Development of Recombinant Vaccines for the Therapy of Carcinomas

Monotherapy and Combination Therapy

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Disclosure

The Laboratory of Tumor Immunology and Biology, Center for Cancer Research, NCI, NIH, has Collaborative Research and Development Agreements (CRADAs) with:

- Bavarian Nordic Immunotherapeutics
- GlobeImmune

concerning the design and development of recombinant cancer vaccines

J. Schlom is an inventor on patents via NCI TTC and NIH OTT.

Drs. Schlom and Madan will discuss experimental therapeutic cancer vaccines in different states of clinical development: PROSTVAC and PANVAC.

STRATEGIC PLAN

Cancer Vaccine Development:

- **Focus on human carcinoma**
- **Focus on development of vaccines that can be widely evaluated**

Ultimate Use:

- **Early in disease process/low tumor burden**
- **Survival as the endpoint**
- **Minimal toxicity**

Immuno-Oncology Platform:

- **Combination immune therapies**
  - **immune stimulation strategies**
  - **reduction of immune inhibitory entities**
- **Combination Therapies: Vaccine plus:**
  - **conventional therapies**
  - **conventional therapies in novel strategies**
  - **other experimental therapies**

Translational Research Programmatic Effort

PRECLINICAL STUDIES:

Laboratory of Tumor Immunology and Biology (LTIB)

James Hodge
Claudia Palena
Al Tsang
Jack Greiner
Jianping Huang

Ingrid Fernando
Benedetto Farsaci
Sofia Gameiro

Laboratory of Molecular Biology

Ira Pastan

Vaccine Branch

Jay Berzofsky

CLINICAL STUDIES:

LTIB/Medical Oncology Branch

James Gulley Ravi Madan
Mary Pazdur

Medical Oncology Branch

William Dahut Tito Fojo
William Figg
Marijo Bilusic Chris Heery

Radiation Oncology

Kevin Camphausen Deborah Citrin

Urologic Oncology

Marston Linehan Peter Pinto
Gennady Bratslavsky

Biostatistics and Data Management Section

Seth Steinberg

NIH Nuclear Medicine

C.H. Paik

NIH Interventional Radiology

Brad Wood

Translational Research Programmatic Effort

CLINICAL STUDIES — EXTRAMURAL:

Georgetown – John Marshall
Dana Farber Cancer Center – Donald Kufe, Paul Eder, Philip Kantoff
Columbia – Howard Kaufman
Cancer Institute of New Jersey – Edward Lattime, Robert DiPaola
Ohio State – William Carson
Duke – H. Kim Lyerly, Michael A. Morse

Eastern Cooperative Oncology Group (ECOG) – Robert DiPaola

CANCER THERAPY EVALUATION PROGRAM (CTEP):

Howard Streicher Jan Casadei

PRIVATE SECTOR:

- **GlobeImmune – David Apelian**
- **BN ImmunoTherapeutics – Wayne Godfrey, Reiner Laus**

NCI Technology Transfer Center: Kevin Brand, Bob Wagner, Karen Maurey

NIH Office of Technology Transfer: Sabarni Chatterjee, Mojdeh Bahar

Recombinant Vaccine Vectors

- Pox vectors

  Vaccinia (rV-) elicits a strong immune response

  – host induced immunity limits its continuous use

  – MVA (replication defective)

  Avipox (fowlpox rF-, ALVAC)

  – derived from avian species

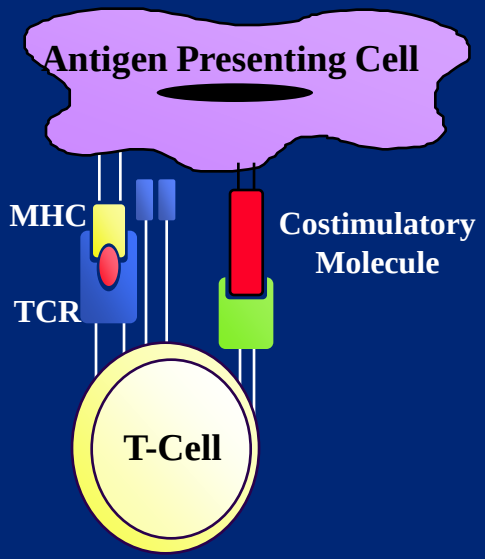
  – safe; does not replicate

  – can be used repeatedly with little if any host neutralizing immunity

- Can insert multiple transgenes
- Do not integrate into host DNA
- Efficiently infect antigen presenting cells including dendritic cells

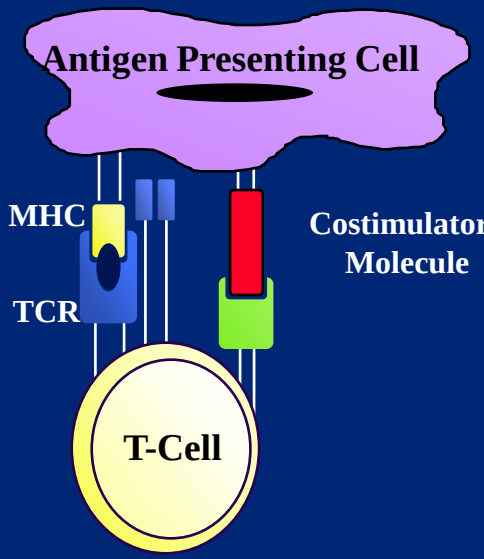
T-Cell Dependence on Costimulation

Signal 1 + Signal 2



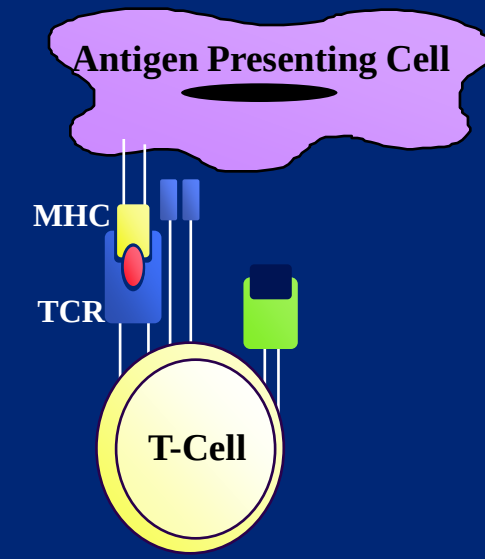
Activation of Antigen-Specific T-cells

No Signal 1



Clonal Anergy
Apoptosis
Ignorance

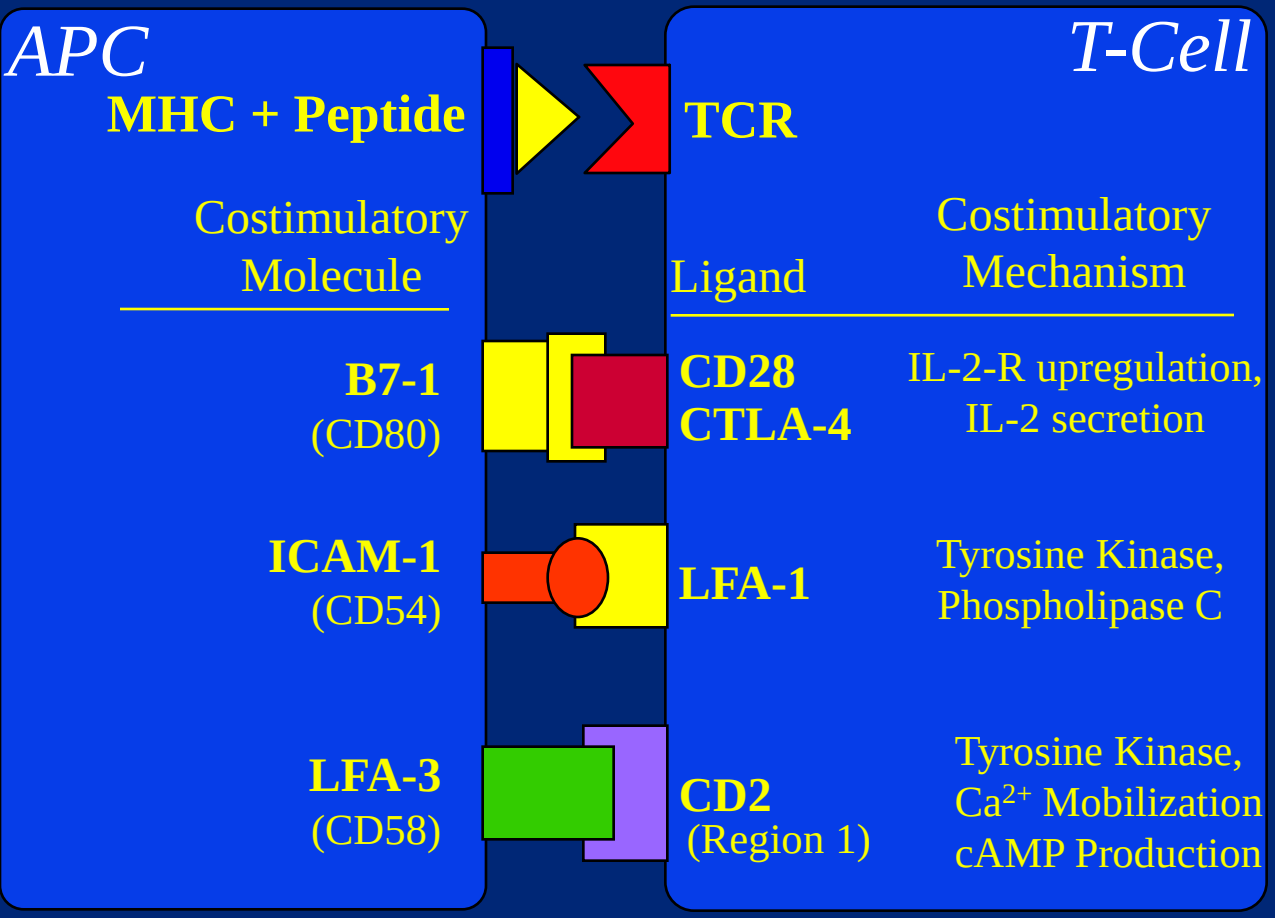
No Signal 2

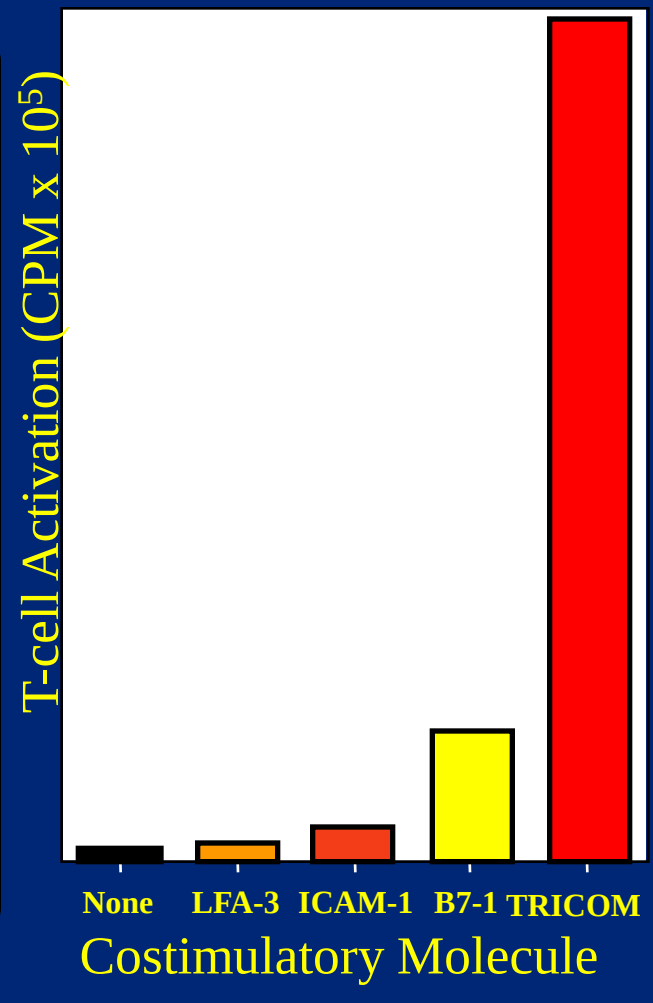


Clonal Anergy
Apoptosis
Ignorance

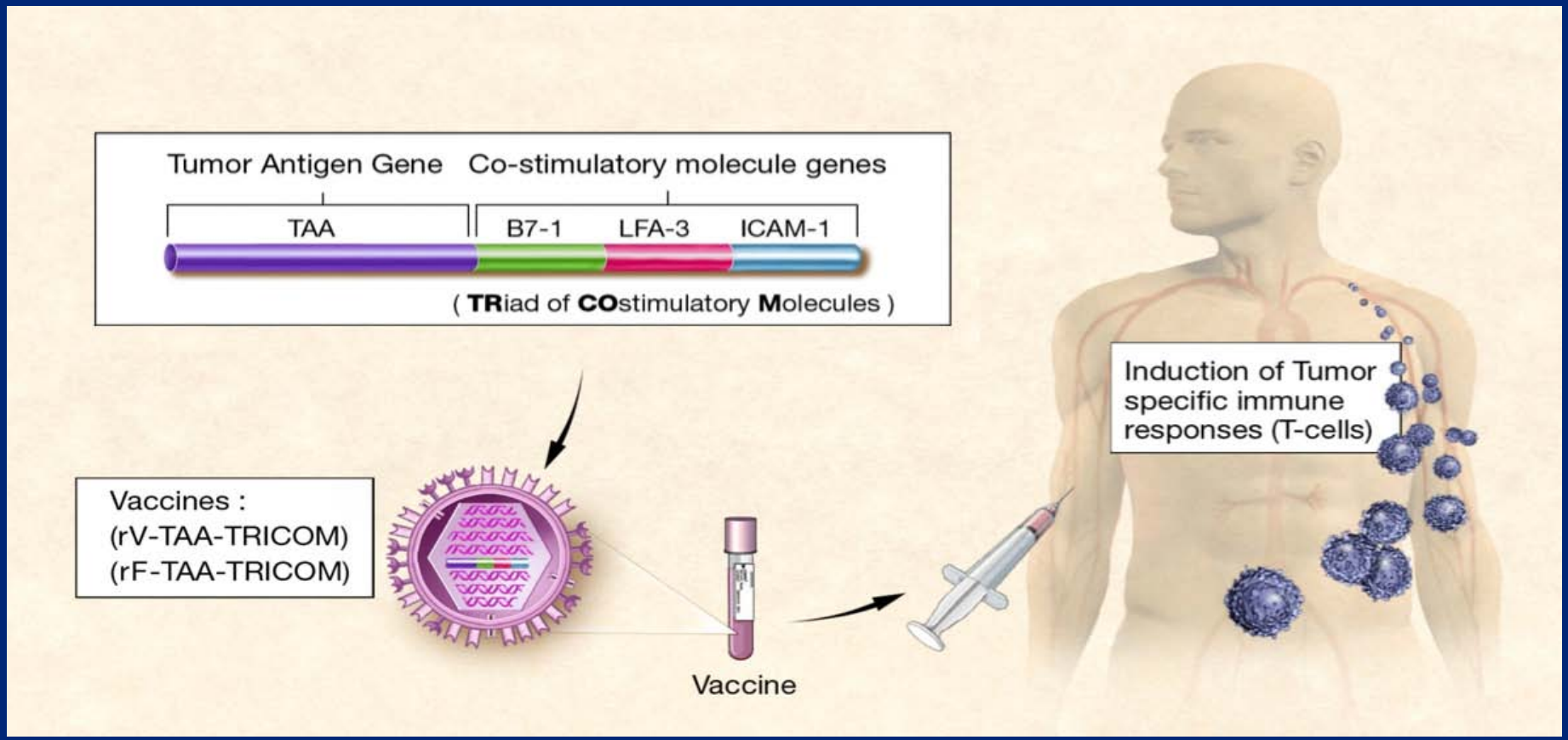
Costimulatory Molecule Candidates

- Major Costimulatory Effect must be on the T-cell
- No Overlap of T-cell Ligands
- No Redundancy of Costimulatory Mechanisms





TRICOM Vaccines



TRICOM
TRIad of COstimulatory Molecules

Costimulatory Molecule	Ligand on T cell
B7-1 (CD80)	CD28/CTLA-4
ICAM-1 (CD54)	LFA-1
LFA-3 (CD58)	CD2

TRICOM = B7-1/ICAM-1/LFA-3

CEA/TRICOM = CEA/B7-1/ICAM-1/LFA-3

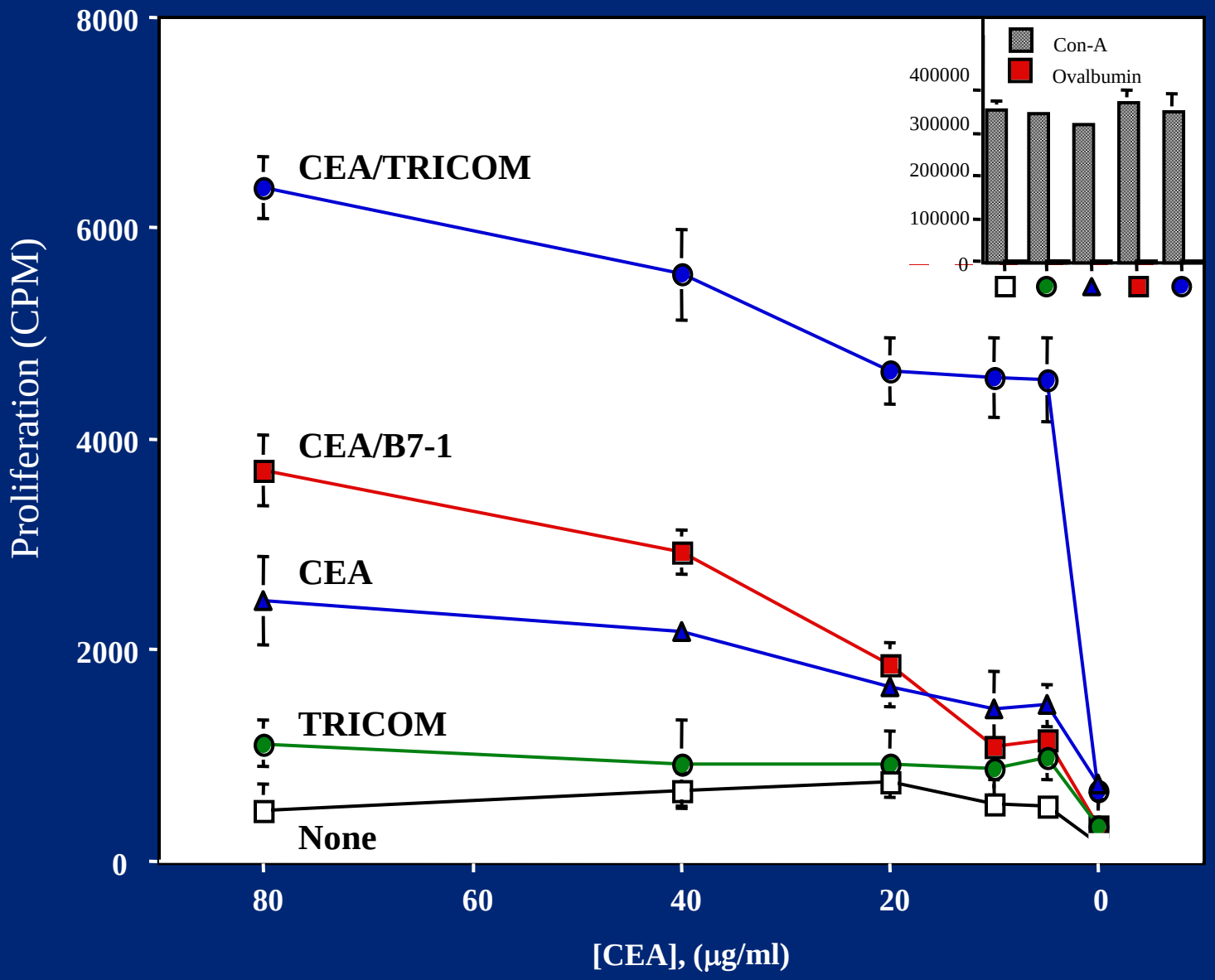
CEA/MUC-1/TRICOM = CEA/MUC-1/B7-1/ICAM-1/LFA-3 (PANVAC)

PSA/TRICOM = PSA/B7-1/ICAM-1/LFA-3 (PROSTVAC)

All vaccines contain: rV- as a prime vaccine
avipox (fowlpox, rF-) as multiple booster vaccines

CEA, MUC-1, and PSA transgenes all contain enhancer agonist epitopes

CEA-specific Lymphoproliferation of T Cells from CEA-Tg Mice Vaccinated with TRICOM Vectors



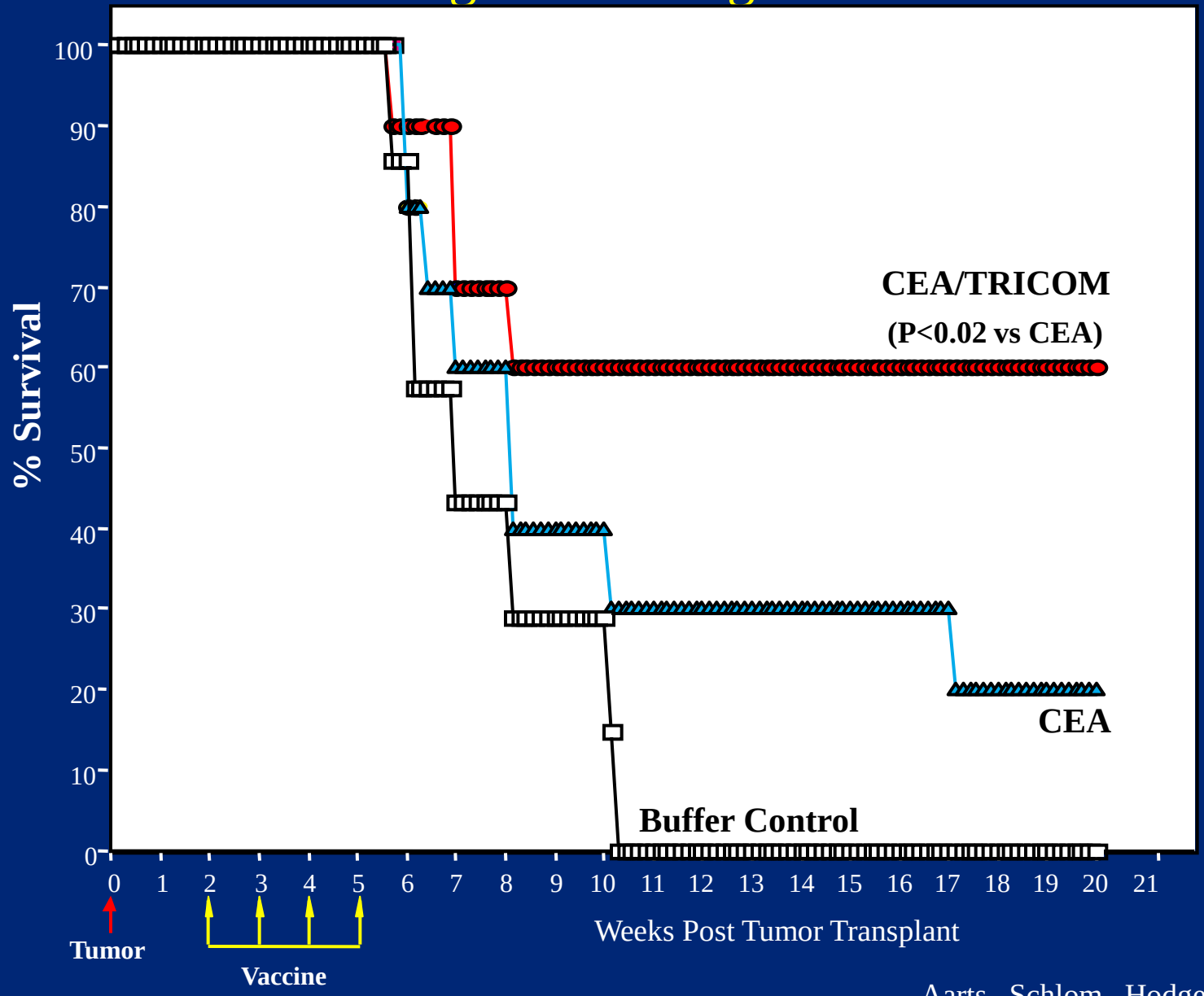
VAAA Regimen

CEA
CEA/B7-1
CEA/TRICOM
TRICOM

All groups with GM-CSF and low dose IL-2

Aarts , Schlom , Hodge. Cancer Res. 62:5770-7.

Therapy of 14-Day Established CEA^{+} Experimental Metastases in CEA-Tg Mice Using CEA/TRICOM Vectors



VAAA Regimen

CEA
CEA/TRICOM

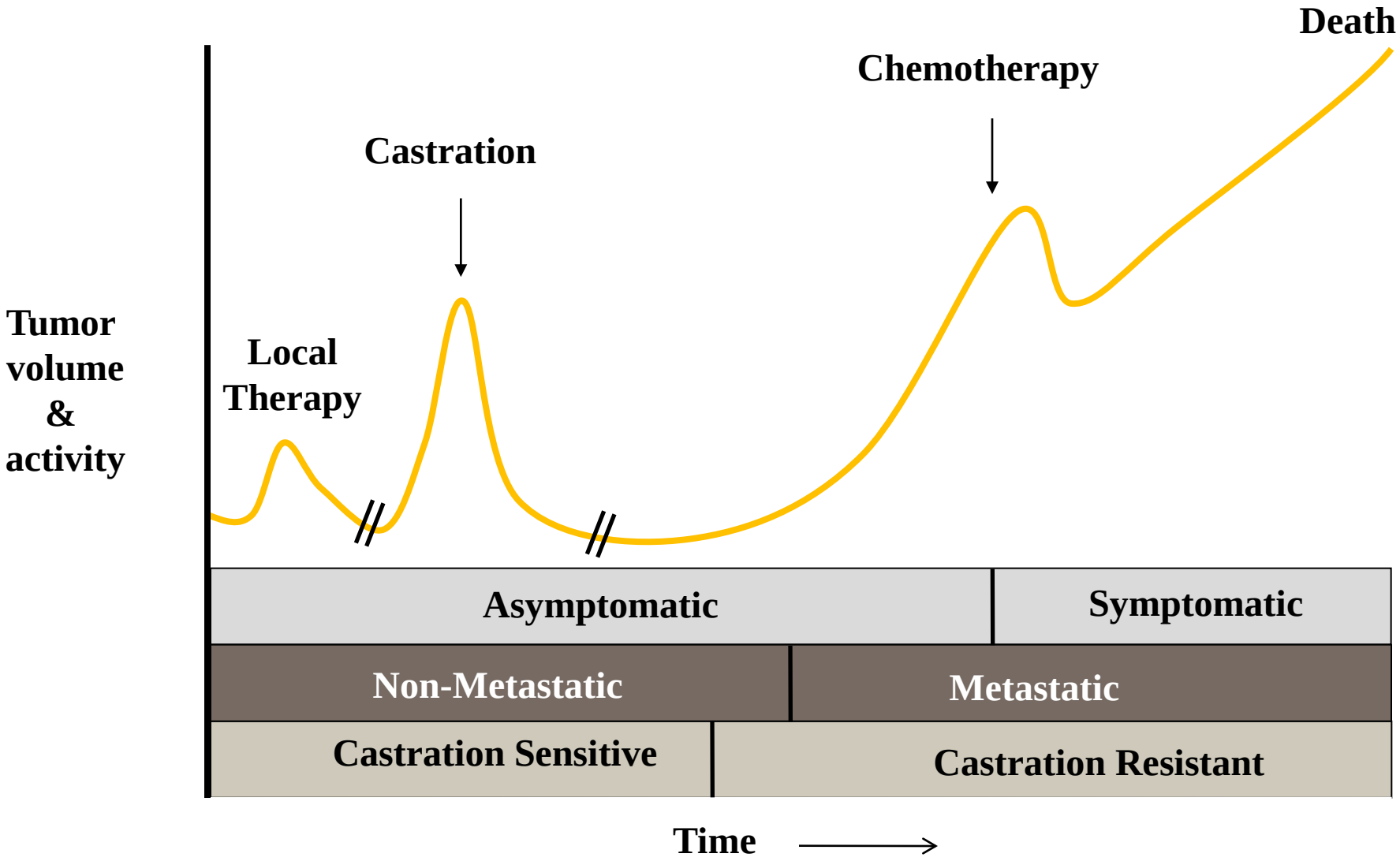
All groups with GM-CSF and low dose IL-2

Aarts , Schlom , Hodge. Cancer Res. 62:5770-7.

Prostate Cancer and Vaccine Therapy

- **Long interval from primary diagnosis to metastatic disease**
- **Serum PSA (doubling time/velocity) as a surrogate for therapeutic benefit or disease recurrence**
- **Nomogram (Halabi) at metastatic disease**
  - **– can predict more indolent vs more aggressive disease**

Natural History of Disease Progression in Prostate Cancer

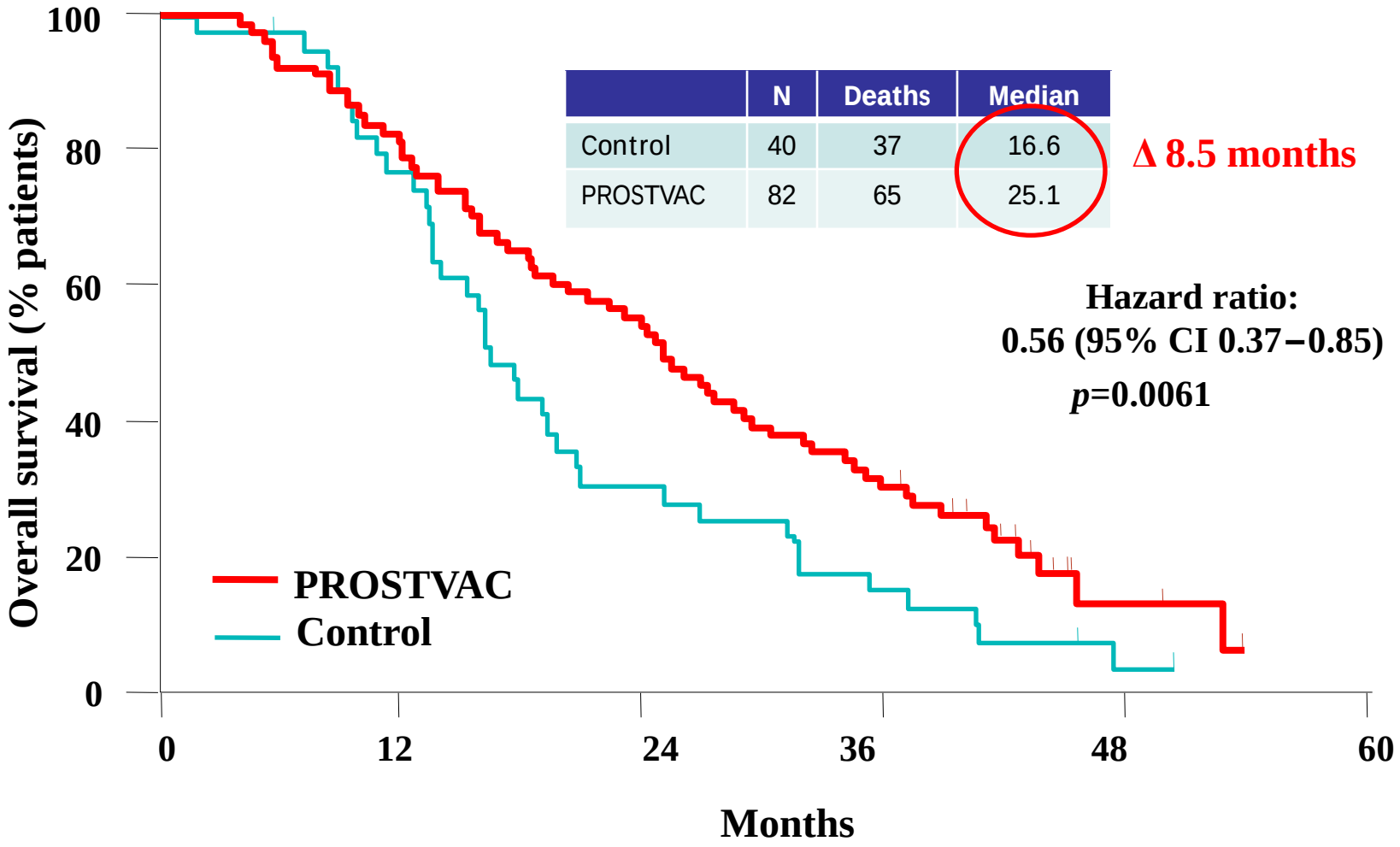


Therapies Shown to Improve Overall Survival in Metastatic Castration-Resistant Prostate Cancer

Agent	Type of therapy	Stop treatment 2º AE	Improvement in median OS	Hazard ratio	Reduction in death rate	Approved
Docetaxel	chemotherapy	11%	2.4 months	0.76	24%	2004
Cabazitaxel	chemotherapy	18%	2.4 months	0.70	30%	2010
Abiraterone	hormone	19%	3.9 months	0.66	34%	2011
Sipuleucel-T	vaccine	1.5%	4.1 months	0.78	22%	2010
Prostvac*	vaccine	~2%	8.5 months	0.56	44%	—

* rV-, rF-PSA-TRICOM – Results of a Phase II randomized, placebo (vector)–controlled, 43-center trial.

PROSTVAC Significantly Extended Overall Survival



Kantoff (Schlom, Gulley) *et al. J Clin Oncol* 2010

Randomized Multicenter Placebo-controlled Vaccine Therapy Trial in Castrate-resistant Metastatic Prostate Cancer Patients

Observations:

A. Time to Progression: no difference in arms

B. Median survival (at 4 years median follow-up)
   Placebo: 16.6 months
   Vaccine: 25.1 months (p=0.006)

C. 44% reduction in death rate in vaccine arm

Phase II Study of PSA-TRICOM

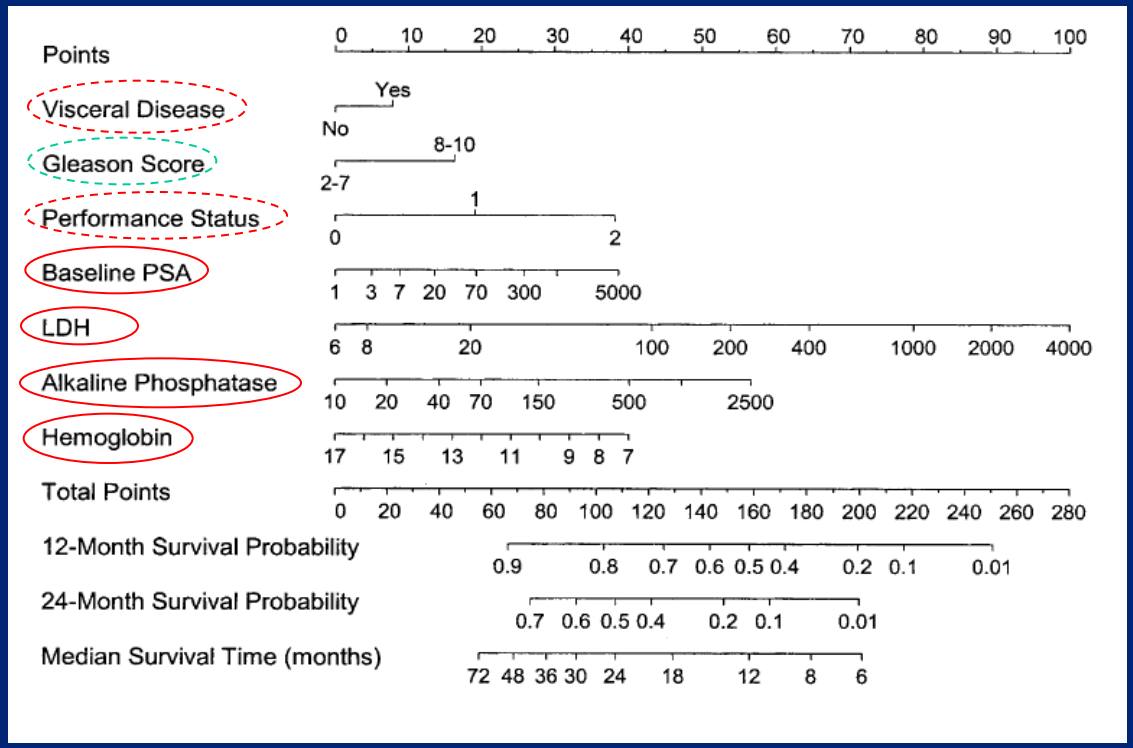
- **32 patients with metastatic castration-resistant prostate cancer (CRPC)**
- **Chemotherapy naive**
- **Primary endpoint: immune response by ELISPOT**
- **Secondary / exploratory endpoints: Response, Survival**

Gulley, (Madan, Schlom) et al., Clin Immunol Immunother, 2010

Prognostic Model for Predicting Survival in Men with Hormone-Refractory Metastatic Prostate Cancer

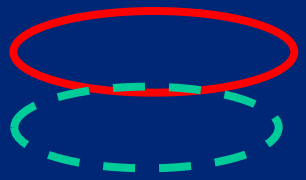
By Susan Halabi, Eric J. Small, Philip W. Kantoff, Michael W. Kattan, Ellen B. Kaplan, Nancy A. Dawson, Ellis G. Levine, Brent A. Blumenstein, and Nicholas J. Vogelzang

J Clin Oncol., 2003



<u>Conclusion:</u>

Can predict survival probabilities.



Volume of disease

Aggressiveness of disease

Predicted Survival by Halabi Score vs Actual Survival

Vaccine: PROSTVAC (n=32)

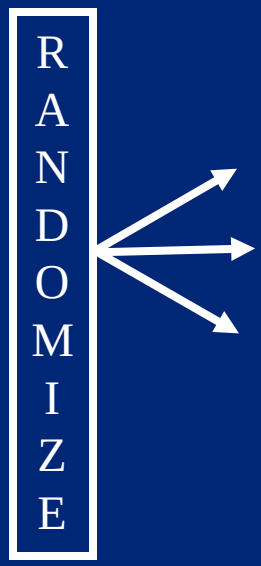
	All patients	Patients with Halabi predicted survival < 18 mos	Patients with Halabi predicted survival ≥ 18 mos
Predicted survival by Halabi score (mos)	17.4	12.3	20.9
Actual median overall Survival (mos)	26.6	14.6	Not reached (8 of 15 pts alive at 37.3 mos)
Difference (mos)	9.2	2.3	≥16.4
Patients survival longer than predicted by Halabi nomogram	22 of 32 (69%)	10 of 17 (59%)	12 of 15 (80%) p = 0.035

Docetaxel therapy (n=22)

Predicted survival by Halabi score (mos)	16.5	13.0	21.0
Actual median overall survival (mos)	15.5	15.4	16.9
Difference (mos)	(-1.0)	2.4	(-4.1)
Patients survival longer than predicted by Halabi nomogram	11 of 22 (50%)	8 of 13 (62%)	3 of 9 (33%)

Planned Phase III

Patient Population: **Metastatic CRPC (Asymptomatic or minimally symptomatic)**



Arm A: PSA TRICOM vaccine with GM-CSF (n=400)

Arm B: PSA TRICOM vaccine + placebo GM (n=400)

Arm C: Empty Vector + placebo GM-CSF (n=400)

Primary endpoint: OS

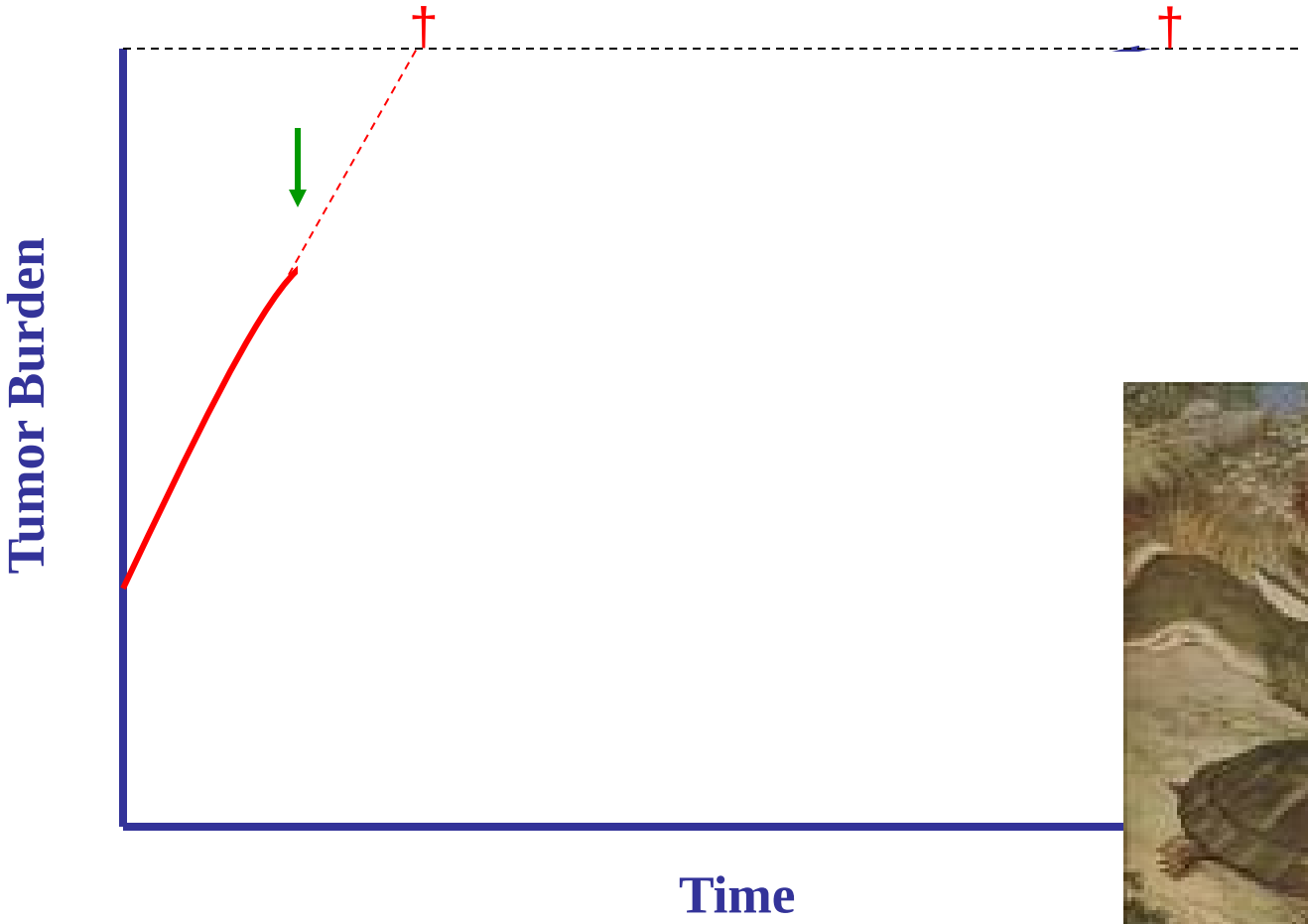
Power = 90% α = 0.005

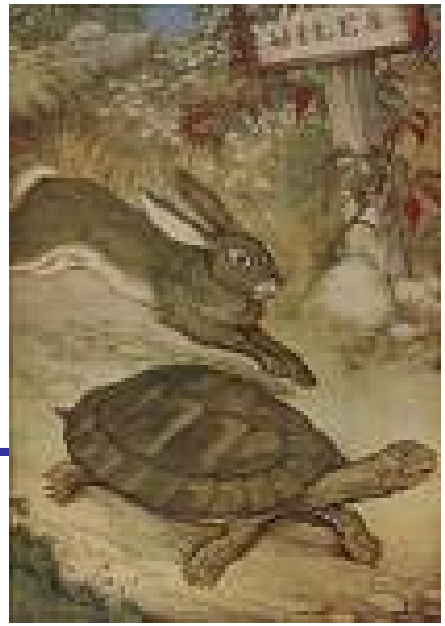
Critical HR 0.8

Expected to open 2011

PI: Gulley

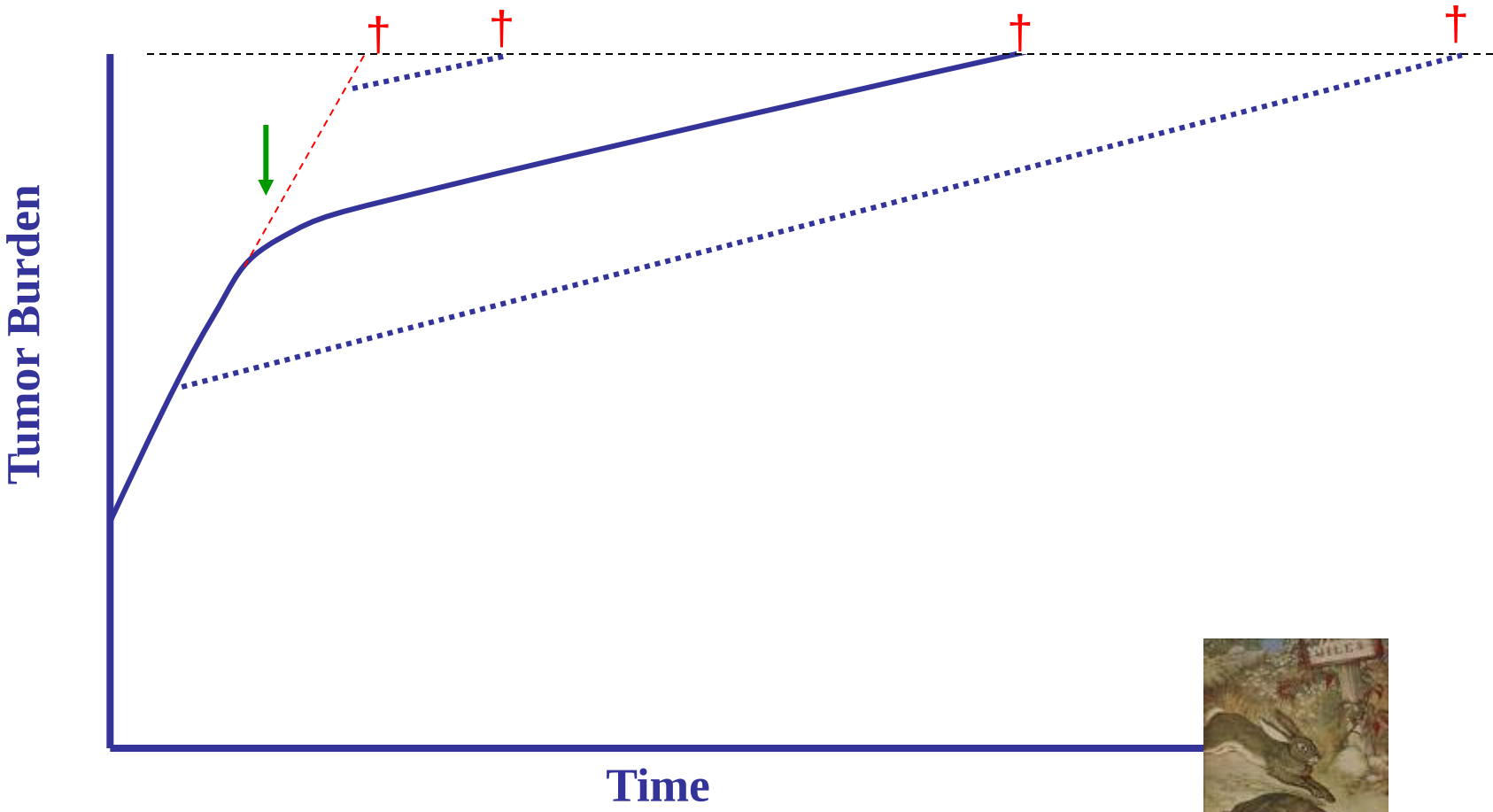
Tumor Growth Rate





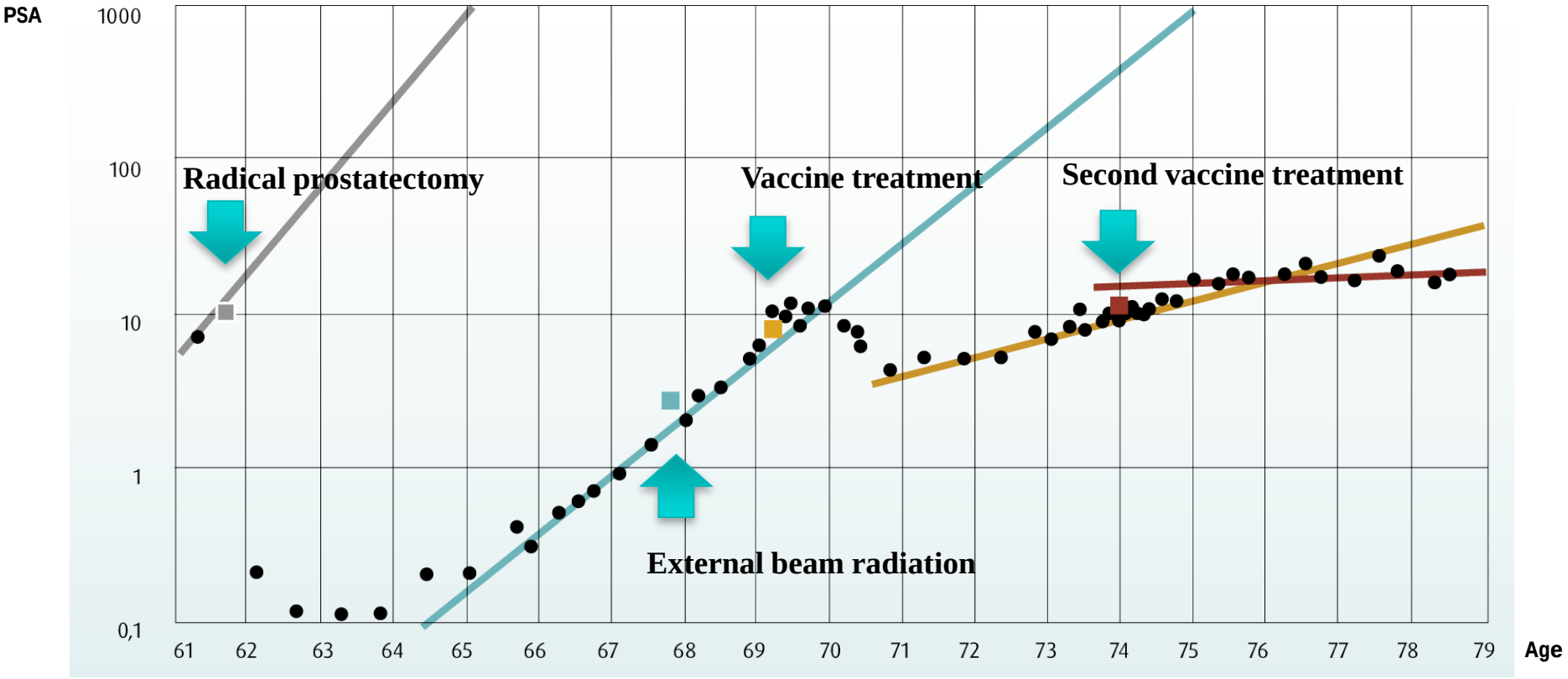
Stein, Gulley, Schlom…Bates, Fojo. Clin Cancer Res. 2010

Tumor Growth Rate



Stein, Gulley, Schlom…Bates, Fojo. Clin Cancer Res. 2010

PROSTVAC – Interesting Case History



Gleason grade: 4 + 3 = 7

	Doubling time	Age at which PSA would equal 1000
Trend before radical prostatectomy	5.8 months	65 years
Trend after radical prostatectomy. External beam radiation	9.6 months	75 years
Trend after first vaccine trial	28.6 months	93 years
Trend after second vaccine trial	27 years	

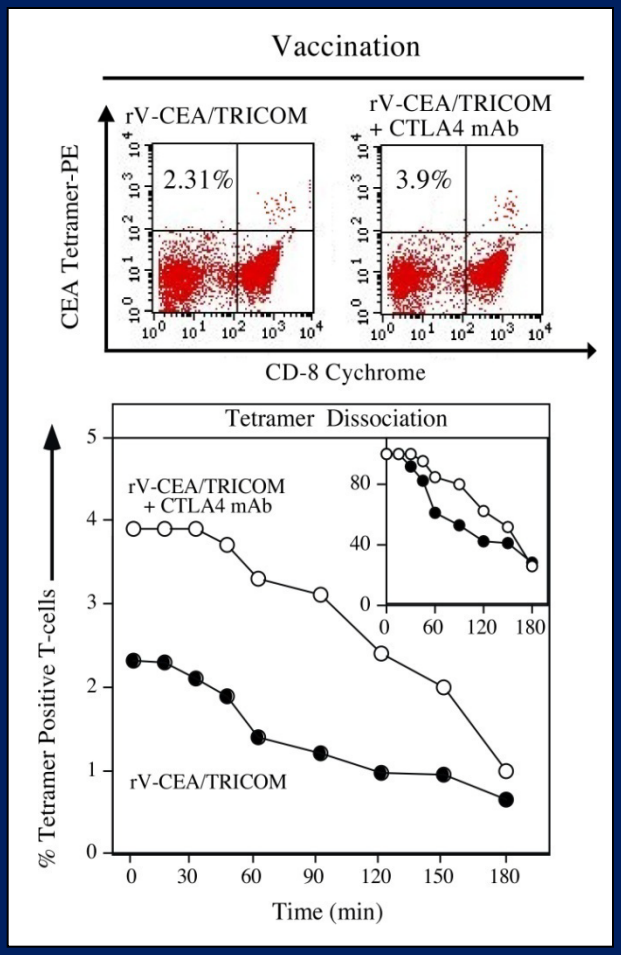
Vaccine Combination Therapies

The use of cancer vaccines with other immune-mediating therapies:

- **enhancers of immune stimulation**
  (e.g., GM-CSF, IL-12, IL-15)
- **immune checkpoint inhibitors**
  (e.g., anti-CTLA-4, MAb, inhibitors of TGF-β)
- **T-cell adoptive transfer therapy**
- **other cancer vaccines**
  TRICOM + yeast

Effect of Multiple Costimulatory Modalities to Enhance CTL Avidity

CEA-Tg

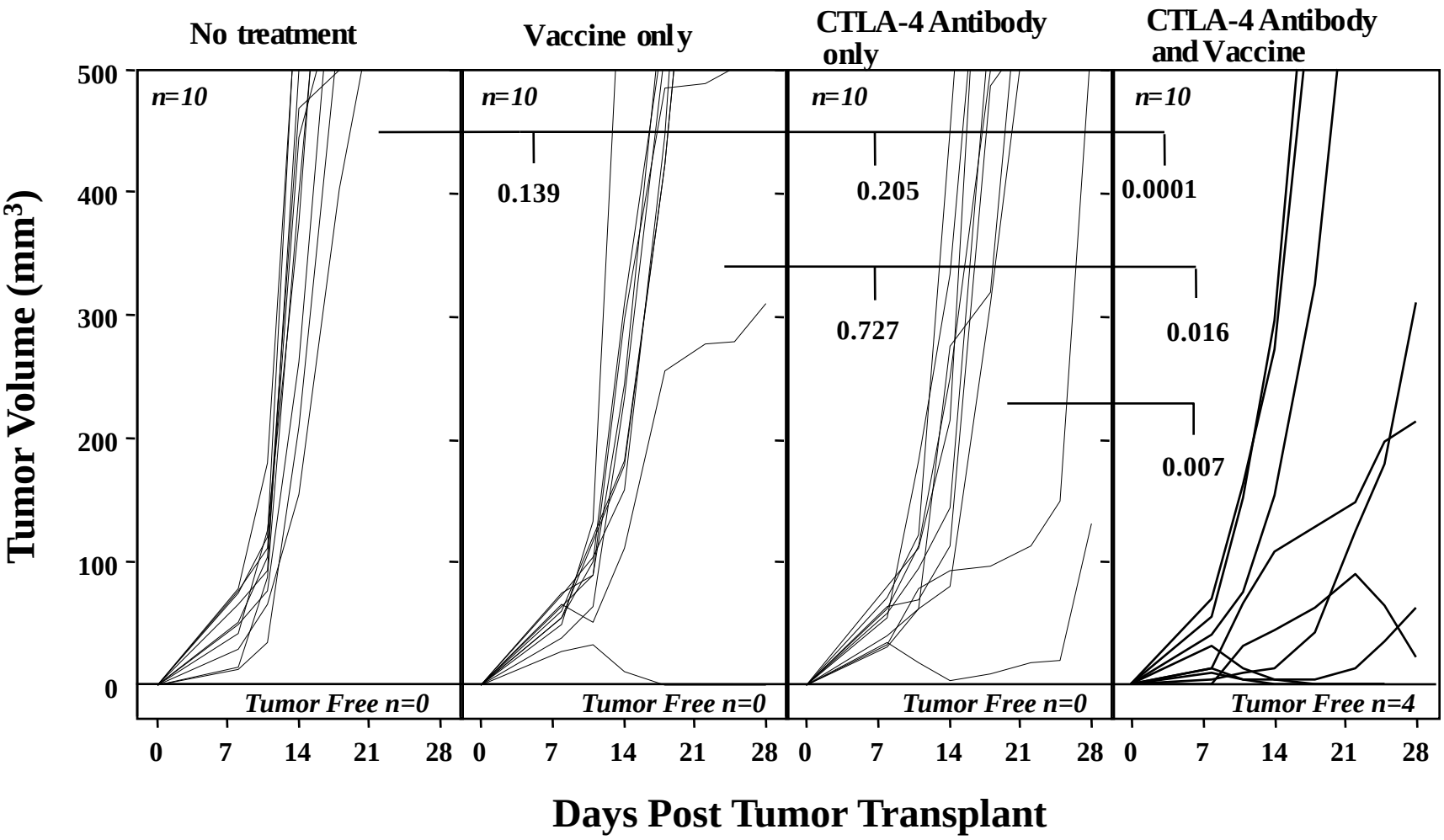


Vaccine Modality	Precursor Frequency/10^5 CD8 T Cells	Δ Precursor	Peptide Concentration for CTL (nM)	Δ Avidity*
rV-CEA	321	1.0x	510	1.0x
rV-CEA/TRICOM	769	2.4x	5	102.0x
rV-CEA/TRICOM+ anti-CTLA-4	1,303	4.0x	0.4	1,275x

- Avidity defined as the natural log of the peptide concentration that results in 50% maximal target lysis. Derby, Berzofsky. J Immunol. 166:1690–7.

Hodge, Chakraborty, Kudo-Saito, Garnett, Schlom. J Immunol. 174:5994-6004.

Combination Therapy: Vaccine and α–CTLA-4



Mouse : CEA/Tg
Tumor : MC32a
Vaccine : Prime on Day 4 and Boost on Day 11,18 and 25
CTLA-4 antibody on Day 4,7 and Day 10

Hodge et al.

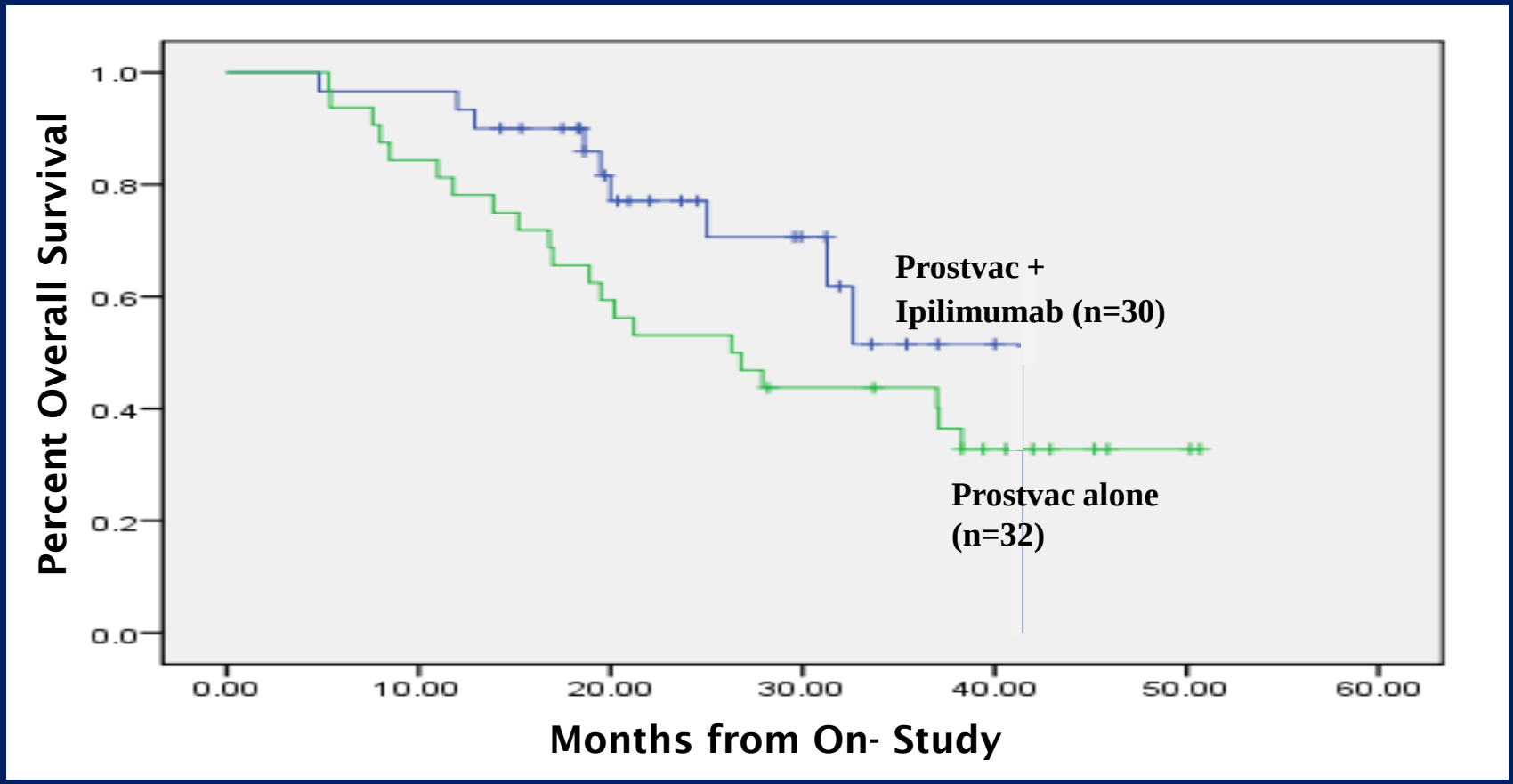
Vaccine + anti-CTLA-4

- Patient population: metastatic CRPC
- Design
  - Phase I
    - fixed dose vaccine
    - dose escalation of ipilimumab (1, 3, 5 and 10 mg/kg)
- Endpoints
  - 1º Safety
  - 2º Clinical responses, PSA kinetics, OS, Immune responses

NCI# 05-C-0167 Gulley PI

Preclinical Data from Hodge et al.

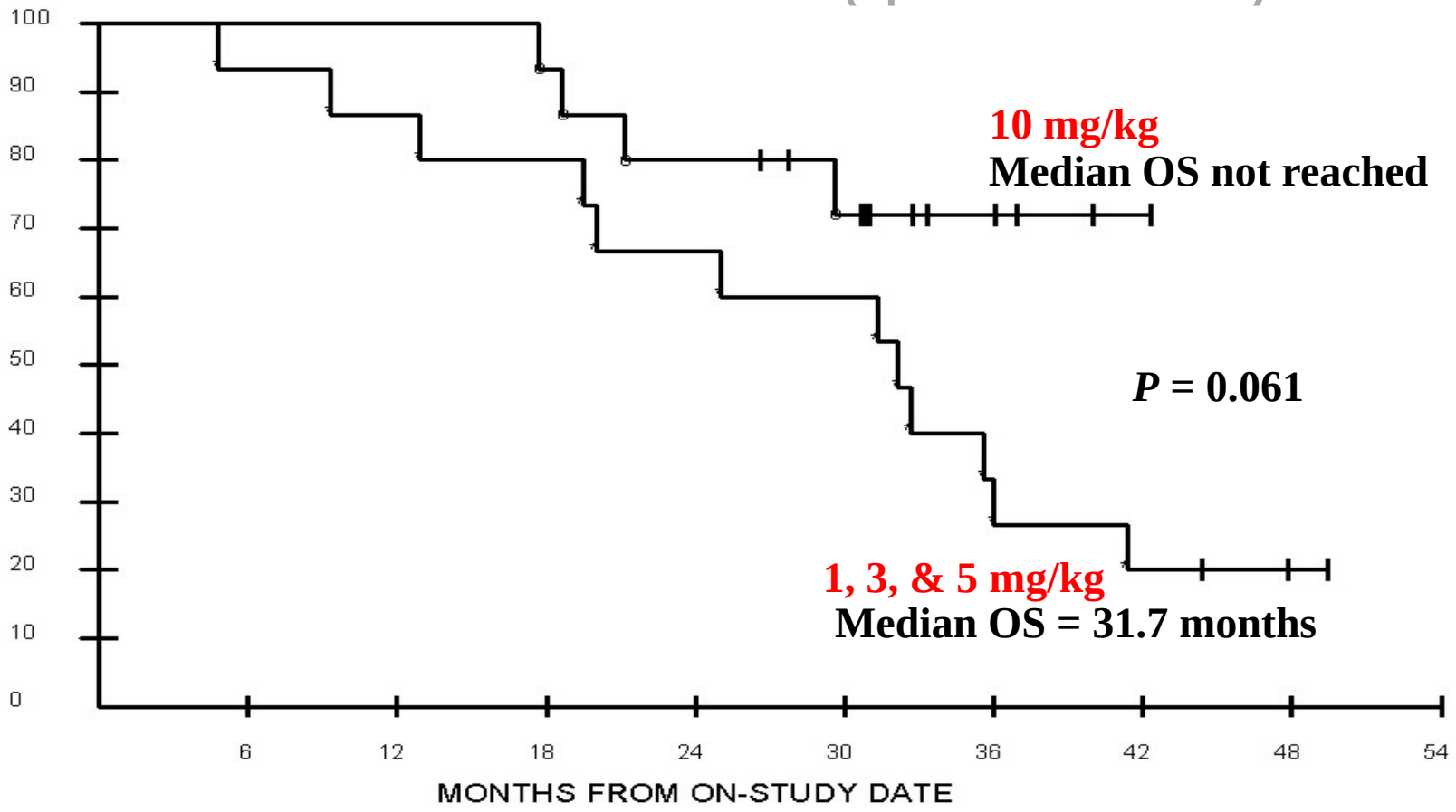
Comparing OS of Prostvac Alone to Prostvac + Ipilimumab



This compares two studies done at the NCI with Prostvac in metastatic CRPC *(Updated 9/21/2010)*

	Median Overall Survival	Halabi Predicted Survival	Δ OS	Alive at 24 mos
Prostvac *alone*	26.3 months	17.2 months	9.1 months	53%
Prostvac *and Ipilimumab*	34.4 months	18.5 months	15.9 months	73.3%

Overall Survival for All Patients (updated 9/21/2010)



	Median Overall Survival	Halabi Predicted Survival	Δ OS	Alive at 24 mos
PSA-TRICOM *alone*	26.3 months	17.2 months	9.1 months	53%
PSA-TRICOM *and Ipilimumab*	34.4 months	18.5 months	15.9 months	73%

The Next Frontier: Vaccine Combination Therapies

The use of cancer vaccines in combination with conventional therapies

- **Chemotherapy**
- **Hormone therapy**
- **Local radiotherapy of tumor**
- **Small molecule targeted therapeutics**

Vaccine Combination Therapies

1. **Vaccines Induce Minimal Toxicity**
   – can act independently of concomitant therapy

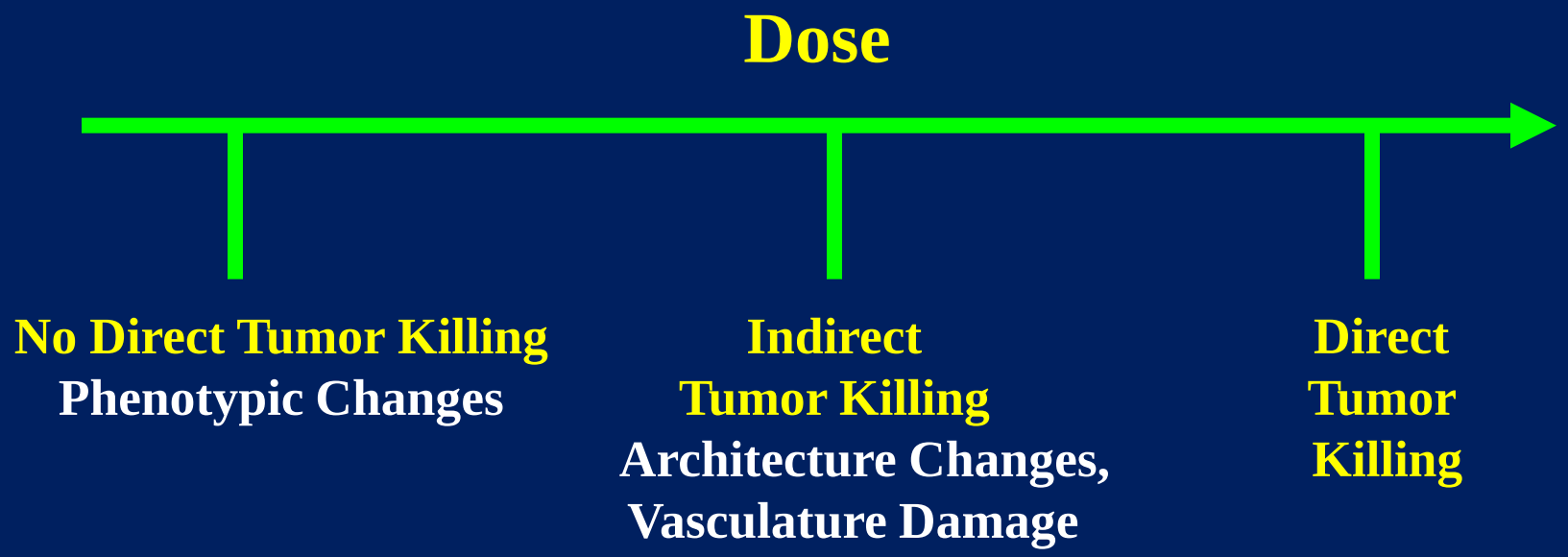
2. **Do NOT confuse**
   multiple therapies used prior to vaccine
   vs.
   therapies used with vaccine or following vaccine

Mode of Action of Vaccine Combination Therapies

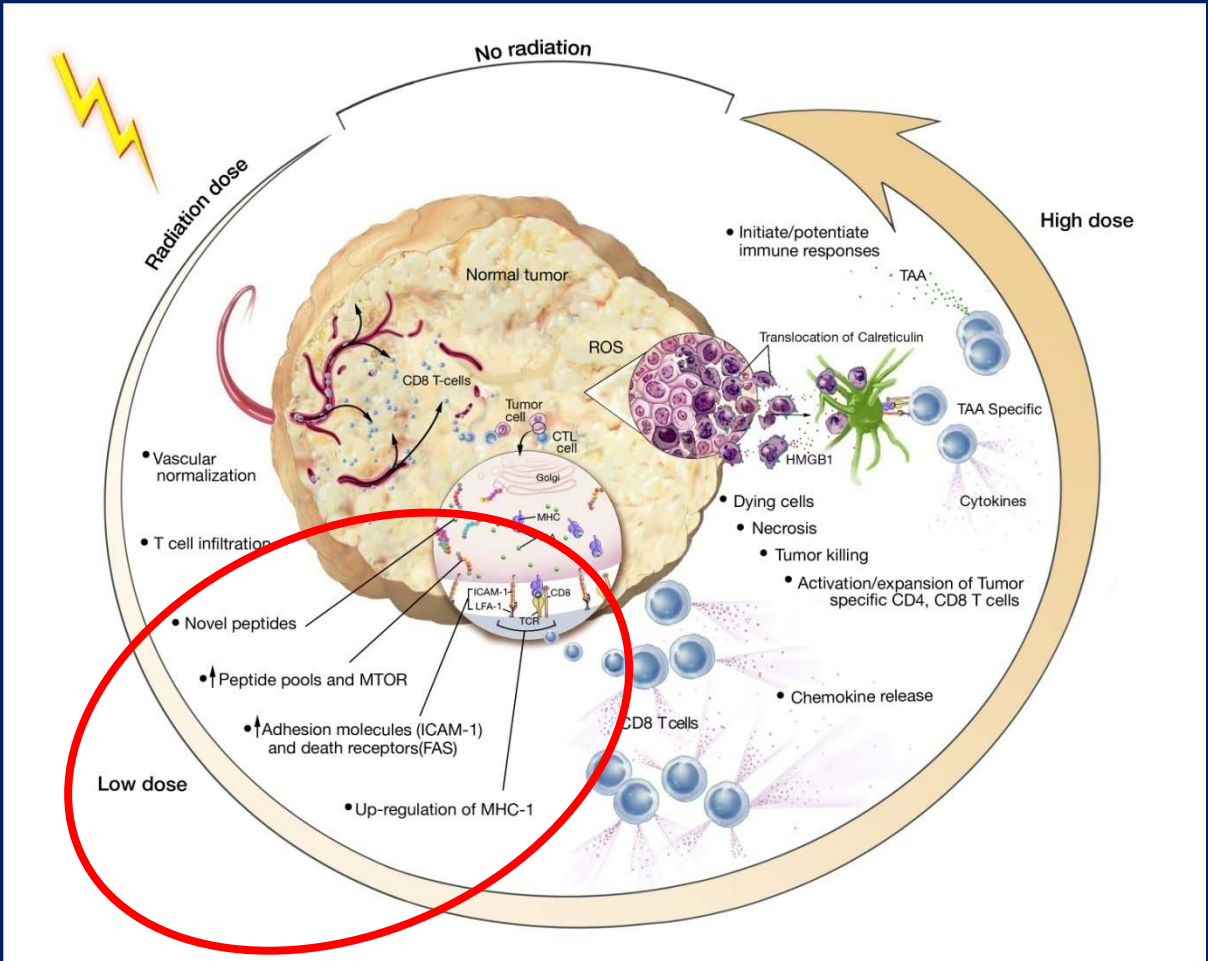
- Certain chemotherapeutics when given post-vaccine therapy will lyse populations of tumor cells acting as a boost for the initial vaccine therapy

- Certain chemotherapeutic agents and/or radiation can alter the phenotype of tumor cells rendering them more susceptible to T-cell–mediated lysis

Potential Multiple Effects of Chemotherapy, Small Molecule Targeted Therapeutics, or Local Irradiation of Tumors

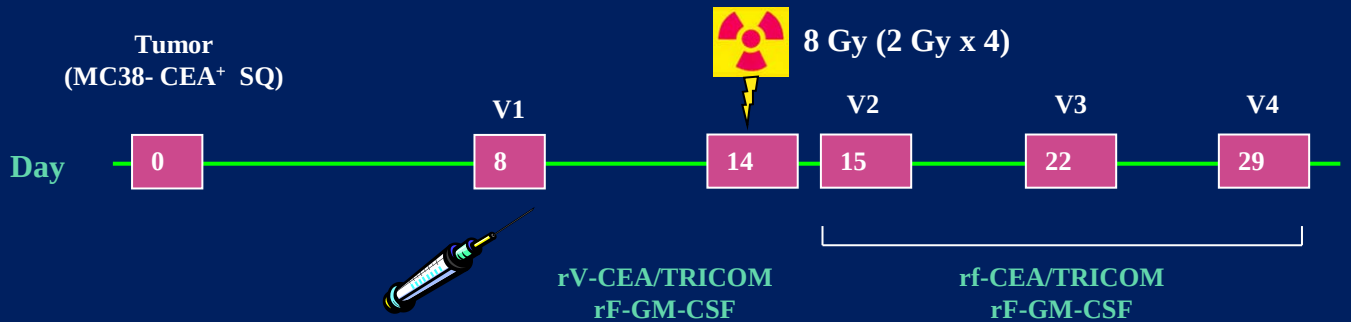


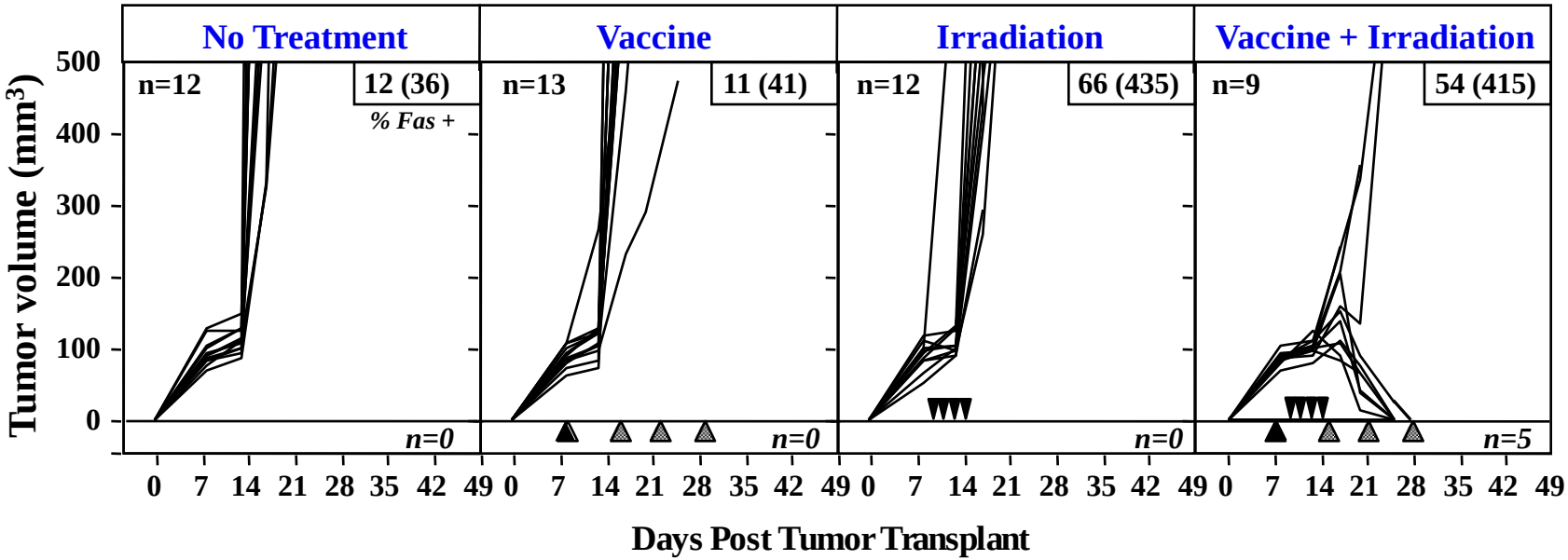
Potential Multiple Effects of Local Irradiation of Tumors



Hodge et al., Oncology 22:1064-70.

Combination Therapy: Vaccine + External Beam Radiation





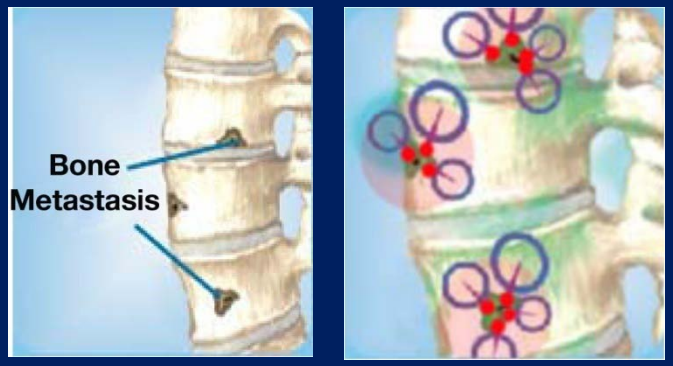
Chakraborty, Abrams…Schlom, Hodge. Cancer Res. 15:4328-37.

QUADRAMET
(SAMARIUM SM-153 LEXIDRONAM INJECTION)

QUADRAMET is a radioactive samarium (^{153}Sm)-chelate:

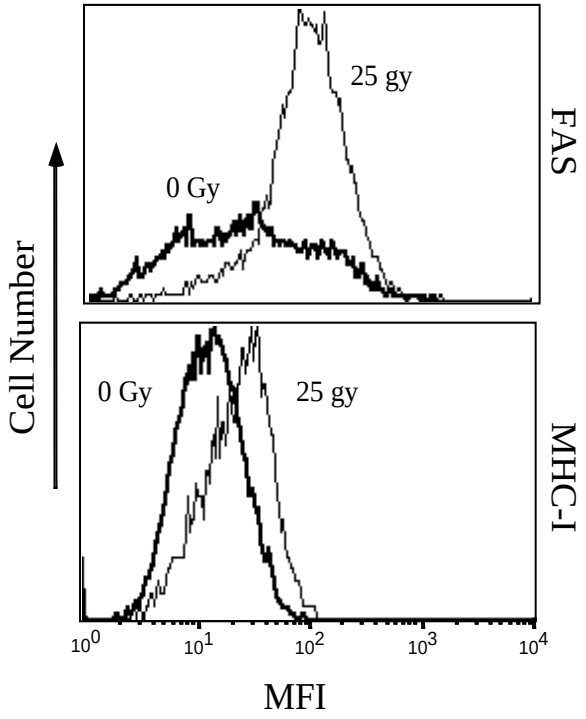
It preferentially binds to osteoblastic metastatic tumor deposits in bone.

^{153}Sm is FDA approved and clinically utilized for palliation of bone metastasis in multiple tumor histologies.



Treatment of LnCaP Prostate Cells with Palliative Levels of ^{153}Sm (Quadramet) Modulates Phenotype, Upregulates TAA, and Increases Sensitivity to Antigen-specific CTL Killing

Treatment of LnCaP prostate cancer cells with palliative doses of ^{153}Sm results in the upregulation of MHC class I and Fas

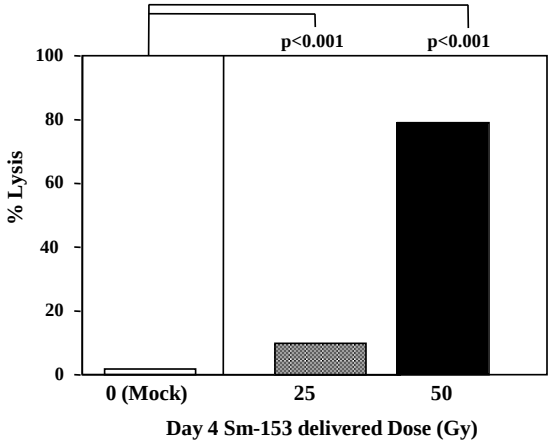


Treatment of LnCaP prostate cancer cells with palliative doses of ^{153}Sm results in the upregulation of TAAs

Tumor antigen genes

	0 Gy	25 Gy
PSA	1	2.79
PSMA	1	4.14
PAP	1	29.0
CEA	1	10.3
MUC-1	1	3.67

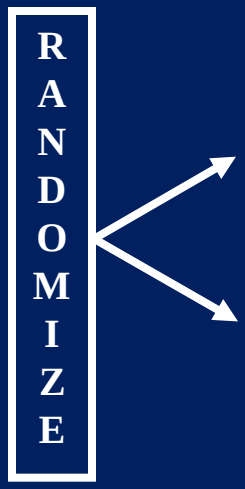
Treatment of LnCaP prostate cancer cells with palliative doses of ^{153}Sm results in increased sensitivity to multiple CTLs



Chakraborty, Wansley…Schlom, Hodge, NCI. Clin Cancer Res. 2008
Collaboration with Nuclear Medicine Branch

^{153}Sm +/- PSA-TRICOM

Patient Population: **CRPC Metastatic to bone**



Arm A: PSA-TRICOM + ^{153}Sm (n=34)

Arm B: ^{153}Sm (n=34)

Vaccine: **rV-PSA/TRICOM s.c. d 1**
rF-PSA/TRICOM s.c. d 15, 29, q 4 wks

^{153}Sm: **1 mCi/kg d 8, may be repeated**
q 12 wks upon hematologic recovery.

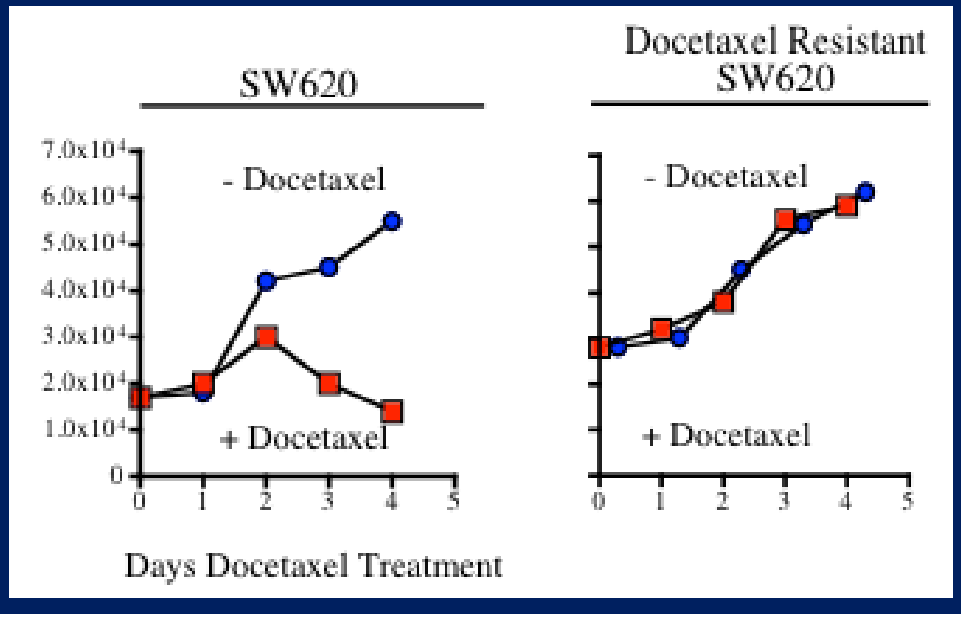
PI Gulley NCI# 7678
in collaboration with Nuc Med

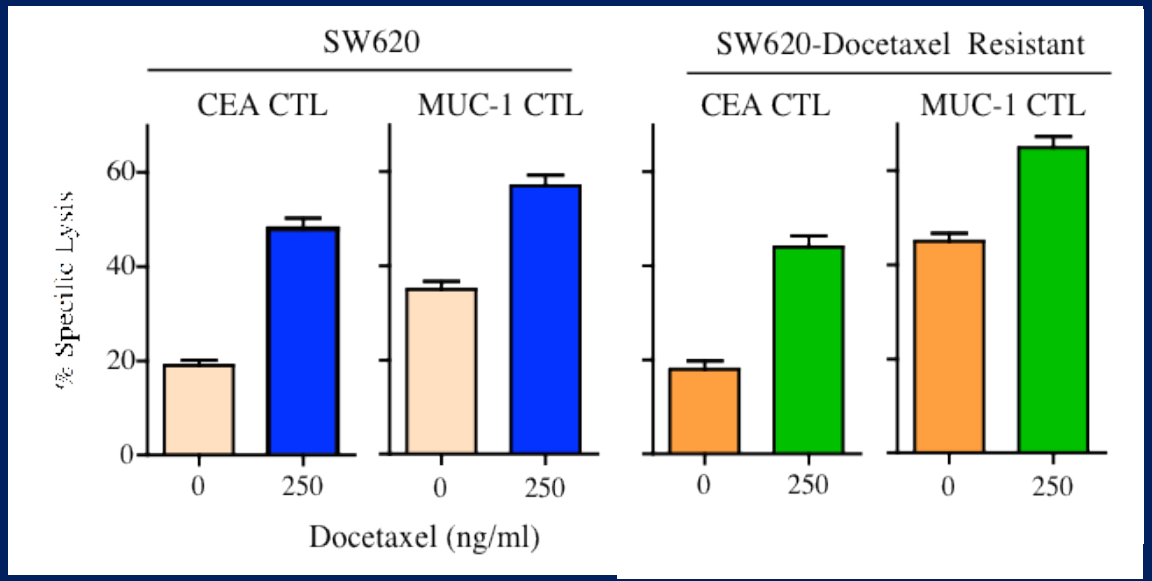
Preclinical Data from Hodge et al.

Mode of Action of Vaccine Combination Therapies

- Evidence of non-coordinate lytic susceptibility of tumor cells
  - — tumor cells have shown differential susceptibilities to killing by chemotherapy/ radiation vs. T cells
- Exploitation of the phenomenon of homeostatic proliferation of T cells post-chemotherapy
  - — certain effector immune cell subsets can be expanded more rapidly vs. regulatory cells

Human Carcinoma Cells Resistant to Chemotherapy Are Sensitive to CTL Killing After Treatment





TRICOM
TRIad of COstimulatory Molecules

Costimulatory Molecule	Ligand on T cell
B7-1 (CD80)	CD28/CTLA-4
ICAM-1 (CD54)	LFA-1
LFA-3 (CD58)	CD2

TRICOM = B7-1/ICAM-1/LFA-3

CEA/TRICOM = CEA/B7-1/ICAM-1/LFA-3

CEA/MUC-1/TRICOM = CEA/MUC-1/B7-1/ICAM-1/LFA-3 (PANVAC)

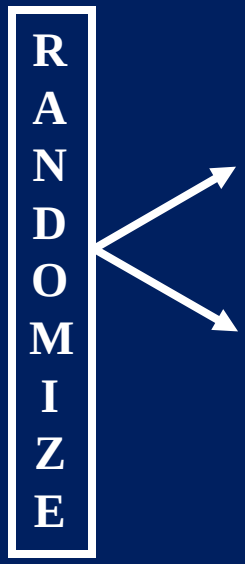
PSA/TRICOM = PSA/B7-1/ICAM-1/LFA-3 (PROSTVAC)

All vaccines contain: rV- as a prime vaccine
avipox (fowlpox, rF-) as multiple booster vaccines

CEA, MUC-1, and PSA transgenes all contain enhancer agonist epitopes

Docetaxel +/- PANVAC

Patient Population: Metastatic Breast Cancer (Docetaxel Naïve) n=48



Arm A: Weekly Docetaxel + PANVAC

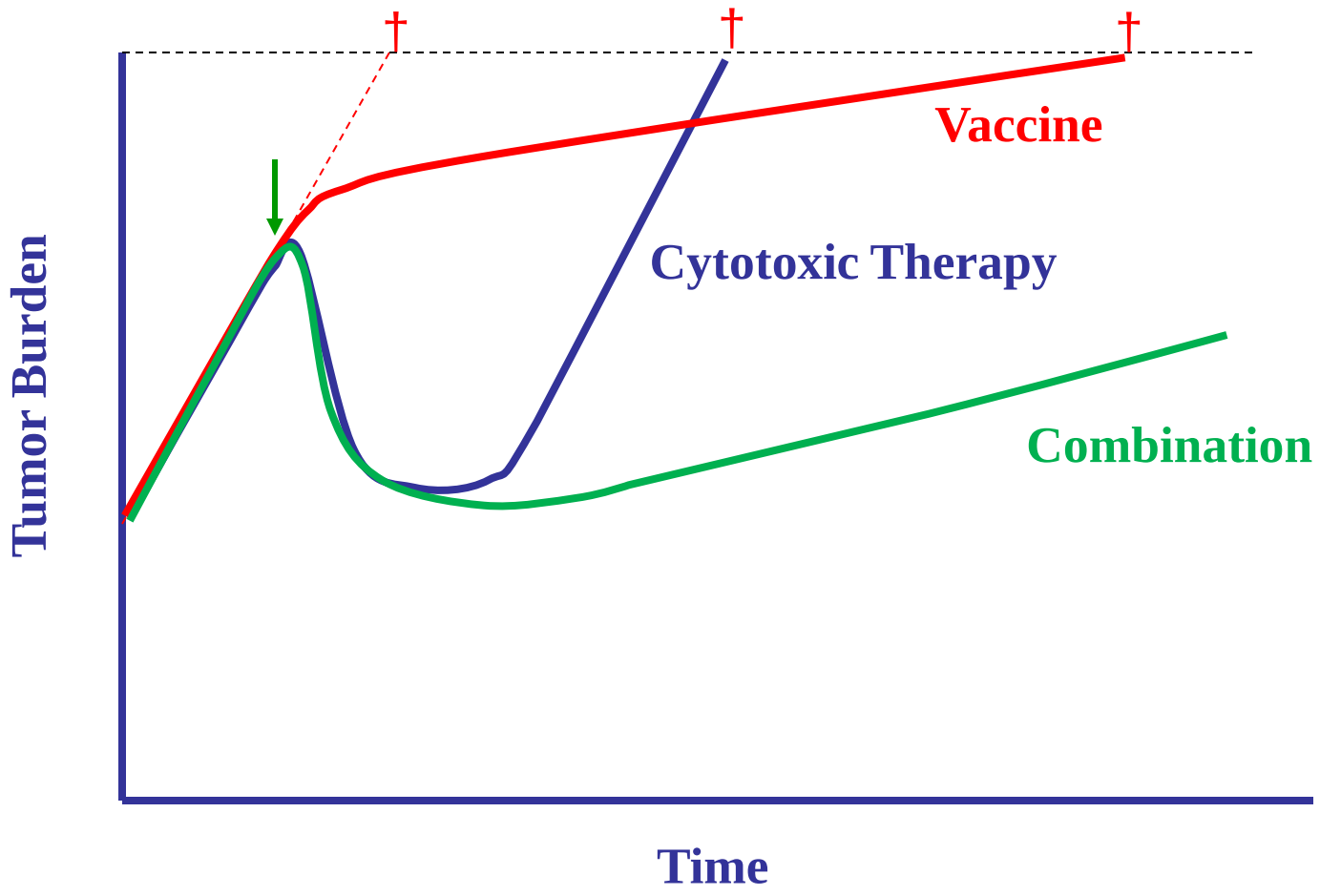
Arm B: Weekly Docetaxel alone

Primary endpoint: TTP

NCI 6977: PI, Gulley

Preclinical Data from Hodge et al.

Tumor Growth Rate



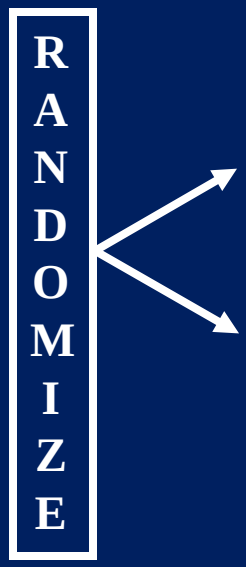
Stein W, Gulley JL, et al. *Clin Ca Res*, 2011

Unique Properties of Therapeutic Cancer Vaccines

- Minimal toxicity
- Effect on the host immune system
  - — indirect effect on the tumor
  - — anti-tumor effects may be delayed
- Overall survival vs RECIST or time to progression as the appropriate primary endpoint
- Induction of host immunity is a dynamic process that can persist post-vaccination
- Potential for an enhanced effect on concomitant or subsequent therapies

Chemotherapy vs. Vaccine Followed by Chemotherapy (ECOG Multicenter Trial)

Patient Population: Metastatic CRPC (Halabi Predicted Survival ≥ 18 months)



Arm A: PSA-TRICOM vaccine → Docetaxel + Prednisone (n=90)

Arm B: Docetaxel + Prednisone (n=45)

Phase II (n=135)
Primary endpoint: OS

Protocol Chair: Doug McNeel
Co-Chair: Gulley