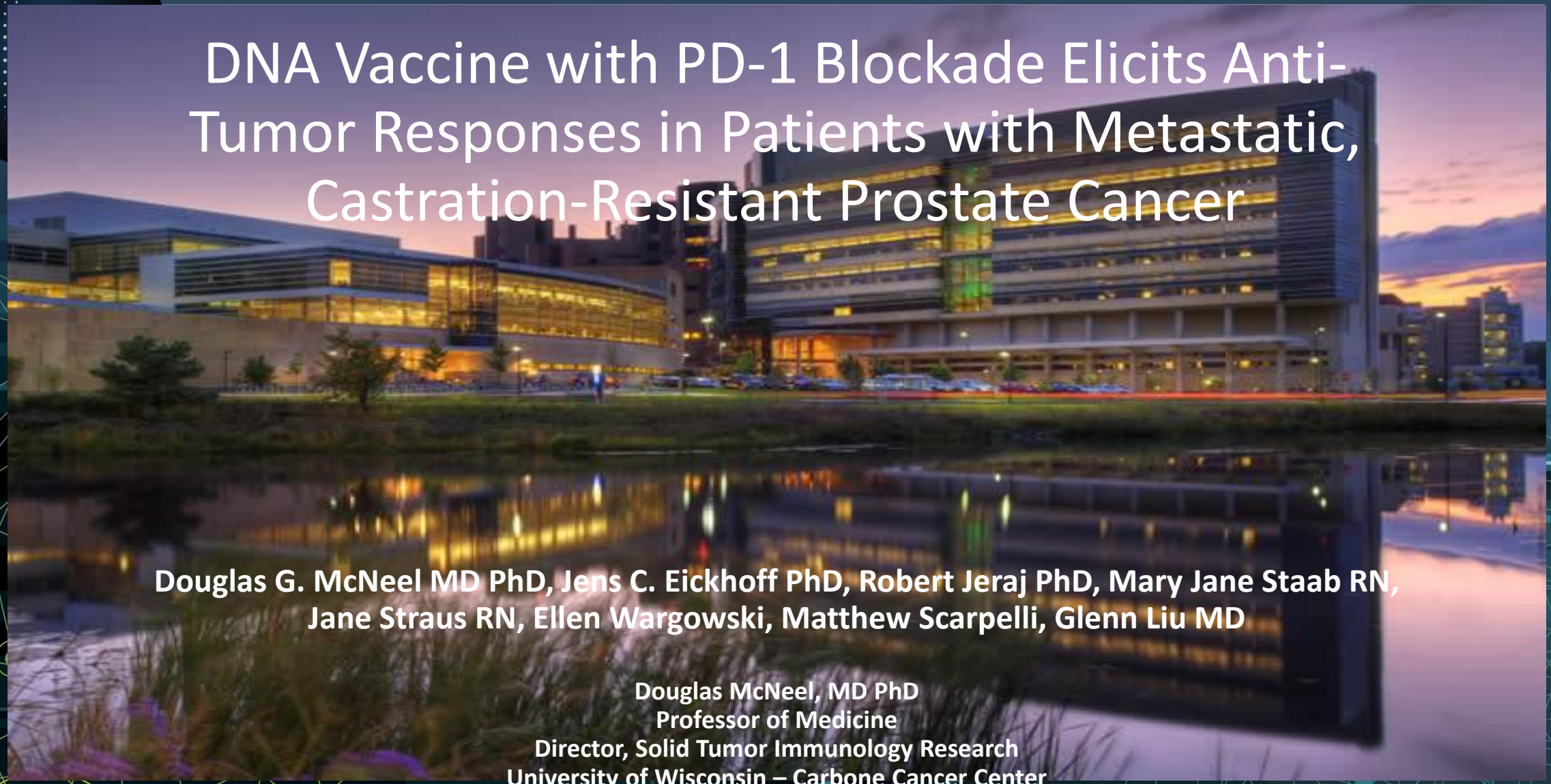

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Society for Immunotherapy of Cancer

November 8-12 • NATIONAL HARBOR, MD

DNA Vaccine with PD-1 Blockade Elicits Anti-Tumor Responses in Patients with Metastatic, Castration-Resistant Prostate Cancer



Douglas G. McNeel MD PhD, Jens C. Eickhoff PhD, Robert Jeraj PhD, Mary Jane Staab RN, Jane Straus RN, Ellen Wargowski, Matthew Scarpelli, Glenn Liu MD

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#SITC2017

Presenter Disclosure Information

Douglas G. McNeel, MD PhD

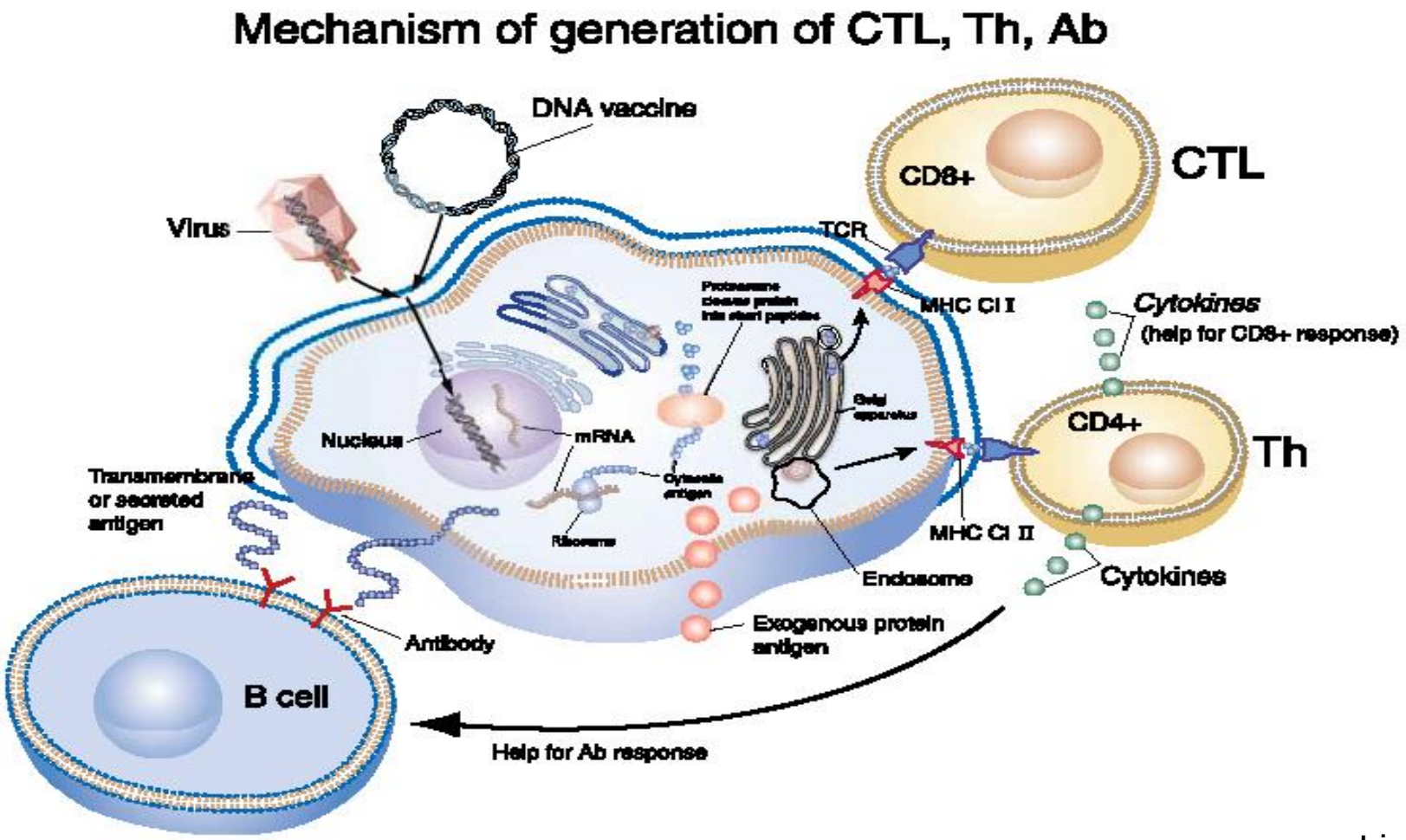
The following relationships exist related to this presentation:

Madison Vaccines Inc. (Founder, consultant, intellectual property)

Vaccines as Cancer Treatments

- Having the “right” kind of T cells in the tumor microenvironment is associated with better long-term outcome
- The ability of vaccines to activate T cells, and augment cytolytic T cells, should have anti-cancer activity
- Clinical activity of single-agent tumor vaccines has been underwhelming
- Animal studies demonstrate vaccines have greater efficacy in tumor prevention and/or minimal residual disease
- Therapeutic cancer vaccines may best be used in combination with methods to block tumor resistance mechanisms

Antigen-Specific DNA Vaccines



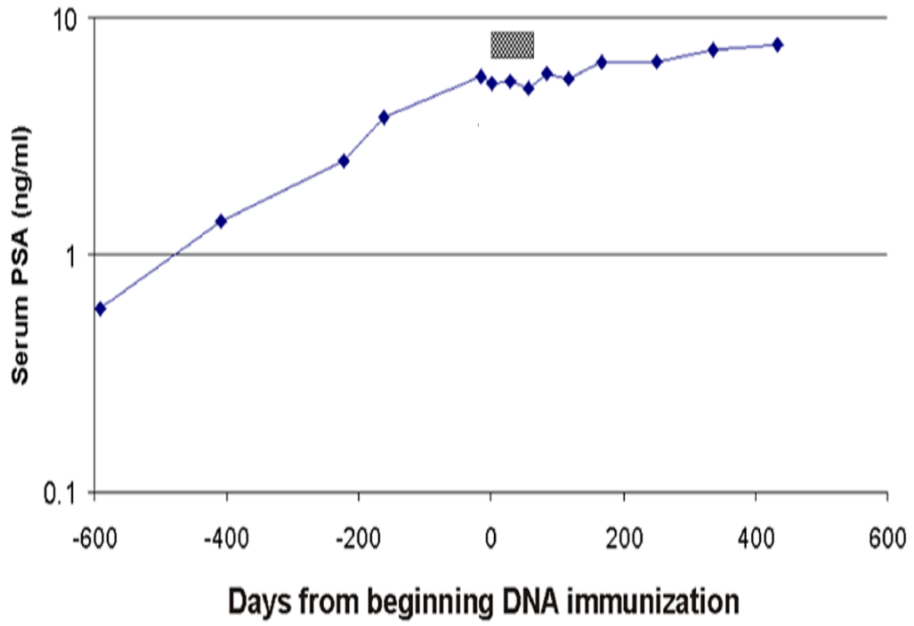
Liu (2003) *J Int Med* **253**:402

Prostatic Acid Phosphatase (PAP) – Vaccine Target Antigen

- Expression essentially restricted to prostate tissue in humans
- Nearly identical prostate-specific rat homologue
- Permits evaluation of serum PSA as an independent assessment of response in human trials
- Previous experience targeting this antigen in rodent models and human clinical trials – same target as FDA approved sipuleucel-T vaccine

Two Phase I/II Trials – DNA Vaccine Encoding PAP - Clinical Stage M0

- PAP-specific T-cell immune responses elicited
  - CD8+ T cells – IFNγ-secreting
  - Th1 bias, no PAP-specific IgG
- No significant adverse events
- Development of persistent PAP-specific IFNγ-secreting T cells associated with favorable change in PSA doubling time
- Development of PAP-specific IFNγ-secreting T cells also associated with PD-L1 expression on circulating tumor cells



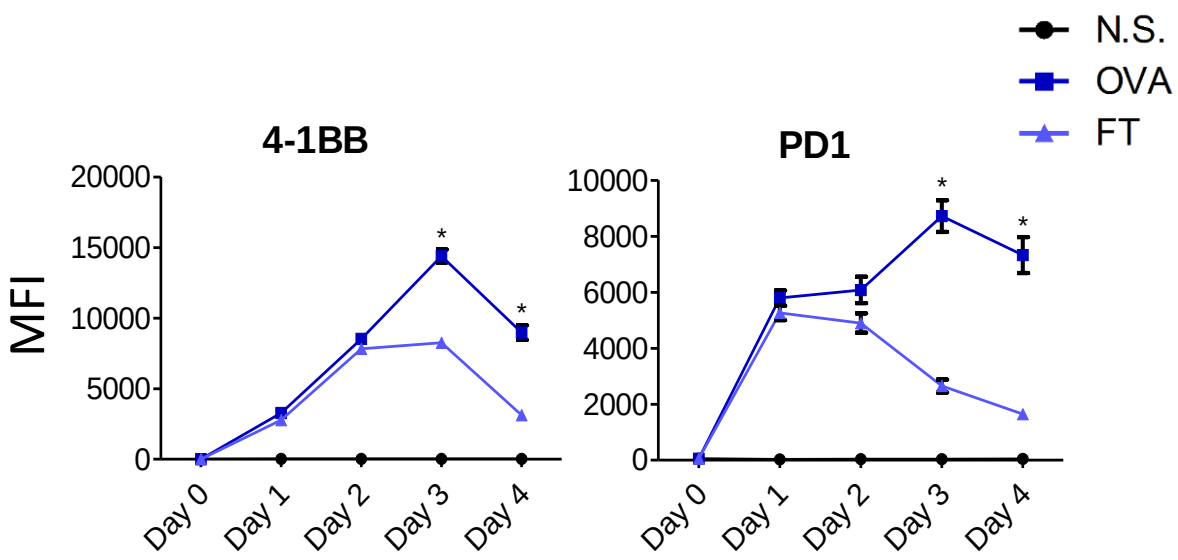
McNeel (2009) *J Clin Onc* **27**:4047
Becker (2010) *J Immunoth* **33**:639
McNeel (2014) *Clin Canc Res* **20**:3692
Rekoske (2016) *Oncoimmunology* **5**:e1165377

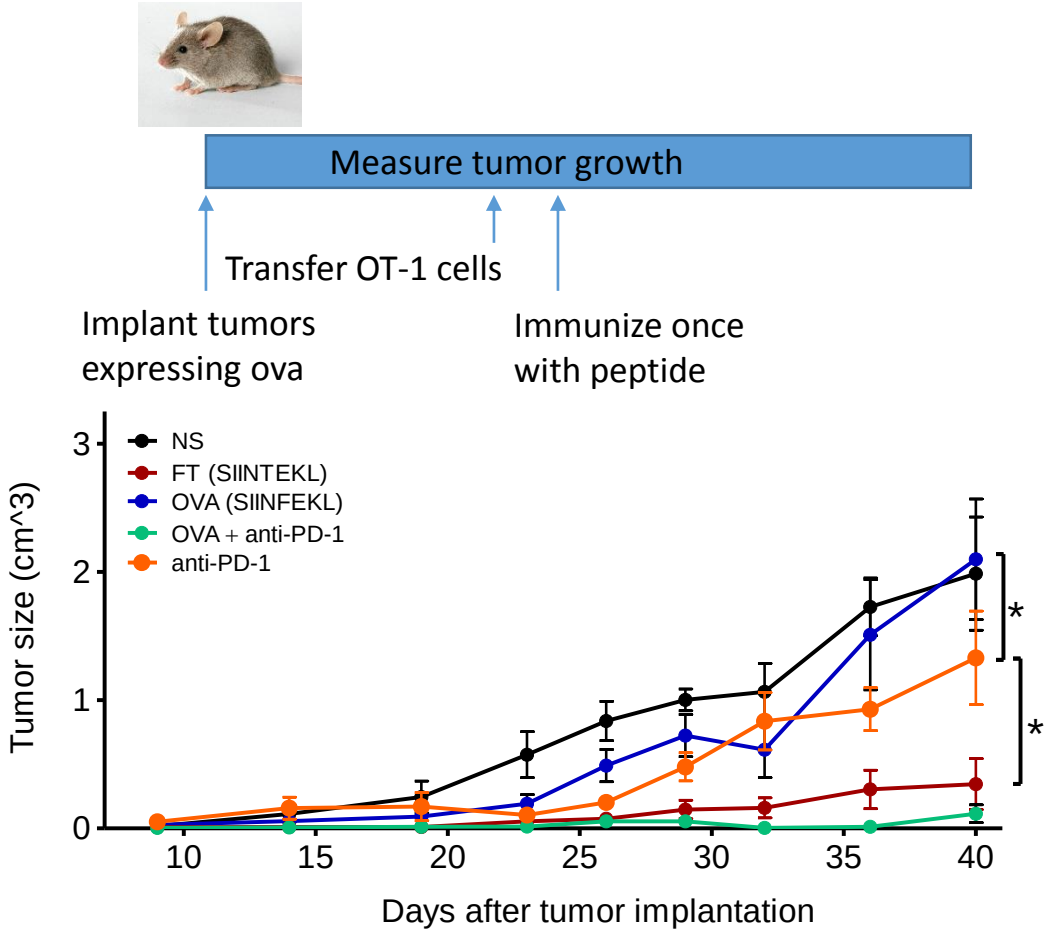
Mechanisms of Immune Resistance following DNA Immunization

- Immunization elicits T cells secreting IFNγ
- This leads to increase in PD-L1 expression on tumor cells
- Encoding epitopes with increased MHC class I affinity elicited CD8+ T cells with increased and persistent PD-1 expression
- Blockade of PD-1 or PD-L1 with vaccination led to improved anti-tumor responses

Smith (2014) *Vaccine* **32**:1707
Rekoske (2015) *Canc Imm Res* **3**:946
Zahm (2017) *Can Imm Res* **5**:630

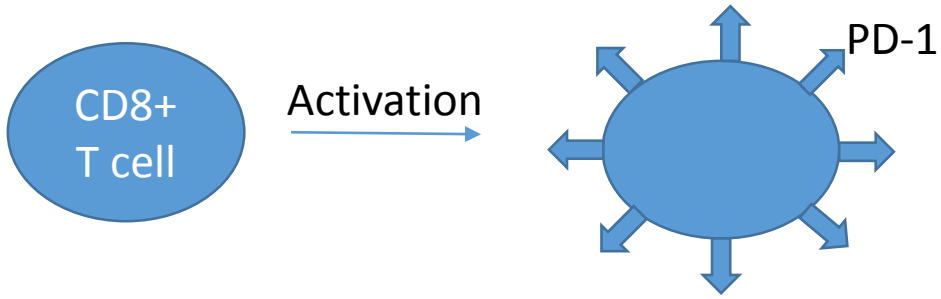
Activation of CD8+ T cells Elicits Increased Expression of PD-1 - Persistent PD-1 Expression Mediates Inferior Anti-Tumor Immunity

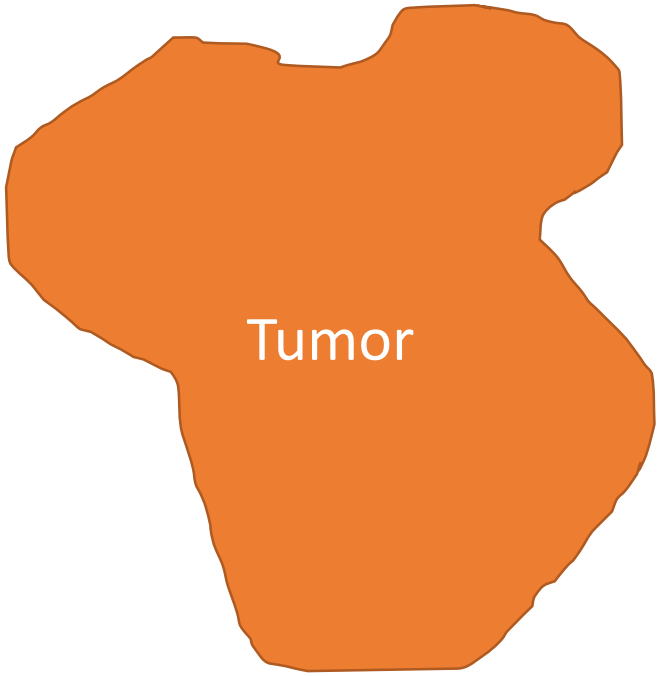




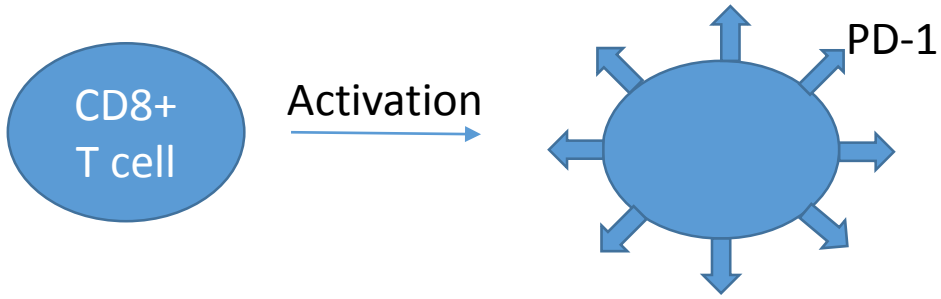
Zahm (2017) *Canc Imm Res* **5**:630

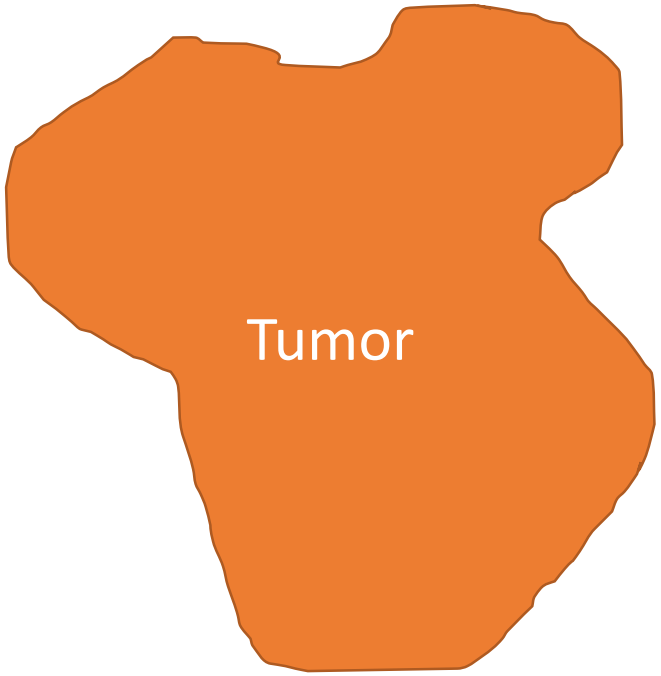
Timing of PD-1 Blockade with Vaccine T-cell Activation: New Model





Timing of PD-1 Blockade with Vaccine T-cell Activation: New Model

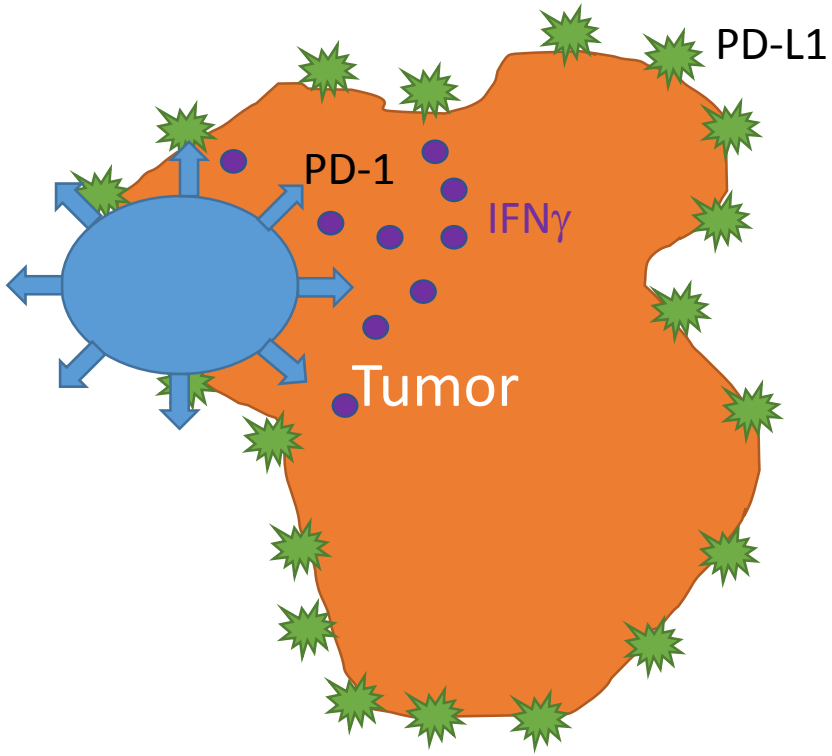




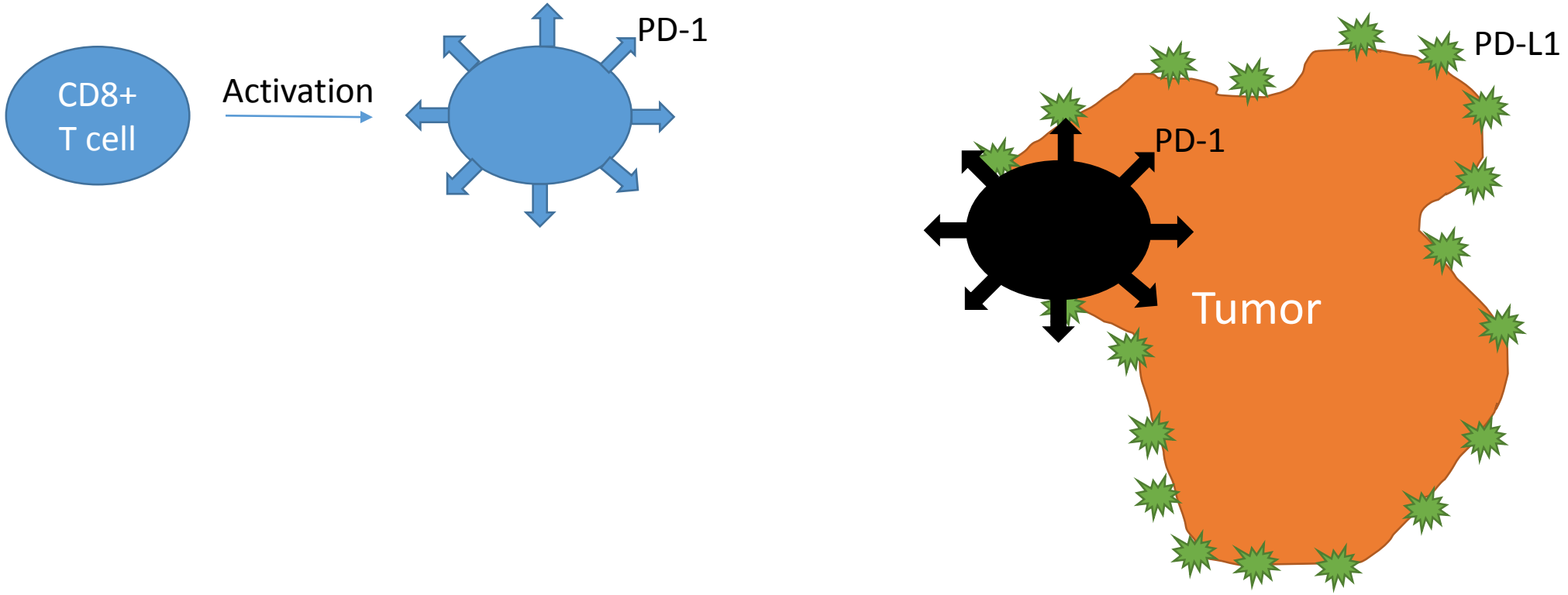
Timing of PD-1 Blockade with Vaccine T-cell Activation: New Model

CD8+ T cell

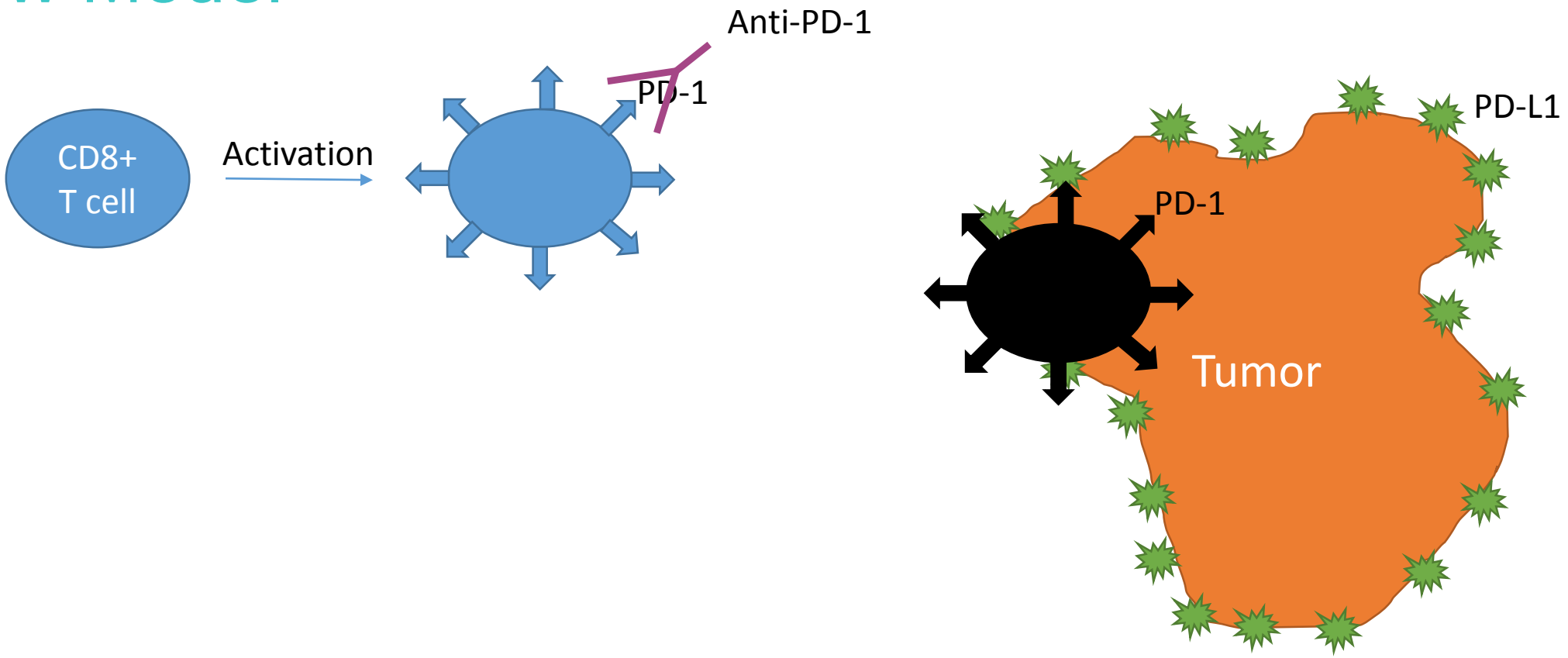
Activation



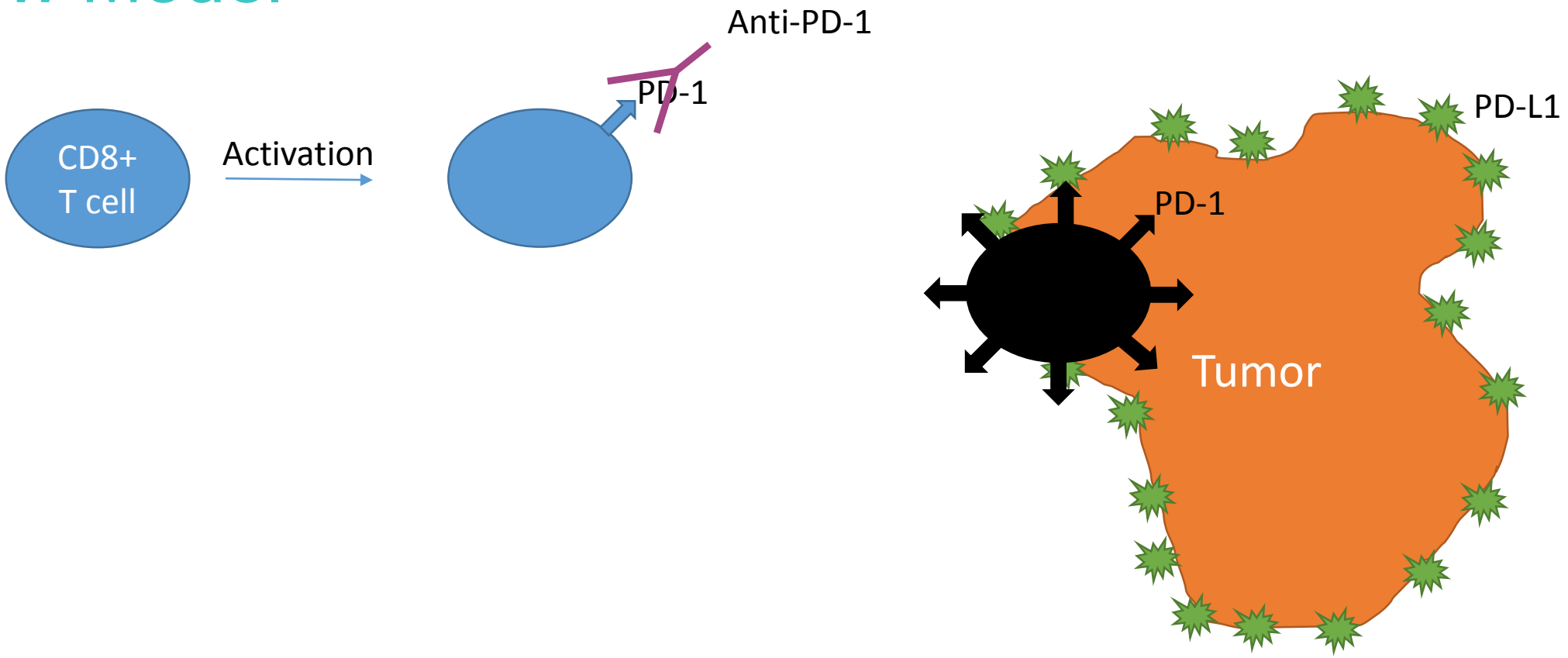
Timing of PD-1 Blockade with Vaccine T-cell Activation: New Model



Timing of PD-1 Blockade with Vaccine T-cell Activation: New Model

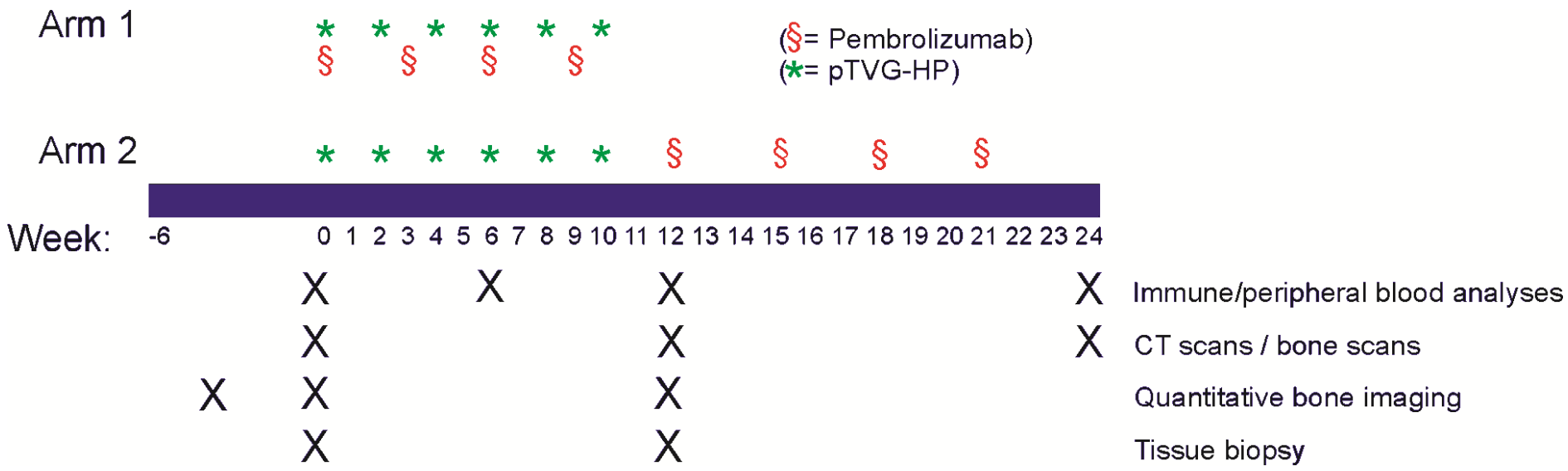


Timing of PD-1 Blockade with Vaccine T-cell Activation: New Model



Clinical Trial Hypothesis and Schema

PD-1 blockade at the time of T-cell activation with vaccination should be more effective than blockade of PD-1-regulated T cells previously elicited with vaccination



Funding Sources: Prostate Cancer Foundation (2014 Challenge Award); Madison Vaccines Inc.

Objectives

Primary:

- Safety
- 6-month progression-free survival and median time to radiographic progression
- To evaluate the anti-tumor response rates (objective response rate and PSA response rate, using PCWG2 criteria)

Secondary:

- Impact of treatment sequence on response, PFS, and PAP-specific immune response

Study Population

- Patients with metastatic, castration-resistant prostate cancer (mCRPC)
- Evidence of disease progression
- No exclusion for prior abiraterone, enzalutamide, or chemotherapy

- Planned enrollment of 32 patients

  (Pilot trial design – to detect a 65% 6m PFS rate in Arm 1 relative to anticipated 25% 6m PFS in Arm 2 with 80% power at 0.10 significance level)

Safety / Adverse Events

Grade 2-3 events:

Fatigue (27%), hypothyroidism (15%), hyperthyroidism (8%), diarrhea (8%), increased AST (8%)

<5%: weight loss, adrenal insufficiency, abdominal pain, constipation, hepatitis, nausea, pancreatitis, hyperglycemia, arthralgia, pain, hot flashes

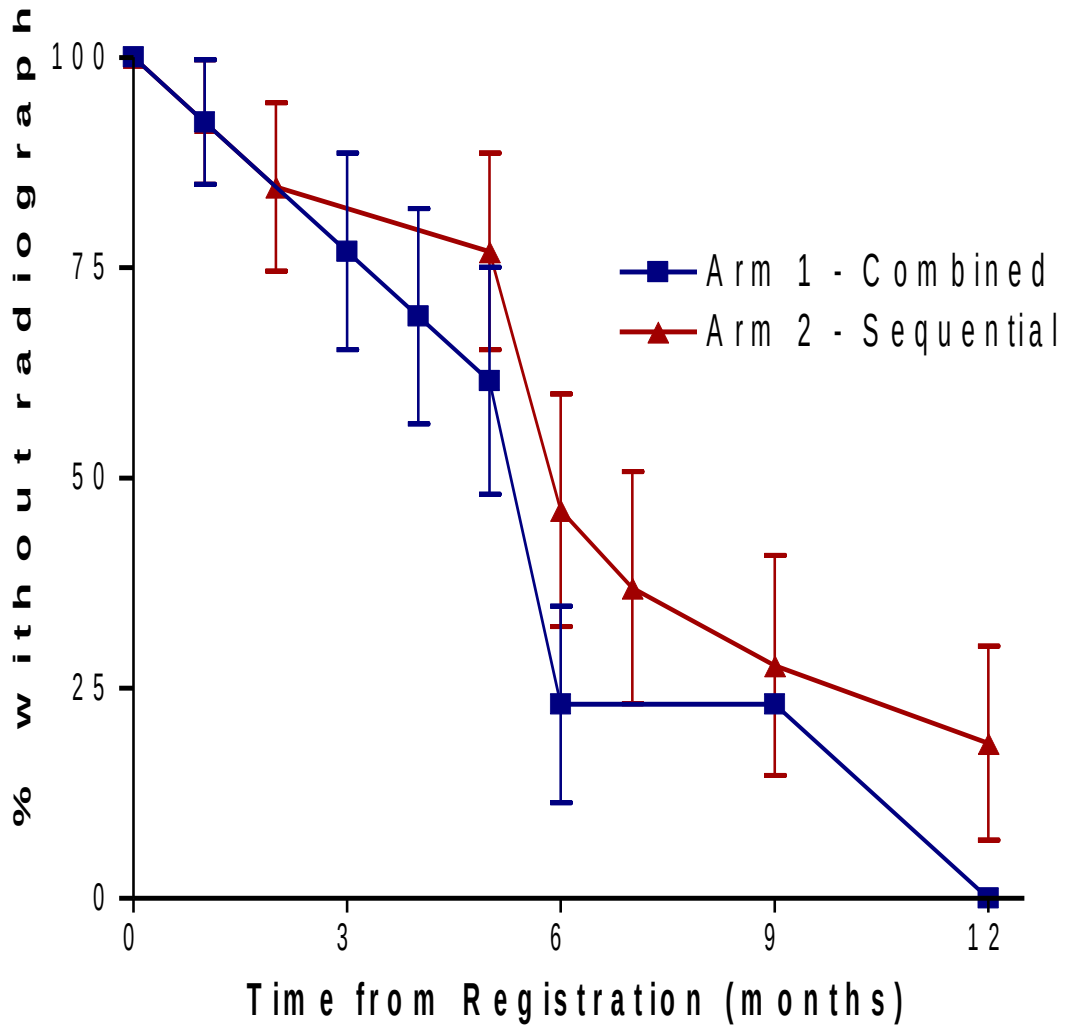
Grade 4 events:

None

Grade 5 events:

Multi-organ failure – 1 patient

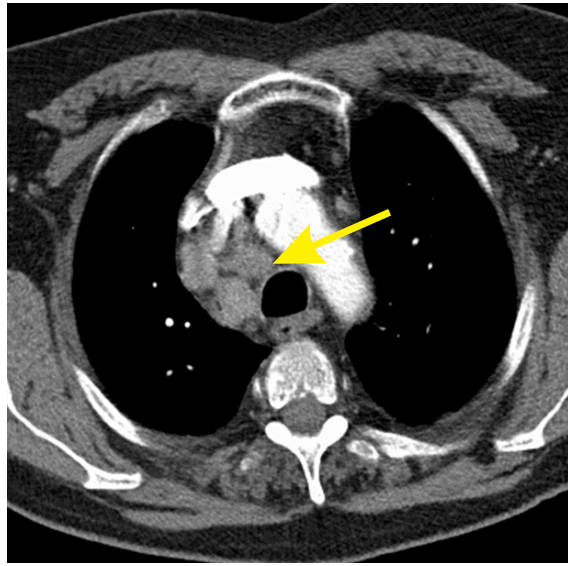
Radiographic Time to Progression



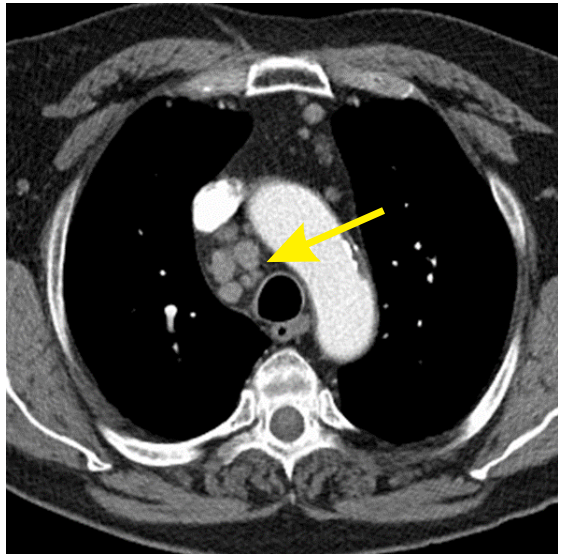
Arm	Best Objective Response – 3m or 6m		
	CR	PR	MR
1 (n=13)	0/8	1/8 (not confirmed)	2/8
2 (n=13)	0/6	0/6	0/6
Total (of 26)	0/14	1/14	2/14

Radiographic Changes

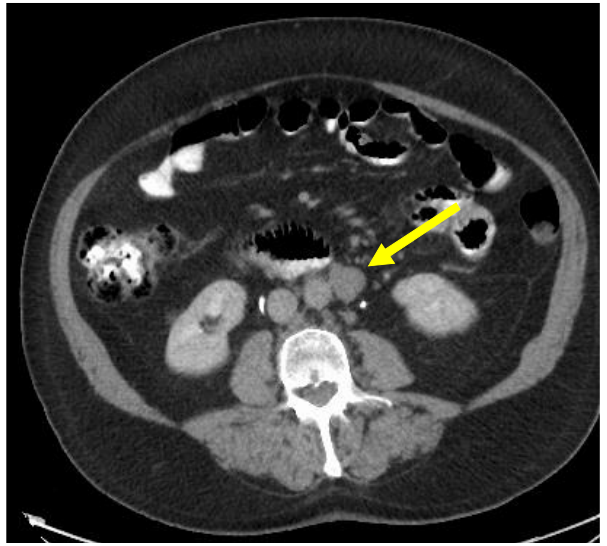
Baseline



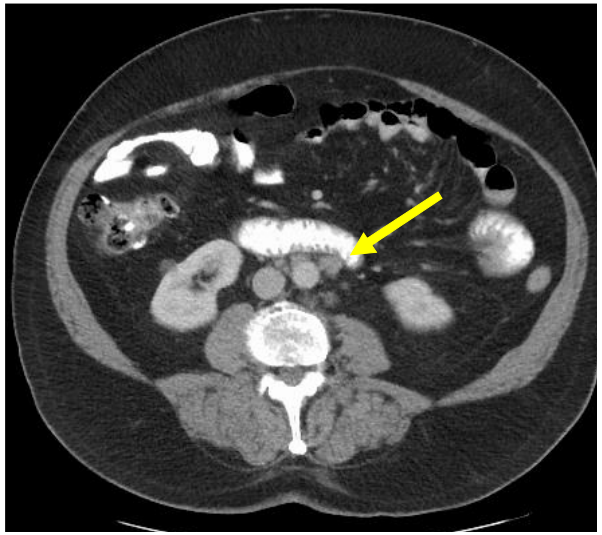
Post-Treatment



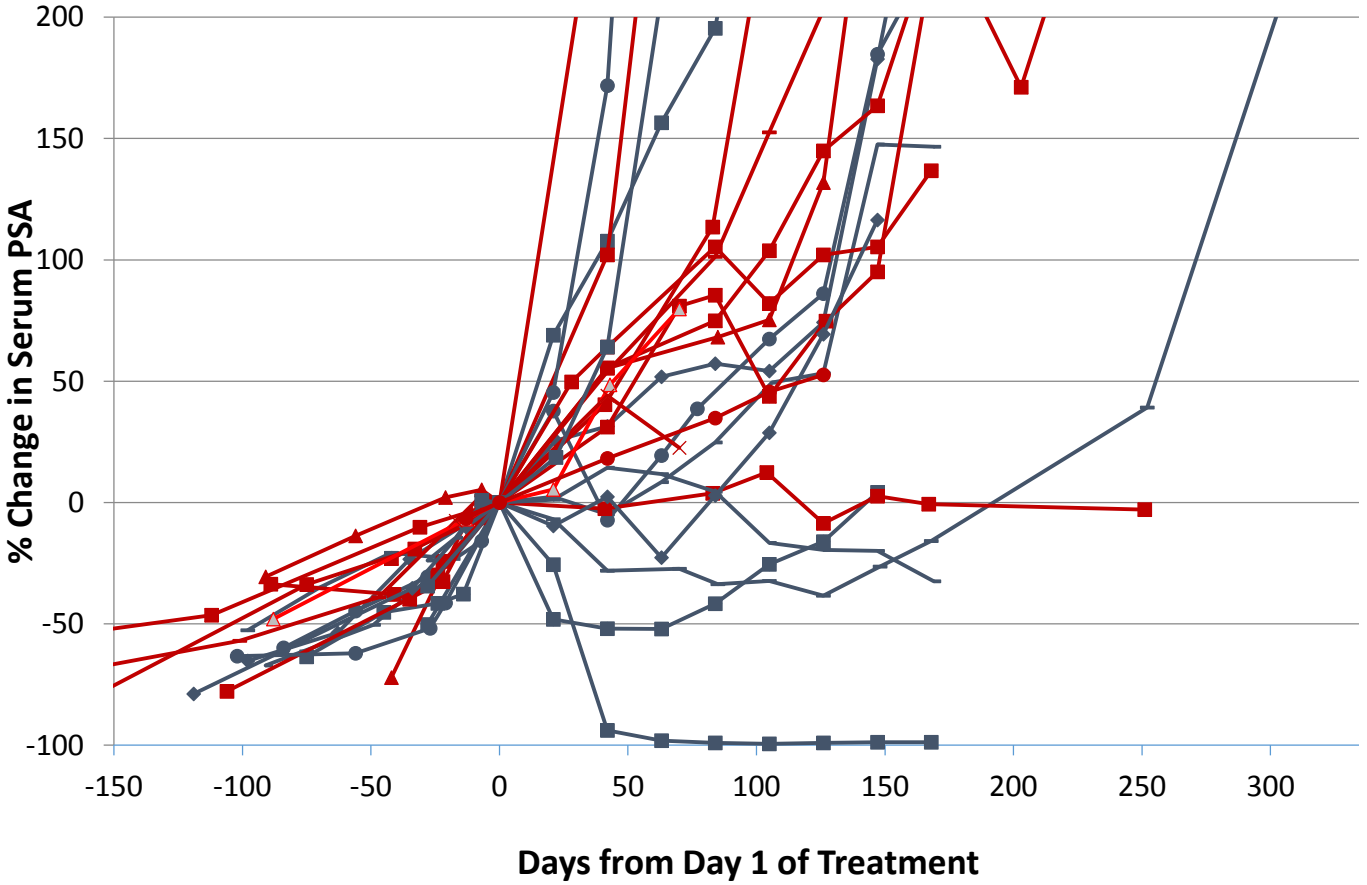
Baseline

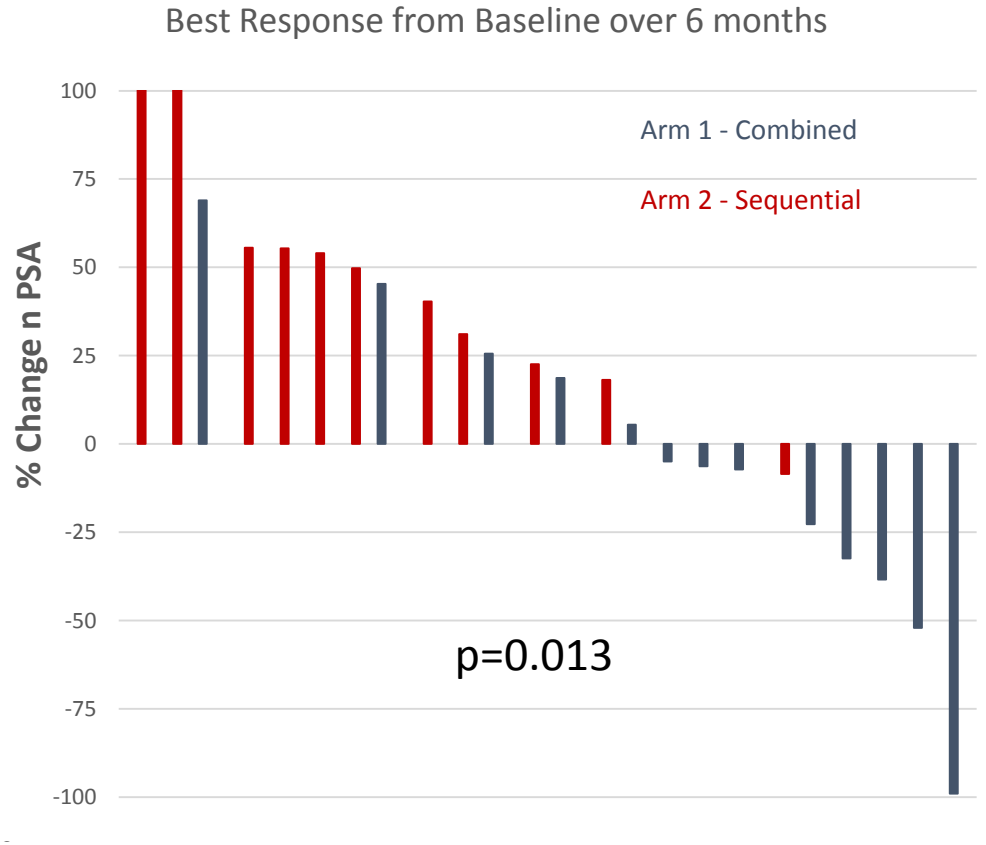


Post-Treatment

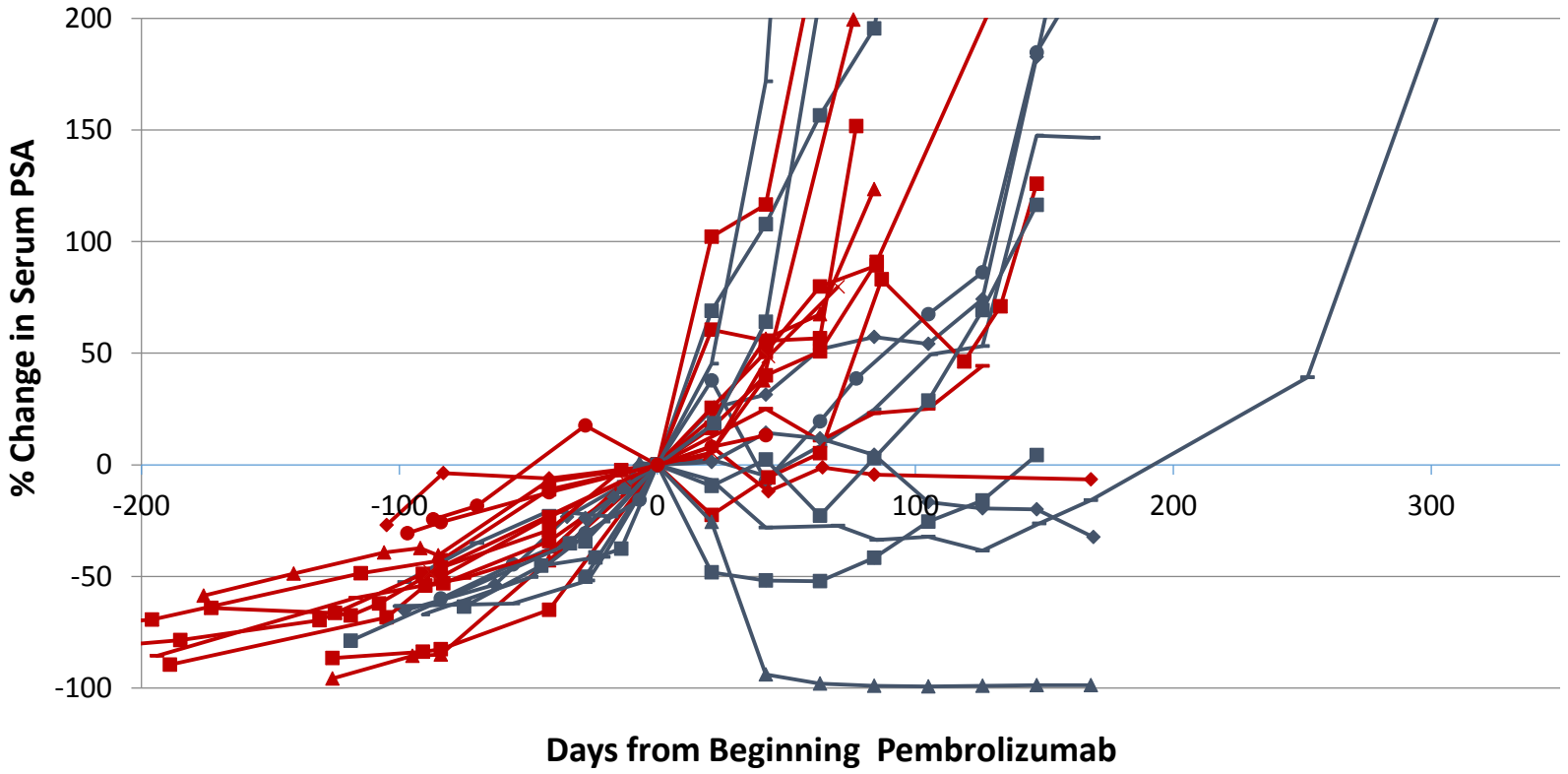


PSA Responses





PSA Responses – Not due to Pembrolizumab

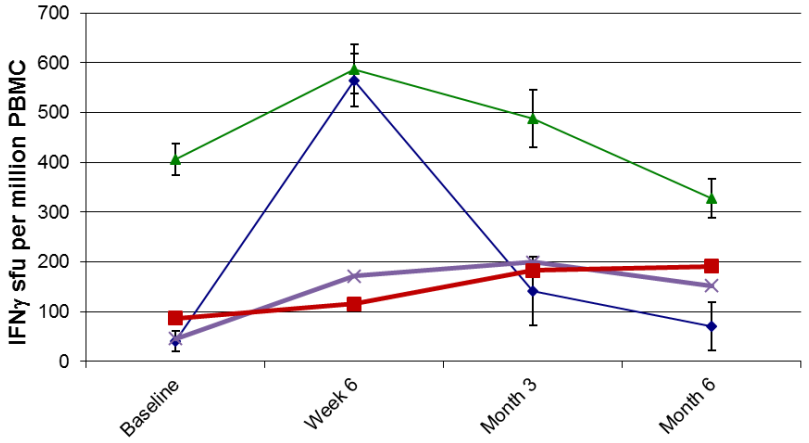


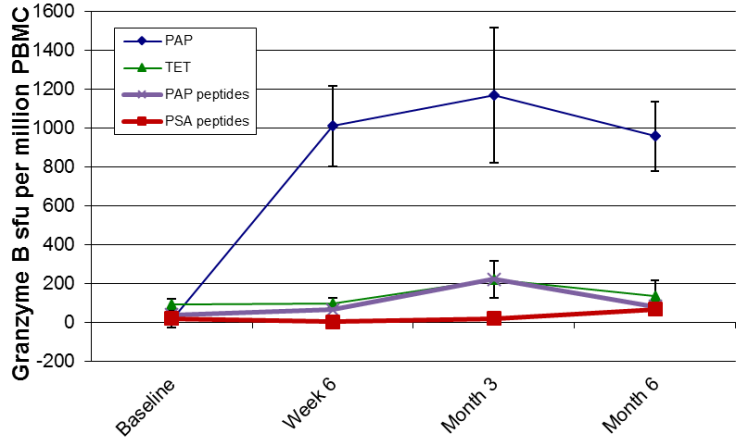
PAP-Specific Immunity – ELISPOT

IFNγ

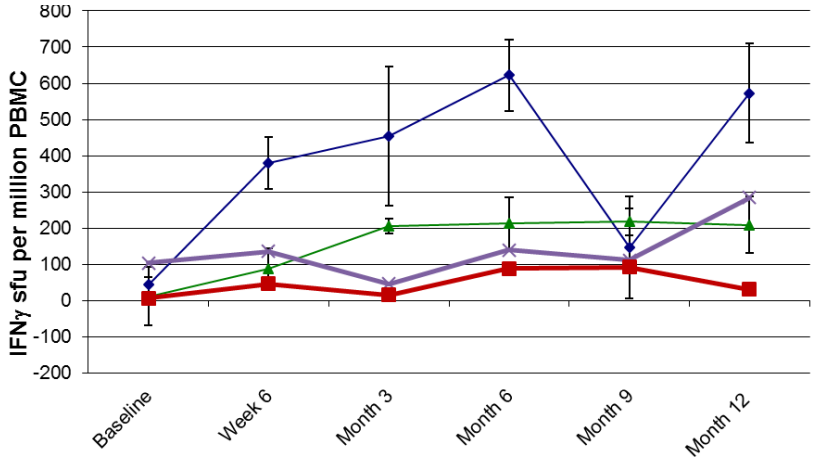
Granzyme B

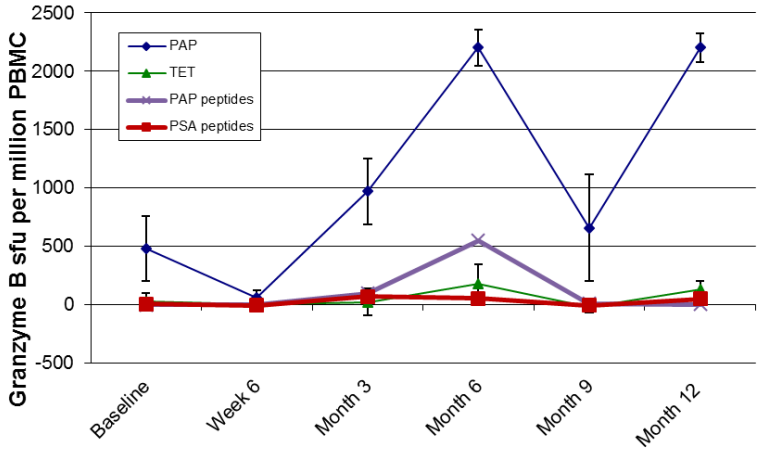
Pt 8



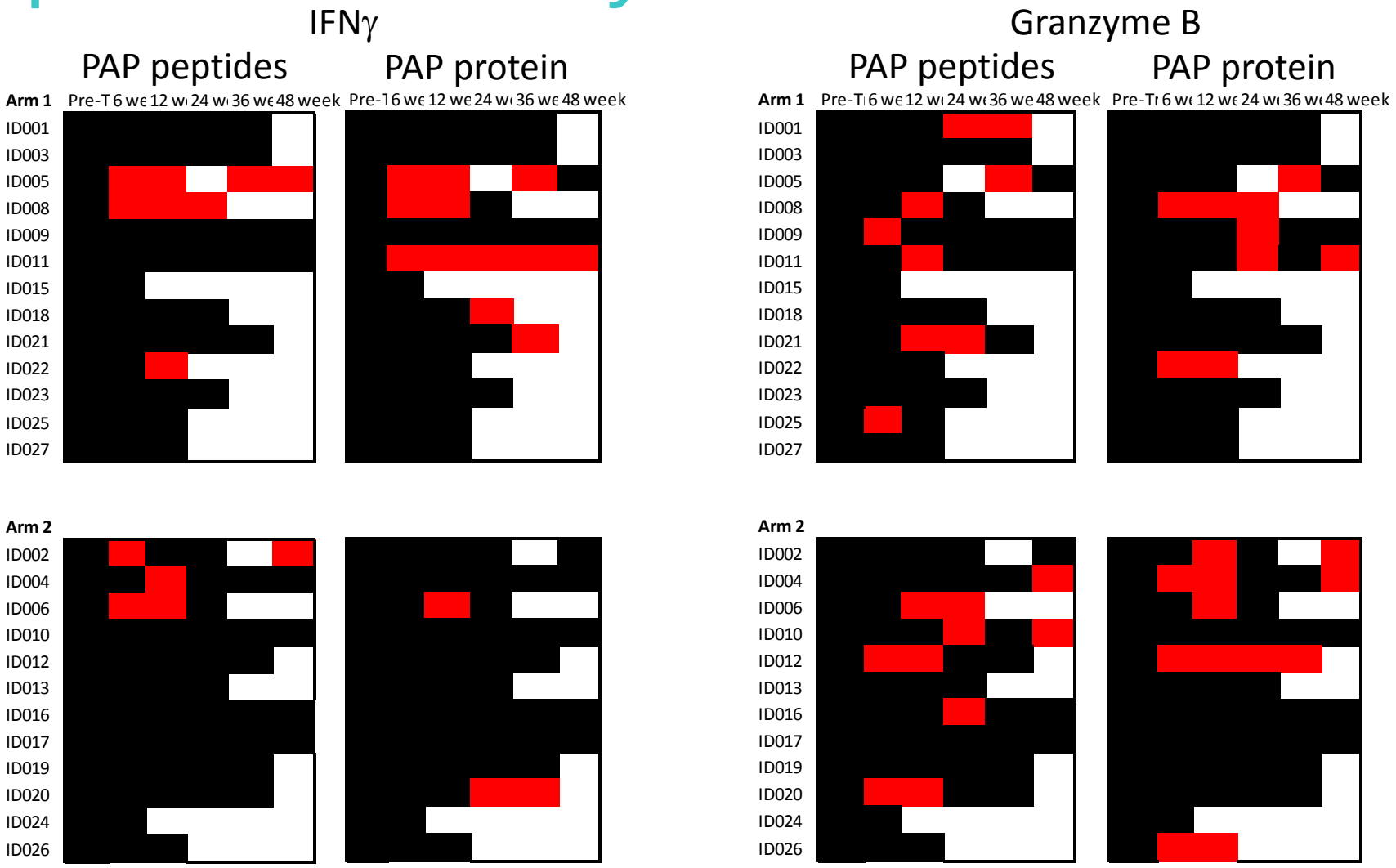


Pt 11



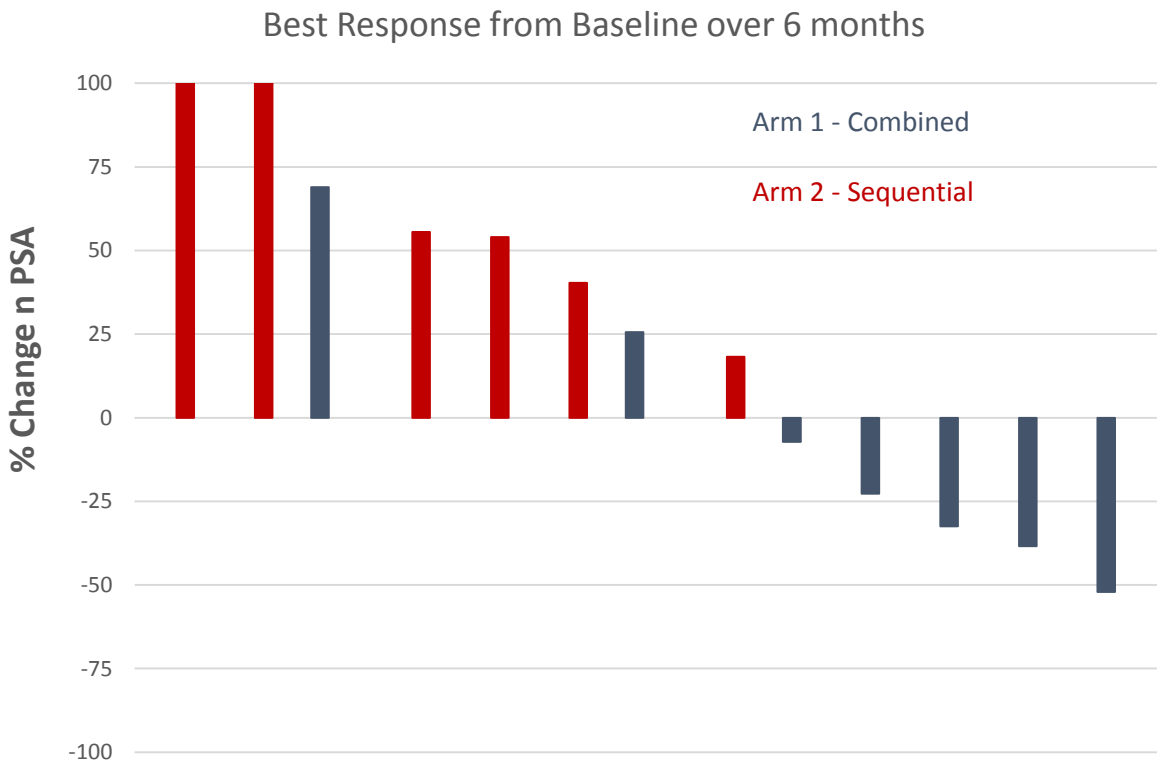


PAP-Specific Immunity – ELISPOT



Ellen Wargowski

PAP-Specific Immunity Is Associated with PSA Decline in Patients Receiving Combination



p=0.021

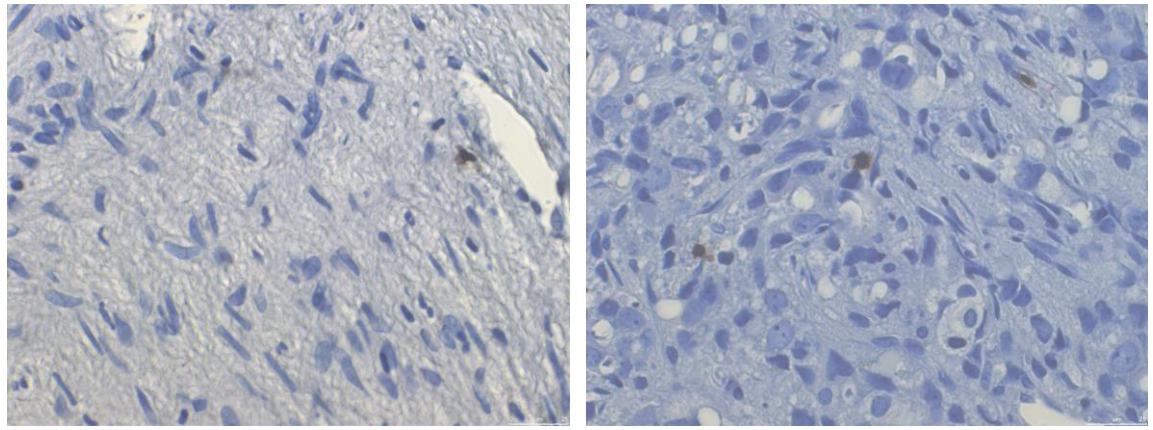
Immunization with PD-1 Blockade Elicits Tumor-Infiltrating CD8+ T cells

Vaccine Alone

Pt 17 Pt 26

Pre

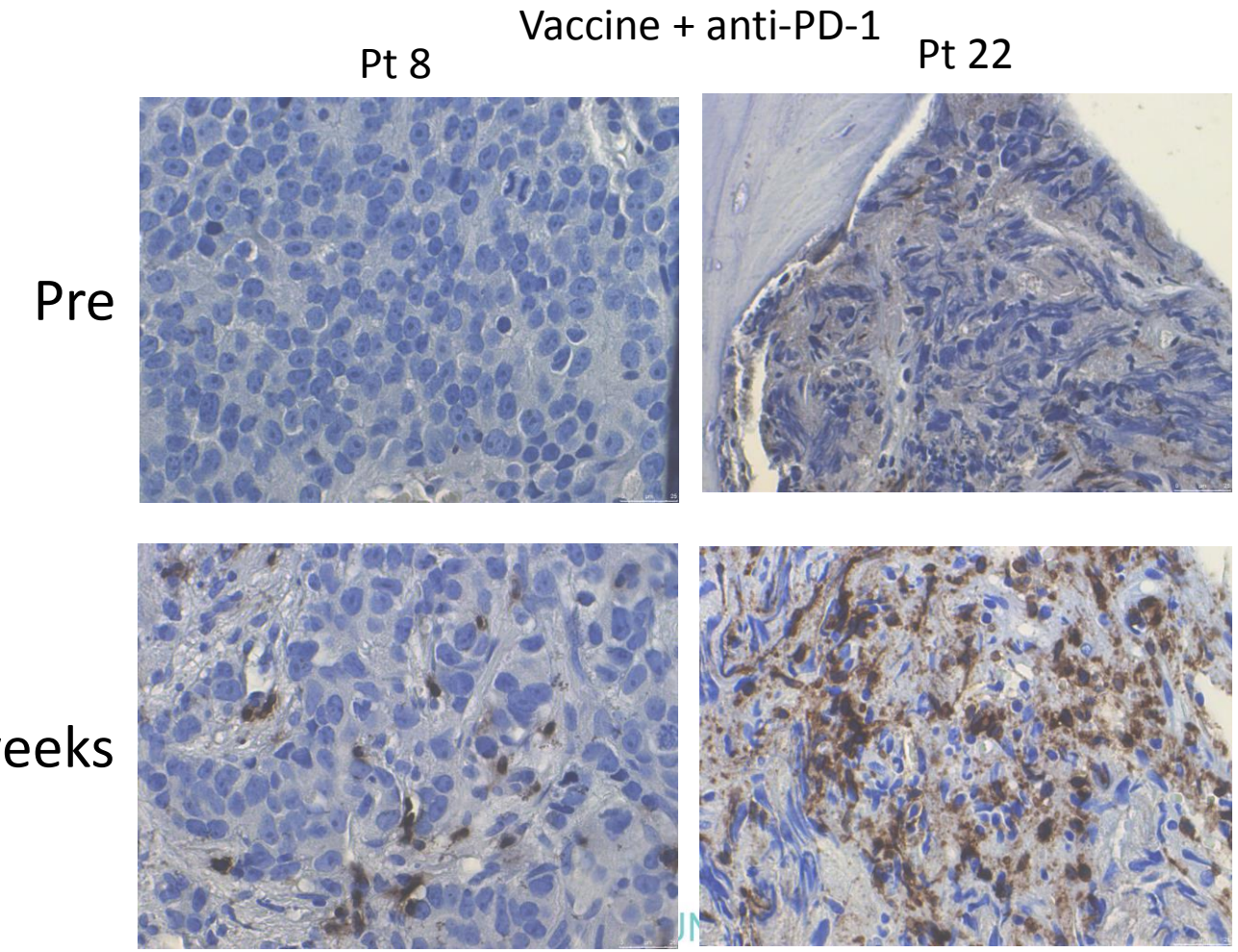
12 weeks



Chris Zahm, PhD

Immunization with PD-1 Blockade Elicits Tumor-Infiltrating CD8+ T cells

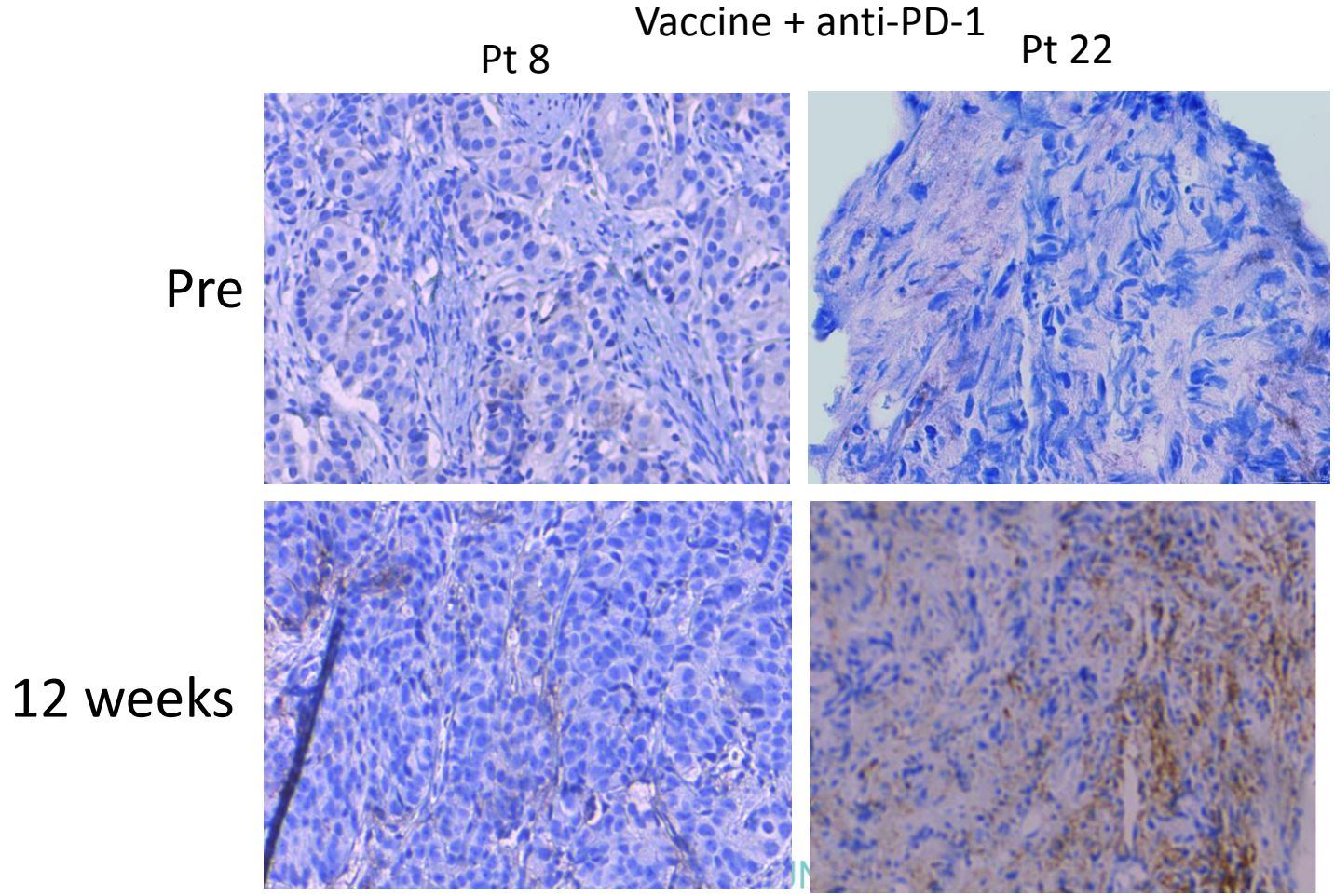
Vaccine + anti-PD-1



Chris Zahm, PhD

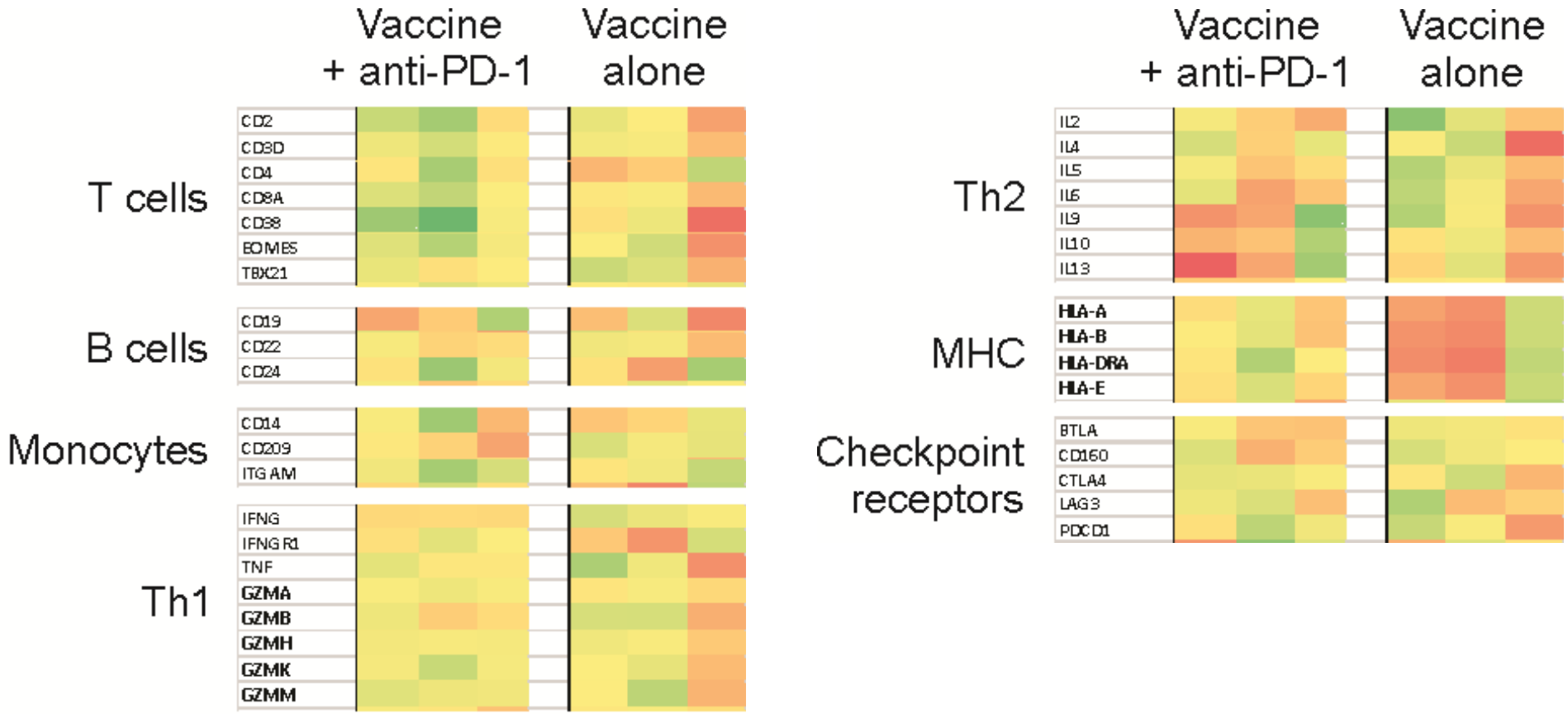
Immunization with PD-1 Blockade Elicits PD-LI Expression in Tumors

Vaccine + anti-PD-1



Chris Zahm, PhD

Immunization with PD-1 Blockade Elicits Changes Associated with CD8+ T cell Activation

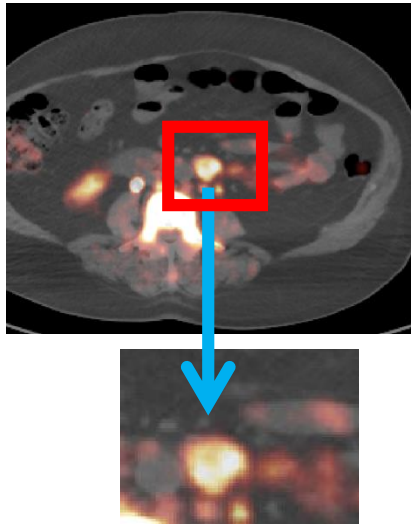


HTG Molecular Diagnostics

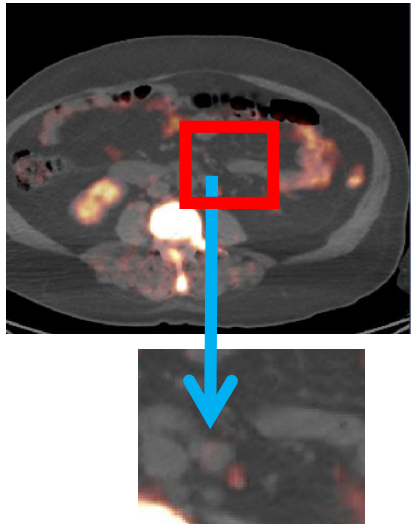
Immunization with PD-1 Blockade Elicits Changes in Proliferation Detected by FLT PET/CT

Change in **Tumor** FLT

Baseline

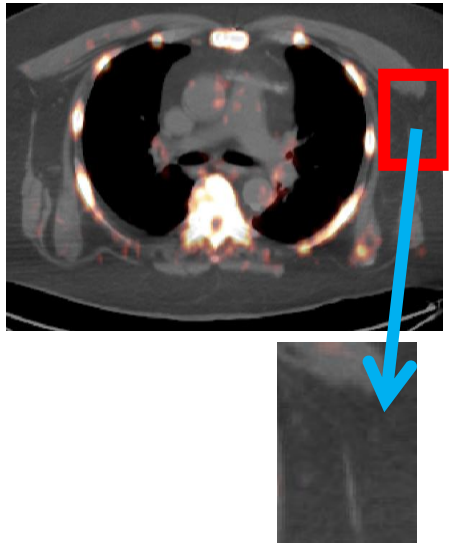


12 weeks

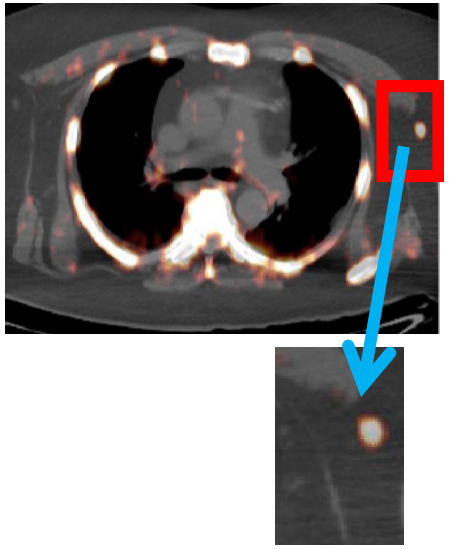


Change in **Axillary Node** FLT

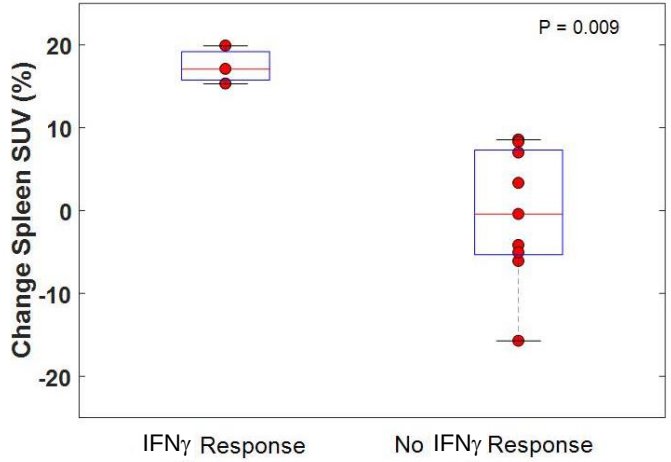
Baseline



12 weeks



Change in **Spleen** FLT



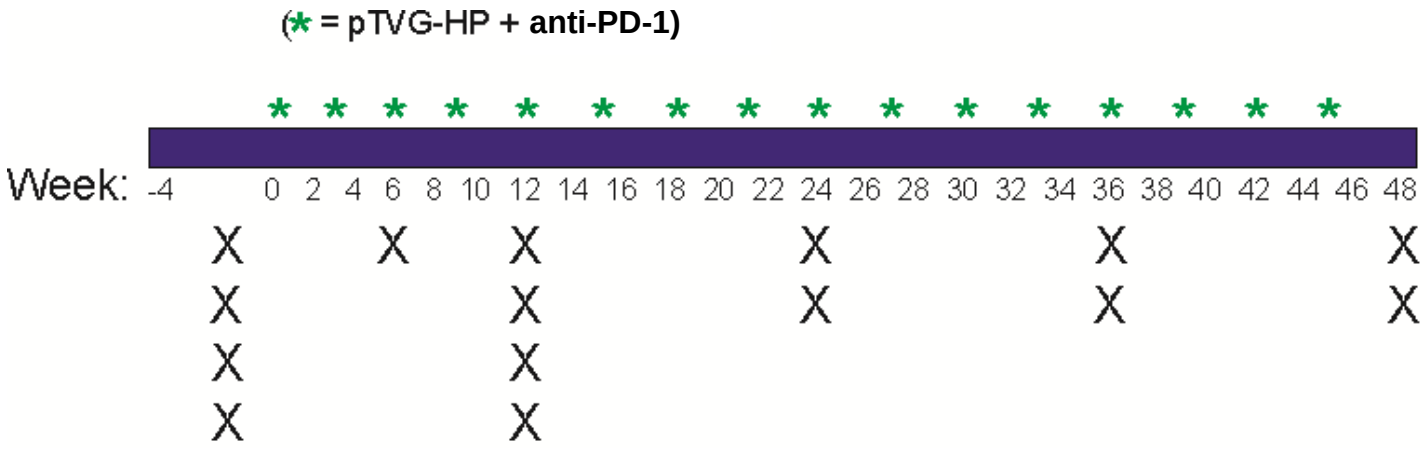
Matthew Scarpelli

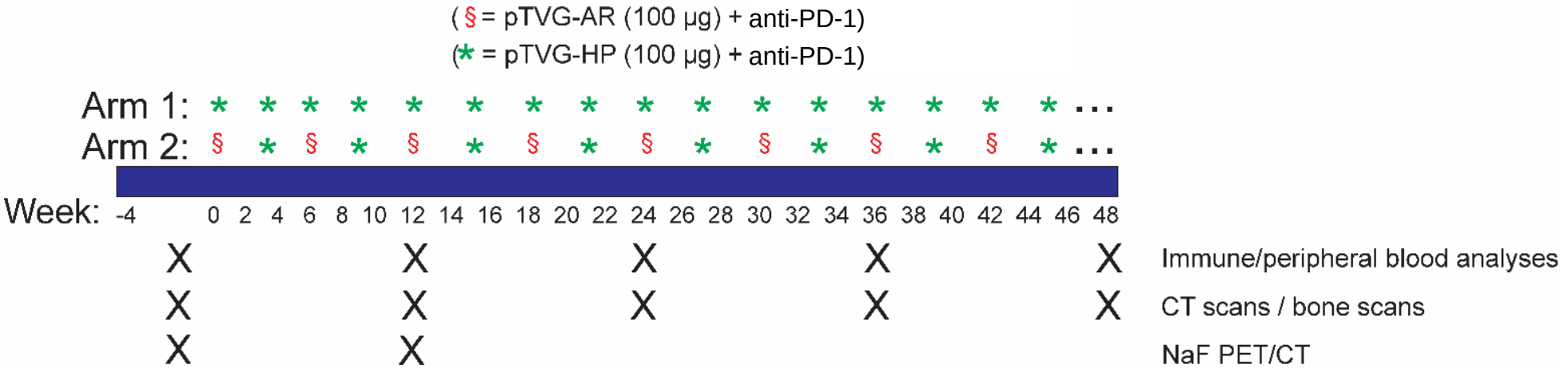
Summary

- Plasmid DNA vaccines elicit antigen-specific CD8+ T cells
- DNA immunization can increase PD-L1 on tumor cells, mediated by T cells
- PD-1 expression increases on CD8+ T cells following vaccine activation
- Blockade of checkpoint molecules with vaccination can lead to improved anti-tumor responses, including radiographic and PSA responses in patients with advanced prostate cancer

- **Anti-tumor vaccines can elicit tumor-specific CD8+ T cells needed to enable PD-1 blockade to work**
- **This has implications for choice of vaccine approach, antigen, and timing of PD-1 blockade**

Ongoing and Future Directions





- Primary endpoints:
  - ORR
  - 6-month PFS

Acknowledgments

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- Laura Johnson, PhD
- Brian Rekoske, PhD
- Heath Smith, PhD
- Sam Tesch
- Ellen Wargowski
- Christopher Zahm, PhD

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NIH National Cancer Institute

Prostate Cancer Foundation Curing Together.

MADISON vaccines incorporated

Carbone Cancer Center
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SCHOOL OF MEDICINE AND PUBLIC HEALTH