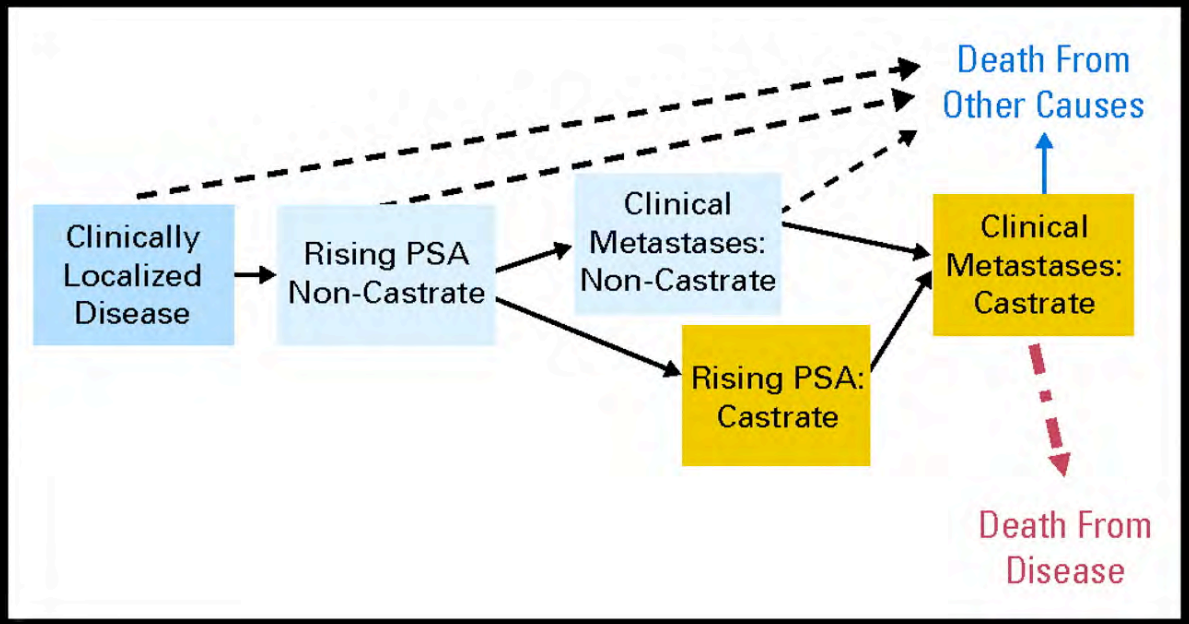
Defining “Response” in Prostate Cancer Immunotherapy

Lawrence Fong

University of California, San Francisco

UCSF

Prostate Cancer Clinical States



- Pre-chemotherapy
- Post-chemotherapy

(Scher et al, JCO 2008)

Randomized Phase III Trial of Sipuleucel-T (Provenge) Targeting PAP

(D9901)

Asymptomatic Metastatic CRPC (N = 127)

- Placebo Q 2wks x 3 (N = 45)
- Provenge Q 2 wks x 3 (N = 82)

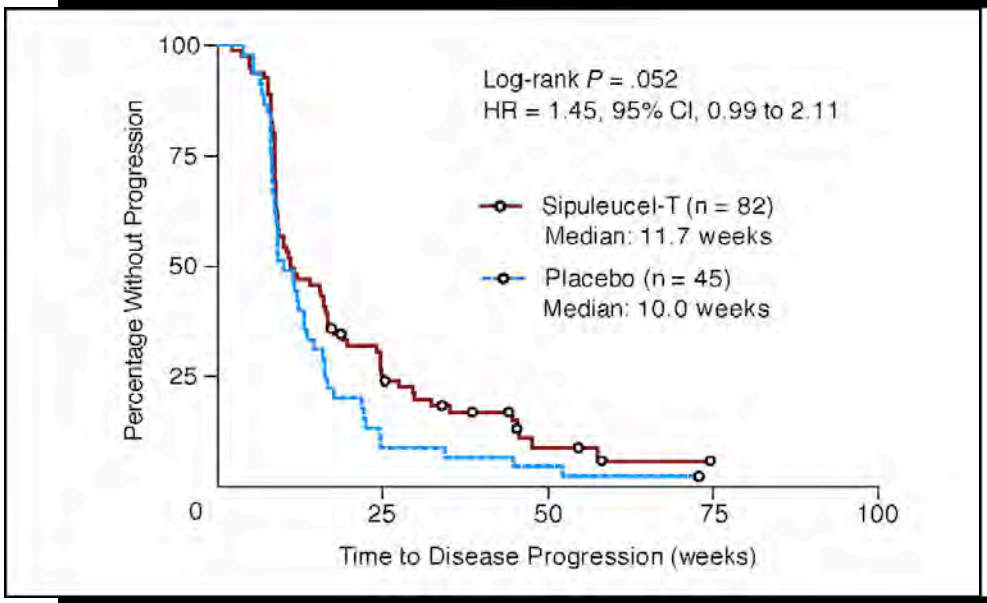
PROGRESSION

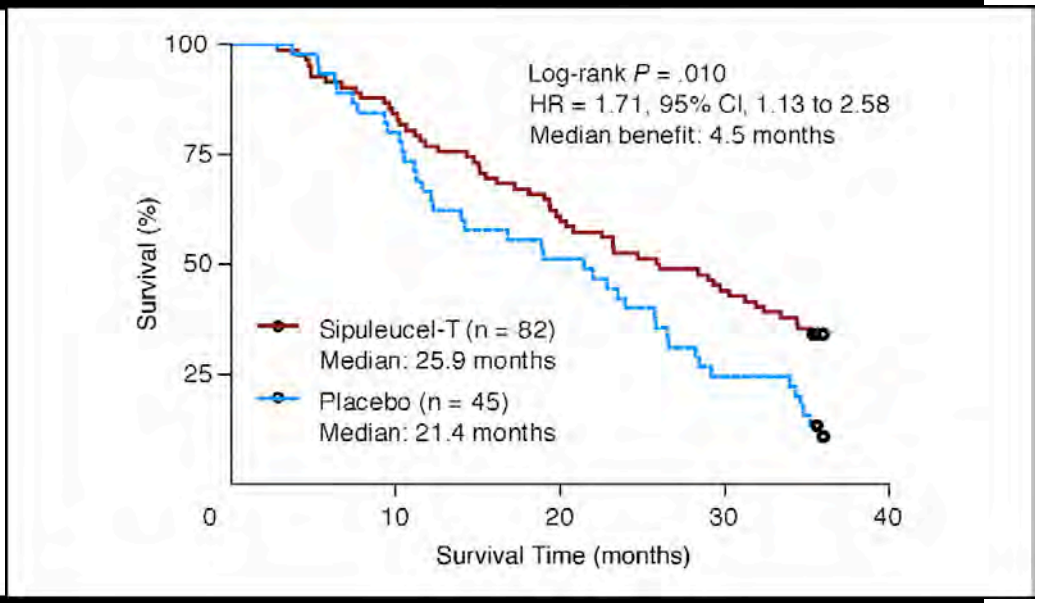
- Provenge Q 2 wks x 3
- Off Study

Primary endpoint: Time to Disease Progression
Radiographic, Clinical or Pain
Not PSA

Secondary endpoint: Overall Survival

Sipuleucel-T is associated with an improvement only in overall survival





(Small et al. JCO 24, 2006)

PROSTVAC: A PSA-targeted viral vaccine

Prime

rV-PSA-Tricom 1x10^9PFU

GM-CSF 100mcg x 3 D

Boost

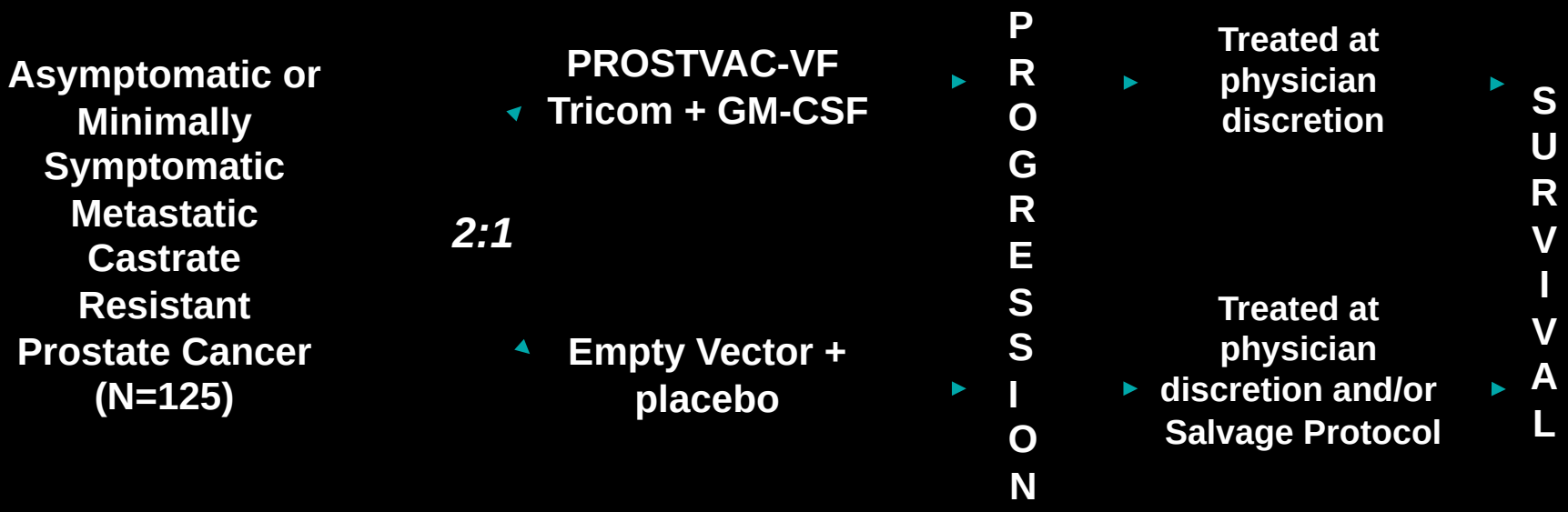
rF-PSA-Tricom 1x10^9PFU

GM-CSF 100mcg x 3 D

Platform: Pox viruses
Antigen: PSA
PSA-3 epitope

Tricom: LFA-3 (CD58)
ICAM-1 (CD54)
B7.1 (CD80)

Randomized Phase II Study of a Vaccine Targeting PSA



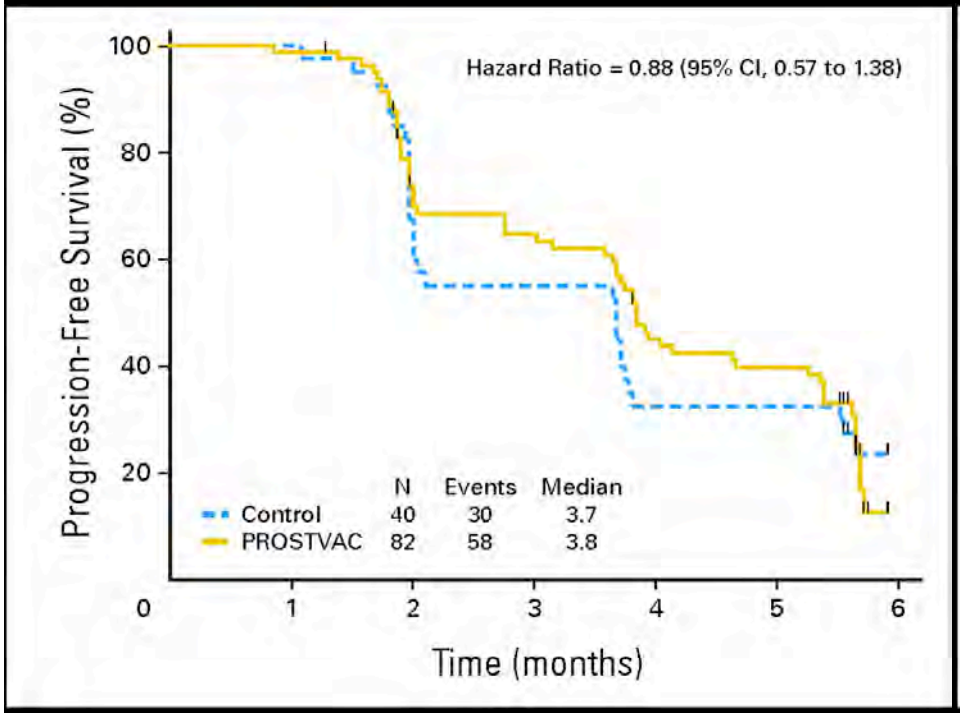
Primary endpoint: Progression Free Survival

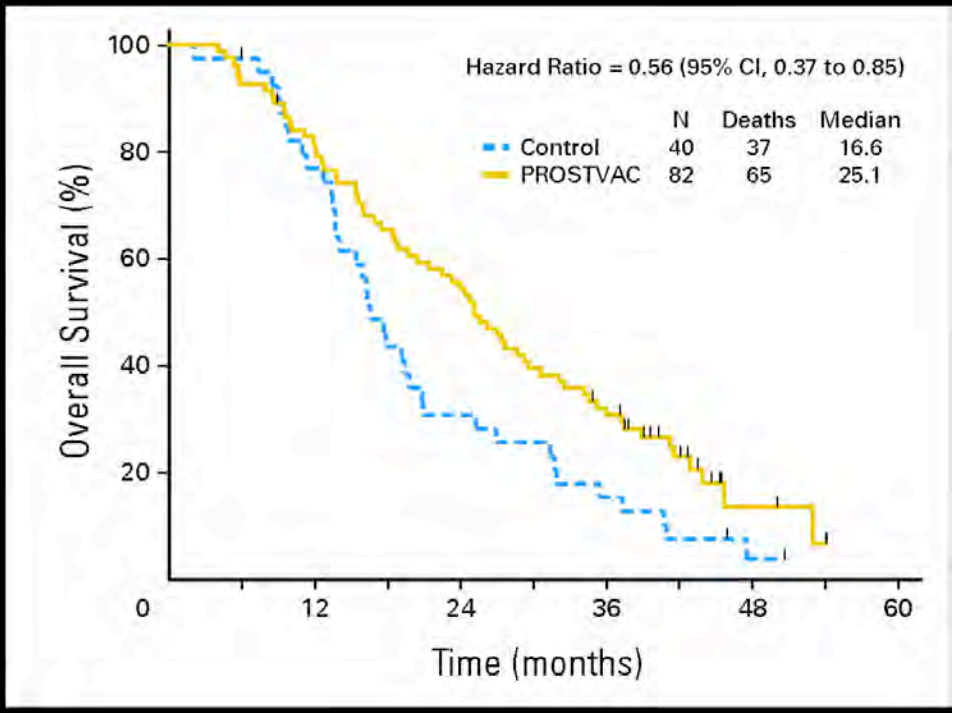
Secondary endpoint: Overall Survival

Therion BCBN

(Kantoff et al. JCO 2010)

PROSTVAC treatment is associated with an improvement only in overall survival





(Kantoff et al. JCO 2010)

Prostate Cancer Immunotherapy 2010

- Sipuleucel-T treatment is associated with an improvement in overall survival in patients with CRPC.
  - No improvement in PFS
- Prostvac treatment is associated with a similar improvement in overall survival.
  - No improvement in PFS
  - Phase 3 planned

Why do we see improvements in overall survival without altering time to progression?

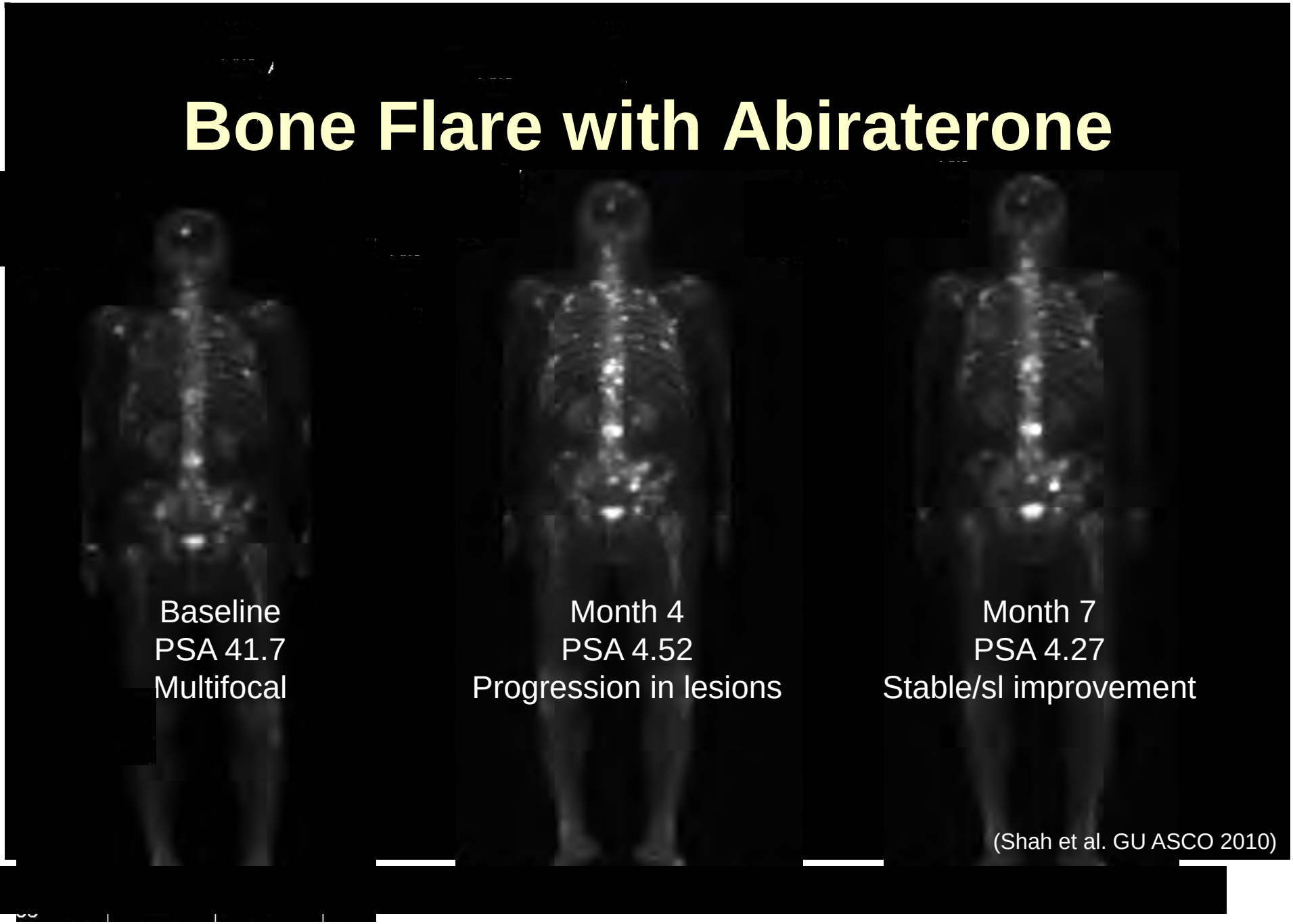
Clinical Endpoints

- PSA doubling time, velocity
- PSA reduction by 50%
- Pain, quality of life
- Time to event
  - Time to progression (TTP)
  - Time to skeletal event
  - Progression free survival (PFS)
  - Overall survival (OS)

Challenges in defining clinical response for prostate cancer

- Slow growing tumor
  - Overall survival as an endpoint can take a long time
- Serologic markers: PSA
  - Easy to follow and are often used to guide treatment
  - May not correlate with clinical response
- Bone tropism for metastasis
  - Bone scans are difficult to measureable
  - Difficult to show a response
  - Most patients do not have measureable disease
- No established surrogate for overall survival

Bone Flare with Abiraterone



Baseline
PSA 41.7
Multifocal

Month 4
PSA 4.52
Progression in lesions

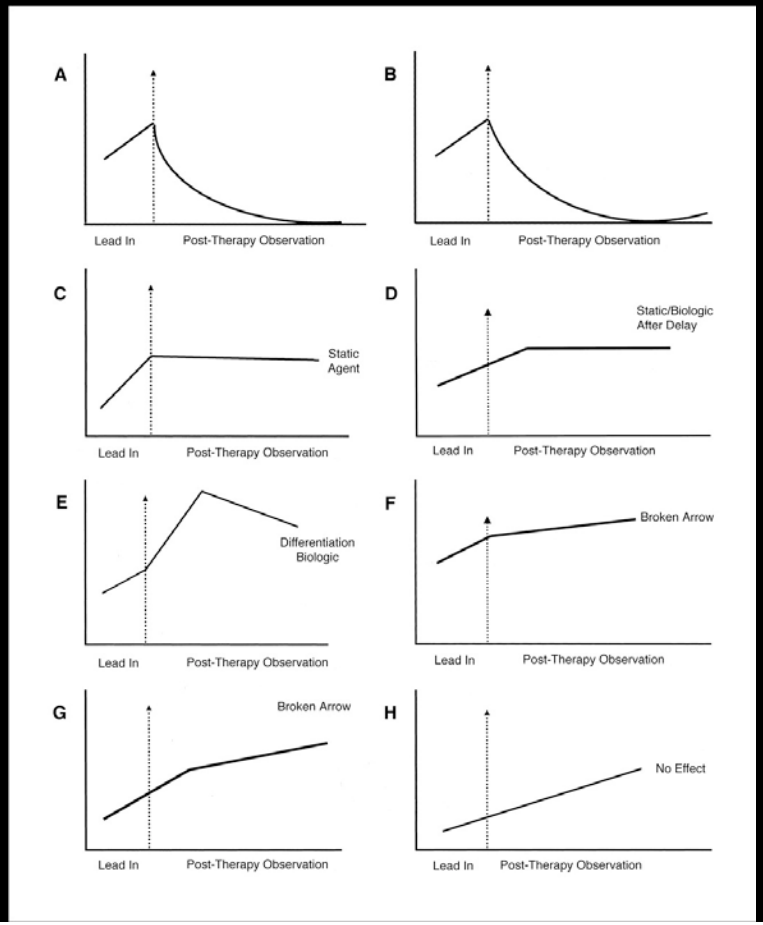
Month 7
PSA 4.27
Stable/sl improvement

(Shah et al. GU ASCO 2010)

Prostate Cancer Clinical Trials Working Group 2(PCWG2)

- Treat for a minimum of 12 wks
- PSA
  - % change from baseline @ 12wks or at any time
  - Time to PSA progression (25% rise from nadir)
- Soft Tissue/Measureable disease
  - RESCIST with caveats
- Bone
  - New lesions must be seen on a confirmatory scan $\geq$ 6 weeks later

12 week window to tolerate early progression



(Scher et al. JCO 2004)

Defining immune responses

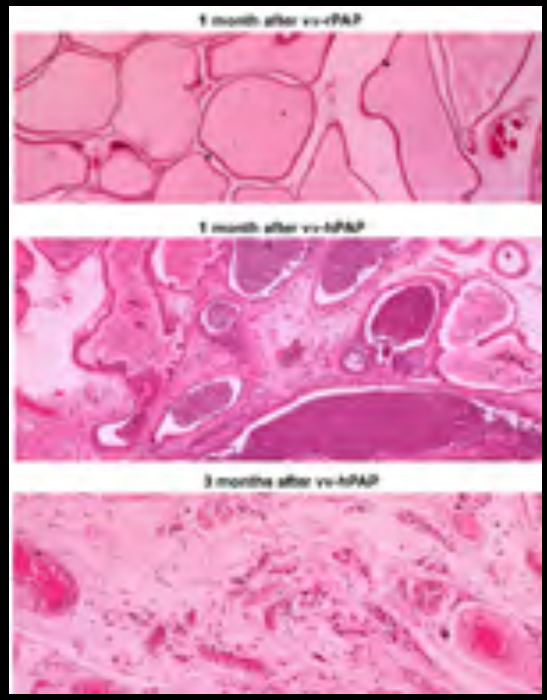
- Immune markers
  - Modulation of immune cell frequency and phenotype
    - APC
    - T cells (activation markers, icos, cytokines)
    - Tregs
  - Antigen specific immune responses
    - Proliferation
    - Cytokine production (IFN γ , polyfunctional, …)
  - Profiling of antigen specific responses

Prostatic acid phosphatase (PAP) is immunogenic in a murine model

Vaccinate rats with recombinant vaccinia virus expressing human PAP

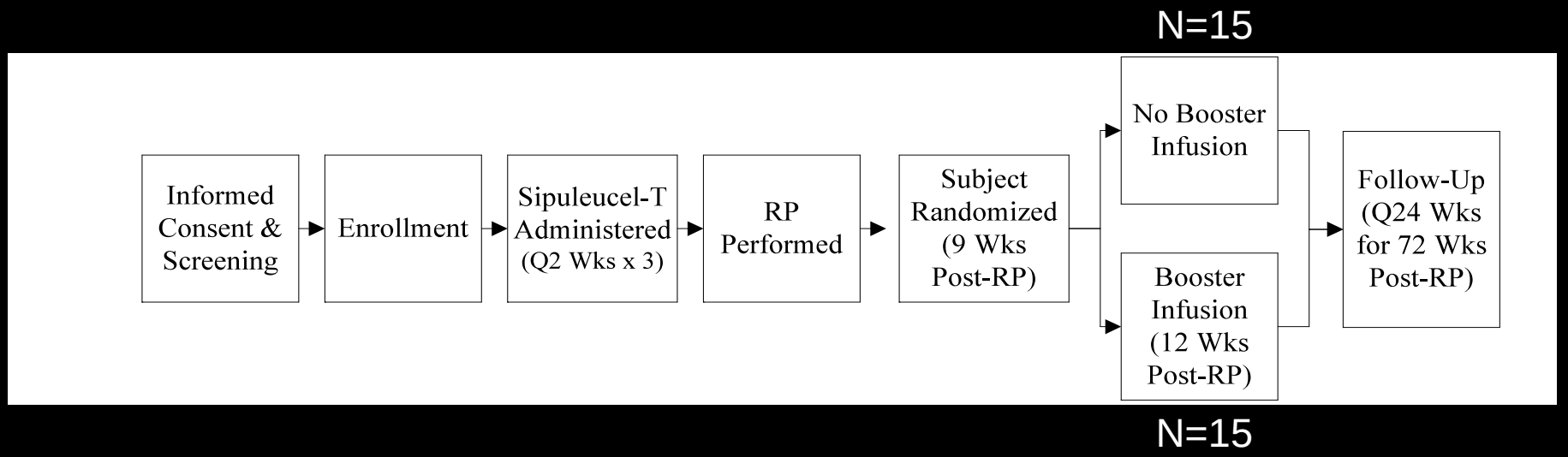
1 month

3 months



(Fong et al., JI 1997)

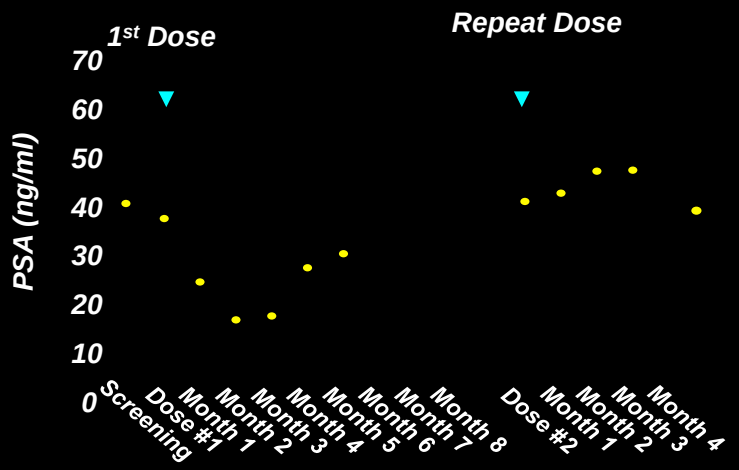
Neoadjuvant Sipuleucel-T



- **Primary endpoint: CD3+ T cells by IHC**
- **Secondary endpoints:**
  - **T cell subset infiltration by IHC**
  - **Antigen-specific T cell responses, pre vs. post induction**
  - **Antigen-specific T cell responses, pre vs. post boost/no boost**

CTLA-4 Blockade: Phase 1 Trial

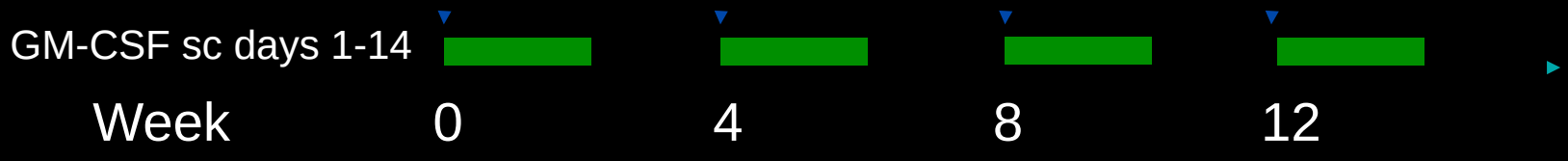
- First-in-man trial conducted in CRPC
- Single dose of Ipilimumab @ 3 mg/kg
- 14 % PSA response rate
- Rash only treatment associated adverse event



(Small, et al., Clin Can Res, 2007)

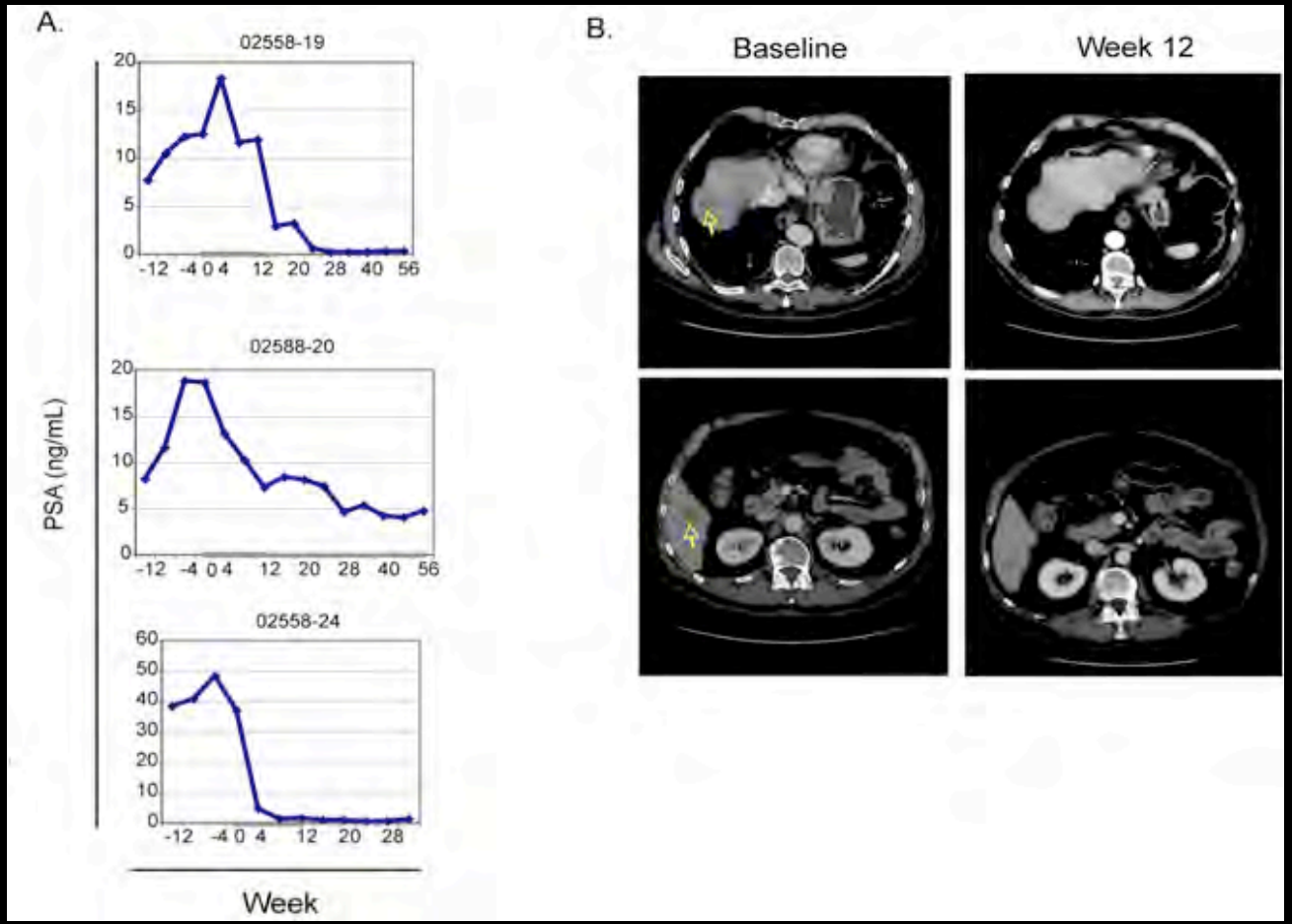
Phase I Combination Trial of Ipilimumab and GM-CSF

- Metastatic CRPC
- Fixed GM-CSF dose (250 mcg/m2/d sc D1-14)
- Escalating anti-CTLA4 antibody dose



Dose Level	Cycle 1	Cycle 2	Cycle 3	Cycle 4	n
1	0.5	0.5	0.5	0.5	3
2	1.5	0.5	0.5	0.5	6
3	1.5	1.5	1.5	1.5	6
4	3	1.5	1.5	1.5	3
5	3	3	3	3	6
6	5	5	5	5	6
7	10	10	10	10	6

Clinical Responses



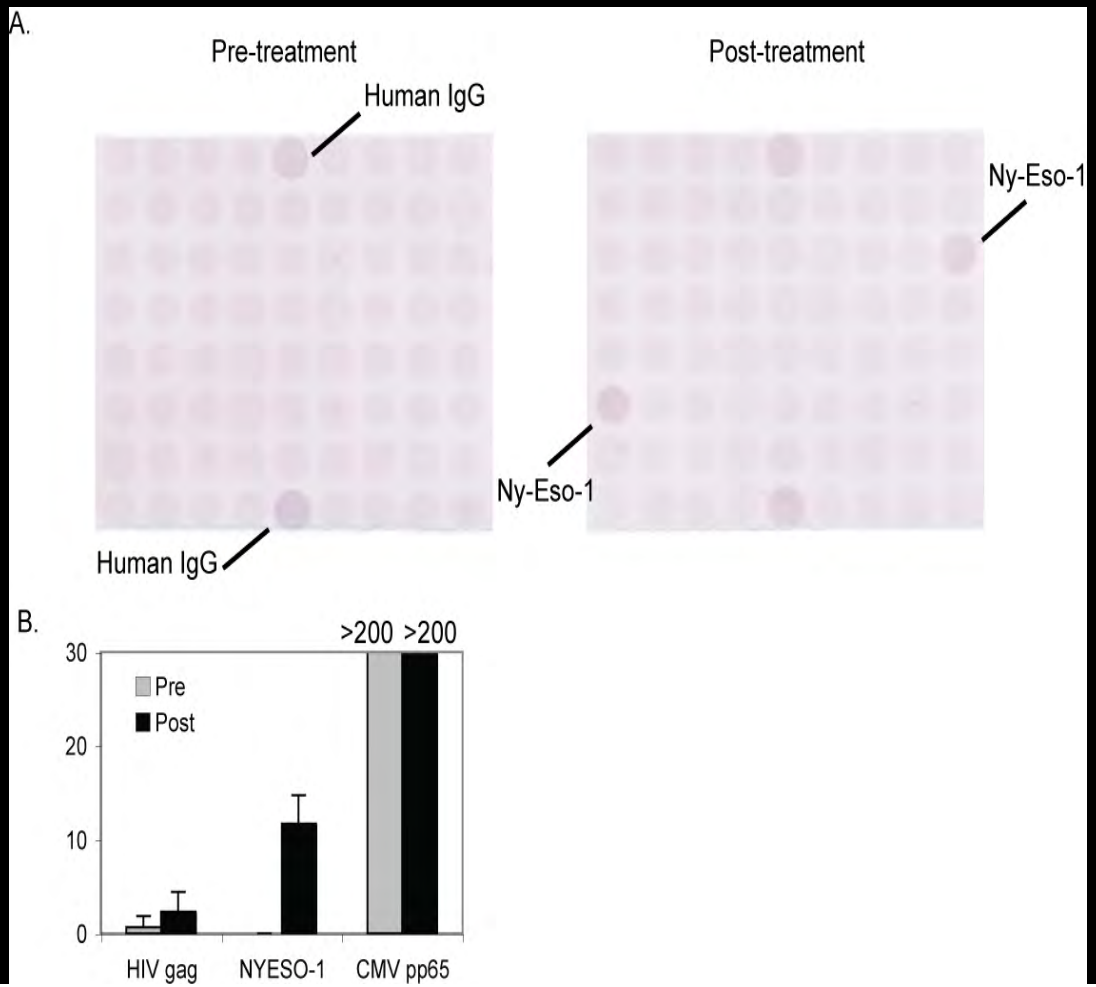
(Fong et al, Can Res 2009)

Array-Based Screening of Antigen-Specific Responses

	1	2	3	4	5	6	7	8	9
A	XAGE-1	FATE1	SSX1	NEG-4	IgG	GAGE-2	PAGE-5	LAGE-1	MAGE-A1
B	TPX1	NY-SAR-35	MAGE-A4	NEG-3	Mp17	GAGE-4	LIP1	PAGE-1	SSX2
C	NXF2	TSP50	MAGE-B2	MAD-CT-2	h-PAP	MAGE-A3	SPA17	MAGE-E1	NY-ESO-1
D	SSX4	ADAM2	MAGE-B1	MAD-CT-1	r-PAP	P53	MAGE-A8	SPANXC	GAGE-7
E	GAGE-7	SPANXC	MAGE-A8	P53	r-PAP	MAD-CT-1	MAGE-B1	ADAM2	SSX4
F	NY-ESO-1	MAGE-E1	SPA17	MAGE-A3	h-PAP	MAD-CT-2	MAGE-B2	TSP50	NXF2
G	SSX2	PAGE-1	LIP1	GAGE-4	Mp17	NEG-3	MAGE-A4	NY-SAR-35	TPX1
H	MAGE-A1	LAGE-1	PAGE-5	GAGE-2	IgG	NEG-4	SSX1	FATE1	XAGE-1

(Hoeppner, et al. Cancer Immunity, 2006)

Treatment can induce immune responses to NY-ESO-1



(Fong et al, Can Res 2009)

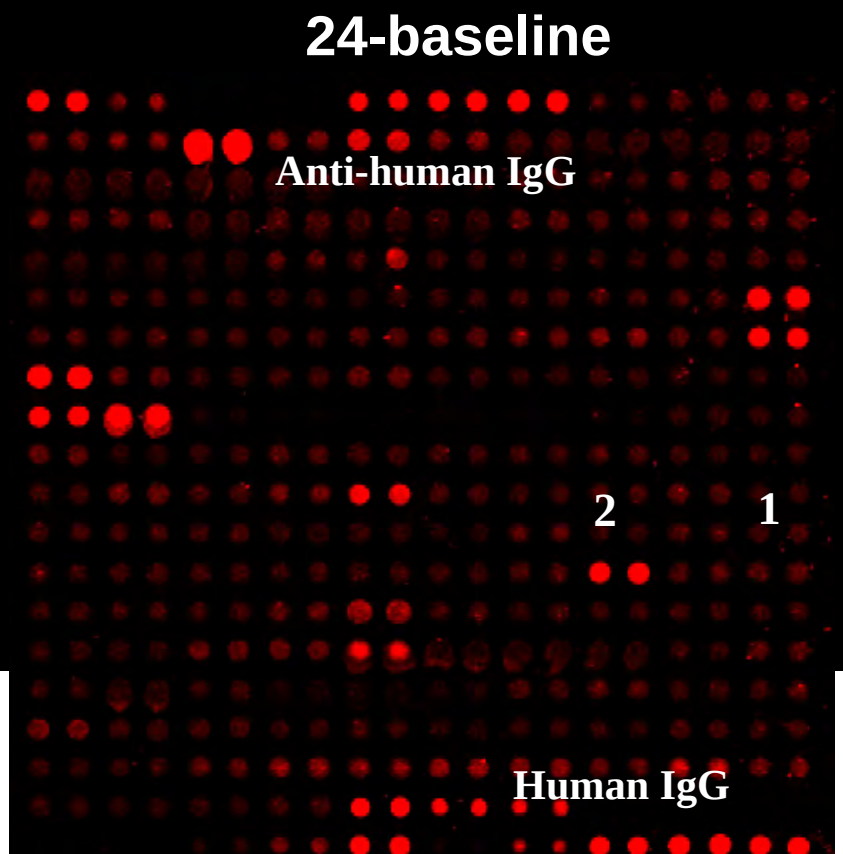
Clinical and Antibody Responses

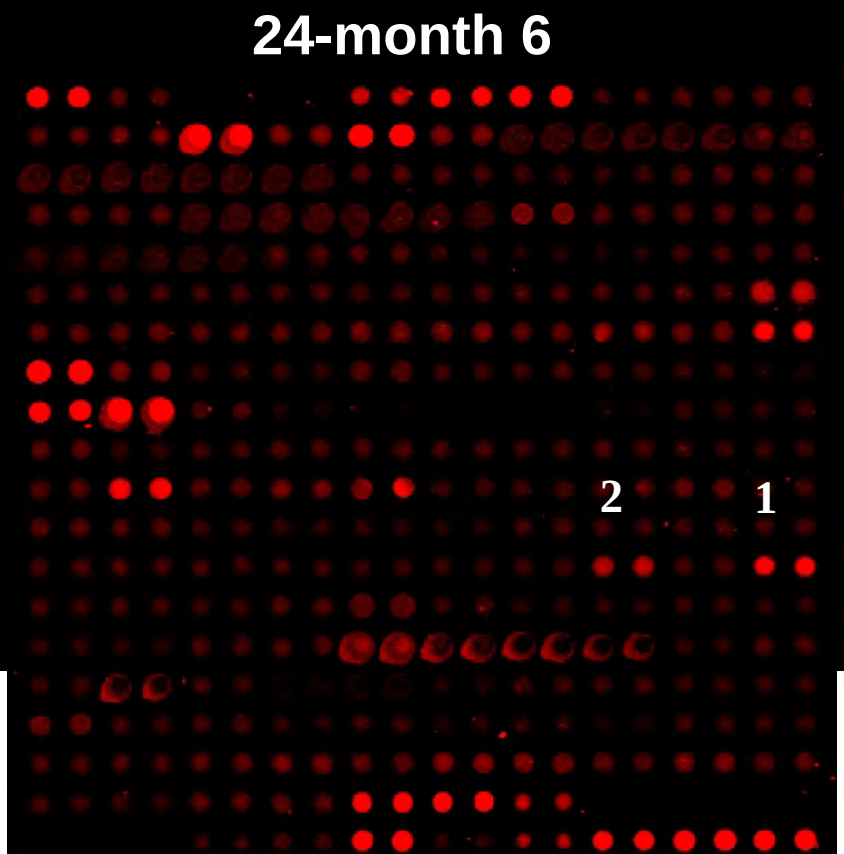
Patient	Dose Level	Number of Cycles	IRAE	Clinical Response	Immune Response	
					Pre	Post
1	1	3			NY-ESO-1, p53	NY-ESO-1, p53
2	1	3				
3	1	7				
4	2	1	G3 CVA			
5	2	3				
6	2	5			NY-ESO-1	NY-ESO-1
7	2	5				
8	2	4				
9	2	2				
10	3	5				
11	3	2	G3 Rash			
12	3	4				
13	3	3				
14	3	2				
15	3	1				
16	4	4				
17	4	6				NY-ESO-1
18	4	3			NY-ESO-1	NY-ESO-1
19	5	5	G3 Panhypopituitarism	PSA		
20	5	24		PSA		NY-ESO-1
21	5	4				
22	5	8				
23	5	5	G3 Temporal Arteritis			
24	5	4	G3 Diarrhea	PSA, CT		

(Fong et al, Can Res 2009)

Profiling of IgG responses with protein arrays

- 8000+ human proteins
- Expressed in baculovirus
- Hybridize with patient sera
- Detect bound IgG by fluorescence





Conclusions

- Overall survival remains the definitive outcome for defining clinical efficacy in prostate cancer, but is not be feasible for early trial development.
- Immunotherapies that induce clinical responses in prostate cancer provide the opportunity to help redefine meaningful immune “responses.”
- Clinical endpoints (PCWG2) that allow for early progression are being used in prostate cancer trials.
- Immune correlates need to be validated in larger trials (with clinical benefit) including Phase 3 trials that are followed for overall survival.

Where do we go from here?

- Introduce mechanistic studies into phase I,II, III trials (cryopreserve samples).
- Exploratory studies to examine the associations between the clinical endpoints and correlative studies may use time to progression and response criteria understanding their caveats.
- Validate associations between clinical (esp. overall survival) and immune responses in subsequent studies.
- Circulating tumor cell measurement (Veridex) currently being looked at in abiraterone and MDV3100 trials – stayed tuned…

David Alajajian
Vinh Dao
Yafei Hou
Dil Kapadia
Brian Kavanagh
Serena Kwek
David Lee
Shaun O'Brien

Vivian Weinberg

Ritu Roy

Eric Small
Charles Ryan
Amy Lin
Andrea Hartzstark

Peter Carroll

Jeffrey Simko
Kyle Kuchinsky

University of Wisconsin
Douglas Mcneel

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