Repetitive DNA Vaccination Elicits PAP Antigen-Specific T-Cell Immune Responses in Patients with Castration-Resistant Prostate Cancer

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Disclosures

Dendreon Corporation – consultant

Intellectual property – WARF

Outline

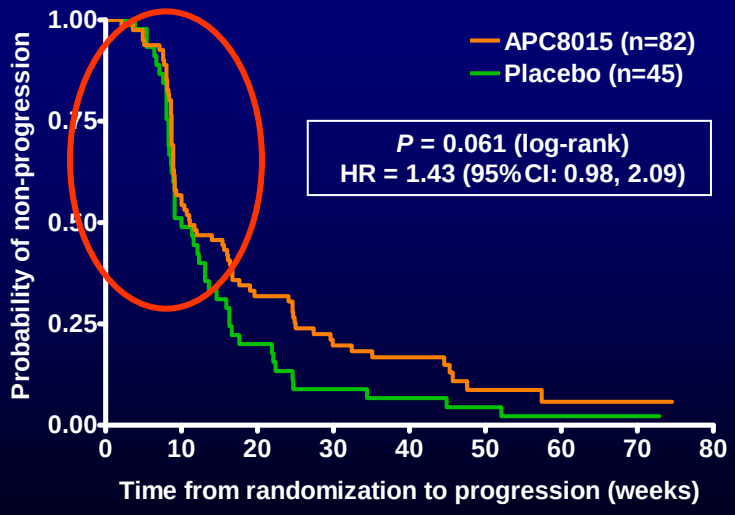
- Background
  - Prostate cancer immunotherapy
  - Previous experience
    DNA vaccine encoding prostatic acid phosphatase (PAP)
- Pilot Clinical Trial
  - Evaluation in patients with non-metastatic prostate cancer
  - Immune monitoring to answer questions of vaccine schedule

Prostate Cancer

- Most commonly diagnosed cancer in the United States
- Second leading cause of cancer-related death in men
- Approximately 1/3 of patients have recurrent disease after “definitive” local therapy
- 240,890 projected new cases in 2011
- 33,720 projected deaths in 2011

Immunotherapy for Prostate Cancer

- Sipuleucel-T approved by FDA in 2010 – first approved anti-tumor vaccine in U.S.
- Approved on the basis of improved overall survival
- Time to progression endpoint in previous trial not met
- Similar findings with PSA-TRICOM vaccine approach



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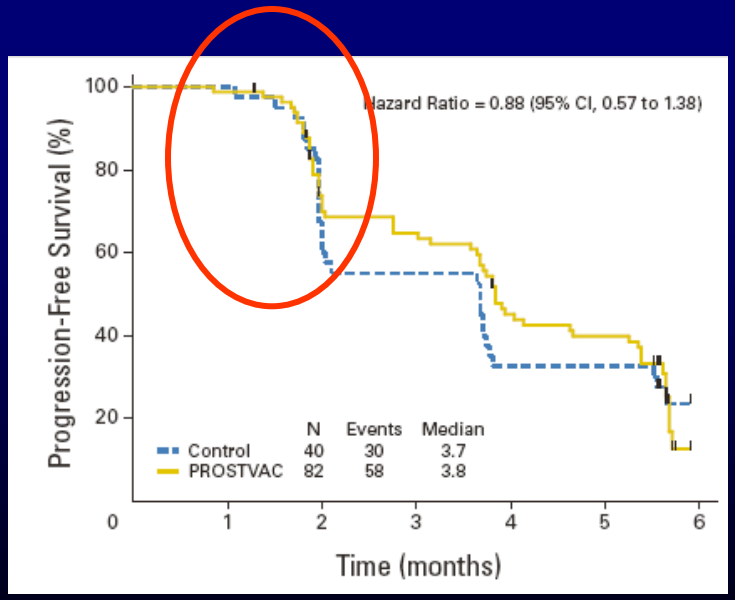
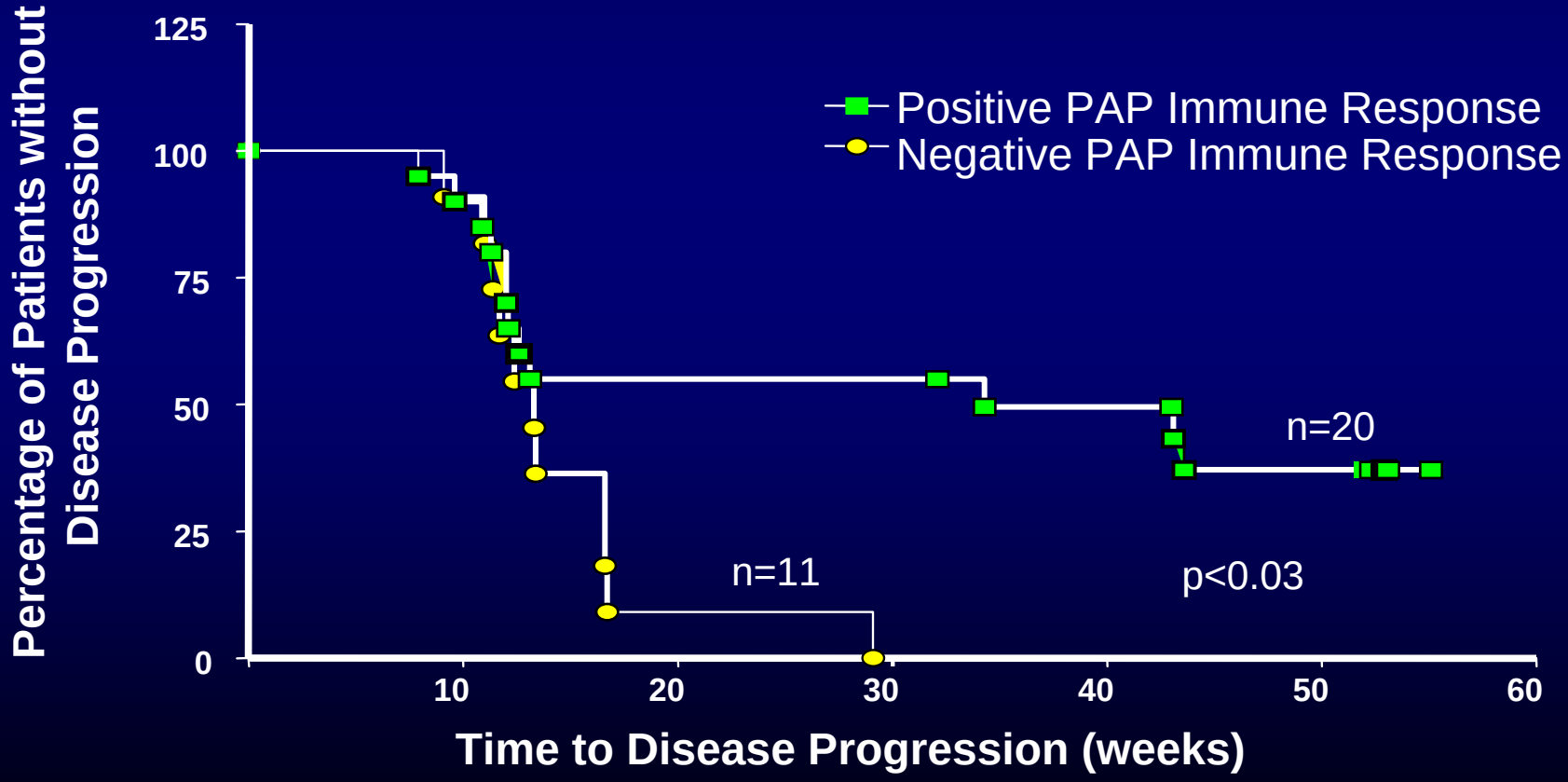


Kantoff (2010) J Clin Onc 28:1099

Questions Regarding Immunotherapy for Prostate Cancer

Why was there no clear association between TTP and OS? Or T-cell immune response and OS or TTP?

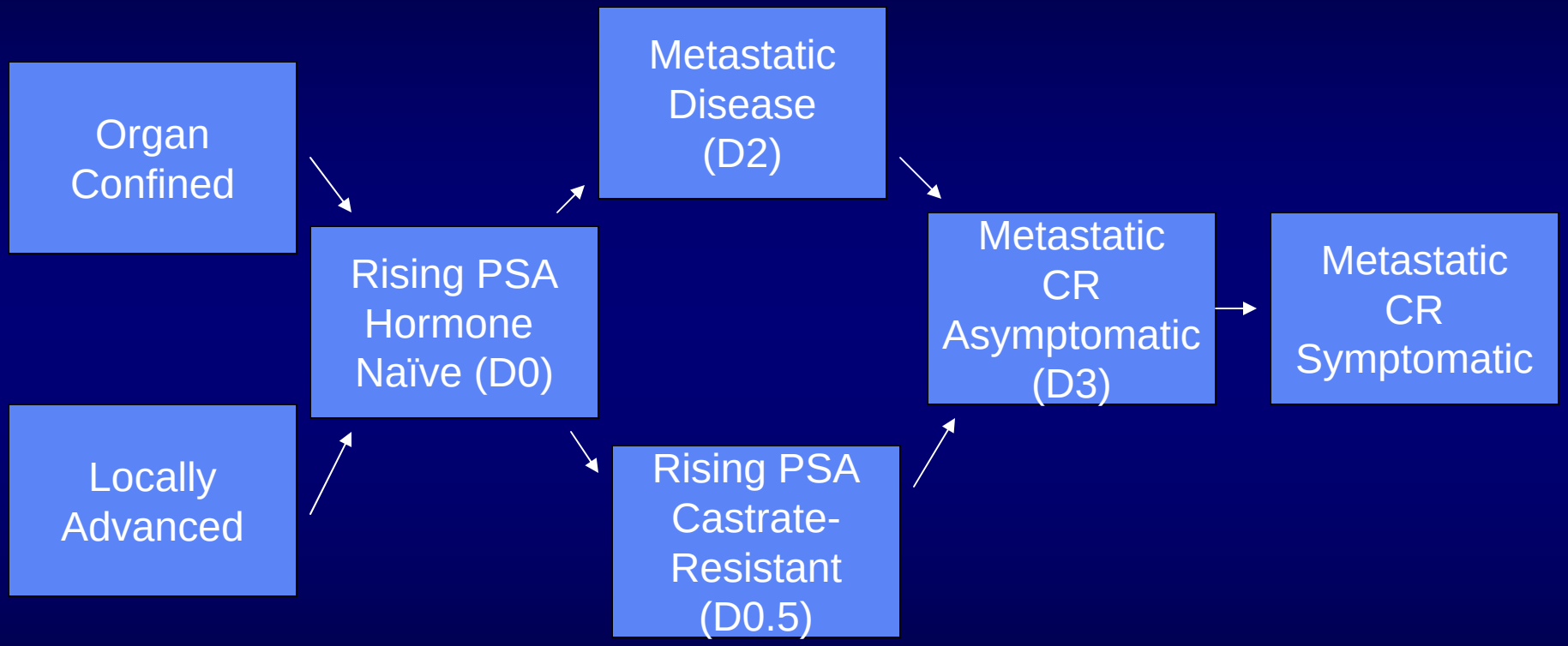


Small (2000) *J Clin Oncol* 18:3894

- Other preclinical studies and anti-tumor vaccine trials have suggested that anti-tumor vaccines might “take time to work” and/or be most effective in the minimal-residual-disease setting.

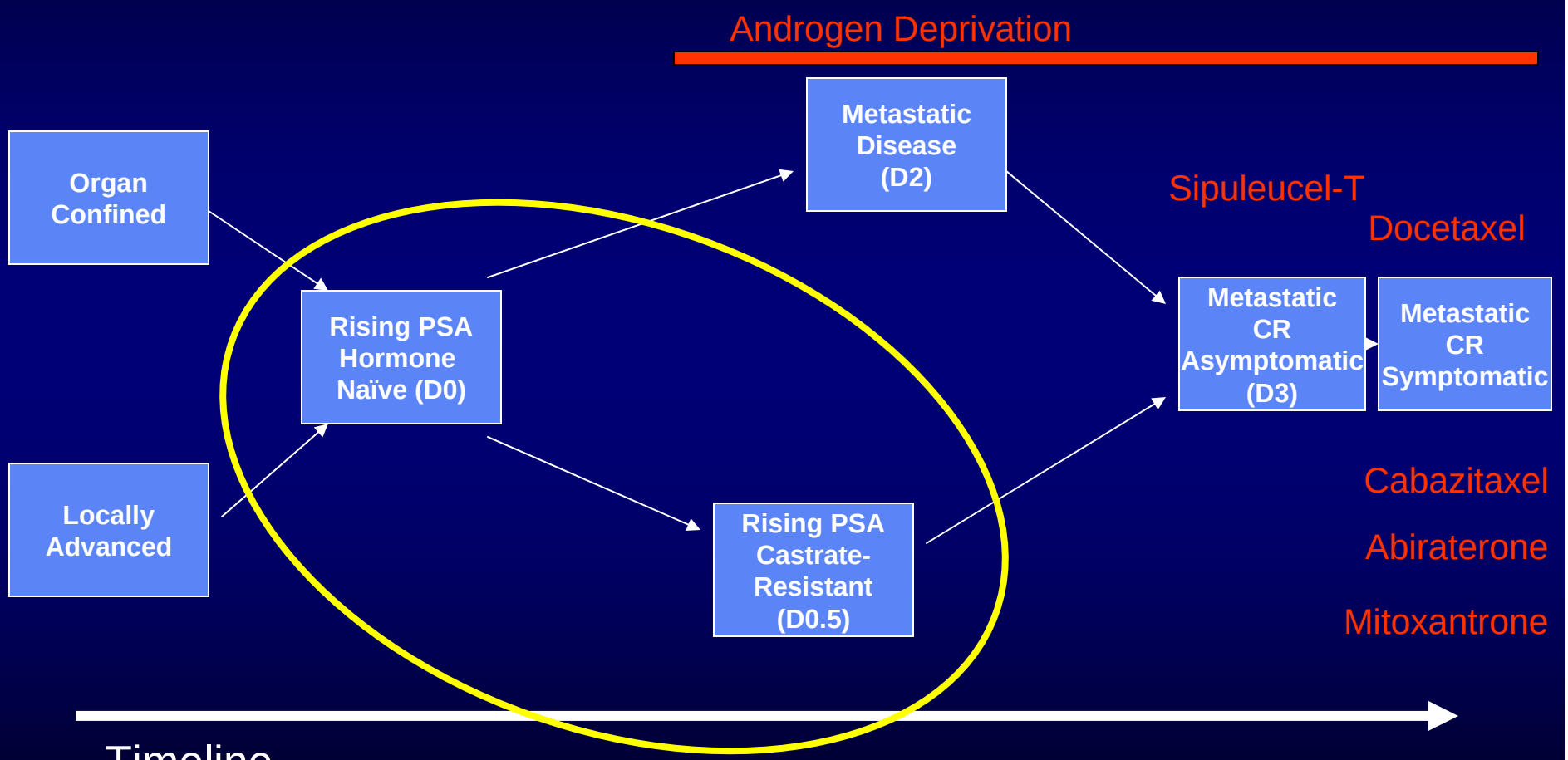
- Is it possible that the advanced stage of prostate cancer that has been most evaluated is not optimal to detect time-to-progression and immunological readouts?

Prostate Cancer



PSA = prostate-specific antigen
CR = castrate-resistant
Modified from: Scher HI, et al. *Urology*. 2000; 55:323-327.

Prostate Cancer



PSA doubling time highly associated with time to progression in stages of disease with only rising PSA

Prostatic Acid Phosphatase – Vaccine Target Antigen

- Expression essentially restricted to prostate tissue in humans
- Permits evaluation of serum PSA as an independent assessment of response in human trials
- Previous experience targeting this antigen in rodent models and human clinical trials:
  - Vaccinia, pulsed dendritic cell (Fong, Stanford)
  - Antigen-presenting cell vaccine (Dendreon corp.)

Antigen-Specific DNA Vaccines

Advantages:

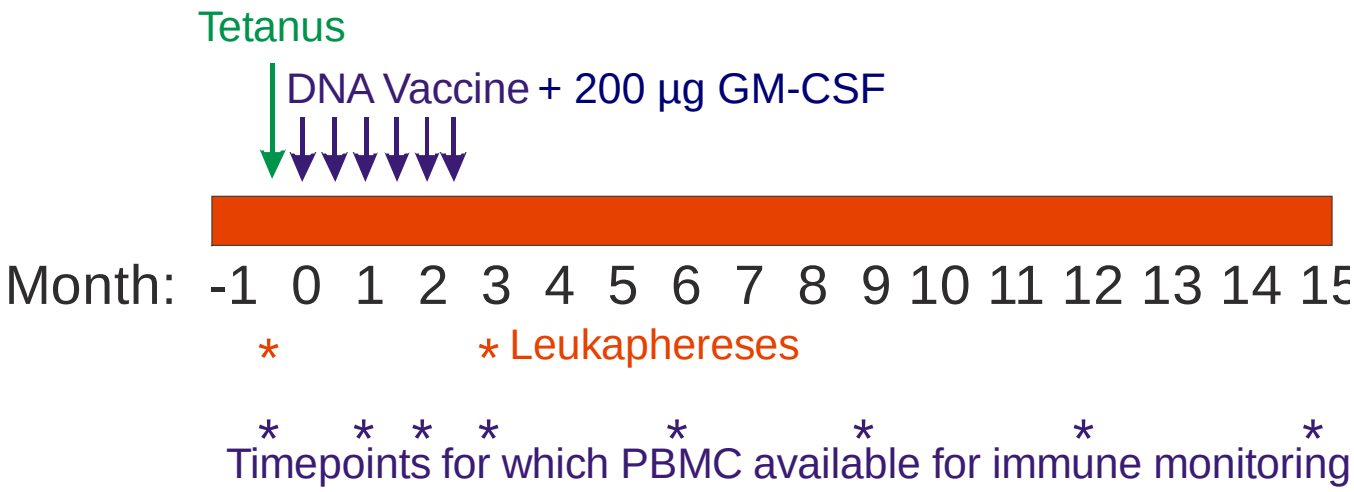
- Simpler, less costly, manufacturing and storage
- Non-autologous
- Not MHC-restricted
- No foreign viral antigens
  - Safety
  - No need for heterologous immunization approach
- Validated in non-human (companion dog) trials

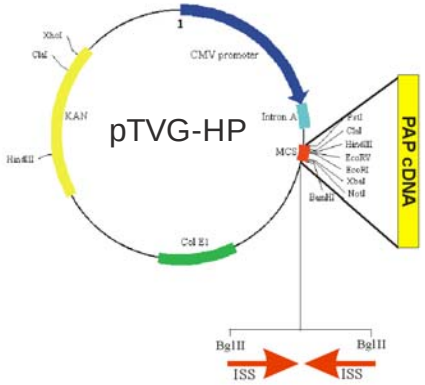
Disadvantage:

- Less immunologically potent

Phase I Trial – DNA Vaccine Encoding PAP Study Design

Patients with stage D0 prostate cancer





Dose Escalation Schedule

Dose Level	pTVG-HP
1	100 µg
2	500 µg
3	1500 µg

McNeel, JCO ’09 27:4047

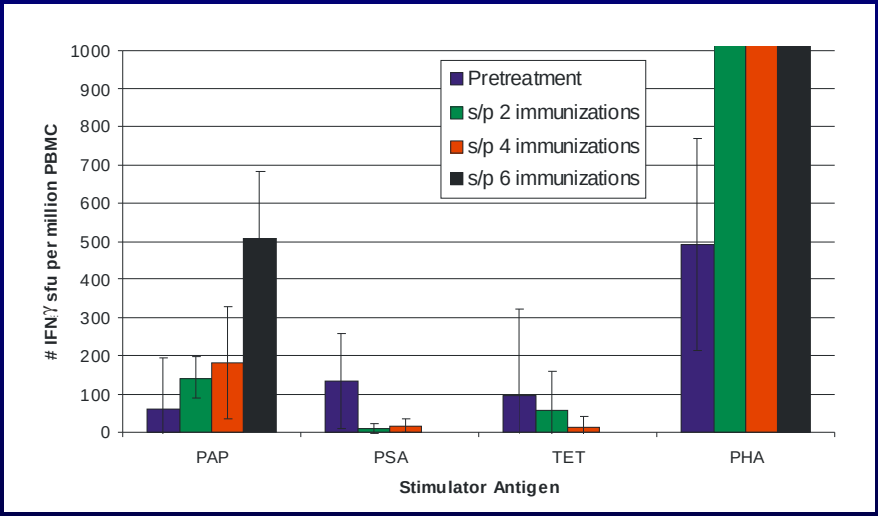
Prostate Cancer – Stage D0 Trial Lessons Learned

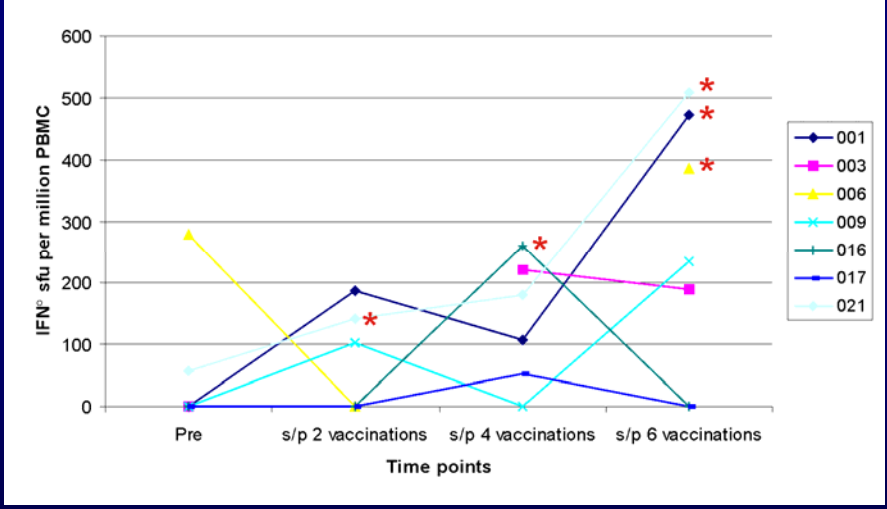
- PAP-specific T-cell immune responses elicited
  - CD8+ T cells – IFNγ-secreting
  - CD4+ and CD8+ T-cell proliferation
  - HLA-A2-restricted cytolytic activity
  - Immune responses elicited irrespective of dose
- No PAP-specific antibody responses elicited

- No significant adverse events

Prostate Cancer – Stage D0 Trial Lessons Learned (cont)

Immune responses detectable after immunization appeared to require several vaccinations





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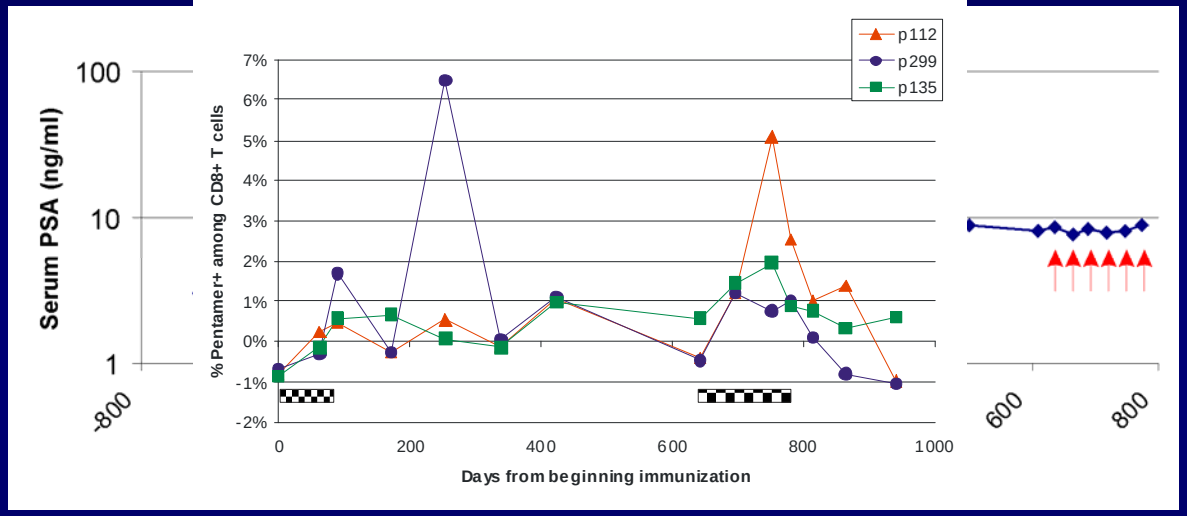
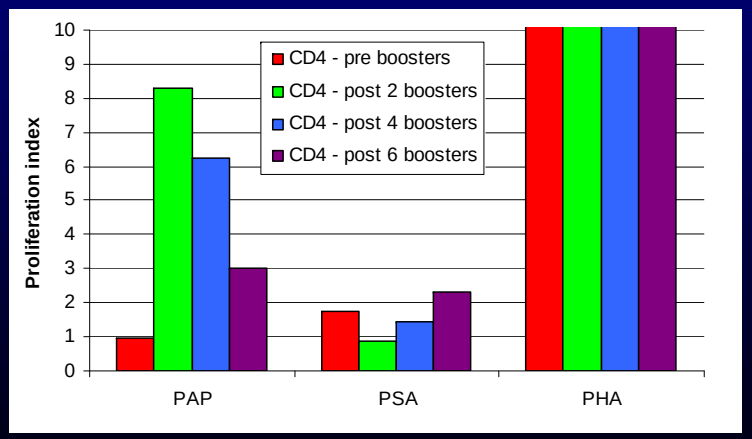
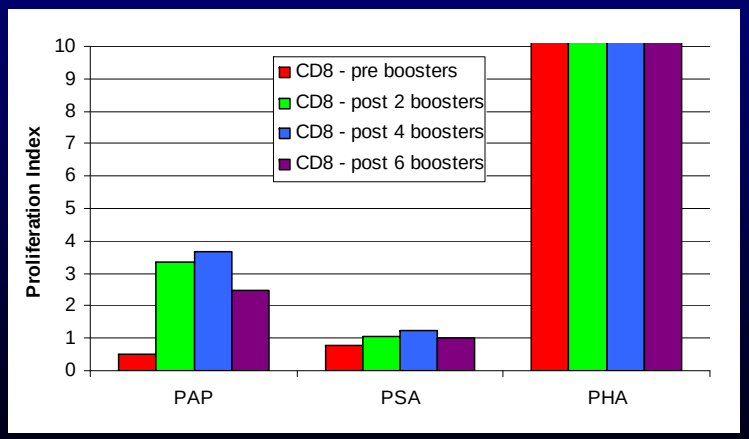
Prostate Cancer – Stage D0 Trial Lessons Learned (cont)

Immune responses were “boostable”







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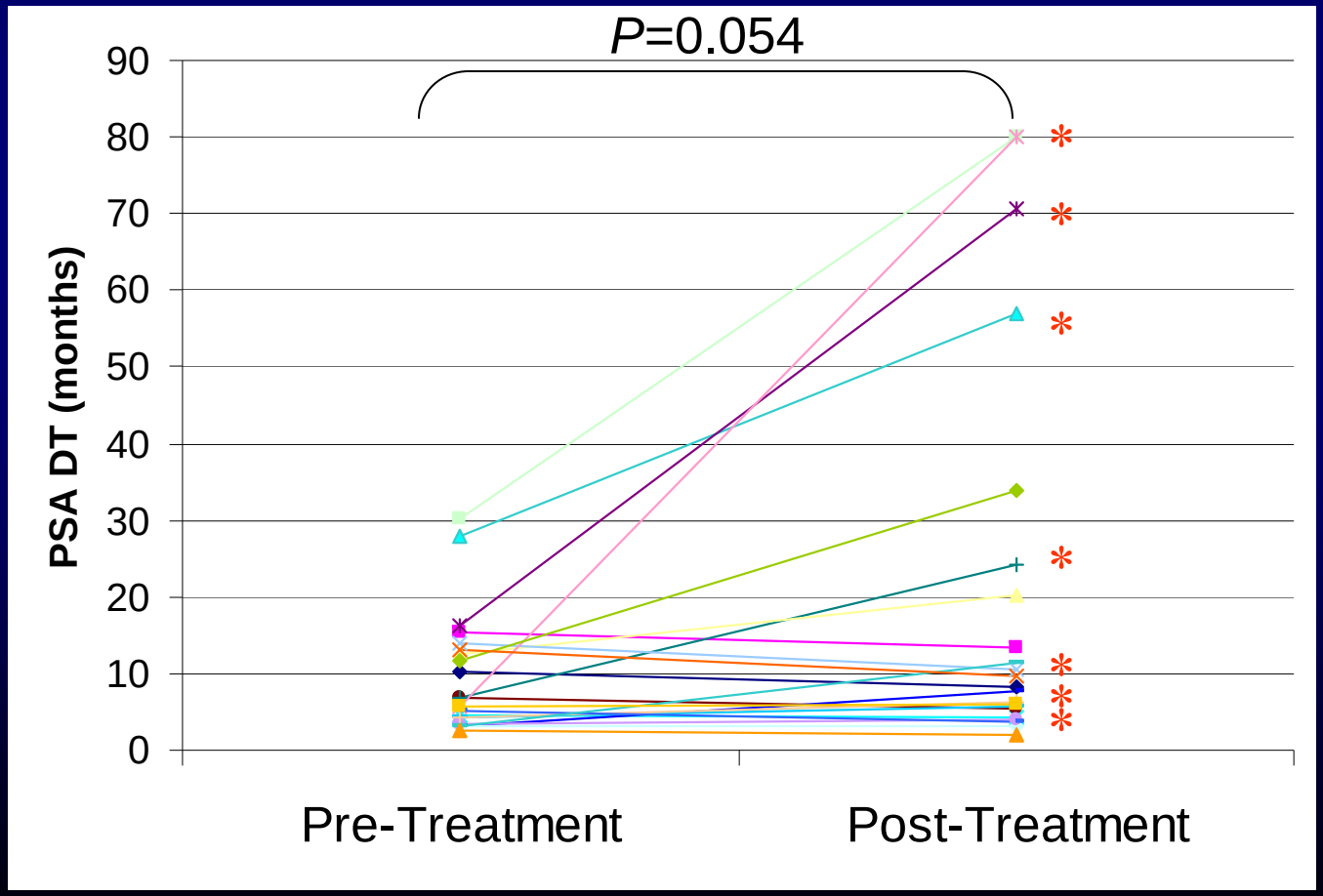
Prostate Cancer – Stage D0 Trial Lessons Learned (cont)

Detection of PAP-specific IFNγ responses at least twice in 1 year of follow up (*) associated with favorable change in PSA doubling time (*P*=0.001)



Hypotheses

- Multiple immunizations may be necessary to elicit responses in some individuals
- Development of long-term, durable memory immune responses may be associated with long-term stable disease
- Periodic booster immunizations may be necessary to maintain Th1-type response

Objectives / Endpoints

Primary Clinical Endpoint:

To determine the safety of multiple serial immunizations in a castrate-resistant, non-metastatic population

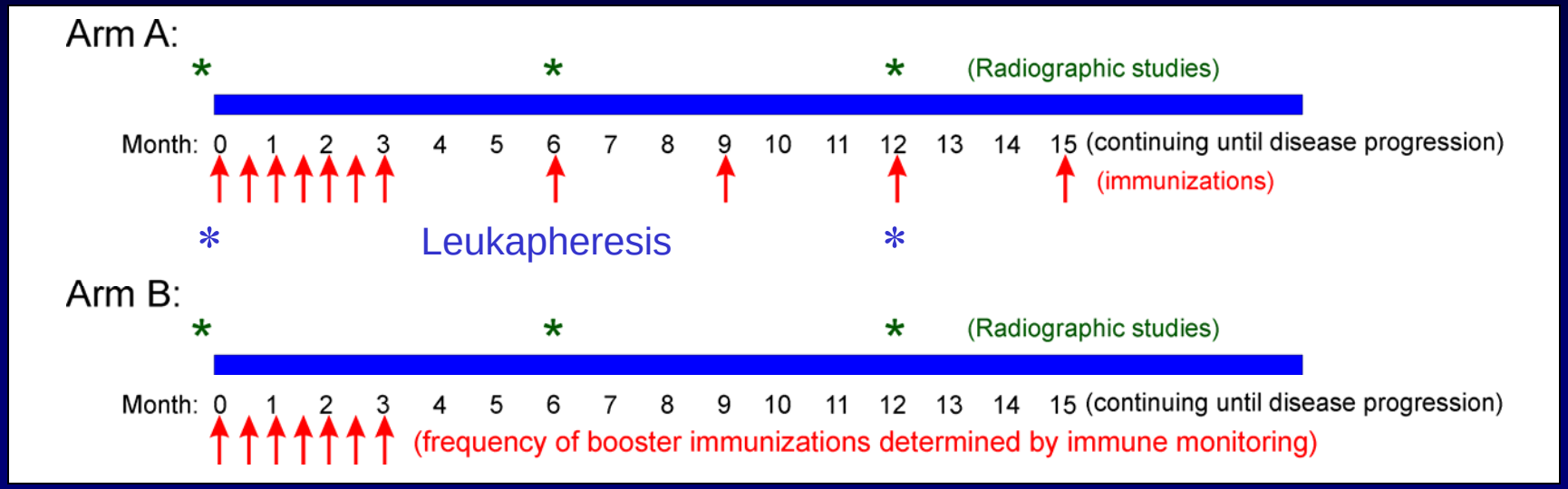
Primary Immunological Endpoints:

- Determine whether long-term, memory PAP-specific T cells can be elicited
- Determine an optimal schedule of immunization to maintain effector/memory T-cell response

Secondary Endpoints:

- Determine if immunization associated with prolonged PSA doubling time
- 1-year metastasis-free survival

Trial Schema



- PAP DNA vaccine 100 µg + 200 µg rhGM-CSF (adjuvant) intradermally
- Tetanus immunization given prior
- Patients remain on study until:
  - Radiographic progression
  - Toxicity
  - Personal choice to discontinue
  - 2 years or maximum of 24 immunizations

Study Population – Entry Criteria

- Stage D0.5 prostate cancer, defined as:
  - Castrate-resistant
  - Rising serum PSA
  - No evidence of metastases by CT or bone scan
- All (minimum of 4) serum PSA values available over a 3-6 month period, last value > 2 ng/mL, all from same clinical laboratory – for pretx PSA DT

- ECOG PS < 2
- Normal hematological, renal, liver function
- Not on immunosuppressive therapy

Trial Conduct

Accrual: 14 patients as of October 2011, of whom
11 have completed 1 year

8 have come off study
2 for PD (6, 15 months)
1 for choice – rising PSA (9 months)
1 for grade 3 allergic reaction (15 months)
4 completed study
3 received 24 immunizations
1 on study for 2 years

9 of 11 have been / were on study $\geq$ 1 year
6 remain on study

Demographics

Age, median:	73.5 years (range 47-86)
Prior treatment:	
Prostatectomy	7 (50%)
Radiation therapy	
Primary treatment	3 (21%)
Salvage treatment	5 (36%)
Gleason Grade	
<7	3 (21%)
7	6 (43%)
8	1 (7%)
9	4 (29%)
Pre-treatment	
PSA, median:	5.35 ng/mL (range 2.3 – 54.4)
PSA doubling time, median:	2.8 months (range 1.36 – 5.48)

Adverse Events

	Grade 2	Grade 3	Grade 4
Allergic / Hypersensitivity	2	1	
Dermatologic			
Injection site reactions	1		
Rash / desquamation	1		
Laboratory / metabolic			
Elevated creatinine	1		

Immune Analysis

Real-Time Immune monitoring:

- PAP-specific CD4+ and CD8+ T-cell proliferation
  (dye dilution to determine precursor frequency)
- PAP-specific IFNγ release (ELISPOT)
- PAP-specific granzyme B release (ELISPOT)

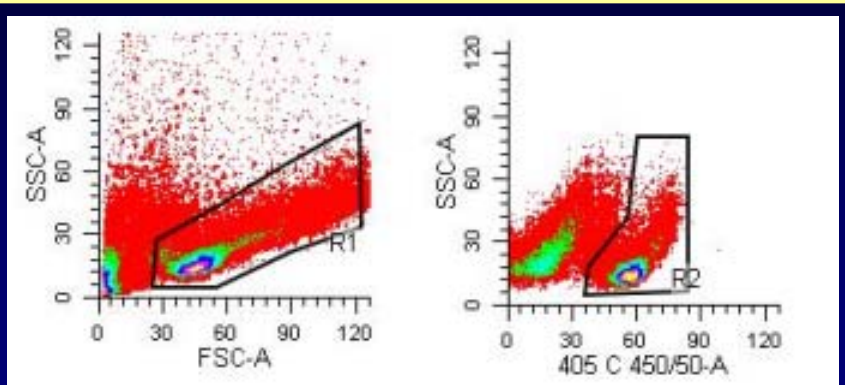
"Response" defined as statistically significant compared with media-only control, and at least 3x baseline value.

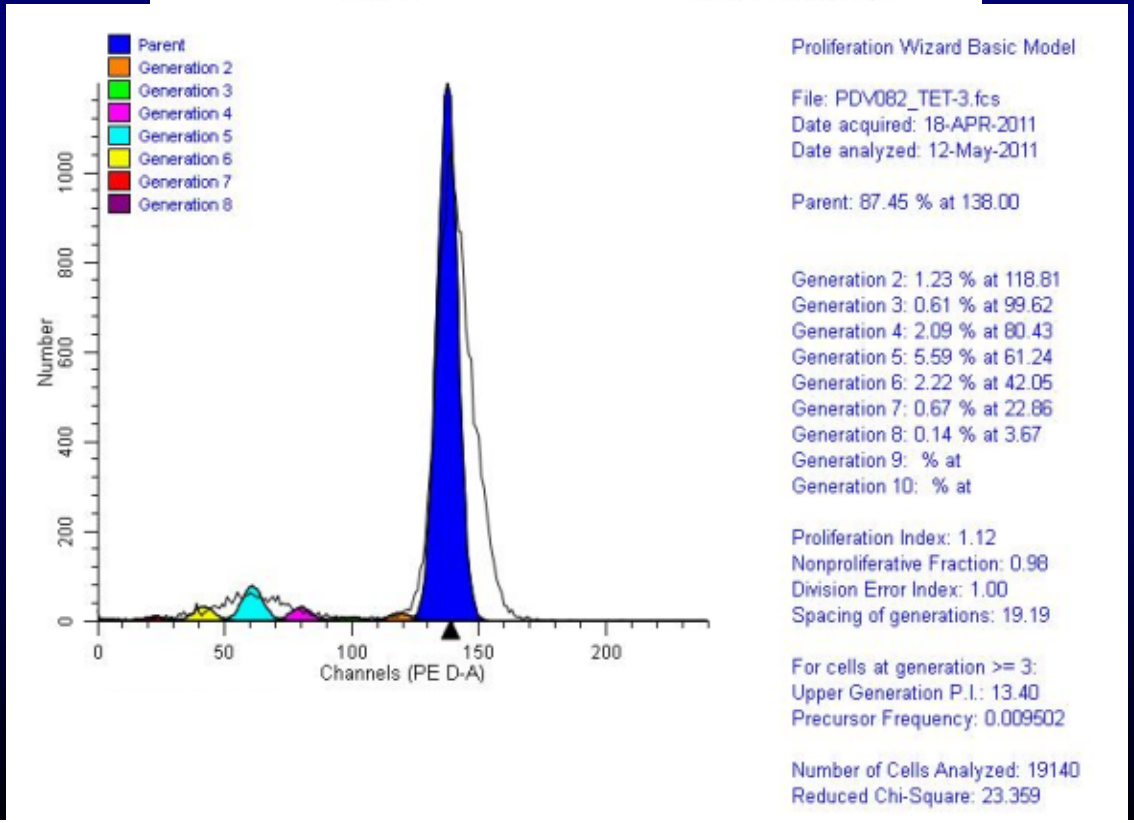
Baseline cryopreserved sample evaluated with each timepoint

Other measures:

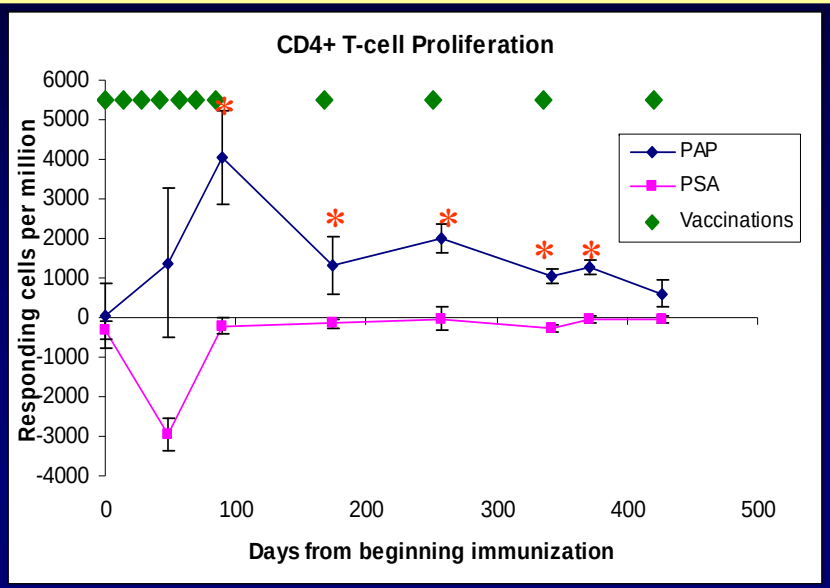
- Memory phenotype of antigen-specific proliferating cells
- Cytokine expression of proliferating cells
- Tetramer analysis of HLA-A2+ individuals
- PAP-specific antibody (IgG) responses

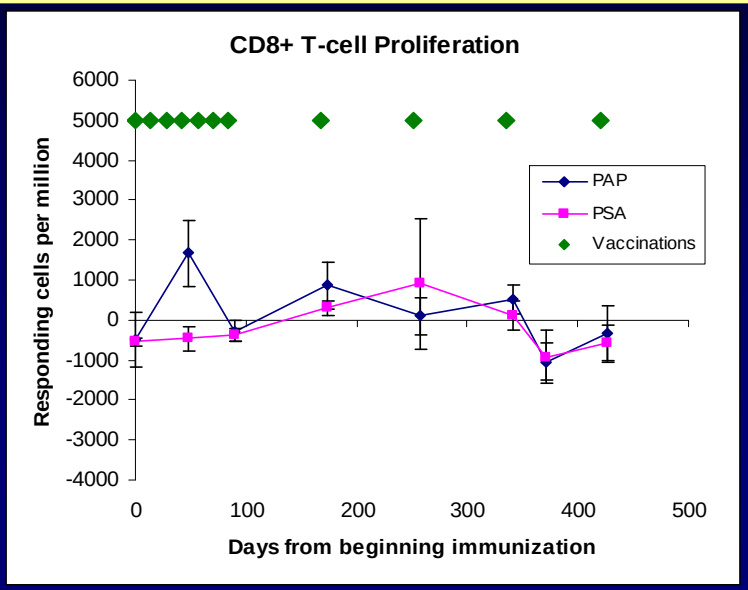
Immune Analysis – T-Cell Proliferation

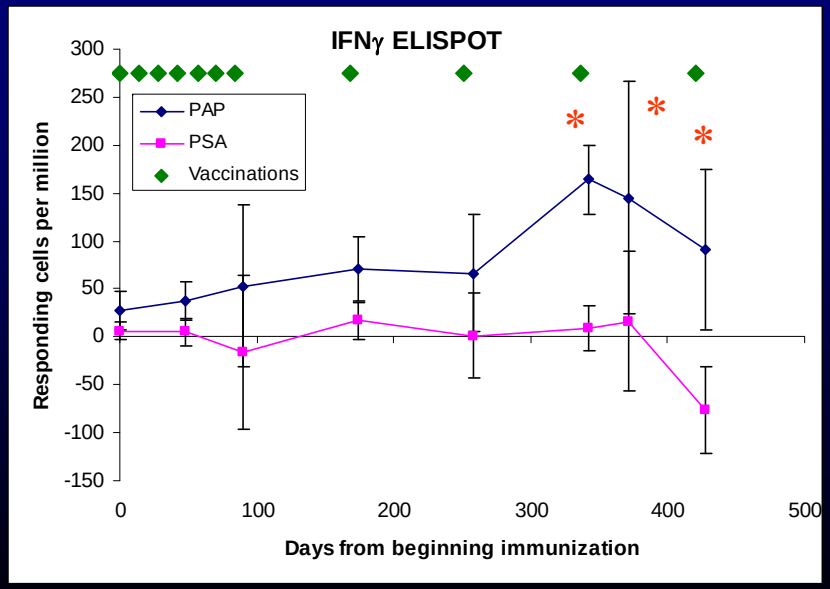


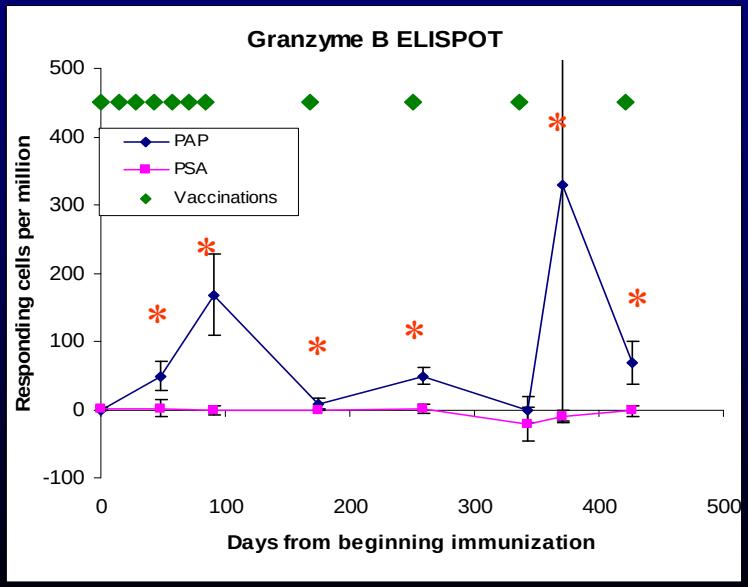


Example Real-Time Immune Analysis Immune Responder

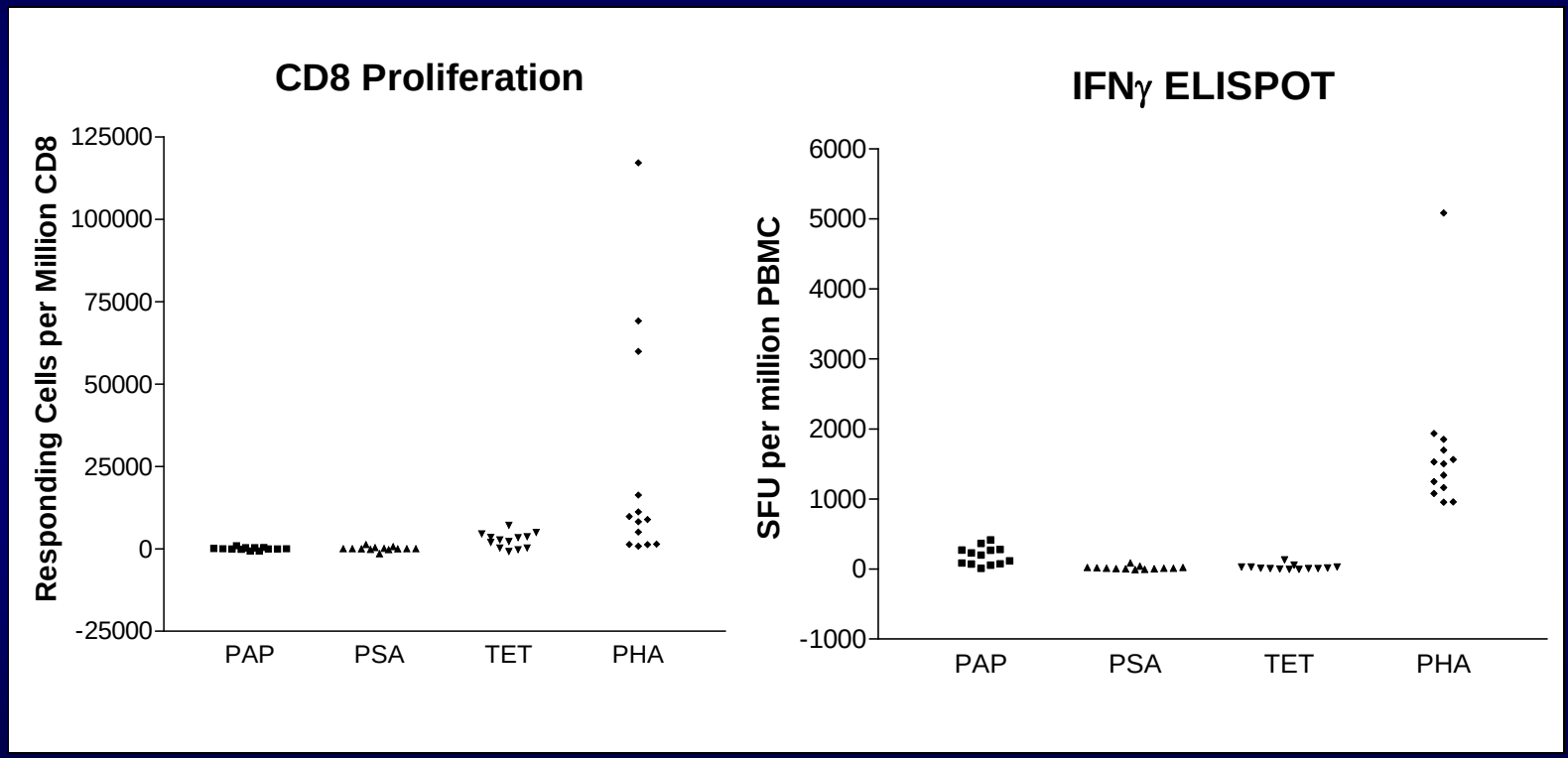




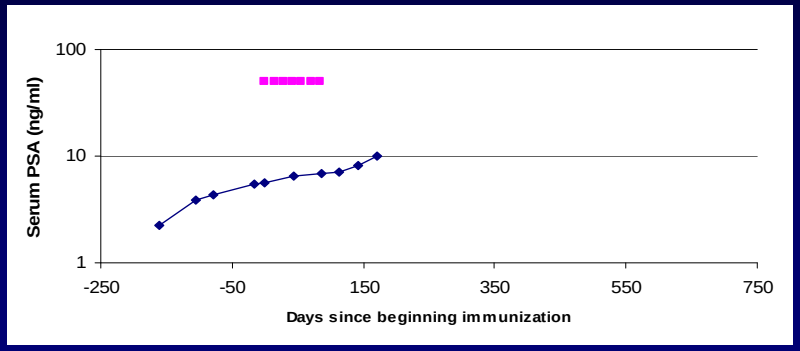


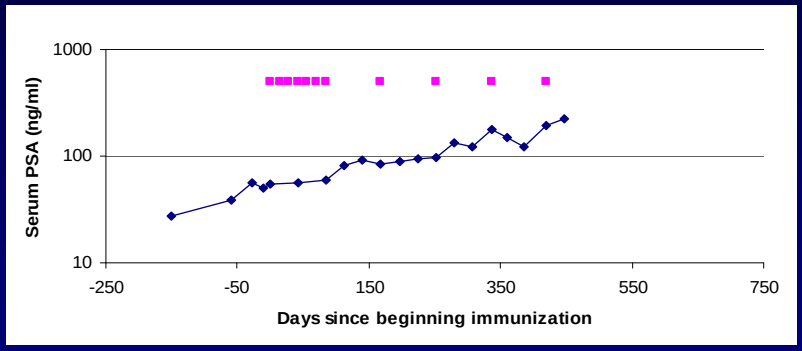


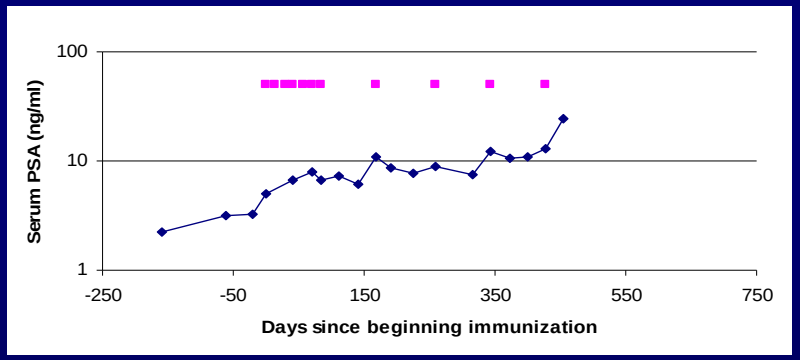
Baseline Immune Analysis Reproducibility over Time

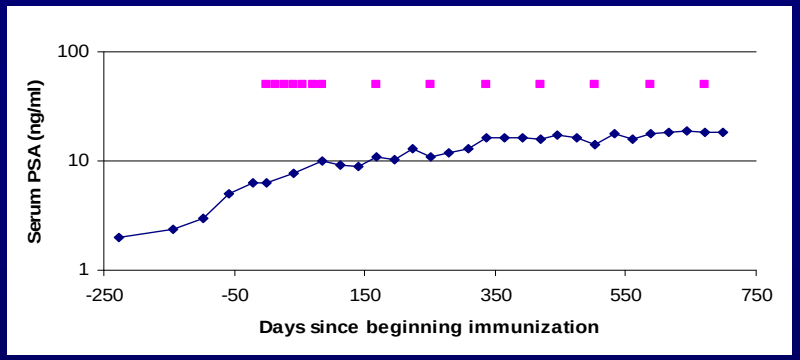


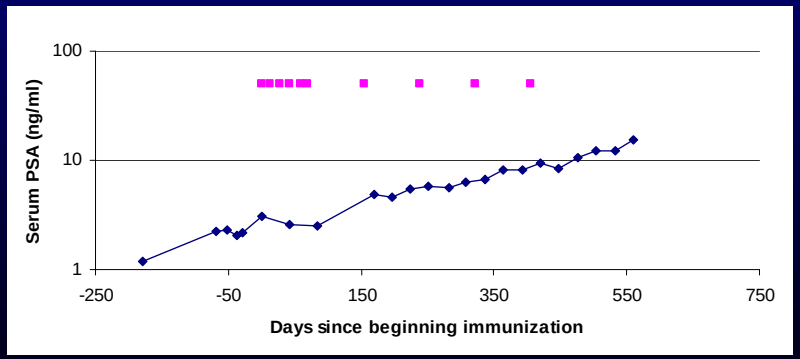
PSA Monitoring with Immunization Fixed Schedule



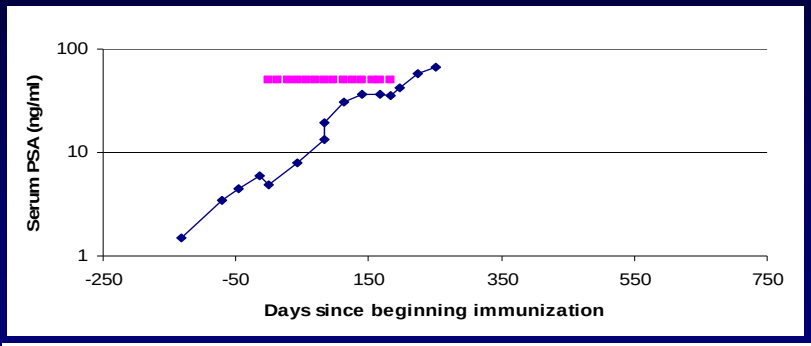


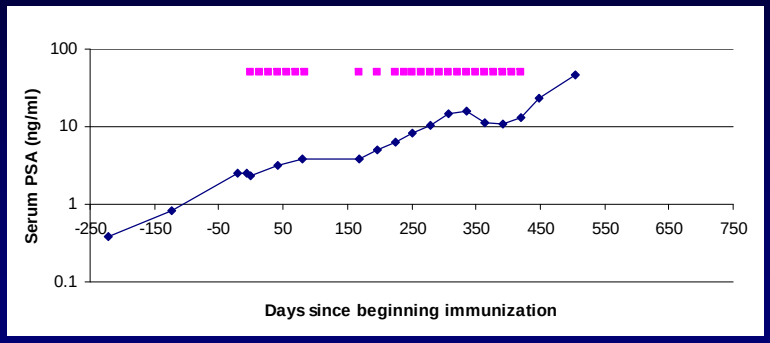


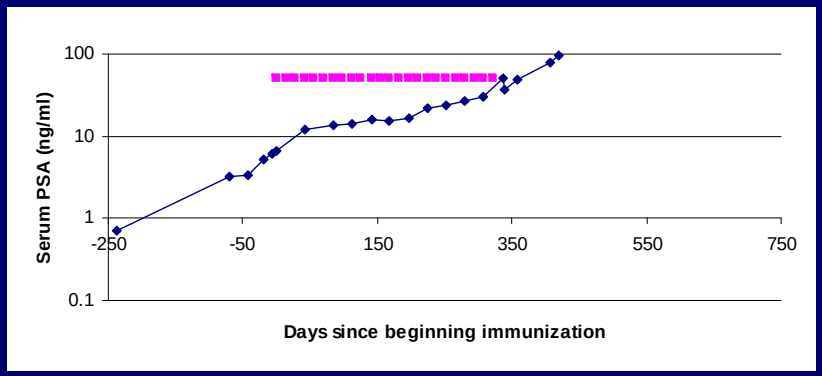


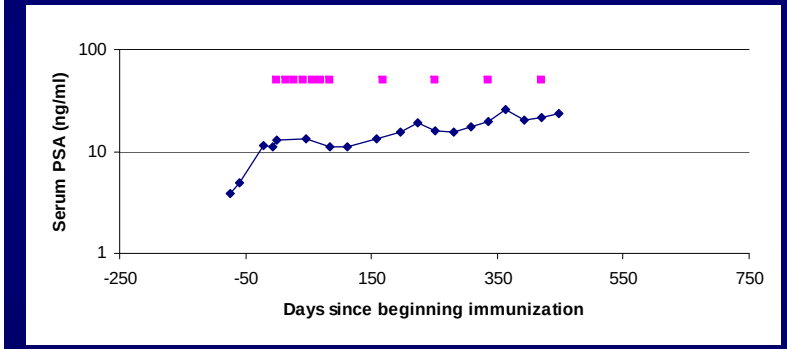


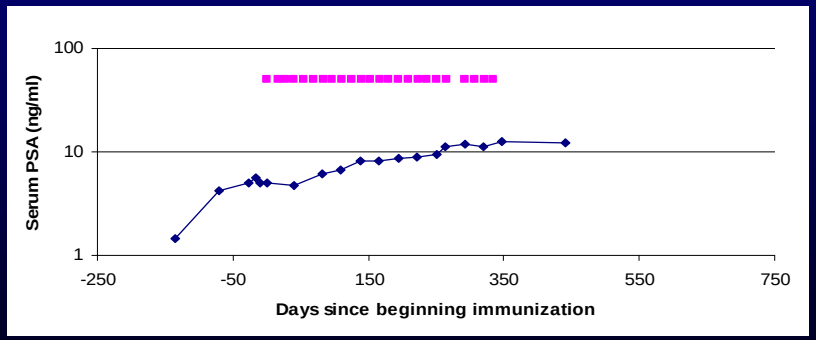
PSA Monitoring with Immunization Variable Schedule with Monitoring

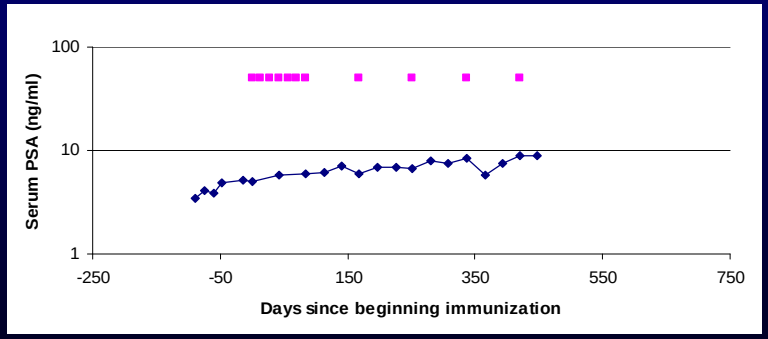




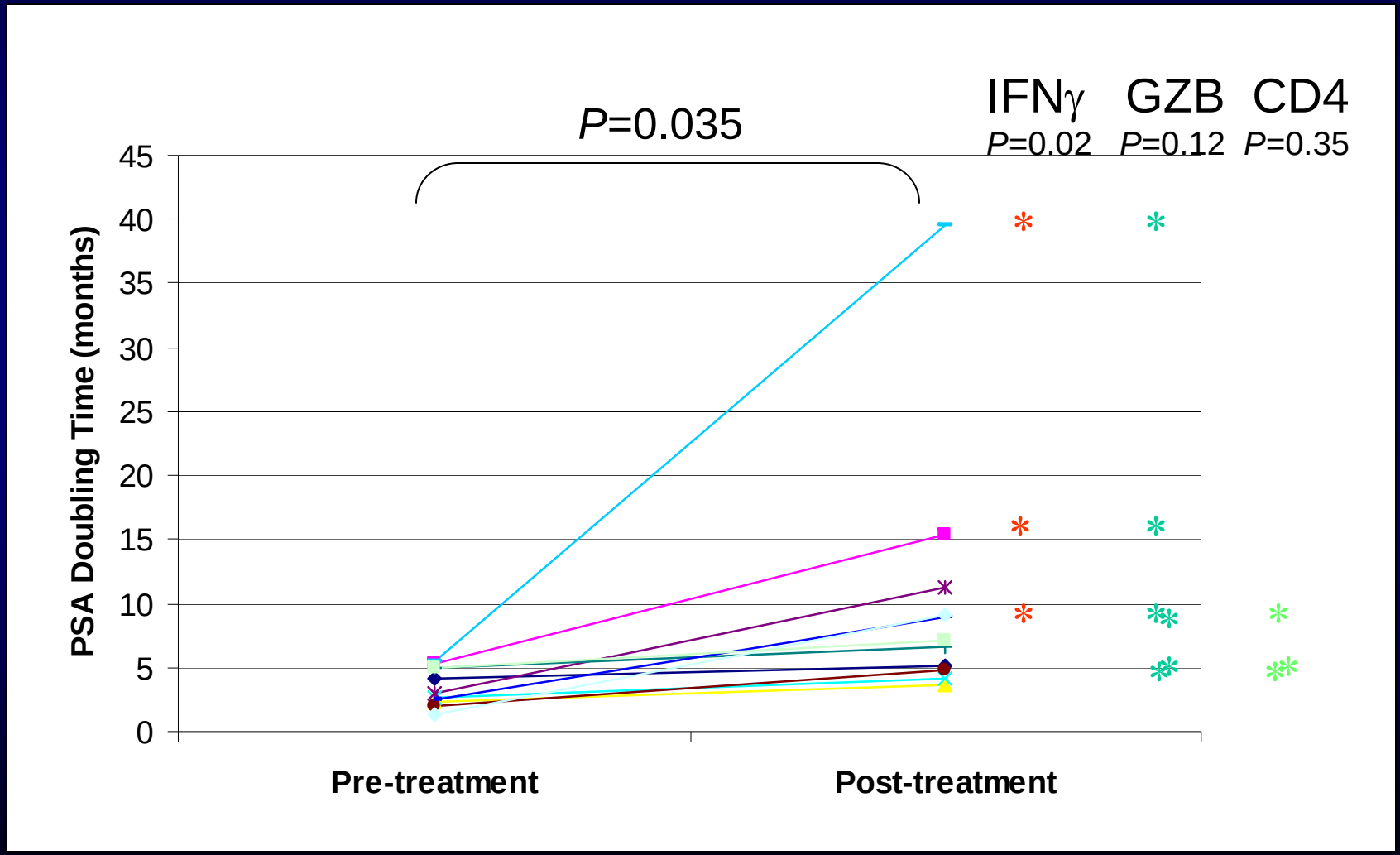








Changes in PSA Doubling Time Associated with Long-Term Th1-Type Immunity



Summary and Preliminary Trial Conclusions

- Multiple repetitive immunizations appears safe
- Long natural disease history appropriate for evaluating long-term effects of anti-tumor vaccines
- Different patterns of immune “response”
- To date, identification of optimal schedule challenging due to delayed immune responses
- IFNγ-secreting responses identified at multiple times after immunization most associated with favorable changes in PSA doubling time

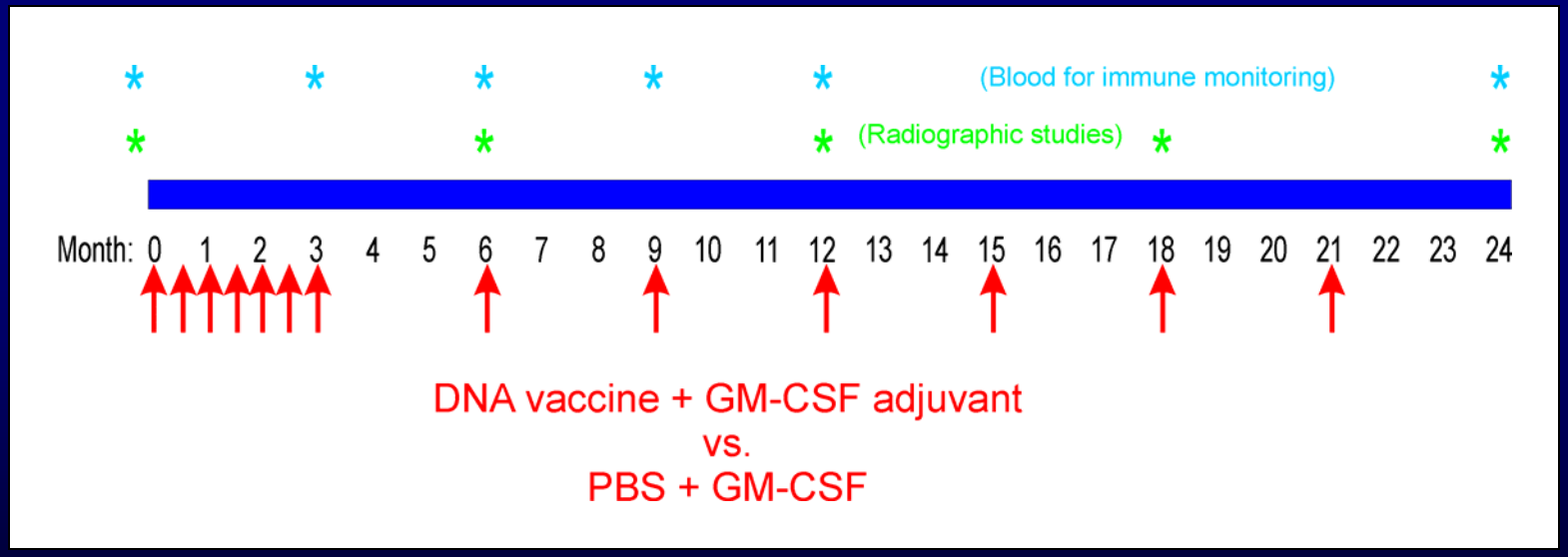
Unanswered Questions and Future Directions

- Does vaccination (and/or change in PSA doubling time occurring after vaccination) affect time to disease progression?
- Does establishment of long-term immune response confer benefit in terms of time to disease progression?
- What differences exist in some patients pre-treatment that make them not “immunizable”?

Ongoing Randomized Phase II Trial

Primary Objective:

To evaluate the 2-year metastasis-free survival of patients with non-castrate, non-metastatic prostate cancer (clinical stage D0) treated with a DNA vaccine encoding PAP, with GM-CSF as an adjuvant, versus GM-CSF only.



Patients with PSA doubling time < 12 months

2-center trial: UWCCC and UCSF (Larry Fong, PI)

Acknowledgements

Lab:

- Jordan Becker
- James Davies
- Ed Dunphy
- Tom Frye
- Laura Johnson, PhD
- Joshua Lang, MD MS
- Matthew Morse, PhD
- Brian Olson, PhD
- Heath Smith
- Stephanie Thiede

Clinical Research Team:

- Justine Bruce, MD
- Jeremy Cetnar, MD
- Jens Eickhoff, PhD
- Dottie Horvath, RN
- Glenn Liu, MD
- Mary Jane Staab, RN
- Jane Strauss, RN
- George Wilding, MD
- Mulusew Yayehyirad, RN

Collaborators:

- William Burlingham, PhD
- Ewa Jankowska-Gan, PhD
- Larry Fong, MD

Funding:

NIH/NCI: K23 RR16489,
R21 CA132267

DOD PCRP: W81XWH-05-1-0404,
W81XWH-08-1-0074

UW Carbone Cancer Center