# Will Immunotherapy Change Your Prostate Cancer Treatment Path?


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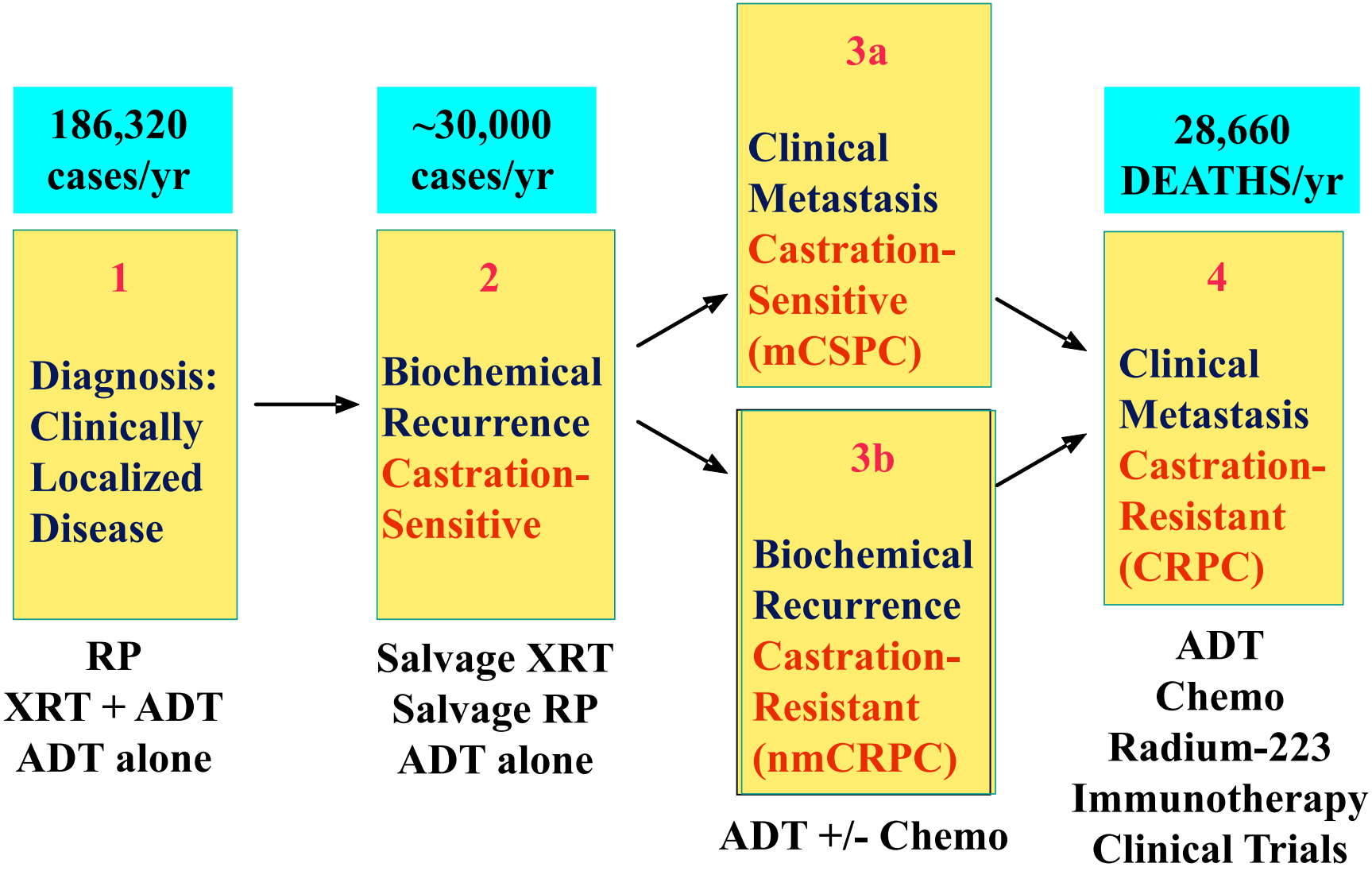
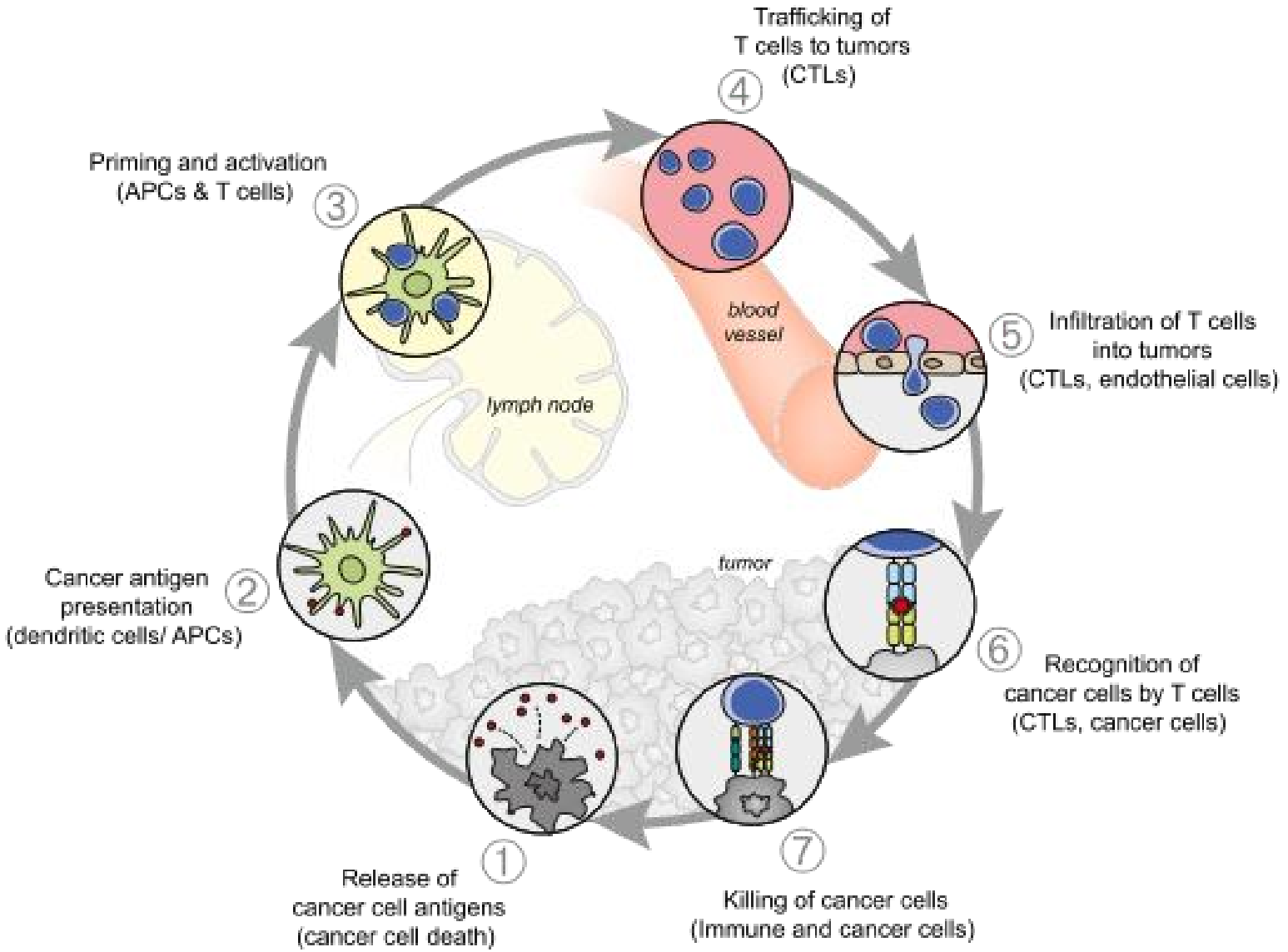
# The Clinical States Model of Prostate Cancer



# Cancer Immunity Cycle




(Chen and Mellman, Immunity 2013)

# Immunotherapy has transformed how we treat cancer patients

Enhancing endogenous immunity

Blocking inhibitors

Stimulating effectors

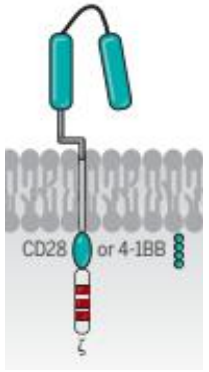
Vaccines

Anti-PD-1

Redirecting immune effectors

Engineering cellular specificities

Colocalizing effectors to tumors



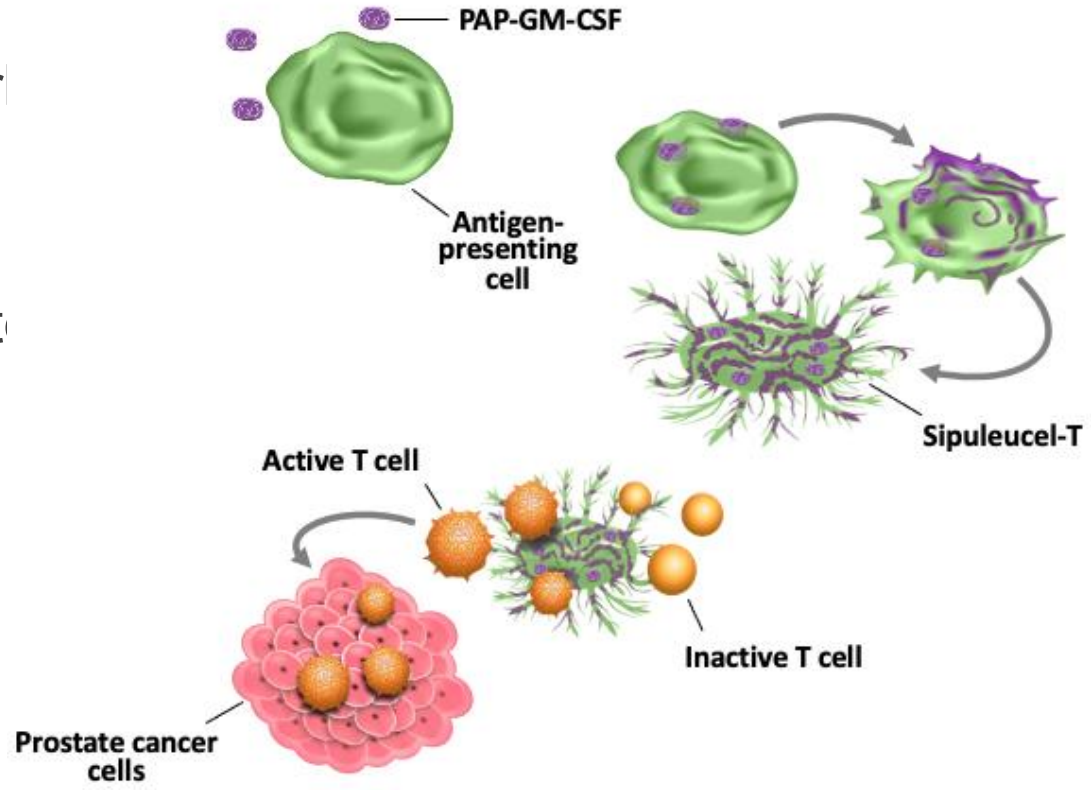

Anti-CD19 CART

Anti-CD19 x anti-CD3

# SIPULEUCEL-T

## First approved prostate cancer immunotherapy

- Autologous cellular immunotherapy that wor as a vaccine
- Targets prostatic acid phosphatase (PAP)
- Induces T and B cell responses that correlat with outcomes

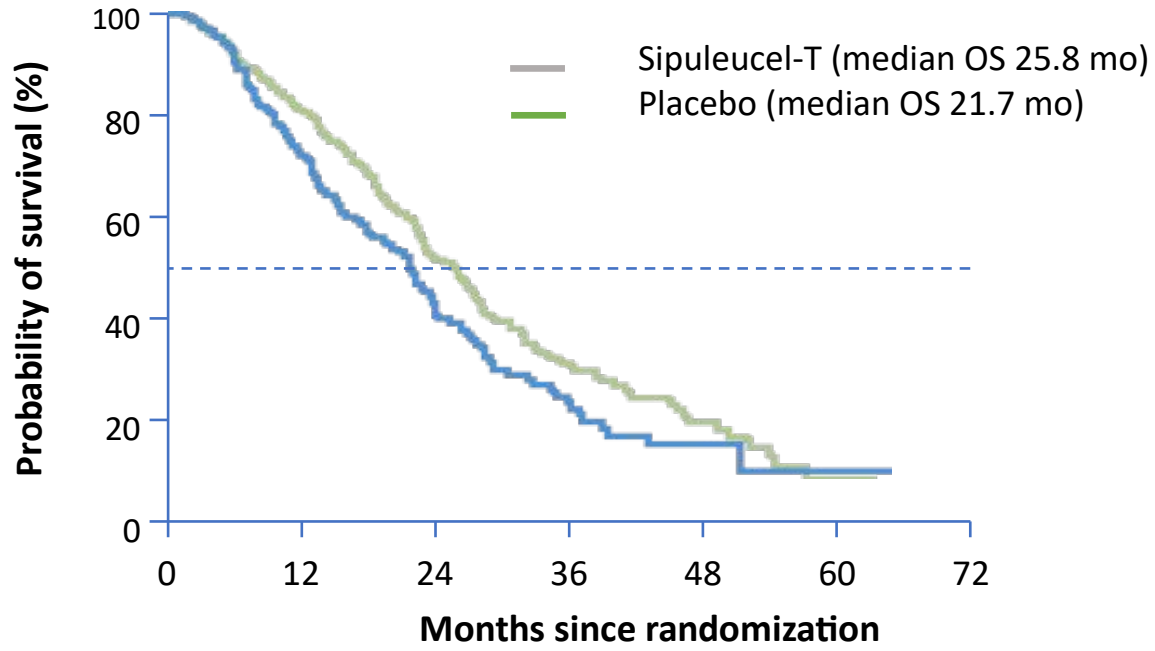



Fong *J Immunol* 1997
Kantoff *NEJM* 2010
Schellhammer *Urology* 2013

# SIPULEUCEL-T

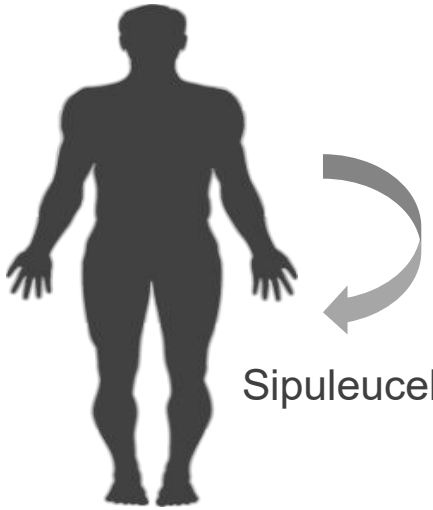
## First approved prostate cancer immunotherapy

- Improved OS without PFS or PSA responses
- Longer OS in patients with lower baseline PSAs




Fong *J Immunol* 1997
Kantoff *NEJM* 2010
Schellhammer *Urology* 2013

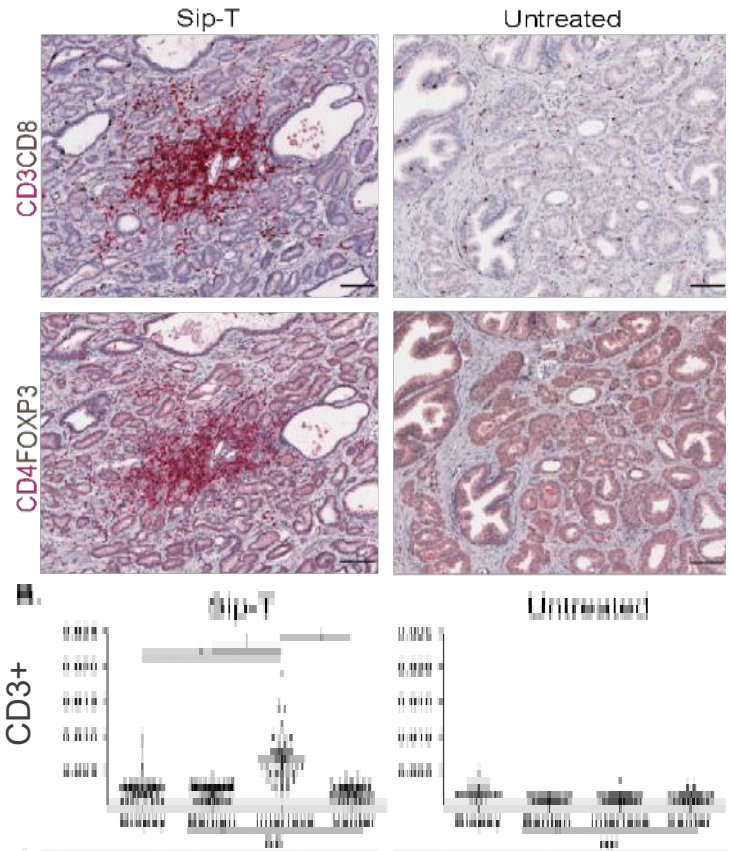
# Neoadjuvant sipuleucel-T induces intratumoral T cells in prostate tumors



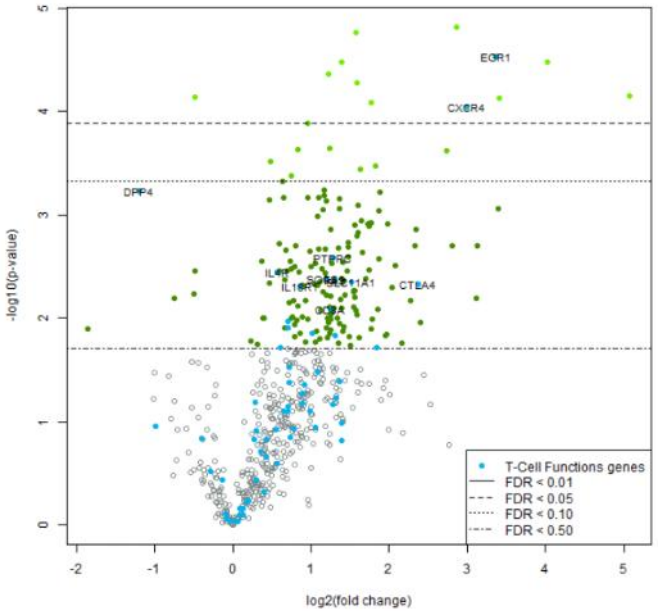
Sipuleucel-T

Radical Prostatectomy

## Immunohistochemistry

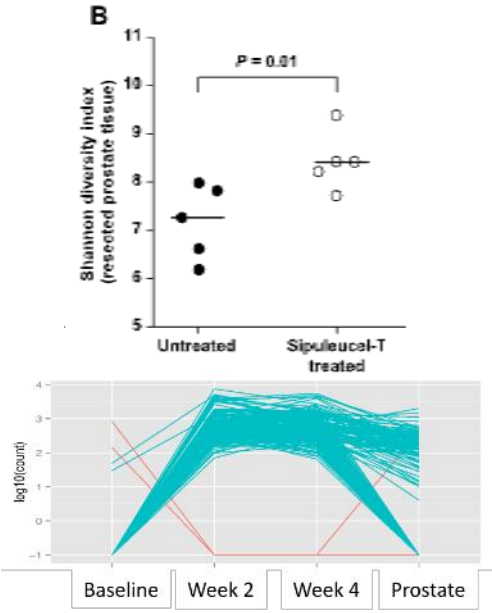



## Gene expression




- Induction of Th1 immunity
- Induction of CTLA-4 and TIGIT (not PDL1, VISTA)

## TCR sequencing

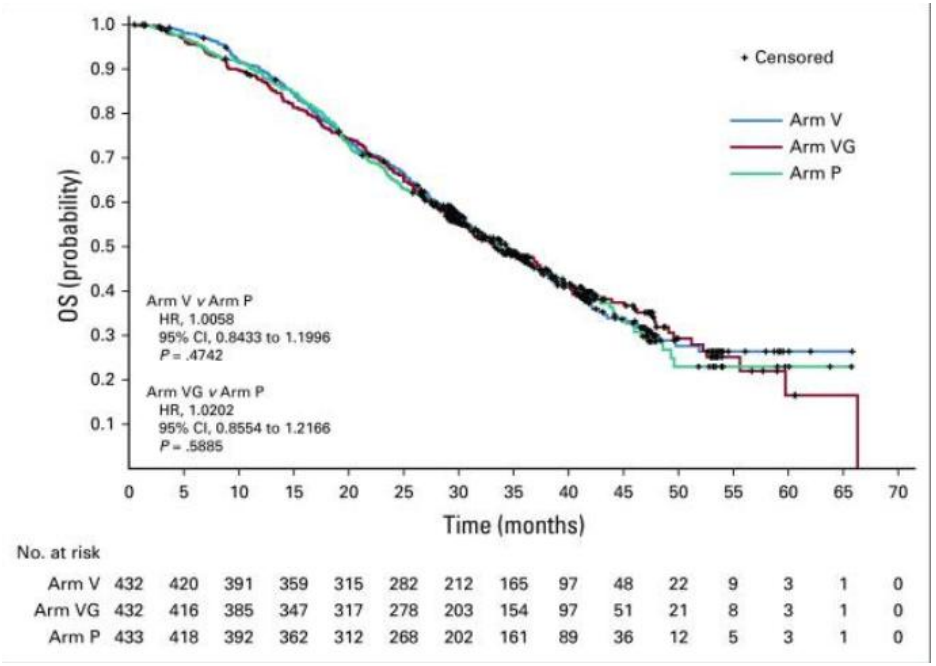



Fong *JNCI* 2014; Hagihara *Oncoimmunol* 2018; Sheikh *Can Res* 2016

# CHALLENGES IN PROSTATE CANCER

## Another cancer vaccine

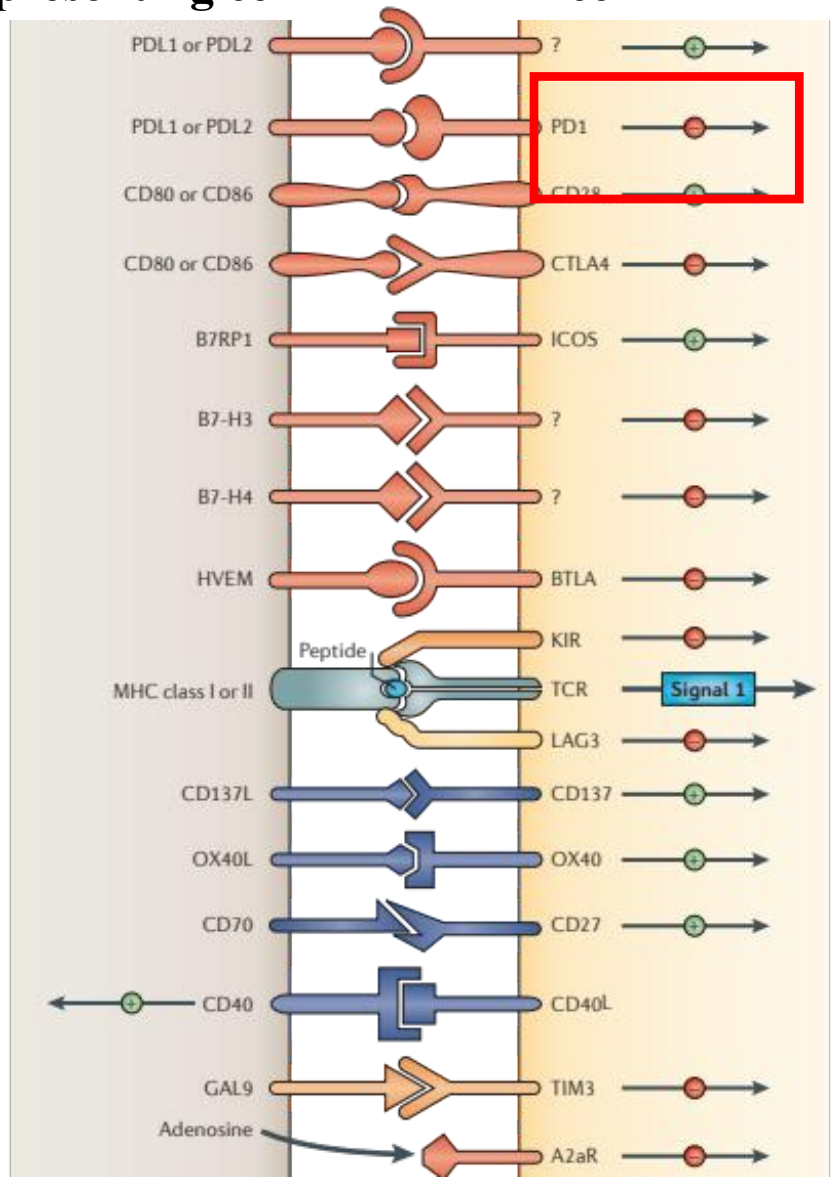
- Negative phase III randomized  of Prostvac-VF




Gulley *JCO* 2019

# Balancing Immune Checkpoints

Antigen recognition via
T cell receptor




**Clinical results**

Huge Success

Toxic

Combination with anti-PD1

No toxicity, no activity

No toxicity, activity as an ADC

Halted in pre-clinical

No efficacy
Multiple neoantigen trials

Limited efficacy in LAG3+ tumors
No toxicity, no activity, ? Combo with anti-PD1

Toxicity, no activity

No toxicity, no activity

Toxicity, limited efficacy

No toxicity, no activity

(Pardoll. *Nat Rev Can* 2012)

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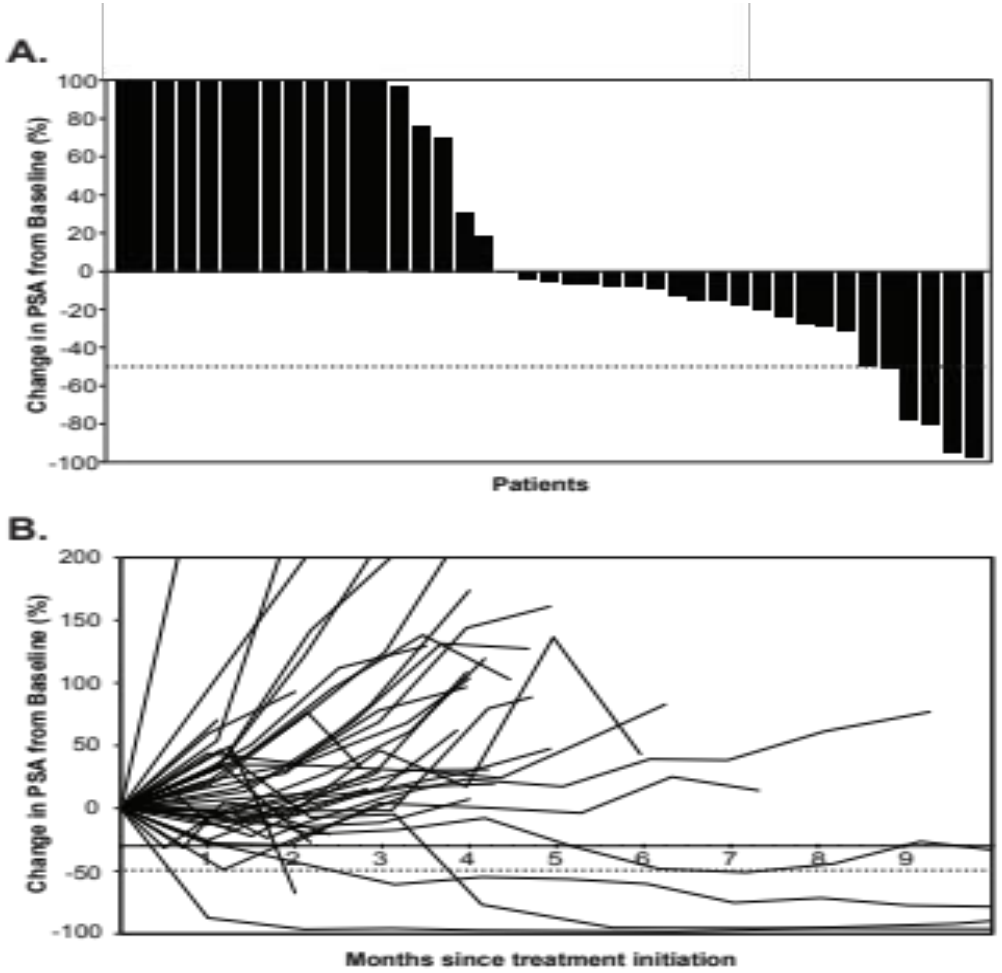
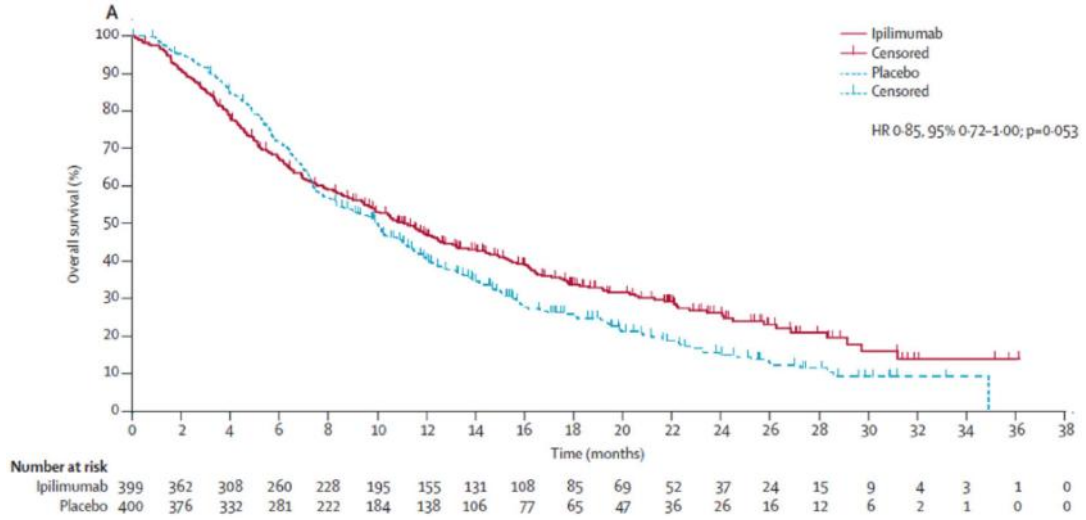
# CTLA-4 blockade in mCRPC




(Fong et al, *Can Res* 2009; Kwek et al, *Can Imm Res*, 2015)

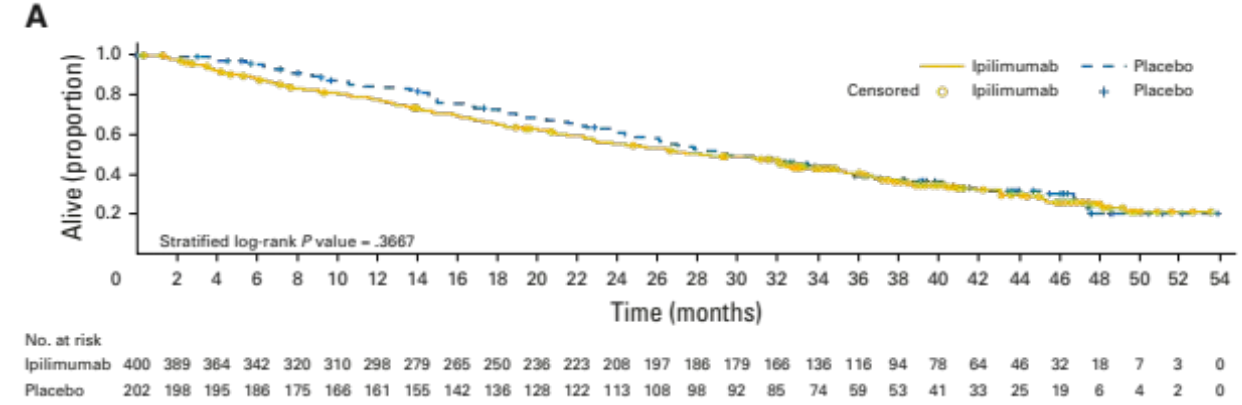
Phase 3 of ipilimumab

Post-chemotherapy




(Kwon et al *Lancet Oncology* 2014)

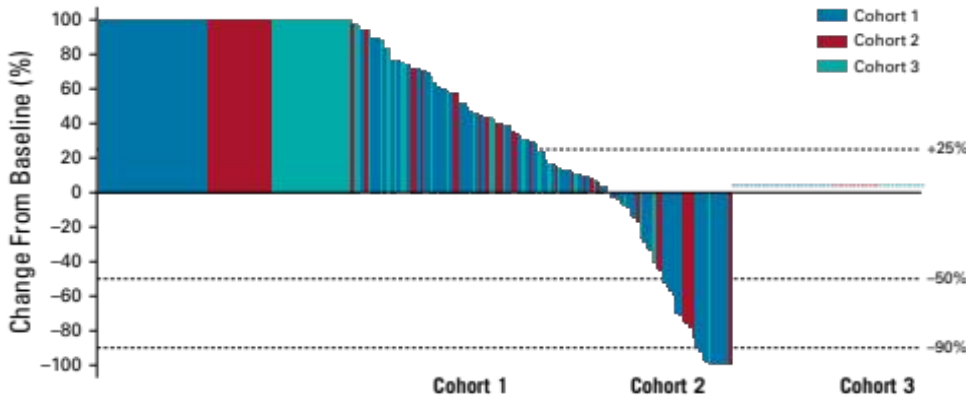
Pre-chemotherapy




(Beer et al *JCO* 2016)

Lawrence Fong

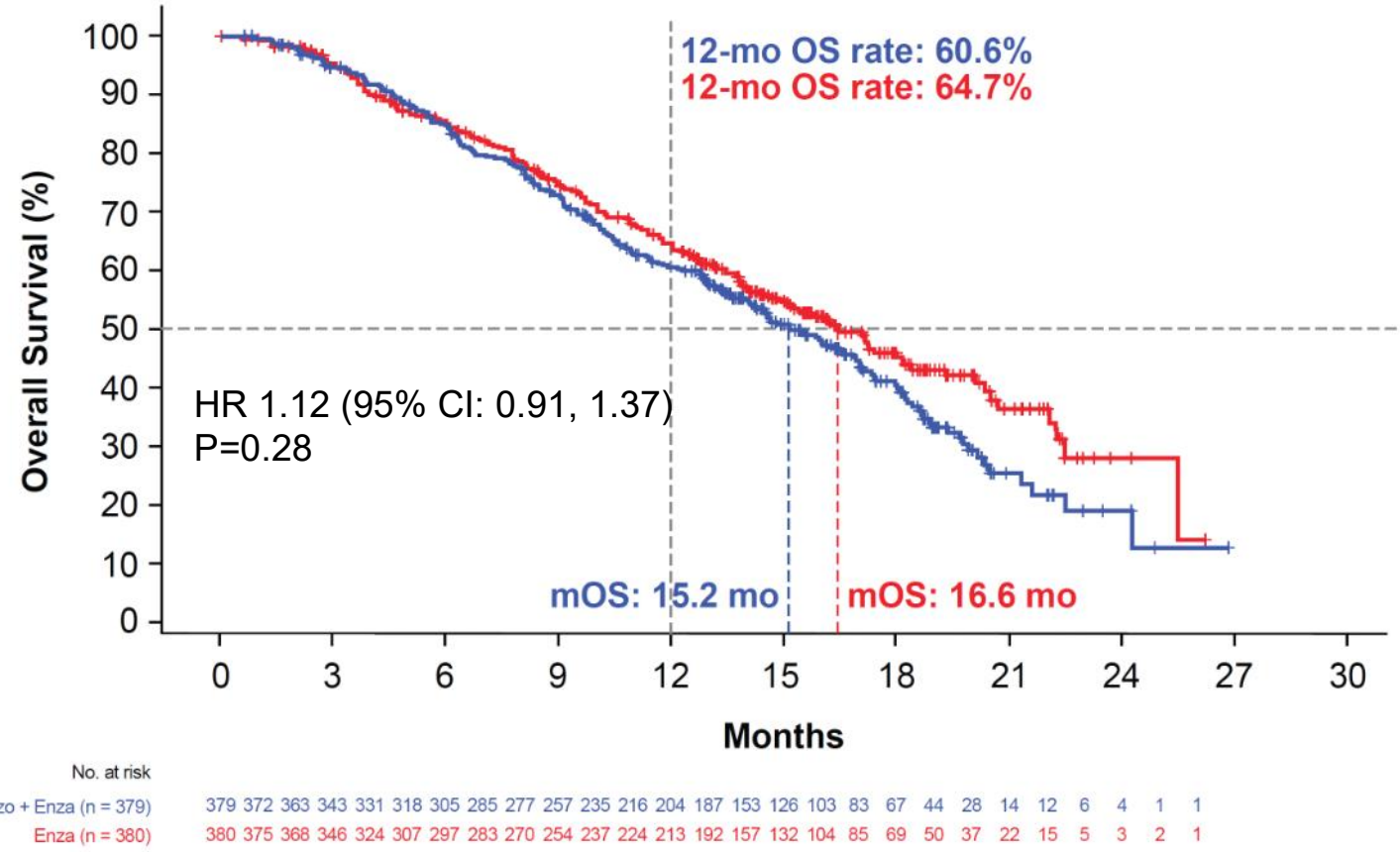
# PD-1/PD-L1 blockade for mCRPC




| Variable | Cohort 1 (PD-L1 positive) | Cohort 2 (PD-L1 negative) | Cohort 3 (bone predominant) |
|---|---|---|---|
| Response assessed per RECIST v1.1 by central radiology review | | | |
| No. of patients | 133 | 66 | 59 |
| ORR, No. (%; 95% CI) | 7 (5; 2 to 11) | 2 (3; < 1 to 11) | — |
| DCR,* No. (%; 95% CI) | 13 (10; 5 to 16) | 6 (9; 3 to 19) | 13 (22; 12 to 35) |
| Response assessed per PCWG3-modified RECIST v1.1 by central radiology review | | | |
| No. of patients | 133 | 66 | 59 |
| ORR, No. (%; 95% CI) | 7 (5; 2 to 11) | 2 (3; < 1 to 11) | — |
| DCR,* No. (%; 95% CI) | 17 (13; 8 to 20) | 12 (18; 10 to 30) | 23 (39; 27 to 53) |
| PSA response† in patients with baseline PSA measurement | | | |
| No. of patients | 124 | 60 | 59 |
| Response rate, No. (%; 95% CI) | 8 (6; 3 to 12) | 5 (8; 3 to 18) | 1 (2; 0 to 9) |

(Antonarakis et al. *JCO* 2020)

Phase 3 of enzalutamide ± atezolizumab

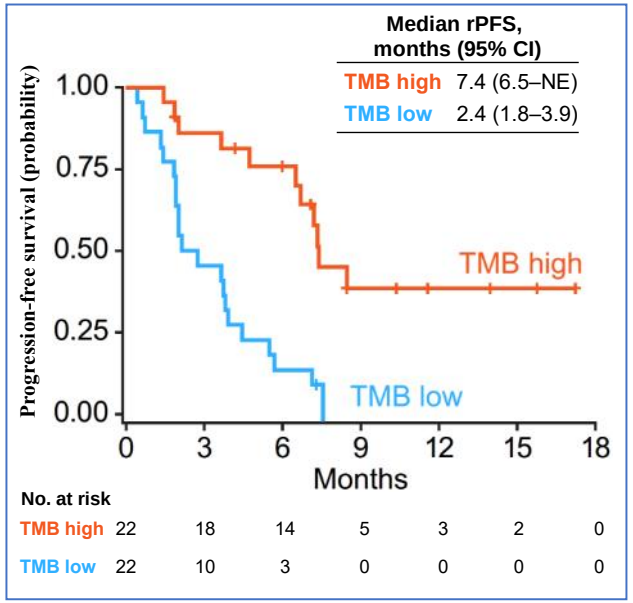



(Sweeney et al. AACR 2020)

# PD-1 + CTLA-4 blockade for mCRPC

| | Pre-Chemotherapy | Post-Chemotherapy |
|---|---|---|
| **Objective response** (measurable disease only)[a] | **Cohort 1 (N = 32)** | **Cohort 2 (N = 30)** |
| **Confirmed ORR, n (%)**<br>95% CI | 8 (25.0)<br>11.5–43.4 | 3 (10.0)<br>2.1–26.5 |
| **Best overall response, n (%)**<br>Complete response<br>Partial response<br>Stable disease<br>Progressive disease<br>Unable to determine | <br>2 (6.3)[b]<br>6 (18.8)[c]<br>13 (40.6)<br>9 (28.1)<br>2 (6.3) | <br>2 (6.7)<br>1 (3.3)<br>11 (36.7)<br>13 (43.3)<br>3 (10.0) |
| **Median time to response, months (Q1–Q3)** | 1.9 (1.9–2.8) | 2.1 (1.9–7.4) |

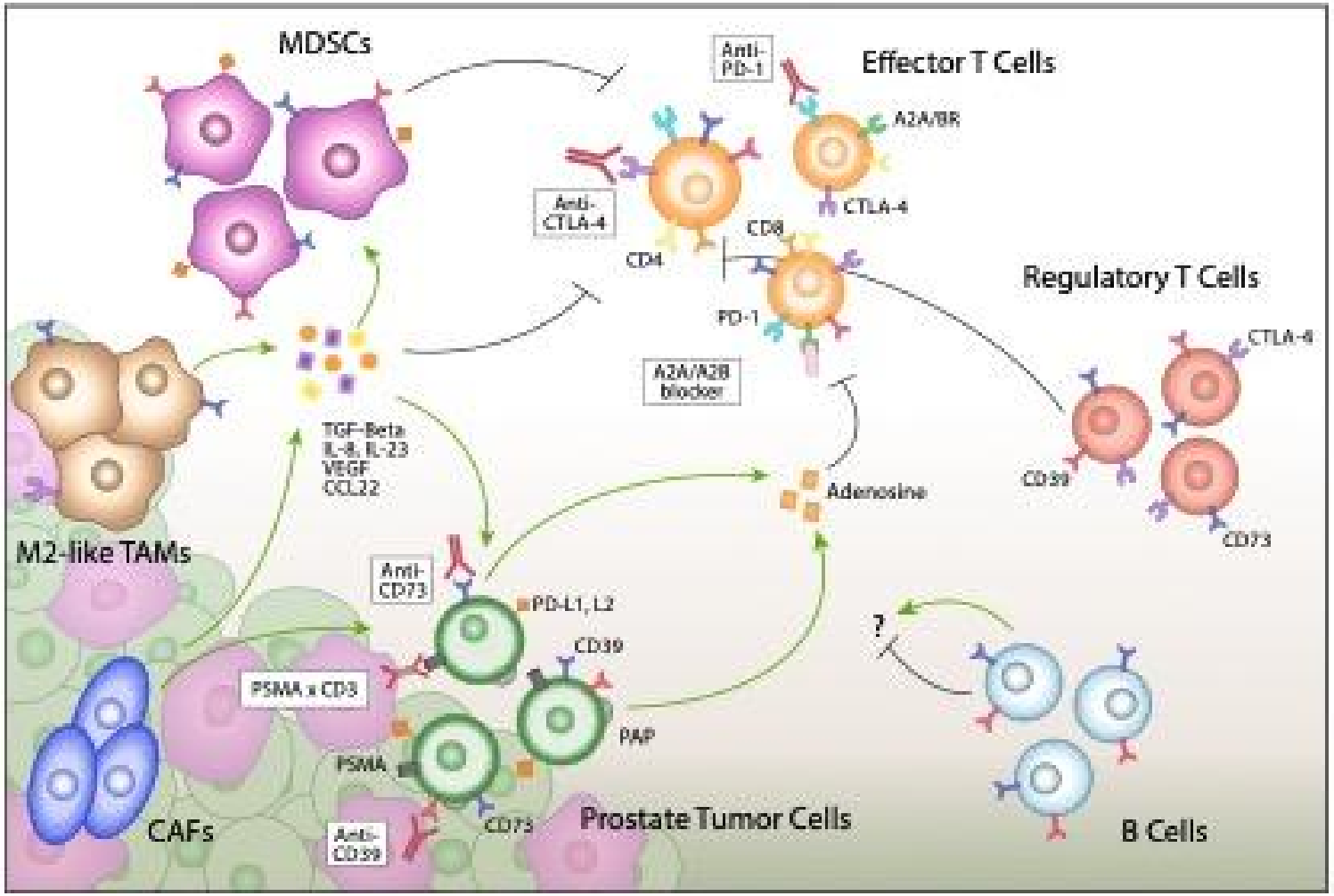
| **PSA response** (measurable/unmeasurable disease in patients with baseline and ≥1 post-baseline PSA result) | **Cohort 1 (N = 34)** | **Cohort 2 (N = 40)** |
|---|---|---|
| **Confirmed PSA response rate, n (%)**[d]<br>95% CI | 6 (17.6)<br>6.8–34.5 | 4 (10.0)<br>2.8–23.7 |
| **Patients with PSA <0.2 ng/mL, n (%)** | 5 (14.7) | 2 (5.0) |
| **Median time to confirmed PSA response, months (Q1–Q3)** | 1.4 (0.8–1.4) | 1.2 (0.8–1.4) |




40-50% Grade 3-4 AEs

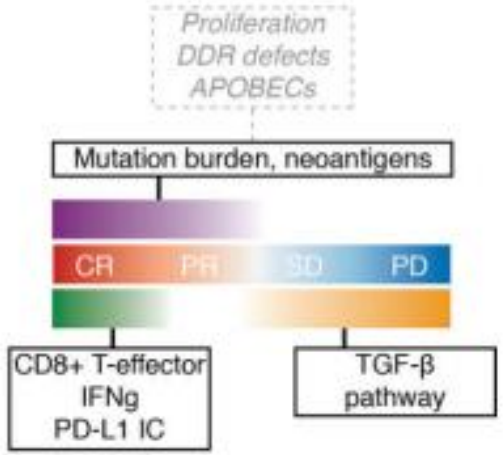
(Sharma et al. ASCO GU 2019)

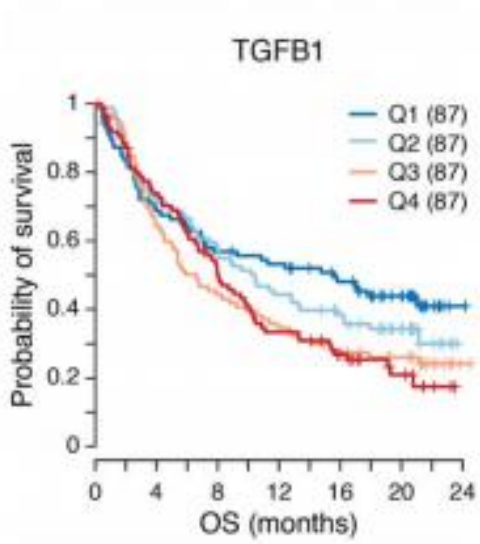
# IMMUNOSUPPRESSIVE TUMOR MICROENVIRONMENT IN PROSTATE CANCER

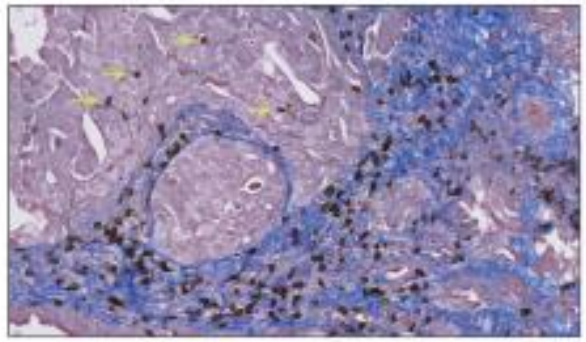


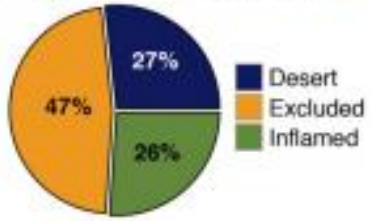

Stultz and Fong. Prostate Can Prostatic Dis 2021

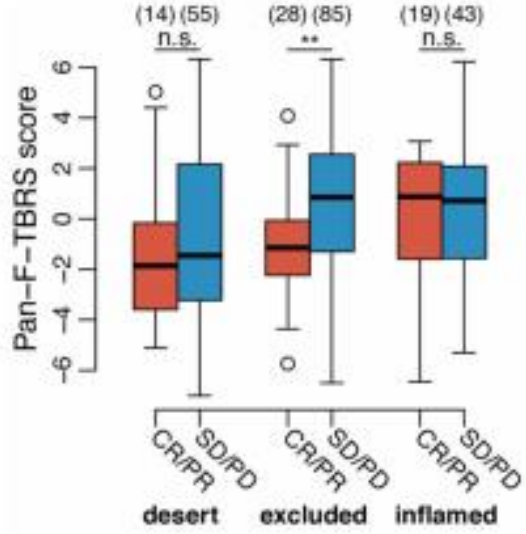
# TGF-β in the "excluded" phenotype

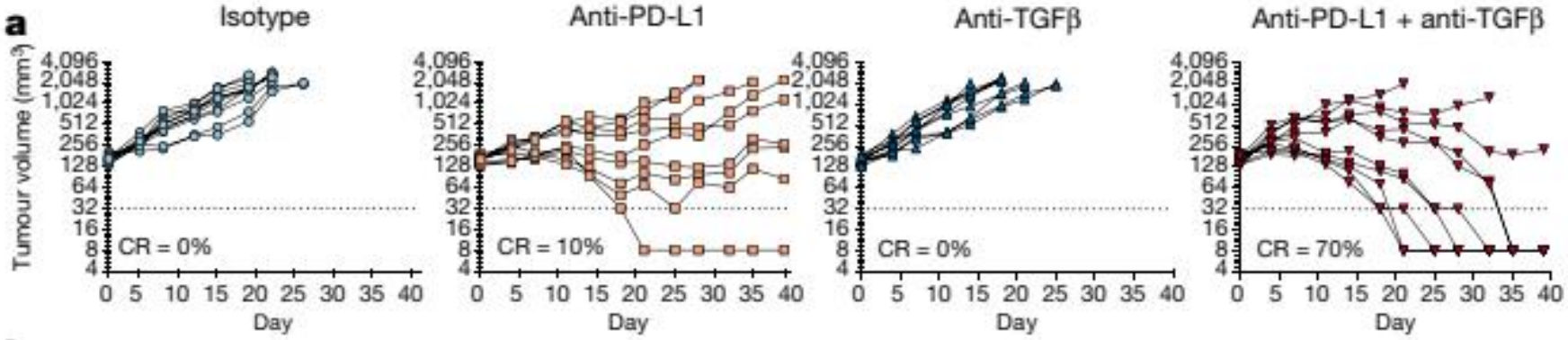




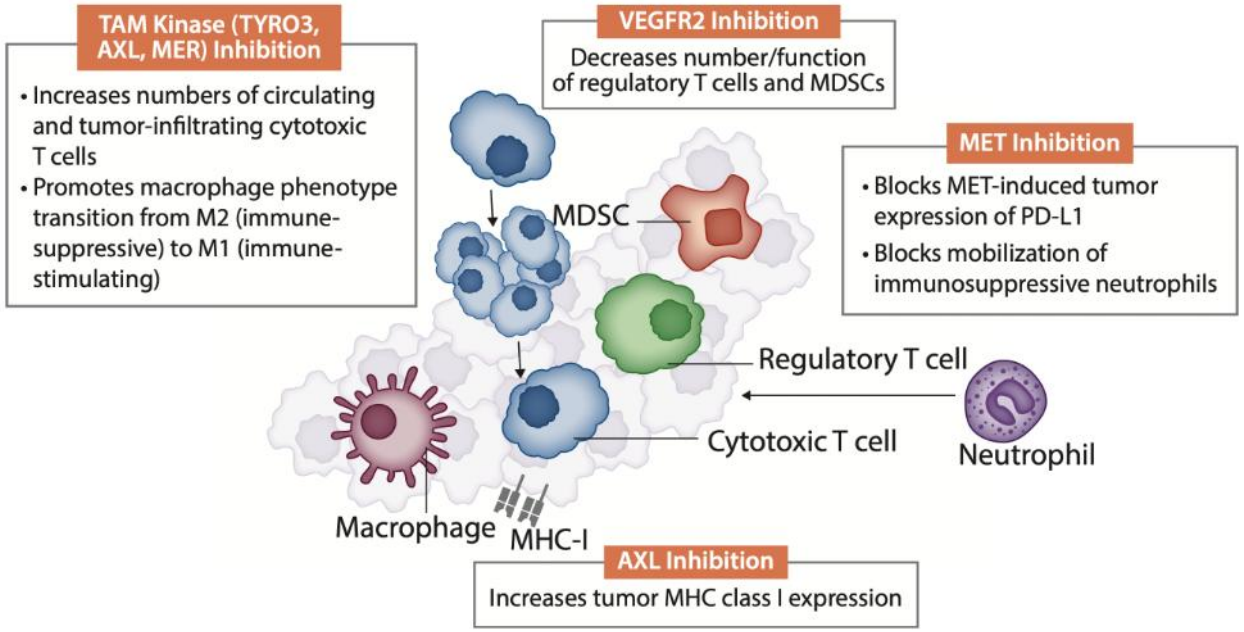



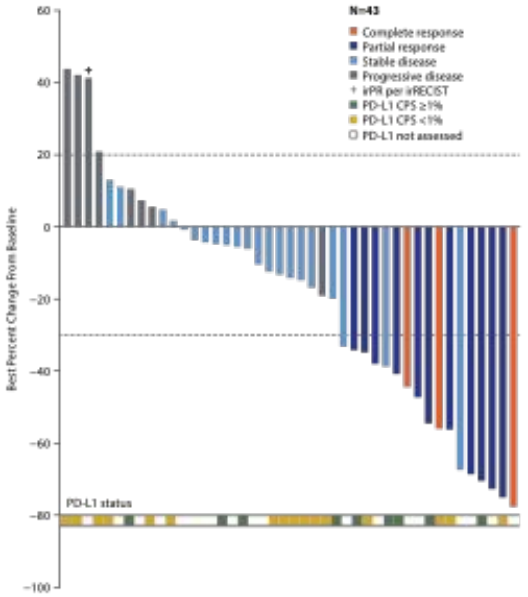

(Mariathasan et al, Nature 2018)

UCSF

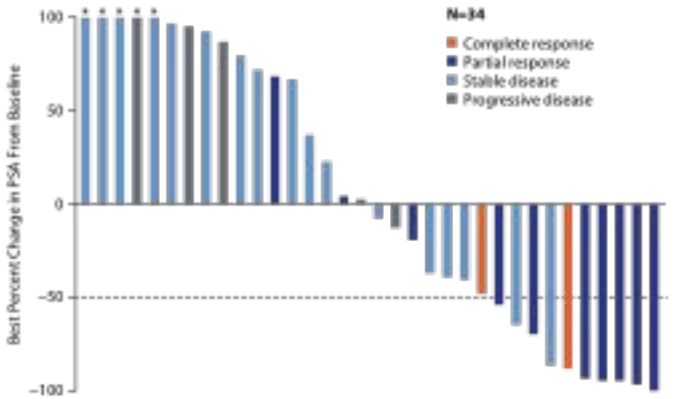
# Targeting myeloid cells with cabozantinib + atezolizumab in mCRPC




RECIST 1.1

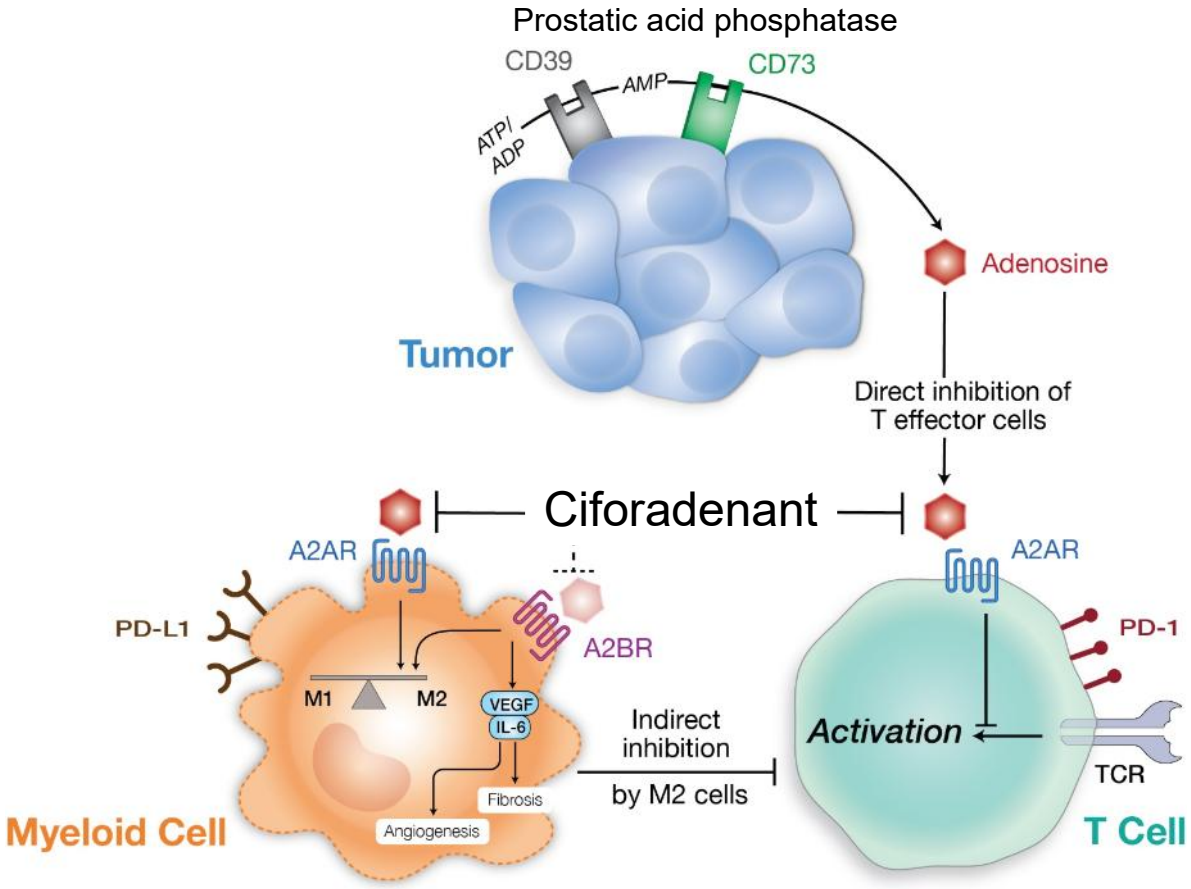



PSA




(Agarwal N et al, ASCO 2020)

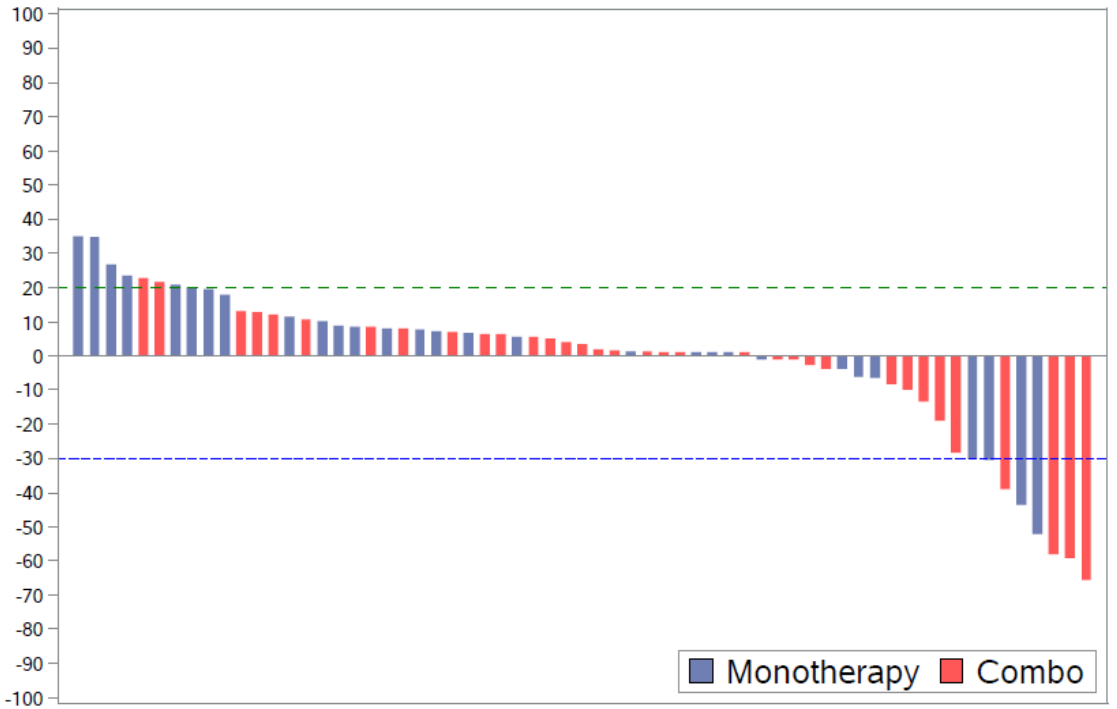
# Targeting the adenosine axis for cancer immunotherapy




**M2 polarization**
**↑ Adenosine Signature**

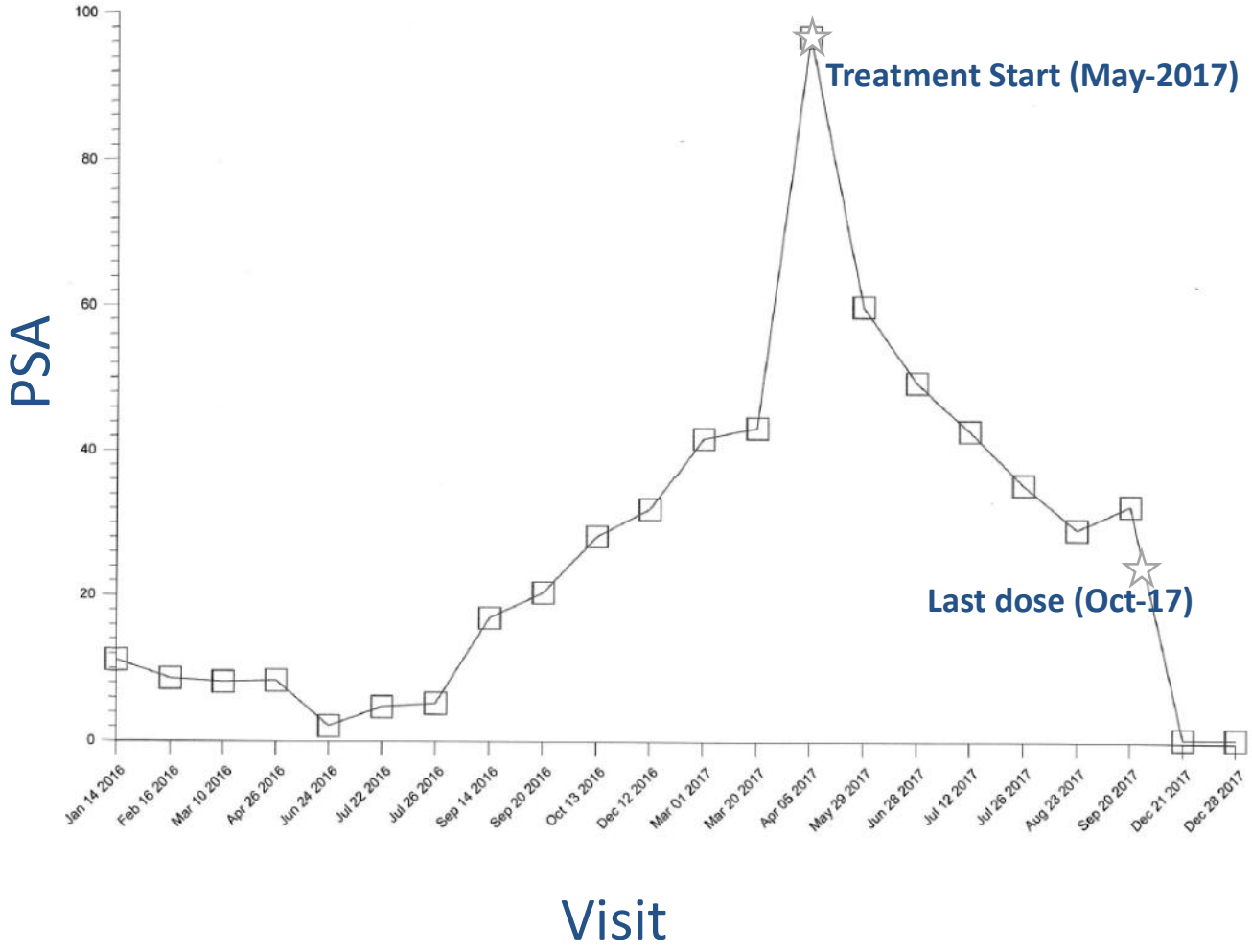
**↑ PD-1 expression**
**↓ IL-2 & IFNγ production**
**↓ Proliferation**

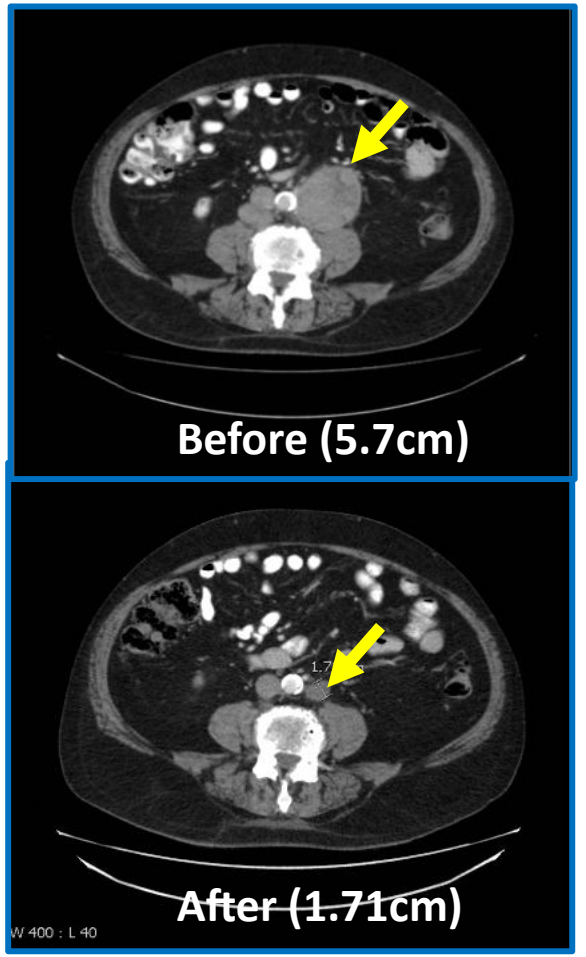
**Tumor response in refractory kidney cancer to A2ARi**



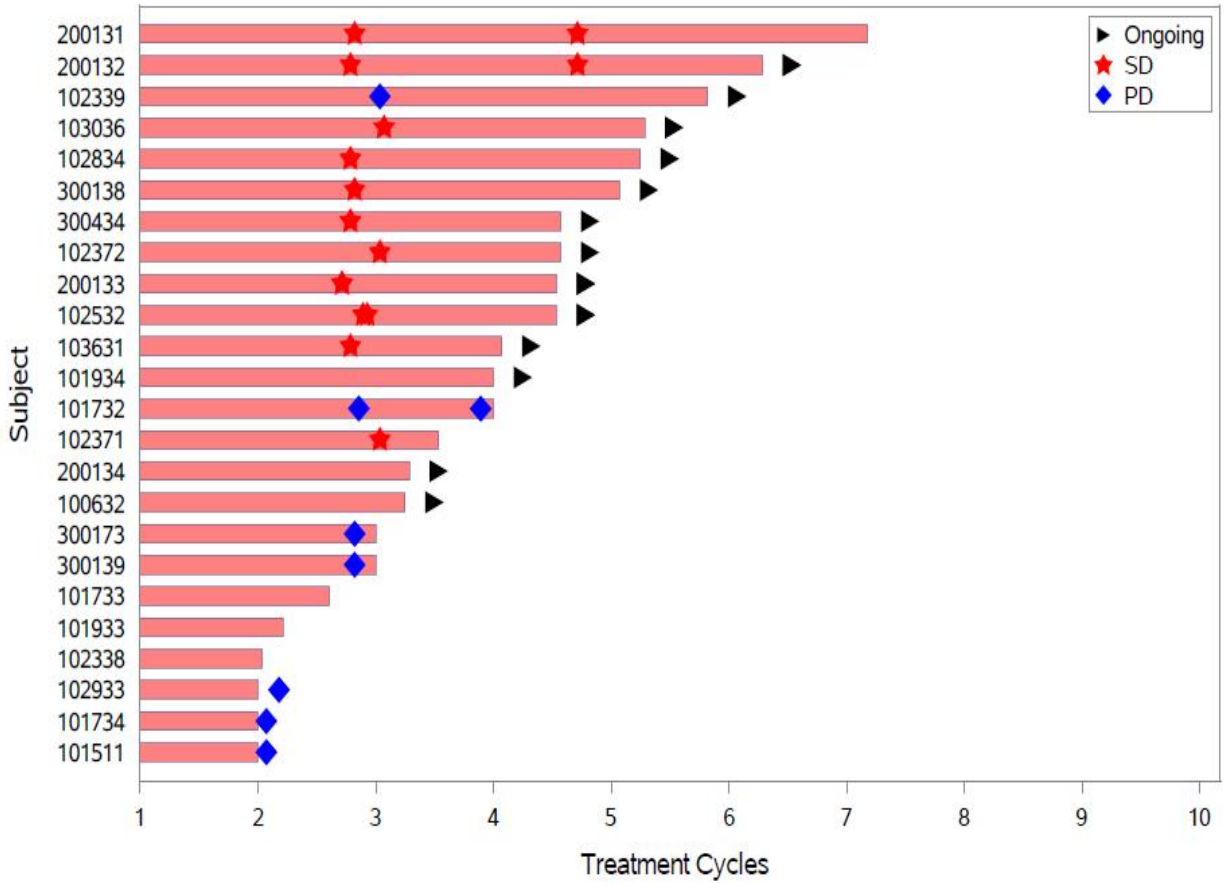

(Fong et al. *Can Discov* 2019)

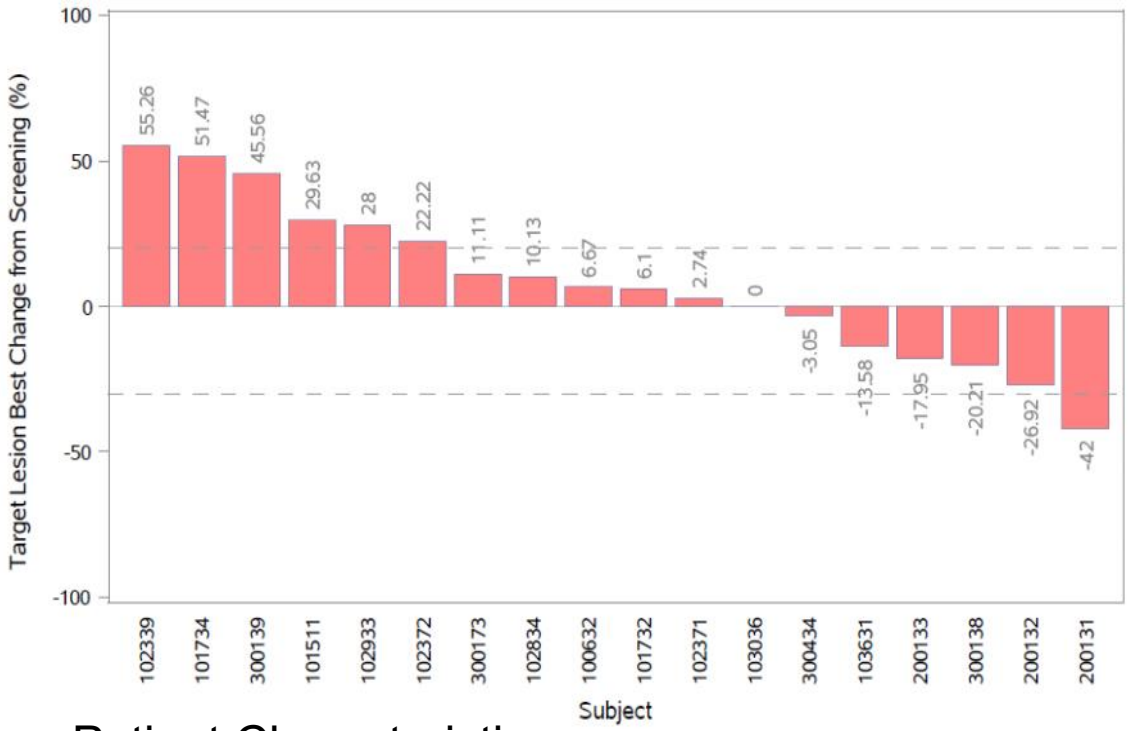
# Clinical activity of ciforadenant + atezolizumab



# Ciforadenant and Atezo in mCRPC



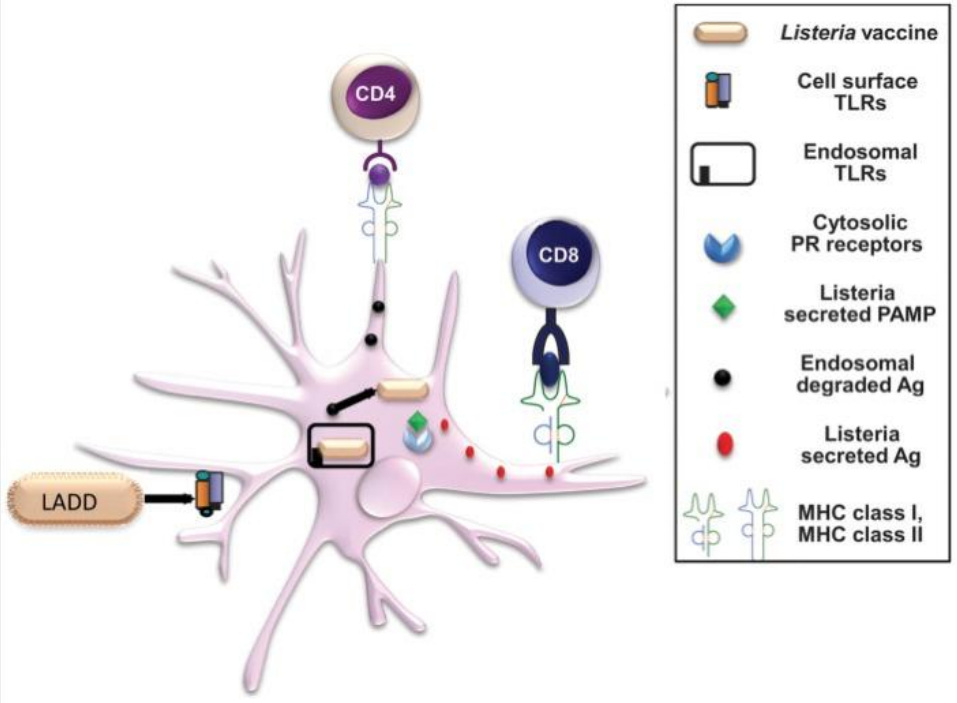



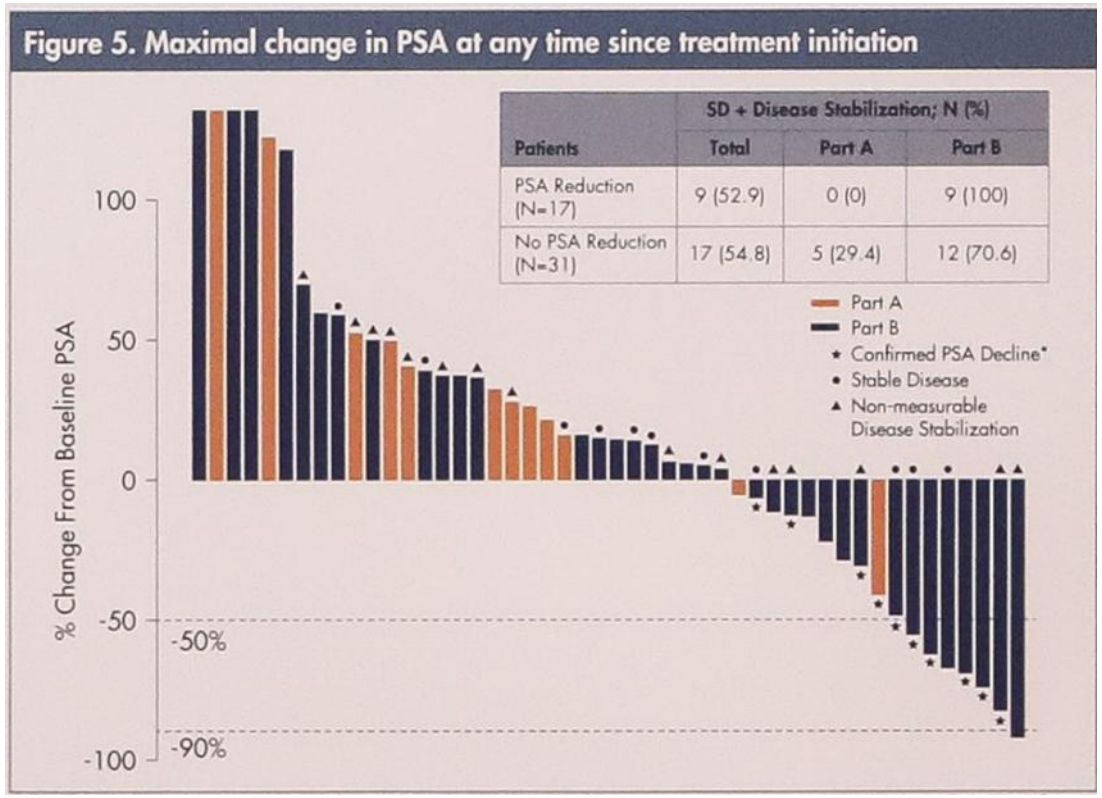

Patient Characteristics:

- Median age 68
- Visceral metastases 46%
- Hormone refractory 96%
- Chemo failures 16%

# VACCINE COMBINATIONS

- **Listeria vaccine (LADD) + CPI**
- KEYNOTE-046: ADXS-PSA +/- pembrolizumab
- Part B: 72% SD, 38% PSA responses, 27% PSA30

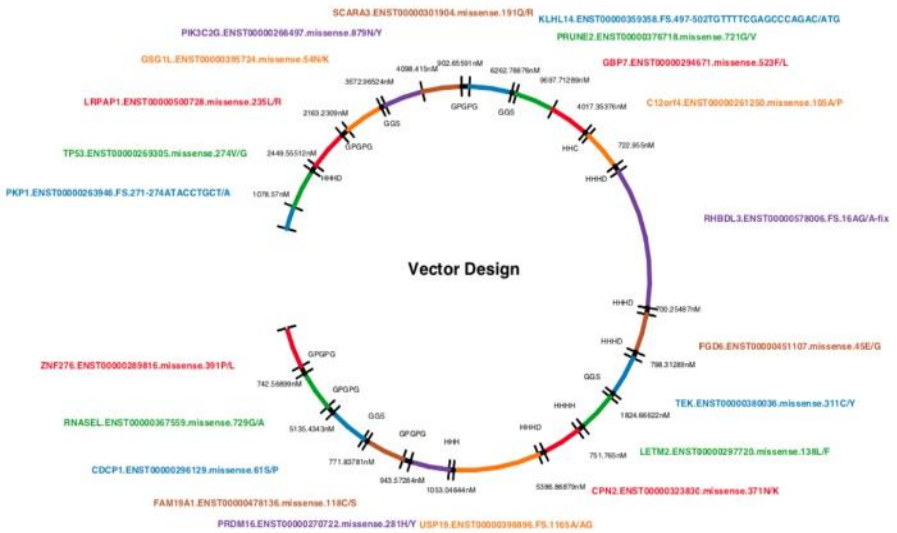


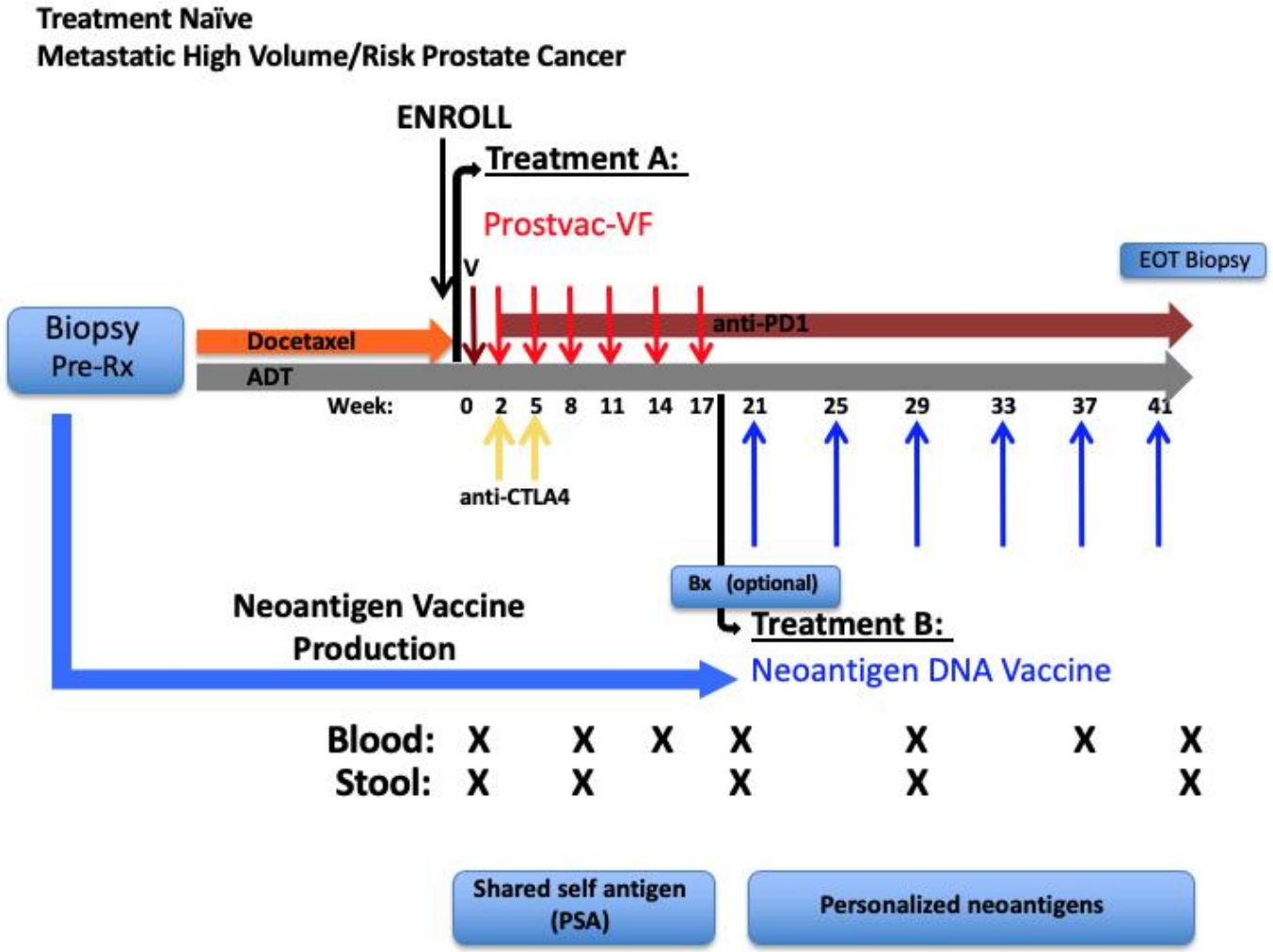




Stein *ASCO* 2018
Stein *GU ASCO* 2020

# VACCINE COMBINATIONS

- **Neoantigen vaccines + CPI**
- mHSPC after tumor burden reduction with docetaxel + ADT
- NCT03532217



# RADIOIMMUNOTHERAPY

- Sipuleucel-T +/- radium-223 (NCT02463799):
  - Improved PSA50 responses (33% vs 0%), PFS/OS
  - Decreased peripheral immune responses

- Radium-223 + atezolizumab (NCT02814669)

- Ongoing: Radium-223 + avelumab + peposertib (M3814) (NCT04071236)

Marshall *ASCO* 2020
Morris *ASCO* 2020

# Immunotherapy has transformed how we treat cancer patients

Enhancing endogenous immunity

Blocking inhibitors

Stimulating effectors

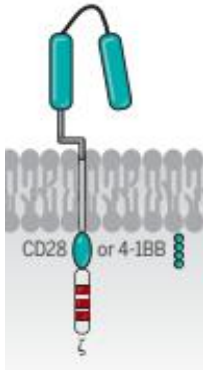
Vaccines

Anti-PD-1

Redirecting immune effectors

Engineering cellular specificities

Colocalizing effectors to tumors

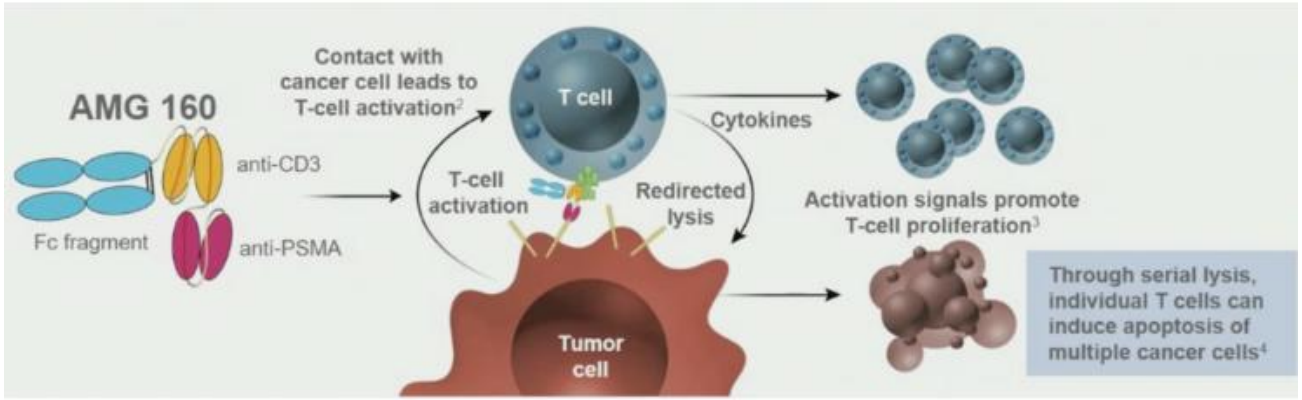



Anti-CD19 CART

Anti-CD19 x anti-CD3

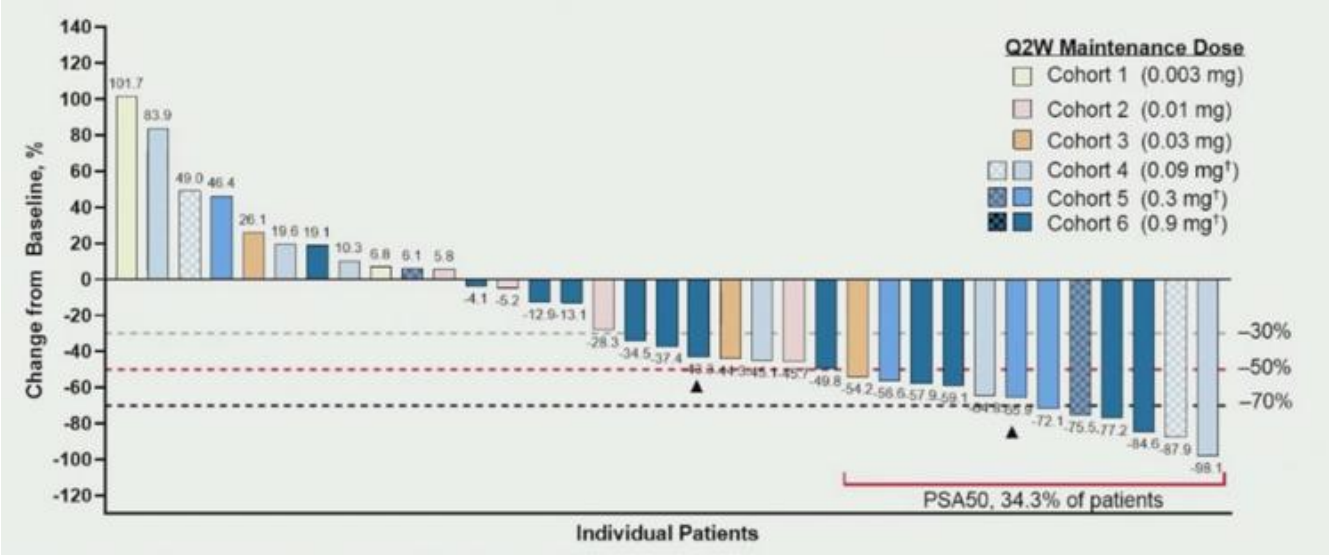
# T CELL BASED

- T cell bi-specifics
  - AMG-160: 34.3% PSA50
  - AMG-509: anti-STEAP




- CAR T-PSMA-TGFβRDN (NCT04227275)

- Will the lack of existing T cells or impedance of trafficking limit efficacy?
- Will toxicity be limiting?




Tran *ESMO* 2020
Kloss *Mol Ther* 2018

# Interim results from a phase 1 study of AMG 160, a half-life extended (HLE), PSMA-targeted, bispecific T-cell engager (BiTE®) immune therapy for metastatic castration-resistant prostate cancer (mCRPC)

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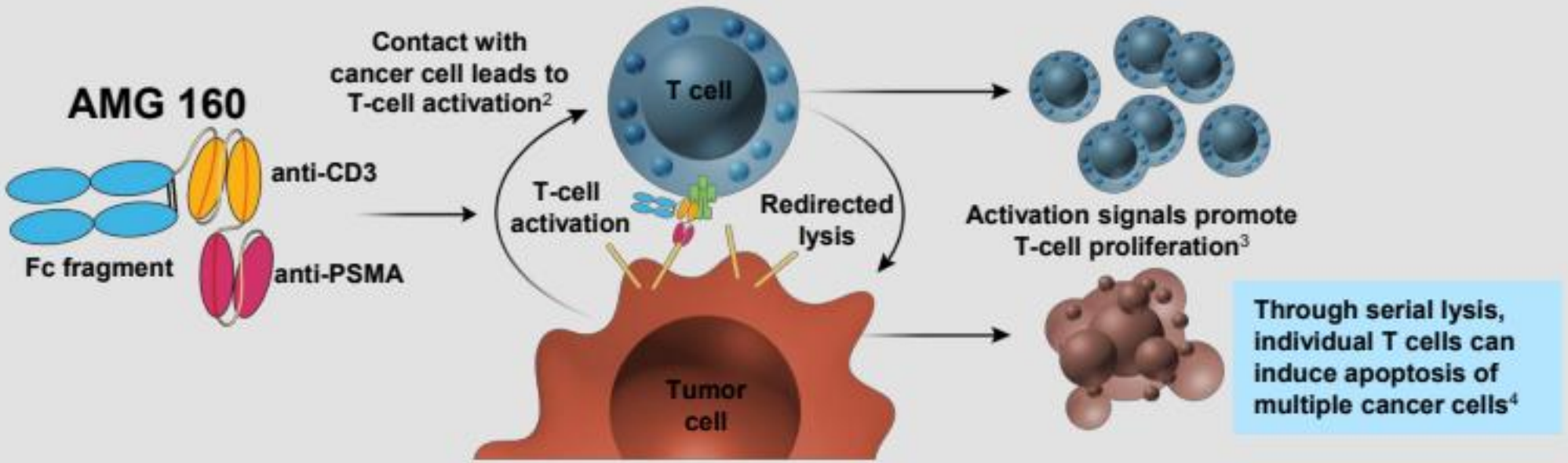
[1]Peter MacCallum Cancer Centre, Melbourne, Australia; [2]Chris O'Brien Lifehouse, Camperdown, Australia; [3]City of Hope, Duarte, CA, USA; [4]University of California, Los Angeles, CA, USA; [5]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [6]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [7]Drug Research Unit, Ghent University, Ghent, Belgium; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [9]Paracelsus Medical University Salzburg, Salzburg Cancer Research Institute-CCCIT and Cancer Cluster, Salzburg, Austria; [10]Indiana University School of Medicine, Indianapolis, IN, USA; [11]Scientia Clinical Research, Randwick, Australia; [12]Amgen Inc., Thousand Oaks, CA, USA; [13]Gustave Roussy, University of Paris Saclay, Villejuif, France

Presented at European Society of Medical Oncology 2020 Virtual Congress, September 19-21, 2020

# AMGEN BITE® (BISPECIFIC T-CELL ENGAGER) IMMUNOTHERAPY




- BiTE® molecules engage a patient's own T cells to attack and eradicate cancer cells[1]
  - T-cell activation induces transient cytokine release and tumor killing[1]
- Blinatumomab (BLINCYTO®, Amgen Inc.) is the first and only bispecific immunotherapy approved in oncology worldwide[1]
- AMG 160 is a half-life extended PSMA x CD3 BiTE® immunotherapy for mCRPC

1. Baeuerle PA, et al. Cancer Res. 2009;69:4941-4. 2. Klinger M, et al. Immun Rev. 2016;270(1):193-208. 3. Bargou R, et al. Science. 2008;321:974-7. 4. Stieglmaier J, et al. Expert Opin Biol Ther. 2015;15(8):1093-9.





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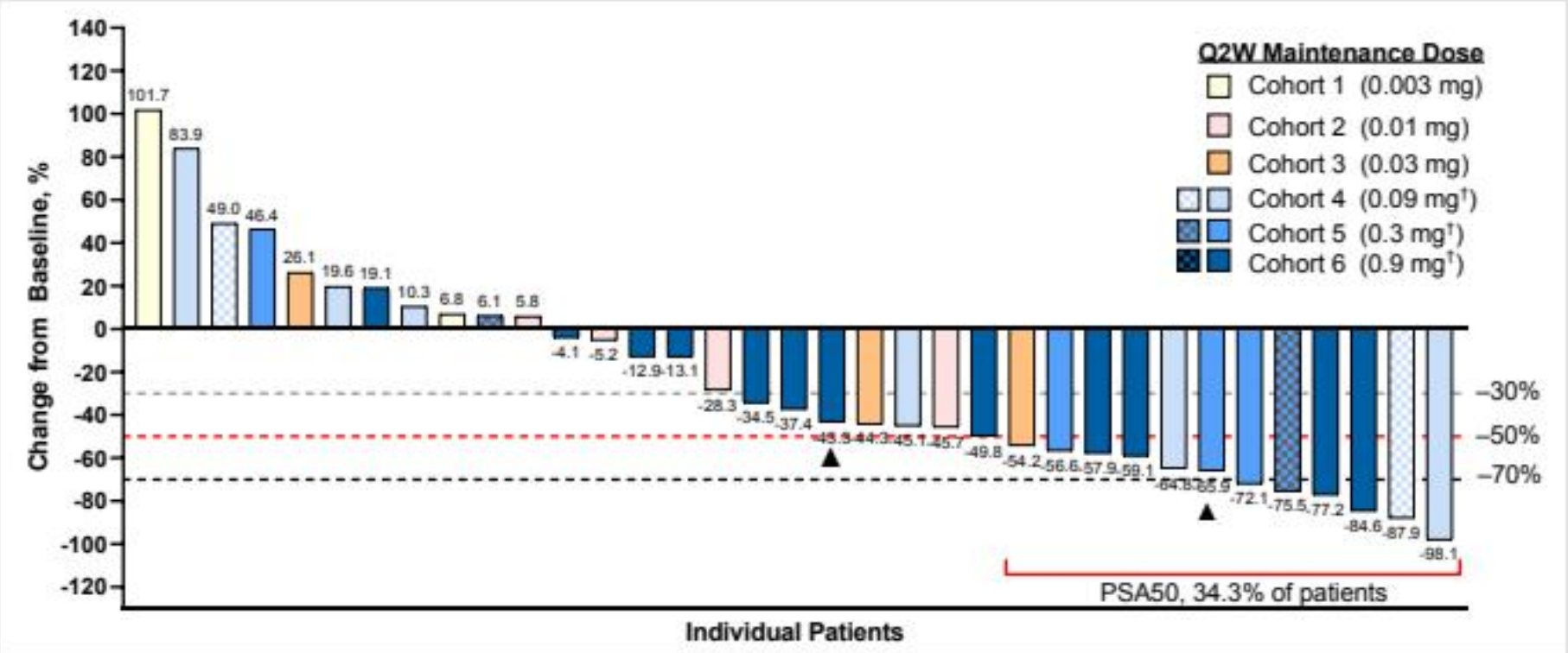
# PSA REDUCTIONS IN THE MAJORITY OF EVALUABLE PATIENTS*

- **PSA reductions (best response) were dose dependent and occurred in 24/35 (68.6%) evaluable patients (20 July 2020)**
- **PSA reductions > 50% occurred in 12/35 (34.3%) evaluable patients**



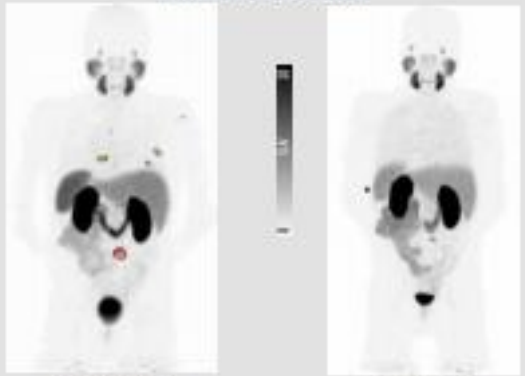

**PSA50 = PSA decrease of ≥ 50%; Q2W = every 2 weeks; * Best PSA reductions at any time point in evaluable patients included those who had received ≥ 1 dose of AMG 160 and had measurable baseline PSA; † Checkered bars indicate cohorts with optimised cycle 1 priming strategies; ▲ Indicates patient who had failed prior LuPSMA treatment**

# EXAMPLES OF DEEP RESPONSES TO AMG 160

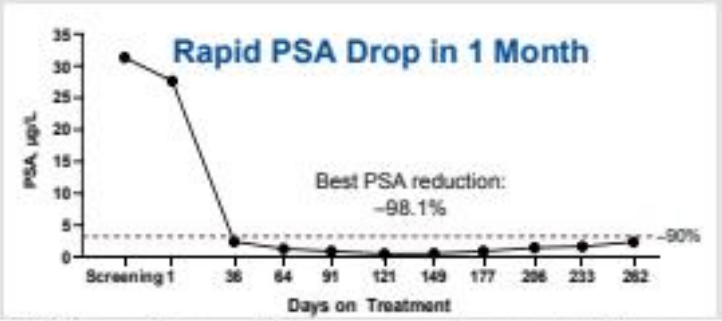
| | |
|---|---|
| **Patient** | 10112001002 |
| **Prior Rx** | Surgery, radiotherapy, docetaxel, enzalutamide, bicalutamide, and talazoparib |
| **Cohort** | 4 (0.09 mg with cycle 1 priming) |

**PR by 3 Months**

PSMA PET/CT



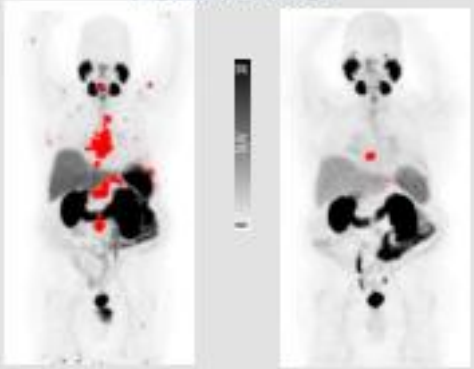
Baseline Week 12



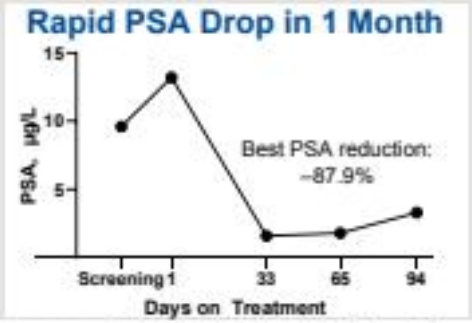

| | |
|---|---|
| **Patient** | 10166004005 |
| **Prior Rx** | Surgery, docetaxel, enzalutamide, sipuleucel |
| **Cohort** | 4 (0.09 mg with optimised cycle 1 priming) |

**Not RECIST evaluable**

PSMA PET/CT

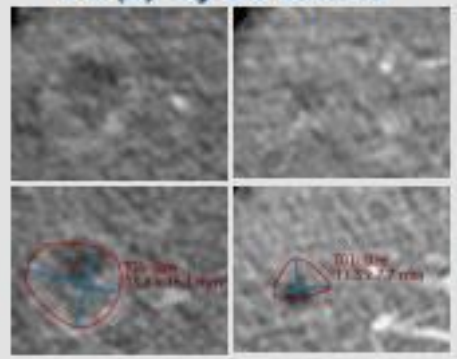


Baseline Week 12



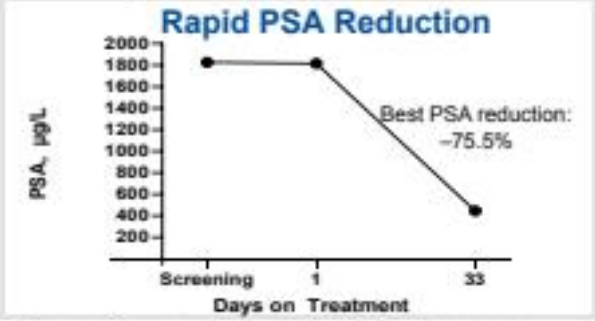

| | |
|---|---|
| **Patient** | 10166004006 |
| **Prior Rx** | Radiotherapy, apalutamide, docetaxel, sipuleucel-T, radium-223 |
| **Cohort** | 5 (0.3 mg with optimised cycle 1 priming) |

**PR (u)* by 2.5 Months**



**Baseline**
T01 Liver Segment VIII

**Week 10**
40% reduction vs baseline




**PET/CT = positron emission tomography–computed tomography; PR = partial response; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RECIST = Response Evaluation Criteria in Solid Tumors; u = unconfirmed; * PR (u) response reported after 20 July, 2020 data cutoff**





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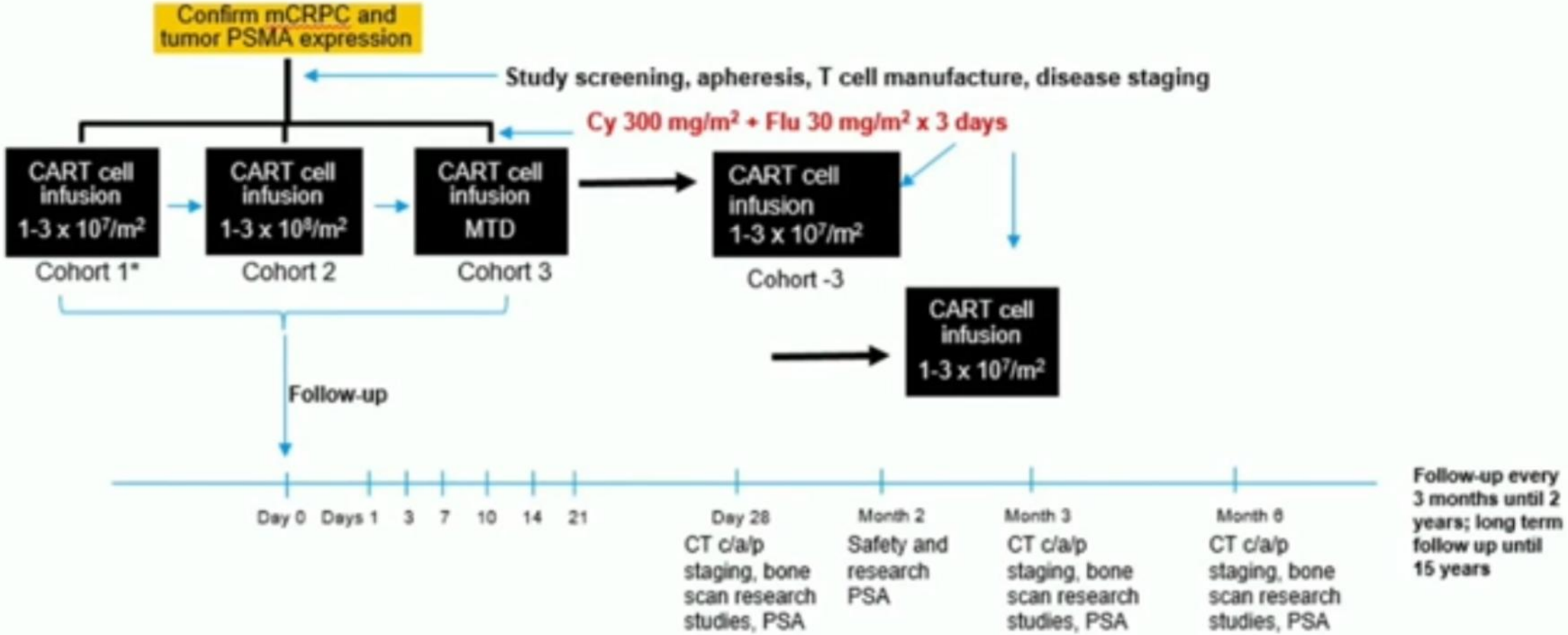
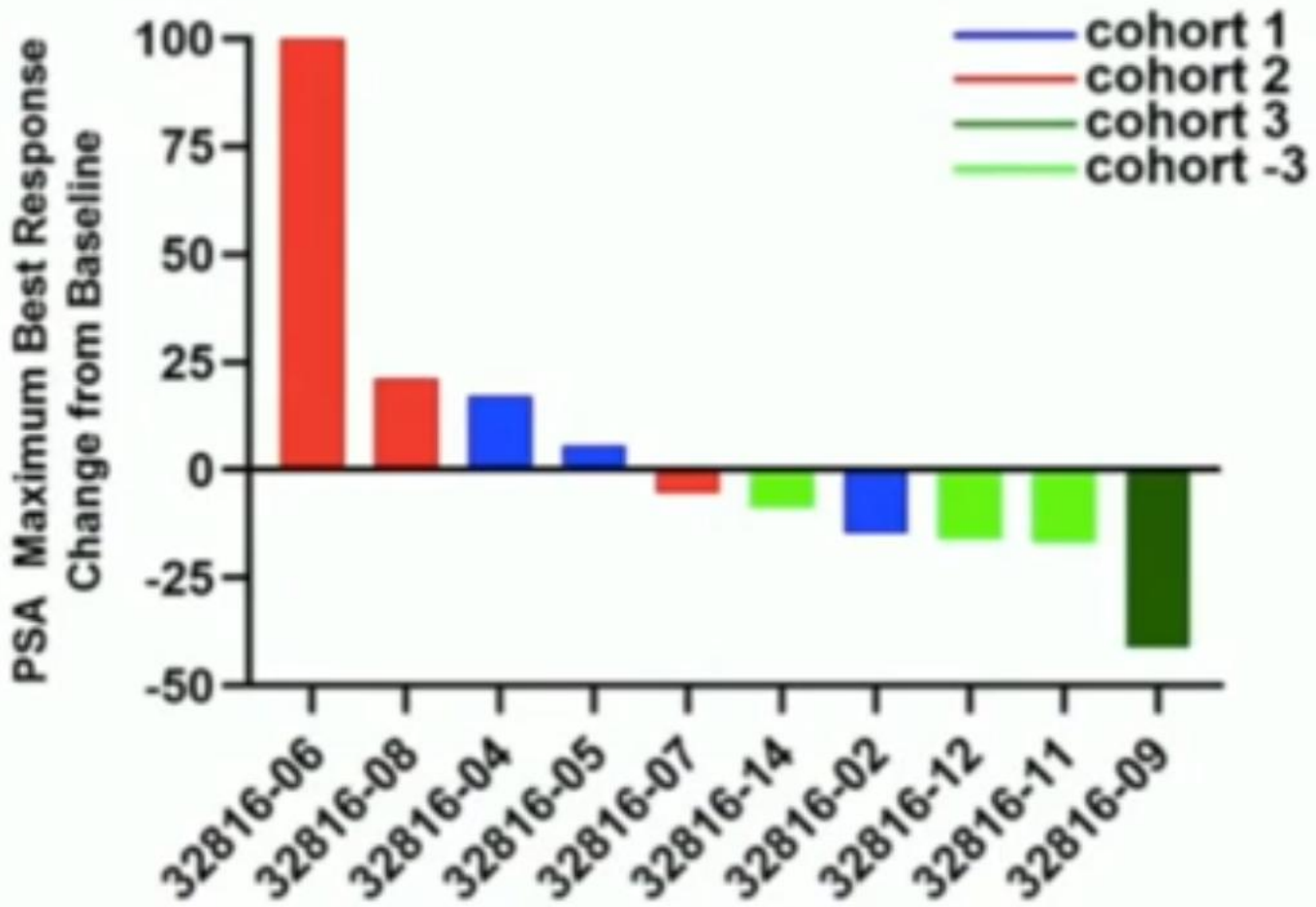
# Study Schema

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




Narayan et al. PCF 2020

# PSA waterfall plot of all treated patients




Narayan et al. PCF 2020

# Conclusions

- Prostate cancer can respond to immunotherapy
- Immune checkpoint inhibition leads to low rates of response.
  - Phase 3 trials have not show benefit in unselected patients.
  - Responses can be very durable.
- Multiple immune resistance mechanisms are operative in prostate cancer.

UCSF

# Future directions

- Treatment combinations will be needed to address multiple resistance mechanisms.
- Empiric -> rationale combinations must be developed through studying our patients.
- Patient selection
  - Tumor intrinsic ($MSI^{hi}$, CDK12-loss)
  - Immune attributes of our patients
- Redirecting T cells (BITE, CART) are showing early signs of clinical activity

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