THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

Immunotherapy for Genitourinary Cancers

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Disclosures

(All Non-University &/or Financial Dealings with Potential, Real, or Perceived Conflicts of Interest)

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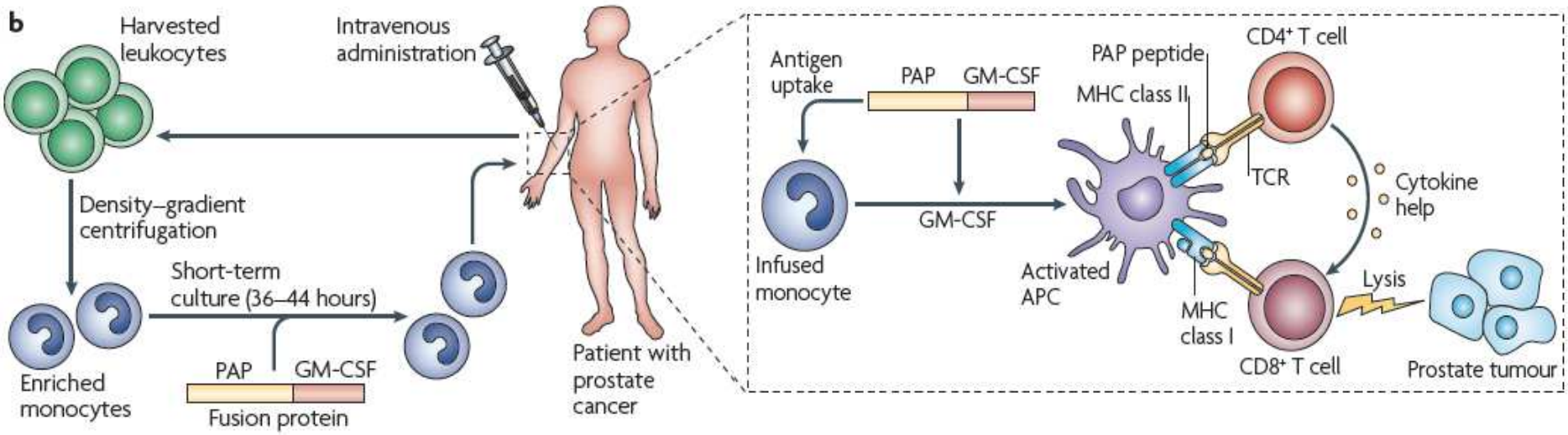
Immunotherapy in Prostate Cancer

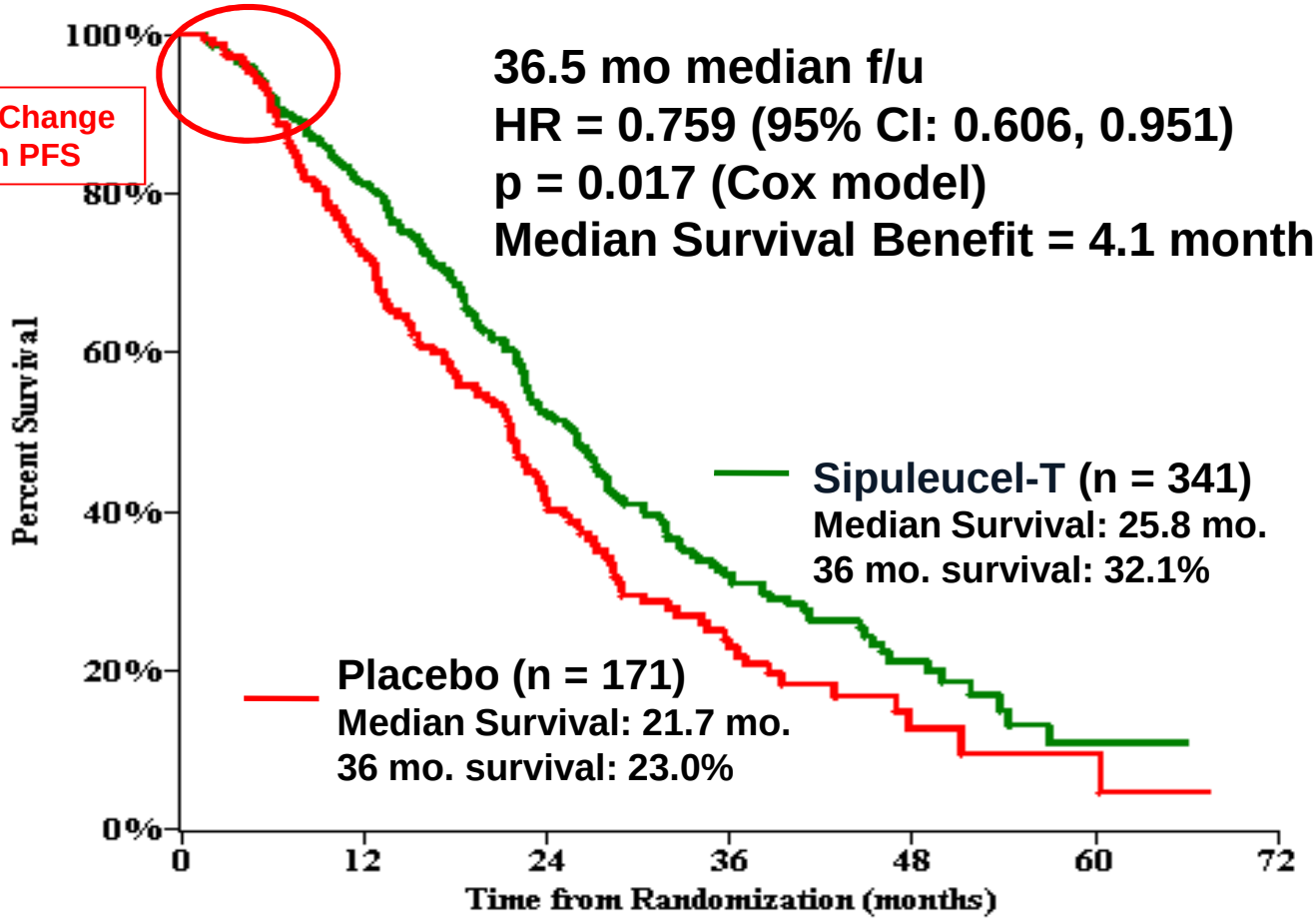
- Increase antigen delivery (e.g. Vaccines)
  - Expose and prime native immune system against specific proteins that are unique to cancer
    - **PSA-TRICOM (ProstVac)**
  - Take out APC's from body and prime *ex vivo*
    - **Sipuleucel-T**
- Repress the native regulation of immunity
  - **Ipilimumab**
- Antibody-dependent cytotoxicity with PC specific antibody
  - **J591**

Vaccination With Fresh (Functional) APCs: Generate ex vivo and Reinfuse



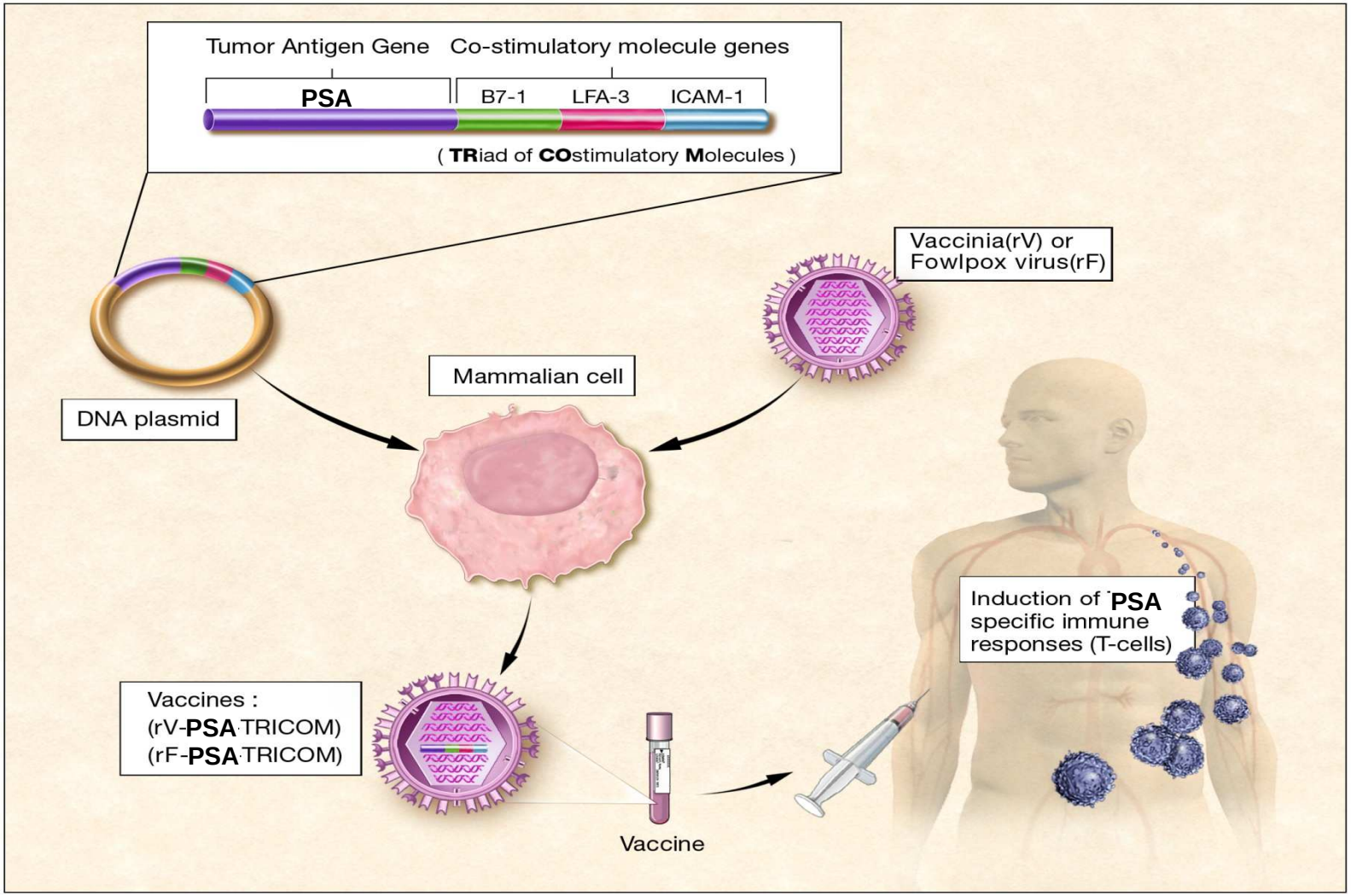
Drake, Nat Rev Immunol. 2010.

Sipuleucel T: IMPACT Overall Survival



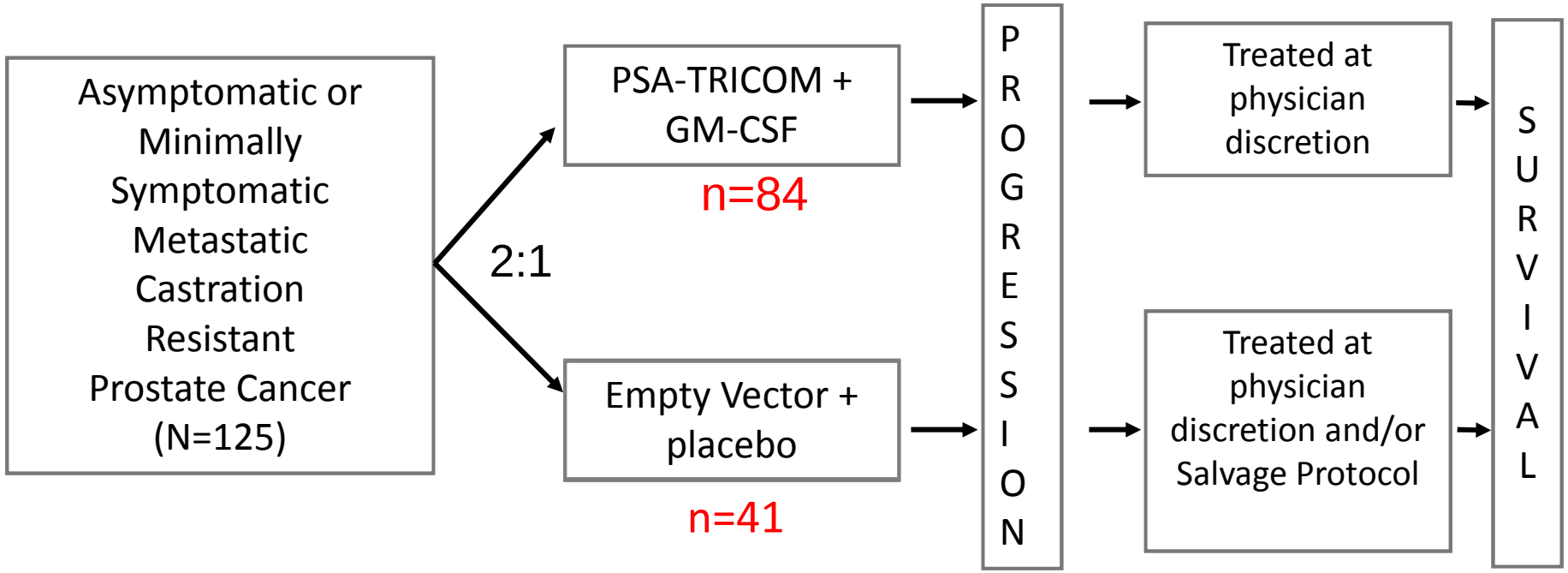
Courtesy of P. Kantoff, presented GU ASCO 2010

ProstVac: Mechanism



Courtesy of C. Drake

ProstVac:Randomized Controlled Double Blind Phase II Study



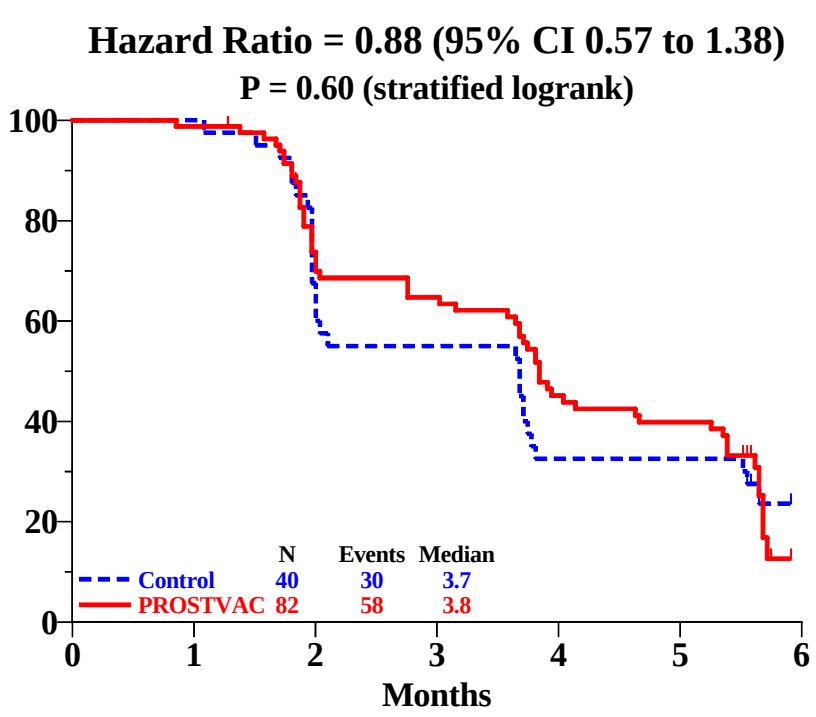
Primary endpoint: Progression Free Survival

Secondary endpoint: Overall Survival

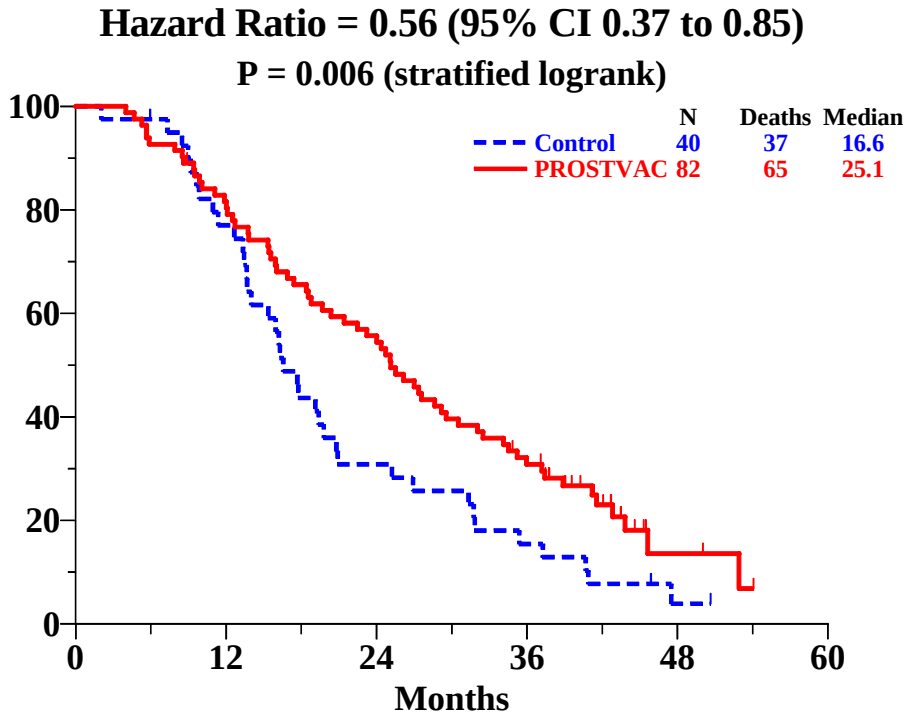
Kantoff, P. W. et al. J Clin Oncol; 28:1099-1105 2010

ProstVac Outcome

Progression Free Survival

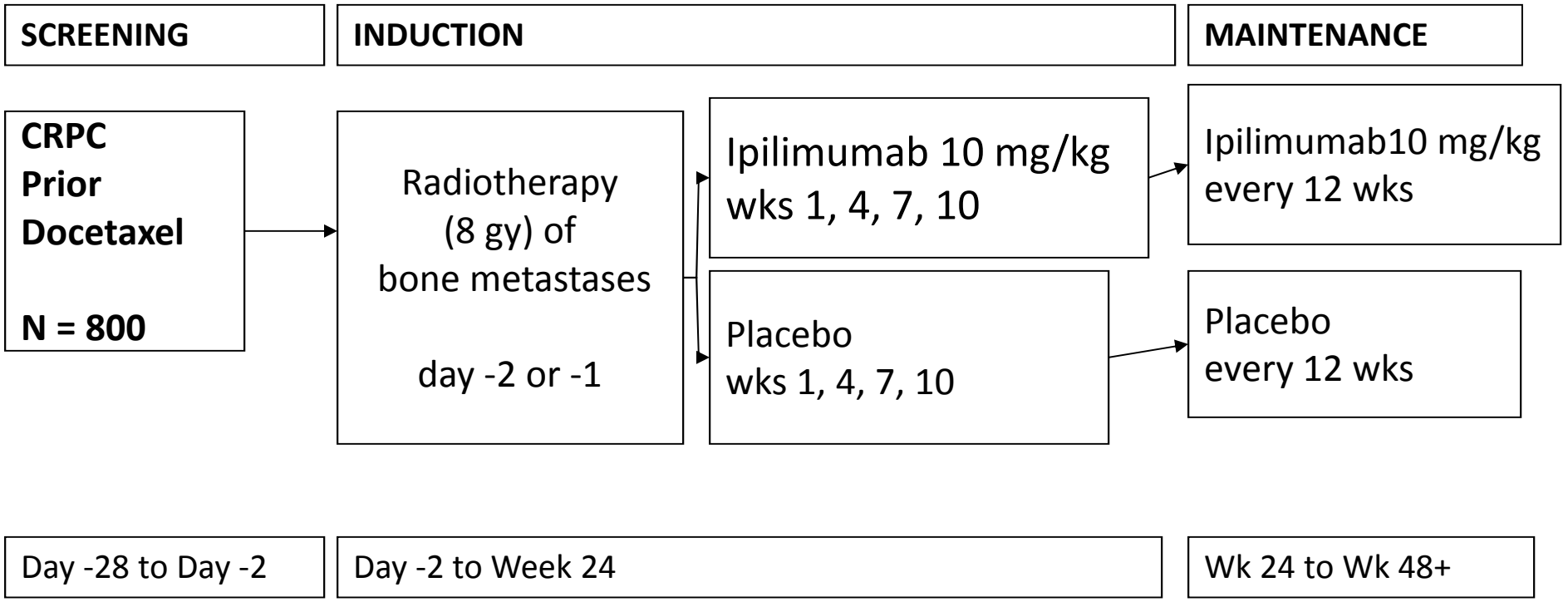


Overall Survival

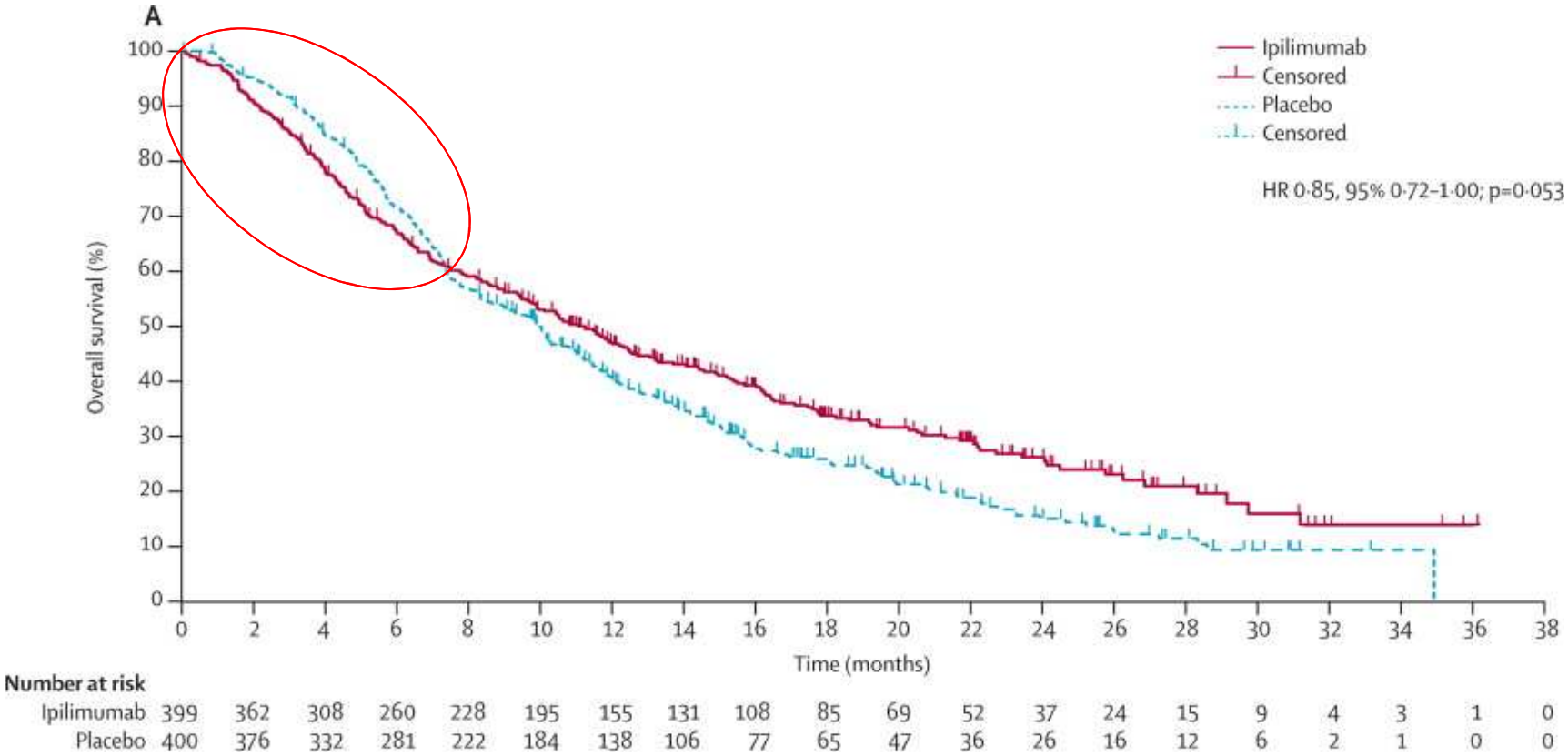


Kantoff, P. W. et al. J Clin Oncol; 28:1099-1105 2010

Phase III Trial Comparing Ipilimumab vs. Placebo Following Radiotherapy in CRPCa



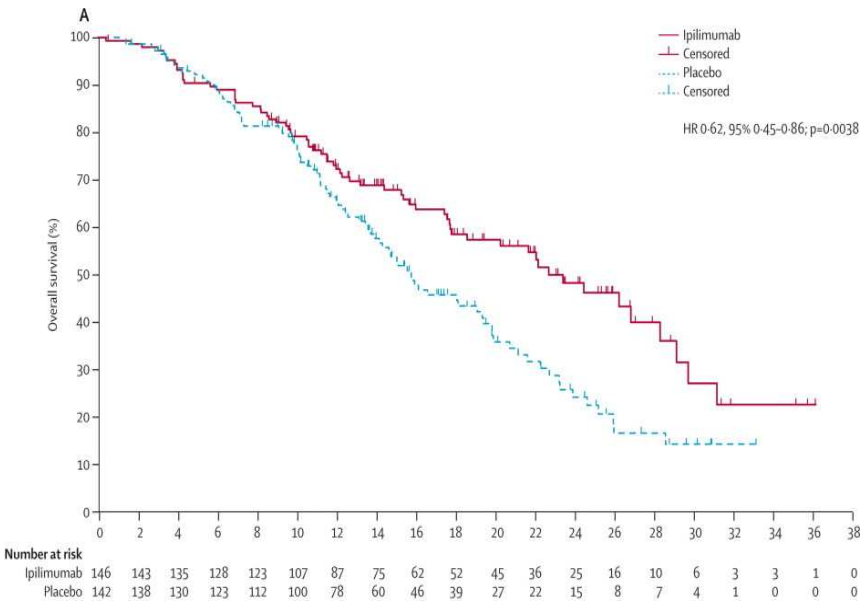
Ipilimumab: Overall Survival



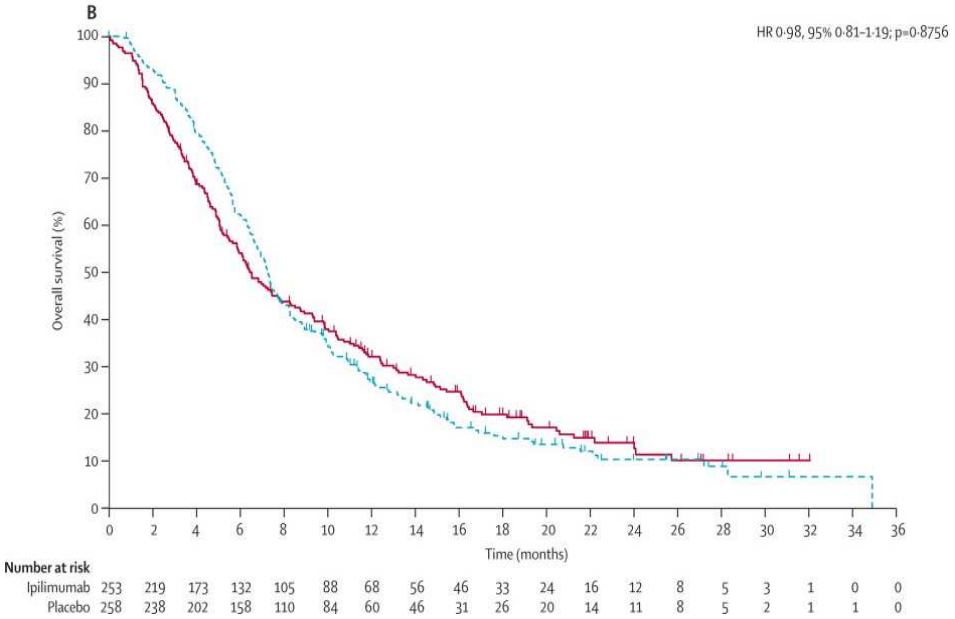
Eugene D Kwon et al, *The Lancet Oncology*, Volume 15, Issue 7, 2014, 700 - 712

Ipilimumab: Post-hoc Analysis

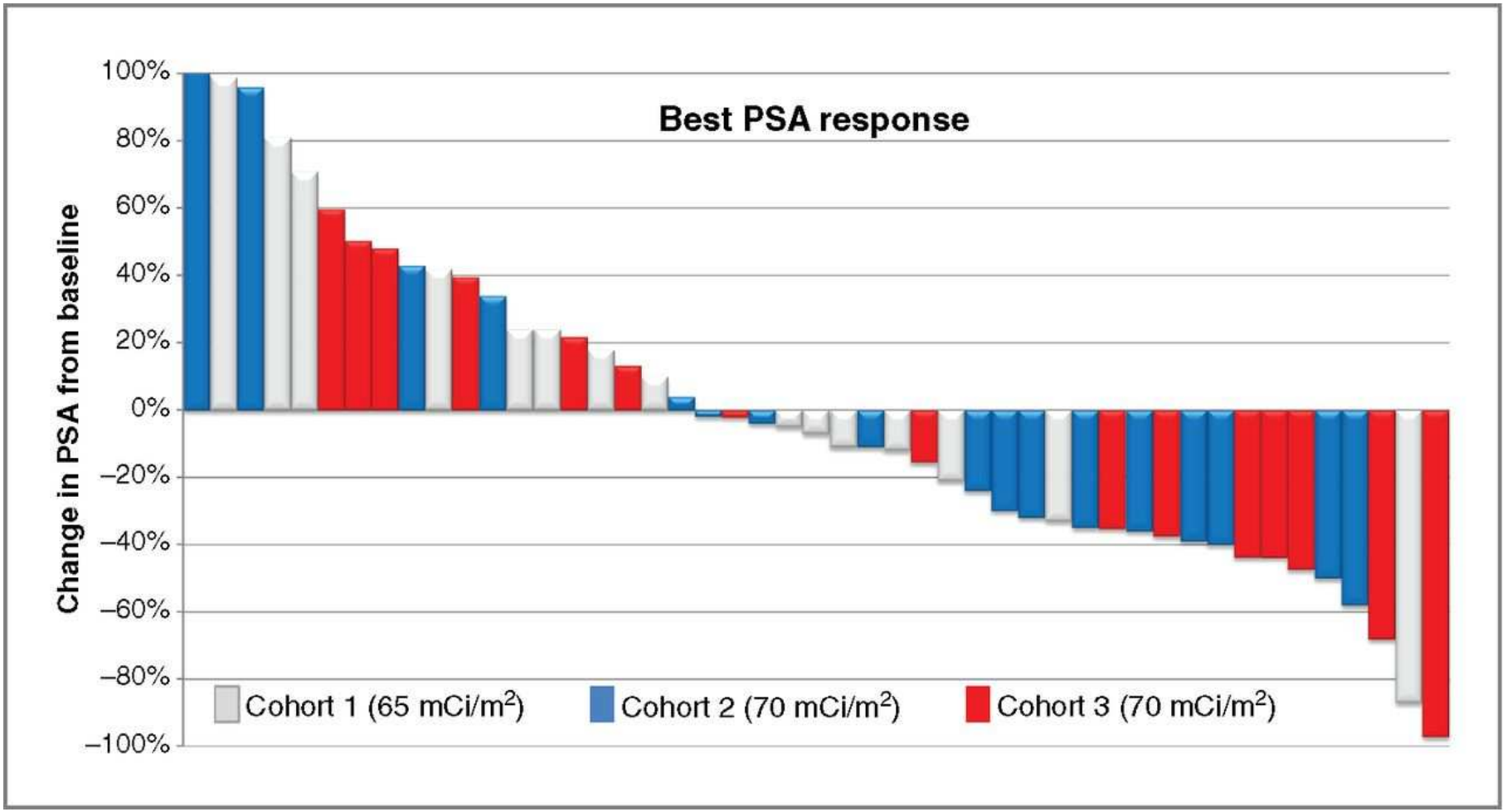
Good Prognosis



Poor Prognosis



PSMA-directed antibody fused to ^{177}Lu (J591)



Prostate Cancer Immunotherapy Conclusions

- Appears to be less responsive to current available immunotherapy
- Checkpoint inhibitors have minimal to no impact
- Nevertheless there are hints of immunotherapy responsiveness that should be pursued
- Mechanisms of immunosuppression?

Renal Cancer: IL2

- Cytokine Working Group trial HD IL2 vs sc IL2/IFNA
  - HD IL2: 600,000 IU/kg q8^{o} x 14 doses
  - sc IL2/IFNA: 5 x 10^6 IU/m^2 4d/wk IL2; 5 x10^6 IU/m^2 2d/wk

	sc IL2/IFNA	HD IL2
Pt number	91	95
Deaths	1	1
CR	3	8 (p= 0.21)
PR	6	14
Resp. Duration	15 mo	24 mo (p=0.18)
Med. Surv.	13 mo	17 mo (p = 0.21)
Durable 3 yr CR	0	7 (p=0.01)

- Selection criteria
  - Non-clear cell have minimal to no benefit
  - Suggestion that post-VEGFR TKI treatment has higher toxicity and lower efficacy

Checkpoint Inhibitors in Renal Cancer

Nivolumab Phase 1/2 Trial

Population	Dose (mg/kg)	Patients (n)	ORR n (%)	Duration of Response (mo)	SD ≥24 wk n (%)	PFSR at 24 wk (%)
ALL RCC	1, 10	33	9 (27)	5.6+ to 22.3+	9 (27)	56
RCC	1	17	4 (24)	5.6+ to17.5+	4 (24)	47
	10	16	5 (31)*	8.4 to 22.3+	5 (31)	67

McDermott, et al. JCO, 2015 33:2013-20

Checkpoint Inhibitors in Renal Cancer

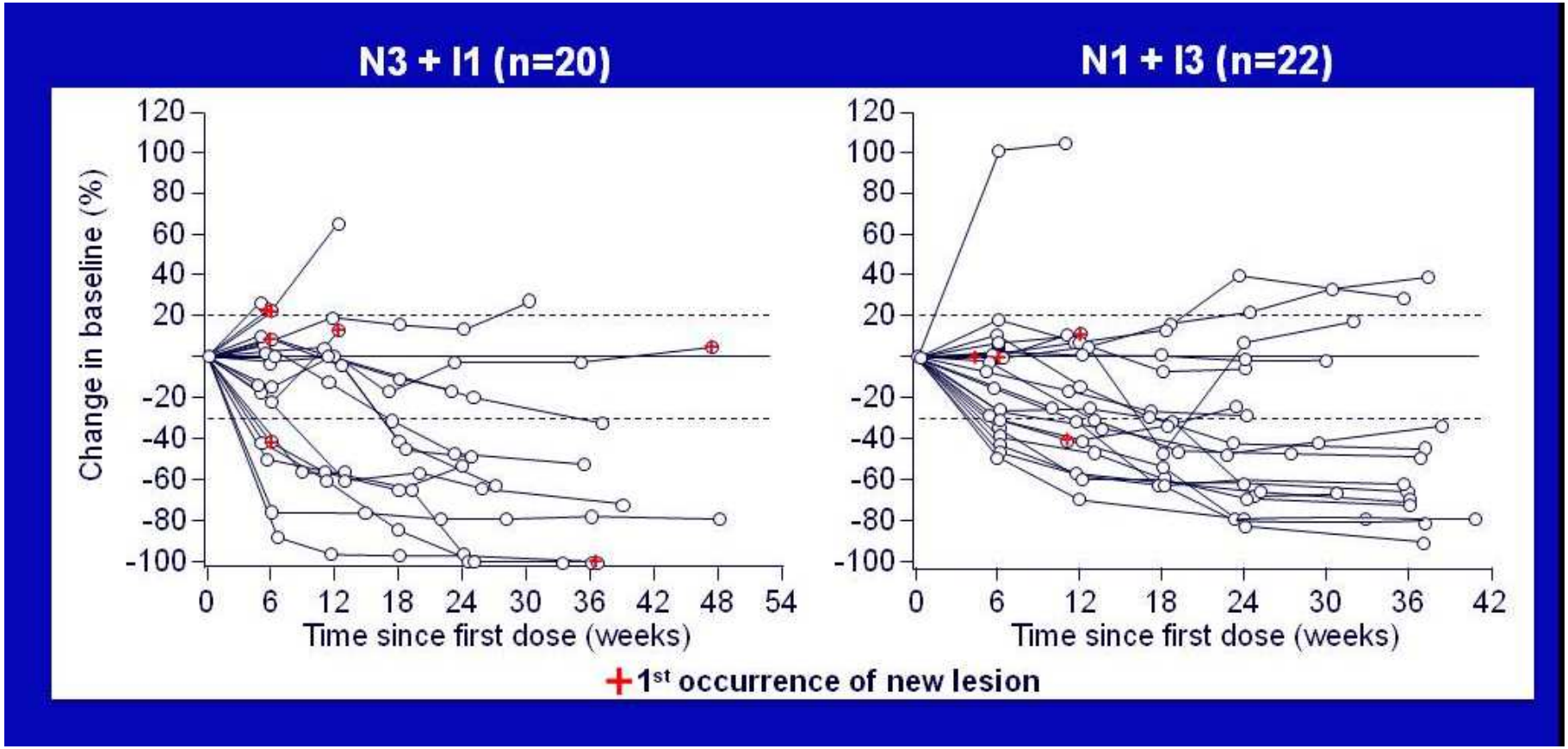
Atezolizumab (MPDL3280a) Phase 1/2

	RECIST 1.1 Response Rate (ORR)	SD of 24 Weeks or Longer	24-Week PFS
Overall population (N = 140)	21%	16%	45%
RCC* (n = 47)	13%	32%	53%
Clear cell (n = 40)	13%	35%	57%
Non-clear cell (n = 6)	17%	0	20%

* 1 patient with unknown histology. Includes sarcomatoid and papillary RCC.
All patients first dosed prior to August 1, 2012; data cutoff February 1, 2013.
ORR includes unconfirmed PR/CR and confirmed PR/CR.

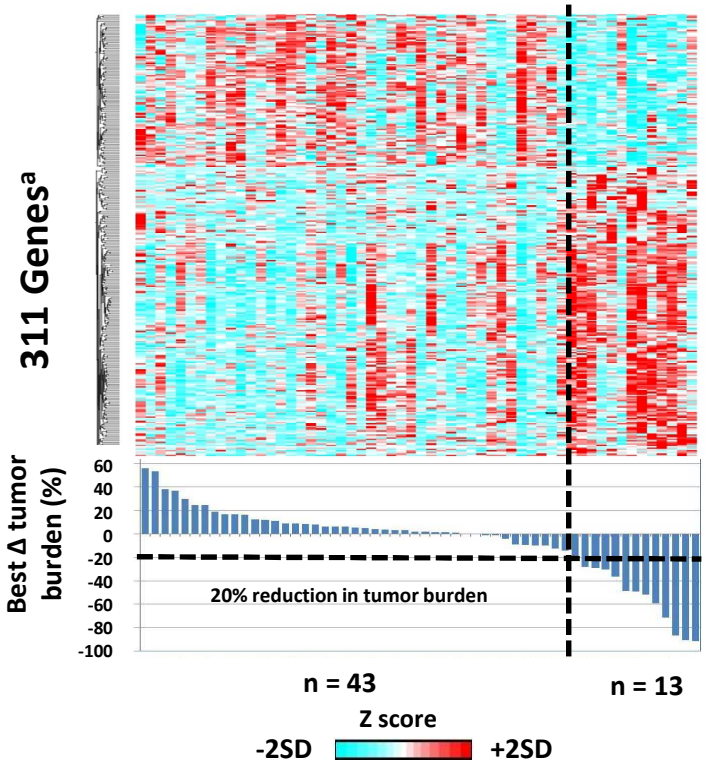
Checkpoint Inhibitors in Renal Cancer

Nivolumab + Ipilimumab



Hammers, et al, ASCO 2014

Baseline Gene Expression Profiling to Predict Nivolumab response



Lower expression

- Establishment of protein localization ($P < 10^{-5}$)
- Negative regulation of epithelial cell proliferation involved in lung morphogenesis ($P < 10^{-4}$)
- Genes downregulated by ipilimumab in melanoma[1] ($P < 10^{-4}$)

Higher expression

- Genes upregulated by ipilimumab in melanoma[1] ($P < 10^{-23}$)
- Immune system (45 genes; $P < 10^{-7}$) IL15Ra, IL1R2, IRF1
- Myeloid lineage: eg, IL1A, LINC00158, PRAM1, SPI1
- Lymphoid lineage: eg, CD3E, AIM2, GZMB, NKG7, CD7, CTSW

[a]Significant at 10% false discovery rate threshold

Bold: denotes gene ontology biological process category

1. Ji RR, et al. *Cancer Immunol Immunother* 2012;61:1019–31.

Renal Cancer Immunotherapy Conclusions

- HD IL2 only known curative therapy
  - Rare long term benefit
  - Role in context of checkpoint inhibitors?
- Checkpoint inhibitors likely to enter therapeutic armamentarium
  - Phase III upfront trials
    - Nivolumab/Ipilimumab vs. Sunitinib
    - Bevacizumab/Atezolizumab (MPDL3280) vs Sunitinib
  - Phase III refractory trials
    - Nivolumab vs. Everolimus (accrual complete)
    - Announced as “positive” in the business pages
- Molecular predictive markers not yet ready for prime time

Urothelial Cancer: BCG

- Effective in non-muscle invasive localized bladder cancer
  - Ta disease: prevent recurrence
  - Tcis/T1 disease: therapeutic/curative
- Historically developed as subcutaneous + intravesicle
  - Subcutaneous BCG does not enhance
  - Requires BCG strain that binds to urothelium
  - Requires an inflammatory reaction
- Mechanism of action not clear

Urothelial Cancer: PD1 Pathway Inhibitors

Atezolizumab (MPDL3280A): PDL1 staining as predictive marker

PD-L1 IHC n = 87[b]	ORR (95% CI), %[a]		CR, n (%)		PR, n (%)	
IC3 (n = 12)	67% (35%-90%)	50% (35, 65)	4 (33%)	9 (20%)	4 (33%)	14 (30%)
IC2 (n = 34)	44% (27%-62%)		5 (15%)		10 (29%)	
IC1 (n = 26)	19% (7%-39%)	17% (7, 32)	-	-	5 (19%)	7 (17%)
IC0 (n = 15)	13% (2%-40%)		-		2 (13%)	

- Responses were observed all PD-L1 subgroups, with higher ORRs associated with higher PD-L1 expression in IC
- Responders also included patients with visceral metastases at baseline: 38% ORR (95% CI, 21%-56%) in 32 IC2/3 patients and 14% (95% CI, 5%-30%) ORR in 36 IC0/1 patients

Petrylak, et al; ASCO 2105

Urothelial Cancer: PD1 Pathway Inhibitors

Pembrolizumab: PDL1 expression as predictive marker

Tumor Cells Only (N = 29 evaluable)		Tumor and Tumor Associated Inflammatory Cells (N = 28 evaluable)	
	ORR (95%CI)		ORR (95%CI)
Negative (N = 11)	9% (0%–41%)	Negative (N = 4)	0% (0%–60%)
Positive (N = 18)	33% (13%–59%)	Positive (N = 24)	29% (13%–51%)

- In order to maximize detecting responders while minimizing the false negative rate, scoring needs to take into account both PD-L1 positive tumor cells and PD-L1 positive tumor associated inflammatory cells

Urothelial Cancer: PD1 Pathway Inhibitors

Pembrolizumab: Immune cell expression profiling as predictive marker

	Nominal One-sided *P*-value*			
Signature	ORR N = 25	Clinical Benefit (CR+PR+SD) N = 25	PFS N = 29	OS N = 29
IFNγ-induced (6-gene)	0.698	0.722	0.406	0.184
Expanded Immune (18-gene)	0.616	0.342	0.115	0.193
T-Cell Receptor Signaling (13-gene)	0.405	0.073	0.024	0.322
De-Novo (33-gene)	0.702	0.322	0.131	0.315

*Using one-sided test from logistic regression for best overall response or Cox regression for PFS.

Urothelial Cancer Conclusions

- Checkpoint inhibitors likely to enter therapeutic armamentarium
  - Phase 3 Trials
    - Refractory: Pembrolizumab vs paclitaxel OR vinflunine
    - Adjuvant: Atezolizumab versus observation
  - Many phase 2 single agent and combination trials
- Ripe for exploration of molecular phenotyping
  - Urothelial cancer may be at least 3 molecular phenotypes
  - FGFR and WNT pathway activation as mediators of “non-inflamed phenotype”