Presenter Disclosure Information

James L. Gulley MD PhD FACP

The following relationships exist related to this presentation:

The NCI has a Collaborative Research and Development Agreement (CRADA) with BN ImmunoTherapeutics (Mountain View, CA):

PROSTVAC (PSA-TRICOM)

PANVAC (CVAC-301)

I have no financial interests to disclose

Combining Vaccines with other therapeutics:
A strategy to accelerate proof of concept studies?

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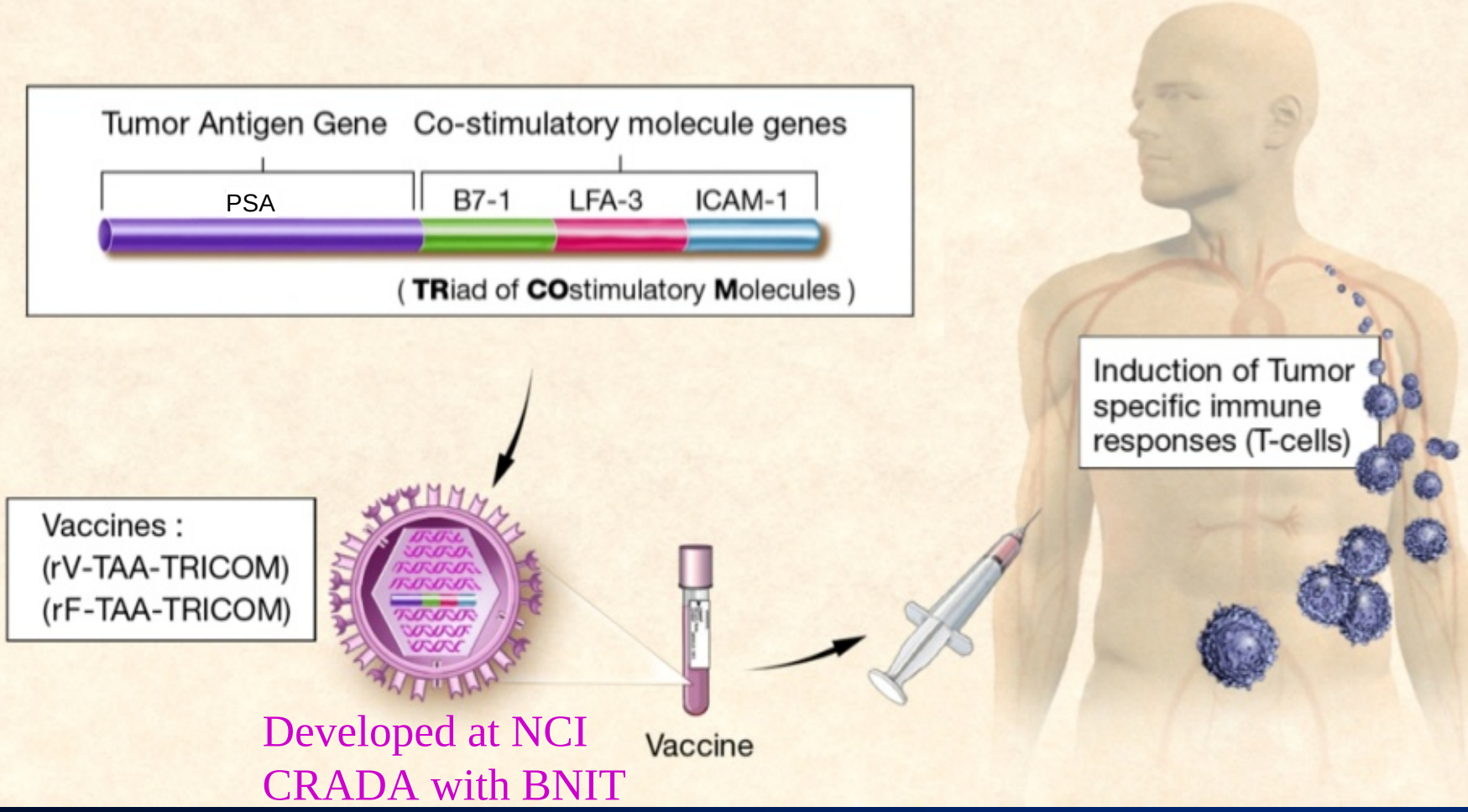
Center for Cancer Research
National Cancer Institute, NIH

Monotherapy

- Randomized controlled studies of immunotherapies alone have suggested that TTP may not be a discriminatory endpoint for clinical trials.
  - Sipuleucel-T (2 phase III studies)
  - Ipilimumab (phase III study)*
  - PROSTVAC (phase II study)

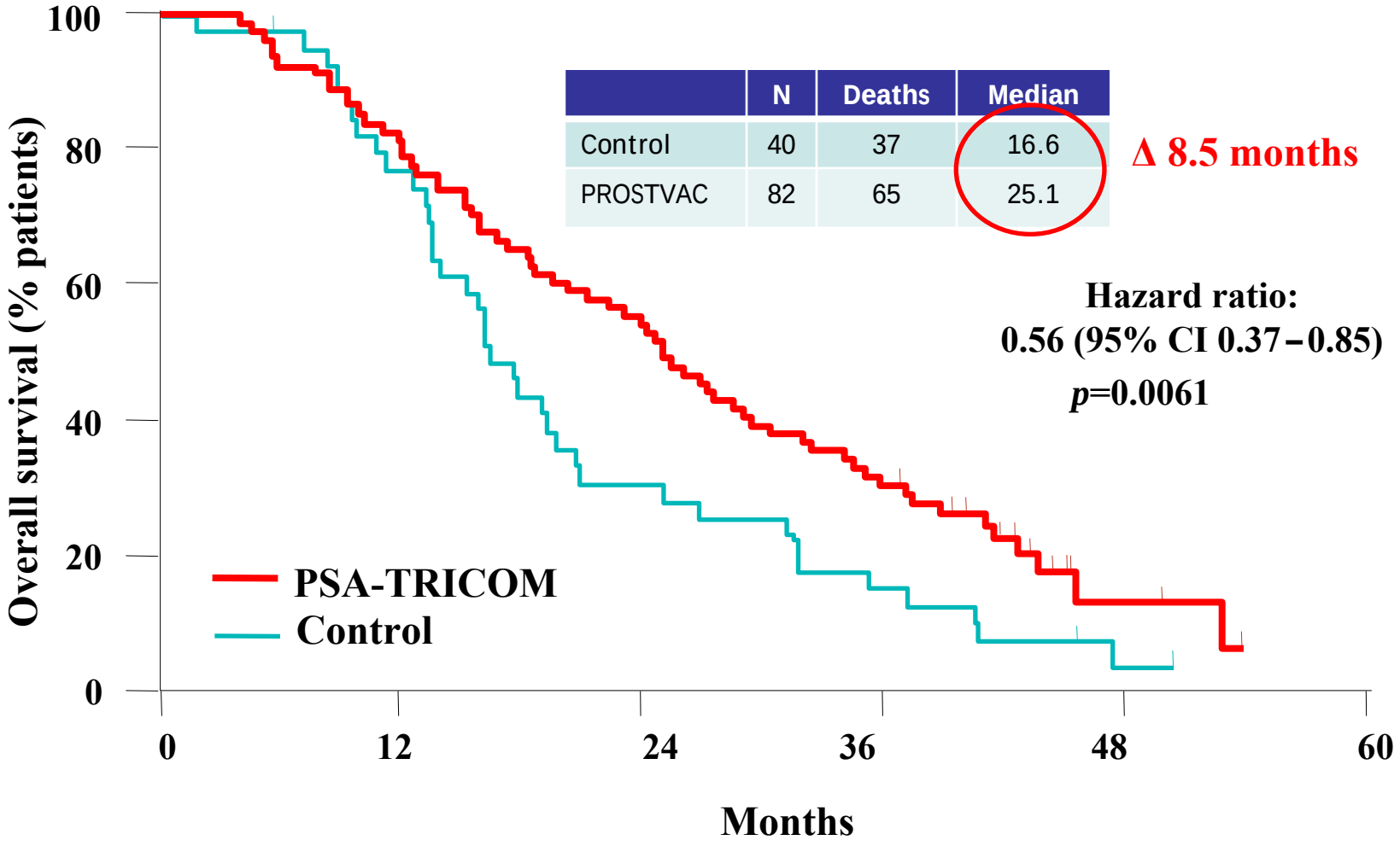
*no improved median TTP

Pox Vector Vaccine: PSA TRICOM (PROSTVAC)



Developed at NCI
CRADA with BNIT

PSA-TRICOM Significantly Extended Overall Survival in a Multicenter Phase II Study



	N	Deaths	Median
Control	40	37	16.6
PROSTVAC	82	65	25.1

Δ 8.5 months

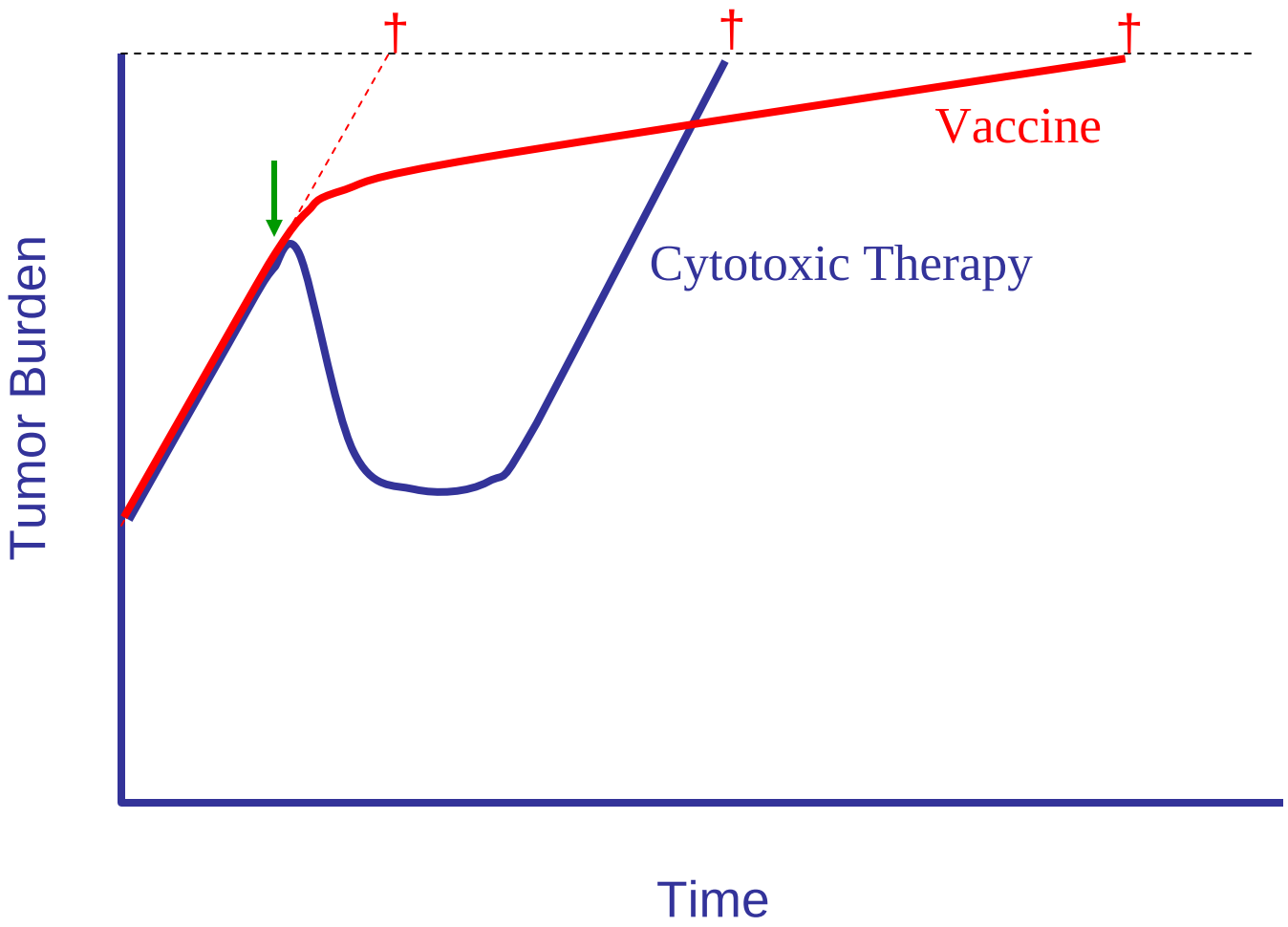
Hazard ratio:
0.56 (95% CI 0.37–0.85)
***p*=0.0061**

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

Therapeutic vaccines vs. Conventional therapy

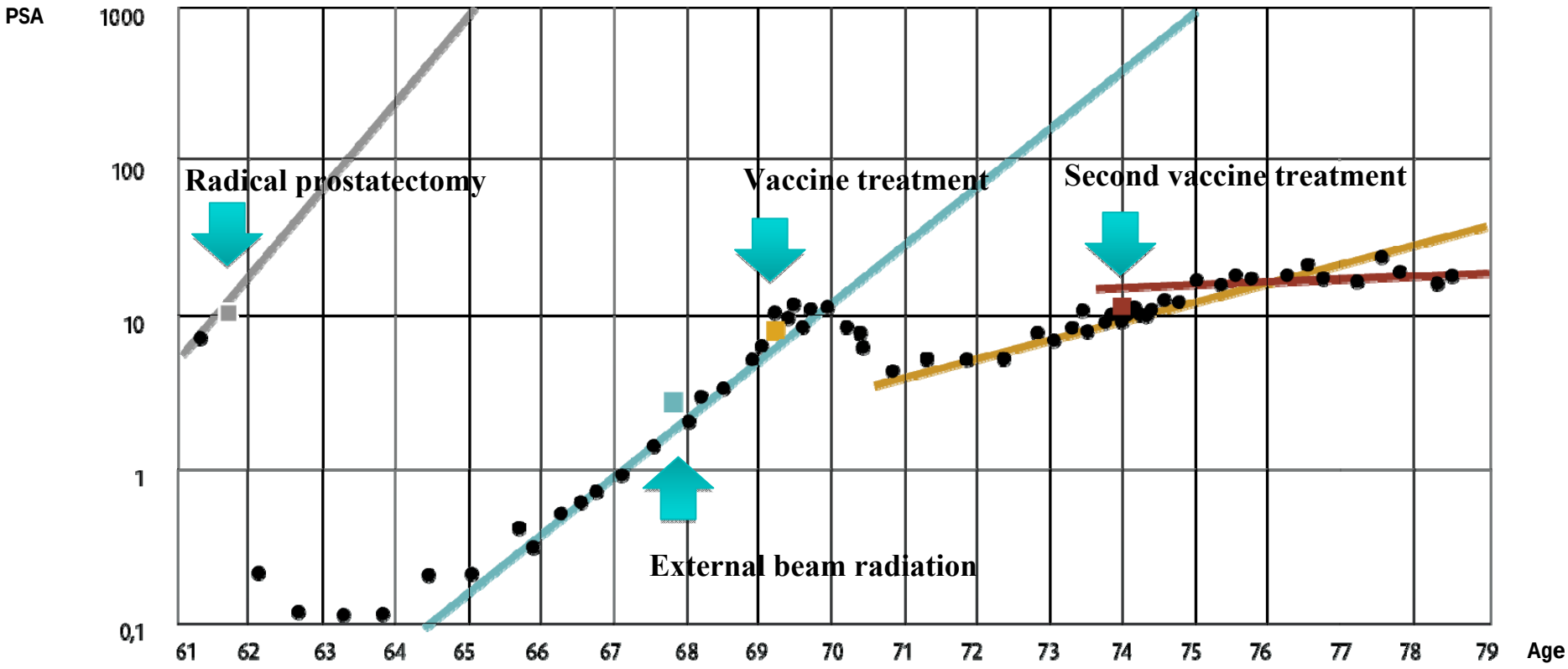
	Conventional Therapy	Therapeutic Vaccines
Target	Tumor or its microenvironment	Immune system
Pharmacodynamics	Often immediate action	Delayed
Memory Response	No	Yes
Limitations	Toxicity	Requires adequate immune system function (both systemically and at tumor site)

Tumor Growth Rate



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

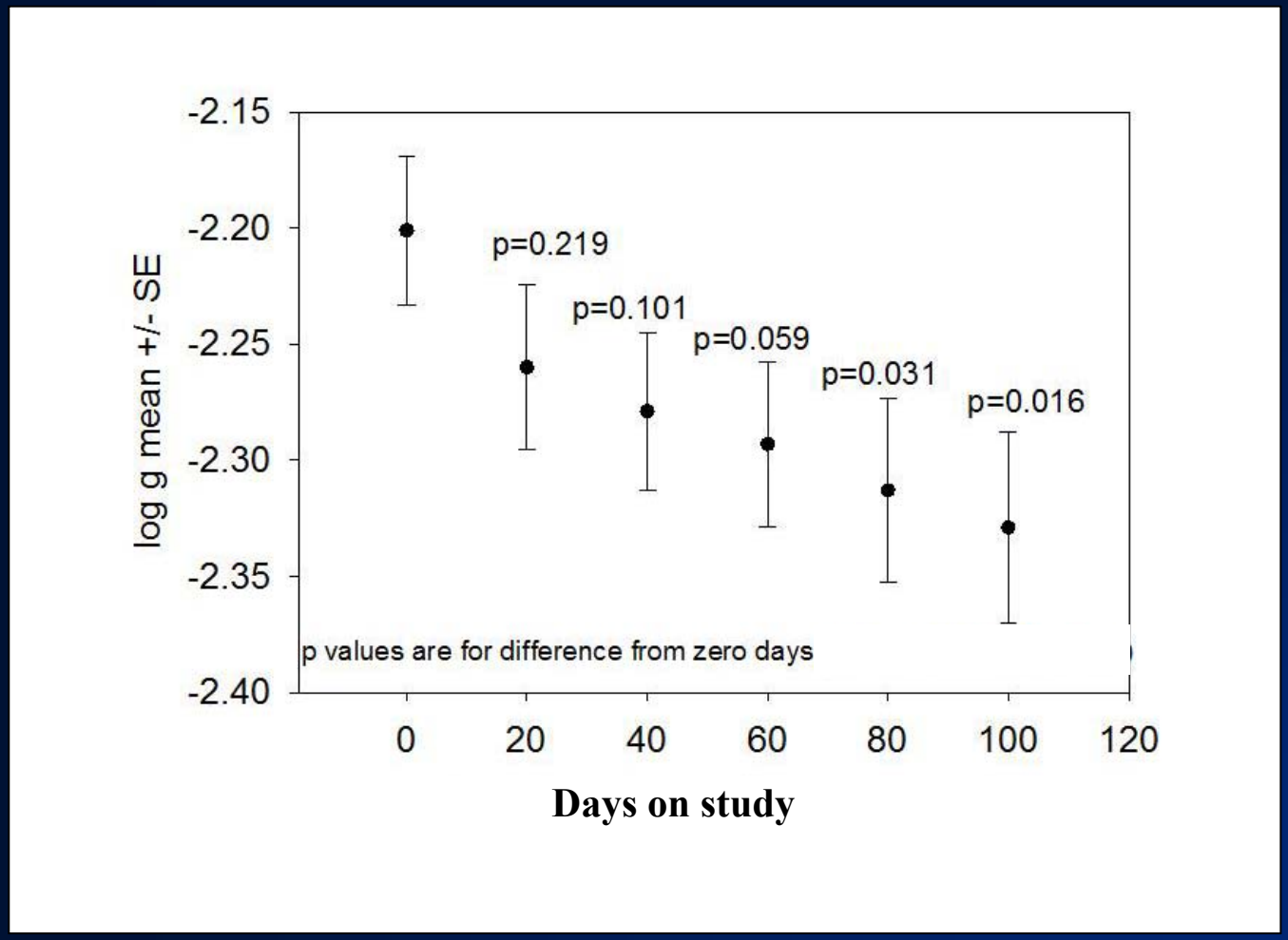
PROSTVAC – Interesting Case History



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	

Decrease in growth rate (PSA) over time following therapeutic vaccination



PROSTVAC treatment starting Day 0 and continued for 6 months, n=50
DiPaola et al, ASCO GU 2009 (E9802)

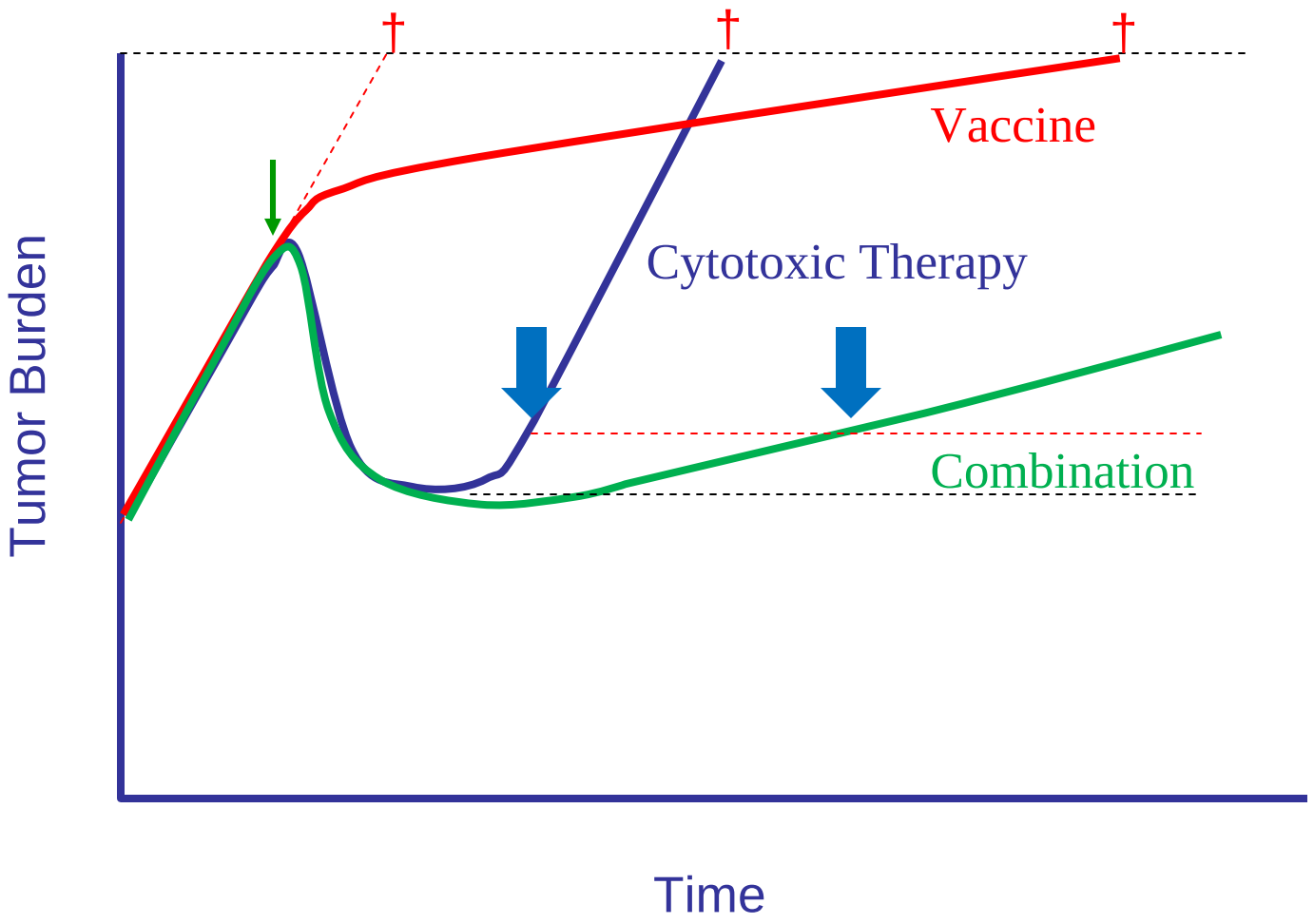
Combination Studies

tumor

immune

- Rationale: added therapy
  - Kill in an immunologic manner (boosting anti-cancer immune responses)
  - Phenotypically alter tumor cell → more amenable to immune mediated killing
    - Killing
      - Fas, improved T-cell binding (ICAM)
    - Recognition
      - MHC, TAA
  - Augment immune effectors / decrease immune regulators

Tumor Growth Rate

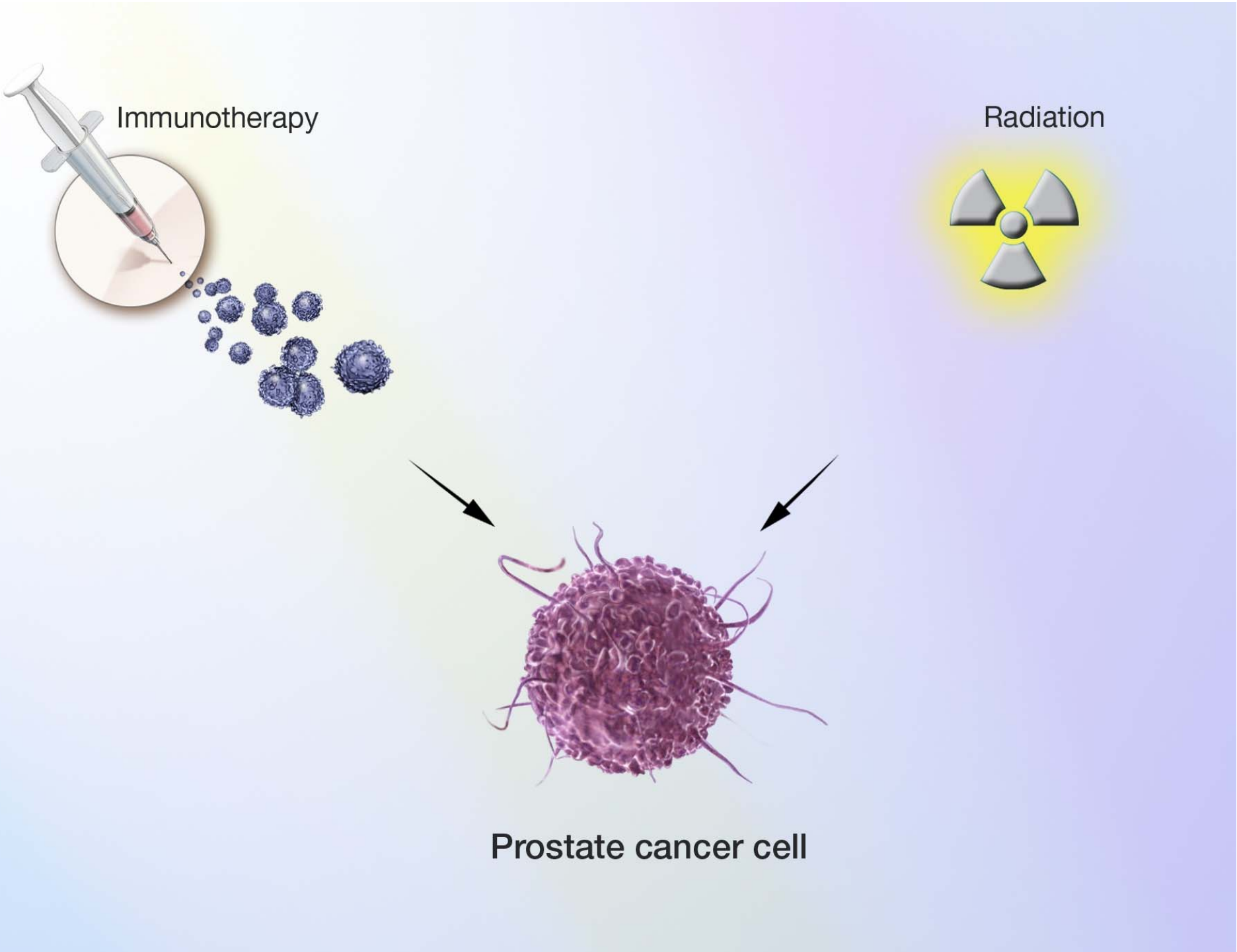


Stein W, Gulley JL, et al. *Clin Ca Res*, 2011

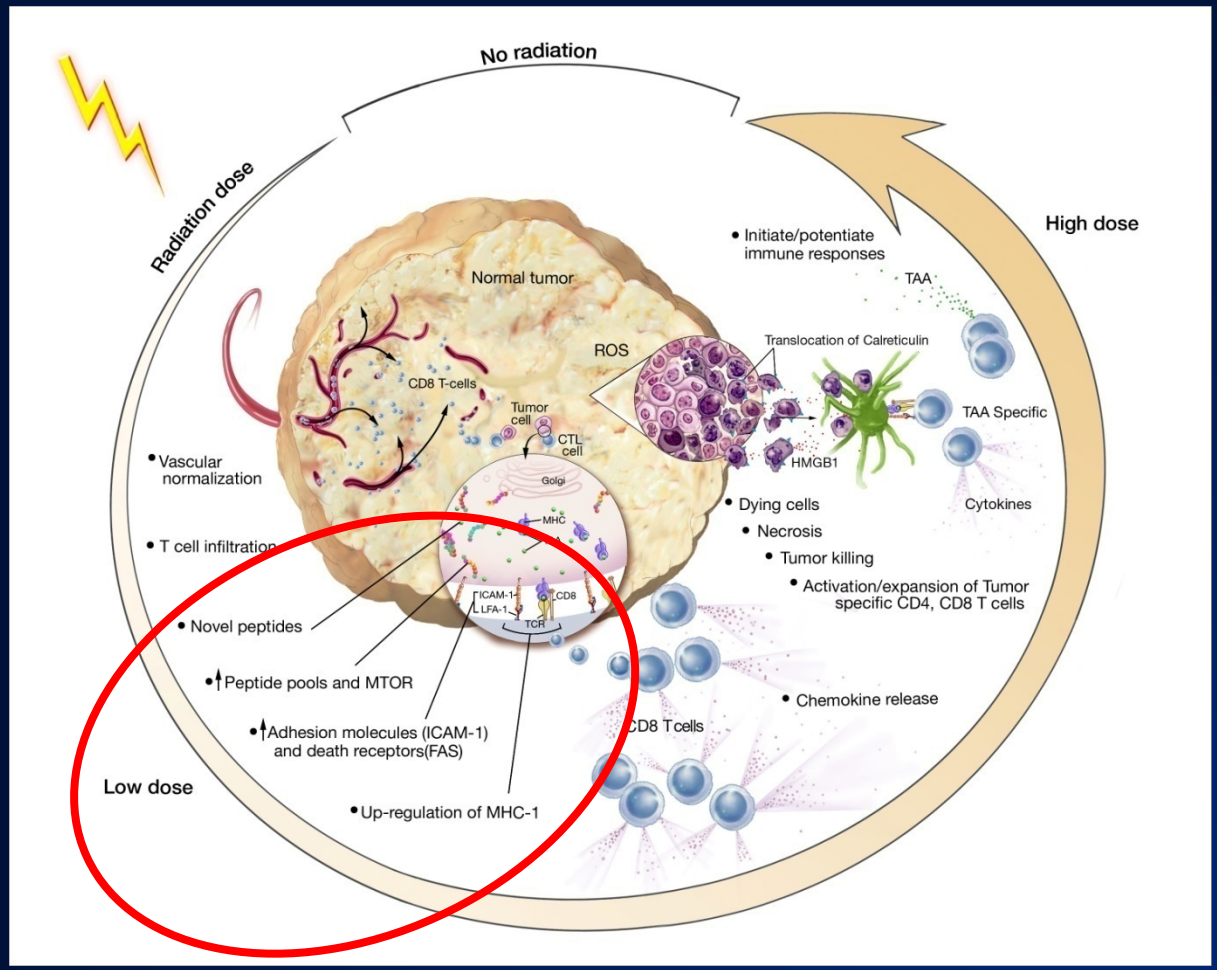
Combination Studies

		Clinical Trials	
	Preclinical Studies	**Immune Endpoint**	**Clinical Endpoint**
Radiation	✓	✓	**ongoing**
Chemotherapy	✓	✓	**ongoing**
Hormonal Manipulation	✓	✓	**ongoing**
Small Molecule	✓		
Immune Checkpoint inhibition	✓	✓	

LTIB Studies, Hodge, Schlom et al.


Immunotherapy
Radiation
Prostate cancer cell

Potential Multiple Effects of Local Irradiation of Tumors



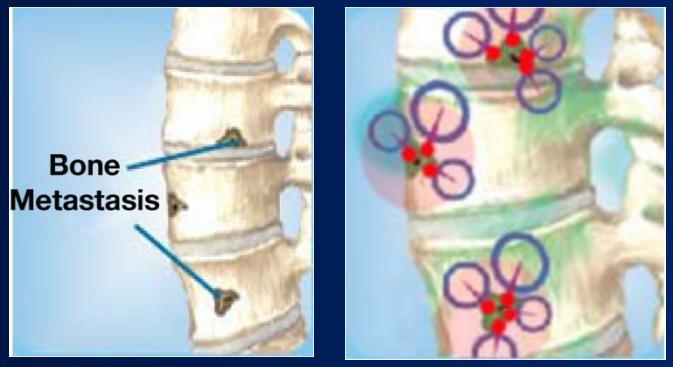
Hodge …Gulley et al., Oncology 22:1064-70.

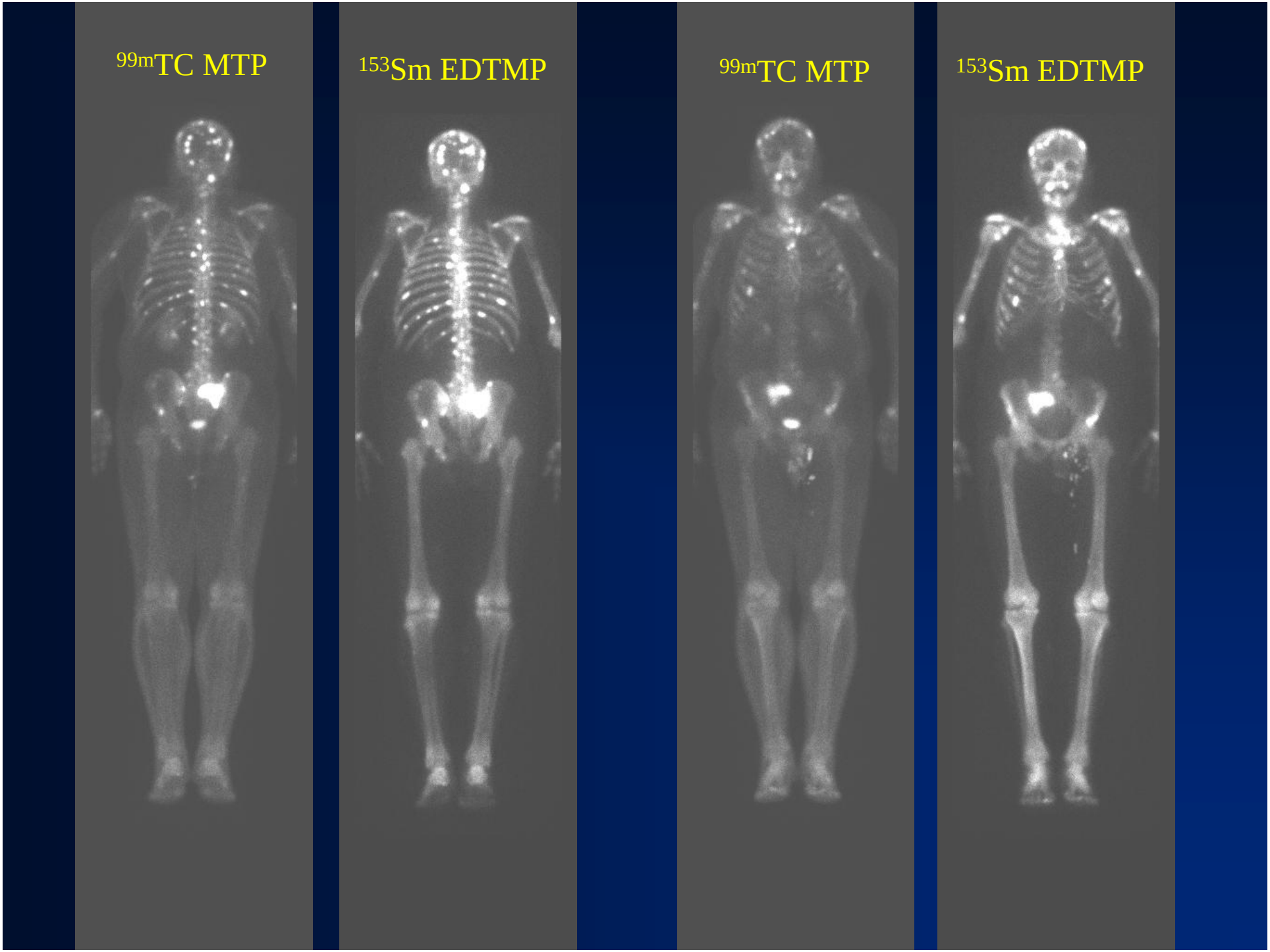
QUADRAMET
(SAMARIUM SM-153 LEXIDRONAM INJECTION)

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

It preferentially binds to osteoblastic metastatic tumor deposits in bone.

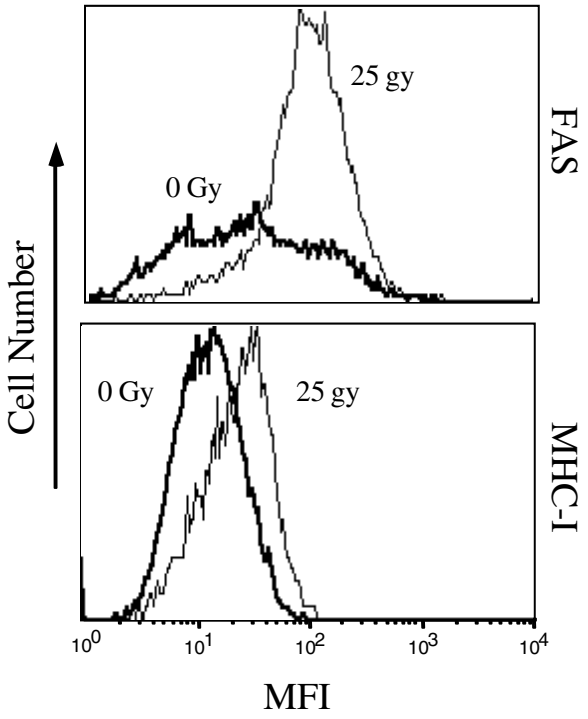
^{153}Sm is currently FDA approved and clinically utilized for palliation of bone metastasis in multiple tumor histologies.




^{99m}TC MTP
^{153}Sm EDTMP
^{99m}TC MTP
^{153}Sm EDTMP

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

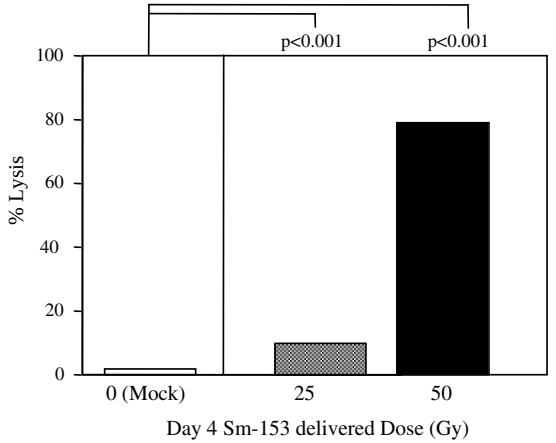
Treatment of LnCaP prostate cancer cells with palliative doses of ^{153}Sm results in the upregulation of MHC class I and Fas



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

	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

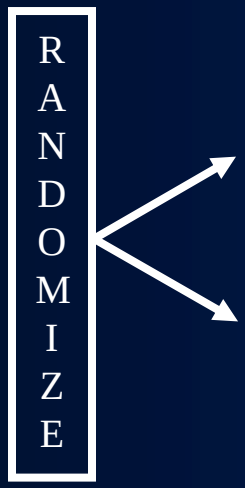
Treatment of LnCaP prostate cancer cells with palliative doses of ^{153}Sm results in increased sensitivity to multiple CTLs



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)

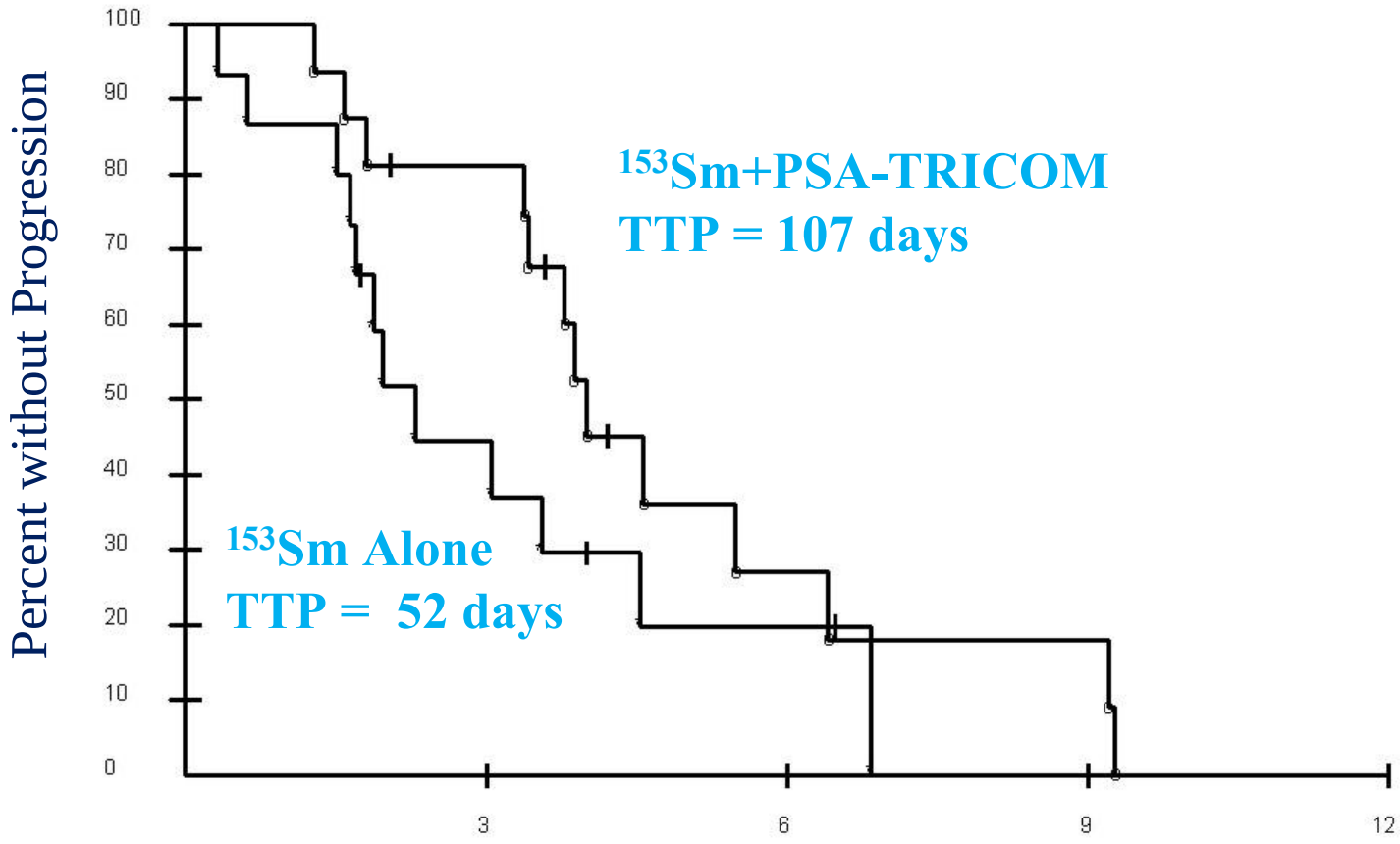
Arm B: ^{153}Sm (n=34)

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.

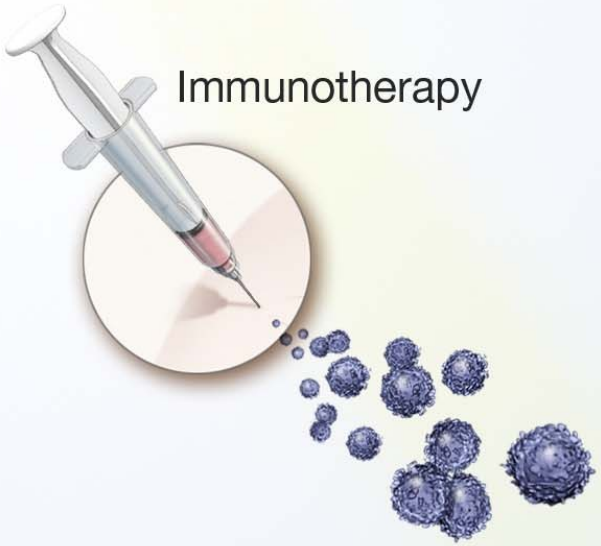
NCI# 7678 PI Gulley
CINJ (DiPaola) and UC (Stadler)

Preliminary Data: ^{153}Sm +/- PSA-TRICOM

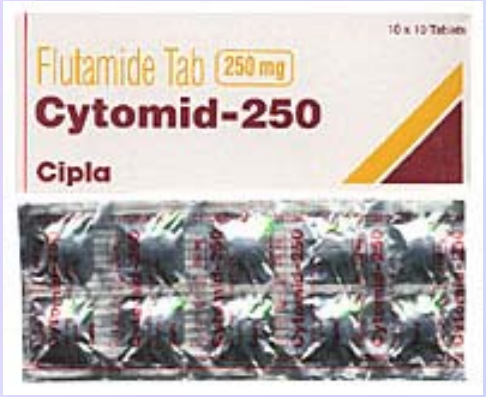


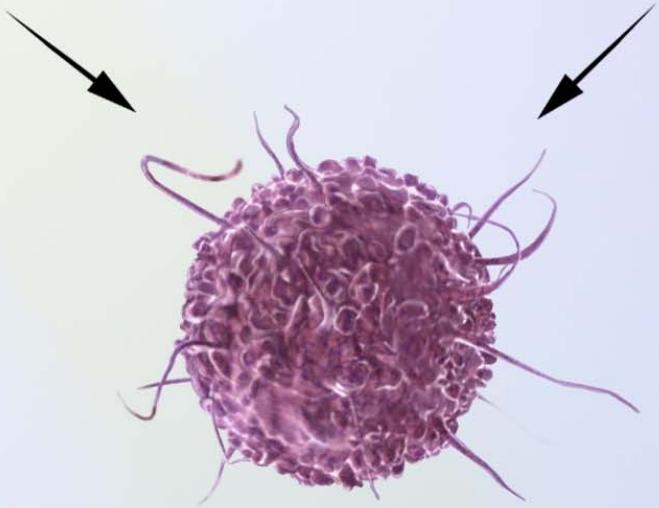
n=37

Immunotherapy



Hormonal Therapy





Prostate cancer cell

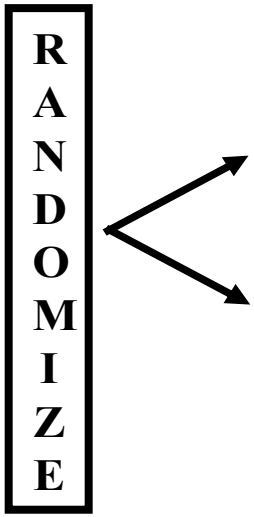
Rationale for Vaccine Combined With Androgen Deprivation Therapy (ADT)

- Increase thymic emigrants (naïve immune cells)
- Increased T-cell trafficking to the prostate
- Decreases immune tolerance to tumor antigens

Drake CG, et al. Cancer cell 2005.
Aragon-Ching JB (Gulley), Front Biosci 2007

ADT+ Fluatmide +/- PSA-TRICOM

Patient Population: D0.5 Prostate Cancer



Arm A: **PSA-TRICOM + Flutamide 250 mg TID** (n=31)

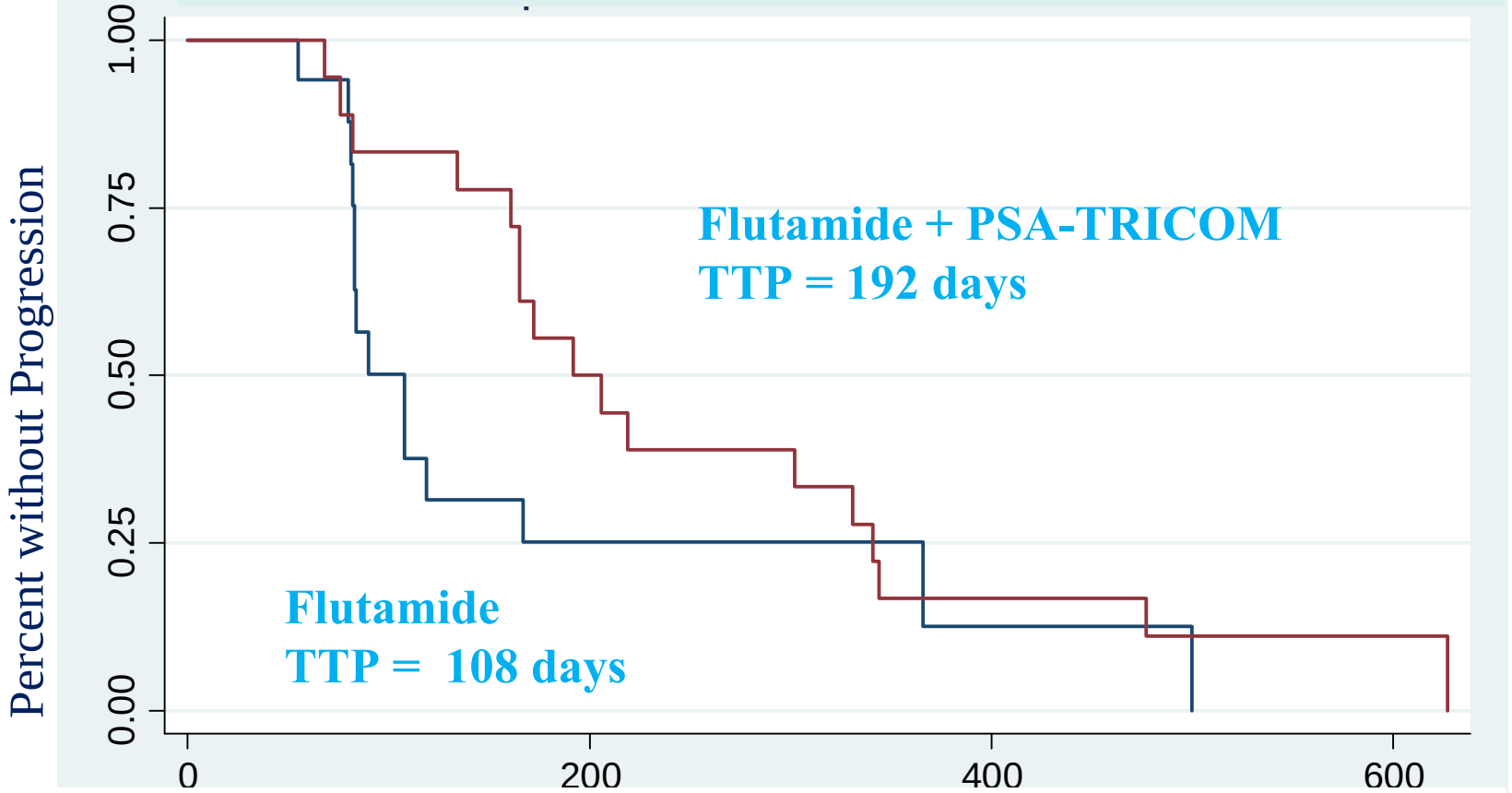
(vaccine given monthly until progression)

Arm B: **Flutamide 250 mg TID alone** (n=31)

Primary End Point: Time To Progression (PSA rise or mets)

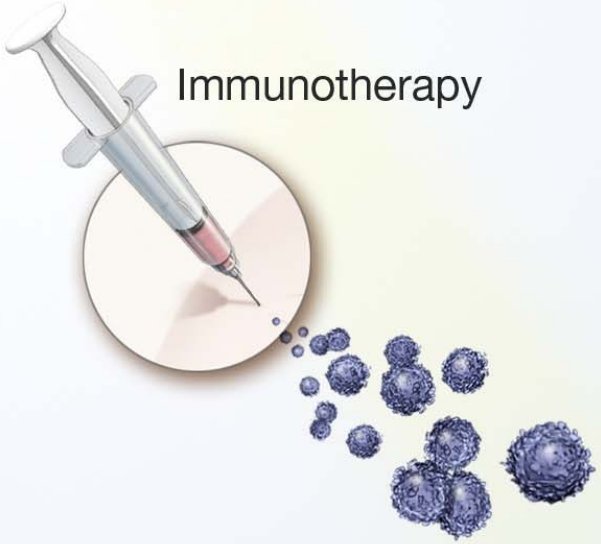
Secondary End Points: Immunologic Response

Preliminary Data: ADT+ Flutamide +/- PSA-TRICOM

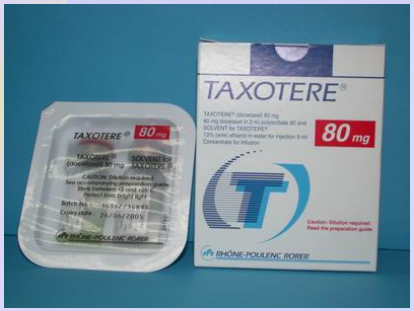


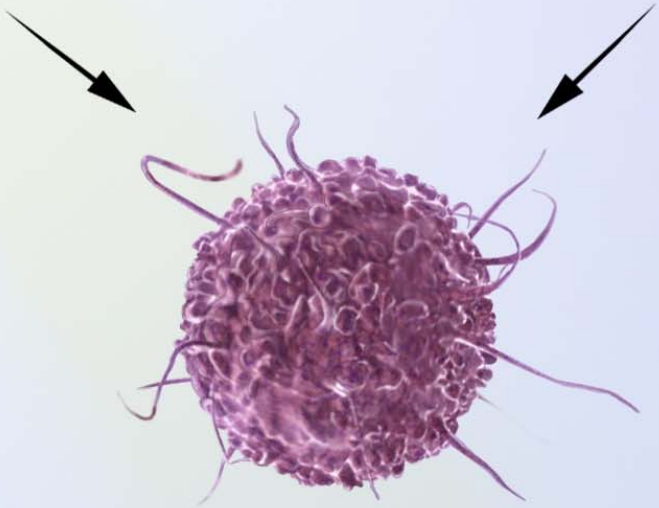
n=41

Immunotherapy



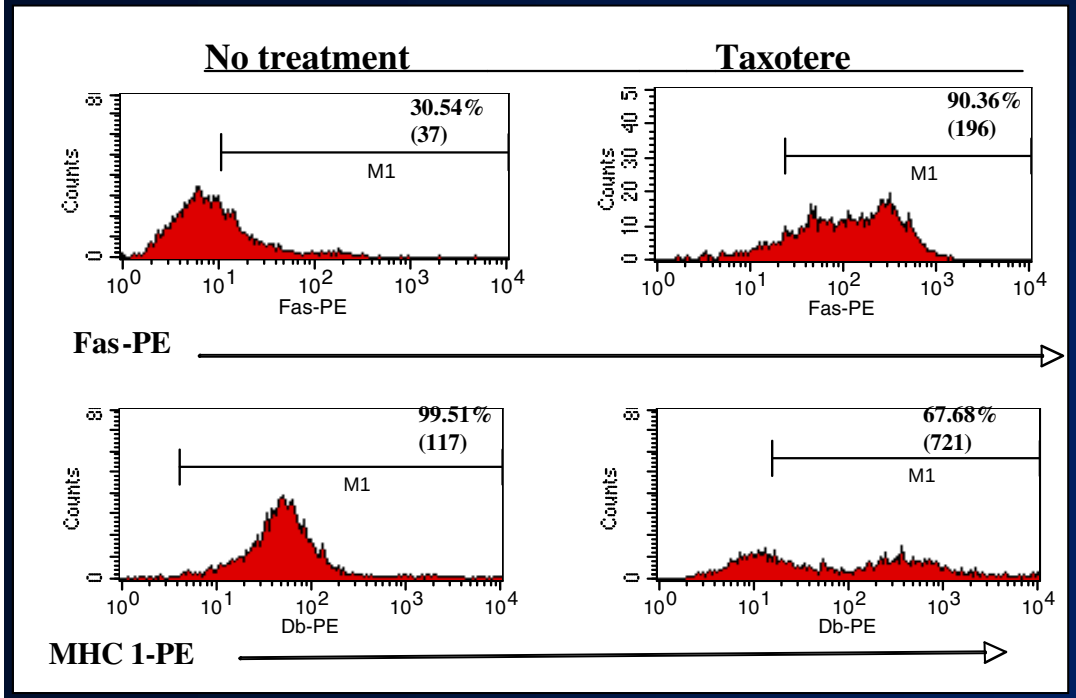
chemotherapy

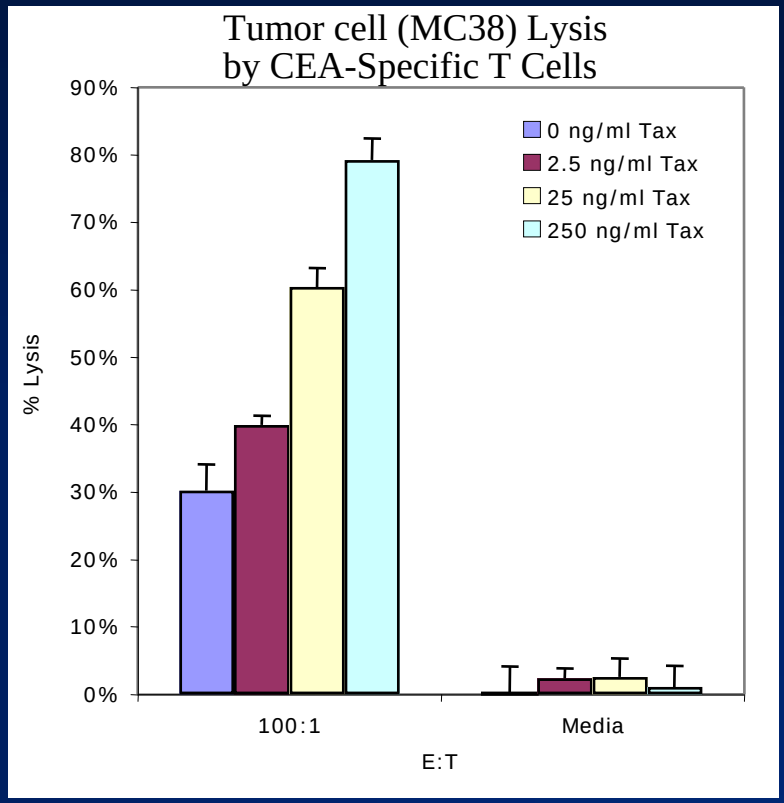




Cancer Cell

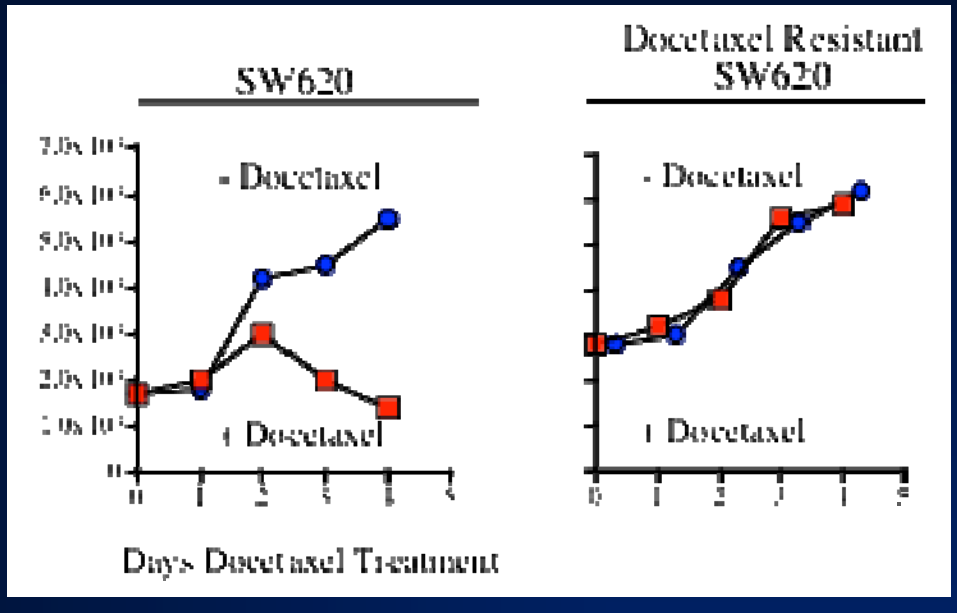
Ability of Docetaxel to Alter Tumor-Cell Phenotype: Enhanced Sensitivity to Antigen-Specific T-Cell Lysis

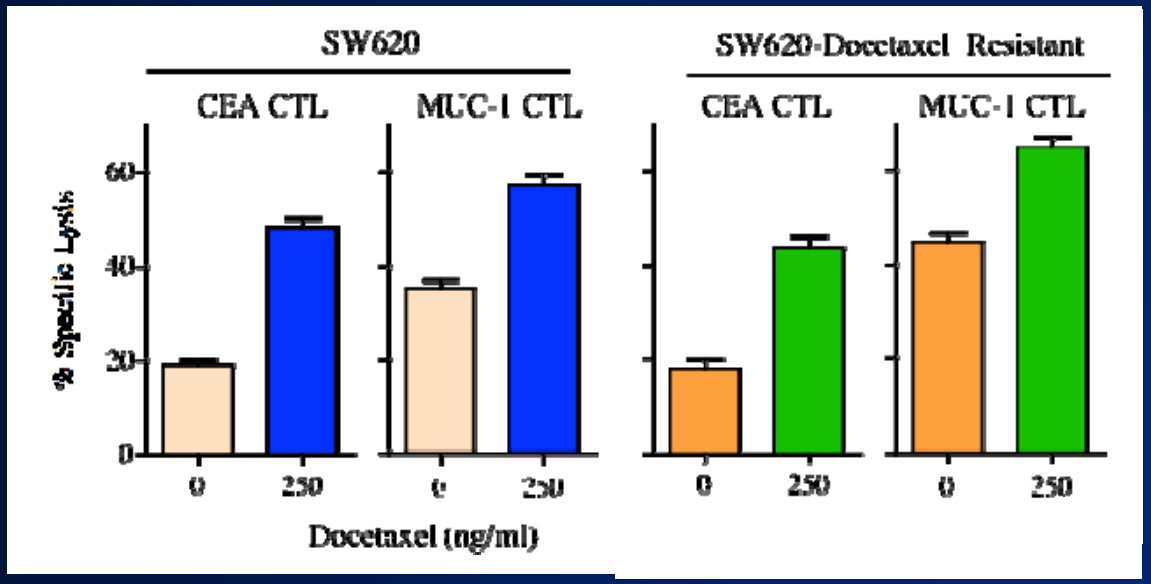




Garnett, Schlom, Hodge, Clin Cancer Res., 2008

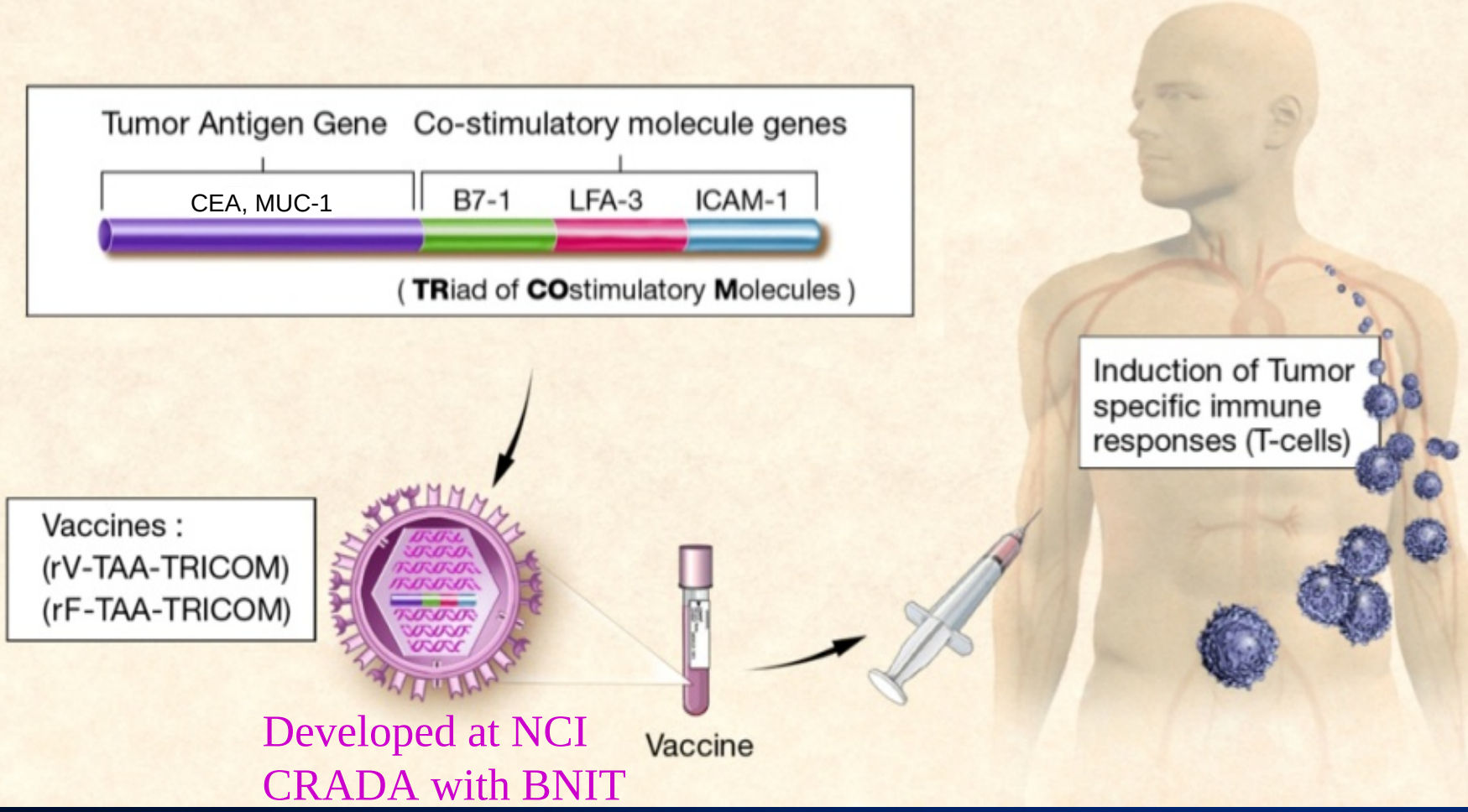
Human Carcinoma Cells Resistant to Chemotherapy Are Sensitive to CTL Killing After Treatment





Preclinical Data from Hodge et al.

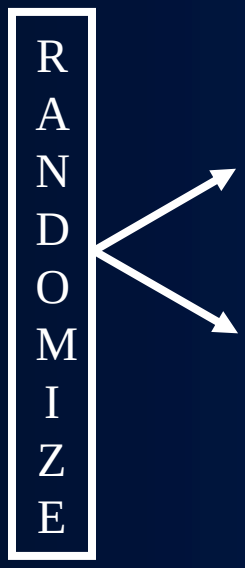
Pox Vector Vaccine: PANVAC



Developed at NCI
CRADA with BNIT

Docetaxel +/- PANVAC

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



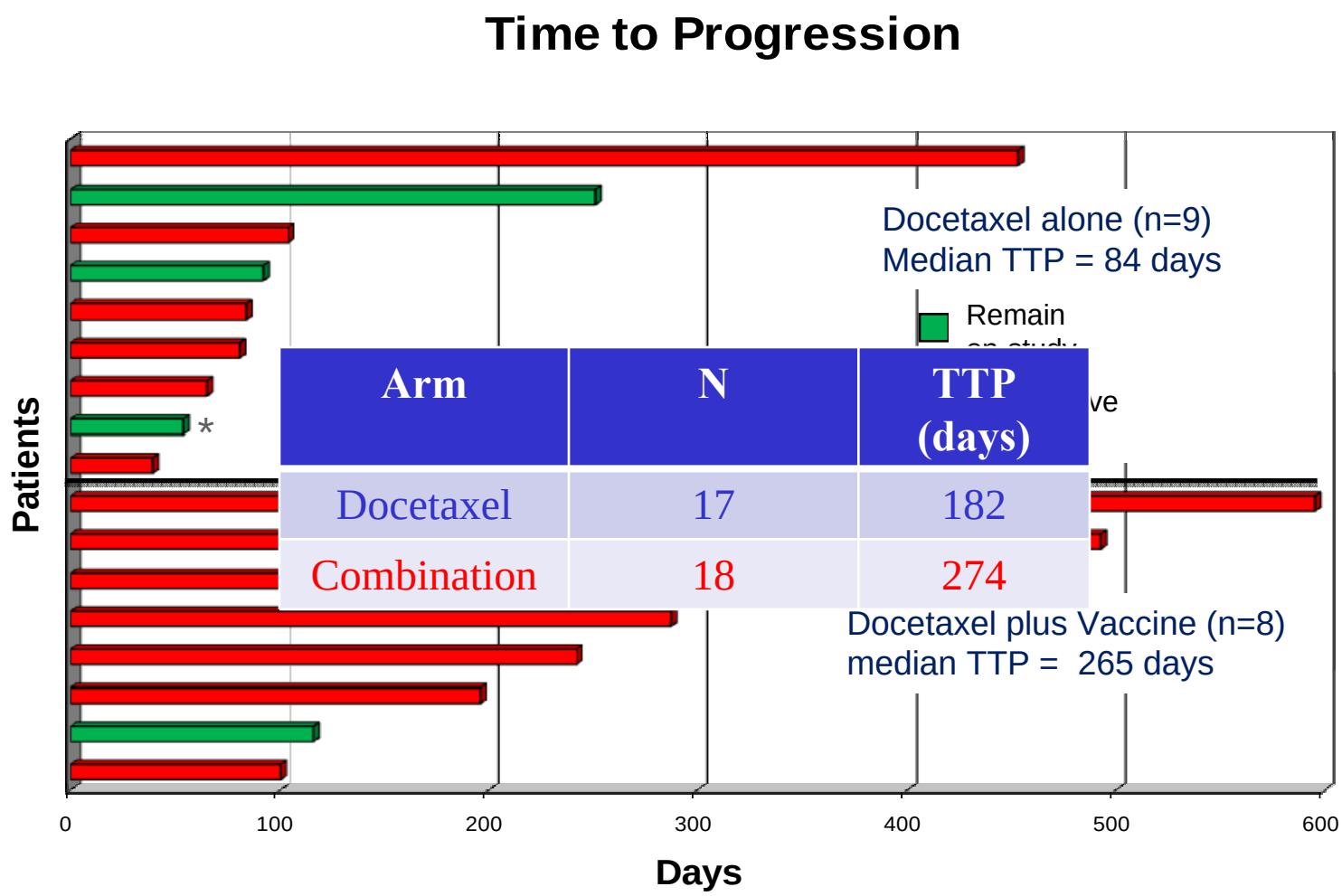
Arm A: Weekly Docetaxel + PANVAC

Arm B: Weekly Docetaxel alone

Primary endpoint: TTP

NCI 6977: PI, Gulley
MDA (Ibrahim)

Preliminary Data: Docetaxel +/- PANVAC



Arm	N	TTP (days)
Docetaxel	17	182
Combination	18	274

Median TTP for docetaxel in 2nd line setting is 4 months (Buzdar et al, *The Breast* 1996)

Conclusions

- Immunotherapy monotherapy does not appear to impact PFS
- However, delayed impact on tumor growth kinetics may eventually lead to improved OS
- Rationally designed combination studies
  - may control tumor burden for long enough → optimal immune mediated tumor growth slowing
  - improved PFS for combination arms vs. standard of care
  - This platform may lead to accelerated proof of concept studies and improved patient outcomes

Laboratory of Tumor Immunology and Biology