SITC 2016

NATIONAL HARBOR, MD
NOVEMBER 9-13, 2016

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Society for Immunotherapy of Cancer

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Challenges and Opportunities for Immunotherapy in Prostate Cancer

James Gulley MD, PhD, NCI

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#SITC2016

Presenter Disclosure Information

James Gulley

The following relationships exist related to this presentation:

No Relationships to Disclose

Immunotherapy Landscape in mCRPC

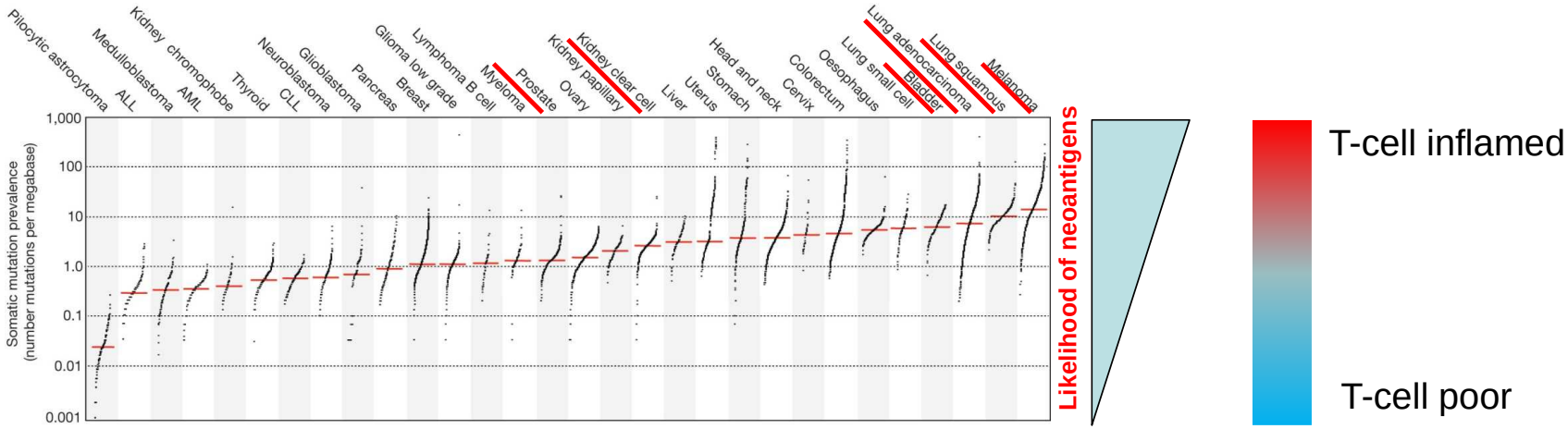
- Approved Vaccine therapy (Sipuleucel-T)
  - Survival: 25.8 versus 21.7 months
  - Earlier use appears to lead to improved outcomes
  - No significant decrease in PSA, tumor size or PFS

- Experimental Vaccine therapy (PSA-TRICOM / Prostvac)
  - Phase 2 study suggested improved OS
  - Phase 3 study enrolled (n=1,297)

- Experimental Checkpoint inhibitor therapy
  - Two negative ipilimumab phase 3 studies (no OS, although responses seen)
  - 0 of 17 patients in a phase I nivolumab study had an objective response to therapy.
  - Preliminary data with pembrolizumab + enzalutamide, durvalumab + olaparib, pembrolizumab + vaccine

NEJM 2010; 363: 411-422, Lancet Oncol 2014; 15: 700-12, NEJM 2012; 366: 2443-2454, Oncotarget 2014, Oncotarget 2016

The prevalence of somatic mutations across human cancer types.

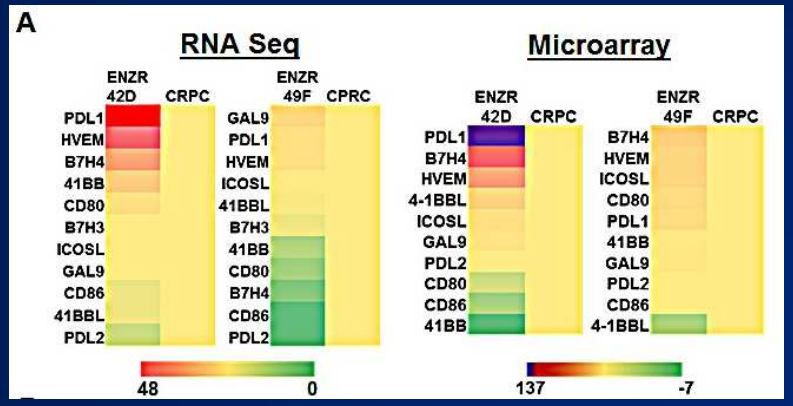


LB Alexandrov *et al. Nature*, 1-7 (2013) doi:10.1038/nature12477

nature

Prostate Cancer and PDL1

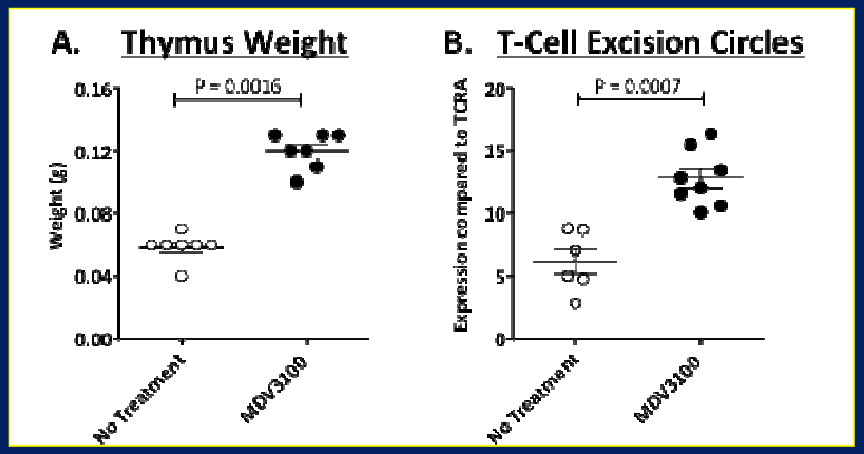
- Minimal PDL1 expression in localized Prostate cancer (3/20) Martin et al., Prostate Ca and Prost. Dis., 2015
- ORR <10% in unselected patients (nivolumab and others).
- PDL1 highly expressed in enzalutamide resistant prostate cancer
  - Murine cell lines
  - In circ. DC in pts



Bishop et al. *Oncotarget*, 2014

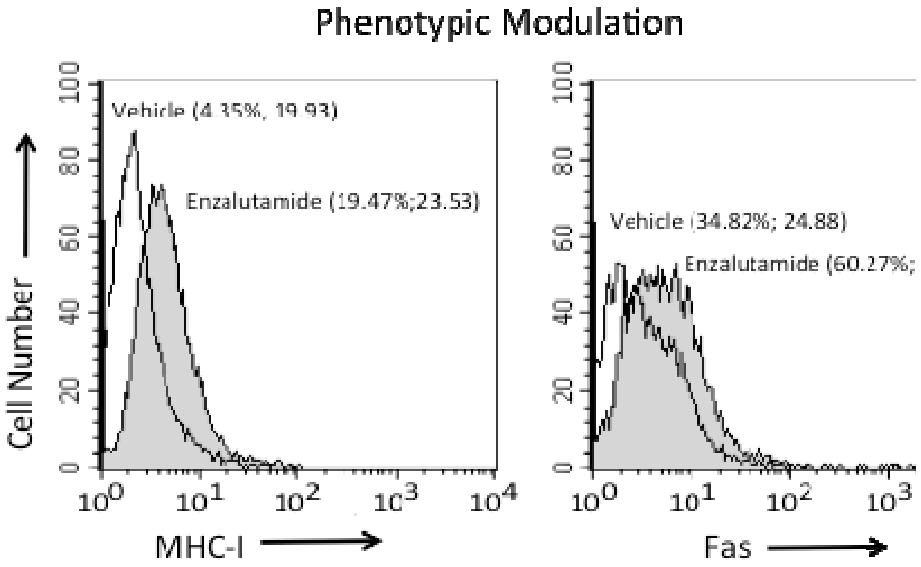
NCI Preclinical Studies with Enzalutamide

- Male C57BL/6 fed Enzaluatmide (MDV3100) in diet
- (A) Increased thymic weights at 14 days
- (B) Increased T-cell receptor excision circles (TRECs), by products of naïve T-cell production



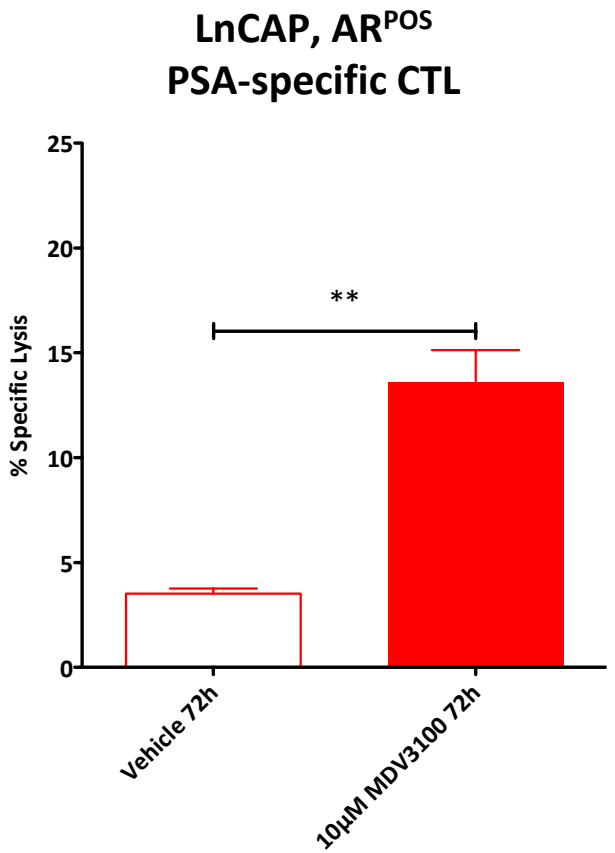
Ardiani et al., *Clin Ca Res*, 2013

Enzalutamide Mediates Immunogenic Modulation in TRAMP-C2 Prostate Cells



MHC Increased ~5-Fold

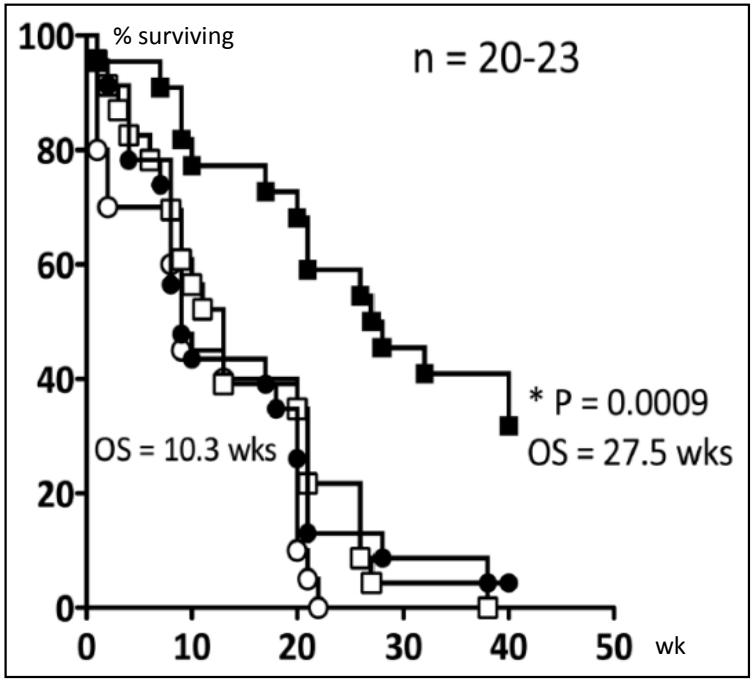
Fas Increased ~1.7-F



Ardiani A et al. Clin Cancer Res 2013
Ardiani A et al. Oncotarget, 2014

Enzalutamide: Synergy with Immunotherapy

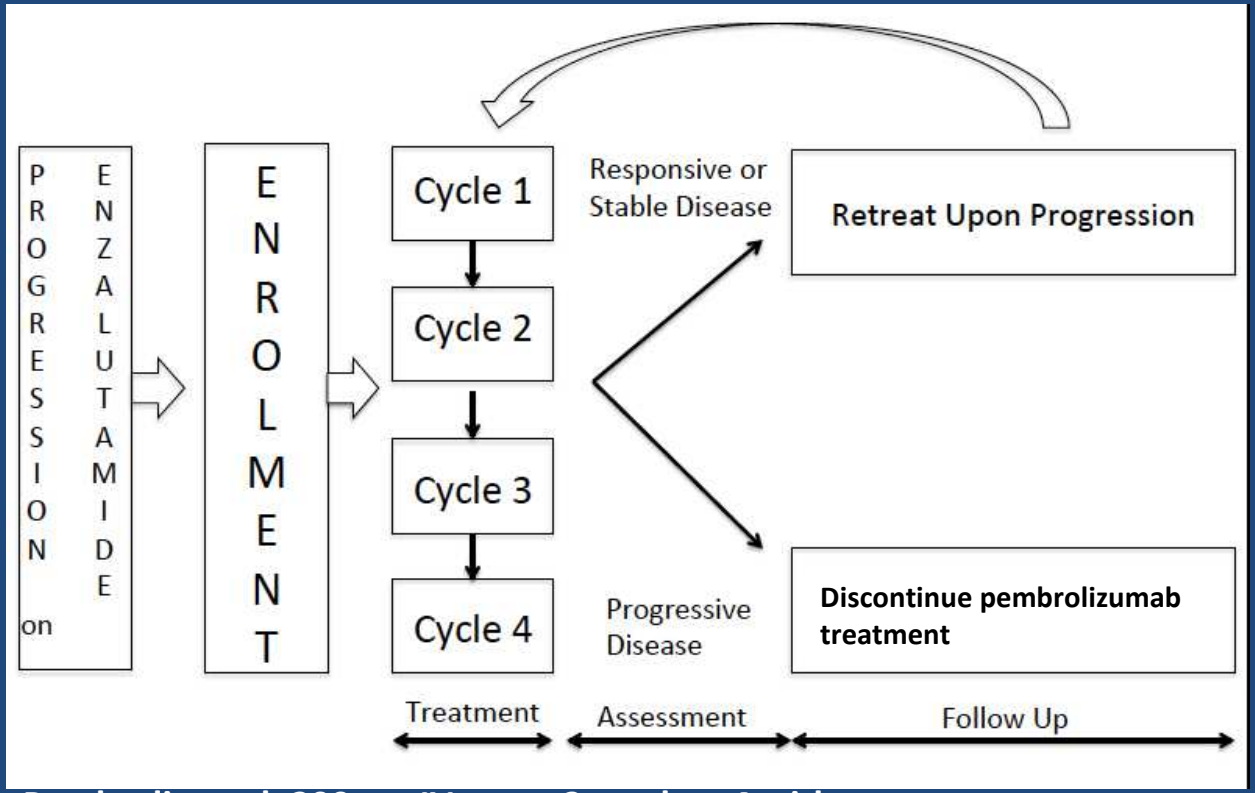
- Enzalutamide combined with a vaccine significantly prolongs OS in TRAMP mice:



Treatment arms:
- no treatment (open circles)
- Vaccine alone (open squares)
- Enzalutamide alone (closed circles)
- Enzalutamide + Vaccine (closed squares)

Ardiani A et al., Clin Cancer Res 2013

Addition of Pembrolizumab Upon Progression on Enzalutamide in Men with mCRPC

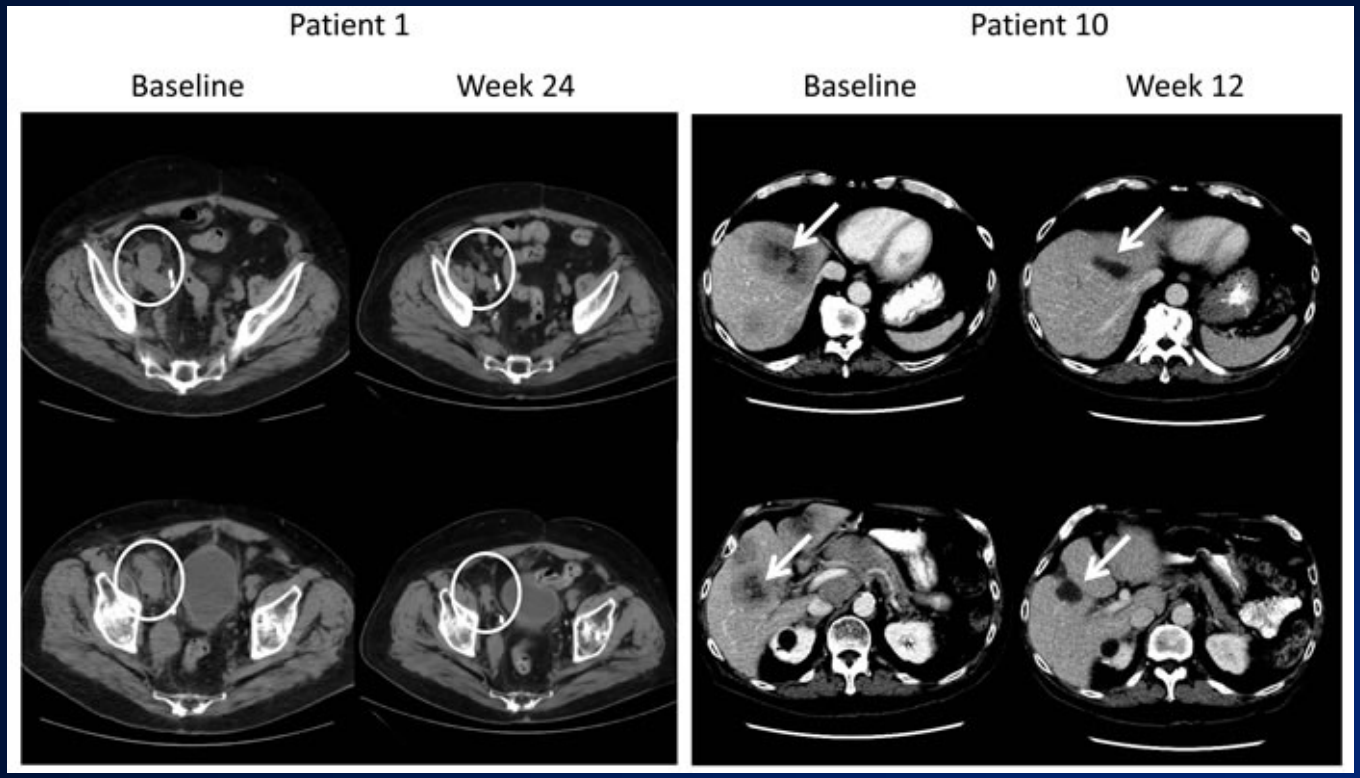


Pembrolizumab 200 mg IV every 3 weeks x 4 with retreatment
Continued Enzalutamide therapy

Graff et al., Oncotarget, 2016

Unpublished data, Courtesy of Julie Graff

Pembrolizumab and Prostate Cancer



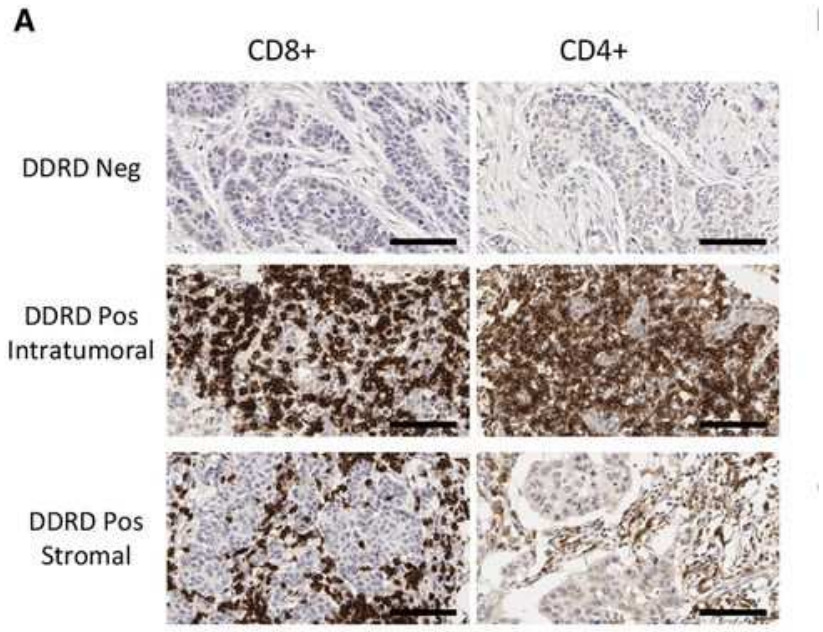
Graff et al., Oncotarget, 2016

Hypermutated Phenotype in mCRPC

- 7/60 (12%)
  - 5/50 Autopsy
  - 3/15 PDX (with overlap from above)
  - All with mismatch repair gene mutations (e.g., MSH2 and MSH6) and MSI (associated with multiple point mutations → neoantigens)
  - Hypermutation status was 100% concordant at different metasatic sites and in 2/2 patients who had primary and mets available.
  - Other Case series have reported lower proportions – 2-12% MSI

Prichard et al., Nature, 2014

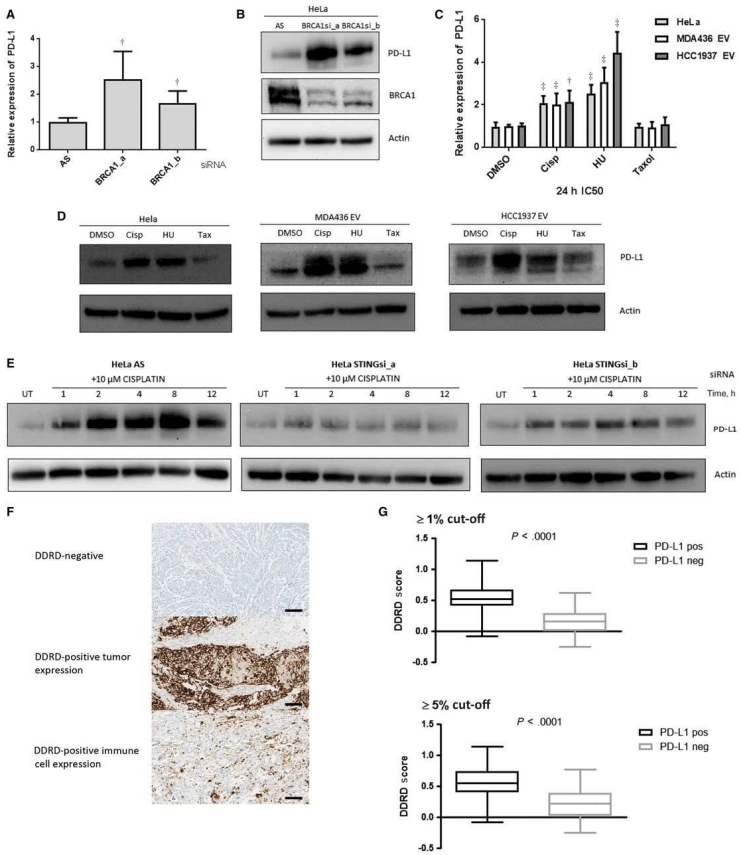
Immune gene expression in FA/BRCA DNA repair pathway loss. (Double strand breaks)



Eileen E. Parkes et al. JNCI J Natl Cancer Inst 2017;109:djw199

JNCI

PD-L1 expression in DNA damage response deficiency.



BRCA1 siRNA → increase PDL1 protein (immunoblot)

DNA damaging chemo increases PDL1 protein

STING mediated (CDDP)

PDL1 staining: DNA damage response–deficient

Eileen E. Parkes et al. JNCI J Natl Cancer Inst 2017;109:djw199

JNCI

The NEW ENGLAND JOURNAL of MEDICINE

Aug 4, 2016

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson

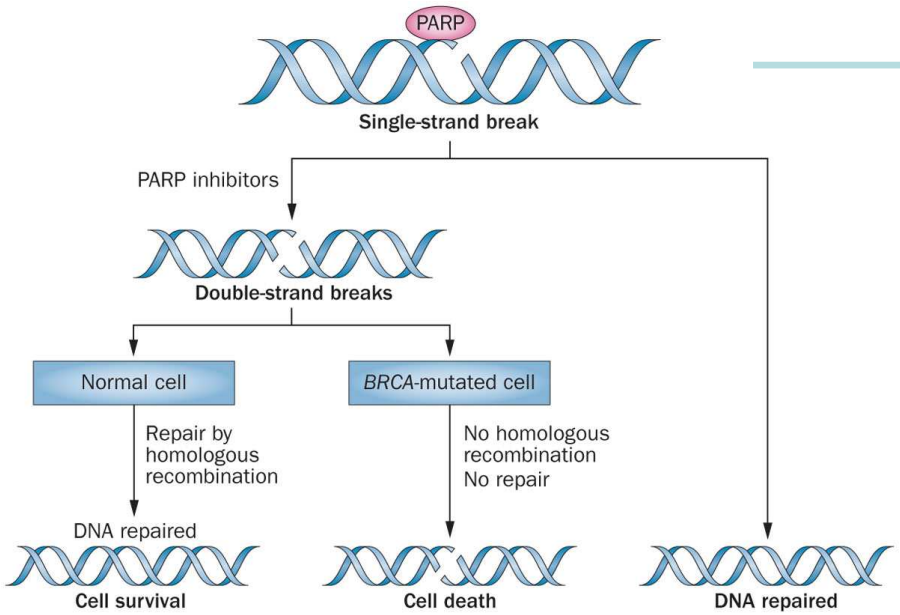
N= 692 mCRPC

11.8% germ-line DNA repair gene mutations

(CGA, n=499 localized PC, 4.6%)

STAND UP TO CANCER

The role of PARP inhibitors in synthetic lethality

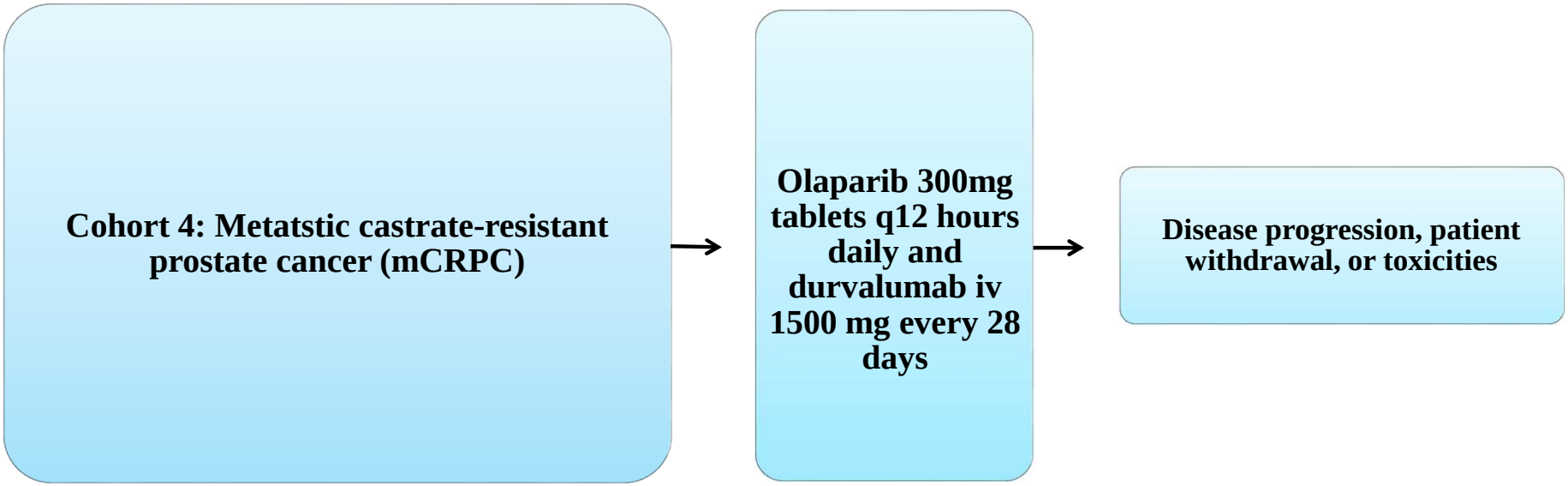


Decrease base excision repair, ? MSI phenotype

Sonnenblick, A. *et al.* (2014) An update on PARP inhibitors—moving to the adjuvant setting *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2014.163

nature REVIEWS CLINICAL ONCOLOGY

Durvalumab + Olaparib



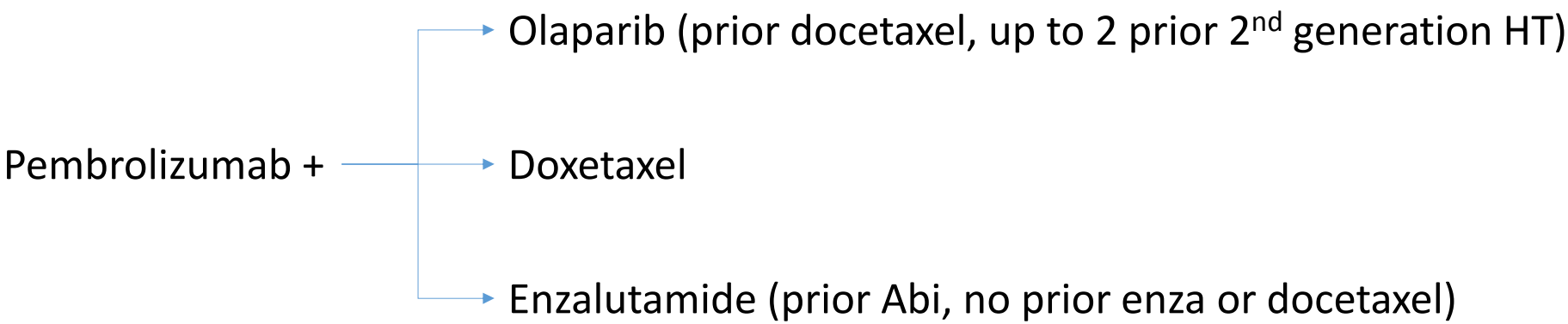
PBMCs: pretreatment, prior to cycle 1 day 15, pre- cycle 3 day 1, and progression

Tumor core biopsy: mandatory pretreatment

PI Lee, NCT02484404

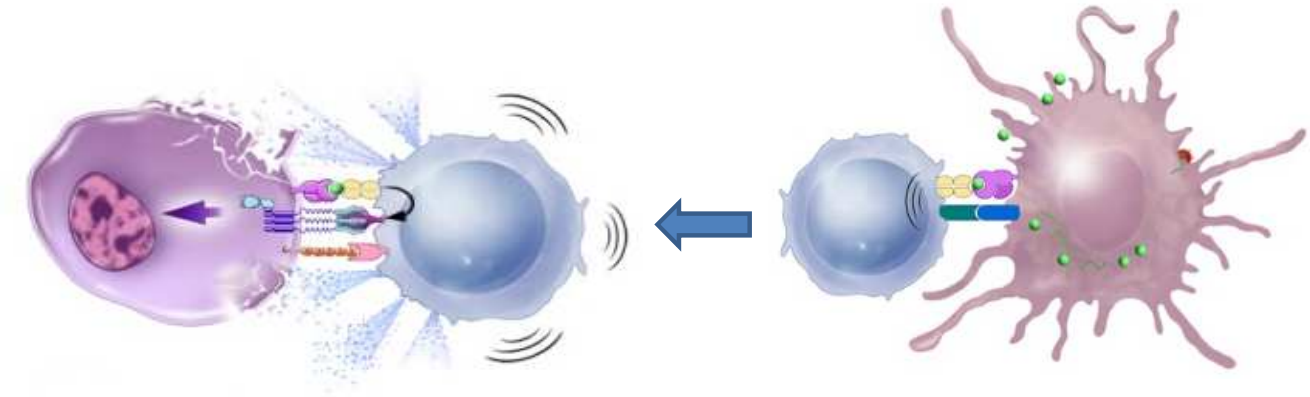
Keynote 365

mCRPC, n=70 per cohort



NCT02861573

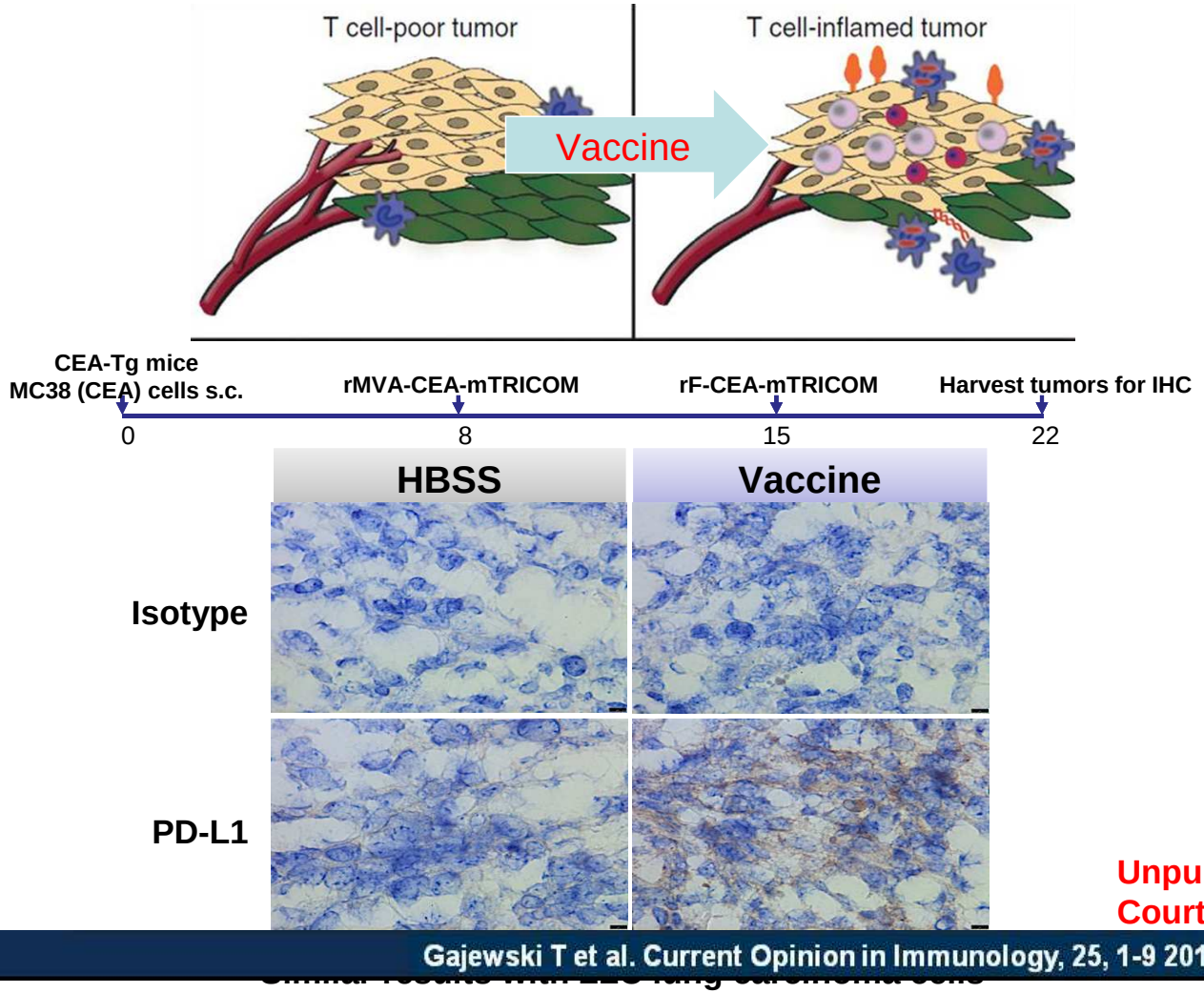
Requirements for Effective Immunotherapy



Effector Cells Functional within Tumor

Generate Immune Response

Effect of Vaccination on Tumor PD-L1 Expression



Unpublished
Courtesy

Gajewski T et al. Current Opinion in Immunology, 25, 1-9 2013

DNA vaccine encoding PAP + Pembrolizumab in mCRPC

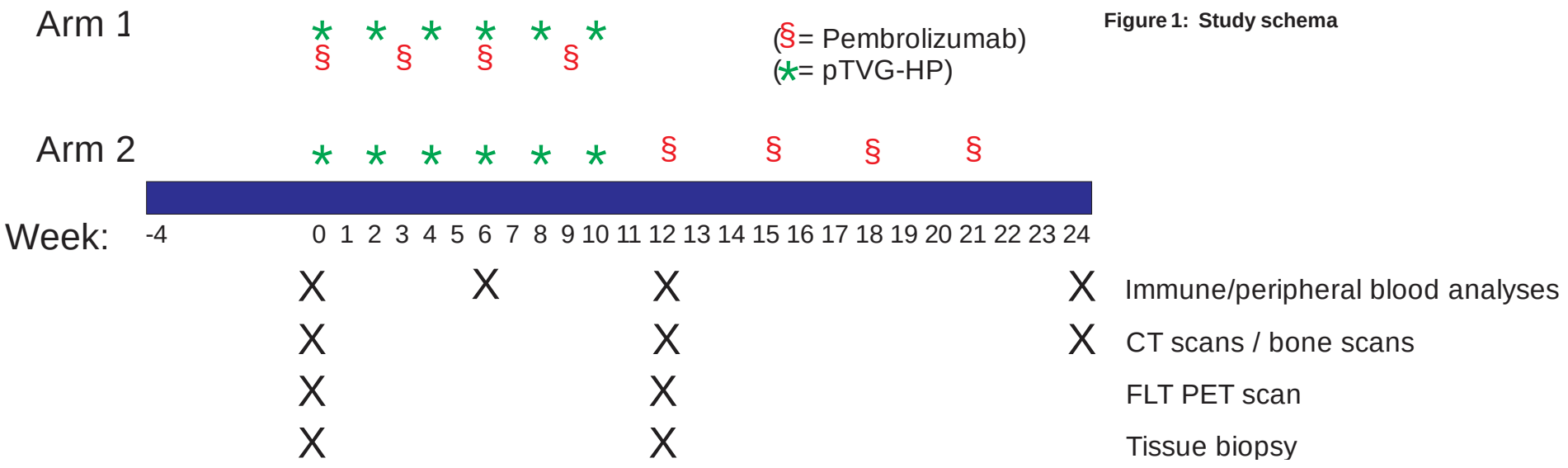


Figure 1: Study schema

McNeel, D. et al., SITC 2016

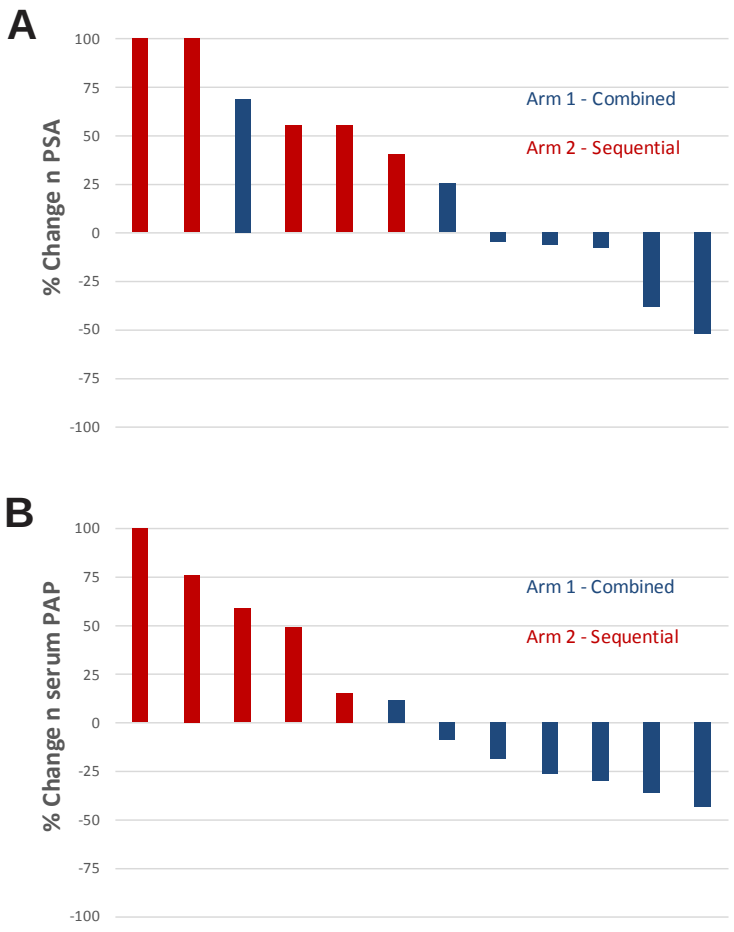


Figure 3: % Change in Serum PSA or PAP. Shown are "best" % change in serum PSA (panel A) or serum PAP (panel B) from D1 of study treatment. Blue indicates patients treated in the concurrent treatment arm, and red indicates patients treated in the sequential treatment arm.

McNeel, D. et al., SITC 2016

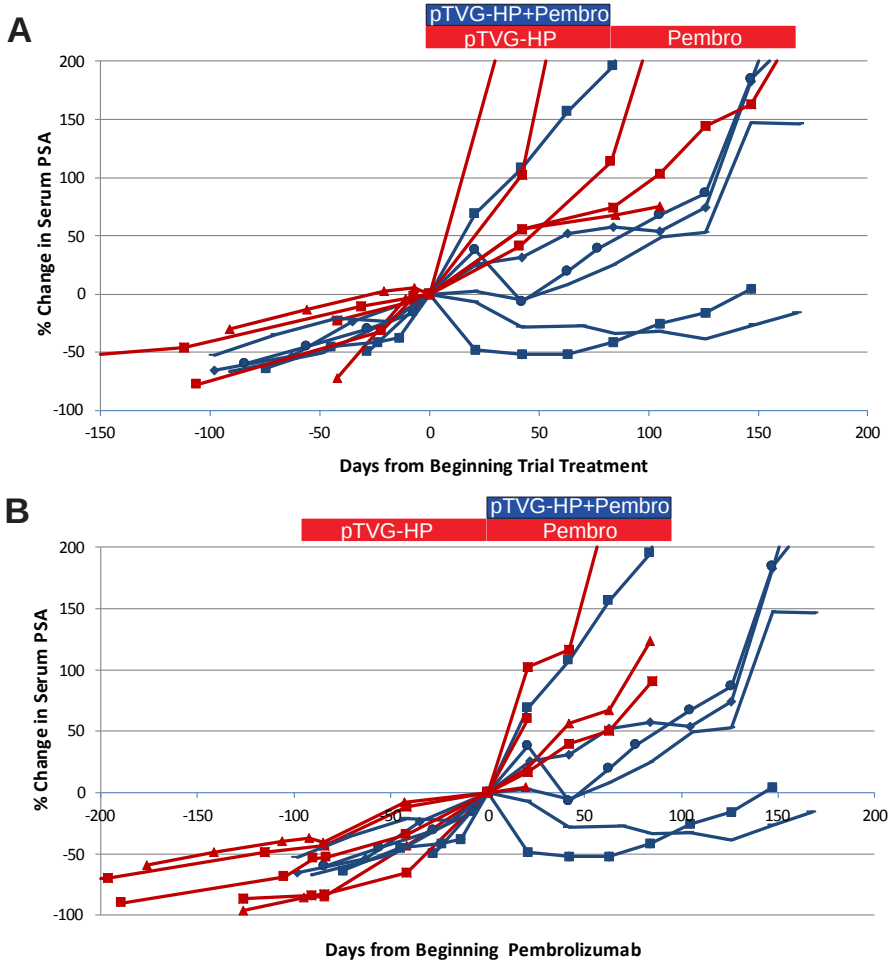


Figure 2: % Change in Serum PSA Shown are % change in serum PSA from (panel A) D1 of study treatment, or (panel B) D1 of receiving pembrolizumab. Blue curves are patients treated in the concurrent pembrolizumab and pTVG-HP treatment. Red curves are patients treated in the sequential treatment arm. Note: One patient with a delayed bicalutamide withdrawal response was removed from this analysis.

McNeel, D. et al., SITC 2016

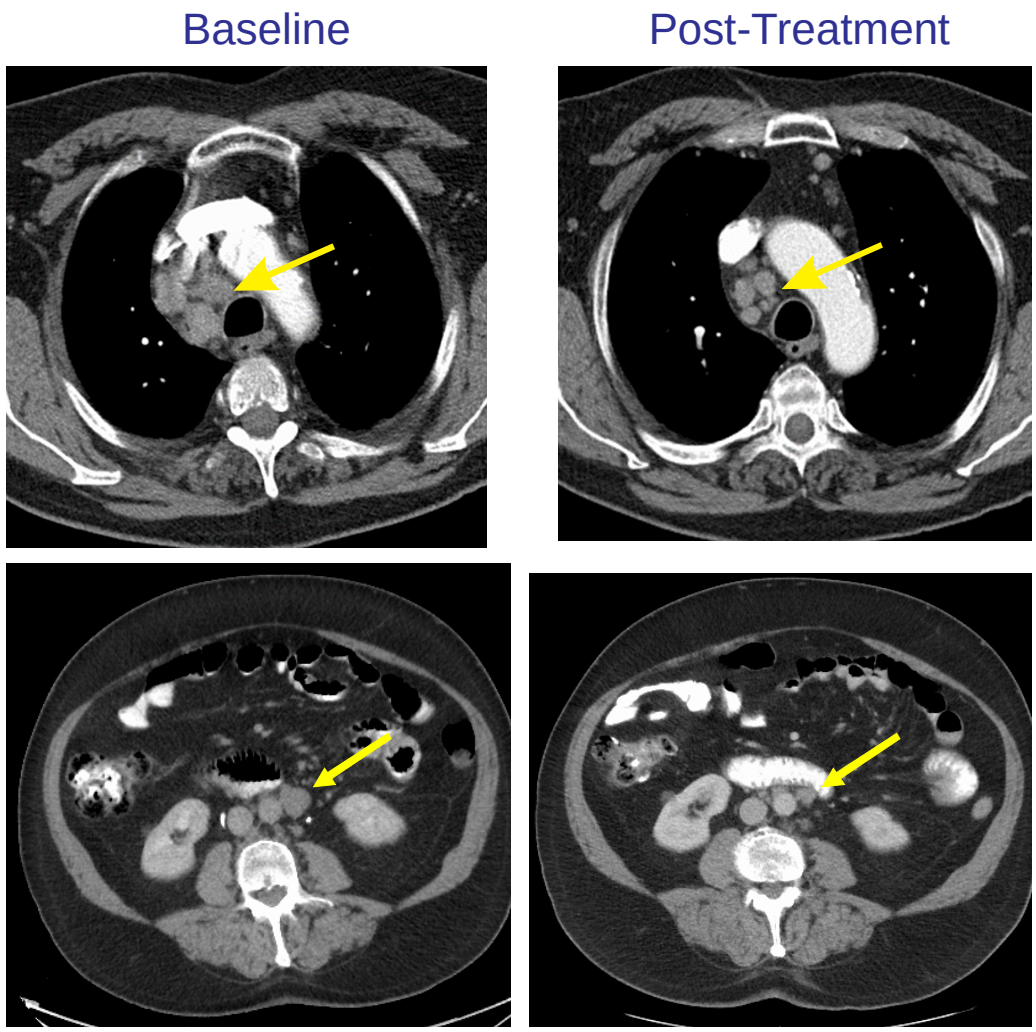


Figure 4: **Objective Tumor Responses.** Shown are baseline and post-treatment (3- or 6-month) CT images from the two patients, treated with the combined pTVG-HP and pembrolizumab schedule, who had the greatest % change in serum PSA.

McNeel, D. et al., SITC 2016

Prostvac + Ipi or Nivo or Comb.

Patient Population: Localized Prostate Cancer, candidates for RP

Cohort 1: Vaccine + Ipi + Nivo (n=10, CRPC)

Cohort 2: Vaccine + Nivo (n=16)

Cohort 3: Vaccine + Ipi (n=16)

Cohort 4: Vaccine + Ipi + Nivo (n=16)

Baseline	Week 0	Week 2	Week 5	Week 8	Week 9
Biopsy	Prostvac-V	Prostvac-F	Prostvac-F	Prostvac-F	RP
		Ipilimumab	**Ipilimumab**	**--**	
		Nivolumab	**Nivolumab**	**Nivolumab**	

Ipilimumab 1 mg/kg, Nivolumab 240 mg

PI Gulley, NCT02933255

Prostvac + Ipi or Nivo or Comb.

Patient Population: Localized Prostate Cancer, candidates for RP

Cohort 1: Vaccine + Ipi + Nivo (n=10, CRPC)

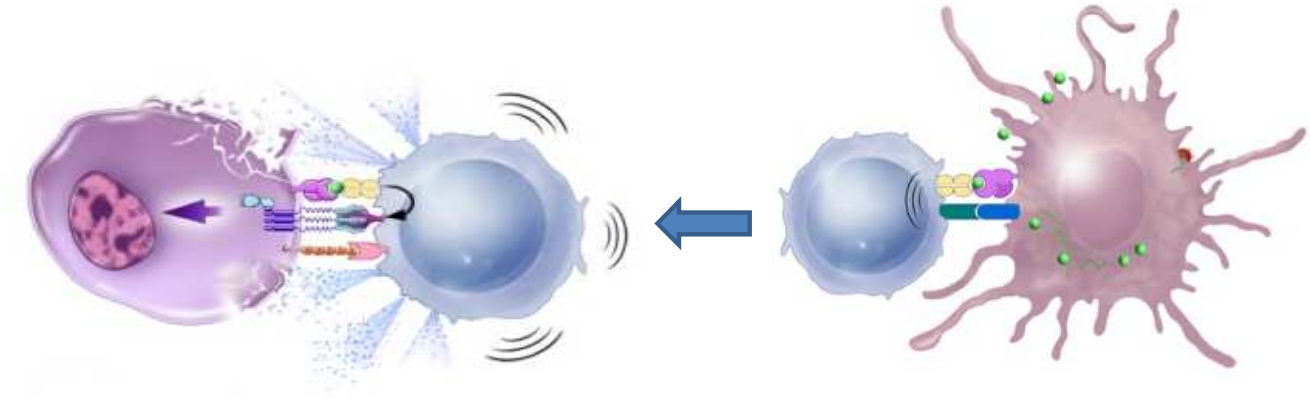
Cohort 2: Vaccine + Nivo (n=16)

Cohort 3: Vaccine + Ipi (n=16)

Cohort 4: Vaccine + Ipi + Nivo (n=16)

Primary analysis: Immune infiltrate by IHC
Secondary: Safety
- Imaging (erMRI)
- Peripheral immune analysis
- In depth analysis of tumor microenvironment
  - -DNA, RNA (immune genes), Protein (Multiplexed IF)

Requirements for Effective Immunotherapy



Effector Cells Functional within Tumor

- PDL1 / PD1
- TGF-β
- IDO
- IL-10
- VEGF (MDSC and immature DC)
- Other immune checkpoints

Generate Immune Response

- Vaccine
- ACT
- CTLA4 blockade
- Intratumoral cytokines (e.g., NHS-IL12)
- NK cells (ACT or cytokines)

Conclusions

Challenges

- Majority of PC are not T-cell inflamed (little to no activity of PD1/PDL1 targeted agents alone)
- Therapeutic vaccine responses may not be optimal as single agents

Opportunities

- If T-cell inflamed / MSI / ?DDRD → ICM monotherapy?
- If not, combination strategies to cause inflammation?
  - Enzalutamide
  - DNA damaging agents
  - Radiation (Ra-223)
  - Vaccine
- Schedule may be important (concurrent vs. sequential)
- Take home: combinations that lead to an active T-cell response and facilitate T-cell activity within the tumor microenvironment may lead to optimal anti-tumor effects

Doug McNeel

Julie Graff