A hot, cold or lukewarm tumor: does immunotherapy work for prostate cancer, or does the environment matter?

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What is immunotherapy?

- Any approach that either uses the body’s own immune cell or antibodies to fight the cancer [Active immunization]
- Can be non-self, ie, use of serum from someone exposed to an infectious agent to treat the disease in another person –Example, Hepatitis [Passive immunization]
- Checkpoint inhibitors (they are antibodies!); Optivo, Yervoy, etc
- Vaccines
- Bispecific T cell engagers (BiTES)
- CAR T cells
- Antibody-Drug conjugates

Nino, et al, eLife 9:e56554; UNSW Sydney 2020 – Cytotoxic T cell swarm by homotypic chemokine signalling

So what’s a “hot tumor”? One answer only please…

1) A tumor that bursts into flames when removed from the body

2) A tumor that grows when you play ‘boogie woogie’ on the radio

3) A tumor that is resistant to therapy

4) A tumor that makes you feel “hot”

5) A tumor that is ‘inflamed’ due to immune cells

And a “cold tumor” is…

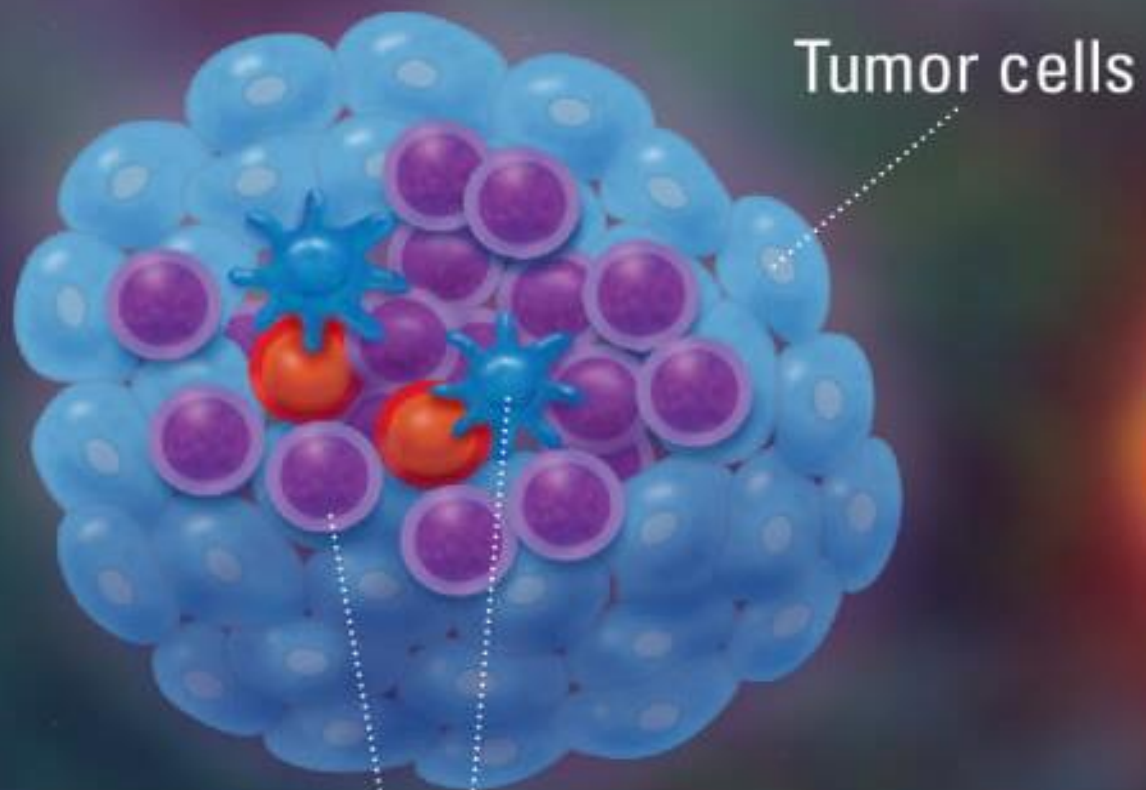
1) A tumor that feels like ice

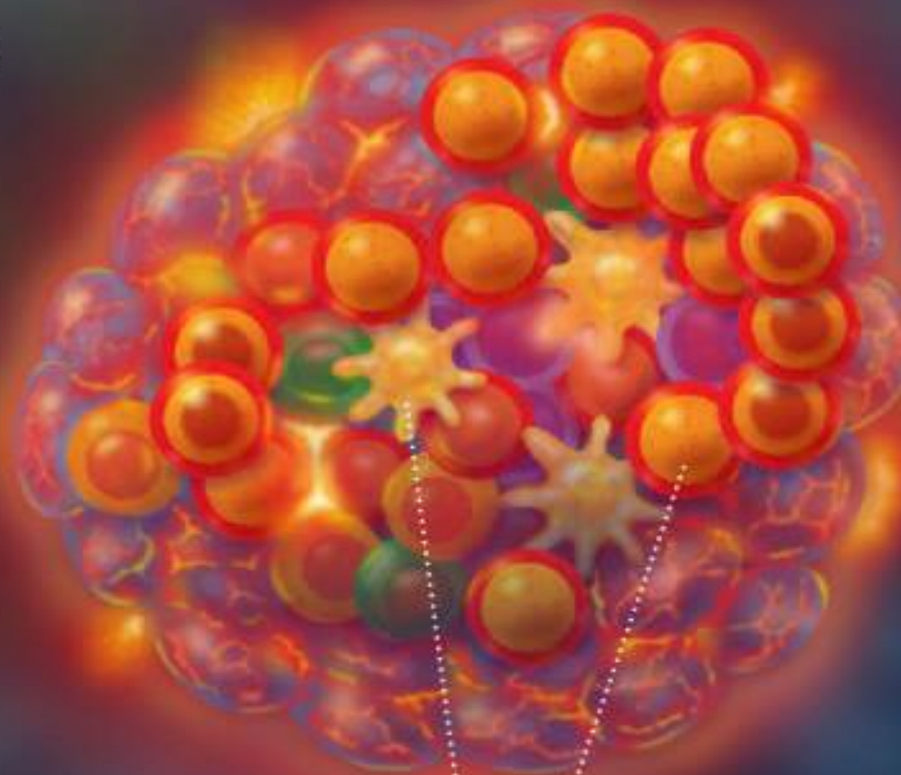
2) A tumor that should be packed in ice

3) A tumor than lacks immune (T cells) cells

4) A tumor cell that is responsive to immune checkpoint agents

5) A tumor that gives you the chills

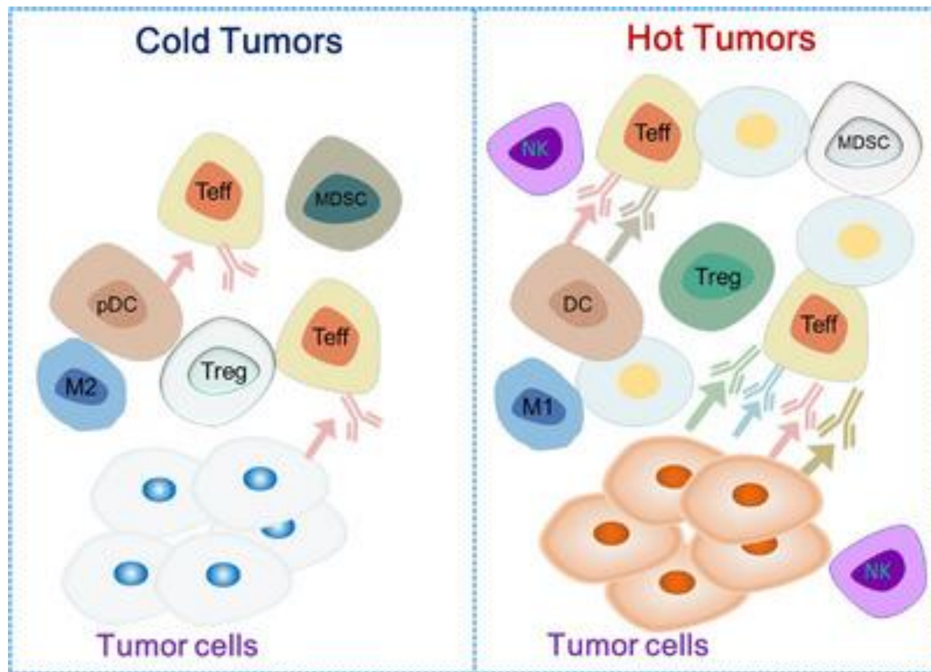


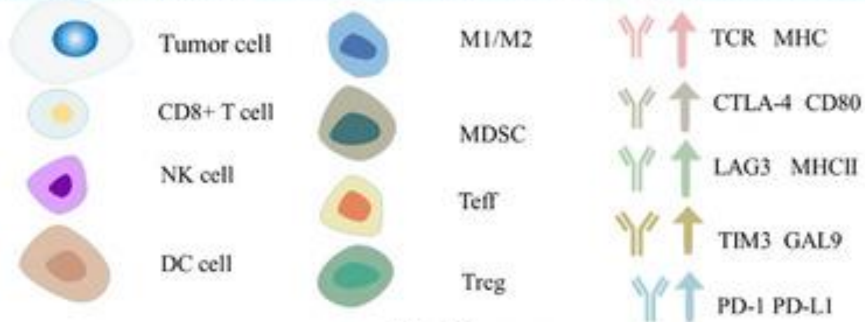


Glimcher, et al, DFCI, 2018

What’s within the prostate gland

- prostate gland - immune-competent organ containing both stromal and infiltrating T and B cells mainly within the fibromuscular stroma and periglandular tissue
- Produces a fluid that mixes with sperm to make semen
- Within the TME - multiple cell types including bone marrow-derived mesenchymal stem cells, cancer-associated fibroblasts, and multiple inflammatory cells.
- Intratumoral niche - contains proinflammatory cytokines, both adaptive and innate immune cells, and fibroblasts all of which contribute to an inflamed TME shown to promote and enhance CaP progression



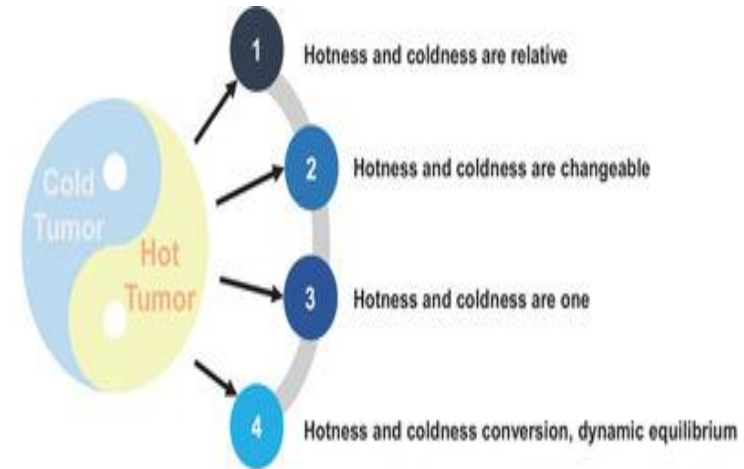


Cold Tumors

Low inflammatory signature
Absent intratumoral CD8+ T cells
low Immunoscore

Hot Tumors

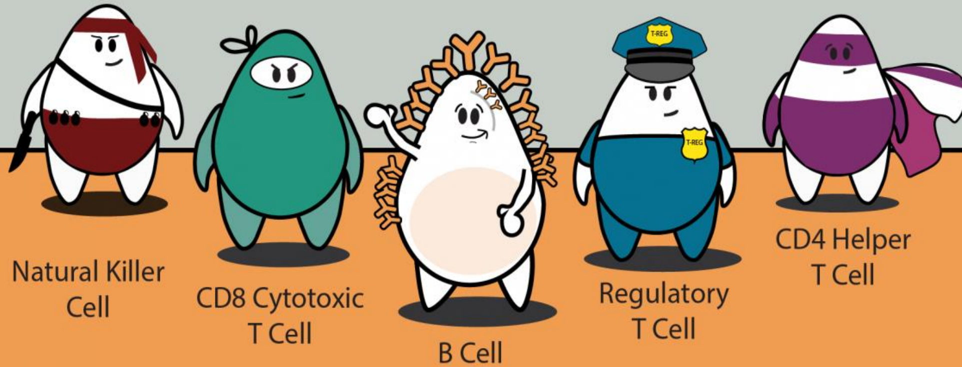
High inflammatory signature
High degree of T cell and cytotoxic T cell infiltration
Checkpoint activation (PD-1, CTLA4, TIM3, LAG3)
high Immunoscore



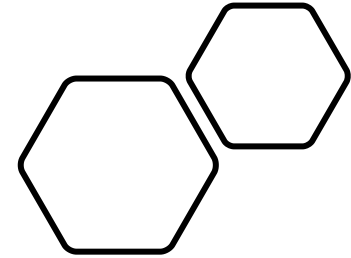
"hot and cold tumor" is consistent with the "Yin and Yang"; essentially these relationships are all "relative"

Wang, et al. MedComm, 2020

Lymphocytes



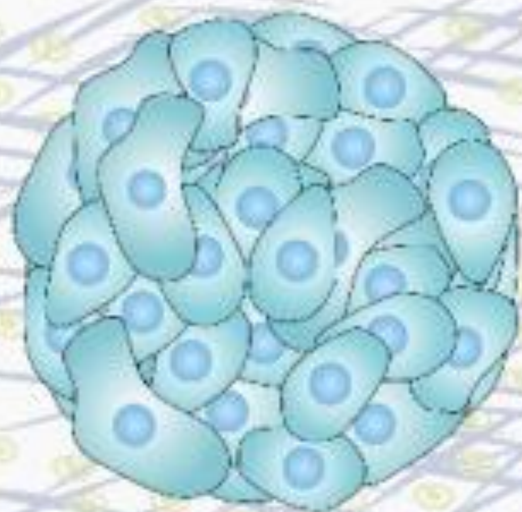
CellCartoons.net



Cold

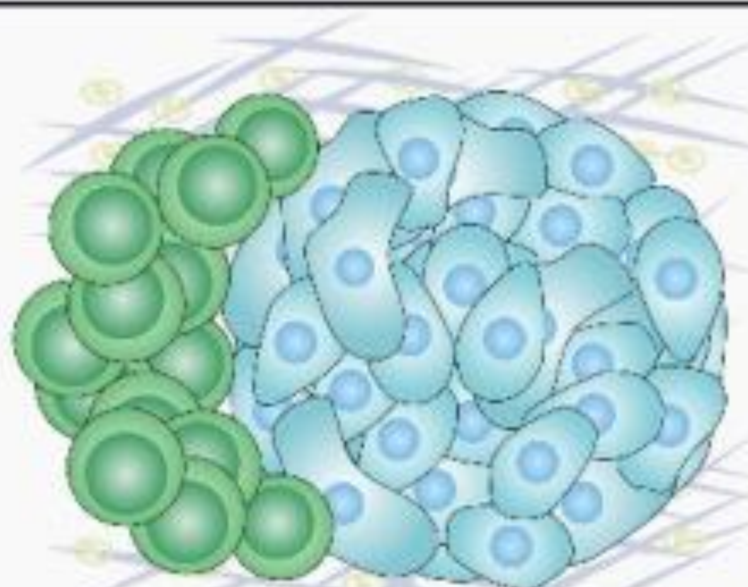
Hot

Desert



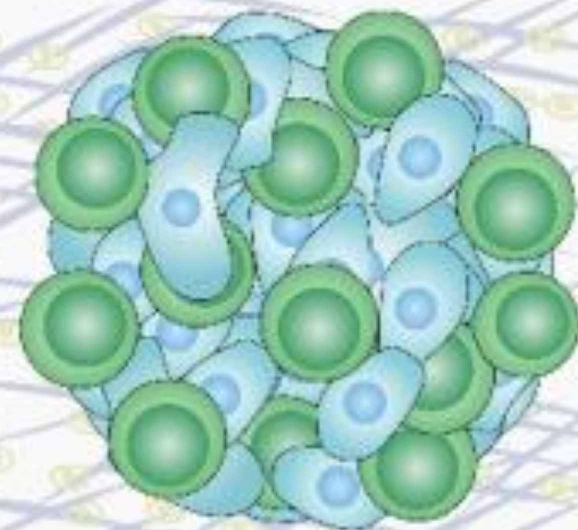
CD8+ T cells are absent from the tumor and its periphery

Excluded



CD8+ T cells accumulated but do not efficiently infiltrate

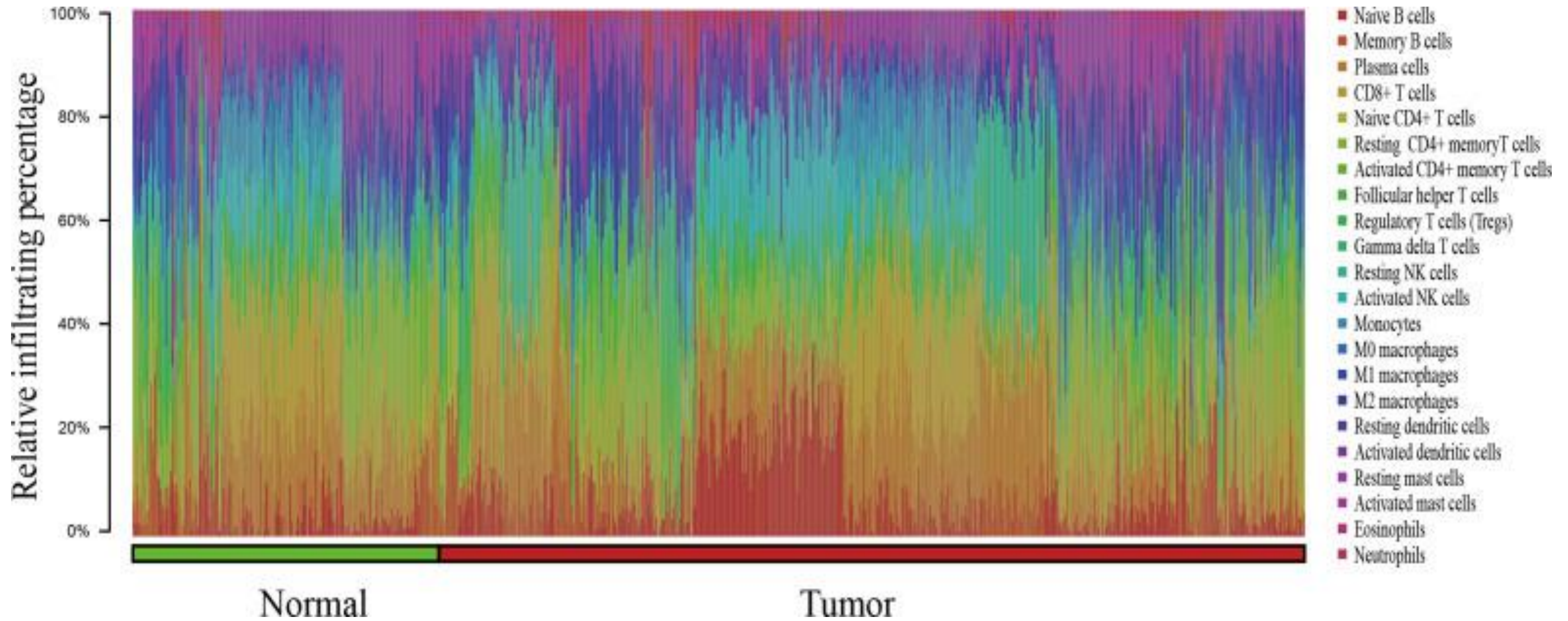
Inflamed



CD8+ T cells infiltrate but their effects are inhibited

Response to immune checkpoint inhibitors

Liu and Sun, Theranostics, 2021

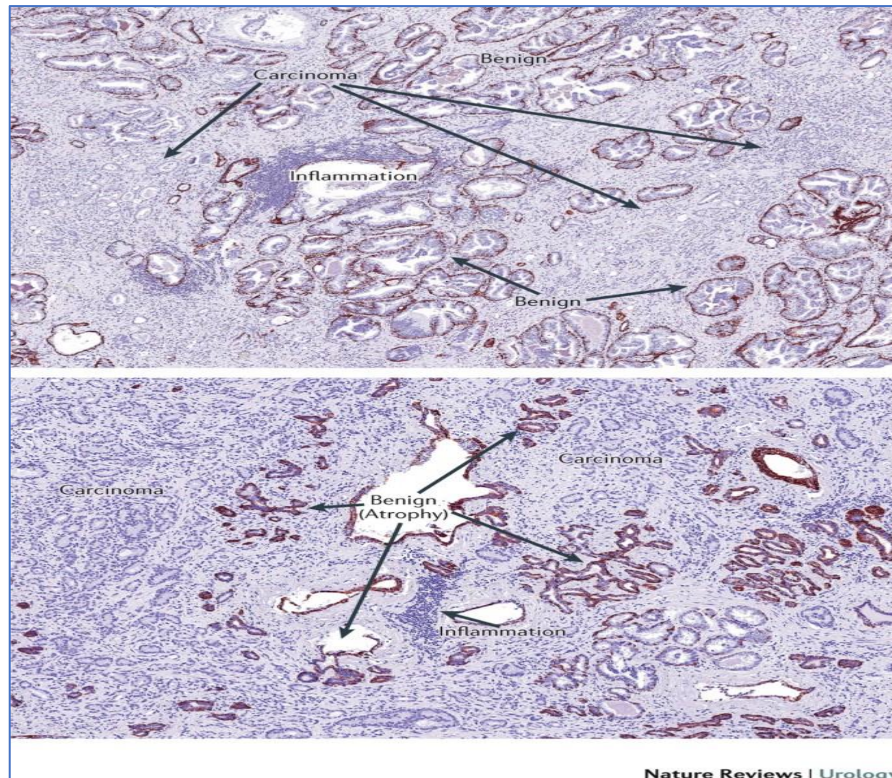


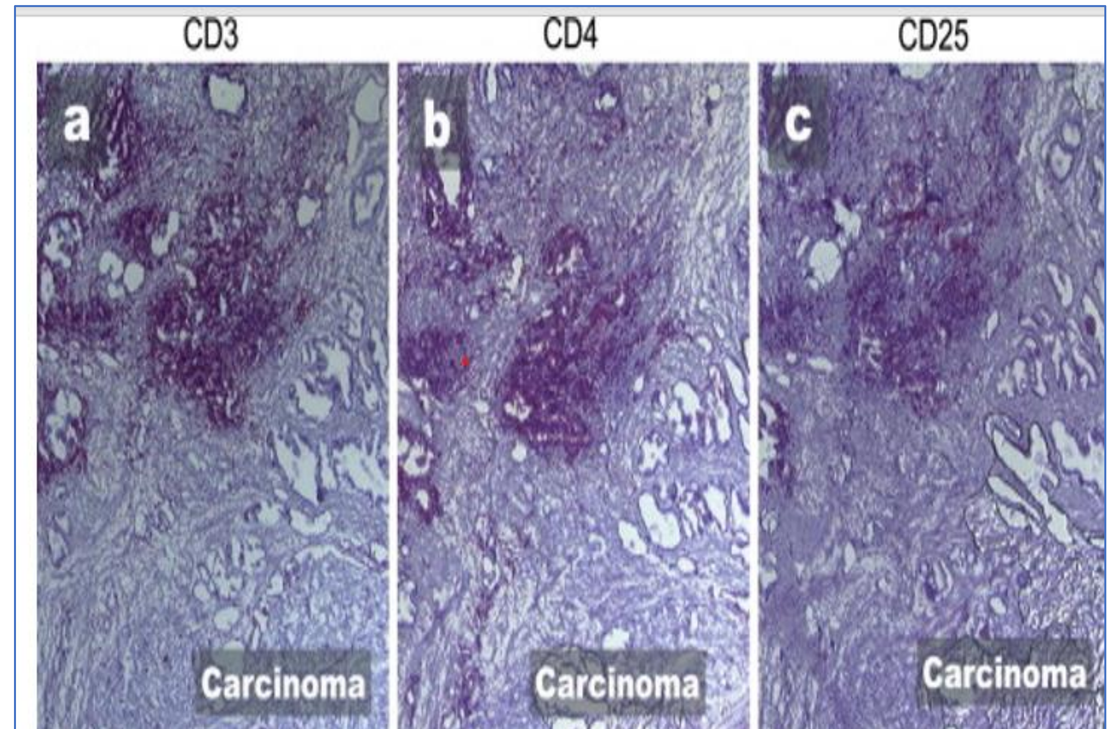
bar chart summarizes the percentage of 22 infiltrated immune cells from normal (n=190) and PCa (n=537) tissues. Each color represents a kind of immune cell, and the length of the bar represents the relative percentage of infiltrating immune cells. The proportion of each infiltrated immune cell is expressed as a percentage of the total 22 immune cells, and the sum infiltrating percentage of 22 immune cells is 100%. (Wu, et al, Front Oncol, 2020)

Does inflammation make the TME more sensitive to treatment? What are we facing in the TME?

Prostate tissue with admixed benign, inflamed, and malignant areas. [Benign prostatic glands are characterized by positive CK903 stain, indicating the presence of basal cells. Prostate carcinoma, which lacks basal cells, is identified by a lack of CK903 staining. Areas of inflammation are characterized by dense clusters of inflammatory cells in the stroma].

Lymphocyte clusters surround prostate cancer lesions. Serial sections stained with anti-human CD3, anti-human CD4. Tumor infiltrating lymphocytes are adjacent to the prostate cancer lesions. Patient with Gleason 6, pT2a. Dense stromal compartment separates the carcinoma area and the lymphocyte clusters.





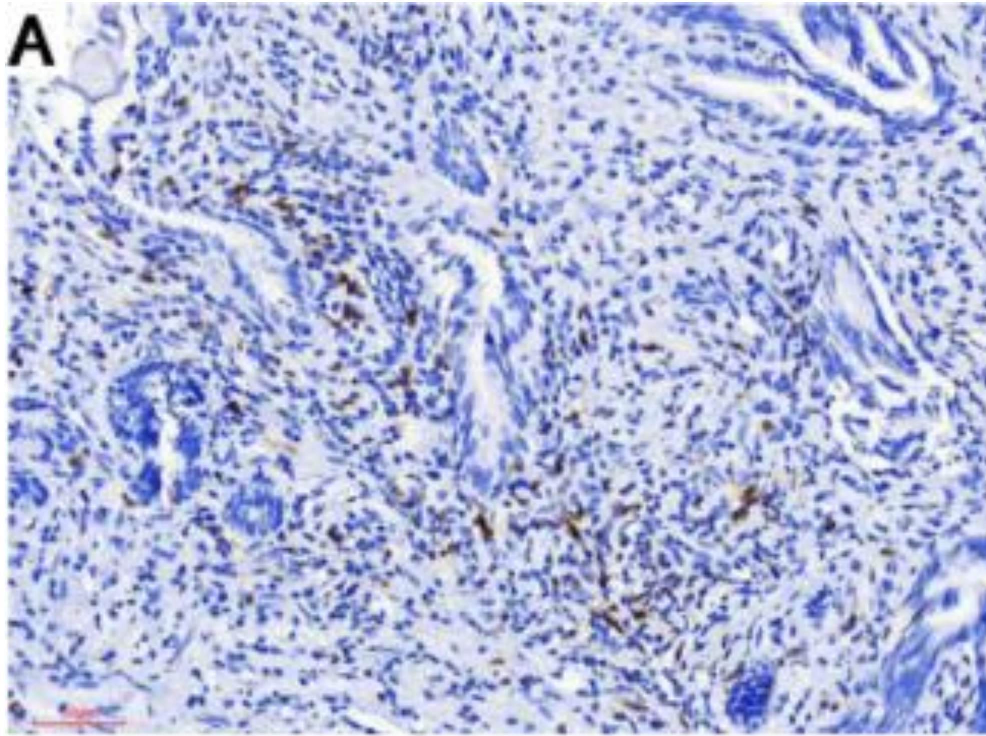
Sfanos, et al, Nature Rev Urol, 2018 Ebelt, et al, Eur J Ca, 2009

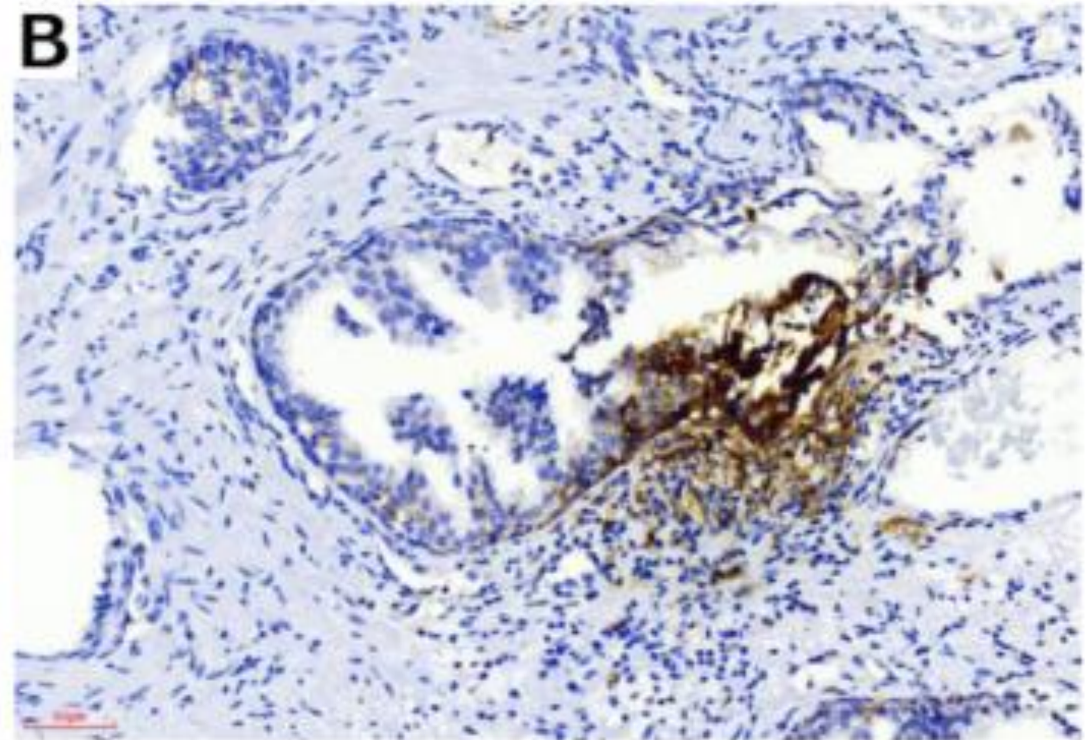
Cells influence cells

- **MDSCs** induce suppression thru nitrous oxide synthase, arginase-1, and indoleamine 2,3 oxygenase – leads to depletion of arginine and tryptophan from the TEM
- Leads to T cell cycle arrest, downregulation of cell surface markers that participate in T cell recognition of tumor cells
- TAMs – seen more frequently in metastases c/w primary tumors

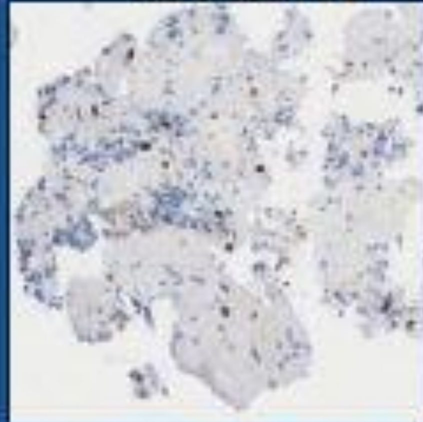
1. **TAM-M2** – Can be associated with lack of effective T cell function
2. TAM-M1 – associated with increased tumor infiltration of specific T cells

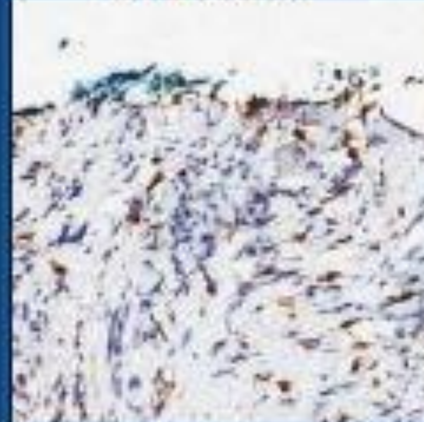
- **CTLA-4** – checkpoint
- **PD-1/-L1**

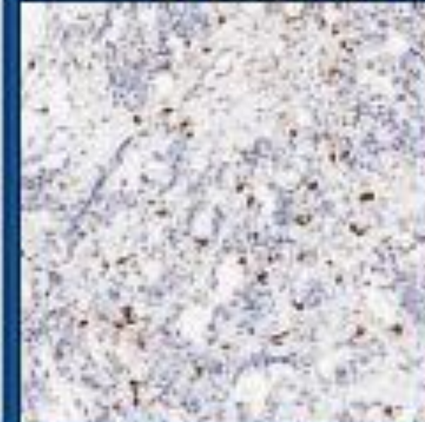


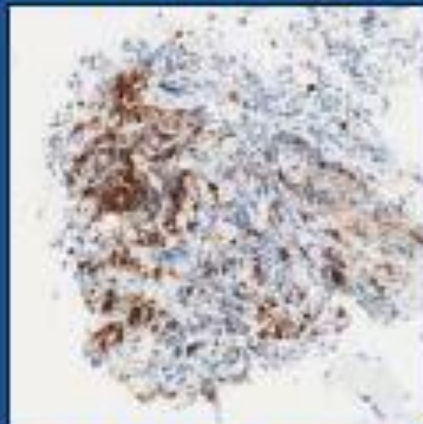


Representative immunohistochemical (IHC) staining of PD1 and PDL1 in BPH. A Representative image showing PD-1 expression in lymphocytes. B Representative image showing PD-L1 expression in epithelial cells and lymphocytes. Original magnification, × 200. PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; BPH, benign prostatic hyperplasia (He, eta l, World J Surgical Oncol, 2021)







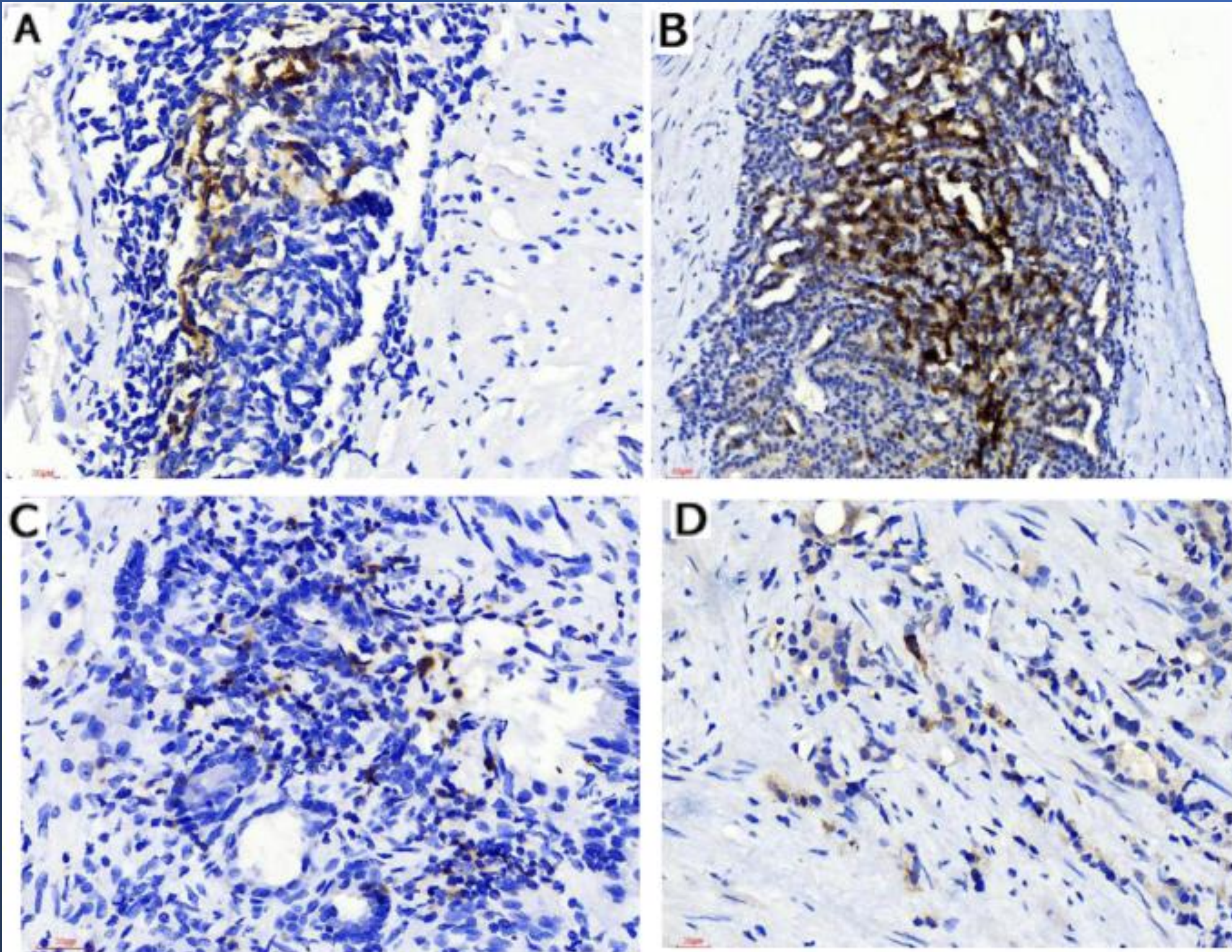


TIL infiltration with clinical response in patients with NSCLC lung cancer who received immunologic treatment

Heat Biologics, biopharmadealmakers.nature.com, 2019

The Programmed Death Family…

- PD-1, along with its complementary ligands PD-L1 and PD-L2act as inhibitory co-receptor-ligand pairs
- maintain balance between immune activation and immunosuppression
- PD-1 is preferentially expressed on regulatory T cells, as well as natural killer cells and activated B cells
- PD-L1 expressed on B cells, T cells, dendritic cells, macrophages, and mast cells



A, **C** Representative images showing PD-1 expression in tumour epithelial cells and lymphocytes, respectively.
B, **D** Representative images showing PD-L1 expression in tumour epithelial cells and lymphocytes, respectively. Original magnification, × 400. PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1

He, et al. World J Surg Oncol 2021

So how do you make something hot that is cold?

- Stick it into boiling water
- Set it aflame
- Steam it
- Pickle it
- Try to understand if there are inhibitory factors such as cytokines or cells or chemical pathways that interfere with normal infiltration of the tumor by immune cells

But is that enough? NO!

How to fix the problem?

Suppress

- In a manner of speaking…. ***Turn on, Tune in, Drop out!***
- What is going on within the TME
- Targeting regulatory T cells, TAM, MDSCs
- Control cytokines secreted by tumor stromal cells/fibroblasts
- Inhibit the inhibitors such as adenosine: adenosine and TGF-G serve as immunosuppressive molecules

But what if TME gets too hot? Is there a middle range?

- Immunosuppression influences efficacy of immunotherapy

Breast cancer:
- Atezolizumab
- Pembrolizumab

NSCLC:
- Atezolizumab
- Durvalumab
- Nivolumab
- Pembrolizumab
- Tremelimab in combination with durvalumab
- Ipilimumab
- Cemiplimab

Small cell lung cancer:
- Atezolizumab
- Nivolumab
- Durvalumab

Mesothelioma:
- Ipilimumab
- Nivolumab

Head and neck squamous cancer:
- Nivolumab
- Pembrolizumab

Classical Hodgkin lymphoma:
- Pembrolizumab
- Nivolumab

Gastric and GEJ carcinoma:
- Pembrolizumab
- Nivolumab

Liver cancer:
- Nivolumab
- Pembrolizumab
- Tremelimab in combination with durvalumab
- Atezolizumab
- Ipilimumab

Renal cell carcinoma:
- Avelumab
- Ipilimumab
- Nivolumab
- Pembrolizumab

MSI-H/dMMR cancers:
- Nivolumab in combination with ipilimumab
- Pembrolizumab

Melanoma:
- Nivolumab
- Pembrolizumab
- Relatlimab in combination with nivolumab (Opdualag™)
- Atezolizumab
- Ipilimumab

Basal cell carcinoma:
- Cemiplimab

Squamous cell carcinoma:
- Cemiplimab
- Ipilimumab
- Nivolumab

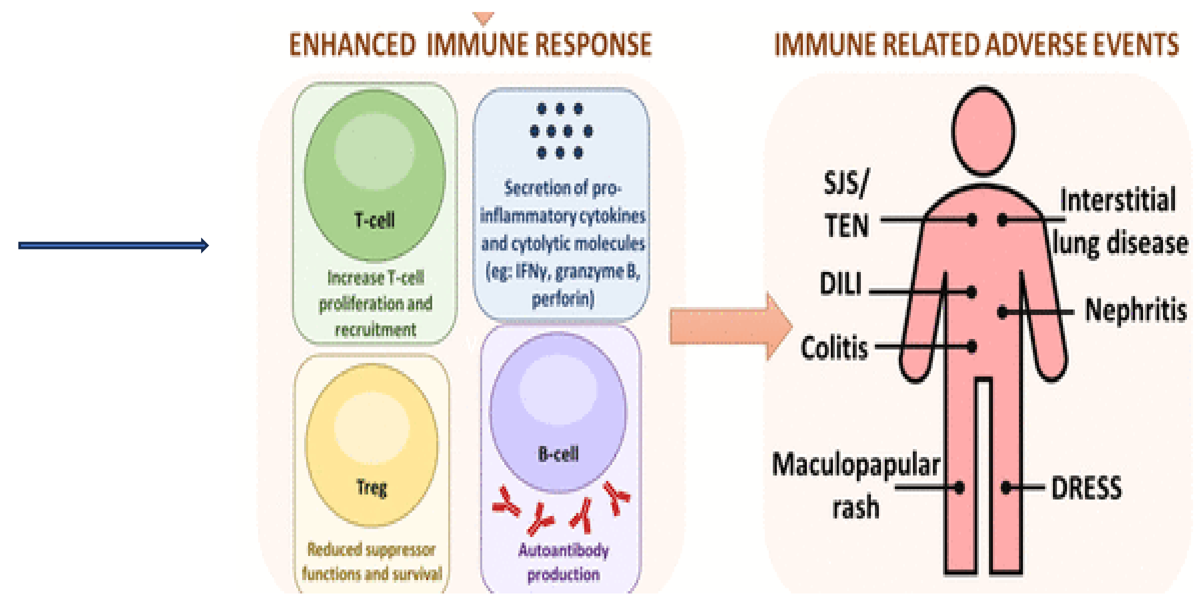
Merkel cell carcinoma:
- Avelumab
- Pembrolizumab
- Retifanlimab

PBMCL:
Pembrolizumab

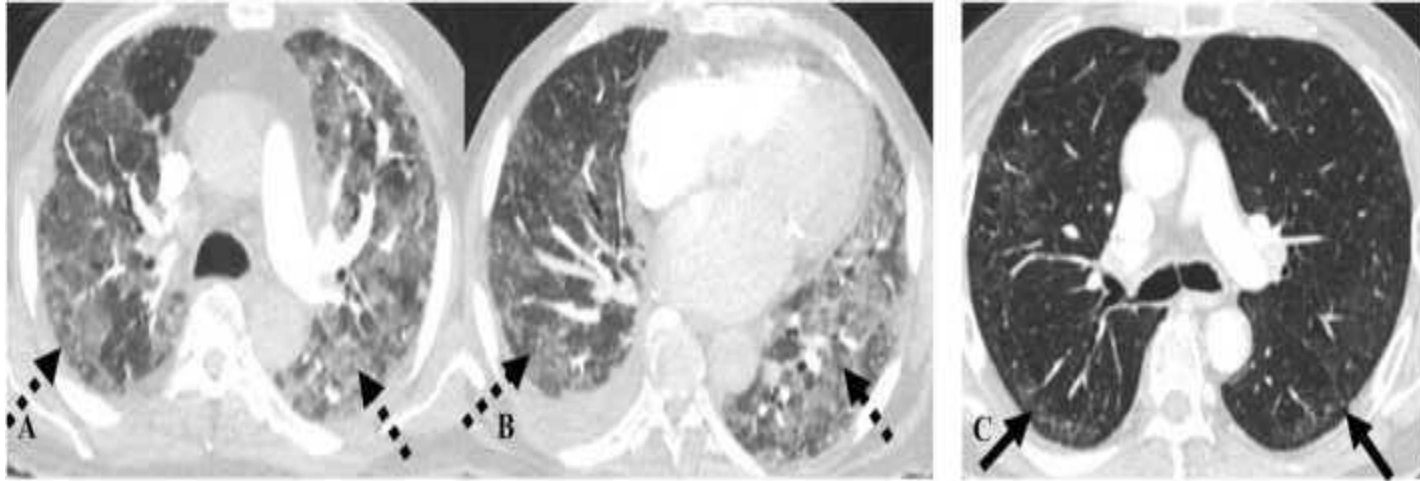
Cervical cancer:
- Pembrolizumab

Endometrial cancer:
- Dostarlimab

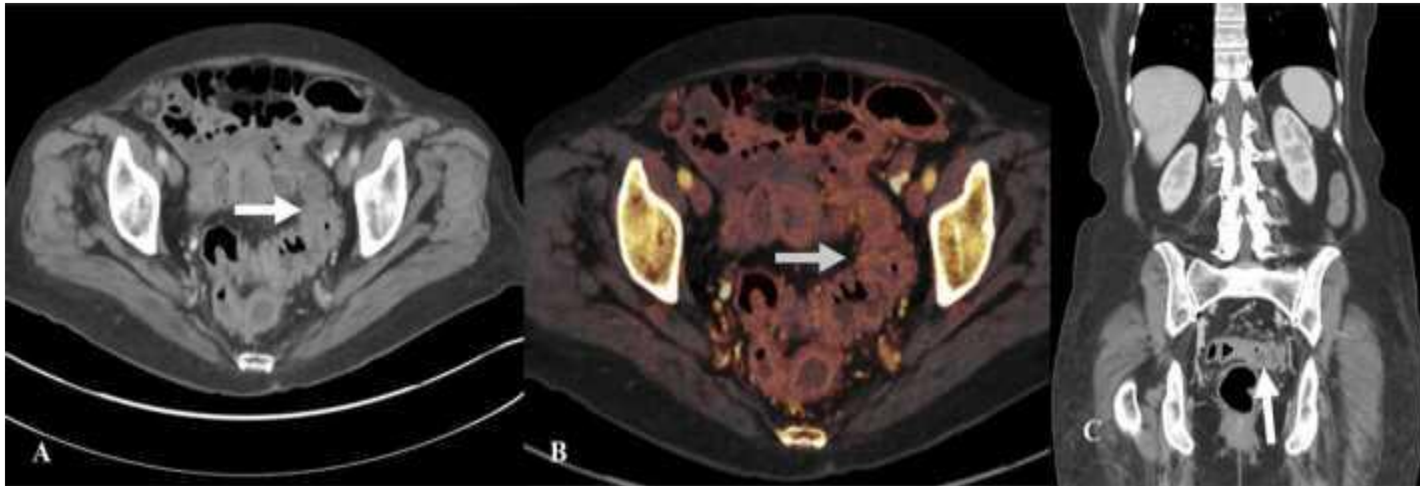
Urogenital cancer:
- Atezolizumab
- Avelumab
- Durvalumab
- Nivolumab
- Pembrolizumab



Grice, et al, Clin Res in Toxicology, 2024

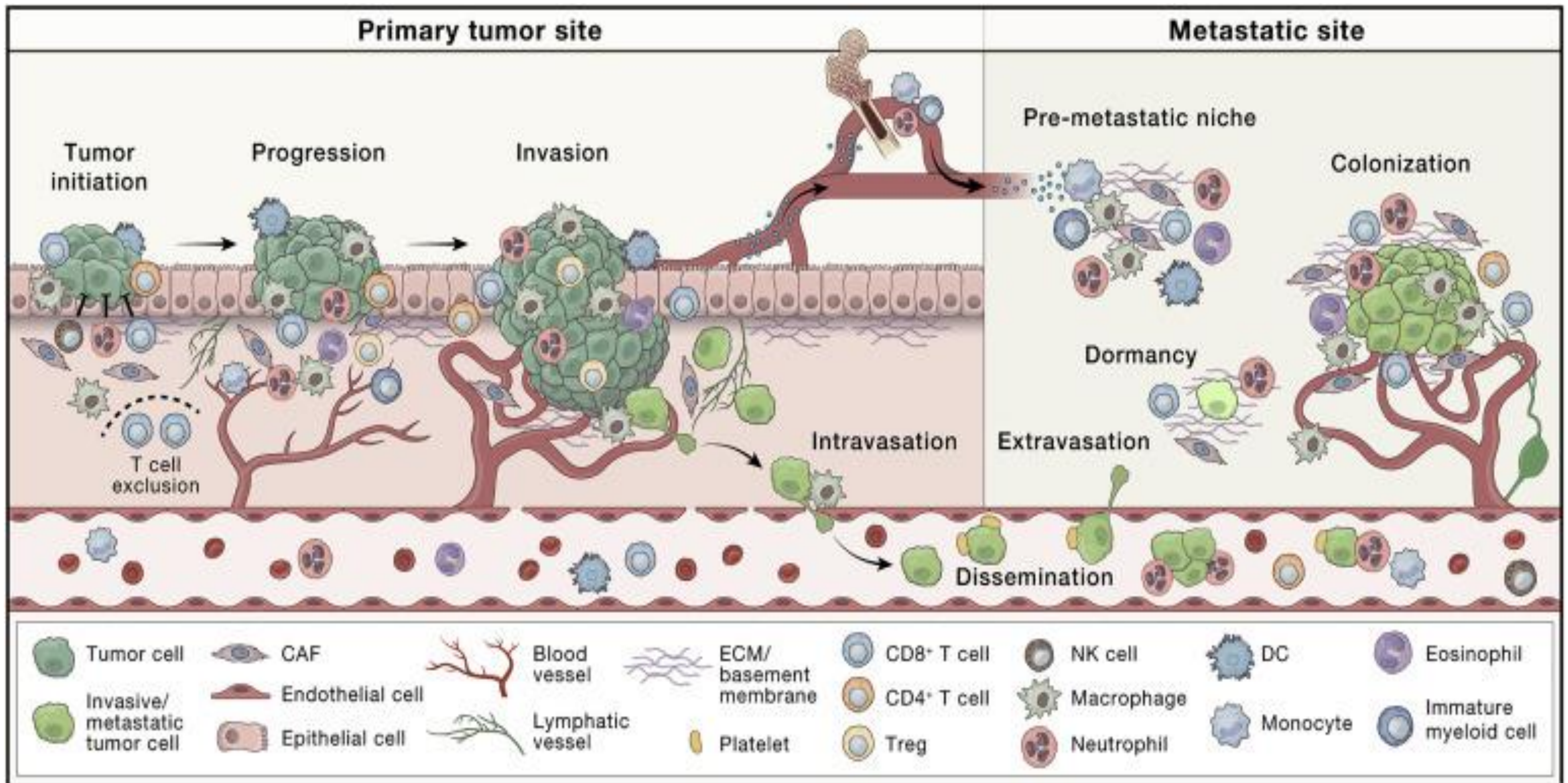


Immune-mediated pneumonitis



Immune-mediated colitis

Gosangi, et al, Eur J Radiol Open, 2022



de Visser, and Joyce, Cancer Cell 2023

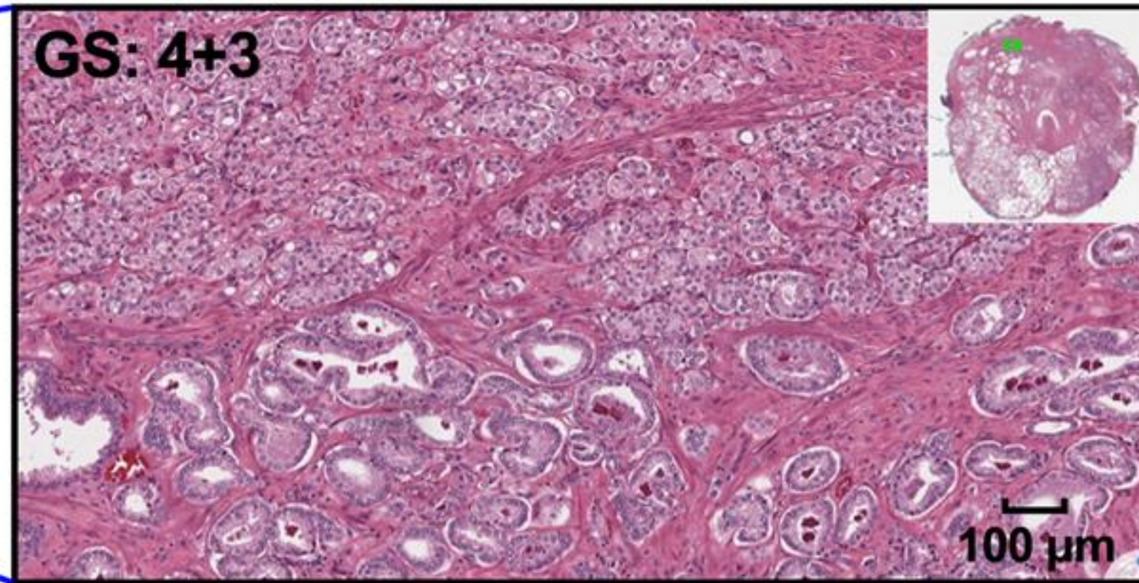
Anterior

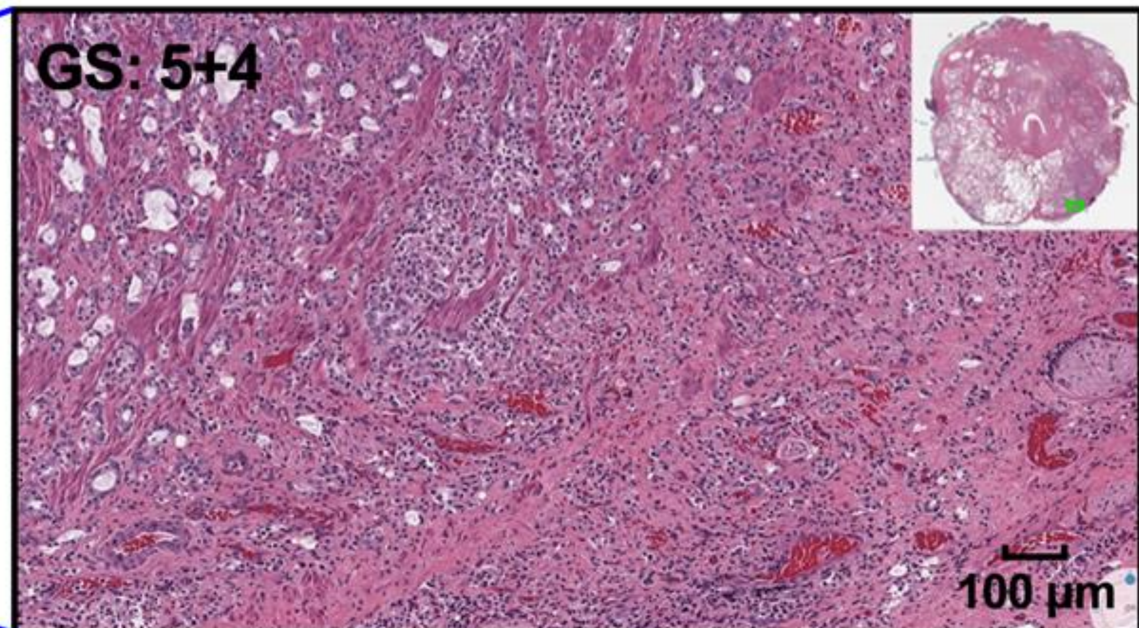
Right

Left

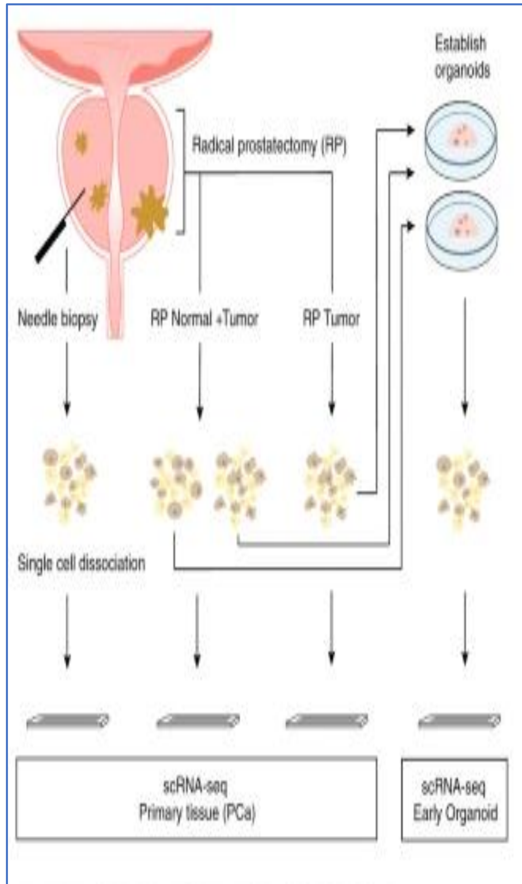
Posterior

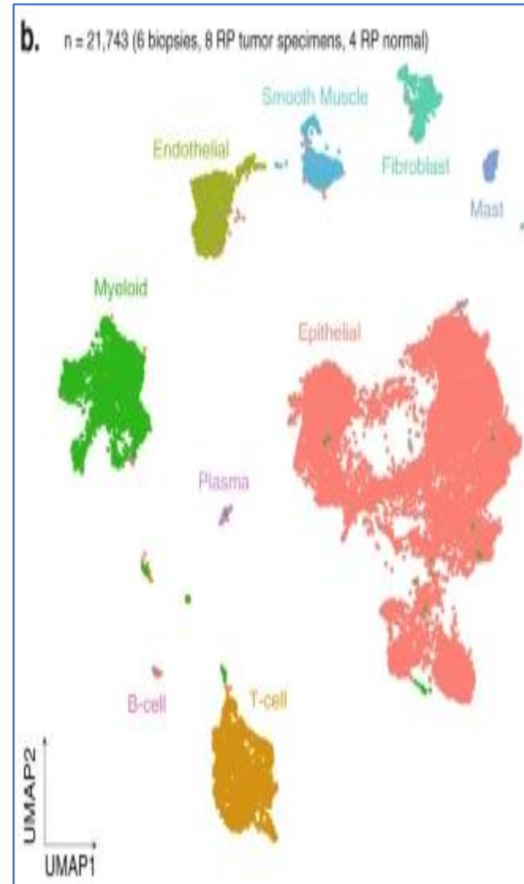
4 mm

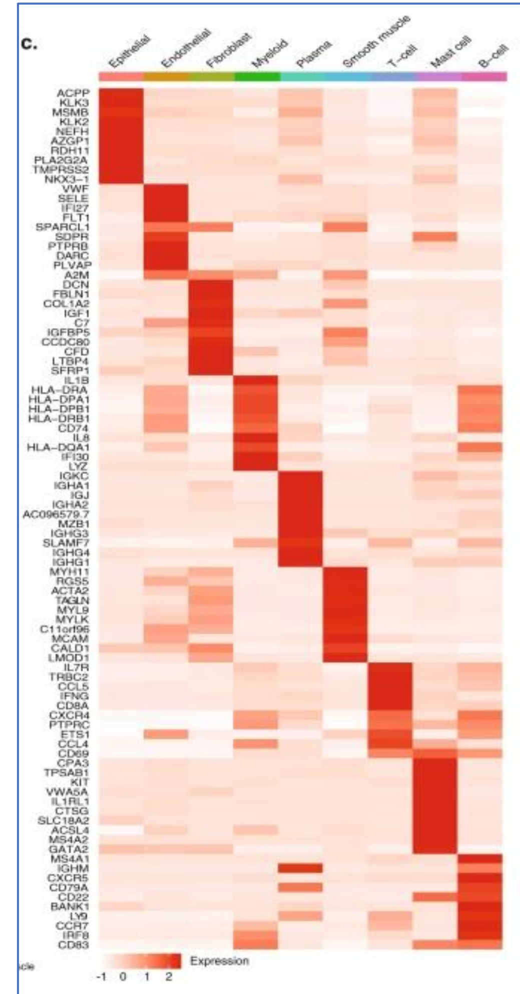


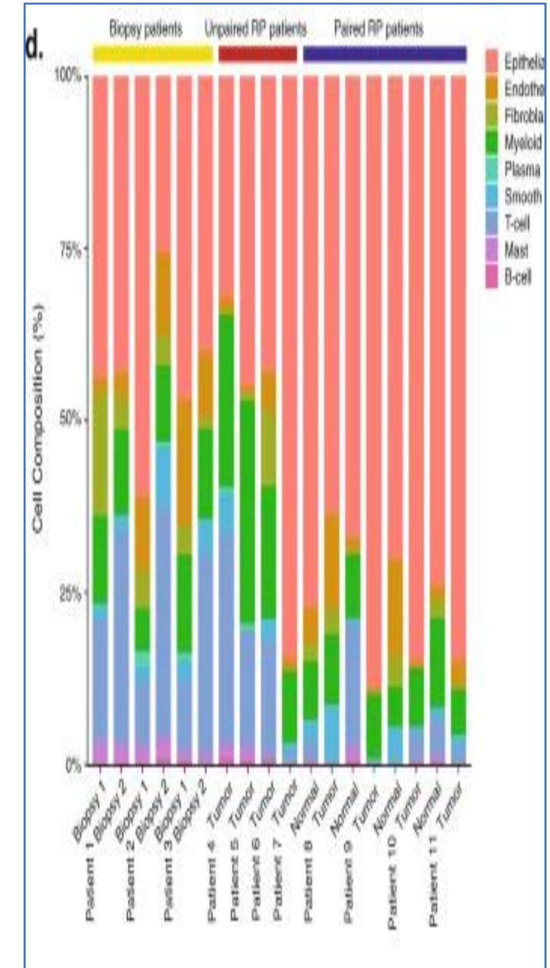


Ge et al. Npj Prec Oncol









Song, et al, Nature Comm

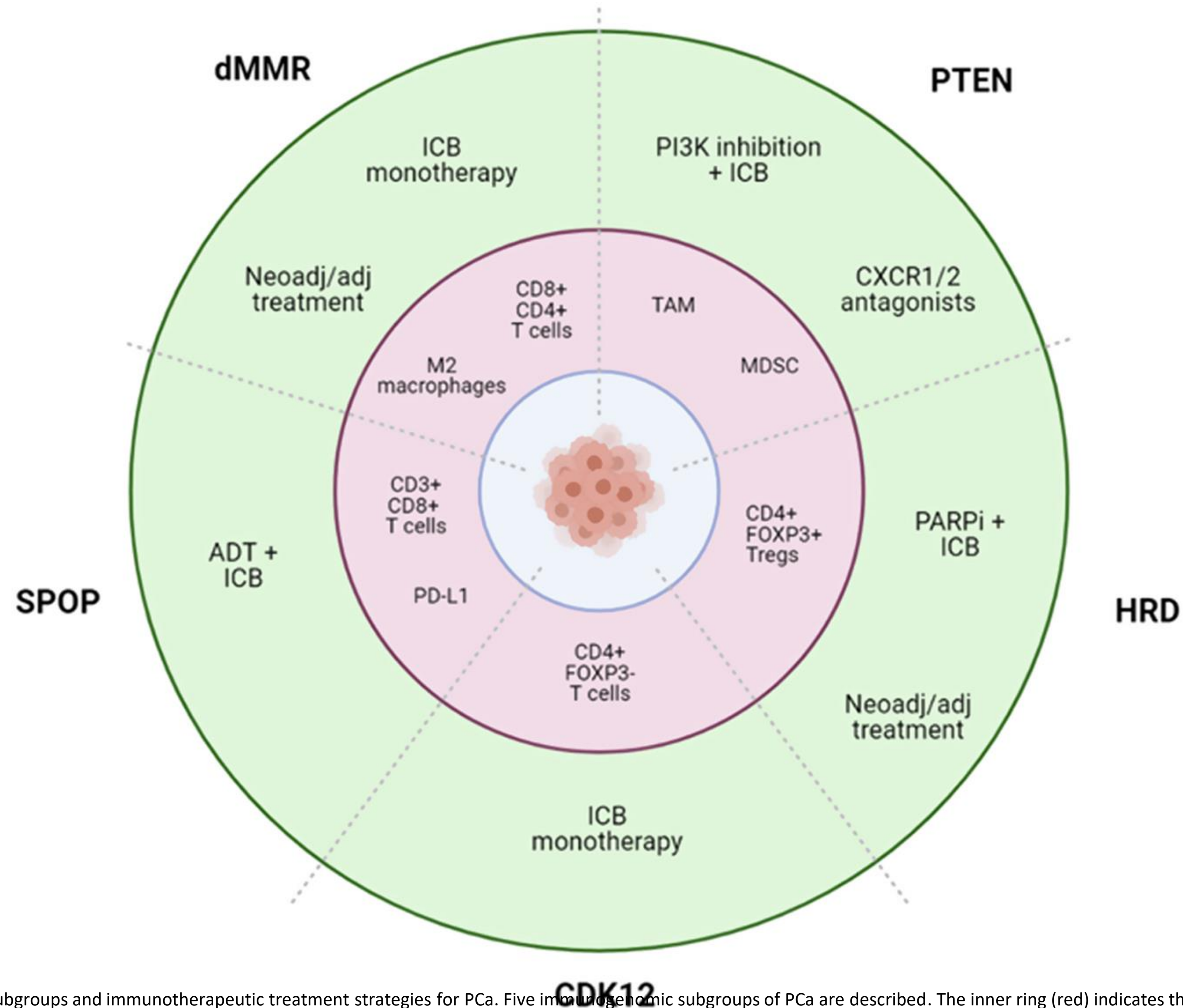
Potential TumorTargets for Immunotherapy via Vaccines, CAR T cells, BiTES, ADC

- **Older studied cell surface antigens:**
- PSMA
- PSCA
- PSA
- PAP
- Globo H
- MUC 1,2
- GM2
- CEA
- NY ESO1
- EPCAM

- **Ongoing studies:**
- B7-H3 – MoAb Enoblituzumab
- B7-H3 - ADC
- STEAP 1 (ADC), STEAP 2 (CAR T)
- DLL3 (neuroendocrine, ADC)
- TROP2 (Sacituzumab Govindan)
- PSCA (CAR T)
- PSMA
- CD40

- *Need for companion imaging and biopsy to confirm responses to therapy

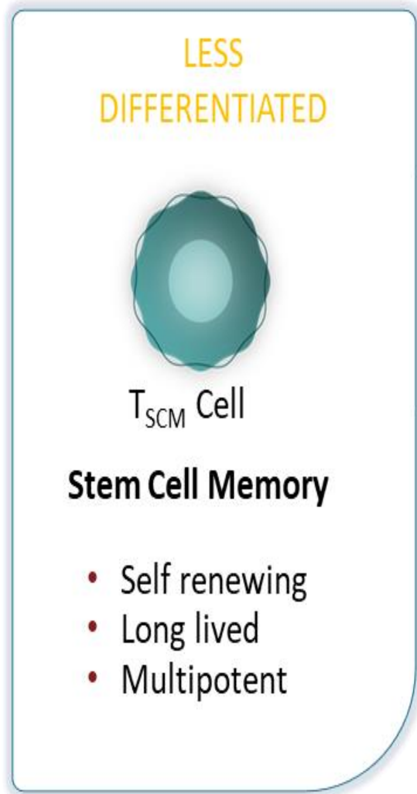
Figure 2



Immunogenomic subgroups and immunotherapeutic treatment strategies for PCa. Five immunogenomic subgroups of PCa are described. The inner ring (red) indicates the immune infiltrate characterised in each subgroup to date. Distinct immune populations are present in different genomic subtypes of PCa, indicating individual immune microenvironments to consider when designing immunotherapeutic treatment approaches. The outer ring (green) indicates potential treatment strategies for each subgroup. dMMR, microsatellite unstable/mismatch repair-deficient; PTEN, PTEN-deficient; HRD, homologous recombination-deficient; CDK12, CDK12-mutated; SPOP, SPOP-mutated; ADT, androgen deprivation therapy; ICB, immune checkpoint blockade.

Kwon, et al, Endo-Rel Cancer, 2021

So how do we go forward with immune strategies is a single therapy doesn’t work?



T_{CM} Cell
Central Memory

T_{EM} Cell
Effector Memory

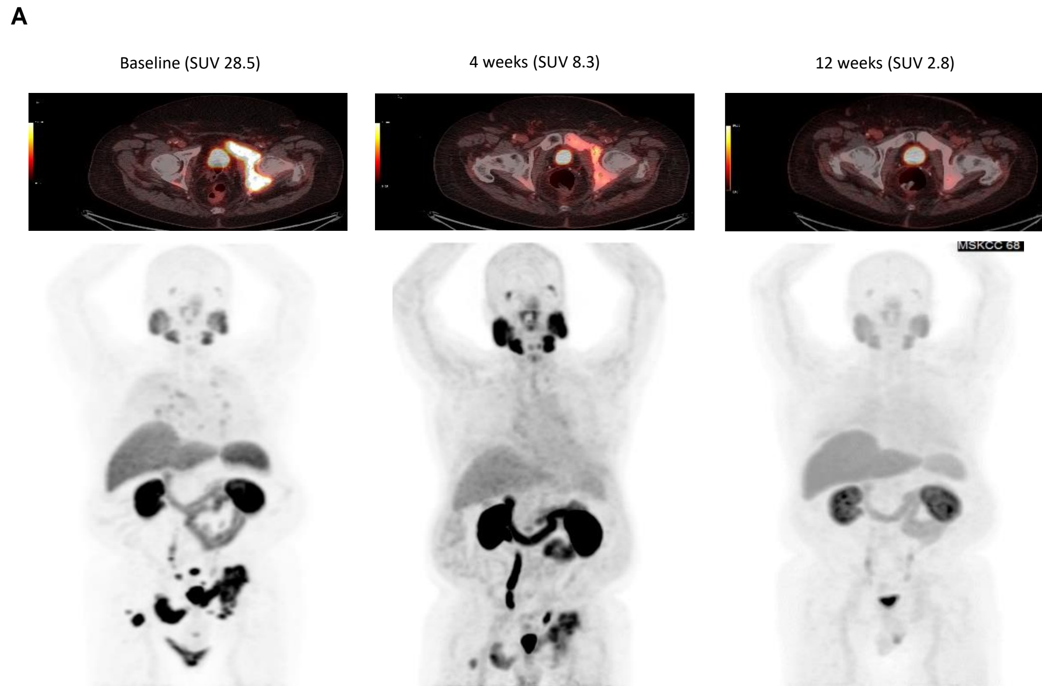
MORE
DIFFERENTIATED

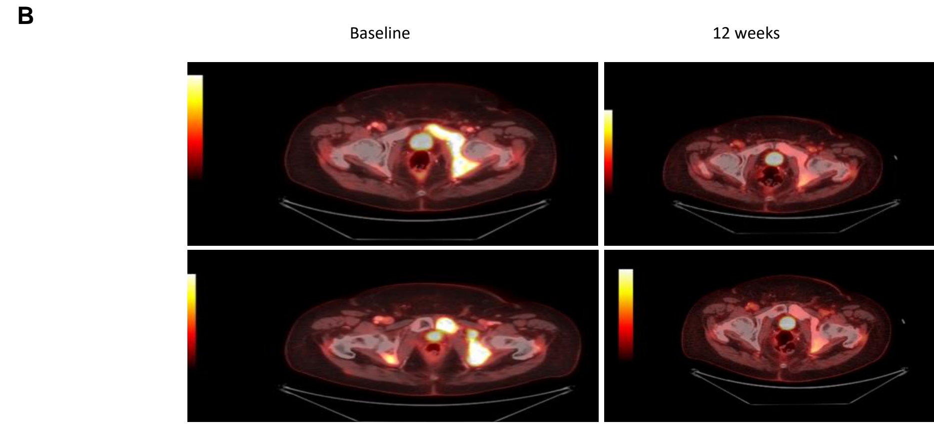
T_{EFF} Cell
Effector T Cell

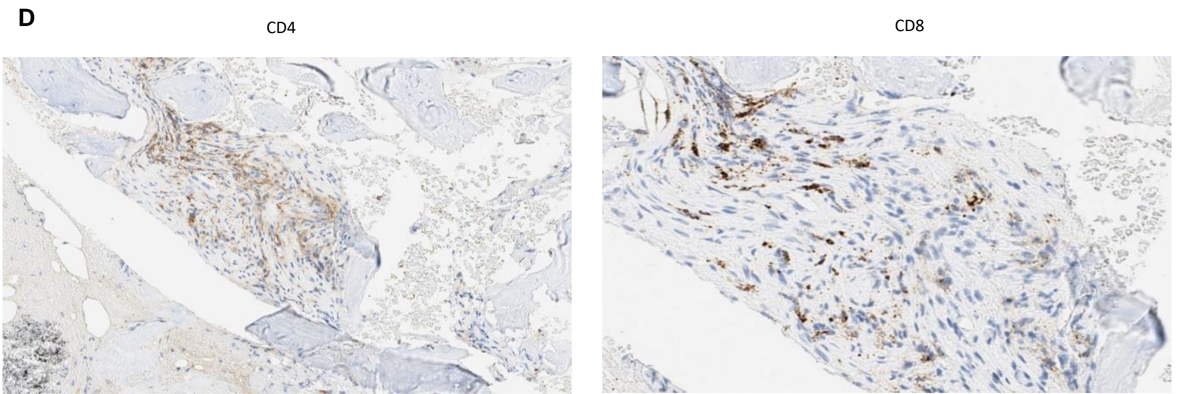
STEMNESS MATTERS

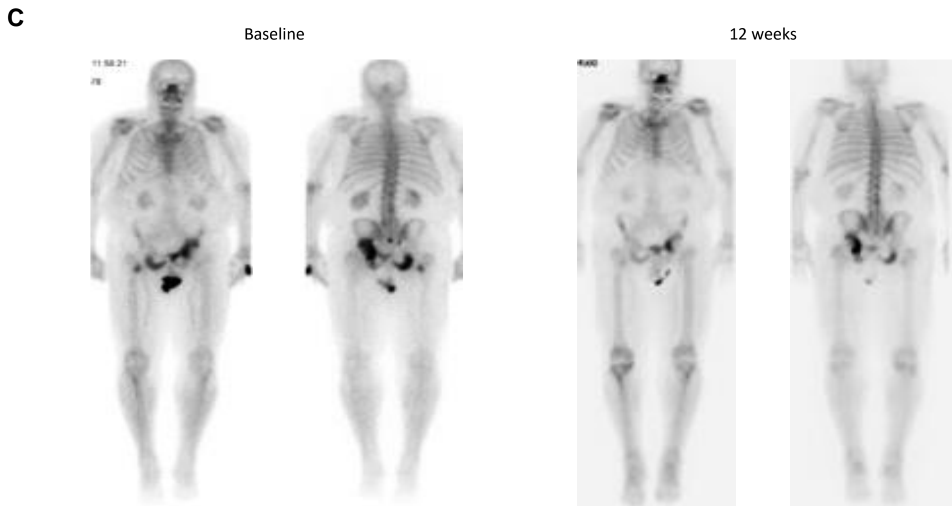
Products with High % of T_{SCM} Cells

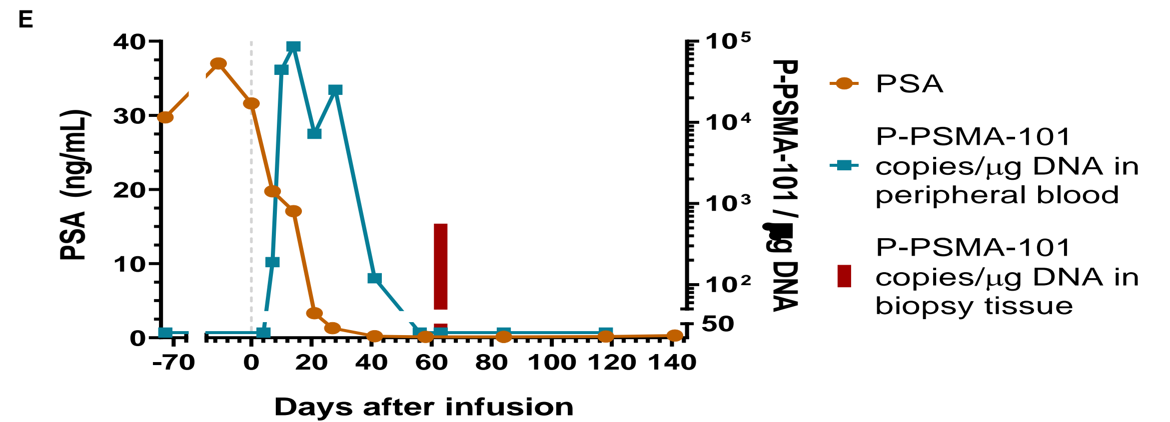
- Strong correlation with best responses in the clinic
- More gradual tumor killing with less toxicity
- Better duration of response and potential for re-response
- **T_{SCM} engrafts in bone marrow – key to CAR-T success in solid tumors**

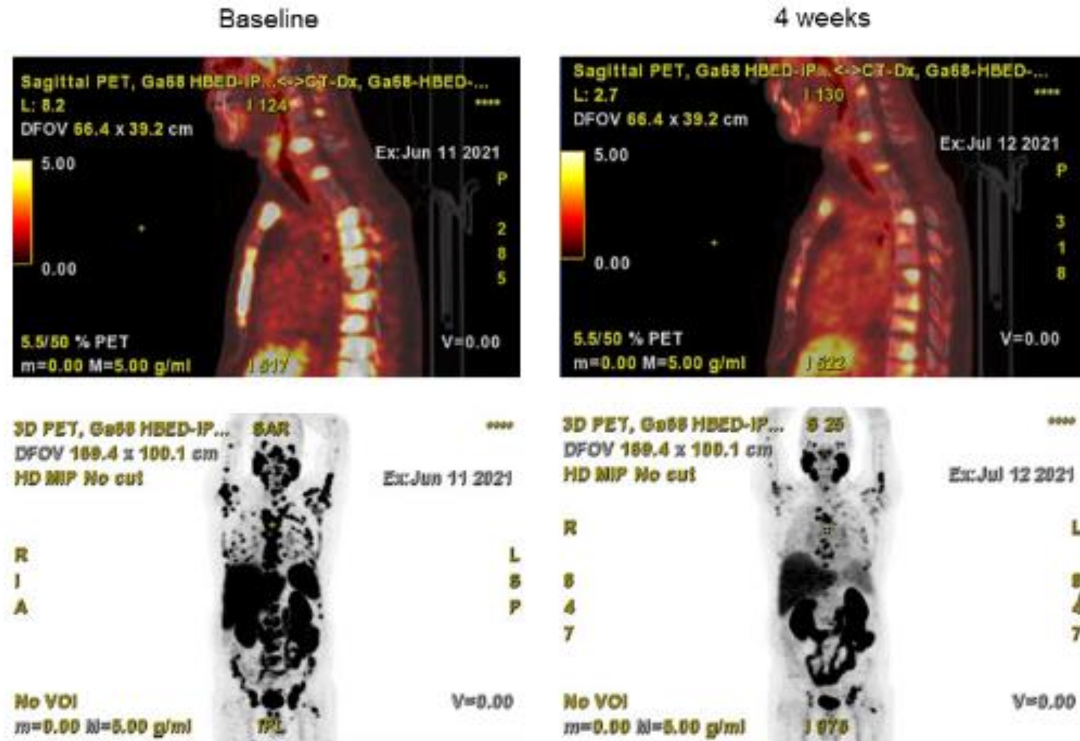

A
Baseline (SUV 28.5)
4 weeks (SUV 8.3)
12 weeks (SUV 2.8)

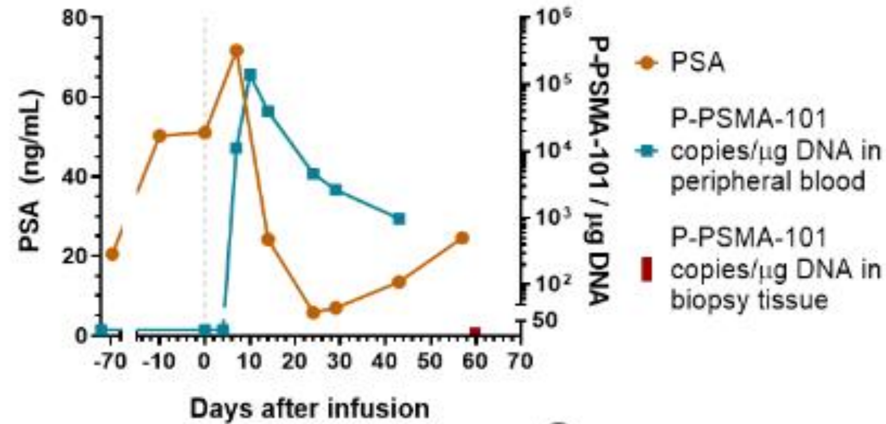

B
Baseline
12 weeks


D
CD4
CD8


C
Baseline
12 weeks


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





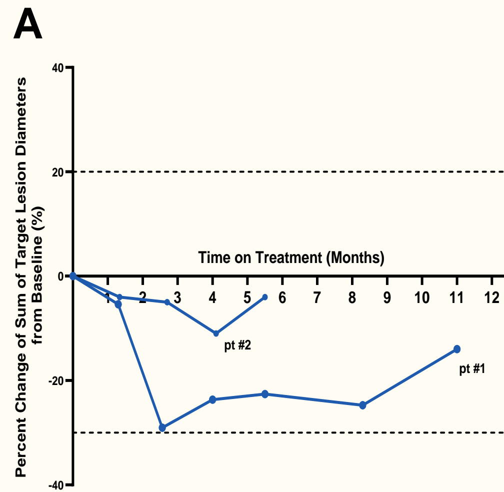
PSMA/FDG PET imaging and differences in biology response

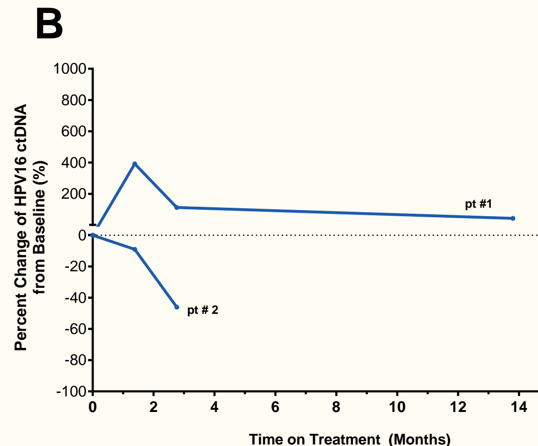
Association of T cell response with best overall response in patients with paired biopsies

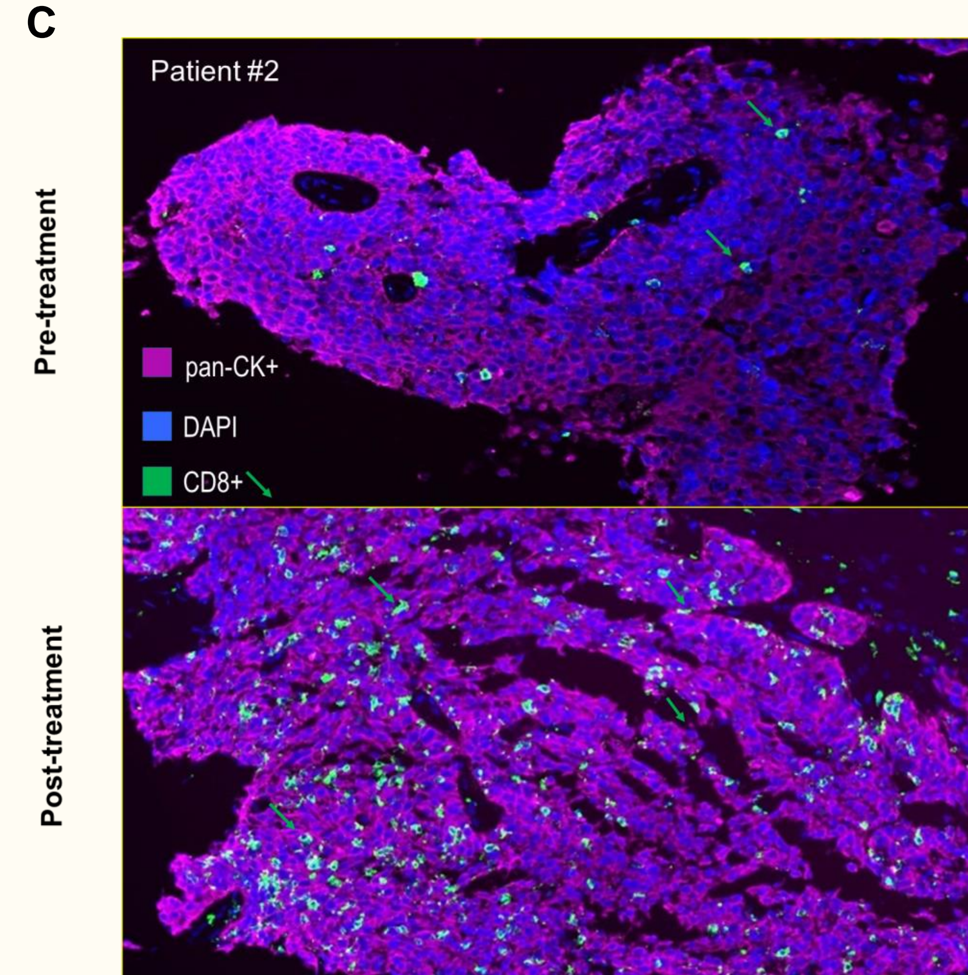
SITC 2023

Paired tumor biopsies of two HNSCC patients treated with HB-200 2-vector therapy at DL2 or DL3 were available for analysis (pt #1 & pt #2):

- Both patients exhibited clinical benefit (stable disease / disease control) (**A**).
- The patients with disease control exhibited only small increases or modest reductions in ctDNA levels (**B**).
- HB-200 therapy induced elevated CD8+ T cell numbers in tumors (**C**).







Wong, et al, SITC,2023 abstr #679

Why are we failing with some immune therapies with an occasional success?

- “Hostile” immune environment – is it as hostile as we think
- Adenosine inhibitors; CXCR inhibitors – but what about cells/cytokines?
- How to deal with MDSCs – blocking agents don’t seem to work
- Is there a benefit for patients pre-chemo rather than post-chemo?
- Does Enzalutamide really modulate the immune environment?
- Are neoadjuvant studies sufficient to endorse a systemic rather than a local effect?

Does immunotherapy work?

- Theoretically, it should
- Not robust at this time
- Responses do exist
- Depending on therapy, responses may be short or long-lived
- Association of immunotherapy response with MSI^{hi} tumors
- Important for genomic profiling to be done on all patients