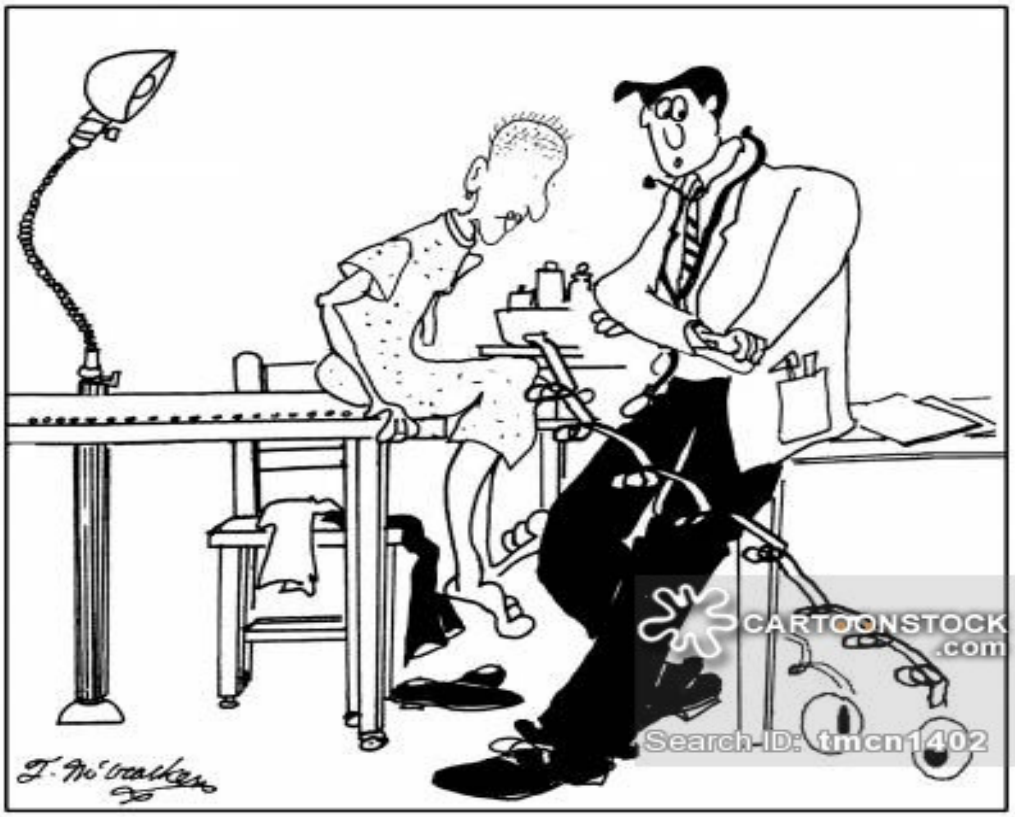
Is Immune Therapy for Prostate Cancer a Riddle Wrapped Up in an Enigma?

Susan F. Slovin, MD, PhD
Attending Physician, Member
Genitourinary Oncology Service
Sidney Kimmel Center for Prostate and Urologic Cancers
Memorial Sloan Kettering Cancer Center
New York, New York



"Oh dear. Your immune system doesn't recognize your eyes."

The checkpoints and autoimmunity???

Vaccination Against Cancer May Result From Discovery By British Medical Experts

Experiments Are Continuing by Research Council and Nata and Important Announcements May Soon Be Expected

CANCEROUS GROWTHS HAVE COMMON VIRUS

(By EDWIN L. JAMES.)
[Special Cable to The Globe and The New York Times. Copyright, 1918.]

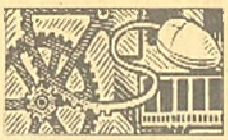
London, July 30.—A new announcement regarding the cancer work of the British Medical Research Council may soon be expected. This announcement will deal with the next step in the work of the Research Council, which announced this week the discovery by Dr. W. E. Gye and F. E. Barnes of a virus believed to cause cancer.

At the same time experiments are being made in causing cancer growths in mice and chickens by means of the newly discovered virus other experiments are being conducted in immunizing these animals against the virus, and in connection with this work the new revelations are to be made.

While it would be an overstatement to say a cure for cancer is in sight, the new announcement is expected to indicate probabilities of finding a method of vaccination against cancer.

Discovery of Results.

CENTURY OF THE MILLENNIUM



July 17, 1925 *William Jennings Bryan thunders his defence of the biblical account during the Scopes Monkey Trial in Tennessee. The evolution-teaching defendant, Jo... be found guilty and lightly fined; the law he broke lives on until 1967.* **Other July 17** *France, British and Indian cavalry charge straight into the guns of astonished Germ... (1918).* **Monday** *Games Are Disrupted As 28 Nations Pull Out (1976)*

Read It in the Morning While It Is News

The Globe.

THE WE... Probabilities: ...

VOL. LXXXII. NUMBER 23566. TORONTO, FRIDAY, JULY 17, 1925.

Rationale for developing immune therapies for prostate cancer

1. Well-characterized cell surface molecules: PSA, PSMA, PAP, STEAP, PSCA, Globo H, GM2, MUC-1,2, Tn, TF, Lewis^{y}.

2. Biomarkers [PSA, CTCs] to study disease progression/response.

3. Widely applicable to all disease states:
   - biochemical relapse thru castration resistant disease.

4. Likely potentiated via combinatorial approaches:
   radiotherapy, chemotherapy, biologic agents (GM-CSF, IL-2), checkpoint inhibitors (anti-CTLA-4, anti-PD-1), antibody-drug conjugates.

In the beginning…why we failed

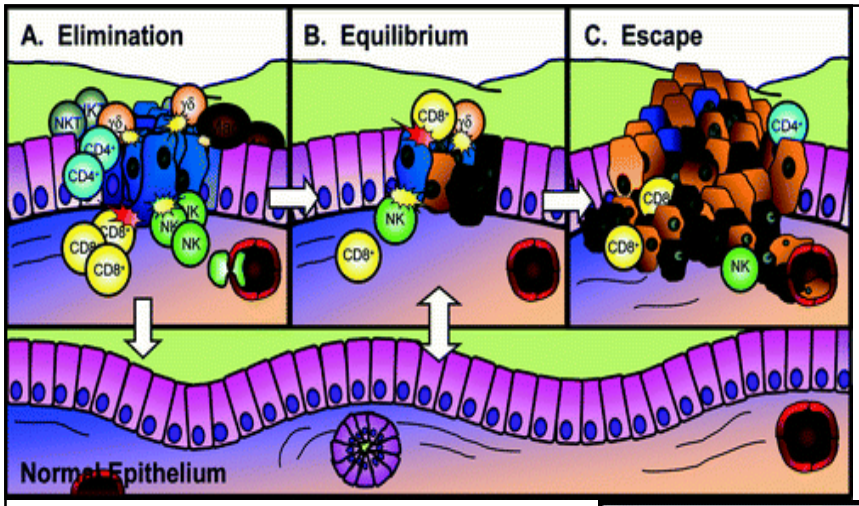
No clinical responses to:

- Cell-based vaccines
- Vector-based vaccines +/- prime boost
- Carbohydrate conjugates (KLH +/- QS-21, alum)

- Concept of “immune desert”

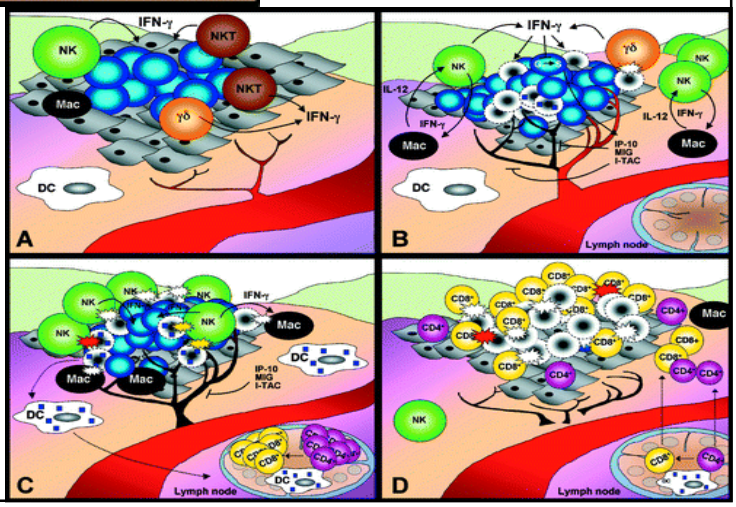
- Understanding the role of immunoediting: Elimination, Equilibrium, Escape [Dunn, et al, Ann Rev Imm 2004]

  Unedited = High immunogenicity
  Edited = Reduced immunogenicity



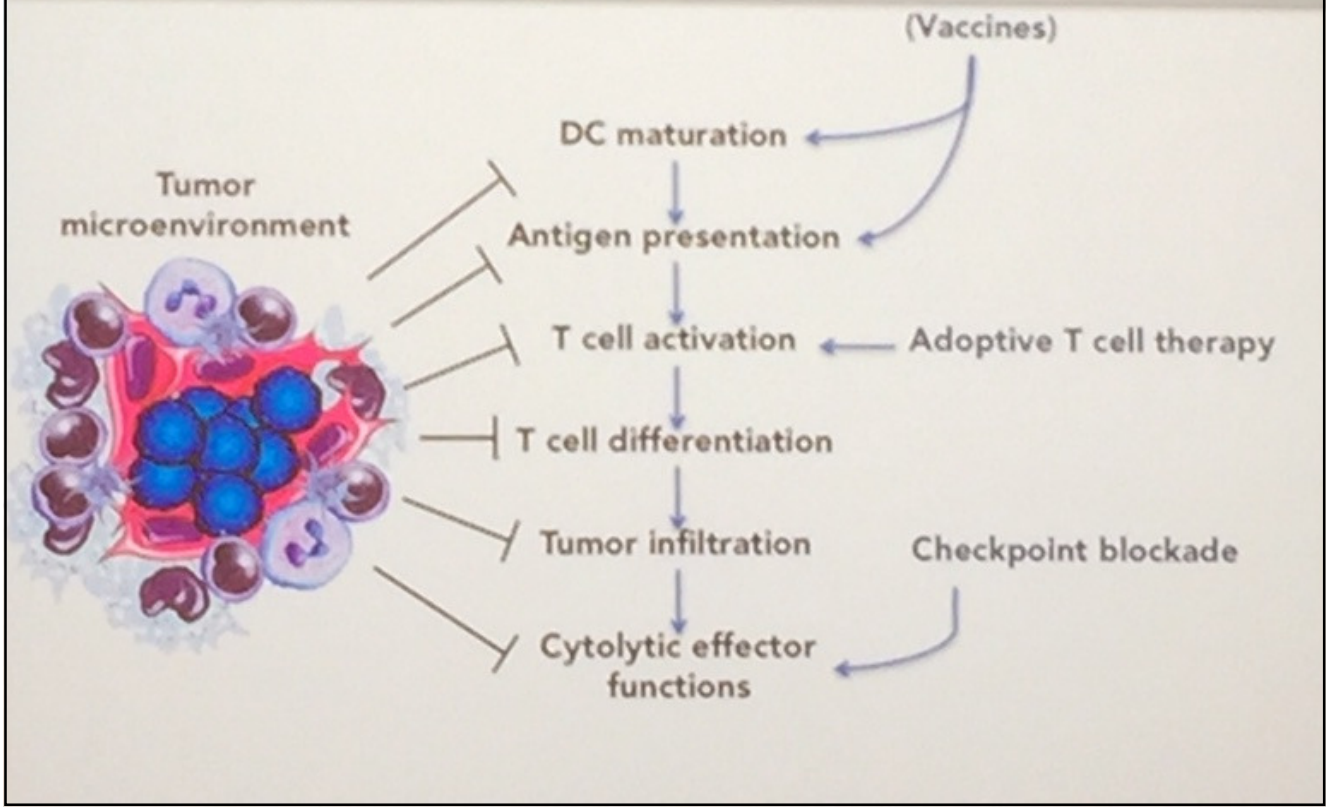
The world reduced to a cycle of immune editing

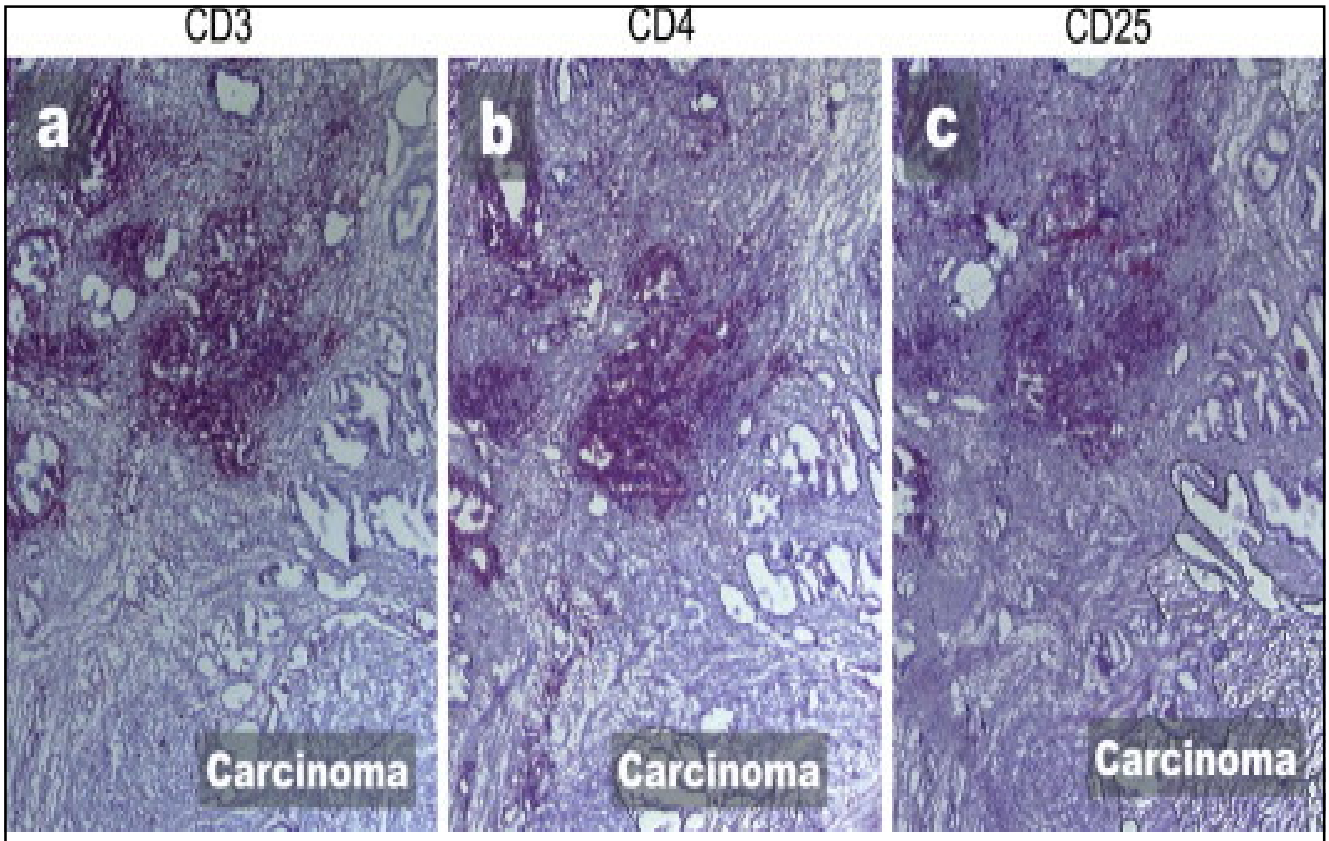
Final – the Elimination phase



Dunn, Old, Schreiber, Ann Rev Imm 2004

Current immunotherapies directly target the T cell and fail to overcome multilayered immunosuppression (T cell exhaustion) by TME





Lymphocyte clusters surround prostate cancer lesions. Serial 5 µm cryosections of prostate cancer-inflicted tissues were stained with anti-human CD3 (dilution 1:5000) (a), anti-human CD4 (dilution 1:1000) (b) and anti-human CD25 (dilution 1:10) (c). (a–c) are overviews (magnification 25×) of prostate cancer-inflicted tissue to demonstrate the cluster formation of tissue-infiltrating lymphocytes adjacent to the prostate cancer lesions (patient 6, Gleason 6, pT2a, as representative example). A dense stromal compartment separates the carcinoma area (lower right corner) and the lymphocyte clusters.
Ebelt, et al, Eur J Ca 2009.

The Challenges of Any Immune Therapy… Therapy must be…

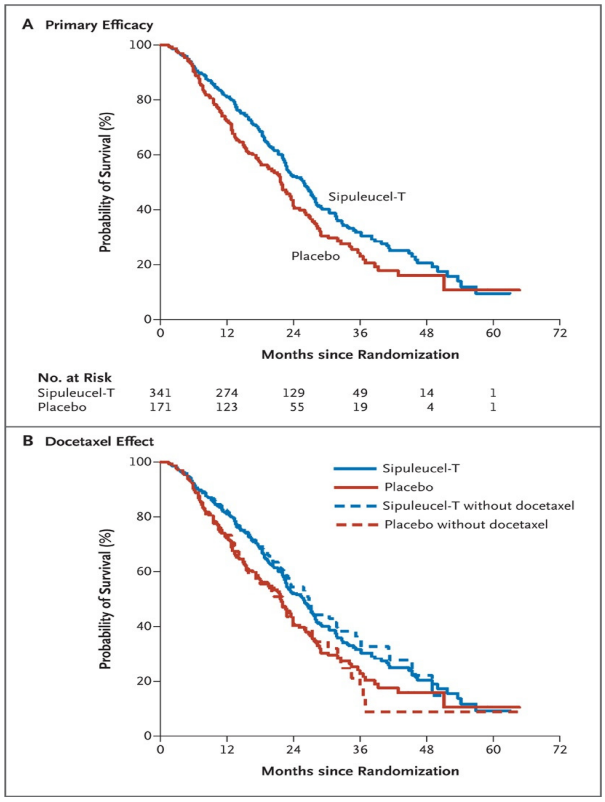
- ***Exportable***: "off the shelf"
- ***Reportable***: need appropriate endpoints
- ***Translatable***: biologic effect*
- ***Time Table***: Anticipated time-to-effect
- ***Radiographic assessment:*** pseudoprogression?

*Immune read-out associated with treatment effect? (Appropriate biomarker)

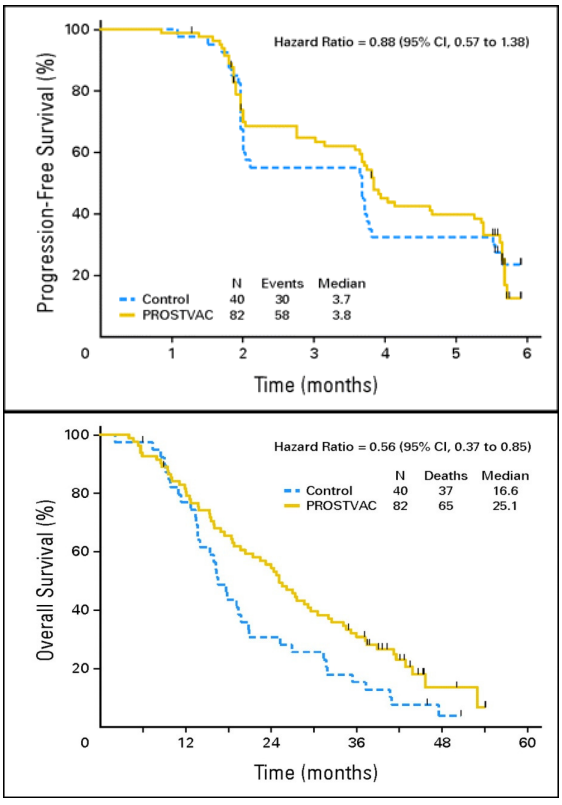
In the beginning…Sipuleucel-T

- ***First*** approved immune therapy for a solid tumor
- ***First*** to show improvement in OS but NOT TTP
- ***First*** as a “personalized” therapy

Vaccines in Prostate Cancer



Kantoff, et al, NEJM 2010.



Kantoff, el al, JCO 2010

PROSTVAC ≠ OS

Prime Boost Strategy:

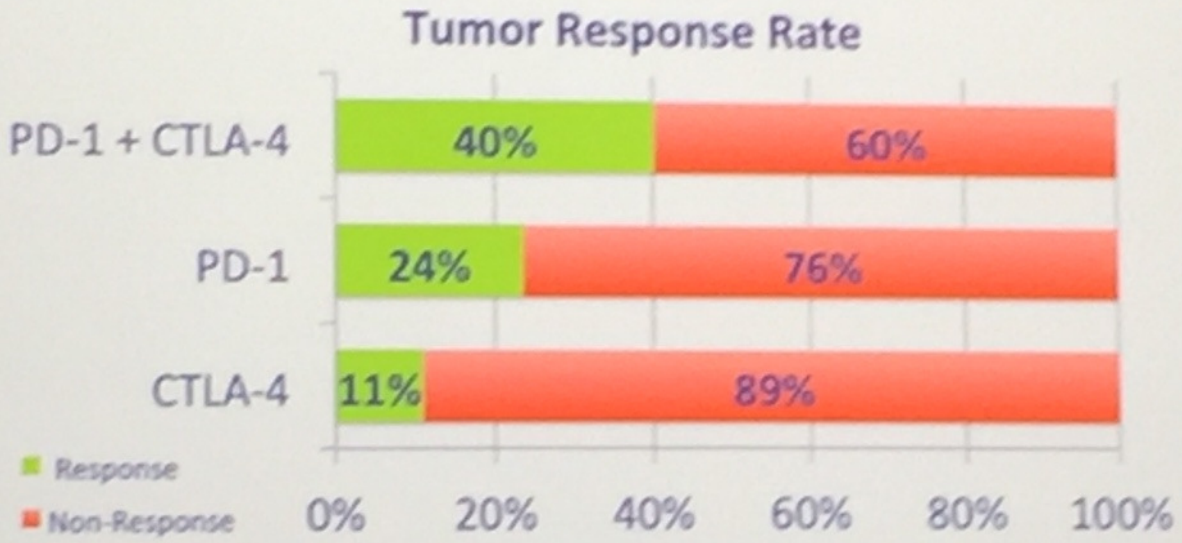
- (Arm V+G) PROSTVAC-V/F plus adjuvant dose GM-CSF
- (Arm V) PROSTVAC-V/F plus GM-CSF placebo
- (Arm P) Double placebo
- Stopped early by DSMB due to futility!

Lessons learned

Prostate cancer vaccine trials – the **"nos"** have it

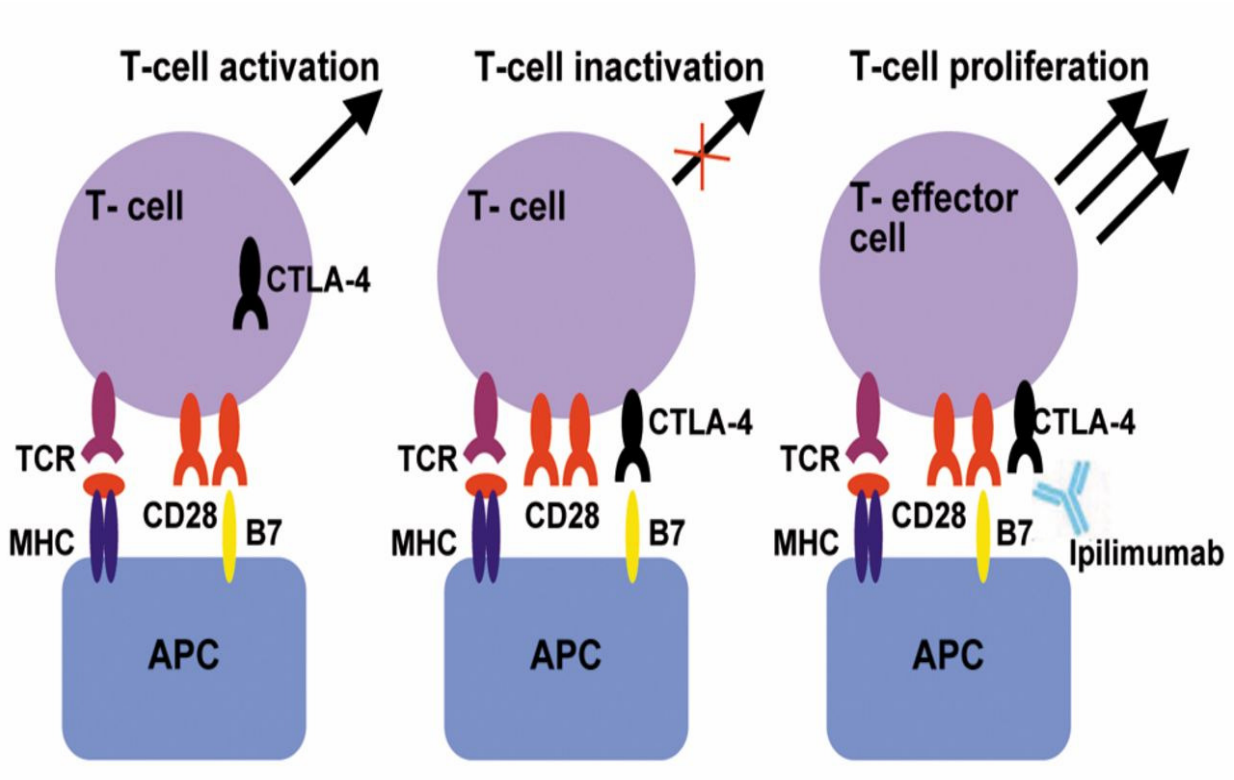
- Prostate ***not*** an "immunologic solid tumor" c/w melanoma, renal, lung, bladder, head and neck
- ***Not*** significantly hyper-mutated
- ↑ doses of vaccine ≠ augmentation of immunogenicity, ie, lower doses likely more immunogenic
- Abs generated specific for immunogen; ***no*** biologic effect seen
- ***NO*** potentiation of T cell responses; role of PD-1, PD-L1 on stromal, TILs, tumor
- *Immunologic signals - not immediate; ? Boosters
- To date, limited efficacy of checkpoint inhibitors, anti-CTLA-4, anti- PD1
- ***No*** evidence of disease pseudoprogression before response
- ***NO*** abscopal effects

Breakthrough immunotherapies still only help a minority of patients

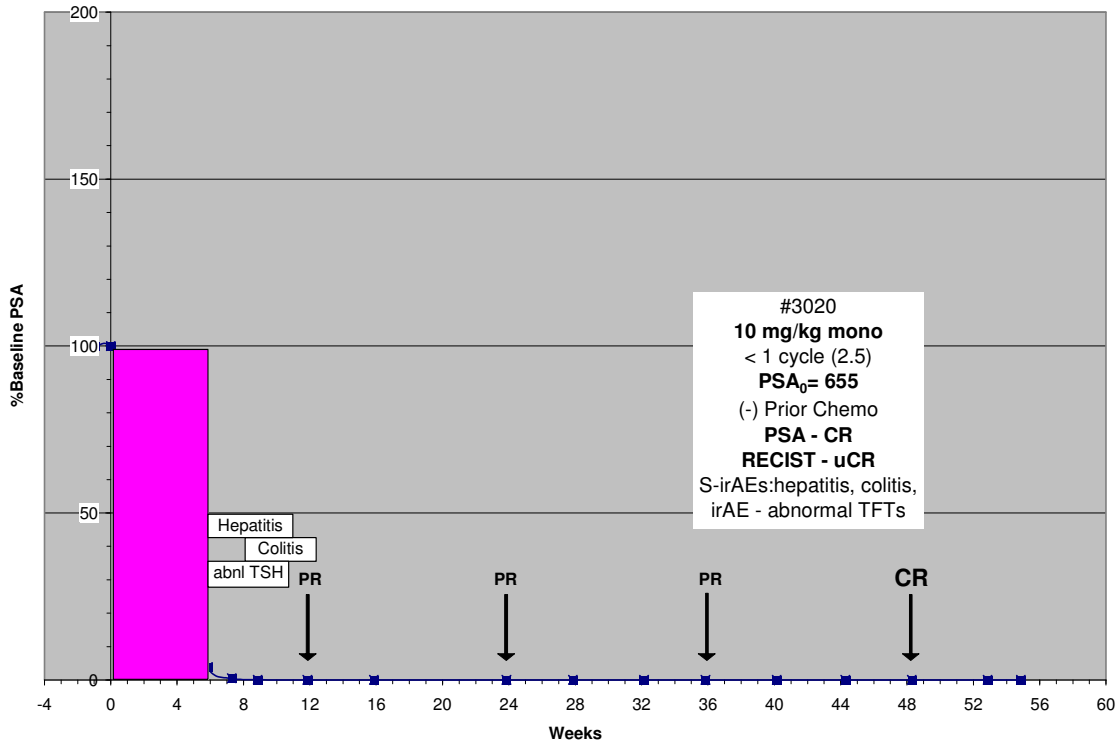


Graphic from Solaris Rx

Melanoma, lung, kidney, bladder, head and neck, Hodgkins, liver, gastro-esophageal


T-cell activation
T- cell
CTLA-4
TCR
CD28
B7
MHC
APC
T-cell inactivation
T- cell
CTLA-4
TCR
CD28
B7
MHC
APC
T-cell proliferation
T- effector cell
CTLA-4
TCR
CD28
B7
MHC
Ipilimumab
APC

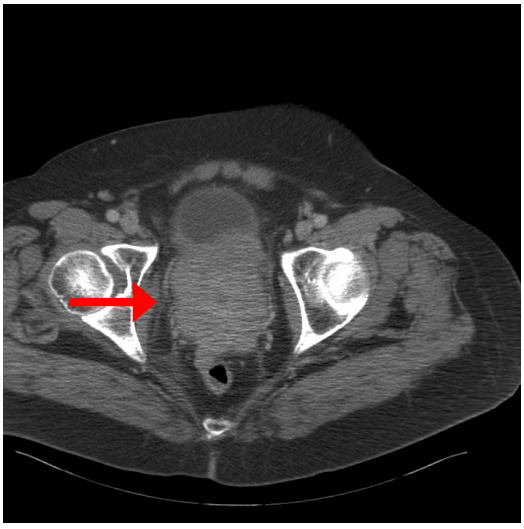
Subject 3020, 10 mg/kg Monotherapy



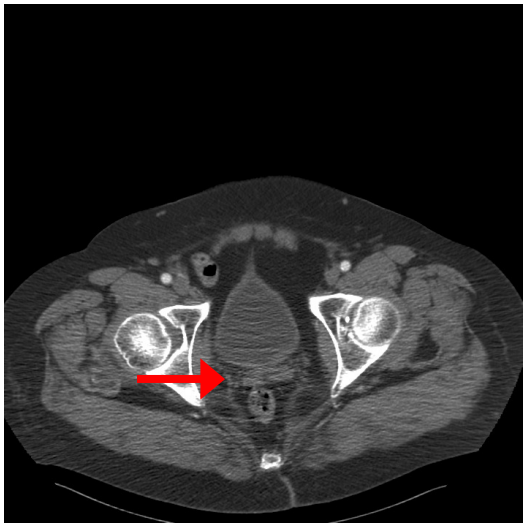
Beer, et al, ASCO 2008

Subject 3020:
Resolution of Prostate Mass

Screening

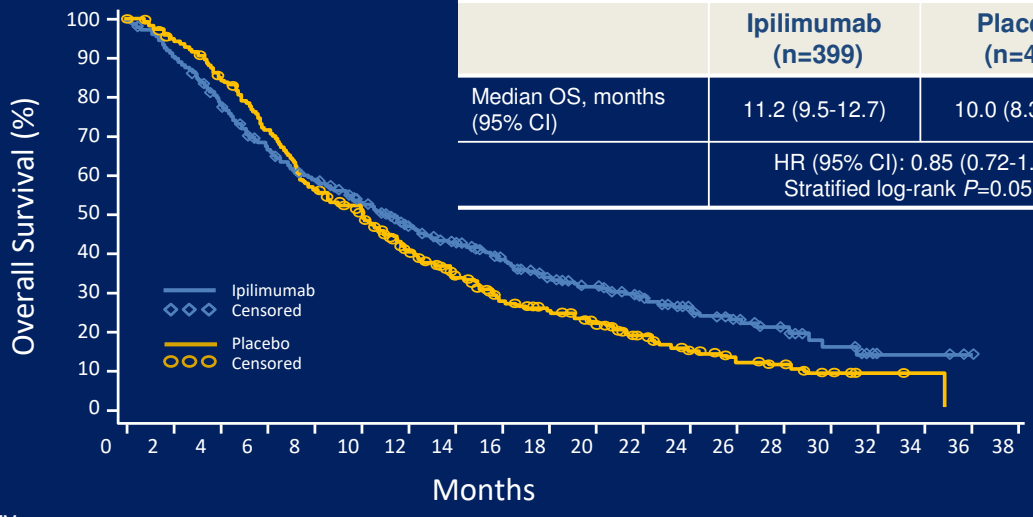


14 months



Phase 3 Study of Ipilimumab in Post-Docetaxel mCRPC (CA184-043)[1]

Primary Endpoint: OS (Intent to Treat [ITT] Population)



	Ipilimumab (n=399)	Placebo (n=400)
Median OS, months (95% CI)	11.2 (9.5-12.7)	10.0 (8.3-11.0)
	HR (95% CI): 0.85 (0.72-1.00) Stratified log-rank *P*=0.0530	

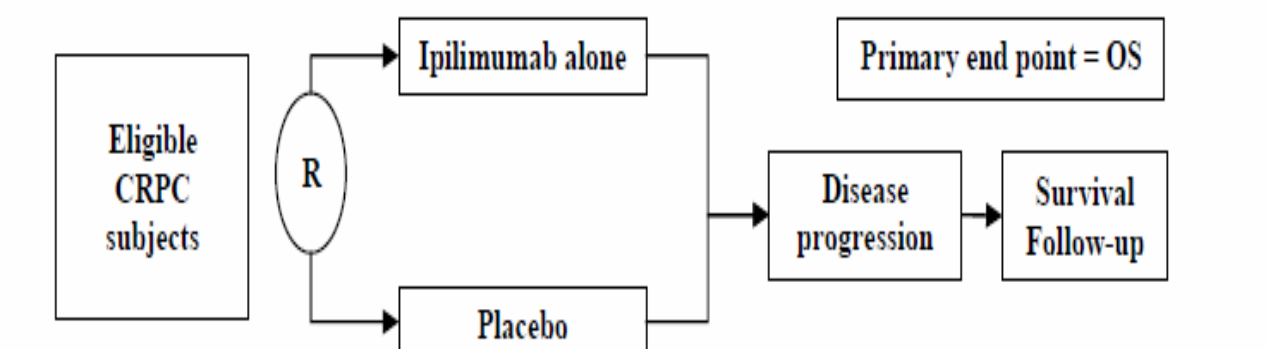
Safety

- Adverse event (AE) profile was consistent with that previously reported for ipilimumab*
  - The most frequent severe immune-related AEs were diarrhea and colitis

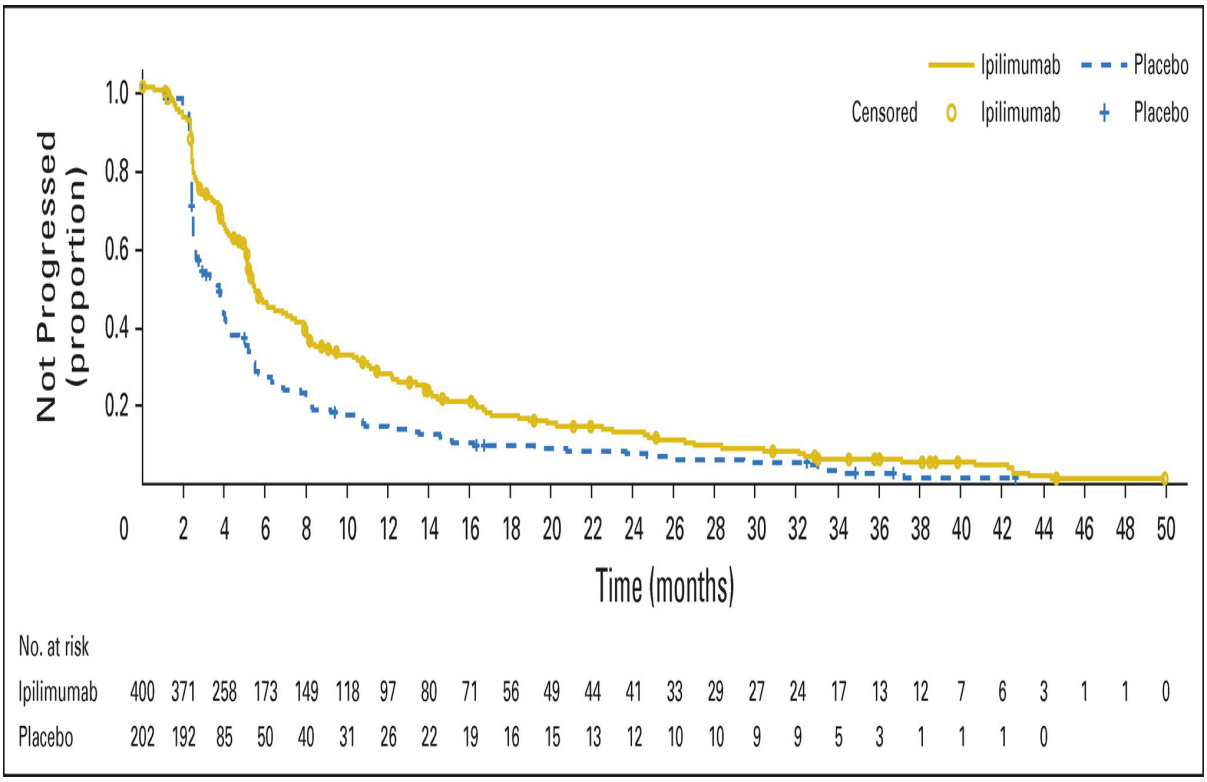
*See poster presentation at this meeting: Beer et al. Abstract ID: 52.

[1]Gerritsen WR et al. Paper presented at: European Cancer Congress 2013; Amsterdam, The Netherlands. Abstract 2850.

Kwon, et al Lancet Onc 2014

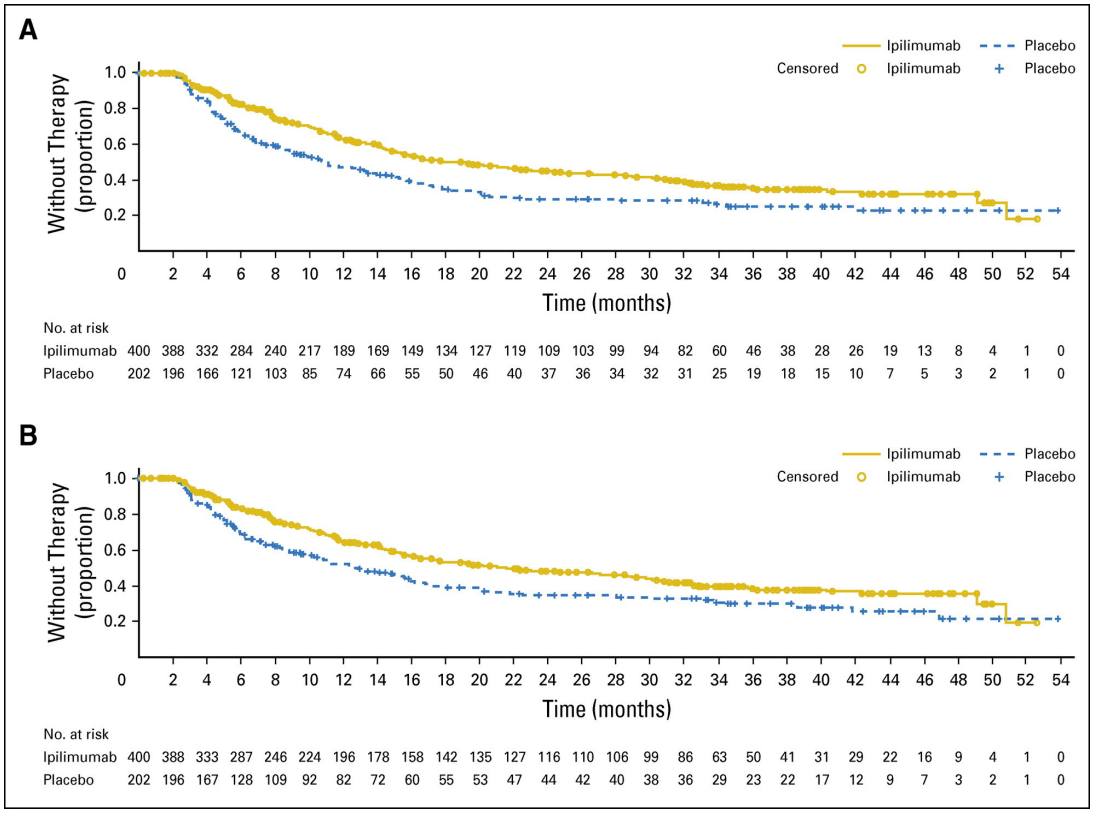


Research Hypothesis: Among subjects with asymptomatic or minimally symptomatic, chemotherapy-naïve castration resistant prostate carcinoma (CRPC) with no visceral metastases, overall survival in subjects randomized to ipilimumab will be superior to overall survival in subjects randomized to placebo.



Progression-Free Survival in Intent-to-Treat Population

Beer, et al, JCO, 2016



Time to (A) nonhormonal systemic therapy or (B) docetaxel therapy

Beer, et al, JCO, 2016

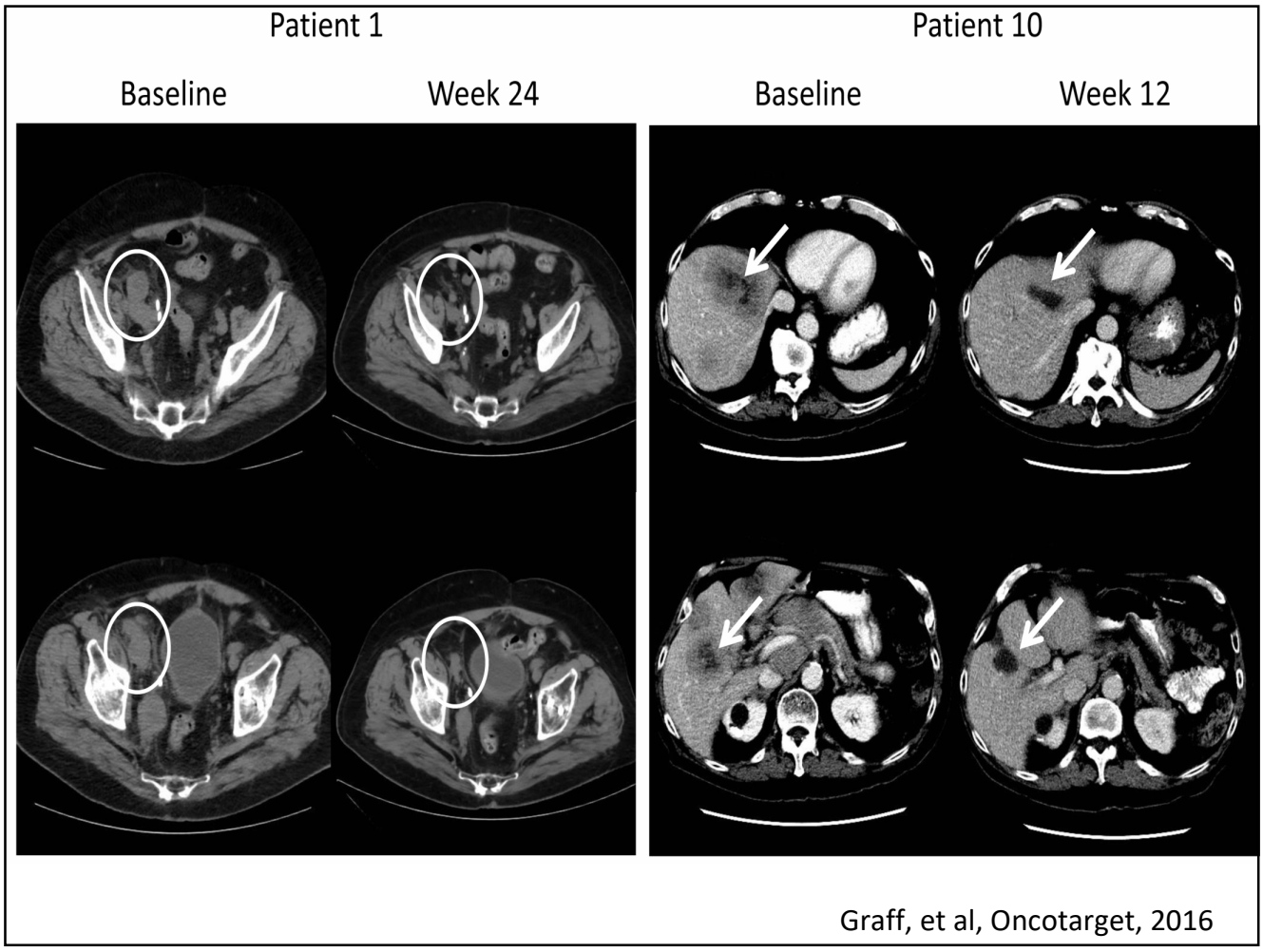
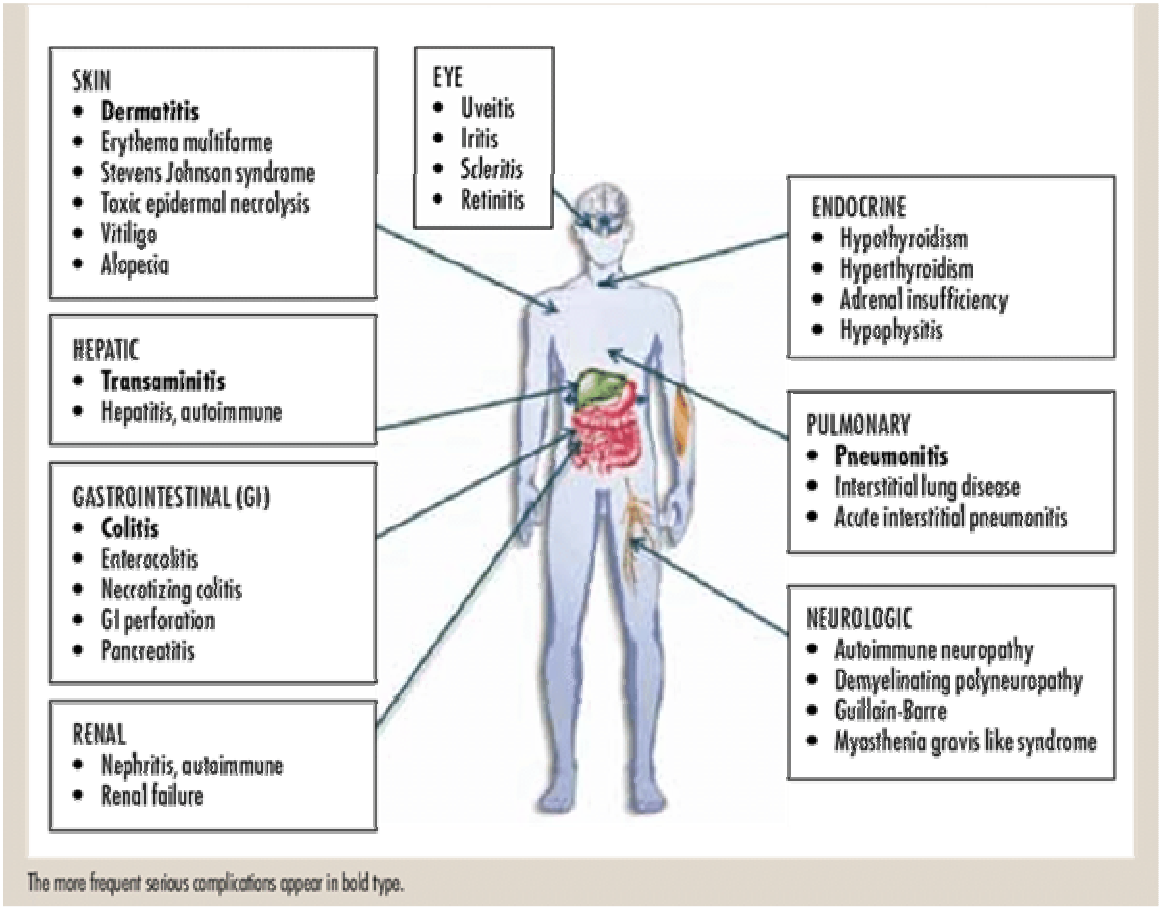

Patient 1
Patient 10
Baseline
Week 24
Baseline
Week 12
Graff, et al, Oncotarget, 2016

Table 2: Responding Patients*

Patient number	Date of cycle 1	PSA (ng/ml) baseline to nadir	Measurable Disease at Baseline	Best Radiologic Response	MSI	Prior Treatment for mCRPC
1	April 2015	70.65 → 0.08	Yes	PR	present	abi, enz
7	October 2015	46.09 → 0.02	No	N/A	n/a	abi, enz
10	January 2016	2502.75 → < 0.01	Yes	PR	absent	enz

* All responding patients remain on study.
PR – partial response; N/A – not applicable (i.e. no baseline biopsy done); MSI – microsatellite instability; abi – abiraterone; enz – enzalutamide

Graff, et al, Oncotarget 2016



The more frequent serious complications appear in bold type.

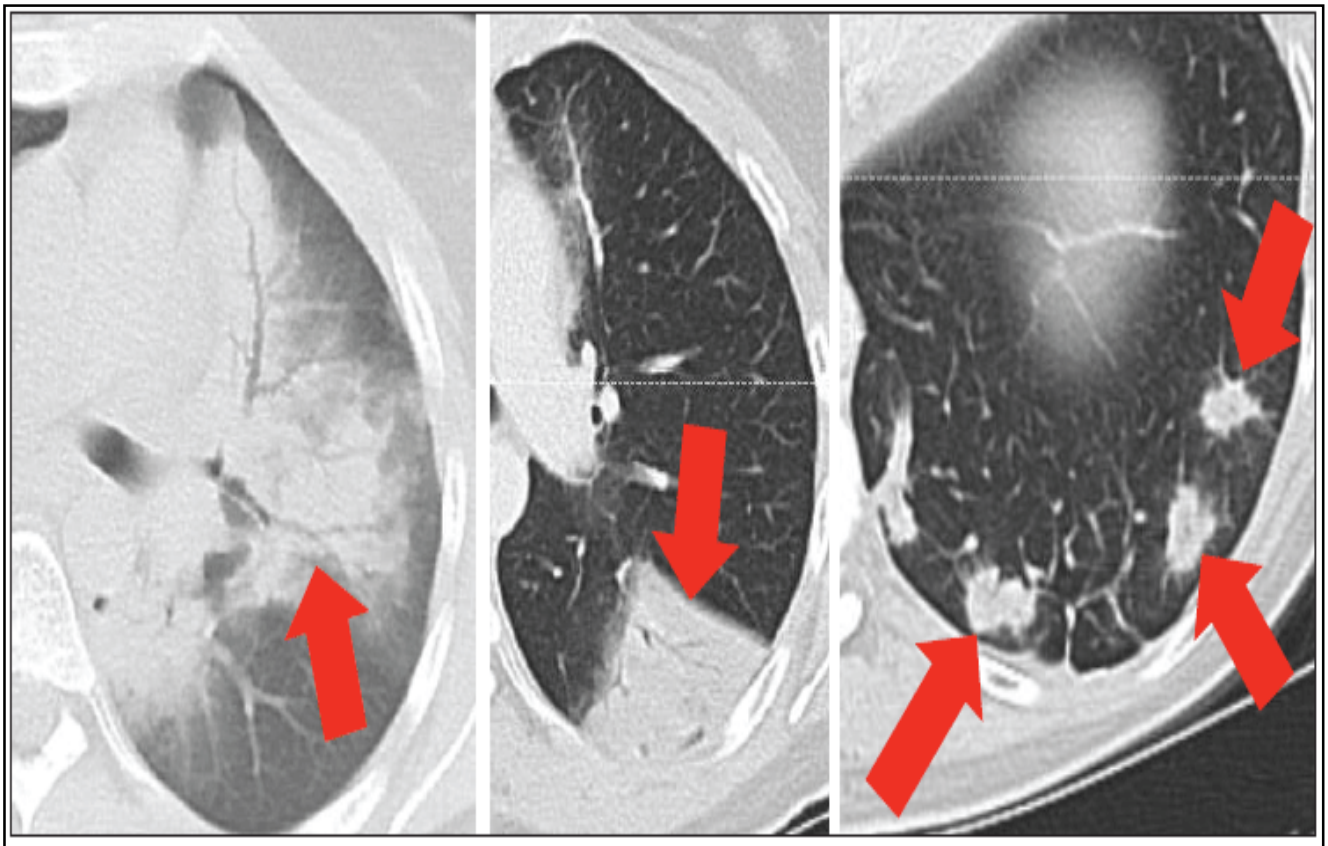


Figure 3: Different Radiographic Patterns of Checkpoint Blockade–Associated Pneumonitis Seen on CT Scanning in a Single Patient Treated With Ipilimumab and Nivolumab—Pneumonitis secondary to ipilimumab is shown in the left-hand panel, and pneumonitis secondary to nivolumab is shown in the center and right-hand panels. Red arrows indicate areas of radiologic abnormality.

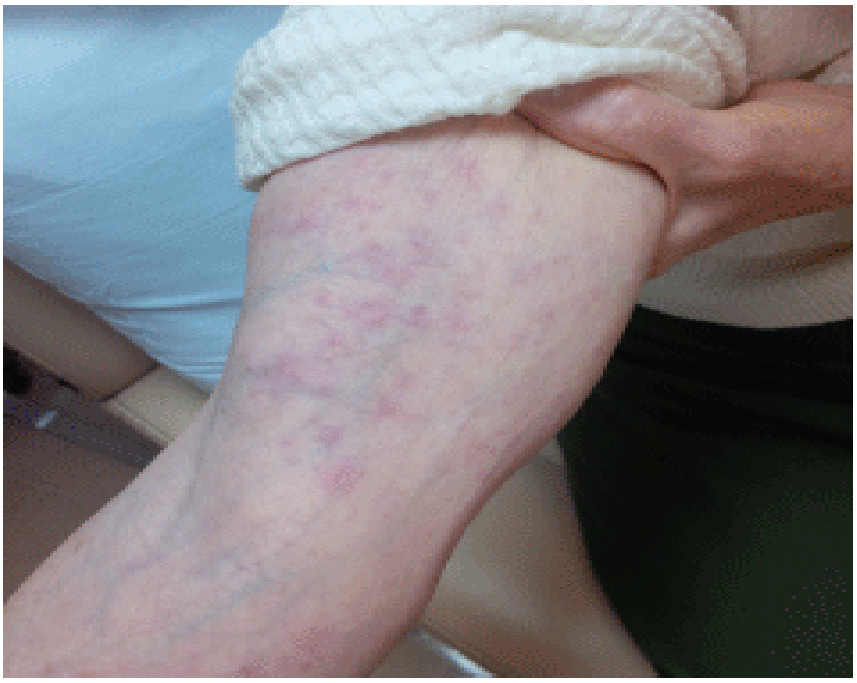


Figure 2: Ipilimumab-Related Autoimmune Dermatitis Manifesting as a Maculopapular Rash on the Arm of a Patient With Metastatic Melanoma. (Photo courtesy of Dr. Michael Postow.)

Programmed Death Ligand-1 (PD-L1) is among the most important immune checkpoint proteins that mediate tumor-induced suppression through T-cell downregulation. PD-L1 expression may indicate a more likely response to immunotherapies.

Microsatellite Instability (MSI) is caused by failure of the DNA mismatch repair (MMR) system. MSI-High correlates to an increase neoantigen burden, which is more likely to respond favorably to immunotherapies.

Total Mutational Load (TML) measures the total number of non-synonymous somatic mutations identified per megabase of the genome coding area. Tumors with high TML likely harbor neoantigens and may respond more favorably to immunotherapies

Unique Immune Approaches

- Focal therapy: VTP
- CAR T cells
- Neoadjuvant vs adjuvant
- Immune modulators: cyclophosphamide, Enzalutamide
- Novel vaccine platforms: DNA vaccine, prime boosts, DCVAC/Pca
- Checkpoints combos

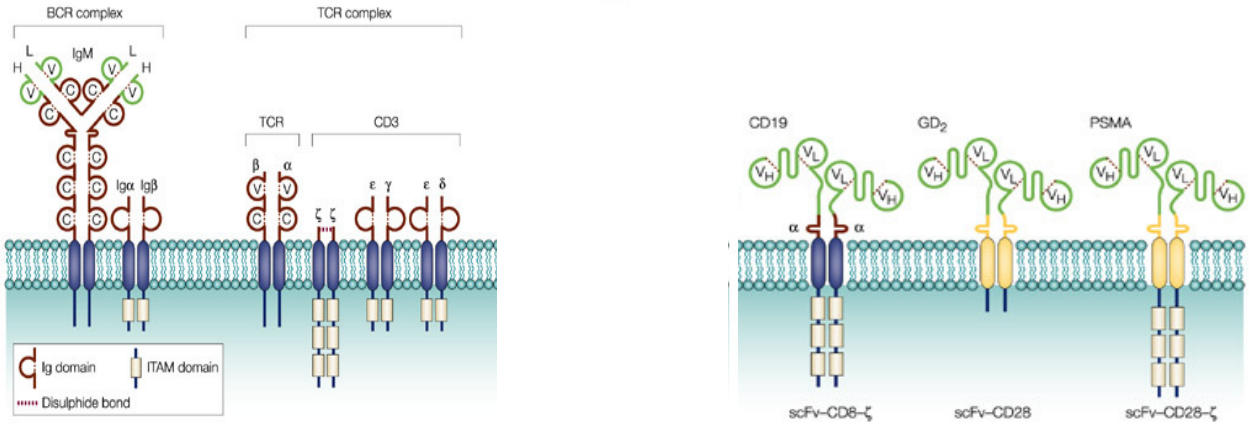
•**Genetic transfer of antigen receptors – rapidly generate tumor-specific T lymphocytes.**

•**Chimeric antigen receptors (CARs) encompass immunoglobulin variable regions or receptor ligands as antigen-recognition elements**

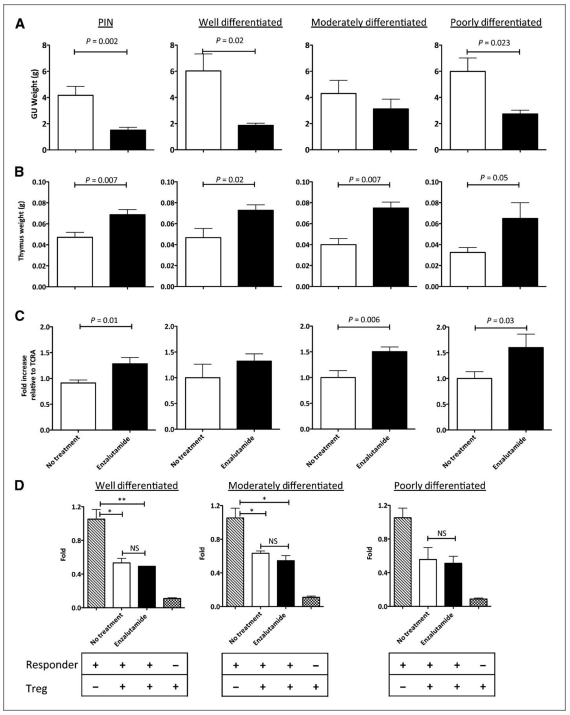
• **Permits T cells to recognize cell surface tumor antigens in the absence of HLA expression**

• **Requirements for genetically targeted T cells to function *in vivo* not clearly defined, hence need to establish *in vivo* conditions**

• **T-cell activation - mediated by the cytoplasmic domain of the CAR, which is typically derived from the CD3ζ chain or the FcRIγ chain**

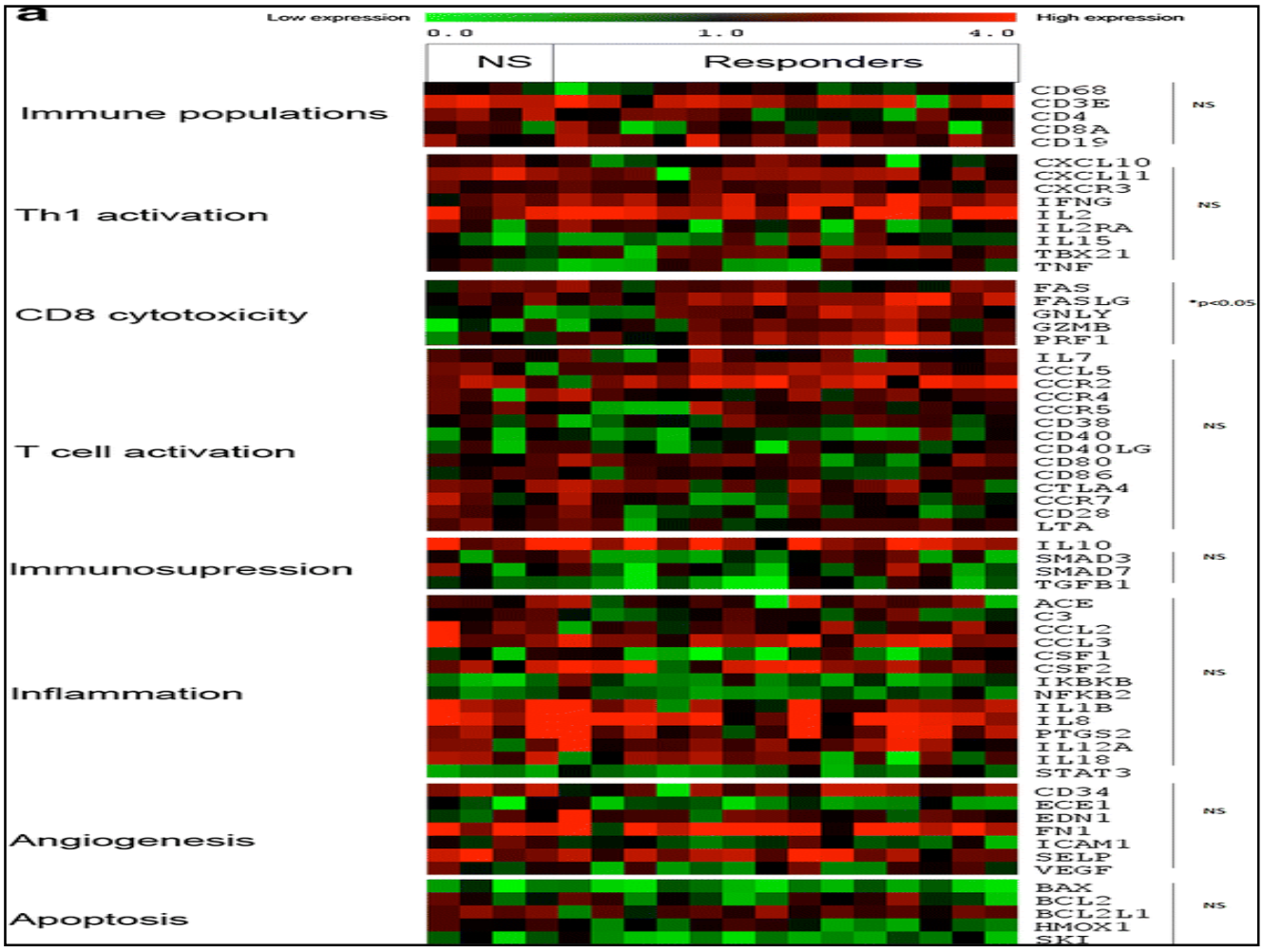


In TRAMP mice, enzalutamide reduces genitourinary tissue weight, enlarges the thymus, and is immune inert.



Andressa Ardiani et al. Clin Cancer Res 2013;19:6205-6218

Clinical Cancer Research
AACR American Association for Cancer Research


a
Low expression
0.0
1.0
4.0
High expression
NS
Responders
Immune populations
CD68
CD3E
CD4
CD8A
CD19
NS
Th1 activation
CXCL10
CXCL11
CXCR3
IFNG
IL2
IL2RA
IL15
TBX21
TNF
NS
CD8 cytotoxicity
FAS
FASLG
GNLY
GZMB
PRF1
*p<0.05
T cell activation
IL7
CCL5
CCR2
CCR4
CCR5
CD38
CD40
CD40LG
CD80
CD86
CTLA4
CCR7
CD28
LTA
NS
Immunosupression
IL10
SMAD3
SMAD7
TGFB1
NS
Inflammation
ACE
C3
CCL2
CCL3
CSF1
CSF2
IKBKB
NFKB2
IL1B
IL8
PTGS2
IL12A
IL18
STAT3
NS
Angiogenesis
CD34
ECE1
EDN1
FN1
ICAM1
SELP
VEGF
NS
Apoptosis
BAX
BCL2
BCL2L1
HMOX1
SKI
NS

Immune Biomarkers and Clinical Trial Designs

- No standards; may need to be based on particular cancer
- Compelling evidence that tumor heterogeneity is influenced at the genetic and epigenetic levels
- Multiplex biomarker panels are being advocated over single markers, which are unlikely to provide definitive stratification of patients.

Mutations, CKIs and prostate cancer: 2 + 2 ≠ 4?

- Mismatch repair (MMR)-deficiency - characterized by microsatellite instability (MSI) and a hypermutated phenotype
- correlates with clinical benefit after PD-1 blockade in patients with metastatic carcinomas. [Brahmer, et al, NEJM, 2015]
- PD-1 blockade in tumors with mismatch-repair deficiency. [Motzer, N Engl J Med. 2015; Alexandrov,et al, Nature, 2013]
- MMR deficiency - present in only a minority (a few percent) of patients with advanced prostate cancer;

Combos

- Up front metastatic disease: choices now

Standard GnRH +/- anti-androgen

GnRH + docetaxel (CHAARTED, STAMPEDE)

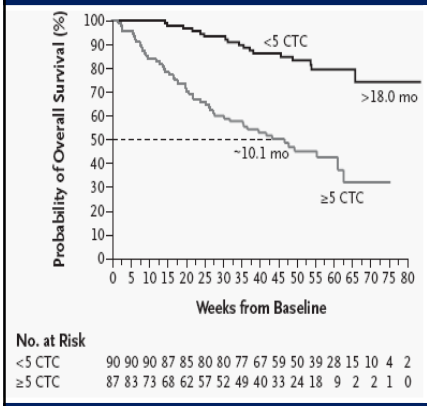
GnRH + abiraterone (LATITUDE, STAMPEDE)

- PARP inhibitors +/- checkpoints, radium-223
- CDK2,4 inhibitors +/- enzalutamide (immune modulator?)
- Future hopeful!

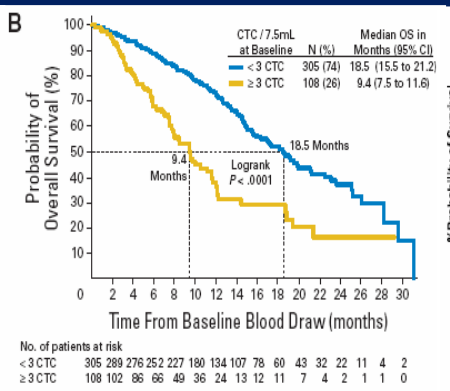
Baseline CTC number is prognostic for survival in patients with colorectal, breast & prostate cancer starting a new chemotherapy

The IMMC Trials

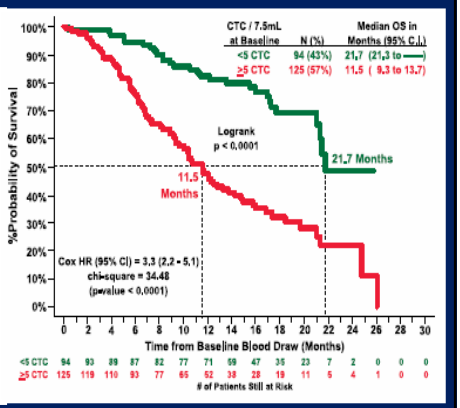
Breast
Christofanilli, NEJM, 2004



Colorectal
Cohen, JCO, 2008



Prostate
De Bono, Clin Can Res, 2008



PROGNOSTIC GROUPS DEFINED BY CUTOFFS

1. Unfavorable: 5 or more CTC's/7.5 ml of blood
2. Favorable: 4 or less CTC's/7.5 ml of blood

Question 1:

Are the checkpoint inhibitors disease specific in their efficacy?

GU: efficacy appears to be bladder >> renal >>>>>>>> prostate

1.Hypermutational status may be one reason

2. Possibility of an “immune desert” in prostate cancer

3. Packed bone marrow by prostate cancer cells may provide antigenic stimulation but with ensuing fibrosis may lead to a “dry” marrow.

Question 2:

Where should immune therapies be positioned in the prostate disease continuum?

- There is rationale for their use any time along the prostate cancer disease continuum.
- Need to have defined endpoint or biomarker to show biologic effect
- PSA not reliable indicator

Question 3:

What is the impact of AR-directed therapies on disease biology; should we use them earlier or later in the disease?

Is there a role for more combinatorial approaches?

1. AR and its relationship to RB continues to play an important role in treatment and clinical trial design
2. Novel therapies include combinations with Rad-223 with atezolizumab, niraparib, olaparib, apalutamide and RT
3. Earlier interventions may identify those patients with differential resistance patterns, ie, innate versus adaptive resistance

Bonus Question 4.

PDL-1 expression in metastatic CRPC specimens is low. What are other relevant markers in this disease?

- Still remain unvalidated: **ICOS, VISTA, MDSC**

  Are they biomarkers?
- Not all commercial antibodies or scoring systems for PDL-1 are the same
- Concerns remain, re: lack of relationship of PD-L1 expression with response in difference malignancies
- Basal vs luminal differences
- Immunologic platforms vary: no firm read out for prostate cancer

Thank you!