Immunotherapy for Advanced Prostate Cancer

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Disclosures

- Consulting Fees: SeaGen, Exelixis, Bayer, Janssen, Pfizer

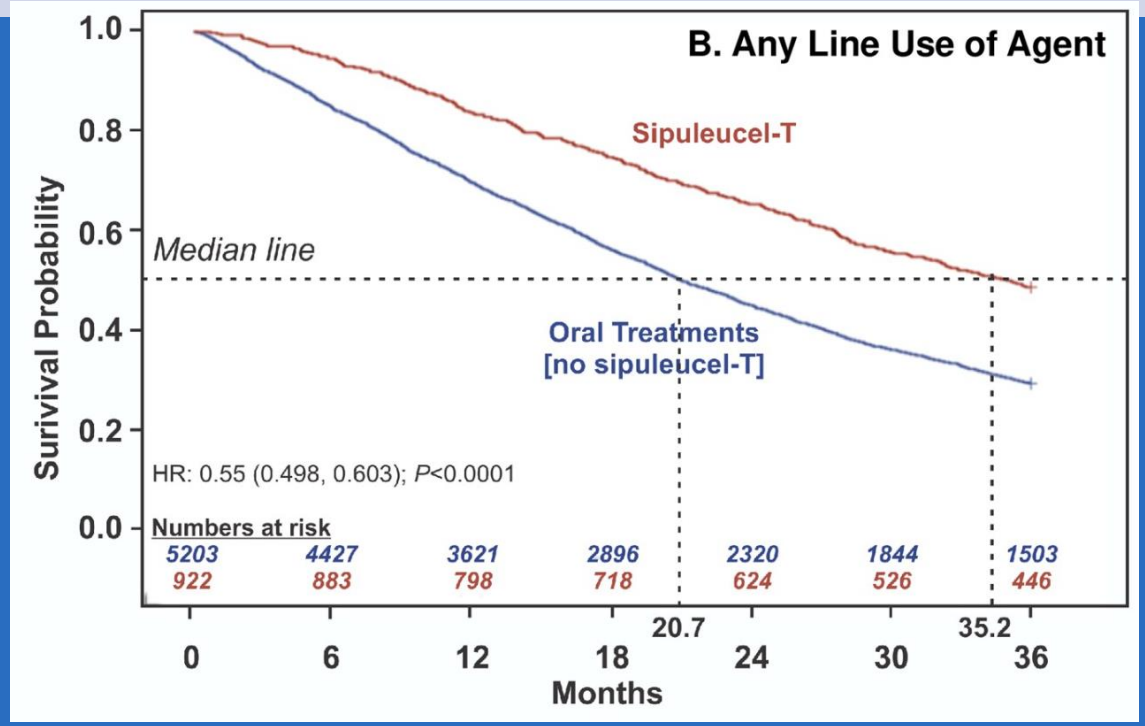
Cellular immunotherapy in mCRPC: past

Sipuleucel-T: approved 2010

OS advantage[1] without rPFS delay or objective responses

Mechanistic support: product parameters[2], CD8 lytic T cell phenotype induction[3]

OS benefit supported in crossover analyses[4] and PROCEED registry, esp AfrAm[5]

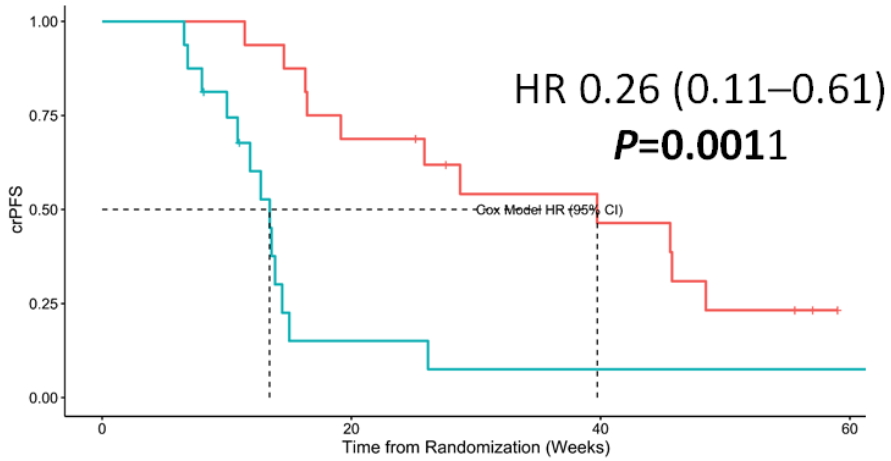


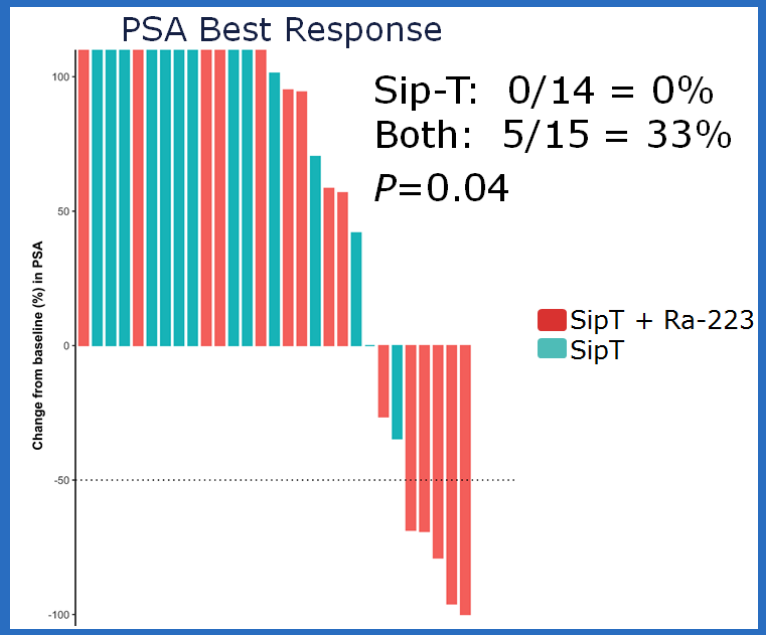
McKay et al, GU ASCO 2020; abstr 42

1. Kantoff PW et al NEJM 2010; 63:411
2. Sheikh N et al Cancer Immunol Immunother 2013; 62:137
3. Antonarakis E et al. Clin Cancer Res 2018
4. George DJ et al Cancer Immunol Res 2015; 3:1063
5. Sartor O et al PCAN 2020; 23:517

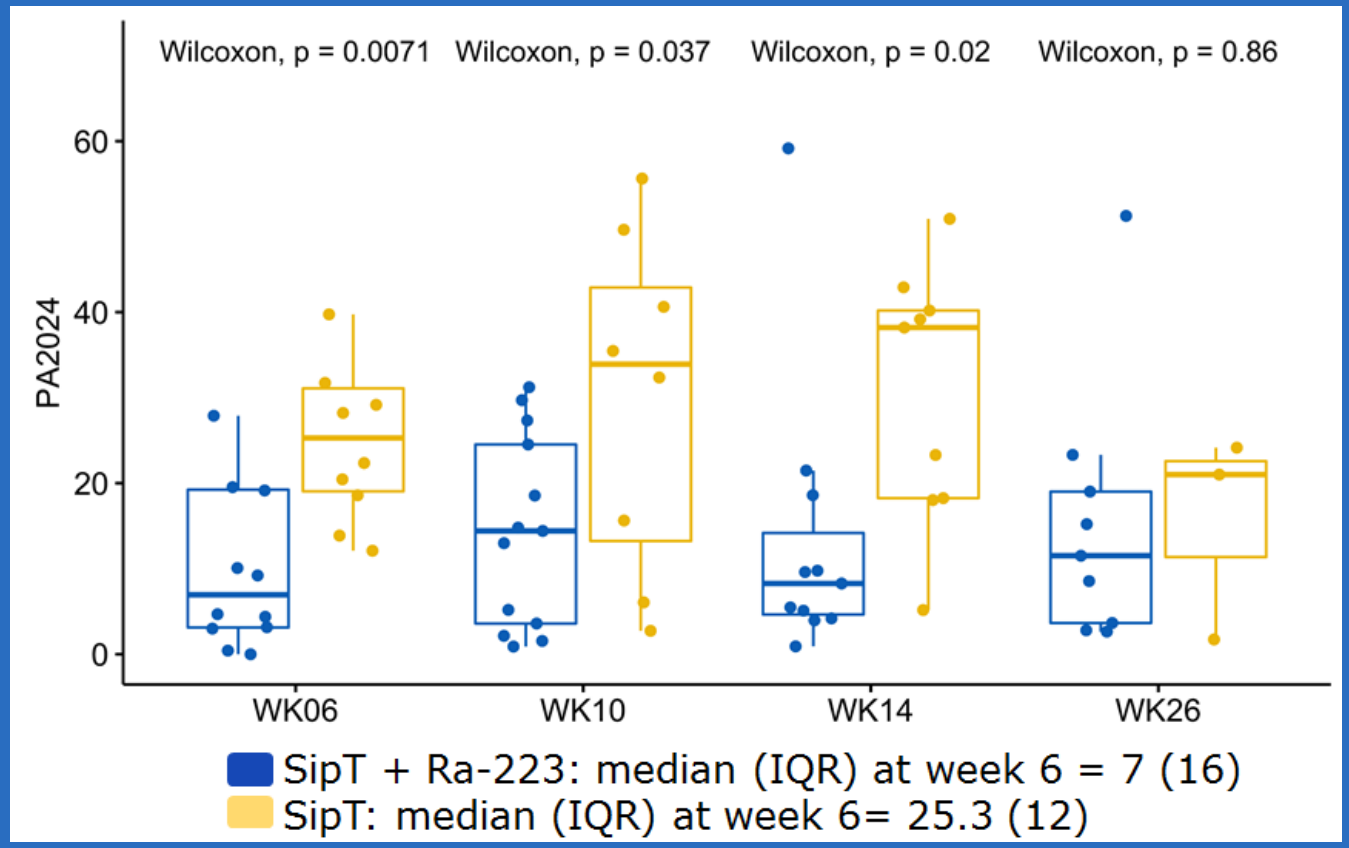
Future directions: SipT + Radium223

Time to radiographic/clinical progression





Marshall CH et al. GU
ASCO abstr 2020



Vaccine approaches

Examples: ProstVAC, GVAX

Advantages:

- Easy administration
- Specific (less toxic)

Disadvantages

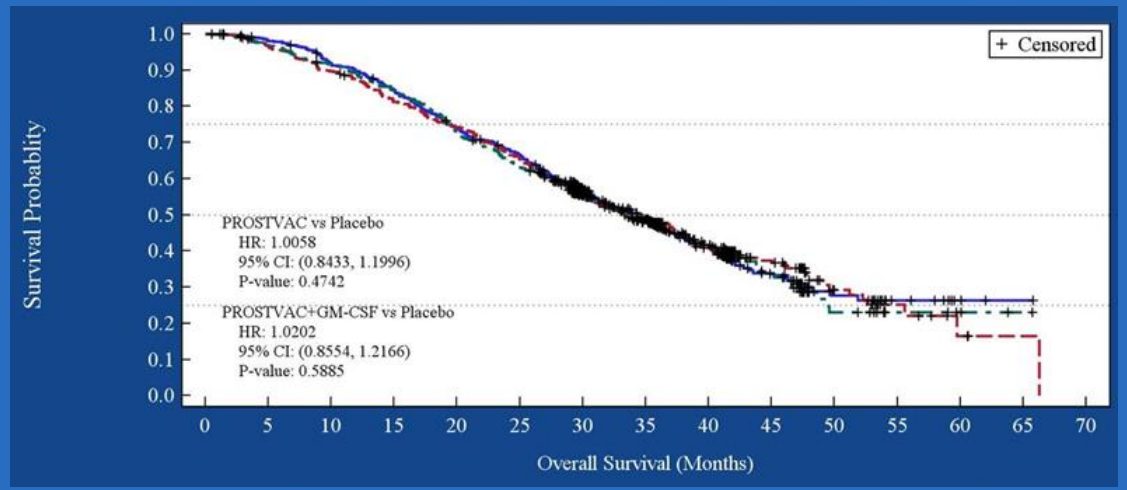
- Single antigen (ProstVAC)
- ? Overcome immune suppression

Future:

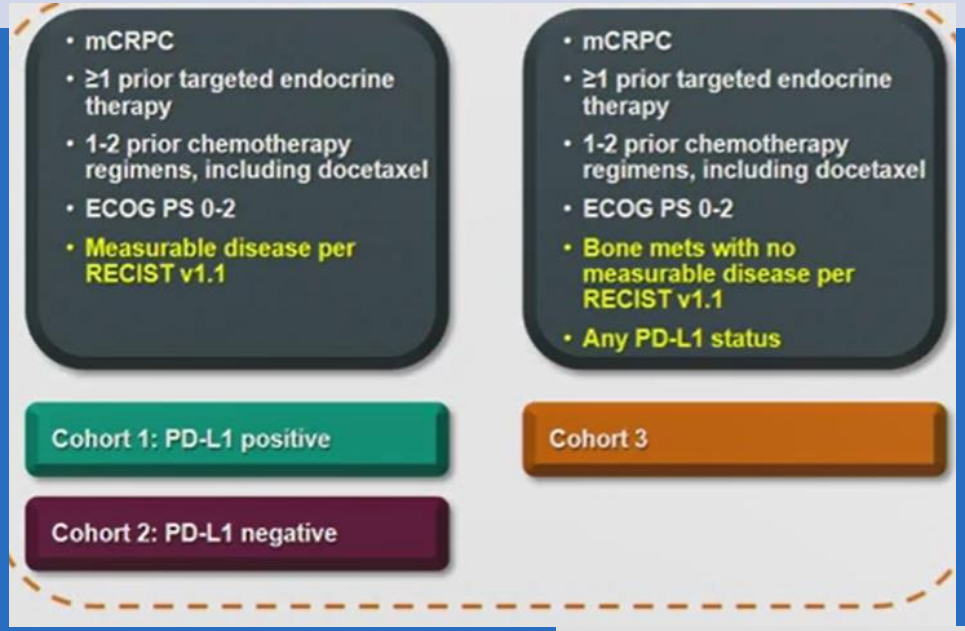
- McNeel (U Wisconsin) AR target w/ GM-CSF
- Oncoimmune (PSA/IL2/GM-CSF)

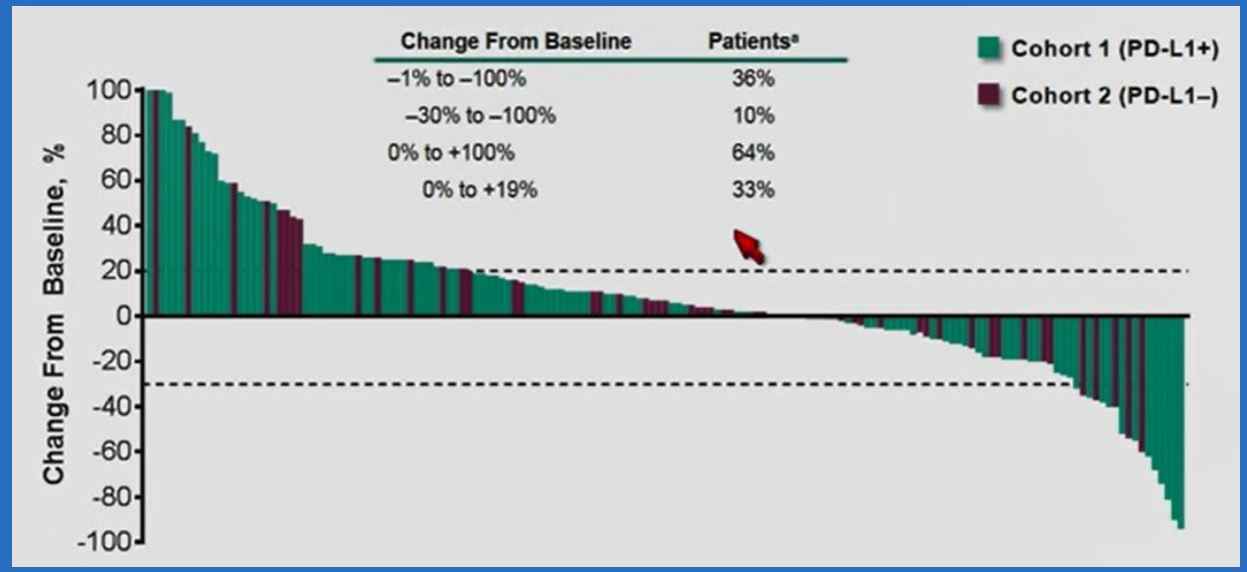
Trial	Med OS	HR (95%CI) p value
GVAX vs Docetaxel + pred	20.7 months 21.7 months	1.03 (0.83, 1.28) P=0.78
GVAX + Docetax Docetaxel	12.2 months 14.1 months	1.7 (1.15, 2.53) P=0.0076

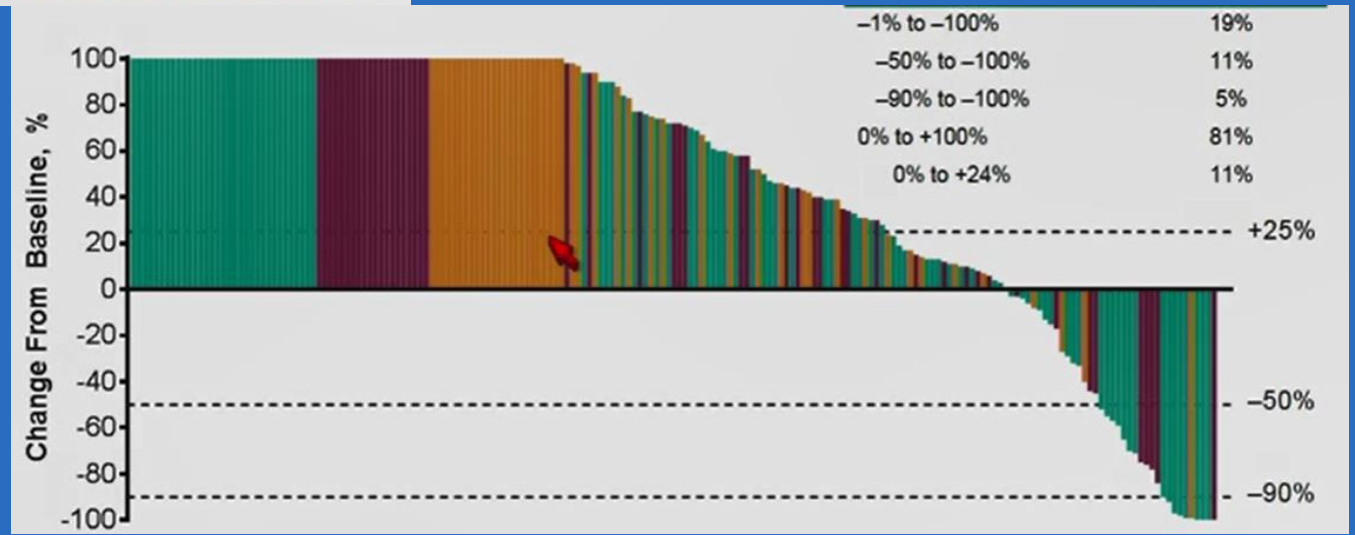
Above: outcomes of phase 3 trials with GVAX
Below: outcome of phase 3 trial of ProstVAC



Immune checkpoint inhibitor therapy in mCRPC: Pembrolizumab (KEYNOTE-199)







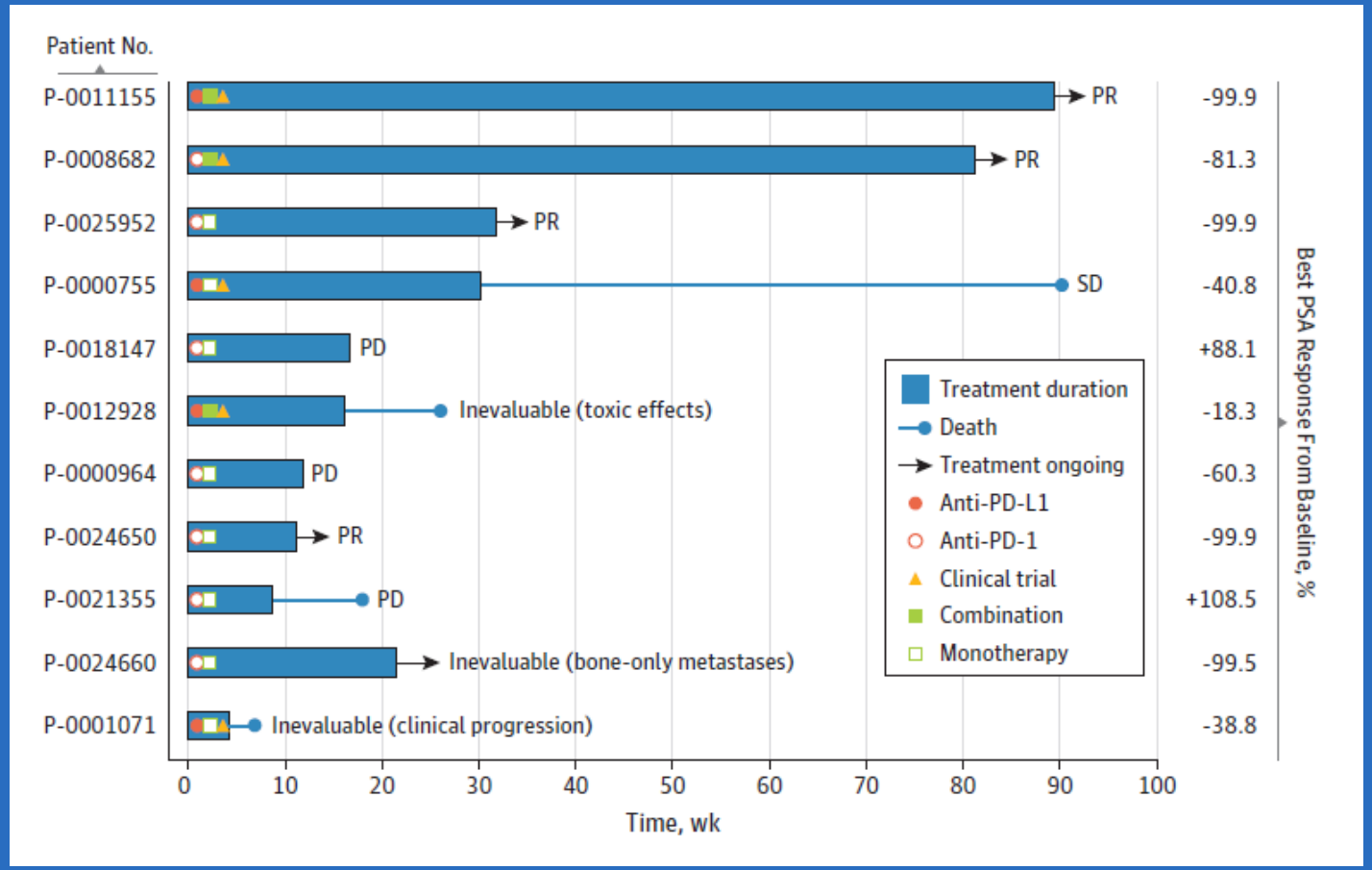
Top right: objective response
Bottom right: PSA changes

DeBono JS. ASCO 2018; oral present

Immune checkpoint inhibitors in mCRPC: selcted by MSI

MSI is present in 3% of prostate cancers

Response to pembrolizumab about 50% (PSA, RECIST)



Abida W et al, JAMA Oncol 2019; 5:471-8

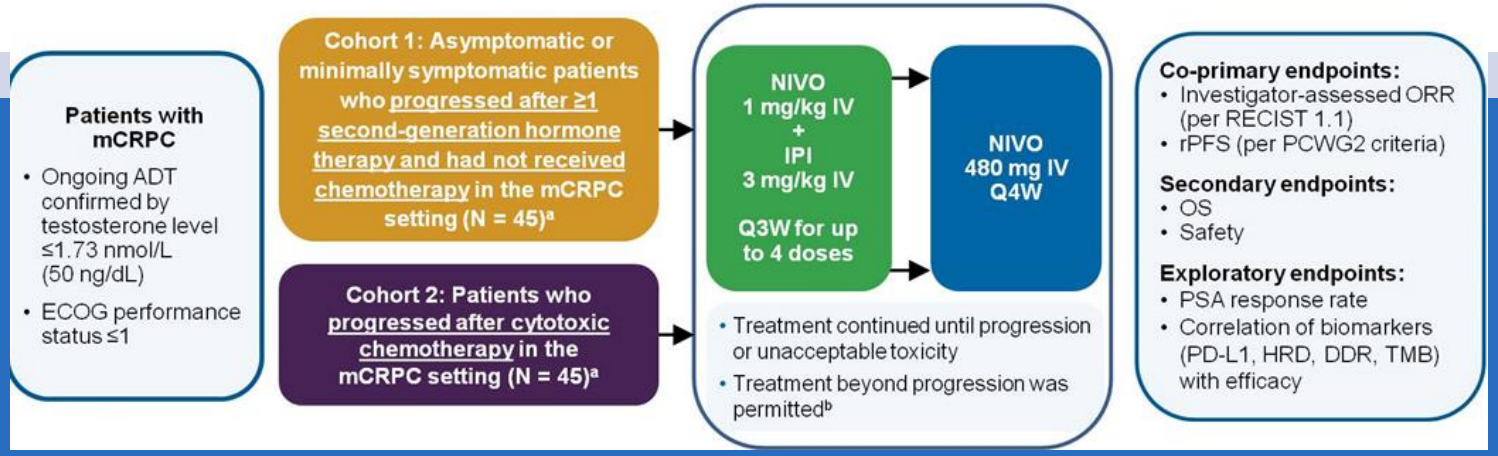
Combinations: checkpoint + checkpoint (Ipi + Nivo)

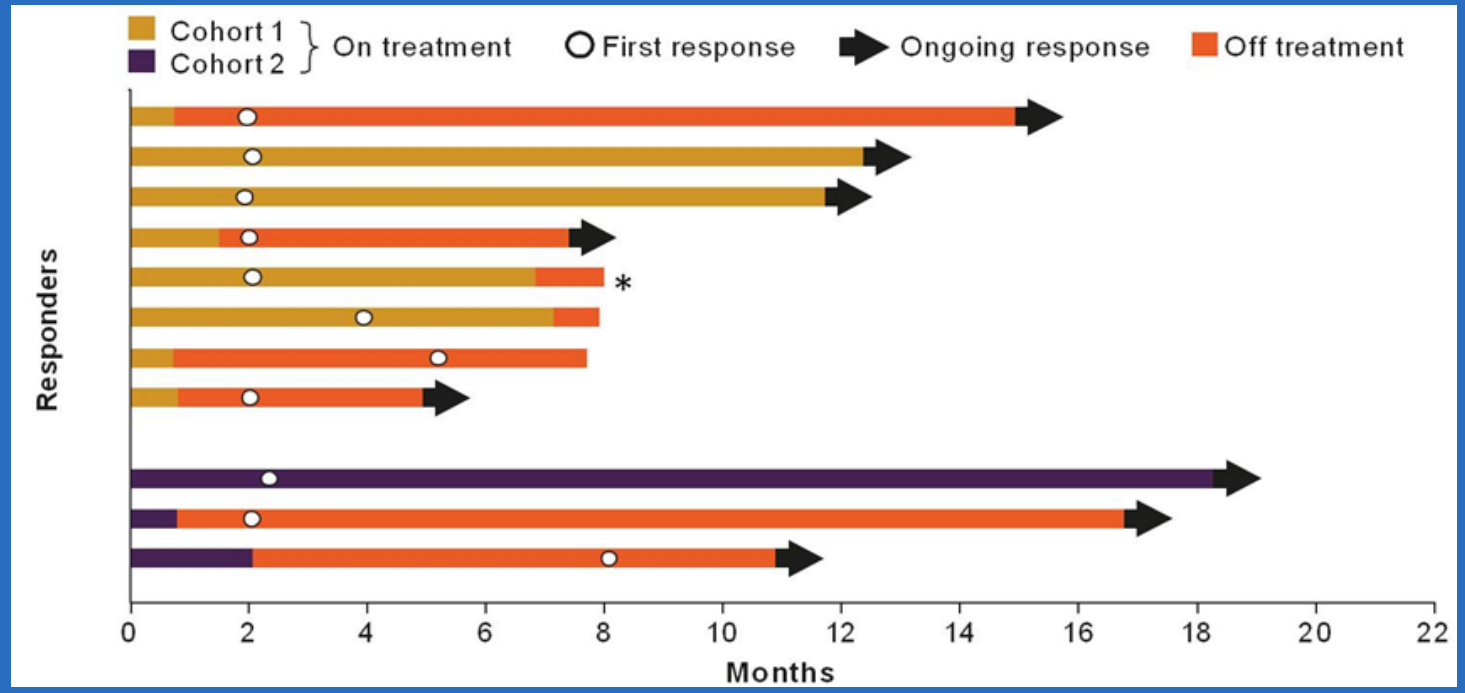
<1/3 received all 4 induction doses

Chemo naïve: 25% objective response with 2 (6%) CR
- PSA response 17.6%

Chemo pre-treated: 10% objective response, 2 (6.7%) CR
- PSA response 10%

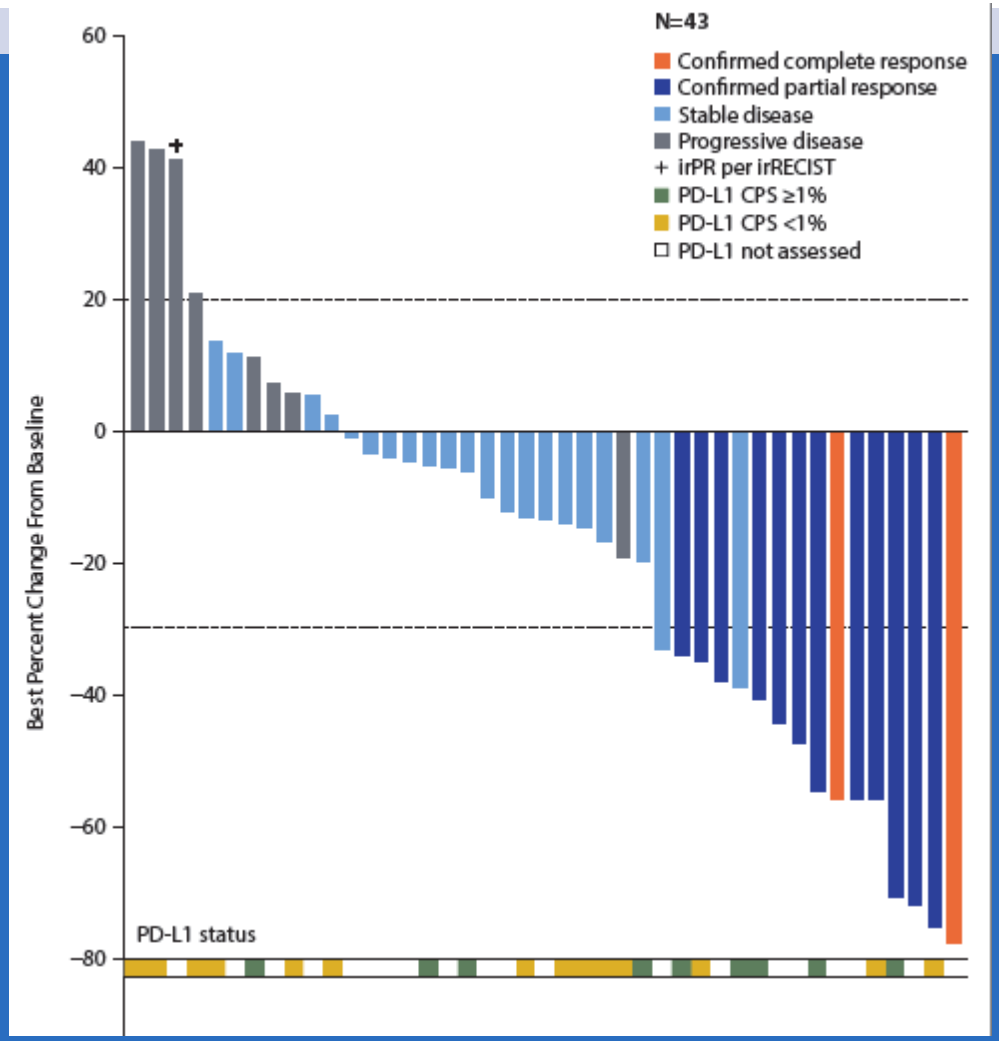
HRD+ had greater response





Sharma P et al, Cancer Cell 2020; 38:489-99

Cabozantinib + Atezolizumab



	CRPC Cohort (N=44)		
	Any Grade	Grade 3	Grade 4
Any AE, n (%)	42 (95)	25 (57)	1 (2.3)*
Fatigue	22 (50)	3 (6.8)	0
Nausea	19 (43)	0	0
Diarrhea	17 (39)	3 (6.8)	0
Decreased appetite	17 (39)	0	0
Dysgeusia	15 (34)	0	0
PPE	14 (32)	1 (2.3)	0
AST increased	11 (25)	2 (4.5)	0
Vomiting	11 (25)	1 (2.3)	0
ALT increased	8 (18)	2 (4.5)	0
Platelet count decreased	8 (18)	0	0
Weight decreased	8 (18)	0	0
White blood cell count decreased	7 (16)	2 (4.5)	0
Hypophosphatemia	7 (16)	1 (2.3)	0
Headache	7 (16)	0	0
Neutrophil count decreased	6 (14)	2 (4.5)	0
Hypertension	6 (14)	1 (2.3)	0
Stomatitis	6 (14)	1 (2.3)	0
Dysphonia	6 (14)	0	0
Hyponatremia	5 (11)	3 (6.8)	0
Arthralgia	5 (11)	1 (2.3)	0
Oral pain	5 (11)	0	0
Rash maculo-papular	5 (11)	0	0

Agarwal N et al. GU ASCO 2020 abstr 139

T cell strategies: BiTE and CarT

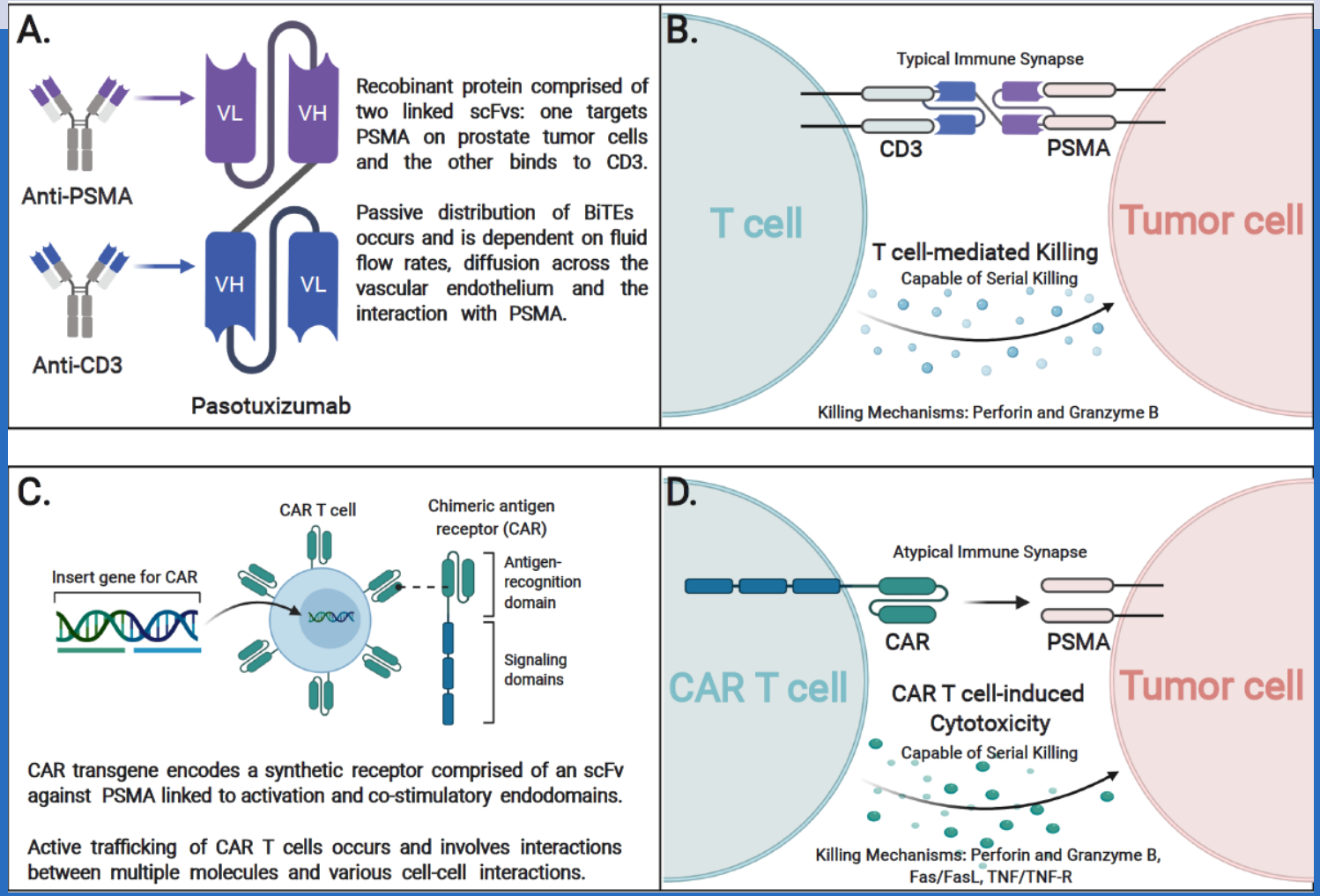
BiTE (A. & B.)

- AMG 160 (PSMA),
- AMG509 (STEAP1)

CarT (C. & D.)

- PSCA (City of Hope)
- PSMA (UPenn, Poseida)

- KLK2-targeted CarT (Janssen)

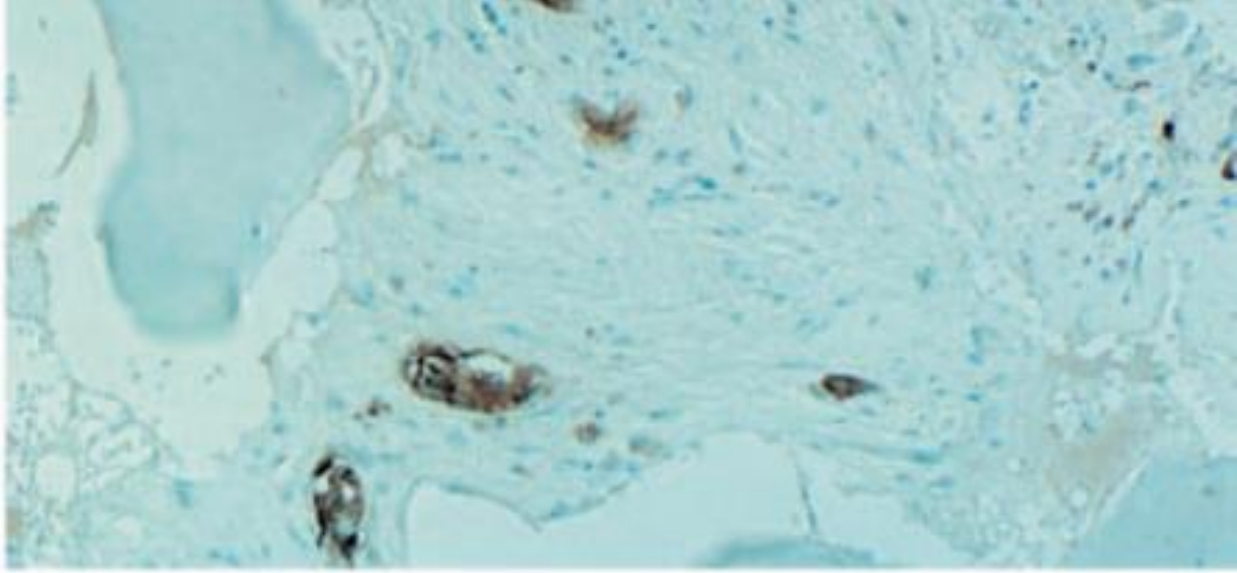


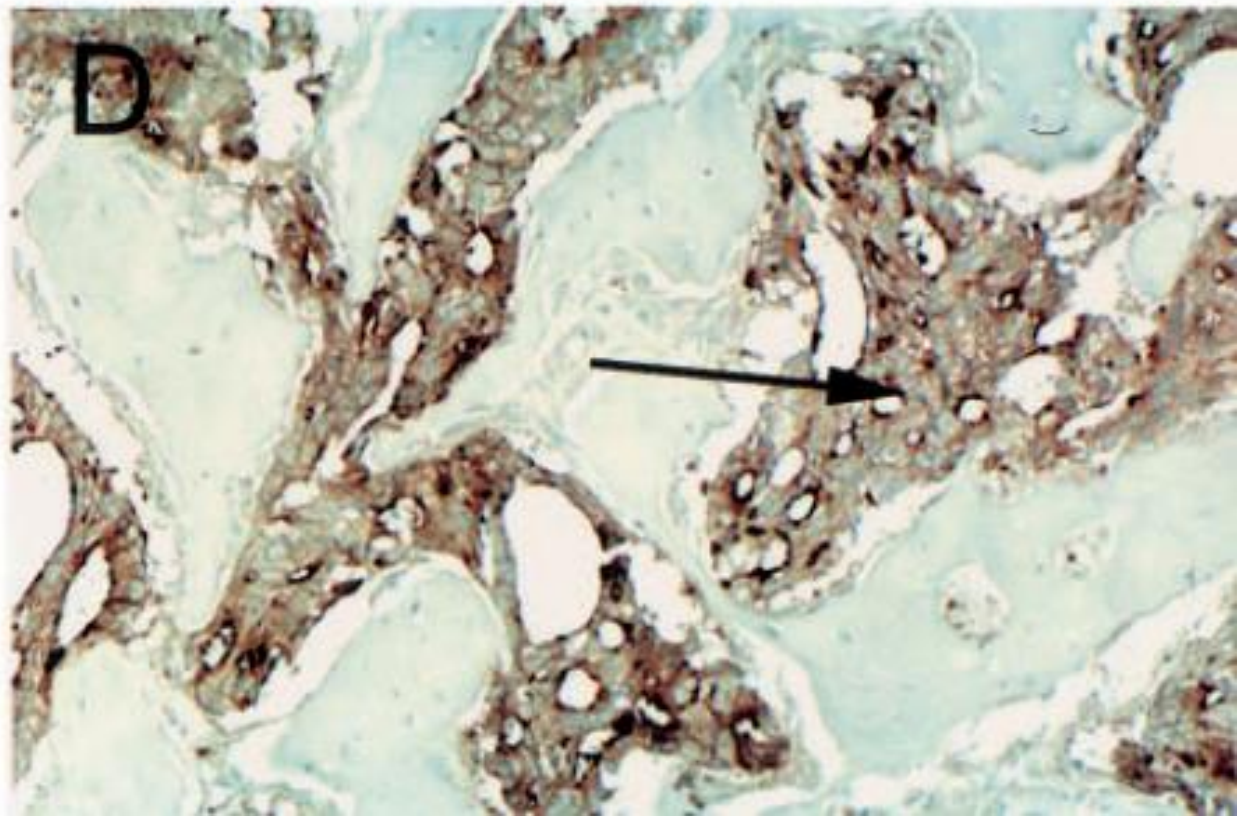
Dorff TB et al. Clin Cancer Res 2021; in press

PSCA as a target

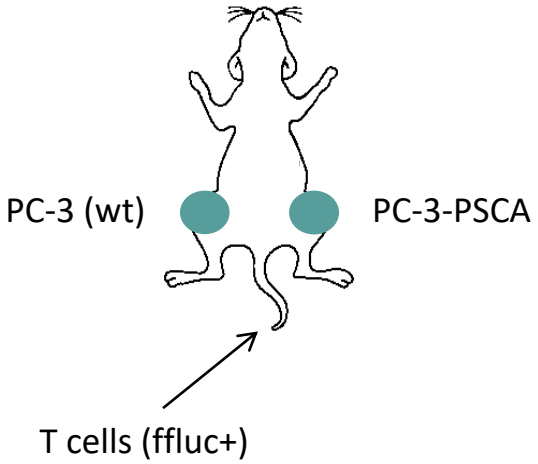
- **Identified by Dr. Reiter in Dr. Witte's lab**
- **Membrane expression**
- **Expressed in 80% of prostate primaries and 90% of metastatic deposits**
- **Downregulated by AR suppression, but overexpressed in castration resistant prostate cancer**
- **Additional cancers: Pancreatic, bladder**

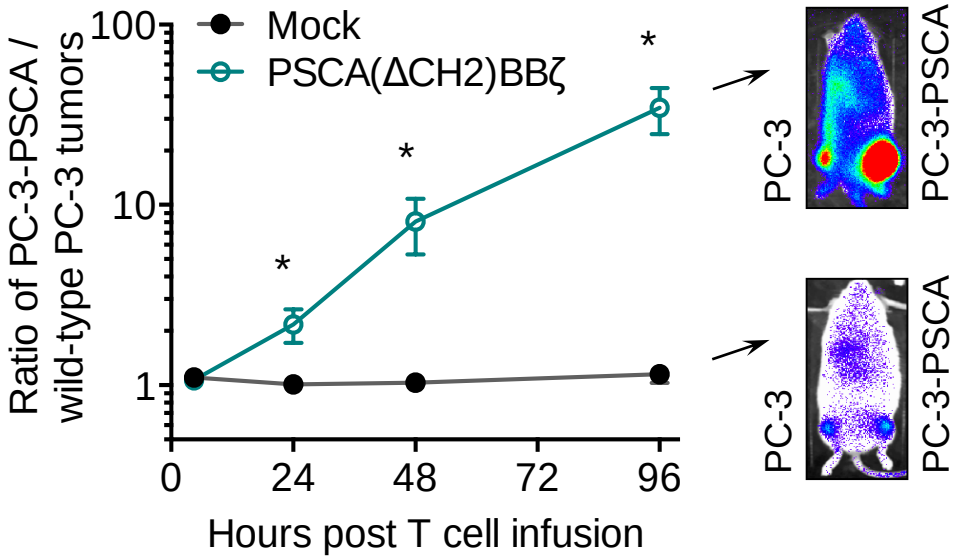
Gu Z et al. Oncogene 2000; 19:1288-96





PSCA-CAR T Cells Home to PSCA^{+} Bone Metastatic Disease in NSG Mice



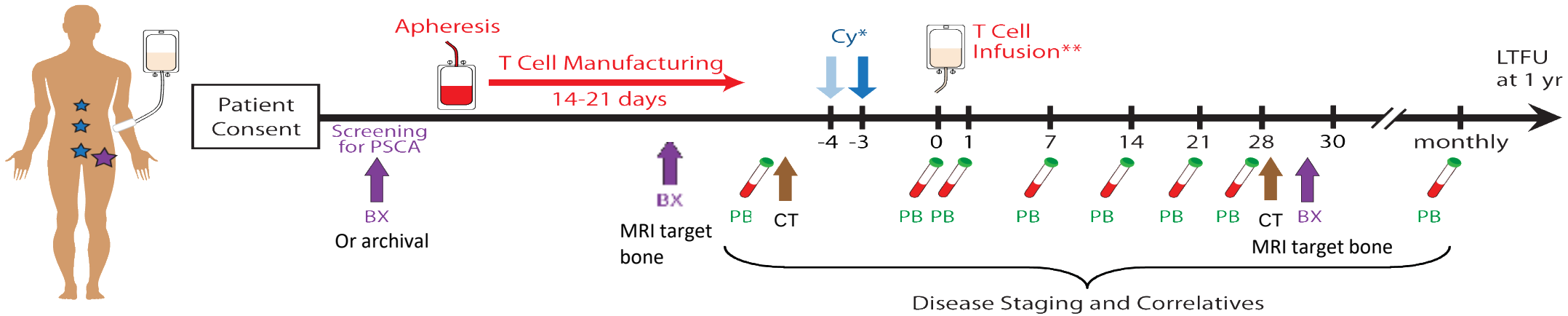


Priceman, et al. OncoImmunology.
2017; doi.org/10/1080/2162402X.2017.1380764

City of Hope

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
PB = peripheral blood

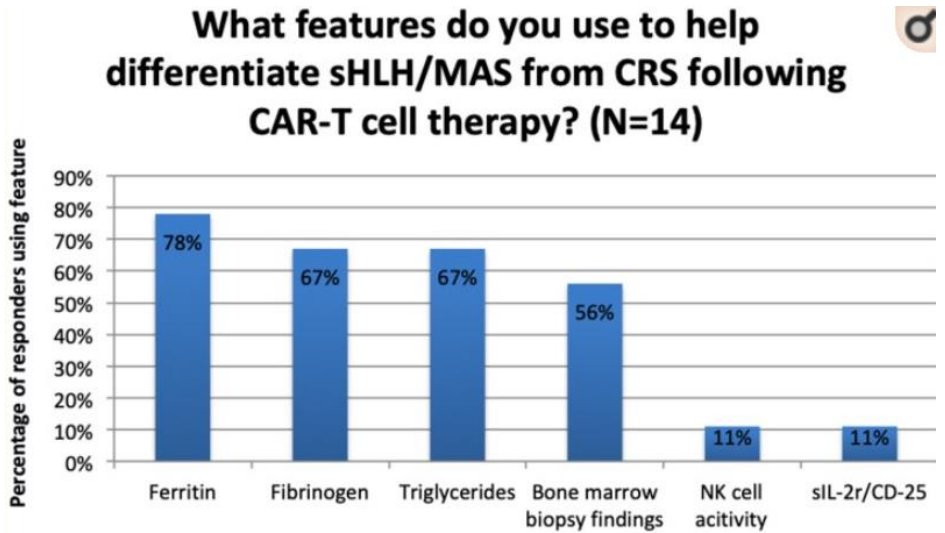
Table 1. CAR+ Cell Dose Schedule				
Dose -1	**Starting Dose 0a**	Dose 0b	Dose 1	Dose 2
50M	**100M**	100M +precond.	300M +precond.	600M + precond.

Toxicities with CAR T for prostate cancer

- Cytokine Release Syndrome in about 1/3
  - Variable onset but typically day 3
  - Have needed tocilizumab
- Cytopenias, infection (from lymphodepletion)
- On target, off tumor
  - PSCA: cystitis
  - PSMA: TBD
- Macrophage activation

- Responses are being achieved!

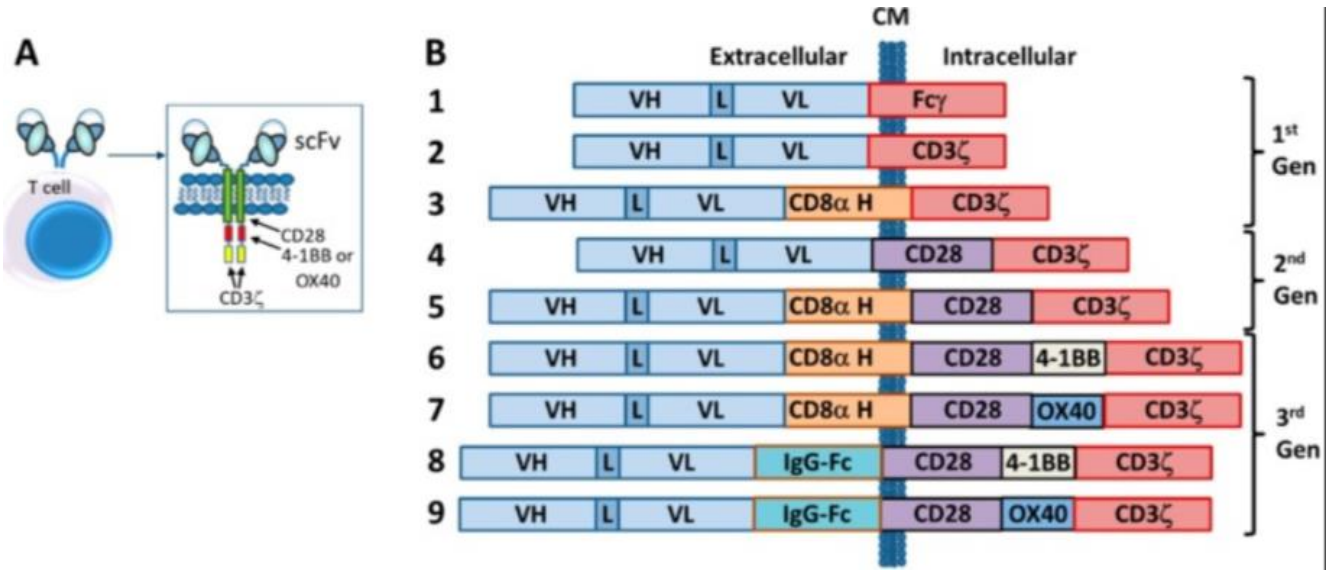
Published criteria	Components of criteria	Centres (%)
HLH-2004 (for fHLH) (24)	Molecular diagnosis consistent with HLH or 5/8 of the following: Fever, splenomegaly, bi or tri-lineage cytopenia, hypertriglyceridaemia ± hypofibrinogenaemia, haemophagocytosis on bone marrow biopsy, no diagnosis of malignancy, low/absent NK cell activity, raised ferritin, raised sIL-2r	43
H-score (for all sHLH/MAS) (25)	Known underlying immunosuppression, fever, organomegaly, mono-, bi-, or tri-lineage cytopenia, ferritin, triglycerides, fibrinogen, AST, haemophagocytosis on bone marrow biopsy. Overall score predicts likelihood of sHLH/MAS	16
Takagi et al. (for SHLH/MAS post-HSCT)	2 major or 1 major and all 4 minor criteria required. Major criteria: (A) engraftment delay, primary or secondary failure or (B) histopathological evidence of haemophagocytosis. Minor criteria: fever, hepatosplenomegaly, elevated ferritin, elevated LDH.	10
PRINTO (for sHLH/MAS in sJIA)	Ferritin > 684 µg/L and 2 of: platelets <181 × 109, AST >48 U/L, triglycerides >256 mg/dL, fibrinogen <360mg/dL	1
MD Anderson (for sHLH/MAS post-CAR-T cell therapy)	Ferritin of > 10,000 µg/L and 2 of: grade > 3 increase in serum transaminases or bilirubin; grade > 3 oliguria or increase in serum creatinine; grade > 3 pulmonary oedema; or histological evidence of haemophagocytosis in bone marrow or organs	7
Combination of the above		23



CAR T vs BiTE

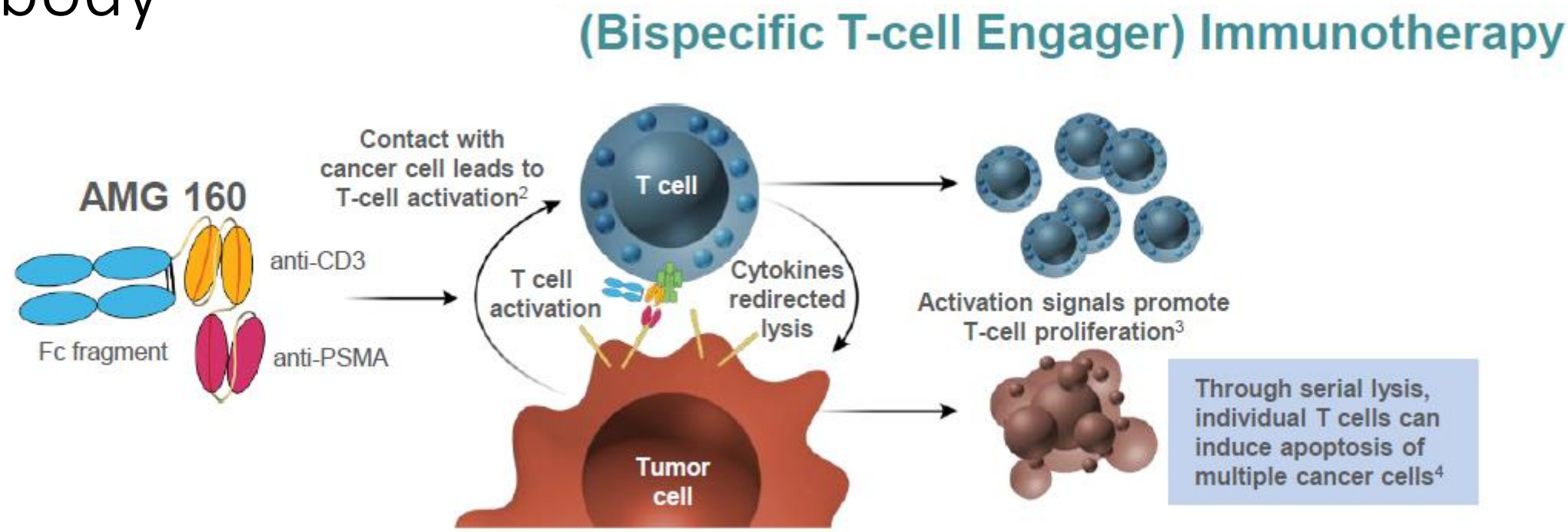
- Cost/scalability
  - CAR NK or other allo methods may improve (CRISPR)
  - BiTE still pricey, depending on hospitalization requirements and supportive medications
- Durability of remissions
- CarT is a very flexible platform

Generations of CarT Cells



Strohl et al. Antibodies 2019;
doi: 10.3390/antib8030041

BiTE antibody therapy

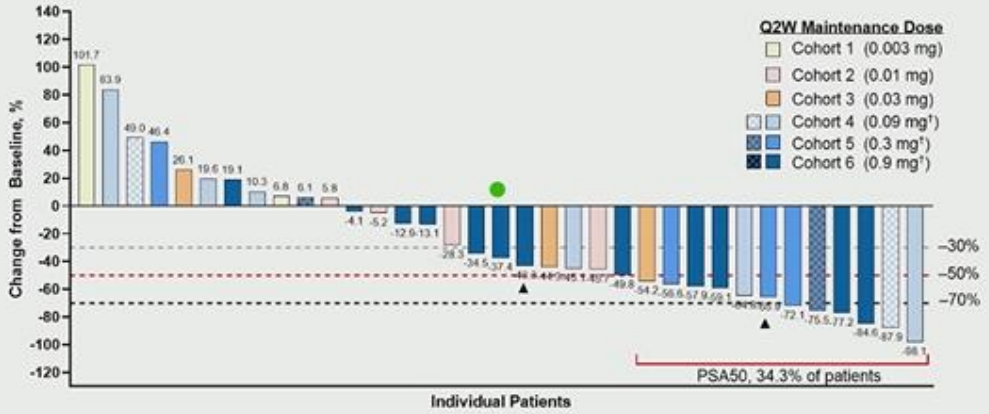


- Only approved BiTE is blinatumomab for ALL.
- AMG160 is half-life extended dual-targeted antibody to PSMA and CD3
  - Dosed every 2 weeks
- AMG509 is 3-headed (2 for target antigen)

Efficacy Results AMG160

dose escalation

- 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



PSA = prostate-specific antigen; 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

Tran, Horvath, Dorff et al.
ESMO 2020

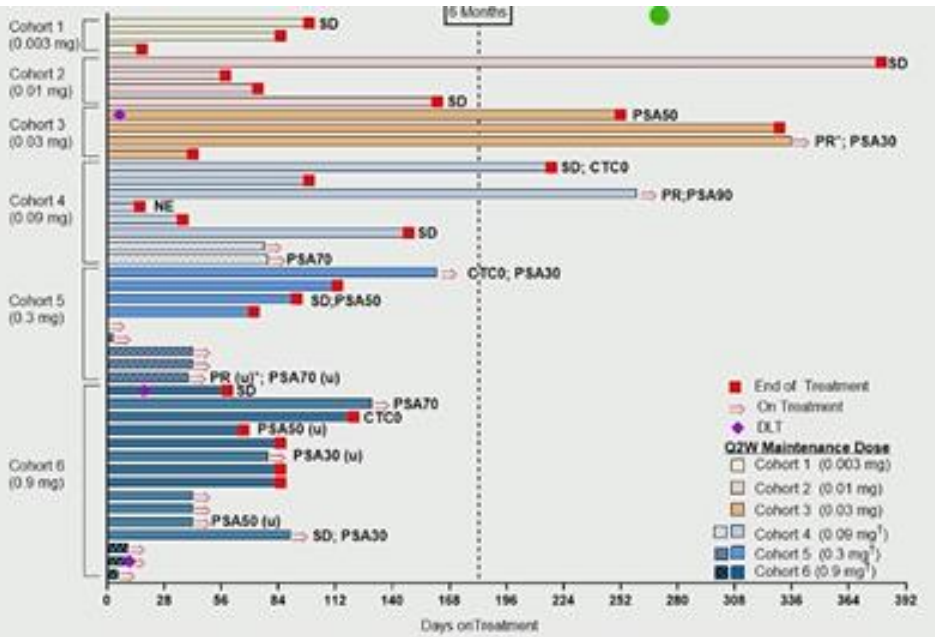
PSA/CTC Responses (n = 13–35)

Response	All, n (%)
PSA response, confirmed*	8 (27.6)
PSA response, unconfirmed†	4 (11.4)
CTC0 response‡	3 (23.1)

RECIST Responses (n = 15)

Response	All, n (%)
Partial response, confirmed	2§ (13.3)
Partial response, unconfirmed	1§ (6.7)
Stable disease	8 (53.3)

* ≥ 30% reduction based on 29 patients with 2 postbaseline PSA results
† ≥ 30% reduction based on 35 patients with measurable PSA at baseline
‡ Based on 13 patients with baseline CTC > 0 and postbaseline CTC assessment
§ 1 PR(u) and 1 PR confirmation occurred after 20 July 2020



CTC = circulating tumor cell; DLT = dose-limiting toxicities; NE = not evaluable; PSA = prostate-specific antigen; PR = partial response; Q2W = every 2 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; (u) = unconfirmed
* PR occurred before but reported after 20 July 2020 data cutoff; PR (u) reported after 20 July 2020 data cutoff
† Checkered bars indicate cohorts with optimised cycle 1 priming strategies

TRAEs in ≥ 20% of patients (N = 43)*

TRAE, n (%)	All Grade, n (%)	Grade 3, n (%)
CRS (Lee criteria)†	39 (90.7)	11 (25.6)
Fatigue	19 (44.2)	1 (2.3)
Vomiting†	19 (44.2)	0 (0)
Nausea†	17 (39.5)	0 (0)
Pyrexia†	16 (37.2)	0 (0)
Headache†	15 (34.9)	0 (0)
Diarrhoea†	14 (32.6)	2 (4.7)
Dry mouth	13 (30.2)	0 (0)
Rash†	12 (27.9)	4 (9.3)
Hypophosphataemia	11 (25.6)	4 (9.3)
Hypotension†	10 (23.3)	5 (11.6)
Chills†	10 (23.3)	0 (0)
Dysgeusia	10 (23.3)	0 (0)
Decreased appetite	9 (20.9)	0 (0)

* 8 patients experienced grade 4 laboratory abnormalities that were clinically non-significant. † CRS-related

CRS = cytokine release syndrome

7

Cytokine Release Syndrome and other AEs with AMG160

- CRS most severe in cycle 1
  - 60% had grade 2 CRS at worst
  - 25.6% had grade 3 CRS
- Mitigation strategies have helped reduce rate of grade 3 CRS
- 9.3% of patients experiences reversible atrial fibrillation in setting of CRS/tachycardia
- Dry mouth is on-target PSMA side effect

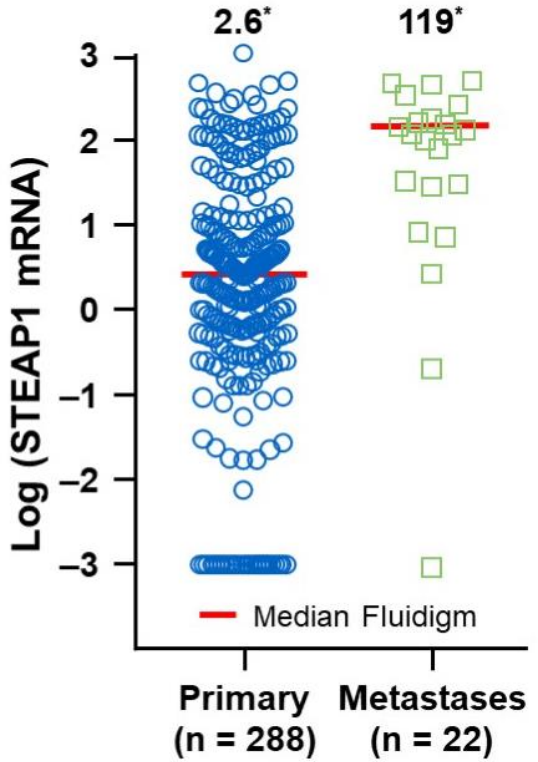
Tran, Horvath, Dorff et al.
ESMO 2020

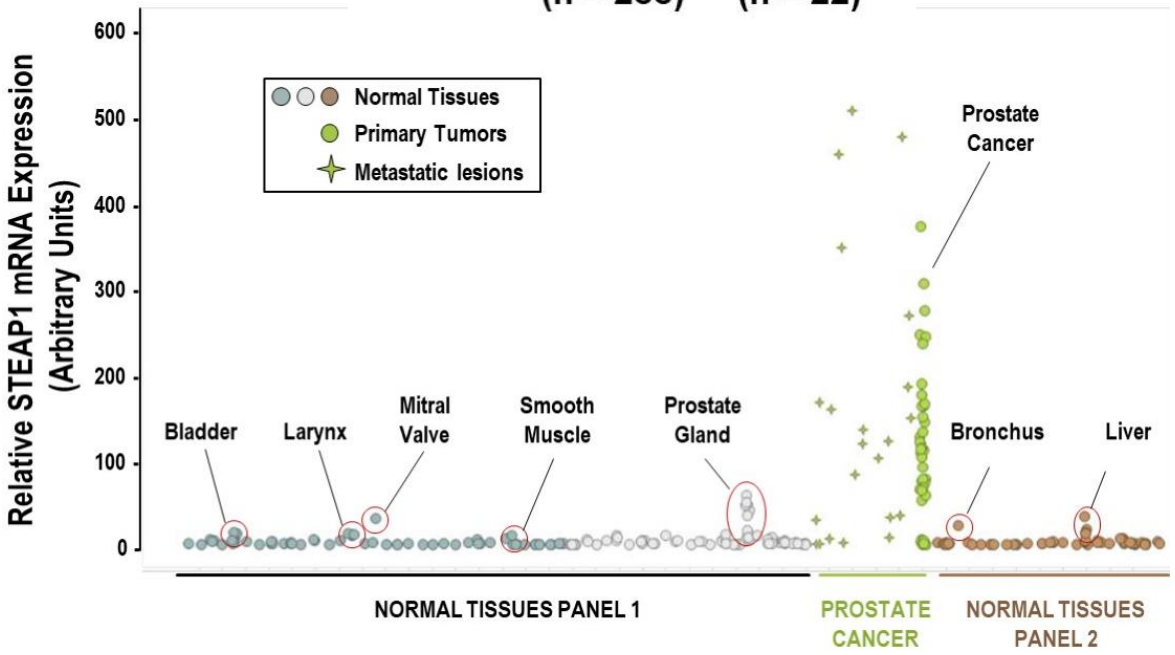
Prophylactic Mitigations in Cycle 1 Priming Cohort		
Dose priming	**Dexamethasone premedication**	**Prophylactic IV hydration**
Lower run-in dose before maintenance target dose	8 mg PO and 8 mg IV before AMG 160 dose*	1L normal saline after AMG 160 dose

STEAP-1 as a target (AMG509)

DSTP3086S: ADCC with MMAE payload

- 18% with PSA 50 when dose was >2 mg/kg IV q3 weeks[2]
- 6% RECIST PR, 59% CTC conversion
- DLTs: grade 3 transaminitis, grade 3 hyperglycemia, grade 4 hypophosphatemia





1. Kelly WK et al. GU ASCO 2021. TPS abstr 183
2. Danila DC et al. JCO 2019; 36:3518-27

Conclusions: immunotherapy for advanced prostate cancer

Sipuleucel-T

- Still an option. OS benefit when used early

- Combination studies. Active Surveillance

Immune Checkpoint inhibitors

- Selected patients only (ex: TMB, MSI)
- Will likely require combination (ex: cabozantinib)

- Radiopharmaceutical partners

BiTE: AMG160 (& AMG509)

- Clearly effective
- CRS is very common, limits dosing
- Anti-drug antibodies may limit efficacy

- Additional targets, additional modifications to reduce toxicity

CarT: PSCA, PSMA, klk2

- Promising early results with objective responses
- CRS very manageable (even MAS can be…)
- On target, off tumor toxicity

- Optimize dosing strategy, possible combinations, “off the shelf”, dual targets