Therapeutic Cancer Vaccines

Douglas G. McNeel, MD PhD

Professor of Medicine

University of Wisconsin Carbone Cancer Center

Madison, WI

Disclosures

Consultant: Dendreon corporation, Madison Vaccines Inc

Founder: Madison Vaccines Inc

I will not discuss off-label use of any agents

Educational Goals

- To understand the rationale for anti-tumor vaccines
- To understand the role of “antigens” as targets for vaccine development
- To identify anti-tumor vaccine approaches approved or in advanced phase clinical trials
- To understand some of the challenges incorporating anti-tumor vaccines into clinical practice

Outline

- Introduction
  - Rationale for anti-tumor vaccines
  - History of vaccines
  - Role of antigens / antigen discovery
- Anti-tumor vaccines in practice/advanced trials
- Paradigm changes for the treating oncologist

Tumor Immunology - Types of approaches

- Infusion of cytokines
- Antibody therapy
- Adoptive immunotherapy

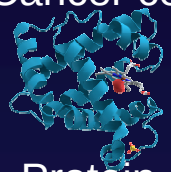
} Passive

- Immunomodulation
- Vaccines

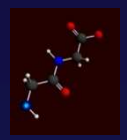
} Active

What is an anti-tumor vaccine and how do they work?

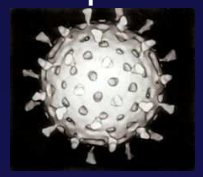
Cancer cell



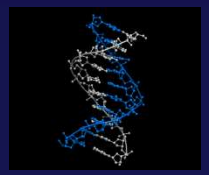
Protein



Peptide



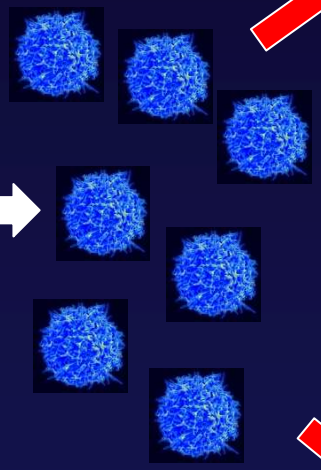
Virus / bacteria



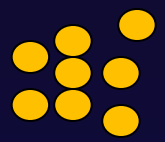
Nucleic acid

ADJUVANT

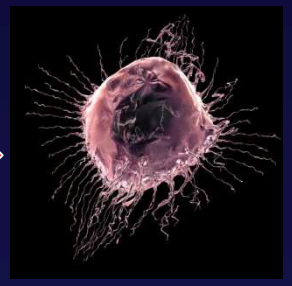
Dendritic cell
(Antigen-presenting cell)



Lymphocytes



Cytokines



Antibodies

Why use vaccines to treat cancers?

- Nature has already given us a specific and adaptive process
- Infectious diseases – “magic bullet”
- Greatest medical accomplishment of the 20th century (?) – vaccines
- Already evidence that immune system plays a role in anti-tumor surveillance
- Lots of evidence that they “work” in experimental models

Challenges with Anti-Tumor Vaccines

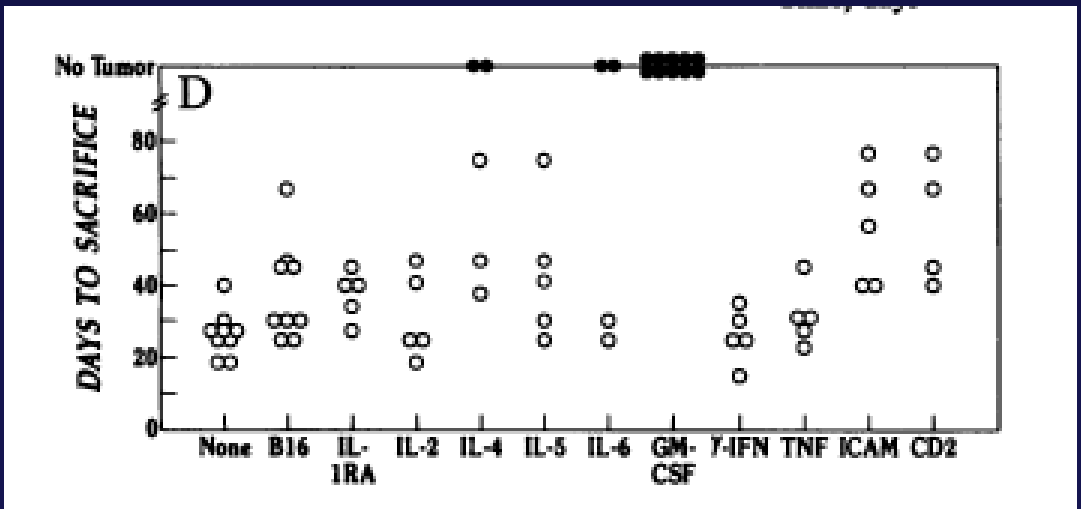
- Self versus non-self
  - Autoimmunity …
- Protection from disease versus treatment of existing disease
- Generating antibody responses (only) may be insufficient
- Compensatory / regulatory mechanisms within tumors are complex

(Brief) History of Anti-Tumor Vaccines

- Discovery of mechanisms of T-cell recognition and action
- Discovery of antigen-presenting cells
- Led to a large effort to identify “tumor-rejection” antigens
- Multiple vaccine approaches to specifically elicit immune cells with anti-tumor activity

(Brief) History of Anti-Tumor Vaccines

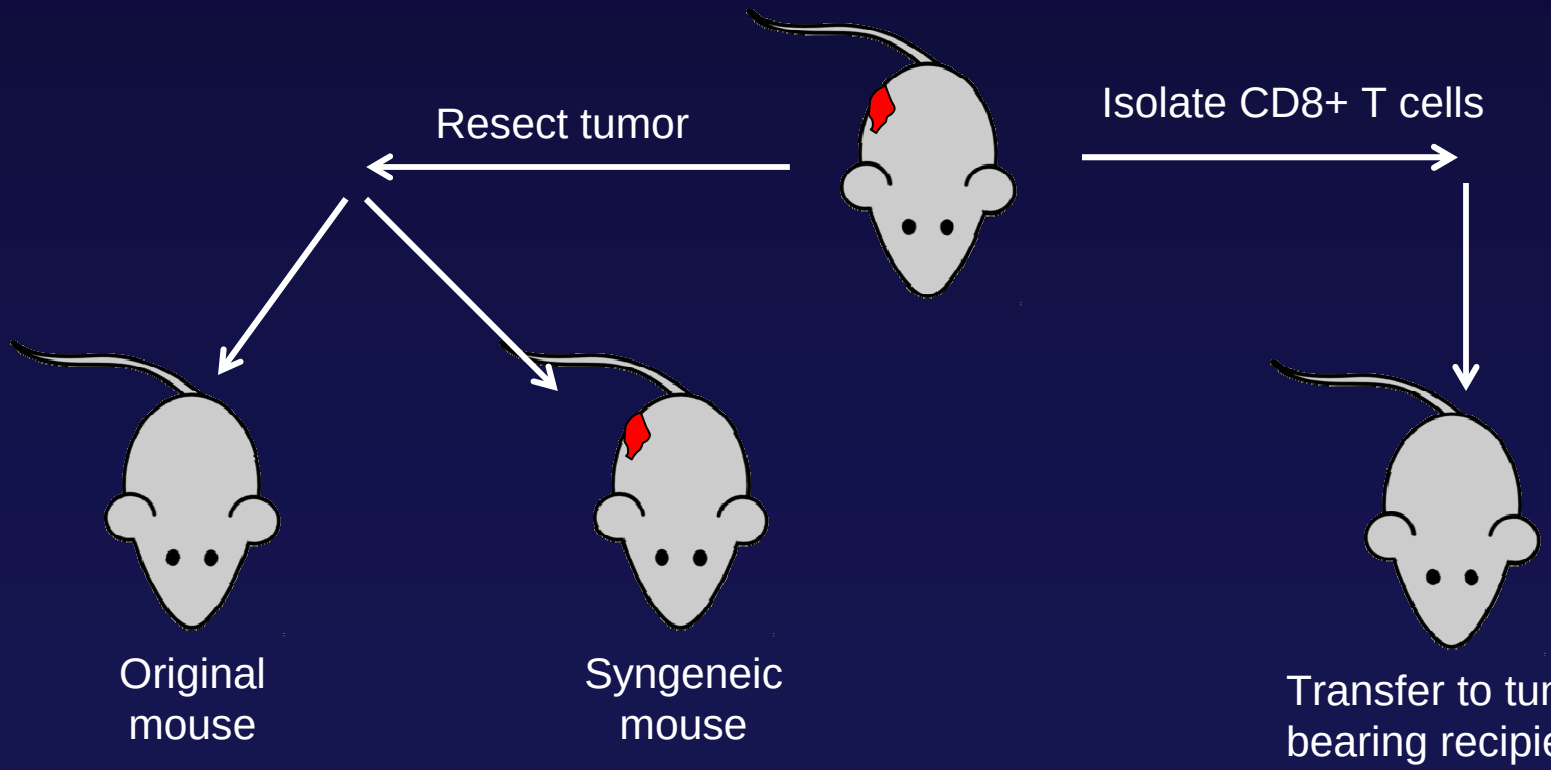
- Early 1900's: Inactivated tumors as vaccines
- Use of adjuvants
  - BCG
  - Cytokines



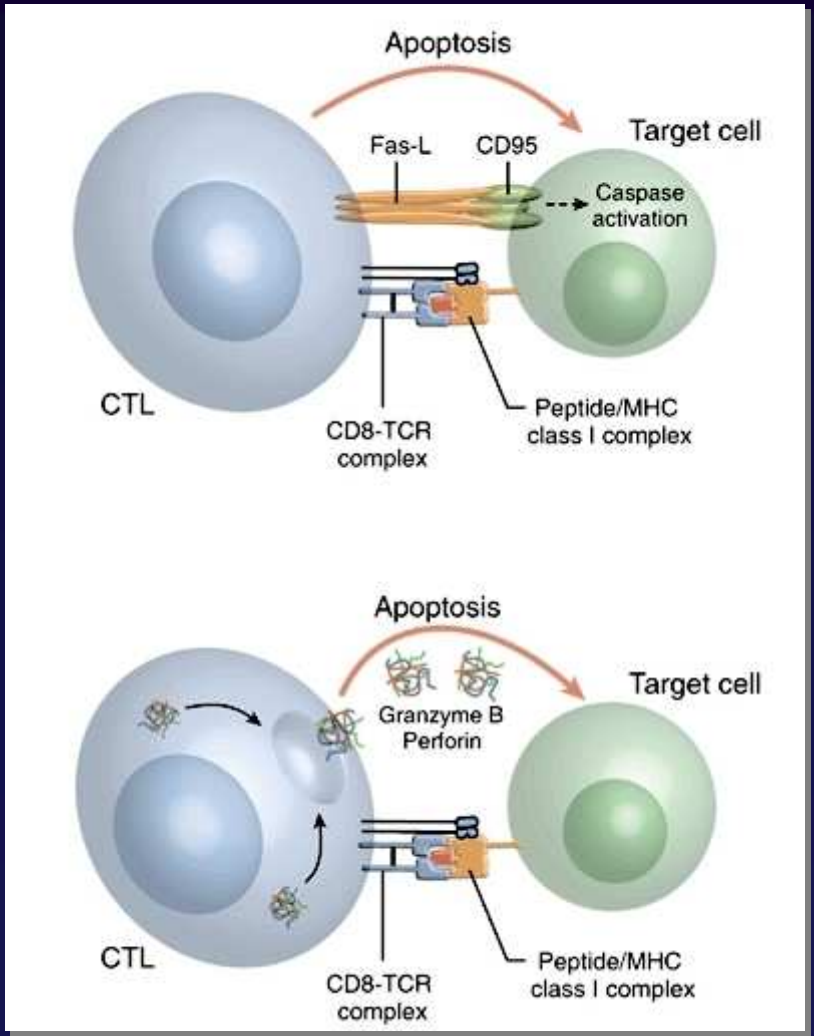
Dranoff '93 PNAS 90:3539

(Brief) History of Anti-Tumor Vaccines

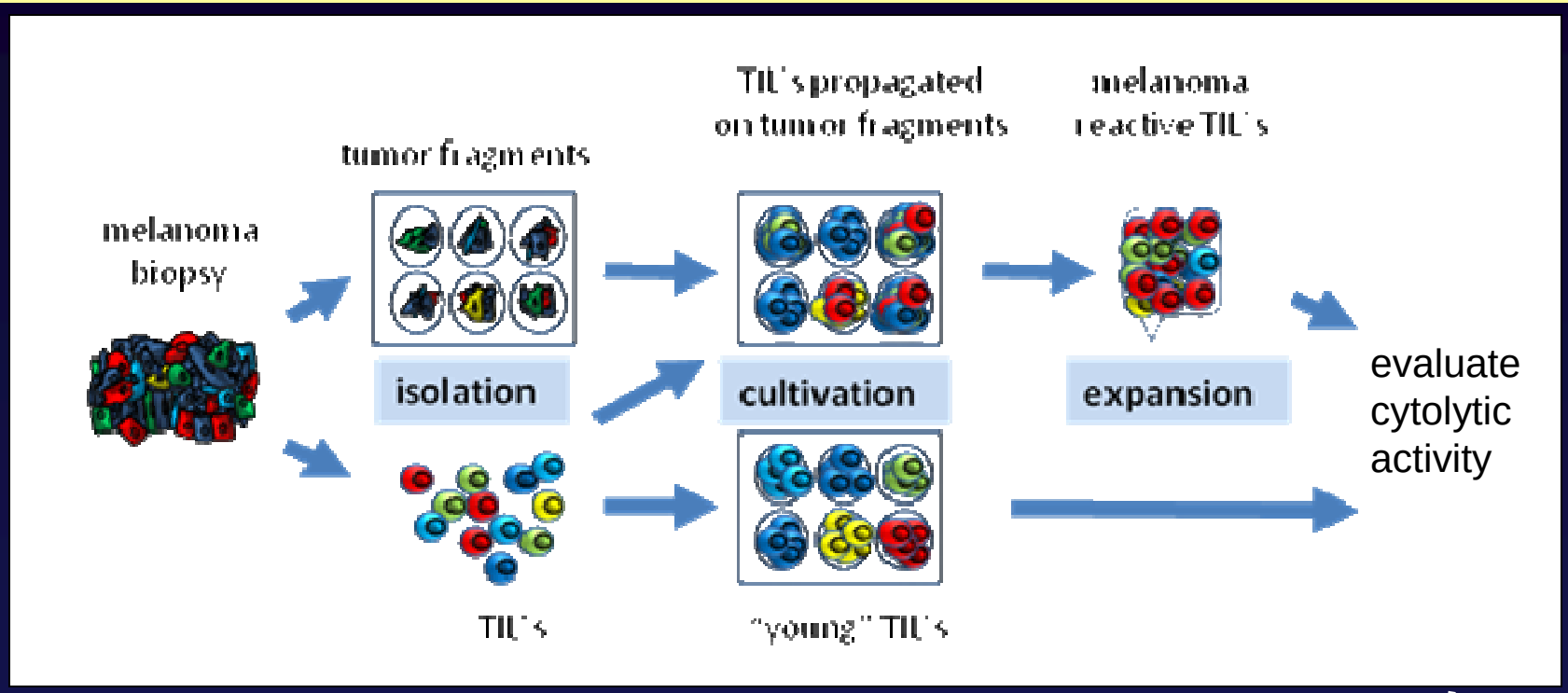
- Inbred mouse strains permitted the demonstration of antigen-specific anti-tumor immunity

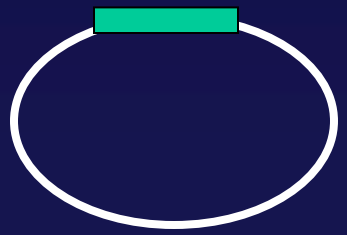


What the cytolytic T cell sees and does



Identification of CTL antigens





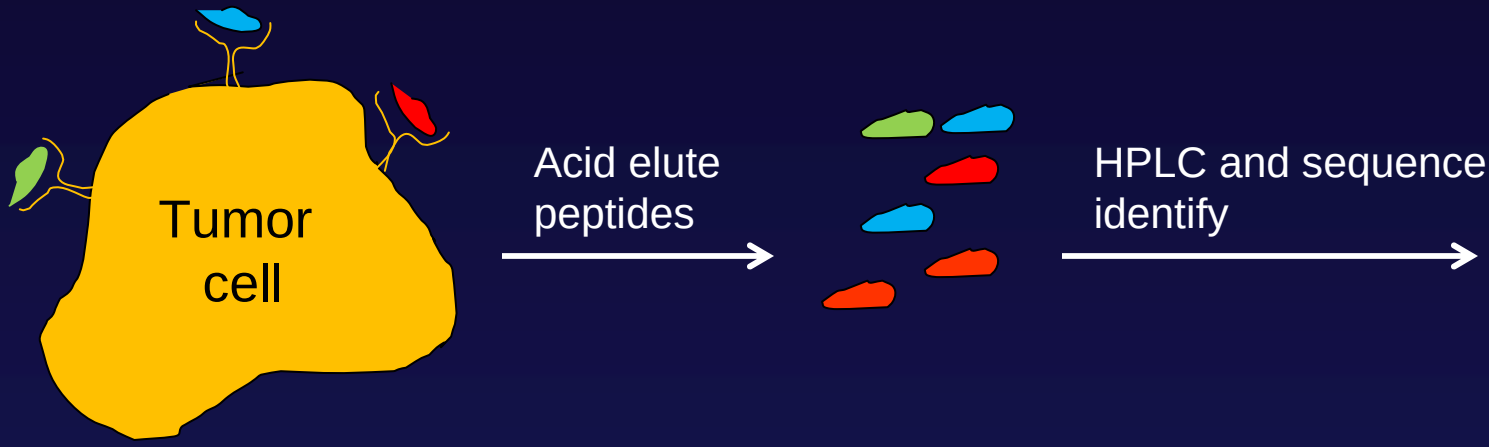
Prepare cDNA library from tumor

Transfect reporter Cell line

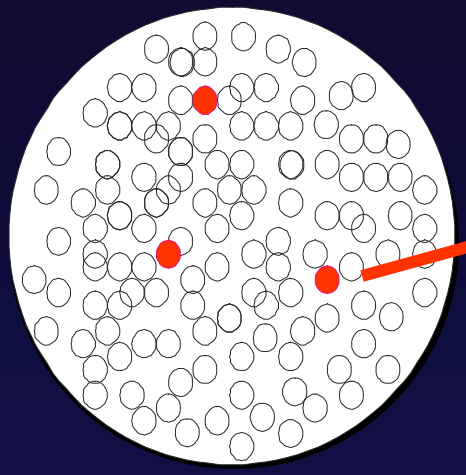
Lysis?

Adapted from: Makalowski '13 DOI:10.5772/53619

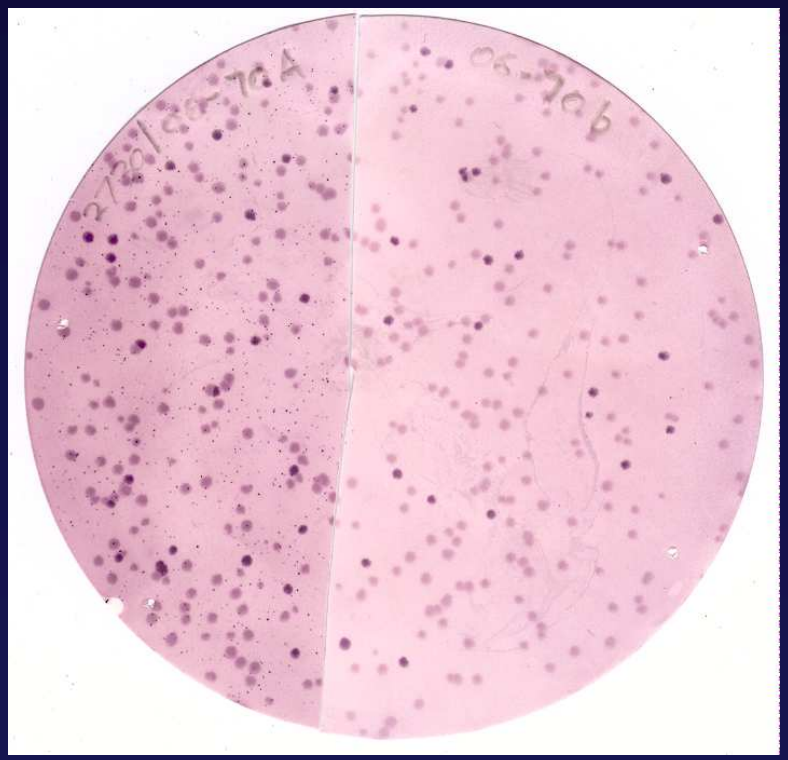
Identification of CTL antigens



Identification of other tumor antigens "SEREX"



Sequence and identify gene encoding phage plaque



Grow bacterial lawn on agar

Transfect – phage cDNA library

Transfer to membrane

Overlay with human sera

Detect IgG

Tumor Vaccine Antigens

- Tumor-specific
  - Expressed only by tumor
  - Mutated, frameshift, translocation event
  - Abnormal post-translational modifications
- Oncofetal, differentiation antigens
  - Germ cell – “cancer-testis” antigens
- Tumor-associated
  - More highly expressed in tumor
- Viral oncogenes

Types of Anti-Tumor Vaccines

- Antigen not defined
  - Whole cell vaccines, cytokine-expressing whole cell vaccines, tumor nucleic acid transfected DC vaccines
- Antigen-specific vaccines
  - Protein
  - Peptide (e.g. binding specific MHC)
  - Genetic (viral, bacterial, plasmid DNA vectors)

Outline

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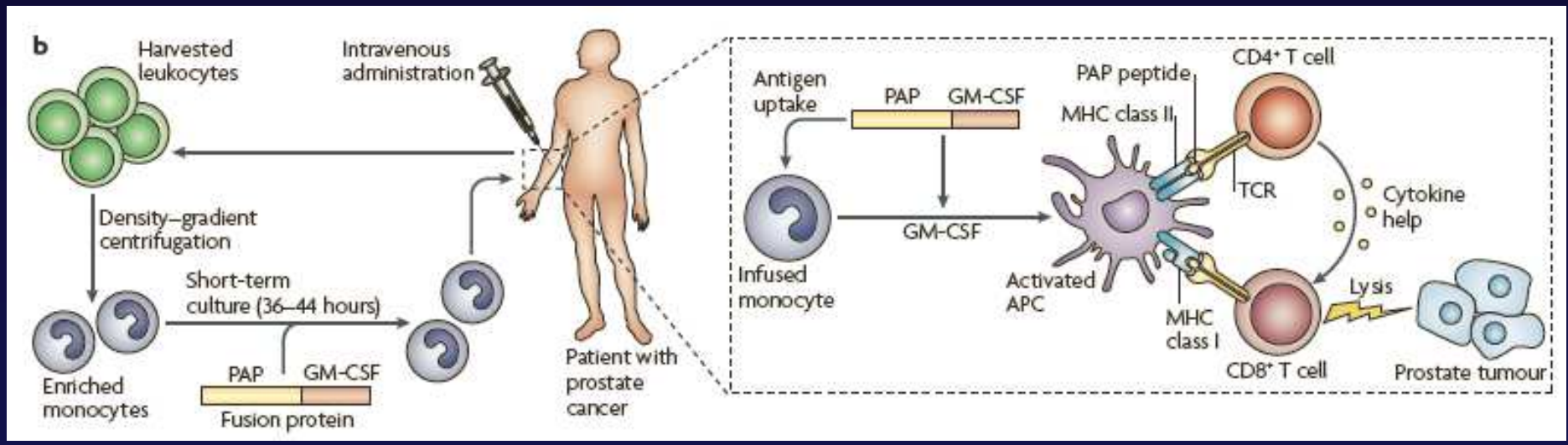
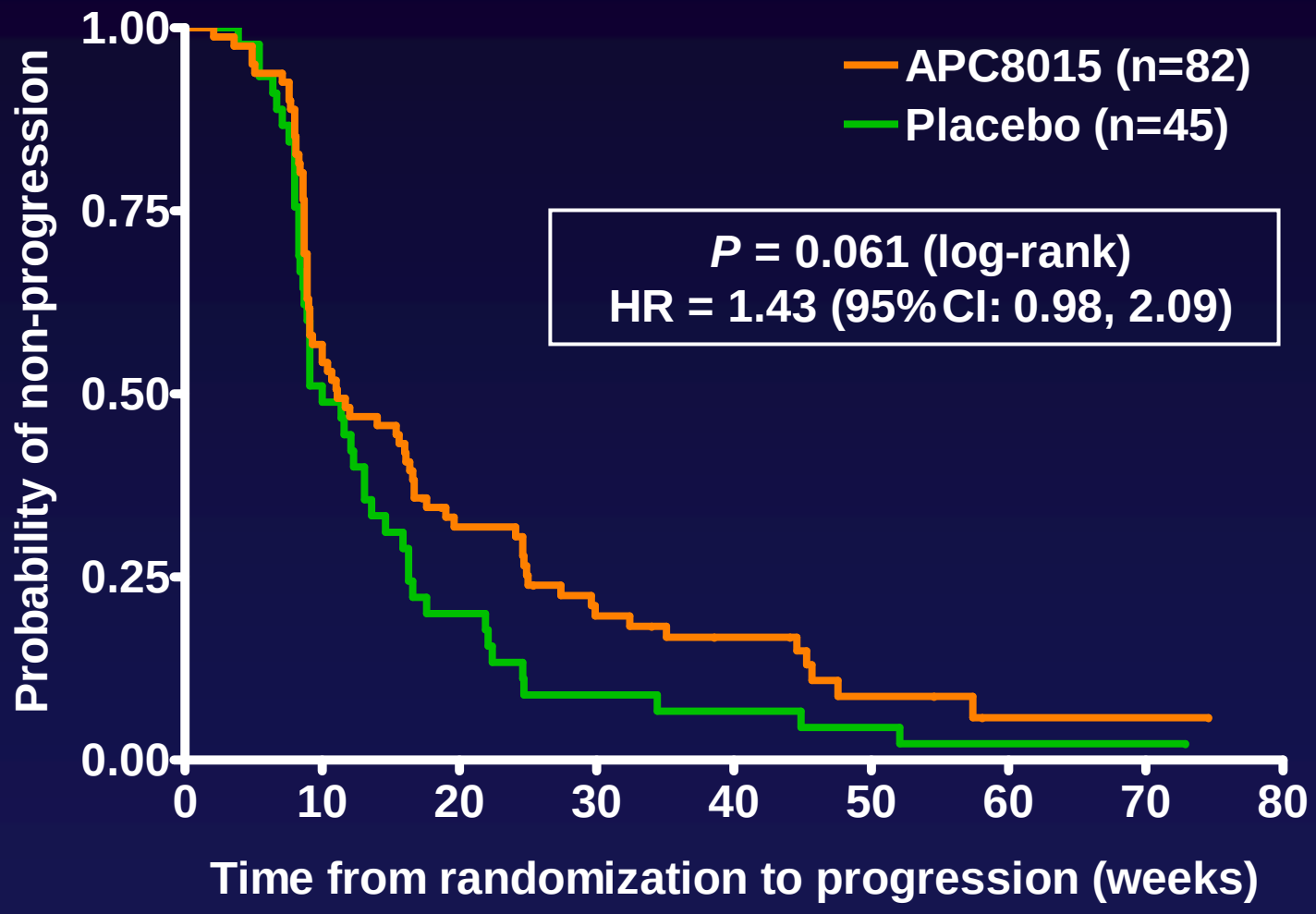
  - Rationale for anti-tumor vaccines
  - History of vaccines
  - Role of antigens / antigen discovery
- Anti-tumor vaccines in practice/advanced trials
- Paradigm changes for the treating oncologist

Antigen-Presenting Cell Vaccines – Sipuleucel-T



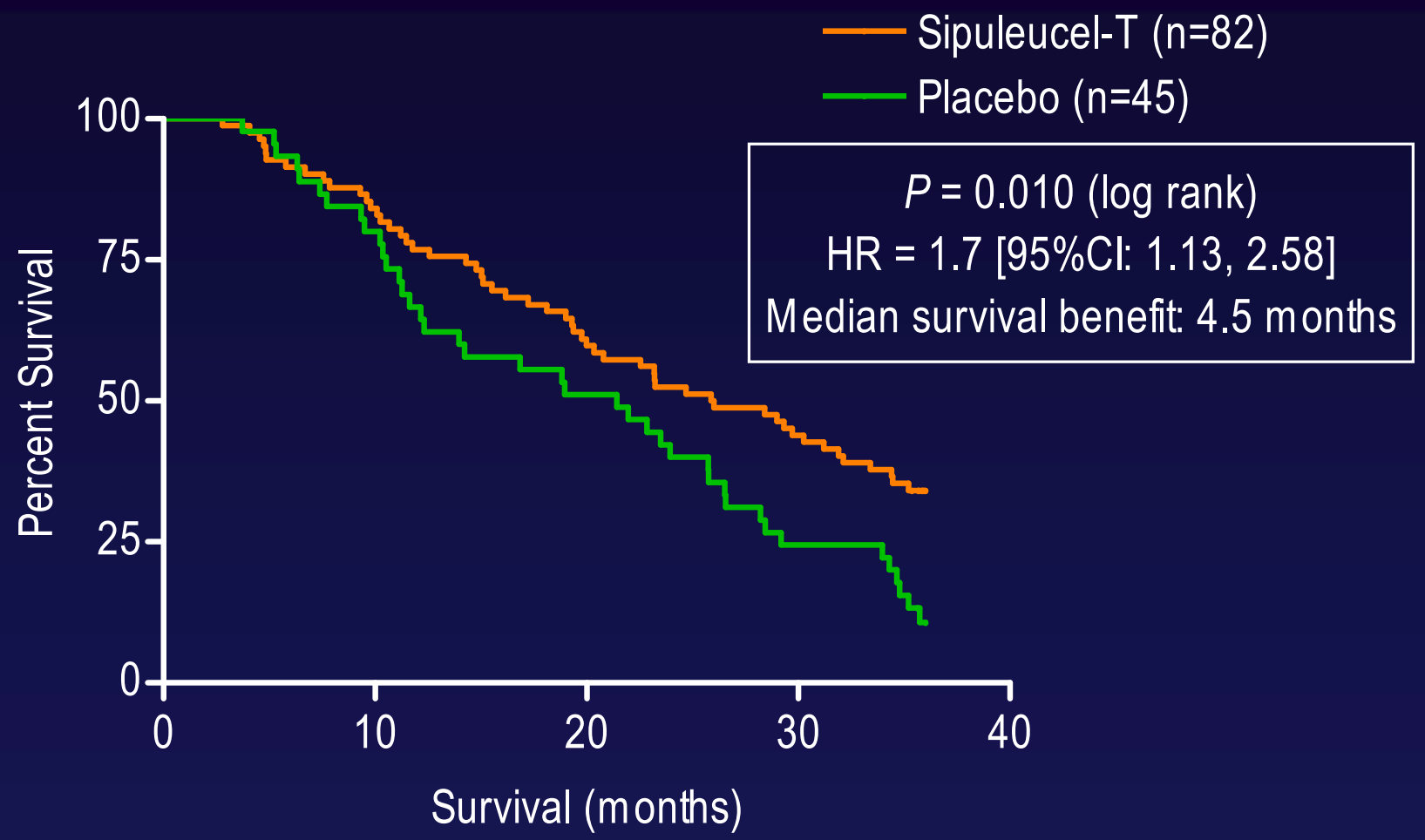
Drake (2010) Nat Rev Imm 10:580

Sipuleucel-T Phase III Trial - D9901



Small (2006) JCO 24:3089

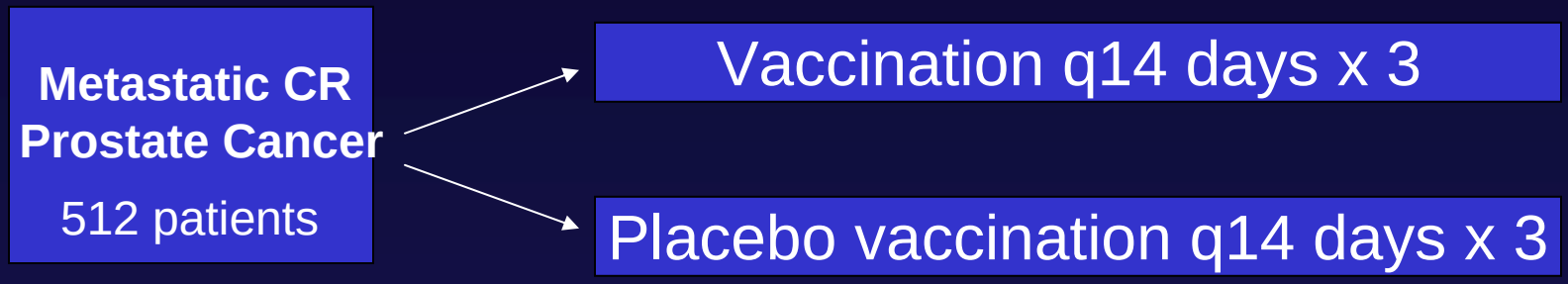
Sipuleucel-T Phase III Trial - D9901



Small (2006) JCO 24:3089

Sipuleucel-T Phase III “Impact” Trial - D9902B

9902B – Phase III “IMPACT” Trial

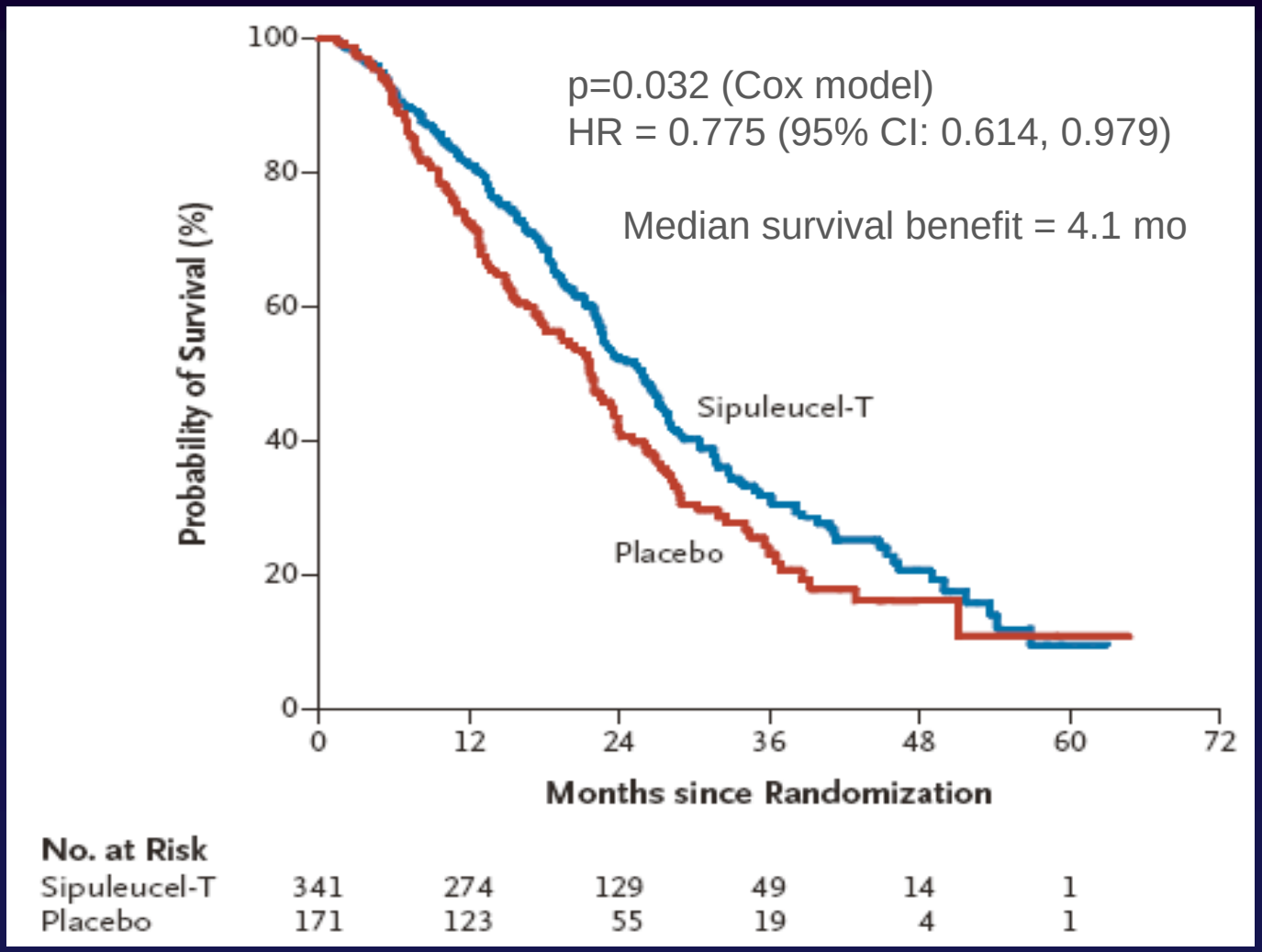


Trial Endpoints:

Primary: **Overall survival**

Secondary: **Symptomatic, radiographic progression**

Sipuleucel-T Phase III “Impact” Trial - D9902B



Kantoff (2010) NEJM 363:411

Adverse Events – IMPACT Trial

Grade 1 or 2 events 2x higher in sipuleucel-T than placebo group:

- Chills
- Fever
- Headache
- Flu-like illness
- Hypertension
- Sweating
- Groin pain

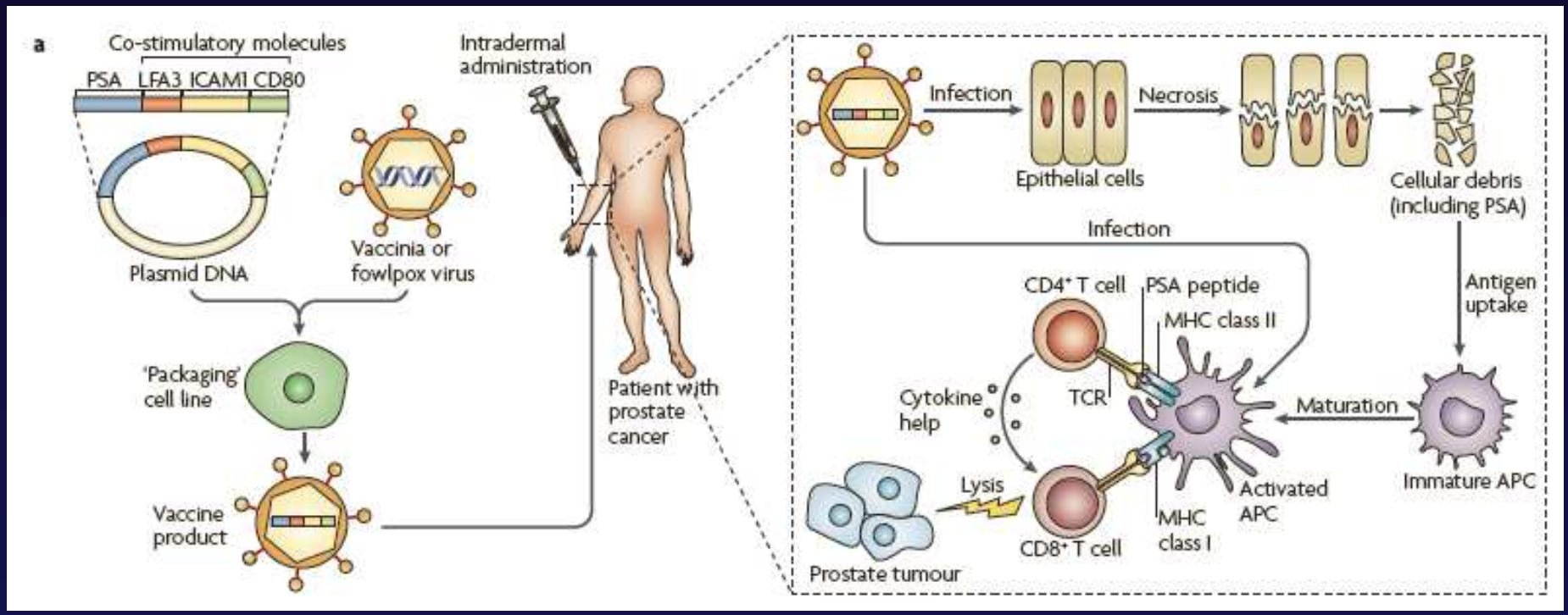
Grade 3 or 4 events: All < 5%

Kantoff (2010) NEJM 363:411

Sipuleucel-T was FDA-approved April 2010 for the treatment of asymptomatic, metastatic, castrate-resistant prostate cancer

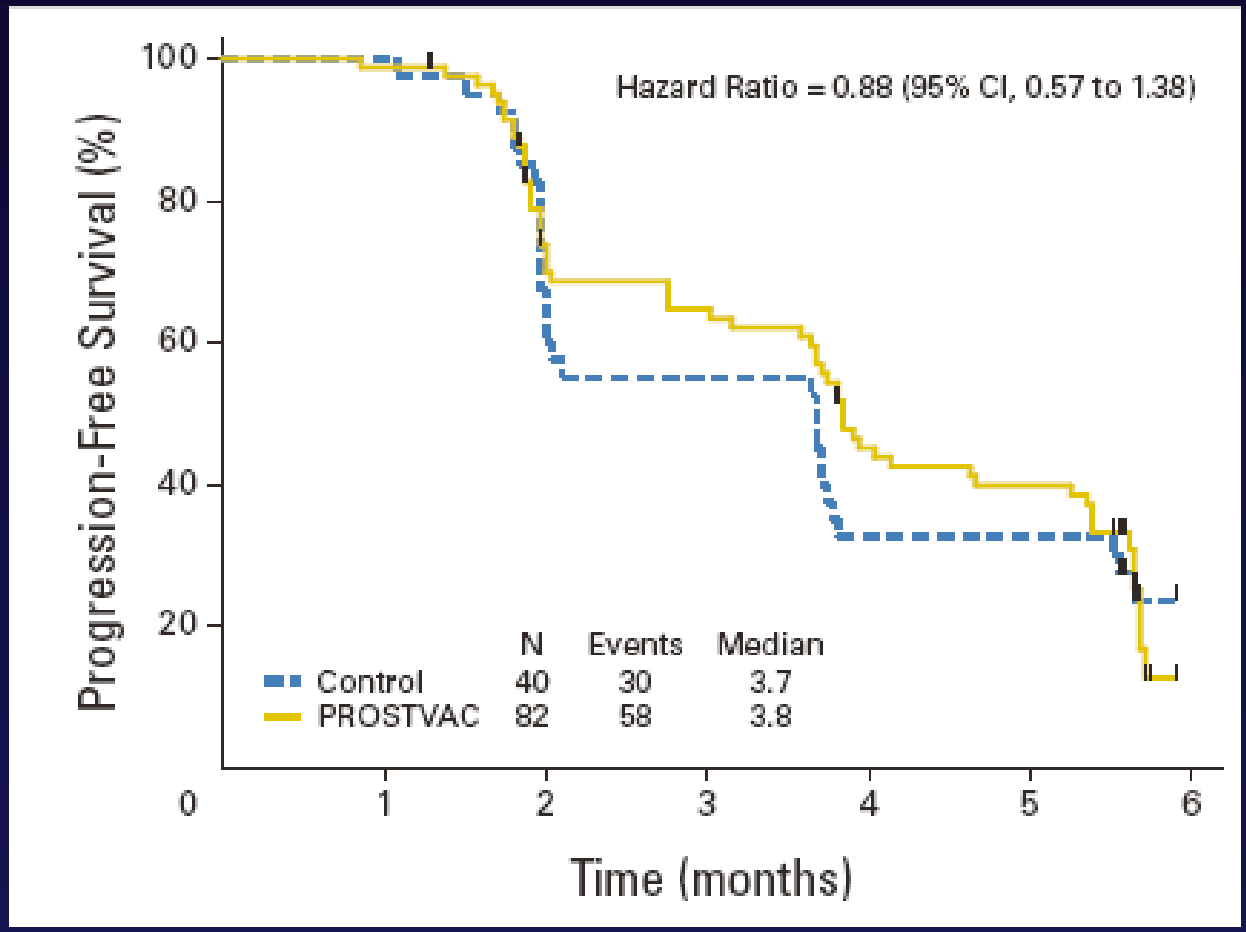
First approval of an anti-tumor vaccine (for humans) in the U.S.

Viral Vaccines – Prostvac-VF



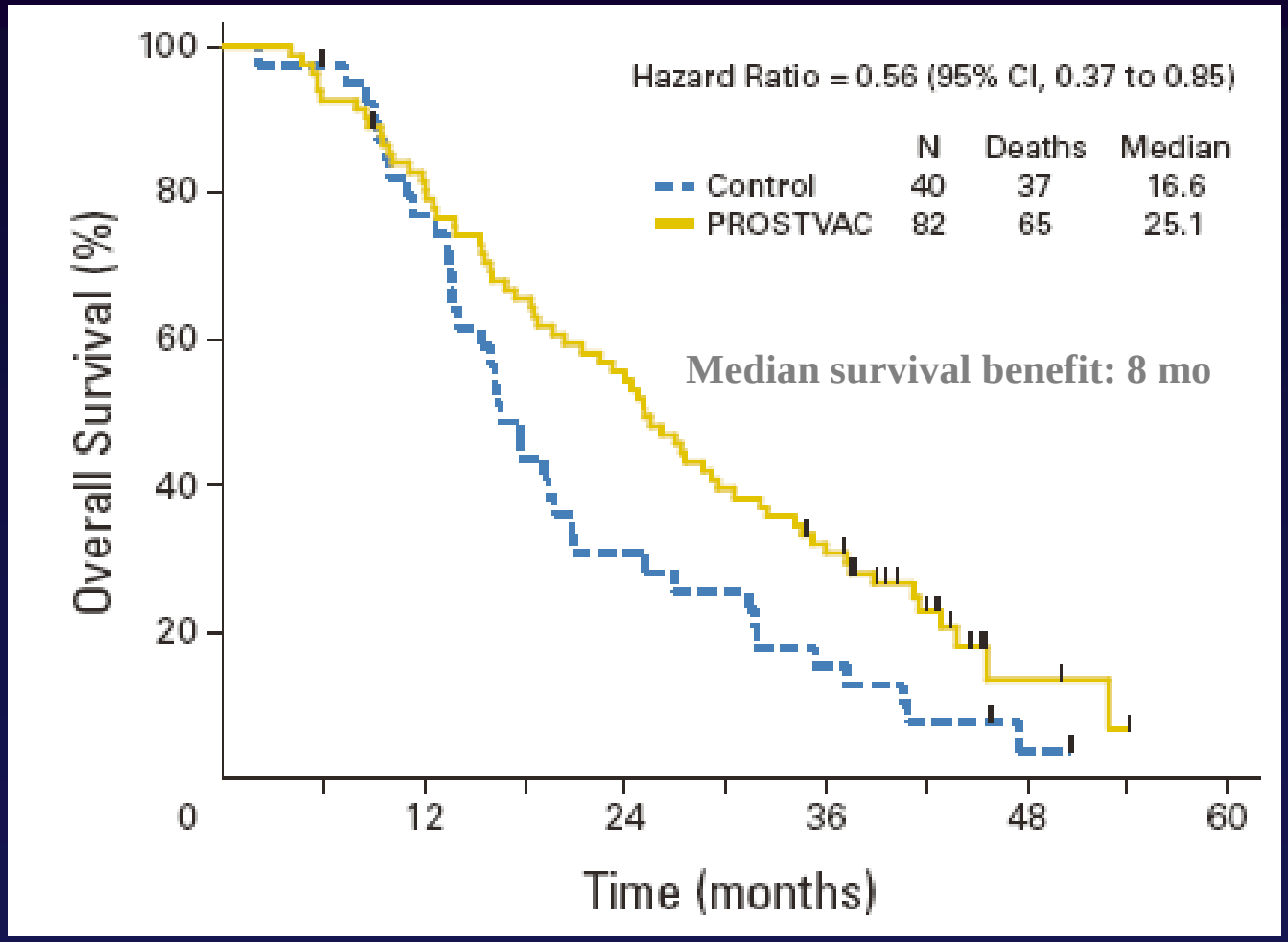
Drake (2010) Nat Rev Imm 10:580

Viral Vaccines – Prostvac-VF Randomized Phase II Trial



Kantoff (2010) J Clin Onc 28:1099

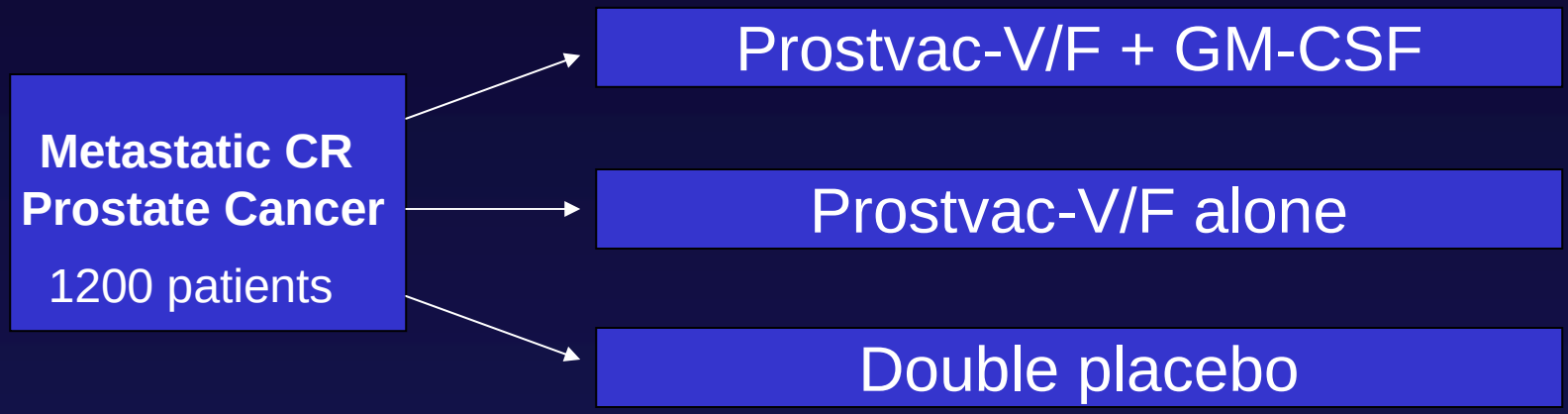
Viral Vaccines – Prostvac-VF Randomized Phase II Trial



Kantoff (2010) J Clin Onc 28:1099

Viral Vaccines – Prostvac-VF Randomized Phase III Trial

"PROSPECT" Trial – NCT01322490



Trial Endpoints:

Primary: **Overall survival**

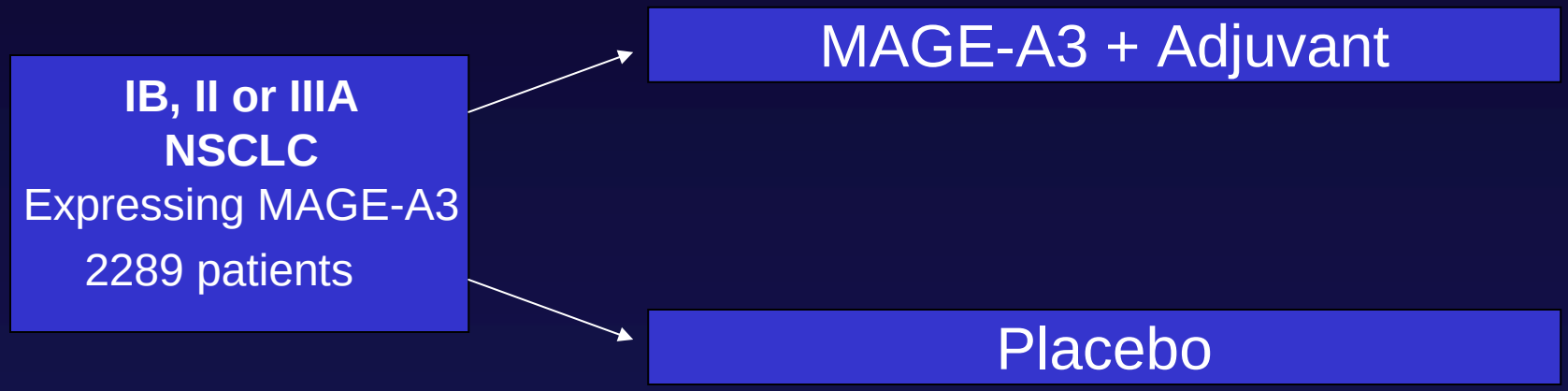
Secondary: **Symptomatic or radiographic progression at 6 months**

What about other diseases?

And simpler vaccines?

Protein Vaccine - NSCLC
MAGE-A3 – Cancer-Testis Antigen

"MAGRIT" Adjuvant Trial – NCT00480025



Trial Endpoints:

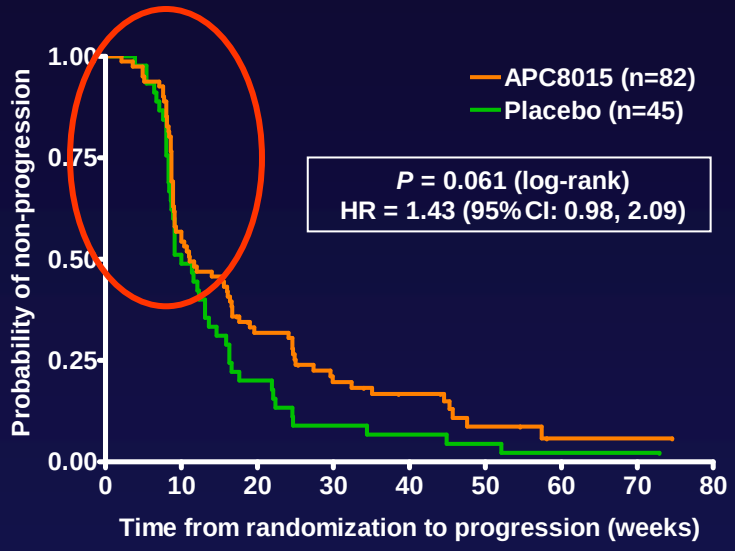
Primary: **Disease-free survival**

Secondary: **Overall survival, lung cancer-specific survival**

Outline

- Introduction
  - Rationale for anti-tumor vaccines
  - History of vaccines
  - Role of antigens / antigen discovery
- Anti-tumor vaccines in practice/advanced trials
- Paradigm changes for the treating oncologist

Why no association with PFS?



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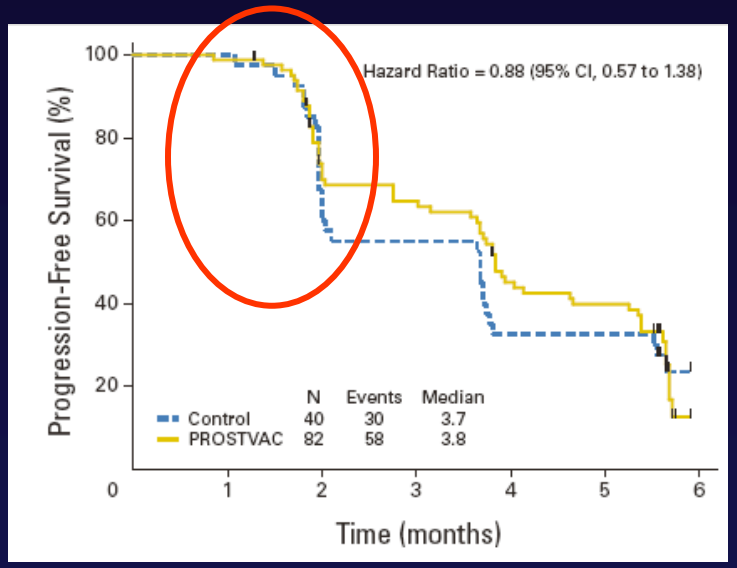
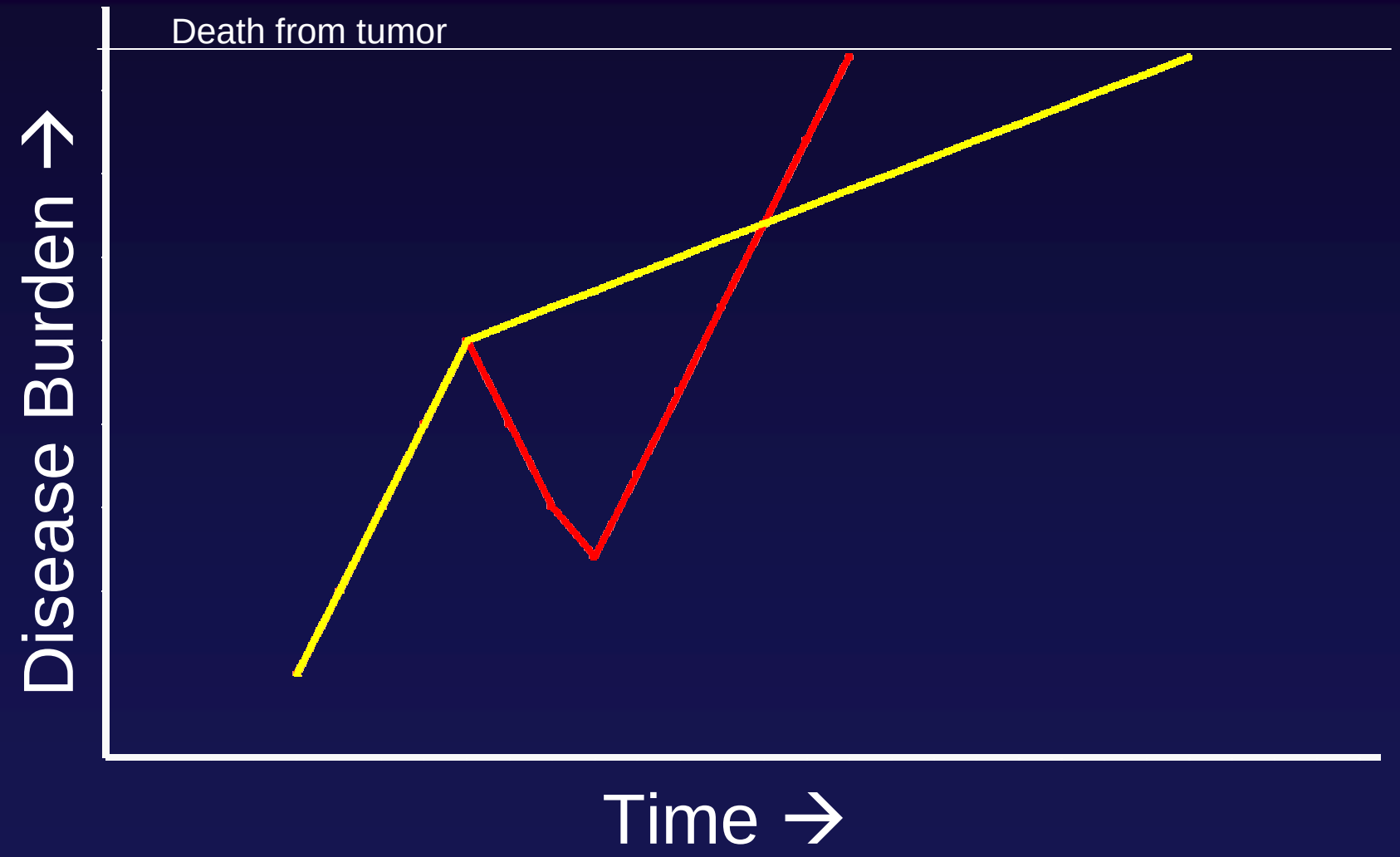


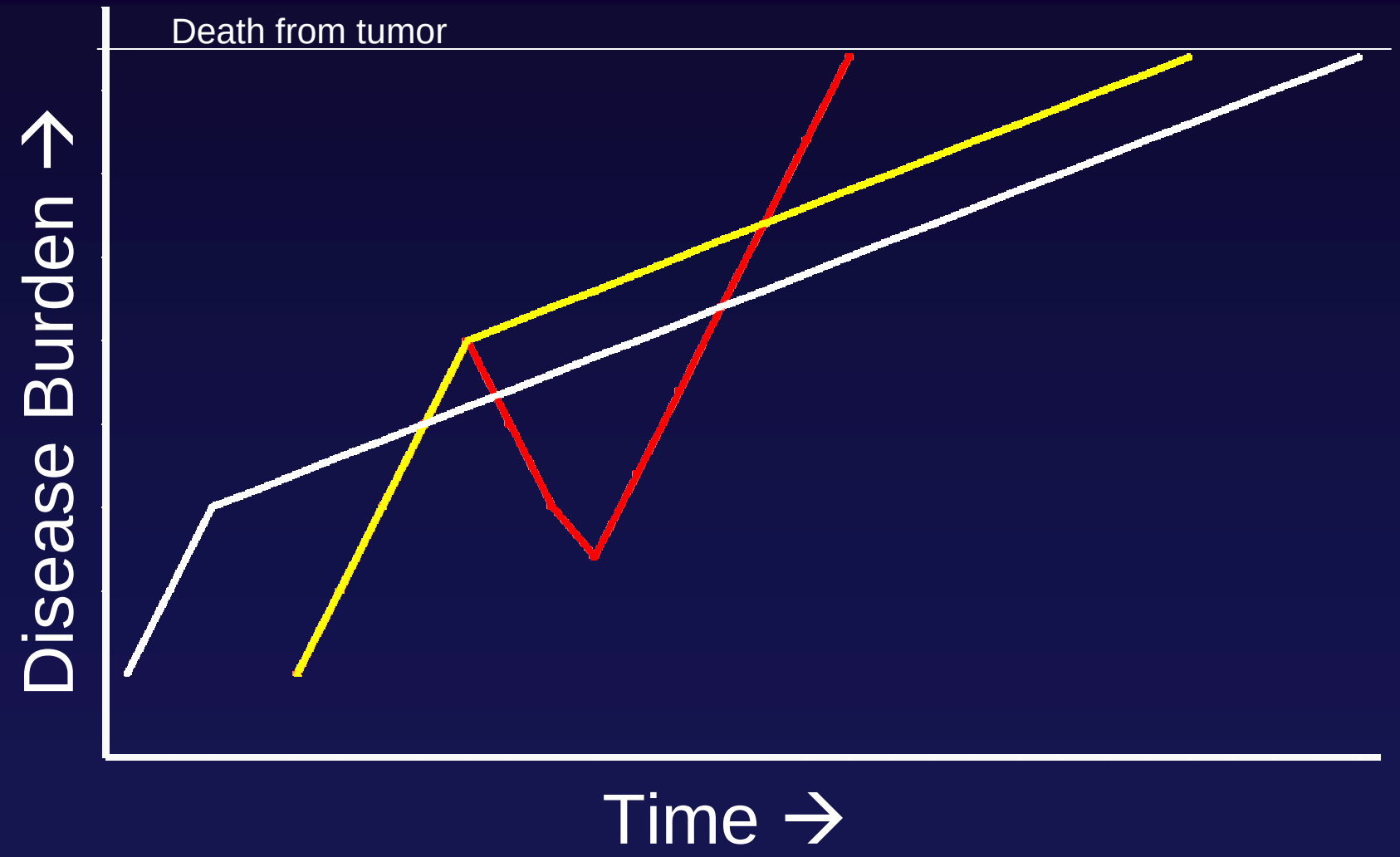
Kantoff (2010) J Clin Onc 28:1099

Model of Treatment Effect Arising from Multiple Immunotherapy Trials



Adapted from: Madan (2010) *Oncologist* 15:969

Model of Treatment Effect Arising from Multiple Immunotherapy Trials



Adapted from: Madan (2010) *Oncologist* 15:969

So What Have We Learned? Guidance for the Treating Oncologist

- Minimal adverse events (compared with traditional anti-cancer therapies)
- No difference in time to radiographic progression, few PSA “responses,” but survival prolonged
- In the case of sipuleucel-T, subgroup analysis suggests magnitude of survival benefit greater in patients with lower disease burden (lower PSA, lower LDH, no prior chemotherapy, greater time from diagnosis)
- “Optimal” treatment time, consequently, not as salvage but rather in early asymptomatic patients who don’t require emergent management

What Else Have We Learned? Challenges for the Treating Oncologist

- Which patients are likely to benefit?

  The future: Which vaccine for which patient?

- No good markers (yet) to know if an individual patient has “benefited”

  (Kind of like adjuvant therapy for metastatic disease)

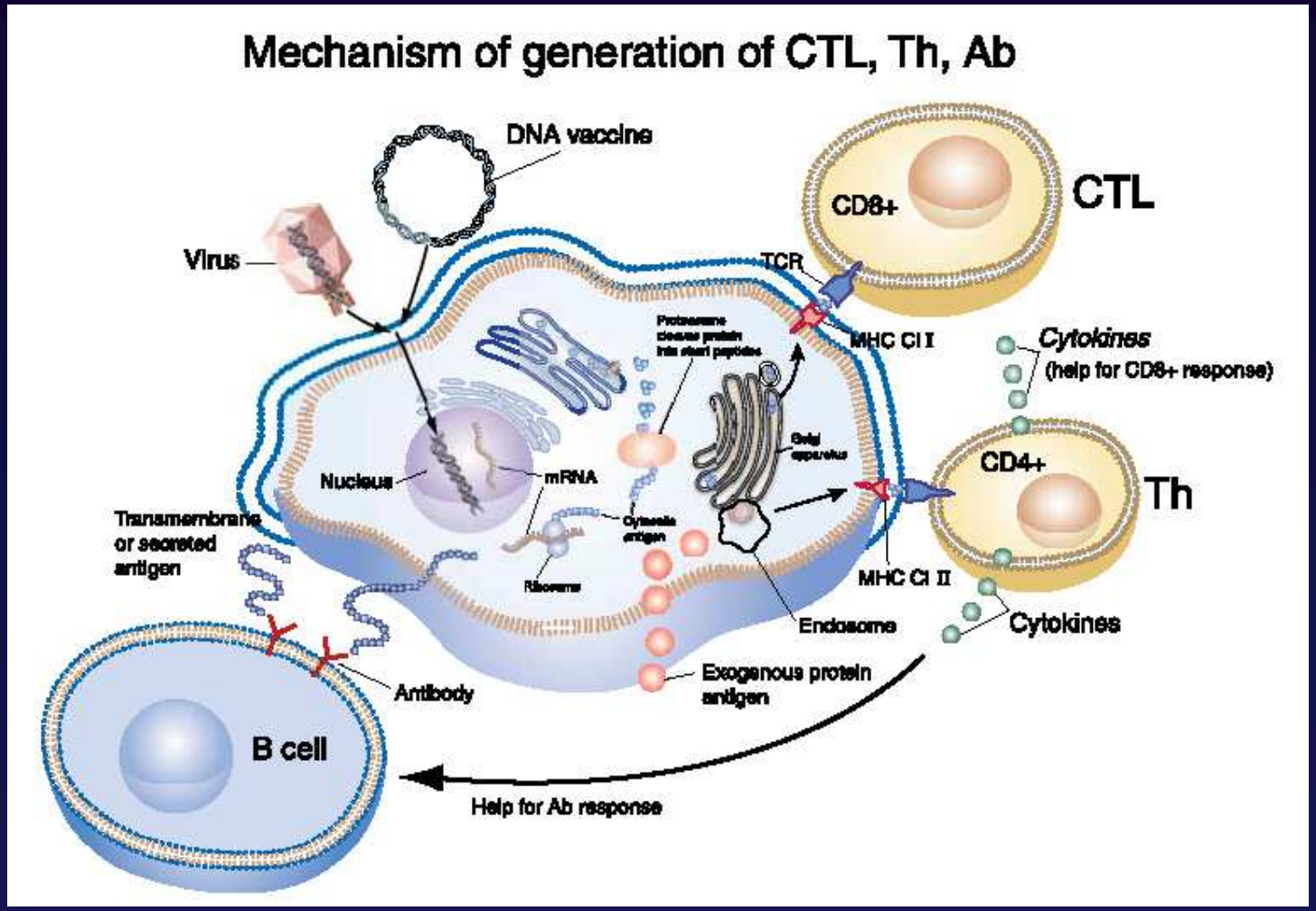
- Difficult to know when to proceed on to next therapy

  How should these be sequenced or used with other therapies (like chemotherapies or corticosteroids)?

So What's in the Future for Cancer Vaccines?

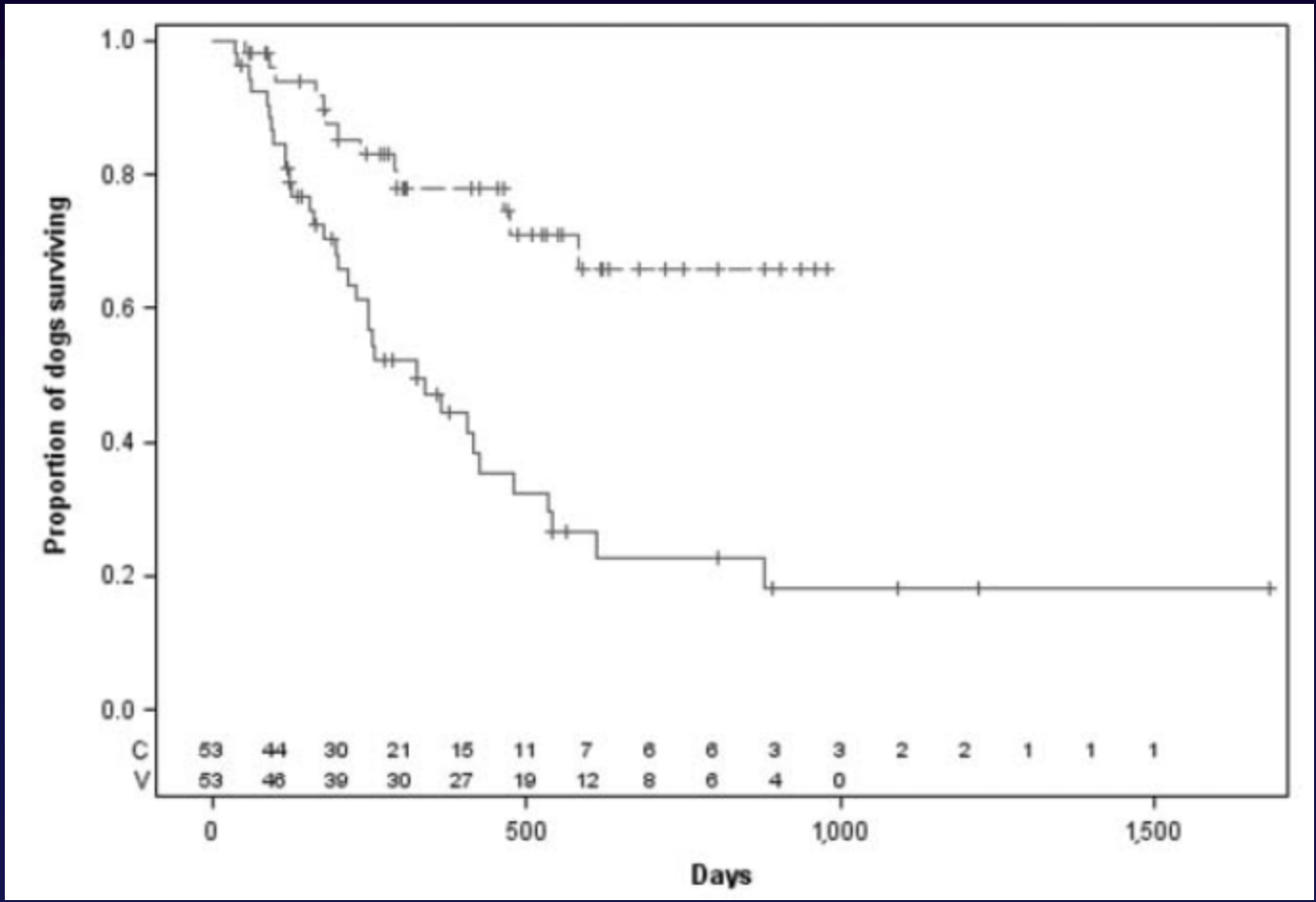
- "Off-the-shelf" vaccines are feasible (and cheaper)
- Earlier stages of disease
- New (better) targets
- Biomarkers of response and likelihood of response ("personalized" medicine)
- Combination with other treatments
  - Traditional therapies
  - Other immunological therapies

Vaccines Don't Need to Be Too Complicated (or Expensive)



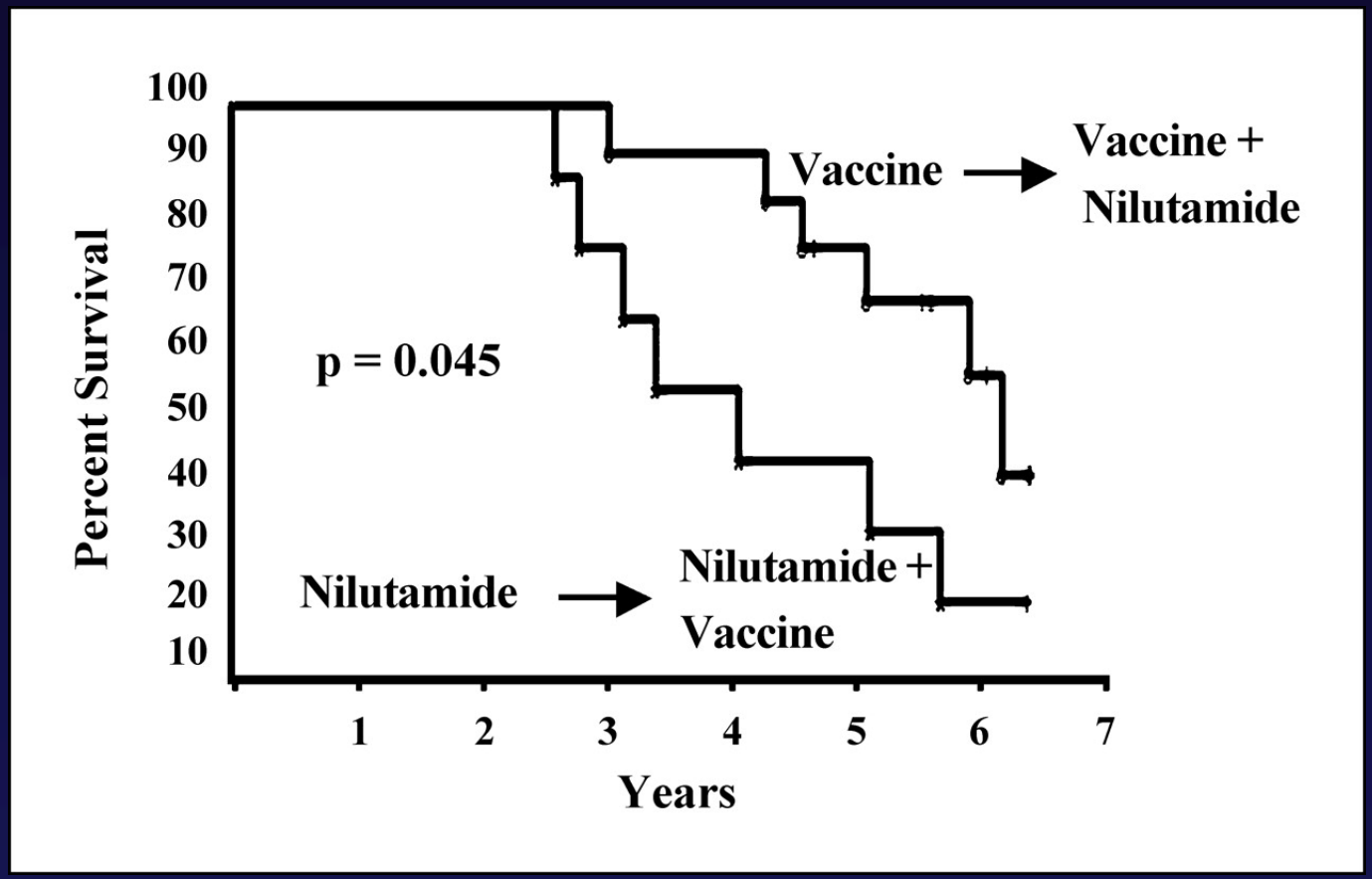
Liu, JIM (2003) 253:402

Antigen-Specific DNA Vaccine - Oncept First Anti-Tumor Vaccine Approved in US



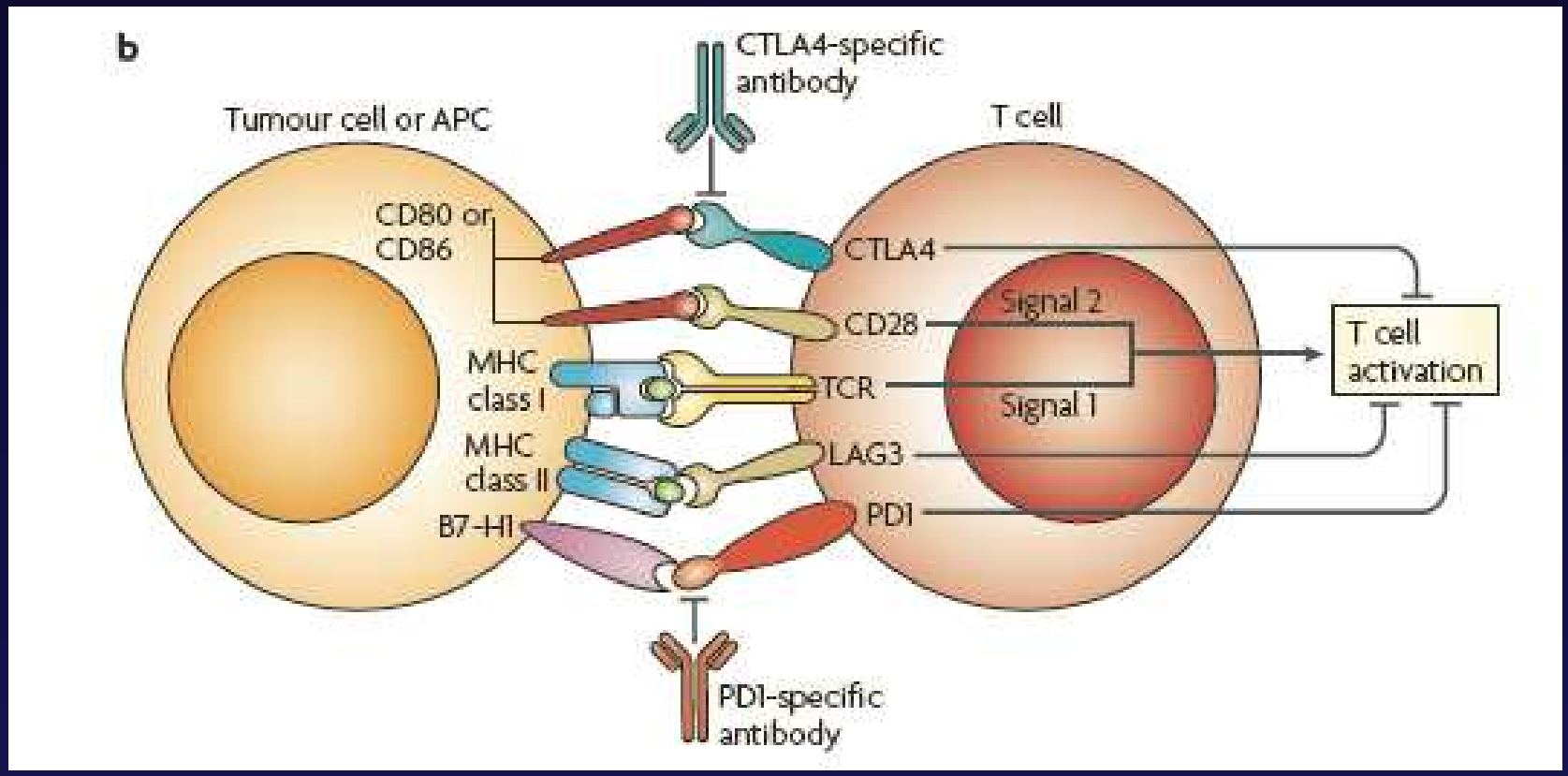
Grosenbaugh, Am J Vet Res (2011) 72:1631

Vaccines May Modulate Effect from Subsequent Therapies



Maddan (2008) Clin Canc Res 14:4526

“Immunomodulation”
Immune Checkpoint Inhibitors



Drake (2010) Nat Rev Imm 10:580

The Future of Vaccines with Other Immunomodulating Agents

Vaccines

Immunomodulating Agents

T-cell checkpoint inhibitors
Tumor µenvironment modulators
Regulatory and immunosuppressive mechanisms

OX-40 agonist
Cytokines