



PROSTVAC

Presentation for the RAC

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Recombinant Vaccine Vectors

- Pox vectors

- Vaccinia (rV-)** elicits a strong immune response

- host induced immunity limits its continuous use

- Avipox (fowlpox rF-)**

- normal hosts are avian species

- does not replicate in mammalian cells

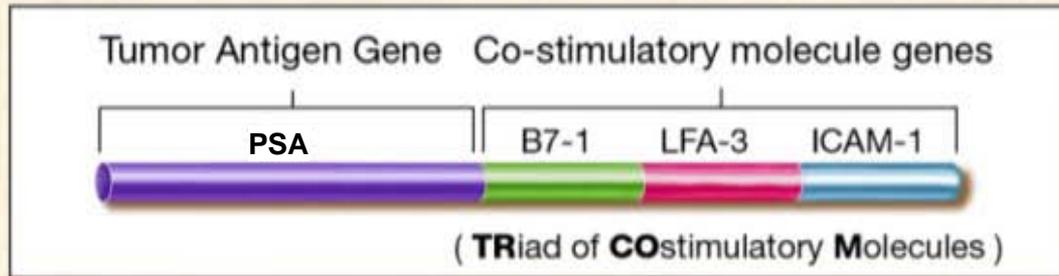
- can be used repeatedly with little if any host neutralizing immunity

- Can insert multiple transgenes

- **Do not integrate into host DNA**

- Efficiently infect antigen presenting cells including dendritic cells

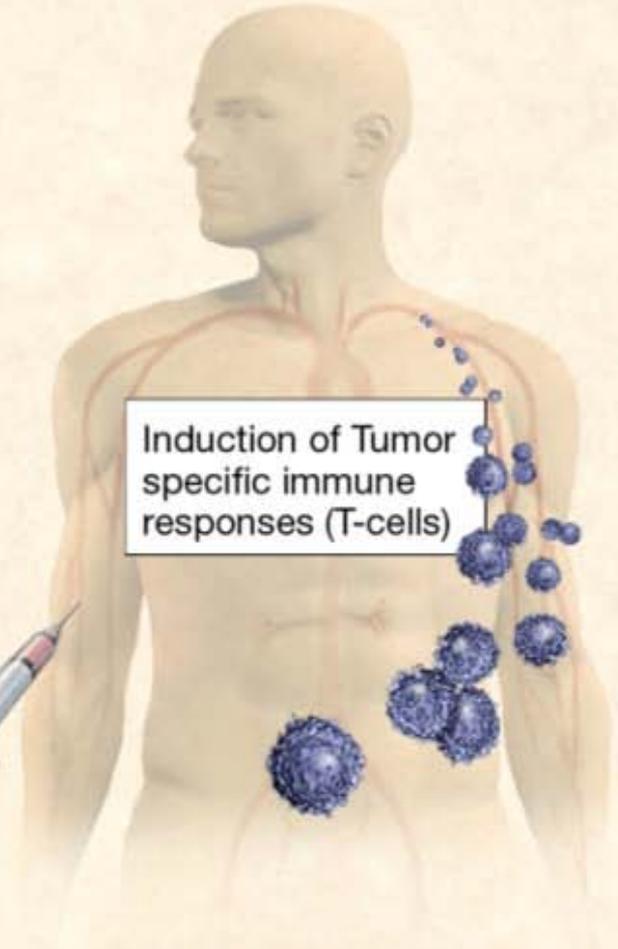
Pox Vector Vaccine: PSA TRICOM (PROSTVAC)



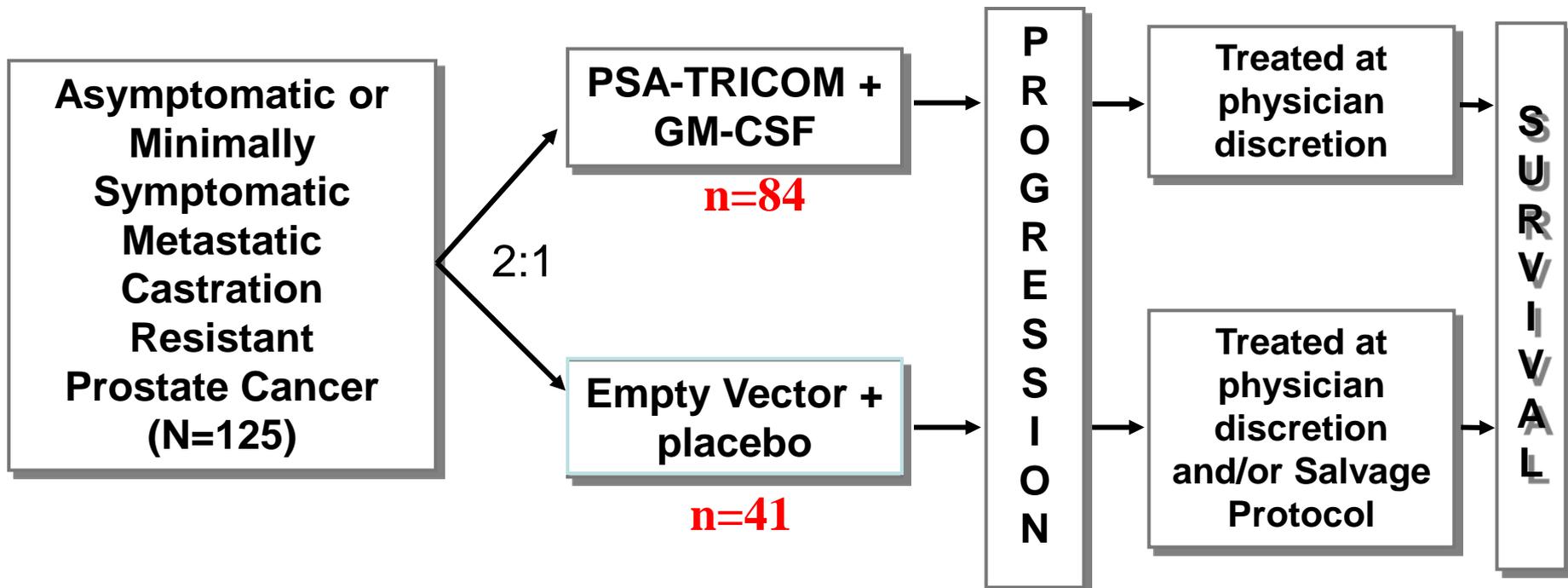
Vaccines :
(rV-TAA-TRICOM)
(rF-TAA-TRICOM)



Developed at NCI
CRADA with BNIT



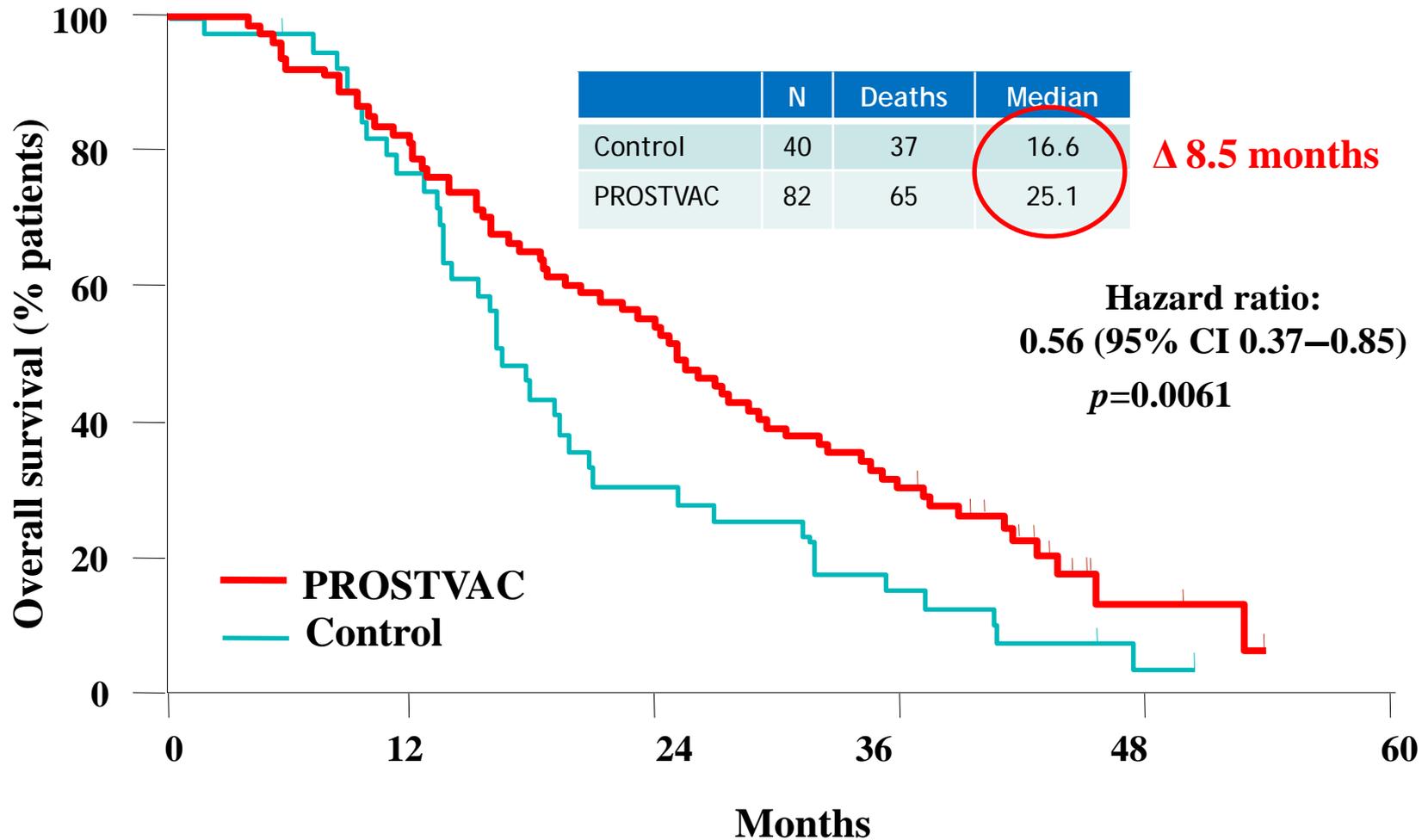
Randomized Controlled Double Blind Phase II Study



Primary endpoint: Progression Free Survival

Secondary endpoint: Overall Survival

PROSTVAC: Overall Survival



Current and Emerging Therapies in CRPC

Phase III data

	Number of patients	Stop treatment 2° AE	PSA ↓ ≥50%	Improvement in Median OS	Hazard Ratio	Reduction in Death Rate	Approved
Docetaxel	1006	11%	45%	2.4 months	0.76	24%	2004
Cabazitaxel	755	18%	39%	2.4 months	0.70	30%	2010
Sipuleucel-T	512	1.5%	2.6%	4.1 months	0.78	22%	2010
Abiraterone	1195	19%	38%	3.9 months	0.66	34%	2011

Phase II PROSTVAC data

	Number of patients	Stop treatment 2° AE	PSA ↓ ≥50%	Improvement in Median OS	Hazard Ratio	Reduction in Death Rate	Approved
Multi-Center	125	~2%	1%	8.5 months	0.56	44%	---
NCI	32	0%	3%	9.1 months*	--	--	---

*compared with validated nomogram

Planned Phase III

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

R
A
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E

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

α (two-sided) = 0.025 per comparison

Critical HR 0.82

Regulatory Review

- Multiple (8) prior submissions of PROSTVAC clinical protocols to OBA for “initial review”
 - Full RAC review not required
- Jan 2010: End of phase II meeting
- Dec 2010: Formal SPA with FDA
- 2009: Scientific Advice with EMA

HS1: Given that GM-CSF has been suggested to have disease modifying effects, comment should be made as to why a 4th arm [GM-CSF alone] was not included.

- GM-CSF is approved for bone marrow reconstitution at high doses
- Effects in Prostate Cancer
 - No defined benefit for “systemic” doses of GM-CSF (high dose)
 - PSA modulation in some patients
- Adjuvant GM-CSF (low dose)
 - Designed for local not systemic effects
 - No changes in WBC subsets at this dose and schedule
 - Undetectable systemic levels 3 days after dose (only time point analyzed).
 - No activity as a single agent in murine models

HS3: How is prior vaccinia experience documented?

- Subject history or medical documentation
- Most subjects over the age of 45 have been vaccinated against smallpox (routine vaccination program ended in 1971).
- To ensure safety, we comply with CDC guidelines for patients who are vaccinia naïve.

HS4: Is the 28 day wash out [for glucocorticoids / immunosuppressives] described in Section 15 sufficient or should patients [with prior Abiraterone + Prednisone] be excluded?

- Safety: Current ongoing studies under FDA and OBA guidance utilize less stringent criteria (no systemic glucocorticoids within 14 days) with no adverse effects.
- Efficacy:
 - In a vaccinia-fowlpox prime-boost randomized phase 2 prostate cancer study with a primary immune endpoint, T-cell responses to PSA were maintained in an arm receiving concurrent weekly docetaxel and steroids (dexamethasone) and identical to the arm receiving vaccine alone.

HS7a/WK1: Given that arms V and P will be compared, it is not clear why a similar comparison between V+GM-CSF vs. V is not included.

- The goal is to determine if either experimental arm is better than the control arm.
- We expect the experimental arms to be relatively similar.
- Tax 327 statistics
 - 3 arm trial
 - No prespecified comparison between two experimental arms

WK2 ...was there any discussion to having any screening of pre-existing Left Ventricular dysfunction in patients since asymptomatic heart failure could certainly be present in this population...perhaps adding BNP levels...

- Exclusion for symptomatic disease utilizing CDC criteria based on careful history and physical exam and on NYHA classification
- BNP can be useful as an adjunct in certain cases however this test is quite variable
- In the smallpox vaccine campaign for first responders (healthy subjects) $n = 37,901$ (no requirement for cardiac screening), 633 per million (0.5 per 800)

JZ1 ...the placebo group will not be given vaccinia primer but instead will get “empty” fowlpox vaccine for both the primary and booster immunizations...Please justify.

- Prime and boost needed for experimental arms (A and B). The purpose of the control arm is to have a blinded non-treatment arm.
- Similar injection site reactions with fowlpox and vaccinia
- For added safety in the placebo arm only fowlpox will be used

Several reviewers had comments related to wording in informed consent form

- We agree with the comments and have provided the committee with a revised informed consent



NT-proBNP levels (in pg/mL) by NYHA functional class

	NYHA I	NYHA II	NYHA III	NYHA IV
5th Percentile	33	103	126	148
Mean	1015	1666	3029	3465
95th Percentile	3410	6567	10,449	12,188

NYHA Classification of Heart Failure

(New York Heart Association)

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Plasma Natriuretic Peptides for Community Screening for Left Ventricular Hypertrophy and Systolic Dysfunction

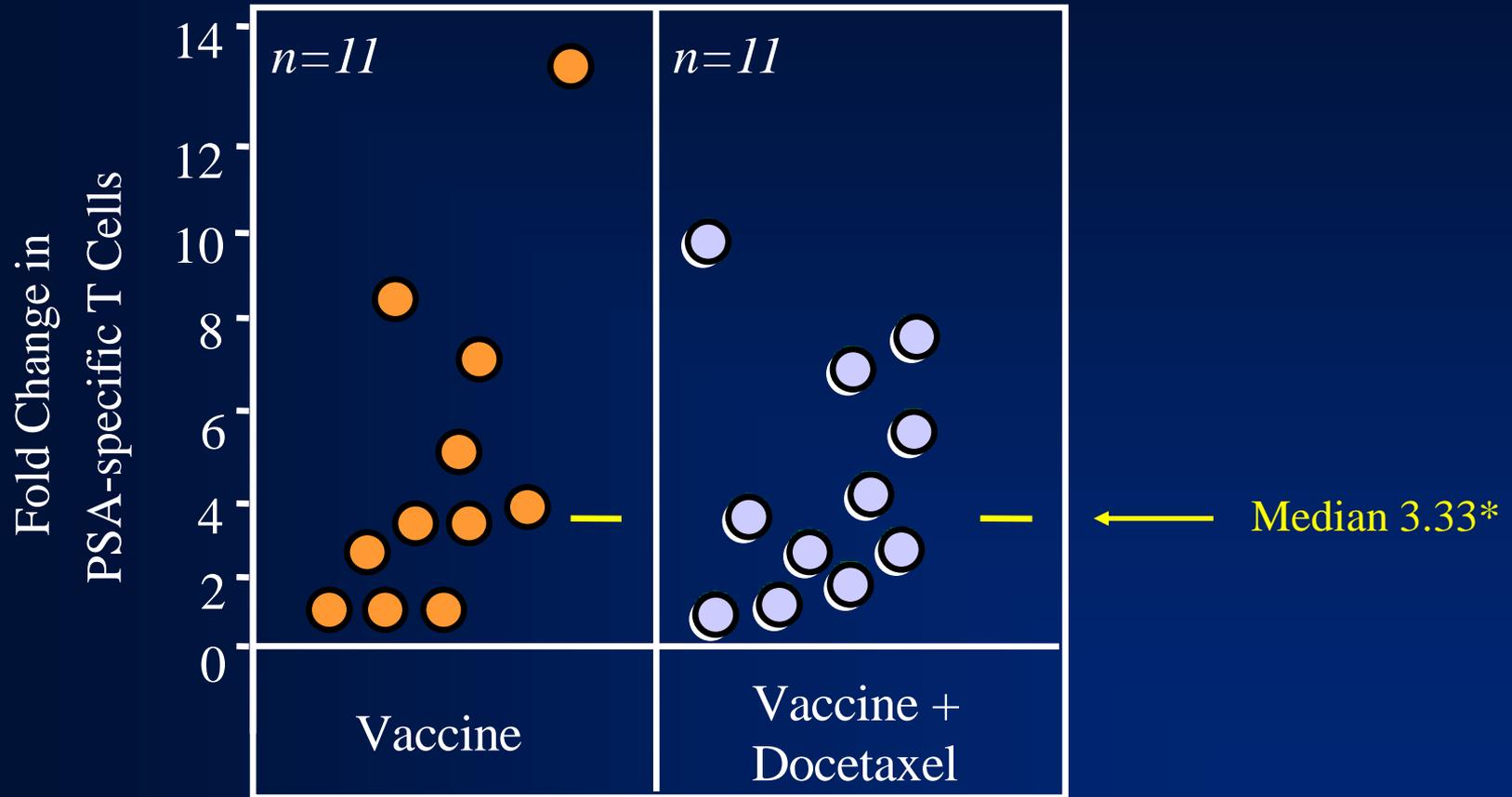
The Framingham Heart Study

JAMA, September 11, 2002—Vol 288, No. 10

Conclusion In our large community-based sample, the performance of BNP and NT-ANP for detection of elevated LV mass and LVSD was suboptimal, suggesting limited usefulness of natriuretic peptides as mass screening tools.

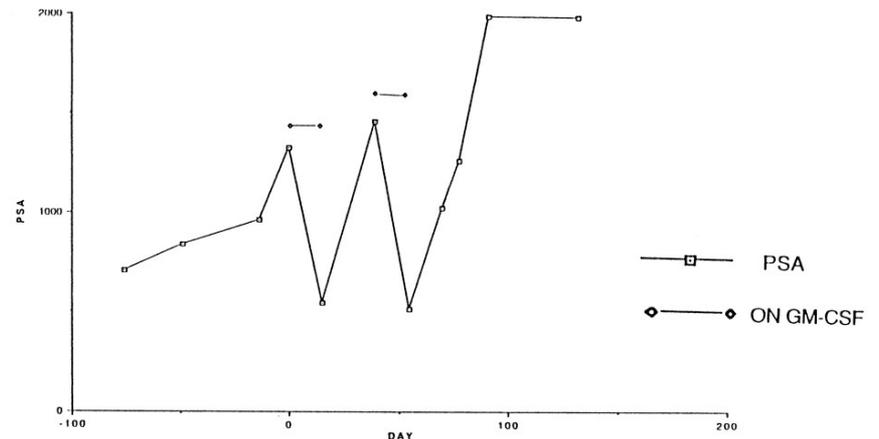
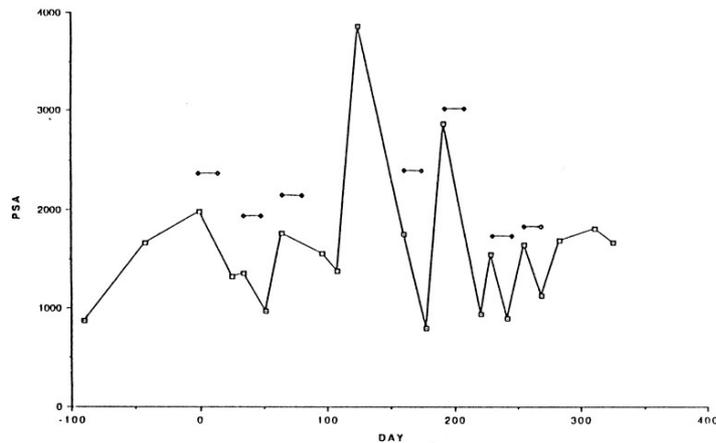
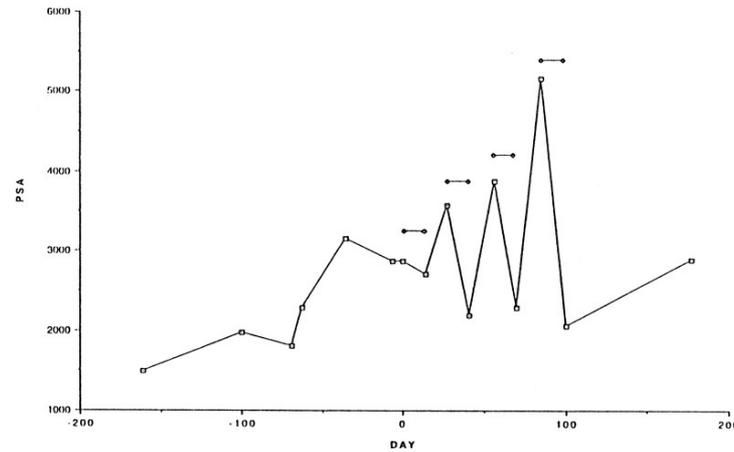
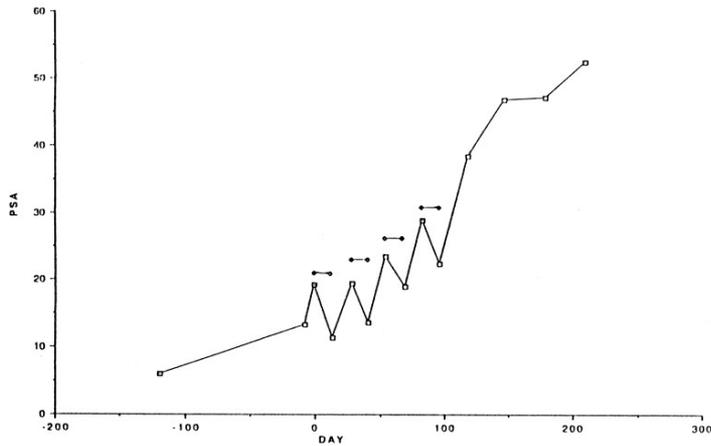
**Good tool for diagnosis or following treatment
may not be a good tool for screening**

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

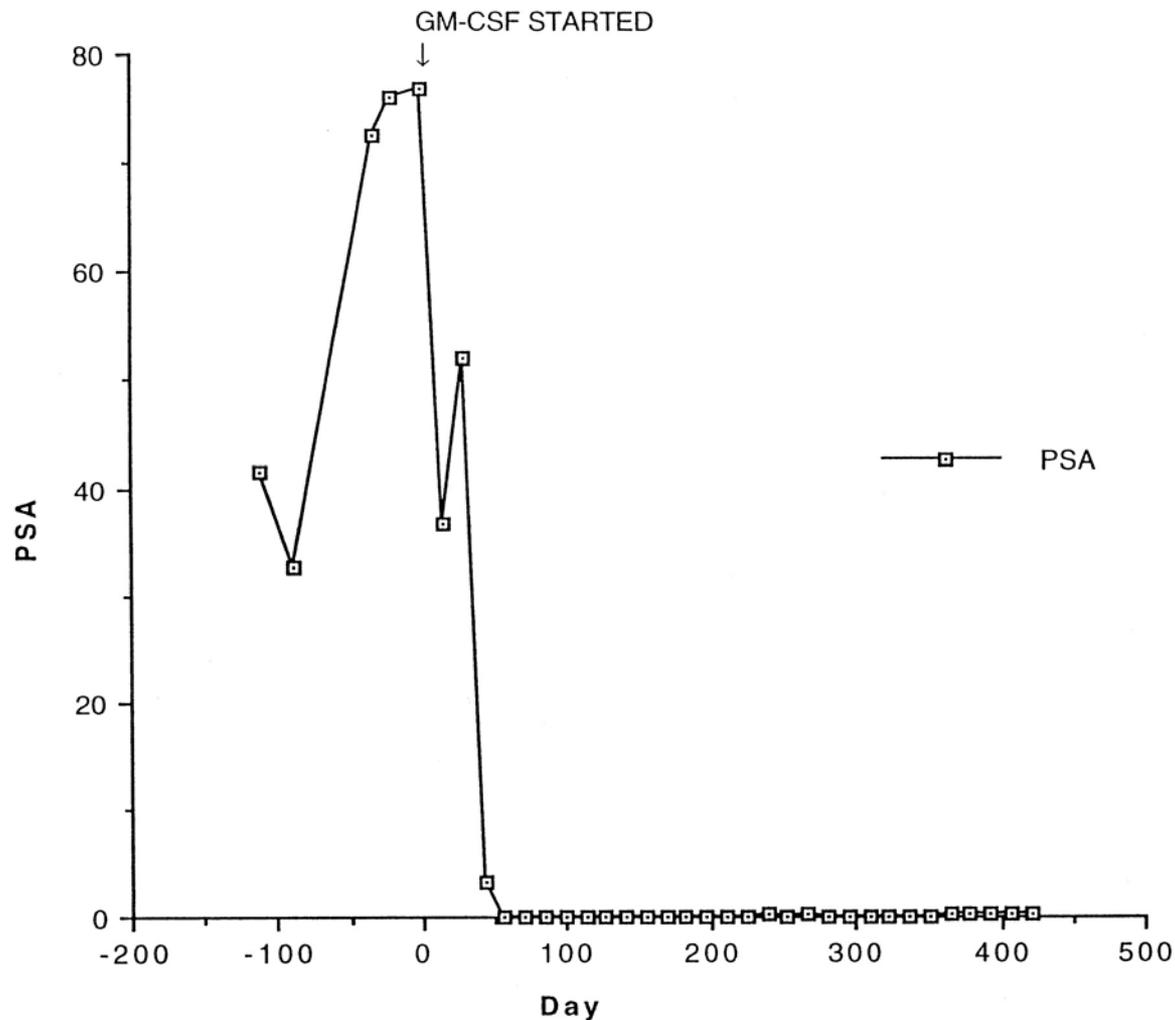
PSA levels from four representative patients from cohort I who developed oscillating PSA values while receiving GM-CSF therapy.



Small E J et al. Clin Cancer Res 1999;5:1738-1744

In a first cohort of patients ($n = 23$), GM-CSF was administered s.c. at a dose of $250 \mu\text{g}/\text{m}^2$ daily for 14 days of a 28-day treatment period.

PSA levels in a patient from cohort II who had a sustained PSA response to GM-CSF therapy.



Small E J et al. Clin Cancer Res 1999;5:1738-1744

Second trial was performed in which patients ($n = 13$) received maintenance GM-CSF ($250 \mu\text{g}/\text{m}^2$ three times weekly) after the first 14 days of daily GM-CSF. 1 pt with PSA decline $>50\%$.

HS7b: The HR reduction in mortality of 32% is “aggressive,” even with the recognition that the phase 2 trial results suggested a 44% reduction, and consideration should be given to increasing the sample size further.

- The critical hazard ratio that is needed for a positive study is HR 0.82. This corresponds to reduction in mortality of 18%.
- This critical HR is more conservative than any drug shown to improve survival and currently approved in the metastatic CRPC setting.

HS9: The secondary efficacy endpoint of radiographic event-free survival is “difficult” to assess without central radiologic review and a dedicated Radiology Charter specifying criteria for soft-tissue changes.

- We agree and plan to have a central radiographic review and a dedicated Radiology Charter.