Combinatorial Immunotherapy for Prostate Cancer:

The "MARCH" Forward

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Disclosure Of Financial Relationships

- Consulting:
  Dendreon, BMS, Medarex

- Sponsored Research Agreements (SRA):
  Cell Genesys

- Institutional:
  Under a licensing agreement between Cell Genesys Inc. and the Johns Hopkins University, the University is entitled to milestone payments and royalties on the sale of immunotherapy products. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

Combinatorial Immunotherapy

- **MA**

  Minimization of Antigen

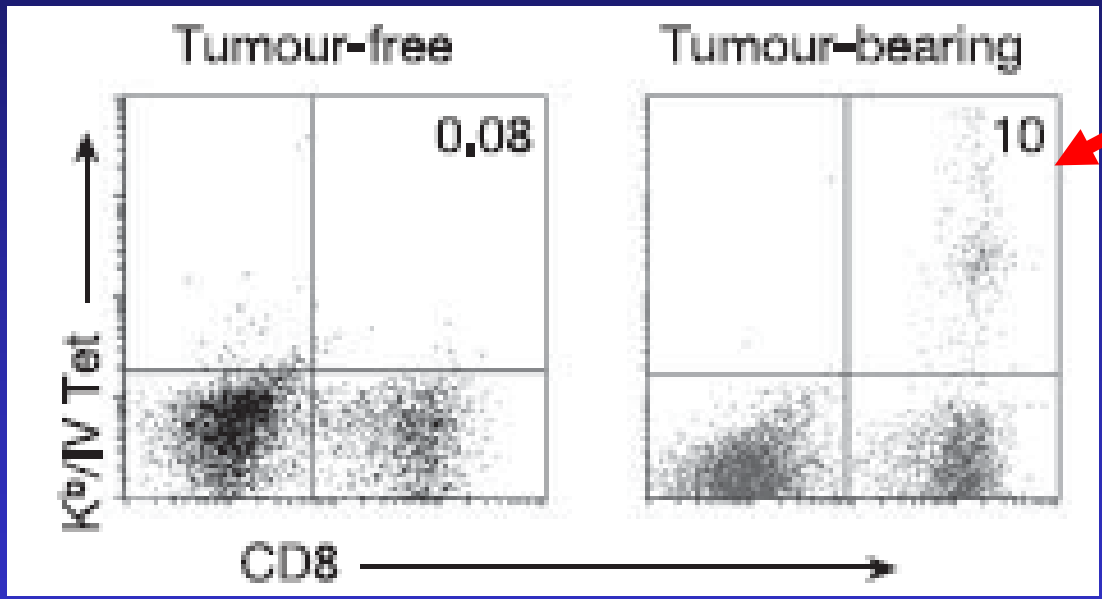
- **R**

  Re-Vaccination*

- **Ch**

  Checkpoint Blockade

Tumor-Bearing MICE (and patients) ALREADY HAVE Anti-Tumor T Cells



Wilimsky, G and Blankenstein T.
Nature, 437: 141-146, 2005.

Re-Vaccines in Clinical Development

Approach	Company	Developmental Phase
Dendritic Cell (Sipuleucel T)	Dendreon	2 Phase III Completed 1 Phase III In Progress
Allogeneic Cell-Based (GVAX)	Cell Genesys	1 Phase III Completed 1 Phase III in progress
Viral-Based (ProstVac VF)	Therion / NIH	Large single agent Phase II completed Multiple Combinatorial Phase II in progress
DNA-Based		Phase I and II
Listeria-Based	Cerus	Preclinical

Immune Checkpoints = The BRAKES

CTLA-4
PD-1
LAG-3
4-1BB
OX-40
iNOS

Vaccine = The GAS

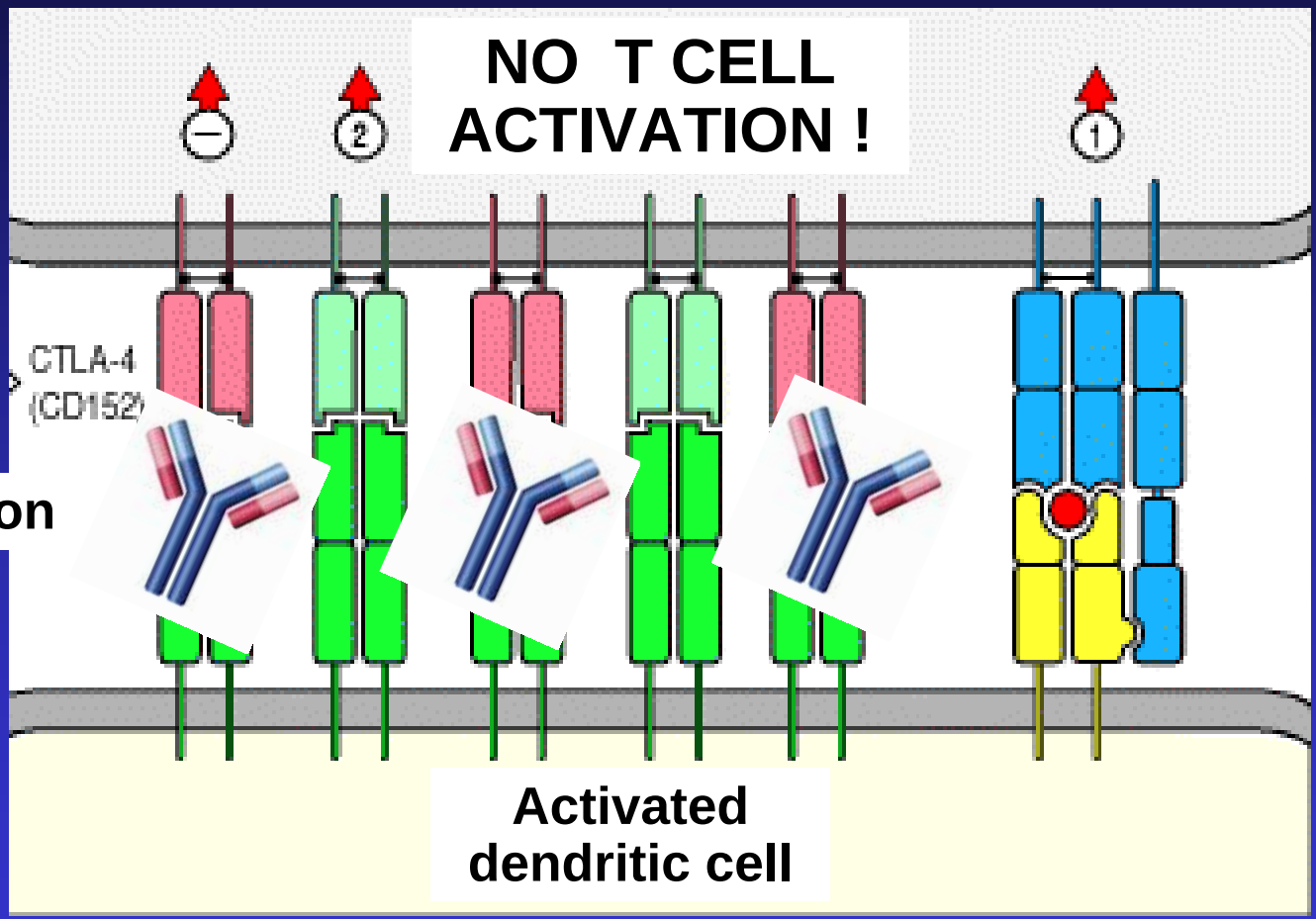
Microarray Analysis Of Prostate-Infiltrating CD4 Treg Cells

Probe ID	Fold Increase	Gene Definition	Gene Symbol	Cellular Component
TNFSF9	122	Tumor necrosis receptor superfamily, member 9 (41BB)	TNFRSF9	Membrane
234895_at	95	cytotoxic T-lymphocyte-associated protein 4	CTLA4	Membrane
206486_at	86	lymphocyte-activation gene 3	LAG3	Membrane
211269_s_at	58	interleukin 2 receptor, alpha (CD25)	IL2RA	Membrane
223851_s_at	31	tumor necrosis factor receptor superfamily, member 18 (GITR)	TNFRSF18	Membrane
224211_at	17	forkhead box P3	FOXP3	Nucleus

The Brakes are On …

Anti-CTLA-4
Taking the foot OFF the Brakes

Co-inhibition



Janeway C. Ed. *Immunobiology*. 6th Edition. 2005:329-330.

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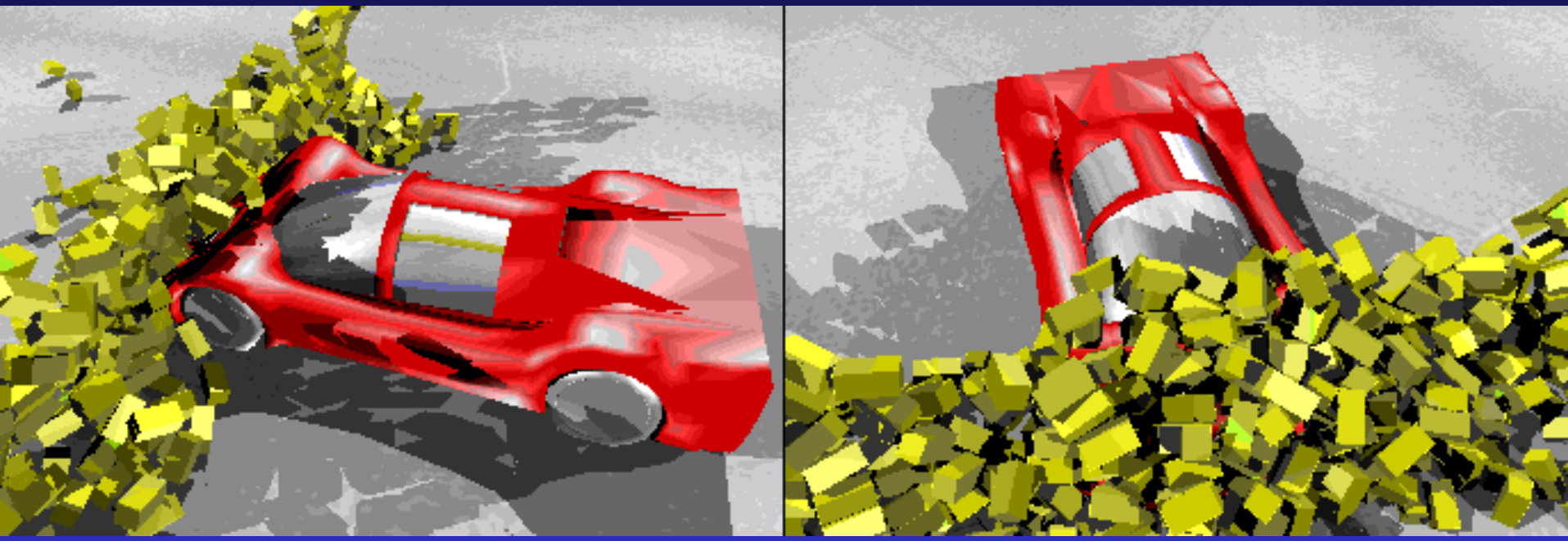
Persistent Antigen = The WALL



The ProHA x TRAMP Mouse (ProTRAMP)

- ProSV40 – Oncogenic
- ProHA – A Tumor / and Tissue Specific Antigen
- Disease grossly identical to TRAMP

What Happens to Tumor-Specific T Cells in Vivo?

HA Specific CD4 Cells (Thy1.1 +)

i.e. Prostate Specific T Cells

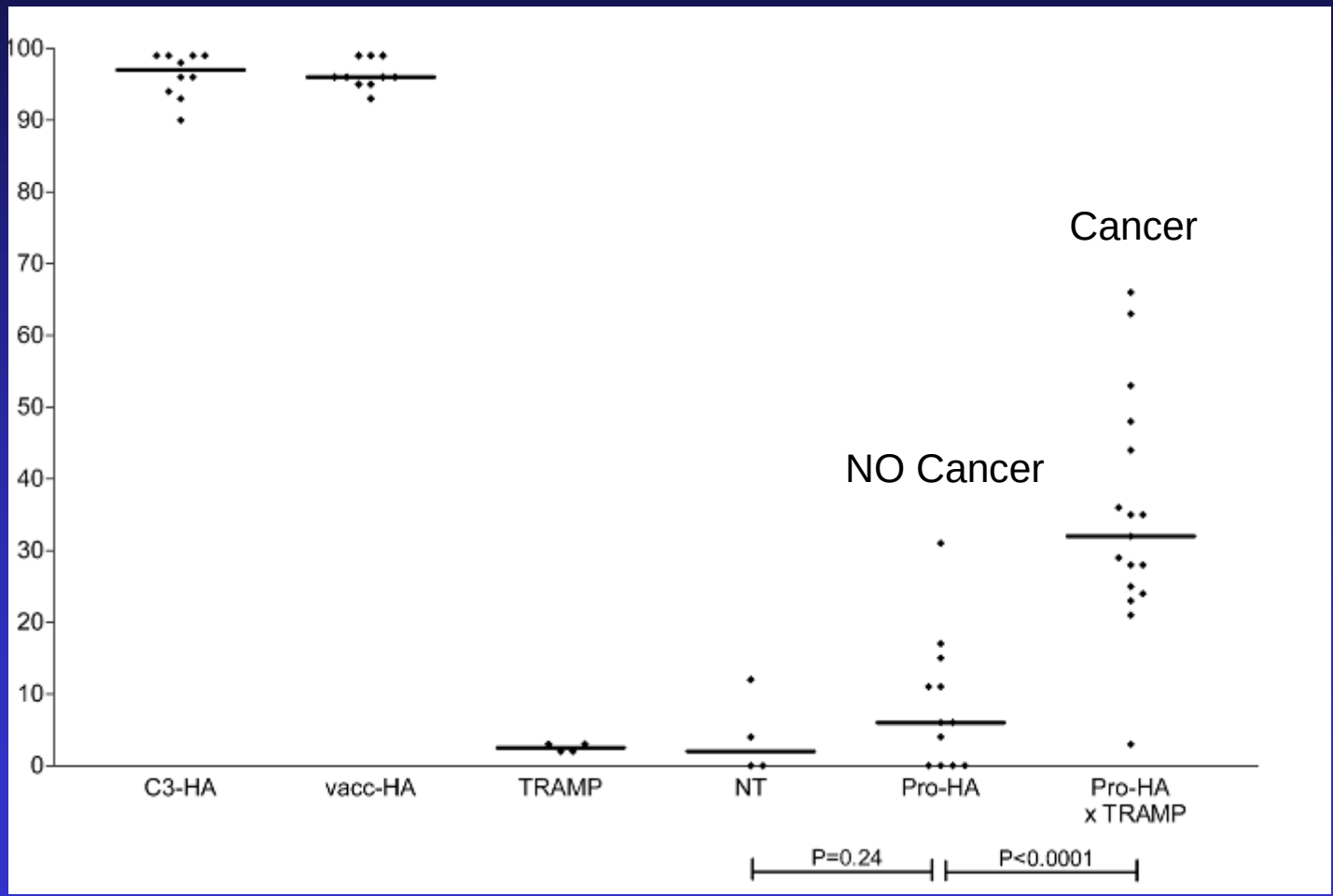
<u>Recipients</u>
C3HA
NonTransgenic + VaccHA
TRAMP d/d
NonTransgenic
ProHA
ProHA x TRAMP

T Cell Expansion
(By CFSE Dilution)

T Cell FUNCTION
Interferon Gamma Production

Tumorigenesis Breaks "Ignorance"

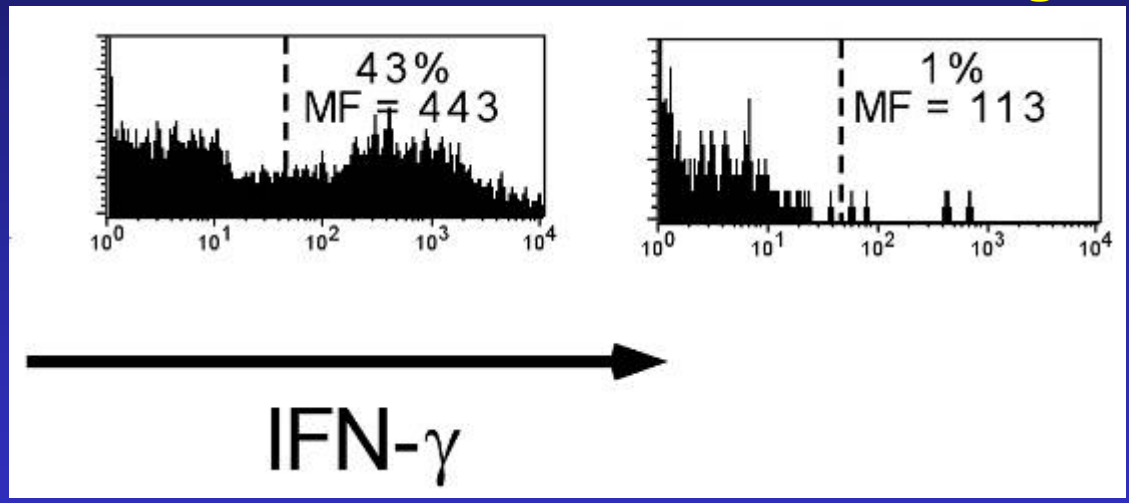
T Cell DIVISION



But …Tumor-Specific CD4 T Cells Are Rendered Tolerant

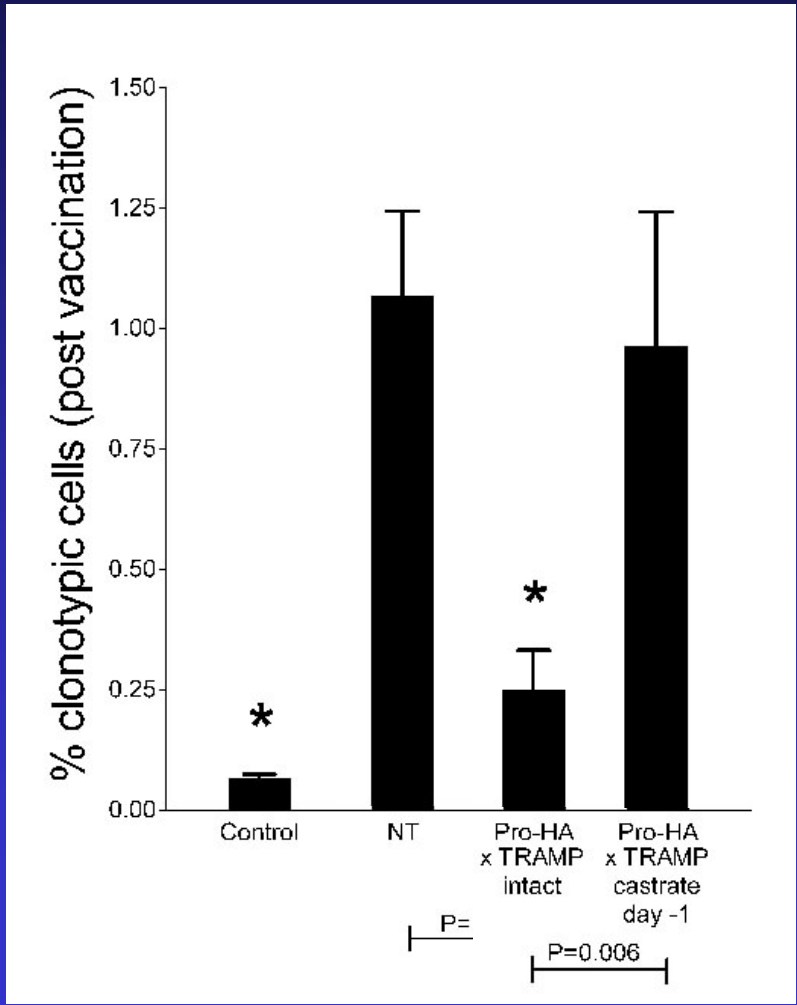
Viral Recognition

Cancer Recognition



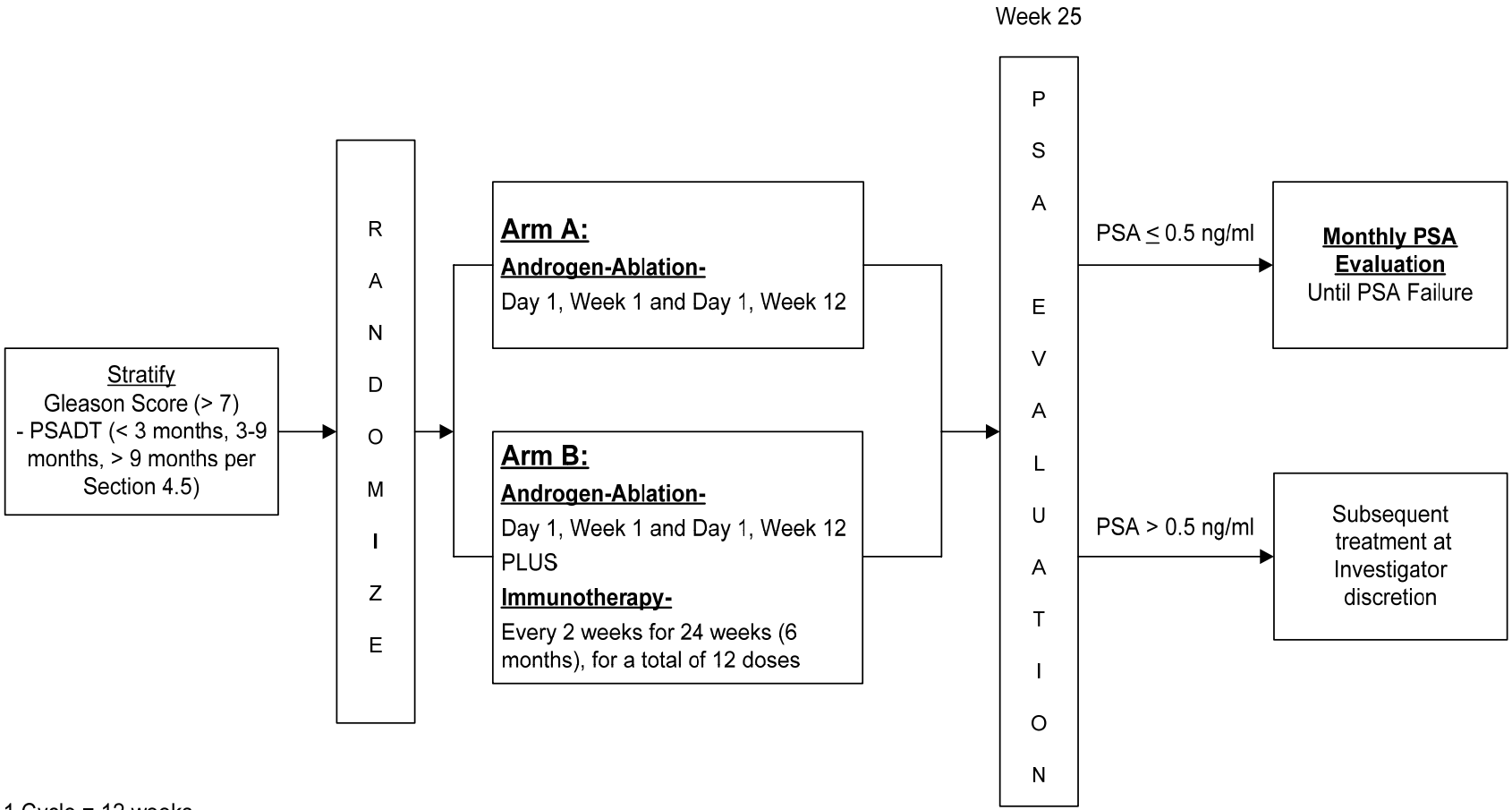
Drake C. et a.. Cancer Cell 2005

Minimization of Antigen…..
(Via Androgen-Ablation)



Drake et al. *Cancer Cell.* 2005;7:239-249.

ECOG 3806



1 Cycle = 12 weeks
Accrual Goal: 126 patients

- Premedication - Bicalutamide 50 mg PO QD for 28 days of treatment beginning 7 days PRIOR to the first androgen ablation treatment until 21 days after.
- PSA Evaluation, Week 25 - Patients on both arms are assessed. PSA > 0.5 ng/ml, patients on either arm are treated at the investigator's discretion and followed. PSA ≤ 0.5 ng/ml, patients stop therapy and have monthly PSA evaluations until PSA progression.

Minimization of Antigen

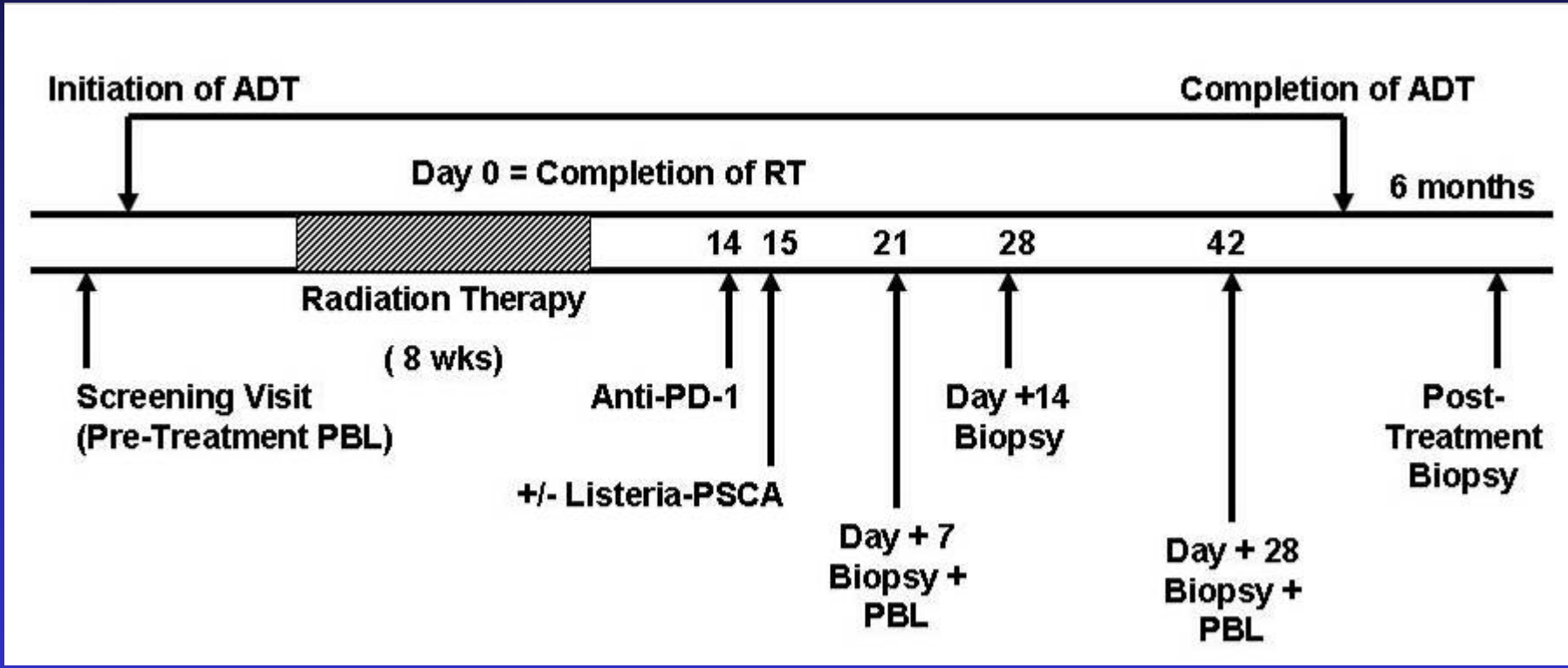
Surgery

Radiation Therapy

Androgen-Ablation

Chemotherapy

Putting it All Together …



Barriers to the MARCH

- FDA ("Bridge" or Barrier)
- Corporate I.P. Issues
- Trial Complexity

Testicular Cancer is NOT CURABLE Using Single-Agent Therapy …