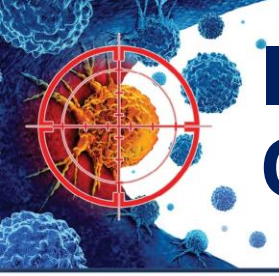

Immunotherapy in prostate cancer: friend or foe? Can the immune system really work to treat cancer?

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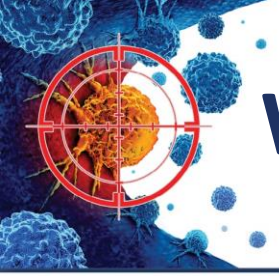
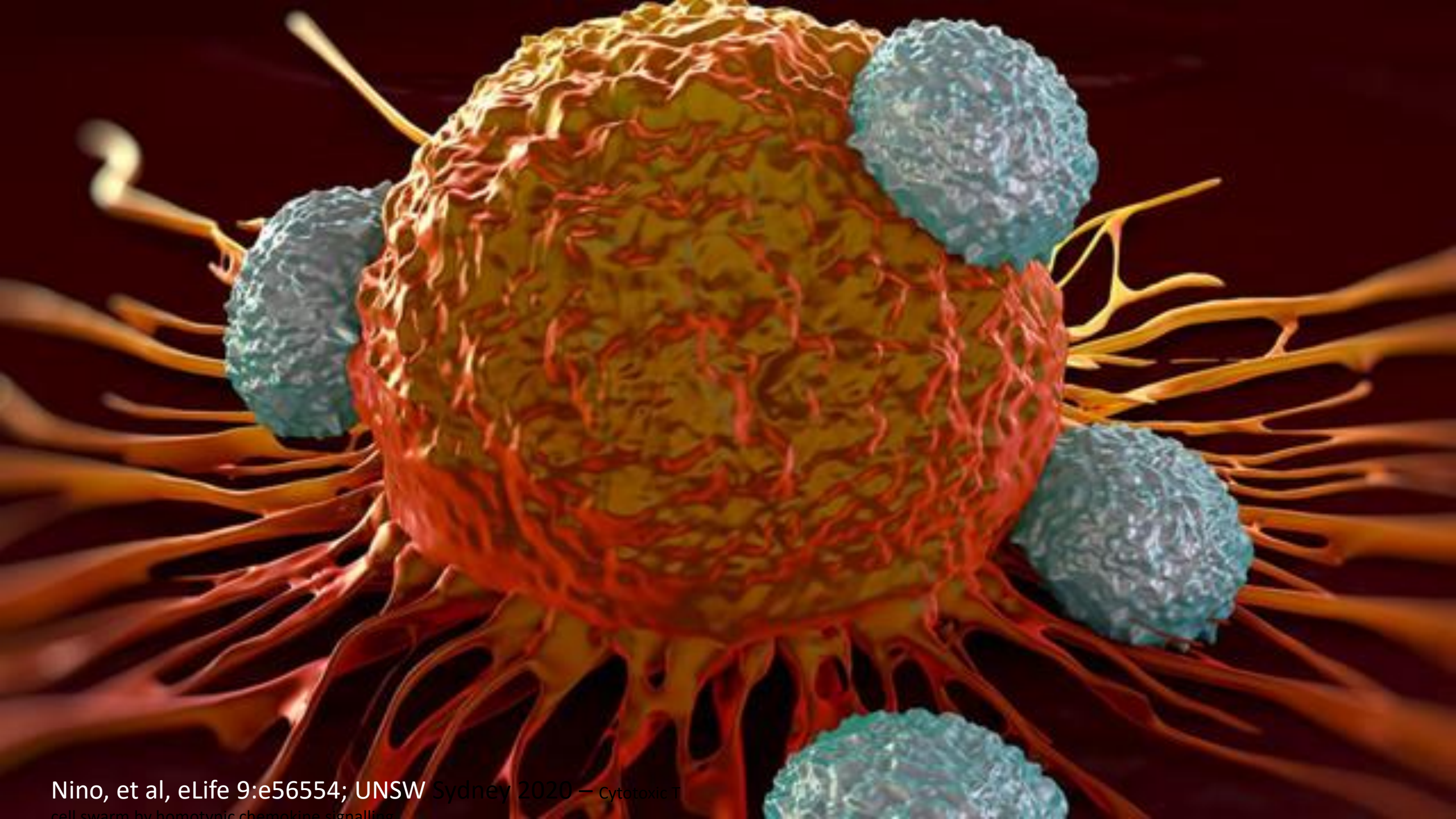
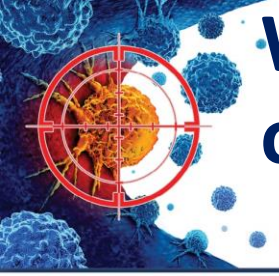


What is Immunotherapy?

- Uses a treatment that tries to use the immune system to fight cancer
- Includes a diversity of approaches; **NOT** limited to immune checkpoint inhibitors (ICIs)
- Vaccines, antibodies, antibody-drug conjugates, bi-specific T cell engagers (BiTES), Chimeric Antigen Receptor T cells (CARs)
- All have the same goal but different platforms
- May not target different components within the tumor microenvironment (TME)
- All are directed at a target on the surface of the prostate cancer cell, although may be expressed at different levels on the tumor cell surface



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



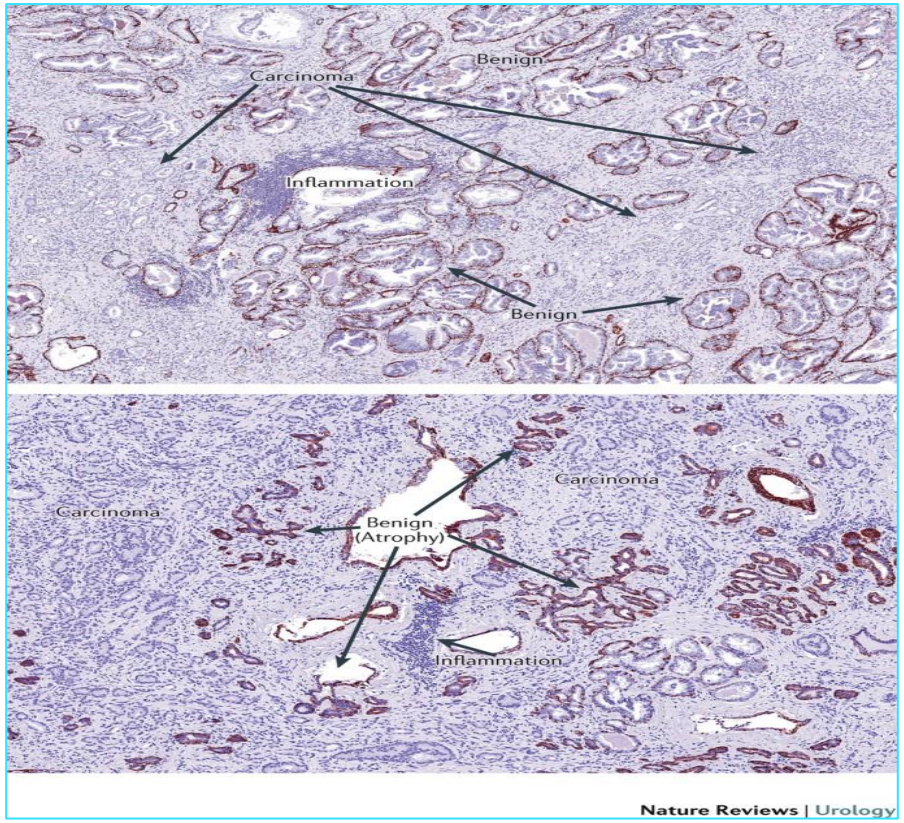
Why are we failing with some immune therapies with an occasional success?

- **Not every tumor** may be susceptible to immune approaches
- Immune therapies for GU tumors: renal, urothelial >>>>> prostate ca
- “Hostile” immune environment – is it as hostile as we think?
- A lot of inhibitory cells and chemical pathways: adenosine; CXCR –
- How to deal with MDSCs – blocking agents don’t seem to work
- Is there a benefit for pts pre-chemo rather than post-chemo?
- Does Enzalutamide really modulate the immune environment?
- Are neoadjuvant studies relevant such that the results may predict systemic behavior of the disease?

Are there tumor microenvironment-related signatures that correlate with prognosis and immunotherapy responses???????

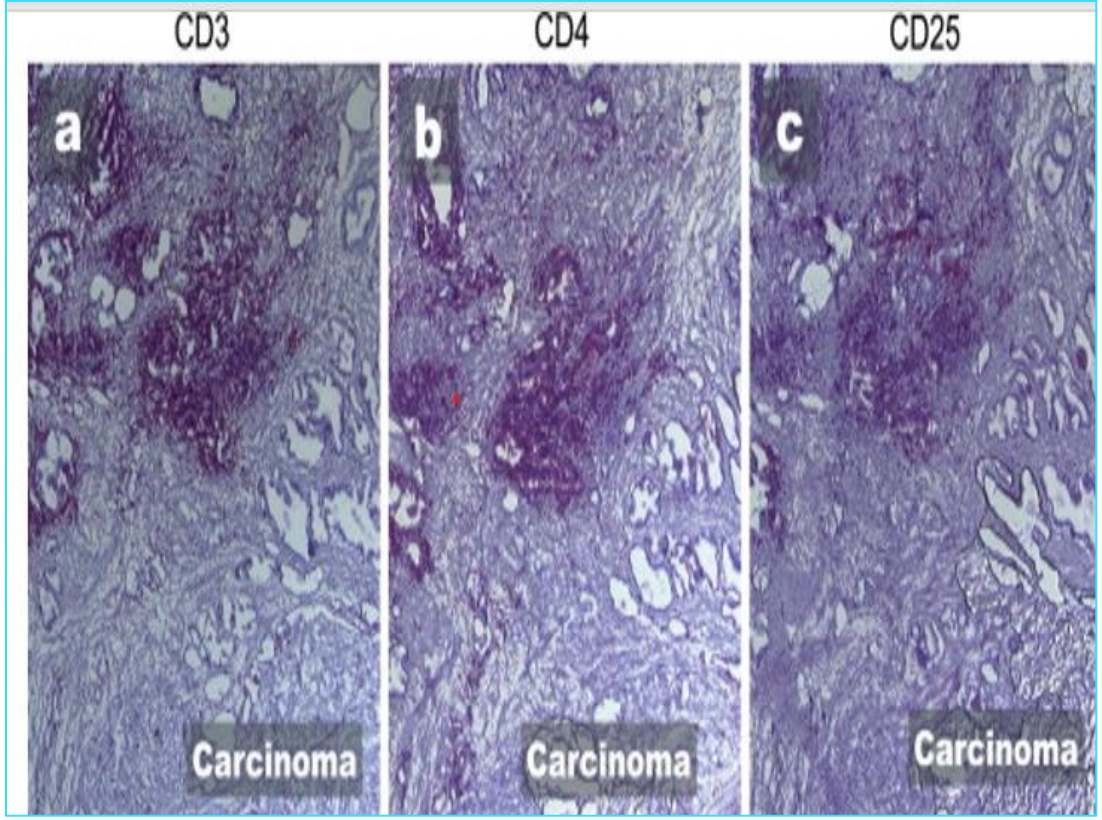
Does inflammation make the TME more sensitive to treatment? What are we facing in the TME?

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.



Sfanos, et al, Nature Rev Urol, 2018

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.

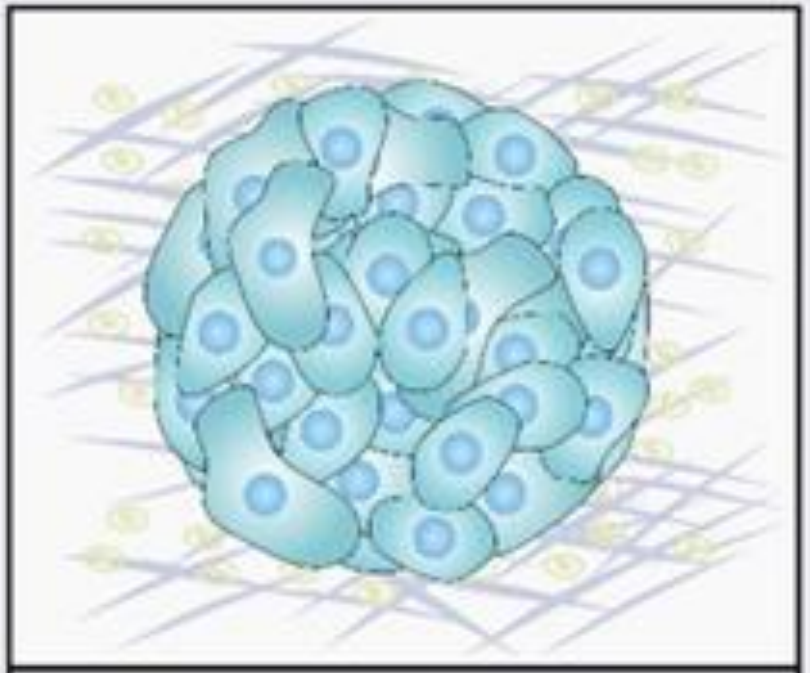


Ebelt, et al, Eur J Ca, 2009

Cold

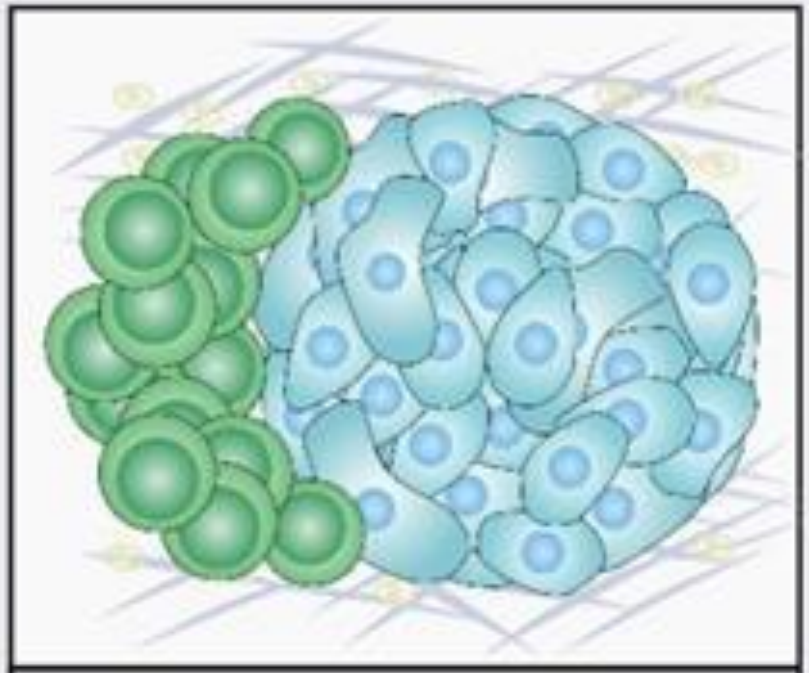
Hot

Desert



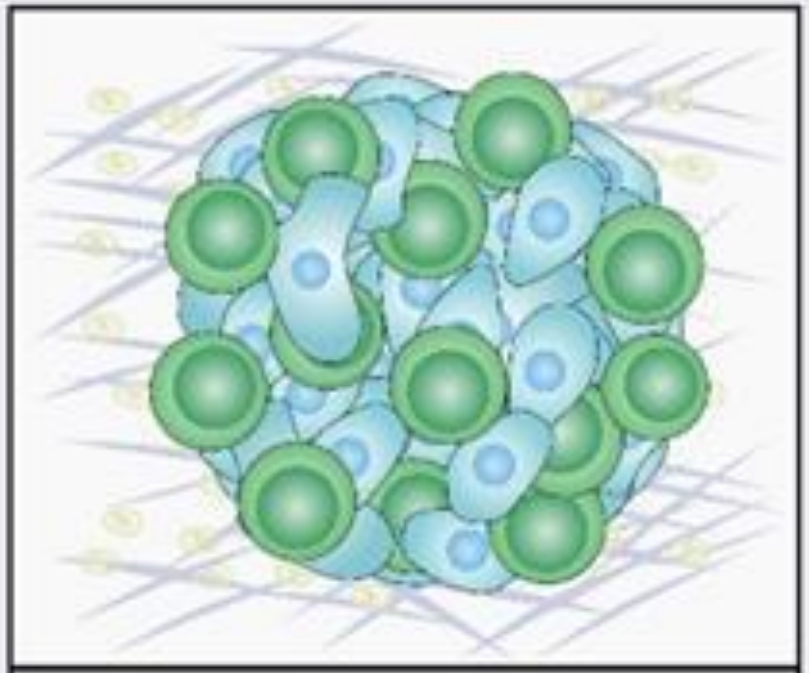
CD8+ T cells are absent from the tumor and its periphery

Excluded



CD8+ T cells accumulated but do not efficiently infiltrate

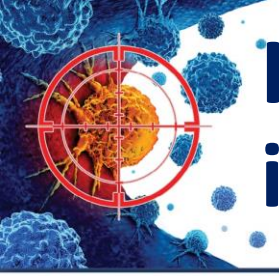
Inflamed



CD8+ T cells infiltrate but their effects are inhibited

Liu YT, Sun ZJ. *Theranostics*. 2021;11(11):5365-5386.

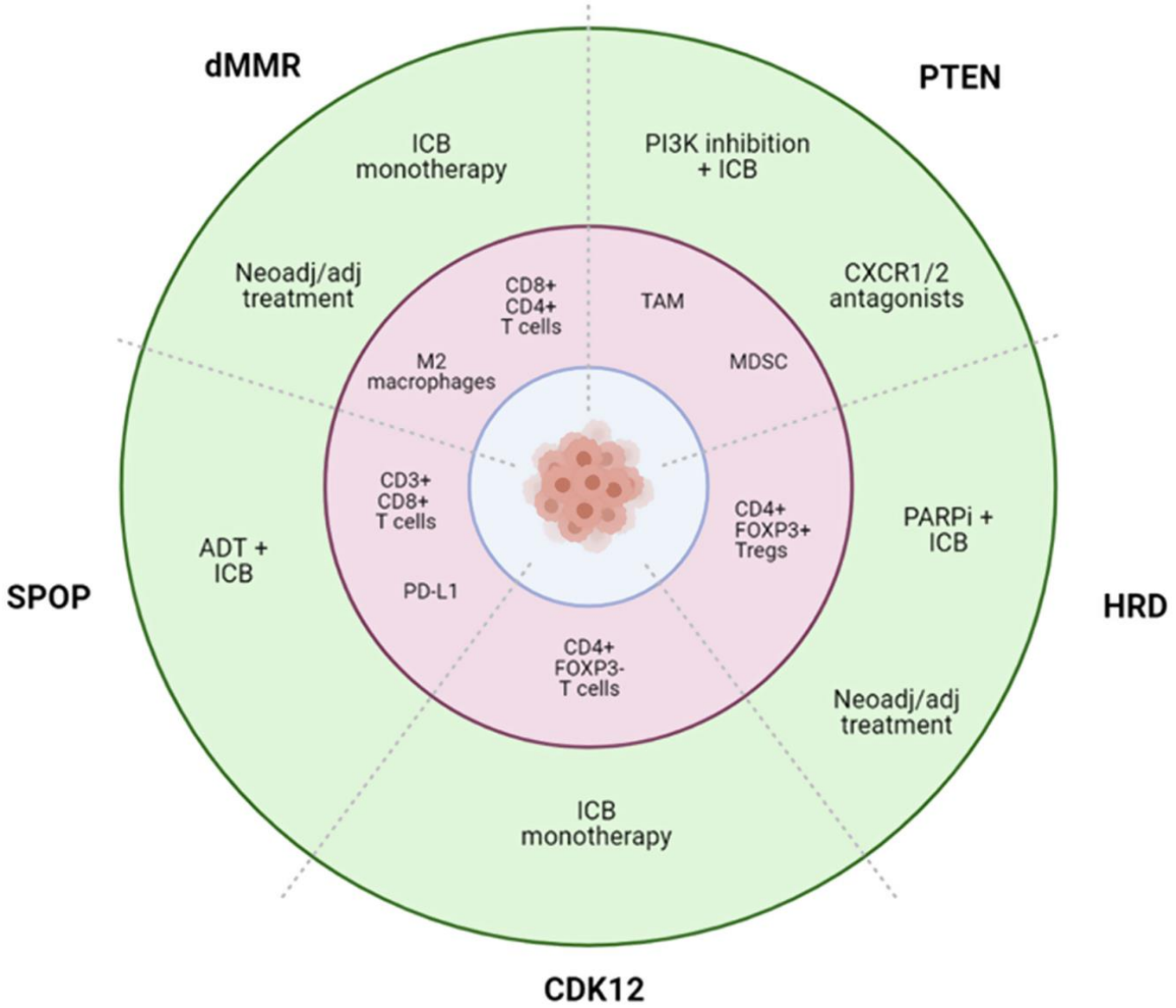
Response to immune checkpoint inhibitors



Is there a recipe for targeting and treating an immunosuppressive microenvironment?

- **prostate gland** - immune-competent organ containing both stromal and infiltrating T and B cells mainly within the fibromuscular stroma and periglandular tissue make up the TME along with multiple cell types including bone marrow-derived mesenchymal stem cells, cancer-associated fibroblasts, pericytes, 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
- Is there a niche within a niche?

Immunogenic subgroups and relationship to genomic environment



Kwon, et al, Endo-Rel Cancer, 2021

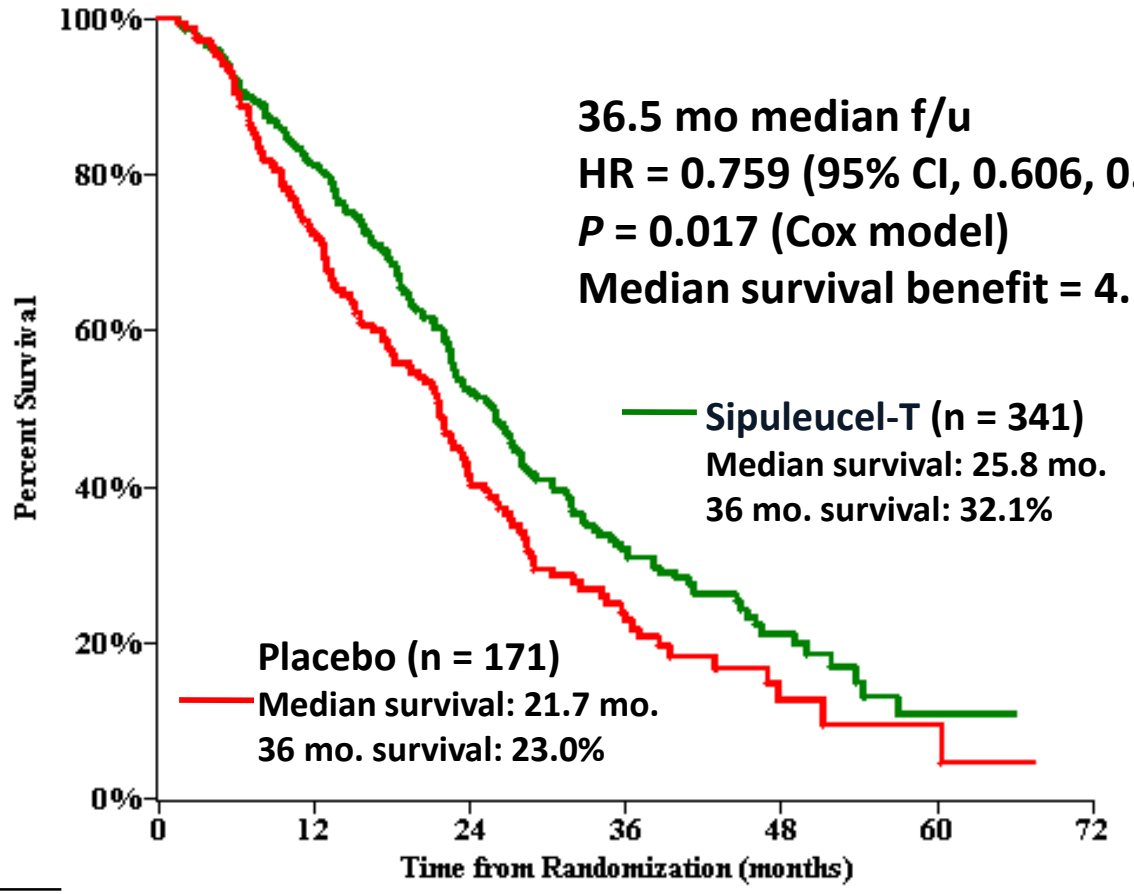
Immunogenomic subgroups and immunotherapeutic treatment strategies for PCa. Five immunogenomic subgroups of PCa are described. The inner ring (red) indicates the immune infiltrate characterised in each subgroup to date. Distinct immune populations are present in different genomic subtypes of PCa, indicating 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.

If you have a target, is it targetable?

Cell surface molecules: PSA, PSMA, PSCA, STEAP, TROP 2, MUC 1, 2, GM2, Globo H, Le^y

Indication:
Asymptomatic of minimally symptomatic mCRPC

IMPACT OS (Sipuleucel-T) Final Analysis (349 events)



No. a						
Sipuleucel-T	341	274	142	56	18	3
Placebo	171	123	59	22	5	2

Kantoff et al NEJM 2010

Polyvalency: are more antigens better? GM2, gly MUC1 Globo G, Le^y, Tn(c), TF(c)

Globo H univalent vaccine

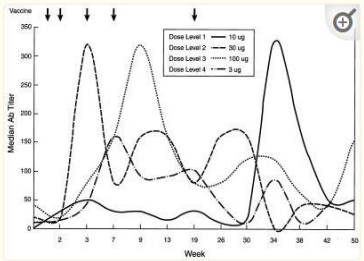


Figure 2

Time course of median IgM antibody titer as determined by ELISA with globo H ceramide after five vaccinations.

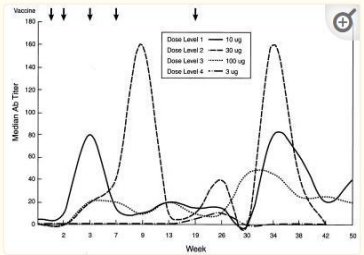
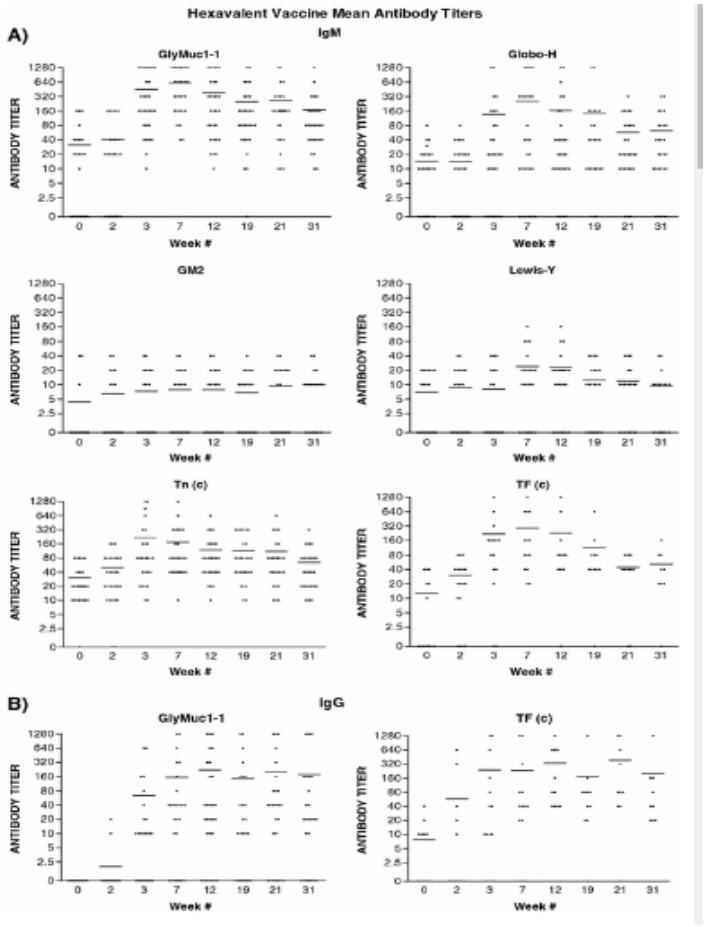


Figure 3

Time course of median IgG antibody titer as determined by ELISA with globo H ceramide after five vaccinations. Note that antibody titers are on a different scale than in Fig. 2.

Slovin, et al, Proc Natl Acad Sci, USA, 1999

Multivalent vaccine



Slovin, et al, Cancer Immunol Immunother, 2007

Potential Tumor Targets 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 Govitecan)
- PSCA (CAR T, BiTE)
- PSMA
- CD40

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

Immunotherapies: CAR T and ADCs

CAR T

Target: PSMA

- Autologous CAR T cells, utilizes transposon platform, generates memory T cells; results in PR/CR, PSA 50 responses

Target: STEAP 2

- First in human
- Autologous CAR T expressing STEAP 2 and a dominant-negative TGFβ receptor II (dnTGFβII) as armoring strategy
- dnTGF component designed to overcome immunosuppression within prostate TME

VACCINE

Target: PSA, PAP

- Prime boost with HB-301 (LCMV) and HB-302 (PICV) are genetically-engineered replicating arenavirus vectors (non-lytic)
- Encoding a non-oncogenic fusion protein of prostatic acid phosphatase (PAP) and prostate-specific antigen (PSA)
- Induce, activate, and migrate antigen-specific cytotoxic CD8+ T cells to tumor; demonstrated in head and neck cancers

Neoadjuvant with MoAb Enoblituzumab

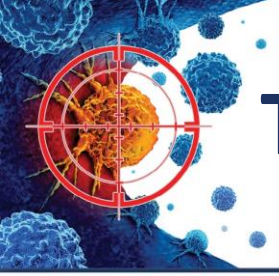
TARGET: B7-H3

- **Enoblituzumab** - humanized, Fc-engineered, B7-H3-targeting antibody that mediates antibody-dependent cellular cytotoxicity
- phase 2 randomized multi-center neoadjuvant trial in 219 men with high risk Gleason 4+3 with high risk features or Gleason 8-10) prostate cancer to determine efficacy

ADC – MGC018

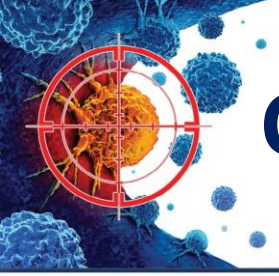
Target: B7-H3

- MGC018 is comprised of the cleavable linker **duocarmycin** payload, valine-citrulline-*seco*-Duocarmycin hydroxyBenzamide-Azaindole (vc-*seco*-DUBA; SYD980), conjugated through reduced interchain disulfides to the anti-B7-H3 humanized immunoglobulin G1 (IgG1) kappa monoclonal antibody MGA017
- Bystander cytotoxic effect of the vc-*seco*-DUBA linker/payload may afford MGC018 therapeutic benefit toward tumors with heterogeneous overexpression of B7-H3.
- In design: Phase III Vobramitamab Duocarmazine in Participants with Metastatic Castration-Resistant Prostate Cancer (TAMARACK)



Targeting PSMA in prostate cancer…

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

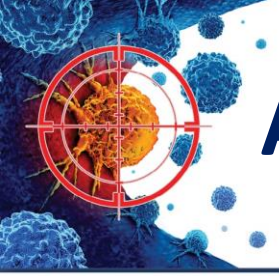


Challenges using CAR T cells in solid tumors

- Retroviral vectors – instability of construct, poor proliferation
- Possible cross-reactivity with normal antigens or unusual sites, ie, brain (PSMA), lung epithelium (HER2) & (Mesothelin), renal (CAIX)- liver toxicity, colon (CEA) – colitis.
- Density of antigen: over- or under-expressed
- Preparative regimens to deplete Tregs may be insufficient to deal with either an immunologically “bland”/“cold” or immunosuppressive tumor microenvironment (TME): inhibitory MØ, adenosine, cytokines, inhibitory fibroblasts
- Are we under- or over-using cyclophosphamide to suppress Tregs?
- High vs low affinity CARs

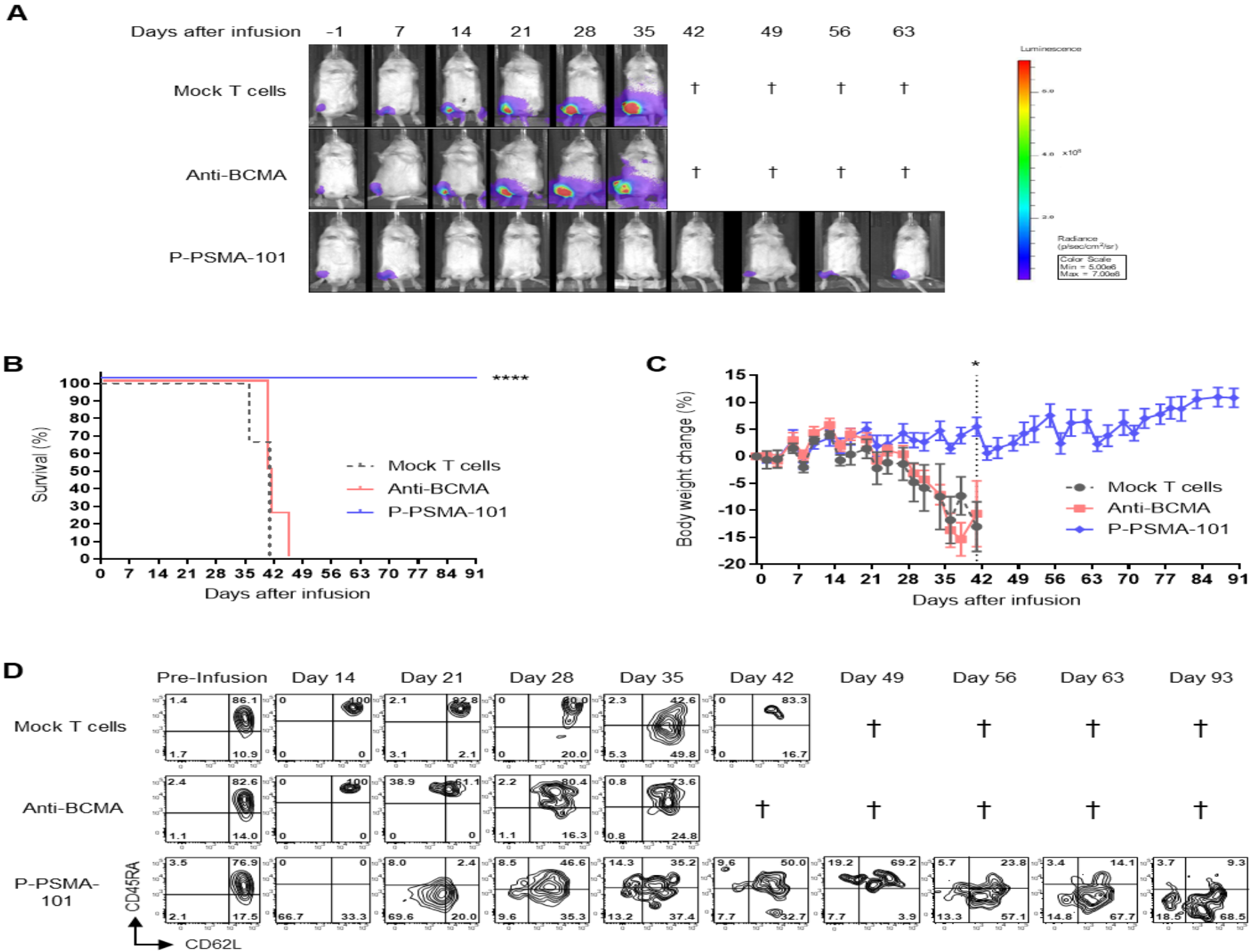
Lessons learned in metastatic castration resistant prostate cancer (mCRPC)…

- First generation CARs in prostate
- Safe, longest persistent of cells up to 2 weeks
- Hard to track migration
- *Ex vivo* labeling of CAR T with possible tracking to PSMA+ lymph node; slight PSA decline and stable disease in lymph nodes but required RT to maintain
- No signal of antitumor effect by PSA
- Combination approaches with IL-2 (Junghans), TGF-β (Haas)



Are there generational differences?…

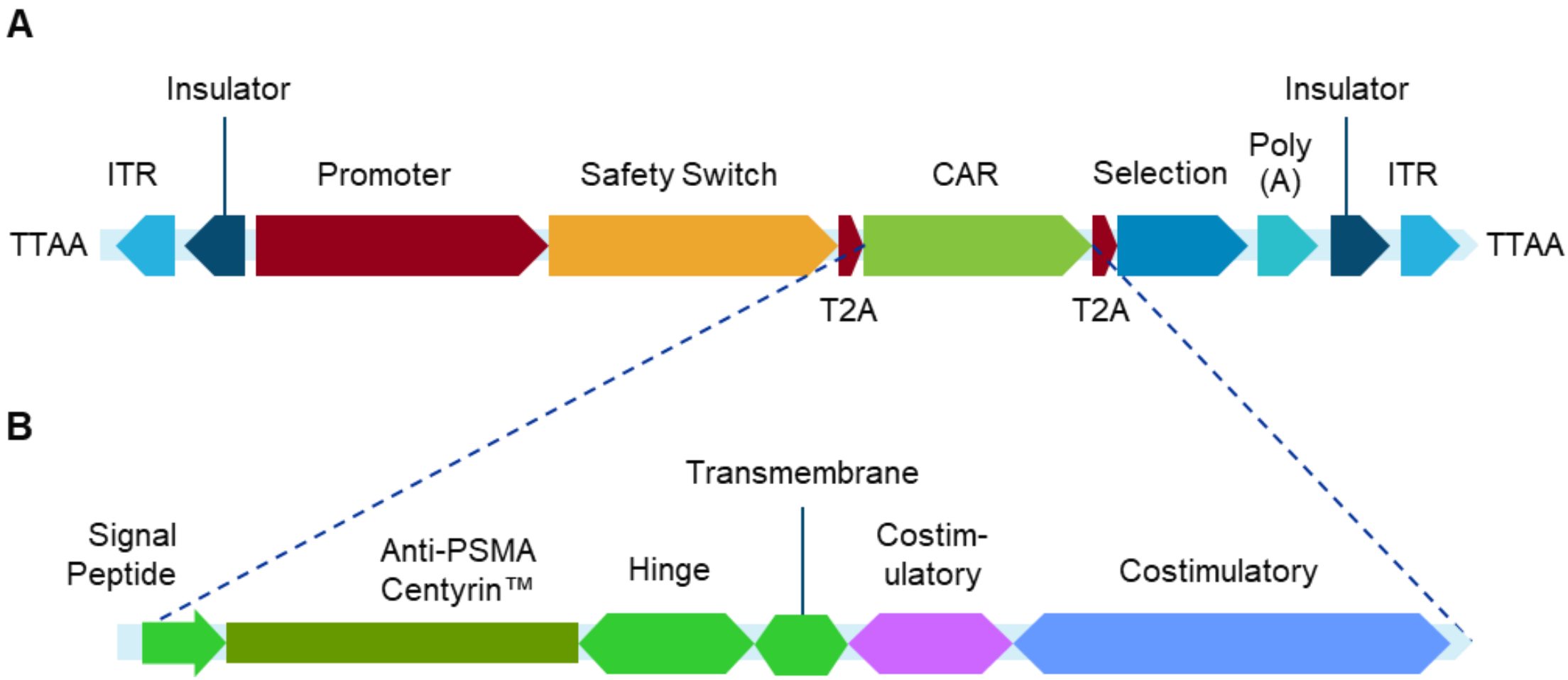
- Third-generation CAR (3G CAR) matched co-stimulation of CD28 with 4-1BB - improves T-effector memory cell differentiation and protects cells from apoptosis
- 3G CAR containing two costimulatory elements, CD28 and 4-1BB co-signaling domains, in addition to CD3ζ. (Zuccolotto, et al, Front Onco 2021).
- the additional costimulatory domain produced detrimental effects - could be attributed to an increased activation-induced cell death (AICD).


A
Days after infusion
-1
7
14
21
28
35
42
49
56
63
Mock T cells
Anti-BCMA
P-PSMA-101
†
Luminescence
Radiance (p/sec/cm²/sr)
Color Scale
Min = 5.00e6
Max = 7.00e8
B
Survival (%)
Days after infusion
****
Mock T cells
Anti-BCMA
P-PSMA-101
C
Body weight change (%)
Days after infusion
*
Mock T cells
Anti-BCMA
P-PSMA-101
D
Pre-Infusion
Day 14
Day 21
Day 28
Day 35
Day 42
Day 49
Day 56
Day 63
Day 93
Mock T cells
Anti-BCMA
P-PSMA-101
CD45RA
CD62L

P-PSMA-101Transposon platform…

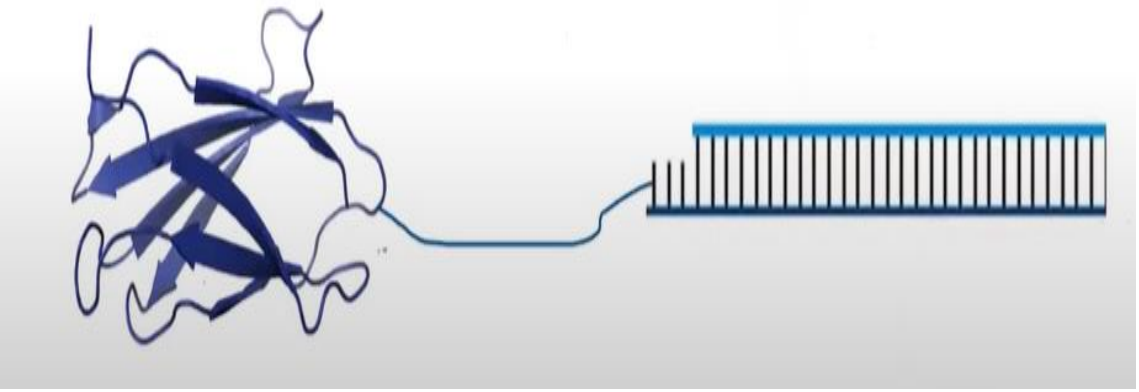
- non-viral transposon system (piggyBac®) - results in a CAR-T product comprised of a high percentage of T stem cell memory (T_{SCM}) cells
- Genes are inserted encoding a PSMA-targeted Centyrin CAR, iCasp9-based safety switch, and DHFR to purify CAR-T cells
- Result: T_{SCM} cells with bone marrow homing capability
- may be particularly relevant to bone tropic solid tumors, ie, prostate adenocarcinoma

PSMA 101 Construct



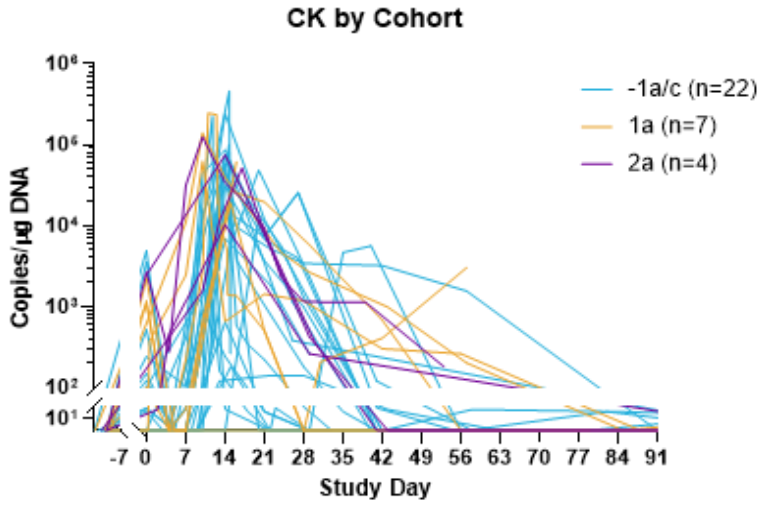
Centyrin platform

- Proprietary antigen binding platform
- Built on human tenascin C FN3 framework
- ~10kd; approx 1/15 size of Moab
- Stable, soluble
- Readily expressed in E. coli
- Structurally simplistic; No glycosylation, no disulfide bonds
- High specificity
- Not a known autoantigen

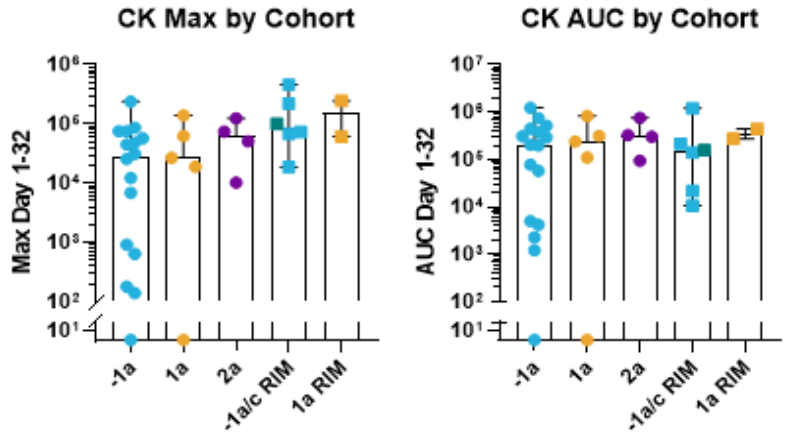


Cellular Kinetics

A.

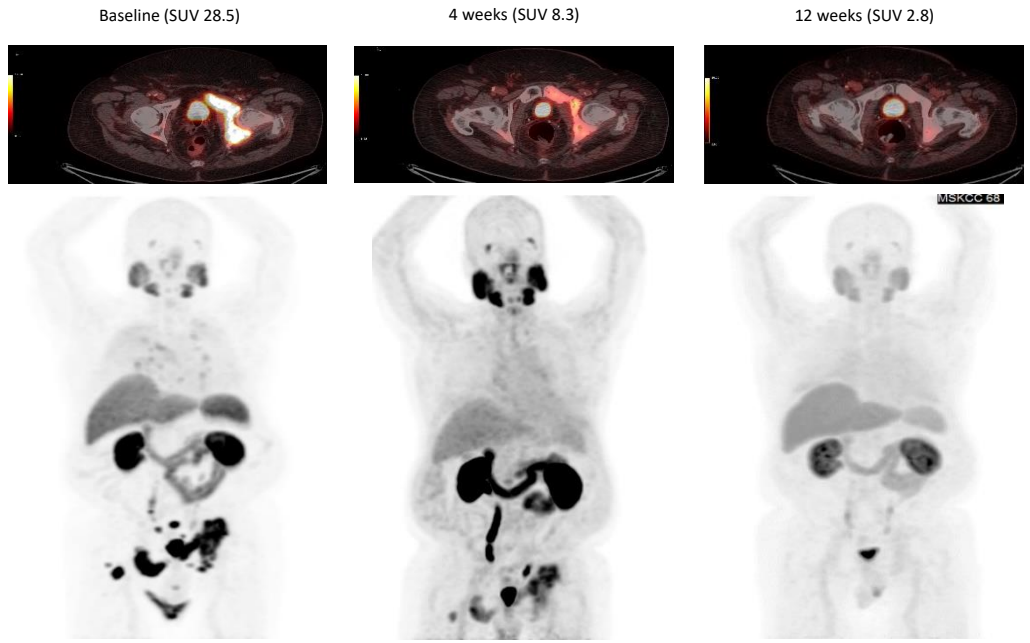


B.

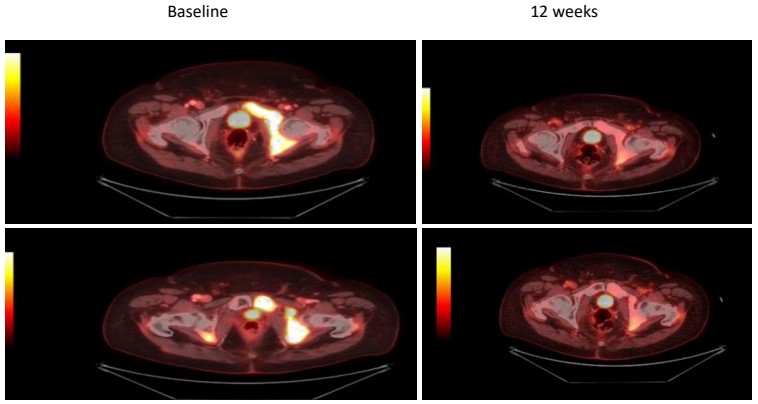


- **Panel A**: Distribution of P-PSMA-101 cellular kinetics (CK) as measured by quantitative PCR (qPCR), expressed in copies of transposon per microgram of DNA (cp/µg DNA). Data are plotted over time from Day 0 to Day 91, with different cohorts color-coded as indicated. The single patient dosed in cohort -1c (rituximab cy/flu low dose) is grouped with cohort -1a.
- *peak expansion occurred between 10–14 days post-infusion. The Limit of Quantification (LOQ) was determined as < 200 cp/µg DNA.
- **Panel B**: Summarizes the maximum cellular kinetics (Cmax) and the area under the curve (AUC) across cohorts for days 1–32. Data are displayed as a bar chart, with individual data points shown as scatter plots. Patients requiring rimiducid are shown as -1a/c RIM and 1a RIM.(note: the one cohort -1c patient shown as green square under -1a/c RIM).

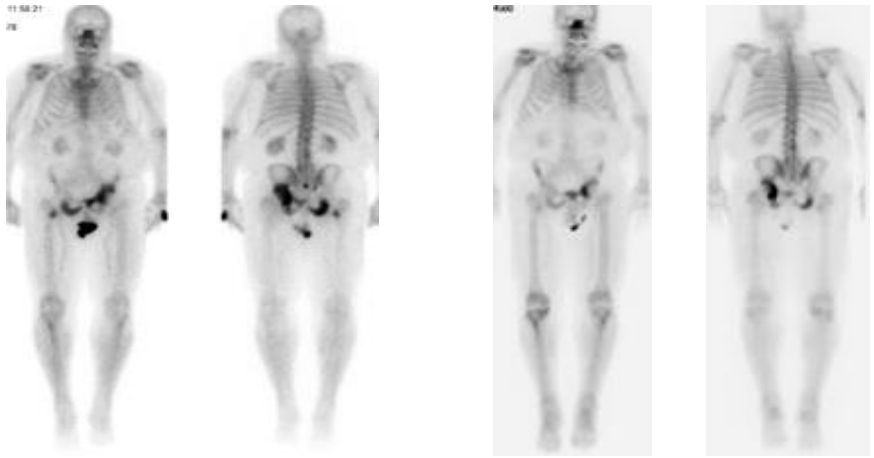
A


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

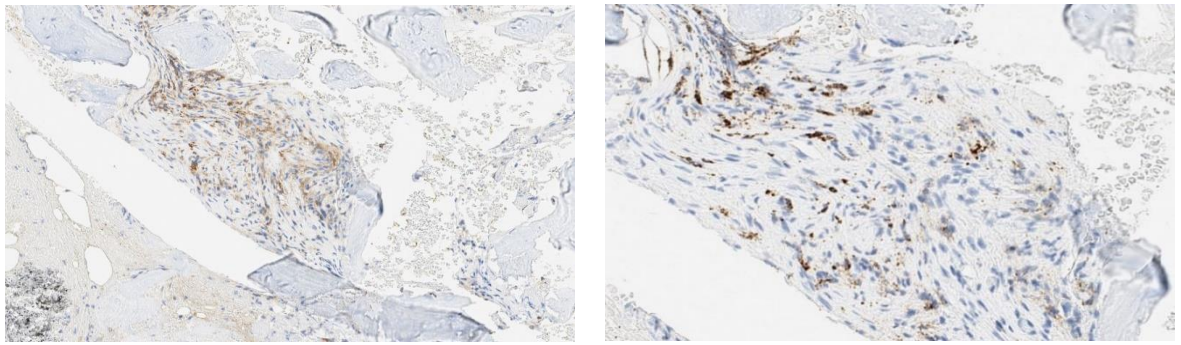
B


Baseline
12 weeks

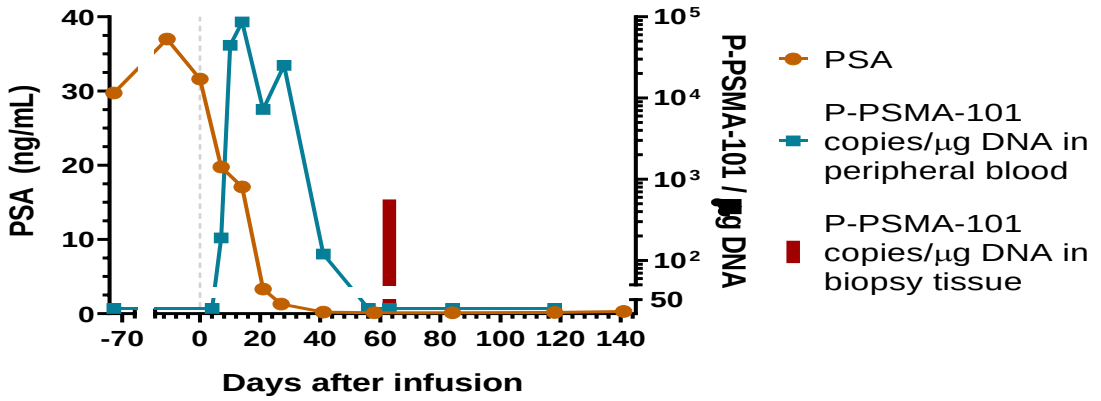
C

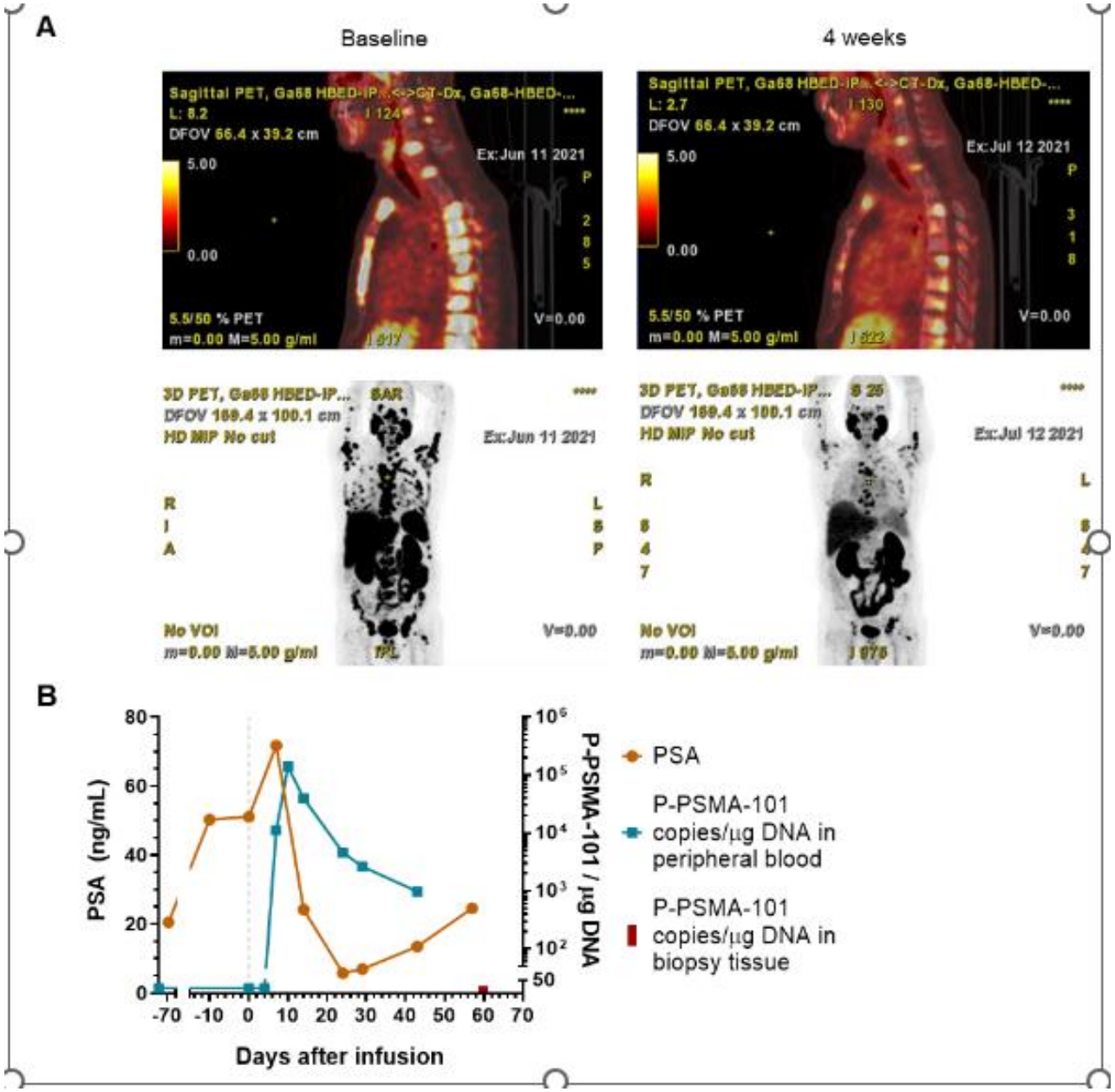

Baseline
12 weeks

D


CD4
CD8

E

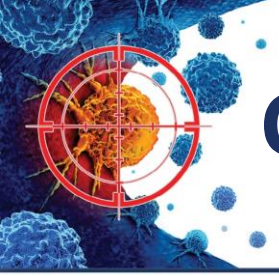

PSA (ng/mL)
P-PSMA-101 / µg DNA
Days after infusion
PSA
P-PSMA-101 copies/µg DNA in peripheral blood
P-PSMA-101 copies/µg DNA in biopsy tissue



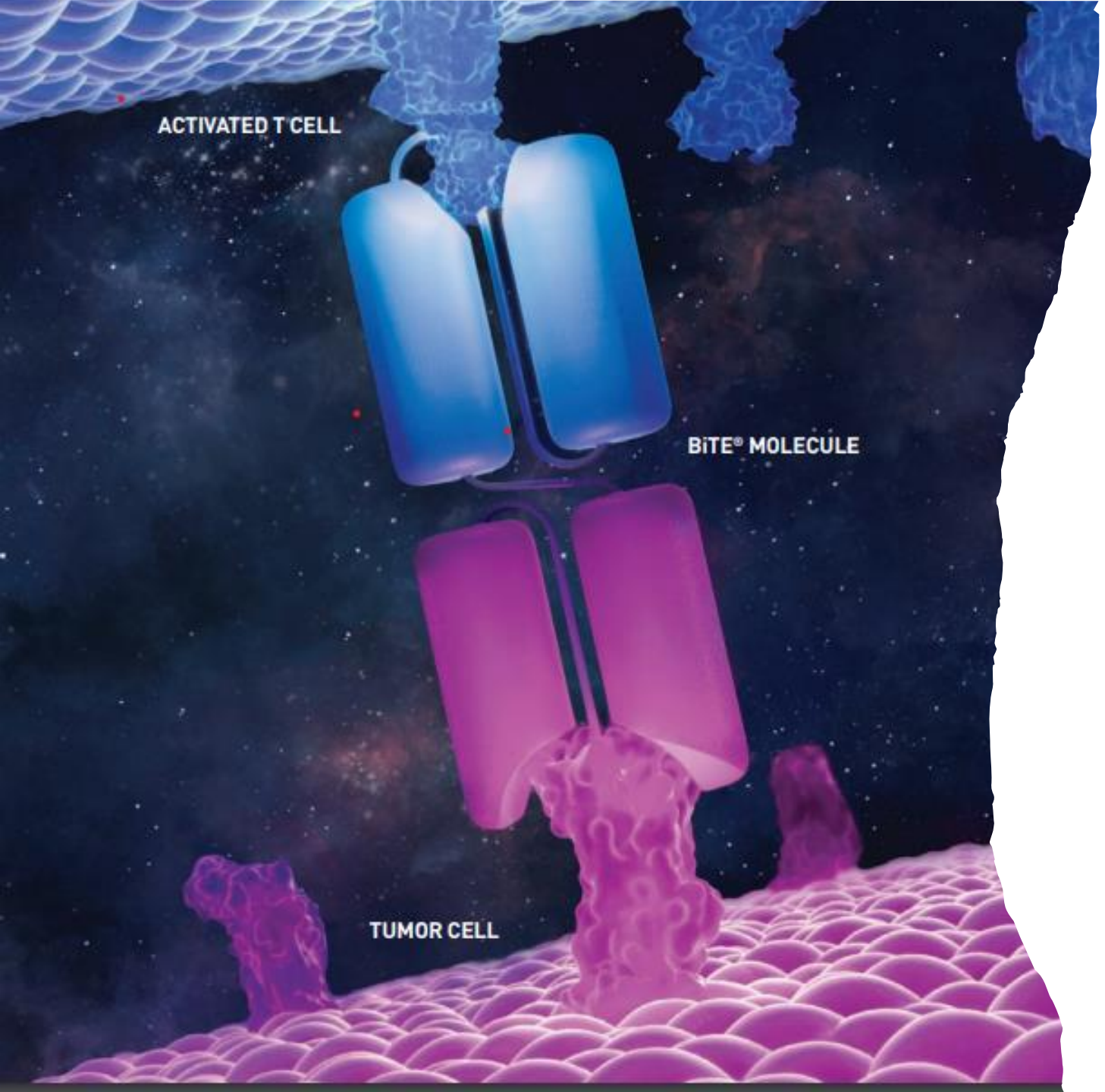
PSMA/FDG PET imaging and differences in biology response

UPDATE…

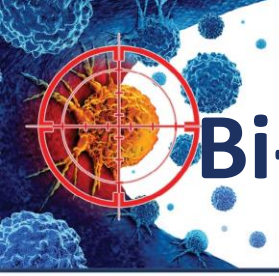
- 33 mCRPC pts received a single infusion of P-PSMA-101: 6/33 (18.2%) pts experienced DLTs including one pt with Grade 4 HLH and subsequent Grade 5 hepatic failure.
- CRS was observed in 61%; HLH seen in 9.1% (3/33).
- 8 mCRPC pts treated with P-PSMA-101 required activation of the iCasp9-based safety switch by rimiducid infusion due to emergence of acute HLH-like syndrome or significant transaminitis.
- **Anti-tumor activity** - PSA declines from baseline in 26 of 33 (79%) of pts with PSA_{50} and PSA_{30} observed in 21% and 33%, respectively.
- **ORR observed** - 6.3% with investigator-assessed best response of CR in one pt and PR in one pt. Stable disease was achieved in 20 of 33 pts (60.6%) with seven (21.9%) remaining stable for ≥ 3 months.
- Two initially treated pts demonstrated marked responses with concordant findings in pharmacokinetics, biomarkers, and imaging. The pts had a >99% and >88% decline in PSA levels within 6 weeks.
- **PSMA-targeted PET** demonstrated a reduction in SUV to levels below liver background for all tumors in one pt and ~50% in the other. Biopsy of bone metastases in both patients demonstrated the presence of P-PSMA-101 CAR-T cells by qPCR, and elimination of tumor cells in one. Both pts improved clinically in mCRPC-related symptoms.
- *Re-dosing was safe and feasible.



Can we take a “BiTE” out of cancer????



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



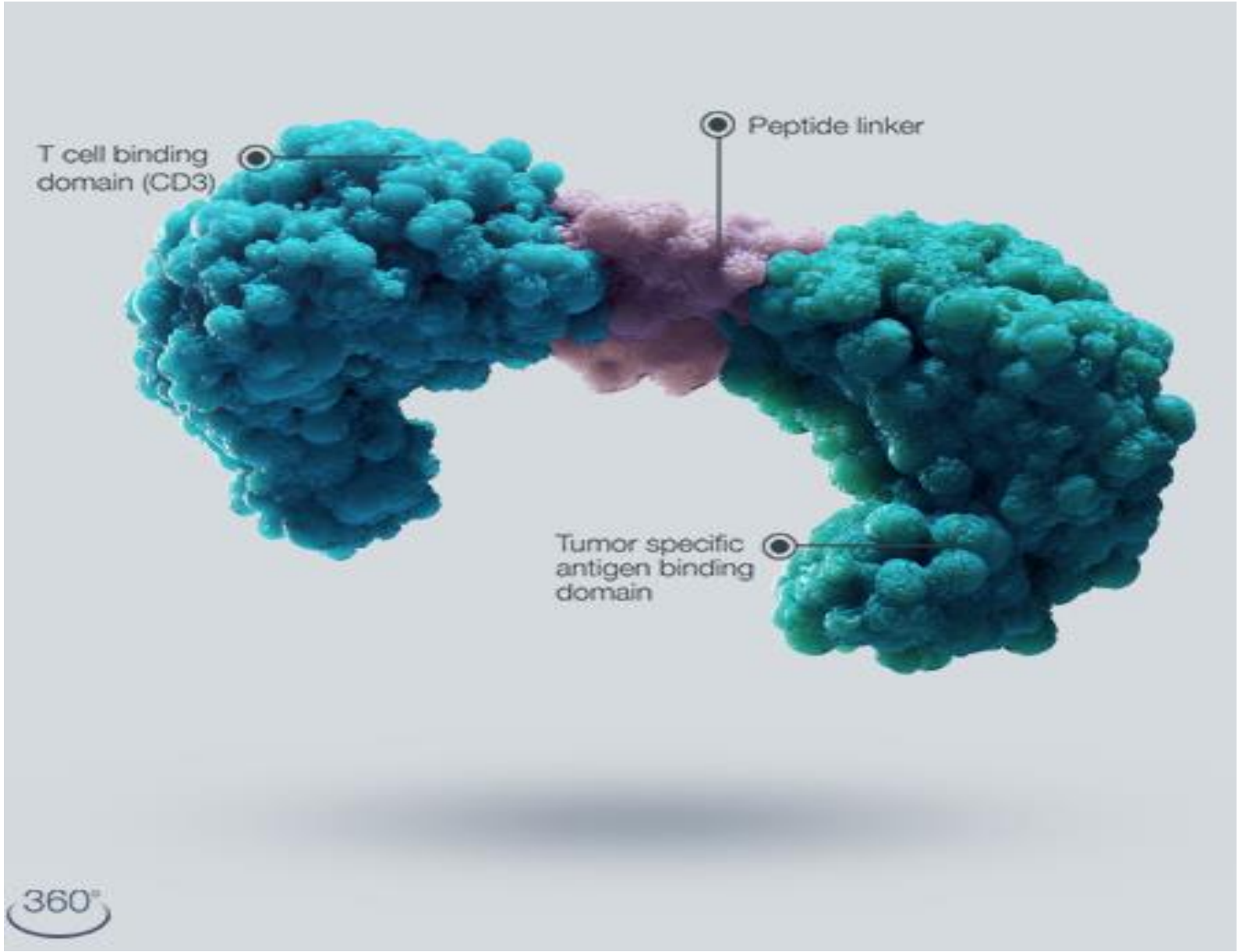
Bi-Specific T Cell Engager (BiTE)…

1. Once T cells are activated by a BiTE® molecule, the T cells may induce further T-cell proliferation and cytokine production.

2. Induces apoptosis; activated T cells release cytokines and produce additional perforin/granzymes that may allow T cells to target surrounding cancer cells

3. potentially results in the serial lysis of multiple cancer cells by a single T cell.

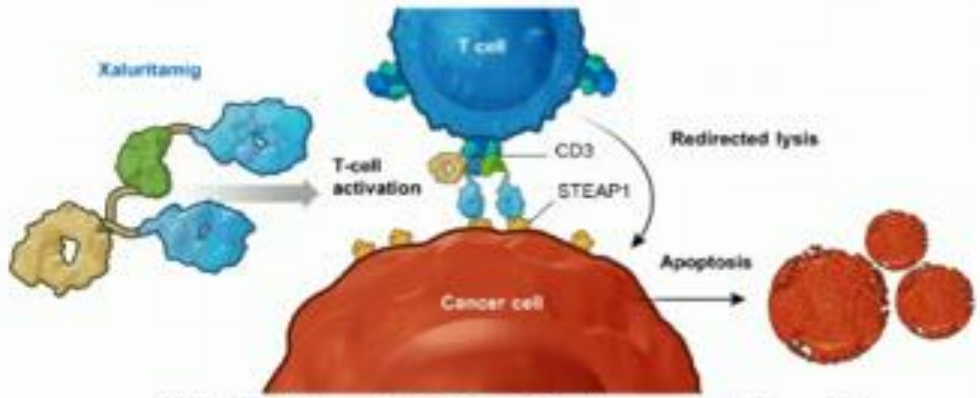
4. Sustained activation of a single activated cytotoxic T cell theoretically results in local proliferation and expansion of polyclonal memory T cells.



Pasotuxizumab: Hummel HD et al. *Immunotherapy.* 2021;13(2):125-141.

Xaluritamig is a STEAP1-targeted T cell engager being evaluated for the treatment of prostate cancer

- Prostate cancer remains a leading cause of cancer deaths worldwide, and patients with mCRPC have a poor prognosis[1]
- STEAP1 is a cell surface antigen highly expressed in prostate cancer and associated with poor survival[2,3]
- In preclinical studies, xaluritamig showed broad anti-cancer effects in prostate cancer xenograft models[3]



Xaluritamig is an XmAb® 2+1 T-cell engager designed to facilitate T cell-mediated lysis of STEAP1-expressing cells[3,4]

XmAb® is a registered trademark of Xencor, Inc.

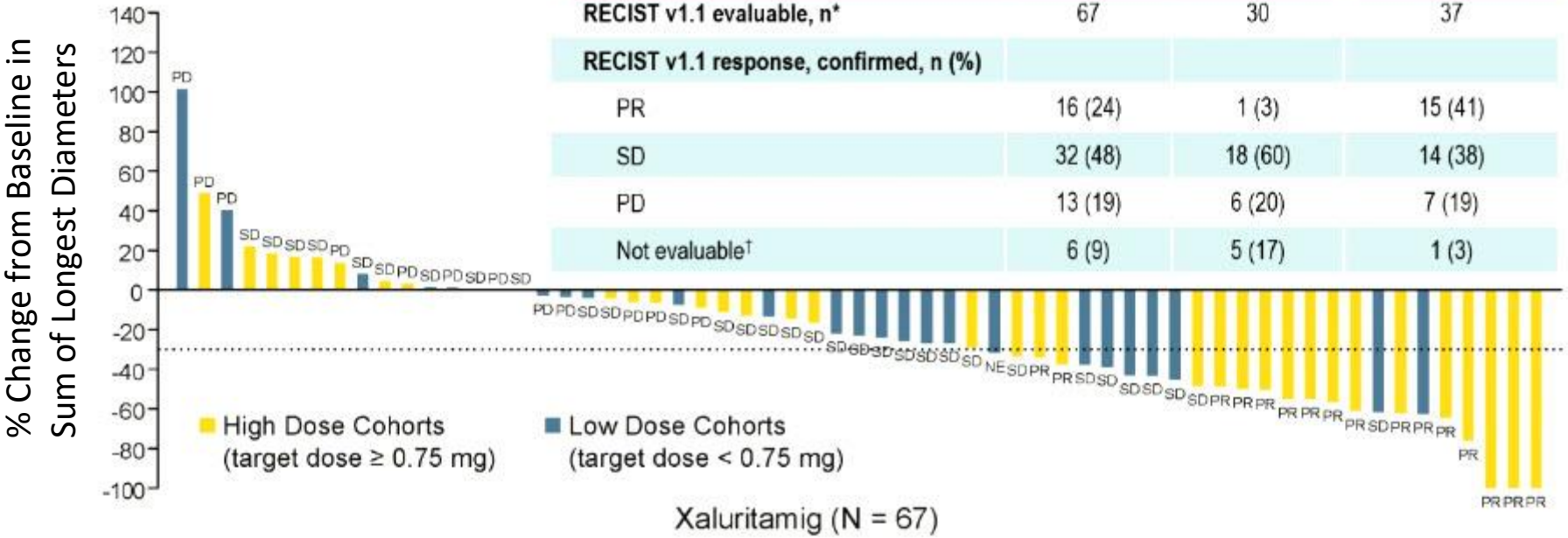
mAb, monoclonal antibody; mCRPC, metastatic castration-resistant prostate cancer; STEAP1, six transmembrane epithelial antigen of the prostate

1. Turco F, et al. *Res Rep Urol*. 2022;14:339-50.
2. Xu M, et al. *Cancers (Basel)*. 2022;14:4034.
3. Nolan-Stevaux O, et al. *Cancer Res*. 2020;80(16_Supplement):CT032-03.
4. Li C, et al. *J Immunother Cancer*. 2020;8:718.

MADRID 2023 ESMO congress

Confirmed RECIST responses occurred more often in high dose cohorts

	All cohorts	Low dose cohorts (1–7a)	High dose cohorts (7b–13)
RECIST v1.1 evaluable, n*	67	30	37
RECIST v1.1 response, confirmed, n (%)			
PR	16 (24)	1 (3)	15 (41)
SD	32 (48)	18 (60)	14 (38)
PD	13 (19)	6 (20)	7 (19)
Not evaluable†	6 (9)	5 (17)	1 (3)



Dashed line indicates 30% reduction in tumor sum of longest diameters from baseline. *Historically, ~40% of mCRPC patients have RECIST measurable disease[1,2]. †BOR of NE includes 5 patients without post-baseline scans and 1 patient without sufficient follow up duration prior to post baseline assessment.

BOR, best overall response; NE, not evaluable; PD, progressive disease; PR, partial response; PSA, prostate specific antigen; RECIST; Response Evaluation Criteria in Solid Tumors; SD, stable disease.

1. Scher HI, et al. *Clin Cancer Res*. 2005;11(14):5223-5232. 2. Lorente D, et al. *Eur Urol Focus*. 2018;4(2):235-244.

Conclusions

- Xaluritamig is the first clinical T cell engager targeting STEAP1
- The MTD was established utilizing step-dosing and premedication
  - 1.5 mg IV QW (3-step, D1 0.1 mg / D8 0.3 mg / D15 1.0 mg / D22+ 1.5 mg)
- The safety profile was clinically manageable with CRS that was generally low grade and primarily in cycle 1
- Observed encouraging antitumor activity in heavily pre-treated patients with mCRPC
  - PSA50 response: 49% (Total) 59% (High-dose)
  - PSA90 response: 28% (Total) 36% (High-dose)
  - RECIST ORR: 24% (Total) 41% (High-dose)
- Dose expansion and optimization is currently ongoing to advance further development of xaluritamig as both a monotherapy and in combination

CRS, cytokine release syndrome; D, day; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; MTD, maximum tolerated dose; ORR, objective response rate; PSA, prostate-specific antigen; QW, weekly; RECIST; Response Evaluation Criteria in Solid Tumors; STEAP1, six transmembrane epithelial antigen of the prostate 1.

HB-301 and HB-302

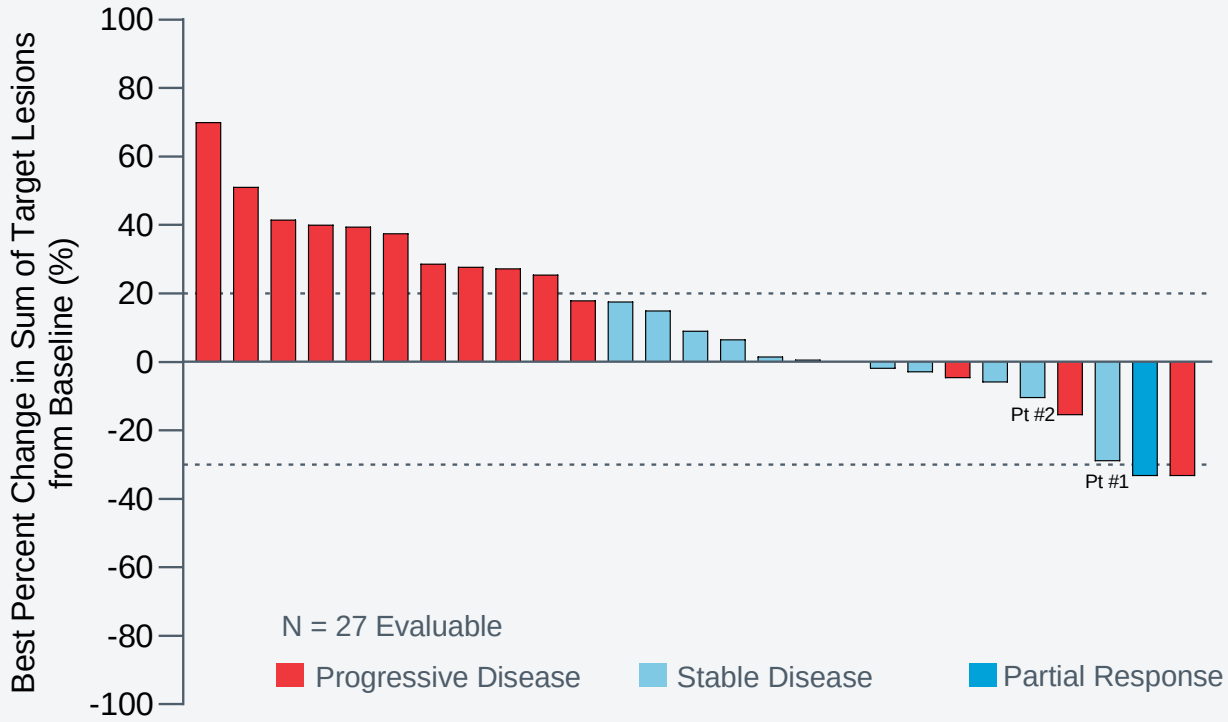
- Arenaviruses are a large family of single-stranded RNA viruses which do not integrate into the human genome.
- HB-301 (LCMV) and HB-302 (PICV) are genetically-engineered replicating arenavirus vectors (non-lytic)
- Encoding a non-oncogenic fusion protein of prostatic acid phosphatase (PAP) and prostate-specific antigen (PSA)
- Induce, activate, and migrate antigen-specific cytotoxic CD8+ T cells to tumor

Tumor response in patients with HNSCC treated with HB-200 at the RP2D or RP2D-1

SITC 2023

- 29 (ITT) patients with HPV16+ HNSCC treated at the RP2D and RP2D-1 of HB-200 alternating 2-vector monotherapy:
  - 27 evaluable (≥ 1 tumor efficacy scan):
    - DCR 44% (1 confirmed PR, 11 SD)
    - 33% had tumor shrinkage in the target lesions.
  - OS data is still maturing with mOS approximately 13 mo and median follow-up time of 6.3 months for the 29 patients as of August 7, 2023.
  - Two patients (patient #1 and #2) had paired biopsies available.

Best percent change in sum of target lesions and overall response per RECIST v1.1



Data cutoff date: August 7, 2023

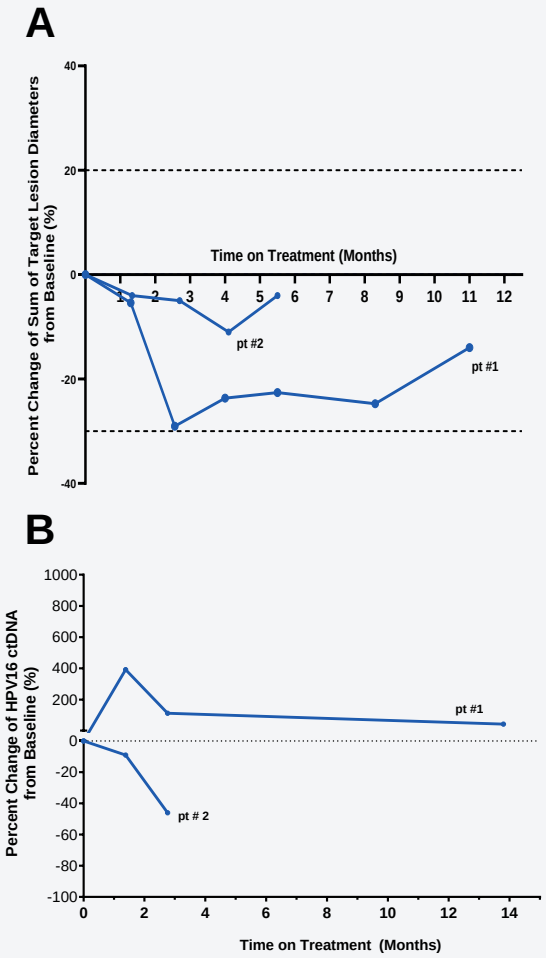
Wong, et al, SITC,2023 abstr #679

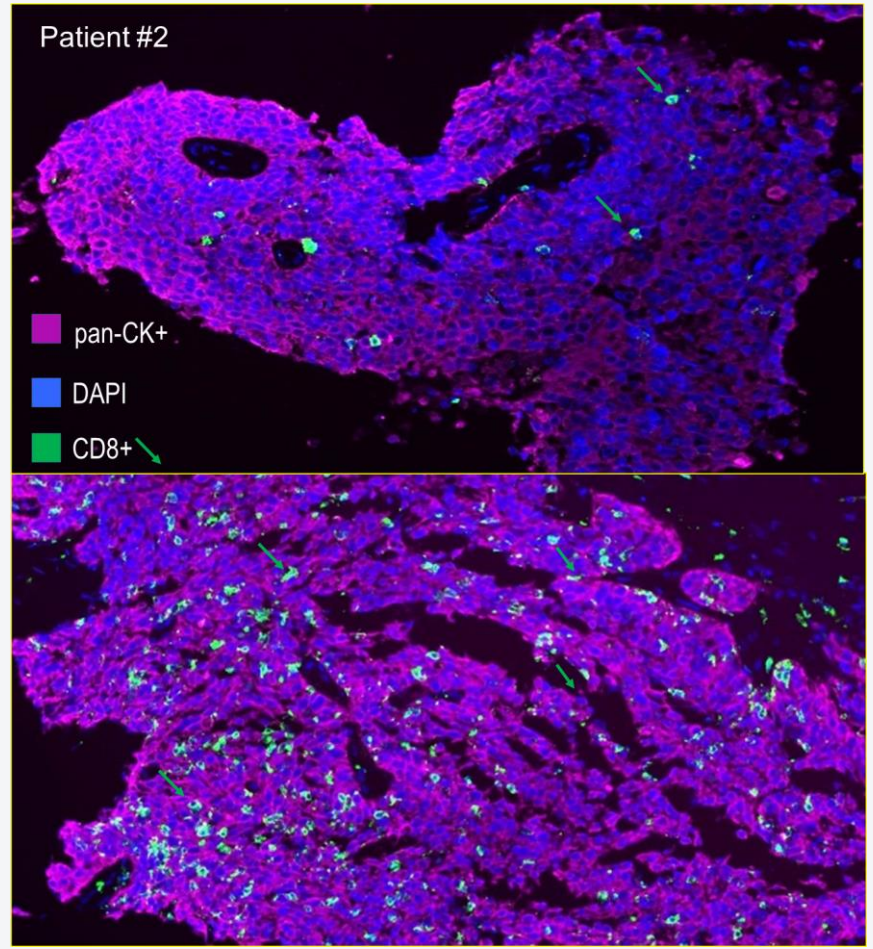
Association of T cell response with best overall response in patients with paired biopsies

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

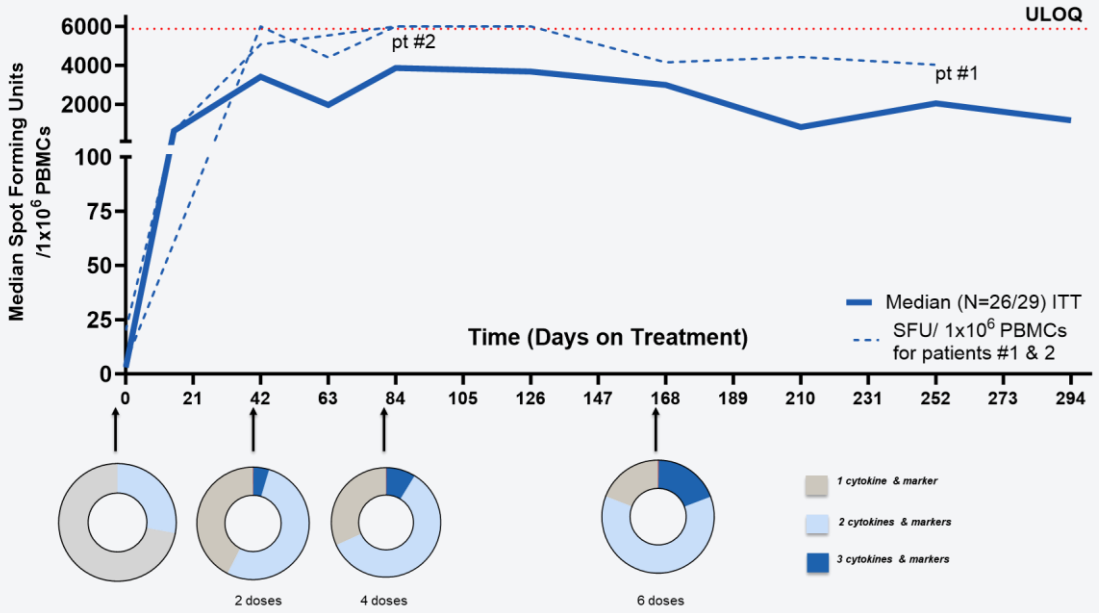
HB-200 achieved rapid induction of functional and long-lasting CD8+ T cell responses & association of tumor-infiltrating CD8+ T cells with BOR

SITC 2023

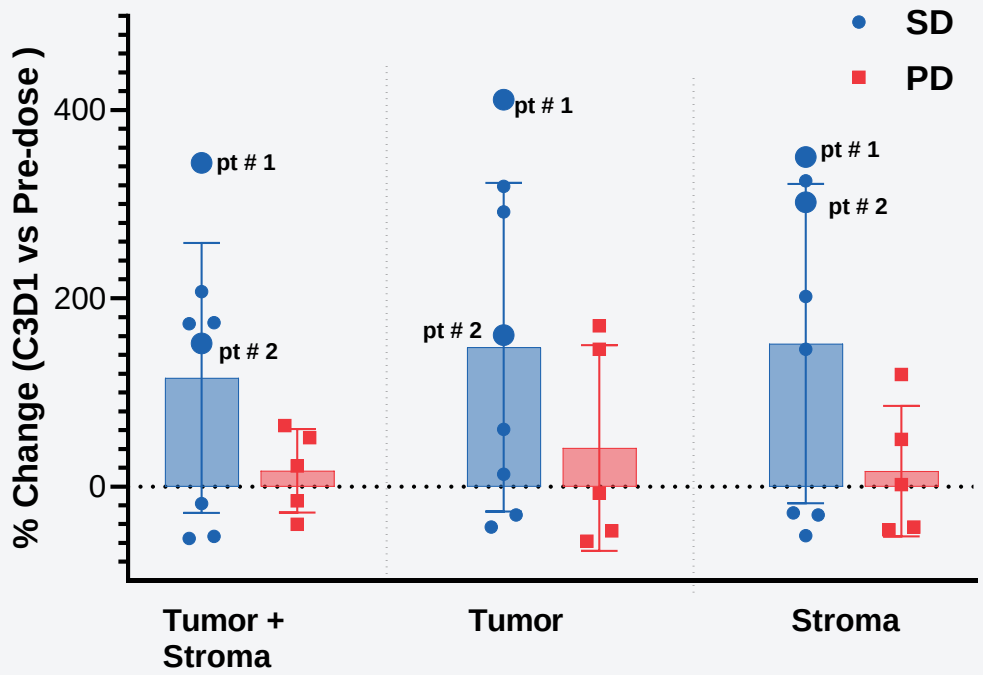
Durability and functionality of tumor-specific CD8+ T cells (N = 35/41 HNSCC patients receiving HB-200 and infiltration of CD8+ T cells in tumors upon therapy in patients with paired biopsies (N = 13 tested out of 93 patients in Phase 1):

- Results showed rapid induction of tumor-specific T cells, sustained for more than 8 months and increasing in polyfunctionality during treatment **(A)**.
- Patients with increased CD8+ T cell influx in tumors during HB-200 treatment tended to show clinical benefit (stable disease vs. progressive disease) **(B)**.

A



B



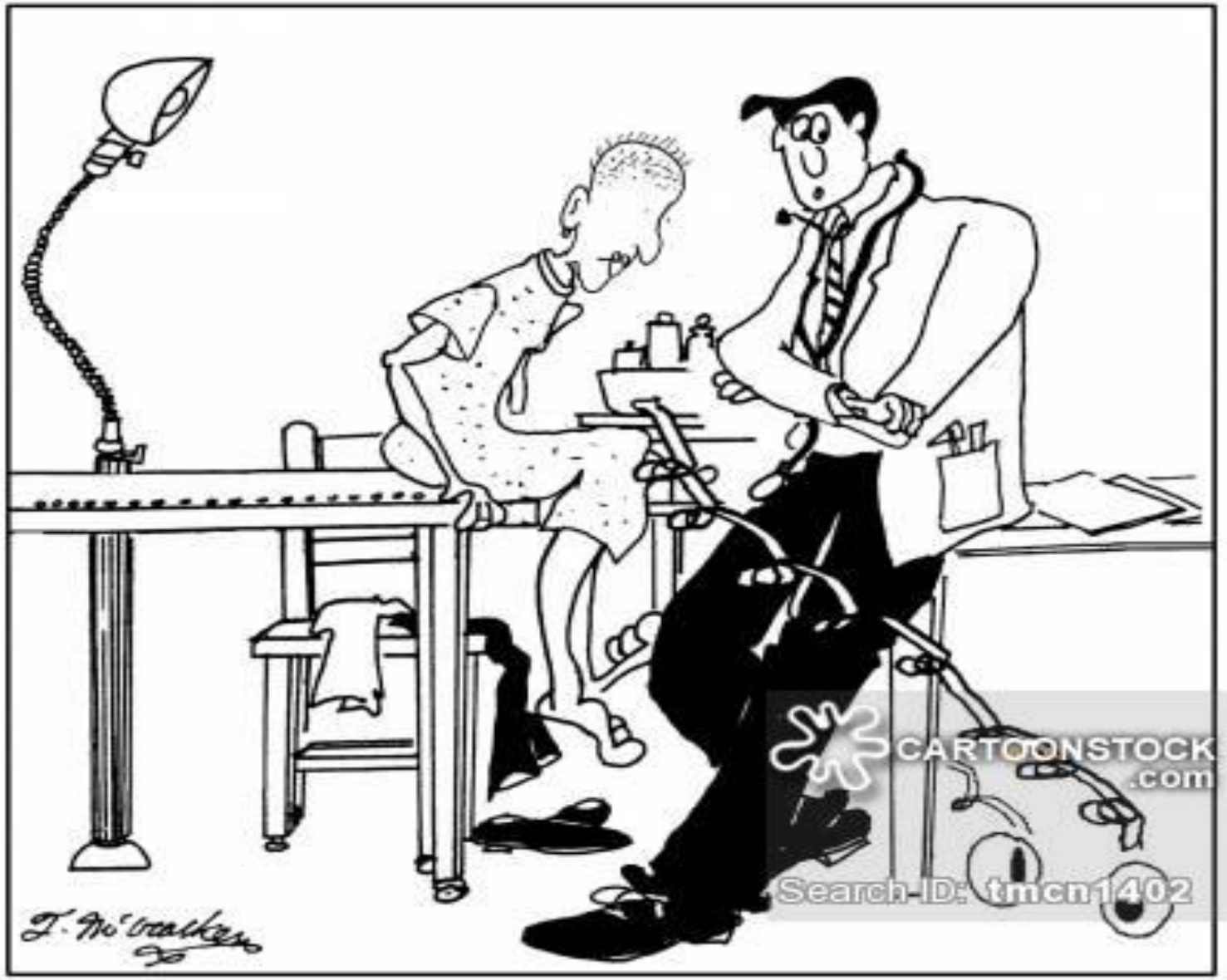
Wong, et al, SITC,2023 abstr #679

What about combinations of immune checkpoint inhibitor (ICI) combos?

- *Multiple industry-sponsored trials have **not** shown efficacy when ICIs are used in combination with androgen-receptor signaling inhibitors (enzalutamide), or with docetaxel*
- **Phase III KEYNOTE-641**: Enza + pembro vs placebo + Enza
- 1244 pts with mCRPC failed to meet dual 1^0 endpoints of rPFS, OS (Graff, et, al ESMO 2023, Abstr #1771MO)
- Modest increased in CRR with pembro + enza vs placebo + enza (7.54% vs 2.7%, respectively); no significant impact on **rPFS** (**median 10.4 mo vs 9 mos**) or **OS** (**median 24.7 mo vs 27.3 mo**).
- Increase incidence of TRAES with pembro c/w placebo + Enza
- Some pts with clinical benefit; likely to have MMR deficiency or microsatellite instability
- Still a need to identify those pts who are likely to derive benefit.

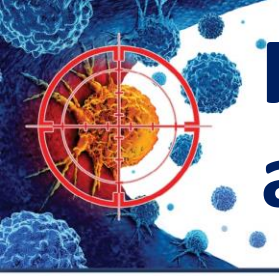
Does the clinical state make a difference in terms of sensitivity to immune combos?

- **KEYNOTE 991**- 1251 pts with mHSPC (Gratze, et al, ESMO 2023, Abstr 1772M0)
- Failed to reach primary endpoint of rPFS
- Increased in TRAES also observed
- Early trial termination
- **PROSTRATEGY** (Arranz, et al, ESMO 2023, Abstr 1783P)
- Hypothesis based on premise that ADT increases immune infiltration in tumors that are enhanced by enza or docetaxel.
- 150 pts with high volume mHSPC
- Ipi and/or Nivo + ADT + docetaxel
- Median f/u of 32.5 mo, no significant decreases in efficacy, rPFS, clinical PFS an OS between arms



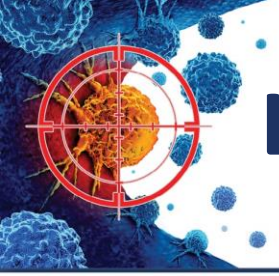
"Oh dear. Your immune system doesn't recognize your eyes."

The checkpoints and autoimmunity???



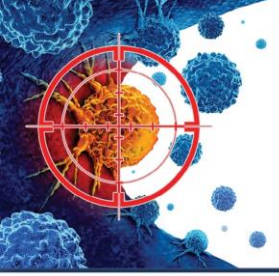
Future development strategies to assess biologic activities…

- Immunologic changes should correspond with a change in the biology of the tumor! **Yes**
- Need for companion diagnostics; how to best integrate functional imaging to assess biologic changes. **Yes**
- How to assess “response” in functional imaging? **Ongoing**
- Are there true immunologic response criteria? **Yes/no/maybe**
- Combinations; is rationale always clear or is it mix and match? **NO!**
- the optimal combination of costimulatory domains for CAR development may need a case by case evaluated evaluation. **Yes**
- Can we safely retreat? **Yes**



Lastly…

- Using immune therapies may not always be appropriate as first line treatment except for certain cancers, ie, urothelial and renal
- Unless MSI^{hi} no role for front line immunotherapy in prostate cancer
- Importance of profiling all tumors from diagnosis to advanced disease
- Immune signatures do exist but may not correlate with biologic behavior



Thank you!