

Innovative Clinical Trial Design for Immune Monitoring

Society for Immunotherapy of Cancer (SITC)

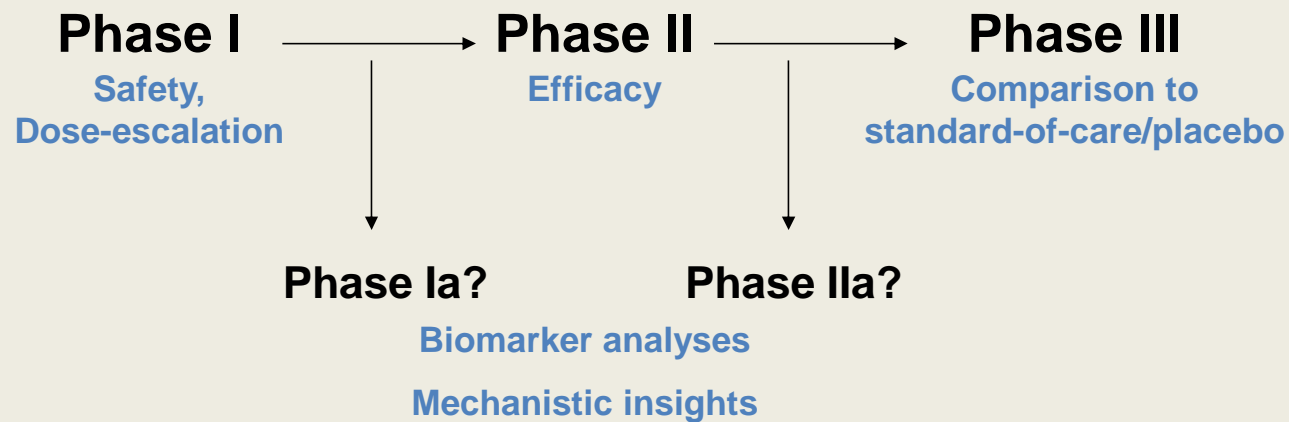
Primer on Tumor Immunology and Cancer Immunotherapy™

November 5, 2015

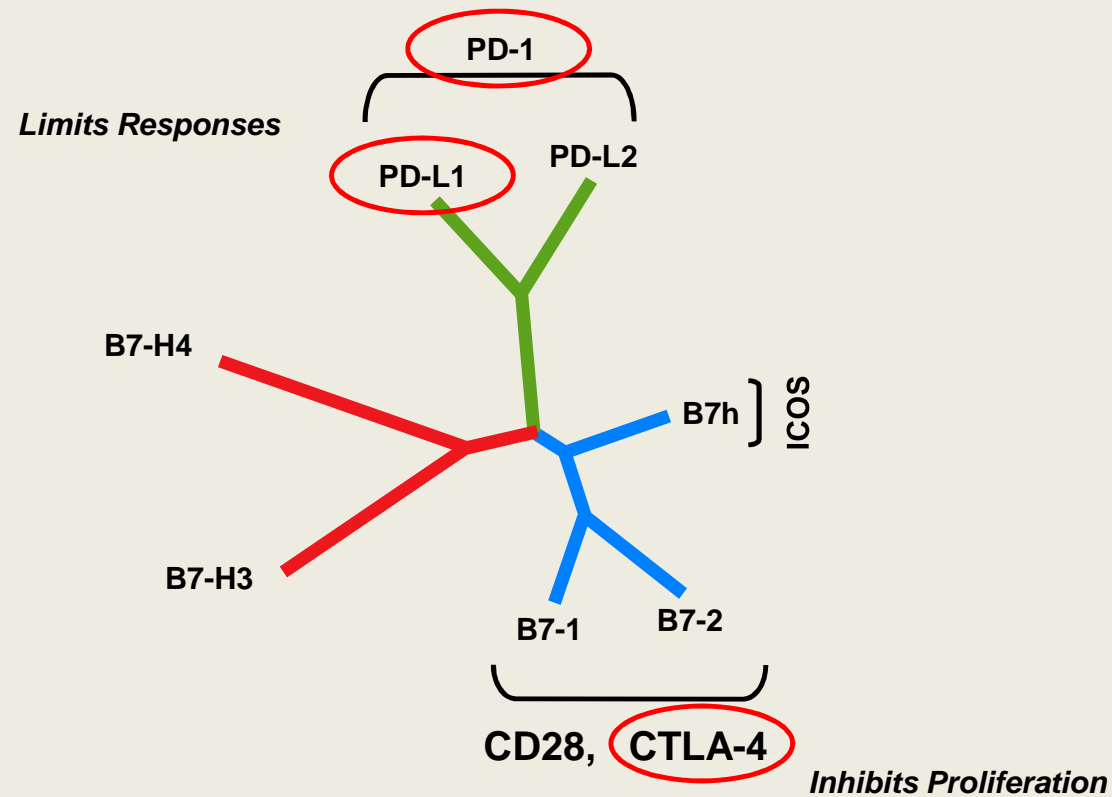
Sumit K. Subudhi, MD, PhD

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



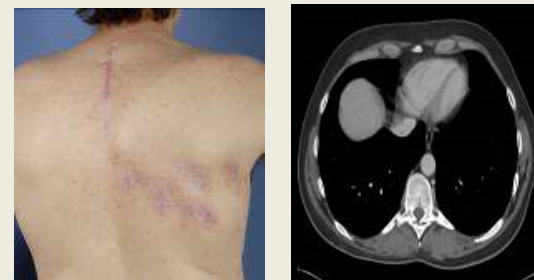
Week 12
Initial increase in
total tumour burden (mWHO PD)



Week 16
Responding



Week 72
Durable & ongoing response



Courtesy of K. Harmankaya

Clinical states model of prostate cancer

Non-castrate

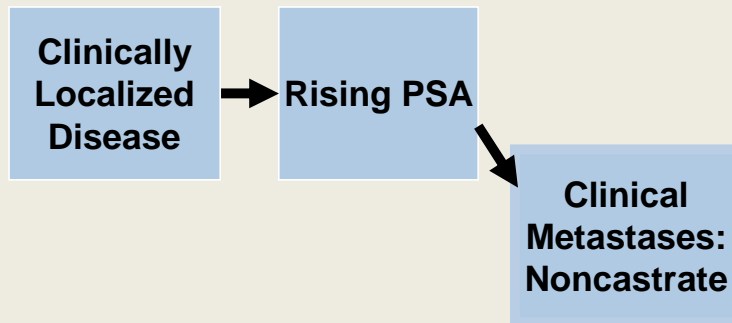
Castration-resistant

Modified from Scher and Heller. *Urology* 2000.

Clinical states model of prostate cancer

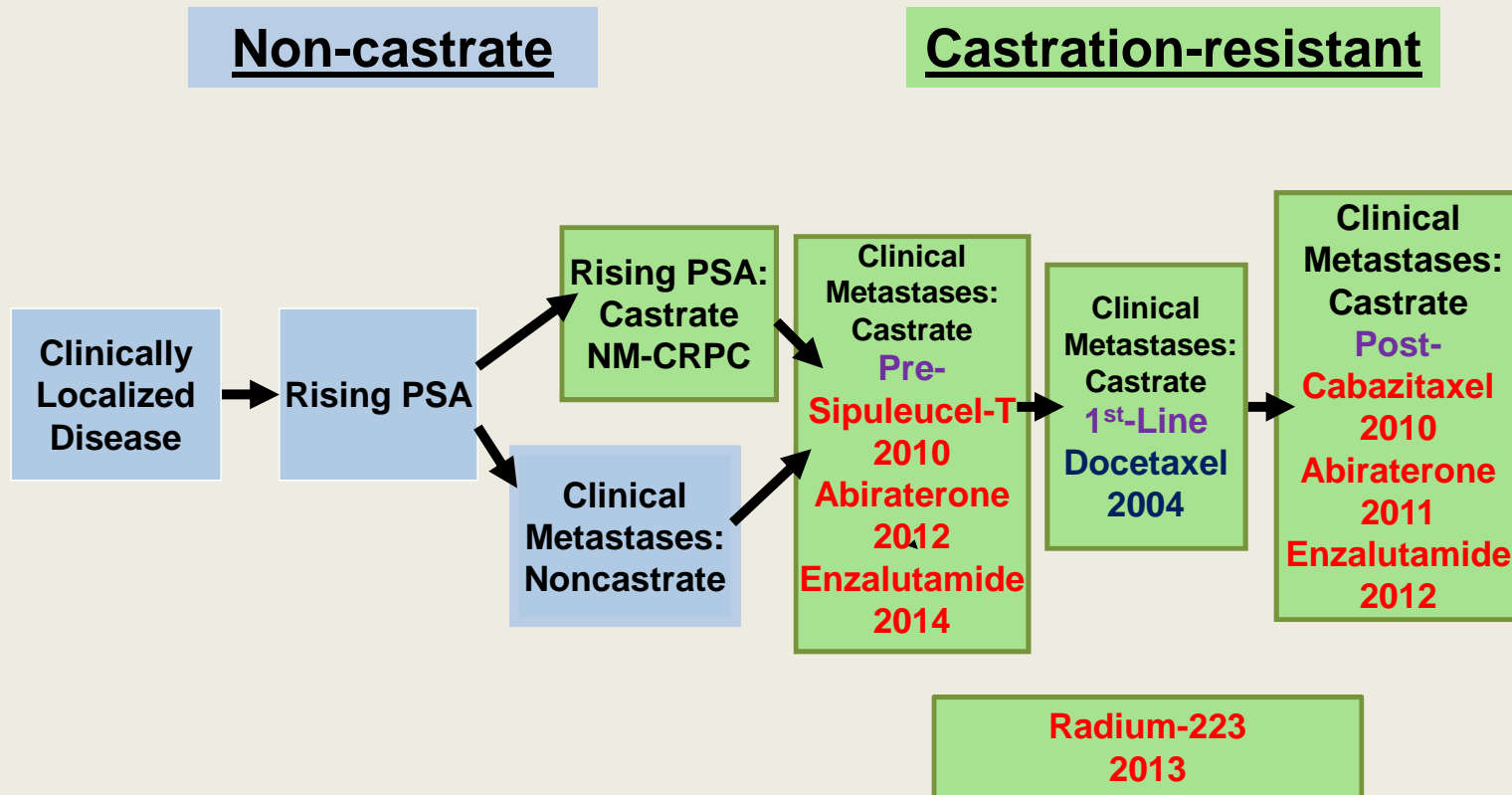
Non-castrate

Castration-resistant



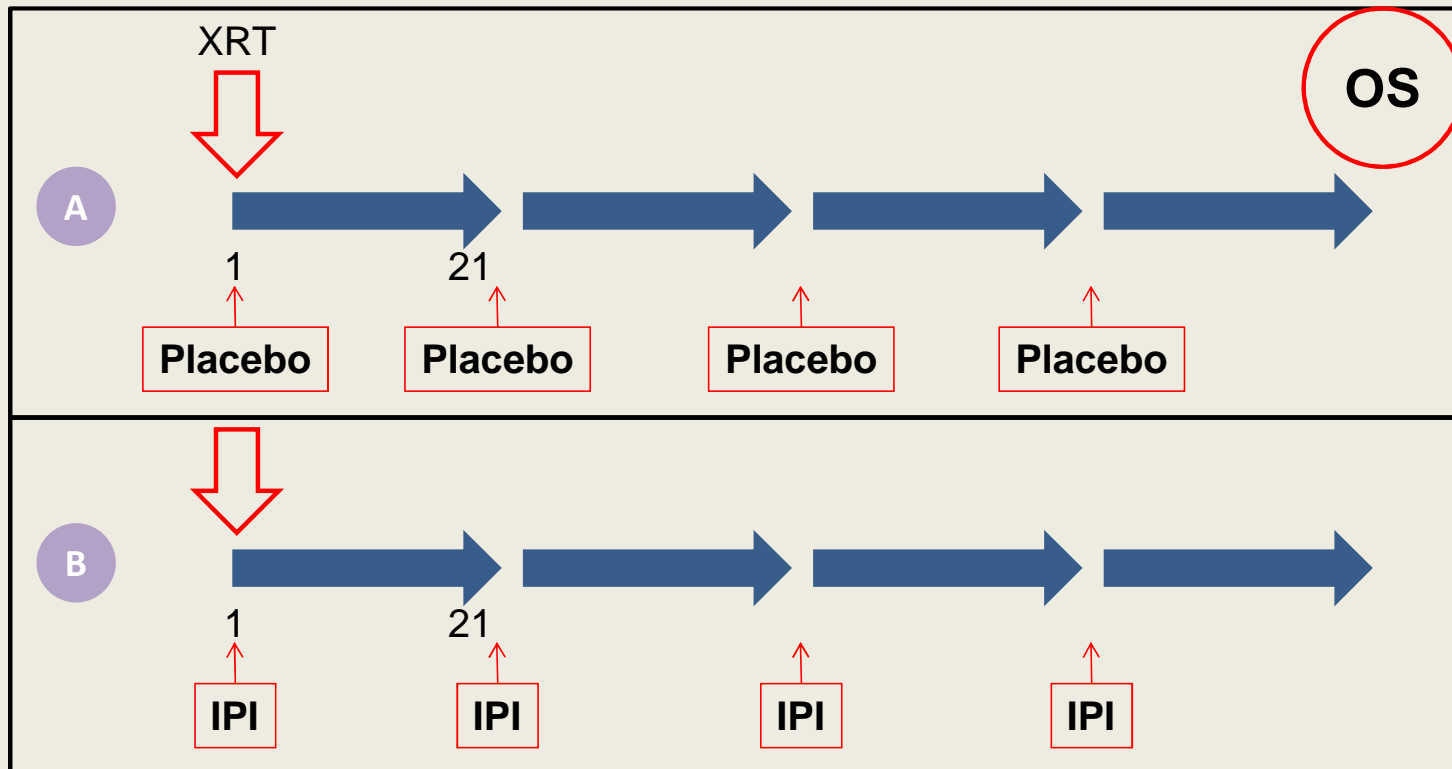
Modified from Scher and Heller. *Urology* 2000.

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)

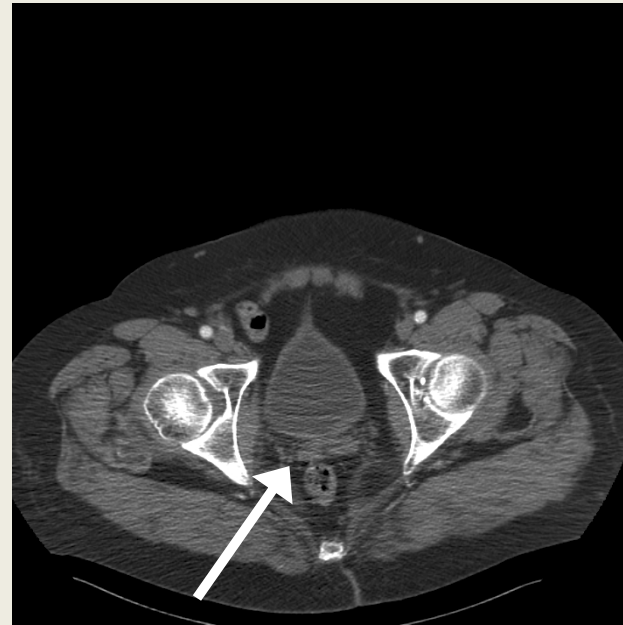
... then q3 months until PD

Complete responder: prostate cancer

Screening



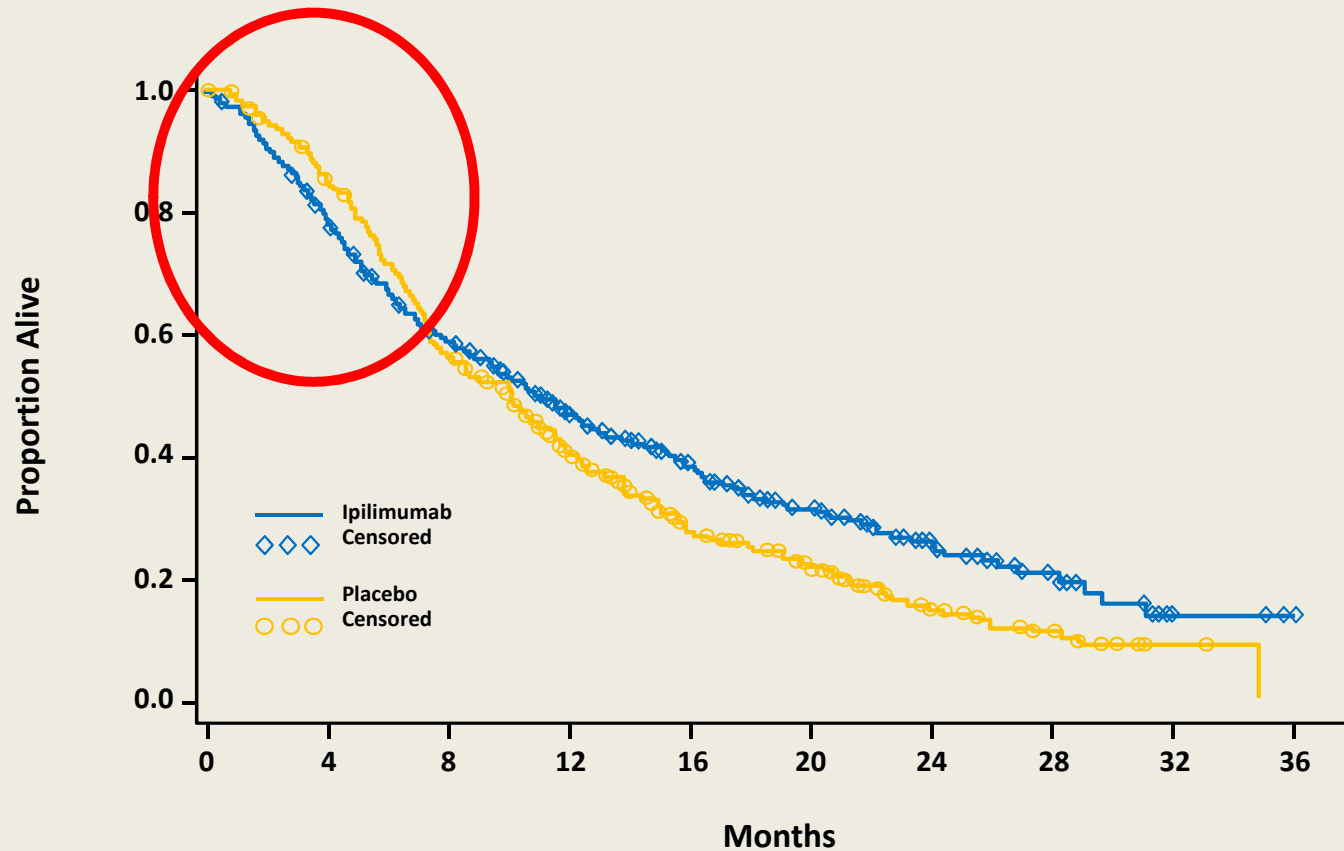
14 months



Phase III trial recently reported

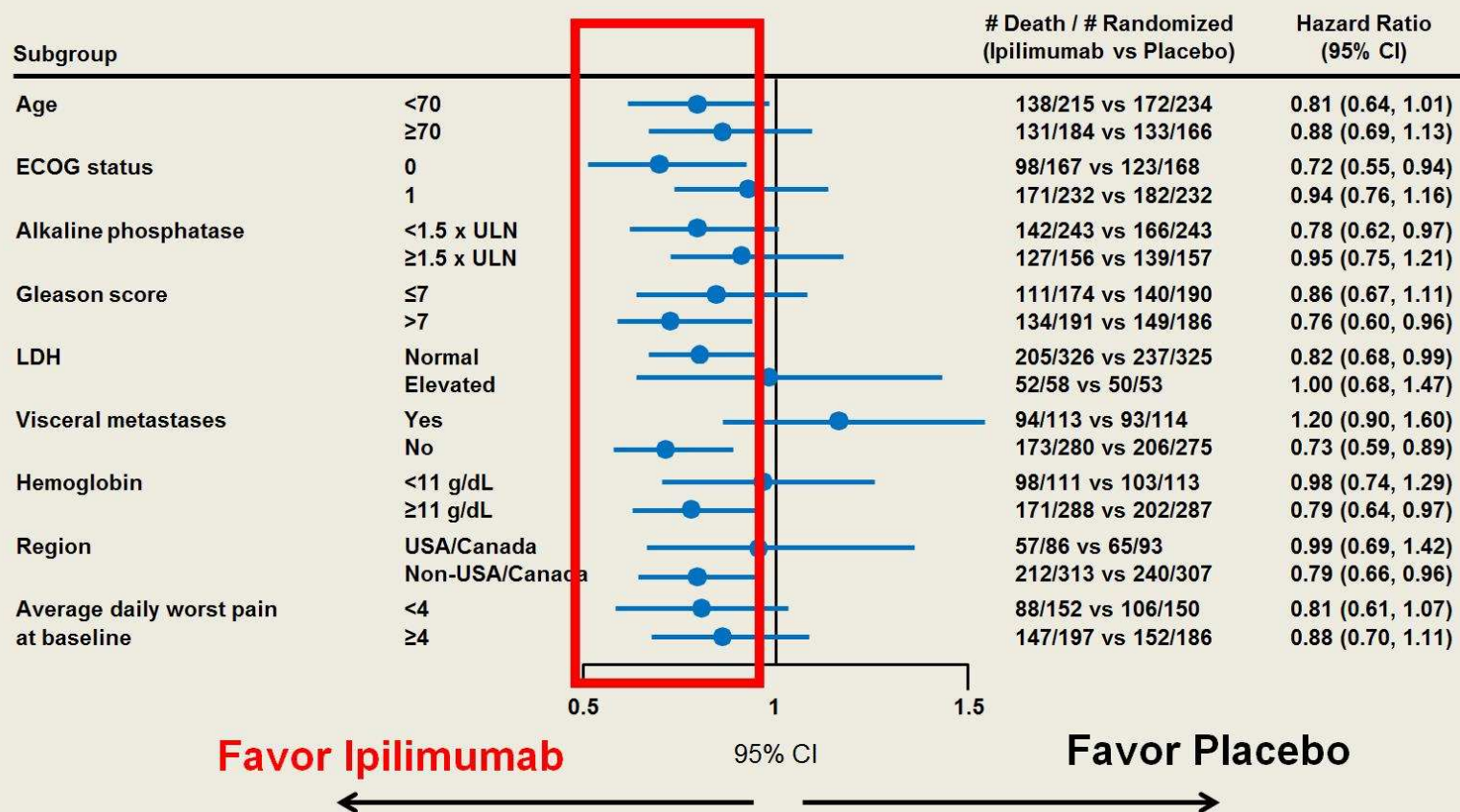
BMS

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

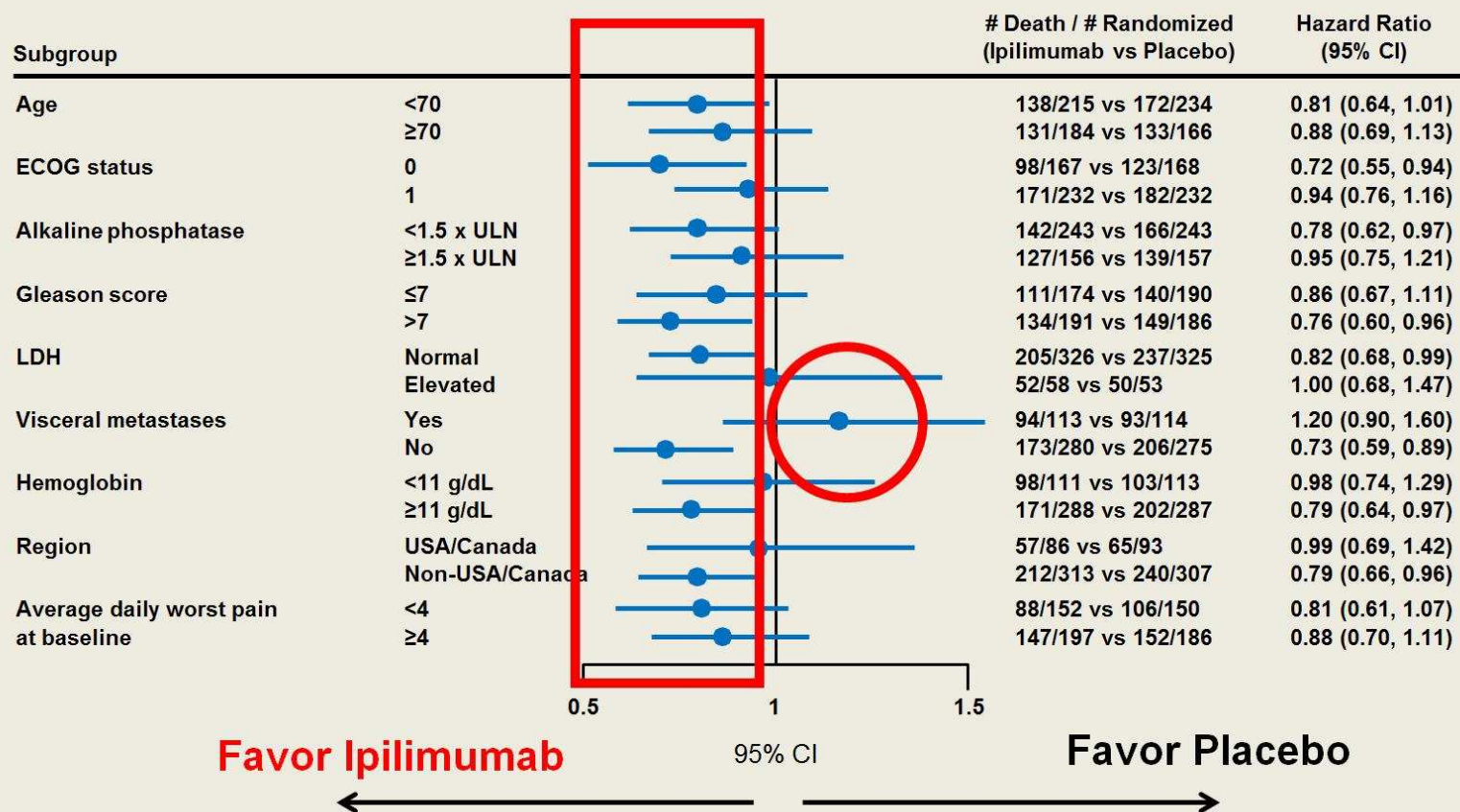


Kwon, ED et al. Lancet Oncol. 2014 Jun;15(7):700-12

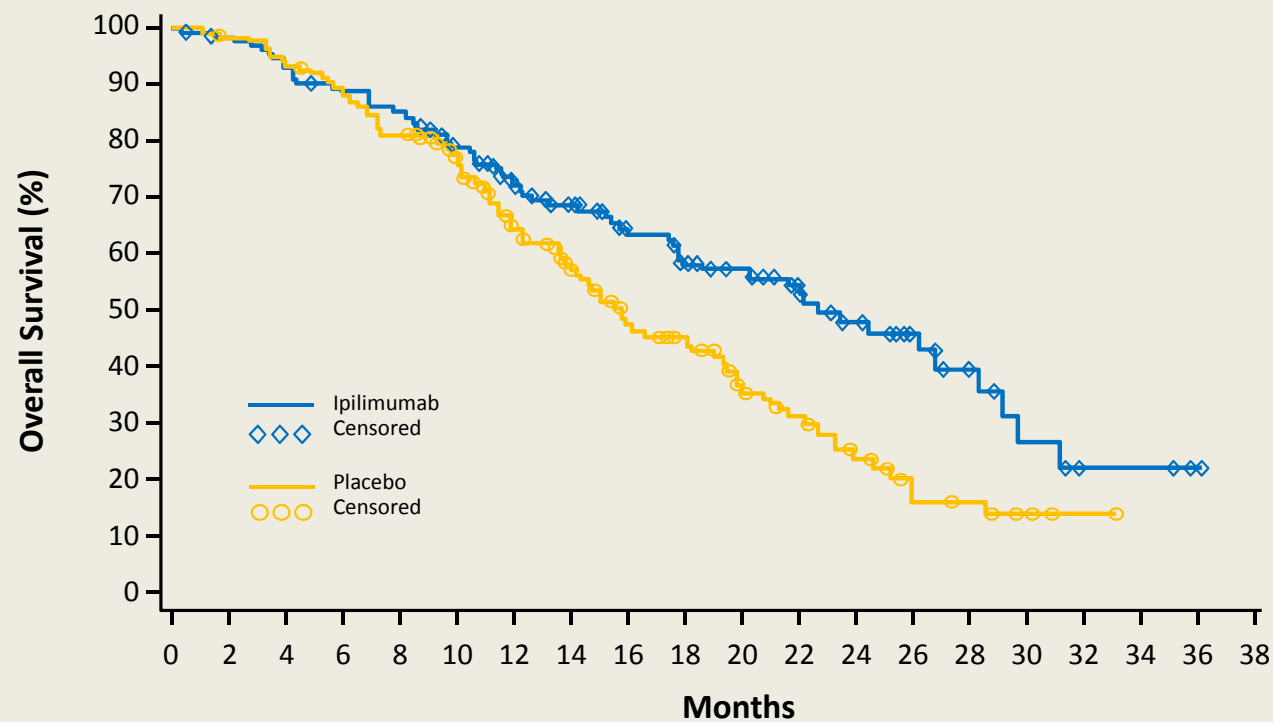
Overall survival: Pre-specified subgroups



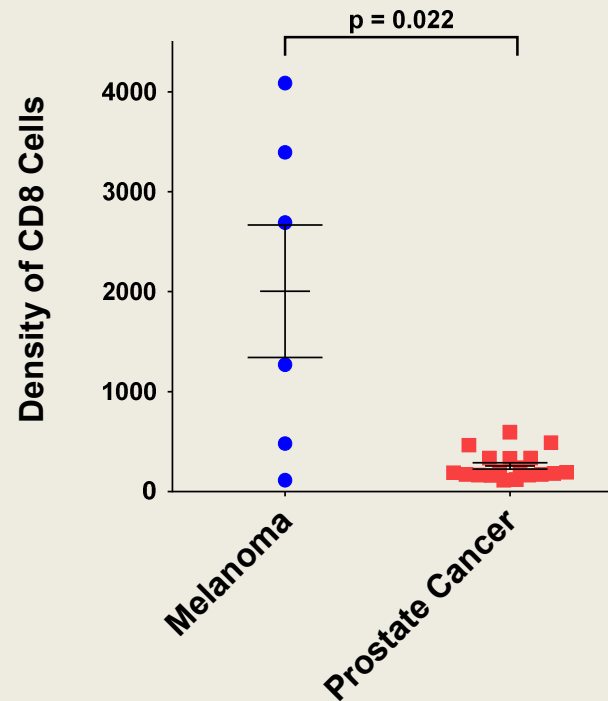
Overall survival: Pre-specified subgroups



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

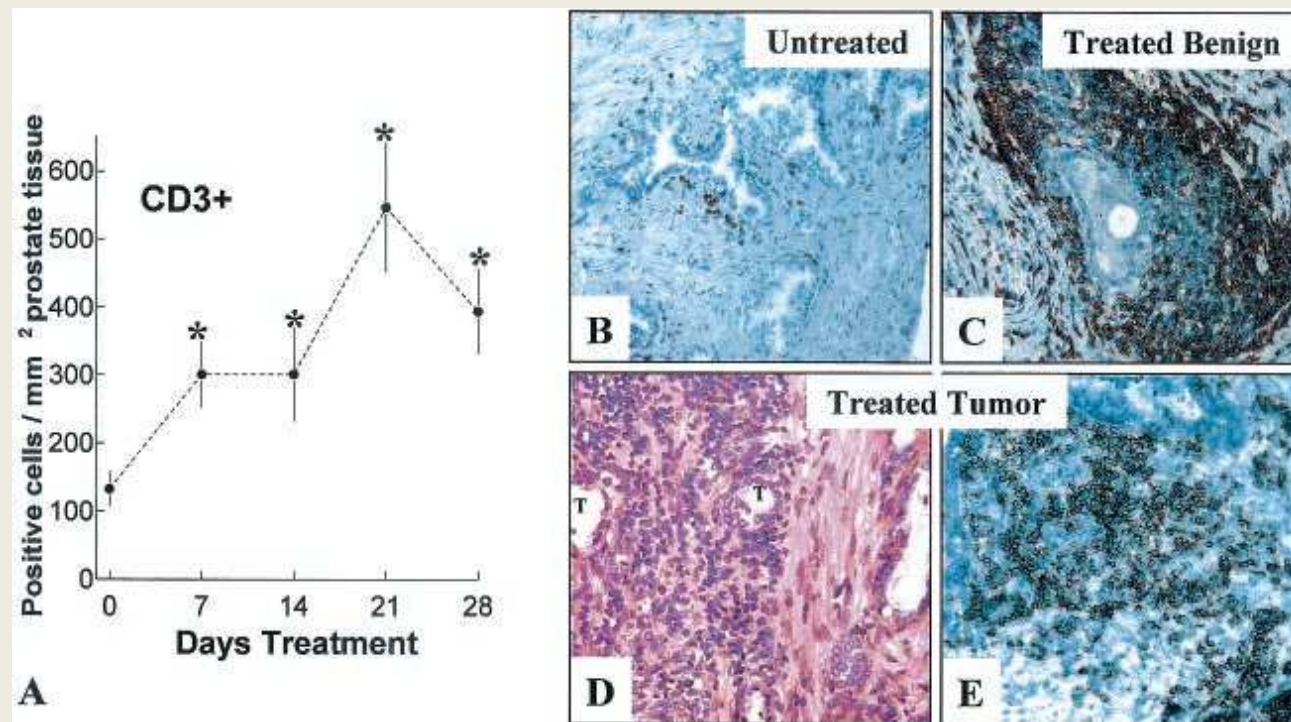
Maria Mercader^{*†}, Barbara K. Bodner^{*†}, Micheal T. Moser^{*†}, Pamela S. Kwon[†], Eugene S. Y. Park^{*†}, Ryan G. Manecke[†], Thomas M. Ellis^{*}, Eva M. Wojcik[‡], Damu Yang^{*}, Robert C. Flanigan[†], W. Bedford Waters[†], W. Martin Kast^{*}, and Eugene D. Kwon^{*†§}

Departments of [†]Urology and [‡]Pathology, and the ^{*}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)

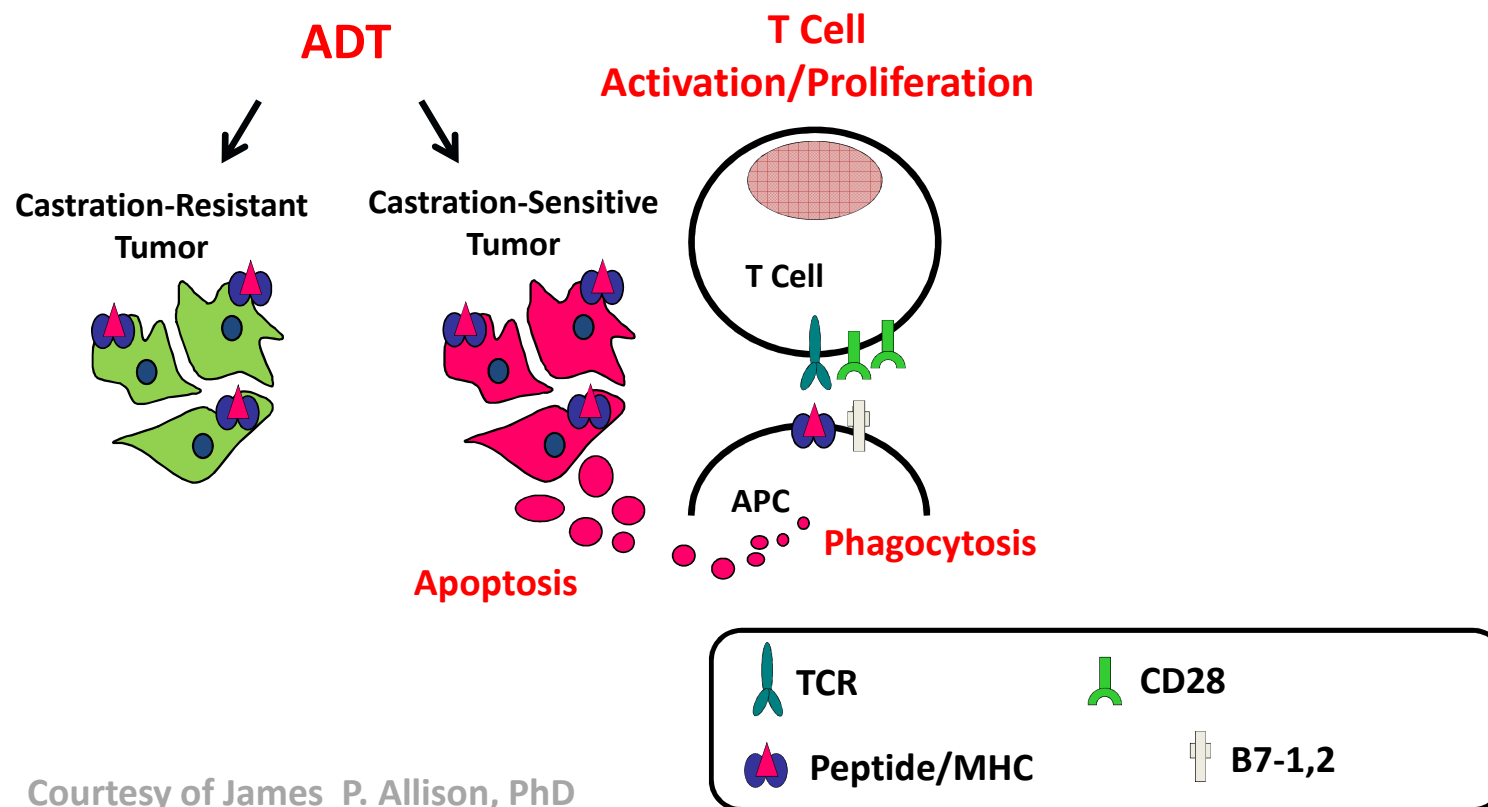
PNAS | December 4, 2001 | vol. 98 | no. 25 | 14565–14570

Androgen Blockade Increases TILs

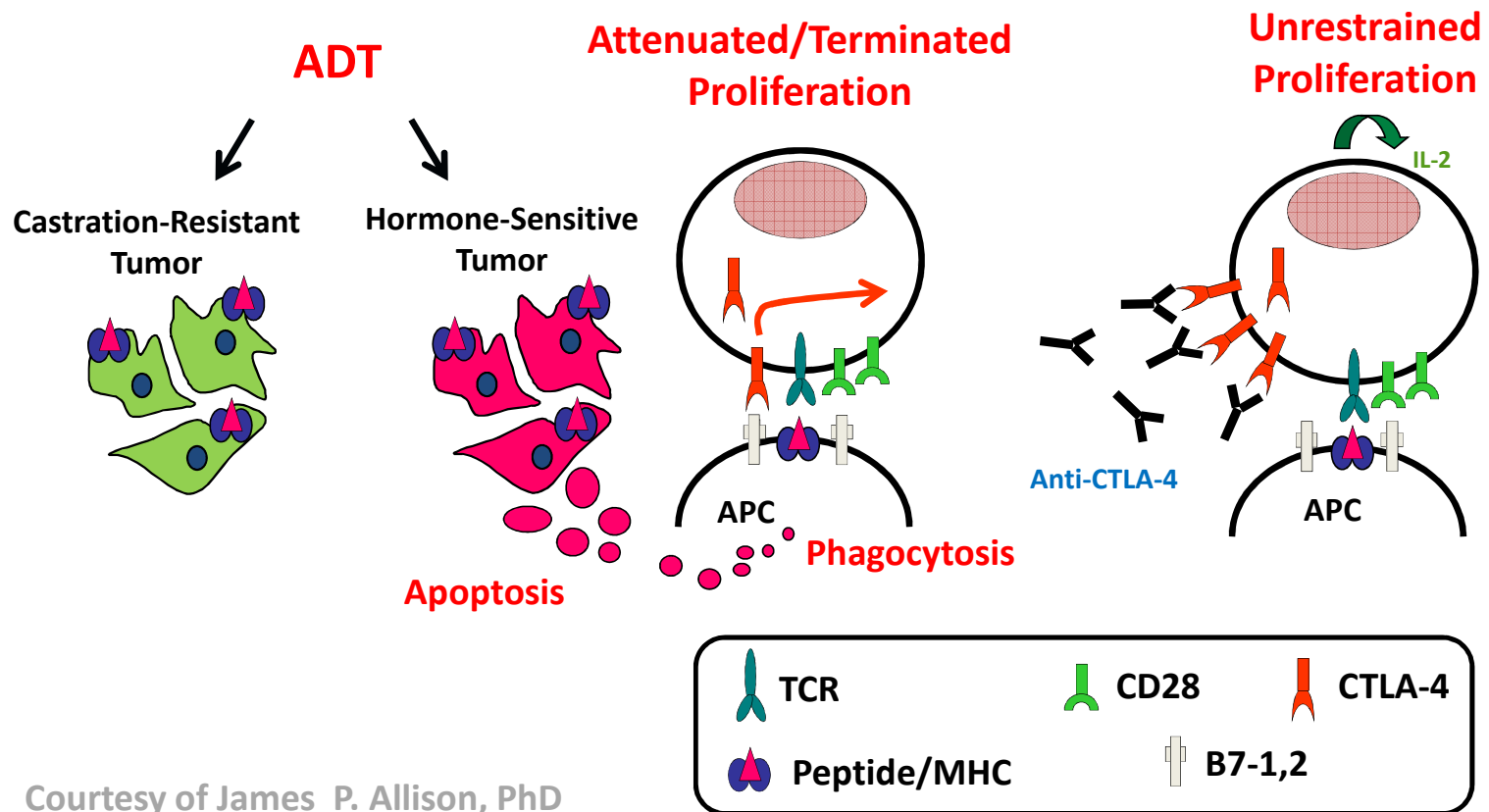


Mercader M et al. PNAS 2001; 98:14565-14570

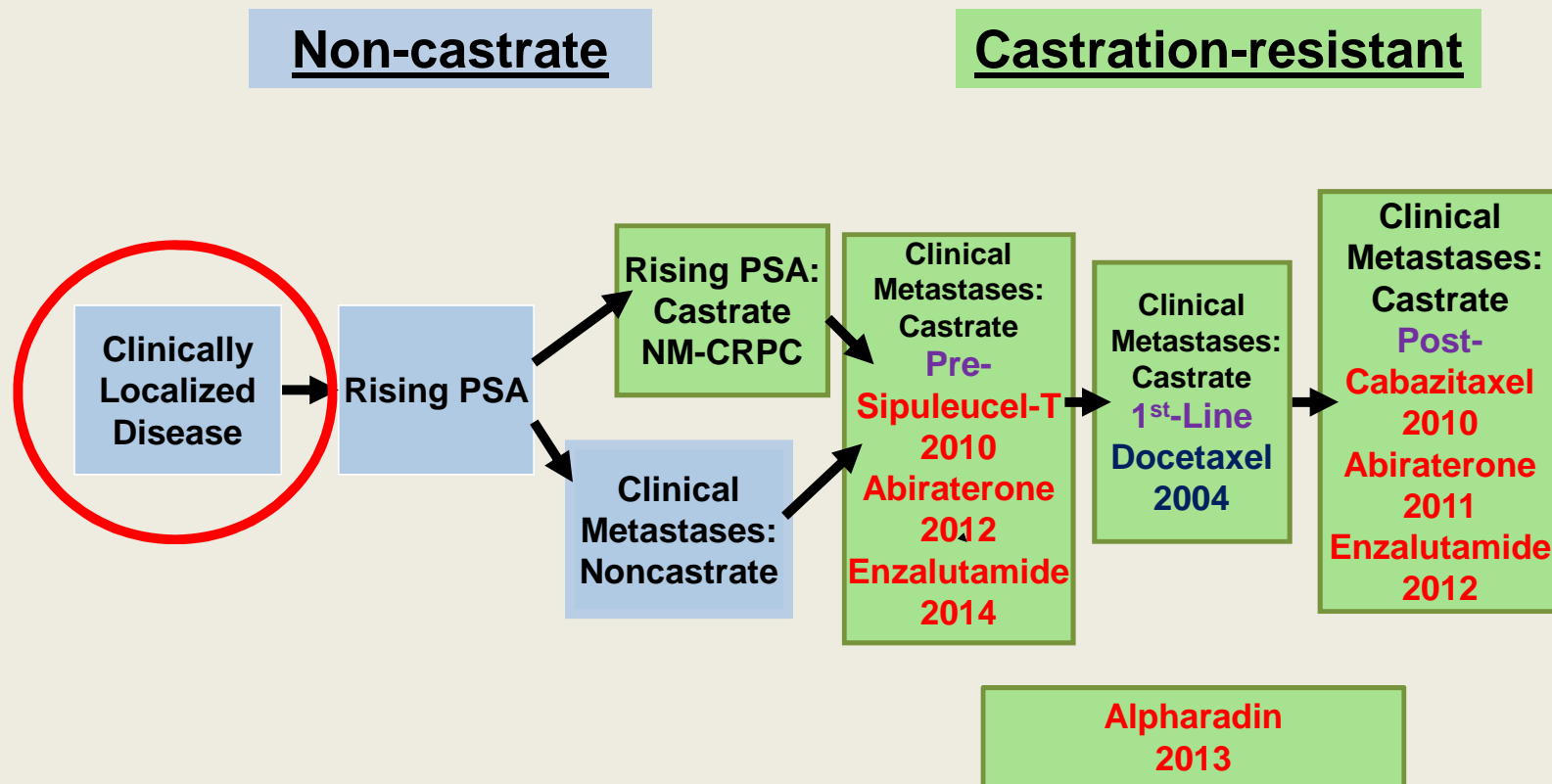
The Effects of Androgen Deprivation Therapy (ADT) on Tumor Cells and the Immune System



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



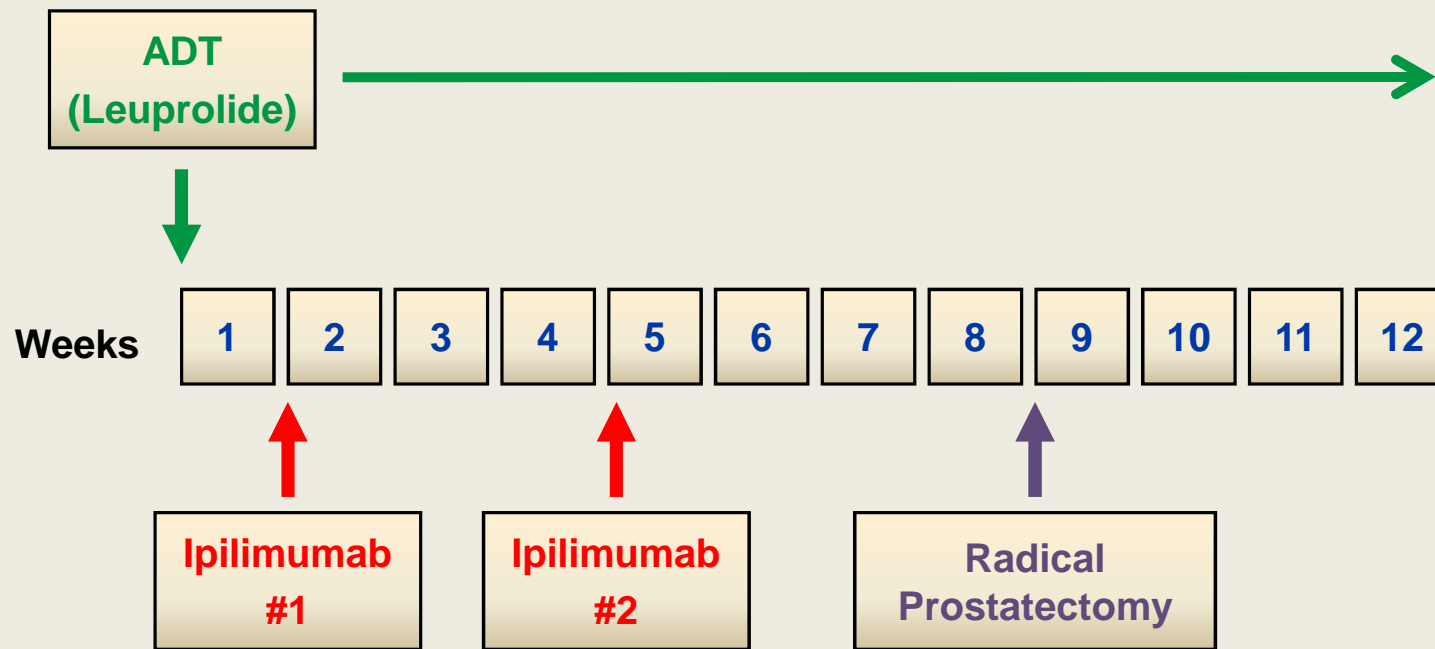
Clinical states model of prostate cancer



Modified from Scher and Heller. *Urology* 2000.

MD Anderson Protocol 2009-0135:

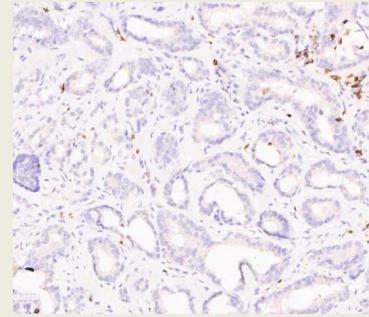
*A Neoadjuvant Phase IIa Study of Ipilimumab Plus
Hormone Ablation in Men with Prostate Cancer
Followed by Radical Prostatectomy*



Padmanee Sharma, MD, PhD

CD3 T-cells within the tumor microenvironment

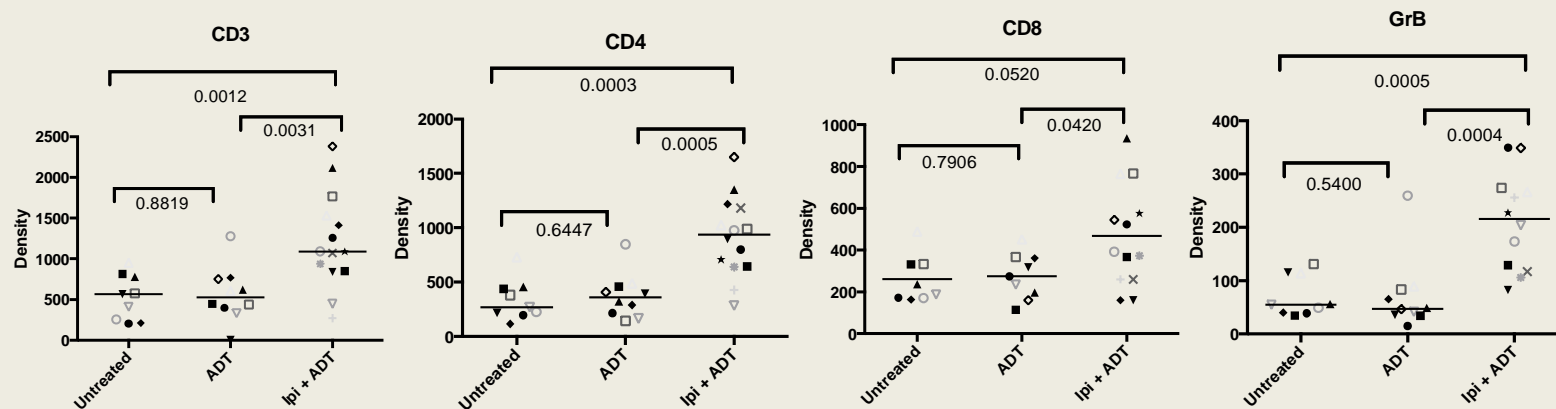
Untreated
(Control)



1X

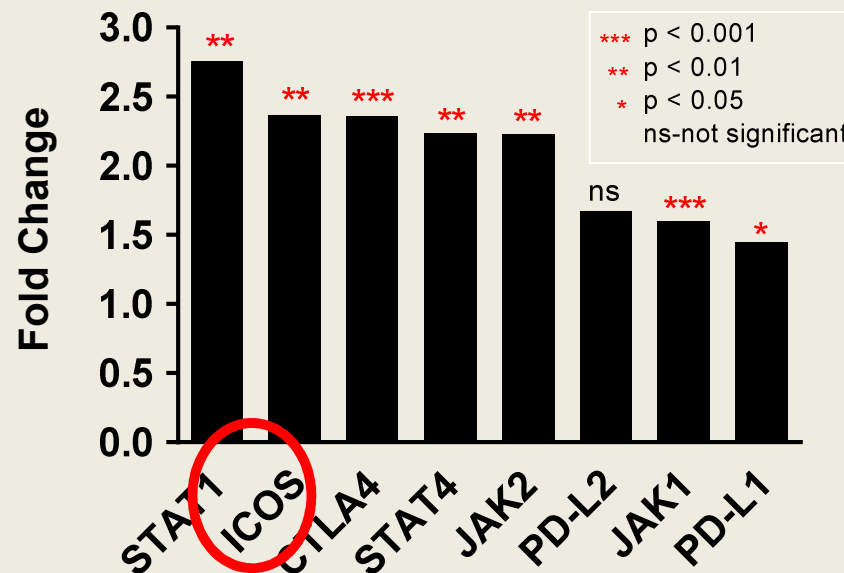
20X

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

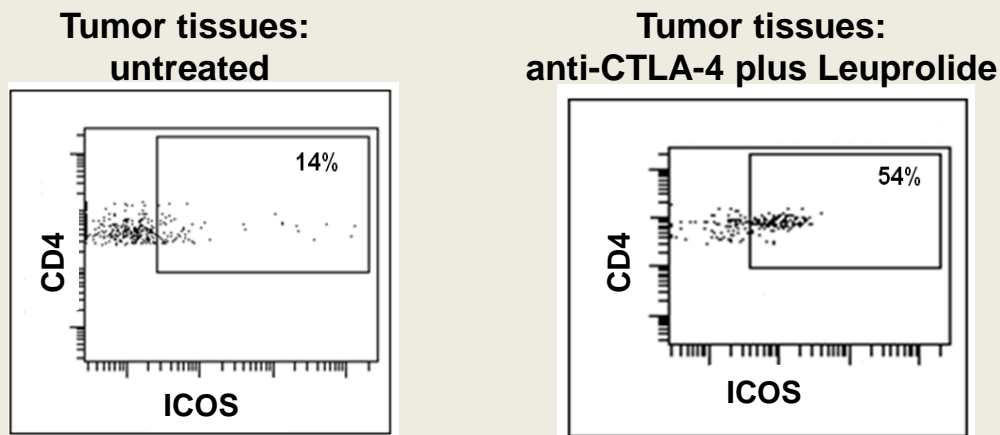


Mann Whitney test, unpaired, two tailed

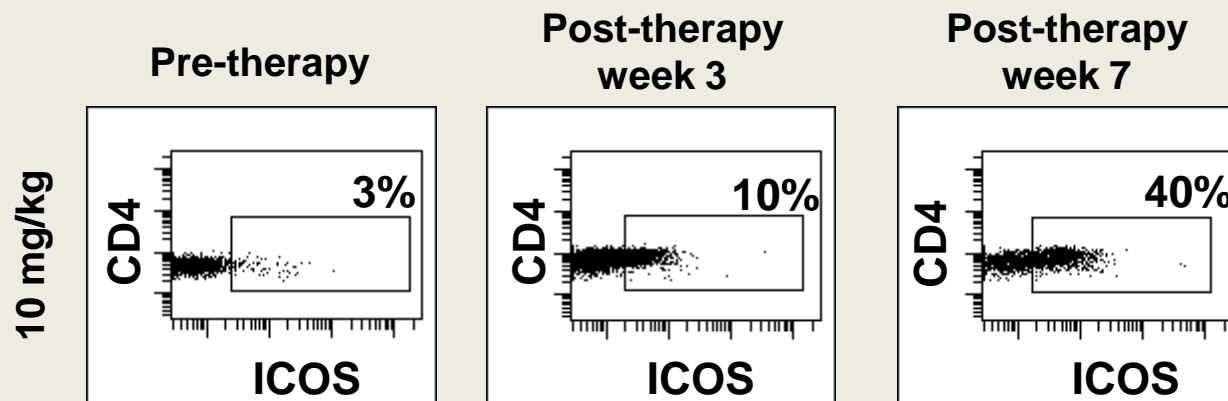
Select immune DEGs in prostate tumor tissues after treatment with ipilimumab plus ADT



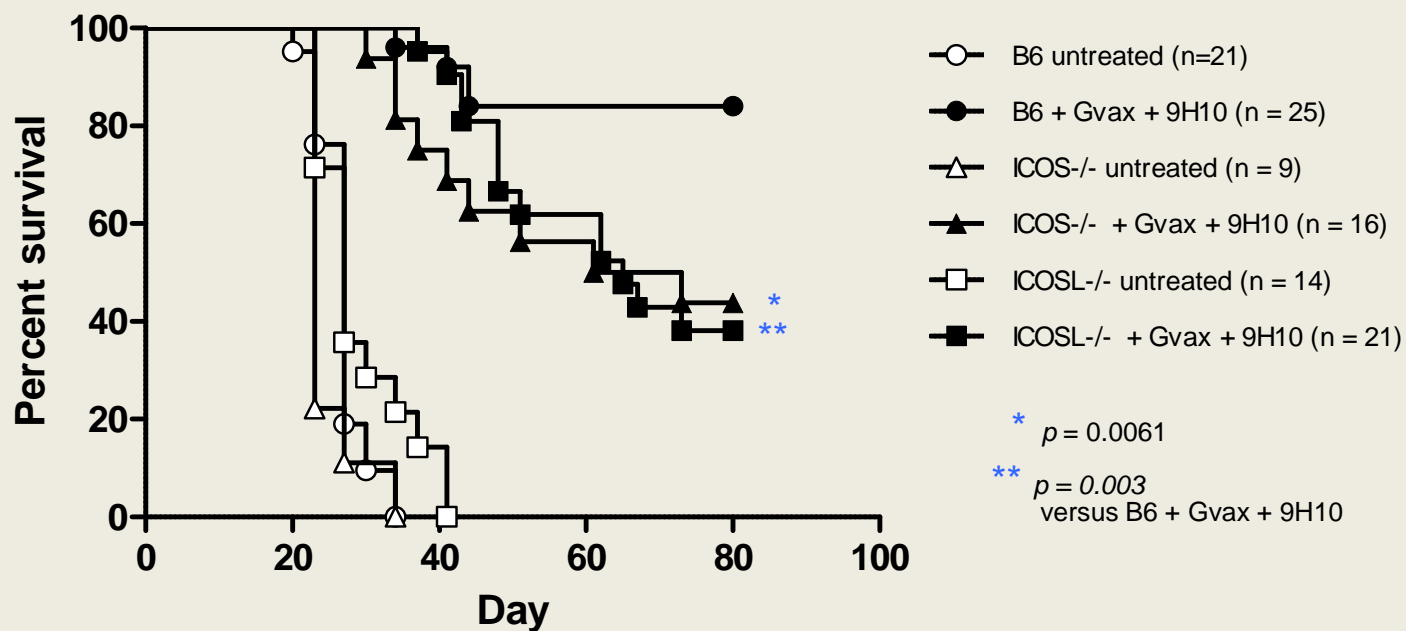
Increased Frequency of ICOS⁺CD4 T Cells in Tumors from Anti-CTLA-4 Treated Patients



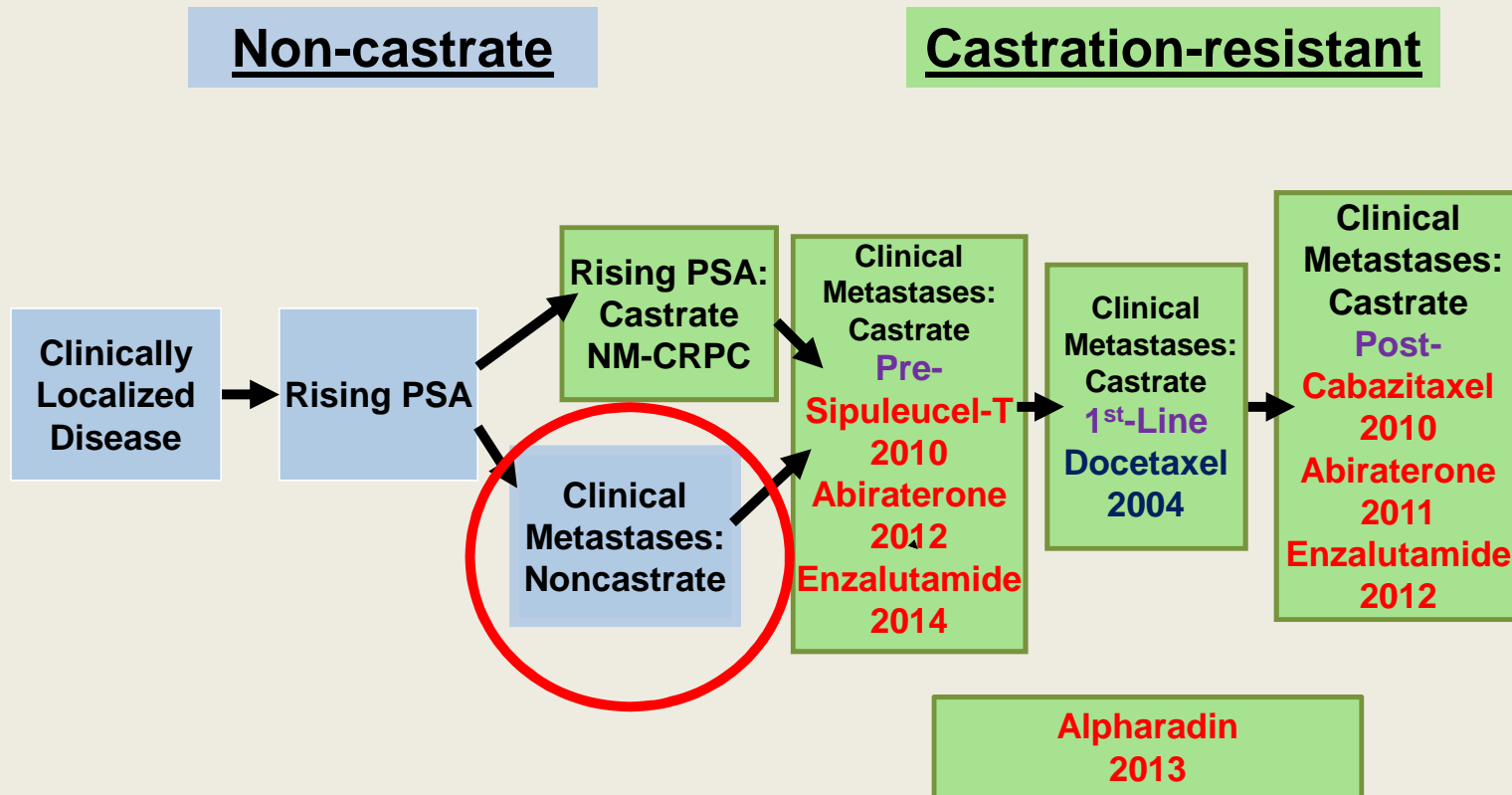
Frequency of ICOS⁺CD4 T cells increase in peripheral blood after treatment with anti-CTLA-4 antibody



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

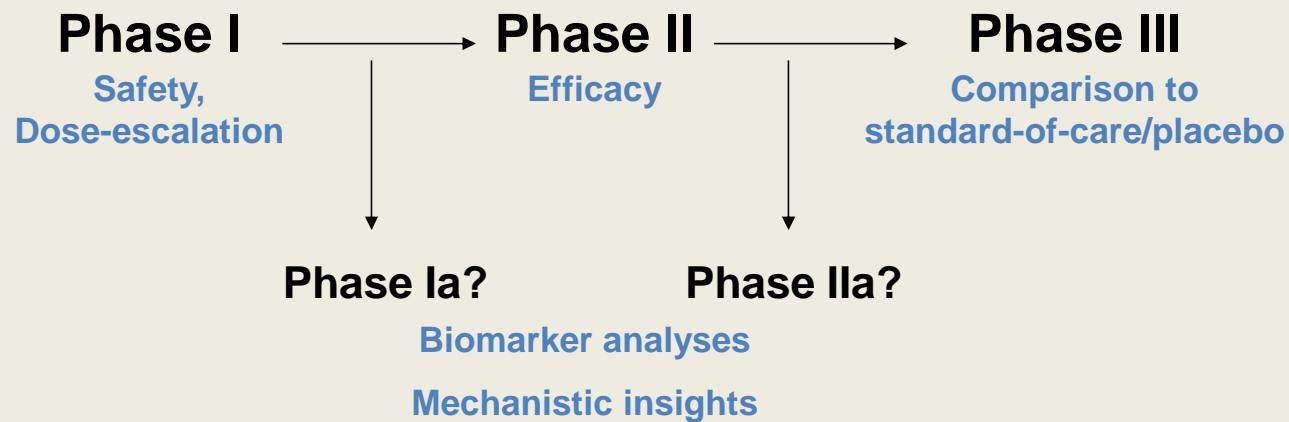


Clinical states model of prostate cancer



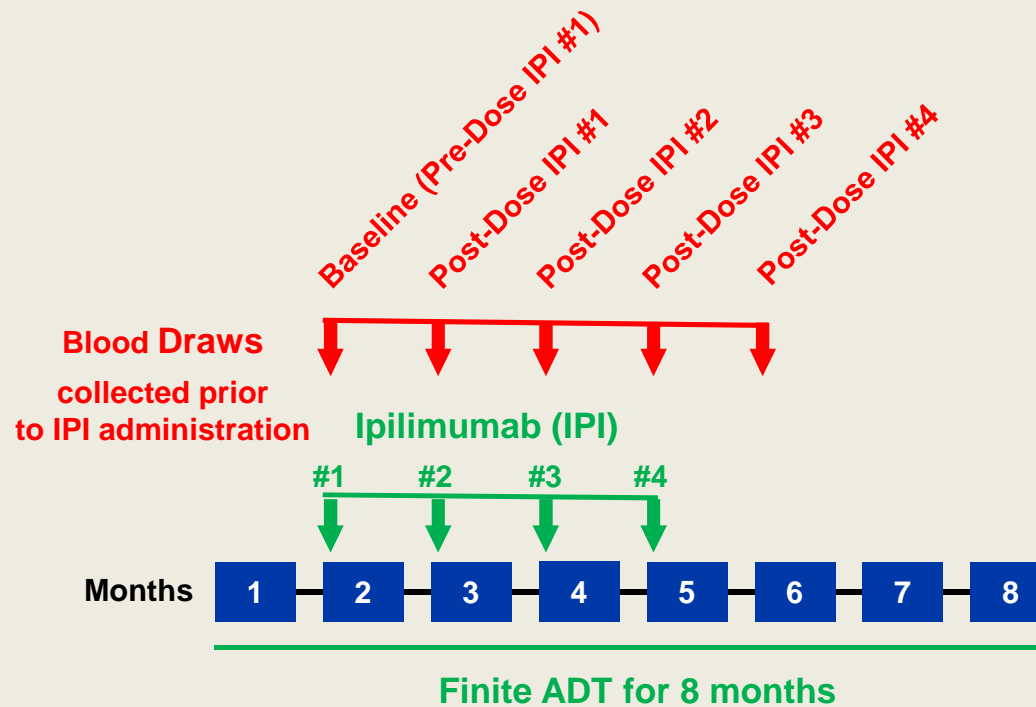
Modified from Scher and Heller. *Urology* 2000.

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

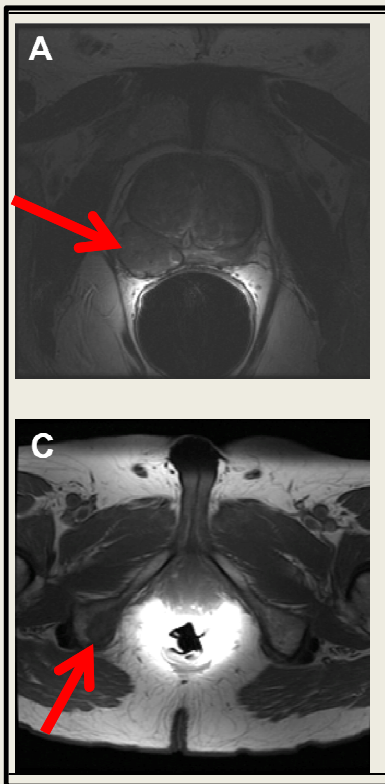
Endpoints

- **Primary:**
 - To estimate rate of PSA ≤ 0.2 ng/ml at 7 months (Maha Hussain, MB, ChB)
- **Secondary:**
 - To assess the time to testosterone recovery (≥ 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

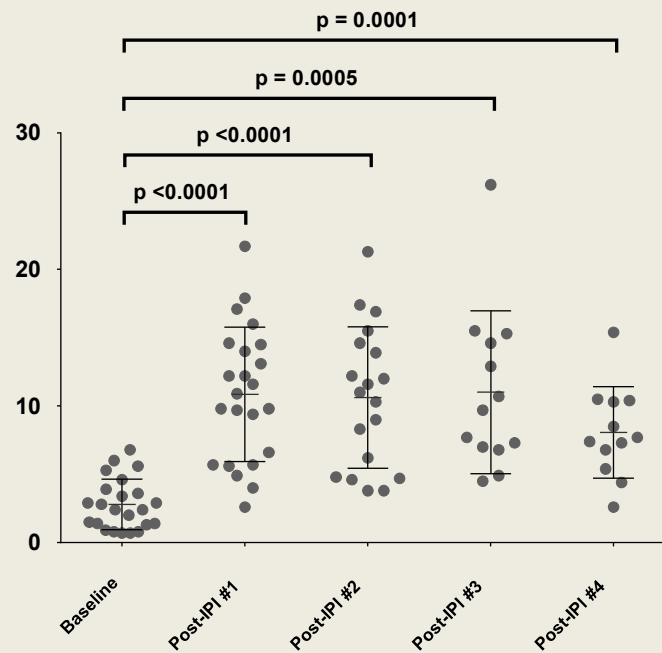
Baseline

07/15/2011

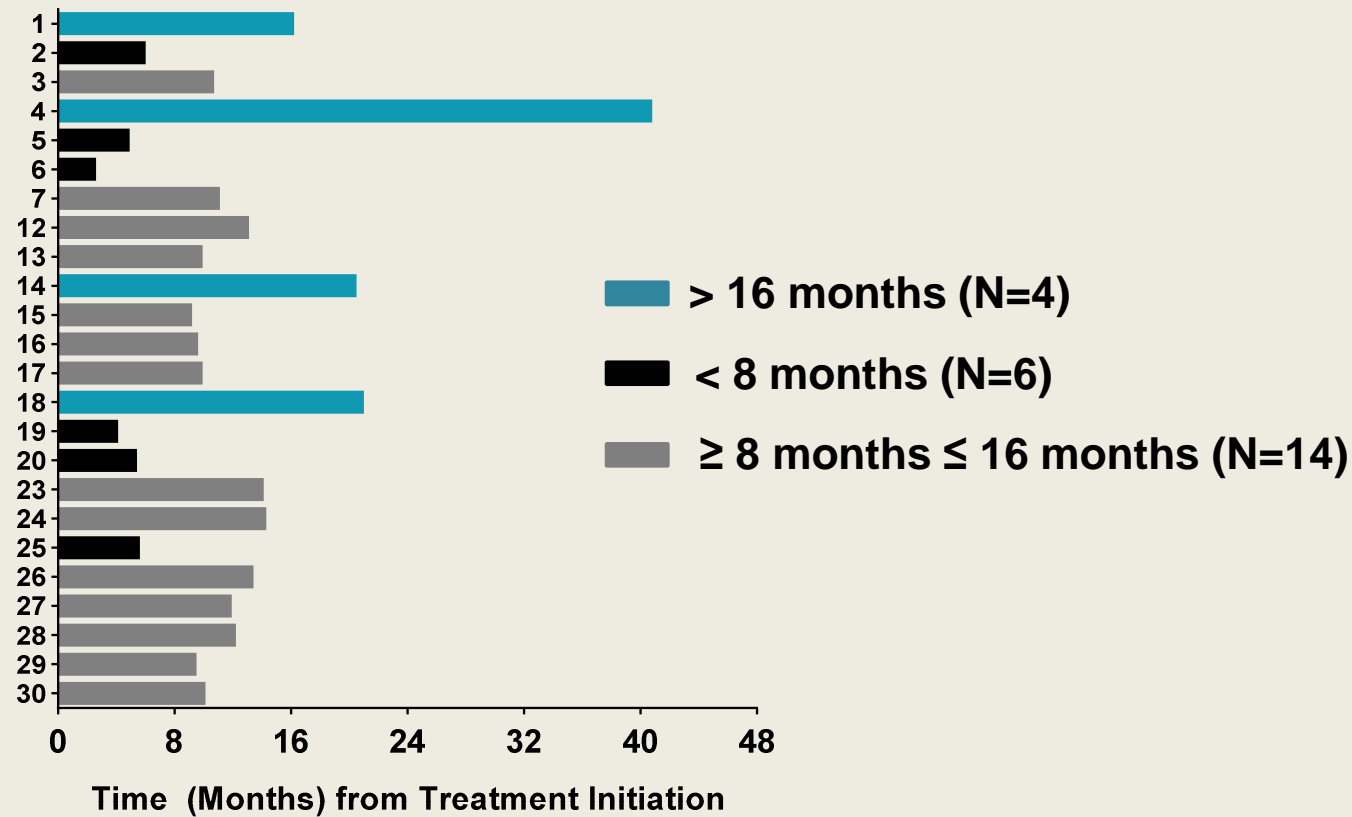


2 of 24 (7%) patients (Patients #1 and #4) achieved complete radiographic responses based on RECIST criteria.

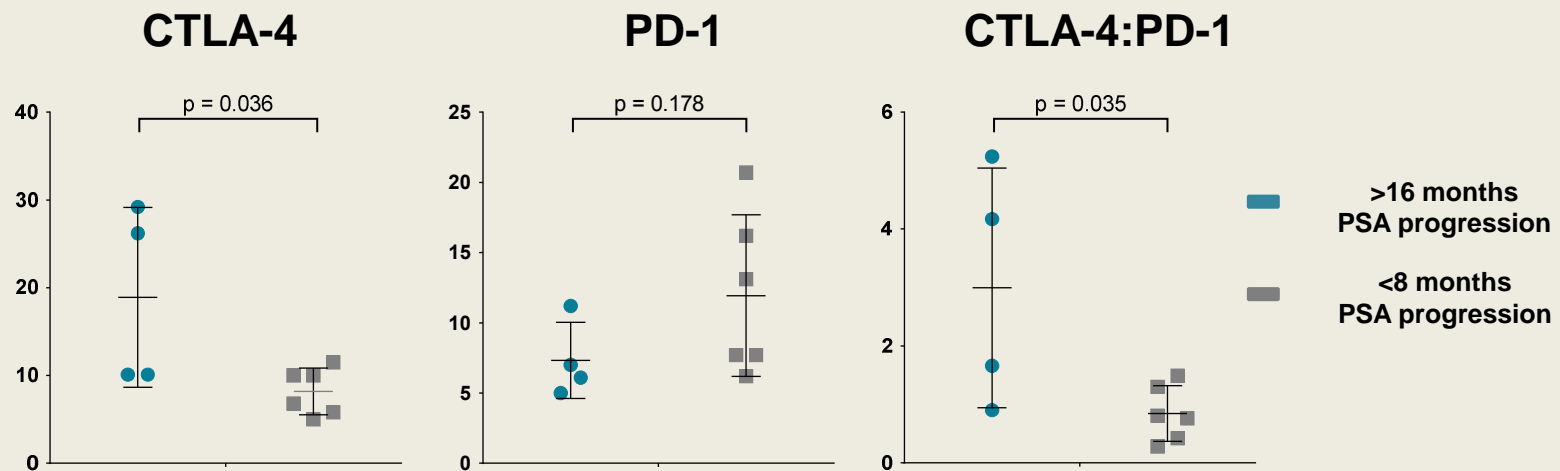
ICOS+CD4 T cells is a pharmacodynamic marker for ipilimumab



Time to PSA progression

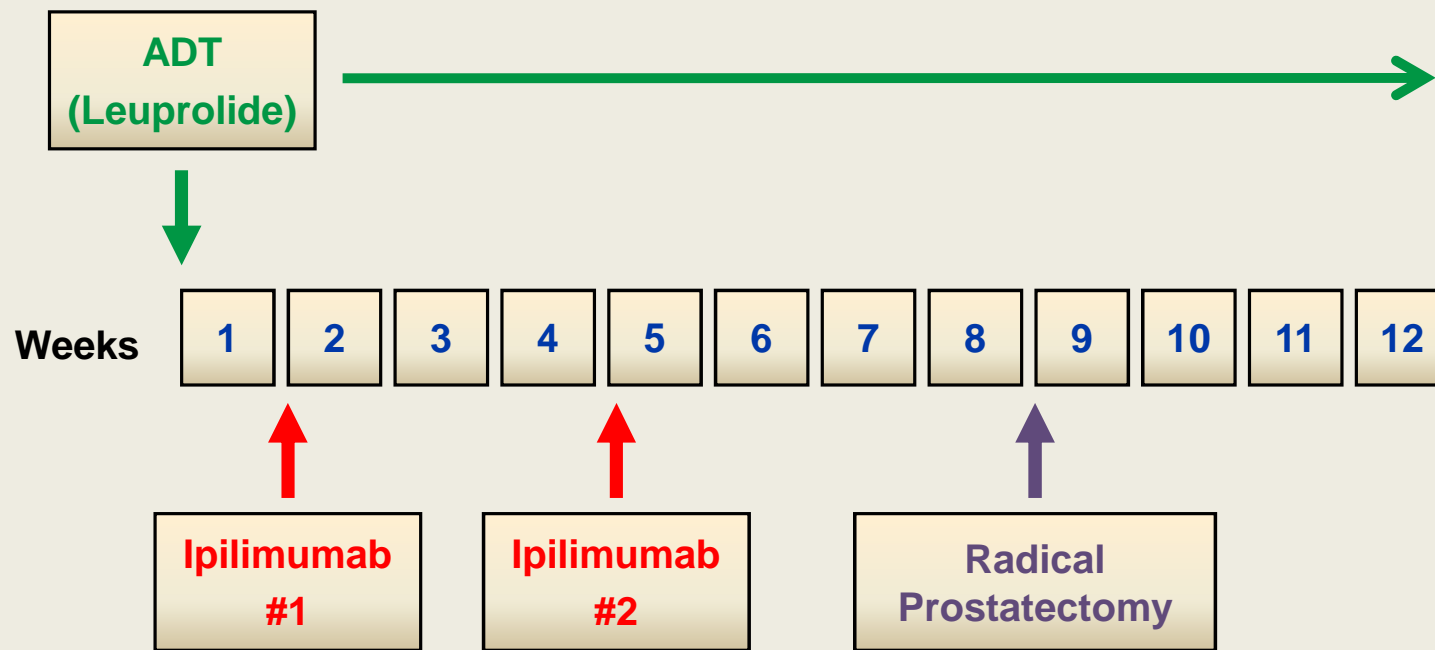


Baseline CD3 T cell biomarkers potentially predictive of clinical benefit



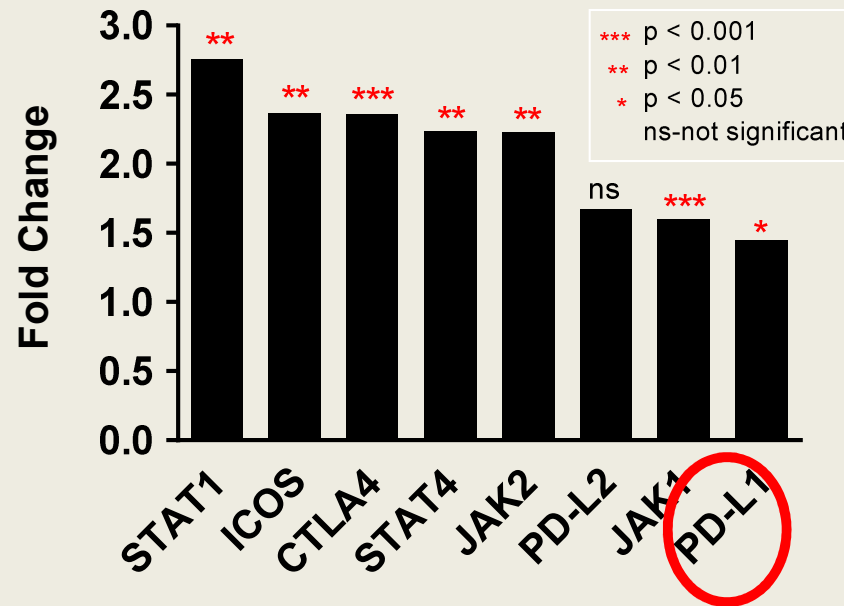
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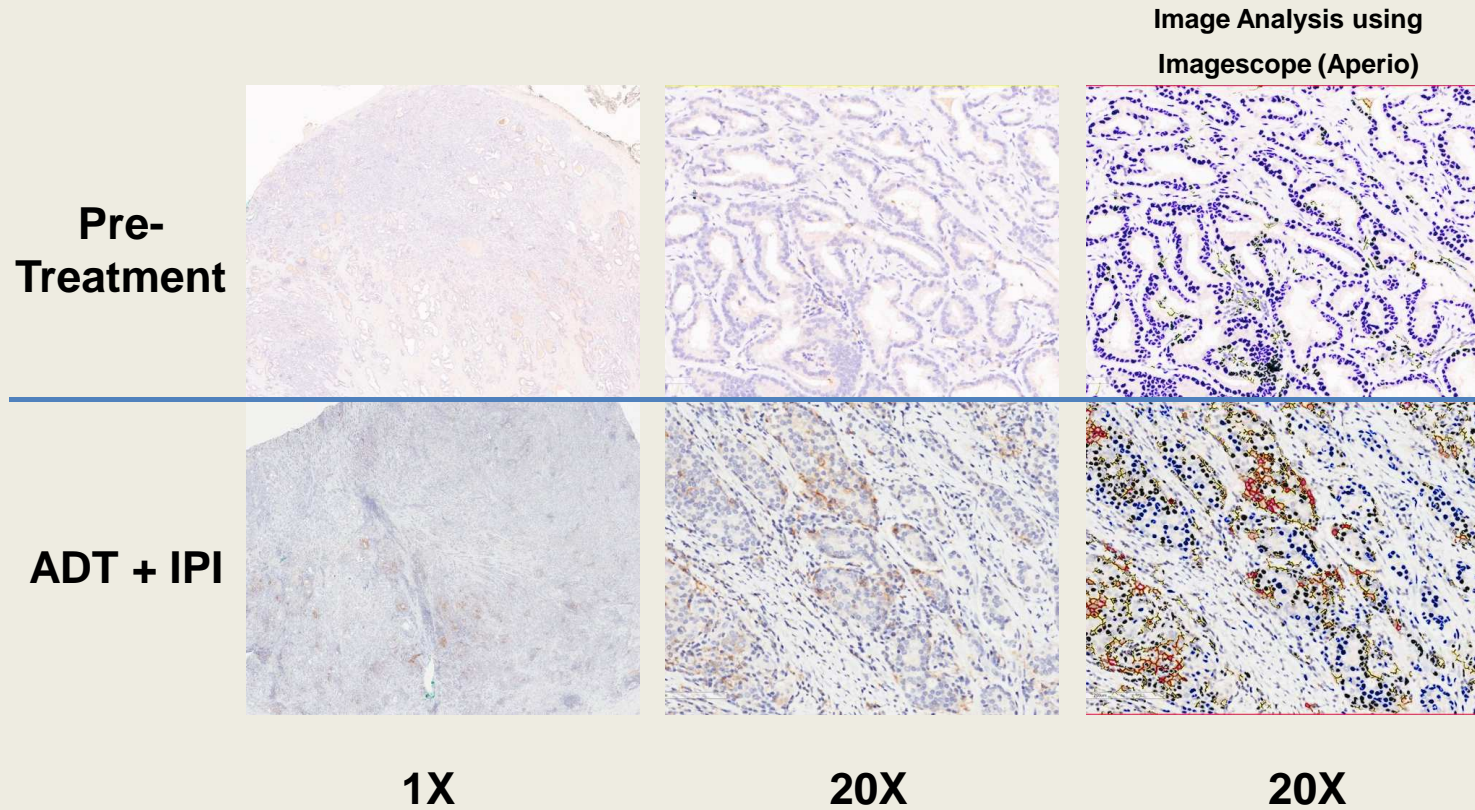


Padmanee Sharma, MD, PhD

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

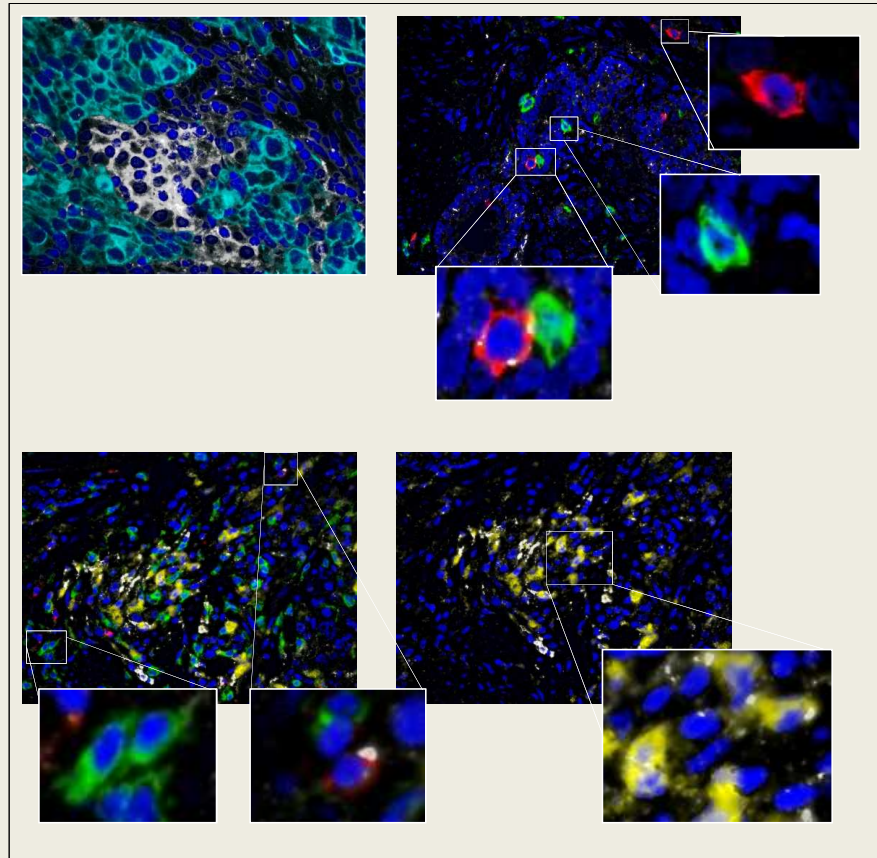


PD-L1 IHC staining

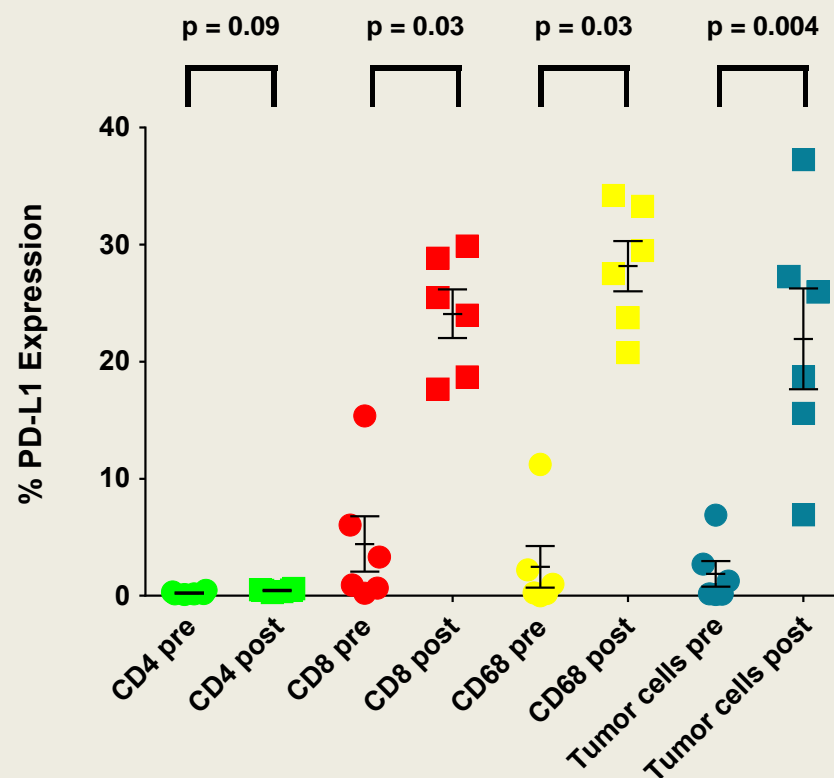


Multiplex analysis of PD-L1 expression status on selected cell subsets

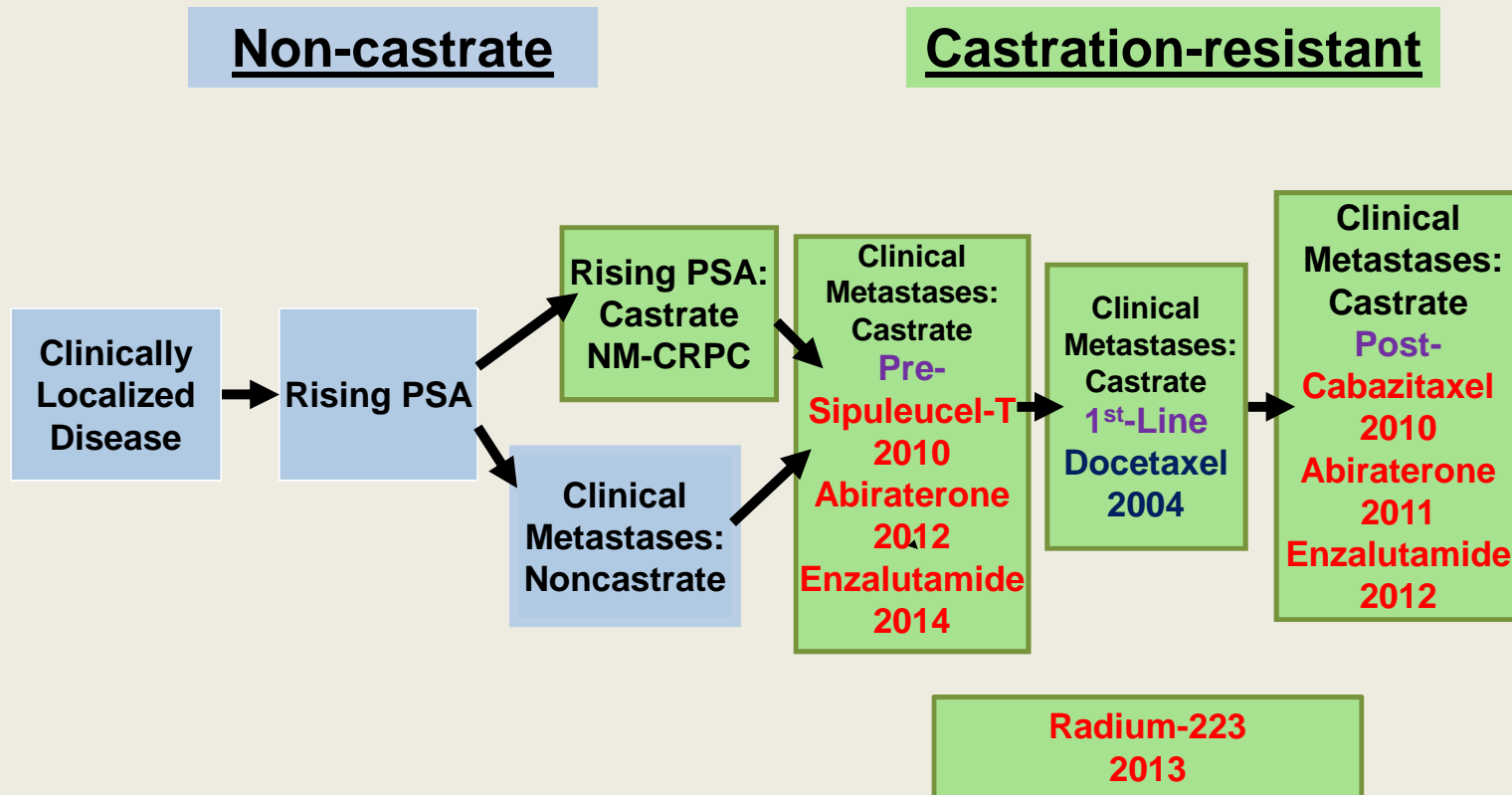
DAPI
Tumor/Epithelial cells
PD-L1
CD4
CD8
CD68



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

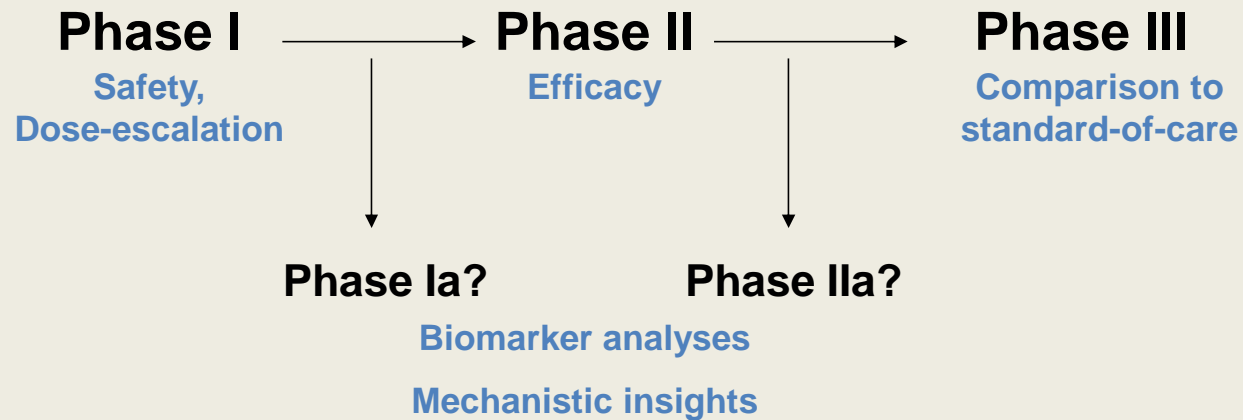


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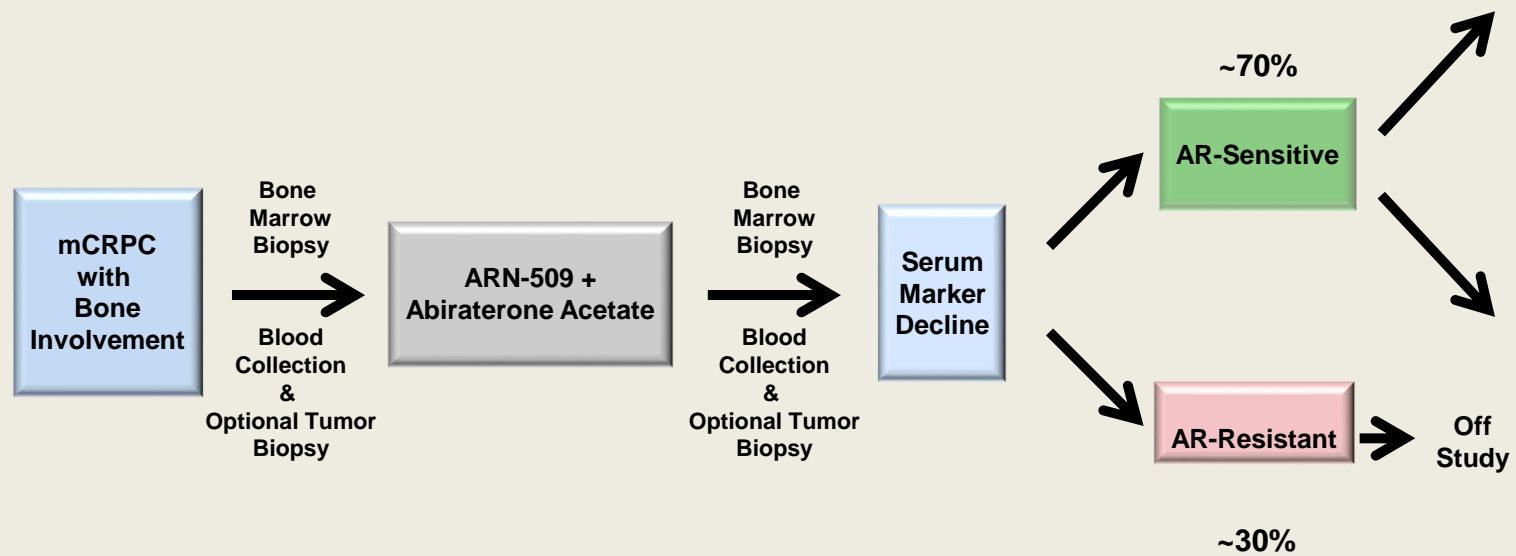
Re-thinking clinical trial design to obtain appropriate samples for biomarker studies



Hypothesis

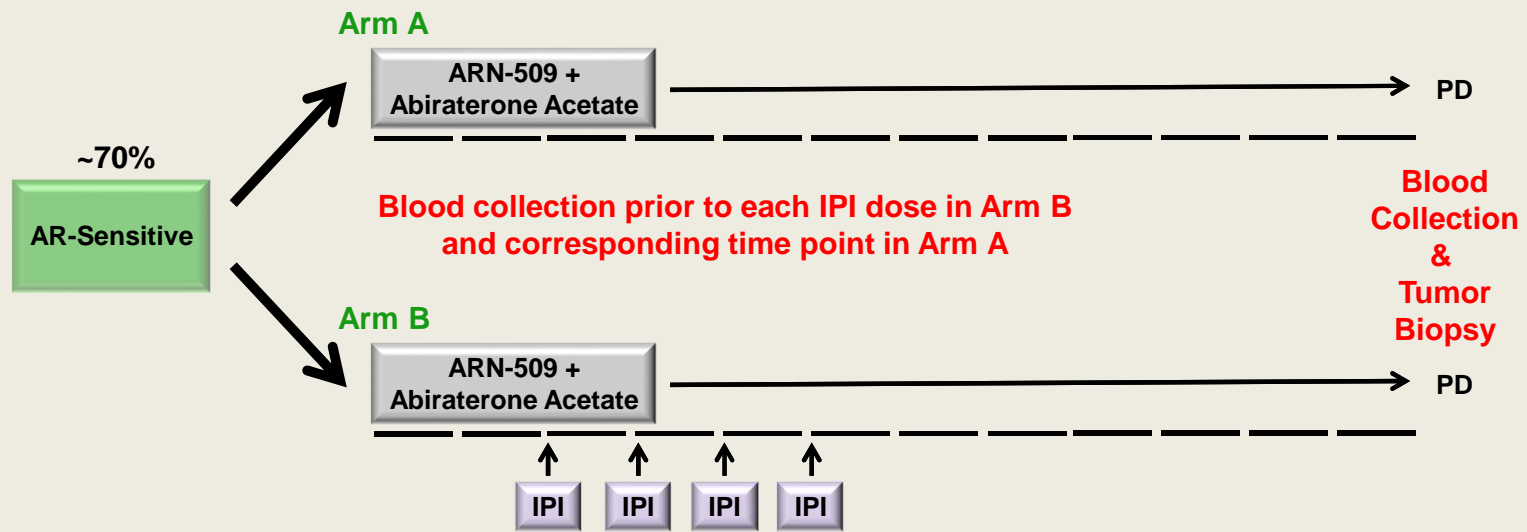
- **Patients identified based on initial responses to optimal targeting of the AR signaling pathway will derive further benefit with ipilimumab.**

Dichotomization of CRPC



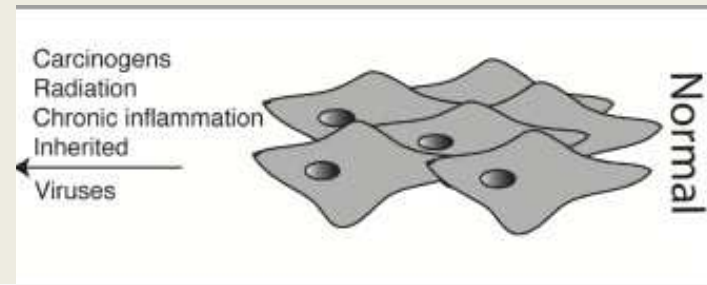
PI: Ana Aparicio, MD

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



Additional biomarker analyses

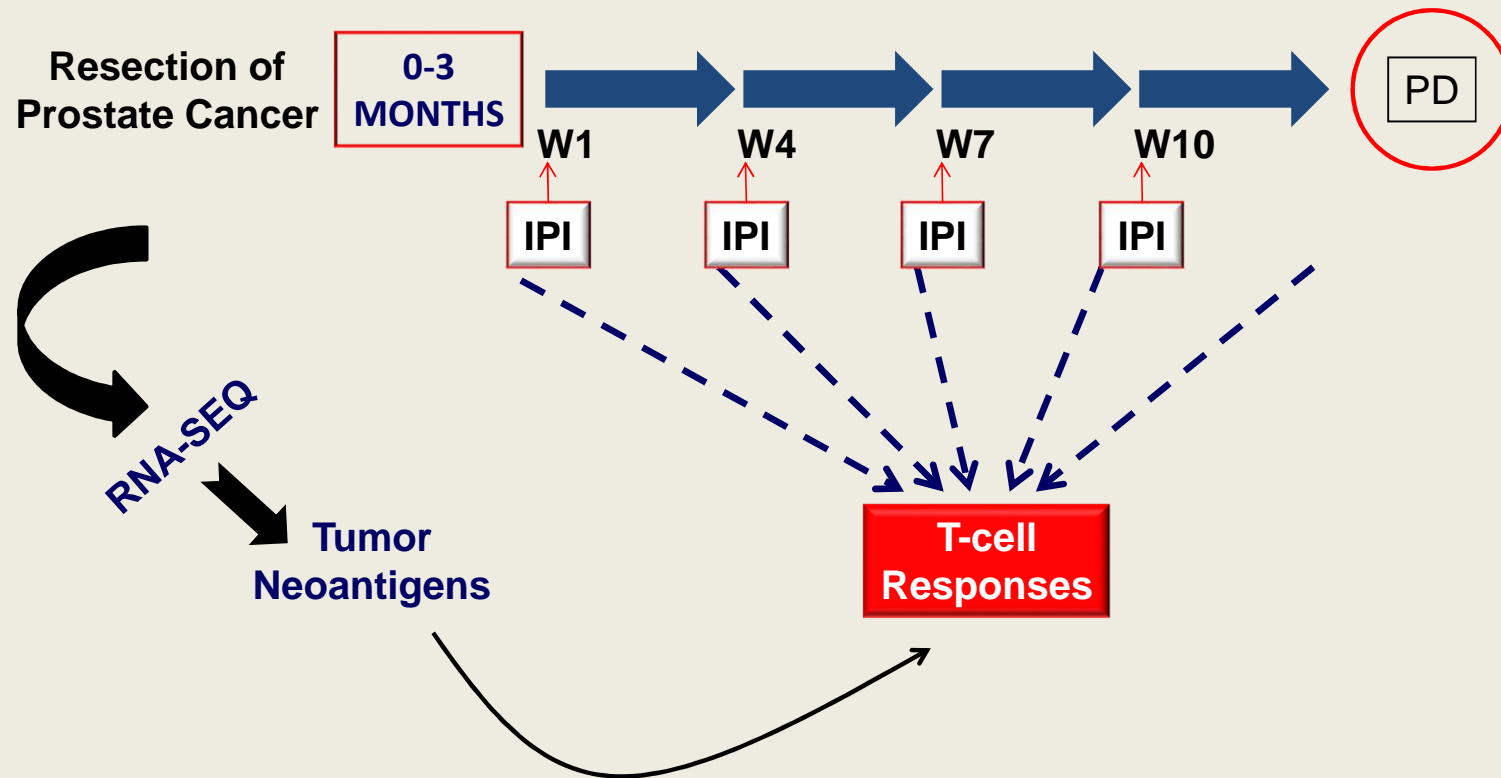
- **Hypothesis**
 - **Induction of effective anti-tumor responses by ipilimumab is mediated by lymphocyte responses to tumor neoantigens.**



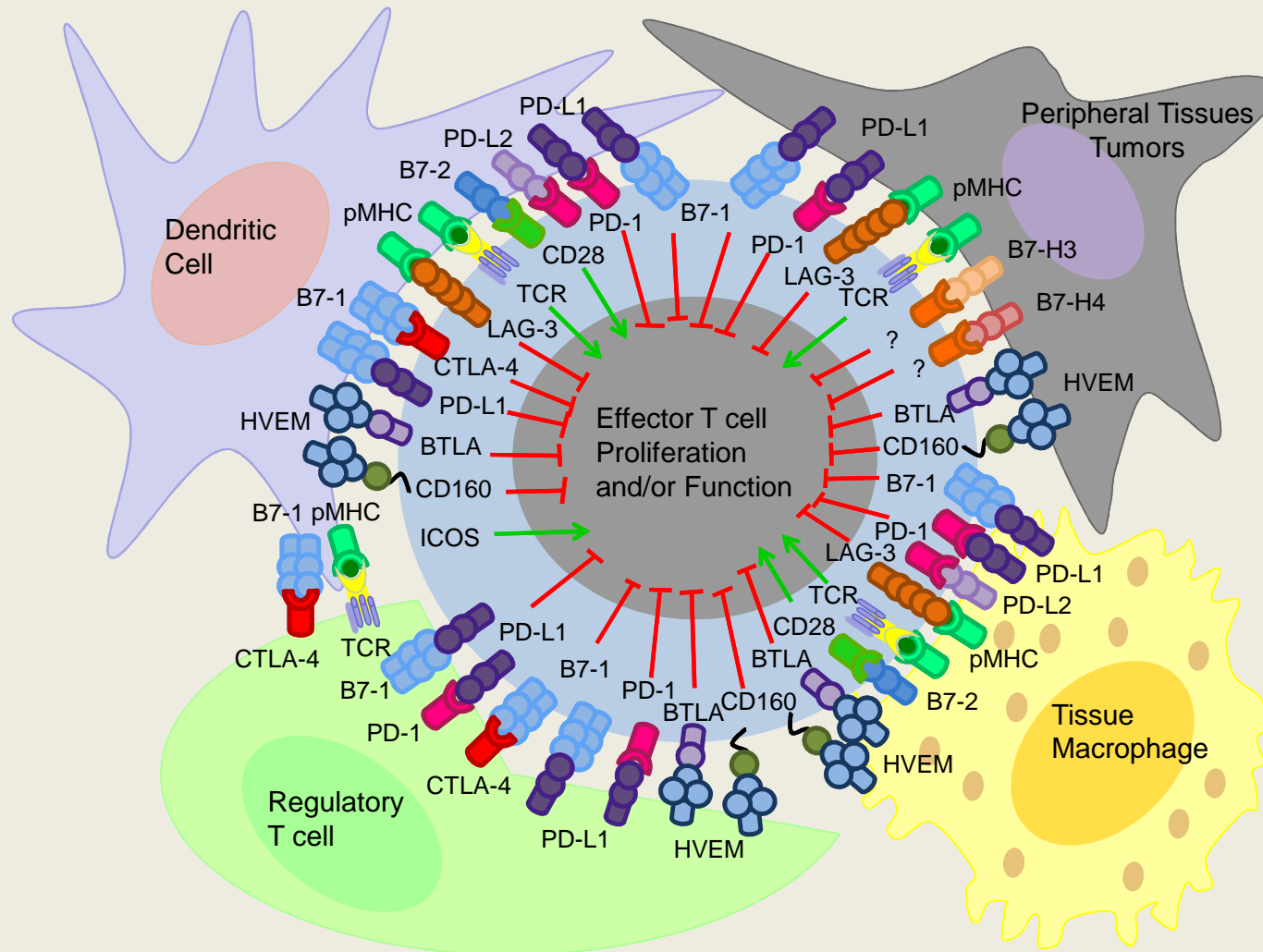
The Immunobiology of Cancer Immunosurveillance and Immunoediting

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
FOR APPLIED RESEARCH OF
GENITOURINARY CANCERS

PATIENTS

Immunotherapy (IMT) Platform

James Allison
Jorge Blando
Padmanee Sharma
Luis Vence
Ignacio Wistuba

Urology

Brian Chapin
John Davis
John Ward

Pathology

Patricia Troncoso

GU Medical Oncology

Ana Aparicio
John Araujo
Paul Corn
Eleni Efstathiou
Jianjun Gao
Christopher Logothetis
Padmanee Sharma
Shi-Ming Tu
Amado Zurita

Radiology

Brinda Rao