Challenges in Development of Vaccines in Early Clinical Trials

reasons to love/hate cancer vaccines

Vaccines: What's Wrong

- Difficult to Demonstrate Efficacy at the clinical level
- Pre-clinical models are neither necessary nor sufficient to support trials
- Immune responses have not correlated with efficacy
- Has the immune system failed us?
  - We have failed to improve on or even follow nature's path
  - Human immunology is a newly emerging science
  - Cancer Immunotherapy is not Immunity
  - Things are changing

What has worked

Provenge – Dendreon PAP GM-CSF protein in APC for Hormone Refractory Prostate Cancer

Reproducible OS advantage in two studies compared to docetaxel 21.7 vs. 25.8 months **N Engl J Med**. 2010 Jul 29;363(5):411-22

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Enormous Value: Paradigm changing----

Proof that a vaccine can reliable increase OS with no increase in RR or PFS in a phase 3 trial

Questions: How do we know it works

- No change in PFS or ORR
  - How does this vaccine work
  - What are the immune mediators
  - Correlates of response or benefit
  - Do we need to use overall survival as the measure of success?
- Is the principle effect relatively subtle influence on tumor growth rates
- Toxicity is minimal– does this reflect the effector response

How well can it work

- What are the essential active components –
  - DC quality measured by CD80 expression
  - Do we need the GM CSF
  - What is the optimal dose schedule
- Individual product – but no PD measures
- Limited Immunologic data and essentially no correlation with clinical outcome
- No patient characterization to be able to predict or select responders

How does it fit into the overall schema of cancer treatments

- Can this platform be extended to other antigens and other histology How do we select antigenic targets
- Is vaccine effectiveness and potency really limited
- Can the clinical results be improved ? Subsequent or concomitant treatment-- combined with hormonal therapy immune therapy (CITN trial with IL-7) Disease setting early, prior to chemotherapy, low disease burden –

Matters for thought

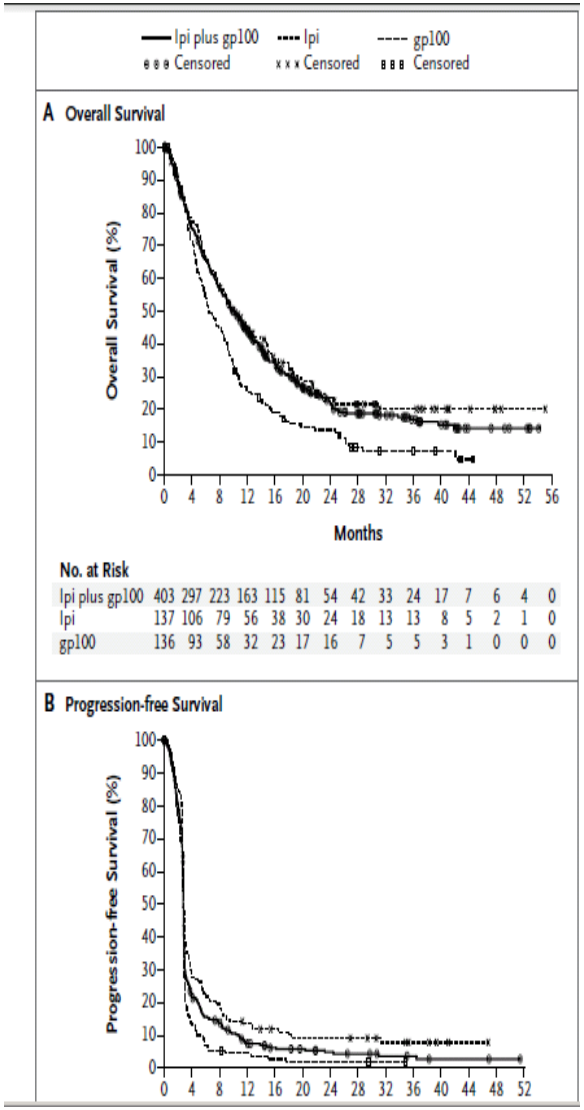
- Many vaccines will improve survival in the right setting – lower disease burden , tumor microenvironment perhaps by changing tumor growth rates (Fojo)
- So far not proven in combination with other immune therapy- CTLA-4 with peptide vaccine
- Not proven in the adjuvant setting
- In some examples OS may be decreased – perhaps by shifting to Th2 responses (E 1629 vs IFN Eggermond ASCO)

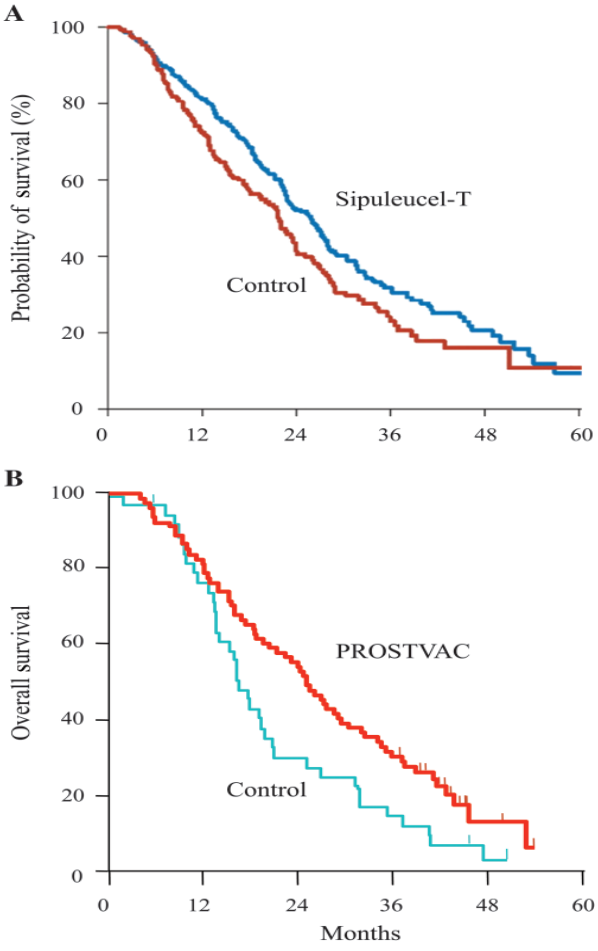
Pharmalot web site 8/30/11 Silverman

Critique

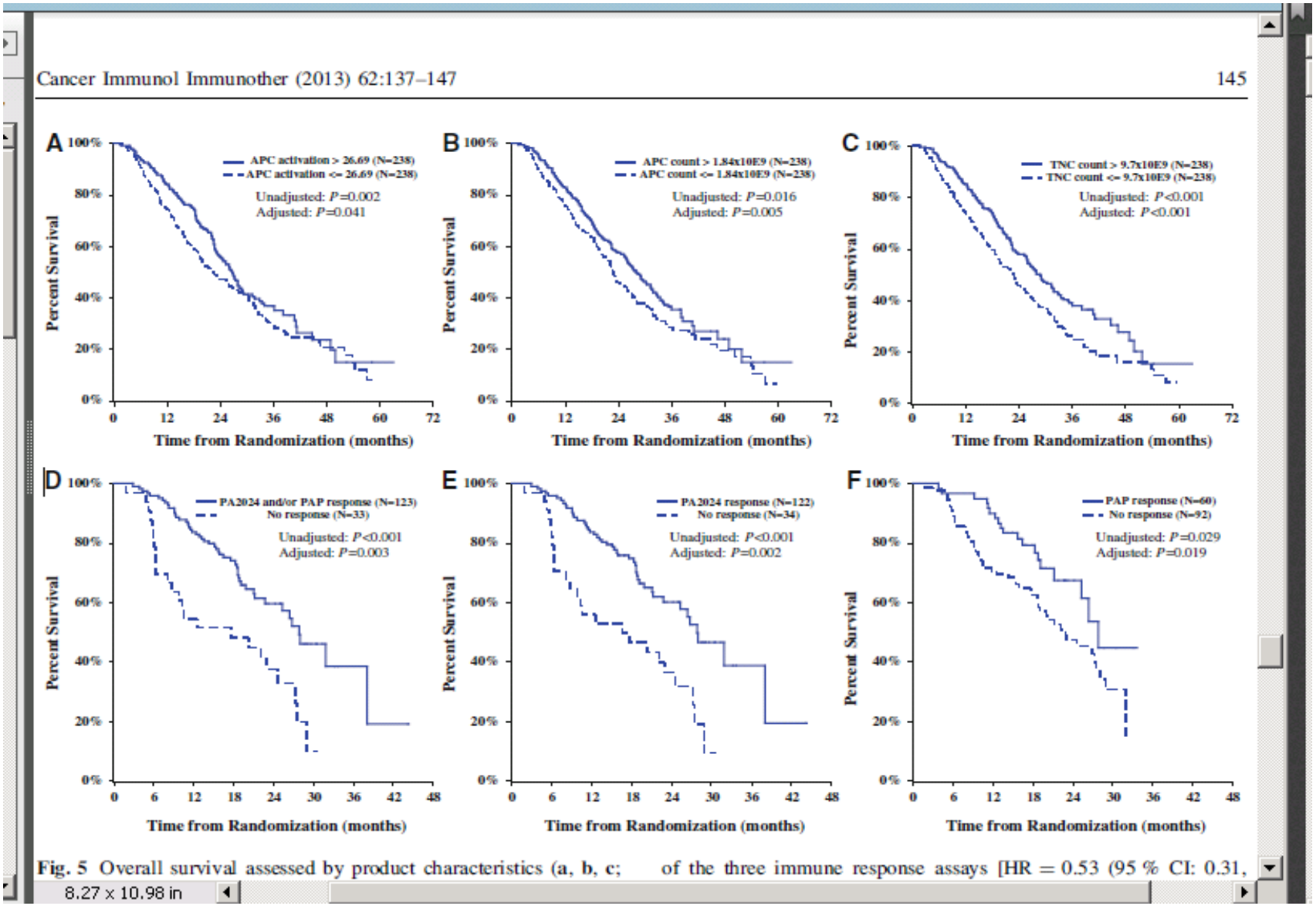
Provenge or a similar life-extending treatment should offer seven months or more more than 30 percent say a medication needs to add at least one year of life, according to Sermo, the web site where docs like to dish The median survival benefit offered by the Dendreon vaccine, which costs $93,000, is 4.1 months.

Survival Curves





Sheikh NA, Petrylak D, Kantoff PW, et al. Sipuleucel-T immune parameters correlate with survival: an analysis of the randomized phase 3 clinical trials in men with castration-resistant prostate



New Phase 2 trial based on pre clinical data

- Phase 2 study under the direction of Principal Investigator Samir N. Khleif, MD, employing Dendreon's Provenge and two drugs shown to shrink tumors. The trial, known as 'Sipuleucel-T, CT-011, and Cyclophosphamide for Advanced Prostate Cancer,' is described on the clinicaltrials.gov Web site. Its objective is to test the effectiveness of Provenge (also known as Sipuleucel-T), CureTech's CT-011, and cyclophosphamide for prostate cancer.
- Dr. Khleif said "[A]lthough the increased overall survival seen with Provenge treatment is a welcome advance in the treatment of prostate cancer, the goal of cancer therapy must be the eradication of disease. Therefore, improvements can be made, and this clinical trial is intended to improve the current standard of care."

ProstVac

- rV or rFp or PSA-B7.1-LFA-4- ICAM-1 Prime and Boost
- Phase 2 trials- Immunologic Data ORR PFS not sig.
- Kantoff NEJM Increased OS
  - overall survival 25.1 versus 16.6 months
- Phase 3 trial- BITN three arms Vaccine +/-GMCSF, P
- Early data with second line hormone-
- Combination with Radiation
- Unique Changes in tumor growth Analyzed by Fojo

Vaccination against HPV-16 Oncoproteins for Vulvar Intraepithelial Neoplasia
N Engl J Med 2009;361:1838-47.

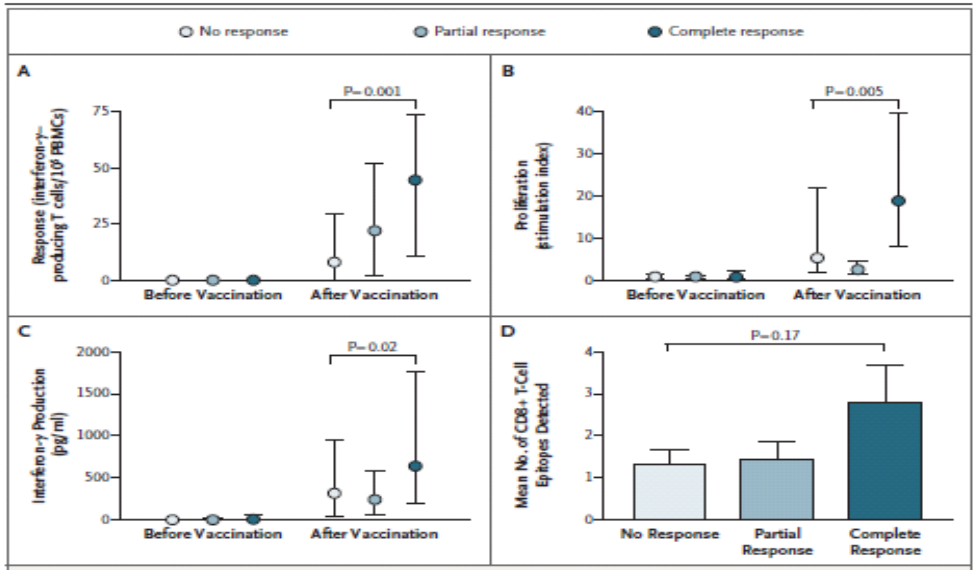


Figure 2. Immune Response before and after Vaccination.

The immune response was analyzed in blood samples obtained from eight patients with no clinical response, seven patients with a partial response, and five patients with a complete response, as observed at 3 months after the last vaccination. Panels A, B, and C show the immune response before the first vaccination and 2 weeks after the last vaccination. These panels also show the strength of the T-cell response that was specific for human papillomavirus type 16 (HPV-16) oncoproteins E6 and E7. The median number of interferon-γ–producing T cells per 100,000 peripheral-blood mononuclear cells (PBMCs) is shown, with the interquartile range (I bars). Panel B shows the strength of proliferation (median stimulation index and interquartile range [I bars]). Panel C shows interferon-γ production (median and interquartile range [I bars]) by proliferating PBMCs that were specific for HPV-16 oncoproteins E6 and E7. The strength of the immune response was determined by calculating the median immune response in all patients in the group on the basis of data on six different peptide pools per patient. Panel D shows the mean number of CD8+ T-cell epitopes detected in the three groups of patients 2 weeks after the last vaccination. The T bars indicate 95% confidence intervals. P values in all four panels were calculated with the Mann–Whitney test.

ated with regression of lesions[35,36] and suppres-

as a member of the steering committee of ISA Pharmaceuticals;

The strength of the immune response was determined by calculating the median immune response in

gp100 Peptide Vaccine and Interleukin-2 in Patients with Advanced Melanoma Schwartzentrubber et al NEJM

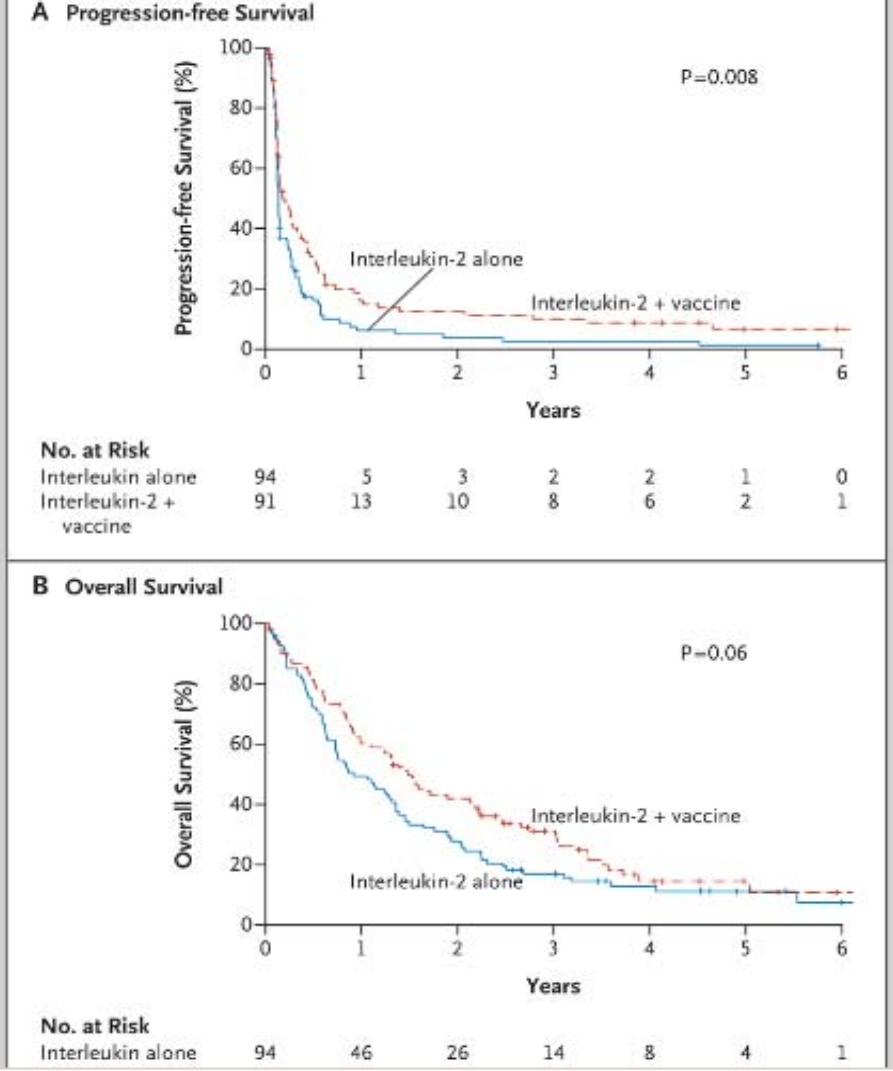


Figure 1. Progression-free and Overall Survival.

Progression-free survival (Panel A) was longer among patients receiving vaccine and interleukin-2 than among those receiving interleukin-2 alone. The median progression-free survival among patients who received the vaccine was 2.2 months (95% confidence interval [CI], 1.7 to 3.9), as compared with 1.6 months (95% CI, 1.5 to 1.8) among patients who did not receive the vaccine. There was a trend toward longer overall survival (Panel B) among patients receiving vaccine and interleukin-2 than among those receiving interleukin-2 alone. The median survival among patients who received the vaccine was 17.8 months (95% CI, 11.9 to 25.8), as compared with 11.1 months (95% CI, 8.7 to 16.3) among patients who did not receive the vaccine.

- Pre-clinical data toxicity difficult to test-
- Models mechanisms-- but don't predict success-
- Toxicity so far has been minimal to most vaccines--- but
- Choice of antigen or epitope not well defined – central tolerance or "self" is only a part of the problem , minor antigens, novel antigens
- Compare to TIL or TCR strength of response is minimal

Major Questions

- Target antigens and Endogenous Responses
- Immune modulation also requires specific antigens
- Adoptive transfer of TIL, TCR, and CAR define targets and cell types
- No biologic measures of activity or potency of the vaccine

Success of Historic Vaccines

Impact of Vaccines in the 20th & 21st Centuries

Comparison of 20th Century Annual Morbidity & Current Morbidity

Disease	20th Century Annual Morbidity*	2010 Reported Cases†	% Decrease
Smallpox	29,005	0	100%
Diphtheria	21,053	0	100%
Pertussis	200,752	21,291	89%
Tetanus	580	8	99%
Polio (paralytic)	16,316	0	100%
Measles	530,217	61	>99%
Mumps	162,344	2,528	98%
Rubella	47,745	6	>99%
CRS	152	0	100%
Haemophilus influenzae (<5 years of age)	20,000 (est.)	270 (16 serotype b and 254 unknown serotype)	99%

Sources:

* *JAMA*. 2007;298(18):2155-2163

† CDC. *MMWR* January 7, 2011;59(52);1704-1716. (Provisional *MMWR* week 52 data)

Failure to stimulate- peripheral anergy
Failure to clear leads to exhaustion
Disease control requires alternative mechanisms

- Tuberculosis- PPD is a failed vaccine alternative immune control granuloma
  - Tons of Immunity IFN-
- Malaria- State of "partial immunity"
  - GSK Vaccine with adjuvant 33% successful in children
- Hepatitis C- fails to clear virus chronic inflammation leads to hepatoma
- HIV antigenic variation-

Quo Vadis

- Many trials including pivotal Mage 3 GSK

  EGRFviii and literally hundreds- 1279 trials on cancertrials.gov-- 355 open--- 30 Phase 3

Empirically driven clinical trials are insufficient to develop new treatment – Systems biology - molecular biologists have tools to unravel biological complexity and the limitations of reductionism H. V. Van RegenmortelEMBO Rep. **5, 1016–1020 (2004).**

Quo Vadis

- We might get lucky with enough studies But we have had trouble building on successes
- Vaccine technology lives in a world of its own
- Little guide to development or how to choose regimes for larger trials – depend on investigator commitment, faith often in a biologic approach and resources
- Look in the right place – tumor biopsies
- Essential to have immunologic results that can be used to develop agents and combination strategies (Butterfield)

- Targeted agents: how to select the winners in preclinical and early clinical studies? Eur J Cancer. 2012 Jan;48(2):170-Goodwin R, Giaccone G, Calvert H, Lobbezoo M, Eisenhauer EA.
- Shifting the equilibrium in cancer immunoediting: from tumor tolerance to eradication Jim Allison Immunol Rev. 2011 May
- Therapeutic Cancer Vaccines: Current Status and Moving Forward Schlom J Natl Cancer Inst 2012;104:599–613