Charles G. Drake MD / PhD
Associate Professor: Medical Oncology, Immunology and Urology
Co-Director: Multi-Disciplinary Prostate Cancer Clinic
Johns Hopkins Kimmel Cancer Center

# Immunotherapy for Prostate Cancer?

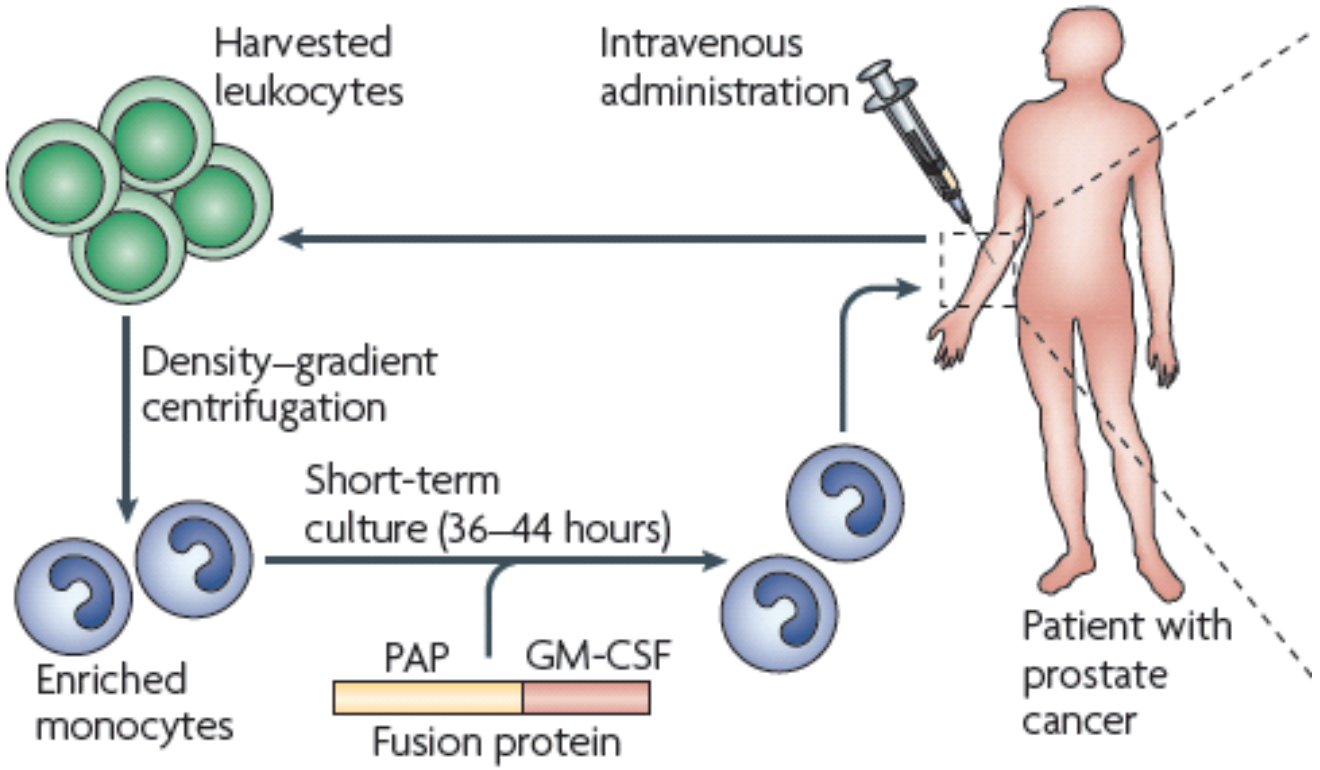
# Disclosure of Financial Relationships

- Consulting:
  Amplimmune, Bristol Myers Squib, Compugen, Dendreon, ImmunExcite, Janssen, NexImmune; Pfizer, Roche-Genentech
- Patents:
  Amplimmune
- Sponsored Research:
  Aduro Biotech, Bristol Myers Squibb, Janssen

# Off Label and Investigational Use

- Anti-PD-1 (Nivolumab) is an investigational agent and is NOT FDA-approved for cancer treatment.
- Anti-CTLA-4 (Ipilimumab) is NOT FDA-approved for the treatment of prostate cancer

# Sipuleucel-T
# (an autologous vaccine)




Drake, *Nature Reviews Immunology,* 2010

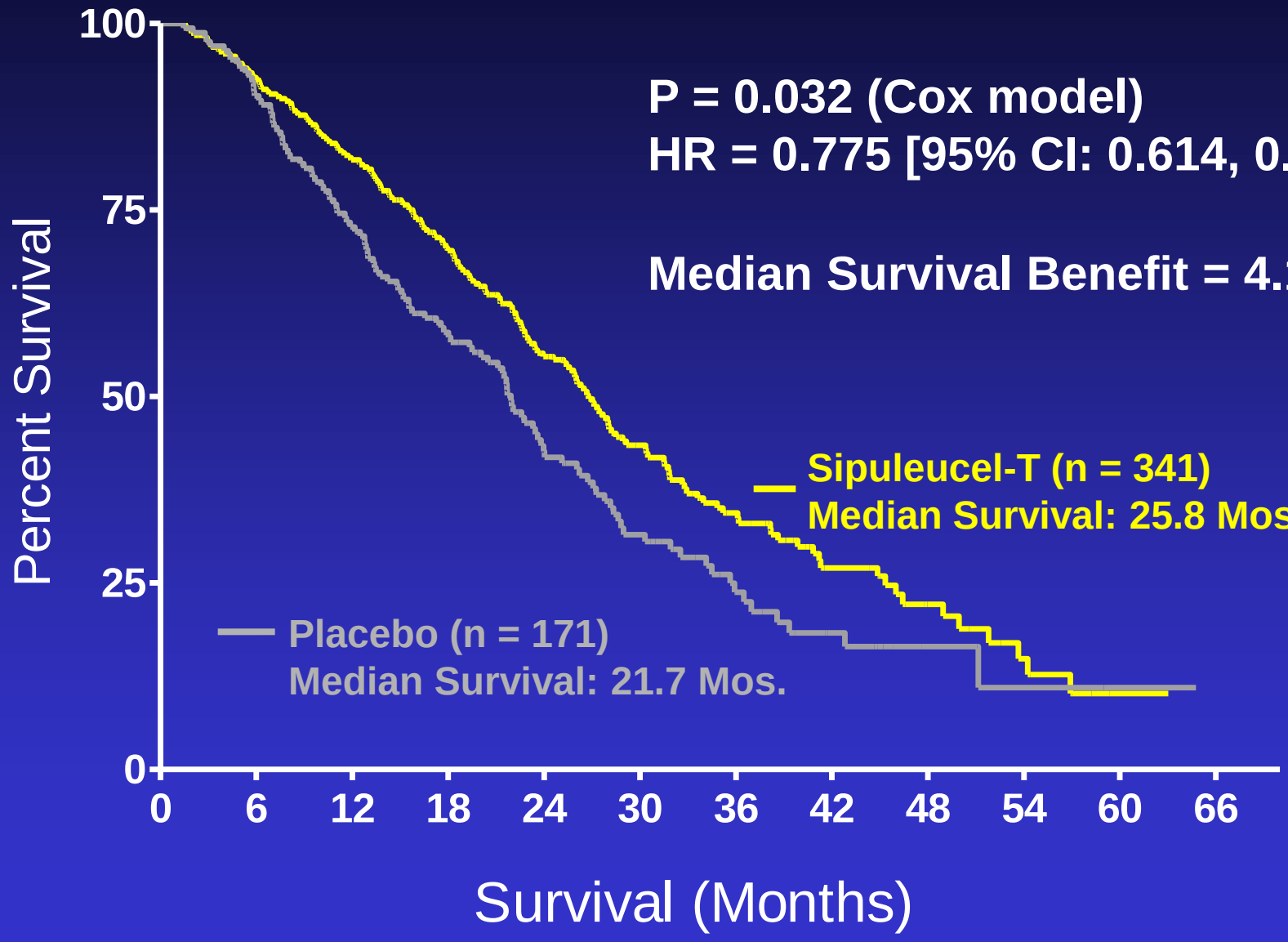
# D9902B – IMPACT

## IMmunotherapy Prostate AdenoCarcinoma Treatment


- Patients: Asymptomatic or minimally symptomatic metastatic CRPC

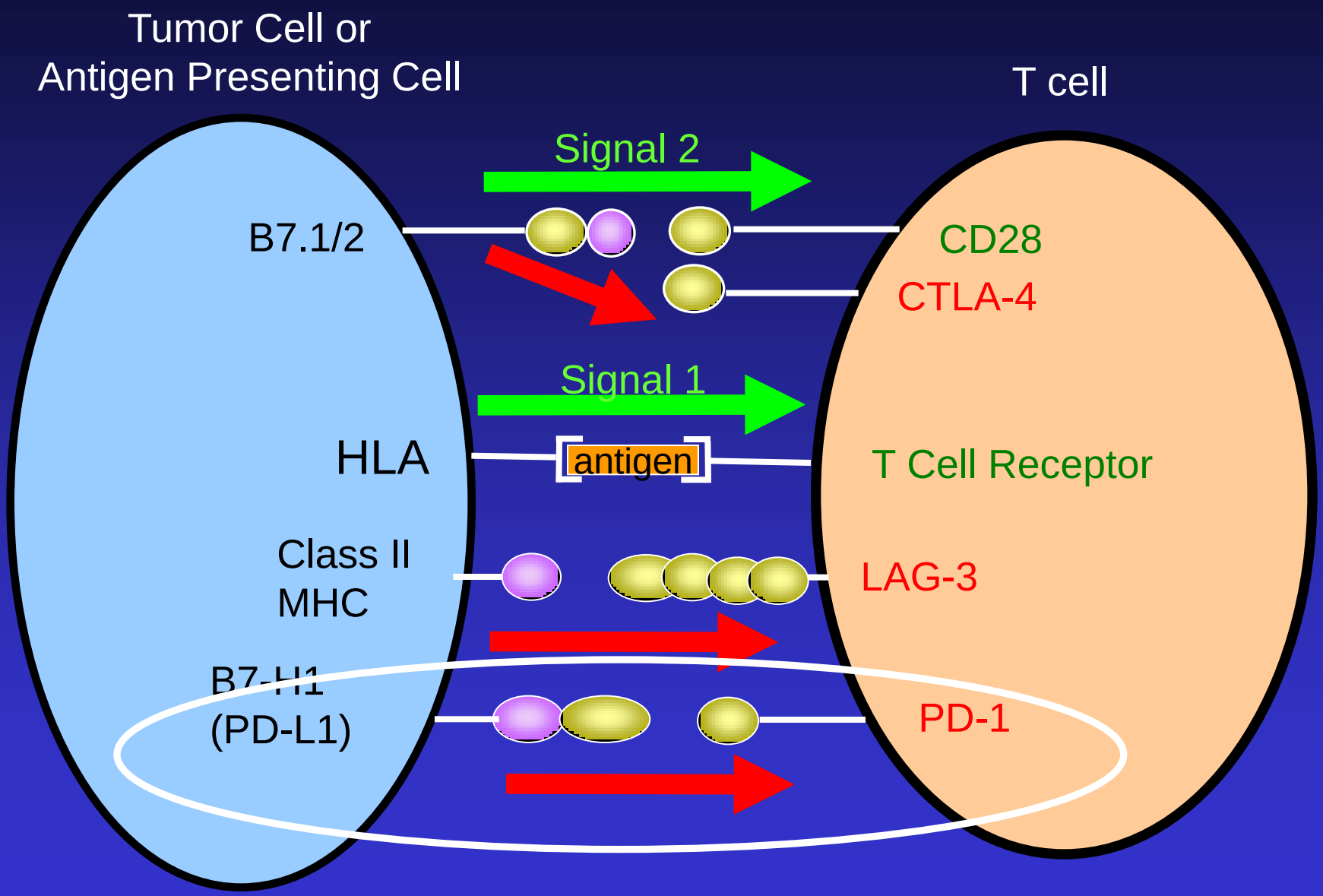
- Primary end point: Overall Survival
- Secondary end point: TTP
- * Prepared from cryopreserved lymphocytes

# Sipuleucel-T: Survival Benefit in Phase III Trial(s)

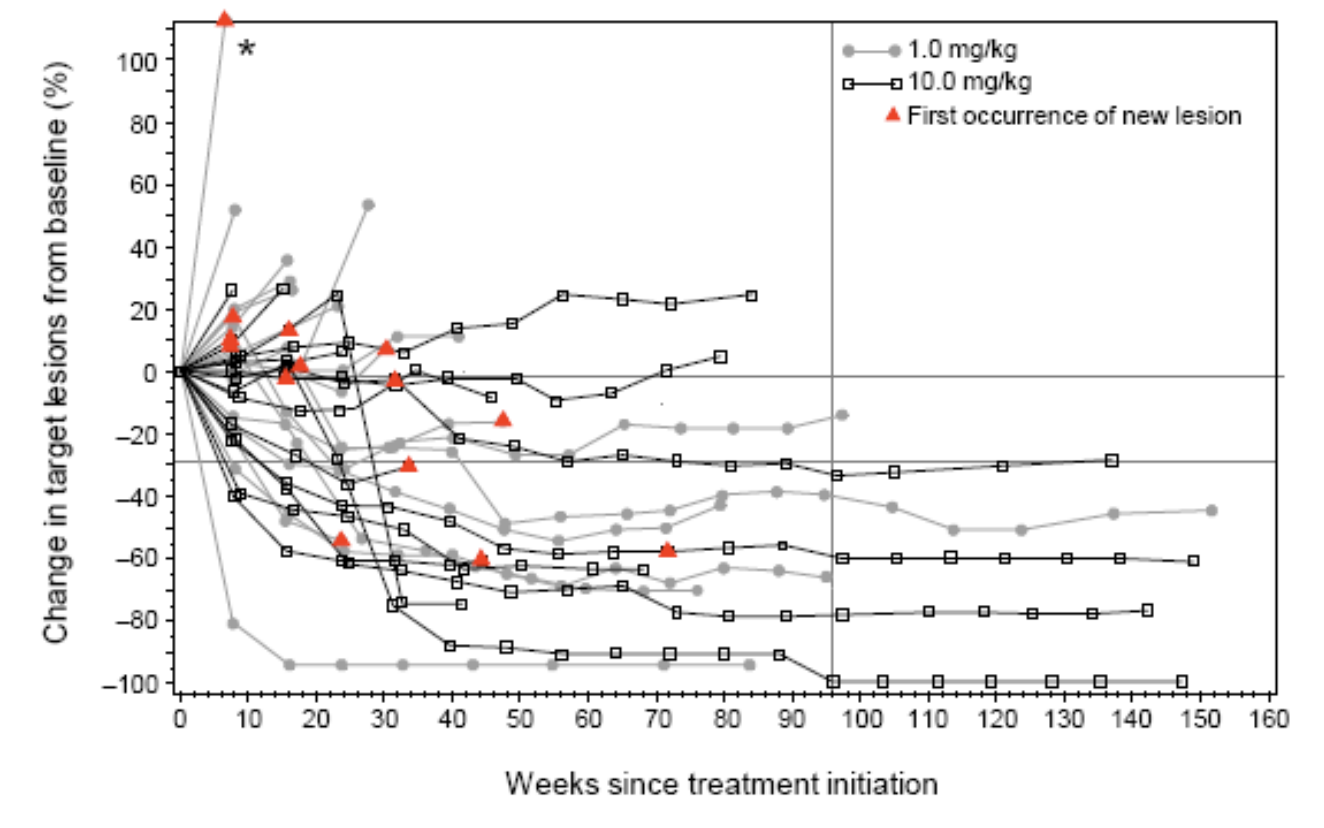



Kantoff et al, *NEJM* 2012

# Immune Checkpoint Blockade



# Response kinetics in patients with mRCC receiving nivolumab 1 or 10 mg/kg




Baseline tumor measurements standardized to zero; tumor burden = sum of longest diameters of target lesions

* = off-scale value of 144%; ▲= indicates first occurrence of new lesion

Vertical line at 96 weeks = maximum duration of nivolumab therapy

Horizontal line at −30% = threshold for defining objective response (partial tumor regression) according to RECIST

Drake CG, McDermott D et al ASCO 2013

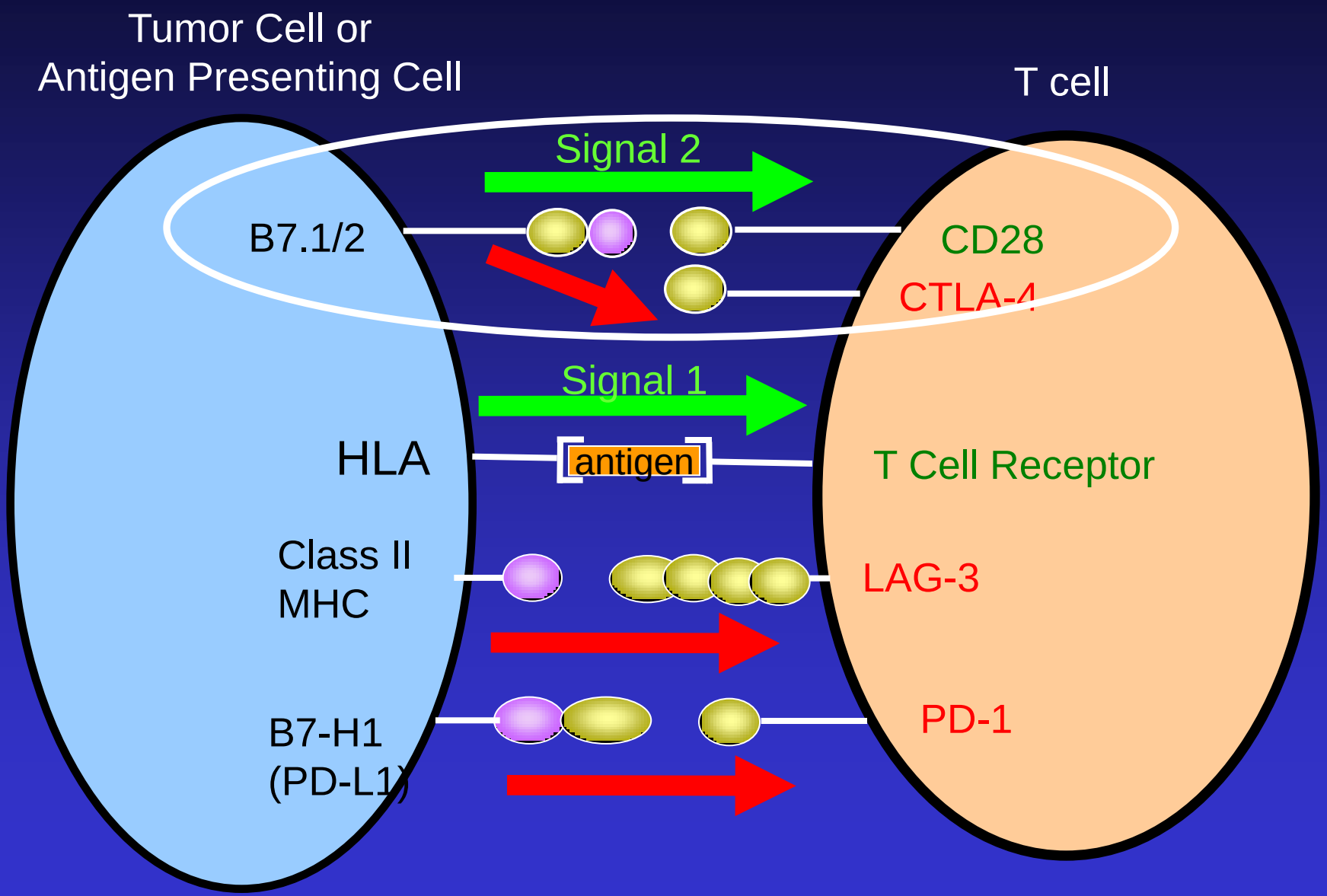
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

# Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

"No objective responses were observed in patients with colorectal or prostate cancer."


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

# 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) |

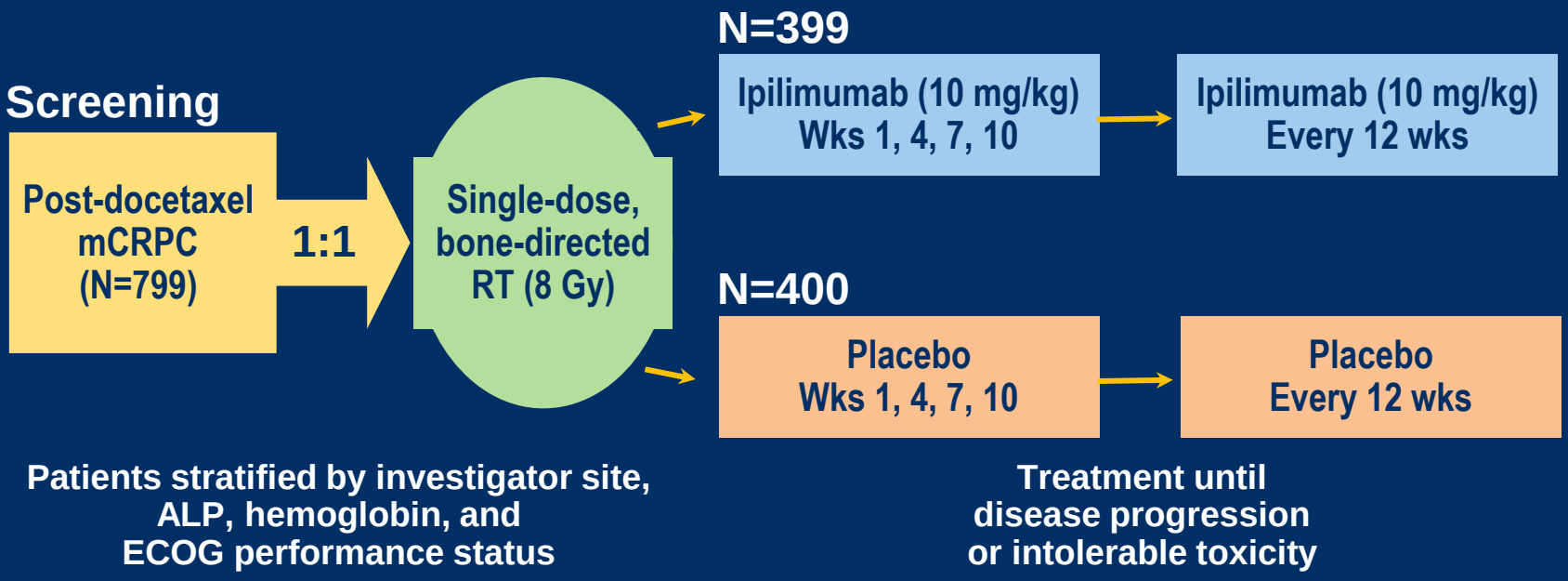
4(27)

[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]

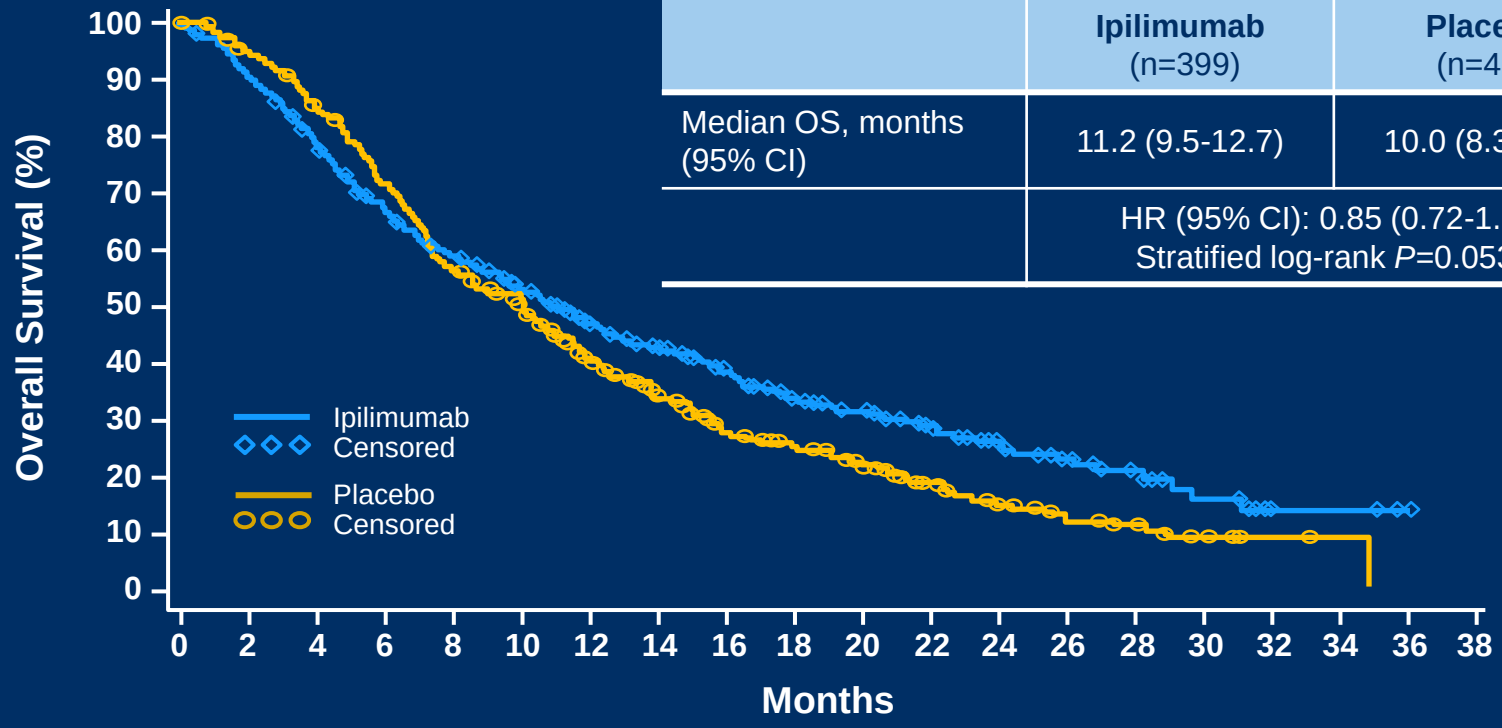



- Primary endpoint: overall survival (OS)
- Secondary endpoints: progression-free survival (PFS), safety
- Exploratory endpoint: prostate-specific antigen (PSA) response rate

*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)<br>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.

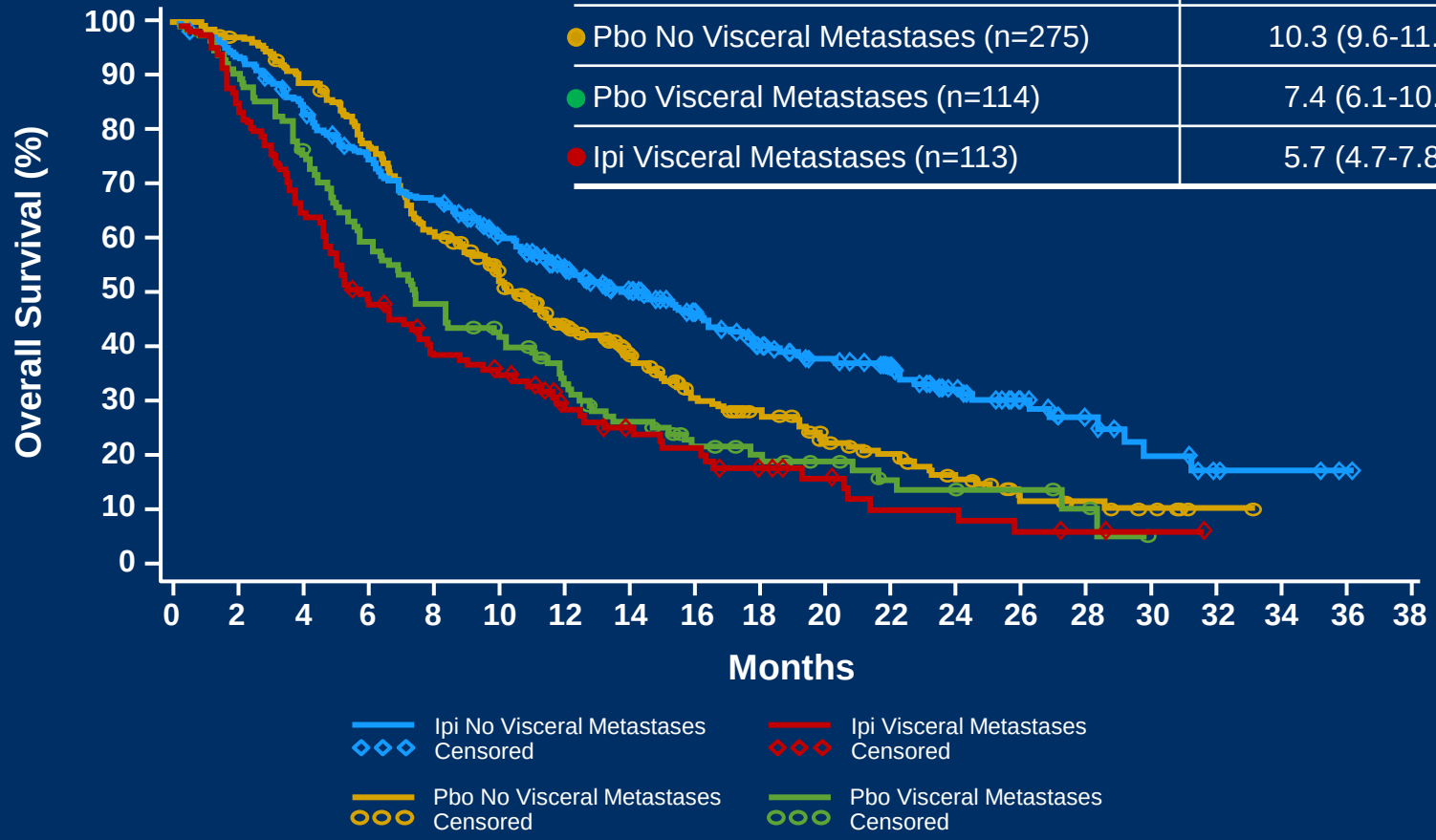
# Presence of Visceral Metastases Appears to Interact With Treatment Effect*

| 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.

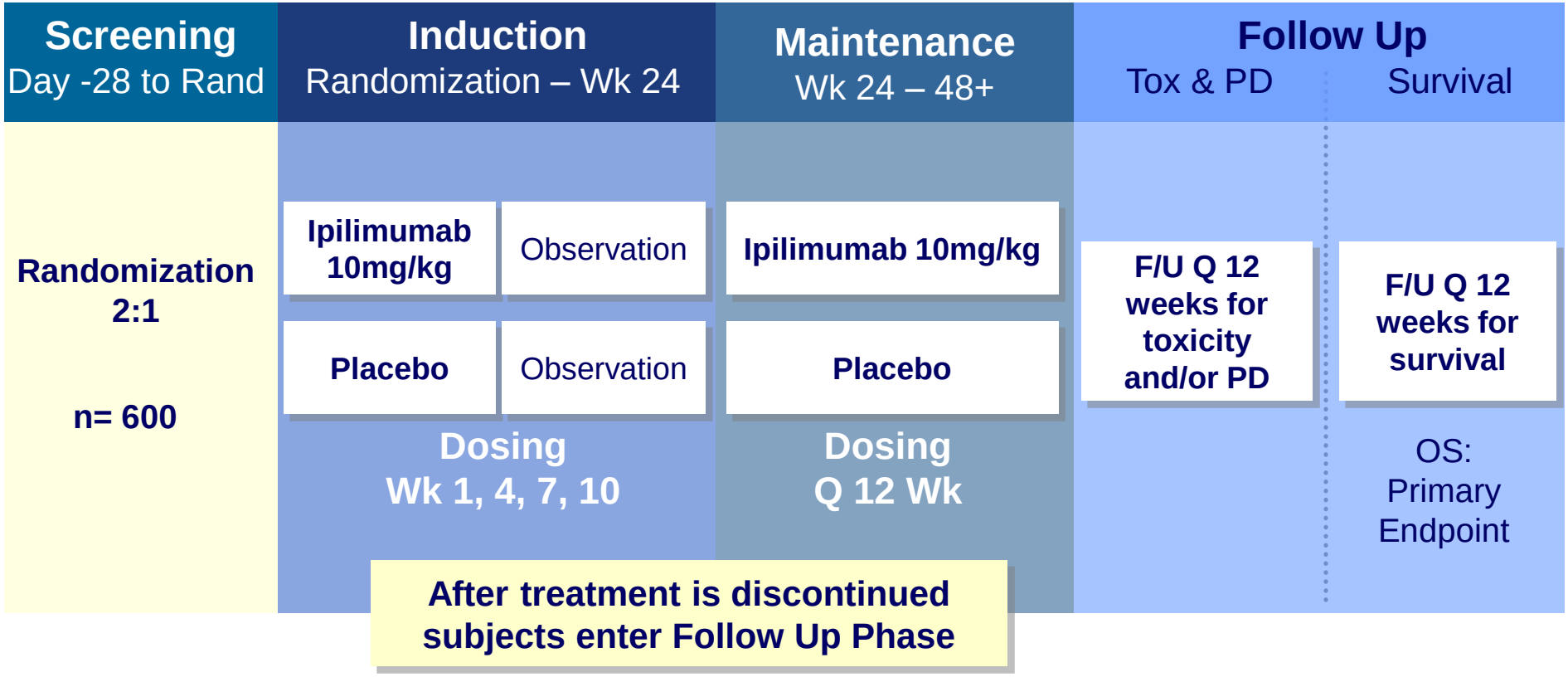
# OS by the Presence of Visceral Metastases at Baseline

| 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) |



Stay tuned …

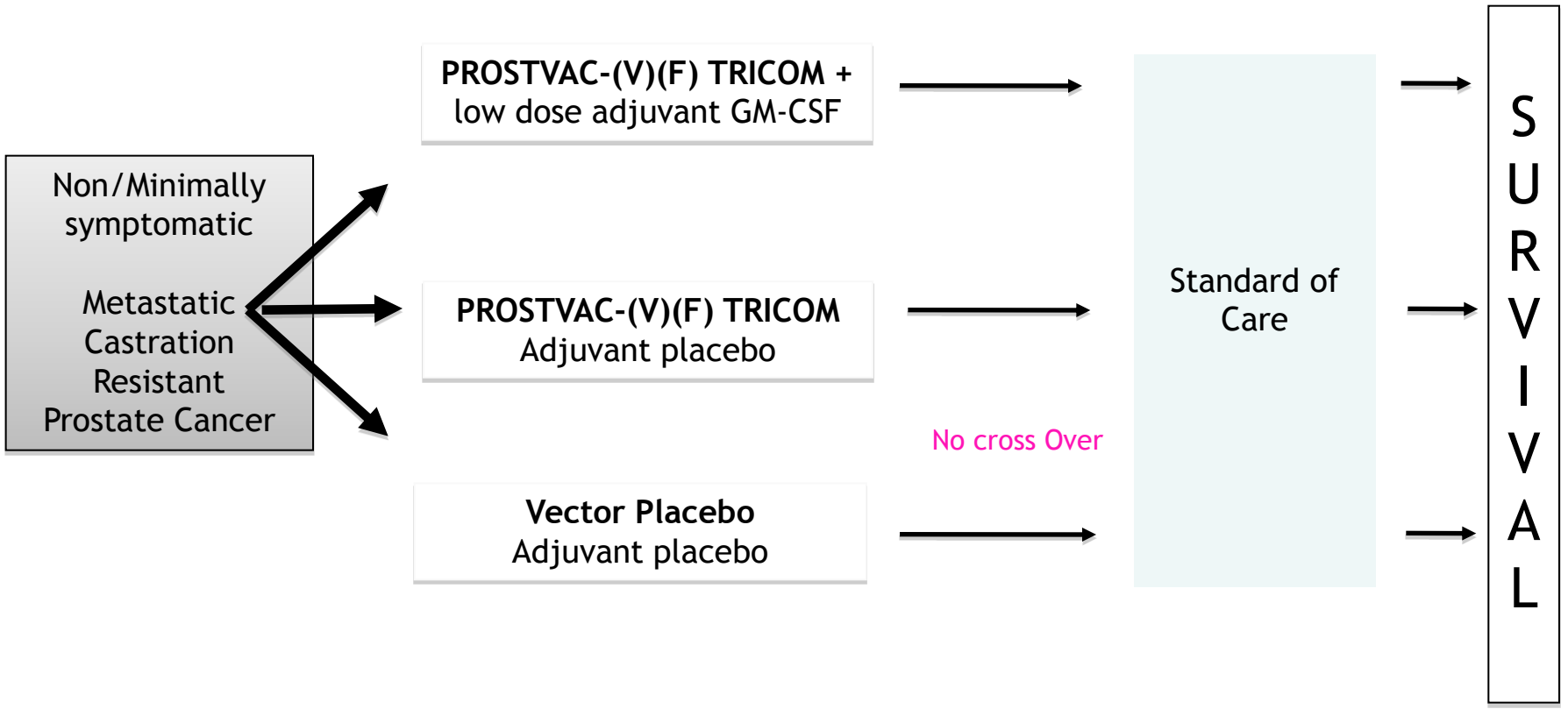
# Phase 3 Study of Ipilimumab in Pre-Docetaxel mCRPC (CA184-095): Study Design




www.clinicaltrials.gov (NCT01057810)

# Prospect Trial: Design (SPA)

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




PRIMARY ENDPOINT: Overall Survival

NATIONAL CANCER INSTITUTE

# Prostate Cancer: Immunologically Challenged

- 12 cytokine / chemokine Signature
- PCA score as a measure of chemokine signal

| Tissue Type | Total # CEL files | # Above 90th percentile | % Above 90th percentile |
|---|---|---|---|
| Bladder | 212 | 27 | 12.74 |
| Brain | 438 | 4 | 0.91 |
| Breast | 3705 | 401 | 10.82 |
| Cervix | 75 | 19 | 25.33 |
| Endometrium | 333 | 14 | 4.20 |
| Esophagus | 90 | 6 | 6.67 |
| Kidney | 850 | 61 | 7.18 |
| Large_Bowel | 2111 | 169 | 8.01 |
| Larynx | 56 | 7 | 12.50 |
| Liver | 116 | 5 | 4.31 |
| Lung | 2708 | 488 | 18.02 |
| Oral_Cavity | 98 | 25 | 25.51 |
| Ovary | 670 | 21 | 3.13 |
| Pancreas | 468 | 15 | 3.21 |
| Peritoneum | 30 | 1 | 3.33 |
| Prostate | 981 | 5 | 0.51 |
| Rectum-Anus | 188 | 10 | 5.32 |
| Renal_Pelvis | 62 | 1 | 1.61 |
| Skin | 569 | 115 | 20.21 |
| Small_Intestine | 52 | 2 | 3.85 |
| Soft_Tissue | 97 | 14 | 14.43 |
| Stomach | 133 | 13 | 9.77 |
| Thyroid | 71 | 5 | 7.04 |
| Tongue | 32 | 8 | 25.00 |
| Uterus | 377 | 13 | 3.45 |

Messina and Mule, *Nature Reports* 2012, 2:765

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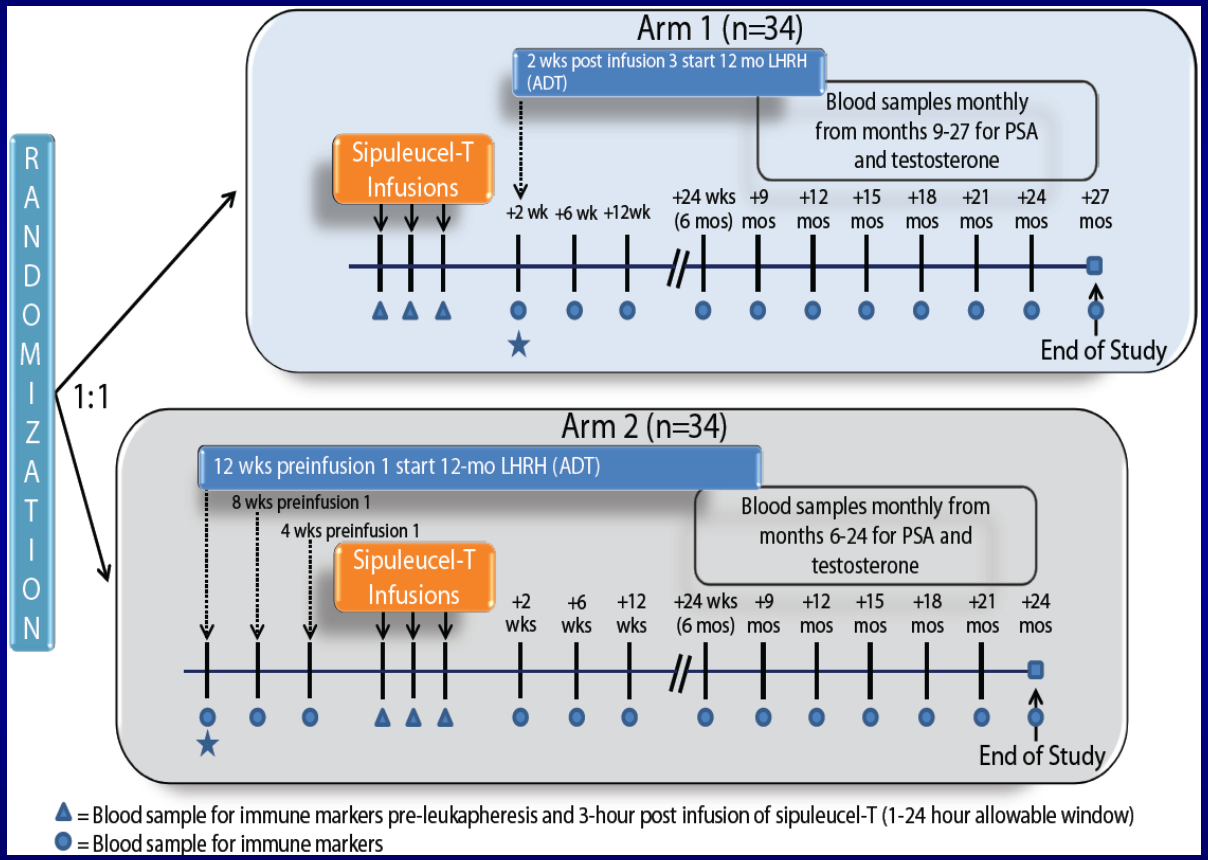
Messina and Mule, *Nature Reports* 2012, 2:765

# Combining Androgen-Ablation with Vaccination

- Biochemically-recurrent prostate cancer following local therapy
- Non-castrate (>150 ng/dl) testosterone
- PSA doubling time ≤12 mo
- No radiographic metastases




**1° endpoint:** Determine whether ADT started before or after sipuleucel-T leads to an enhanced immune response.

**2° endpoints:** Humoral immune responses, cellular immune responses, cytokine responses, PSA responses, time to PSA progression, metastasis-free survival.

**Antonarakis ES, et al. *J Clin Oncol.* 2013;31(Suppl 6): Abstract 34.**

# Acknowledgements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