Cancer Vaccine Combination with Conventional Therapies

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The following relationships exist related to this presentation:

No Relationships to Disclose

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

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

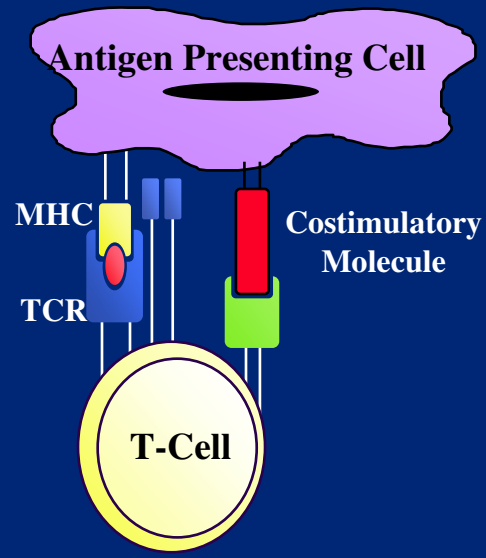
  – safe; does not replicate

  – 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

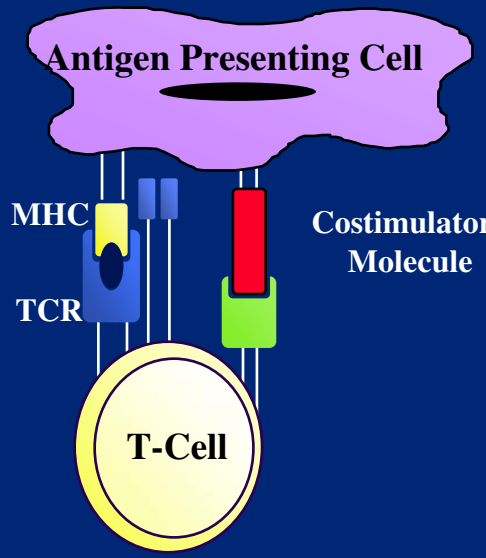
T-Cell Dependence on Costimulation

Signal 1 + Signal 2



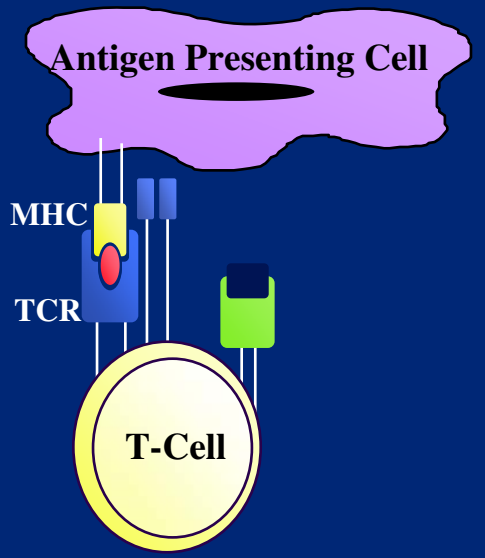
Activation of Antigen-Specific T-cells

No Signal 1



Clonal Anergy
Apoptosis
Ignorance

No Signal 2



Clonal Anergy
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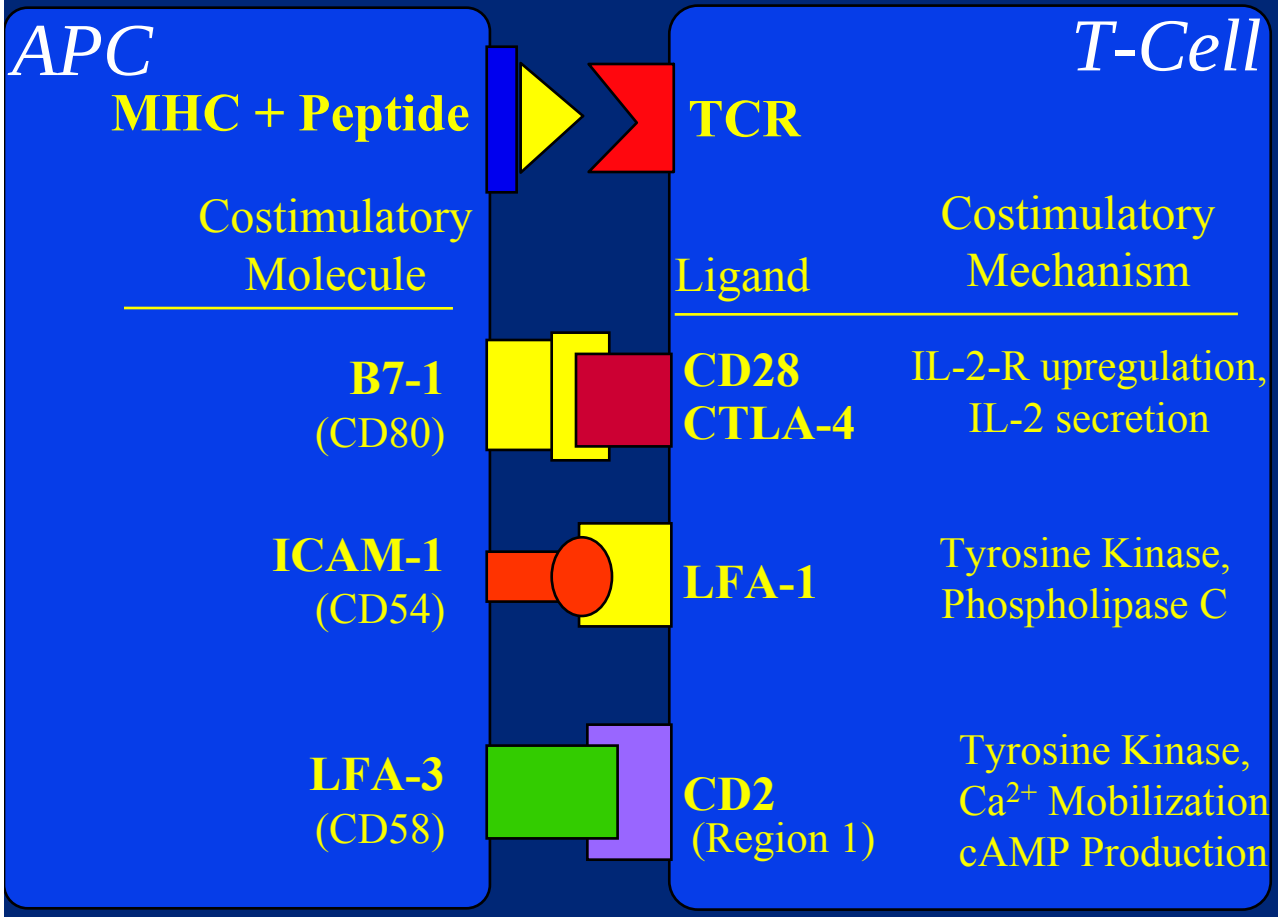
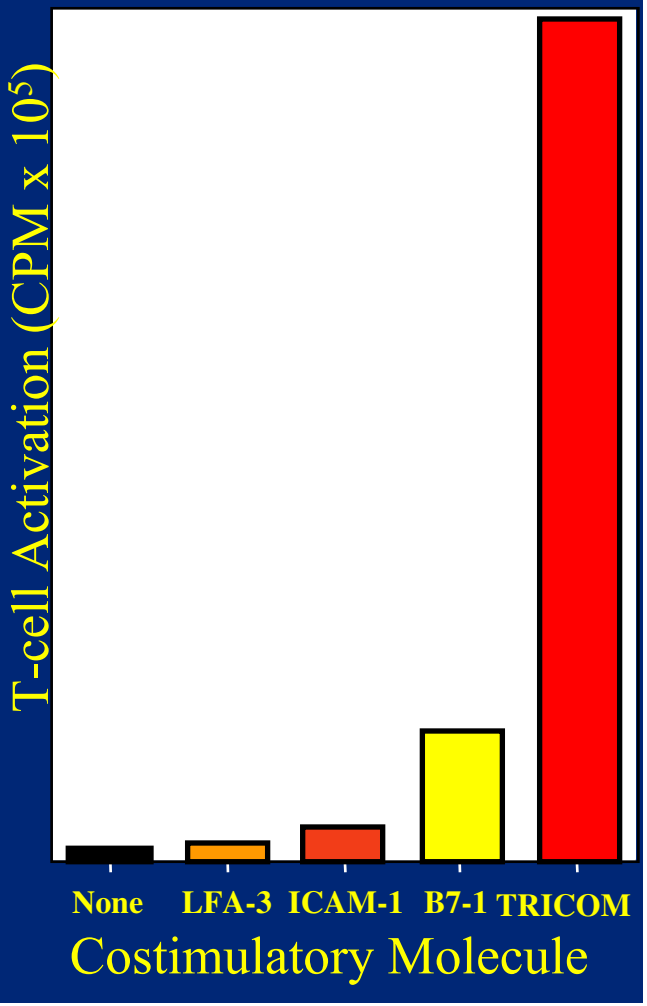
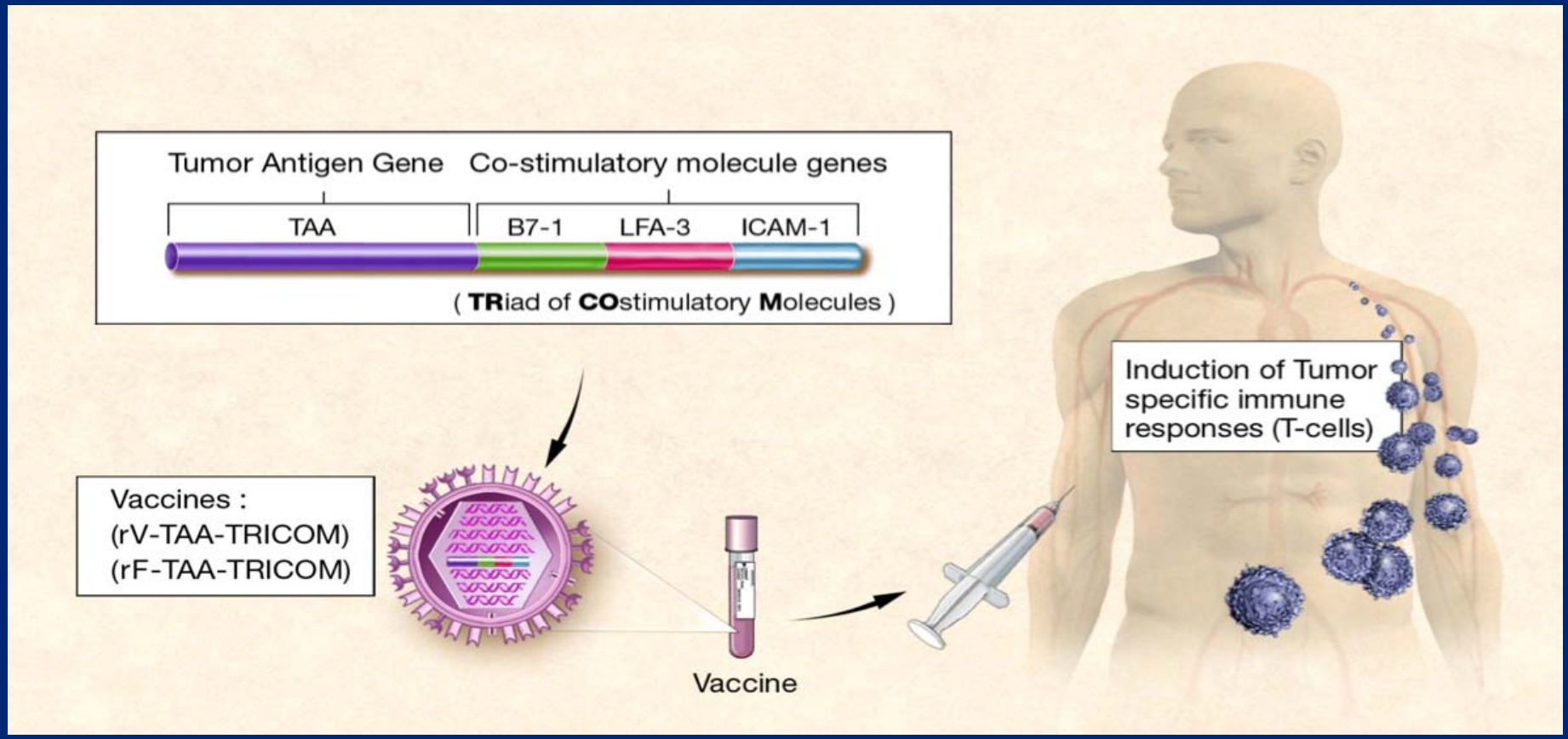
Costimulatory Molecule Candidates

- 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

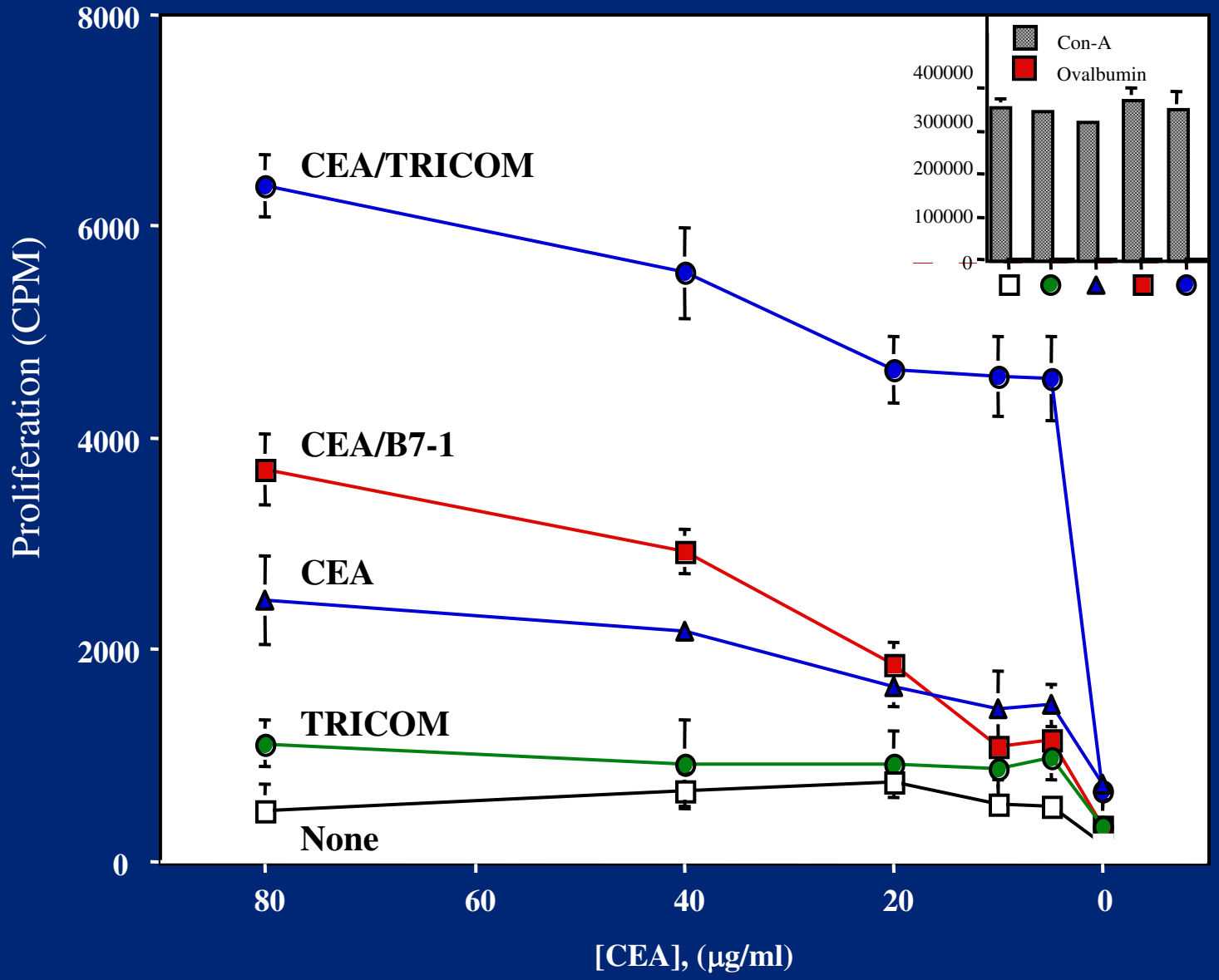
CEA/MUC-1/TRICOM = CEA/MUC-1/B7-1/ICAM-1/LFA-3 (PANVAC)

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



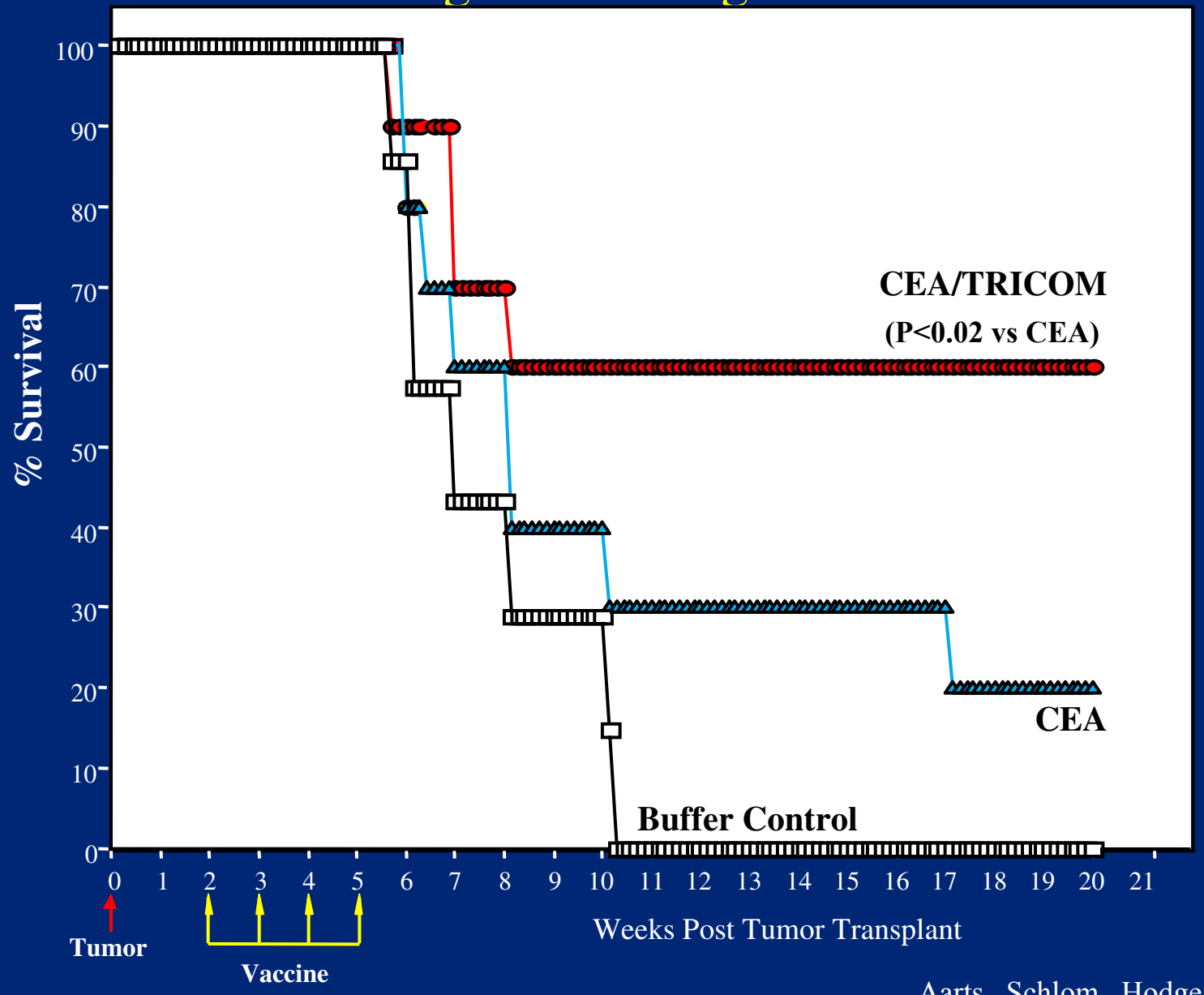
VAAA Regimen

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

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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

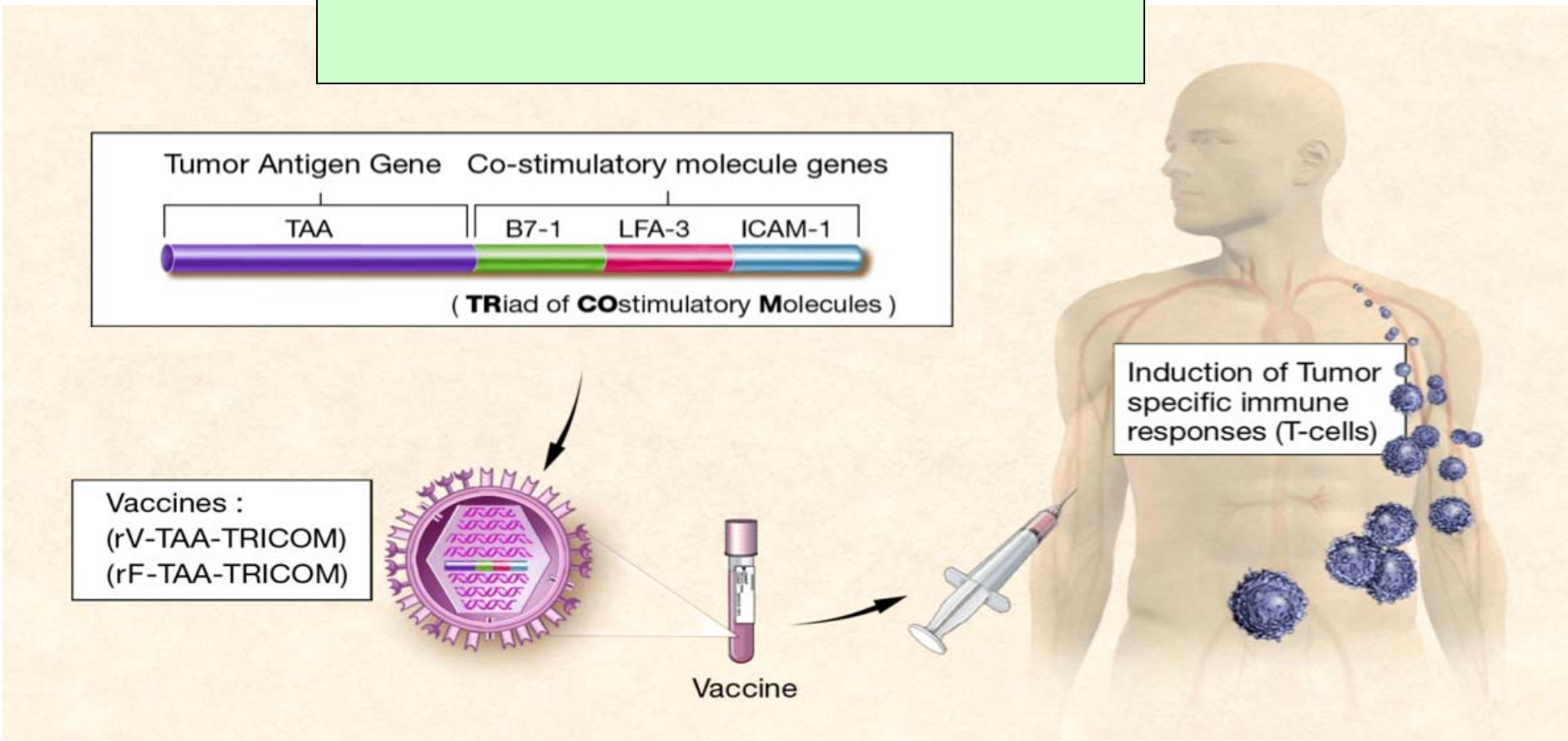
Therapies Shown to Improve Overall Survival in Metastatic Castration-Resistant Prostate Cancer

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%	—

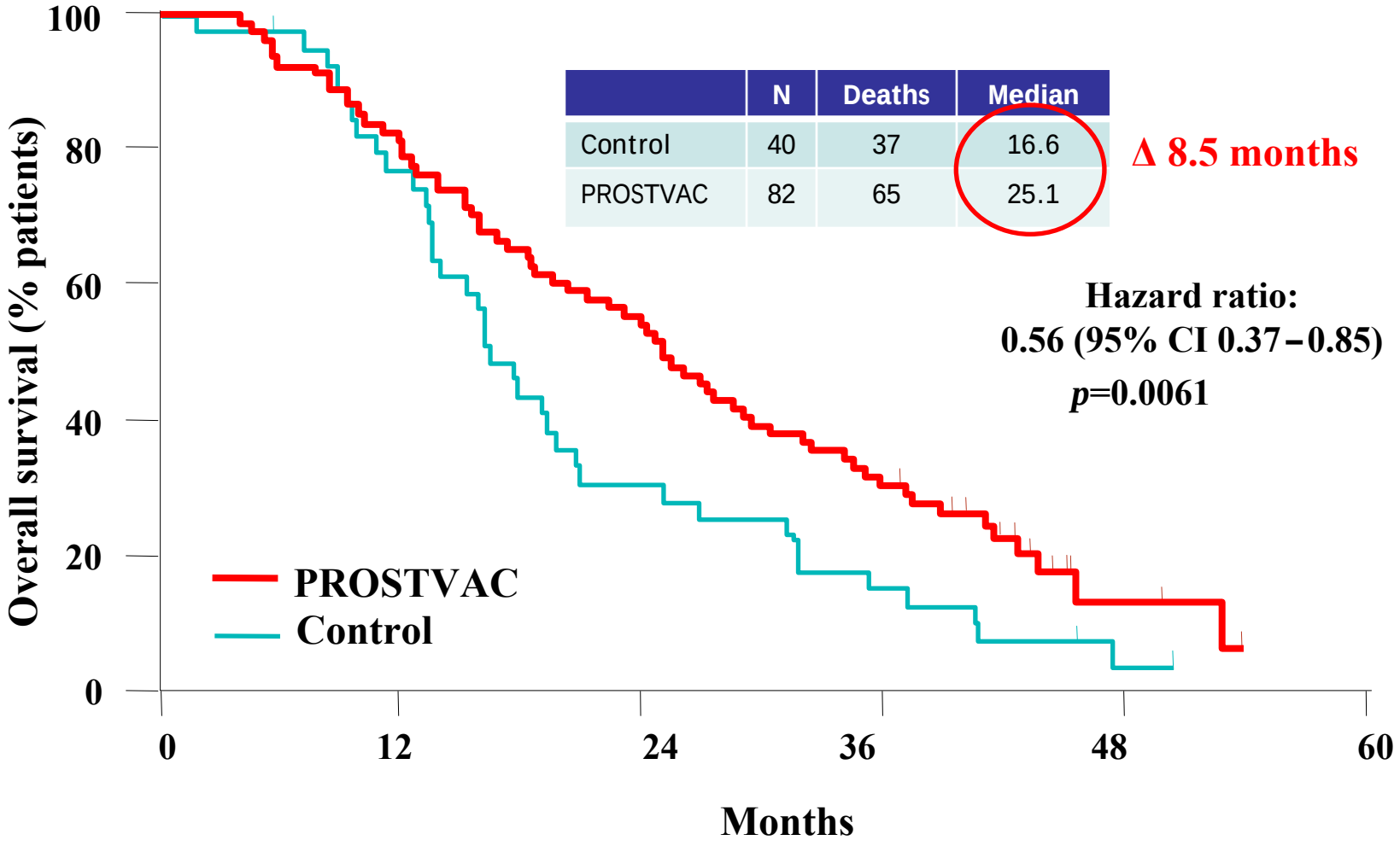
* rV-, rF-PSA-TRICOM – Results of a Phase II randomized, placebo (vector)–controlled, 43-center trial.

PROSTVAC
PSA and a TRIad of COstimulatory Molecules

TAA: PSA: PROSTVAC



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

NCI Phase II Trial:

MOS: 26.6 mo

HPS: 17.4 mo

The Next Frontier: Vaccine Combination Therapies

The use of cancer vaccines in combination with conventional therapies

- **Hormone therapy**
- **Radiotherapy of tumor**
- **Chemotherapy**

Vaccine Combination Therapies

The vaccine induction of a dynamic host immune response can be boosted by

- concomitant or subsequent therapies

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(a) can alter the phenotype of tumor cells, rendering them more susceptible to T-cell killing

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Vaccine Combination Therapies

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– concomitant or subsequent therapies

(a) can alter the phenotype of tumor cells, rendering them more susceptible to T-cell killing

(b) can lyse populations of tumor cells which, in turn, act as a booster for tumor-specific immune cells

(c) can kill or inhibit regulatory T cells and thus boost the immune response

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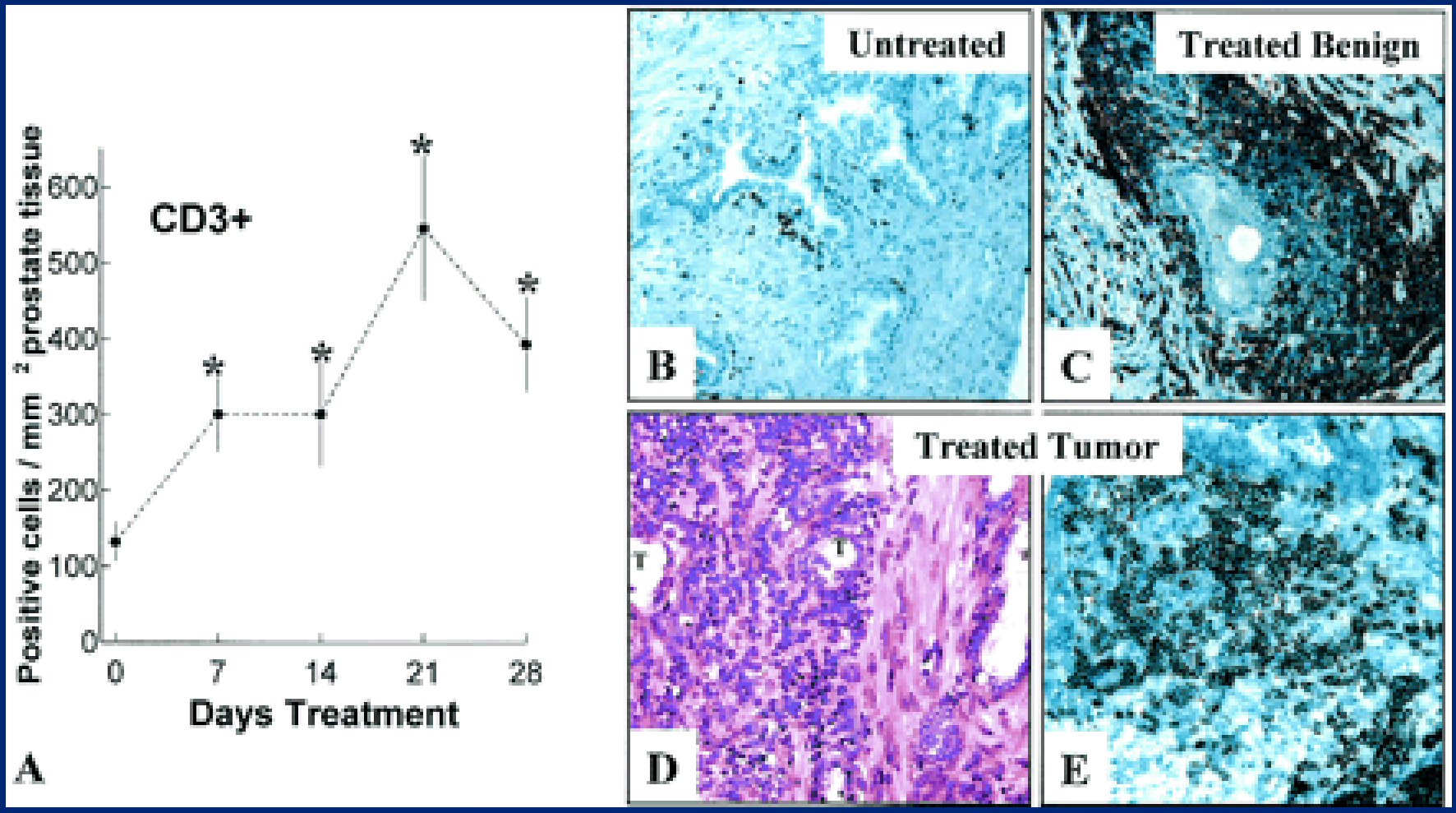
Dosing Regimens of Anti-androgen Therapy

Combination with Testosterone lowering therapy (CAB)

- Flutamide
  - 250 mg three times daily – total 750 mg per day
- Bicalutamide
  - 50 mg daily
- Nilutamide
  - 300 mg once a day for 30 days followed thereafter by 150 mg per day

T cell infiltrate after ADT

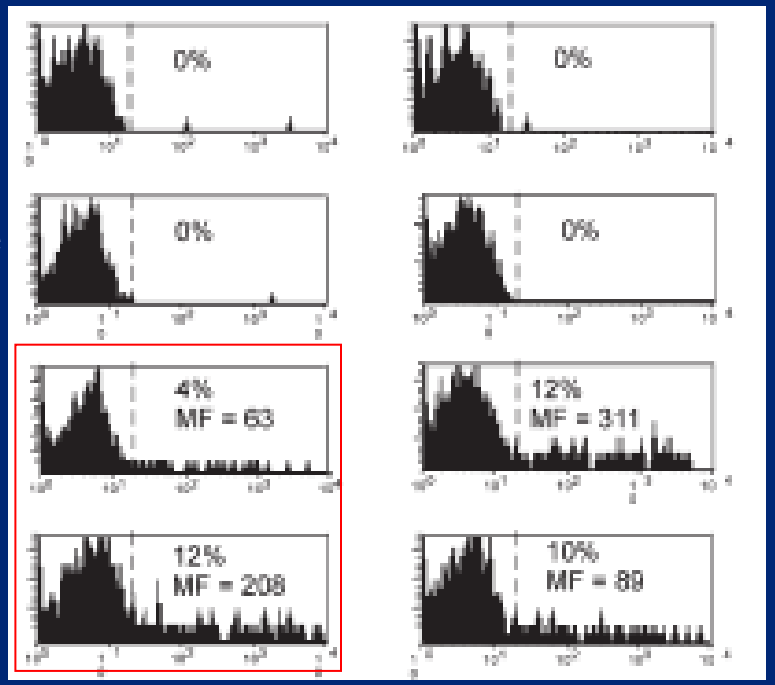


Mercader M et al. Proc Natl Acad Sci U S A 2001 Dec 4;98(25):14565-70

Androgen ablation mitigates tolerance to a prostate/prostate cancer-restricted antigen

Charles G. Drake,[1,*] Amy D.H. Doody,[2] Marianne A. Mihalyo,[2] Ching-Tai Huang,[1,3] Erin Kelleher,[1] Sowmya Ravi,[1] Edward L. Hipkiss,[1] Dallas B. Flies,[1] Eugene P. Kennedy,[1] Meixiao Long,[2] Patrick W. McGary,[2] Lee Coryell,[2] William G. Nelson,[1] Drew M. Pardoll,[1] and Adam J. Adler[2,*]

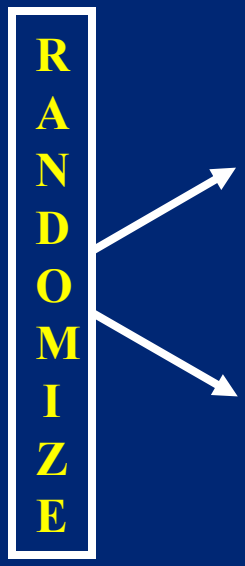
12- to 14-week-old NT or ProHA × TRAMP mice were adoptively transferred with 1 × 10^7 clonotypic HA targeted CD4 cells 1 week prior to castration. After 1 additional week, animals were challenged with vacc-HA and cells harvested 5 days later.



Cancer Cell, 2005

Vaccine/Androgen Receptor Antagonist Therapy

Patient Population: Androgen Independent Prostate Cancer with Rising PSA and No Radiographic Evidence of Disease (D = 0.5)



Arm A: Vaccine* (n=21)

rV-PSA + rV-B7-1 prime, rF-PSA boosts monthly IL-2 low dose x 5 days, recombinant GM-CSF x 4 days

Arm B: Nilutamide* (n=21)

(Androgen Receptor Antagonist)

*If patient progressed by PSA but still NED radiographically, they could add in the therapy of the other arm

Arlen, et al. J. Urol. 174:539-46, 2005

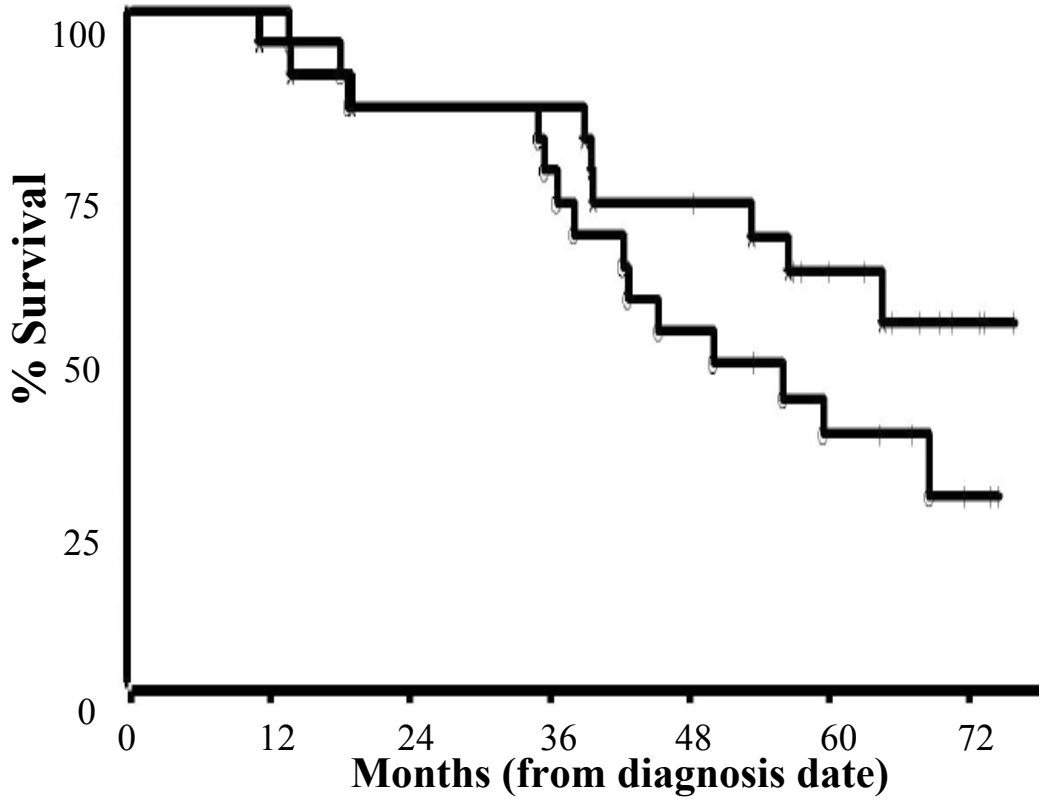
Time to Treatment Failure

Regimen	n	PSA ↓ 50%	Median Time to Treatment Failure
Vaccine	21	1	9.9 months
Nilutamide	21	10	7.6 months
Vaccine → Vaccine + Nilutamide	12	7	13.9 months (after cross-over)*
Nilutamide → Vaccine + Nilutamide	8	1	5.2 months (after cross-over)

Treatment failure includes progressive disease (radiographic or PSA), or discontinuation due to toxicity.

*Median time to cross-over was 12.0 months.

Overall Survival: Randomized Trial in Patients with Nonmetastatic HRPC Receiving Vaccine (rV-PSA/B7.1, rF-PSA) vs. Androgen Receptor Antagonist (Nilutamide) with Crossover at Progression



Five-Year Overall Survival:

38%: Nilutamide first

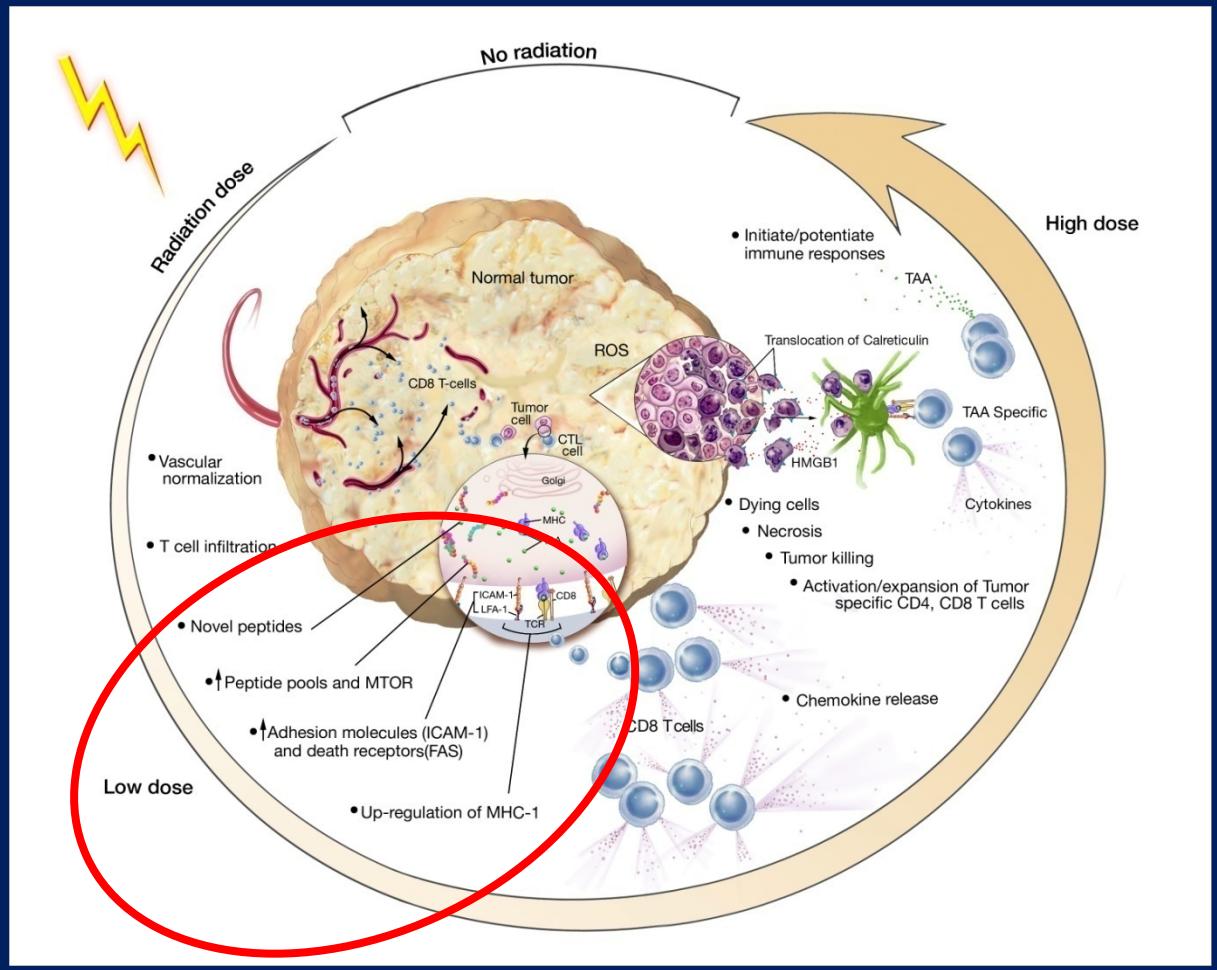
59%: Vaccine first

The Next Frontier: Vaccine Combination Therapies

The use of cancer vaccines in combination with conventional therapies

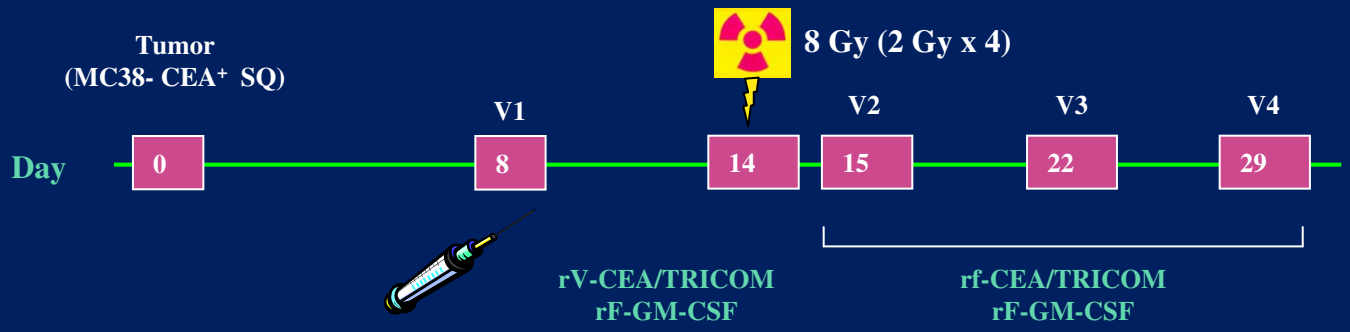
- **Hormone therapy**
- **Radiotherapy of tumor**
- **Chemotherapy**

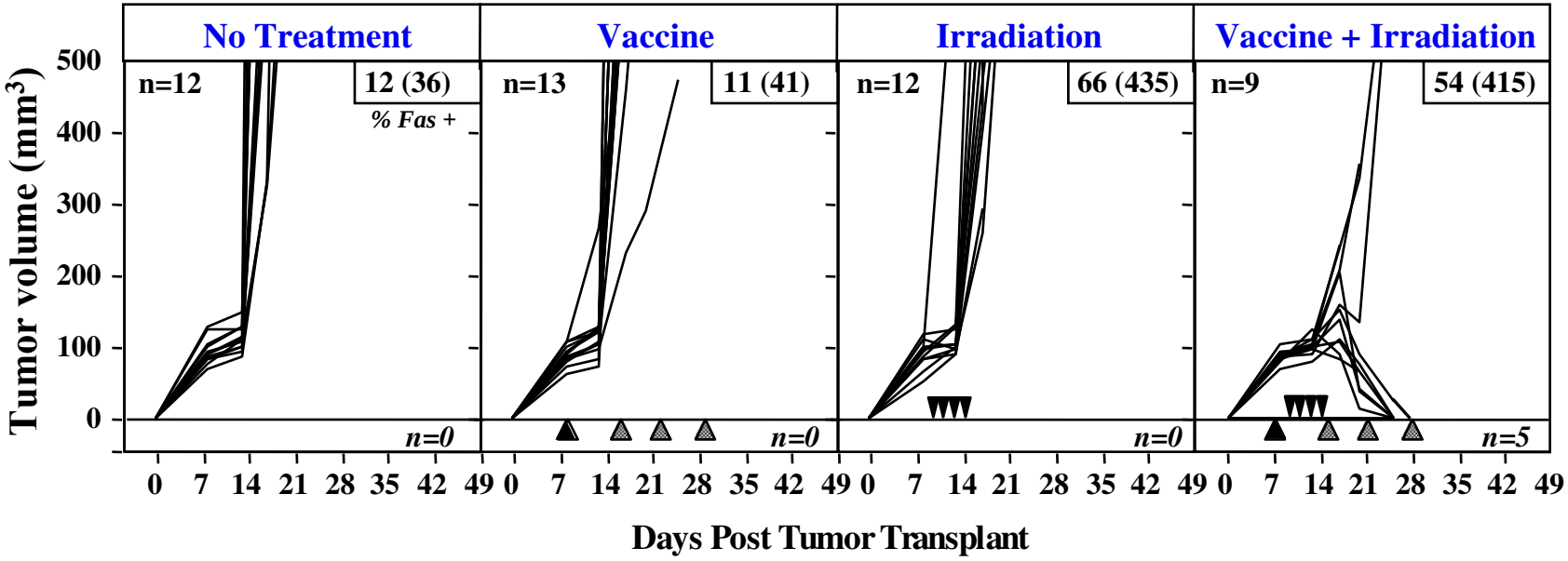
Potential Multiple Effects of Local Irradiation of Tumors



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

Combination Therapy: Vaccine + External Beam Radiation





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

Antigen Cascade (Epitope spreading)

– Generation of T-cell responses to antigens not in vaccine

Tumor Therapy Model

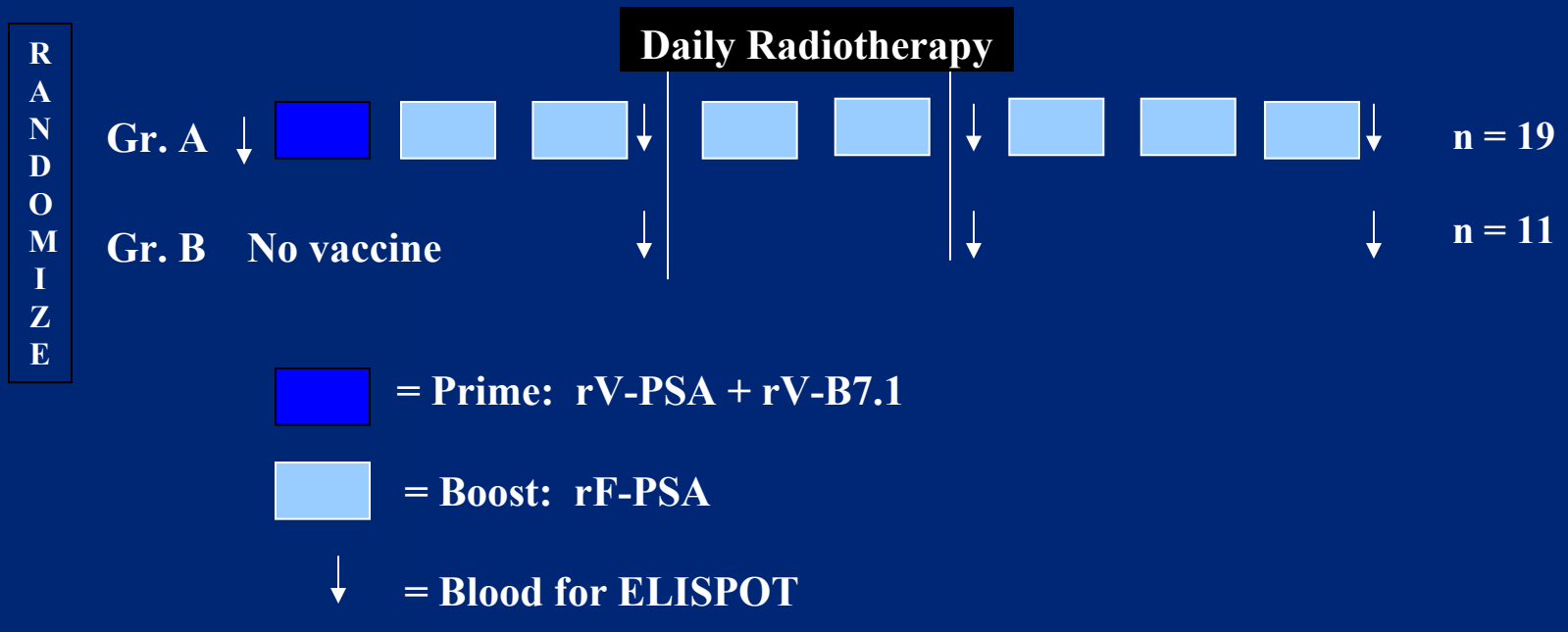
– Antigen cascade T-cell responses greater in responders (tumor cure) vs. non-responders (tumor growth)

* Cascade antigen T-cell responses
  – can be more potent than those directed against antigen in vaccine
    - clinical implications

Kudo-Saito C, Schlom J, and Hodge JW. Clin. Cancer Res. 11:2416-2426, 2005
Kudo-Saito C, Schlom J, and Hodge JW. Clin. Cancer Res. 10:1090-1099, 2004
Kudo-Saito C, Schlom J, Camphausen K, Coleman CN, and Hodge JW. Clin Cancer Res. 11:4533-4544, 2005
Chakraborty M, Abrams SI, Coleman CN, Camphausen K, Schlom J, and Hodge JW. Cancer Res. 64:4328-4337, 2004

Trial : Radiotherapy ± Vaccine

Background: ~1/3 have PD after radiation therapy, often 2° to occult metastasis
Perhaps this could be improved with a well tolerated systemic therapy (vaccine)
The addition of vaccines to radiation → minimal risk of toxicity, potential synergy
Hypothesis: Immune responses can be raised to TAA despite local RT



All vaccines given with GM-CSF and IL-2

Gulley, Arlen, …Tsang, Camphausen, Coleman, Schlom, Dahut Clin Ca Res, 11(9):3353-3362 (2005)

Immune response

- 13 of 17 evaluable patients in the vaccine arm had increases of their PSA-specific T-cells of at least 3-fold following vaccination as measured by ELISPOT assay
- None of 8 evaluable patients tested on the radiation only arm had any measurable increase in their PSA-specific T-cells ($p<0.0005$)
- Hypothesis: Effective immune mediated killing → induction of immune response to prostate cancer antigens not in the vaccine (prior to RT).
- 6/8 pts tested had ≥2-fold increase in immune response to PAP, PSMA, PSCA and / or MUC-1
- Cells isolated from a pt who had both MUC-1 and PSA responses could specifically lyse PSA or MUC-1 containing tumors

Gulley, Arlen, …Tsang, Camphausen, Coleman, Schlom, Dahut Clin Ca Res, 11(9):3353-3362 (2005)

Antigen Cascade

Patient	Sample	PSA3	PSMA	PAP	PSCA	MUC-1
Pt 3	pre vac	-	-	-	-	-
	post 3	+	-	+	+	+
Pt 6	pre vac	-	-	-	-	-
	post 3	+	+	-	-	+
Pt 7	pre vac	-	-	-	-	-
	post 3	+	-	+	-	-
Pt 8	pre vac	-	-	-	ND	-
	post 3	+	+	-	ND	+
Pt 11	pre vac	-	-	-	-	-
	post 3	+	-	-	-	+
Pt 12	pre vac	-	-	-	-	-
	post 3	+	-	-	-	+

Controls:

Flu

HIV

No peptide

The Next Frontier: Vaccine Combination Therapies

The use of cancer vaccines in combination with conventional therapies

- **Hormone therapy**
- **Radiotherapy of tumor**
- **Chemotherapy**

Mode of Action of Vaccine Combination Therapies

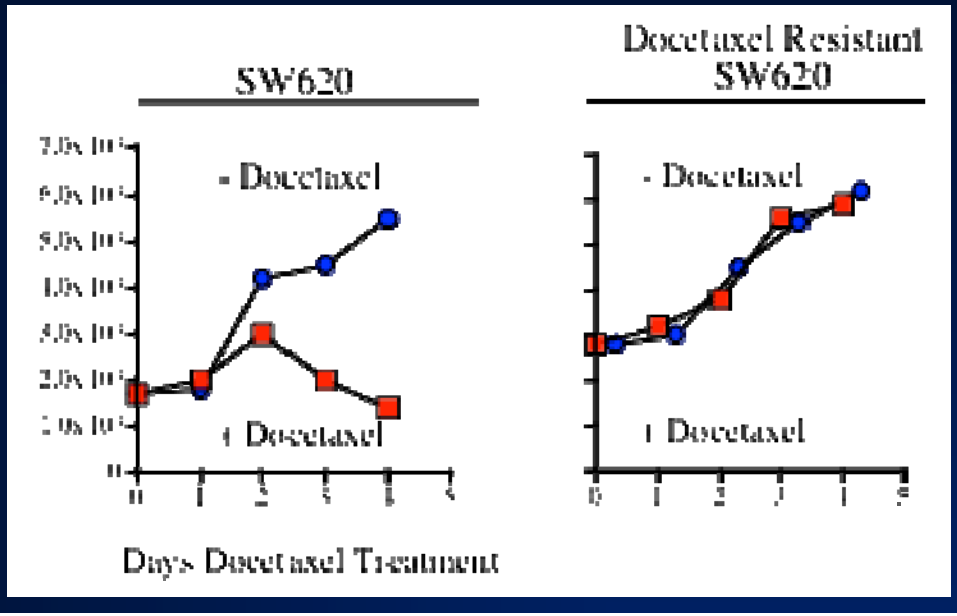
- Exploitation of the phenomenon of homeostatic proliferation of T cells post-chemotherapy

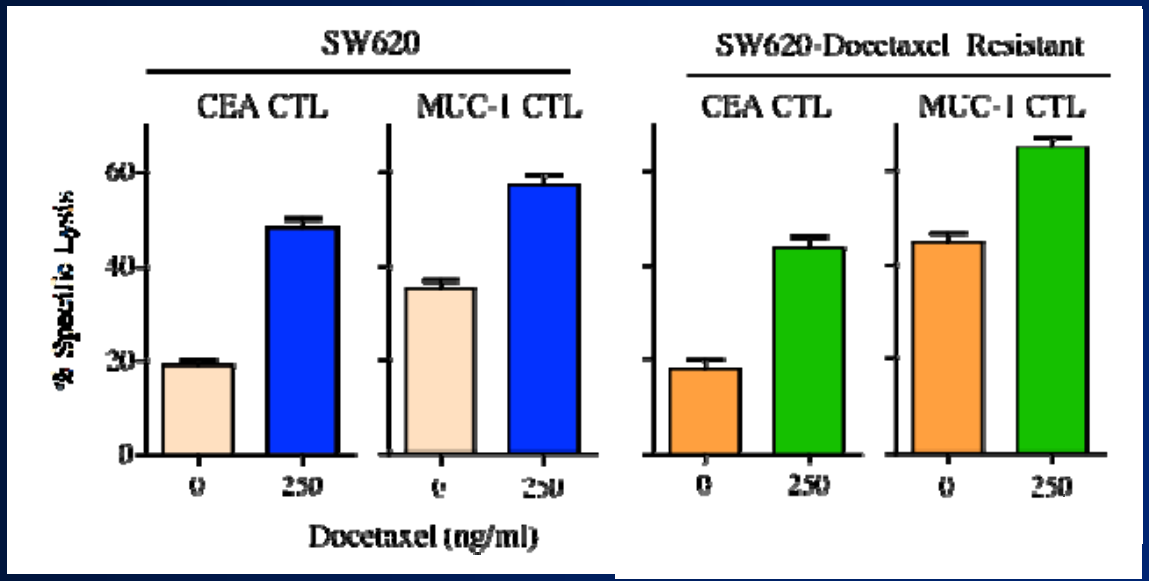
  — certain effector immune cell subsets can be expanded more rapidly vs. regulatory cells

- Evidence of non-coordinate lytic susceptibility of tumor cells

  — tumor cells have shown differential susceptibilities to killing by chemotherapy/radiation vs. T cells

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



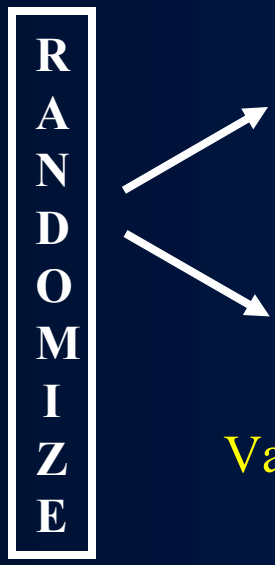


Vaccine/Docetaxel Combination Therapy

Patient Population: Metastatic Androgen Independent Prostate Cancer (AIPC)

Primary endpoint: Fold change in PSA specific T-cell precursors post-vaccine

Secondary endpoints: Change in PSA velocity after 3 months, median time to disease progression



Arm A: Vaccine + Docetaxel (n=14)

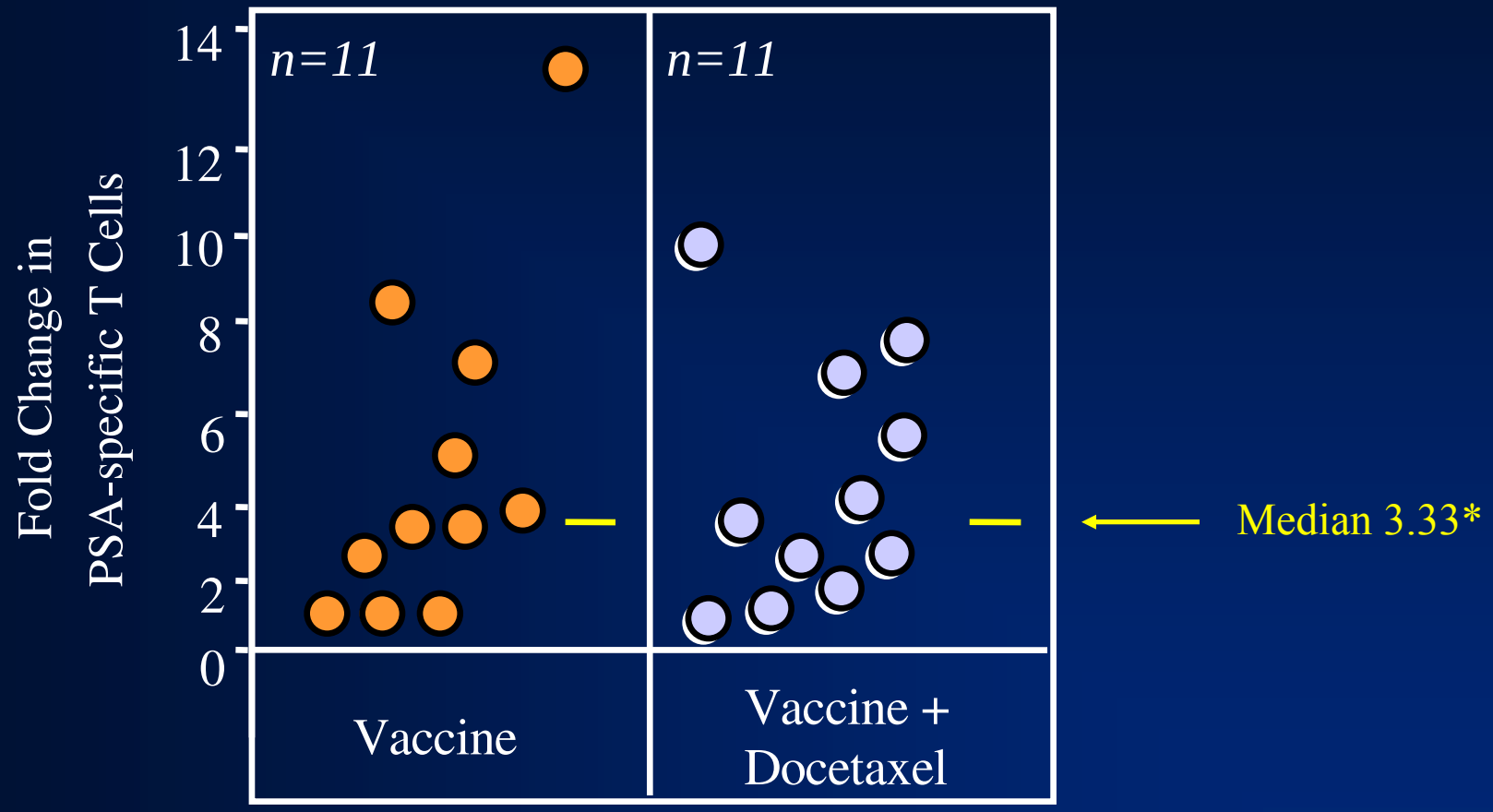
Arm B: Vaccine alone (n=14)*

Vaccine: rV-PSA + rV-B7.1 prime on day 1;
rF-PSA boosts on days 15, 30, and 58

*At time of PD, vaccine could be stopped and docetaxel added.

Arlen, Gulley…Tsang…Steinberg…Schlom, and Dahut.
Clin. Cancer Res. 12:1260-1269, 2006

Fold Increase in PSA-specific T Cells post Vaccination for Patients Receiving Vaccine vs. Vaccine plus Docetaxel (plus Steroid)



*p = 0.92 using Wilcoxon Sum Rank Test

Vaccine/Docetaxel Combination Therapy

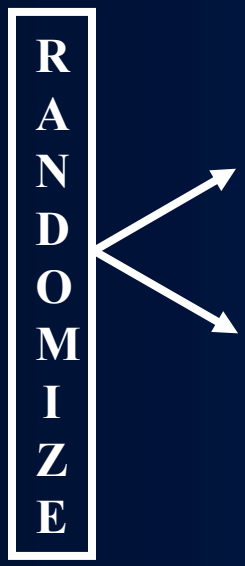
Time to Progression

Regimen	n	>50% PSA decline	Median time to progression
Vaccine alone	14	0/14 (0%)	1.8 months
Vaccine + docetaxel	14	3/14 (21.4%)	3.2 months
Docetaxel post-progression on vaccine	11	5/11 (45.5%)	6.1 months
Docetaxel alone*	25	9/24 (37.5%)	3.7 months

*Historical control with same dose and schedule of docetaxel in similar patient population at same institution (Dahut et al., J. Clin. Oncol. 2004)

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)

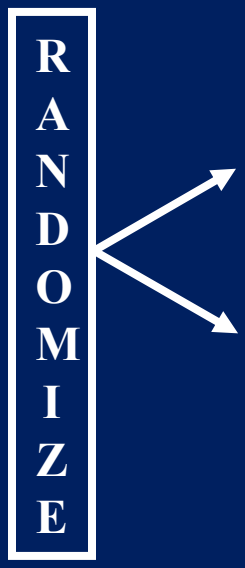
Arm B: Docetaxel + Prednisone (n=45)

Phase II (n=135)
Primary endpoint: OS

Protocol Chair: Doug McNeel
Co-Chair: Gulley

Docetaxel +/- PANVAC

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



Arm A: Weekly Docetaxel + PANVAC

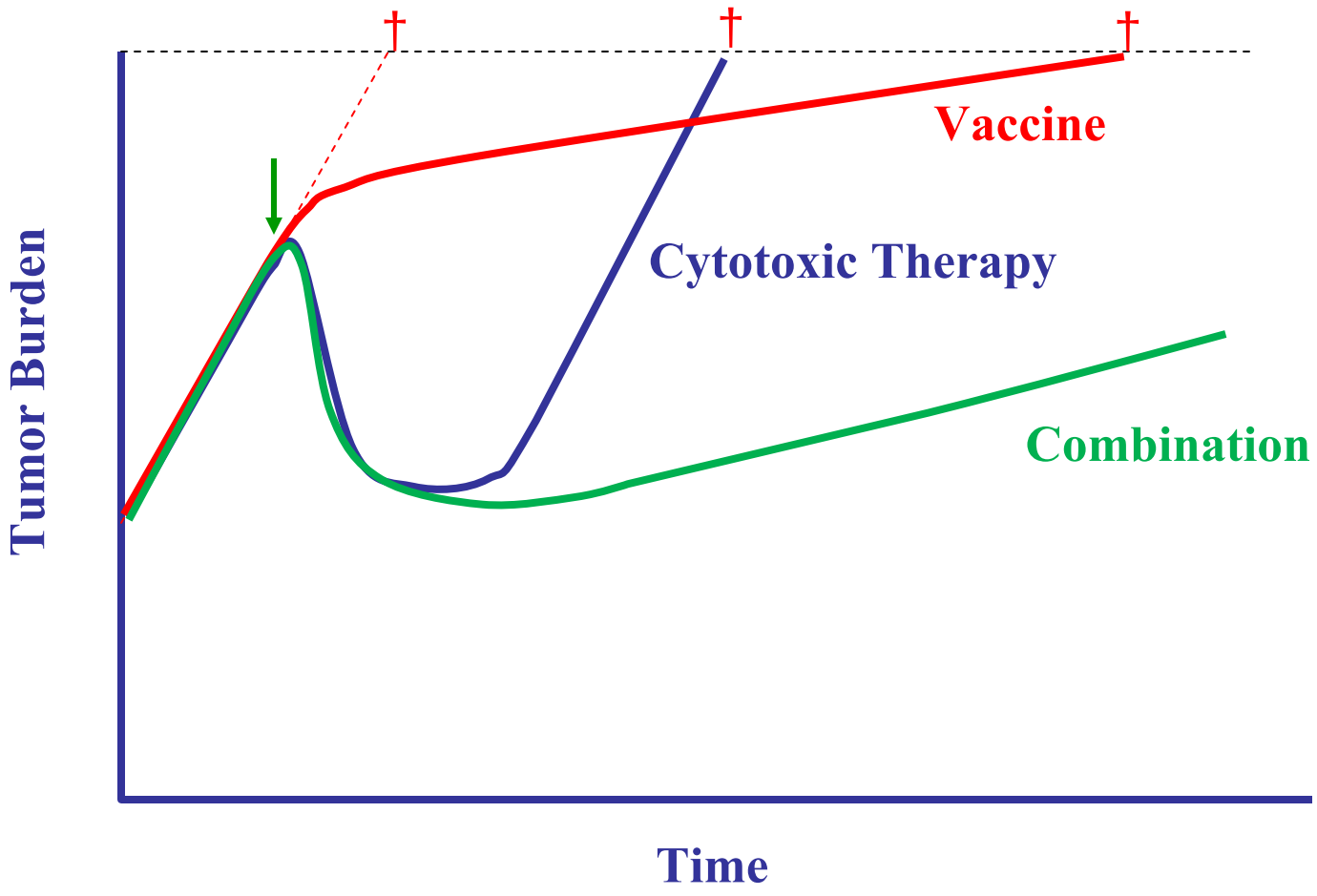
Arm B: Weekly Docetaxel alone

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

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, Alain Delcayre
Merck/EMD Serono – Helen Sabzevari , Jens-Oliver Funk

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

NIH Office of Technology Transfer: Sabarni Chatterjee, Mojdeh Bahar