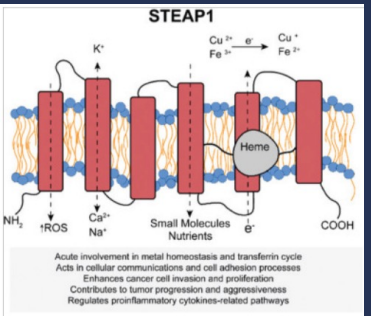
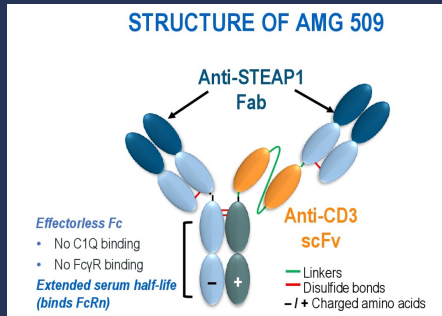
Immunotherapy and BiTe Updates in Prostate Cancer

MLS Cleveland
Precision Medicine and Immunotherapy

April 13, 2024

Leonard J. Appleman MD PhD

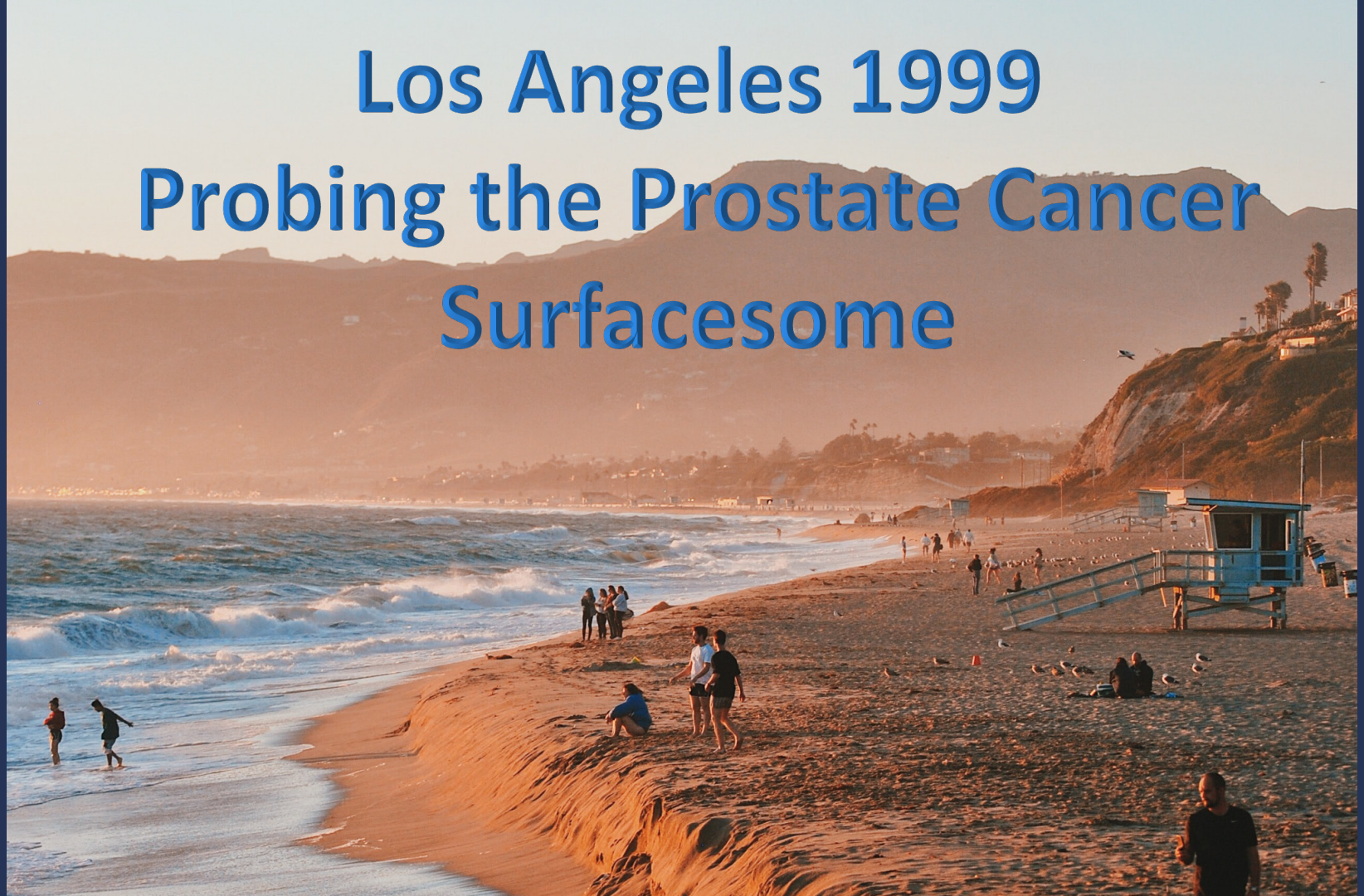


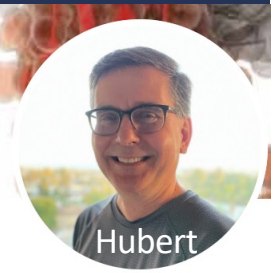


Prostate Cancer- Left behind the immunotherapeutic revolution?

- Limited activity of immune checkpoint inhibitorsin unselected patients
- Sipuleucel-T was first approved immunotherapy for any cancer in 2010, but enthusiasm has waned.
- **Cold tumor?**
  - Low neoantigen load/Tumor mutational burden. MSI rare.
  - TGF-β-rich TME
  - Down-regulated MHC class I

Los Angeles 1999
Probing the Prostate Cancer Surfacesome





STEAP: A prostate-specific cell-surface antigen highly expressed in human prostate tumors

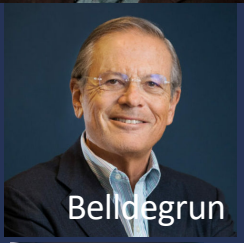
Rene S. Hubert*, Igor Vivanco*, Emily Chen, Shiva Rastegar, Kahan Leong, Steve C. Mitchell, Rashida Madraswala, Yanhong Zhou, James Kuo, Arthur B. Raitano, Aya Jakobovits, Douglas C. Saffran, and Daniel E. H. Afar†

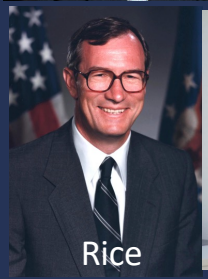
UroGenesys Inc., 1701 Colorado Avenue, Santa Monica, CA 90404

Communicated by Robert N. Eisenman, Fred Hutchinson Cancer Research Center, Seattle, WA, October 13, 1999 (re

Six Transmembrane Epithelial Antigen of Prostate

Suppression subtraction hybridization (SSH) of **LAPC-AD xenograft** (Sawyers) cDNA **vs. BPH**





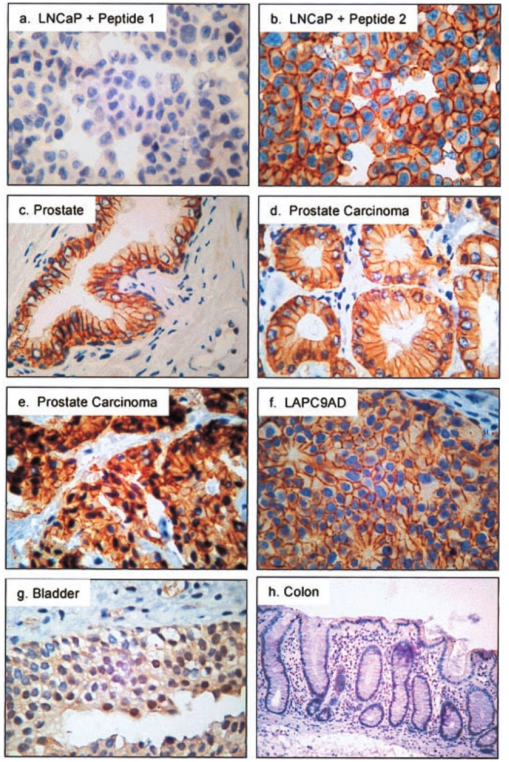
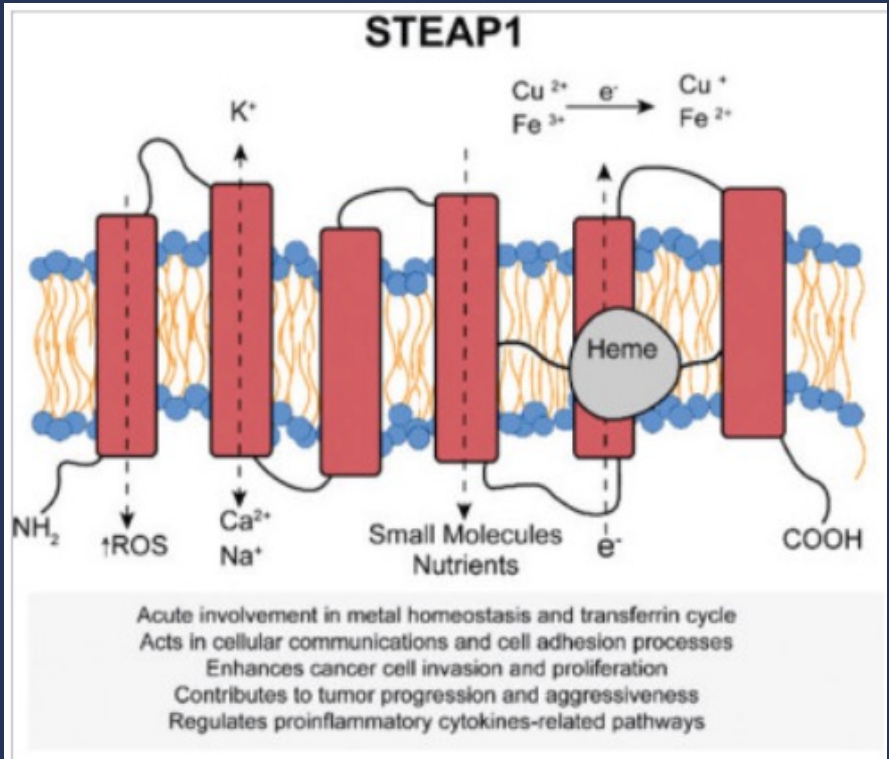


Fig. 4. Immunohistochemical analysis of patient samples with anti-STEAP antibodies. Samples include: LNCaP cells probed in the presence of amino-terminal STEAP peptide 1 (*a*), LNCaP plus nonspecific peptide 2 (*b*), normal prostate tissue (*c*), grade 3 prostate carcinoma (*d*), grade 4 prostate carcinoma (*e*), LAPC-9 AD xenograft (*f*), normal bladder (*g*), and normal colon (*h*). (×400.)

STEAP-1

Six Transmembrane Epithelial Antigen of Prostate



STEAP1-4:

- Metal ion homeostasis
- Reduction of metal ion complexes
- Proliferation
- Invasion
- Apoptosis
- Cell Stress
- Pro-inflammatory
- Associated with ER/Lysosomal compartment

Rocha *et al.* 2021

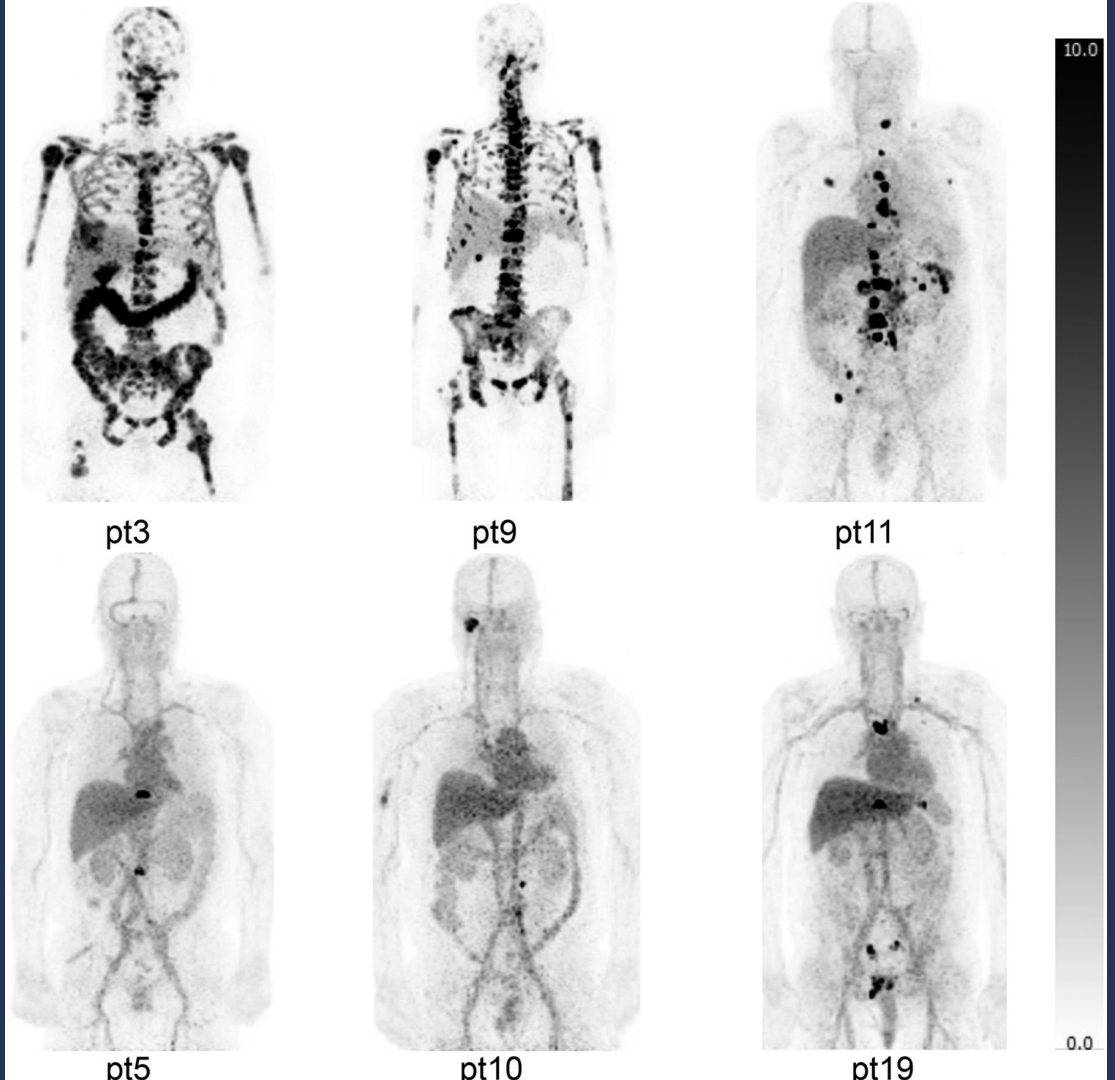
Fast forward 20 years

Imaging Patients with Metastatic Castration-Resistant Prostate Cancer Using ^{89}Zr-DFO-MSTP2109A Anti-STEAP1 Antibody

Jorge A. Carrasquillo[1–3], Bernard M. Fine[4], Neeta Pandit-Taskar[1–3], Steven M. Larson[1–3], Stephen E. Fleming[1], Josef J. Fox[1], Sarah M. Cheal[1], Joseph A. O'Donoghue[5], Shutian Ruan[1], Govind Ragupathi[6], Serge K. Lyashchenko[7], John L. Humm[5], Howard I. Scher[6,8], Mithat Gönen[9], Simon P. Williams[4], Daniel C. Danila*[6,8], and Michael J. Morris*[6,8]

[1]Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, New York; [2]Department of Radiology, Weill Cornell Medical Center, New York, New York; [3]Center for Targeted Radioimmunotherapy and Diagnosis, Ludwig Center for Cancer Immunotherapy, New York, New York; [4]Genentech, South San Francisco, California; [5]Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, New York; [6]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York; [7]Radiochemistry and Molecular Imaging Probes Core, Memorial Sloan Kettering Cancer Center, New York, New York; [8]Joan and Sanford I. Weill Department of Medicine, Weill Cornell Medicine, New York, New York; and [9]Biostatistics Service, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York

J. Nucl. Med 2019



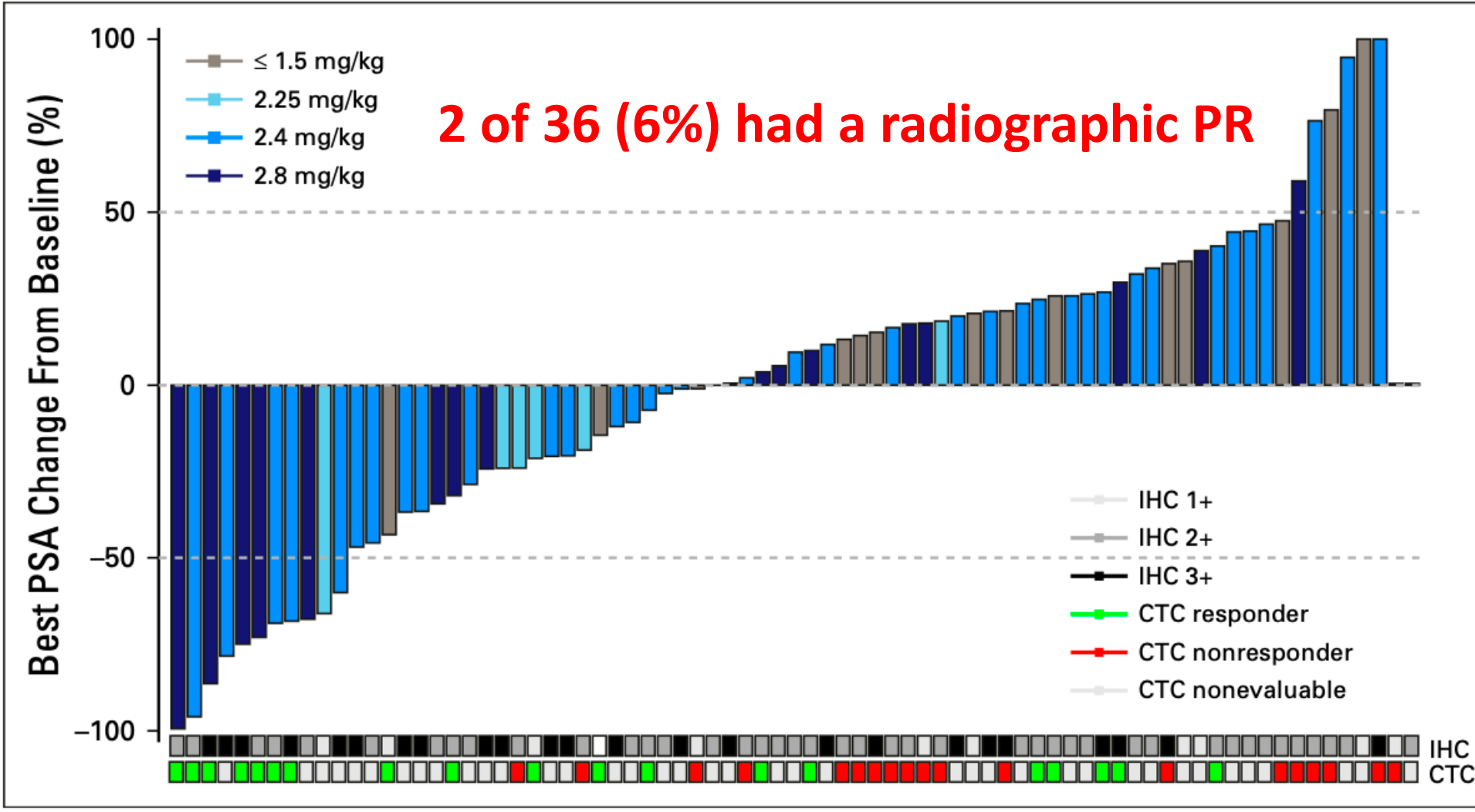
Carrasquillo et al 2019

Phase I Study of DSTP3086S, an Antibody-Drug Conjugate Targeting Six-Transmembrane Epithelial Antigen of Prostate 1, in Metastatic Castration-Resistant Prostate Cancer

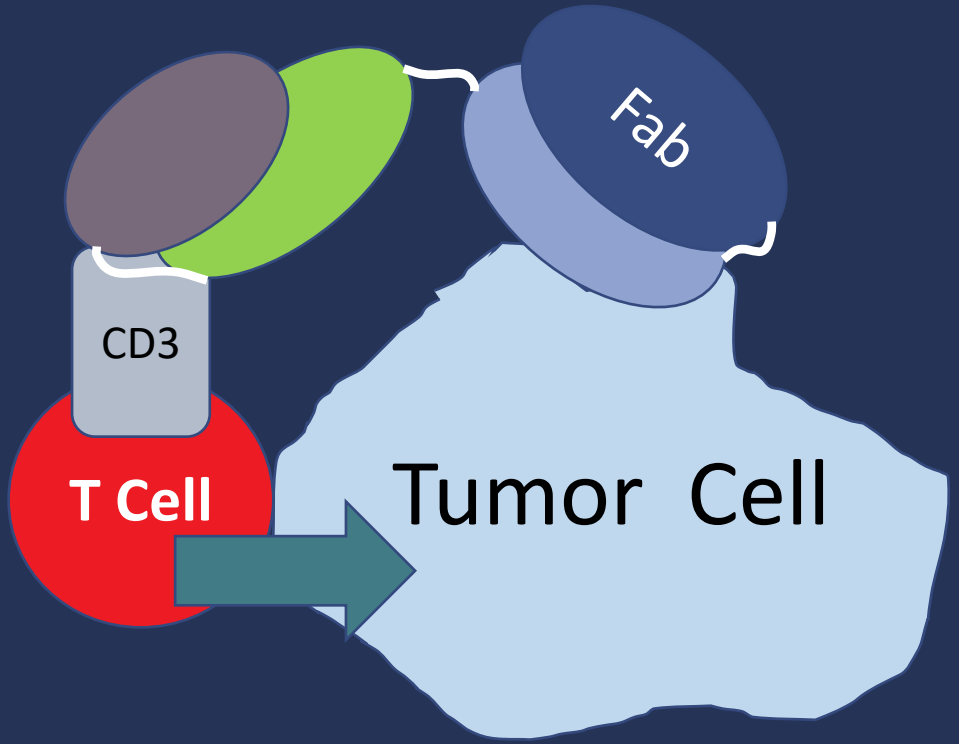
Daniel C. Danila, MD[1]; Russell Z. Szmulewitz, MD[2]; Ulka Vaishampayan, MD[3]; Celestia S. Higano, MD[4]; Ari D. Baron, MD[5]; Houston N. Gilbert, PhD[6]; Flavia Brunstein, MD, PhD[6]; Marija Milojic-Blair[6]; Bei Wang, MS[6]; Omar Kabbarah, PhD[6]; Michael Mamounas, PhD[6]; Bernard M. Fine, MD, PhD[6]; Daniel J. Maslyar, MD[6]; Alexander Ungewickell, MD, PhD[6]; and Howard I. Scher, MD[1]

JCO **2019**

vandortuzumab vedotin (MMAE)


2 of 36 (6%) had a radiographic PR
Best PSA Change From Baseline (%)
100
50
0
−50
−100
≤ 1.5 mg/kg
2.25 mg/kg
2.4 mg/kg
2.8 mg/kg
IHC 1+
IHC 2+
IHC 3+
CTC responder
CTC nonresponder
CTC nonevaluable
IHC
CTC

Bi-specific T cell redirectors/engagers

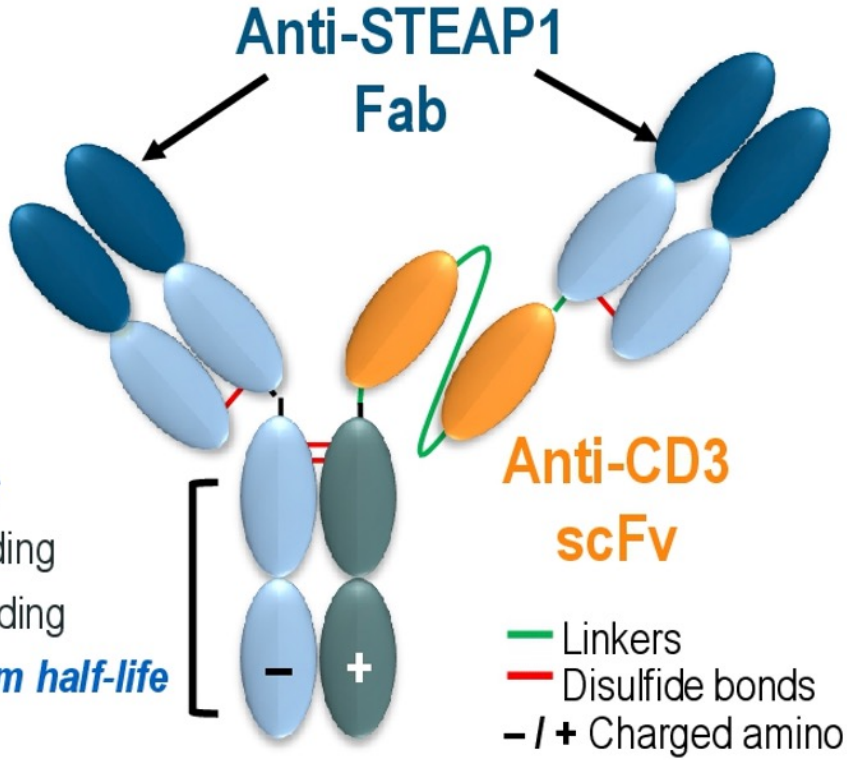


Bi-Specific T Cell Redirectors/Engagers

- 2014: Blinatumomab (anti-CD19/CD30) approved for refractory B precursor ALL. (Topp et al.)
- 2022: Teclistamab (anti-BCMA/CD3) for refractory myeloma (Moreau et al.)
- 2023: Glofitamab (anti-CD20/CD3) for refractory diffuse large B cell lymphoma
- 2022: Tebentafusp (gp100-HLA-A2/CD3 ImmTAC) for uveal melanoma (Nathan et al).
- Tarlatamab (anti-DLL3/CD3) for refractory small cell lung cancer (Ahn et al). Targeted FDA review June 12 2024

What about a BiTE targeting STEAP1 in Prostate Cancer?

STRUCTURE OF AMG 509



Danila et al. ASCO 2022. Trials in Progress NCT04221542

MADRID 2023 ESMO congress

Interim Results From a Phase 1 Study of Xaluritamig (AMG 509), a STEAP1 x CD3 XmAb® 2+1 Immune Therapy, in Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC)

William K. Kelly, Daniel C. Danila, Chia-Chi Lin, Jae-Lyun Lee, Nobuaki Matsubara, Patrick J. Ward, Andrew J. Armstrong, David W. Pook, Miso Kim, Tanya Dorff, Stefanie Fischer, Yung-Chang Lin, Lisa Horvath, Christopher Sumey, Zhao Yang, Gabor Jurida, Jamie Connarn, Hweixian L. Penny, Julia Stieglmaier, Leonard J. Appleman

RESEARCH ARTICLE

Xaluritamig, a STEAP1 × CD3 XmAb 2+1 Immune Therapy for Metastatic Castration-Resistant Prostate Cancer: Results from Dose Exploration in a First-in-Human Study

William K. Kelly[1,2], Daniel C. Danila[3,4], Chia-Chi Lin[5], Jae-Lyun Lee[6], Nobuaki Matsubara[7], Patrick J. Ward[2,8], Andrew J. Armstrong[9], David Pook[10], Miso Kim[11], Tanya B. Dorff[12], Stefanie Fischer[13], Yung-Chang Lin[14], Lisa G. Horvath[15], Christopher Sumey[16], Zhao Yang[17], Gabor Jurida[17], Kristen M. Smith[18], Jamie N. Connarn[18], Hweixian L. Penny[17], Julia Stieglmaier[19], and Leonard J. Appleman[20]

Cancer Discovery. Oct 20, 2023 Online before print. PMID 37861461

Key inclusion criteria:

- **mCRPC refractory to prior novel hormonal therapy and 1–2 taxane regimens***
- ECOG PS 0–1

Key exclusion criteria

- Histology other than adenocarcinoma
- Active autoimmune disease

Patient Characteristics	All cohorts, Part 1 (N = 97)
Age, median (range), years	67 (40, 86)
Race,† n (%)	
White	59 (61)
Asian	32 (33)
Black / African American	5 (5)
ECOG PS 0 / 1, n (%)	45 (46) / 52 (54)
Number of prior lines of therapy,‡ median (range)	4 (1, 9)
≥ 5, n (%)	27 (28)
Prior taxane, n (%)	82 (85)
Prior PSMA-targeting radioligand therapy, n (%)	4 (4)
Baseline PSA, ng/mL, median (range)	113.0 (0.2, 5808.9)
Visceral metastases, n (%)	51 (53)
Liver	19 (37)
Median (range) duration of follow-up, months	8.1 (0.5, 29.2)

Kelly *et al.* 2023

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Kelly *et al.* 2023

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Dose exploration with step-dosing to determine the MTD

Dosing schedule: 28-day cycles; QWeekly 60 min IV dosing; treatment until progression or unacceptable toxicity

24 hour inpatient admission for monitoring (through 1st infusion at target dose).

Dexamethasone pre-medication 8 mg x 2 doses at 6-12 and 1 hour: mandatory through 1st infusion at target dose, then optional.

BLRM			
No Step	**1-Step**	**2-Step**	**3-Step**
C1: 0.001 mg **C2:** 0.003 mg **C3:** 0.01 mg **C4:** 0.03 mg **C5:** 0.1 mg **C6:** 0.3 mg	**C7a:** 0.1 → 0.3 mg **C8:** 0.3 → 1.0 mg **C10:** 0.1 → 1.0 mg	**C7b:** 0.1 → 0.3 → 1 mg **C7c:** 0.1 → 0.3 → 1 mg (Q2W) **C9:** 0.1 → 0.3 → 0.75 mg	**C11:** 0.1 → 0.3 → 1 → 1.5 mg **C12:** 0.1 → 0.3 → 0.75 → 1.5 mg **C13:** 0.1 → 0.3 → 1 → 2 mg

MTD → **Xaluritamig dose expansion**

Pre-medication adjusted during C7a →

Not tolerable MTD

MTD: 0.1 mg→0.3 mg→1.0 mg→1.5 mg

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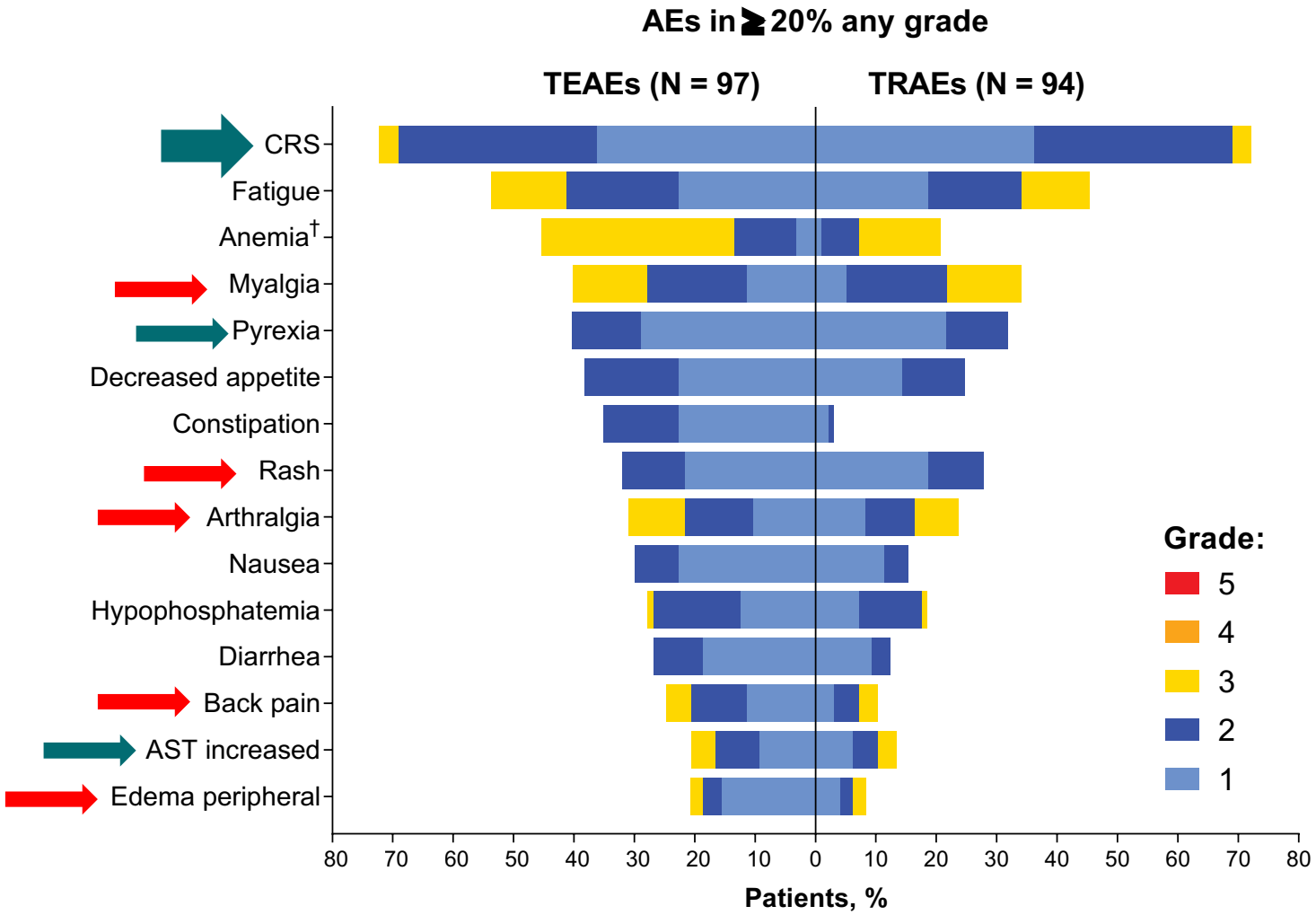
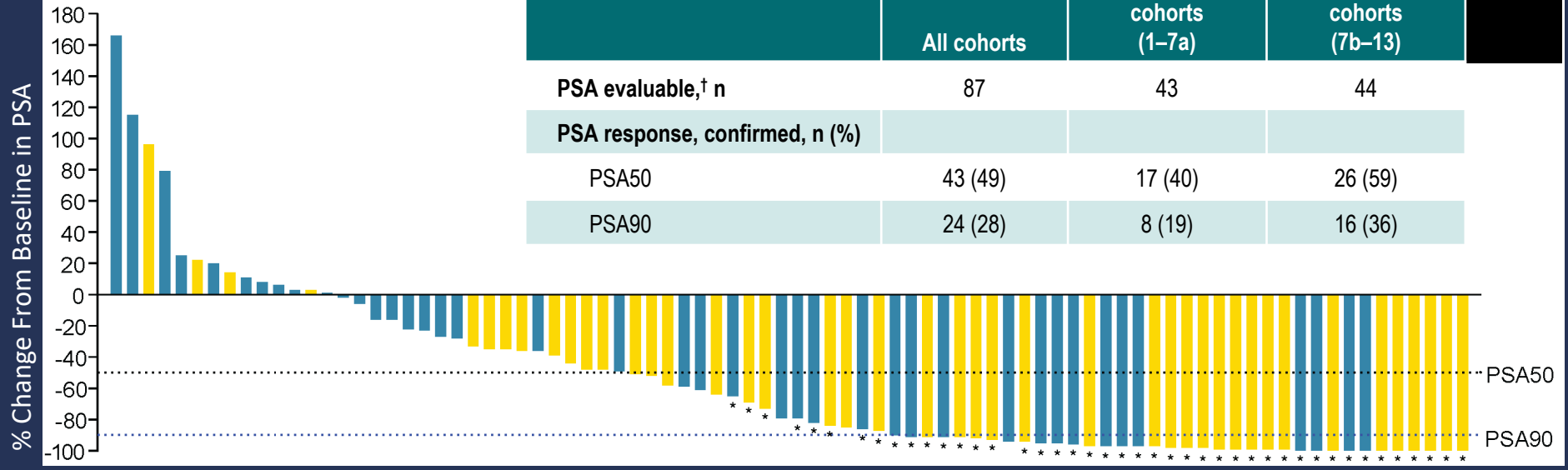

AEs in ≥ 20% any grade
TEAEs (N = 97)
TRAEs (N = 94)
CRS
Fatigue
Anemia†
Myalgia
Pyrexia
Decreased appetite
Constipation
Rash
Arthralgia
Nausea
Hypophosphatemia
Diarrhea
Back pain
AST increased
Edema peripheral
Grade:
5
4
3
2
1
80 70 60 50 40 30 20 10 0 10 20 30 40 50 60 70 80
Patients, %

Confirmed PSA Responses

	All cohorts	Low-dose cohorts (1–7a)	High-dose cohorts (7b–13)
PSA evaluable,† n	87	43	44
PSA response, confirmed, n (%)			
PSA50	43 (49)	17 (40)	26 (59)
PSA90	24 (28)	8 (19)	16 (36)



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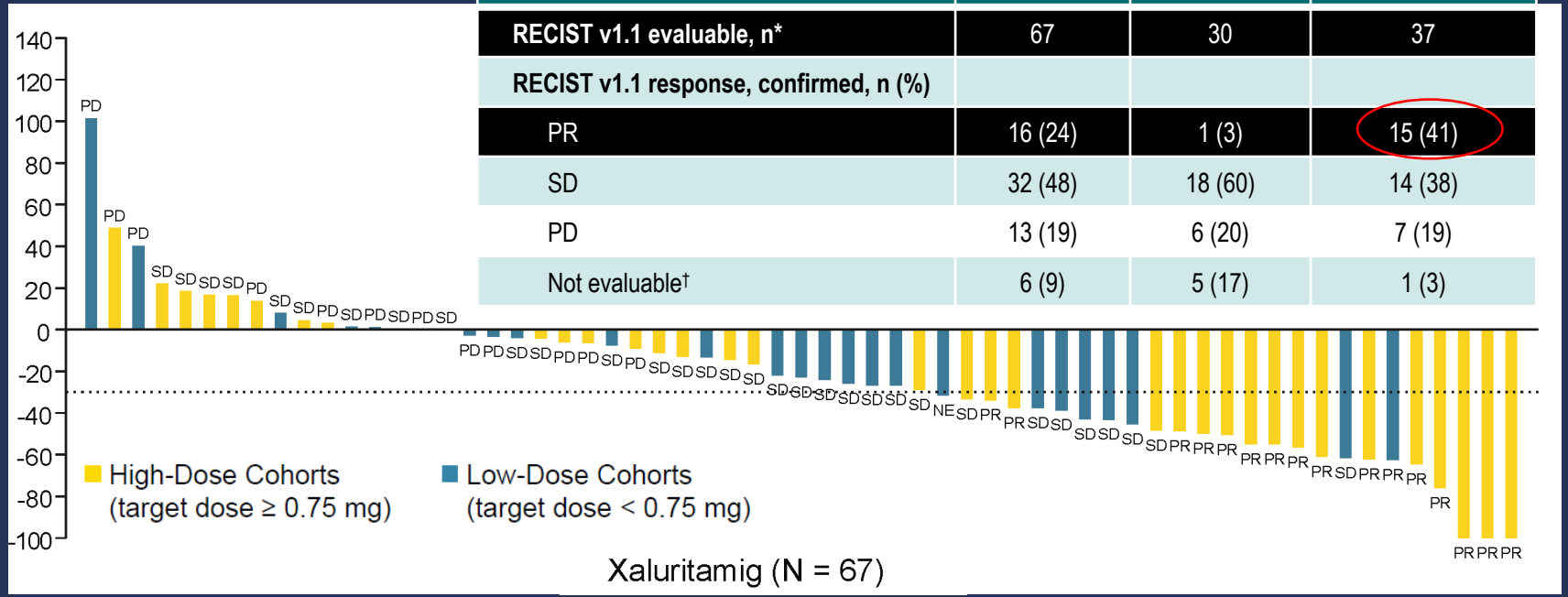
Confirmed RECIST responses in patients with measurable disease (n=67)

	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)



Median duration of Response 9.2 months (1.9 - 17.7+)
10/16 with PR still responding

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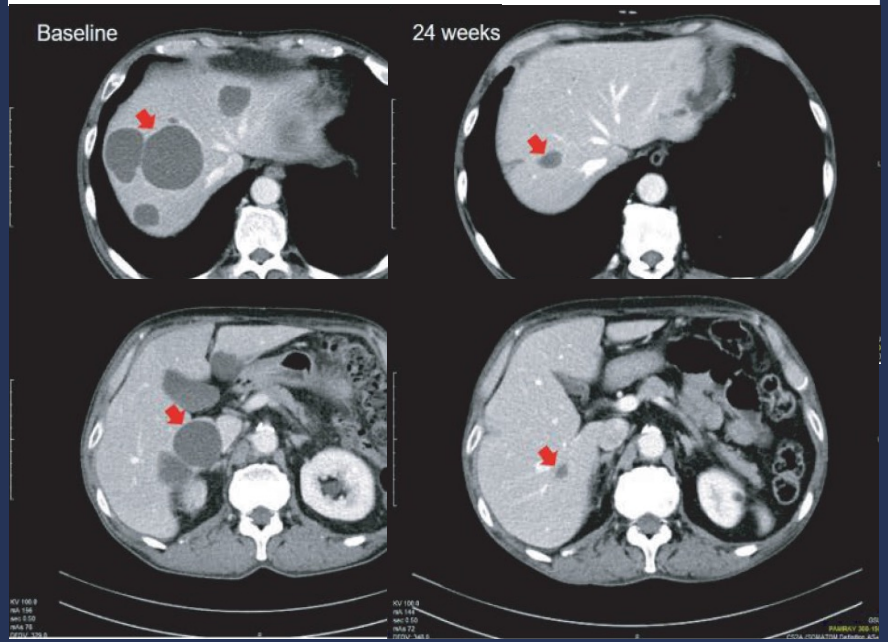
CT Scan

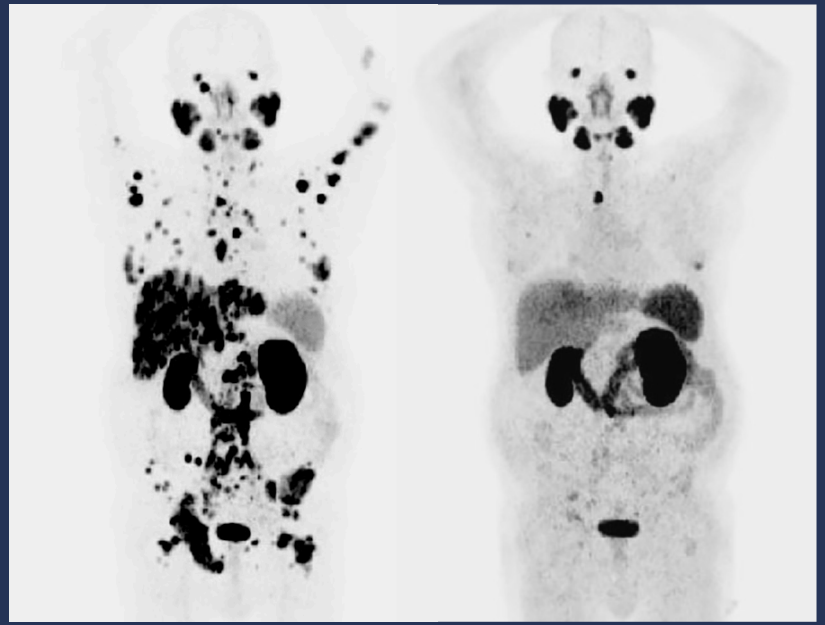
Baseline	Week 24



65-year-old heavily pre-treated patient with mCRPC. Patient was enrolled in cohort 11 and achieved a confirmed RECIST and PSA90 response.

PSMA PET

Baseline	Week 12



56-year-old heavily pre-treated patient with mCRPC. Patient was enrolled in cohort 12 and achieved a confirmed PSA90 response (not RECIST evaluable).

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CONCLUSIONS

- Xaluritamig (AMG 509) is a bi-specific T cell engager targeting STEAP-1
- Using a weekly IV schedule, **step-dosing** of xaluritamig is safe and tolerable
  0.1 mg→ 0.3 mg → 1 mg→ 1.5 mg.
- Toxicities: Cytokine release syndrome, and **musculoskeletal inflammation** (myalgias, edema, rash) - manageable with corticosteroids and tocilizumab.
- Response observations in mCRPC:

	Total	High Dose
– **PSA_{50} response:**	**49%**	**59%**
– **PSA_{90} response:**	**28%**	**36%**
– **RECIST ORR:**	**24%**	**41%**

What's Next?

Further study of AMG 509 (xaluritamig)

- Combinations
- Earlier disease states
- Randomized Phase III study(ies)
  - What would your control arm be?
  - Allow cross-over?

Other Targets and Strategies

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

A Phase I Study of Acapatamab, a Half-life Extended, PSMA-Targeting Bispecific T-cell Engager for Metastatic Castration-Resistant Prostate Cancer

Tanya Dorff[1], Lisa G. Horvath[2], Karen Autio[3], Alice Bernard-Tessier[4], Matthew B. Rettig[5,6], Jean-Pascal Machiels[7], Mehmet A. Bilen[8], Martijn P. Lolkema[9,10], Nabil Adra[11], Sylvie Rottey[12], Richard Greil[13], Nobuaki Matsubara[14], Daniel S.W. Tan[15], Alvin Wong[16], Hiroji Uemura[17], Charlotte Lemech[18], Johannes Meran[19], Youfei Yu[20], Mukul Minocha[21], Mason McComb[21], Hweixian Leong Penny[22], Vinita Gupta[23], Xuguang Hu[23], Gabor Jurida[24], Hosein Kouros-Mehr[25], Margit M. Janát-Amsbury[26], Tobias Eggert[26], and Ben Tran[27]

Dorff et al 2024

Table 2B. Worst grade ≥3 TEAEs noted in greater than 5% of patients in dose expansion.

TEAE	Dose expansion ($N = 56$)	
	Any grade *n* (%)	Grade ≥ 3 *n* (%)
Cytokine release syndrome	55 (98.2)	9 (16.1)[a]
Anemia	20 (35.7)	11 (19.6)
Hypophosphatemia	20 (35.7)	9 (16.1)
Alanine aminotransferase increased	12 (21.4)	3 (5.4)
Aspartate aminotransferase increased	11 (19.6)	3 (5.4)
Platelet count decreased	8 (14.3)	3 (5.4)[a]
Hypertension	4 (7.1)	3 (5.4)
Neutropenia	4 (7.1)	4 (7.1)[a]

Note: TEAEs were coded using MedDRA version 25.0 and graded using CTCAE version 5.0 criteria.
Abbreviation: MedDRA, Medical Dictionary for Regulatory Activities.
[a]Includes 1 patient who experienced a grade 4 event.

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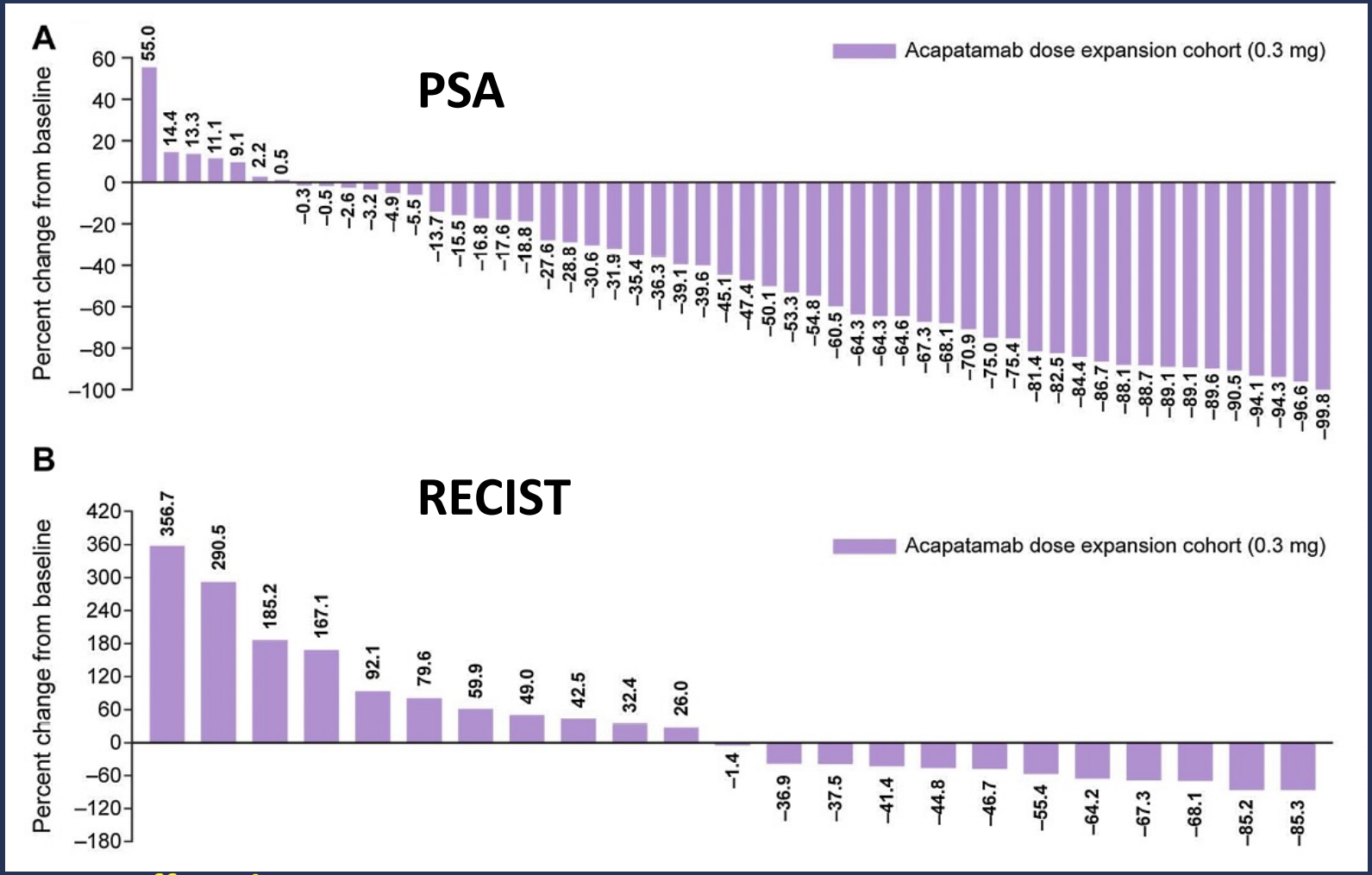


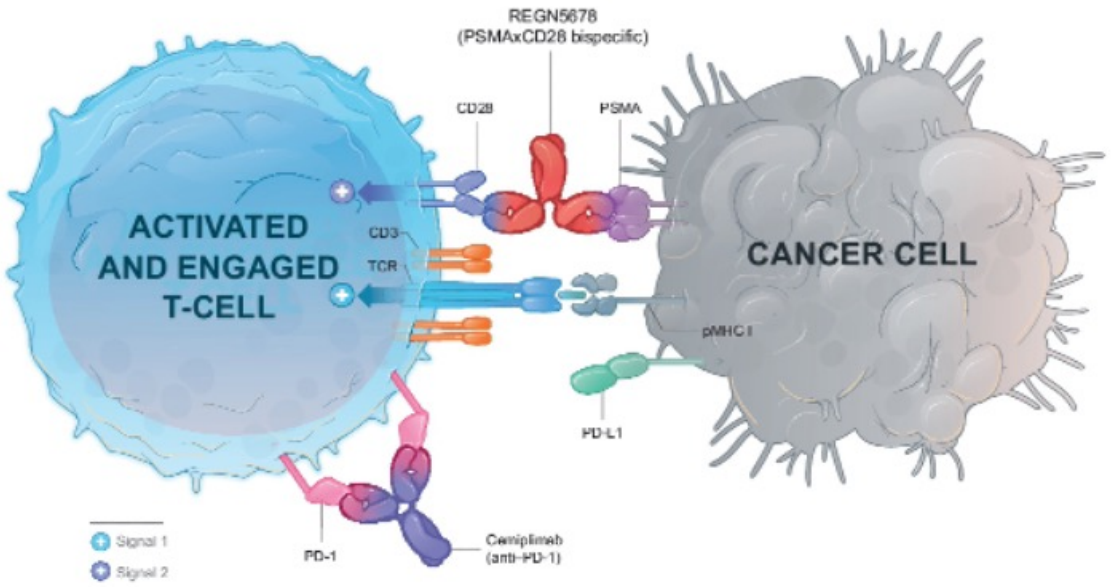
Dorff et al 2024

Preliminary results from a Phase 1/2 study of the co-stimulatory bispecific PSMAxCD28 antibody REGN5678 in patients with metastatic castration-resistant prostate cancer

Mark N Stein,[1] Jingsong Zhang,[2] William Kelly,[3] David R Wise,[4] Che-Kai Tsao,[5] Benedito A Carneiro,[6] Gerald Falchook,[7] Fang Fang,[8] Shilpa Govindraj,[8] Hung-Kam Cheung,[8] Min Zhu,[8] Nathalie Fiaschi,[8] Jennifer S Sims,[8] Dimitris Skokos,[8] Frank A Seebach,[8] Israel Lowy,[8] Pradeep Thanigaimani,[8] Sabina Sandigursky,[8] Elizabeth Miller[8]

[1]Columbia University Medical Center, New York, NY, USA; [2]Moffitt Cancer Center, Tampa, FL, USA; [3]Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA; [4]NYU Langone Perlmutter Cancer Center, New York, NY, USA; [5]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [6]Legorreta Cancer Center at Brown University, Providence, RI, USA; [7]Sarah Cannon Research Institute at HealthONE, Denver, CO, USA; [8]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

Figure 1. Mechanism of action of REGN5678

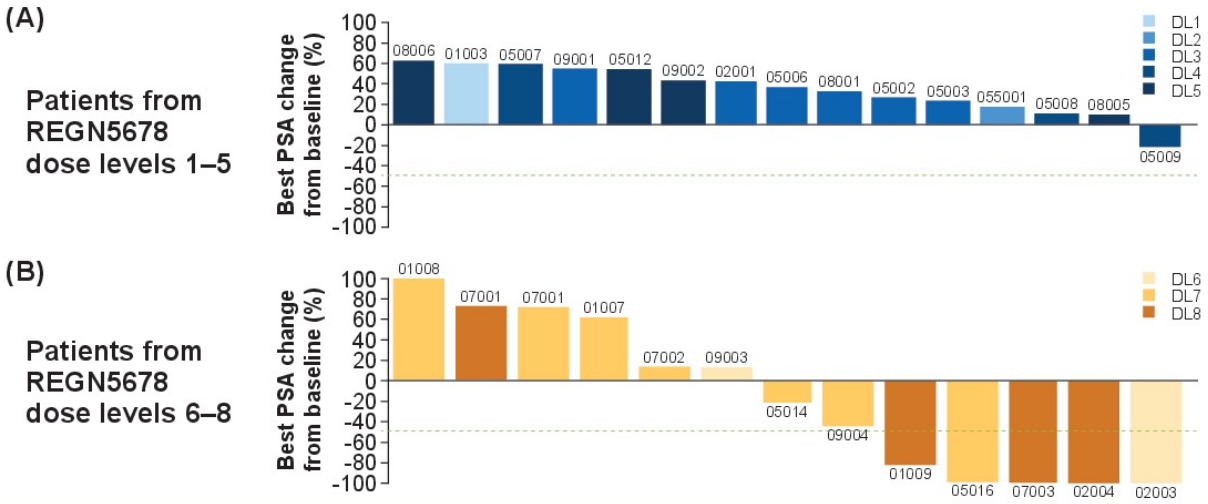


PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; pMHC I, peptide (antigen)-bound major histocompatibility complex class I; TCR, T-cell receptor.

Efficacy

- Preliminary efficacy measurements include decline in PSA from the start of combination treatment, and radiographic response from baseline.
- There were minimal signs of efficacy at lower doses (REGN5678 0.1–10 mg), with only 1/17 (6%) patients showing a PSA decline (**Figure 3A**).
- At the top 3 dose levels (REGN5678 30–300 mg), 7/16 (44%) patients showed PSA declines, with 4 (25%) showing deep responses ranging from 82–100% decreases (**Figure 3B**).
- Grade ≥3 imAEs occurred only in patients who had a decline in PSA level.

Figure 3. Decline in PSA levels from start of combination dosing



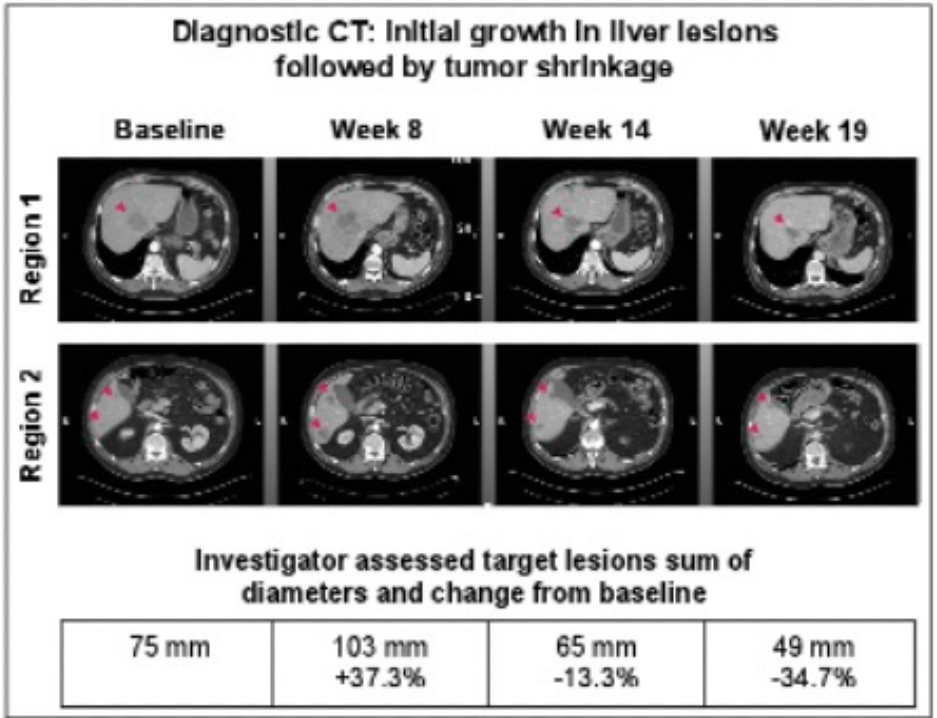
The waterfall plots only include patients who have baseline PSA read-out and post baseline PSA read-out.
DL, dose level; imAE, immune-mediated adverse event; mCRPC, metastatic castration-resistant prostate cancer; PD-1, programmed cell death-1; PSA, prostate-specific antigen.

Stein et al. 2023

(A) Number of RECIST responses among patients with measurable disease and ≥1 on-treatment scan

Dose level	30 mg	100 mg	300 mg
Number of responses	1/3	1/4	1/1
RECIST response	Complete response	Unconfirmed partial response	Partial response

(B) Shrinkage in PSMA-low liver lesion along with decreased uptake in bone lesions (patient in 100 mg cohort)



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What about CAR-T?

ARTICLES | FOCUS
https://doi.org/10.1038/s41591-022-01726-1

nature medicine

Check for updates

PSMA-targeting TGFβ-insensitive armored CAR T cells in metastatic castration-resistant prostate cancer: a phase 1 trial

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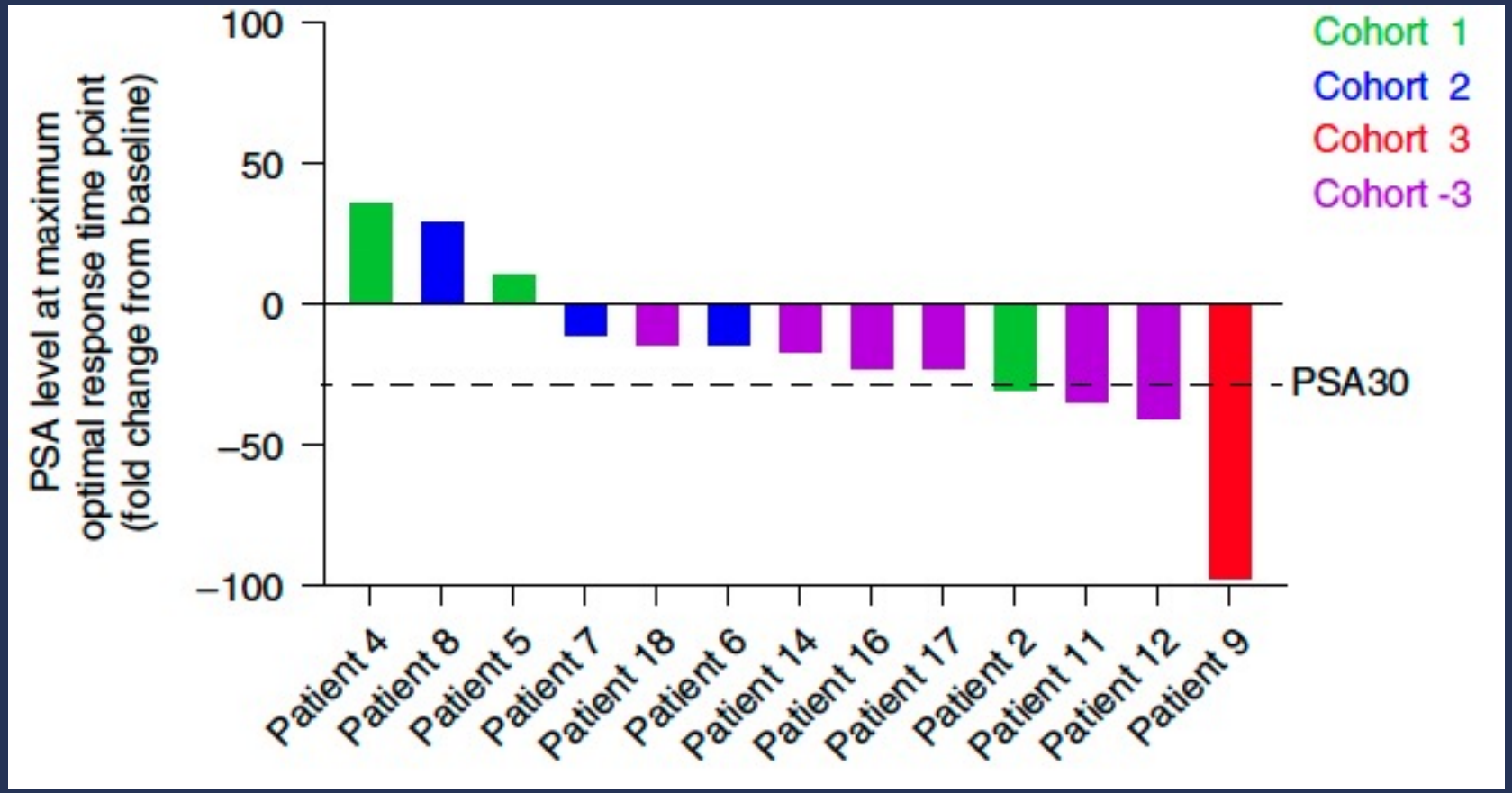

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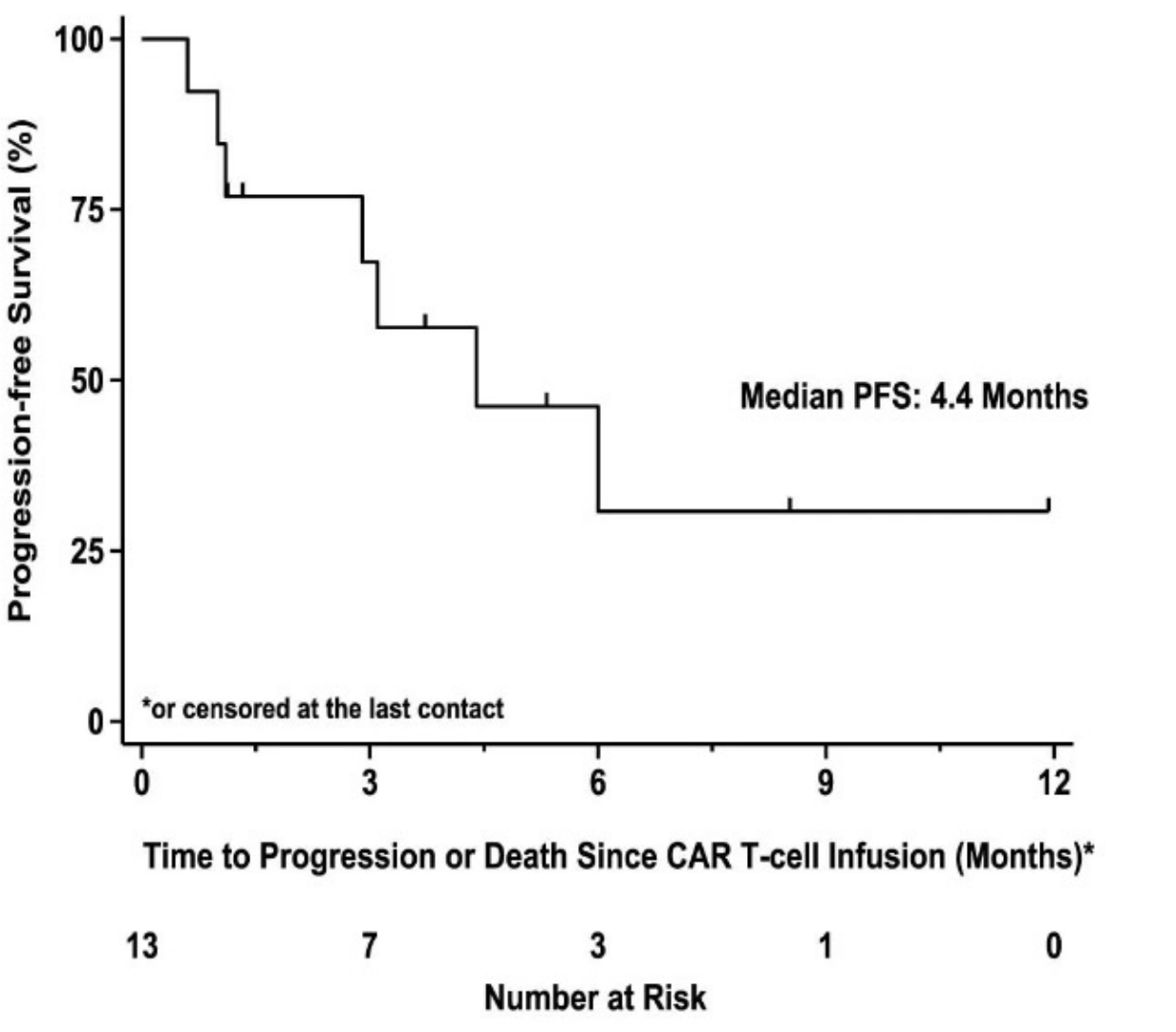

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Immunotherapy Targeting Prostate Cancer: 2024

Targets:
PSMA
STEAP1
STEAP2
?

Vehicles:
CAR-T
ADC
BiTEs
IMMTacs
?

Enhancers:
CD28
CD137
dnTGFβRII
4-1BB
PD-1/CTLA-4

THANK YOU