



Development of Recombinant Vaccines for the Therapy of Carcinomas

Monotherapy and Combination Therapy

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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

Immunologic 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

Al Tsang

Claudia Palena

Jack Greiner

Connie Rogers

Benedetto Farsaci

Sofia Gameiro

Matteo Vergati

Mary Litzinger

Ken Hance

Laboratory of Molecular Biology

Ira Pastan

Vaccine Branch

Jay Berzofsky

CLINICAL STUDIES:

LTIB/Medical Oncology Branch

James Gulley

Philip Arlen

Ravi Madan

Mary Pazdur

Medical Oncology Branch

William Dahut

Tito Fojo

William Figg

Radiation Oncology

Kevin Camphausen

Urologic Oncology

Marston Linehan

Peter Pinto

Biostatistics and Data Management Section

Seth Steinberg

NIH Nuclear Medicine

Jorge Carrasquillo

C.H. Park

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

Eastern Cooperative Oncology Group (ECOG) – Robert DiPaola,
Howard Kaufman, Louis Weiner

CANCER THERAPY EVALUATION PROGRAM (CTEP):

Howard Streicher

Jan Casadei

PRIVATE SECTOR:

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

NCI Technology Transfer Center: Kevin Brand, Karen Maurey

NIH Office of Technology Transfer: Mojdeh Bahar

Strategies to Enhance Vaccine Potency

1. Mode of Delivery of the Vaccine
 - place the gene for the tumor antigen into a vector
2. Diversified Vaccine Prime and Boost
3. T-cell Costimulation
 - these molecules are essential for vigorous T-cell activation
 - place costimulatory molecule into vaccine vector
4. Alter the a.a. sequence of the tumor antigen to enhance the immune response “epitope enhancement”
5. Combination therapies

Vaccine Platforms

- ❖ Recombinant poxviruses
 - vaccinia; (MVA)
 - fowlpox
- ❖ Recombinant *saccharomyces* (yeast)
- ❖ Chitosan / nanoparticles

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

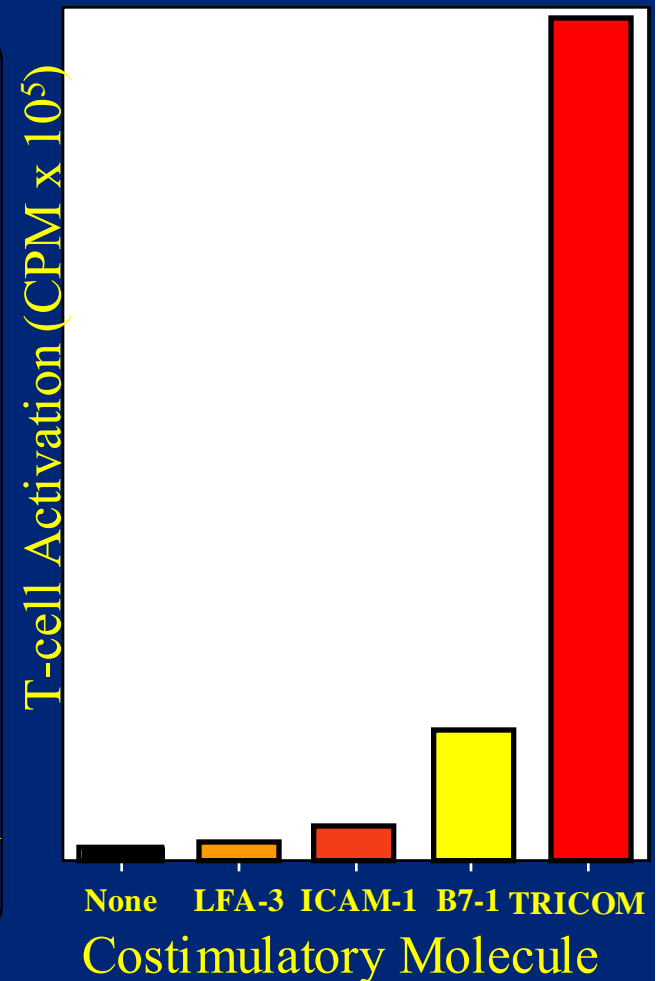
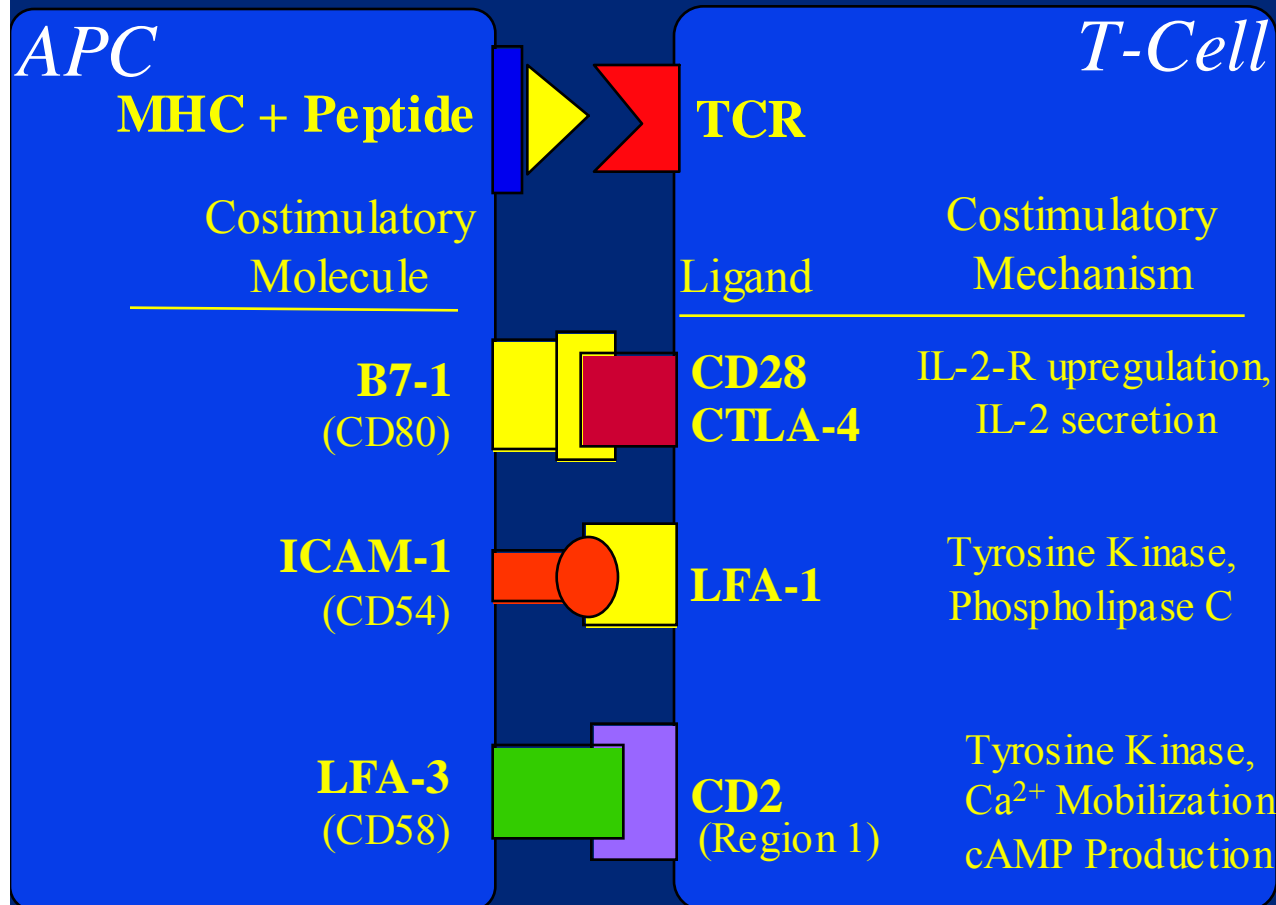
- **Can insert multiple transgenes**

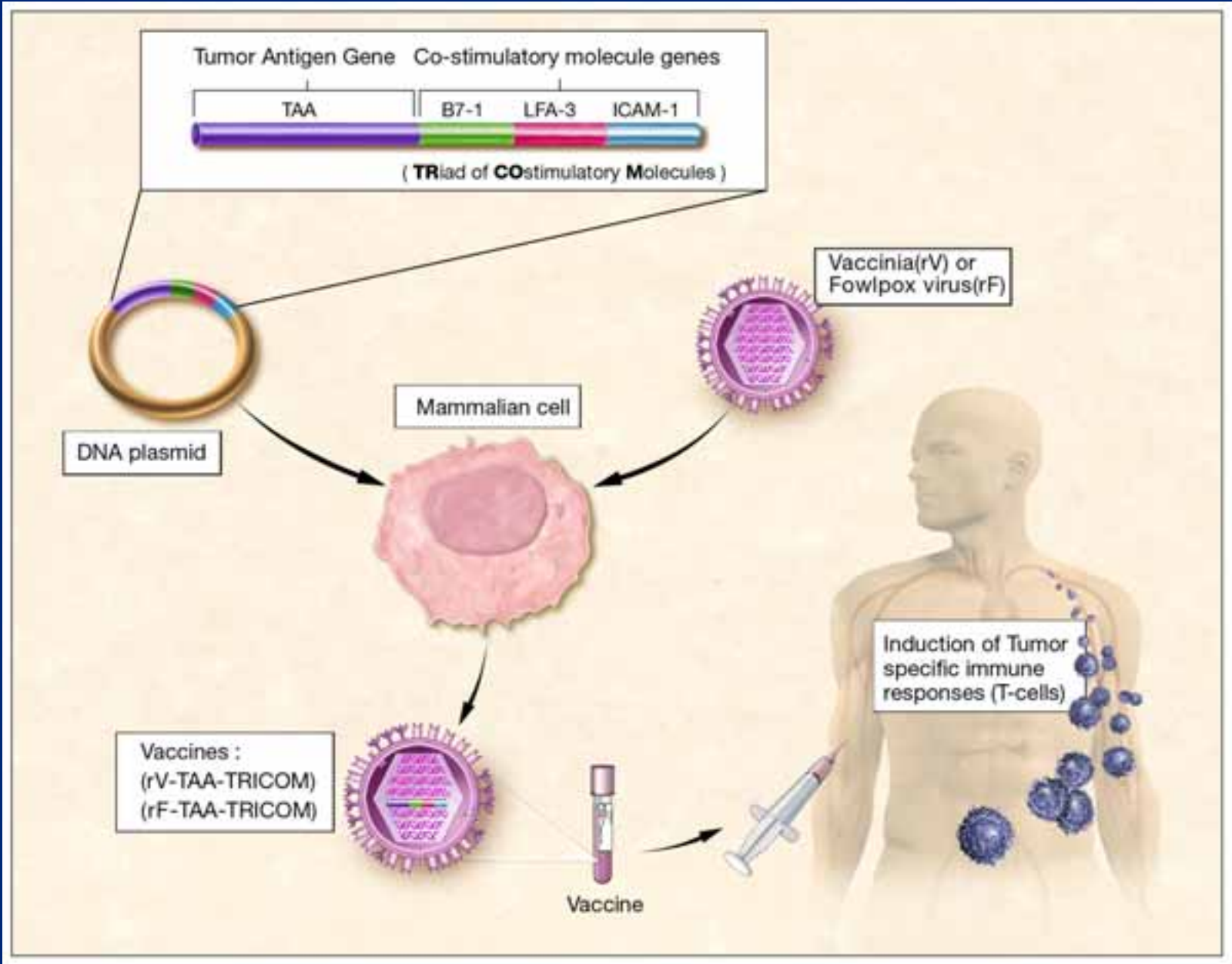
- Do not integrate into host DNA

- Efficiently infect antigen presenting cells including dendritic cells

Costimulatory Molecule Candidates:

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





TRICOM

TRIad of COstimulatory Molecules

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

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

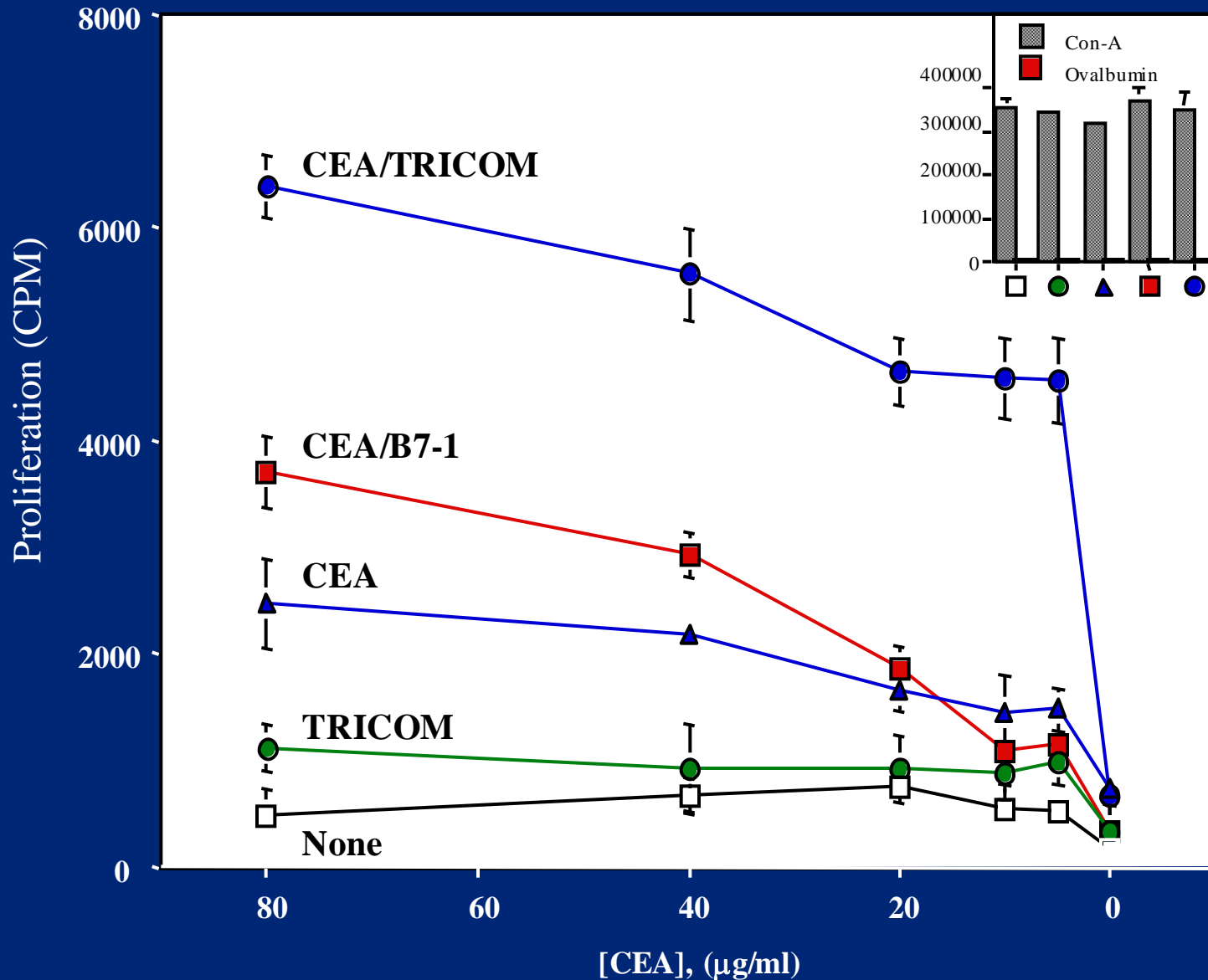
CEA/TRICOM = CEA/B7-1/ICAM-1/LFA-3

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

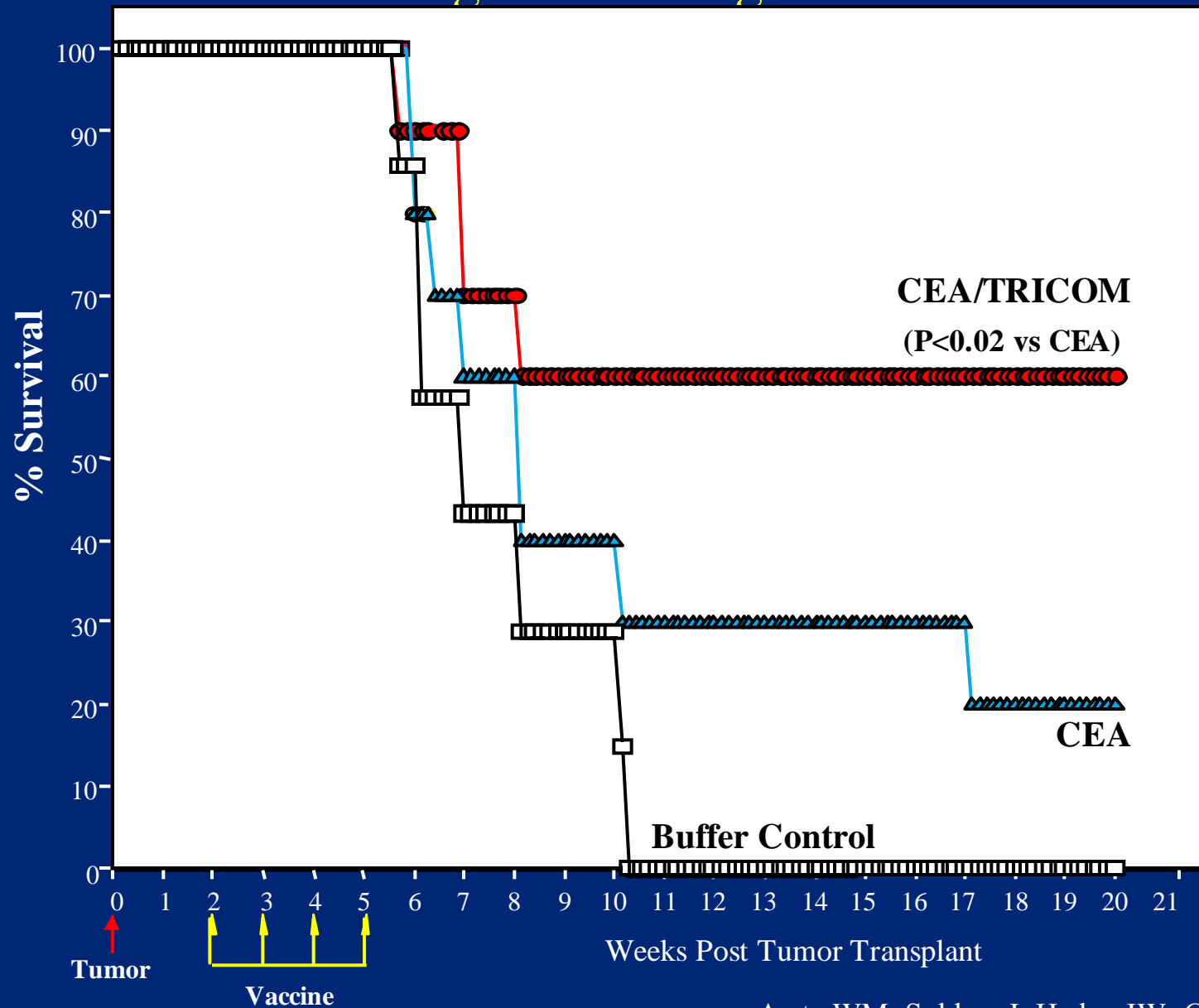


VAAA Regimen

CEA
CEA/B7-1
CEA/TRICOM
TRICOM

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

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

The Next Frontier: Combinatorial 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

Vaccine Combination Therapies

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

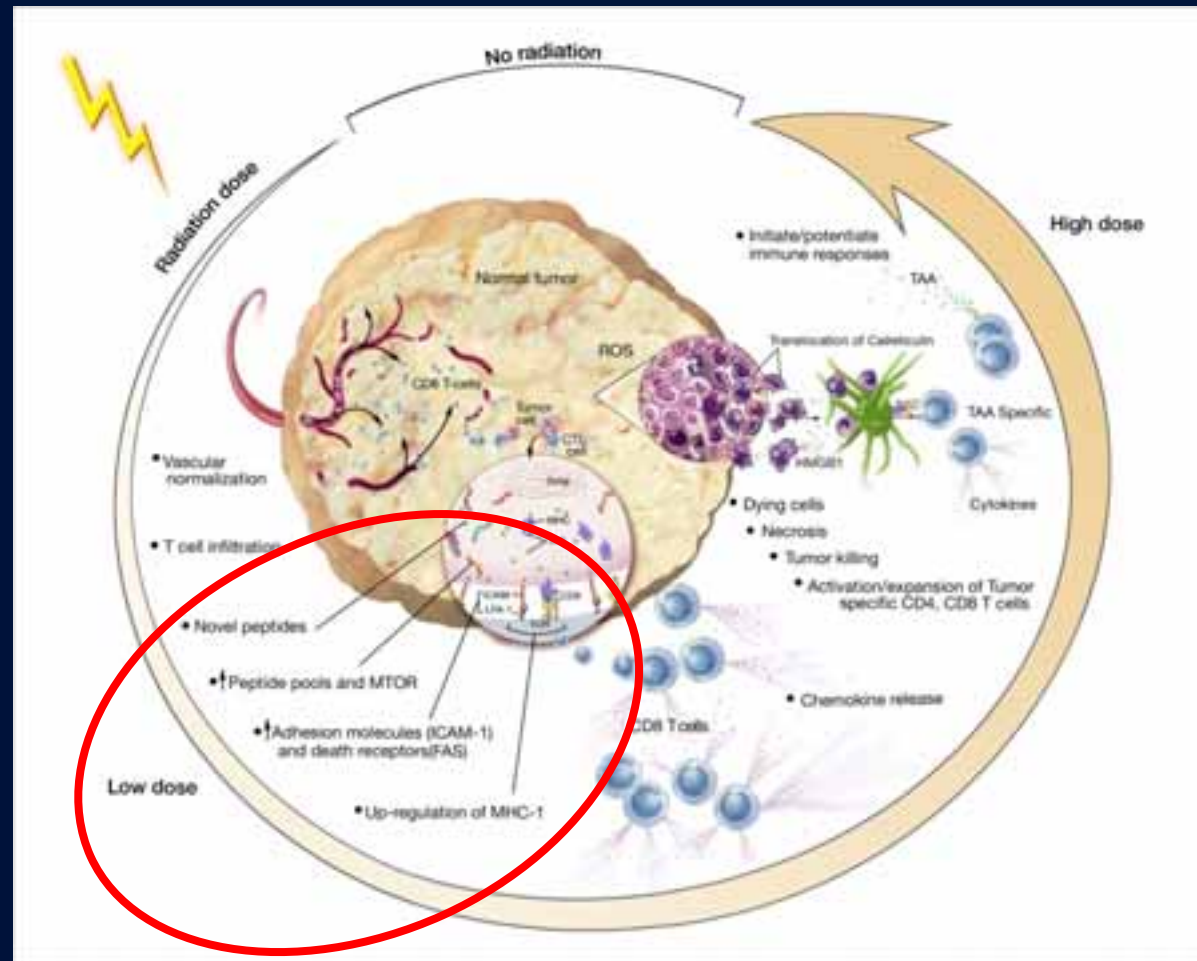
– concomitant or subsequent therapies

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

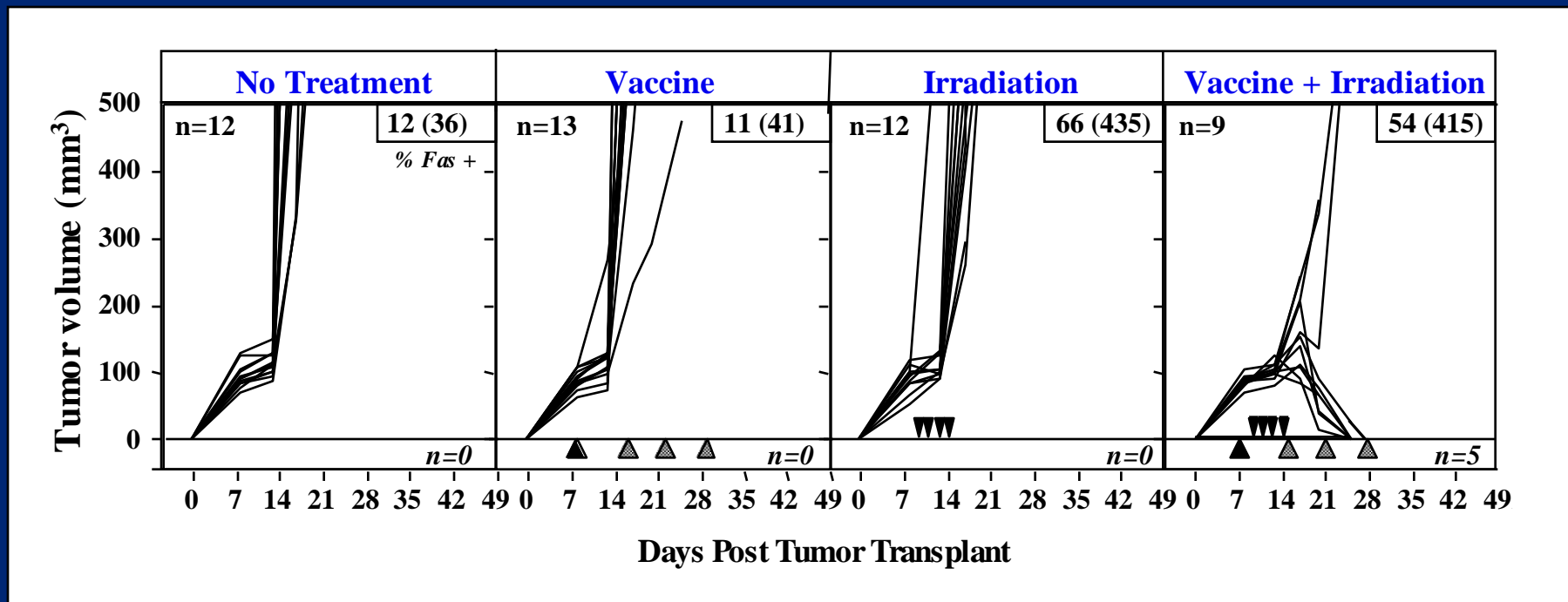
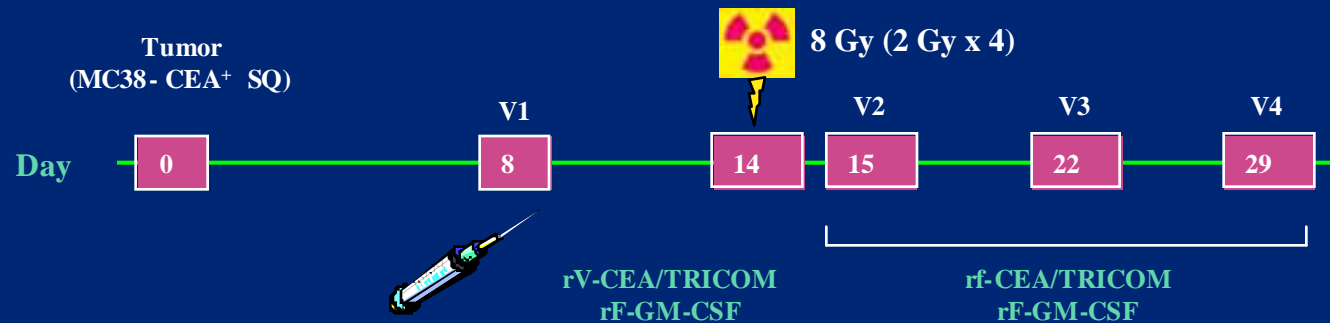
(b) can lyse populations of tumor cells which, in turn, act as a booster for tumor-specific immune cells

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

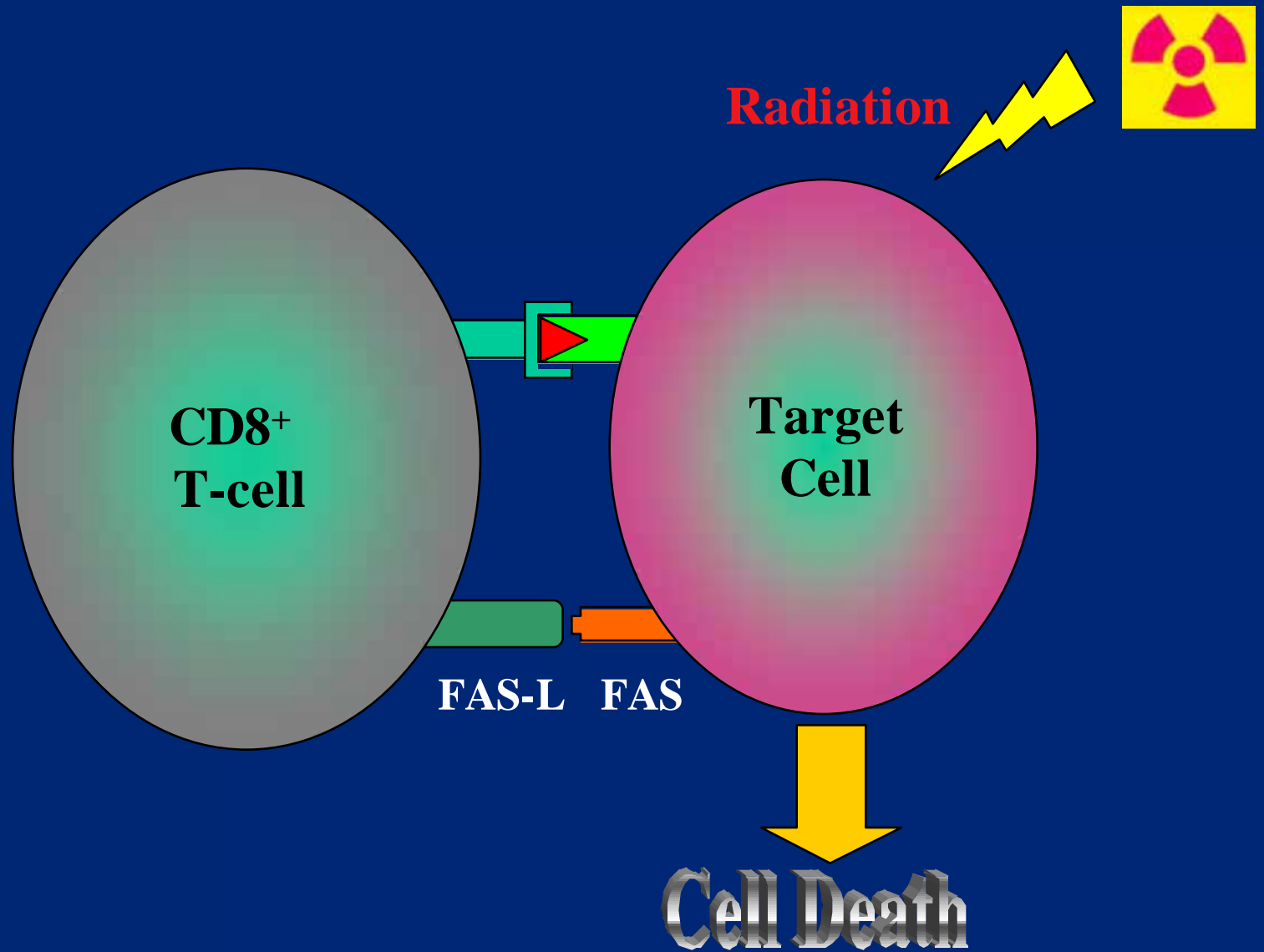
Potential Multiple Effects of Local Irradiation of Tumors



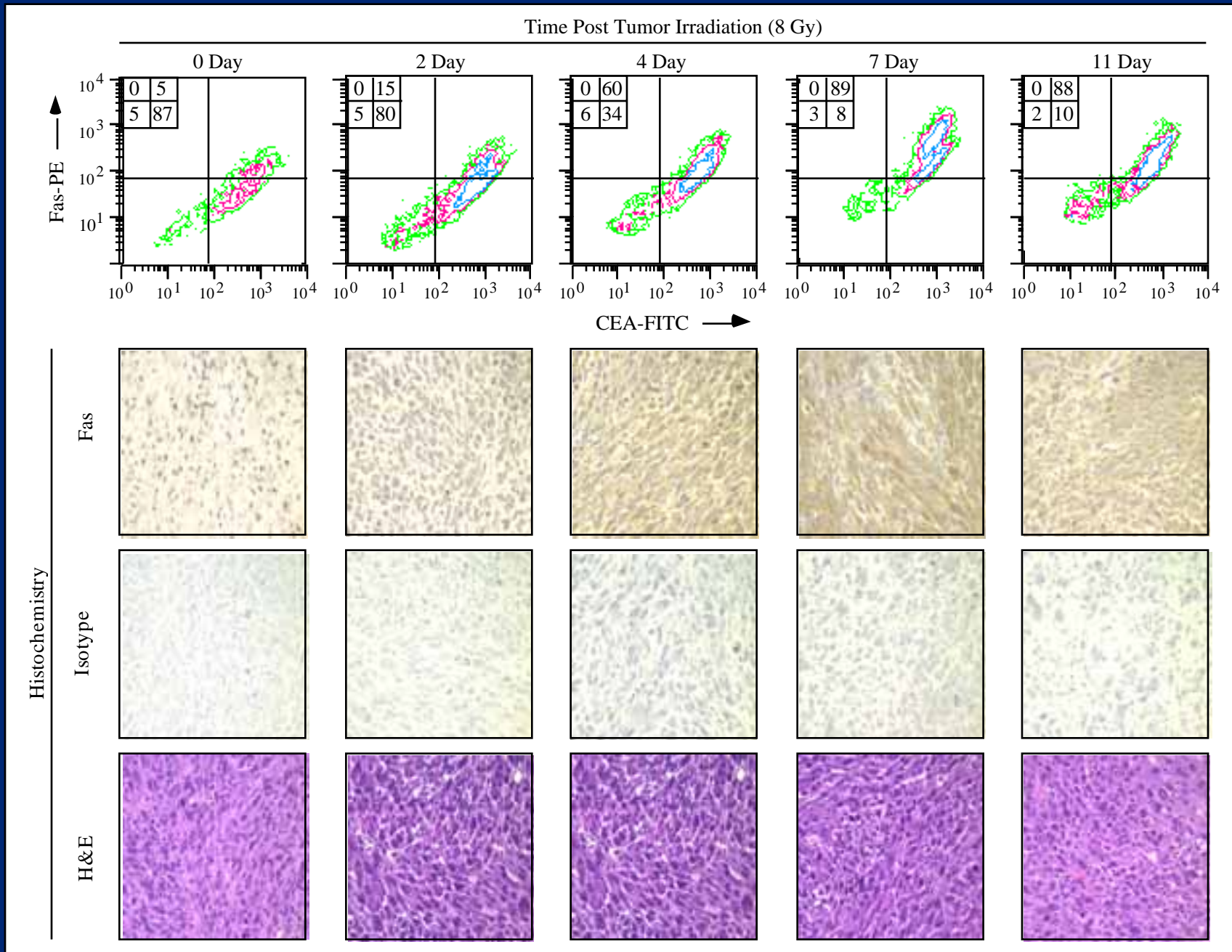
Combination Therapy: Vaccine + External Beam Radiation



Radiation-Enhanced Antigen-Specific Lysis of Tumor Cells



Persistence of Fas Upregulation on MC38-CEA⁺ Tumors After External-Beam Irradiation



QUADRAMET is a therapeutic agent consisting of radioactive samarium (^{153}Sm) and chelator.

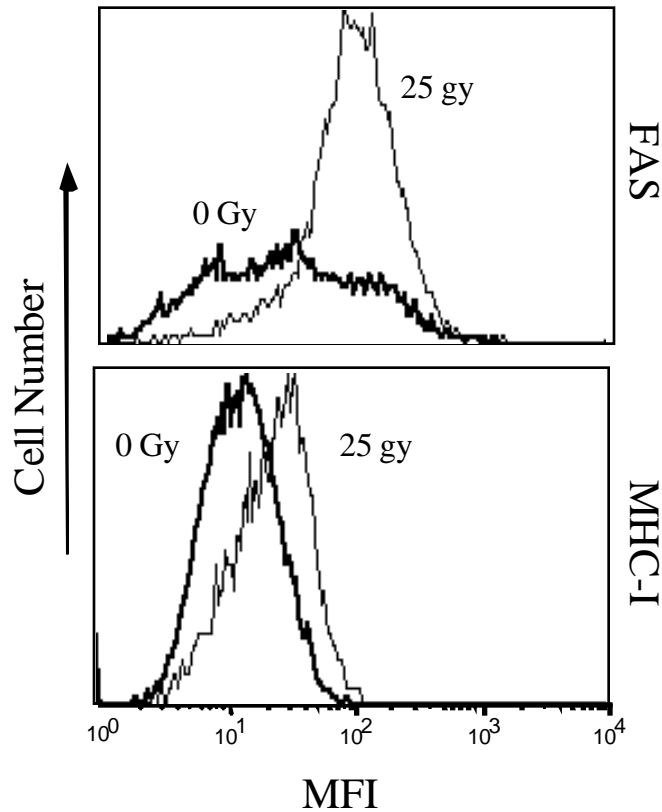
It preferentially binds to osteoblastic metastatic tumor deposits in bone.

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



Low Dose Radiation (25 Gy) of LnCaP Human Prostate Cell Line

Treatment of LnCaP prostate cancer cells with low dose radiation results in the upregulation of MHC and Fas



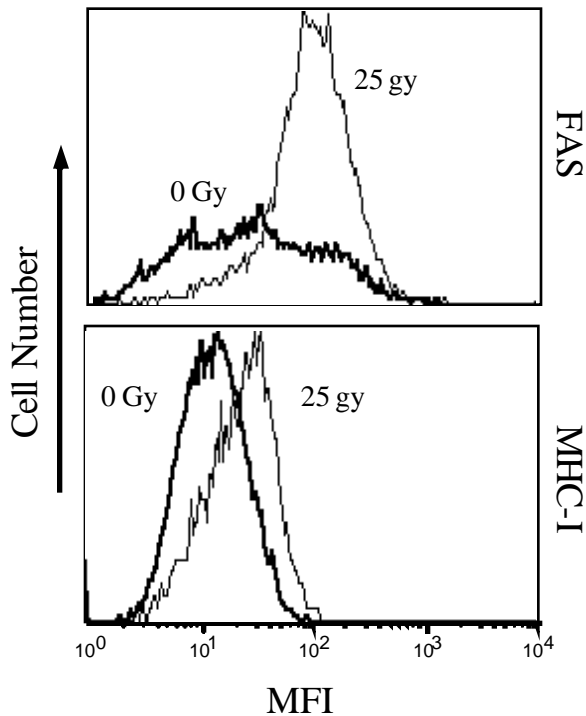
Gene Expression in LnCaP cells RT-PCR

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 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

Gene Expression in LNCaP cells after Sm-153 treatment

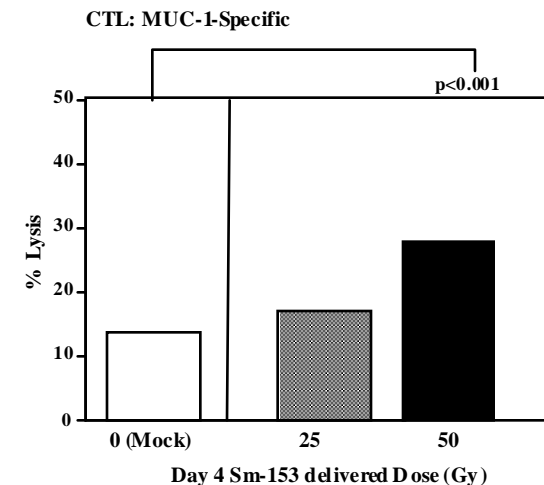
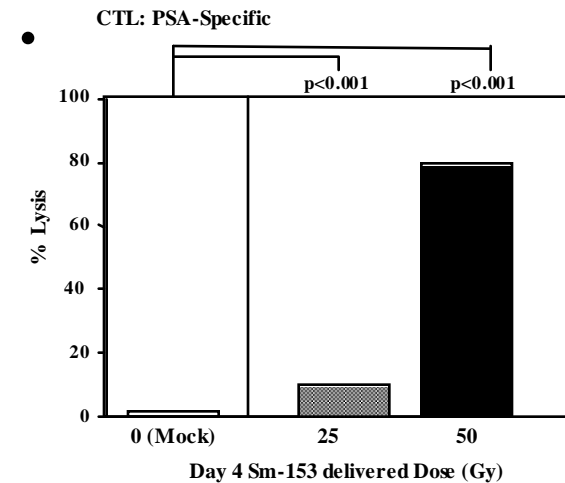
Accessory Genes

	0 Gy	25 Gy
Fas	1	1.96
ICAM-1	1	29.1

Tumor Antigen Genes

	0 Gy	25 Gy
PSA	1	2.79
MUC-1	1	3.67

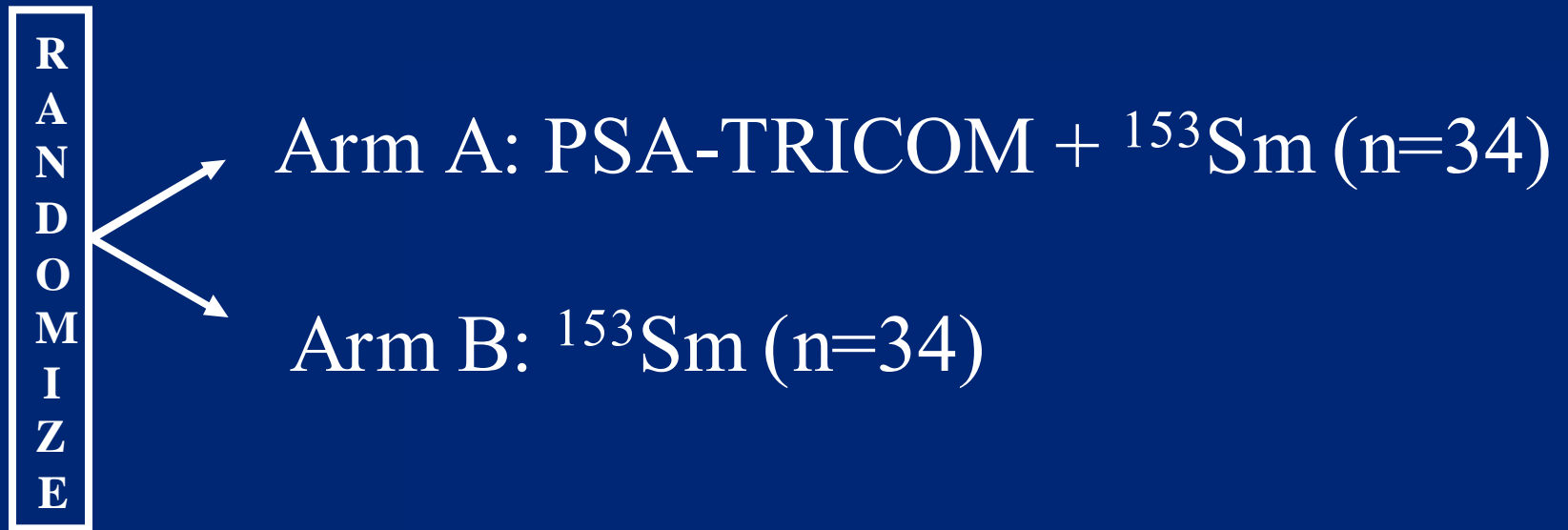
Treatment of LnCaP prostate cancer cells with Palliative doses of ^{153}Sm results in increased sensitivity to multiple CTLs



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

PSA-TRICOM + ^{153}Sm

Patient Population: Metastatic Androgen Independent Prostate Cancer

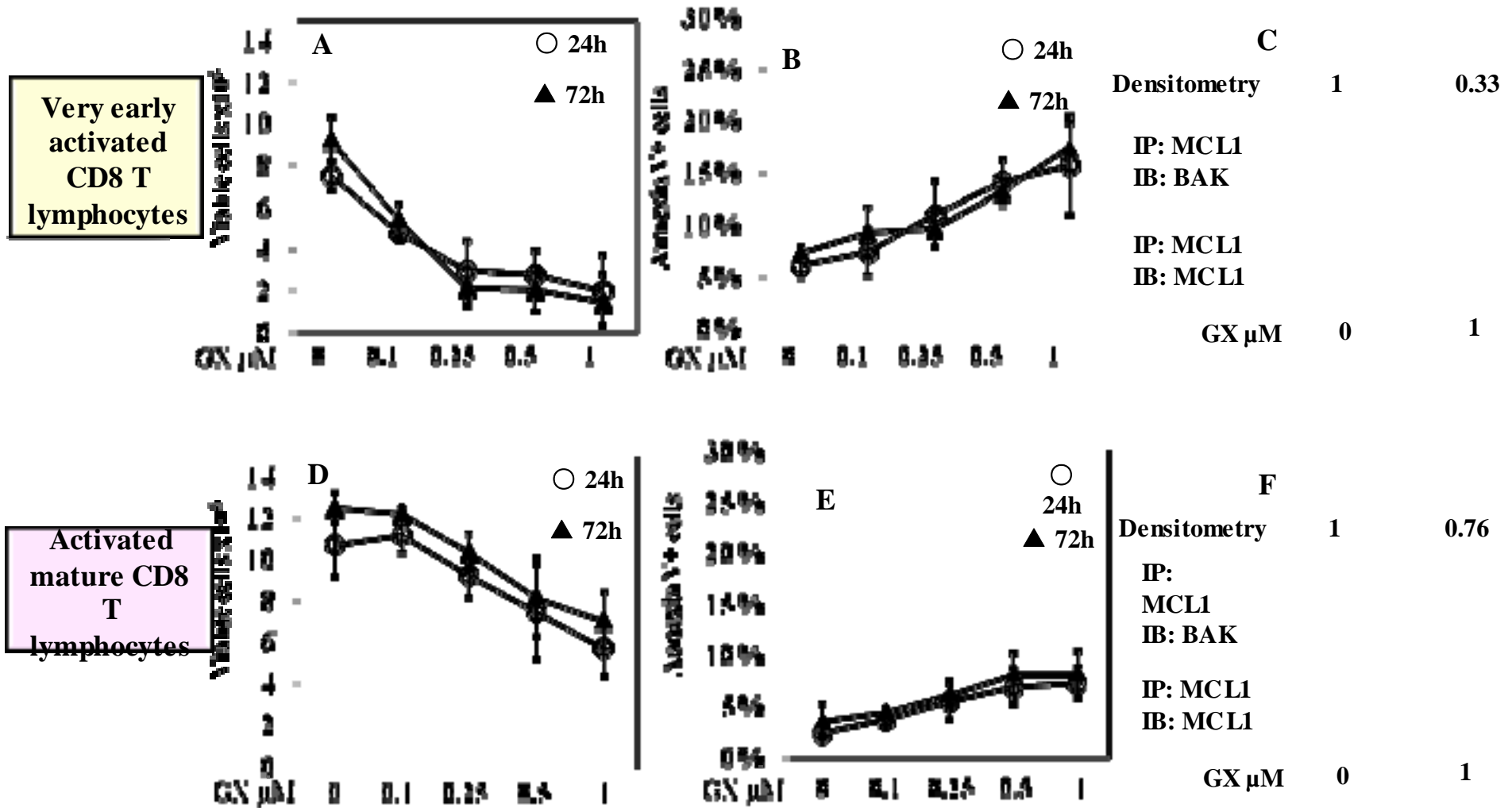


Vaccine: rV-PSA/TRICOM s.c. d 1
rF-PSA/TRICOM s.c. d 15, 29, q 4 wks
All vaccines given with GM-CSF 100 μg s.c. x 4 d

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

**Effect of the *pan* Bcl-2 Inhibitor GX15-070
on the Immune System:
Preclinical Studies**

Activated mature CD8 T lymphocytes are more resistant to GX15-070 than very early activated



- NON *SELF*-CEA LUNG TUMOR MODEL (C57BL/6 MICE)

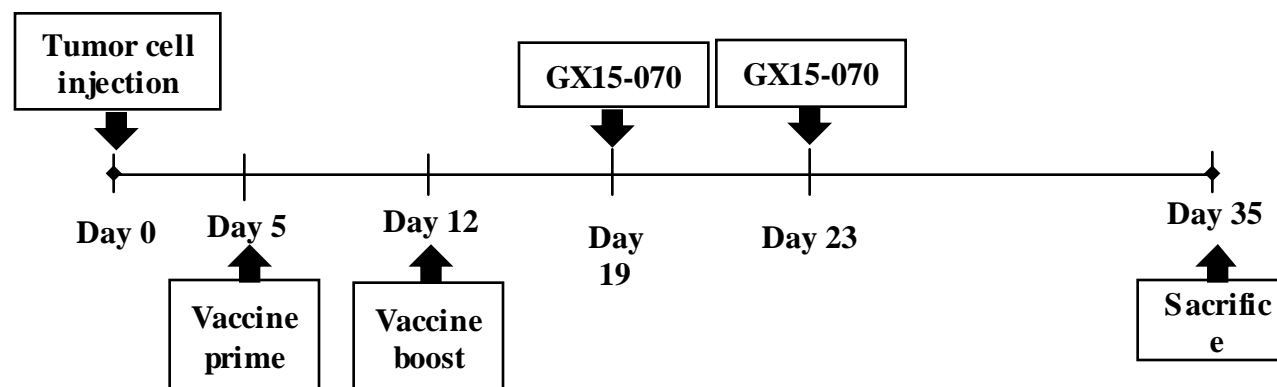
- *SELF*-CEA LUNG TUMOR MODEL (CEA-TG MICE)

Experimental setup

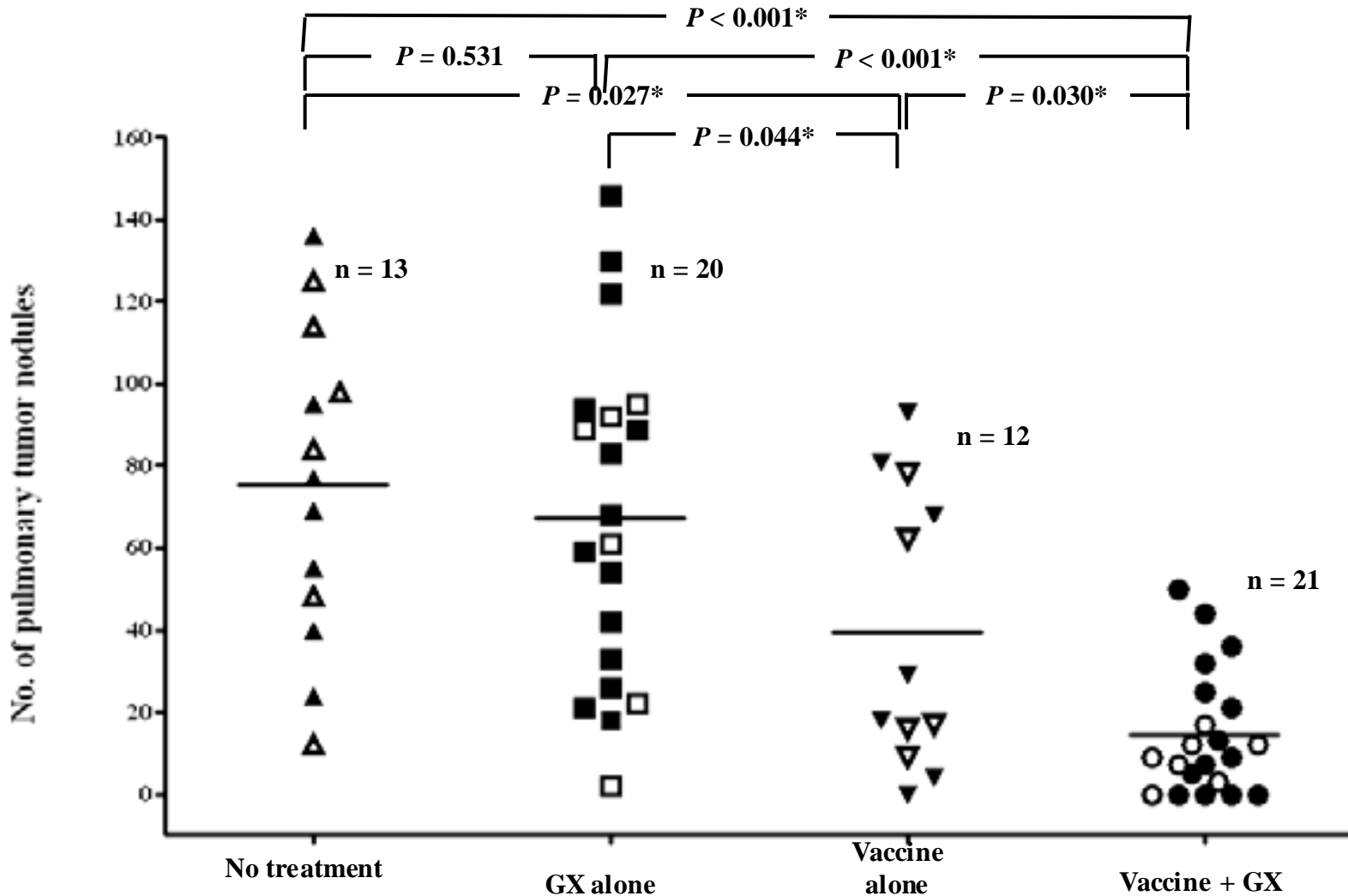
- Mice: C57BL/6 or CEA-Tg, female
- Tumor cells: LL2-CEA 3×10^5 cells/mouse (i.v.)
- Type of tumor model: Pulmonary tumor nodules
- Vaccine prime: PFU 1×10^8 rV CEA-TRICOM + PFU 1×10^7 rF GM-CSF / mouse (s.c.)
- Vaccine boost: PFU 1×10^8 rF CEA-TRICOM + PFU 1×10^7 rF GM-CSF / mouse (s.c.)
- Inhibitor: GX15-070 0.5 or 2 mg/Kg/mouse (i.v.)
- Groups (6 mice/group):
 1. No treatment
 2. GX15-070 alone
 3. Vaccine alone
 4. Vaccine + GX15-070

Assays

- IFN- γ production from splenocyte bulk cultures
- Pulmonary tumor nodules count

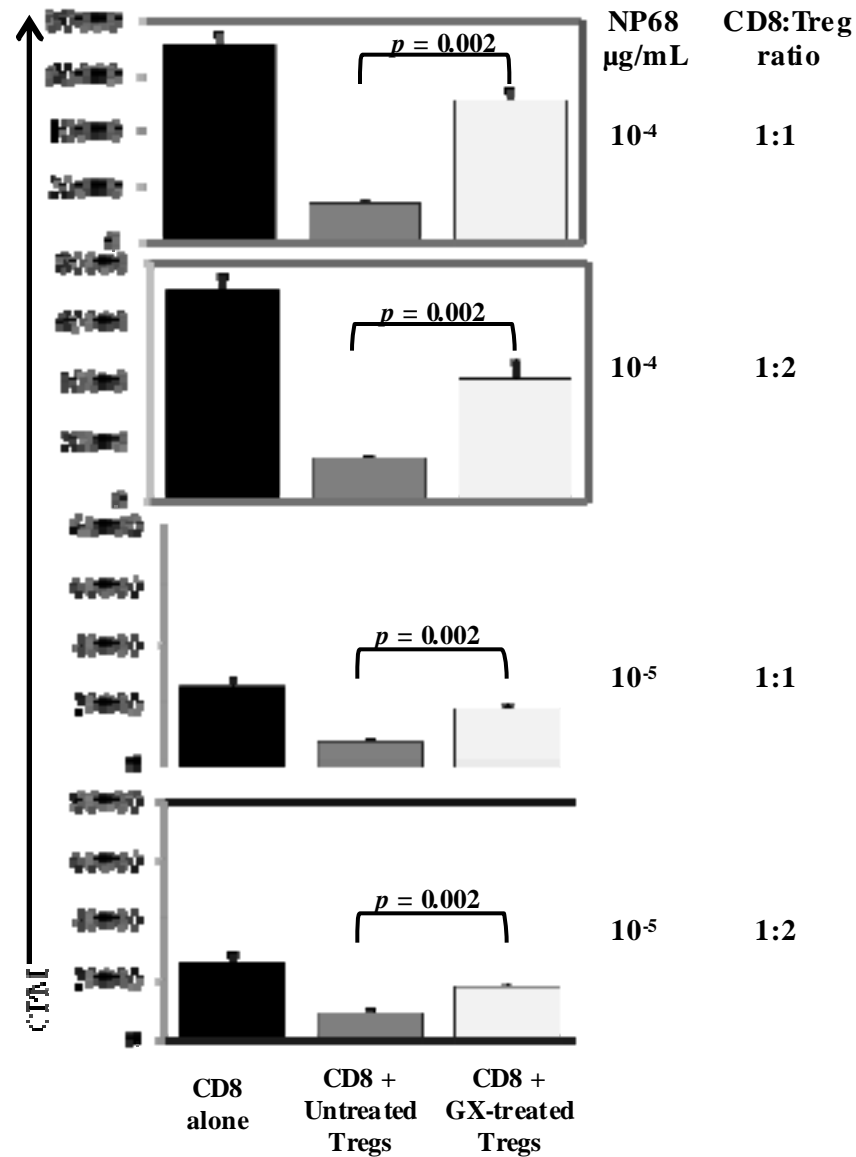


Pulmonary tumor meta-analysis

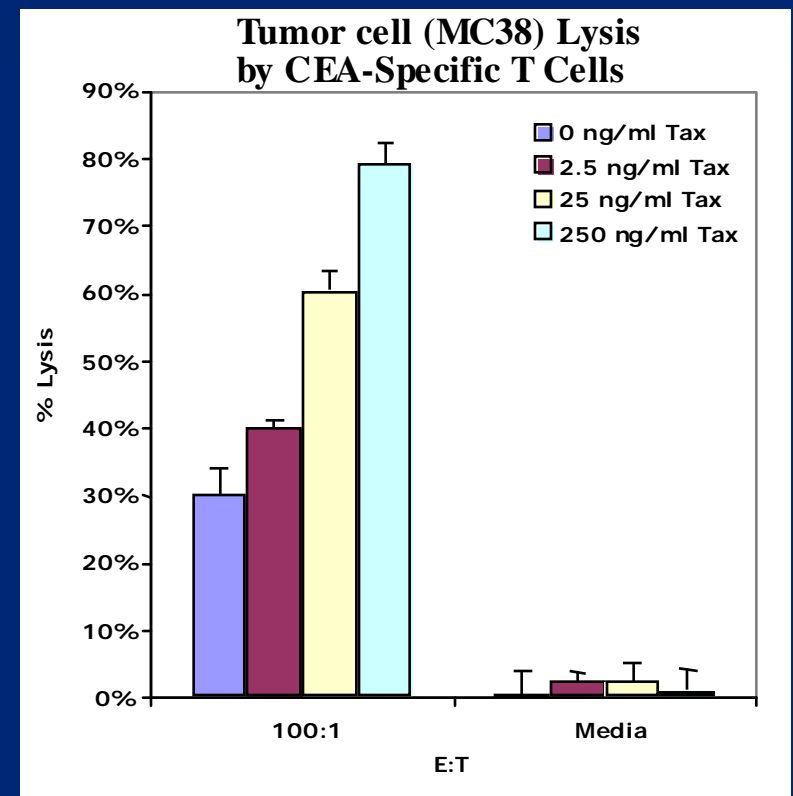
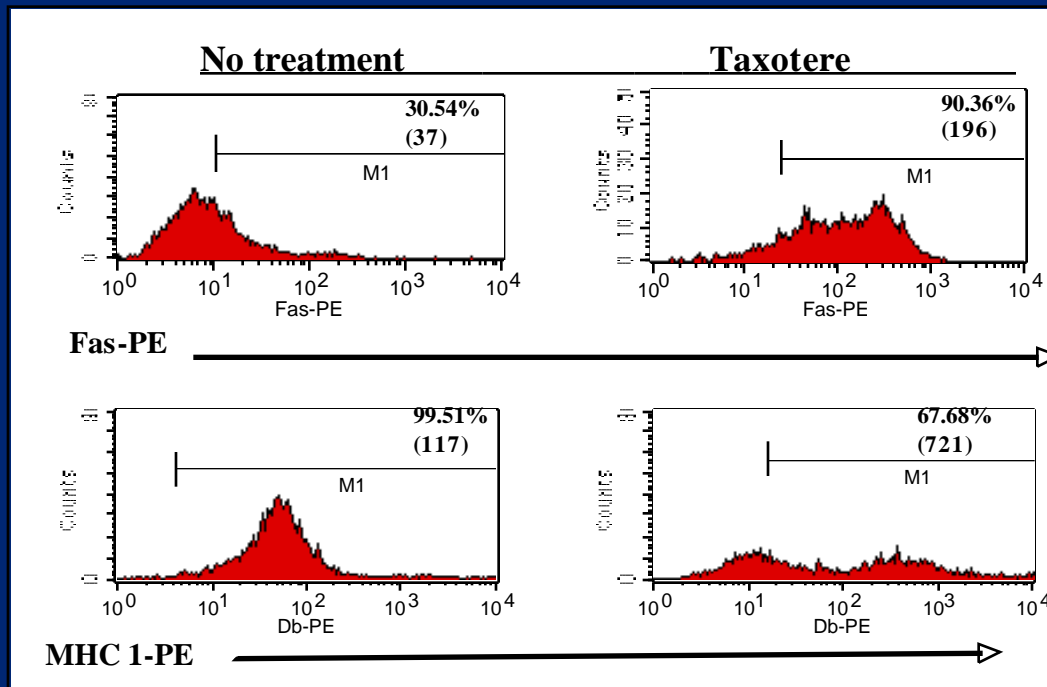


Closed symbols: CEA-Tg mice. Open symbols: C57BL/6 mice.
 * = Statistical significance from two-tailed Mann-Whitney test, 95% confidence interval.

GX15-070 inhibits Treg function

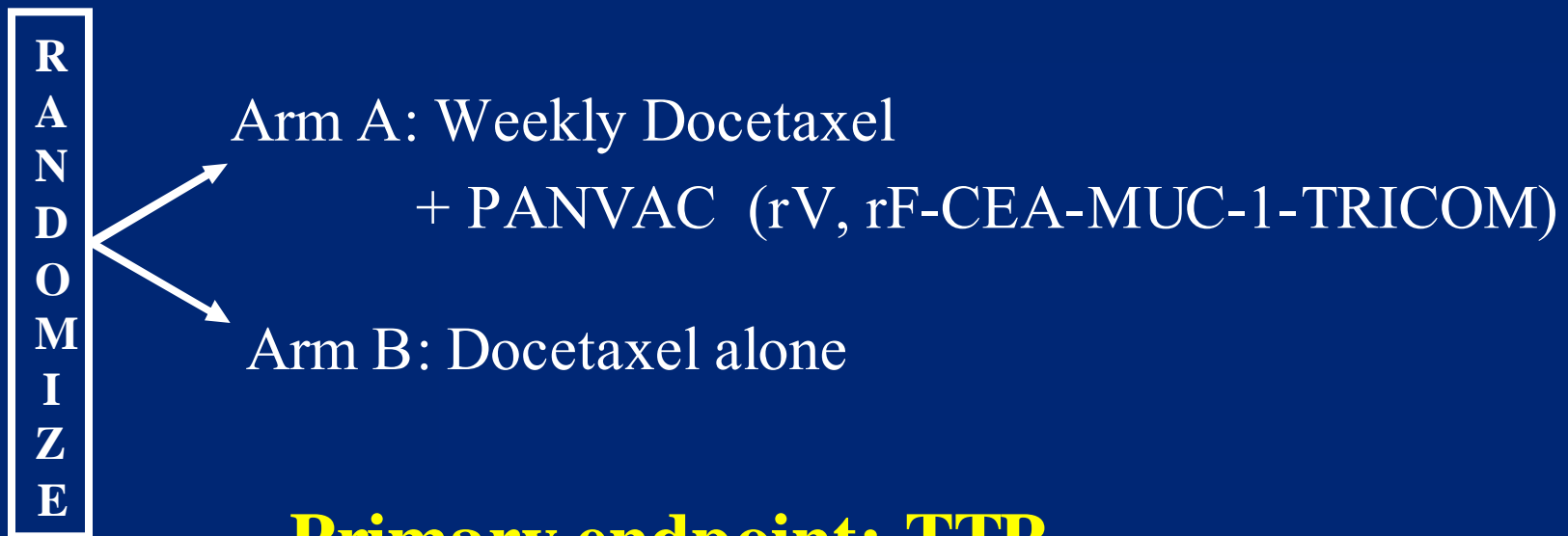


Ability of Docetaxel to Alter Tumor-Cell Phenotype: Enhanced Sensitivity to Antigen-Specific T-Cell Lysis



Docetaxel +/- PANVAC

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



Primary endpoint: TTP

Preliminary Data: 14 patients enrolled

	<u>Arm A</u>	<u>Arm B</u>
Median TTP	10.5 months	2 months
# on >6 months	5/6 (1 too early)	1/7

Prostate Cancer Vaccine Program

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

Vaccine/Androgen Receptor Antagonist Therapy

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

R
A
N
D
O
M
I
Z
E

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

Time to Treatment Failure

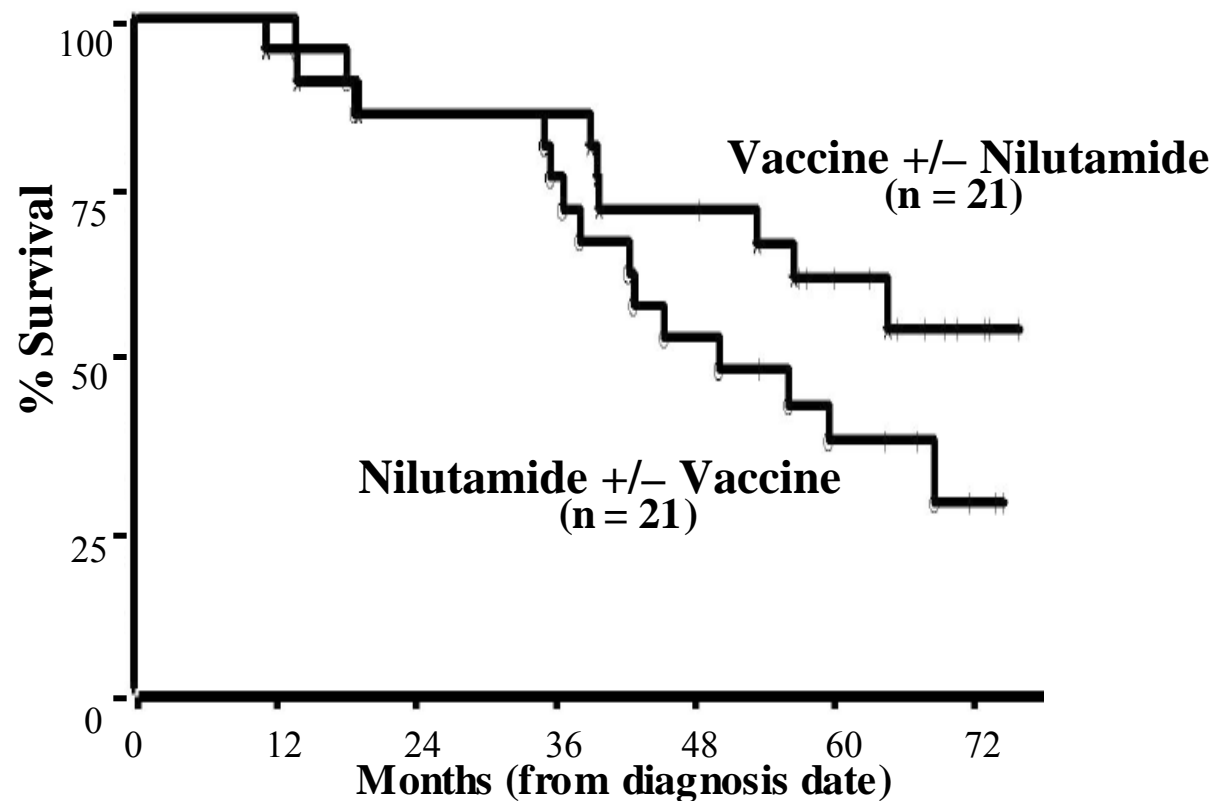
<u>Regimen</u>	<u>n</u>	<u>Median time to treatment failure</u>
Vaccine	21	9.9 months
Nilutamide	21	7.6 months

Time to Treatment Failure After Cross-Over

<u>Regimen</u>	<u>n</u>	<u>Median time to treatment failure</u>
Vaccine → Vaccine + nilutamide	12	13.9 months (after cross-over)* 25.9 months (from initiation of therapy)
Nilutamide → Nilutamide + vaccine	8	5.2 months (after cross-over) 15.5 months (from initiation of therapy)

* 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



At progression, patients continued initial therapy and crossed over to also receive other therapy.

Five-Year Overall Survival:

38%: Nilutamide first

59%: Vaccine first

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

Patients (n = 125)

- Metastatic prostate cancer (CT or bone scan +)
- Gleason score ≤ 7 ; no visceral disease
- Chemotherapy naïve

Vaccine: rV, rF-PSA-TRICOM (PROSTVAC) + GM-CSF

Control arm: empty vector

Randomization: 2:1 (double blind)

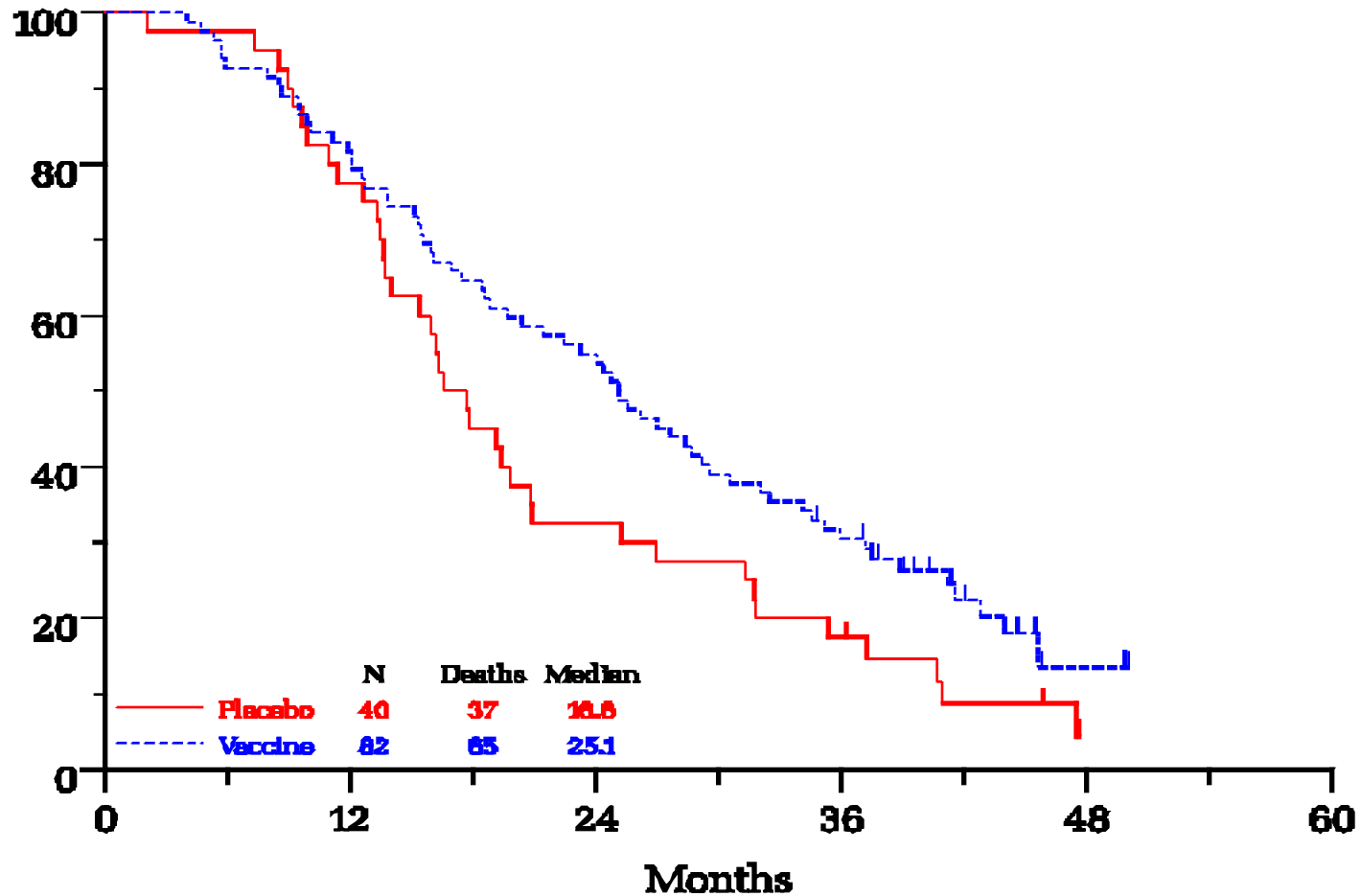
P.I.: P. Kantoff, Dana-Farber Cancer Center

Analyses: W. Godfrey, BNIT
B. Blumenstein, statistician

Survival Full Analysis Set

P = 0.006 (stratified logrank)

Hazard Ratio = 0.601 (0.396 to 0.912)



Kantoff PW, Schuetz TJ, Blumenstein BA, Glode LM, Billhartz DL, Gulley JL, Schlom J, Laus R, Godfrey WR. Overall survival (OS) analysis of a phase II randomized controlled trial (RCT) of a poxviral-based PSA targeted immunotherapy in metastatic castration-resistant prostate cancer (mCRPC). 2009 ASCO Annual Meeting, Orlando, FL, May 29-June 2, 2009.

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
 - Placebo: 16.6 months
 - Vaccine: 25.1 months (p=0.006)
- C. 40% reduction in death rate in vaccine arm

Phase III Trial Planned

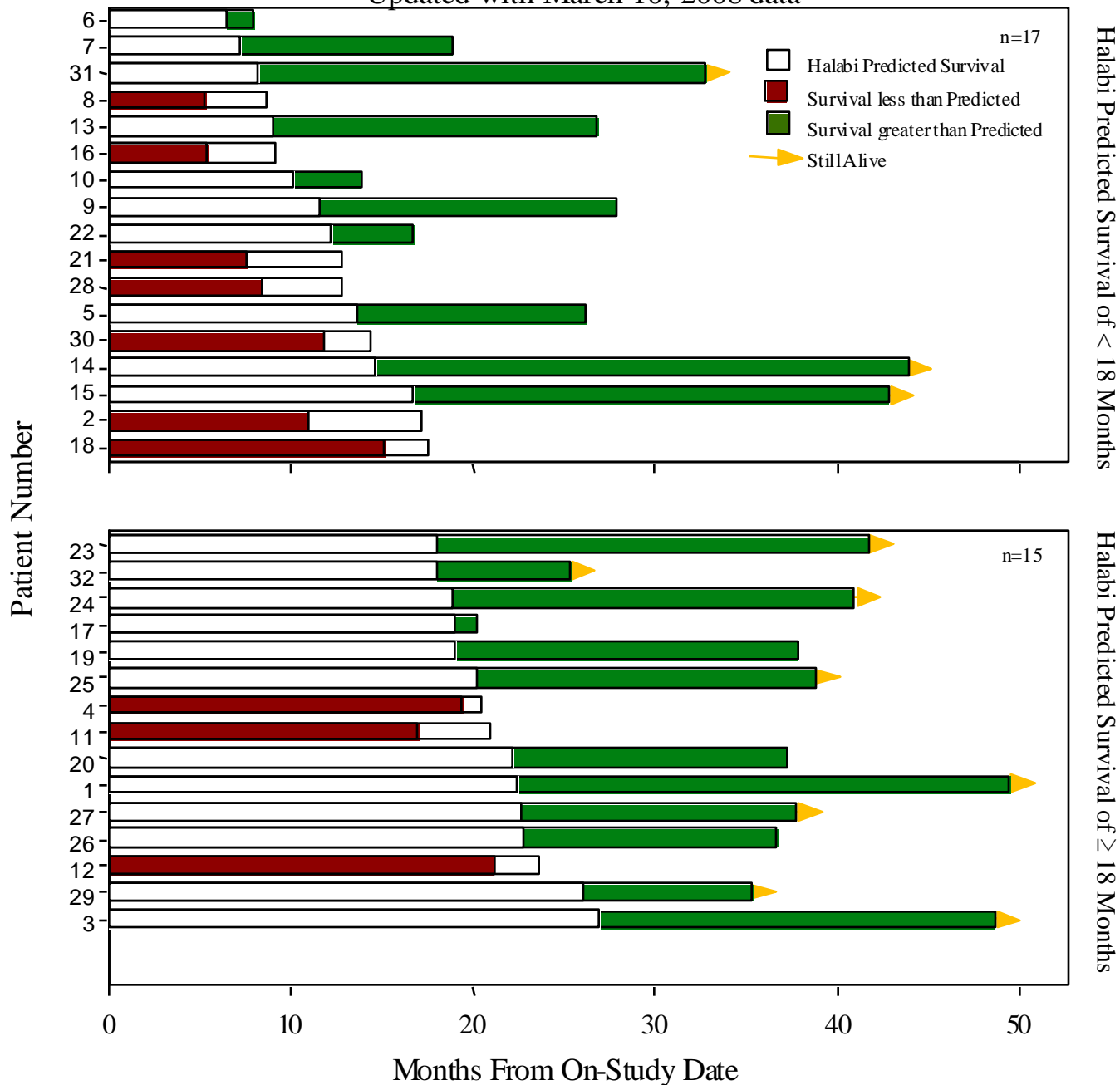
Overall survival analysis of a Phase II study of PSA-TRICOM in the treatment of metastatic, castrate-resistant prostate cancer

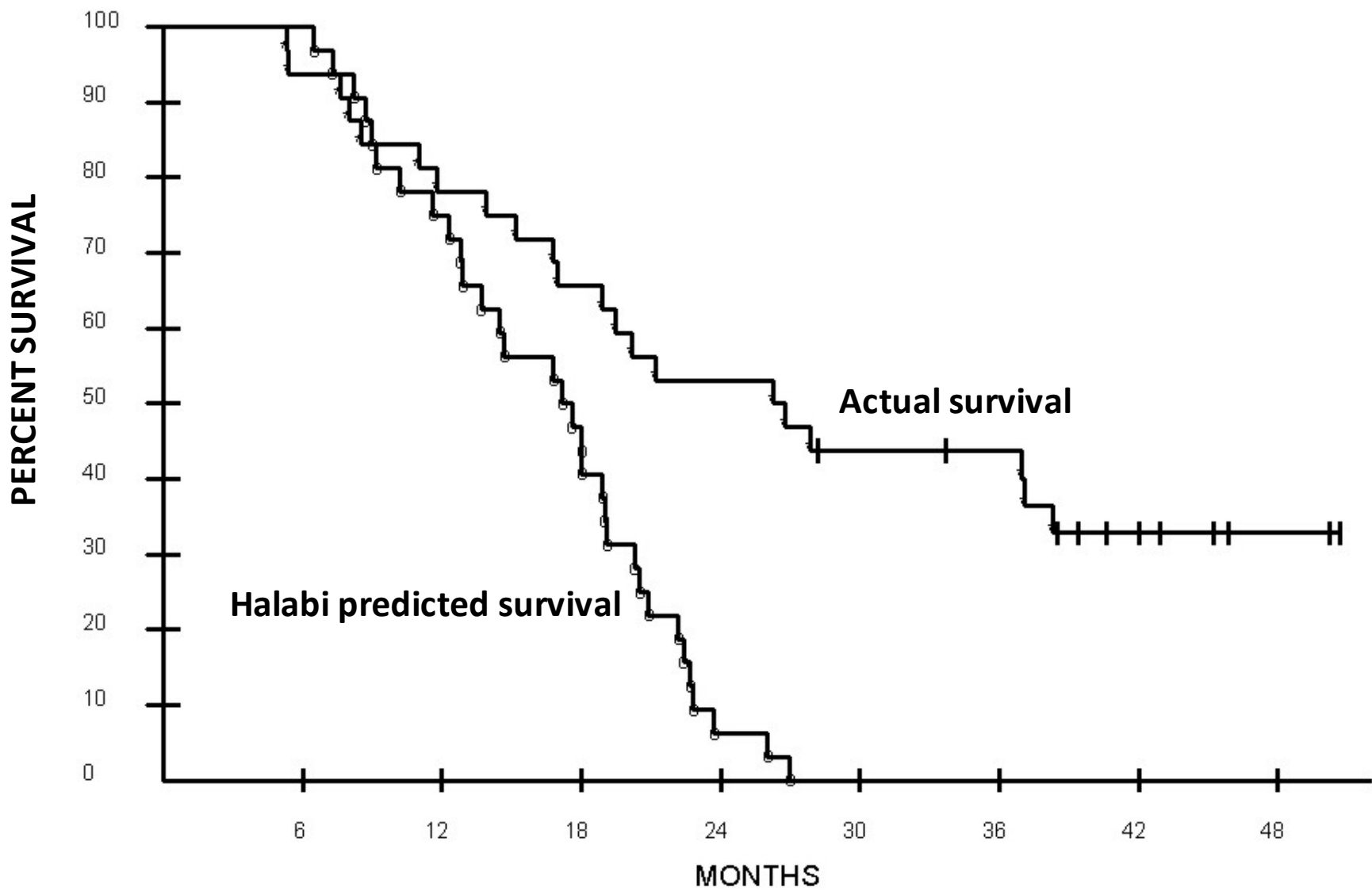
Ravi A. Madan¹, James L. Gulley¹, William L. Dahut², Kwong Y. Tsang¹, Seth M. Steinberg³, Jeffrey Schlom¹ and Philip M. Arlen¹

¹Laboratory of Tumor Immunology and Biology, ²Medical Oncology Branch, and ³Biostatistics and Data Management Section, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, Maryland

Predicted vs. Actual Survival of PSA-TRICOM Patients

Updated with March 10, 2008 data





Actual survival (*) compared with the Halabi predicted survival (o).

Phase II/III Trials: Metastatic Prostate Cancer

Median Overall Survival

Phase III

Mitoxantrone	16.4 mo	
Docetaxel (weekly)	17.3 mo	Δ 0.9 mo
Docetaxel (3 weekly)	18.9 mo	Δ 2.5 mo

NCI Phase II

Docetaxel (HPS 16.5 mo)	15.5 mo	(Δ 1.0 mo)
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Randomized Phase II

Vector control	16.3 mo	
PSA-TRICOM (p = 0.006) (HR = 0.6)	24.4 mo	Δ 8.1 mo

NCI Phase II

PSA-TRICOM (HPS 17.4 mo)	26.6 mo	Δ 9.2 mo
(ave HPS 12.3 mo)	14.6 mo	Δ 2.2 mo
(ave HPS 20.9 mo)	≥37.3 mo	Δ ≥16.4 mo

Vaccine Combination Therapies

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

– 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