Exploring the inner complexity of prostate cancer through immunotherapy… is immunotherapy a reasonable treatment option for prostate cancer?

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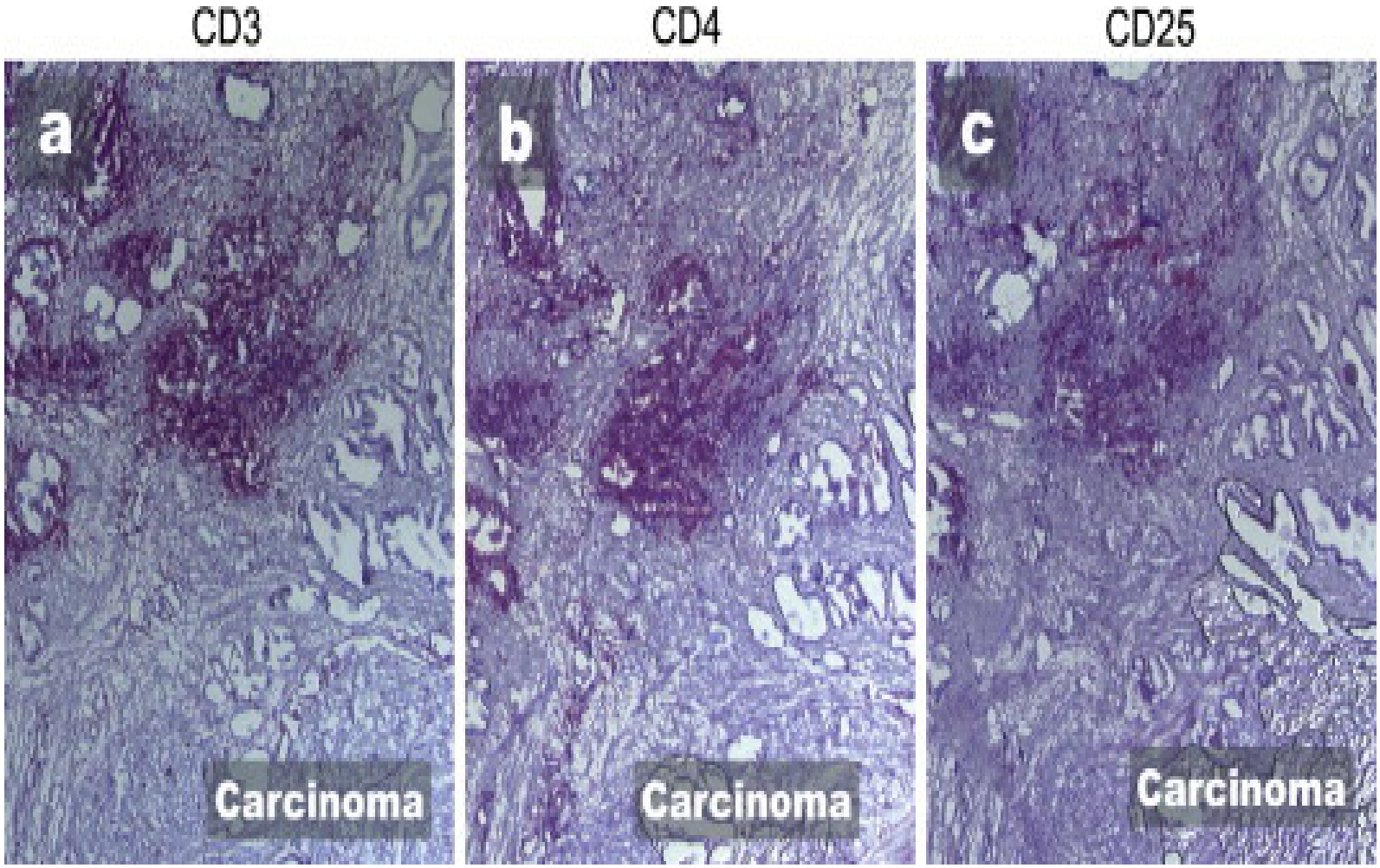
Prostate cancer…

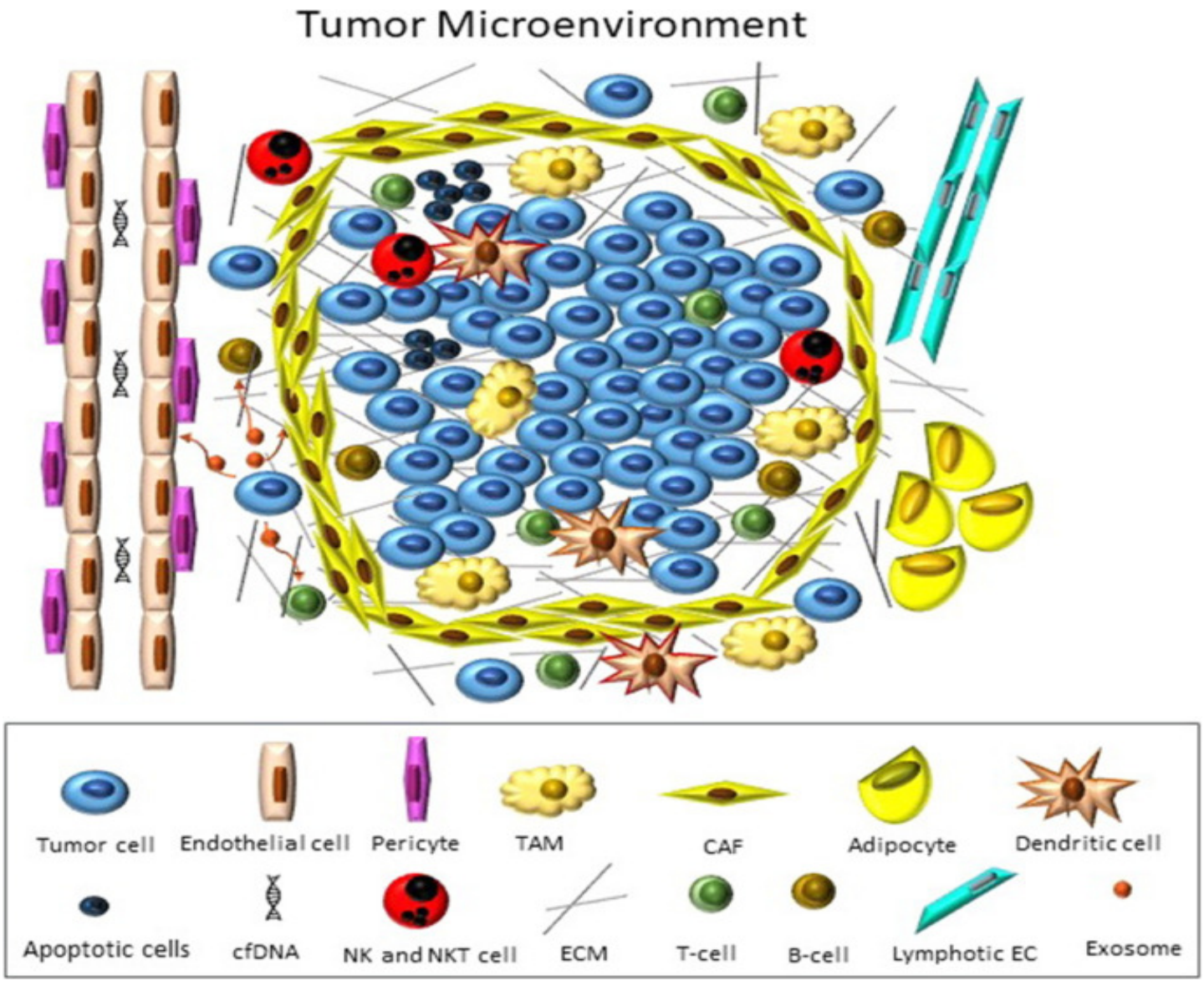
- Considered a “bland” or “cold” tumor
- Tumors that are rich with a variety of immune cells often respond better to immune therapies such as checkpoint inhibitors
- Prostate can be “hot” especially at diagnosis
- Trying to convert a “cold” tumor into a “hot tumor” – not easy despite multiple approaches



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.

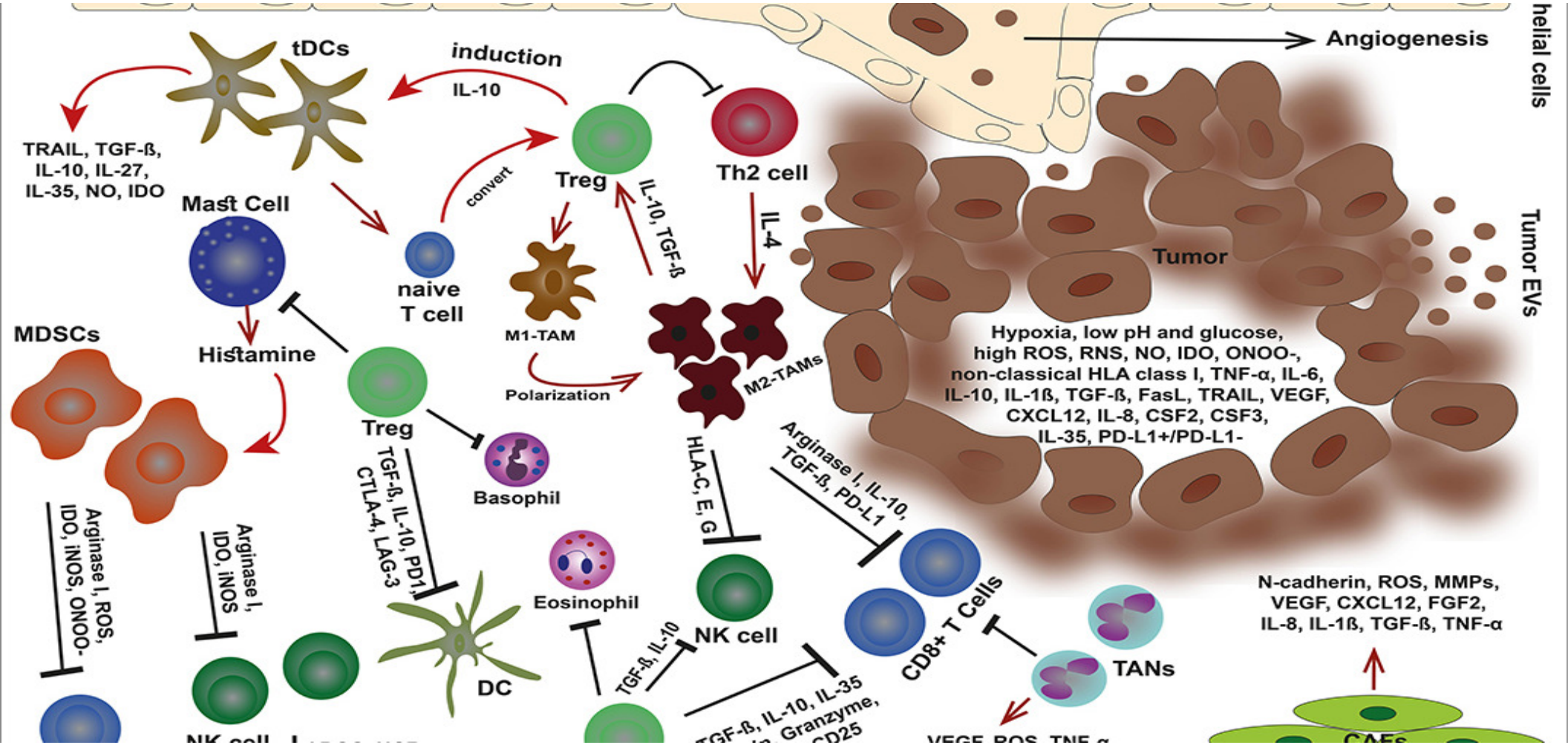
The tumor microenvironment (TME)…

- The area where the tumor is actively growing, an ecosystem that surrounds a tumor inside the body.
- Can be bone or an organ
- Implies the “milieu” or environment that fosters growth of the tumor cells
- includes immune cells, the extracellular matrix, blood vessels and other cells, like fibroblasts that can support growth.
- Other factors can inhibit an immune response within the TME by Inhibitory cells Tregs, adenosine



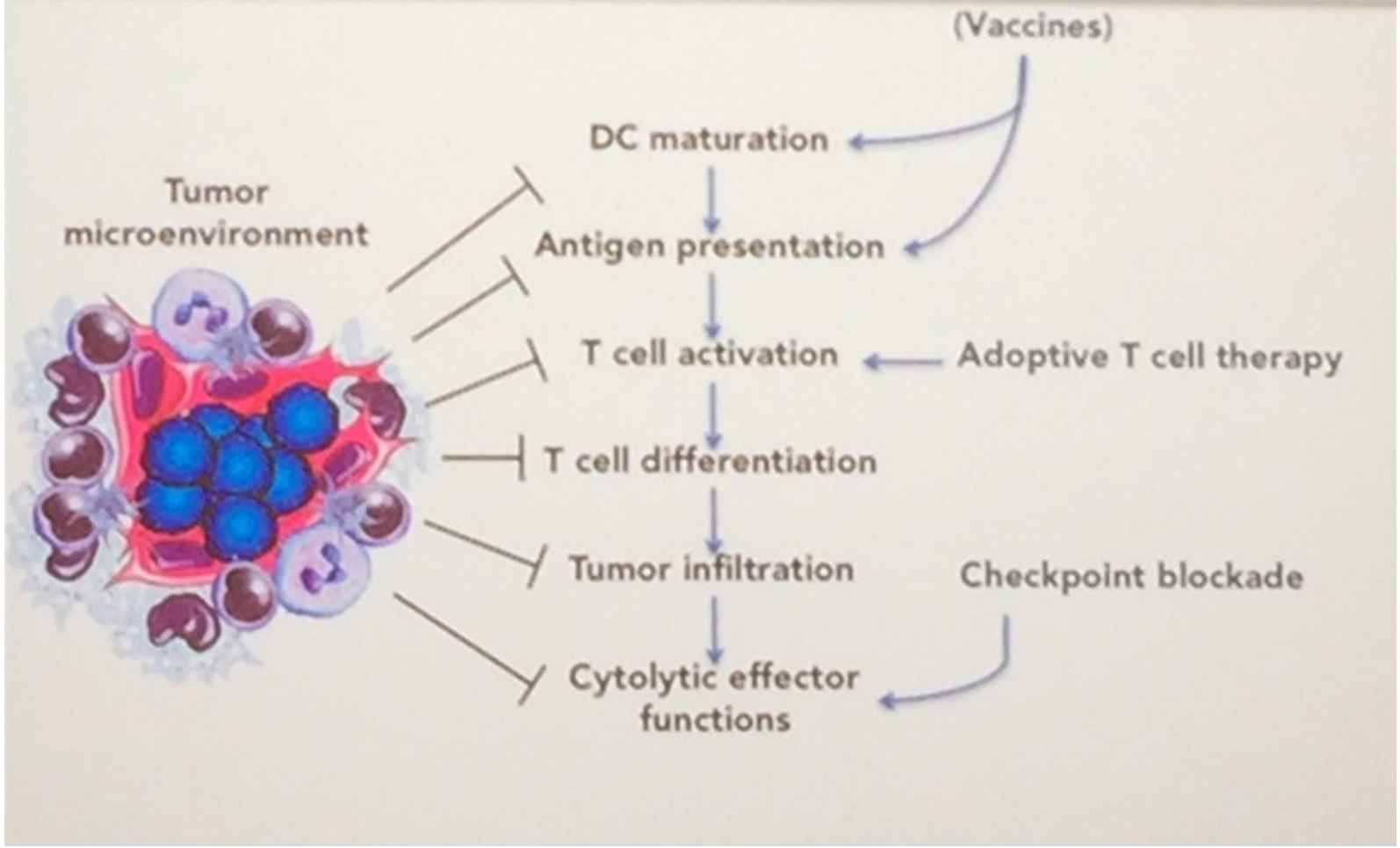
Baghban, et al, Cell Communication & Signalling, 2020

Overview of TME



Labani-Motbagh, et al, Front Immunol, 2020

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



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

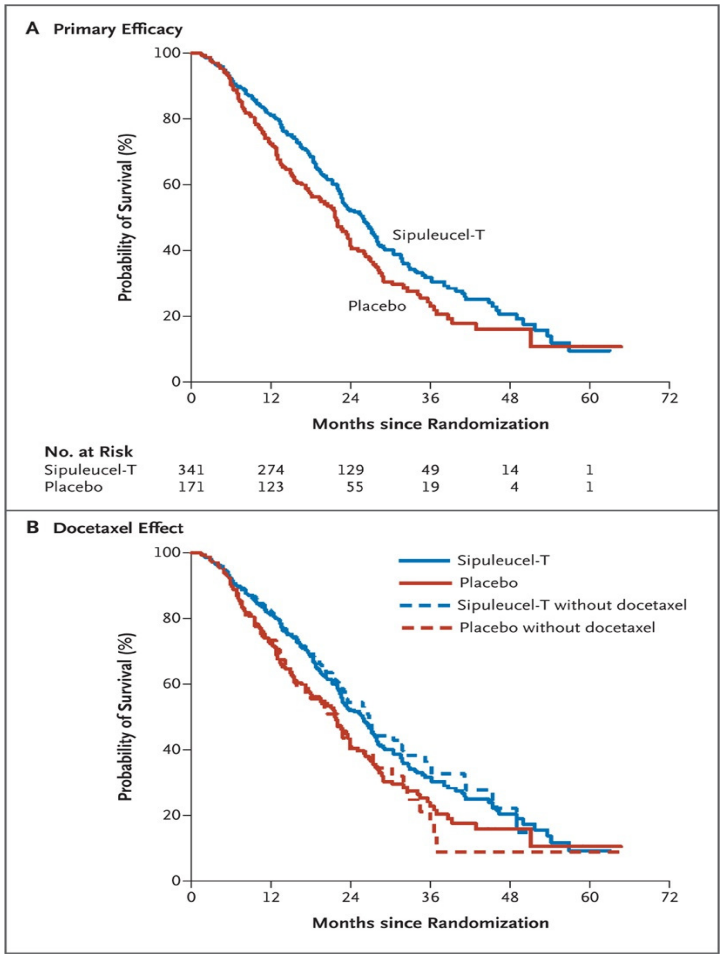
The Challenges of Any Immune Therapy…
Therapy must be…

- ***Exportable***: "off the shelf" – *many still "boutiquish*"
- ***Reportable***: need appropriate endpoints – *Is PSA enough?*
- ***Translatable***: biologic effect* - *can we demonstrate immune cells at the tumor site?*
- ***Time Table***: Anticipated time-to-effect – <u>no immediacy</u>
- ***Radiographic assessment:*** pseudoprogression? – *use of FDG PET, PSMA PET*

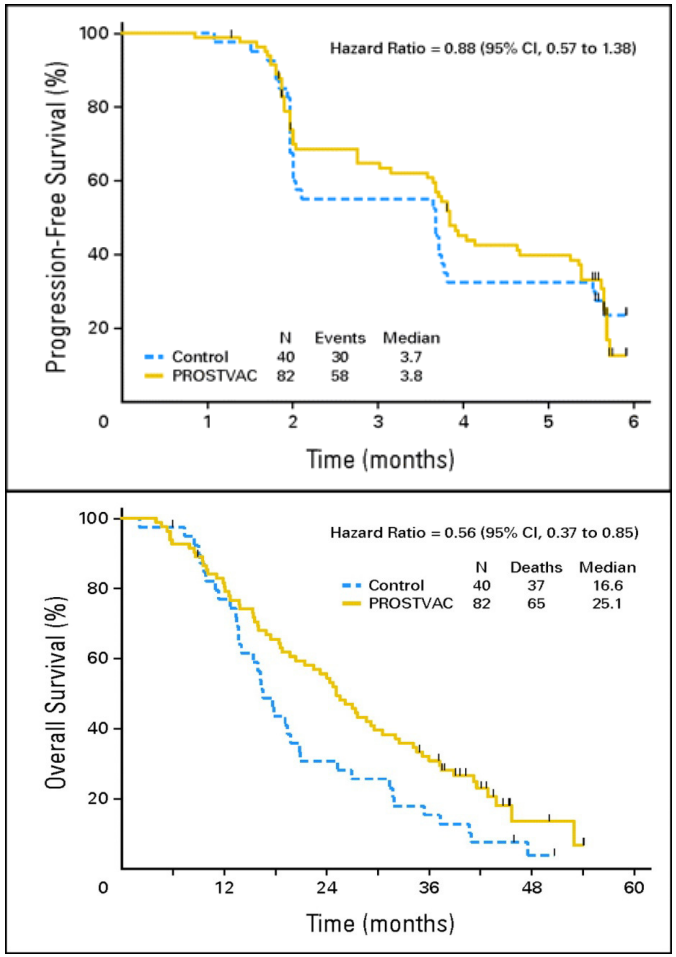
In the beginning…Sipuleucel-T, aka Provenge

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

Vaccines in Prostate Cancer



Kantoff, et al, NEJM 2010.

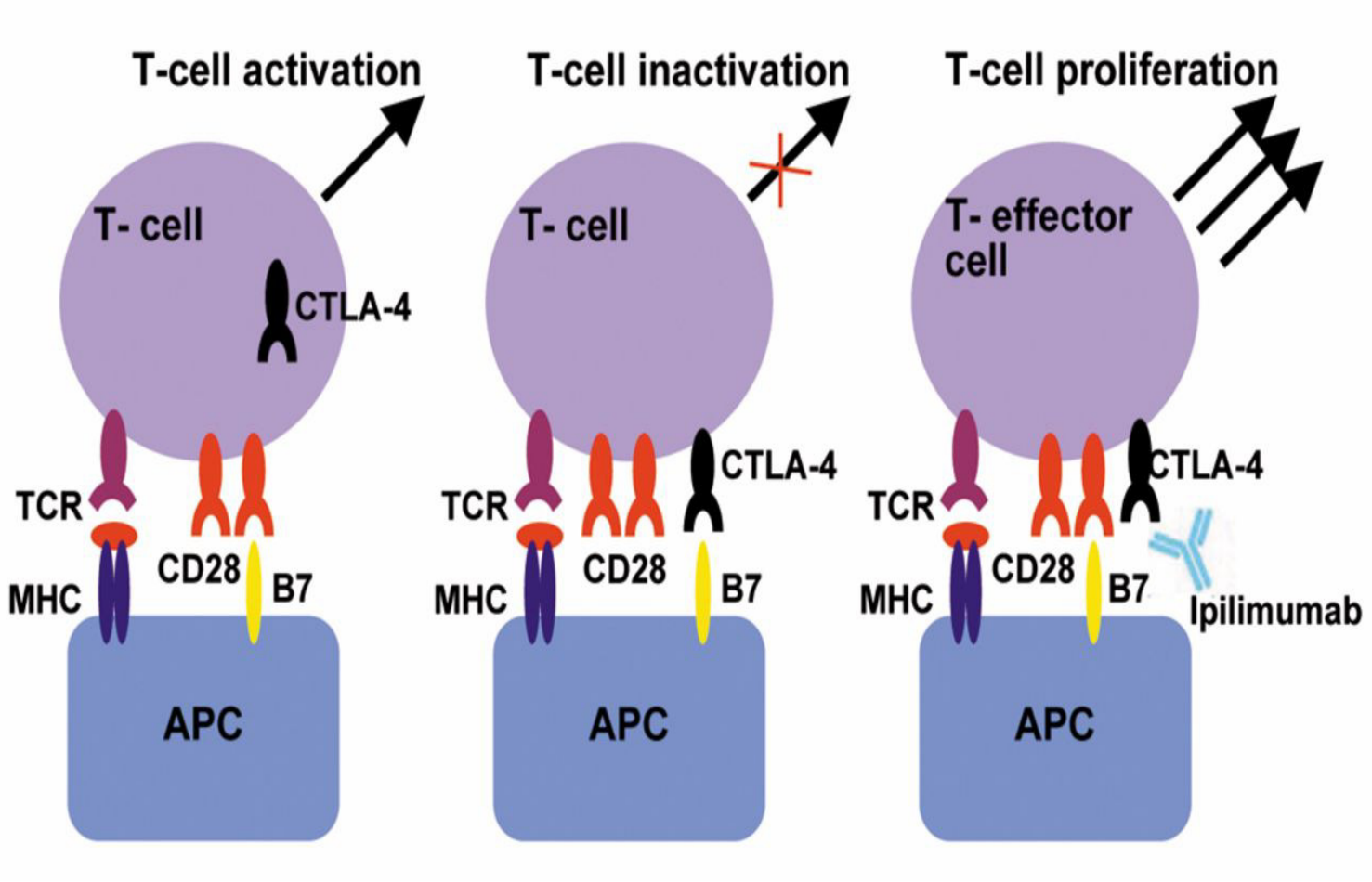


Kantoff, el al, JCO 2010

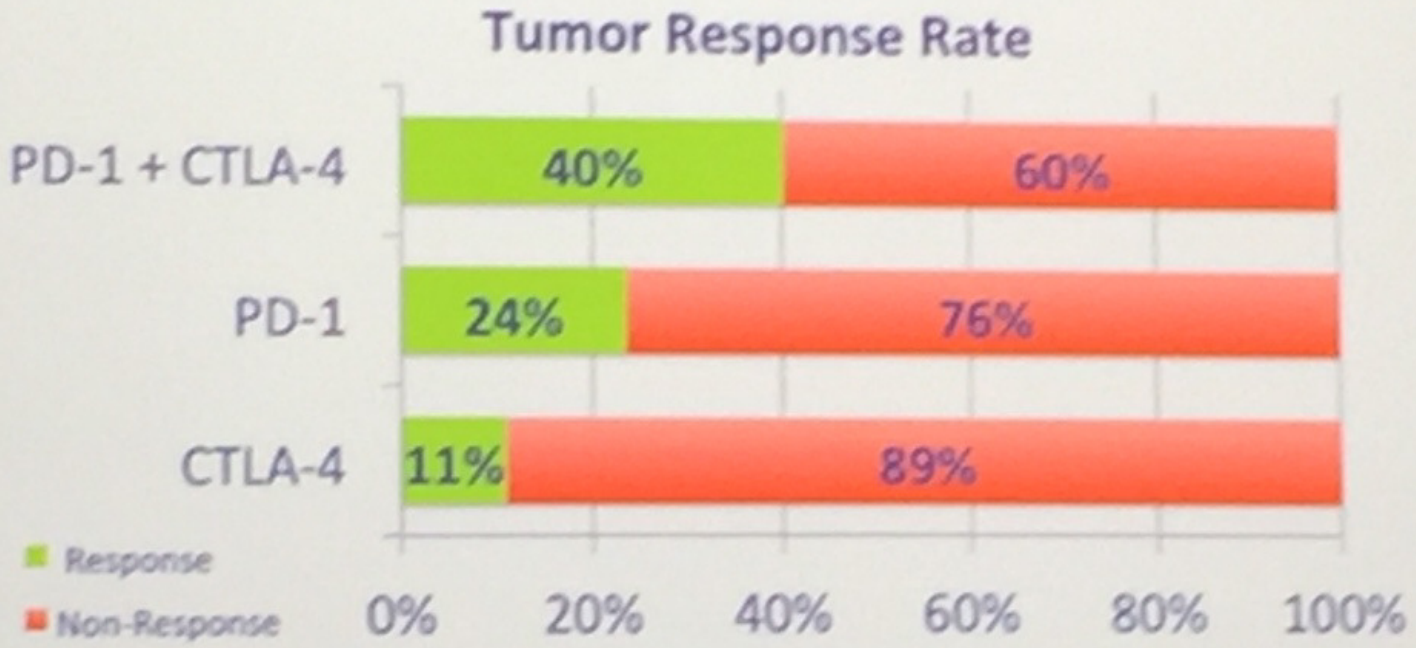
PROSTVAC ≠ OS

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!


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

Breakthrough immunotherapies still only help a minority of patients

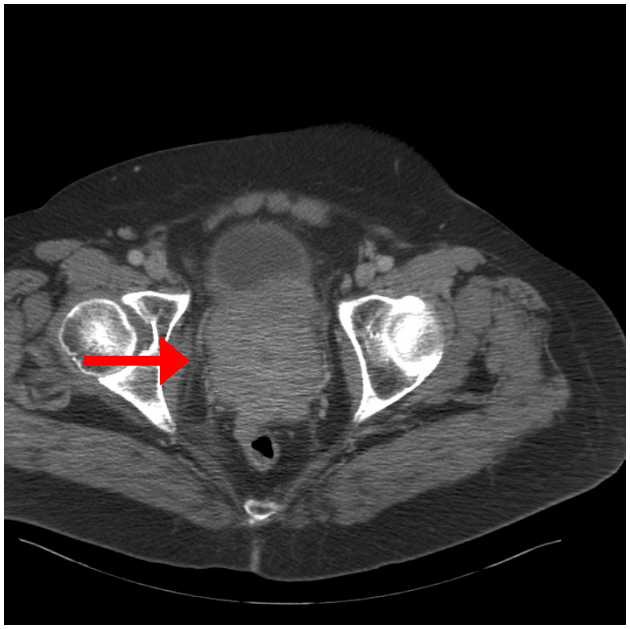


Graphic from Sidaraudka

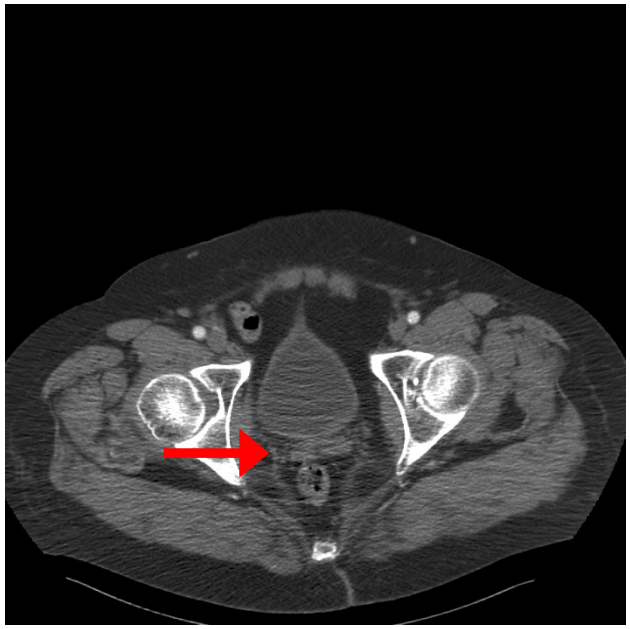
Melanoma, lung, kidney, bladder, head and neck, Hodgkins, liver, gastro-esophageal

Subject 3020:
Resolution of Prostate Mass

Screening

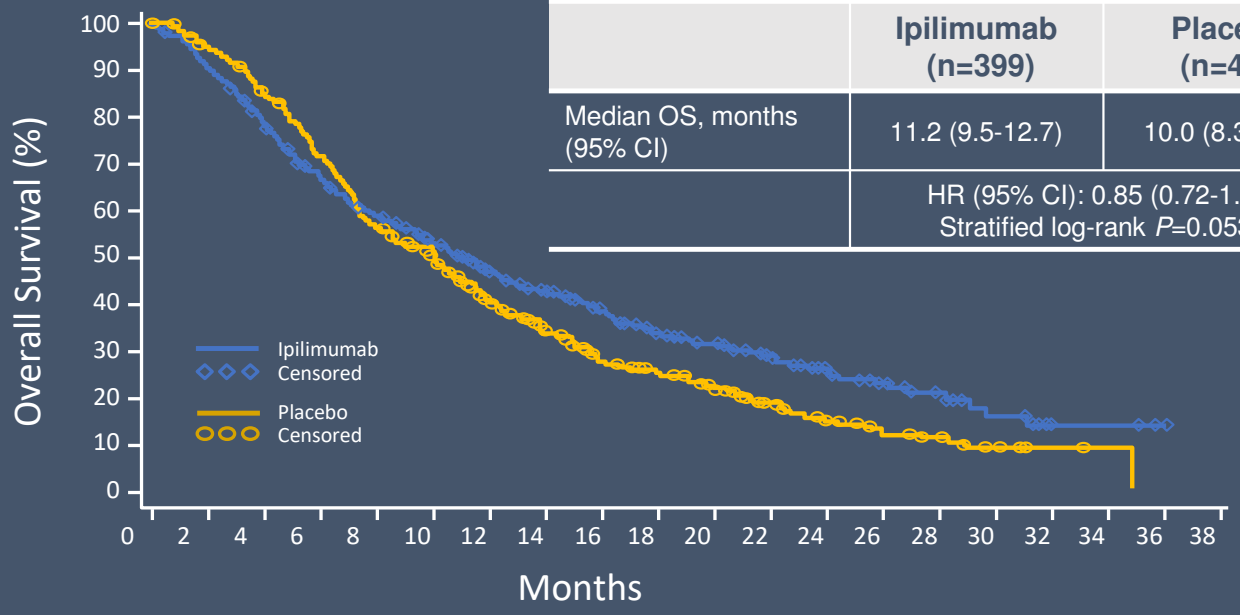


14 months



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	

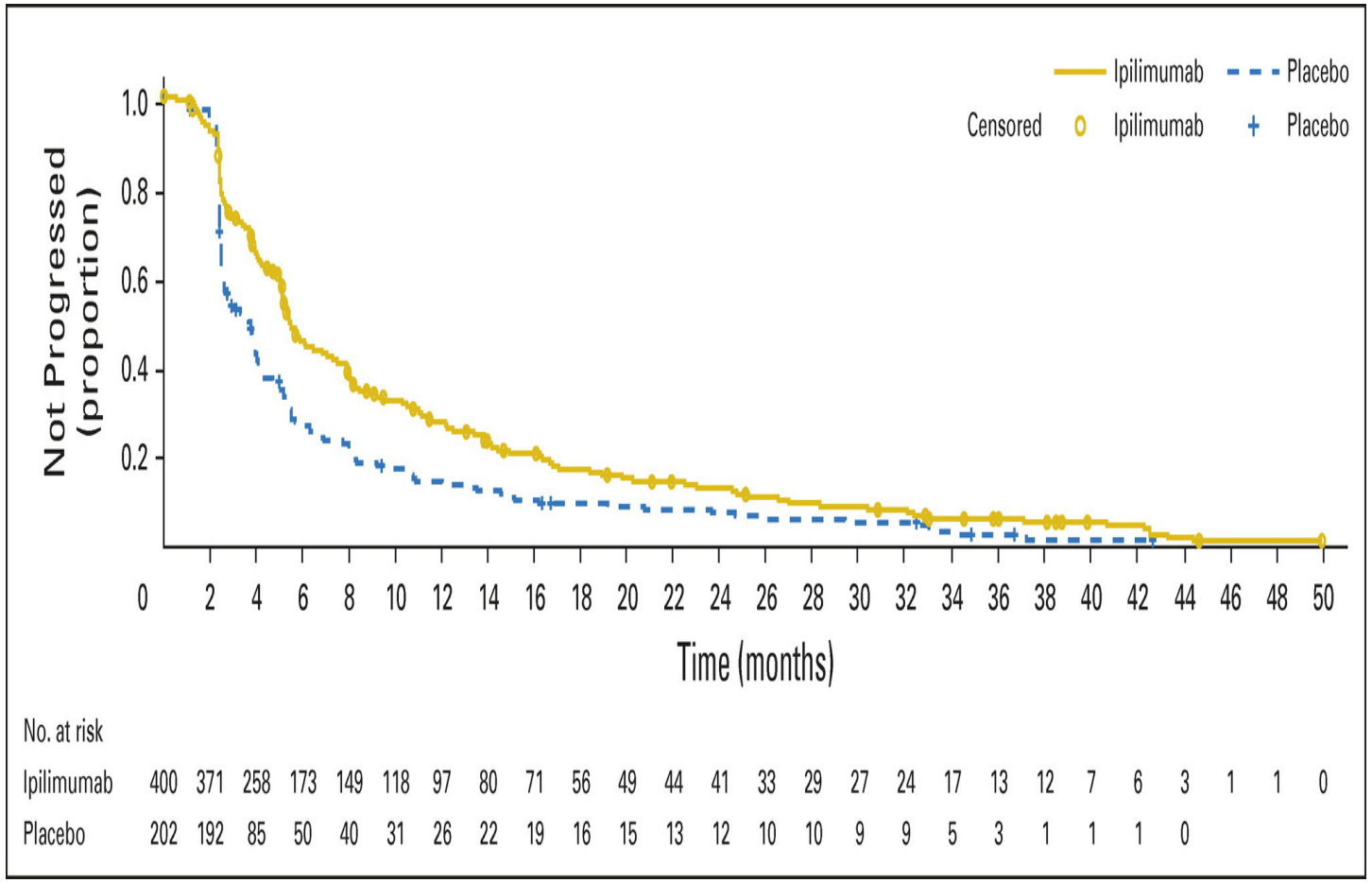
Safety

- 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.

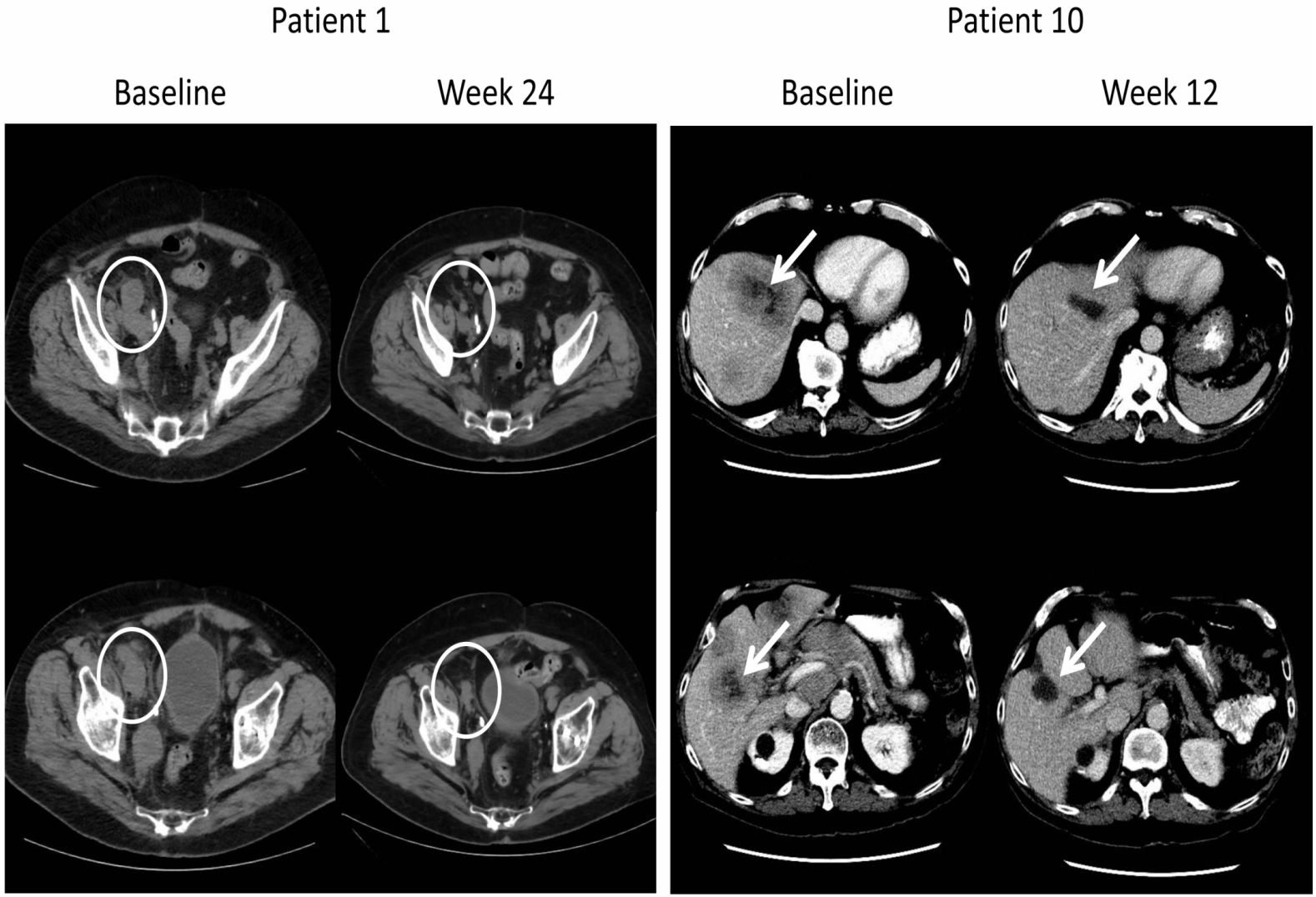
[1]Gerritsen WR et al. Paper presented at: European Cancer Congress 2013; Amsterdam, The Netherlands. Abstract 2850.

Kwon, et al Lancet Onc 2014



Progression-Free Survival in Intent-to-Treat Population

Beer, et al, JCO, 2016



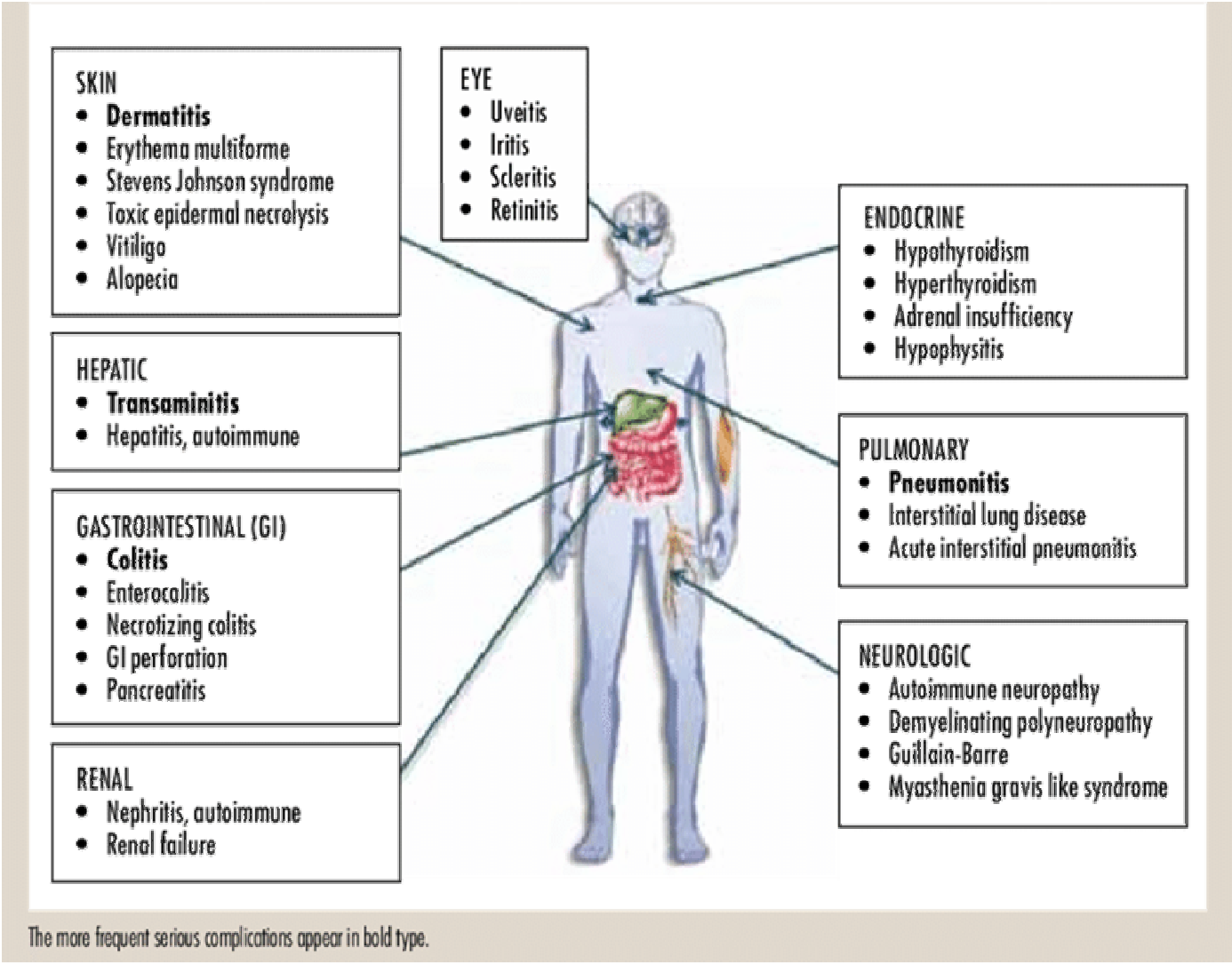
Graff, et al, Oncotarget, 2016

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.

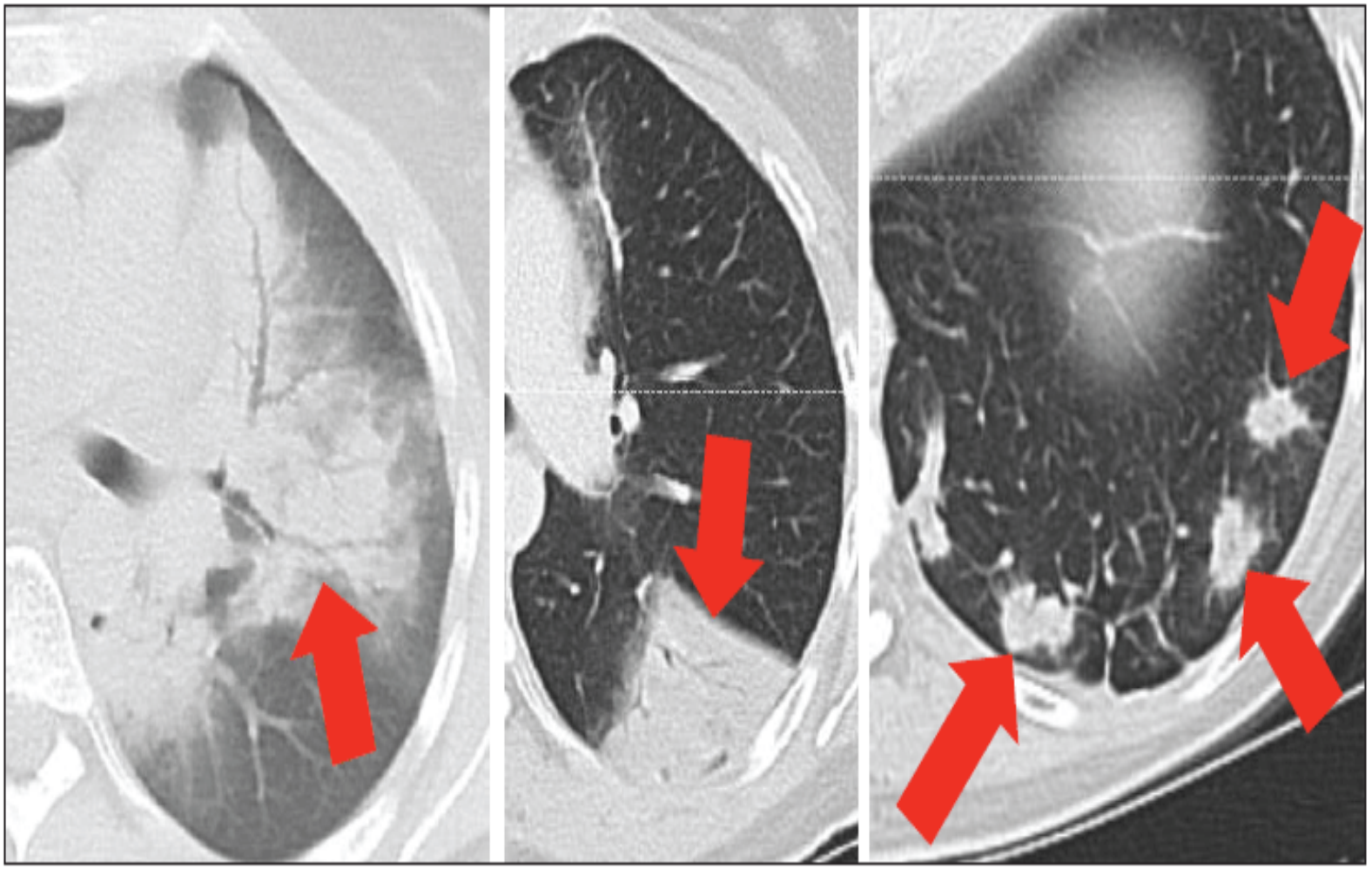


Figure 3: Different Radiographic Patterns of Checkpoint Blockade–Associated Pneumonitis Seen on CT Scanning in a Single Patient Treated With Ipilimumab and Nivolumab—Pneumonitis secondary to ipilimumab is shown in the left-hand panel, and pneumonitis secondary to nivolumab is shown in the center and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

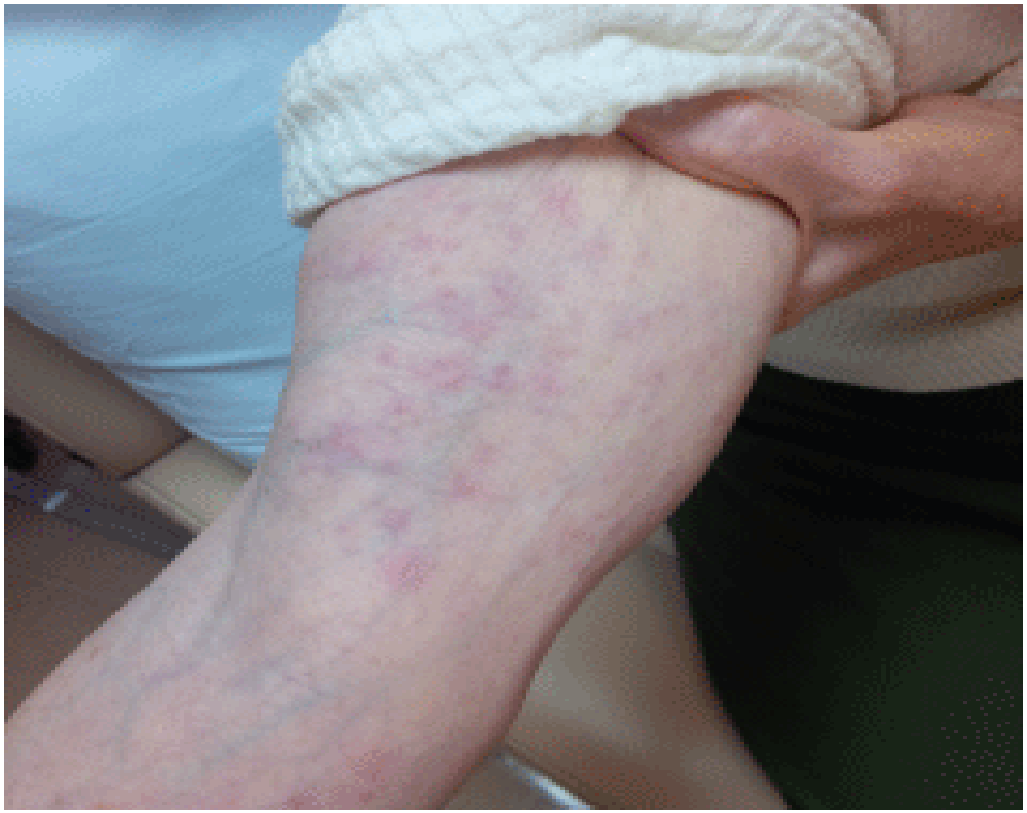
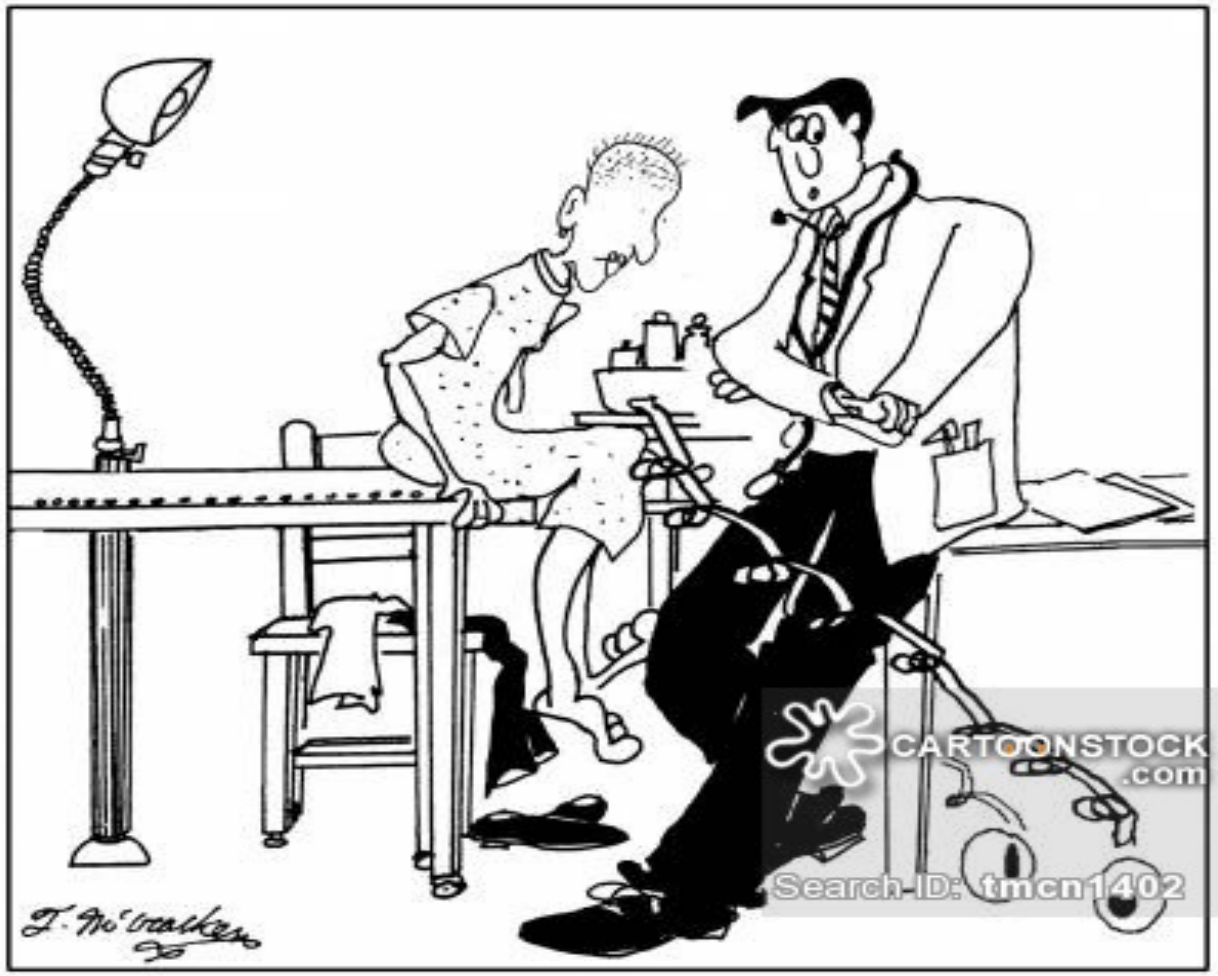


Figure 2: Ipilimumab-Related Autoimmune Dermatitis Manifesting as a Maculopapular Rash on the Arm of a Patient With Metastatic Melanoma. (Photo courtesy of Dr. Michael Postow.)



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

The checkpoints and autoimmunity???

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

Knowing your Patient's Tumor Profile: Example – Prostate Ca

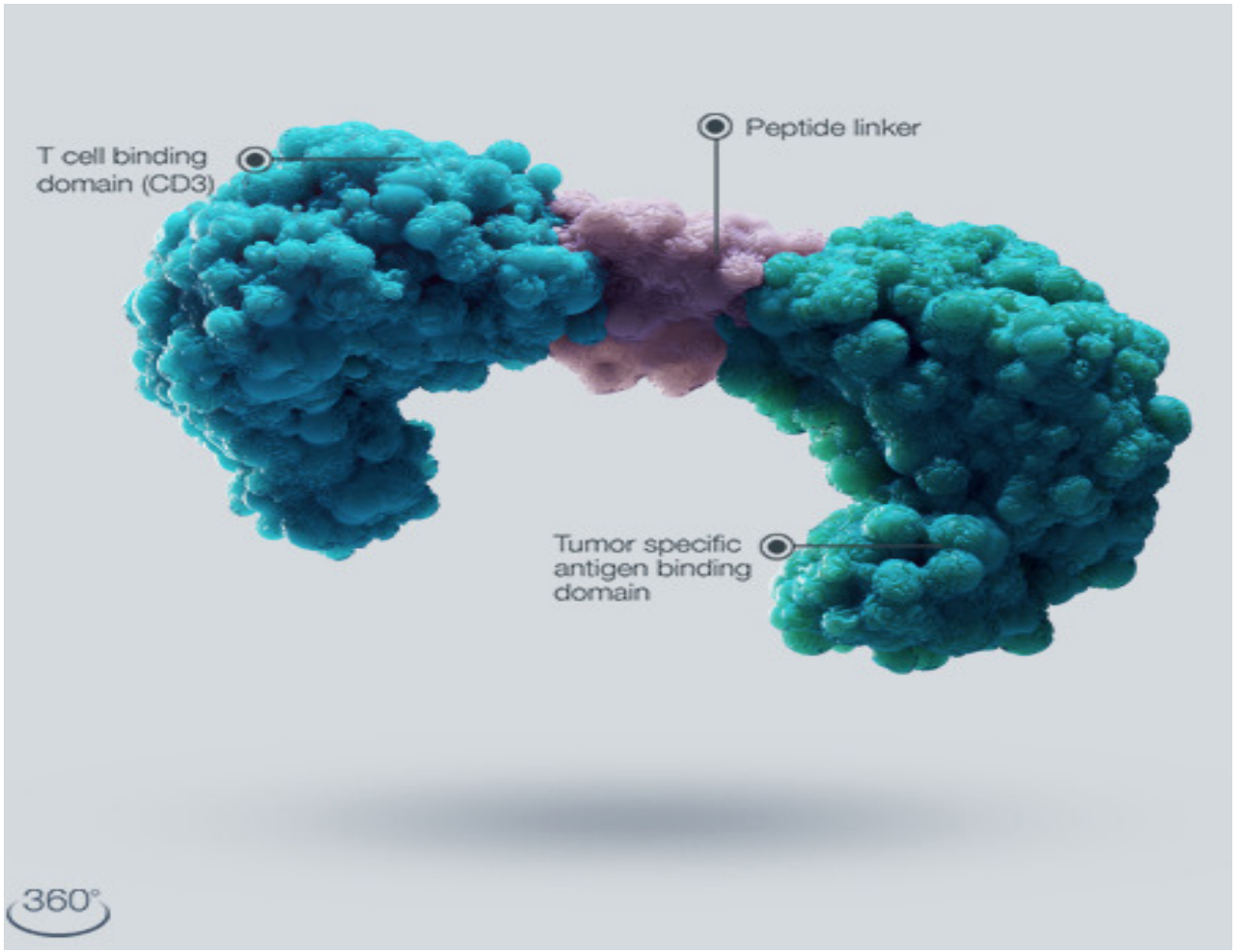
- Precision Medicine - In form of medicine that uses information about a person's own genes or proteins to prevent, diagnose, or treat disease.
- Uses specific information about a person's tumor to help make a diagnosis, plan treatment, find out how well treatment is working, or make a prognosis.
- Precision Medicine may be key to identifying drugs that may attack a particular genomic alteration and lead to improved survival
- Precision imaging may also allow for more directed therapy with radiopharmaceuticals, radioligands, and immune therapies

Approval for checkpoint inhibitors in any cancer, including prostate

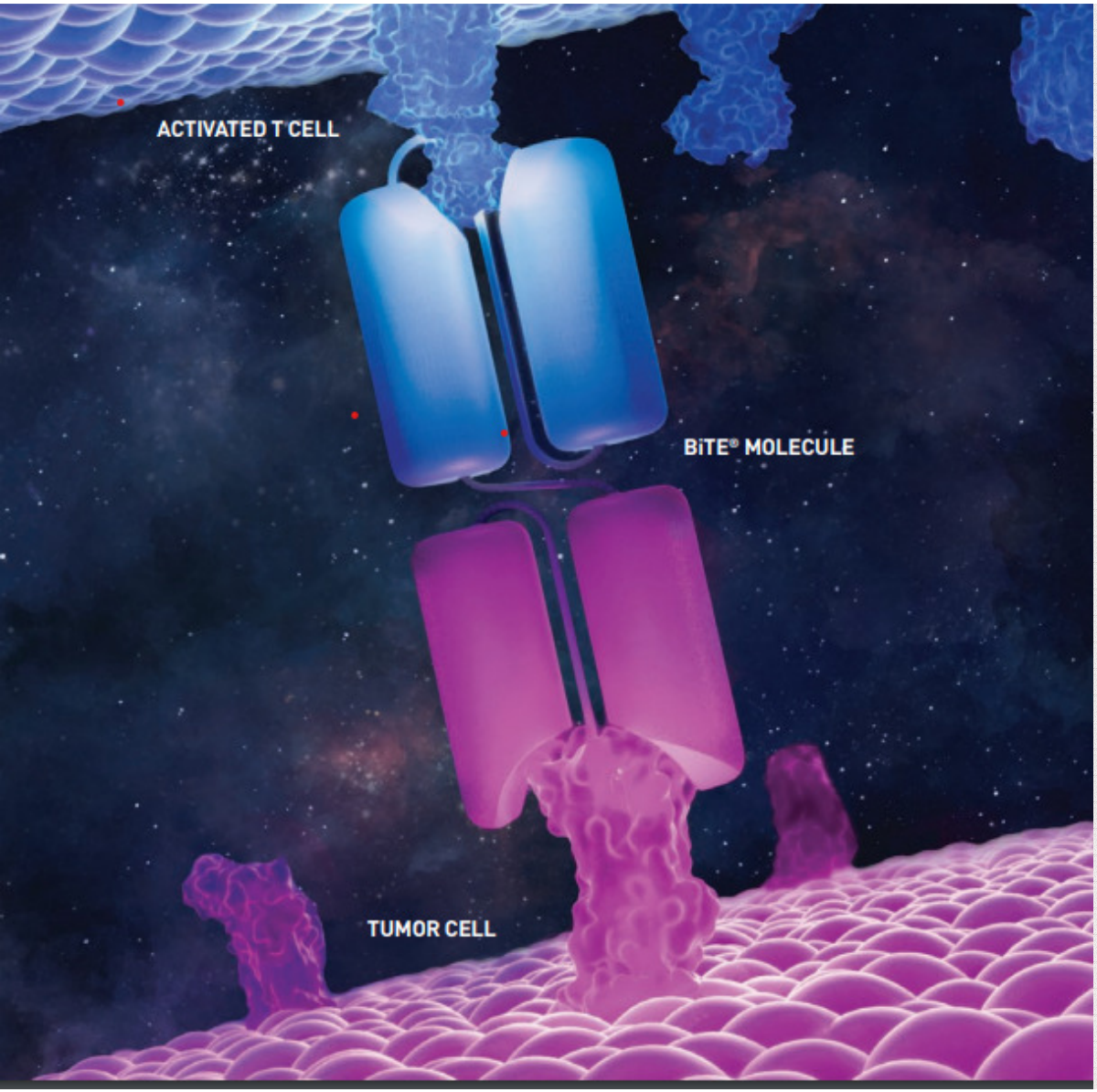
- Agnostic indication
- Pembrolizumab for MSI^{hi}
- Not approved for prostate unless mutation noted
- Not without potential for side effects
- Combinations with ARSI and chemotherapy

Targeting PSMA in prostate cancer…

- Over-expressed with resistant disease
- Expressed on neovasculature, biliary system and brain
- Immune and radiographic target
- Focus of immunotherapies such as BiTE and CAR T cells
- Can we target PSMA with a novel treatment platform using the patient's own cells?



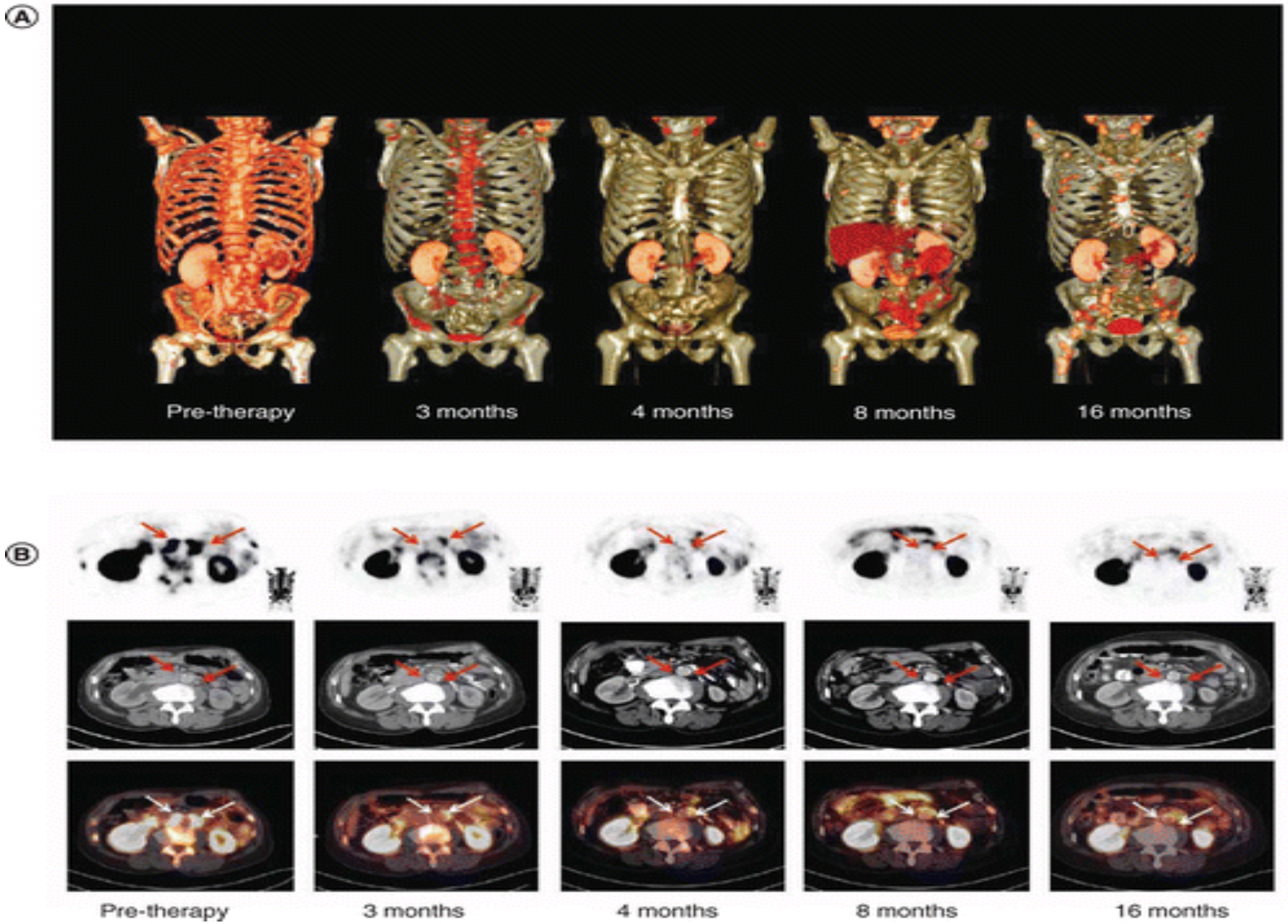
Pasotuxizumab; Hummel, et al, Immunother, 2020

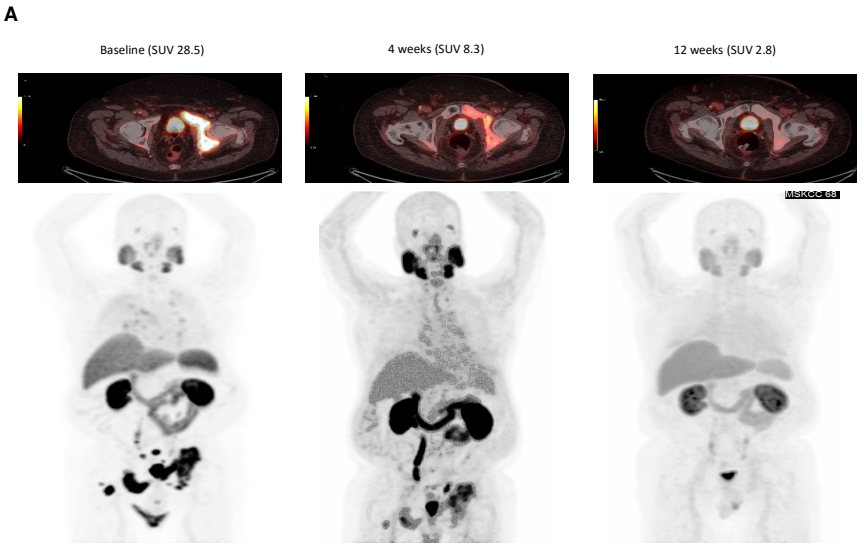


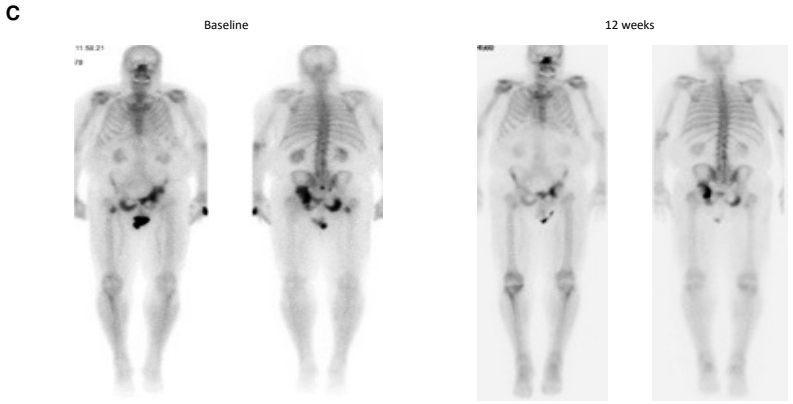
two flexibly linked, single-chain antibodies, with one that is specific for a selected tumor-associated antigen and the other that is specific for CD3 found on T cells

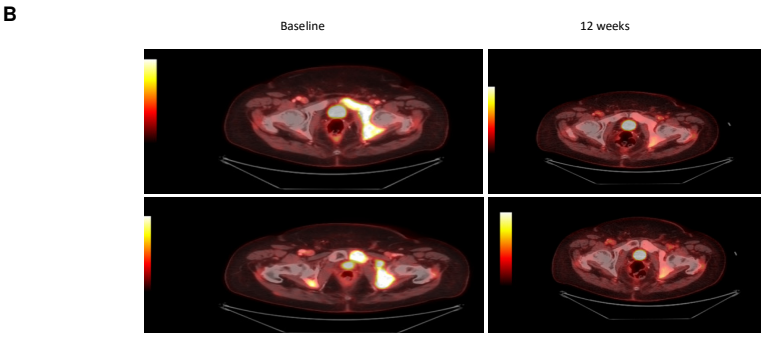
Bi-Specific T cell engager (BiTE)…

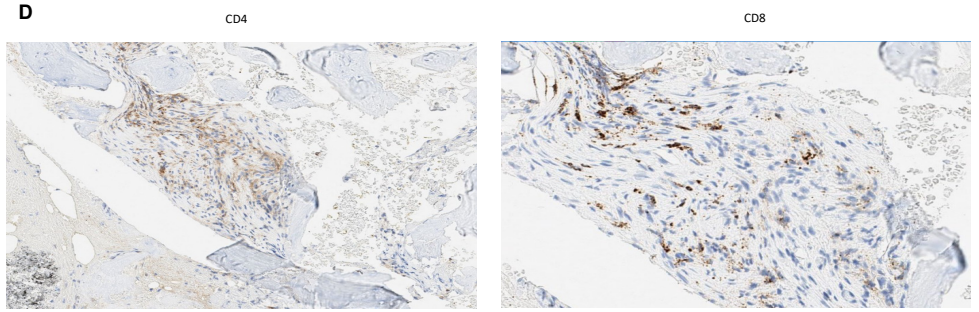
- Once T cells are activated by a BiTE® molecule, the T cells may induce further T-cell proliferation and cytokine production.
- Following cancer cell apoptosis, activated T cells release cytokines and produce additional perforin and granzymes that may allow T cells to target surrounding cancer cells, potentially resulting in the serial lysis of multiple cancer cells by a single T cell.
- Sustained activation of a single activated cytotoxic T cell theoretically results in local proliferation and expansion of polyclonal memory T cells.

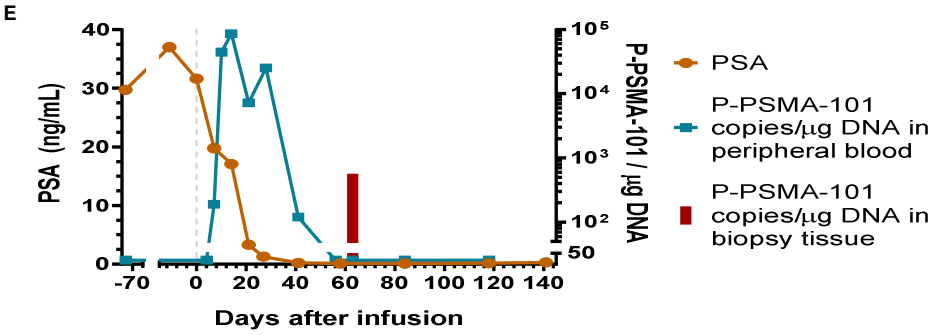

A
Pre-therapy
3 months
4 months
8 months
16 months
B
Pre-therapy
3 months
4 months
8 months
16 months


A
Baseline (SUV 28.5)
4 weeks (SUV 8.3)
12 weeks (SUV 2.8)

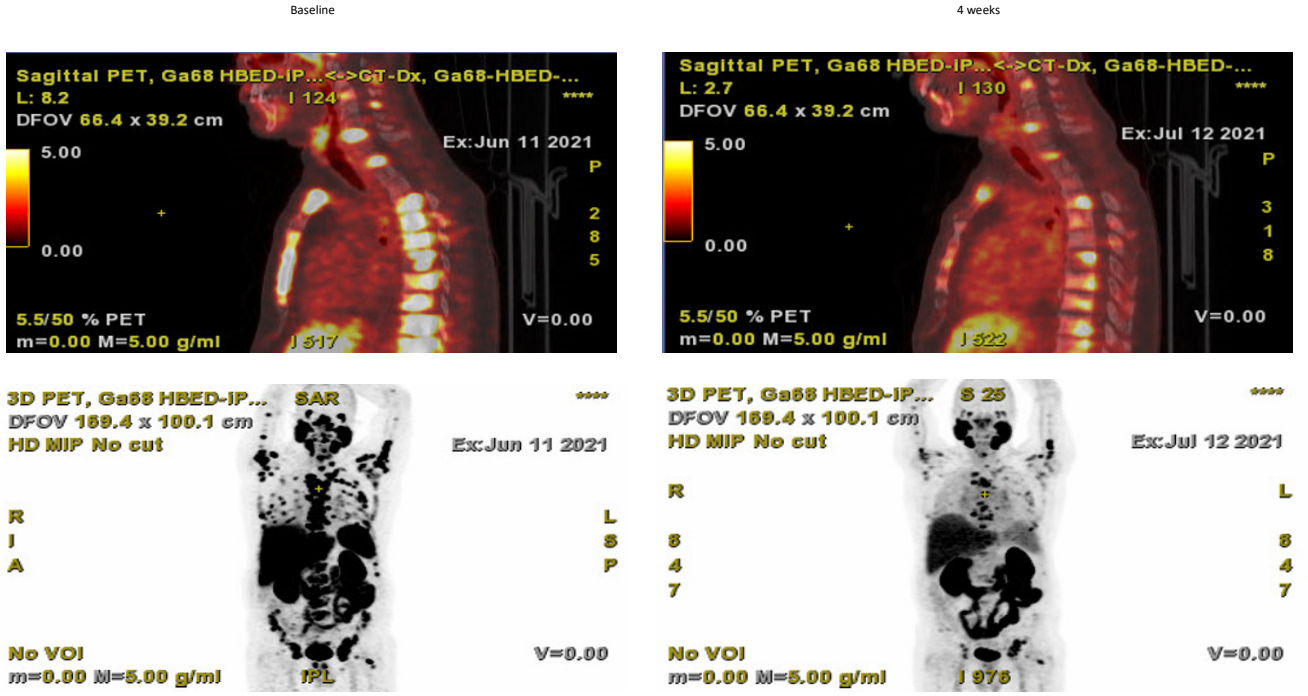

C
Baseline
12 weeks


B
Baseline
12 weeks

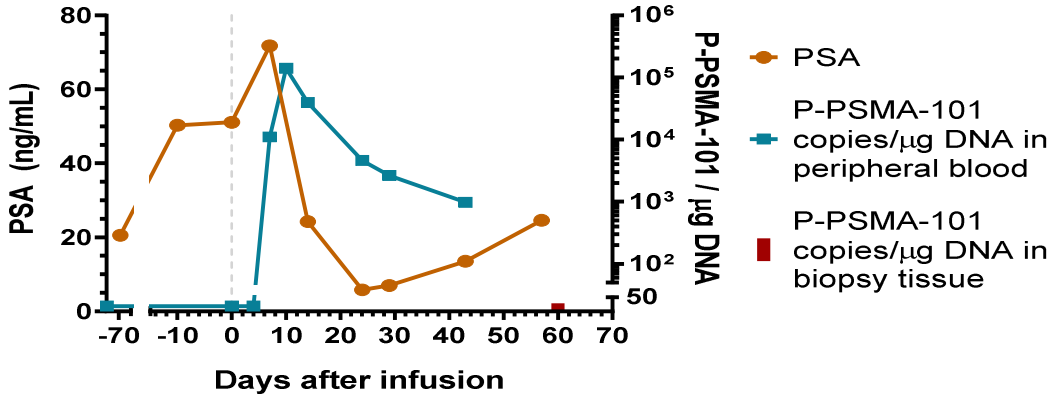

D
CD4
CD8

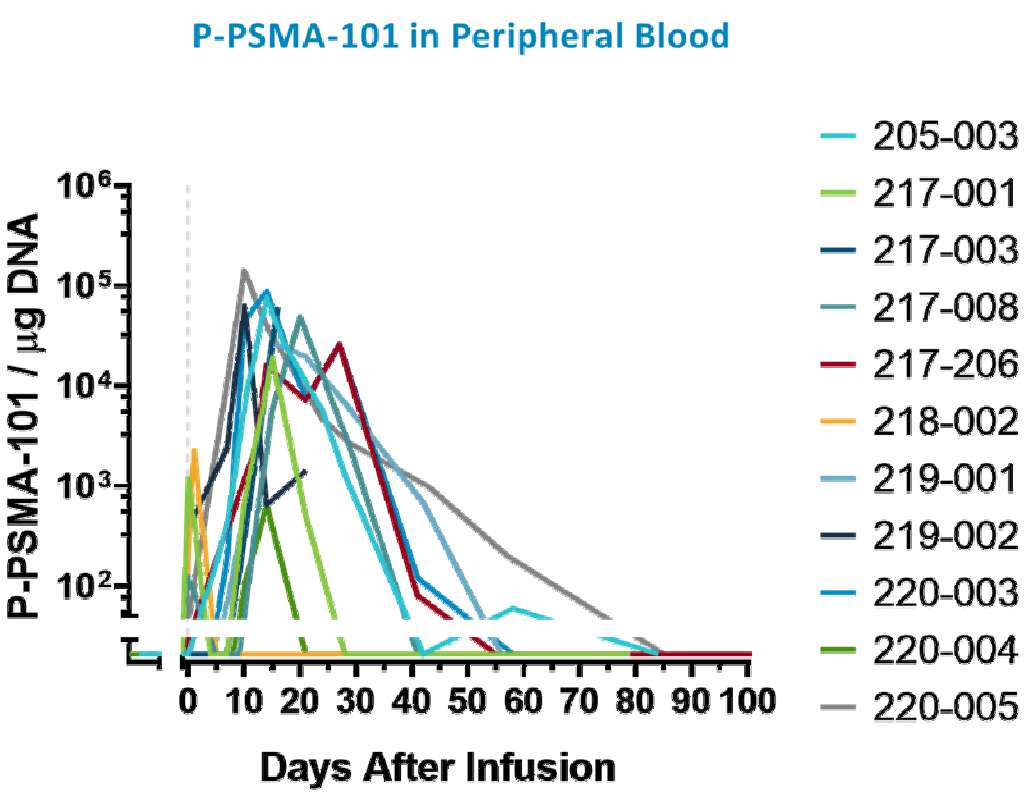

E
PSA (ng/mL)
P-PSMA-101 / µg DNA
Days after infusion
PSA
P-PSMA-101 copies/µg DNA in peripheral blood
P-PSMA-101 copies/µg DNA in biopsy tissue

A


Baseline
4 weeks
Sagittal PET, Ga68 HBED-iP...<->CT-Dx, Ga68-HBED-...
L: 8.2
I 124
DFOV 66.4 x 39.2 cm
Ex:Jun 11 2021
5.00
0.00
5.5/50 % PET
m=0.00 M=5.00 g/ml
I 517
V=0.00
Sagittal PET, Ga68 HBED-iP...<->CT-Dx, Ga68-HBED-...
L: 2.7
I 130
DFOV 66.4 x 39.2 cm
Ex:Jul 12 2021
5.00
0.00
5.5/50 % PET
m=0.00 M=5.00 g/ml
I 522
V=0.00
3D PET, Ga68 HBED-iP...
SAR
DFOV 169.4 x 100.1 cm
HD MIP No cut
Ex:Jun 11 2021
No VOI
m=0.00 M=5.00 g/ml
IPL
V=0.00
3D PET, Ga68 HBED-iP...
S 25
DFOV 169.4 x 100.1 cm
HD MIP No cut
Ex:Jul 12 2021
No VOI
m=0.00 M=5.00 g/ml
I 976
V=0.00

B


PSA (ng/mL)
P-PSMA-101 / µg DNA
Days after infusion
PSA
P-PSMA-101 copies/µg DNA in peripheral blood
P-PSMA-101 copies/µg DNA in biopsy tissue



- Most patients have **significant CAR-T cell** expansion in peripheral blood to levels generally associated with efficacy in CAR-T products
- Many CAR-T products show **peak expansion between 10-21 days**
- P-PSMA-101 shows **peak expansion between 10-28 days**

Conclusions…

- CAR T cells that have tropism for bone-predominant tumors have therapeutic potential
- Safe, well-tolerated
- Serum ferritin possible biomarker for CRI
- CRI moderate, responsive with tocilizumab, anakinra prn
- Eye grounds with chemosis, macular effusions; eye not an immunologically privileged site
- Combinations with other biologic agents under study.

Future development strategies to assess biologic activities…

- Need for companion diagnostics; how to best integrate functional imaging
- How to assess “response” in functional imaging
- Are there true immunologic response criteria?
- Combinations; is rationale always clear or is it mix and match?
- the optimal combination of costimulatory domains for CAR development may need a case by case evaluated evaluation.
- Can we safely retreat?