The QuEST for an effective immunotherapy for Prostate Cancer

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Disclosure Information

James L. Gulley

I have the following financial relationships to disclose:

The NCI has a Cooperative Research and Development Agreement (CRADA) with a number of pharma partners including

Bavarian Nordic, ImmunityBio, Incyte, EMD Serono and has a clinical trial agreement (for biologics) with BMS

The CRADAs provide drug and may provide resources for co-development in clinical trials.

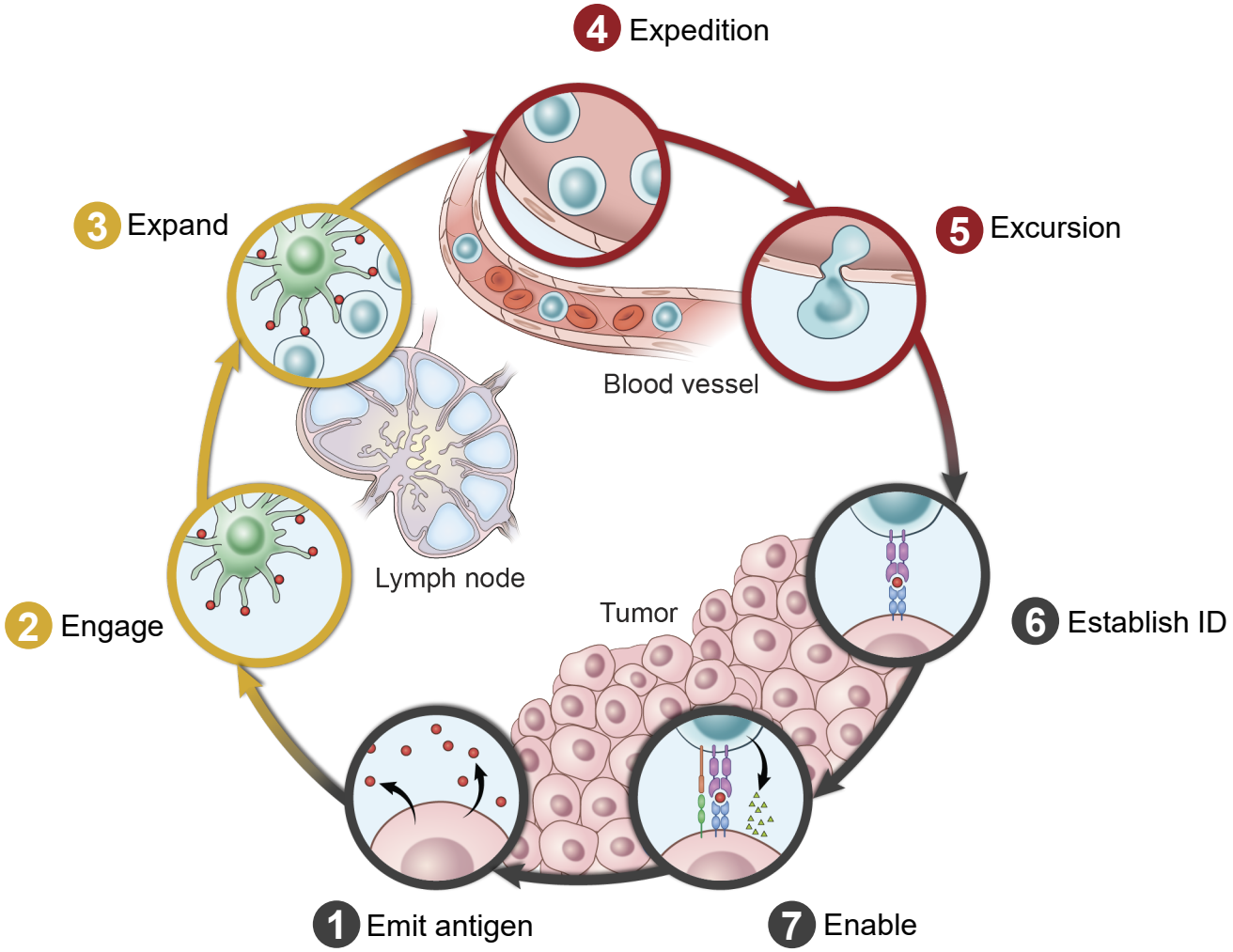
- and -

I will discuss the following off label use and/or investigational use in my presentation:

Ipilimumab

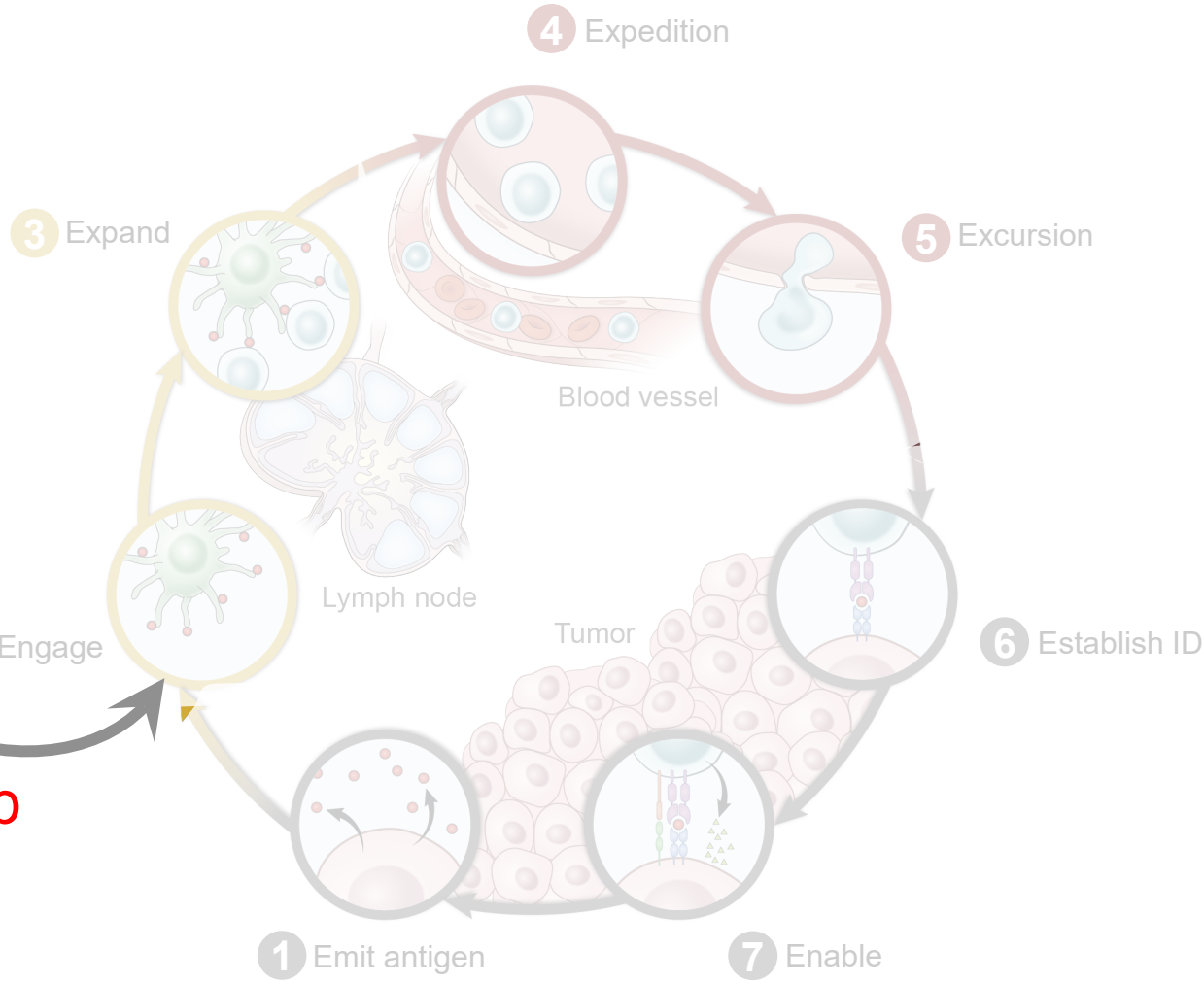
Nivolumab

Cancer Immunity Cyclical Evolution (E^8)



Modified from Chen and Mellman, *Immunity* 2013

Cancer Immunity Cyclical Evolution (E^8)

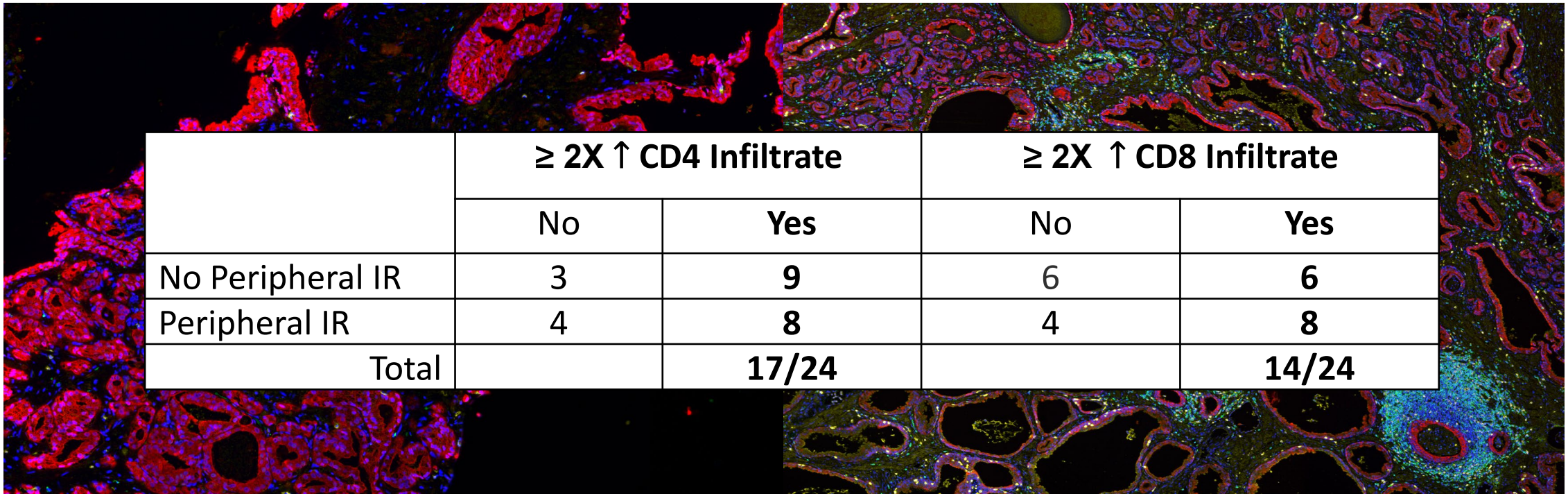


Vaccine
CAR-T
Bispecific Ab

Excursion

Prostvac increases intra/peritumoral immune infiltrate in patients with localized prostate cancer undergoing radical prostatectomy (NCT02153918) (n=27)

Baseline	Day 1	Day15	Day 29	Day 57	64
Biopsy	Priming Vaccination s.c.	Booster Vaccination s.c.	Booster Vaccination s.c.	Booster Vaccination s.c.	RP

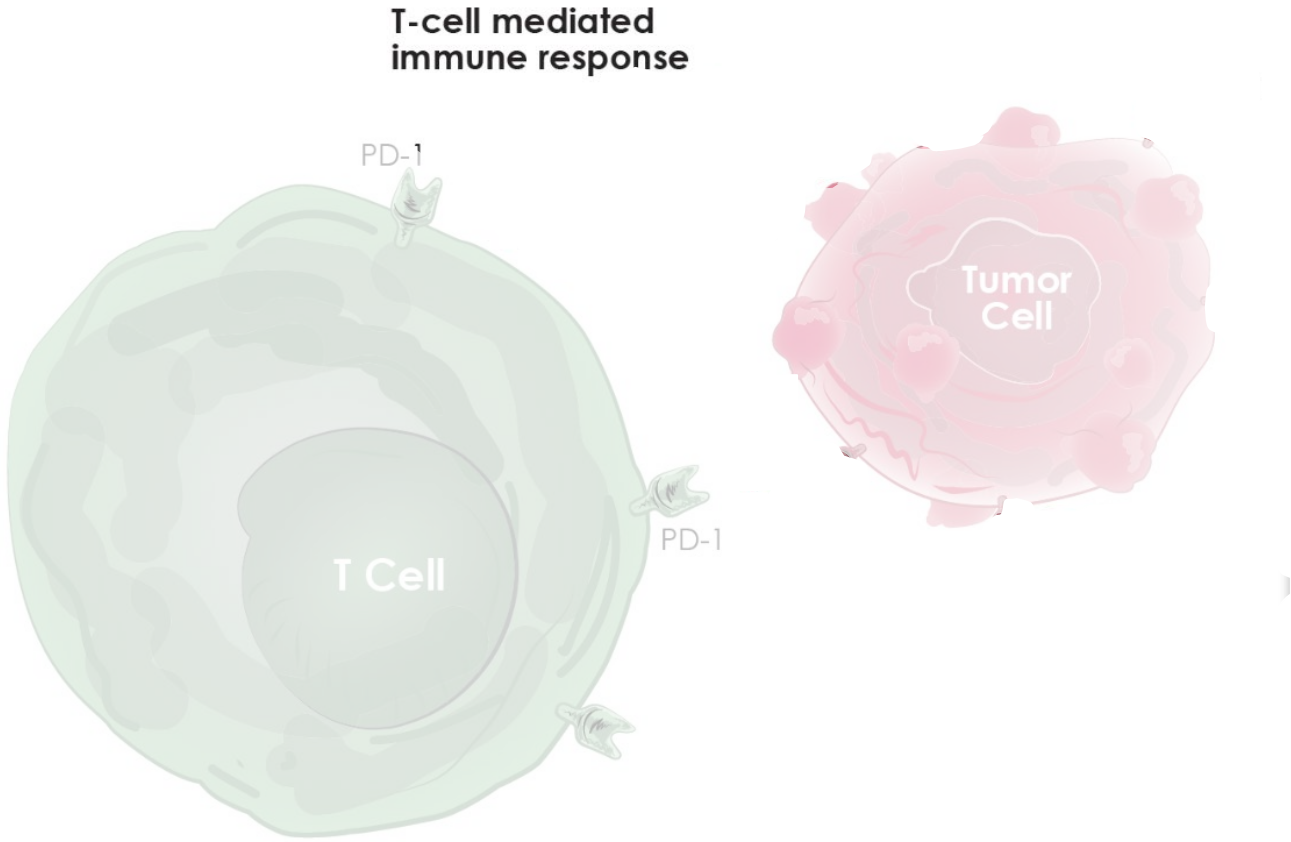


	≥ 2X ↑ CD4 Infiltrate		≥ 2X ↑ CD8 Infiltrate	
	No	**Yes**	No	**Yes**
No Peripheral IR	3	**9**	6	**6**
Peripheral IR	4	**8**	4	**8**
Total		**17/24**		**14/24**

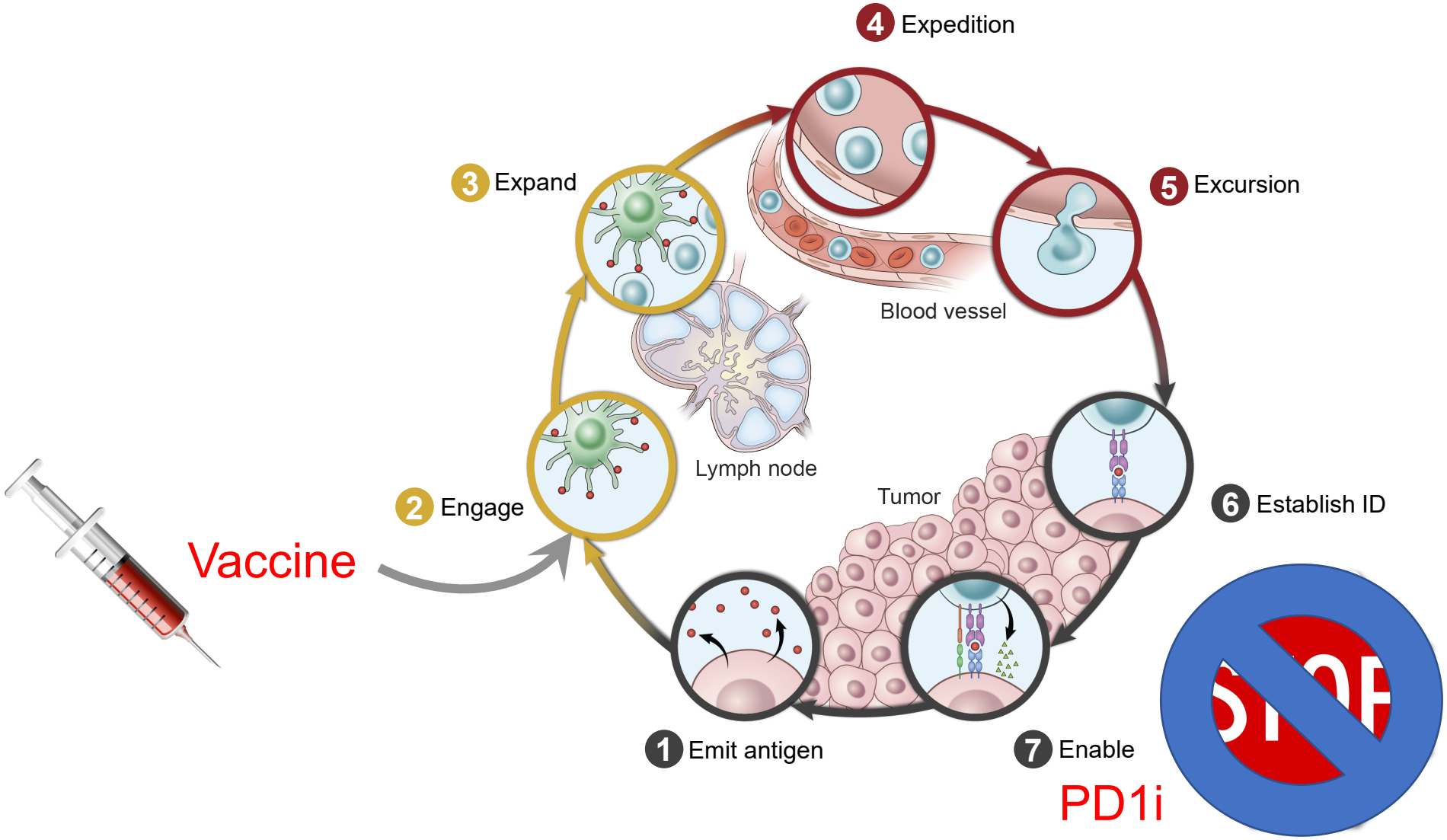
RNA expression profiles consistent with an activated immune response post vaccine

Houssein et al., *JITC* 2020

Importance of PD-1/PD-L1 blockade

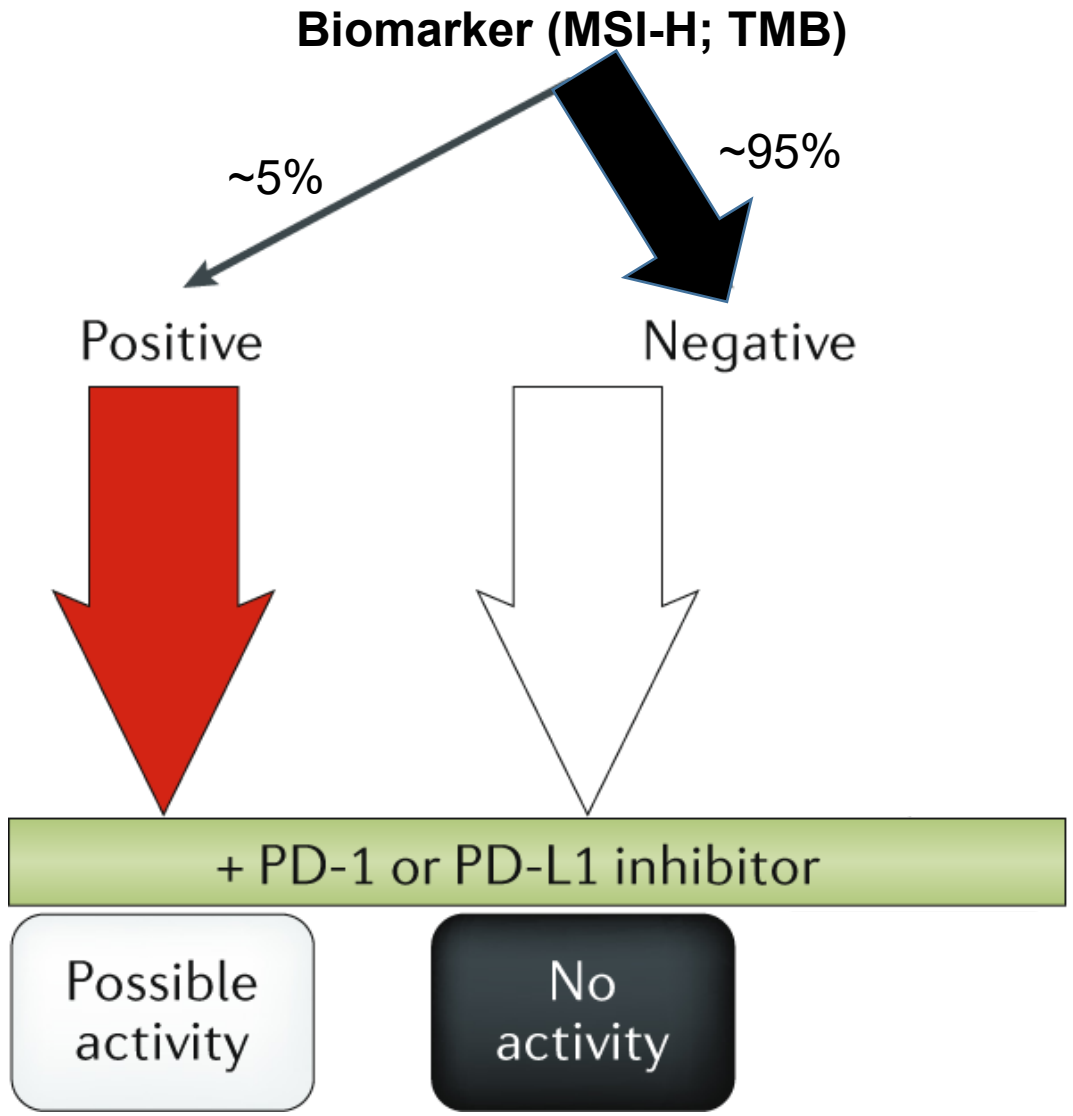


Cancer Immunity Cyclical Evolution



Modified from Chen and Mellman, *Immunity* 2013

Experimental algorithm for immunotherapy for mCRPC



FDA Approved

Pembrolizumab
~50% response

Madan and Gulley *Nature Rev. Urology*, 2018

Prostvac (+ Ipilimumab) + Nivolumab (NCT02933255)

- Eligibility (n=12)
  - mCRPC
  - No prior chemotherapy

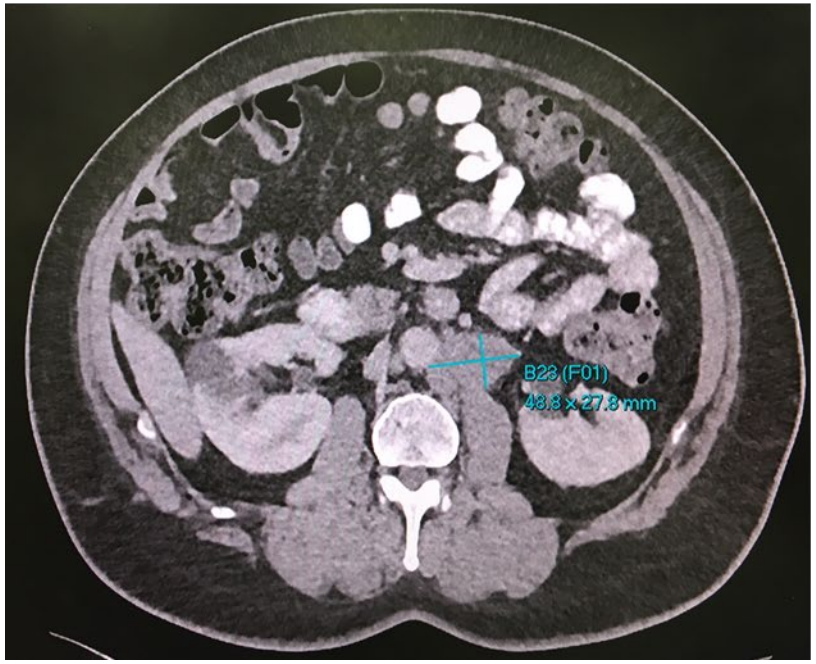
- Treatment
  - Prostvac Vaccine
  - Immune checkpoints
    - Ipilimumab 1 mg/kg
    - Nivolumab 240 mg

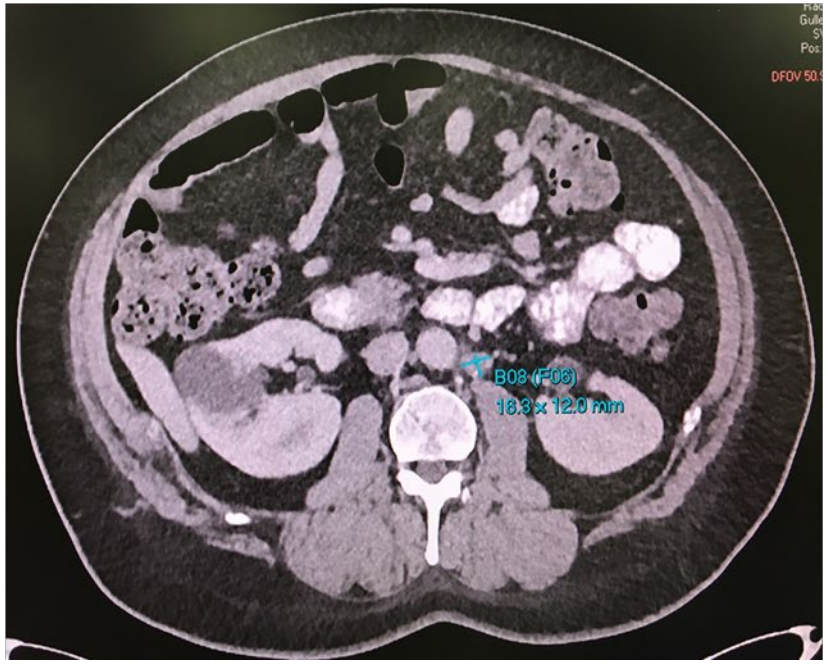
NCT02933255

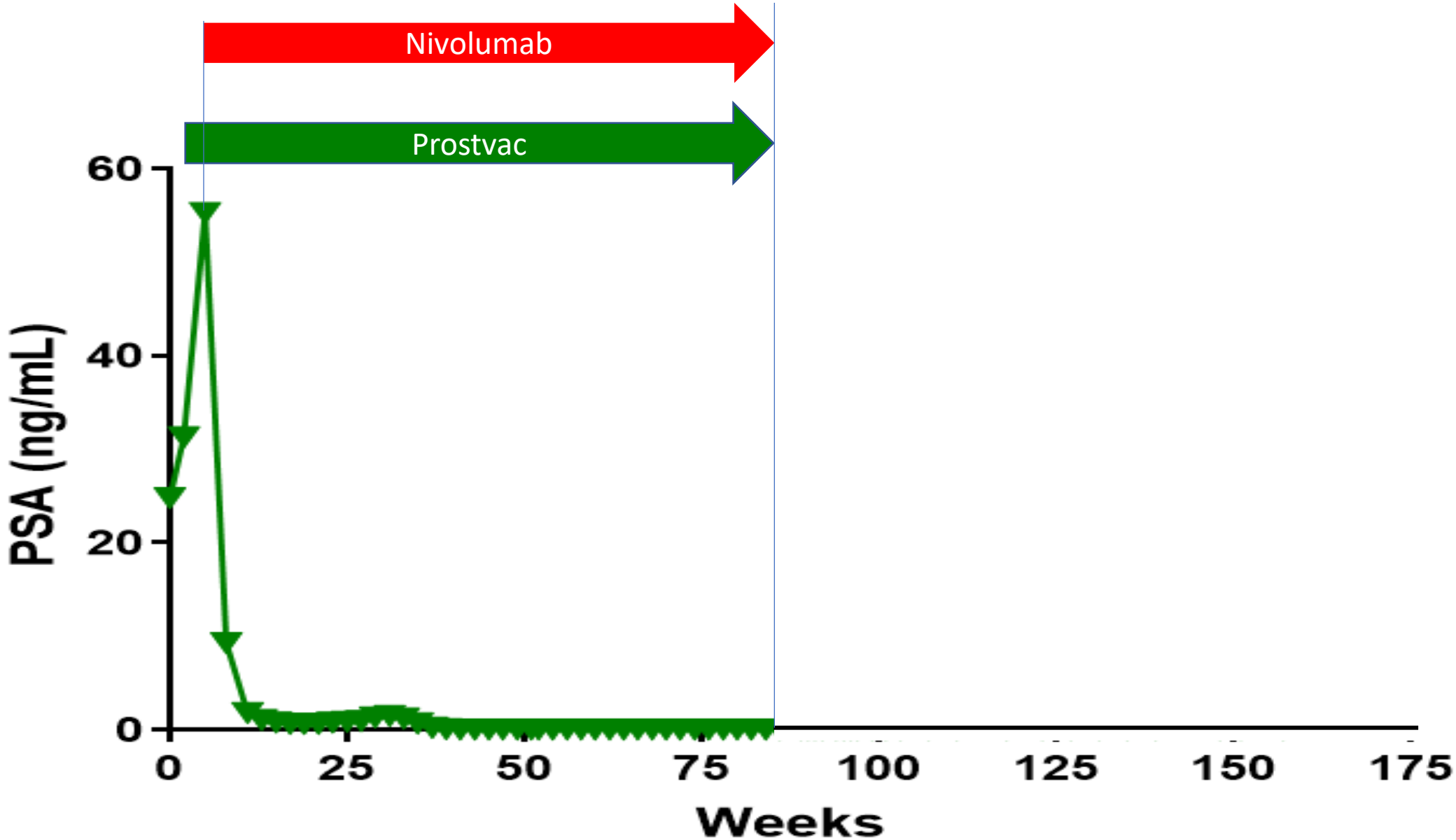
Vaccine, anti-CTLA4, antiPD-1

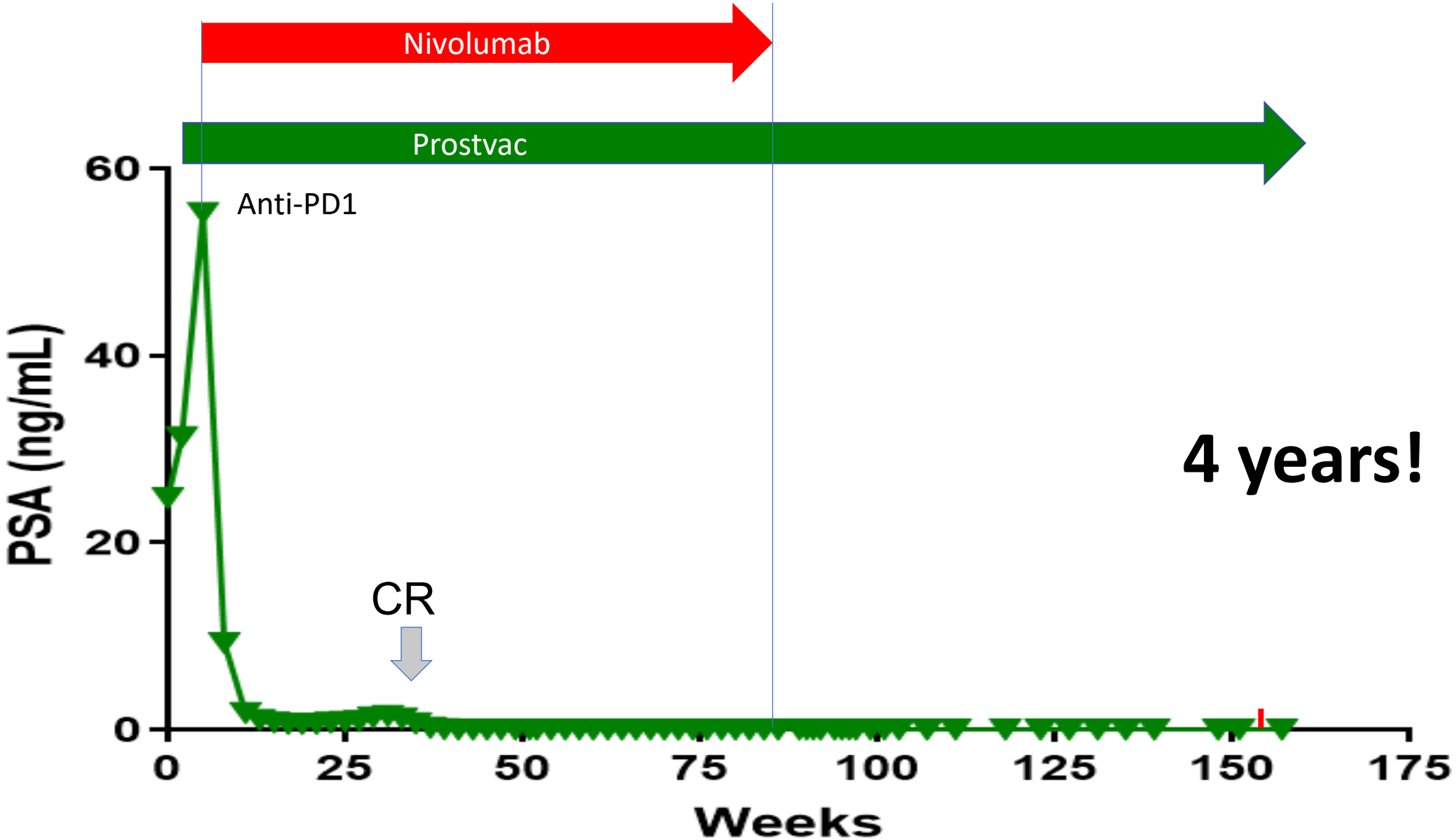
4/11/17

6/22/17

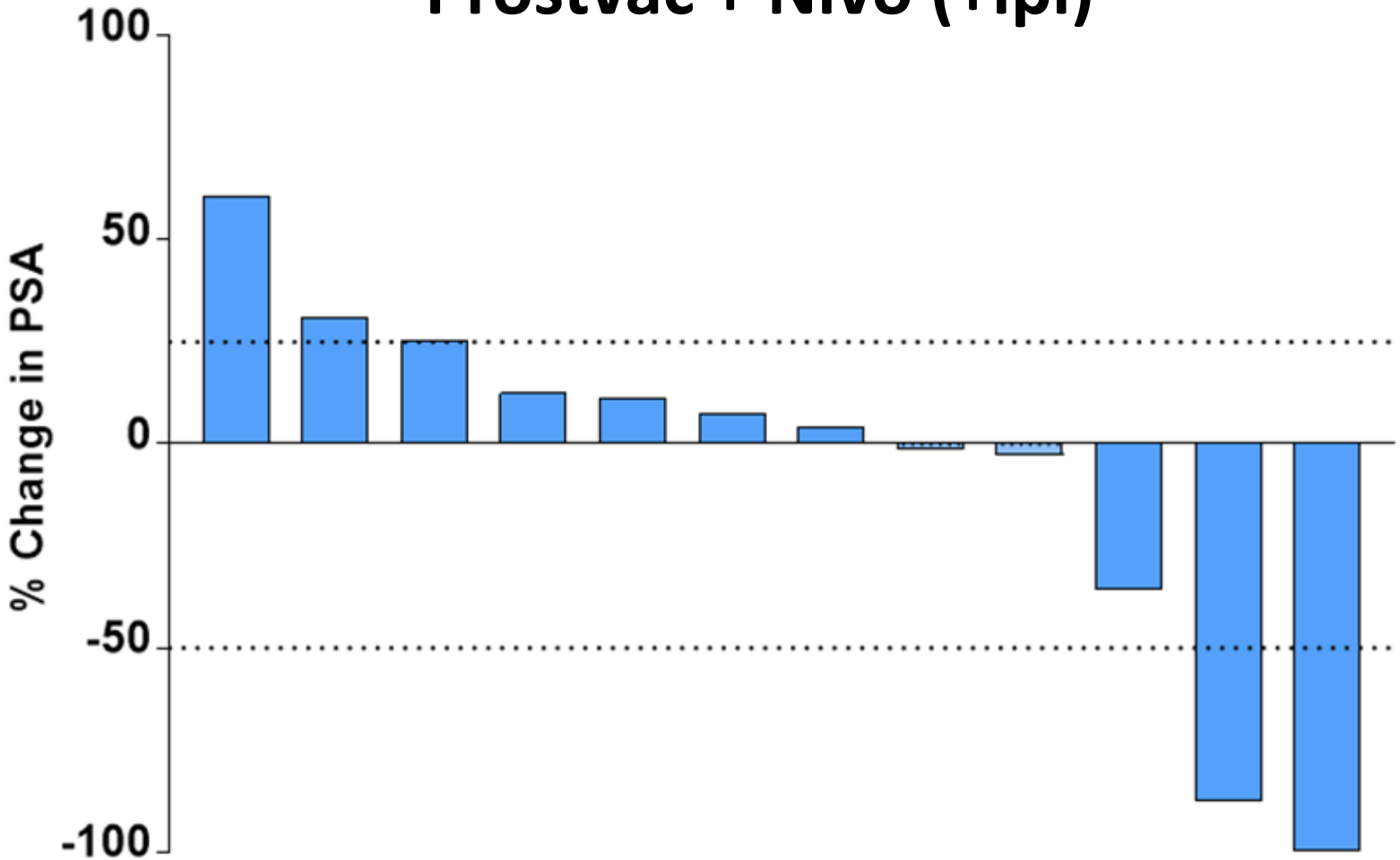




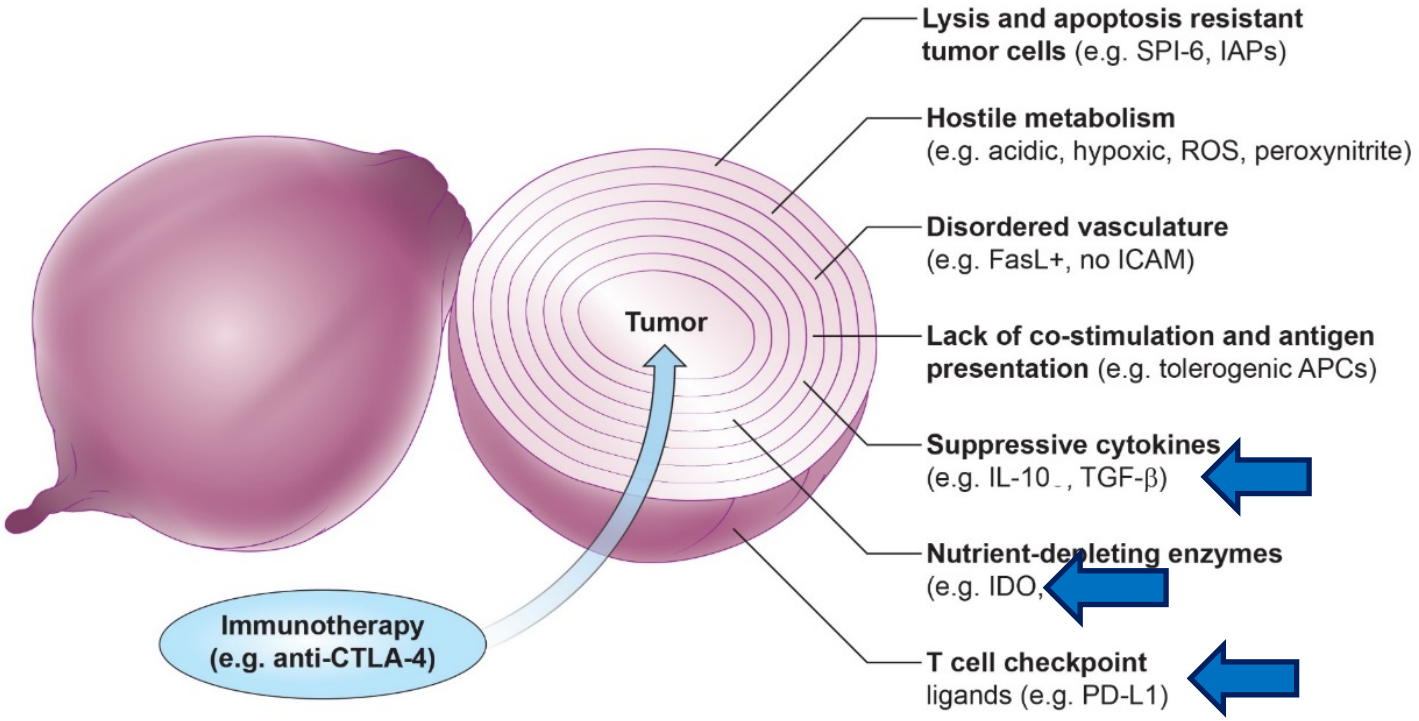

Nivolumab
Prostvac
PSA (ng/mL)
60
40
20
0
0
25
50
75
100
125
150
175
Weeks


Nivolumab
Prostvac
Anti-PD1
CR
PSA (ng/mL)
60
40
20
0
0
25
50
75
100
125
150
175
Weeks
4 years!

Prostvac + Nivo (+ipi)



Multi-layered immunosuppression



- Tumors insulate themselves with dense layers of immunosuppressive stroma
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can "peel back" the layers of local immune suppression, thereby restoring the capacity of T cells to eradicate the tumor

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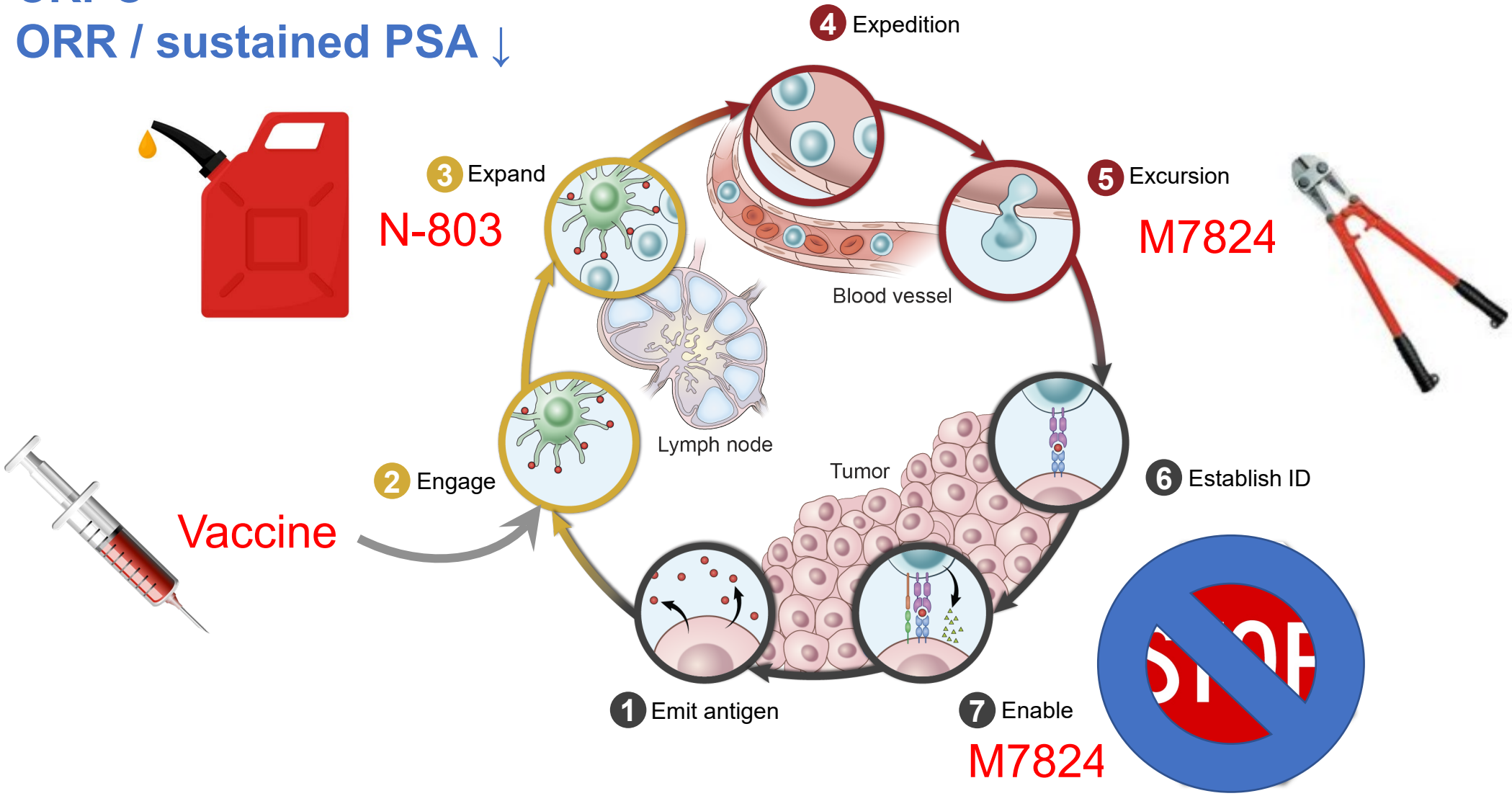
QuEST-1 (Quick Efficacy Seeking Trial)

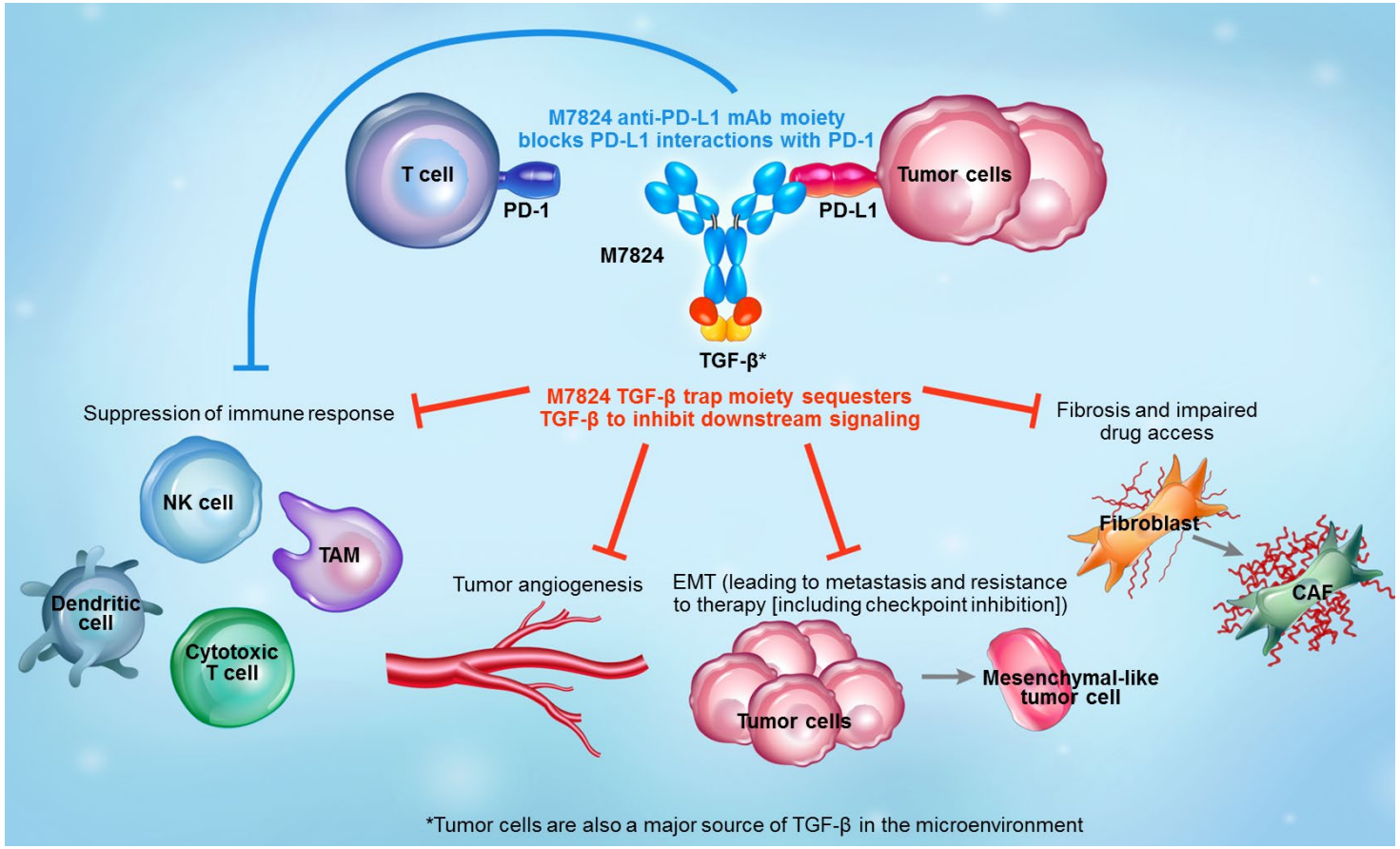
Ongoing study (QuEST1)

- CRPC
- ORR / sustained PSA ↓

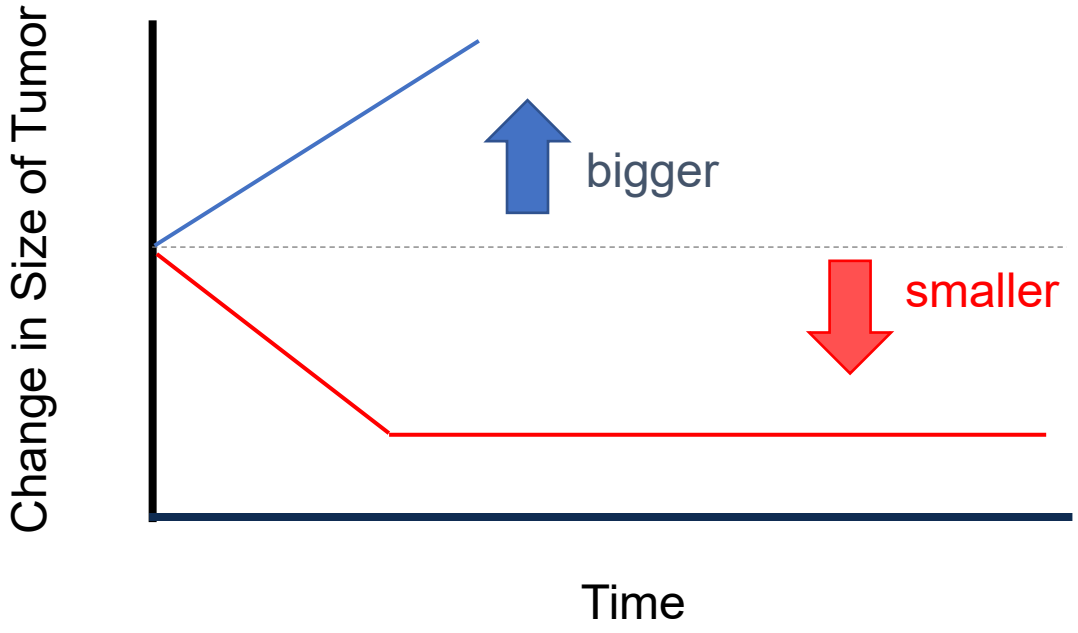


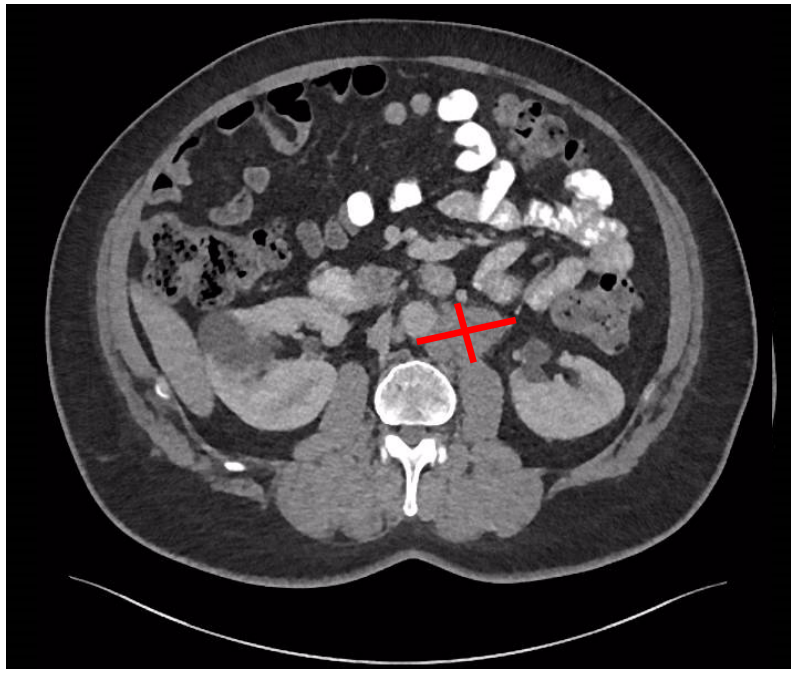
Redman et al., ***JITC*** Sept 2018

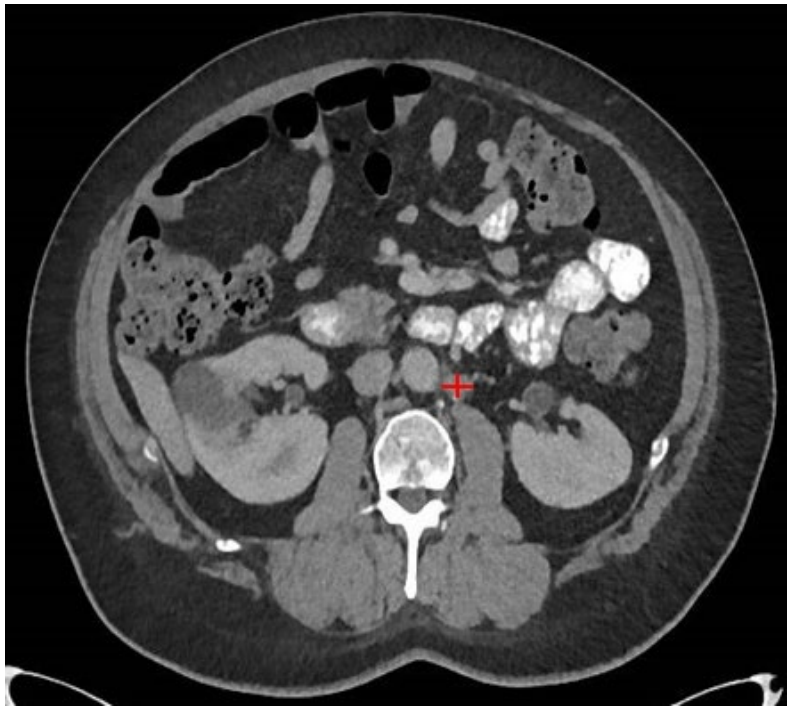
Bintrafusp alfa preclinical work



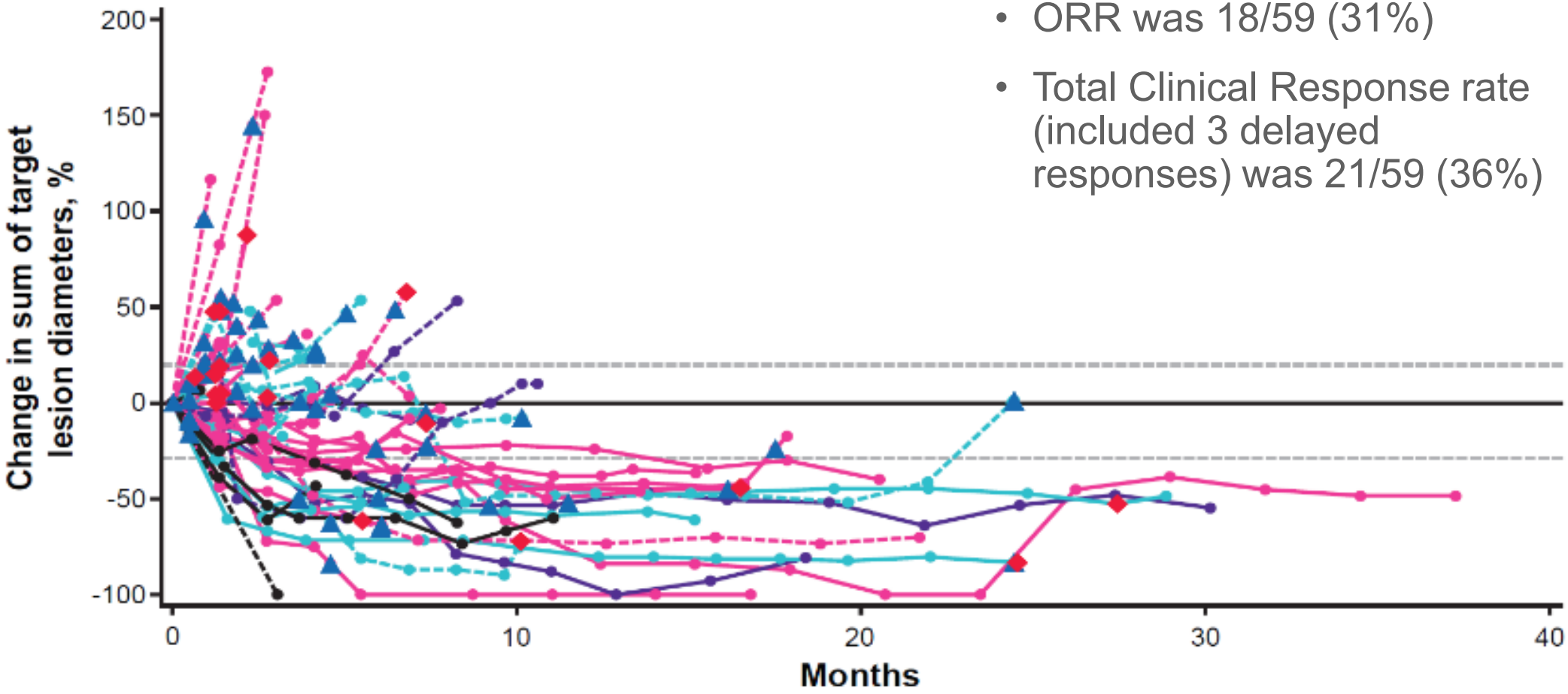
Spider Plot







Bintrafusp alfa in HPV Associated Malignancies



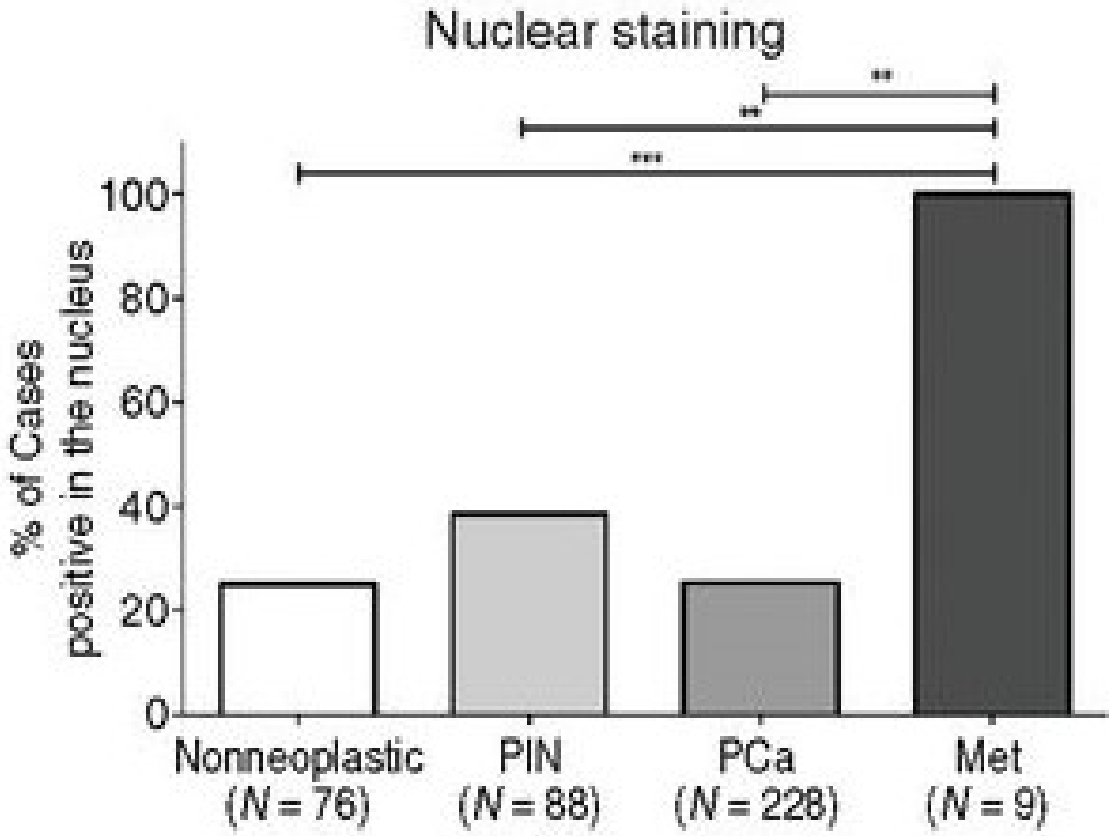
- ORR was 18/59 (31%)
- Total Clinical Response rate (included 3 delayed responses) was 21/59 (36%)

[a]Includes 2 patients with SCC rectal tumors, 1 patient (each) with neuroendocrine cervical, vaginal, and vulvar tumors from study 012.

Strauss…Gulley, *JITC 2020*

Targeting Brachyury

- Brachyury (TBXT)
  - Overexpressed in tumor vs. normal tissue
  - Involved in EMT / drug resistance / cellular plasticity
  - Expression associated with NE markers and PTEN loss in prostate cancer
  - T-cells specific for brachyury can kill brachyury expressing cells in an MHC restricted manner



Pinto et al, Clin Ca Res 2014

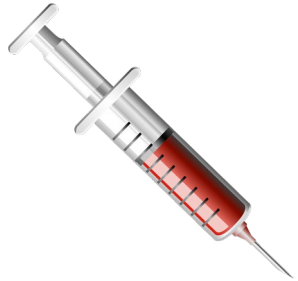
Nov 2017

Cancer Therapy: Clinical

Clinical Cancer Research

Phase I Study of a Poxviral TRICOM-Based Vaccine Directed Against the Transcription Factor Brachyury

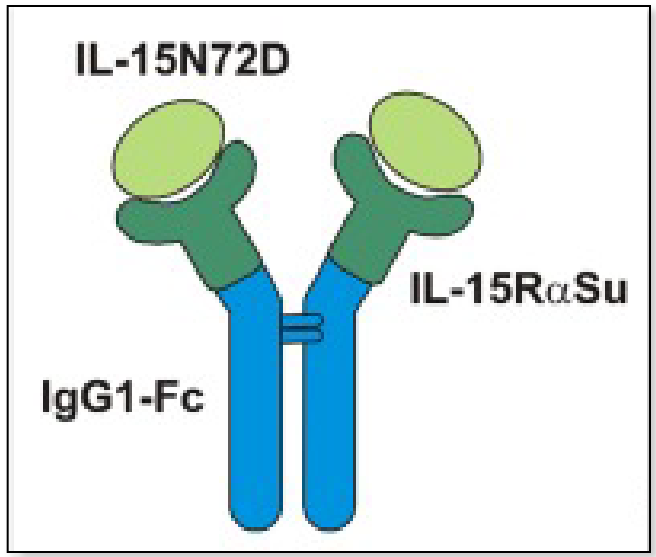
Christopher R. Heery[1], Claudia Palena[1], Sheri McMahon[2], Renee N. Donahue[1], Lauren M. Lepone[1], Italia Grenga[1], Ulrike Dirmeier[3], Lisa Cordes[2], Jenn Marté[2], William Dahut[2], Harpreet Singh[2], Ravi A. Madan[2], Romaine I. Fernando[1], Duane H. Hamilton[1], Jeffrey Schlom[1], and James L. Gulley[2]



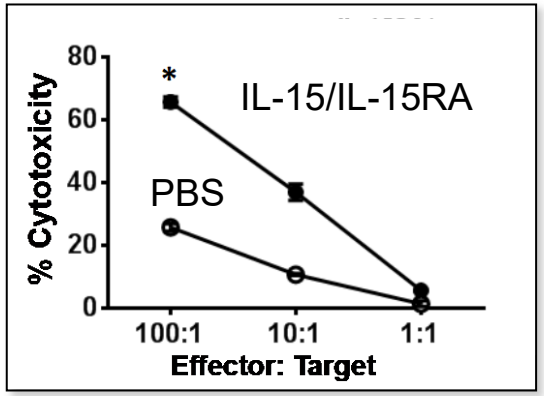
- Well tolerated (no DLT)
- 28 of 34 (82%) patients developed brachyury-specific CD4 and/or CD8 T-cell responses after vaccination

N-803

- Improved affinity for IL2/15R-β (CD122) expressing immune cells (NKs and T cells)
- Longer serum half-life than native IL15 (25 h vs. 40 min) in mice

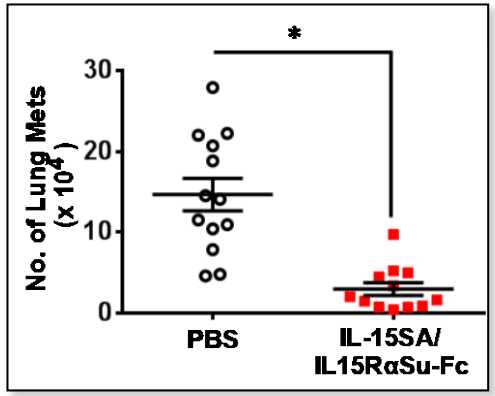


Increased NK function on a per-cell basis



Balb/C mice injected with IL-15/IL15RA-Fc (1ug/IP). Purified NK cell activity tested on day 3.

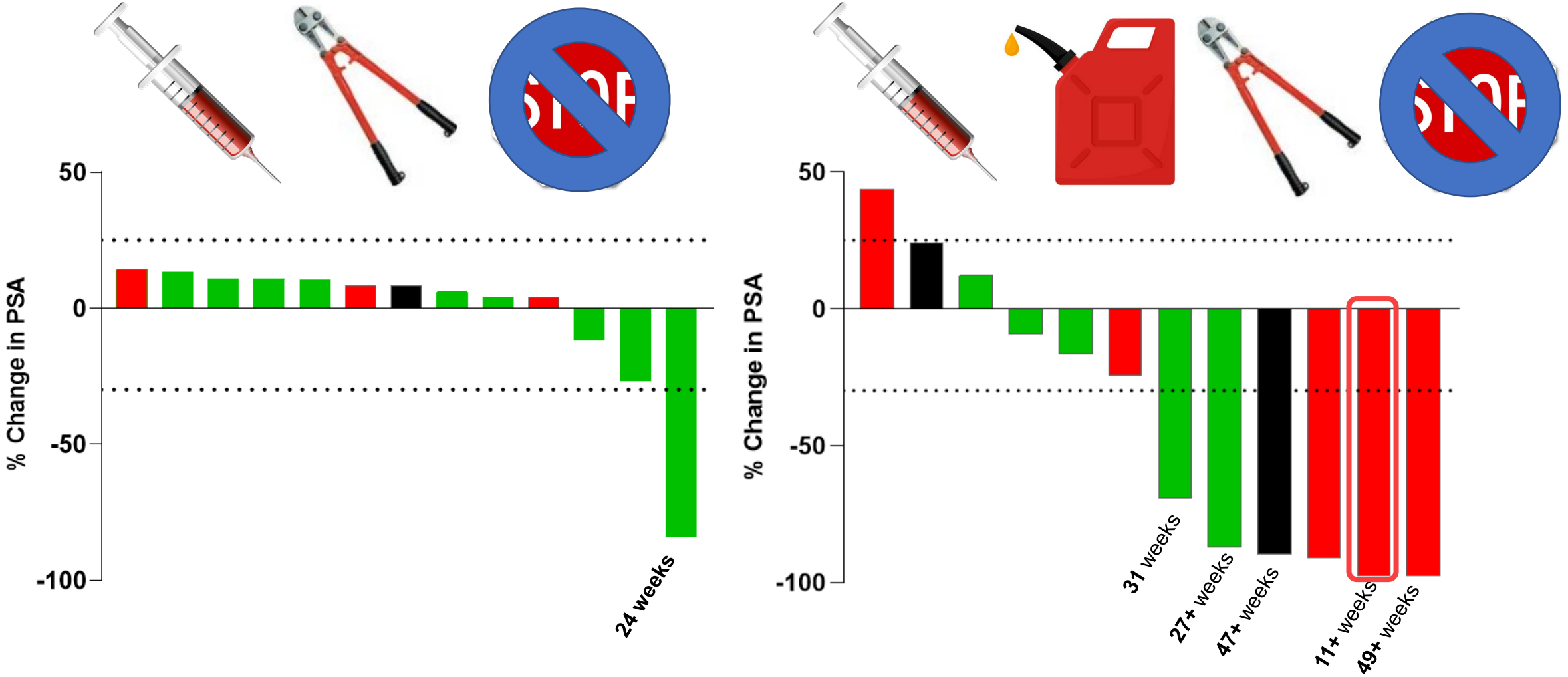
Anti-metastatic activity



4T1 tumor bearing Balb/C mice injected with IL-15/IL15RA-Fc (1ug/IP) on day 7. Tumor metastases counted on day 26. -dependent on CD8 and NK cells

Kim et al, Oncotarget, 2016

Best PSA Responses

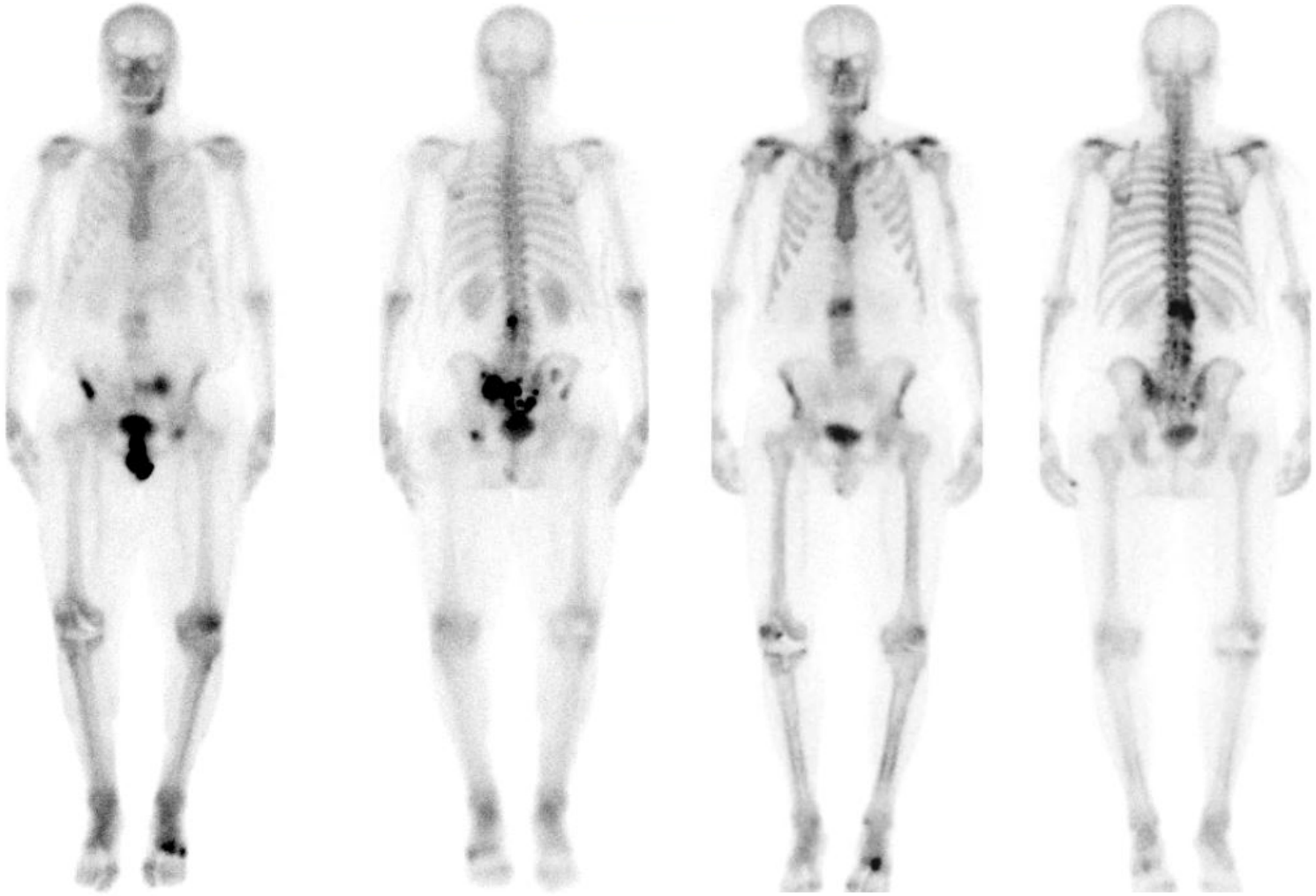


Redman…Gulley, ESMO 2020

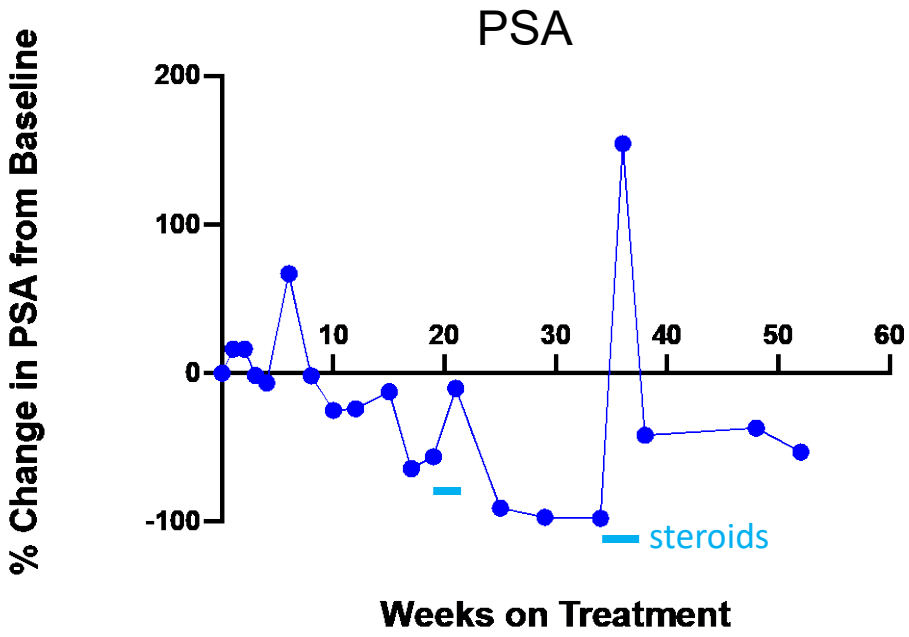
Patient 34

Baseline

~1 Year On Treatment



Prior Treatment
-Sipuleucel-T
-Enzalutamide
-Radium-223 + Niraparib (Trial)
-Adenoviral vaccine targeting PSA, MUC1, Brachyury



Conclusions

- Immunotherapy can be powerful, and can lead to complete responses which are durable
- Despite the impressive results seen in subsets patients in some cancer, unselected patients with prostate cancer rarely have objective responses to current immunotherapy monotherapy
- In order to harness the potential power of immunotherapy in prostate cancer, one must address the critical elements that are necessary for an immune response
- Approaches that (a) stimulate a relevant immune response, (b) expand number and function of those immune cells and (c) facilitate functionality in the TME may be essential for “immune deserts” like mCRPC.

Clinical Cancer Immunotherapy Program

- Ravi Madan MD
- Marijo Bilusic MD PhD
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- Fatima Karzai MD
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- Arun Rajan MD
- Anish Thomas MD
- Tom Waldmann MD
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- Jennifer Jones MD PhD
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Patients and their Families