Modified from Scher and Heller. *Urology* 2000.

# Clinical states model of prostate cancer



Modified from Scher and Heller. *Urology* 2000.

# Trial schema



NCT00861614; BMS

Estimated Enrollment: 800

Study Start Date: May 2009

Estimated Study Completion Date: September 2013

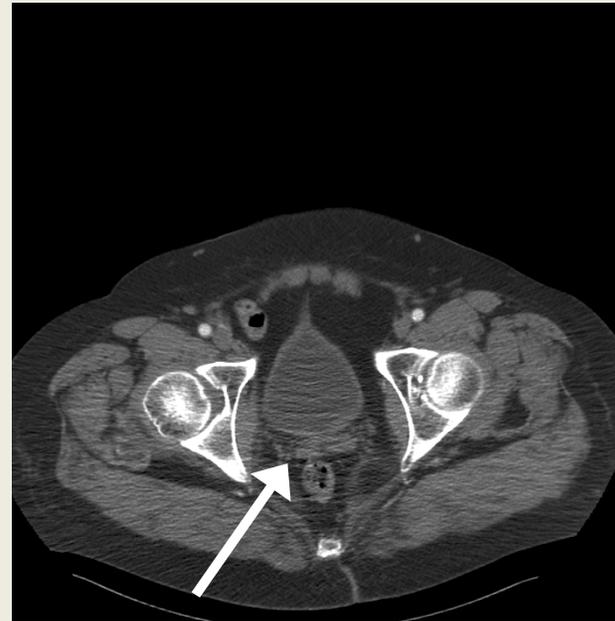
Estimated Primary Completion Date: September 2013 (Final data collection date for primary outcome measure)

# Complete responder: prostate cancer

Screening



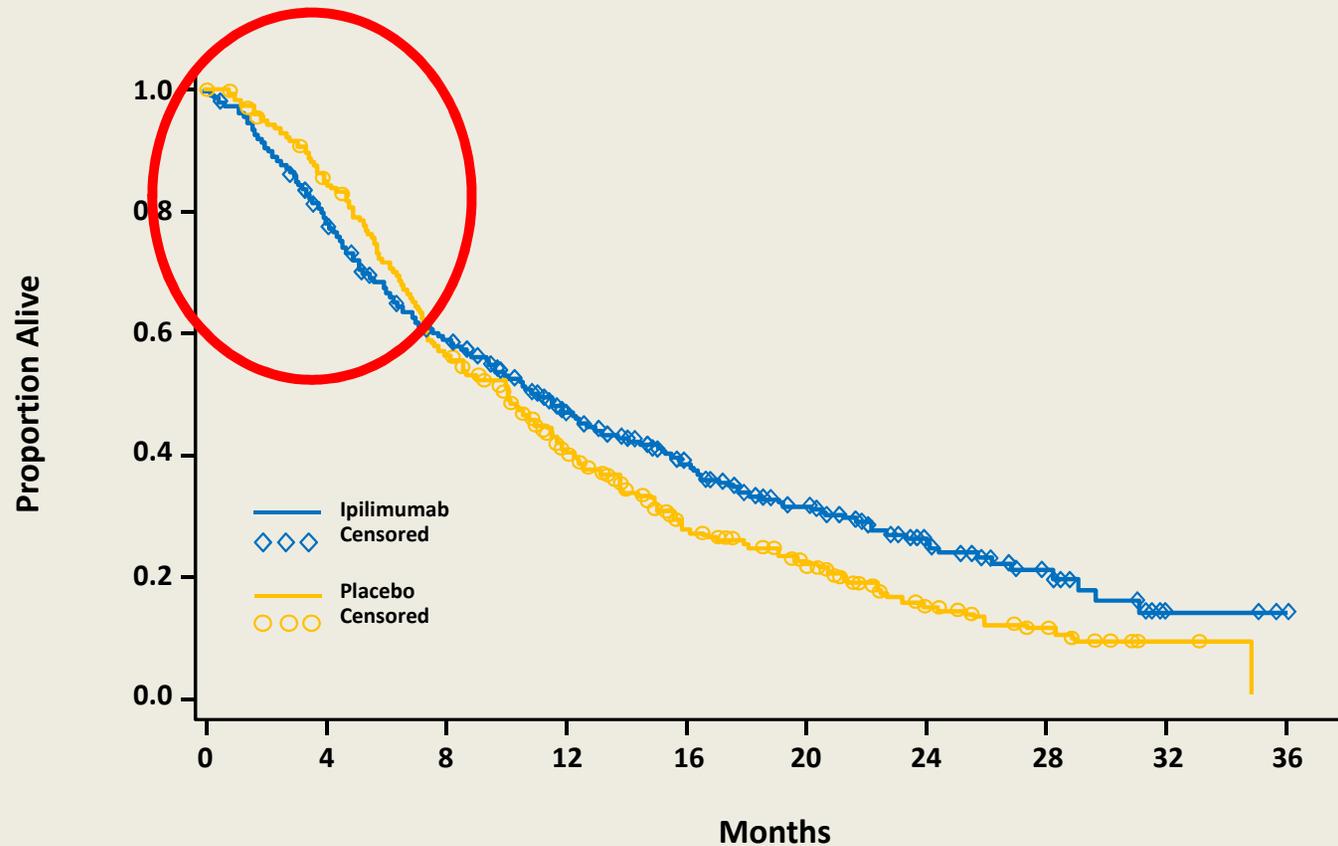
14 months



Phase III trial recently reported

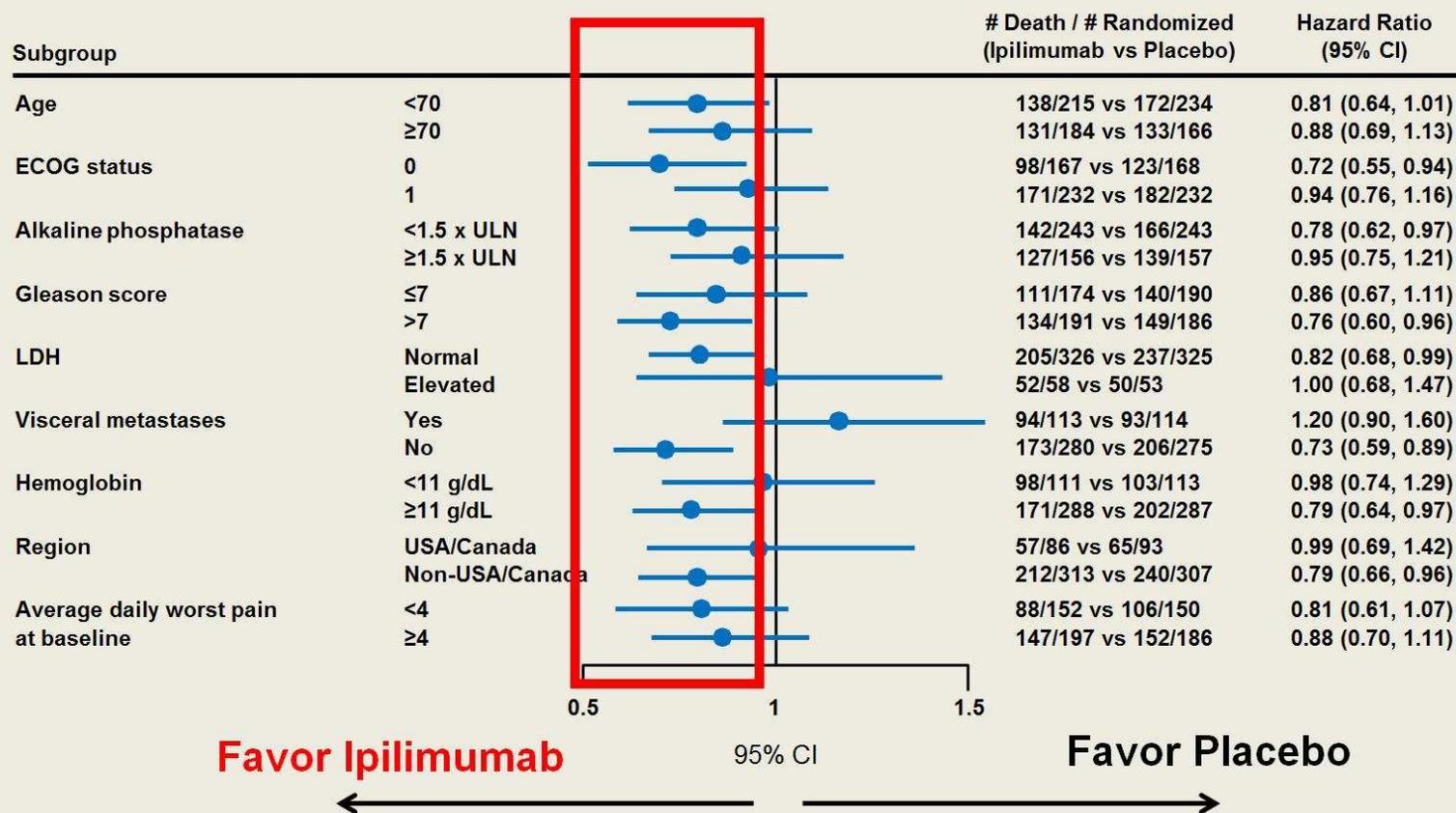
**BMS**

# Ant-CTLA-4 (ipilimumab) + radiation therapy in castration-resistant prostate cancer (CRPC)

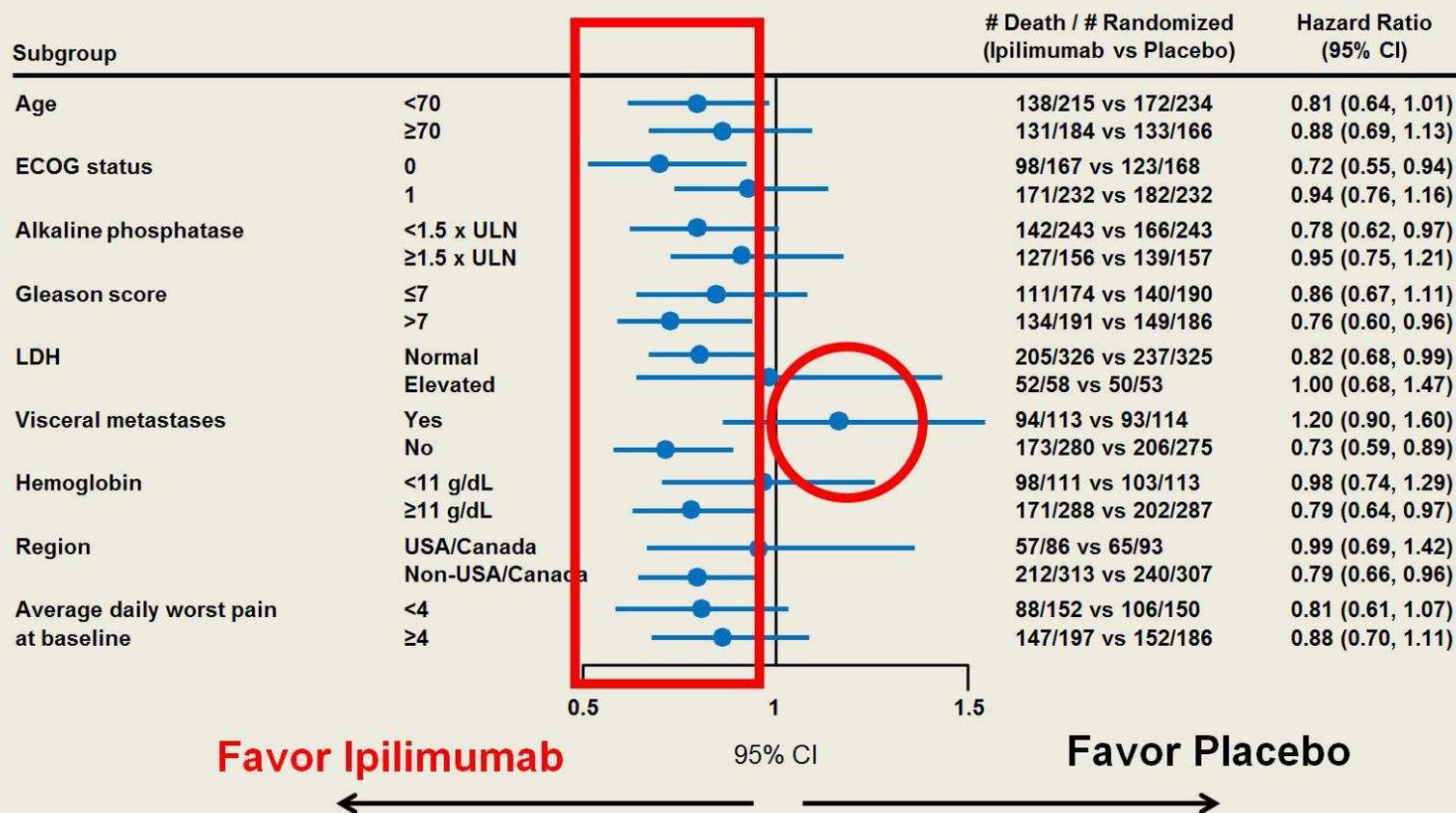


Kwon, ED et al. Lancet Oncol. 2014 Jun;15(7):700-12

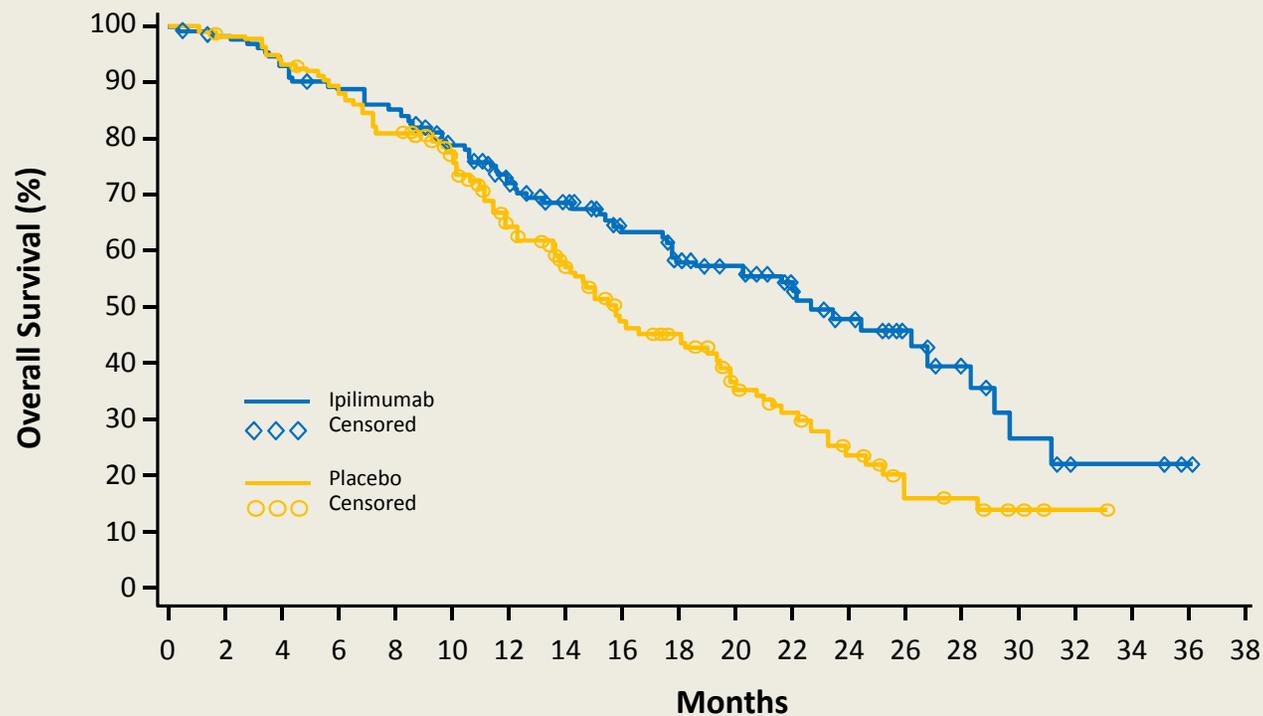
# Overall survival: Pre-specified subgroups



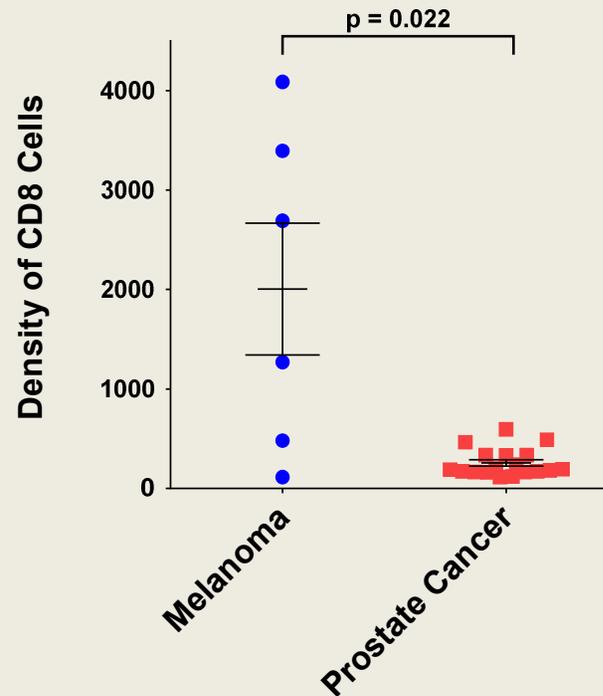
# Overall survival: Pre-specified subgroups



# Exploratory subgroup analysis of OS in CRPC patients treated with ipilimumab



# Lower frequency of CD8 T cells in prostate cancer (non-immunogenic) versus melanoma (immunogenic)



# T cell infiltration of the prostate induced by androgen withdrawal in patients with prostate cancer

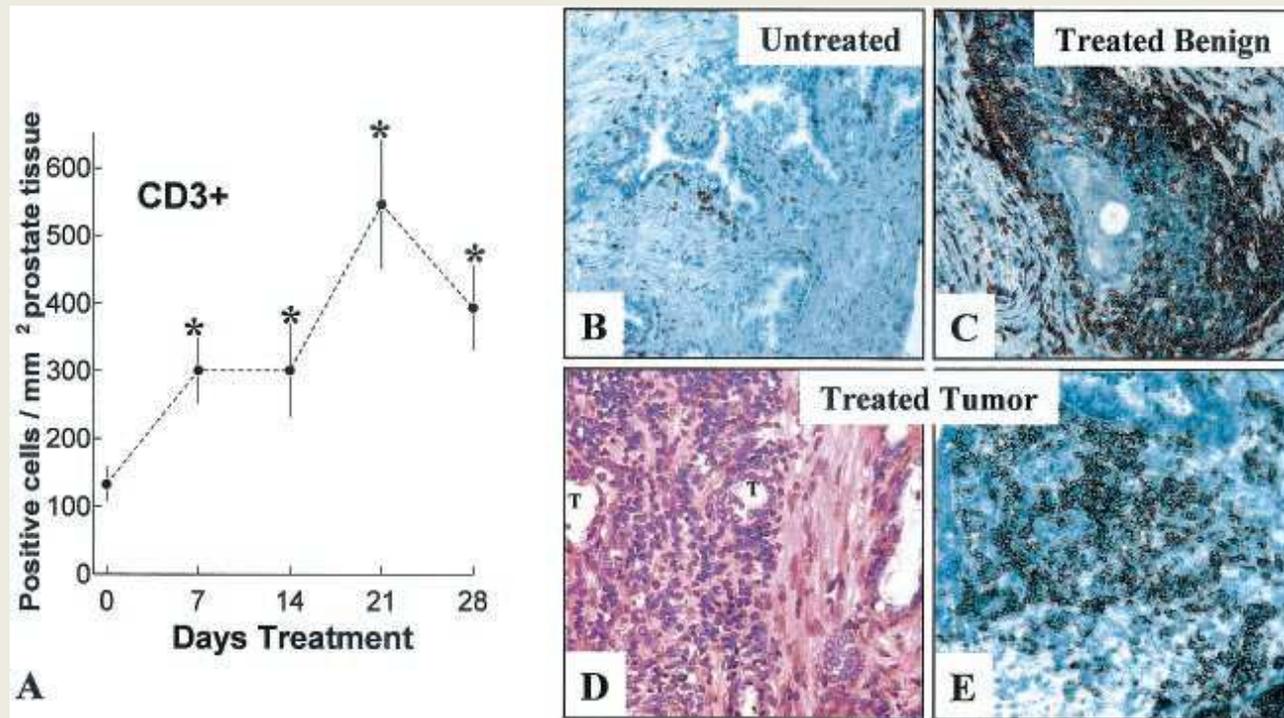
Maria Mercader<sup>\*†</sup>, Barbara K. Bodner<sup>\*†</sup>, Micheal T. Moser<sup>\*†</sup>, Pamela S. Kwon<sup>†</sup>, Eugene S. Y. Park<sup>\*†</sup>, Ryan G. Manecke<sup>†</sup>, Thomas M. Ellis<sup>\*</sup>, Eva M. Wojcik<sup>‡</sup>, Damu Yang<sup>\*</sup>, Robert C. Flanigan<sup>†</sup>, W. Bedford Waters<sup>†</sup>, W. Martin Kast<sup>\*</sup>, and Eugene D. Kwon<sup>\*†§</sup>

Departments of <sup>†</sup>Urology and <sup>‡</sup>Pathology, and the <sup>\*</sup>Cancer Immunology Program of the Cardinal Bernardin Cancer Center, Loyola University of Chicago, Maywood, IL

Edited by James P. Allison, University of California, Berkeley, CA, and approved October 8, 2001 (received for review March 22, 2001)

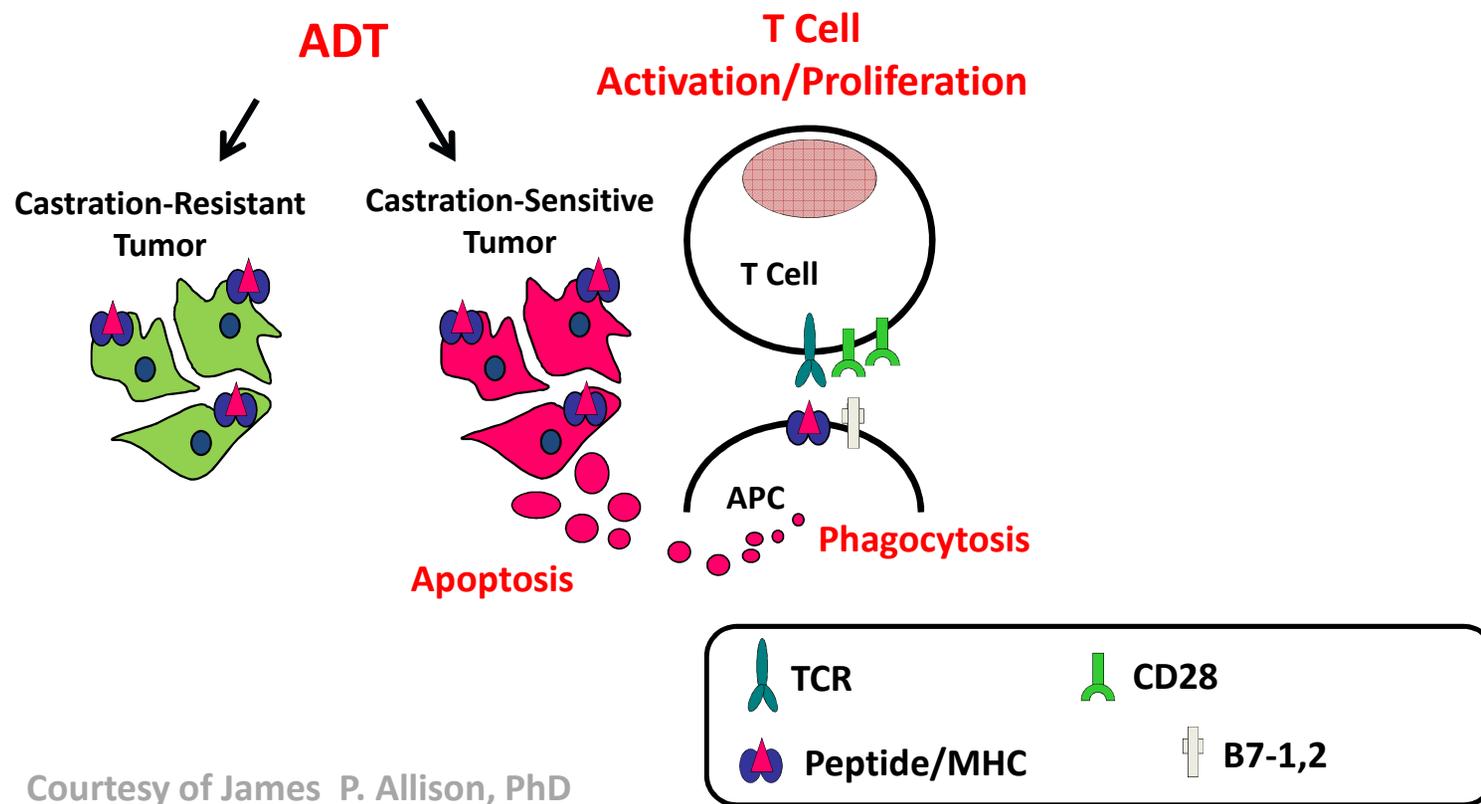
PNAS | December 4, 2001 | vol. 98 | no. 25 | 14565–14570

# Androgen Blockade Increases TILs



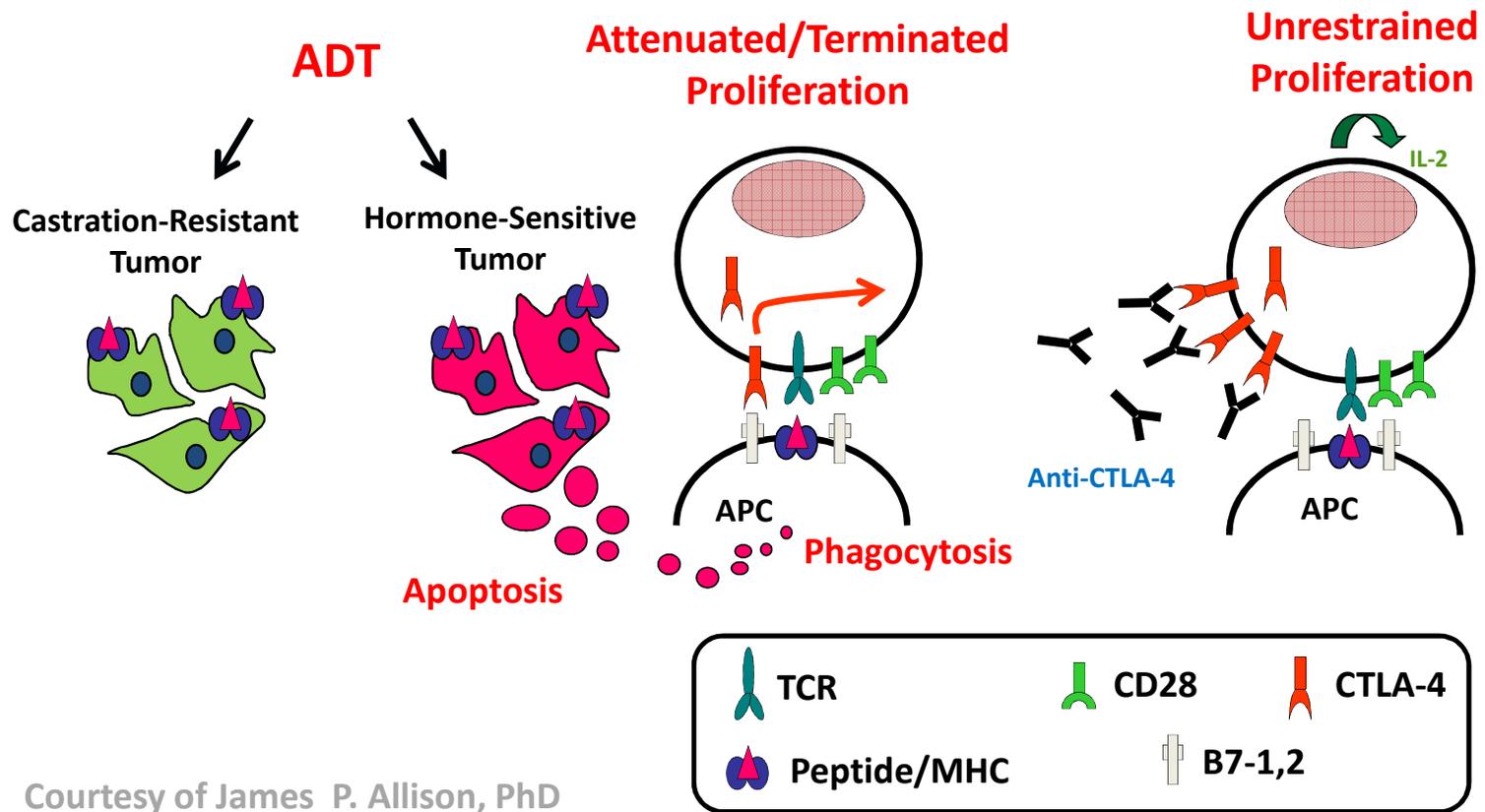
Mercader M et al. PNAS 2001; 98:14565-14570

# The Effects of Androgen Deprivation Therapy (ADT) on Tumor Cells and the Immune System



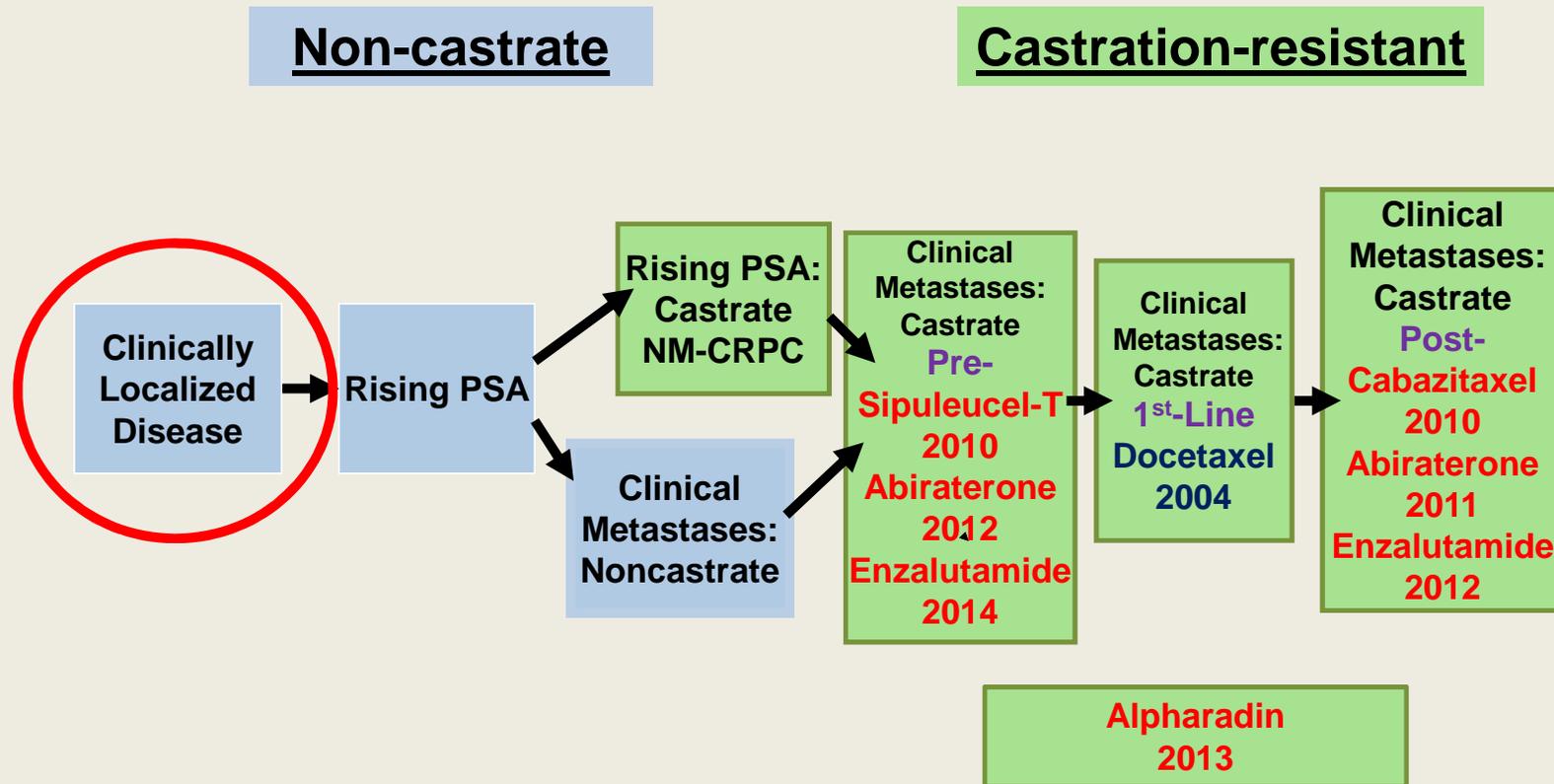
Courtesy of James P. Allison, PhD

# Enhancing the Anti-Tumor Effects of Anti-CTLA-4



Courtesy of James P. Allison, PhD

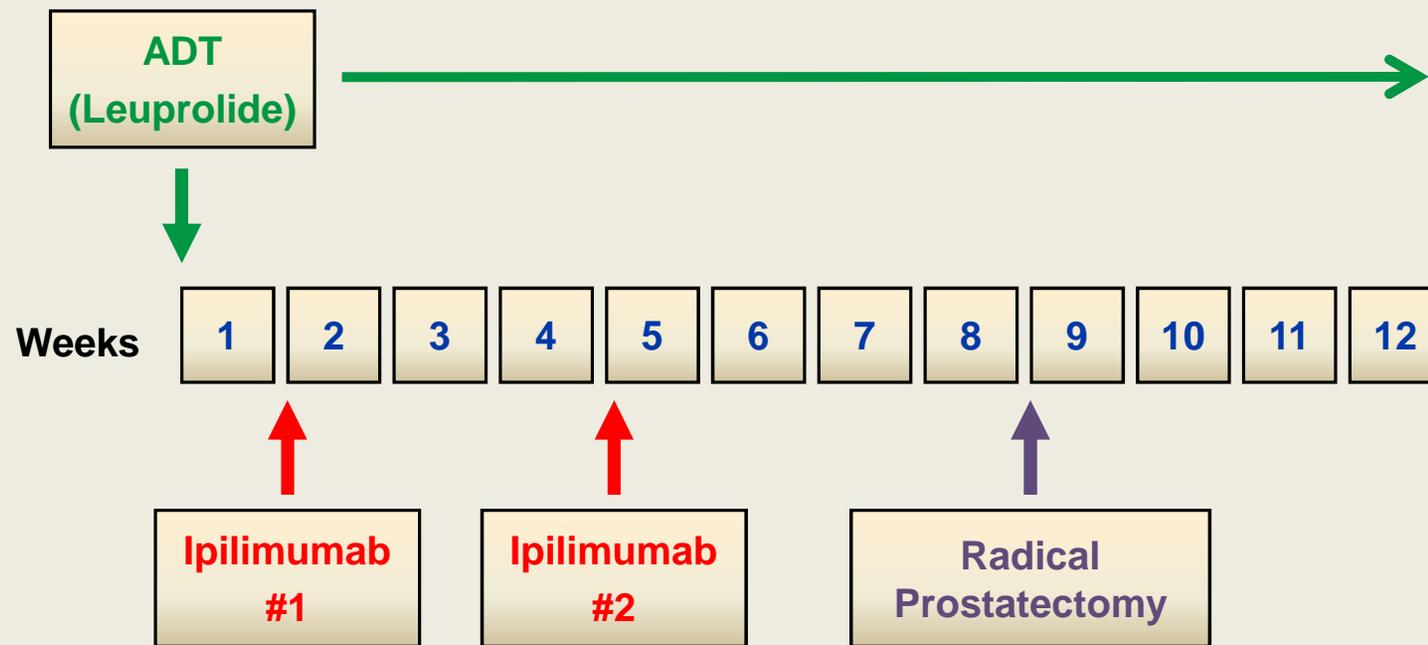
# Clinical states model of prostate cancer



Modified from Scher and Heller. *Urology* 2000.

# MD Anderson Protocol 2009-0135:

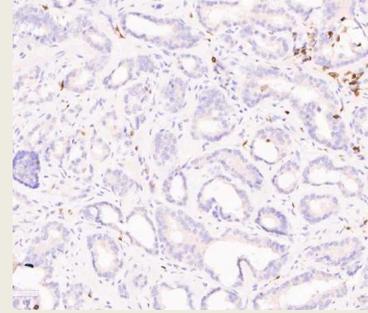
*A Neoadjuvant Phase IIa Study of Ipilimumab Plus  
Hormone Ablation in Men with Prostate Cancer  
Followed by Radical Prostatectomy*



Padmanee Sharma, MD, PhD

## CD3 T-cells within the tumor microenvironment

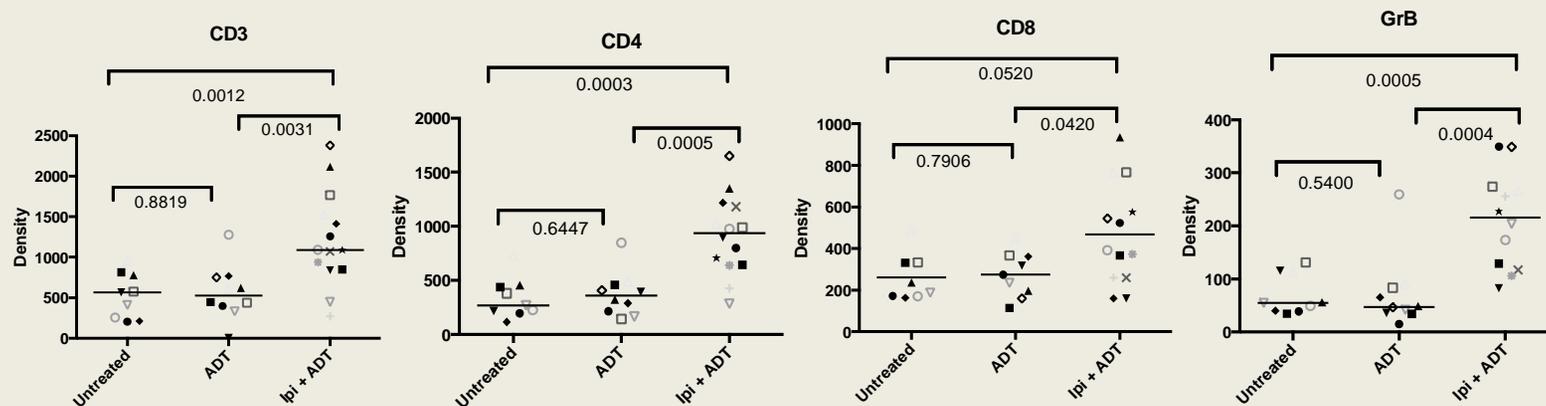
Untreated  
(Control)



1X

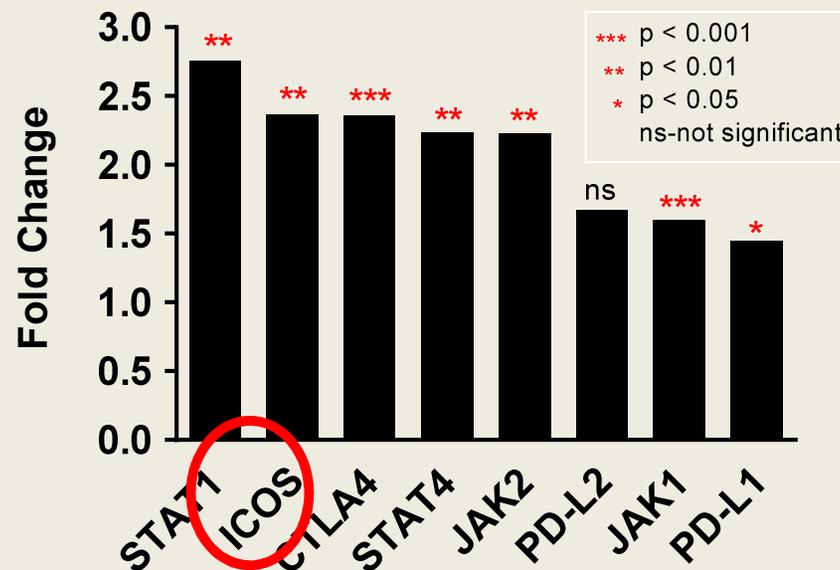
20X

# Targeting AR signaling plus CTLA-4 increases CD3, CD4, CD8 and GrB cells within the tumor microenvironment

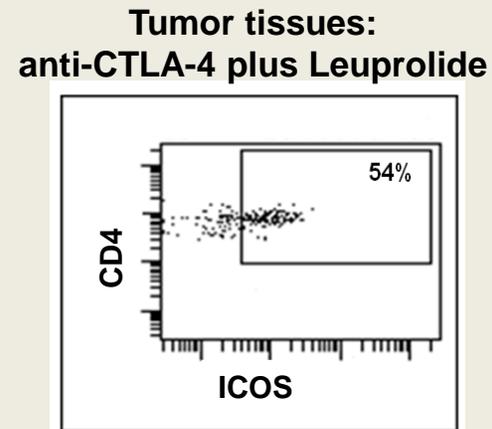
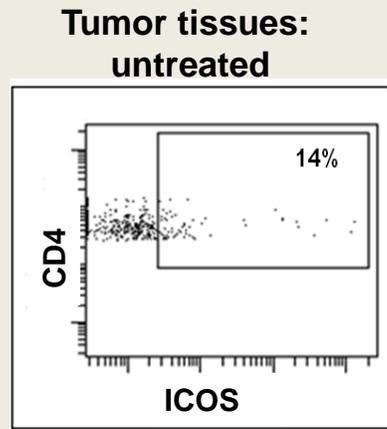


Mann Whitney test, unpaired, two tailed

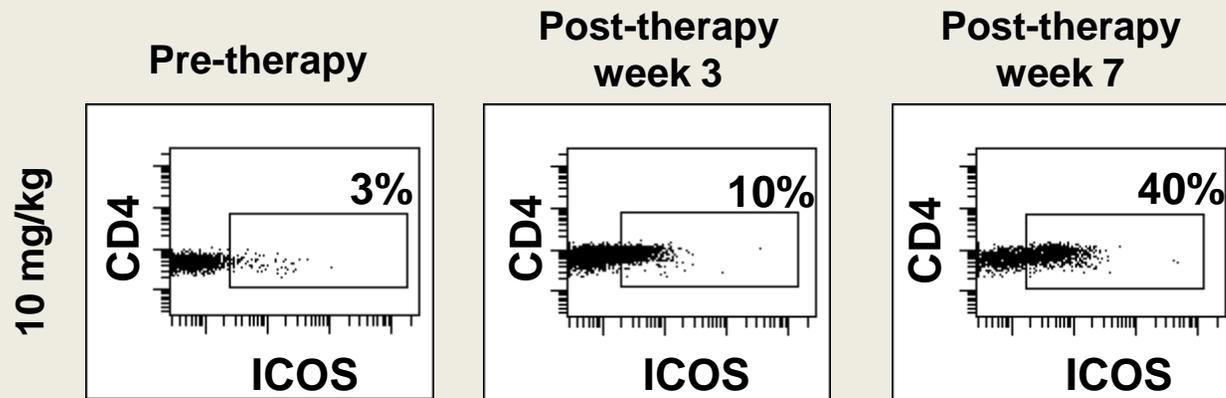
# Select immune DEGs in prostate tumor tissues after treatment with ipilimumab plus ADT



# Increased Frequency of ICOS<sup>+</sup>CD4 T Cells in Tumors from Anti-CTLA-4 Treated Patients

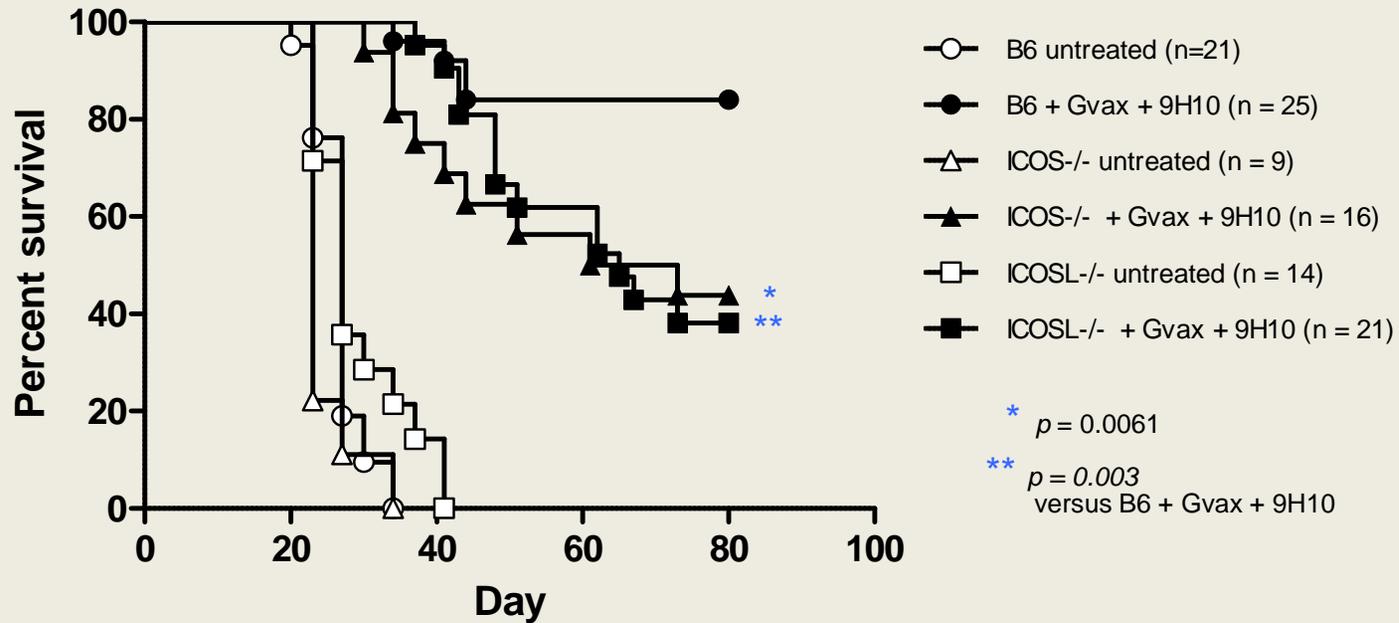


# Frequency of ICOS<sup>+</sup>CD4 T cells increase in peripheral blood after treatment with anti-CTLA-4 antibody

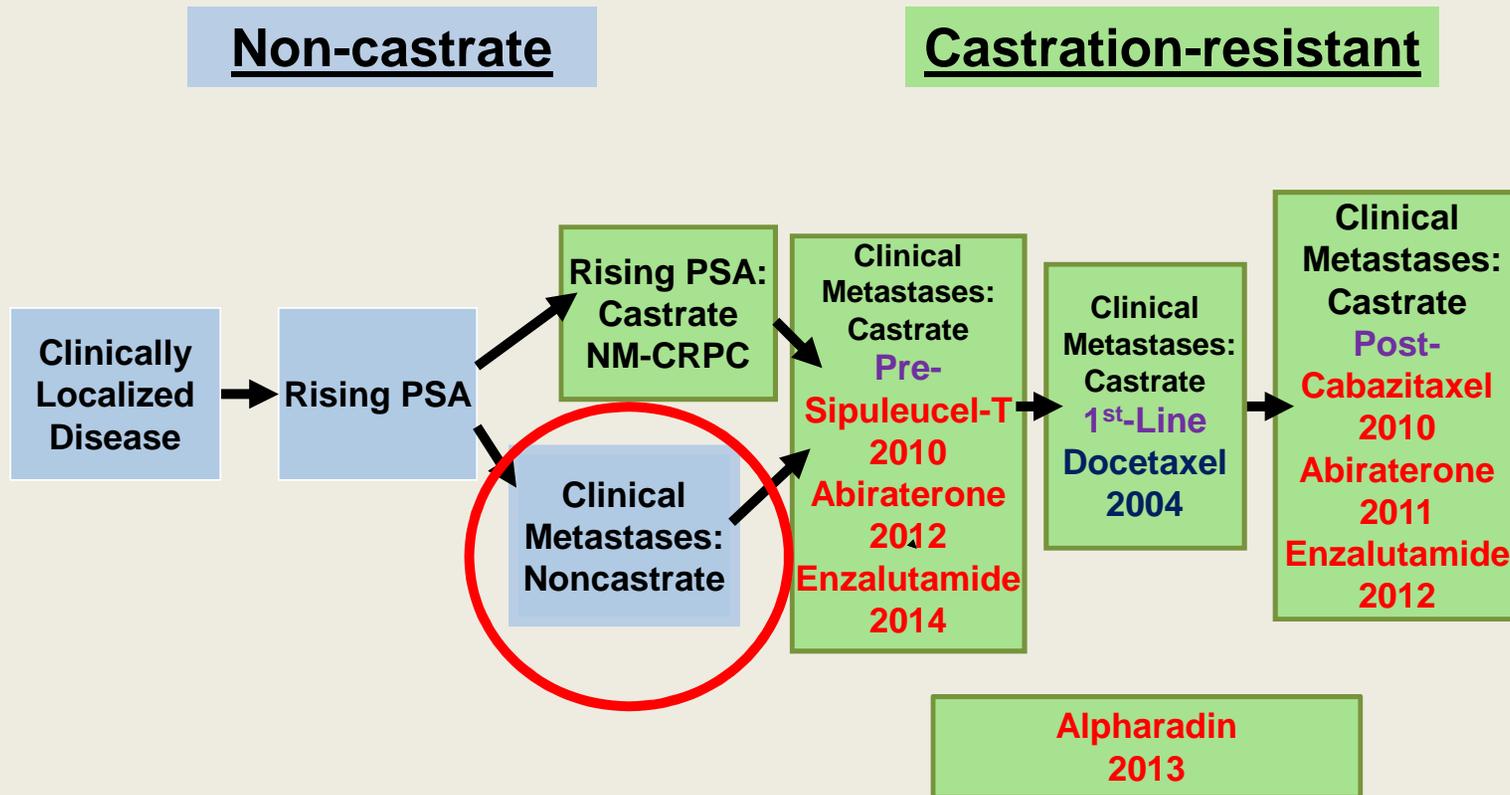


Carthon et al., *Clinical Cancer Research*, 2010

# ICOS/ICOSL pathway is necessary for optimal anti-tumor responses in the setting of CTLA-4 blockade

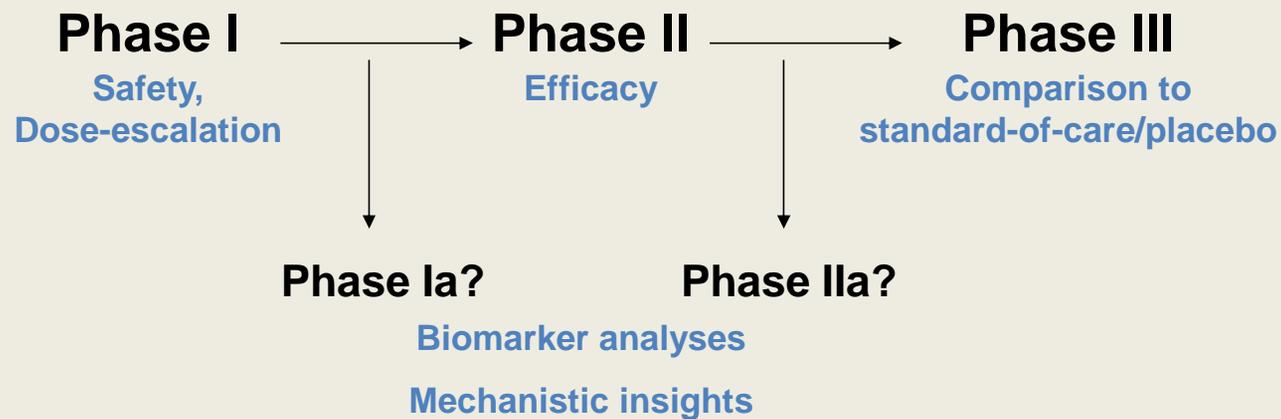


# Clinical states model of prostate cancer



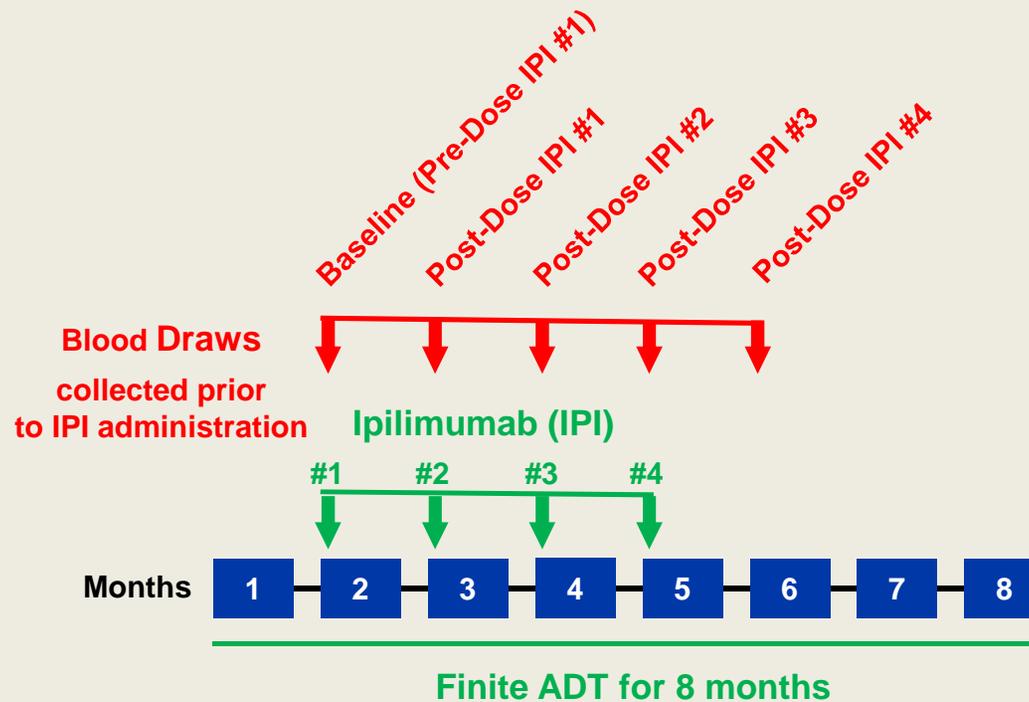
Modified from Scher and Heller. *Urology* 2000.

# Re-thinking clinical trial design to obtain appropriate samples for biomarker studies



# MD Anderson Protocol 2009-0378:

*A Phase II Study of Ipilimumab plus ADT  
in Non-Castrate Prostate Carcinoma*



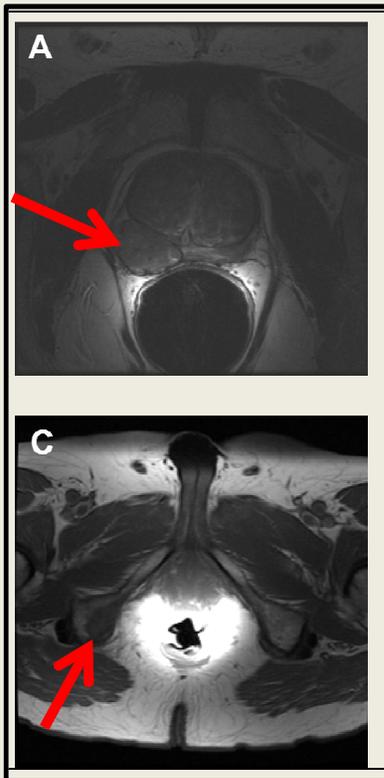
Ana Aparicio, MD

# Endpoints

- **Primary:**
  - To estimate rate of PSA  $\leq 0.2$  ng/ml at 7 months (Maha Hussain, MB, ChB)
- **Secondary:**
  - To assess the time to testosterone recovery ( $\geq 50$  ng/dl)
  - To assess time to progression of disease off ADT
  - To characterize safety and drug-related adverse events of ipilimumab combined with ADT
  - To determine overall survival
  - To profile immunological changes

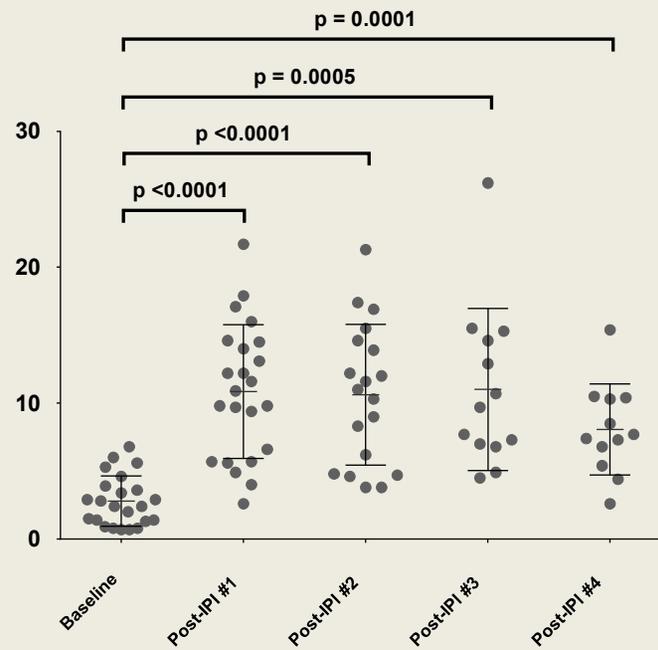
# Radiographic Responses: Patient #1

Baseline  
07/15/2011

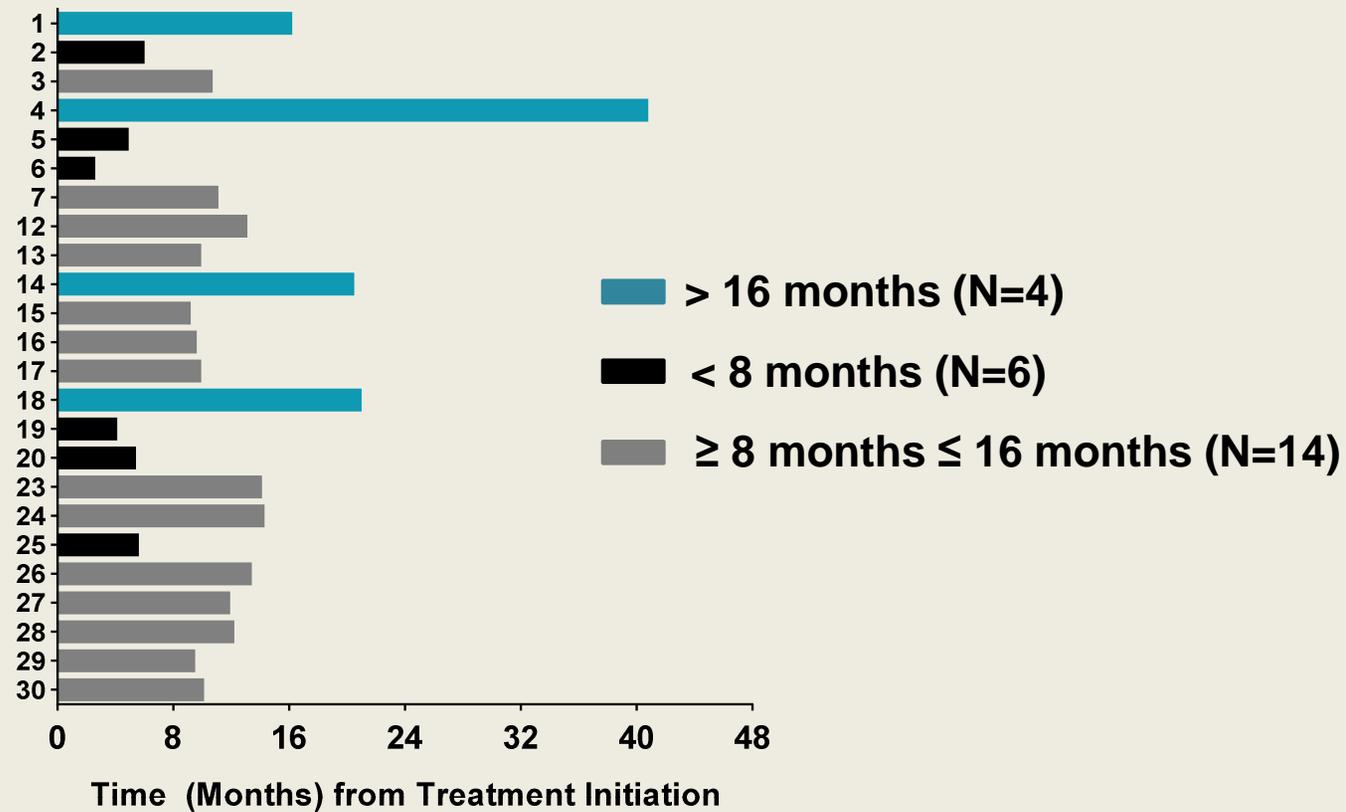


2 of 24 (7%) patients (Patients #1 and #4) achieved complete radiographic responses based on RECIST criteria.

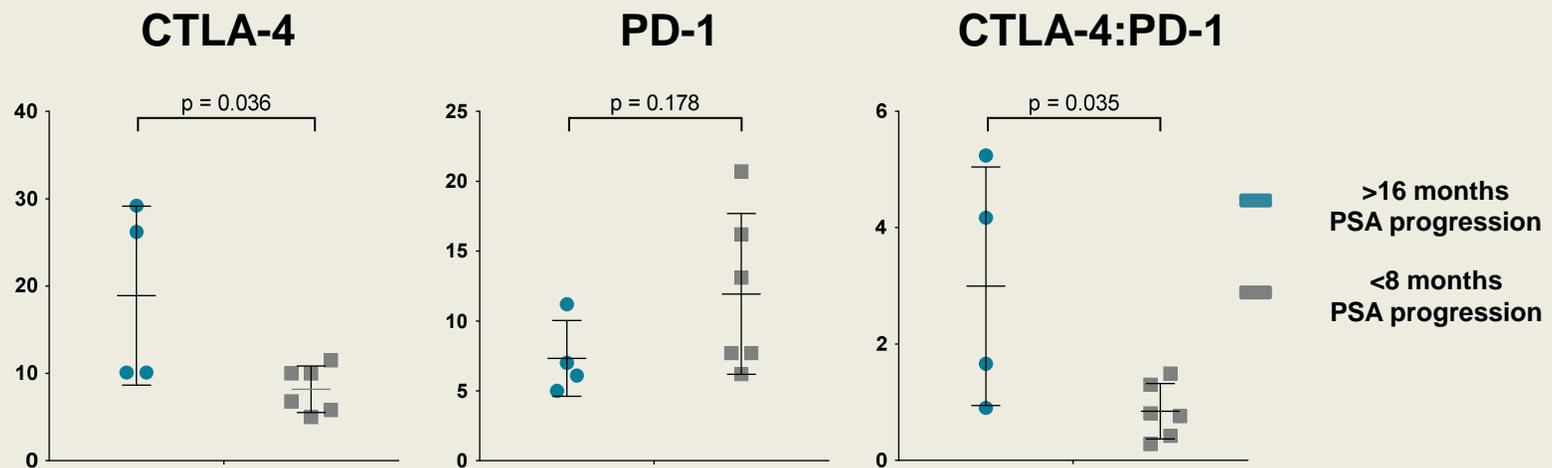
# ICOS+CD4 T cells is a pharmacodynamic marker for ipilimumab



# Time to PSA progression

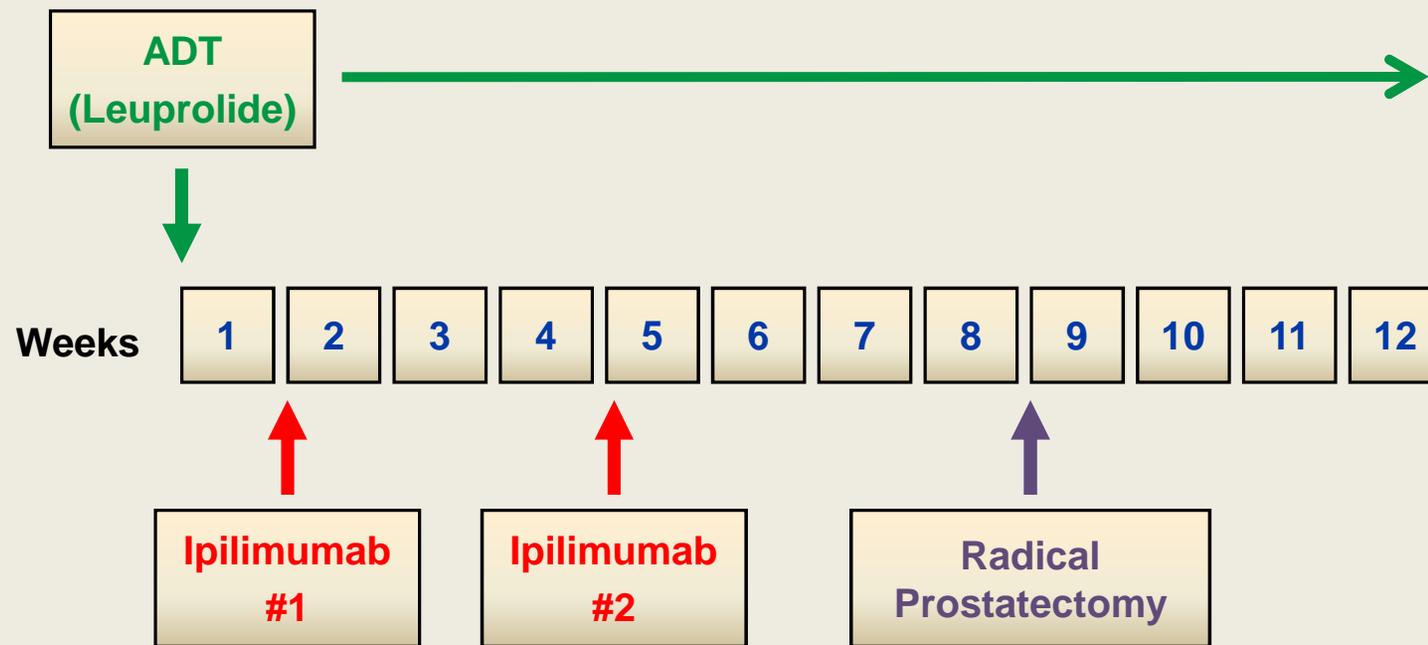


# Baseline CD3 T cell biomarkers potentially predictive of clinical benefit



# MD Anderson Protocol 2009-0135:

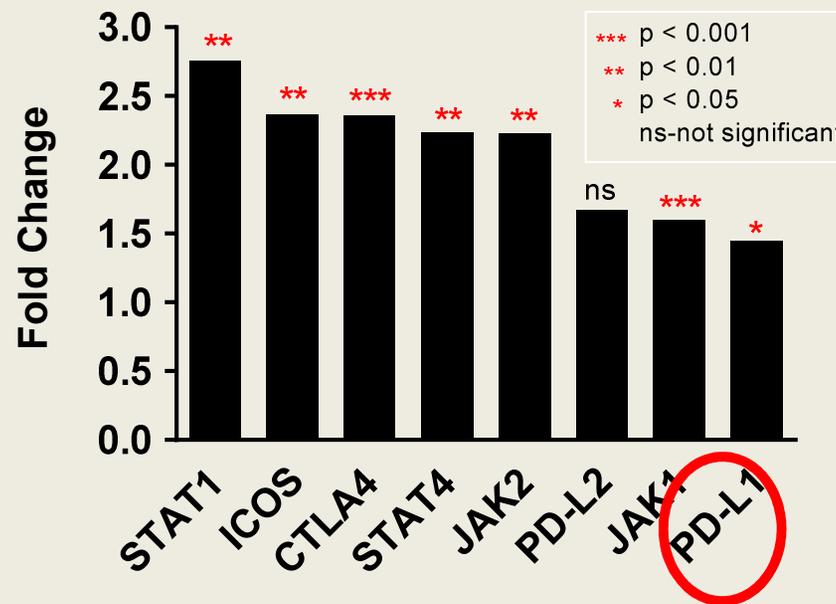
*A Neoadjuvant Phase IIa Study of Ipilimumab Plus  
Hormone Ablation in Men with Prostate Cancer  
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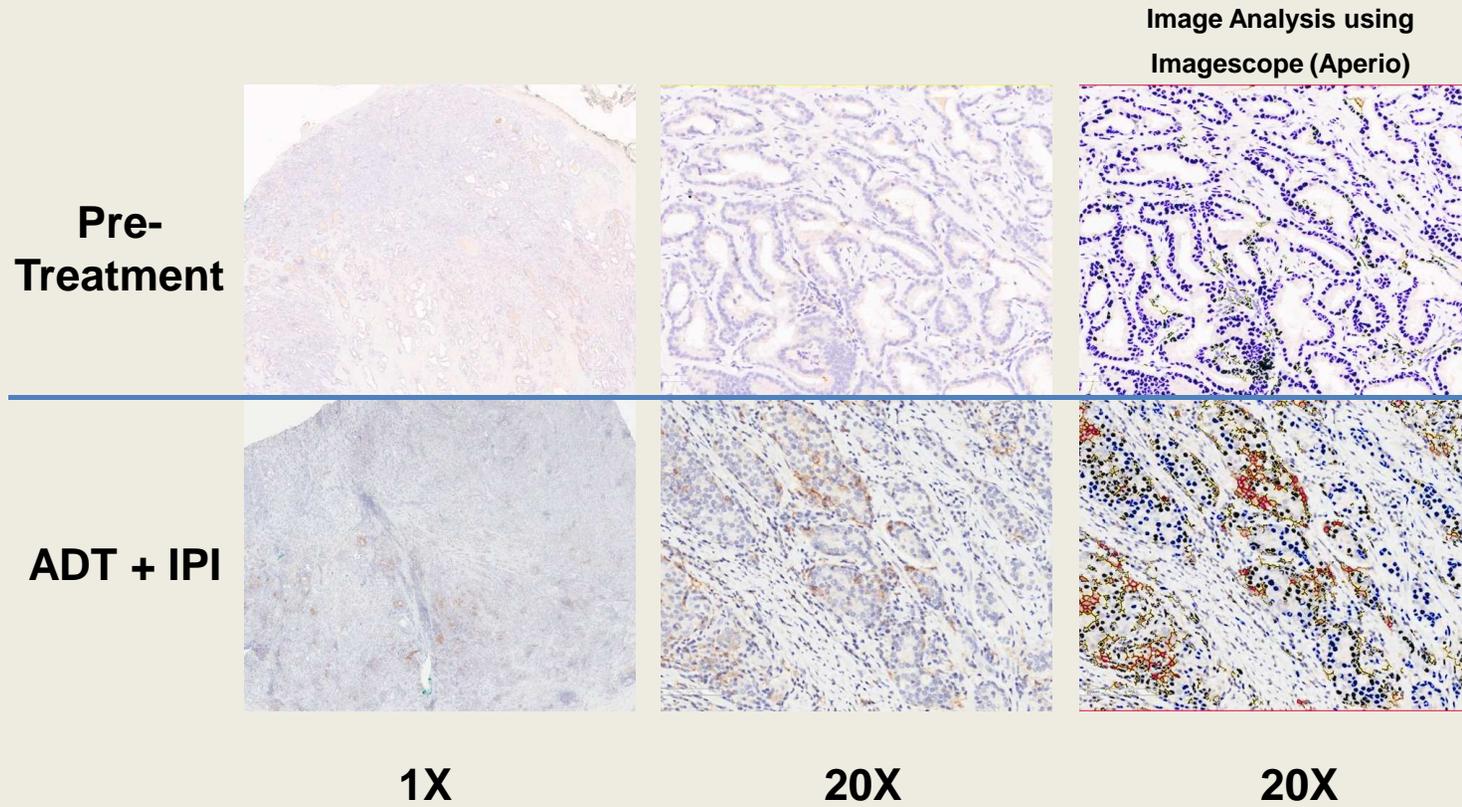
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Padmanee Sharma, MD, PhD

# Select immune DEGs in prostate tumor tissues after treatment with ipilimumab plus ADT

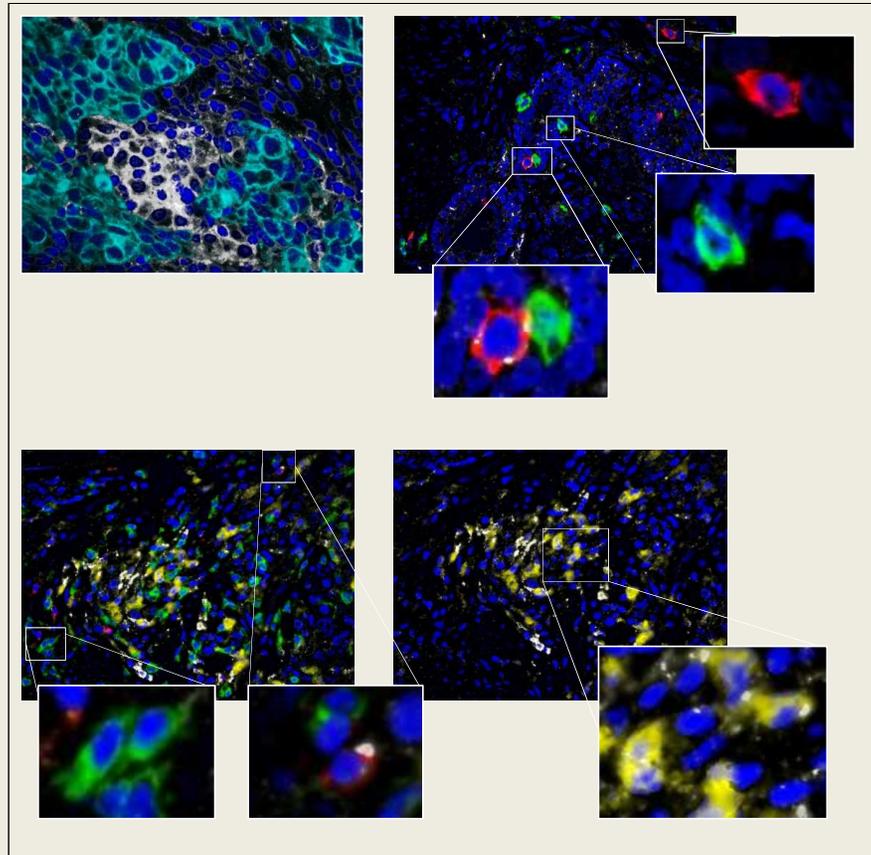


# PD-L1 IHC staining

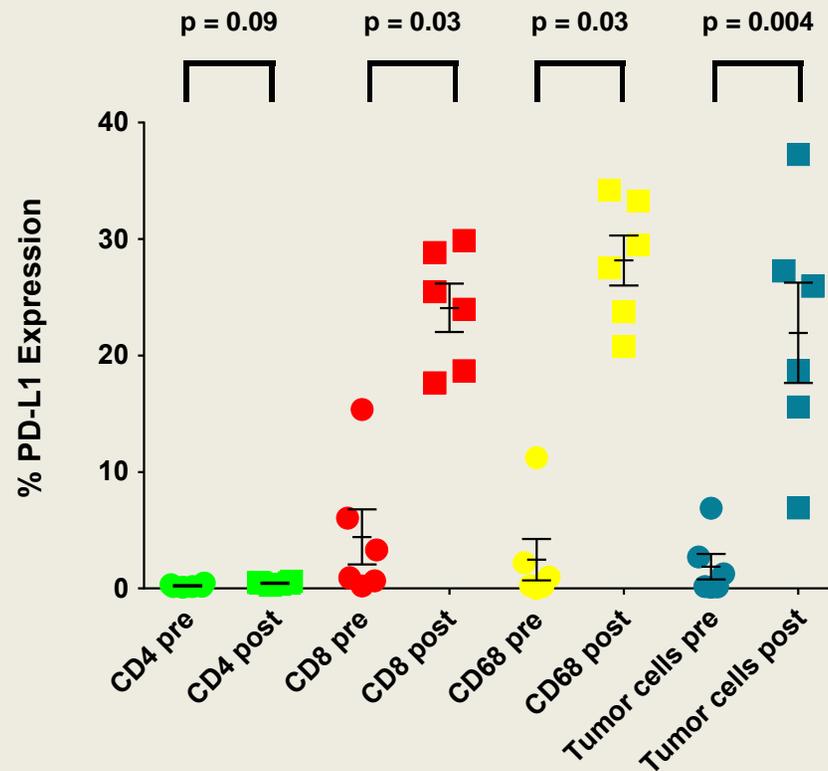


# Multiplex analysis of PD-L1 expression status on selected cell subsets

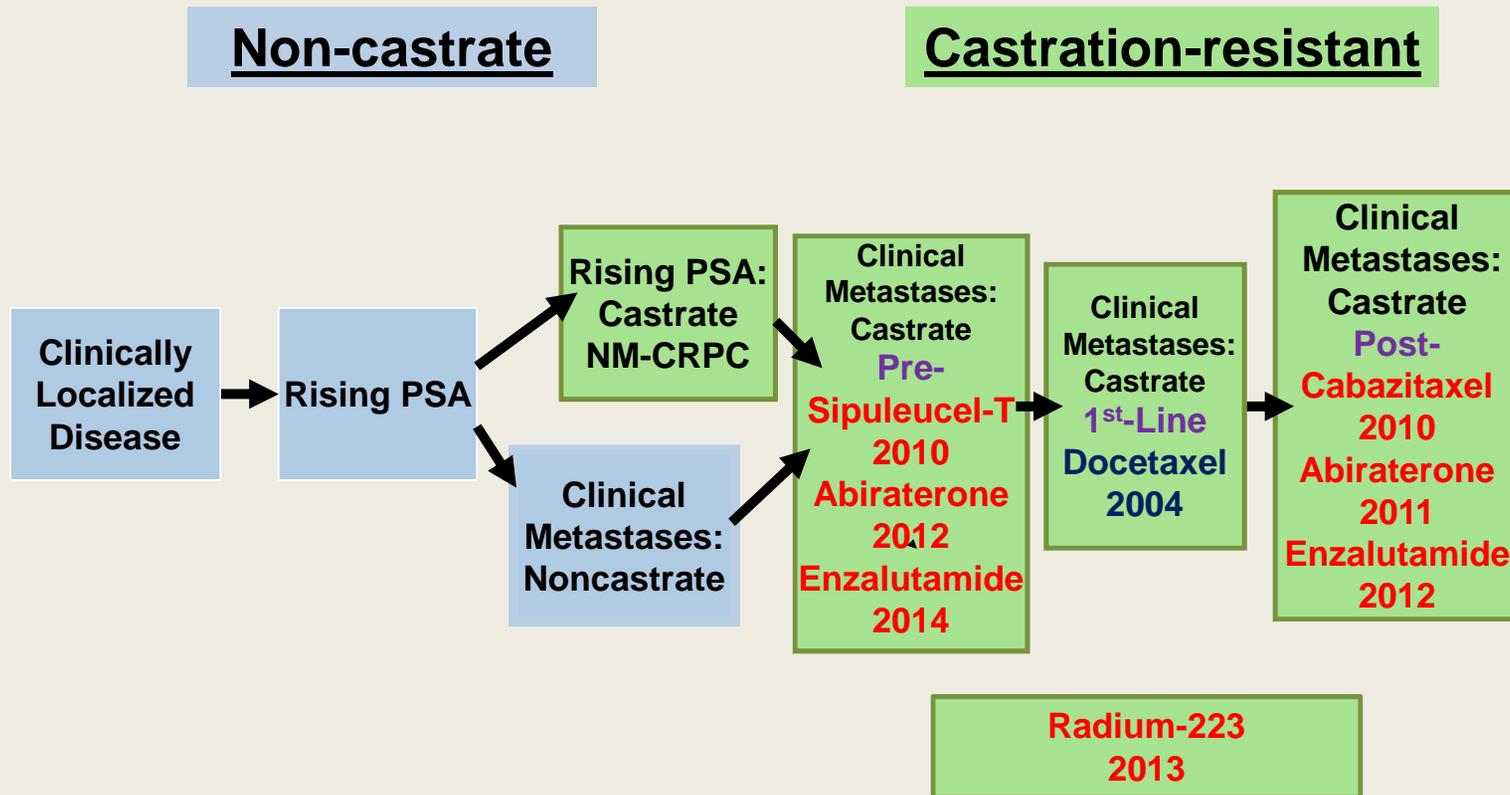
DAPI  
Tumor/Epithelial cells  
PD-L1  
CD4  
CD8  
CD68



# Multiplex analysis of PD-L1 expression status on selected cell subsets

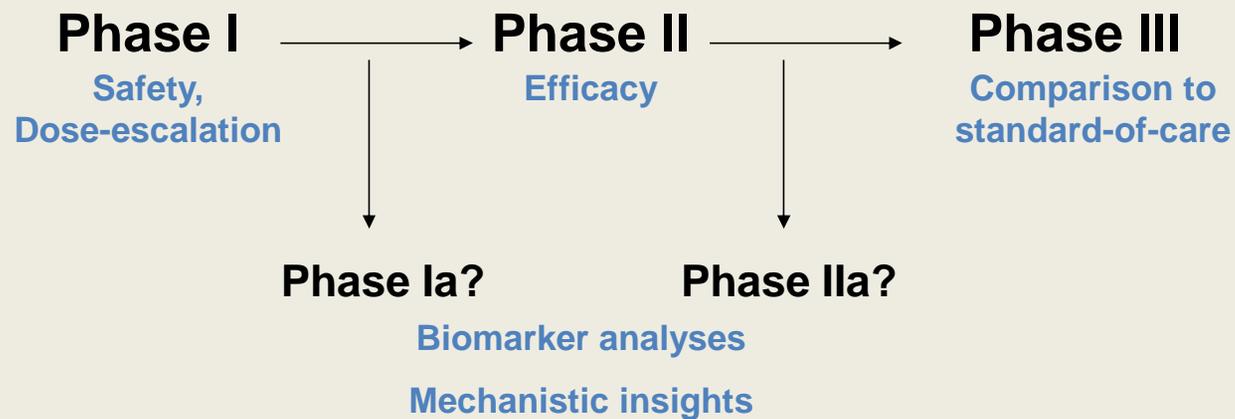


# Clinical states model of prostate cancer



Modified from Scher and Heller. *Urology* 2000.

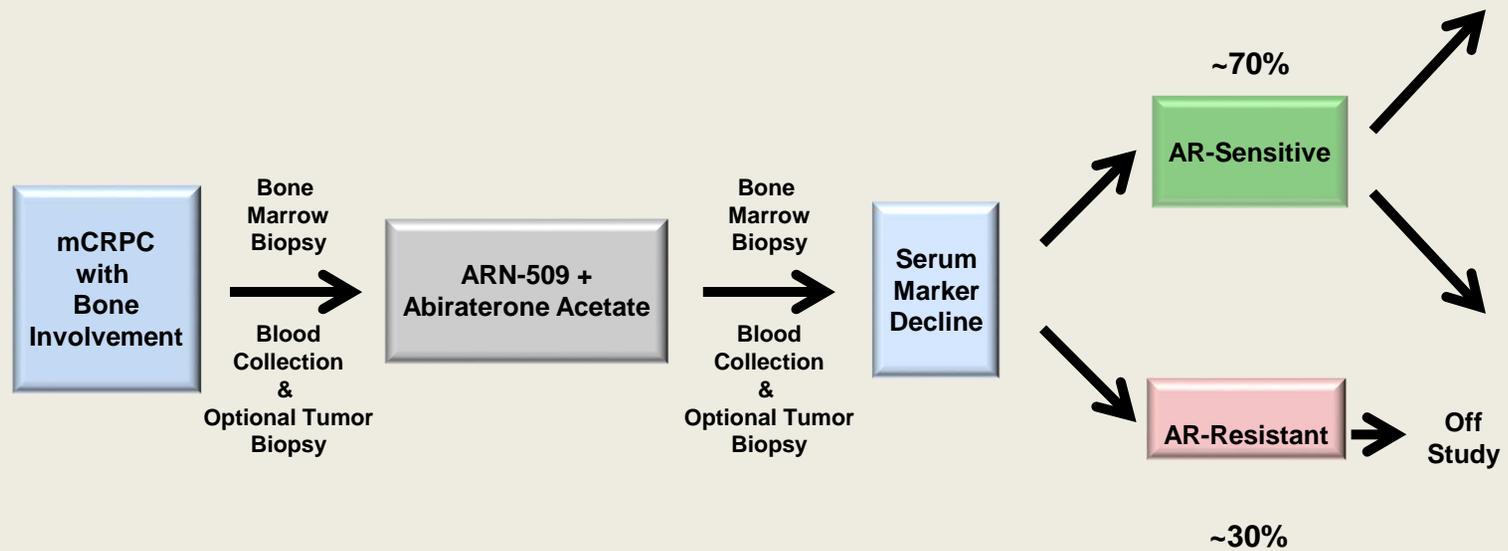
# Re-thinking clinical trial design to obtain appropriate samples for biomarker studies



# Hypothesis

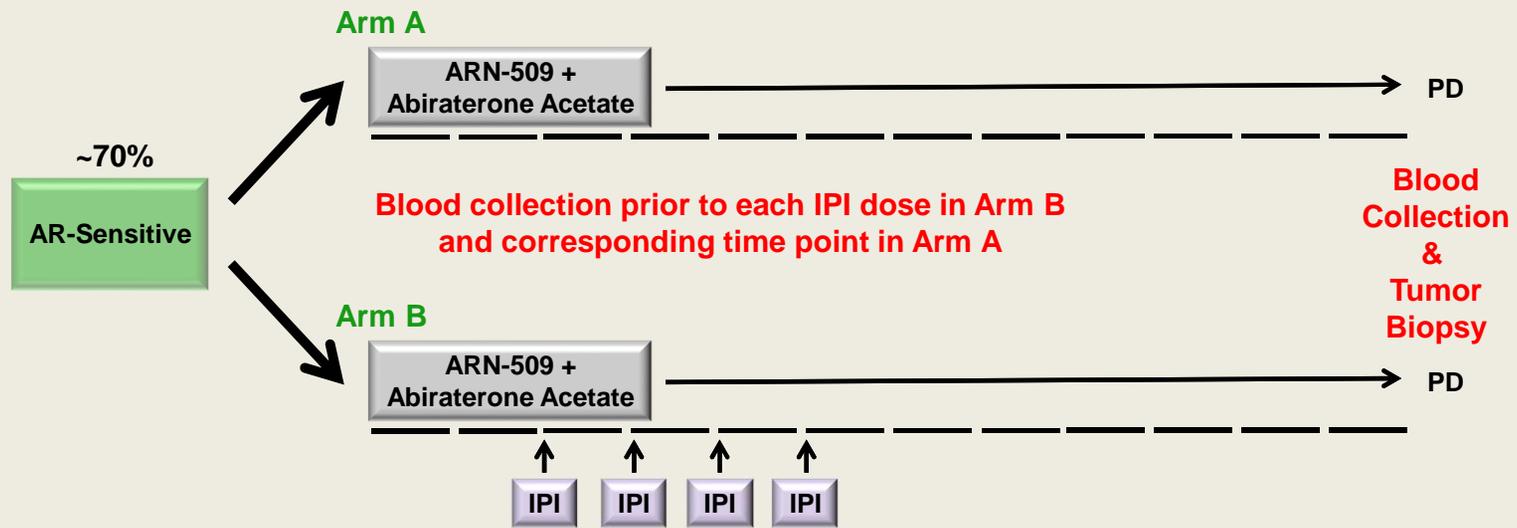
- **Patients identified based on initial responses to optimal targeting of the AR signaling pathway will derive further benefit with ipilimumab.**

# Dichotomization of CRPC



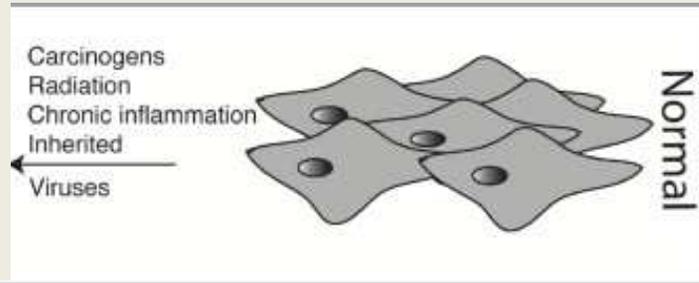
PI: Ana Aparicio, MD

# Elucidating the link between targeting the AR signaling pathway and the immune system



# Additional biomarker analyses

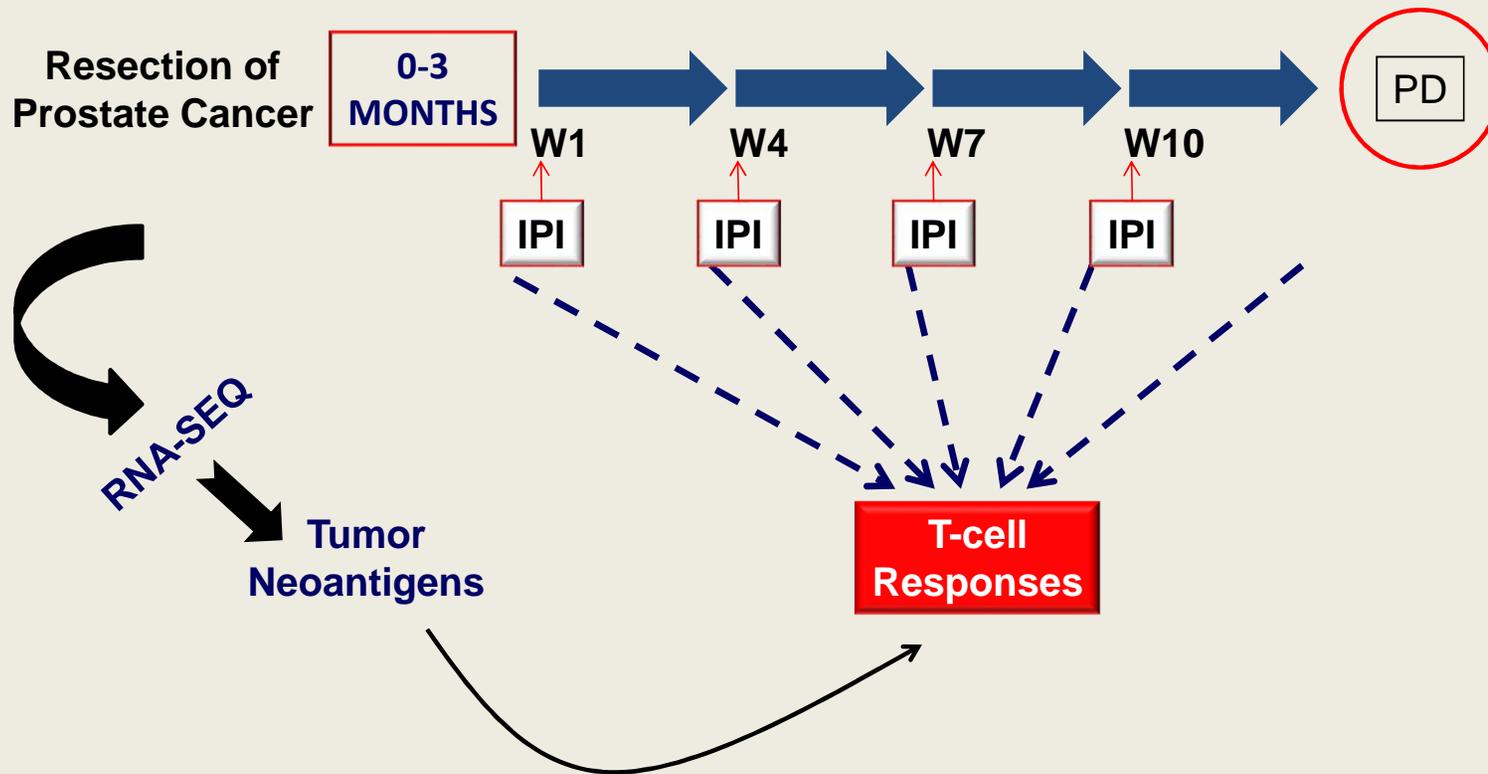
- **Hypothesis**
  - **Induction of effective anti-tumor responses by ipilimumab is mediated by lymphocyte responses to tumor neoantigens.**



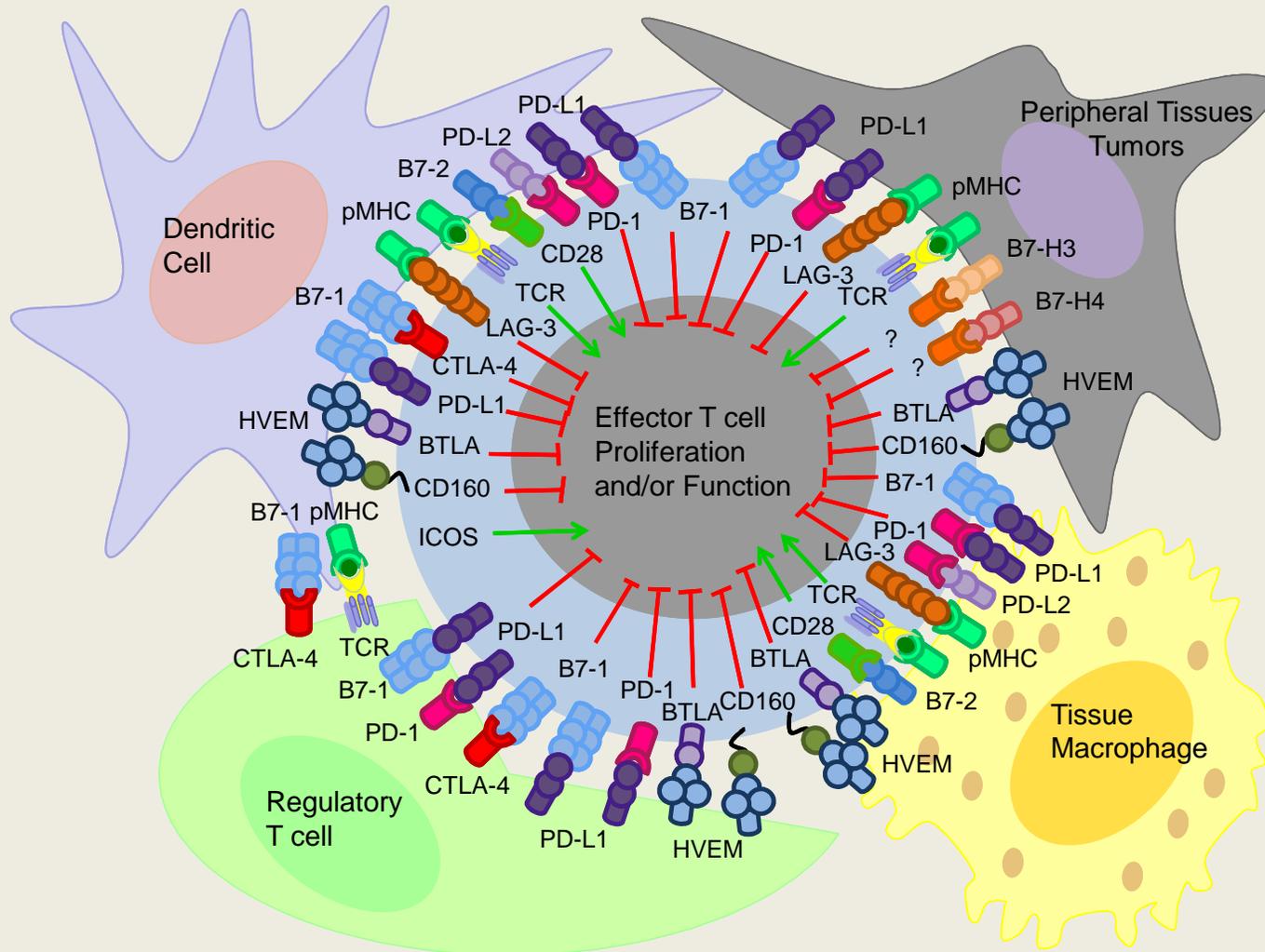
**The Immunobiology of Cancer Immunosurveillance and Immunoediting**

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

# Identifying neoantigens



# Novel immunotherapy targets





# Acknowledgements

DAVID H. KOCH CENTER  
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## PATIENTS

### Immunotherapy (IMT) Platform

James Allison  
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Luis Vence  
Ignacio Wistuba

### Urology

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John Davis  
John Ward

### Pathology

Patricia Troncoso

### GU Medical Oncology

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Jianjun Gao  
Christopher Logothetis  
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Amado Zurita

### Radiology

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