Clinical Development:

Prostate and Kidney Cancer

Charles G. Drake M.D. / Ph.D.
Associate Professor: Medical Oncology, Immunology and Urology
Johns Hopkins Kimmel Cancer Center

Disclosures

- Consulting:
  - Bristol Myers Squibb
  - Compugen
  - Dendreon
  - ImmunExcite
  - Merck
  - Novartis
  - Pfizer
  - Potenza
  - Roche

- Patents Licensed: AZ / Medimmune, Potenza

- ProstVac VF, AGS-003, Ipilimumab (Anti-CTLA-4) and Nivolumab (anti-PD-1) are experimental agents, and are not FDA approved for use in prostate or kidney cancer

Outline

- Cancer Vaccines:
  - FDA-Approved (Sipuleucel-T) for Prostate Cancer
  - Vaccinia – Based Vaccine In Phase III
  - Two Vaccines in Phase III in RCC

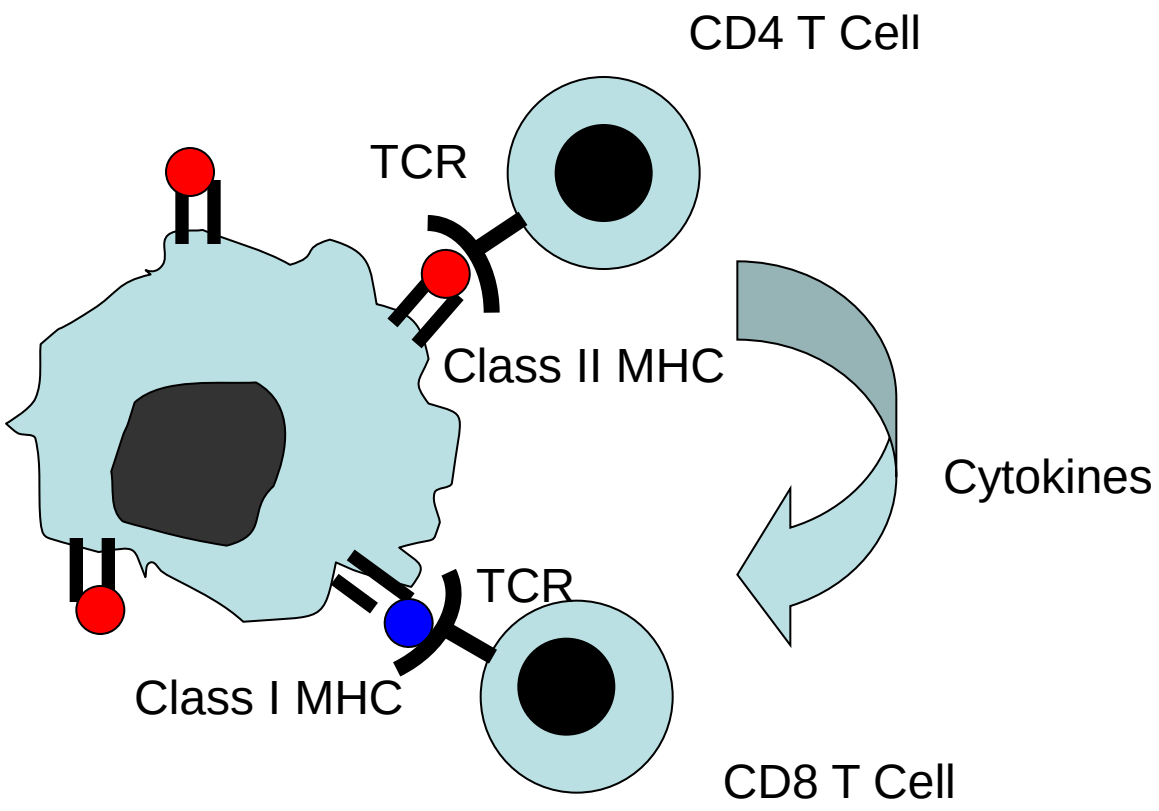
- Immune Checkpoint Blockade:
  - Anti-CTLA-4 (Ipilimumab) a Near Miss in Prostate Cancer
  - PD-1 Phase III Completed Enrollment in Kidney Cancer

- Combination Immunotherapy in the Clinic

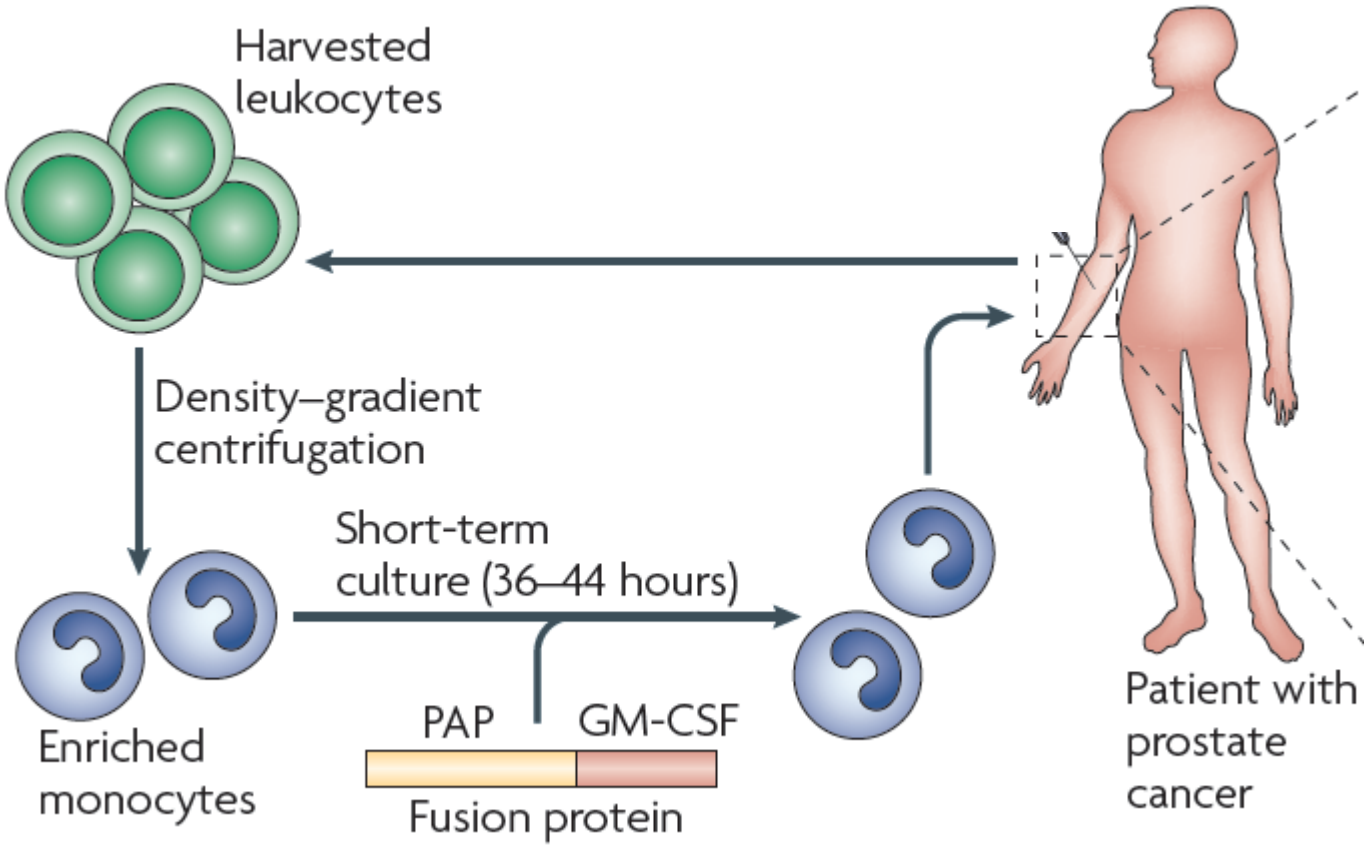
Vaccines

Cancer Vaccine Goal ….

Dendritic Cells Traffic and Present Antigen To Specific CD4 and CD8 T Cells in the Draining Lymph node

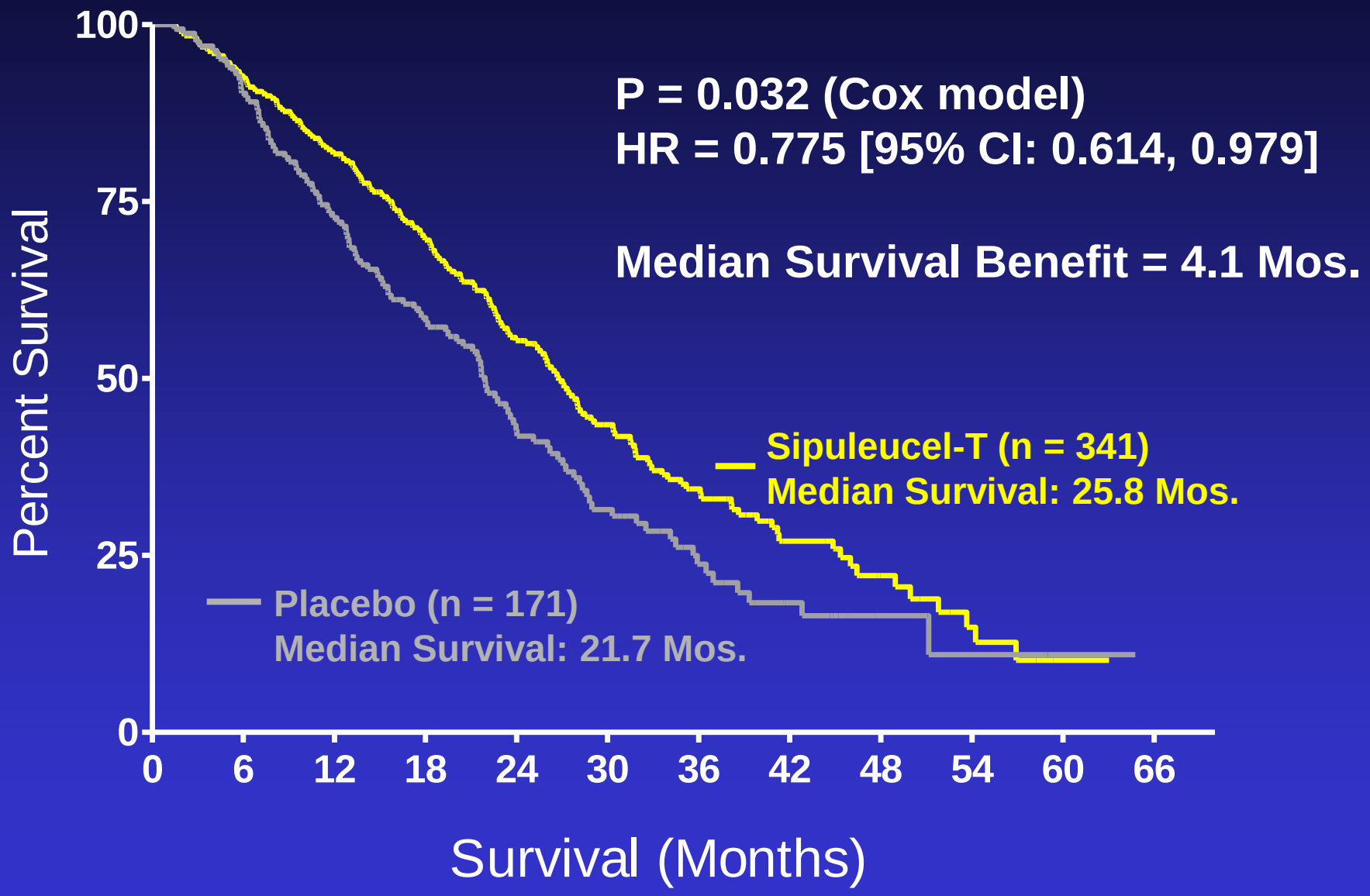


A “Dendritic Cell” Vaccine: Sipuleucel T

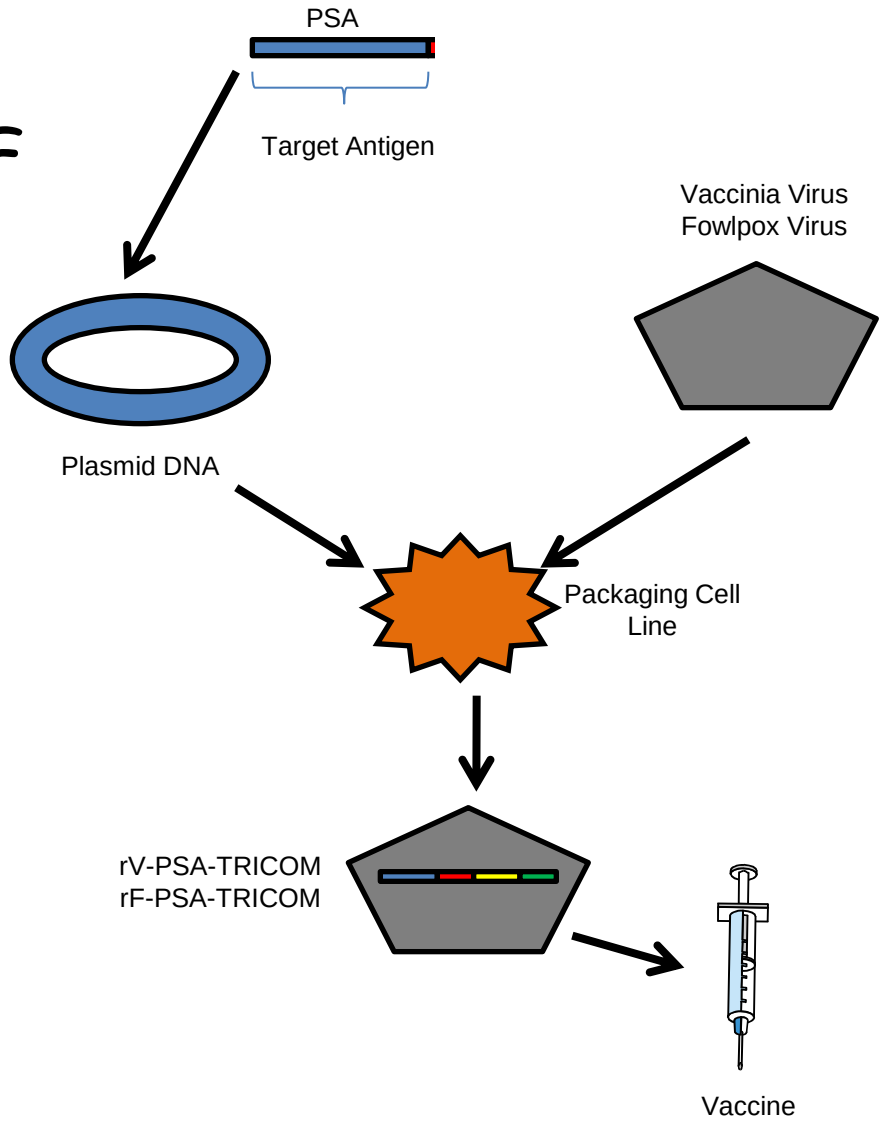


Drake CG *Nat Rev Immunol.* 2010;10:580-93.

IMPACT Overall Survival: Primary Endpoint
Intent-to-Treat Population

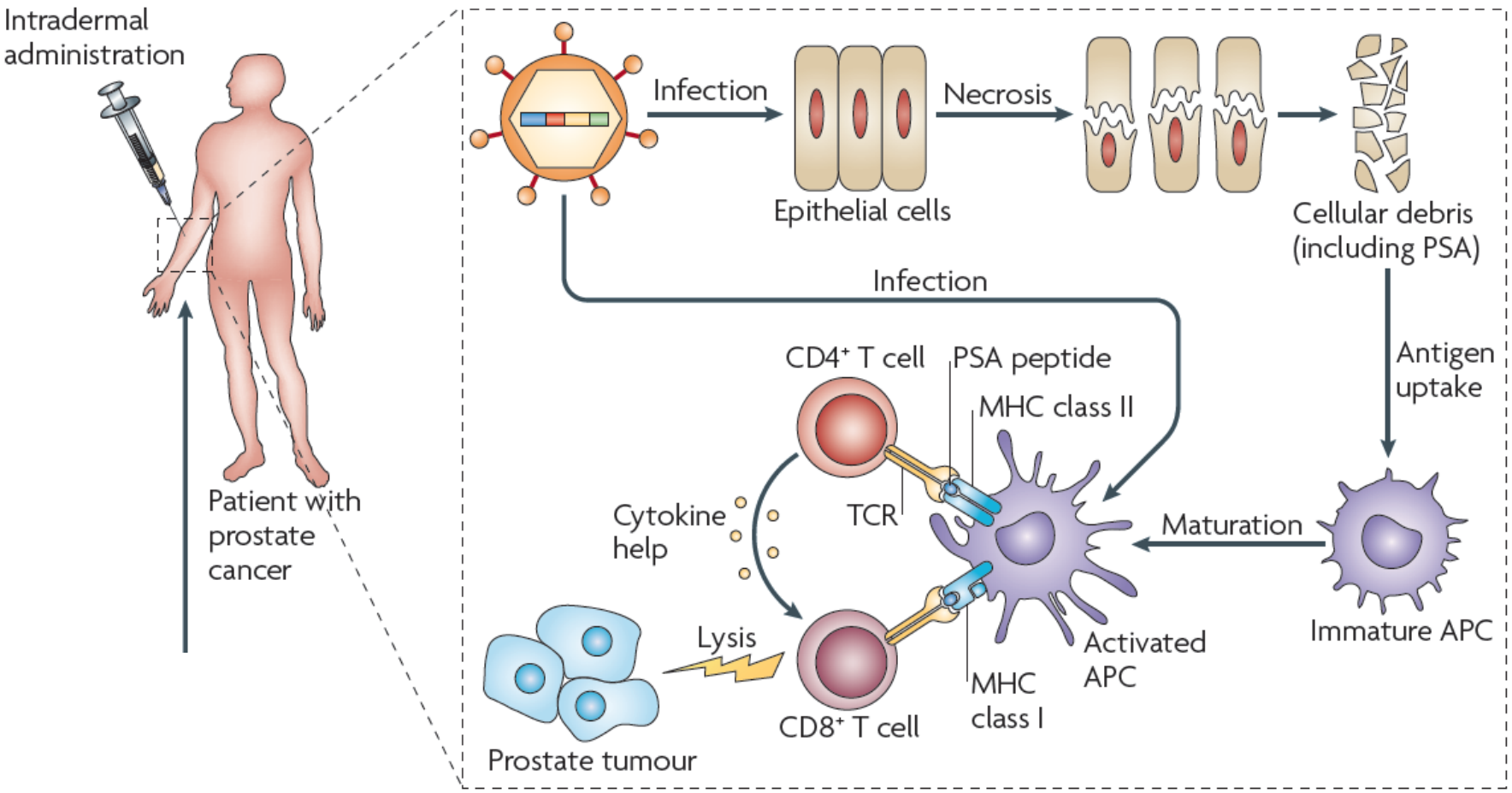


A "**Vector**" Vaccine For Cancer: ProstVac VF



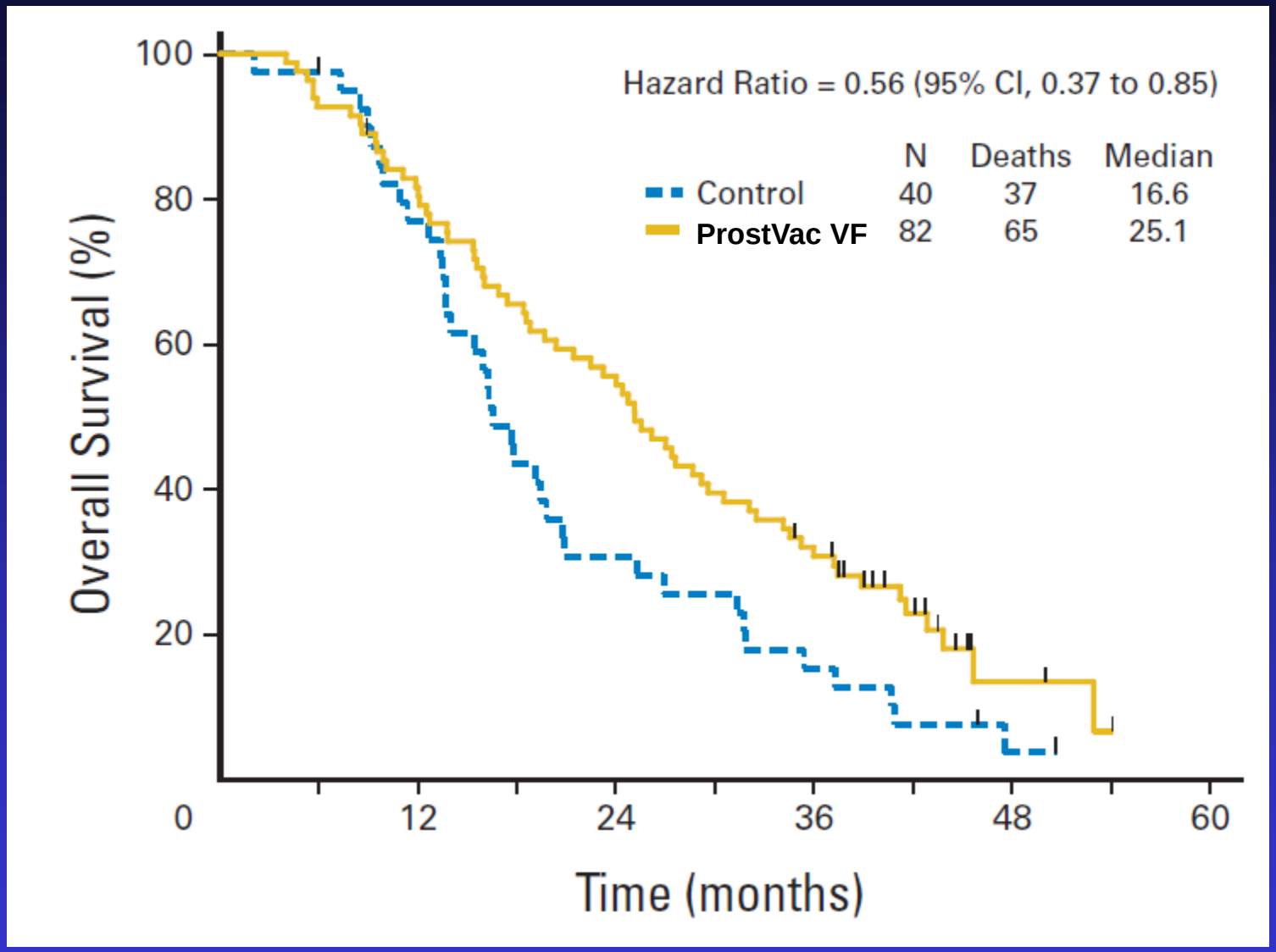
Drake C., *Nature Reviews Immunology*, 2011

Prost Vac VF In Patients



Drake CG *Nat Rev Immunol.* 2010;10:580-93.

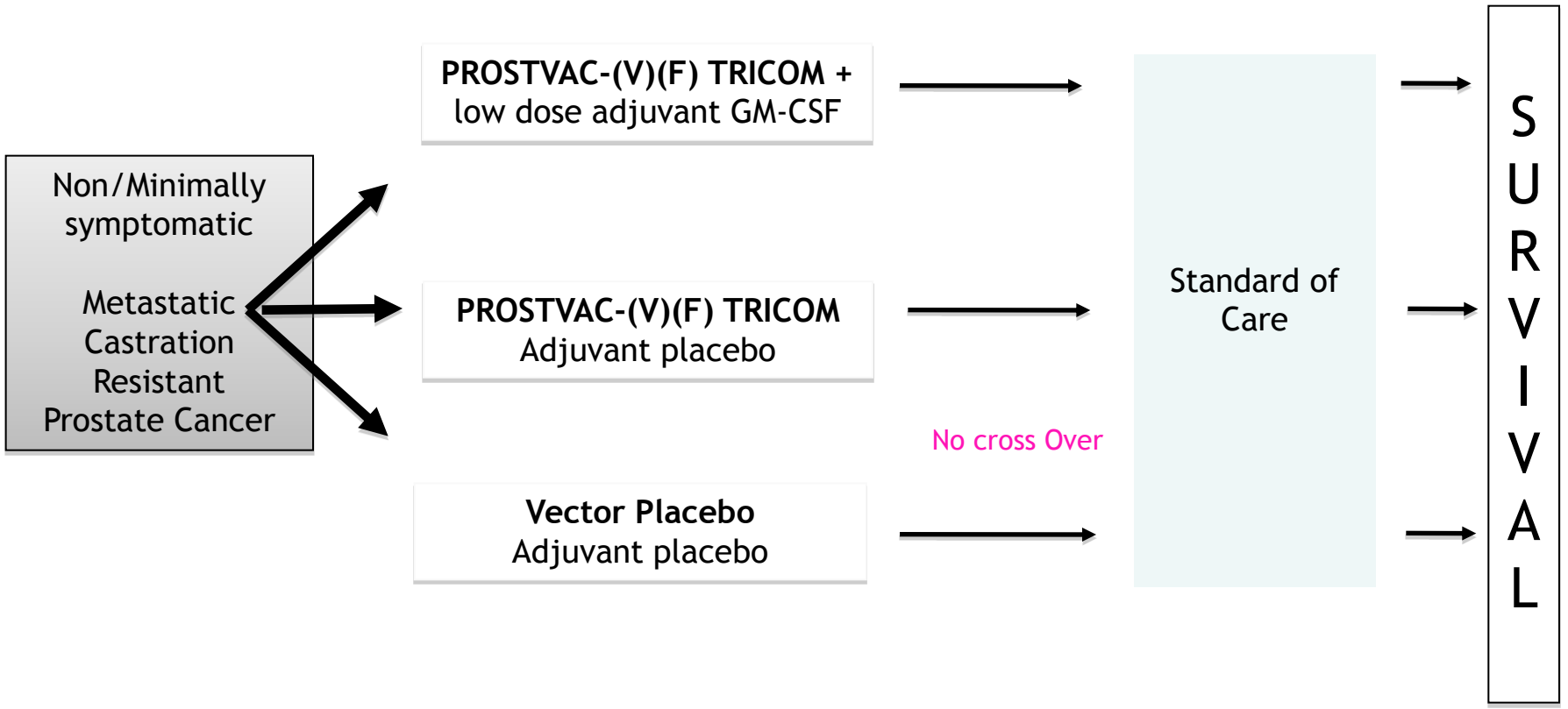
ProstVac Survival Data



Kantoff et al *JCO* 2010, Epub 1/25/2010

Prospect Trial: Design (SPA)

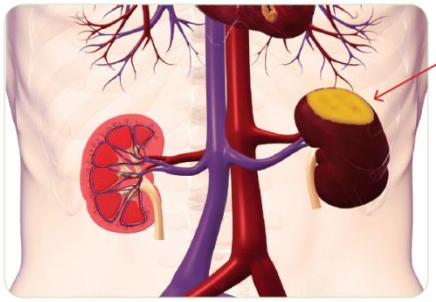
Phase 3 Global (US-CAN-AUS/WE/EE/Latin America)



PRIMARY ENDPOINT: Overall Survival

NATIONAL CANCER INSTITUTE

Using RNA to Load Dendritic Cells: Argos AGS-003



Kidney Cancer Sample

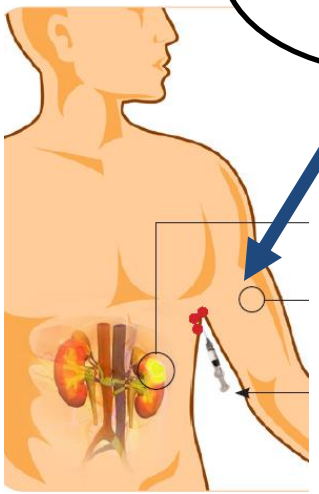
Leukapheresis Product

Tumor RNA Isolation

DC Manufacture

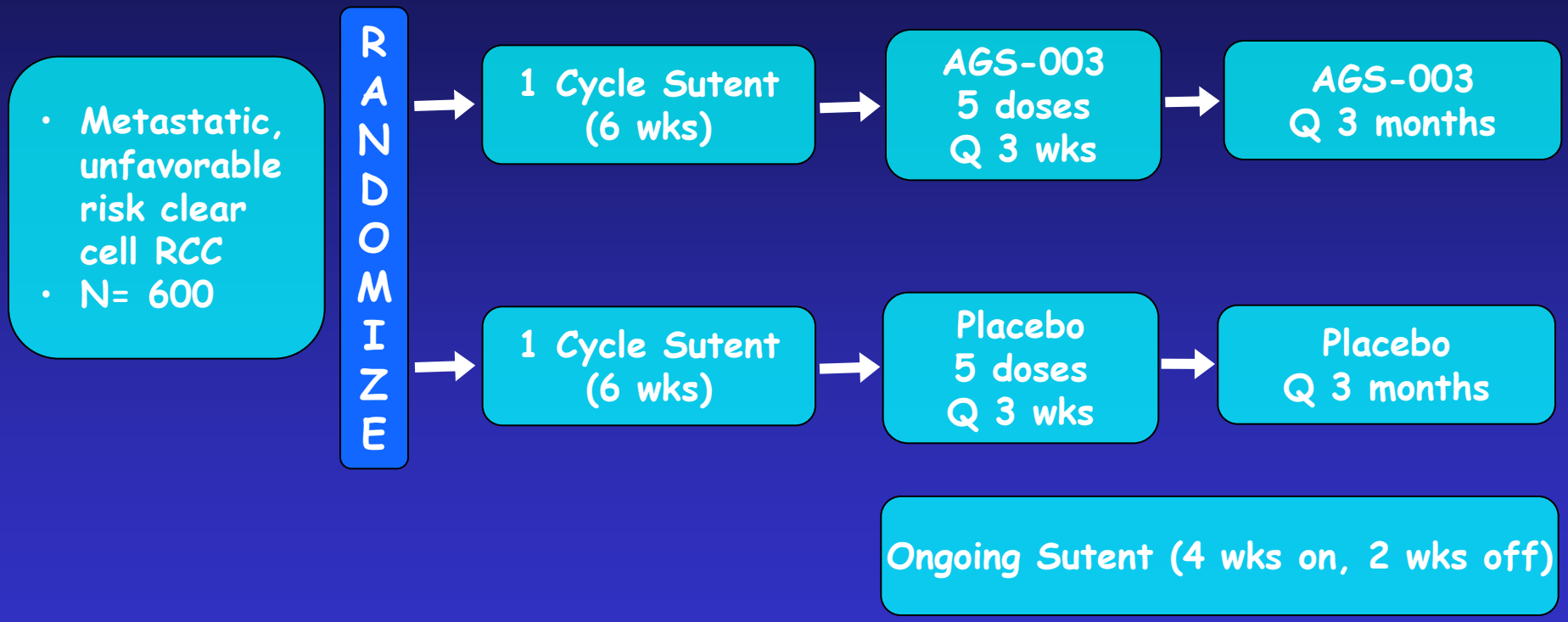
Load DC With RNA And Activate (AGS-003)

Cryopreserve



Intranodal Injection

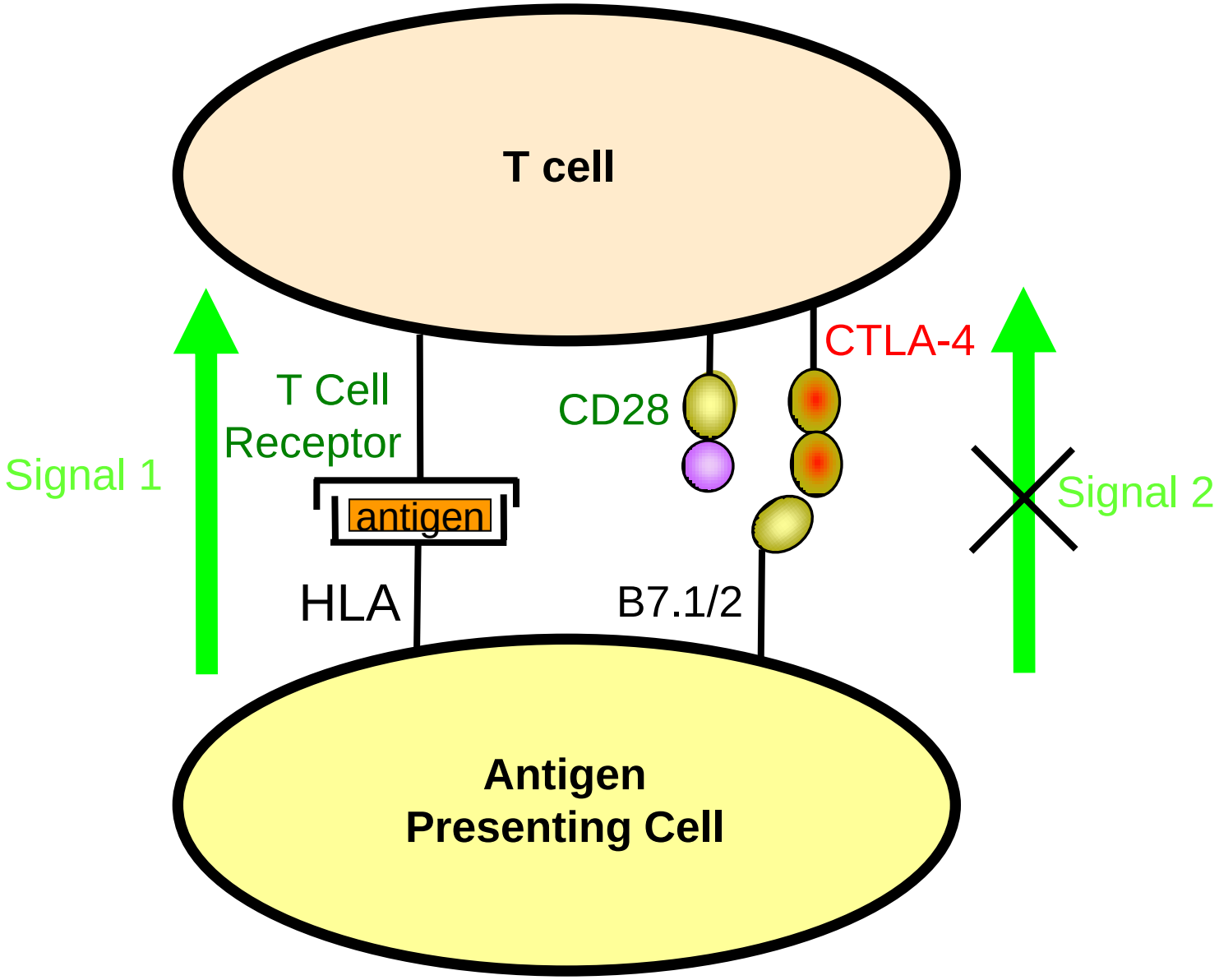
ADAPT:
Autologous Dendritic Cell Immunotherapy with AGS-003 Plus Sunitinib for the Treatment of Advanced RCC



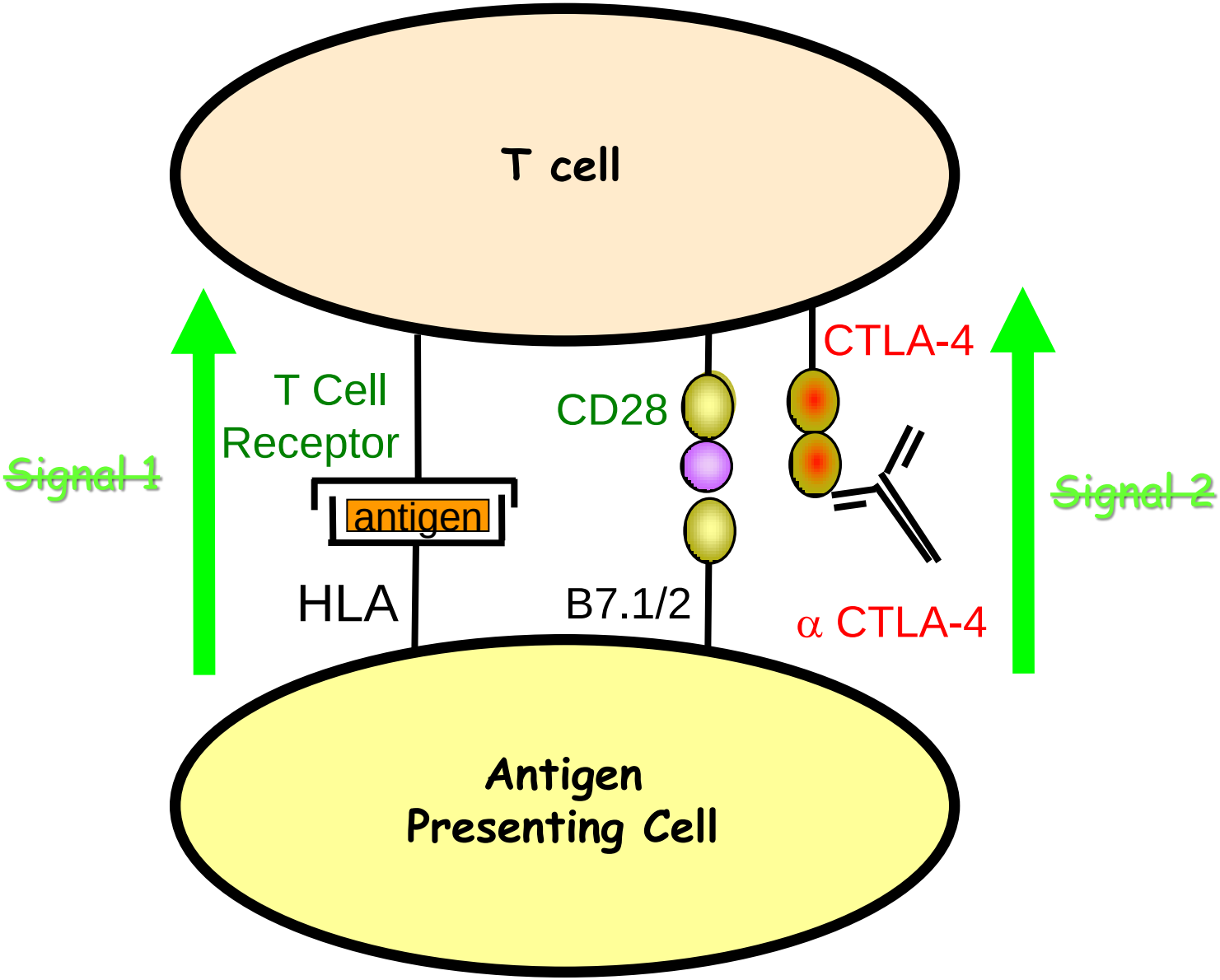
- Primary end point: PFS (30% increase)
- Secondary end point: ORR, OS, Safety

Immune Checkpoint Blockade: CTLA-4

CTLA-4 Prevents Normal T Cell Activation



Ipilimumab (Anti-CTLA-4) Blocks the CTLA-4 Checkpoint, RestoringT Cell Activation



Phase I/II Evidence for Anti-CTLA-4 Activity In Prostate Cancer

Characteristics	Ipilimumab dose					
	3 mg/kg		5 mg/kg	10 mg/kg		
	−XRT ($n = 8$)	+XRT ($n = 7$)	−XRT ($n = 6$)	−XRT ($n = 16$; %)	+XRT ($n = 34$; %)	±XRT ($n = 50$; %)
PSA-evaluable patients	8	6	6	16 (100)	34 (100)	50 (100)
PSA decline by day 85	1	0	1	3 (19)	4 (12)	7 (14)
PSA decline at any time	2	2	1	4 (25)	4 (12)	8 (16)
Tumor-evaluable patients	1	2	1	8 (100)	20 (100)	28 (100)
Complete response	0	0	0	1 (13)	0	1 (4)
Partial response	0	0	0	0	0	0
Partial response (unconfirmed)	0	0	0	1	1	2 (4)
Stable disease	1	1	1	1 (13)	5 (25)	6 (21)
Progressive disease	0	1	0	3 (38)	5 (25)	8 (29)
Unknown	0	0	0	2 (25)	9 (45)	11 (40)

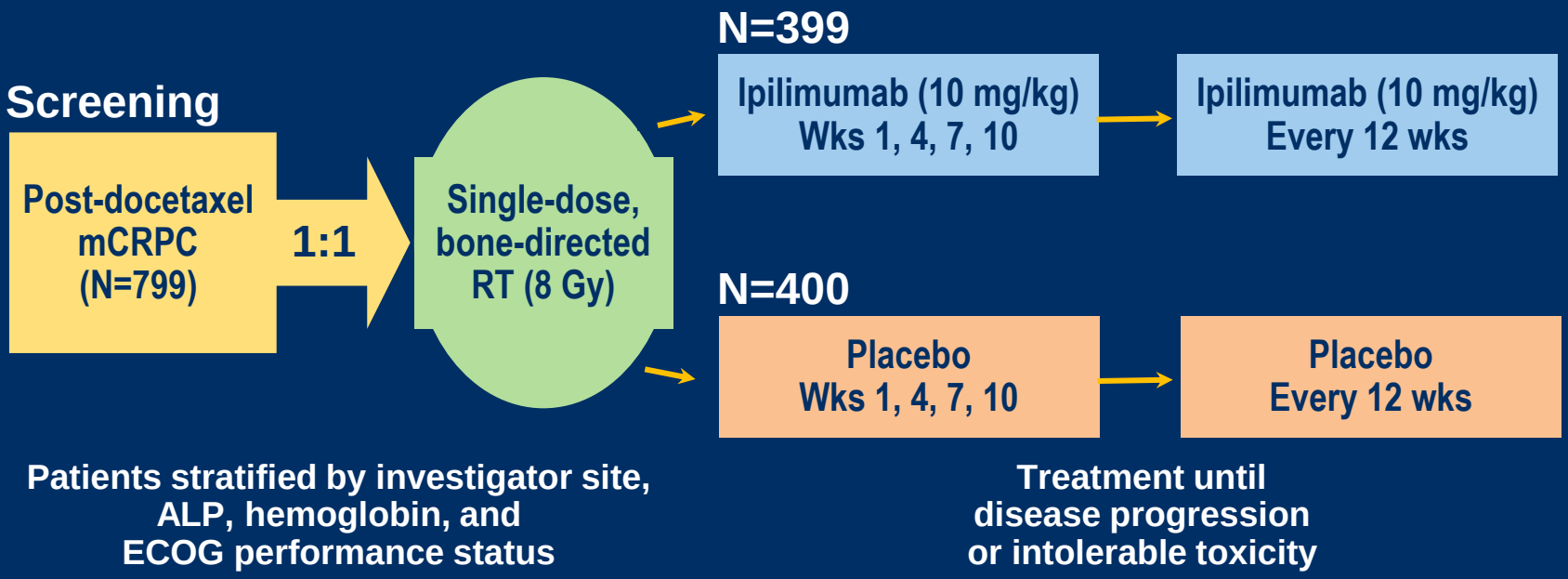
4(27)

[a]PSA decline of ≥50% from baseline (day 85 and at any time) and tumor response (at any time) were confirmed by a second assessment at least 28 days after the initial assessment.

XRT, external-beam radiotherapy; PSA, prostate-specific antigen.

Slovin S et. al. *Annals Oncology*. 2013

Phase 3 Study of Ipilimumab in Post-Docetaxel mCRPC (CA184-043): Study Design*[1]

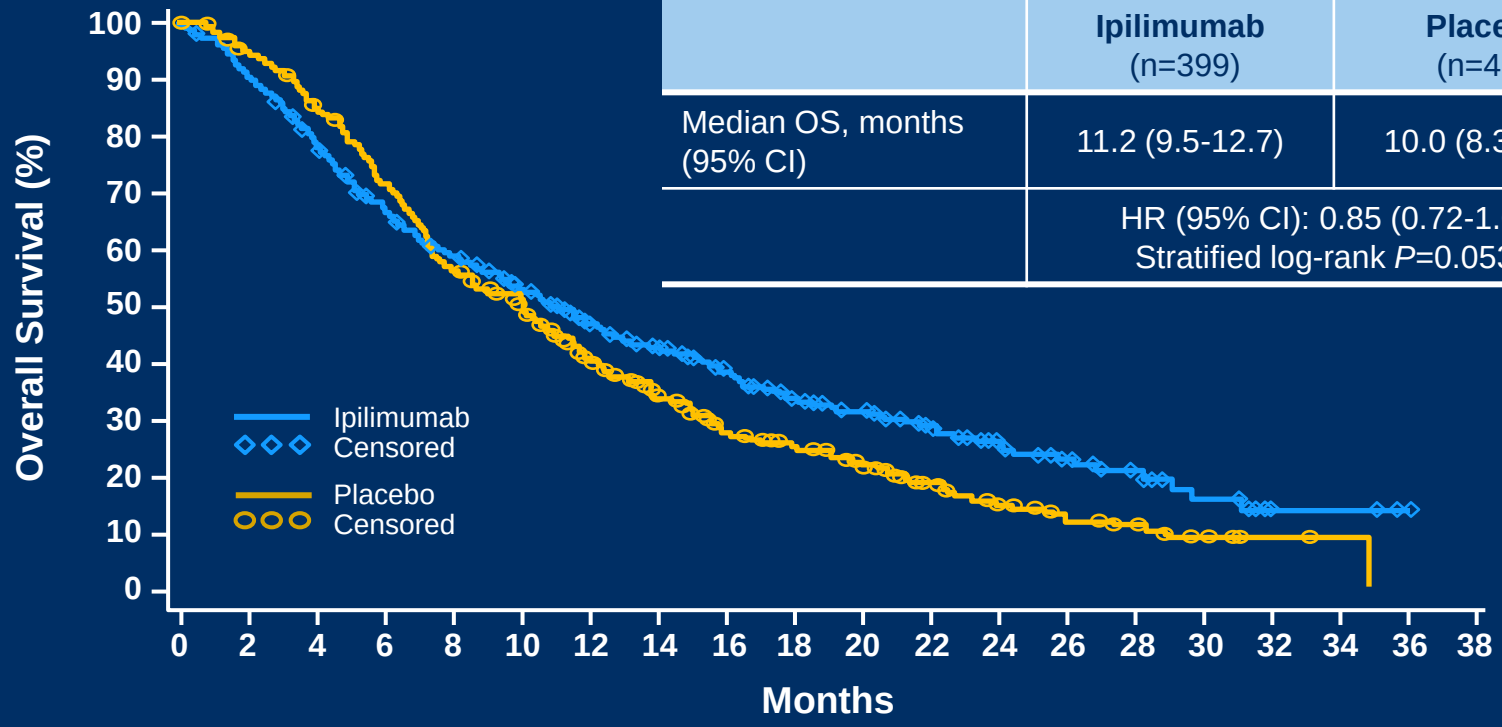


- Primary endpoint: overall survival (OS)
- Secondary endpoints: progression-free survival (PFS), safety
- Exploratory endpoint: prostate-specific antigen (PSA) response rate

*ClinicalTrials.gov Identifier: NCT00861614.
ALP=alkaline phosphatase; ECOG=Eastern Cooperative Oncology Group; RT=radiotherapy.
[1]Gerritsen WR et al. Paper presented at: European Cancer Congress 2013; Amsterdam, The Netherlands. Abstract 2850.

Phase 3 Study of Ipilimumab in Post-Docetaxel mCRPC (CA184-043)[1]

Primary Endpoint: OS (Intent to Treat [ITT] Population)



	Ipilimumab (n=399)	Placebo (n=400)
Median OS, months (95% CI)	11.2 (9.5-12.7)	10.0 (8.3-11.0)
	HR (95% CI): 0.85 (0.72-1.00) Stratified log-rank *P*=0.0530	

Safety

- Adverse event (AE) profile was consistent with that previously reported for ipilimumab*
  - The most frequent severe immune-related AEs were diarrhea and colitis

*See poster presentation at this meeting: Beer et al. Abstract ID: 52.

[1]Gerritsen WR et al. Paper presented at: European Cancer Congress 2013; Amsterdam, The Netherlands. Abstract 2850.

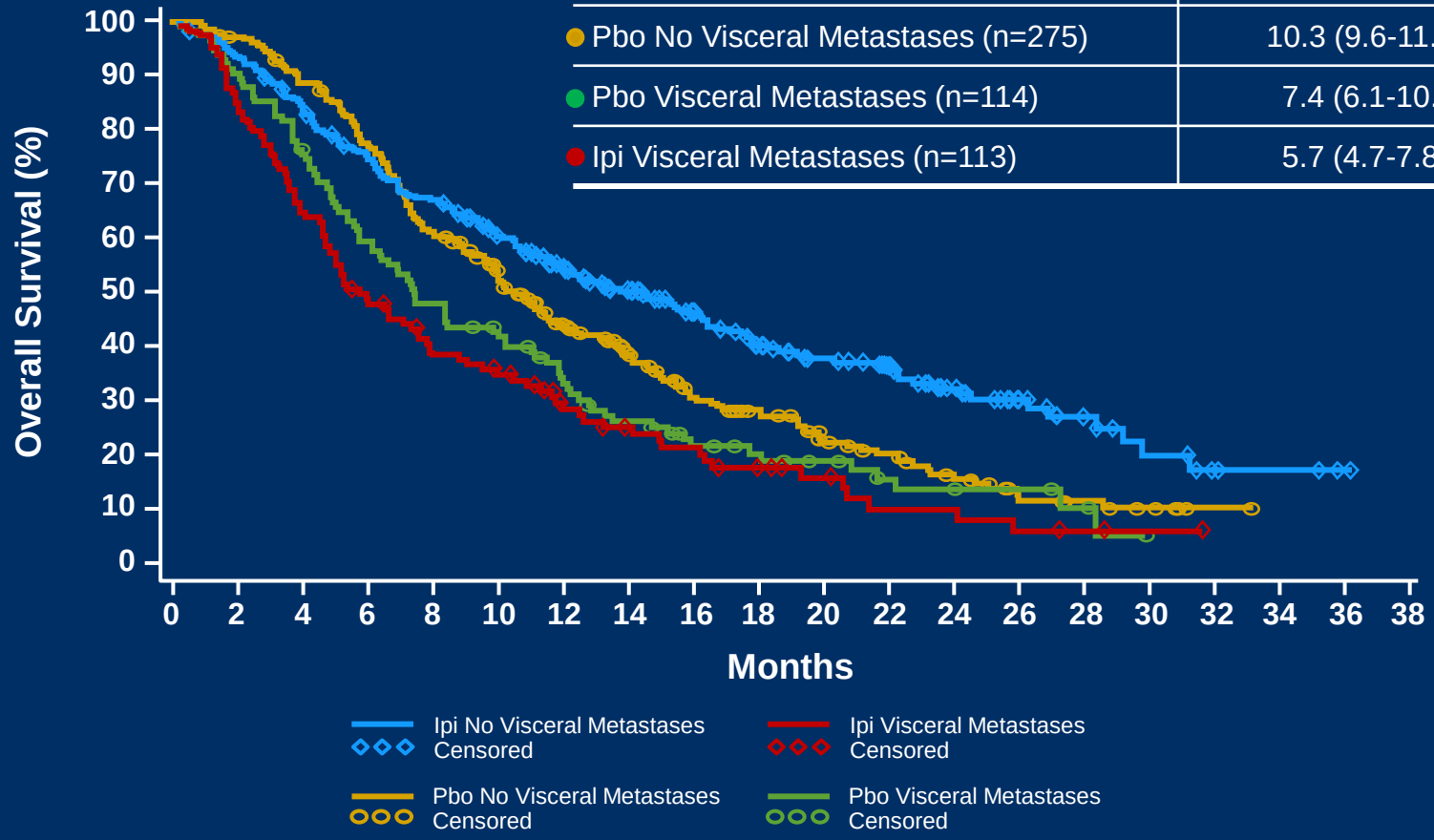
Presence of Visceral Metastases Appears to Interact With Treatment Effect*

Prognostic Feature	*P* Value**	HR (95% CI)**
Age (<70 years, ≥70 years)	0.6764	1.073 (0.772-1.491)
ECOG performance status	0.1655	1.271 (0.906-1.782)
ALP	0.3304	1.178 (0.847-1.637)
Gleason score	0.4971	0.888 (0.631-1.250)
LDH	0.3778	1.214 (0.789-1.870)
Visceral metastases	**0.0056**	**1.644 (1.157-2.336)**
Hemoglobin	0.3257	0.842 (0.597-1.187)
Average daily worst pain (<4, ≥4)	0.7645	1.057 (0.735-1.519)
Log PSA	0.4105	0.951 (0.845-1.071)
Bone metastases	0.8077	0.954 (0.655-1.391)
Bone regions with metastases	0.4526	1.156 (0.792-1.689)

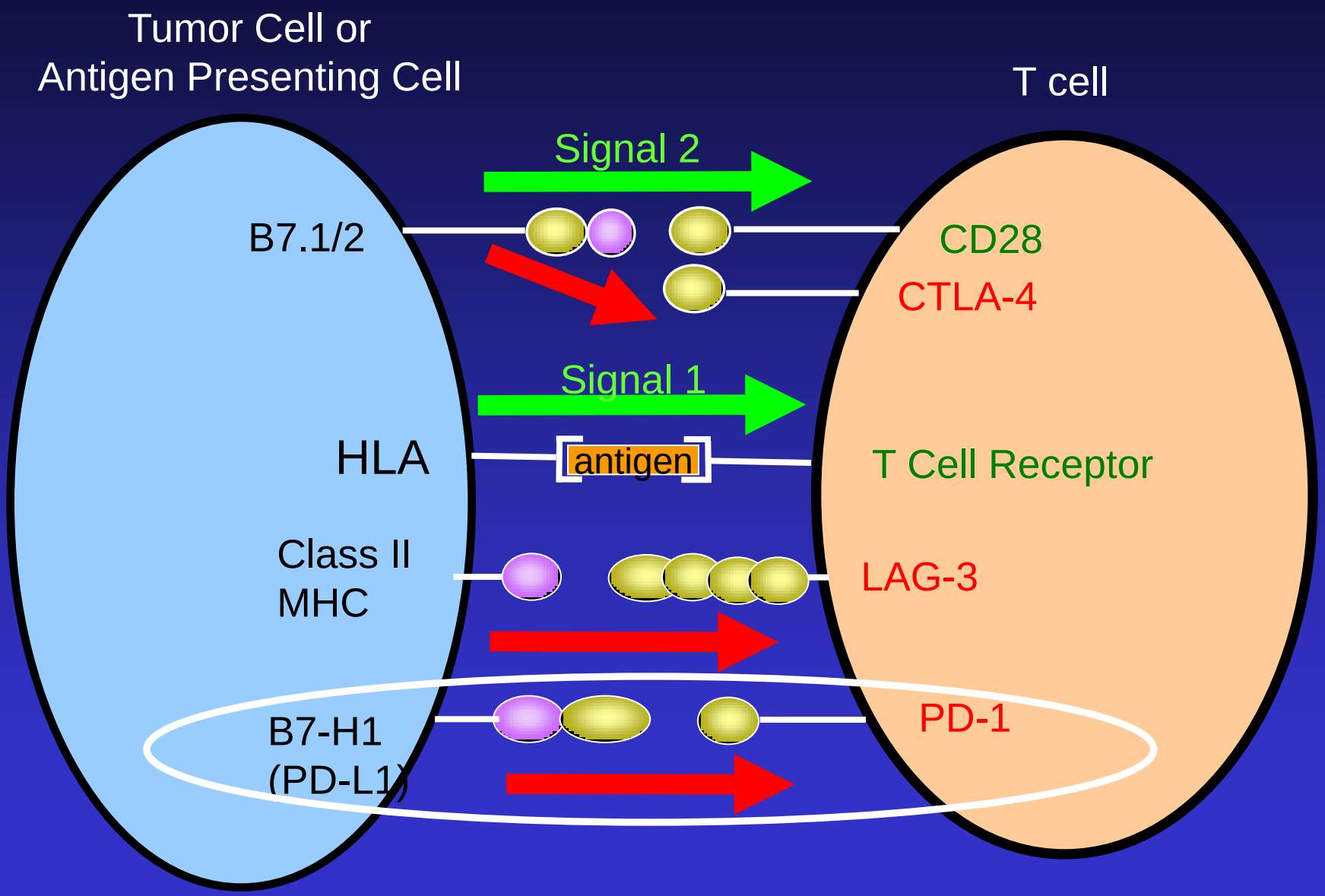
*No multiplicity adjustment.
**For descriptive purposes only.

OS by the Presence of Visceral Metastases at Baseline

Group	Median OS, months (95% CI)
Ipi No Visceral Metastases (n=280)	14.4 (11.5-16.4)
Pbo No Visceral Metastases (n=275)	10.3 (9.6-11.7)
Pbo Visceral Metastases (n=114)	7.4 (6.1-10.2)
Ipi Visceral Metastases (n=113)	5.7 (4.7-7.8)



PD-1


Tumor Cell or
Antigen Presenting Cell
T cell
Signal 2
B7.1/2
CD28
CTLA-4
Signal 1
HLA
antigen
T Cell Receptor
Class II
MHC
LAG-3
B7-H1
(PD-L1)
PD-1

66 year old with RCC

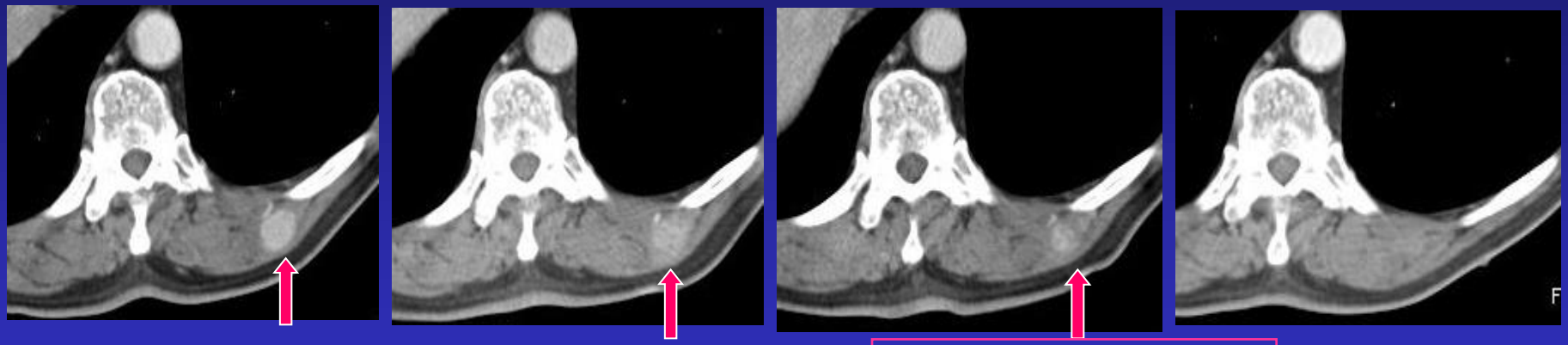
2001 - nephrectomy at JHU = (T3b, NX, MX)

2003 – CT Scan = Multiple Pulmonary Nodules
Multiple treatments, including clinical trials

2007 – CT Scan = Progressive Disease (Pulmonary mets, soft tissue disease, bone dz)

2008 – First dose (10 mg/kg) MDX-1106 on 1/29

01/15/08 (pre-Rx) **03/25/08** **04/22/08** **07/22/08**



- **Received 2 additional on-study treatments (10 mg/kg)**
- **Stable PR -> off study**

US-guided biopsy: No viable tumor

VOLUME 28 · NUMBER 19 · JULY 1 2010
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

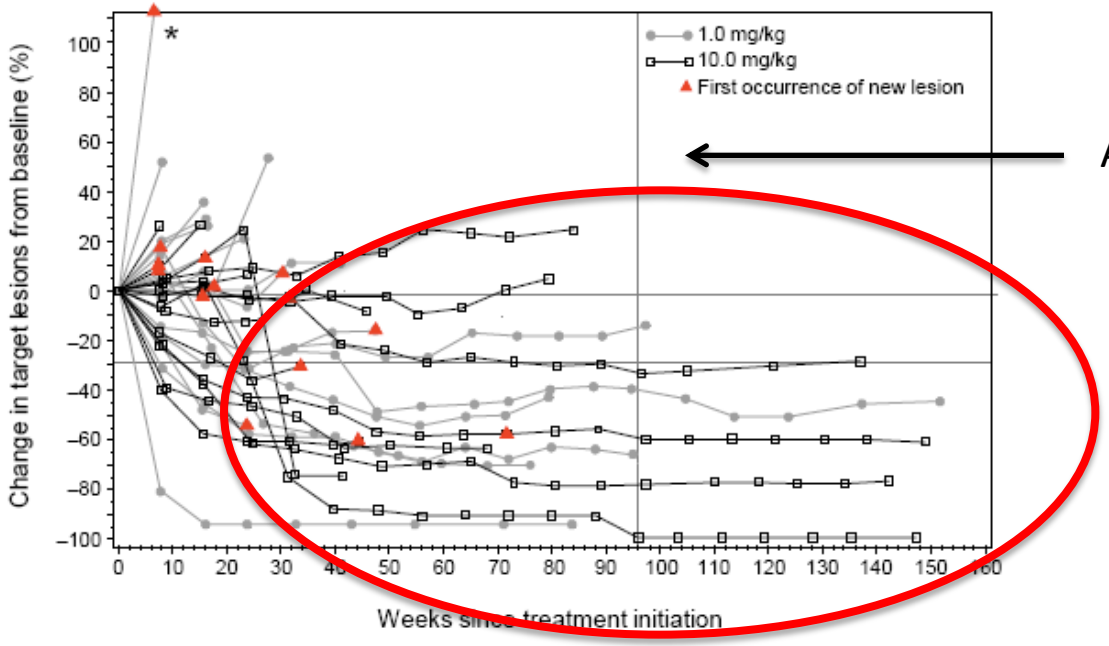
Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates

Julie R. Brahmer, Charles G. Drake, Ira Wollner, John D. Powderly, Joel Picus, William H. Sharfman, Elizabeth Stankevich, Alice Pons, Theresa M. Salay, Tracee L. McMiller, Marta M. Gilson, Changyu Wang, Mark Selby, Janis M. Taube, Robert Anders, Lieping Chen, Alan J. Korman, Drew M. Pardoll, Israel Lowy, and Suzanne L. Topalian

Update: Phase I Nivolumab: RCC cohort (n=34)

- Generally tolerable: fatigue, rash, pruritus, diarrhea
  - 3 deaths: pneumonitis (non-RCC)

- Preliminary efficacy in heavily pre-treated patients:
  - 29% objective responses
  - Median PFS 7.3 months

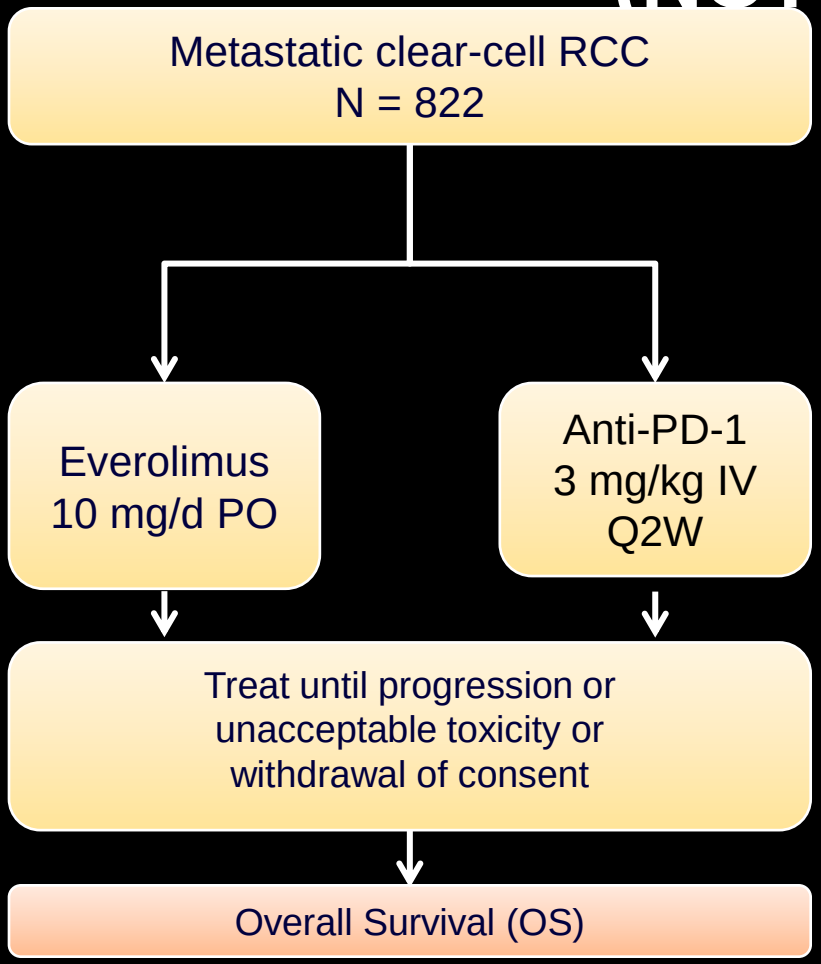


All stopped therapy

Durability of Response Even Off Drug

Drake CG et al Journal of Clinical Oncology, 2013 ASCO Annual Meeting Abstracts. Vol 31, No 15_suppl (May 20 Supplement), 2013: 4514 ASCO 2013

Phase III Study of Anti-PD-1 vs Everolimus in Patients With Previously Treated mRCC (NCT01668784)



Start Date: October 2012
Estimated Study Completion Date: February 2016
Estimated Primary Completion Date: February 2016
Status: Recruiting

Primary Endpoints
- OS

Secondary Endpoints
- PFS
- ORR
- Duration of objective response
- Duration of overall survival
- Safety
- Disease related symptom progression rate

Key Eligibility Criteria
- Confirmed RCC with clear-cell component
- 1/2 prior anti-angiogenic therapies in advanced / metastatic setting
- ≤ 3 prior systemic treatment regimens and evidence of progression on or after last treatment and within 6 months of enrollment
- Karnofsky Performance Score ≥ 70%
- No CNS metastasis

Summary

- There is ONE cancer vaccine that is US FDA-approved for in the treatment setting (Sipuleucel-T)
- Ongoing Phase III Vaccine Trials in Prostate and Kidney Cancer:
  - ProstVac VF in prostate cancer
  - Argos RNA-loaded DC vaccine in kidney cancer
  - Immatics peptide vaccine in kidney cancer

- Immmune Checkpoint Blockade is NOT FDA-approved to treat either prostate OR kidney cancer
  - Phase III trial of anti-CTLA-4 a “near miss” in post-chemotherapy prostate cancer
  - Phase III trial of anti-CTLA-4 (ipliimumab) pre-chemotherapy prostate cancer
  - Not much activity for anti-PD-1 in advanced prostate cancer
  - Phase III trial of anti-PD-1 completed enrollment in kidney cancer

- Earlier Phase Combination trials ongoing (lots !)
  - Toxicity a concern