

Immunotherapy for Metastatic Castrate Resistant Prostate Cancer



Charles G. Drake MD / PhD

Director GU Medical Oncology

Co-Director: Immunotherapy Program

Associate Director for Clinical Research

Professor of Oncology and Urology

Herbert Irving Cancer Center at Columbia University



**COLUMBIA UNIVERSITY
MEDICAL CENTER**

Herbert Irving Comprehensive Cancer Center

 **NewYork-Presbyterian**

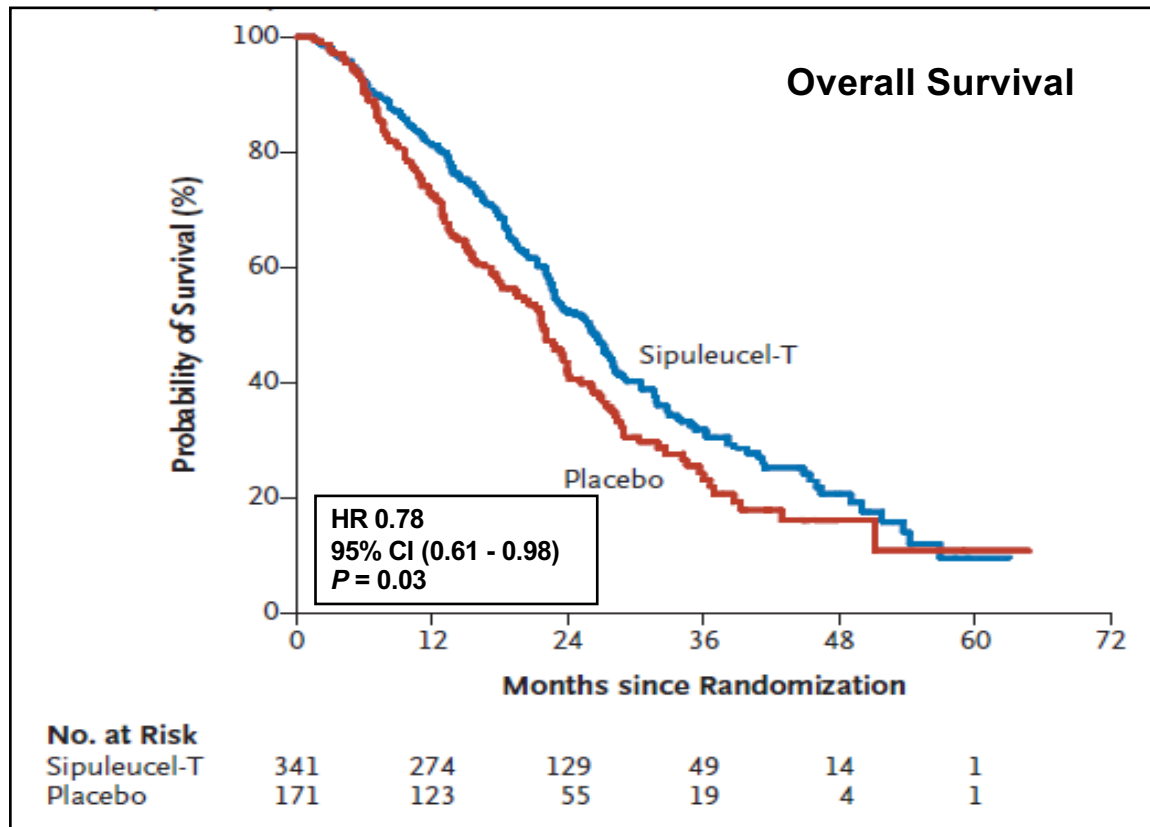
Complete Disclosure

- Consulting:
Bayer, BMS, F-Star, Genocera, Janssen, Merck, Merck-Serono, Pfizer, Pierre Fabre, Roche / Genentech, Shattuck Labs
- Patents (held by Johns Hopkins University)
Amplimmune, BMS, Janssen
- Options
Harpoon, Kleo, Tizona, Werewolf

Outline

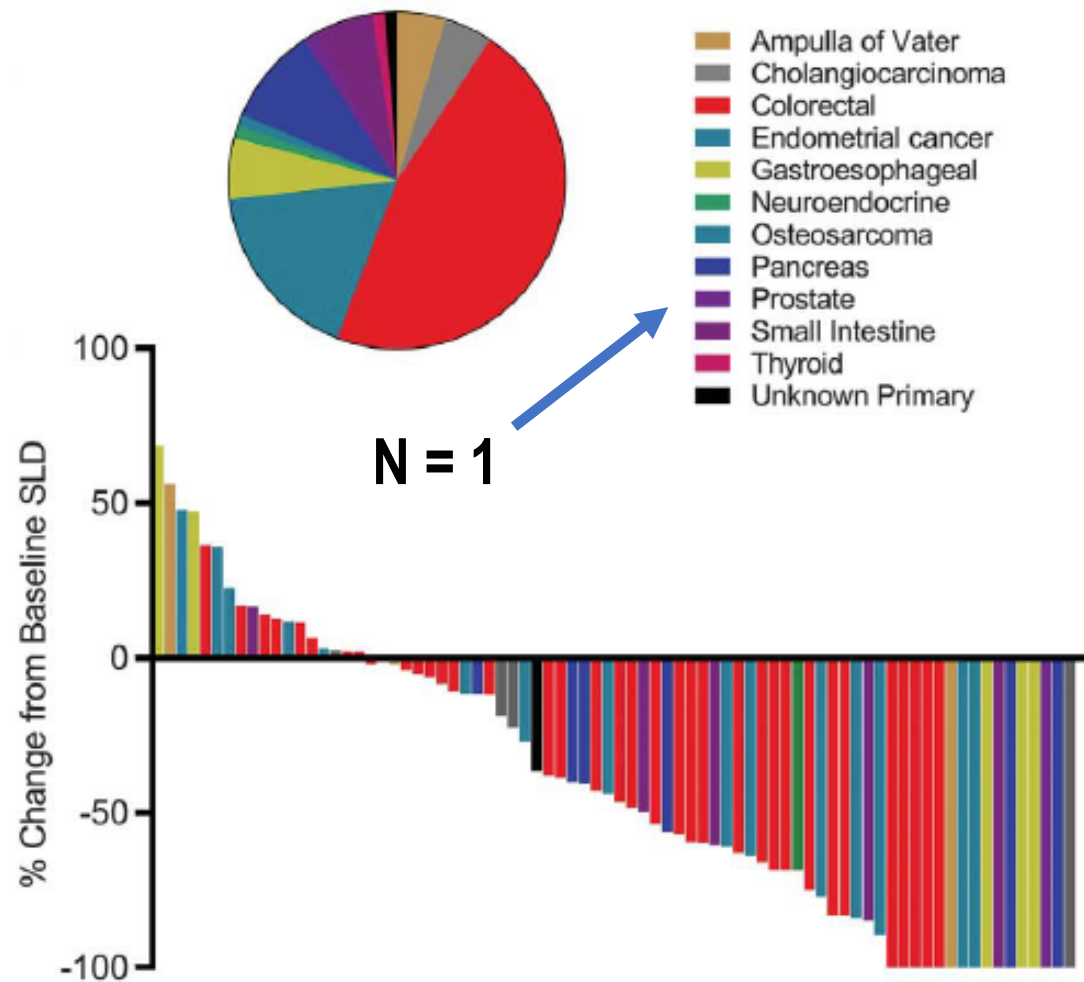
- Sipuleucel-T
- Patient Selection
 - Microsatellite Instability (MSI)
 - CDK12
 - DRD
- Combinations
 - Next Gen Anti-Androgens
 - Chemotherapy
- Could immunotherapy be more active in the CS setting ?

IMmunotherapy for Prostate AdenoCarcinoma Treatment (IMPACT)



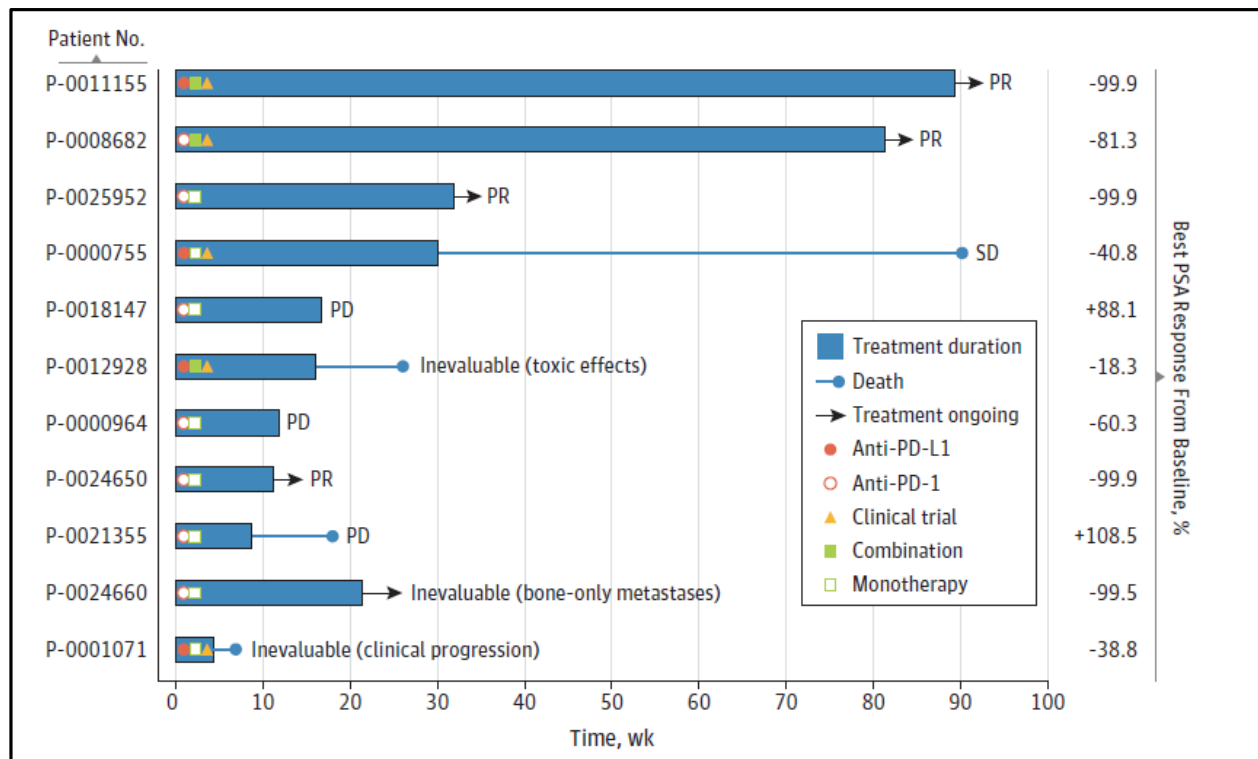
Kantoff *et al*, NEJM 2010

Anti-PD-1 (Pembrolizumab) is US FDA Approved for MSI+ Tumors



Le DT, et al. *Science*. 2017

Activity of PD-1 Blockade in MSI+ Prostate Cancer



- 1300 PC pts with genomic testing - MSK IMPACT Panel
- MSI Incidence = 2%
- 5/10 treated pts with evidence of activity (SD or PR)

Wasim Abida et al, JAMA Oncology 2018

CDK12 and Potential Response to PD-1 Blockade

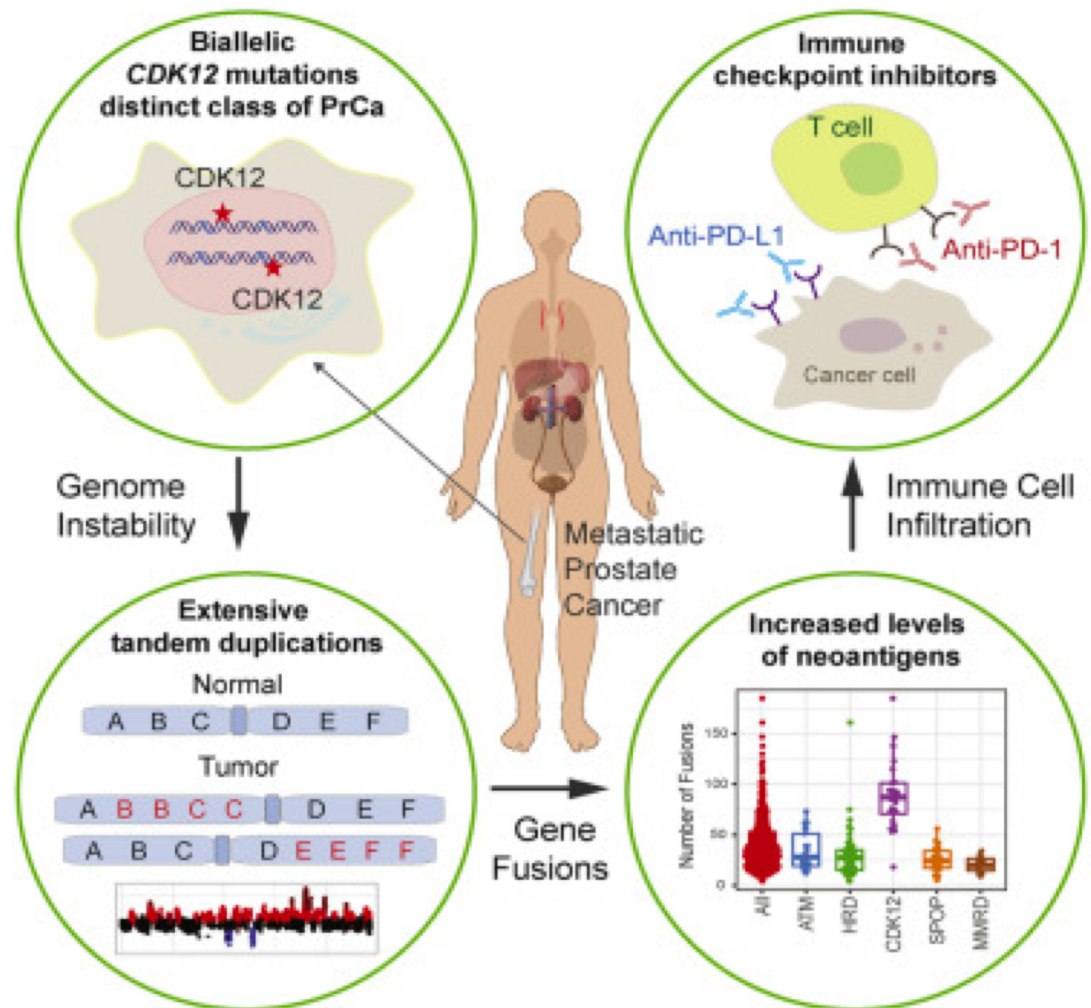
Immunotherapy in Patients With Metastatic Cancers and CDK12 Mutations (**IMPACT**)

NCCT: NCT03570619

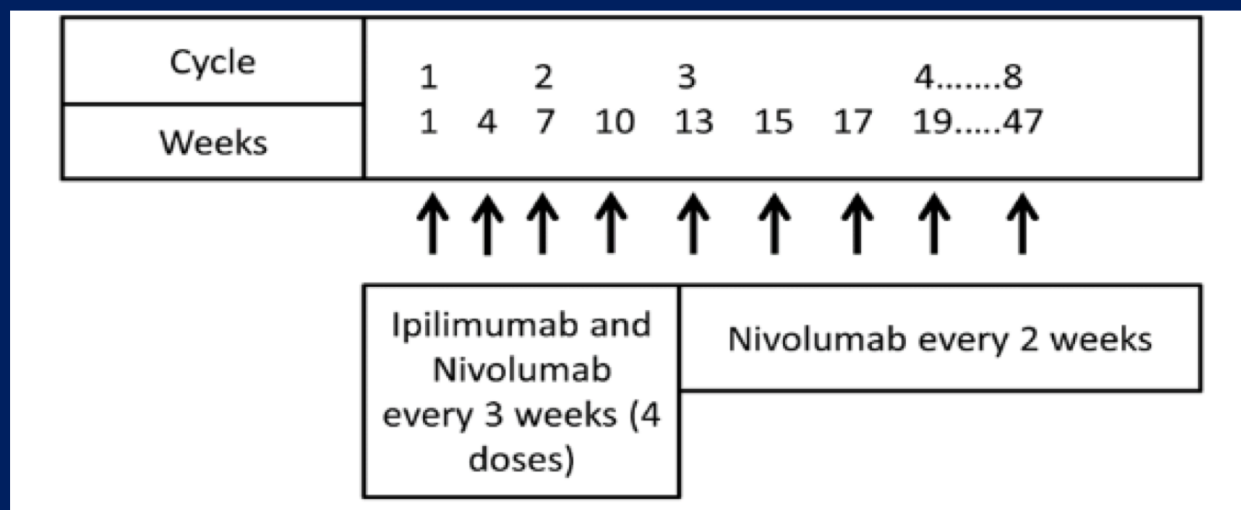
PI: Ajjai Alva, MD

N = 40

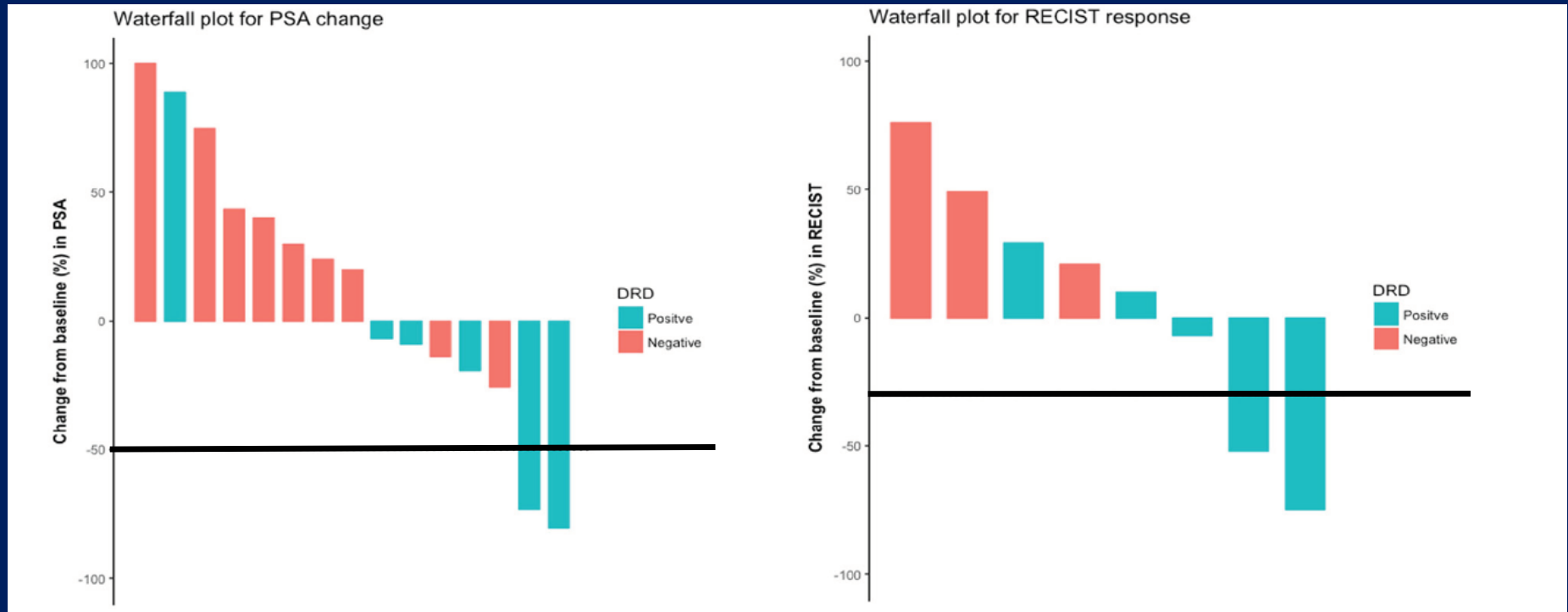
Wu YM, et al. *Cell*. 2018; 173(7):1770-1782.e14.



STARVE-PC: Biomarker-Driven Phase-2 Study of Ipilimumab plus Nivolumab for AR-V7-Expressing Metastatic Castration-Resistant Prostate Cancer



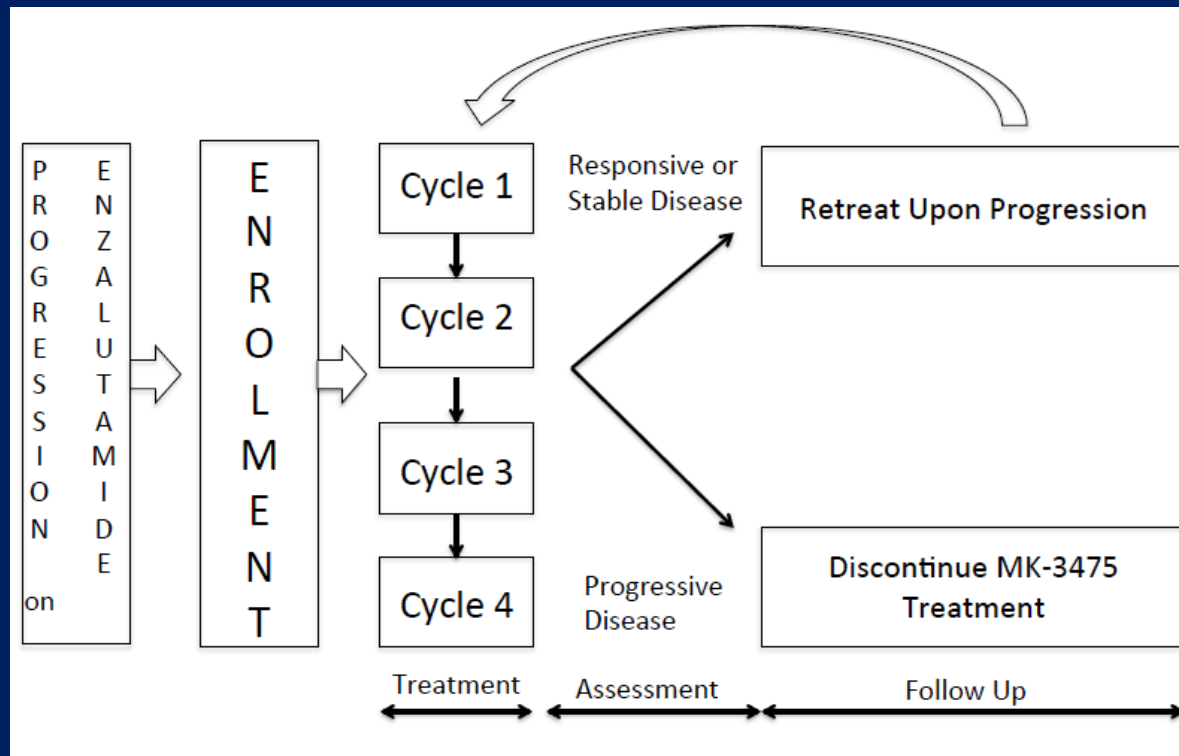
Nivolumab 3mg/kg + ipilimumab 1mg/kg - given every 3 weeks for 4 doses, followed by **nivolumab 3mg/kg** alone every 2 weeks (for up to 1 year)



**2/8 RECIST Evaluable Pts With PR to Anti-PD-1 + Anti-CTLA-4
(note – BOTH had DRD)**

Boudadi K, Drake CG, Antonarakis. *Oncotarget* 2018

Adding PD-1 Blockade To Enzalutamide



**Pembrolizumab 200 mg IV
every 3 weeks x 4**

**Continued Enzalutamide
Treatment**

Courtesy of J. Graff OSHU

Objective Responses to PD-1 Blockade in mCRPC

Patient number	Date of cycle 1	PSA (ng/ml) baseline to nadir	Measurable Disease at Baseline	Best Radiologic Response	MSI	Prior Treatment for mCRPC
1	April 2015	70.65 → 0.08	Yes	PR	present	abi, enz
7	October 2015	46.09 → 0.02	No	N/A	n/a	abi, enz
10	January 2016	2502.75 → < 0.01	Yes	PR	absent	enz

* All responding patients remain on study.

PR – partial response; N/A – not applicable (i.e. no baseline biopsy done); MSI – microsatellite instability; abi – abiraterone; enz – enzalutamide

Julie N. Graff^{1,2}, Joshi J. Alumkal¹, Charles G. Drake³, George V. Thomas⁴, William L. Redmond⁵, Mohammad Farhad^{5,6}, Jeremy P. Cetnar¹, Frederick S. Ey¹, Raymond C. Bergan¹, Rachel Slottke¹ and Tomasz M. Beer¹

Oncotarget 2016 (Update coming!)

IMbassador250: A Phase III Trial in Patients With Metastatic Castration-Resistant Prostate Cancer Comparing Atezolizumab Plus Enzalutamide vs Enzalutamide Alone

Key Eligibility Criteria

- Histologically confirmed mCRPC
- Progressed on an androgen synthesis inhibitor
- Failure of, ineligible for or refused a taxane regimen

Safety Run-In

Atezolizumab
1200 mg IV q3w
+
Enzalutamide
160 mg oral qd
N = 10

N ≈ 720
Randomisation
1:1

Atezolizumab 1200 mg IV q3w
+
Enzalutamide 160 mg oral qd

Key Stratification Factors

- Prior taxane-containing regimen for mCRPC
- Presence of liver metastases

Enzalutamide 160 mg oral qd

Primary efficacy objective: overall survival (OS)

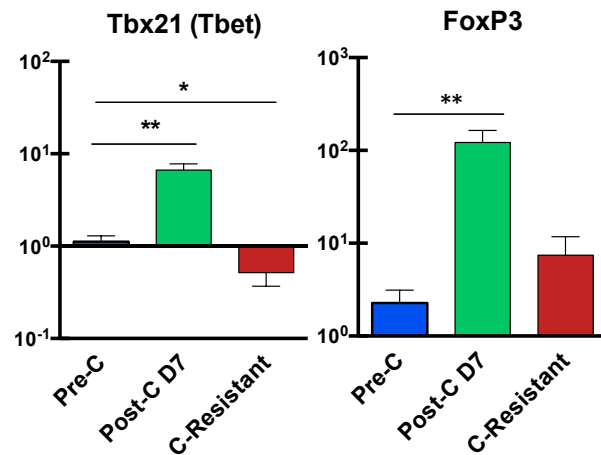
Key secondary objectives: landmark 1-year and 2-year OS rates, time to cancer-related pain progression, time to first SSE, investigator-assessed radiographic PFS and ORR per PCWG3 criteria, PSA response rate, time to PSA progression, safety and tolerability

IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; PCWG3, Prostate Cancer Working Group 3; PFS, progression-free survival; PSA, prostate specific antigen; qd, daily; q3w, every 3 weeks; SSE, symptomatic skeletal event.

T Powles PI

ADT Increases Infiltration With Regulatory T Cells (Treg)

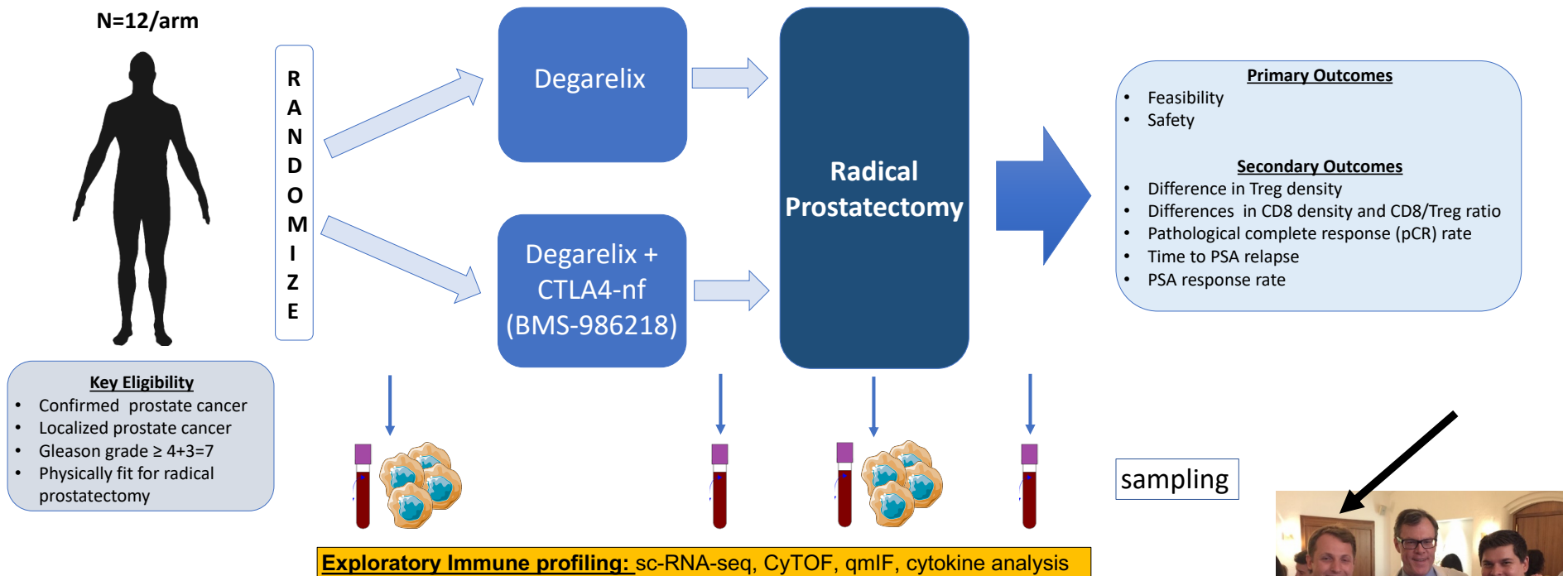
Murine Model



NeoAdjuvant Trial in Patients

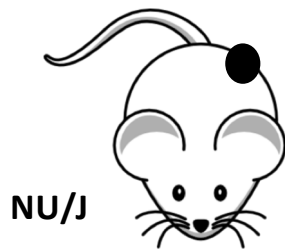
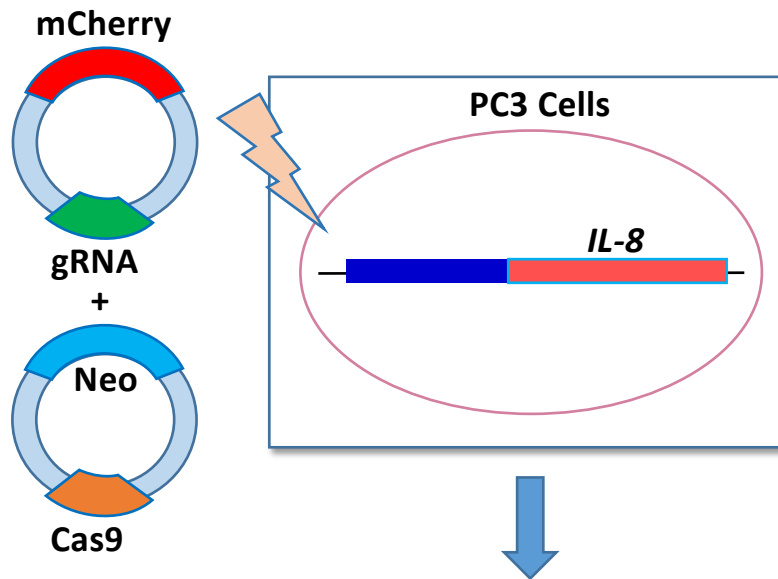
	Cohort C (Control) N=20	Arm A (ADT) N=15	P-value
CD8+ T cell density (mean, 95%CI)	96 (72–120)	205 (121–289)	0.03 (A vs C)
Treg cell density (mean, 95%CI)	29 (21–36)	59 (34–85)	0.02 (A vs C)
CD8+ / Treg ratio (mean, 95%CI)	3.7 (2.9–4.6%)	4.0 (2.7–5.3%)	0.68 (A vs C)

Neo-RED-P: Neoadjuvant Trial of Regulatory t cell Depletion

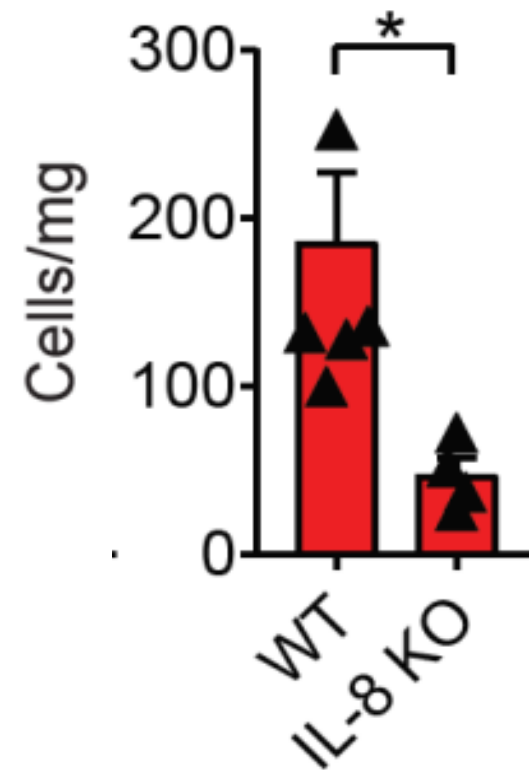


IL-8 Drives PMN-MDSC Recruitment

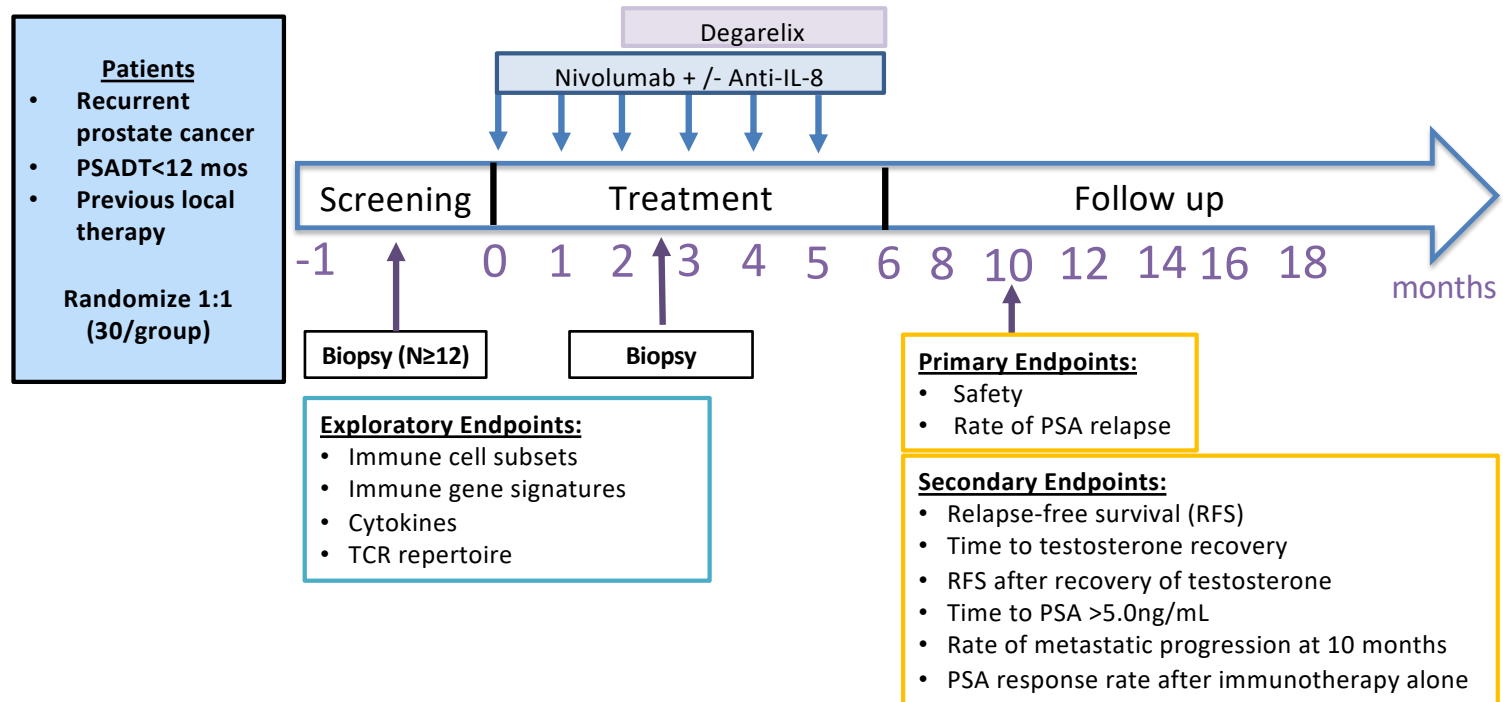
CRISPR IL-8 KO Human Cell Line



PMN-MDSCs



MAXimizing ADT ImmunoGenicity With Anti-IL-8 (MAGIC-8)



***Labs:** Safety, PSA, testosterone (screening; monthly during treatment; every 2 months for year 1 follow up; every 3 months year 2 follow up)

***Imaging:** CT c/a/p and bone scan (screening; 6 months; 10 months)

***Sera/PBMCs:** C1D1, C3D1, EOT, 10 months, 14 months, 18 months

Open and Accruing: NCCT03689699

Ongoing

- Immunotherapy Combinations in CRPC Phase III
 - + Chemo
 - + ADT
 - + PARPi
- Anxiously awaiting data
 - Not soon

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