CAR T Prostate Cancer Trials

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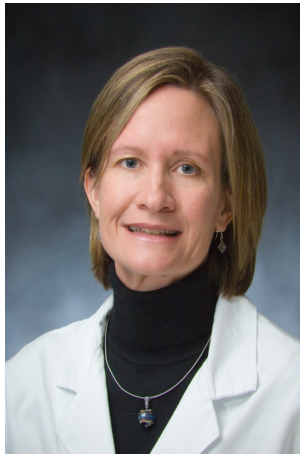
CART PSMA-TGFβRDN Team



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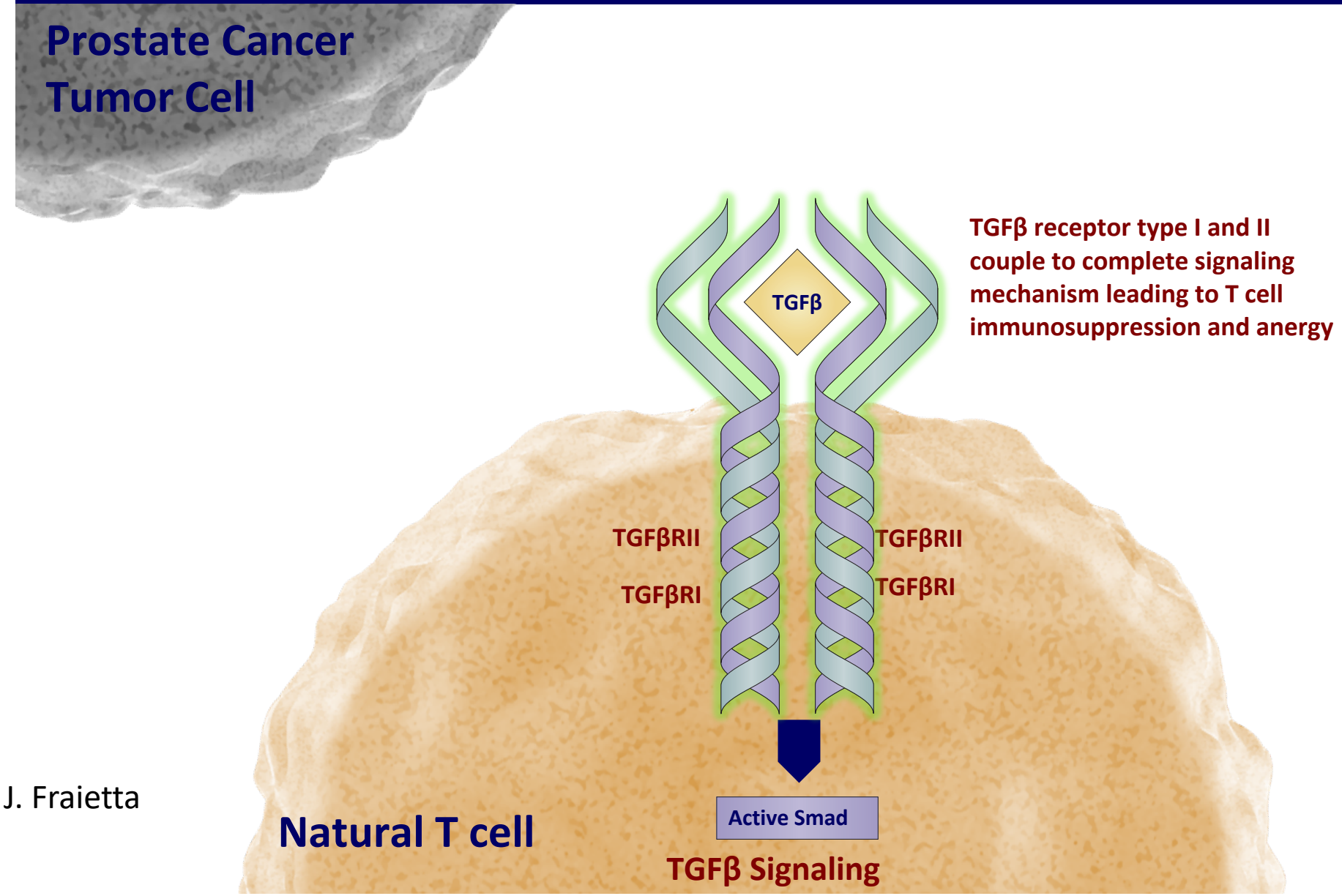
Prostate cancer CAR T trials in perspective

- First PSMA CART trial in CRPC (NCT01140373) used conditioning regimen cyclophosphamide one day prior to CART 1 x 10^7 up to 3 x 10^7 CAR+ T cells/kg with with increased levels of IL-4, IL-8, IP-10, sIL-2ra and IL-6 (https://ascopubs.org/doi/abs/10.1200/jco.2013.31.15_suppl.tps3115)

Key differentiator: TGFβ (Transforming growth factor beta)

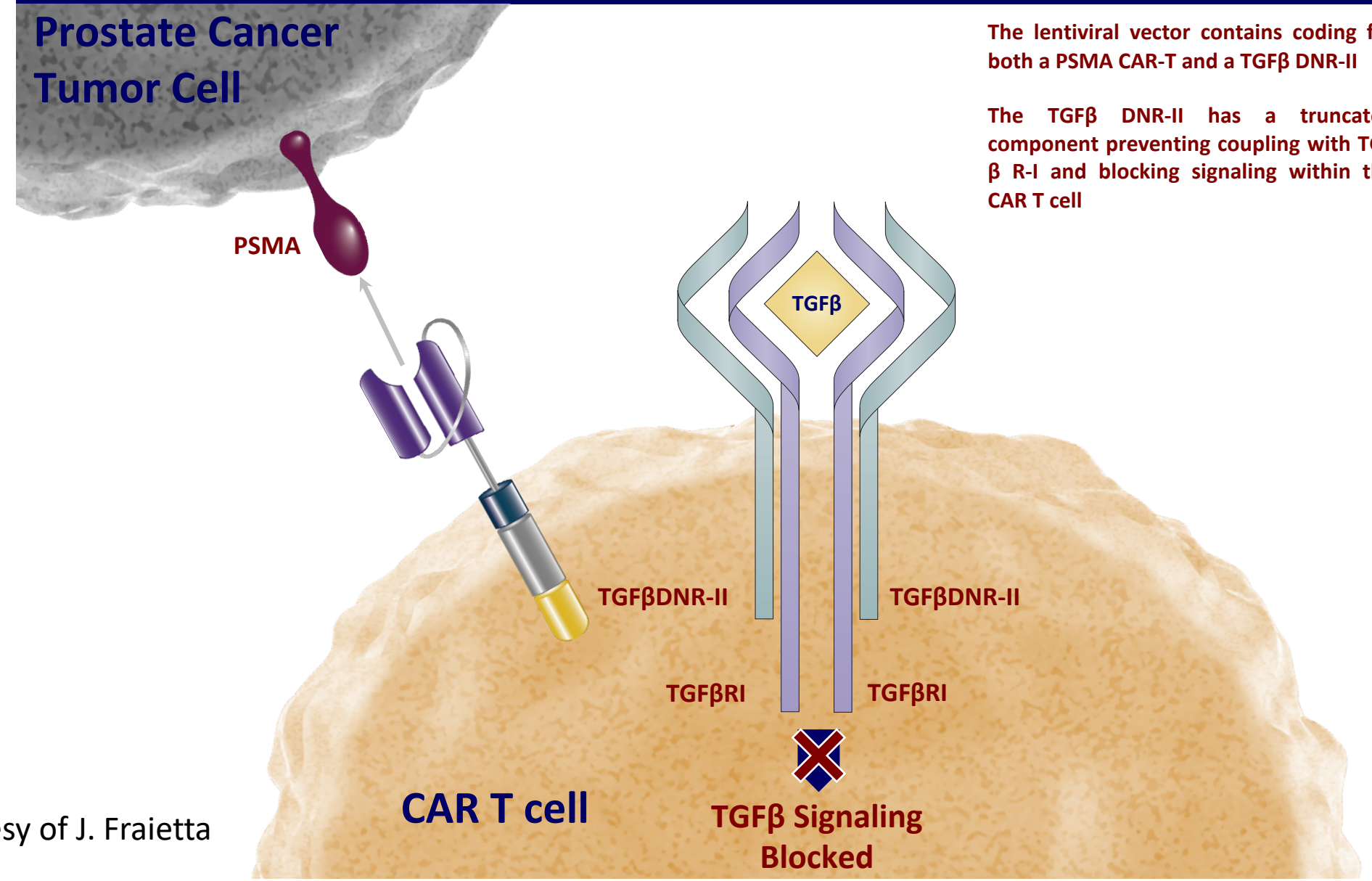
A Potent Immunosuppressor of T cells Expressed in Prostate Cancer Tumor Microenvironment



Courtesy of J. Fraietta

Key differentiator: TGFβ (Transforming growth factor beta)

A potent immunosuppressor of T cells expressed in prostate cancer tumor microenvironment



The lentiviral vector contains coding for both a PSMA CAR-T and a TGFβ DNR-II

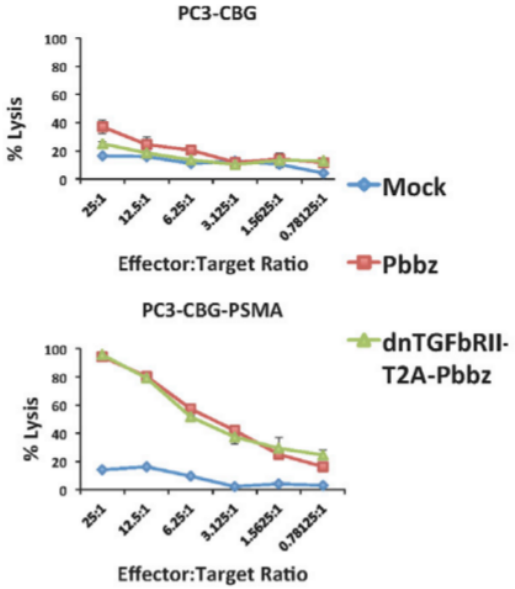
The TGFβ DNR-II has a truncated component preventing coupling with TGF β R-I and blocking signaling within the CAR T cell

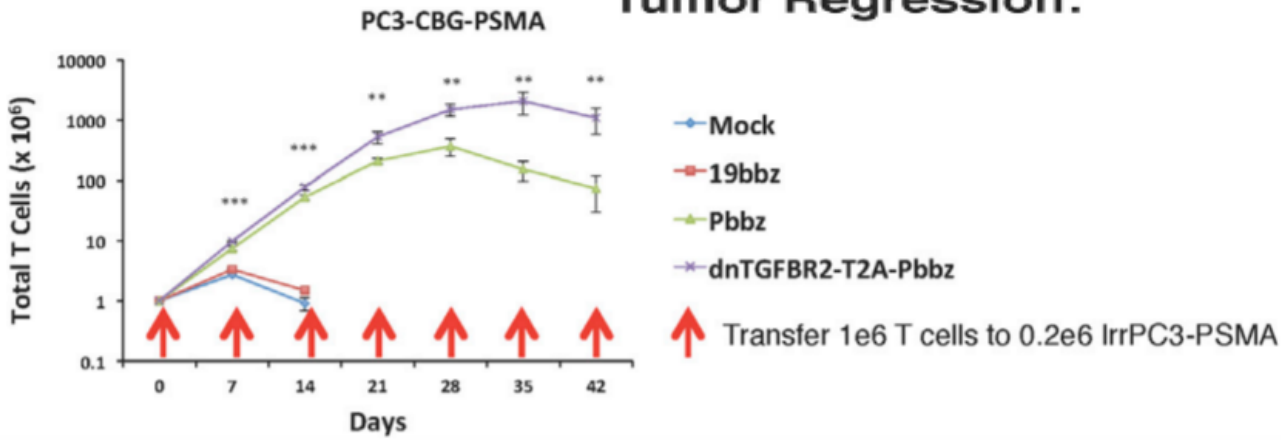
Courtesy of J. Fraietta

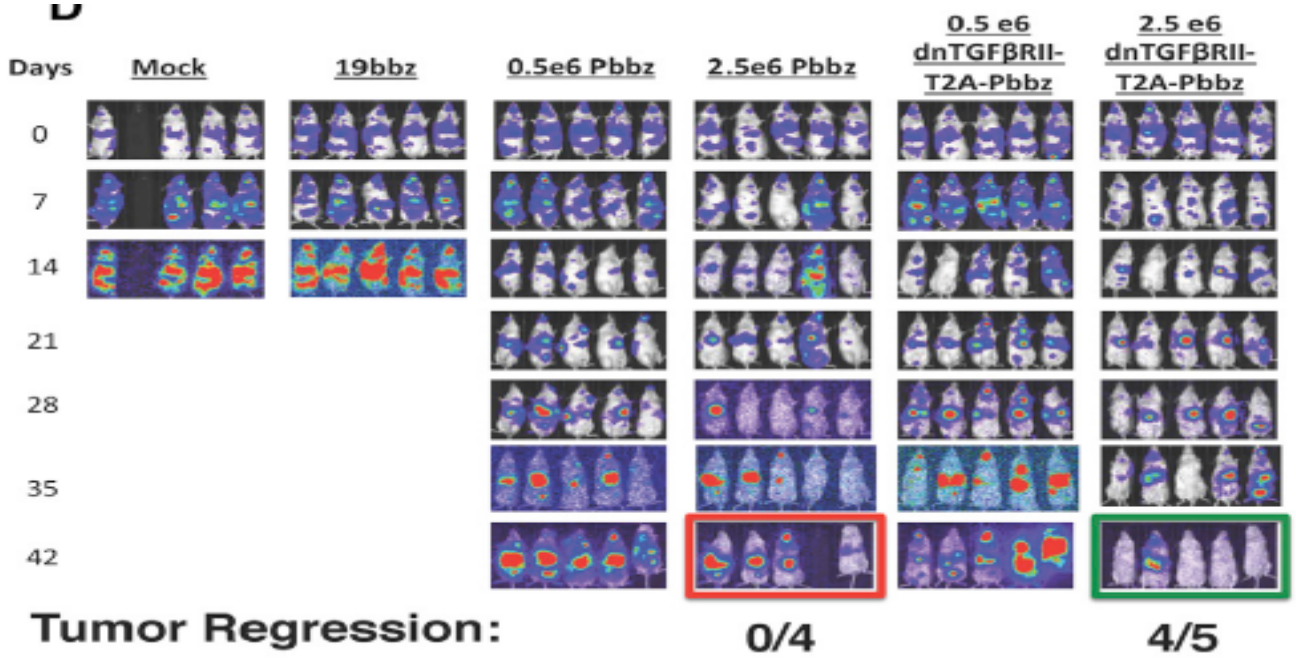
Molecular Therapy
Original Article

Dominant-Negative TGF-β Receptor Enhances PSMA-Targeted Human CAR T Cell Proliferation And Augments Prostate Cancer Eradication

Christopher C. Kloss,[1,4] Jihyun Lee,[1,5] Aaron Zhang,[1] Fang Chen,[1] Jan Joseph Melenhorst,[1,2,3] Simon F. Lacey,[1] Marcela V. Maus,[1,6] Joseph A. Fraietta,[1,2,3] Yangbing Zhao,[1,2] and Carl H. June[1,2,3,4]







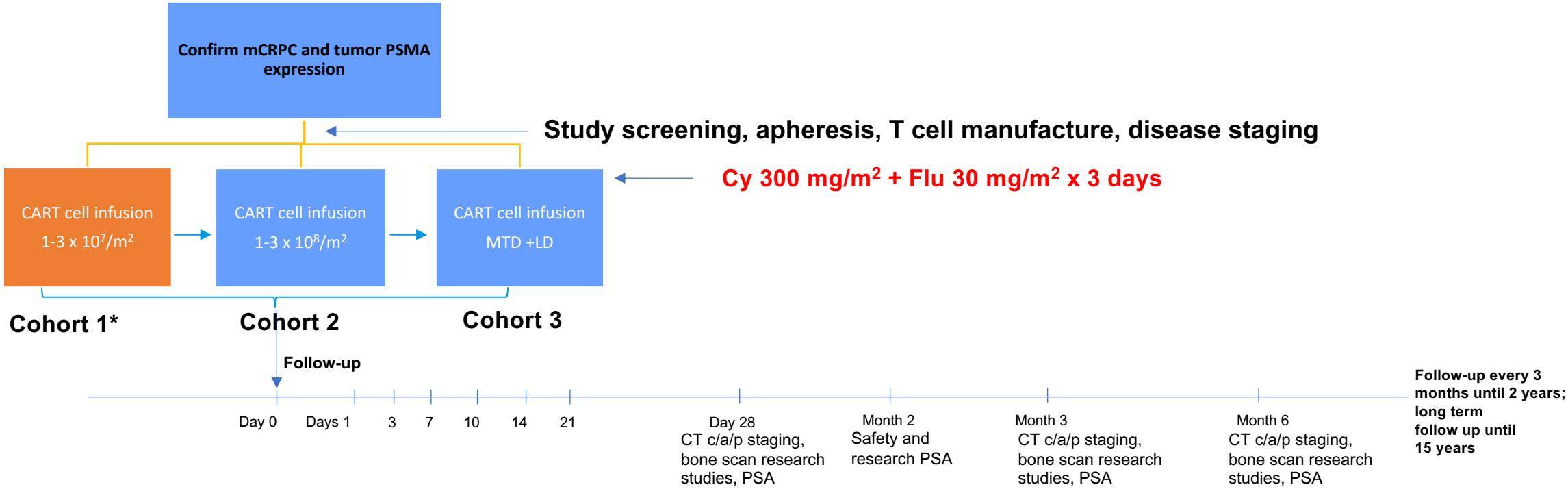
Kloss, C…June, C. *Mol Ther*. 26(7) 1855-1866. 2018.

CART-PSMA-TGFβRDN Schema:

Lentivirally-transduced modified T cell expressing PSMA CAR and TGFβ dominant negative receptor transgene

scFv derived from the J591 antibody

3+3 dose escalation design



*** Enrollment follows in succession from Cohort 1 to Cohort 3**

Key eligibility

- Metastatic Castration Resistant Prostate Cancer (measurable or bony-only)
- ≥ 10% tumor cells expressing PSMA by IHC analysis on fresh tissue
- ECOG Performance Status 0-1
- Evidence of disease progression per PCWG2 criteria
- Prior therapy with at least one standard 17α lyase inhibitor

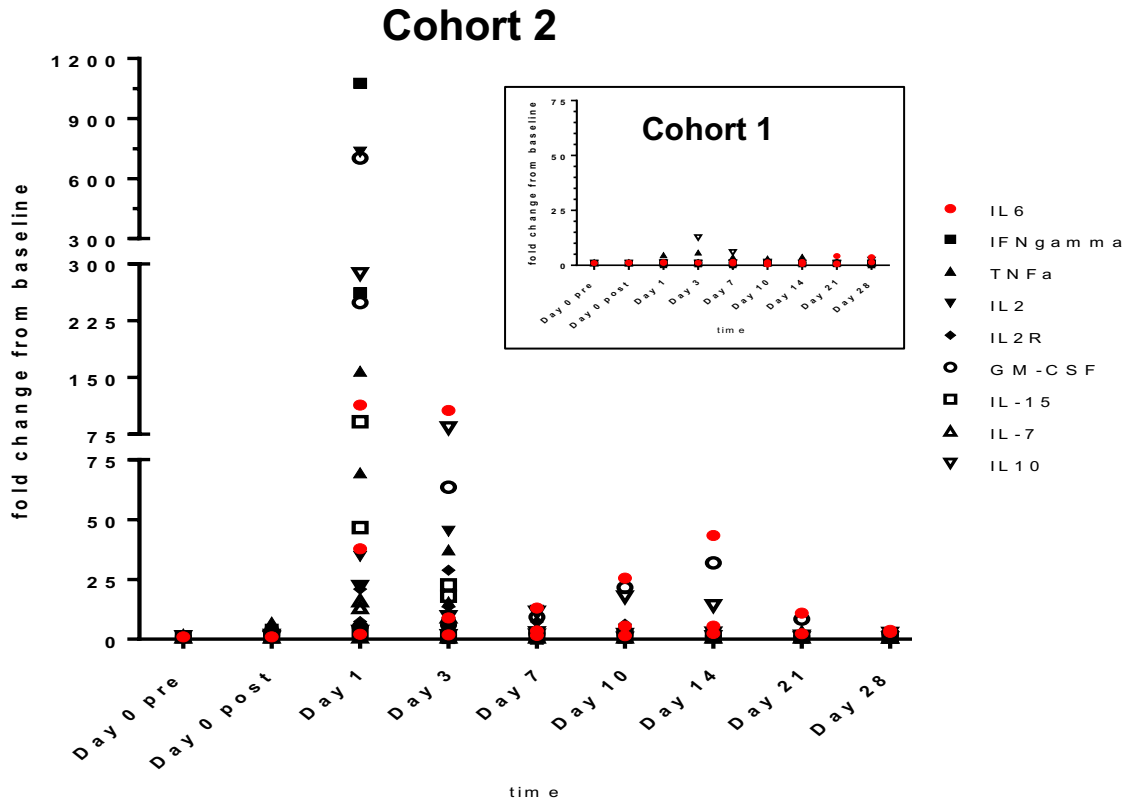
or second-generation anti-androgen therapy for CRPC

ClinicalTrials.gov Identifier: NCT03089203. PI: N. Haas.

Summary of Initial Cohorts (without LD chemotherapy)

- No evidence of CAR T cell activity in Cohort 1
  - No related Adverse Events
  - Little cytokine activity (Figure Inset)

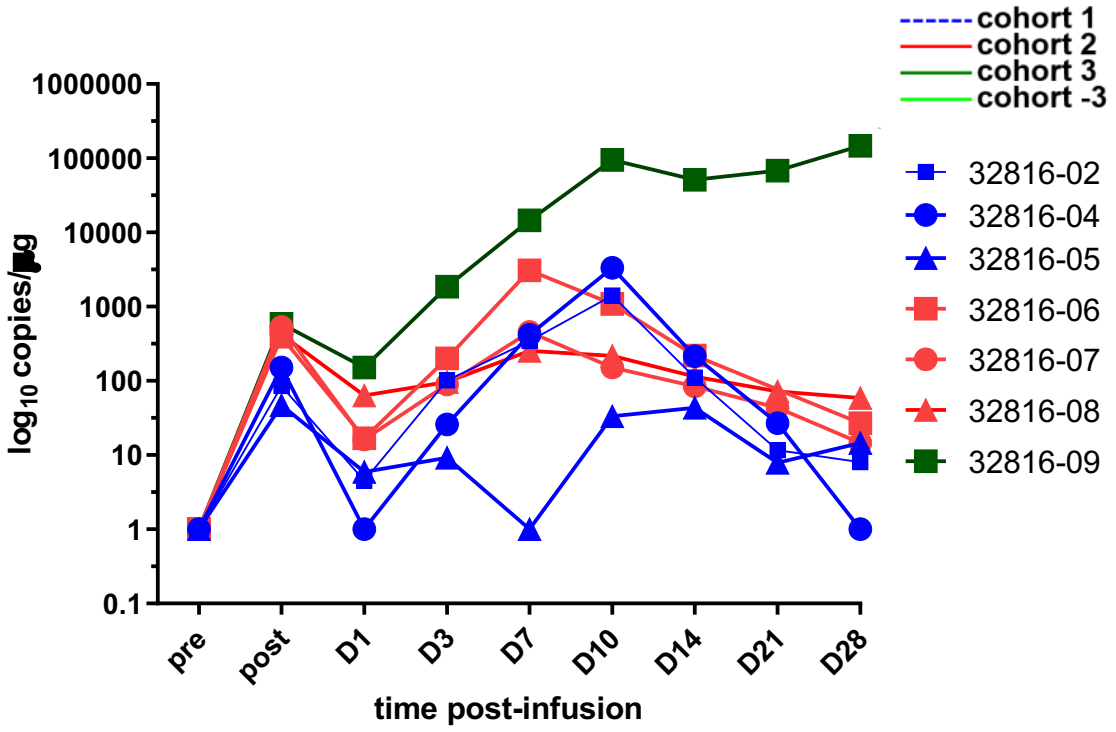
- Evidence of anti-tumor CAR T cell activity in Cohort 2
  - Grade 3 CRS within hours of CAR T cell infusion
  - Adverse events were reversible
  - Robust cytokine activity in patients with Gr3 CRS
  - First indications of CRS in solid tumor patients

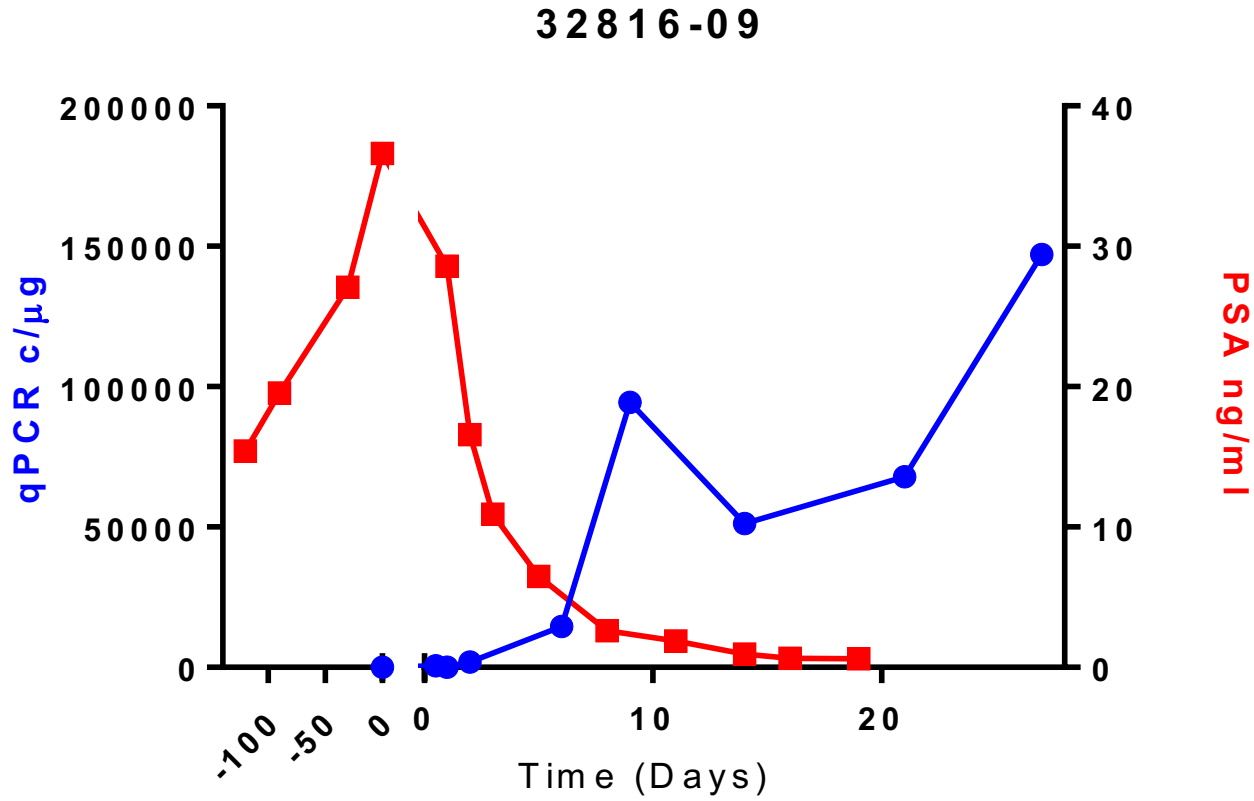


Conclusions:

- **CART-PSMA-TGFβRDN cells are safe at $3x10^8/m^2$ CAR+ cells without conditioning chemotherapy.**
- **There is a dose dependent relationship with cytokine detection.**

Dose- and LD Chemo-Dependent CAR T Cell Expansion in Peripheral Blood

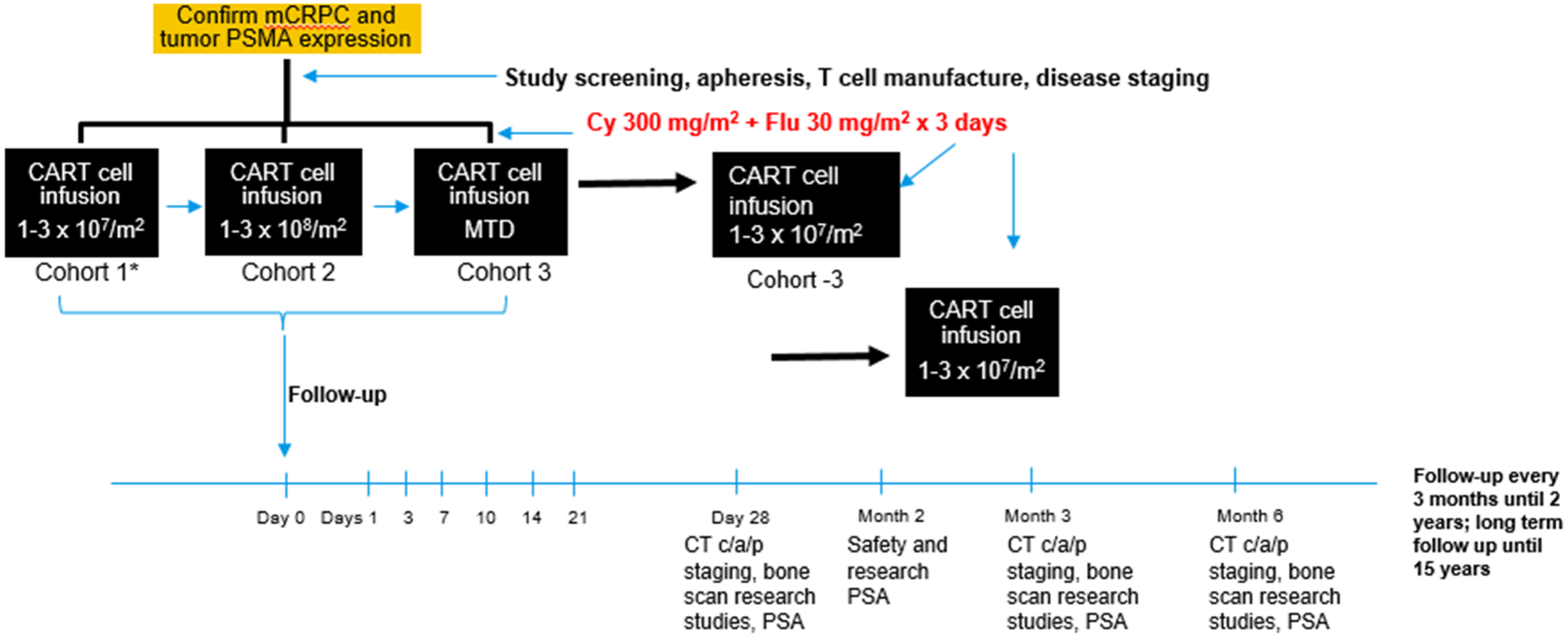




Correlation between CART-PSMA-TGFβRDN expansion and PSA reduction

Revised Study Schema

CART-PSMA-TGFβRDN:
Lentivirally-transduced modified T cell expressing PSMA CAR and TGFβ dominant negative receptor transgene
scFv derived from the J591 antibody
3+3 dose escalation design

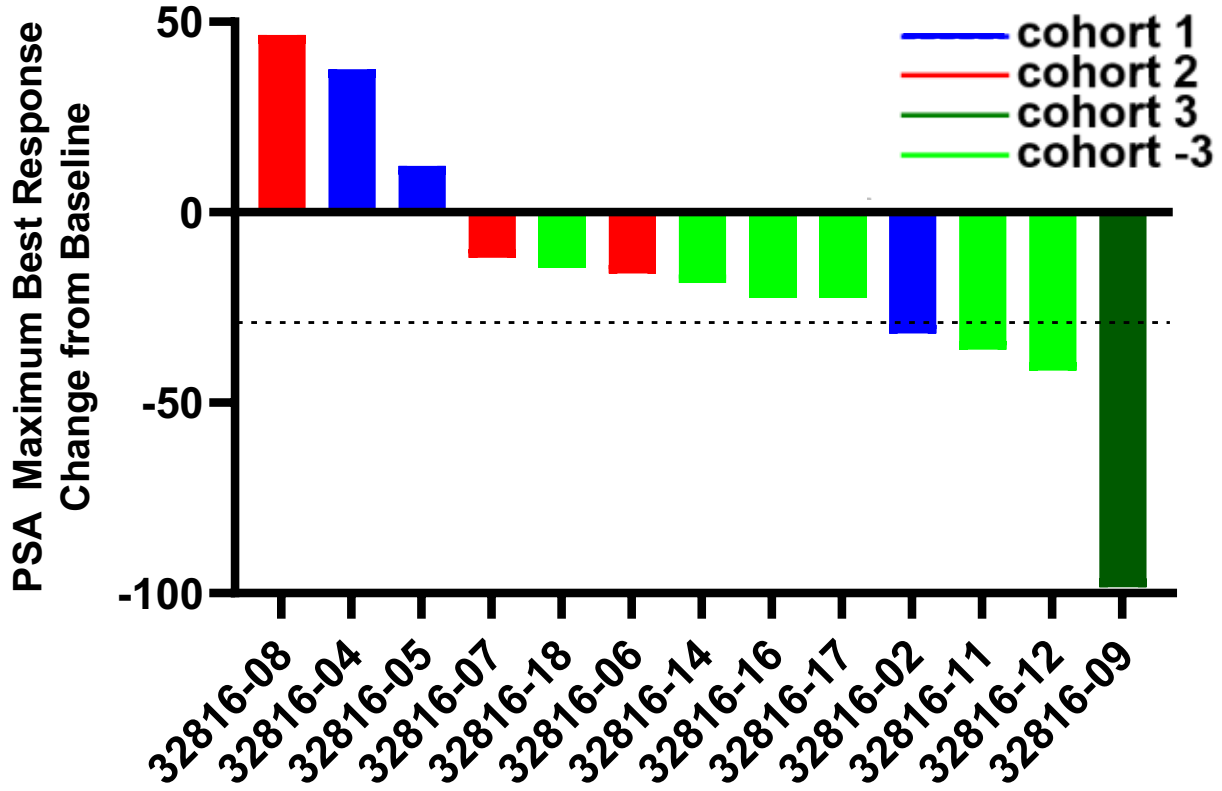


ClinicalTrials.gov Identifier: NCT03089203. PI: N. Haas.

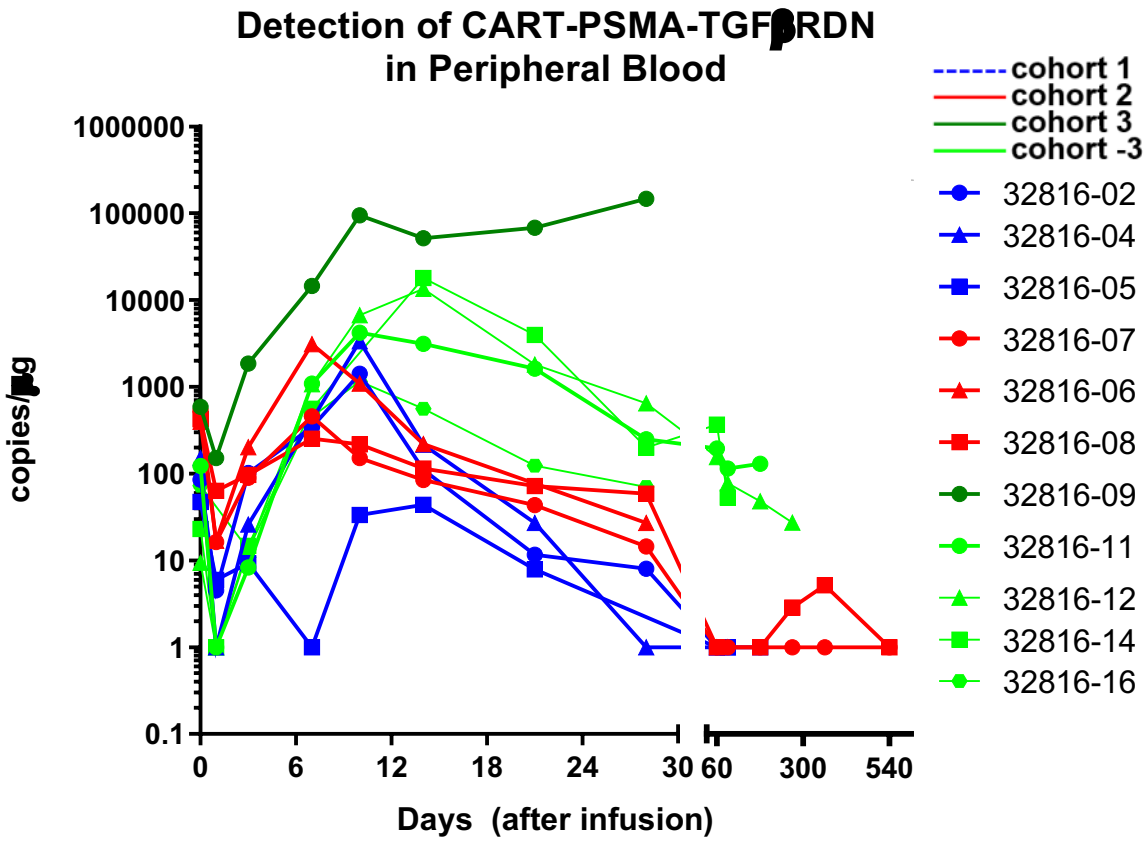
Phase I CART-PSMA-TGFβRDN Toxicity

Cohort	Dose (n=#)	Toxicity
1	$3x10^{7}/m^{2}$ (n=3)	1 Gr3 unrelated hip fracture 1 Gr4 hematuria
2	$3x\ 10^{8}/m^{2}$ (n=3)	7 Gr3 events including encephalopathy, CRS, hypotension and AKI 1 Gr4 hypotension
3	$3x10^{8}/m^{2}$ +LD (n=1)	1Gr5 with Gr4 hypotension, CRS, AKI with recovery and later sepsis
-3	$3x10^{7}/m^{2}$+LD (n=6)	4 Gr3 including CRS, hypoxia and SIADH

Preliminary Evidence for Dose-Dependent and LD-Chemo Dependent Anti-Tumor Response



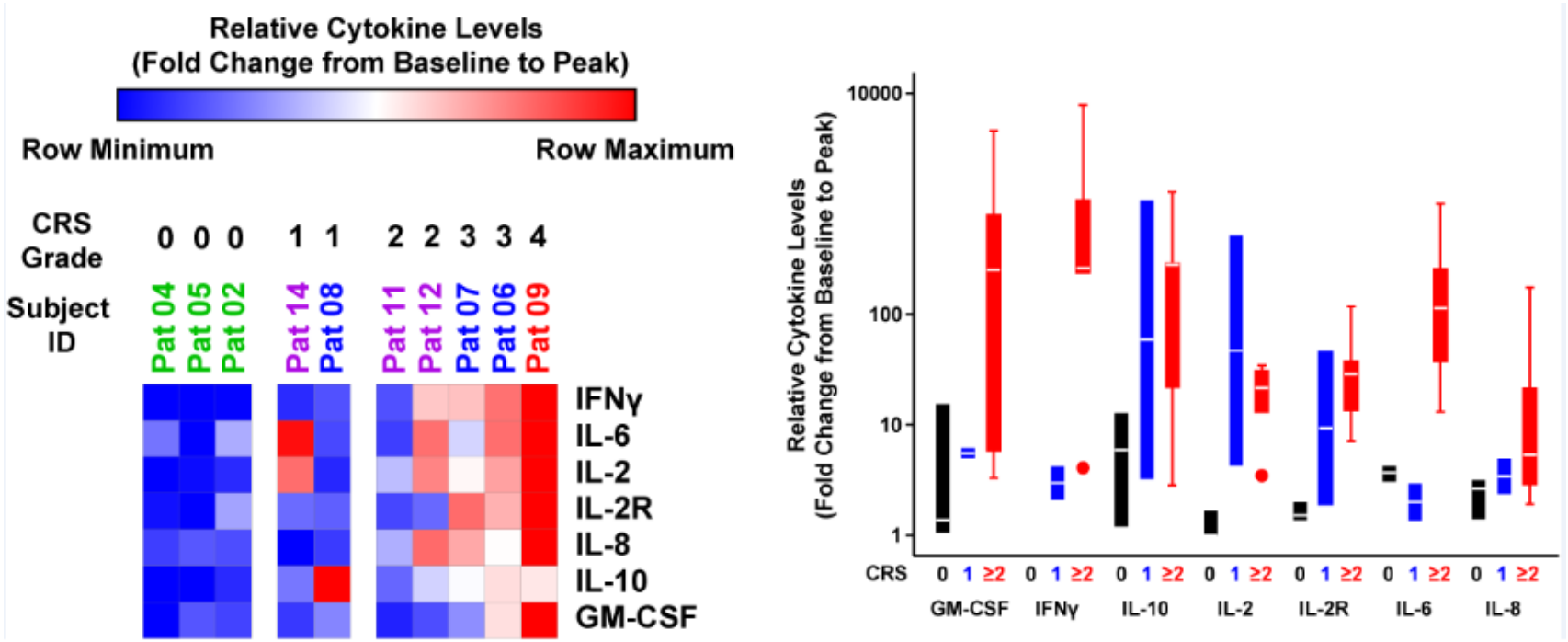
CART-PSMA-TGFbRDN Cell Engraftment (qPCR in peripheral blood)



CAR-T peak expansion increased with dose-escalation and incorporation of Cy / Flu LD chemotherapy

Courtesy S. Lacey

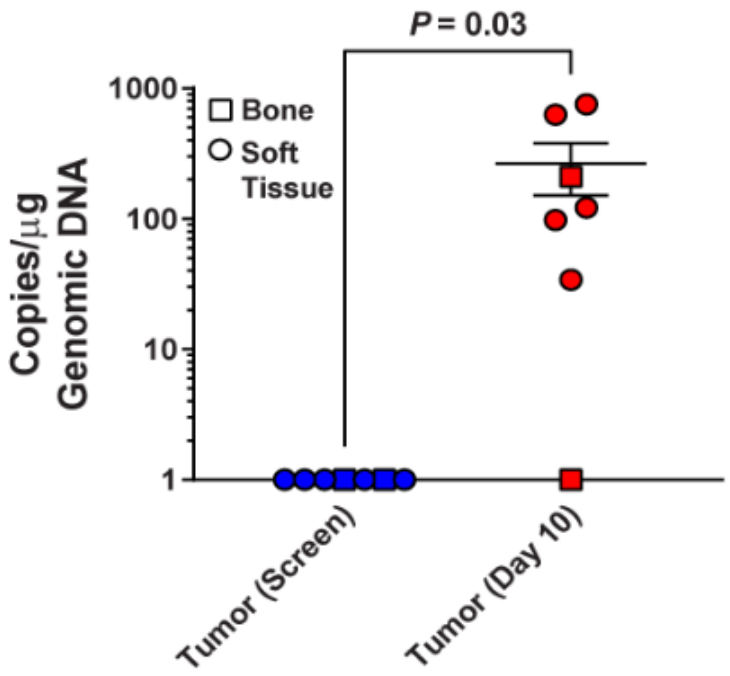
Peak Fold-Change in Pro-Inflammatory Cytokine Production

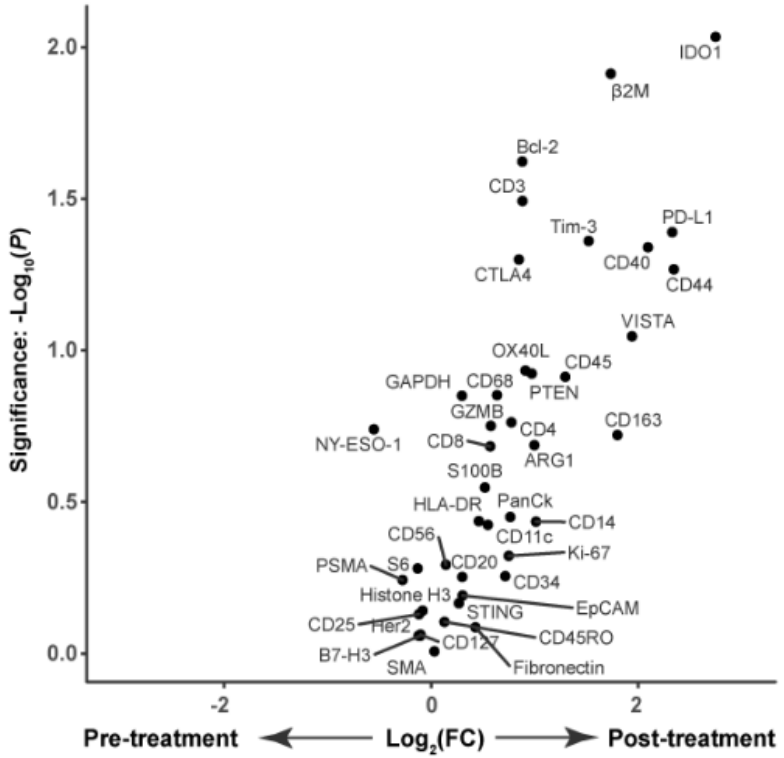


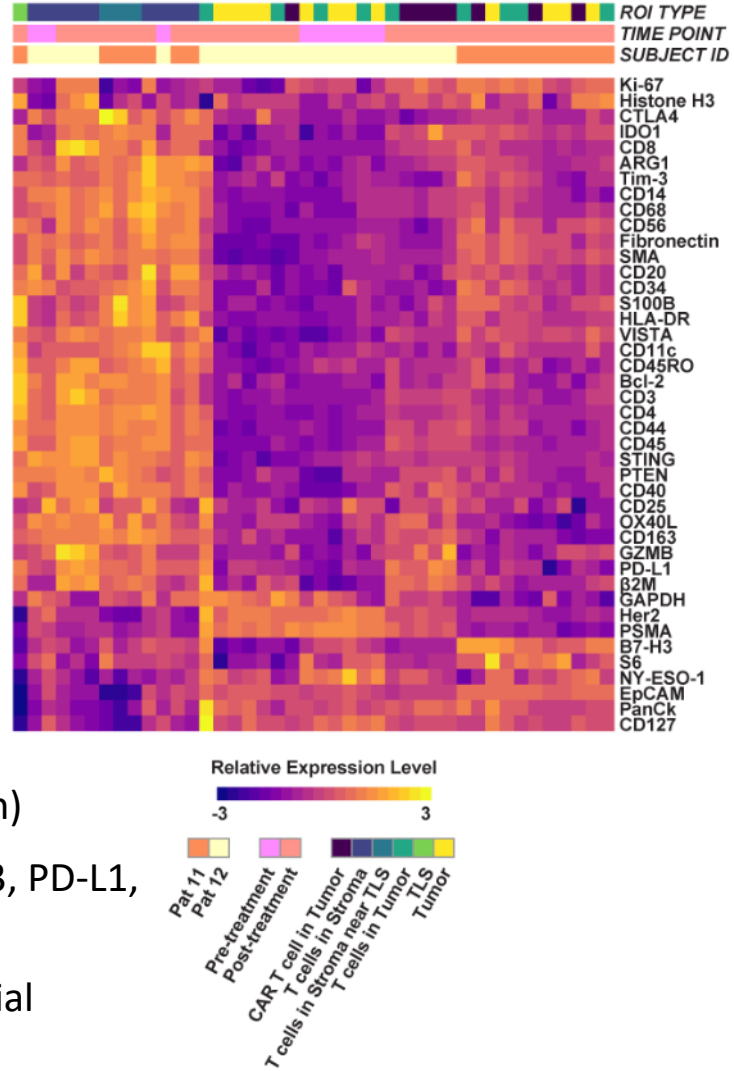
- Higher grade CRS was associated with a greater magnitude of fold change in pro-inflammatory analytes post-infusion.

Courtesy J Barber-Rotenberg

Tumor Trafficking and Tumor Microenvironment







- Observed tumor tissue trafficking in 6 of 7 available metastatic biopsies (~10 days post-infusion)
- Protein-based DSP analyses of TME: Increased expression of inhibitory molecules (IDO1, Tim-3, PD-L1, CTLA-4, VISTA) within T cell-rich regions
- Preliminary anti-tumor effector functions are accompanied by upregulation of multiple potential immunosuppressive resistance mechanisms within the TME

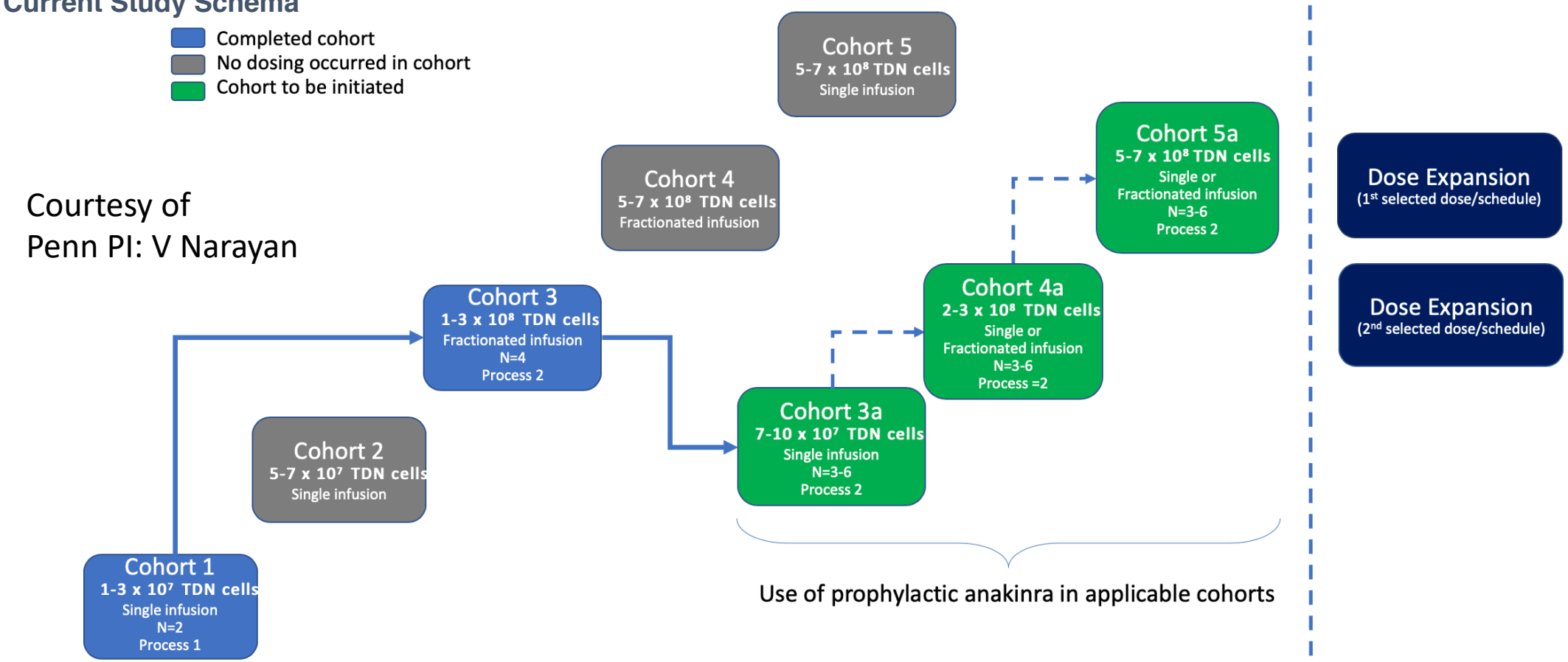
Courtesy J. Fraietta

Conclusions

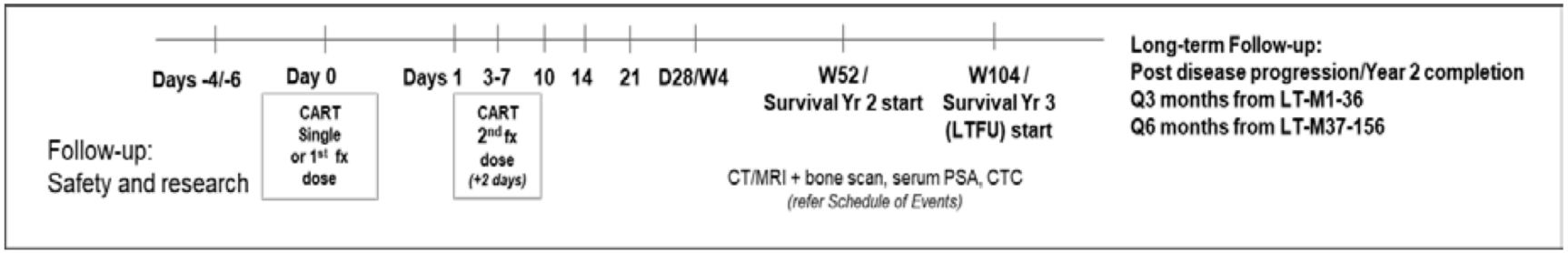
- PSMA TGFβRDN CART (NCT03089203) is feasible and safe at current dosing
- Response is dose dependent and enhanced with lymphodepletion
- Serial dosing is likely to be safe and more effective
- Accrual to other solid tumor types planned using this CART
- Nanostring T cell sequencing, CTC, cytokine, and CART trafficking analysis are all ongoing.
- Phase I/II Multi-Center Industry Trial (NCT04227275) using serial dosing is ongoing

CART-PSMA-TGFβRDN-02: A Phase 1 Open-Label Multi-Center Study of PSMA Targeted Genetically Modified Chimeric Antigen Receptor T-cells in Patients with Metastatic Castration Resistant Prostate Cancer

Current Study Schema



Courtesy of
Penn PI: V Narayan

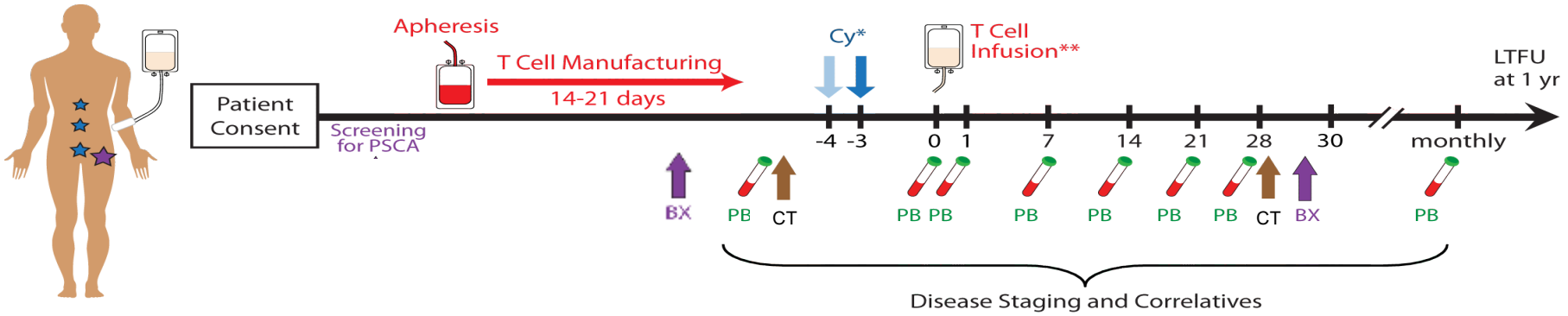


Lymphodepleting Chemotherapy (D-6 to D-4)
- Cyclophosphamide 300 mg/m2 x3-days
- Fludarabine 30 mg/m2 x3-days

TMUNITY

Phase I Clinical Trial to Evaluate PSCA-BBζ CAR T Cells in mCRPC

- **PSCA+ metastatic castration resistant prostate cancer**
  (Clinical PI: Tanya Dorff, MD, Research PI: Saul Priceman, PhD) – enrolling



Cy* = cytoreductive chemotherapy
Bx = biopsy
CT = imaging
PB = peripheral blood

Table 1. CAR+ Cell Dose Schedule				
Dose -1	**Starting Dose 0a**	Dose 0b	Dose 1	Dose 2
50M	**100M**	100M +precond.	300M +precond.	600M + precond.

Prostate Cancer Foundation
Curing Together.

City of Hope