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CANCER INSTITUTE

Advances in Immunotherapy for Prostate Cancer

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Disclosure Information

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The following relationships exist relevant to this presentation:

- Dr Kantoff has served on the Scientific Advisory Board or is an advisor to Sanofi, Novartis, Amgen, BN-IT, Dendreon, Janssen, Bellicum and Bayer.

Immunotherapeutic Approaches

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- Provenge (Sipuleucel-T)
- PROSTVAC-VF Tricom
- Ipilimumab

- Sipuleucel-T (Provenge)

Sipuleucel-T: Mechanism of Action

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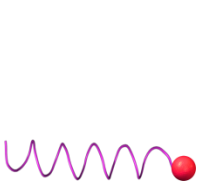
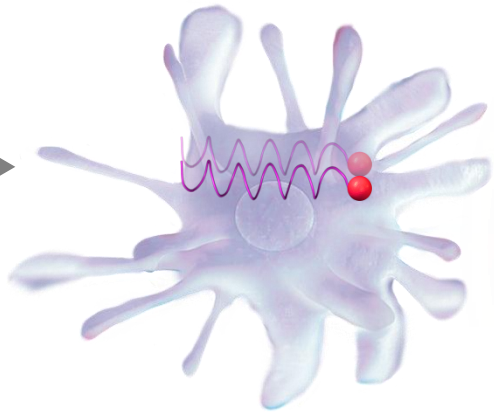
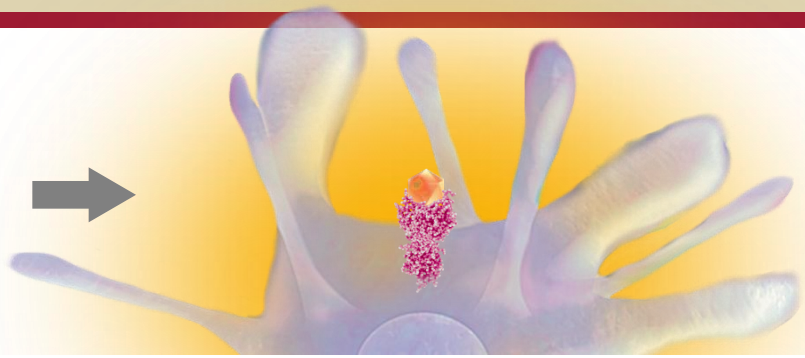


Antigen (PAP-GMCSF) is exposed to an Antigen Presenting Cell (APC)



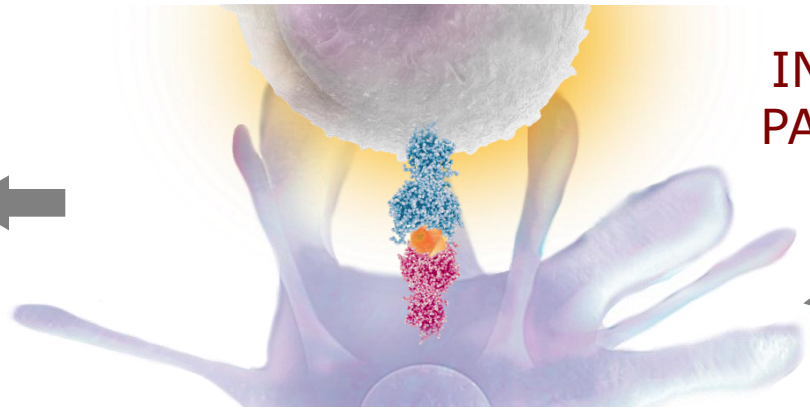
APC takes up the antigen



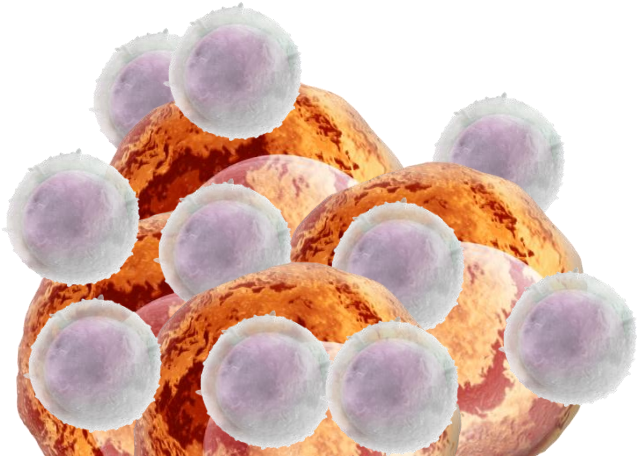
Antigen is processed and presented on surface of the APC

Fully activated, the APC is now sipuleucel-T and is collected

INFUSE PATIENT



sipuleucel-T activates T-cells in the body



T-cells proliferate and attack cancer cells

Sipuleucel-T: Logistics of Therapy

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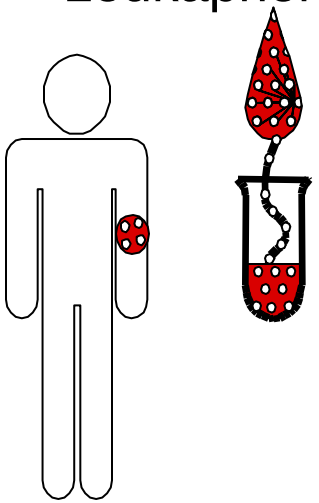
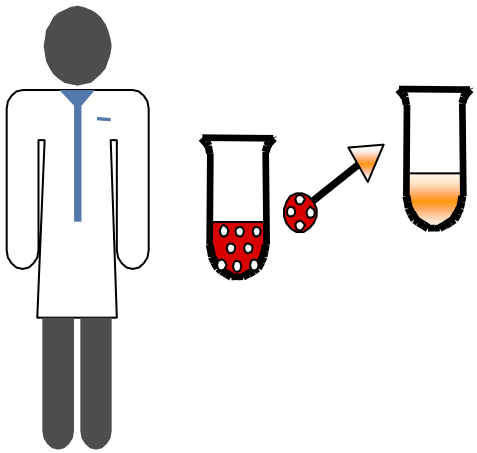
Day 1
Leukapheresis



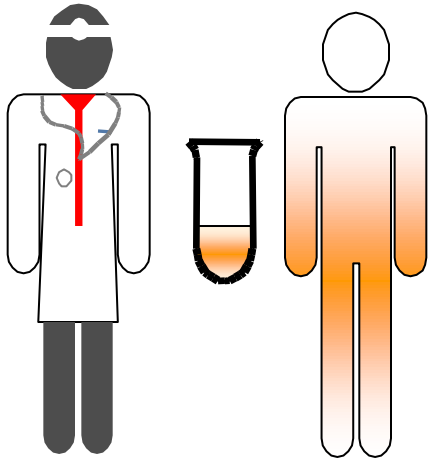
Apheresis Center

Day 2-3
Sipuleucel-T is manufactured



Central Processing

Day 3-4
Patient is infused



Doctor's Office

COMPLETE COURSE OF THERAPY:
Weeks 0, 2, 4

Randomized Phase III Trial of Sip-T in CRPC (D9901)

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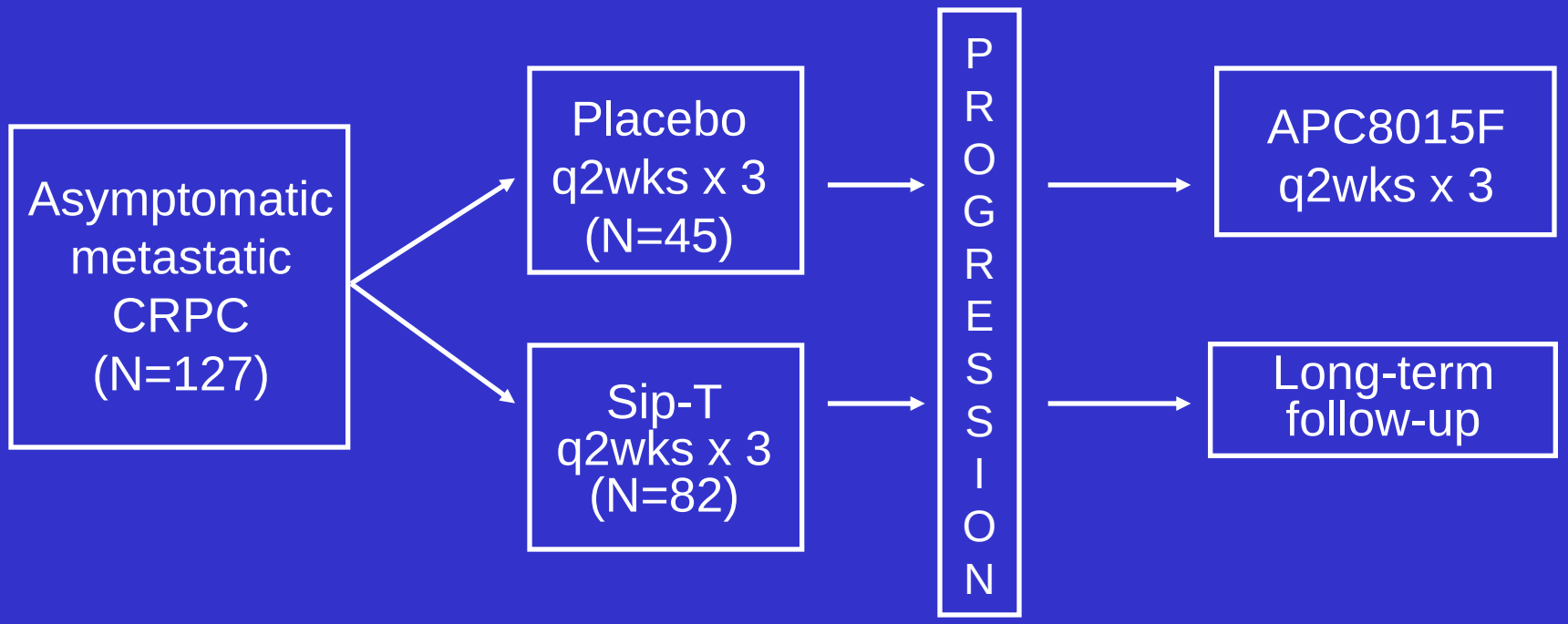

Primary endpoint-TTP

Small et al. JCO 2006

Results: Time to Objective Progression

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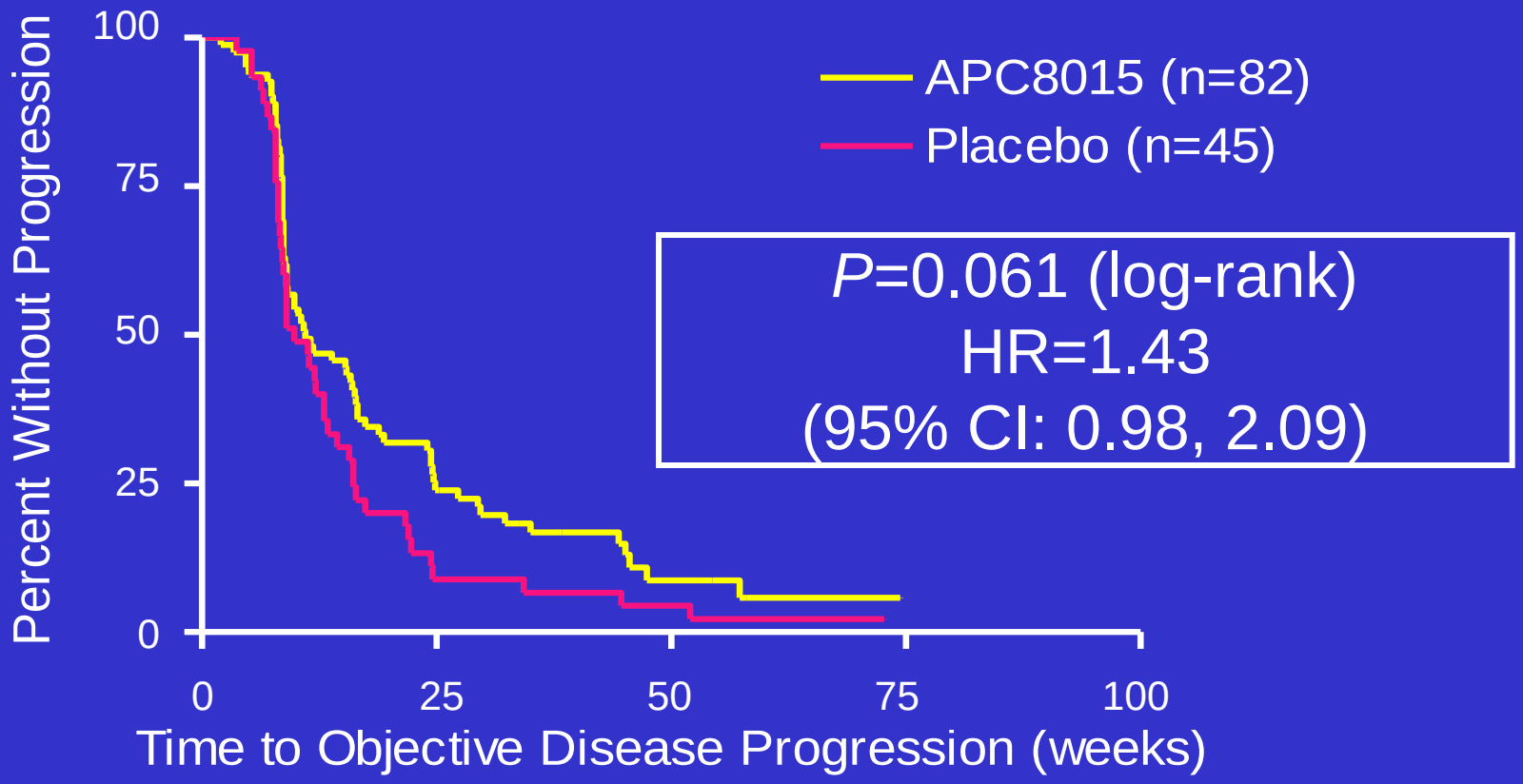

Small et al. JCO 2006

Results: Overall Survival

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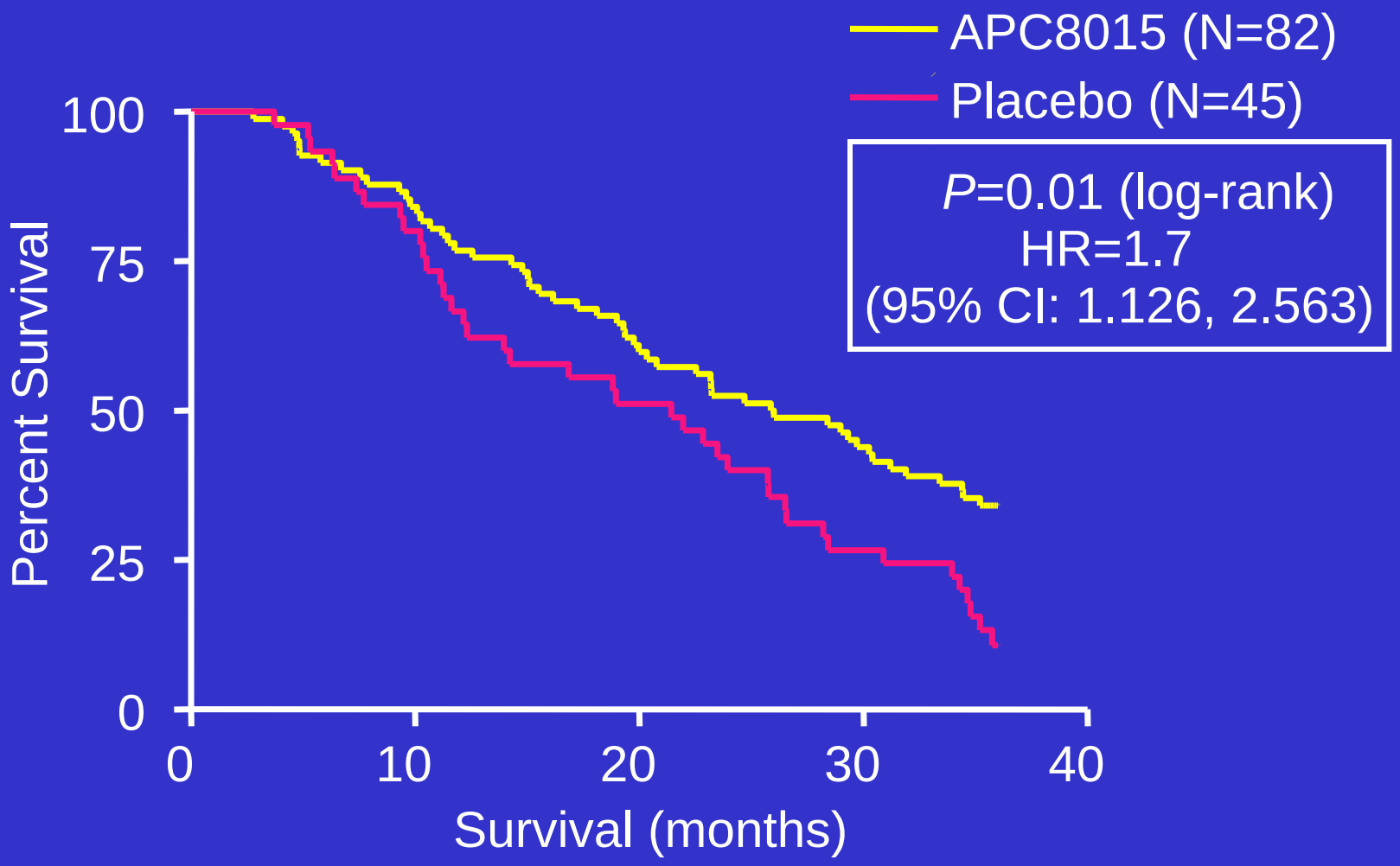

Small et al. JCO 2006

Randomized Phase 3 IMPACT Trial

(IMmunotherapy Prostate AdenoCarcinoma Treatment)

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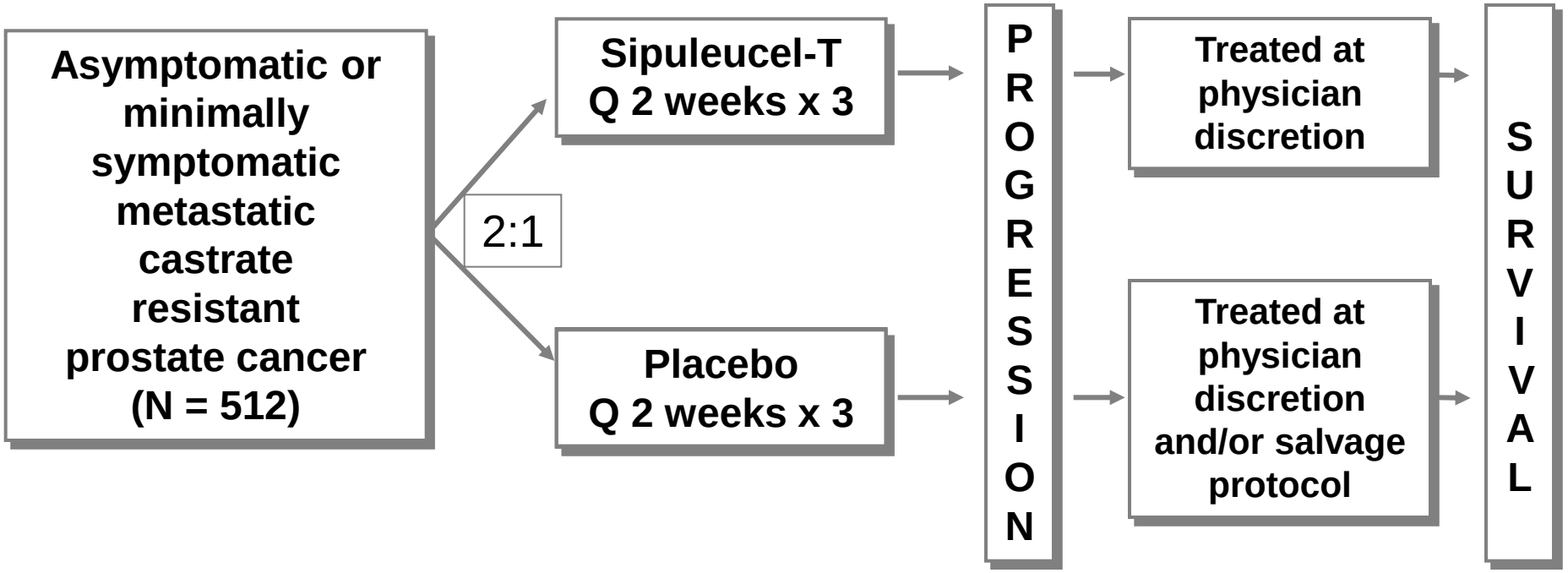

Primary endpoint: Overall survival

Secondary endpoint: Objective disease progression

Kantoff et al NEJM 2010

IMPACT Overall Survival
Final Analysis (349 events)

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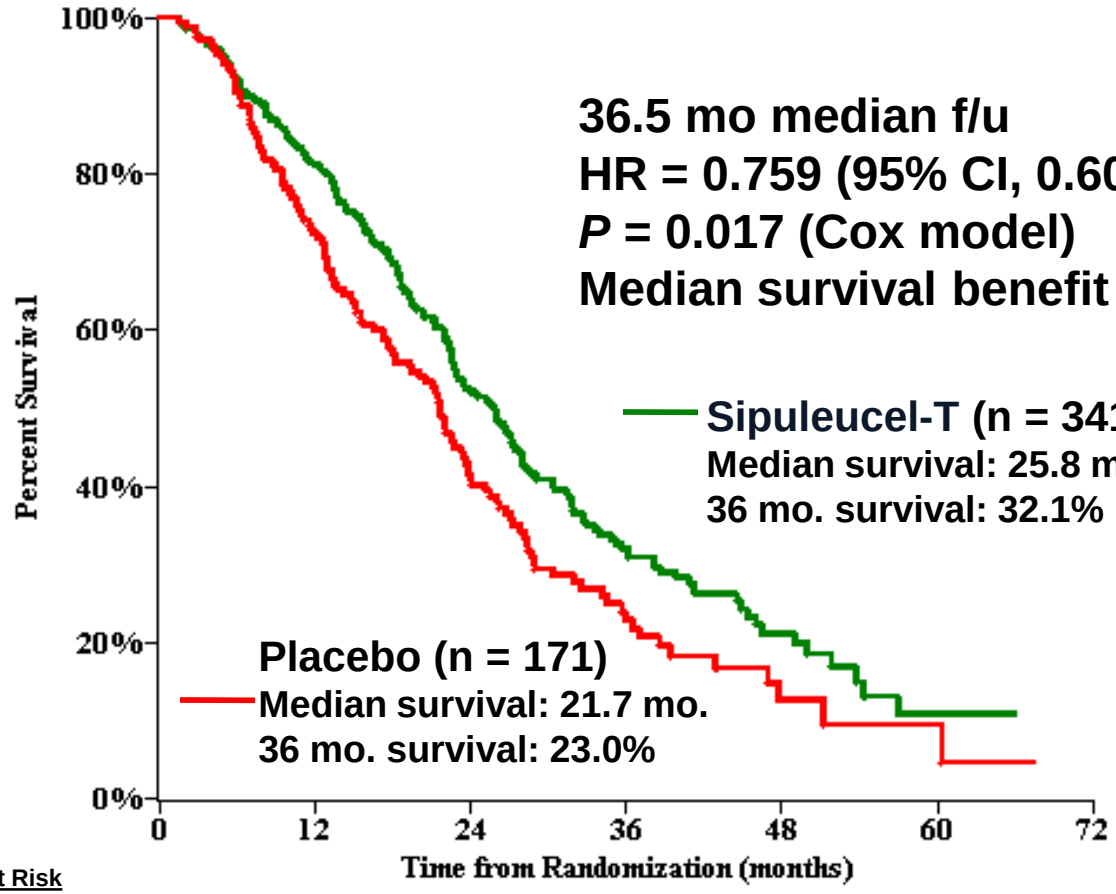

No. at Risk						
Sipuleucel-T	341	274	142	56	18	3
Placebo	171	123	59	22	5	2

Kantoff et al NEJM 2010

Unresolved Issues

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- Adoption has been slower than expected
  - Controversial MOA with few PSA declines
  - Predicting who will benefit
  - Lack of markers of benefit
  - Other agents with of MOAs have been developed
- What is appropriate timing?
  - Most appropriate patient has very early mCRPC asymptomatic and slowly progressing

Time to Disease Related Pain

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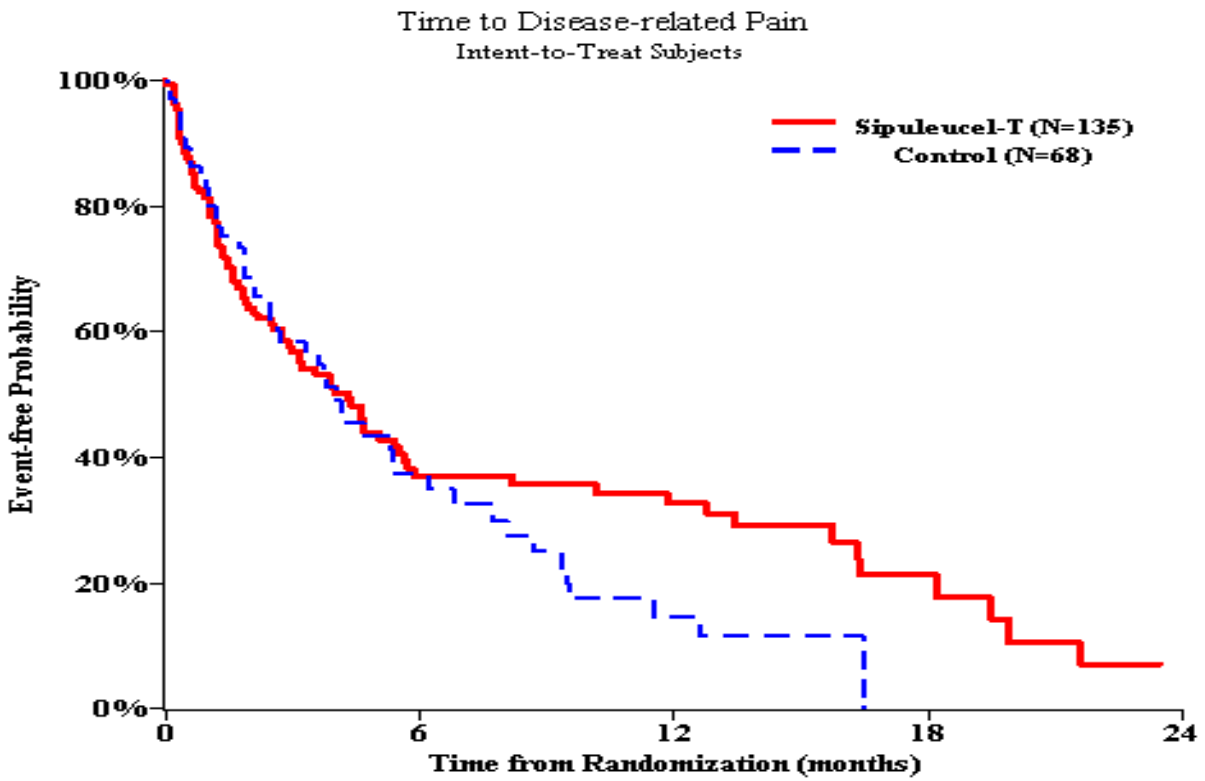

Survival rate estimate (95% CI)				
Sipuleucel-T	37.0% (27.8, 46.3)	32.7% (23.3, 42.1)	21.3% (10.9, 31.6)	7.1% (0.0, 15.8)
Control	37.2% (24.4, 49.9)	14.5% (3.9, 25.2)	0	0

Small et all (submitted)

Hazard ratios for treatments with different MOAs

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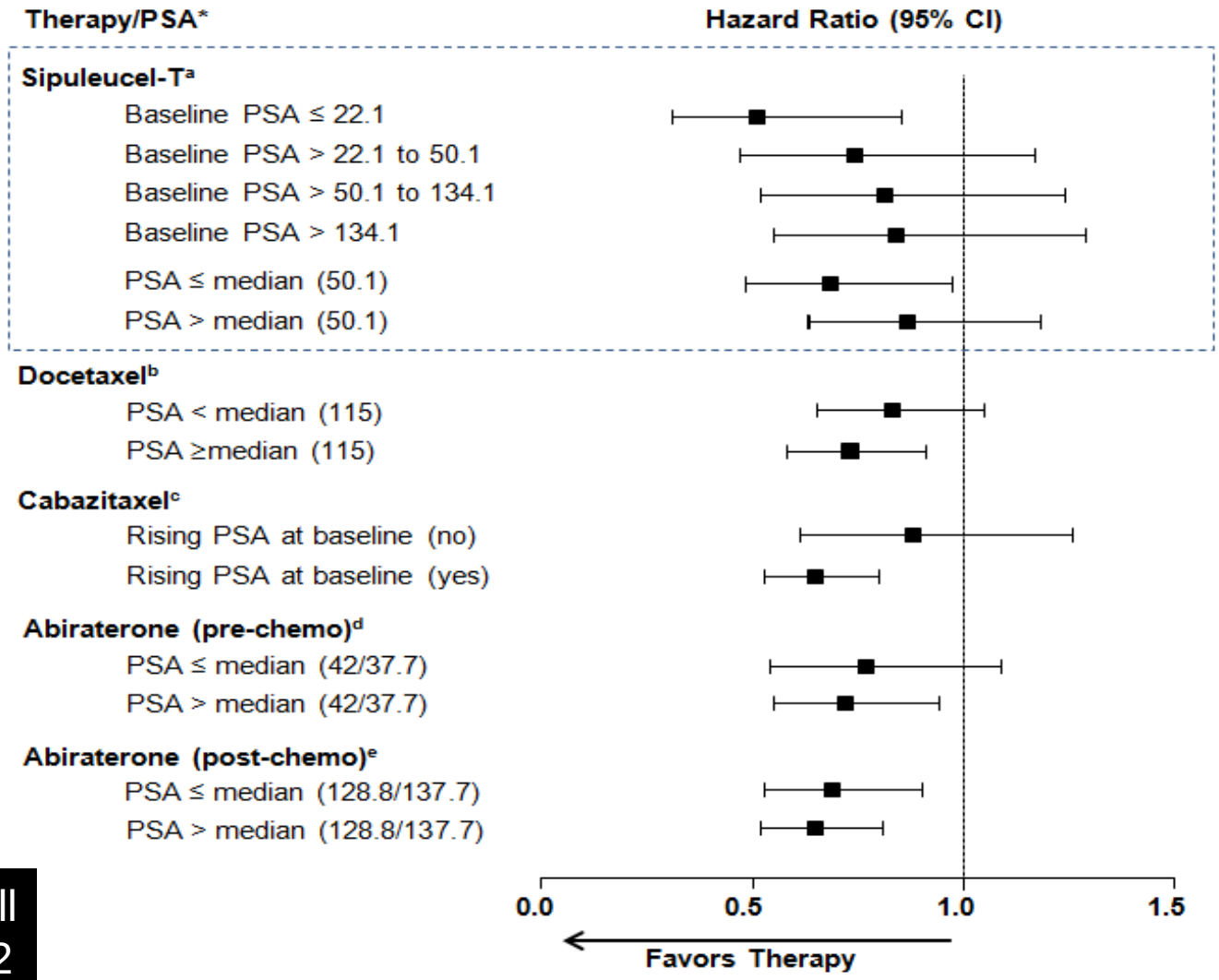

Kantoff et all
ESMO 2012

Does sipuleucel-T activate the immune system?

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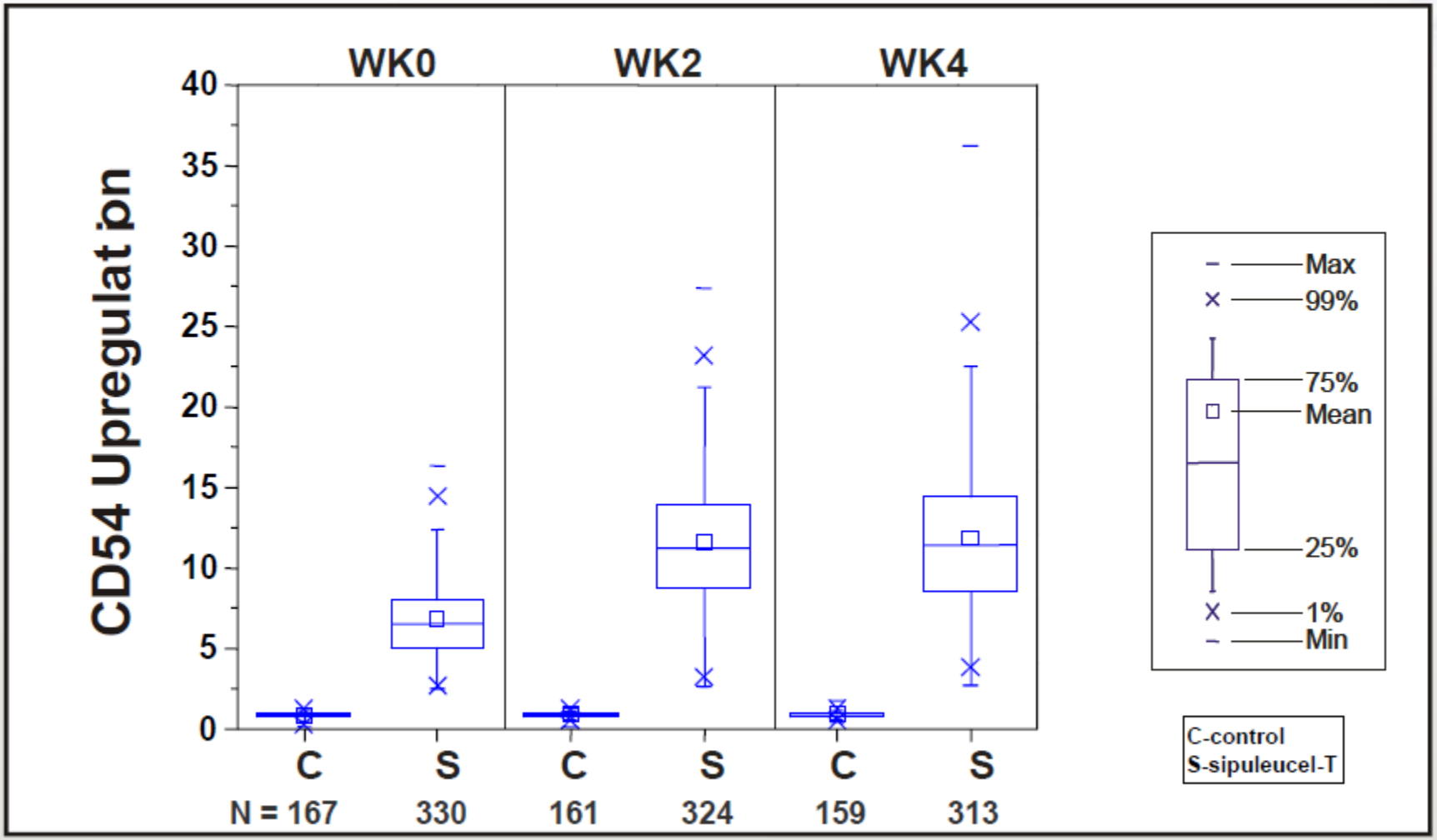
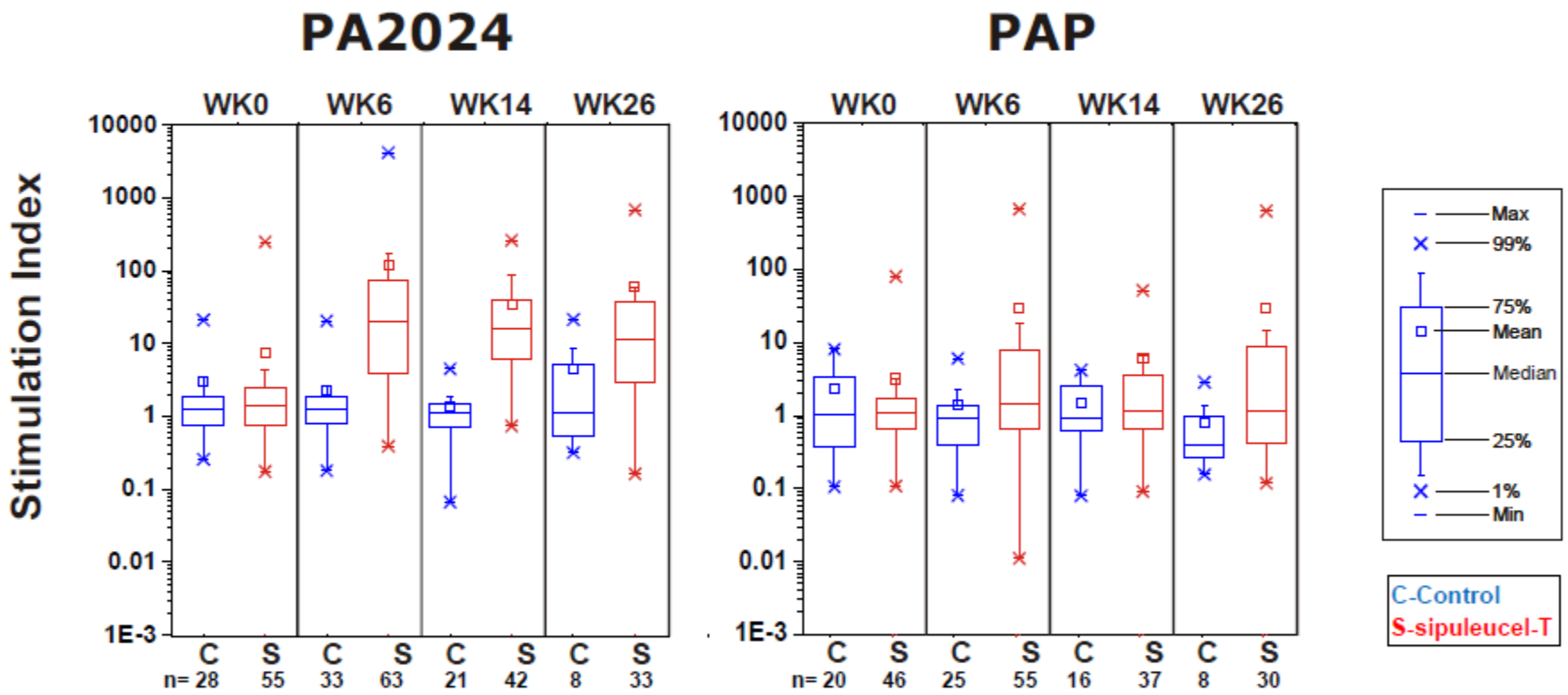
IMPACT Trial: APC Activation Increases after Initial Sipuleucel-T Treatment



Sheikh et al Cancer Immunology and Investigation 2012

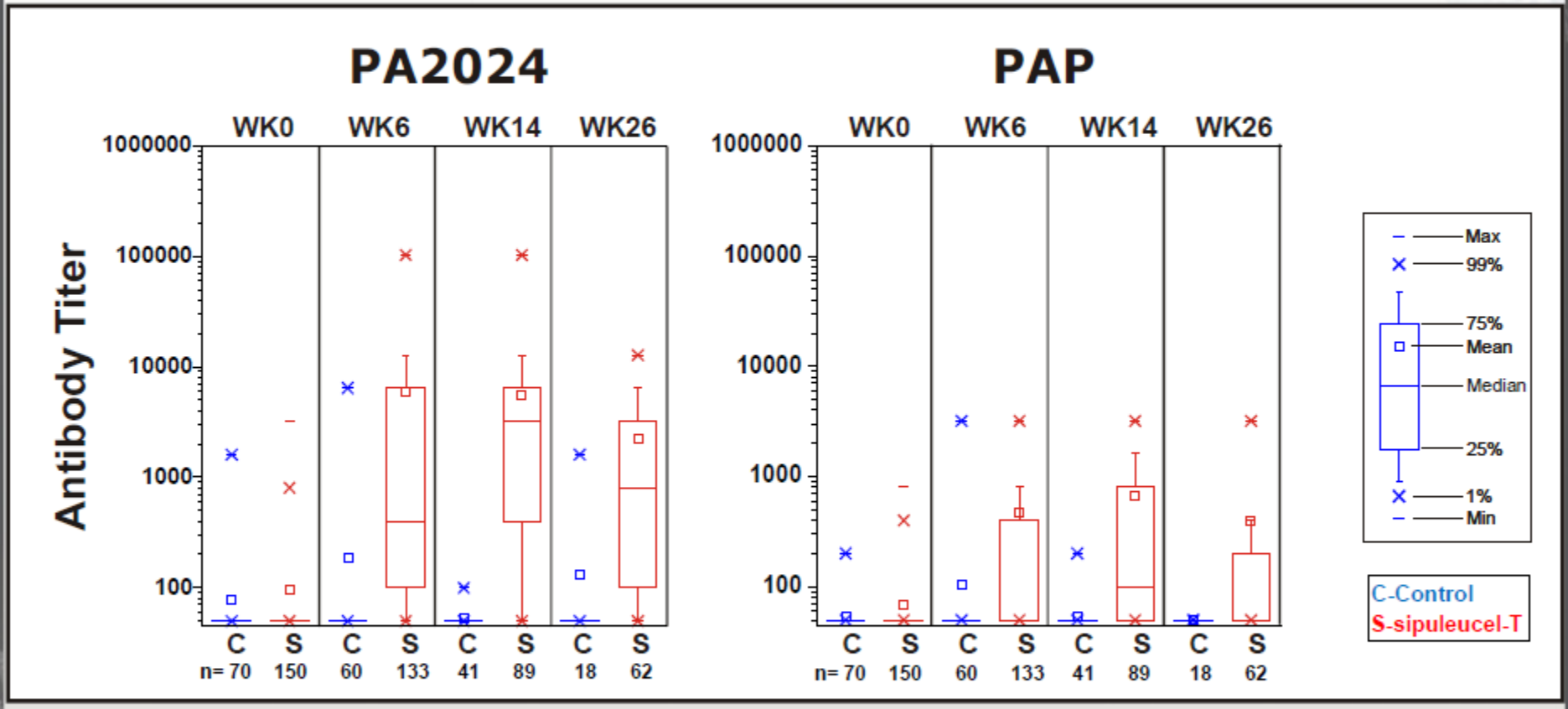
IMPACT Trial: Sipuleucel-T Induces Proliferative Responses to PA2024* and PAP



*PA2024 = PAP-GM-CSF recombinant antigen

Sheikh et al Cancer Immunology and Investigation 2012

IMPACT Trial: Sipuleucel-T Generates Persistent Antigen-specific Humoral Responses



Sheikh et al Cancer Immunology and Investigation 2012

PROSTVAC VF-Tricom

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Development of PROSTVAC VF-Tricom

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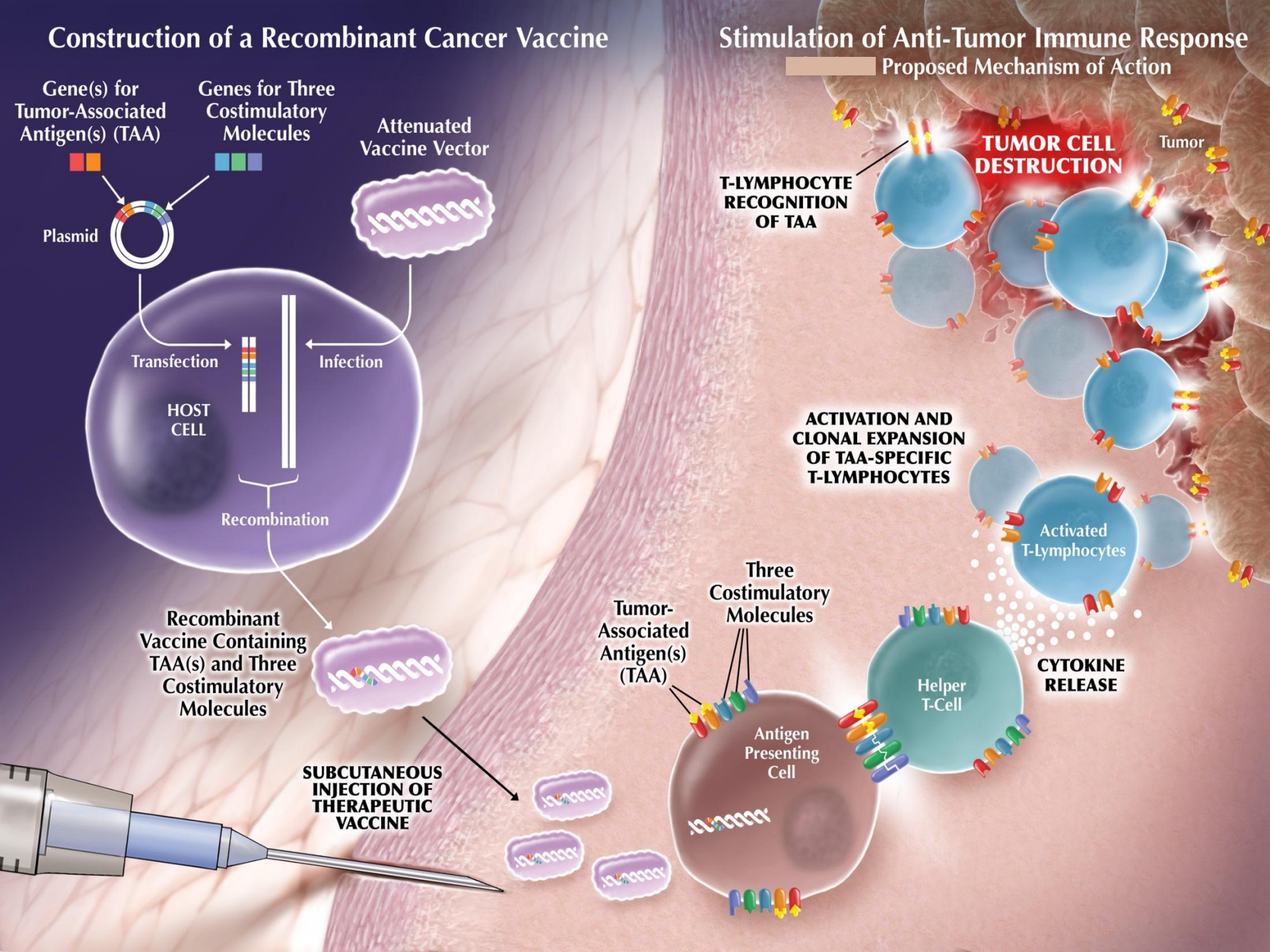
- Vaccinia
  - Potent immunological priming agent
- Fowlpox
  - Minimally/non-cross-reactive with vaccinia
  - Enables boosting
- Slightly altered PSA transgene
  - Modified HLA-A2 epitope. Increased HLA-A2 binding and immunogenicity.
- Tricom
  - Lymphocyte function-associated antigen LFA-3 (CD58)
  - Intercellular adhesion molecule ICAM-1 (CD54)
  - Costimulatory molecule for the T-cell receptor B7.1 (CD80)


Construction of a Recombinant Cancer Vaccine
Gene(s) for Tumor-Associated Antigen(s) (TAA)
Genes for Three Costimulatory Molecules
Attenuated Vaccine Vector
Plasmid
Transfection
Infection
HOST CELL
Recombination
Recombinant Vaccine Containing TAA(s) and Three Costimulatory Molecules
SUBCUTANEOUS INJECTION OF THERAPEUTIC VACCINE
Stimulation of Anti-Tumor Immune Response
Proposed Mechanism of Action
T-LYMPHOCYTE RECOGNITION OF TAA
TUMOR CELL DESTRUCTION
Tumor
ACTIVATION AND CLONAL EXPANSION OF TAA-SPECIFIC T-LYMPHOCYTES
Activated T-Lymphocytes
CYTOKINE RELEASE
Tumor-Associated Antigen(s) (TAA)
Three Costimulatory Molecules
Antigen Presenting Cell
Helper T-Cell

Randomized Phase II Study

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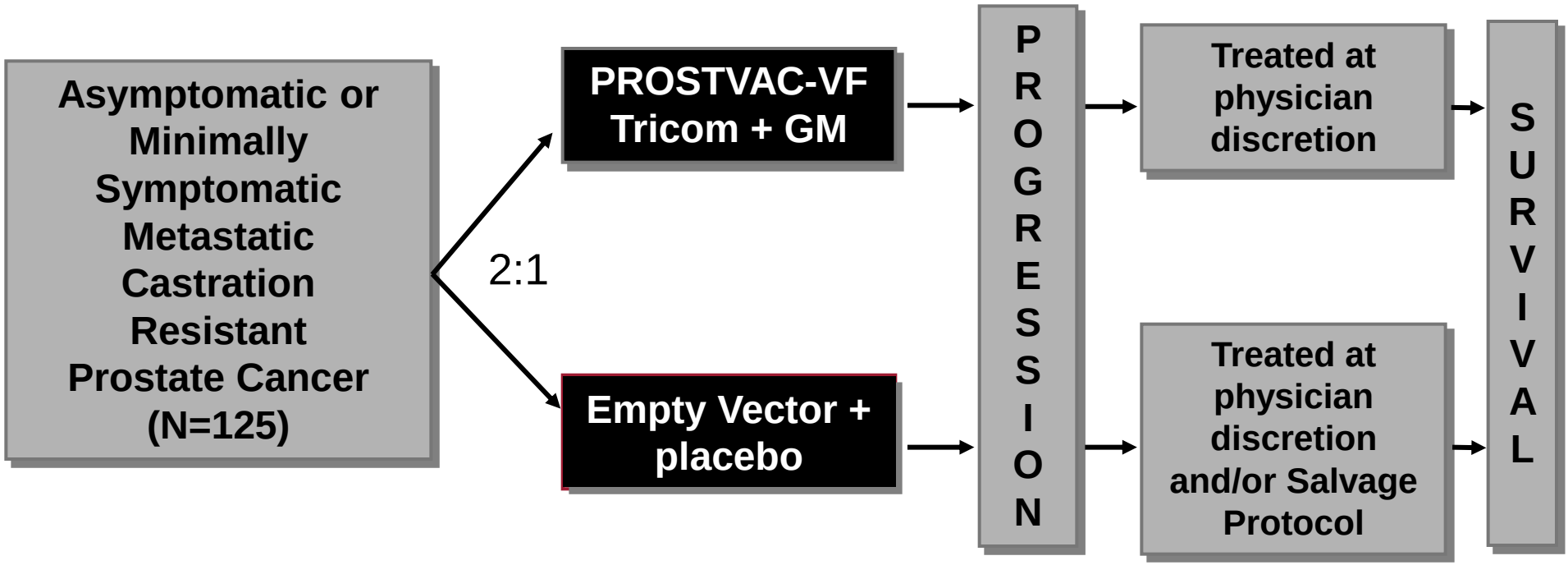

Primary endpoint: Progression Free Survival

Secondary endpoint: Overall Survival

Kantoff et al. J Clin Oncol 2010

Progression Free Survival

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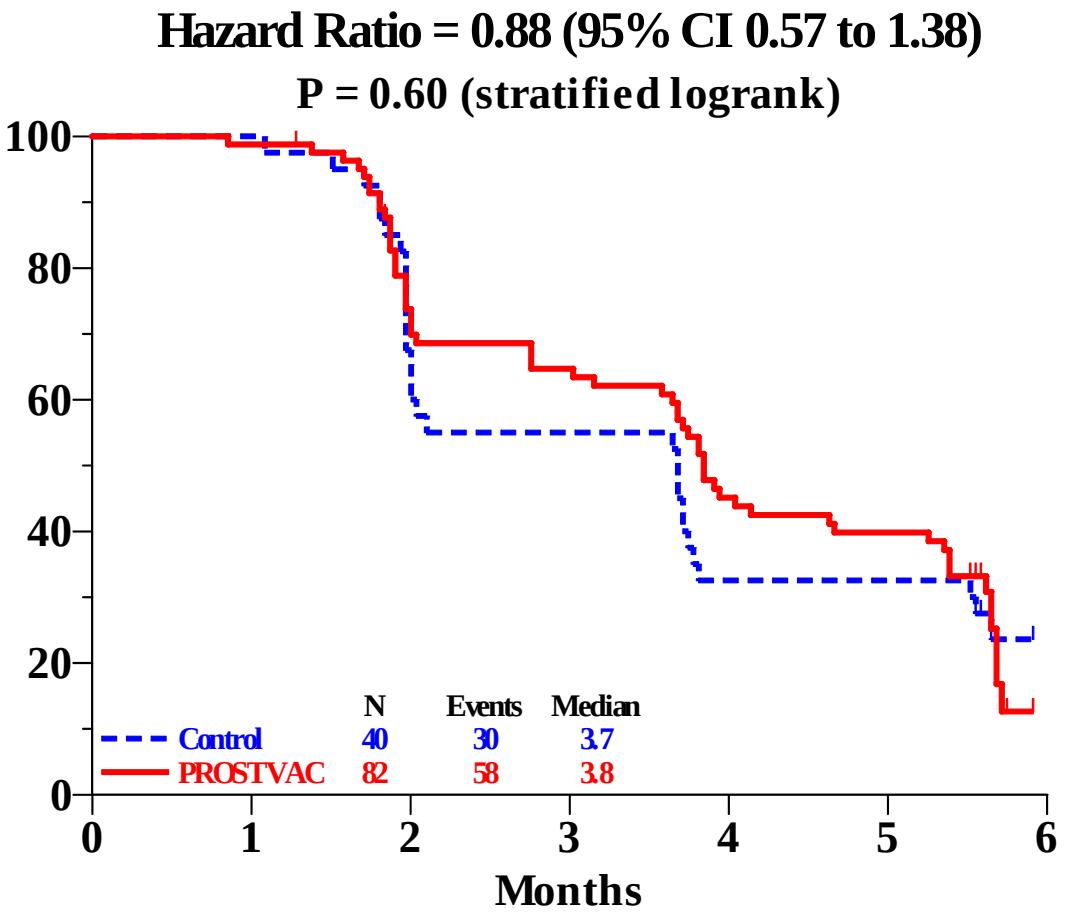

Kantoff et al. J Clin Oncol 2010

Overall Survival

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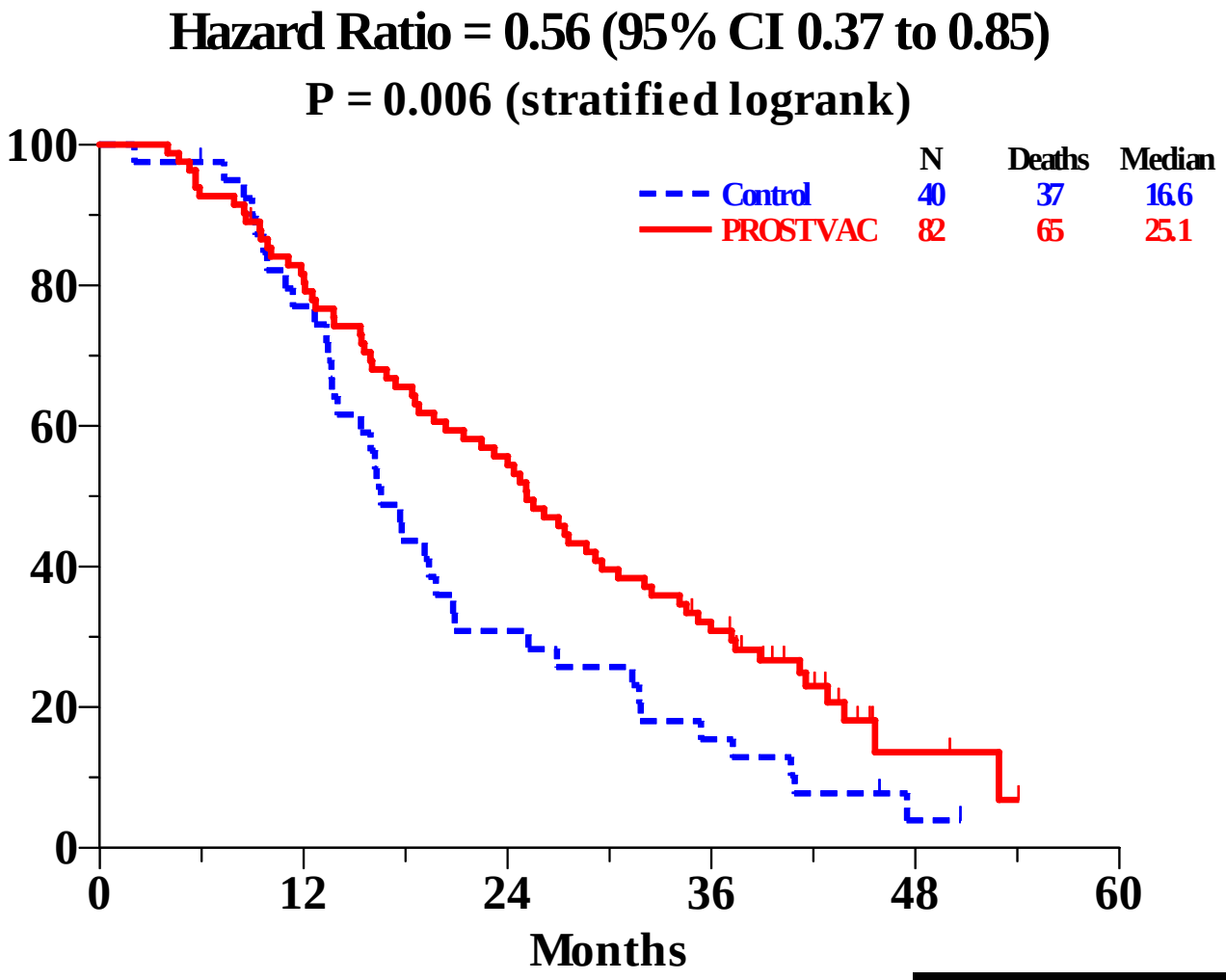

Kantoff et al. J Clin Oncol 2010

PROSPECT Trial-Phase III Global Trial

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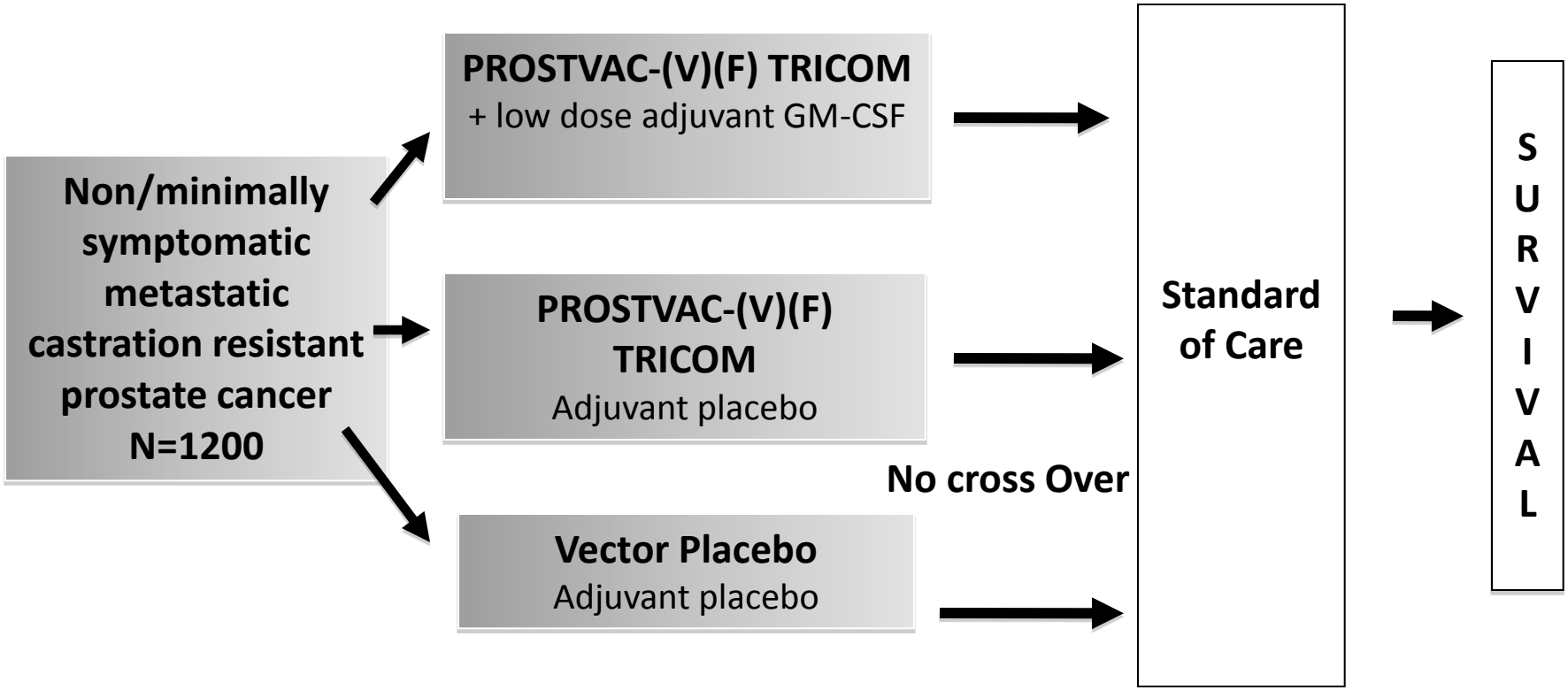

Gulley J and Kantoff P

Ipilimumab

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Phase I/II CRPC Treatment Schema

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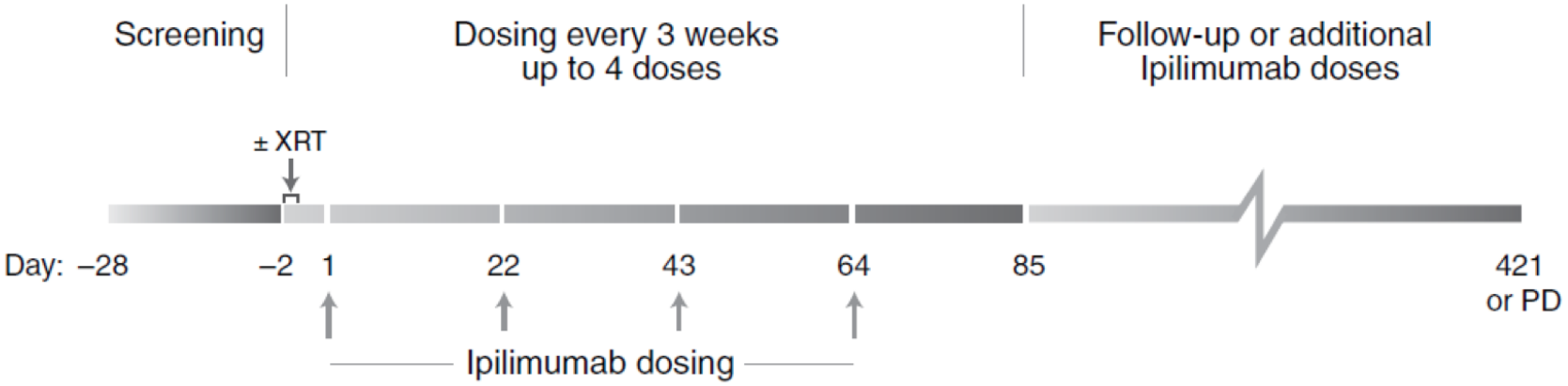

Design:

- Phase 1 – Dose escalation: 3, 5 or 10 mg/kg Ipi, then 3 or 10 mg/kg Ipi ± XRT (single dose of 8 Gy/lesion, up to 3 lesions per patient)
- Phase 2 – Cohort expansion: 10 mg/kg ± XRT cohorts

Endpoints:

- Safety
- PSA response at Day 85, overall PSA response, and tumor response by RECIST

Response assessments:

- PSA: Days 22, 43, 64, 85, then monthly
- Tumor: Day 85, then every 3 months

Slovin et al submitted 2011

PSA Waterfall Plot on Day 85

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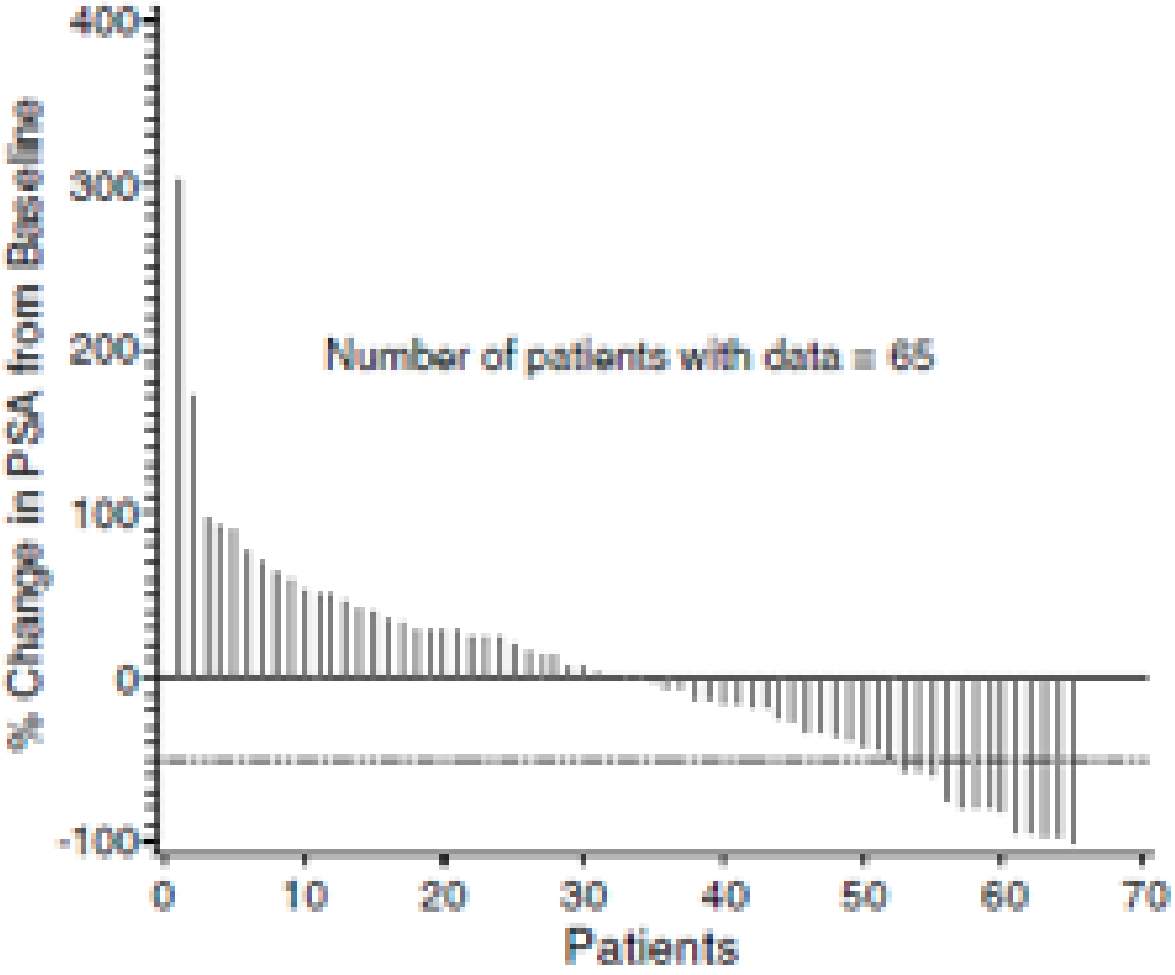

Slovin et al submitted 2011

Ipilimumab Randomized Phase II in advanced CaP

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- 108 patients with advanced CaP were randomized to ADT alone (54 patients) or to ADT plus 3 mg/kg ipilimumab
- Primary endpoints were safety and efficacy as measured by PSA and clinical response
- No baseline differences between the treatment groups.
- Percent decline in testosterone level was > 97% in both arms
- Patients treated with ipilimumab + ADT were more likely to have an undetectable PSA by 3 months (55% vs. 38%)

Tollefson et al. 2010 GU Cancers Symp

Ipilimumab Phase III studies in CRPC

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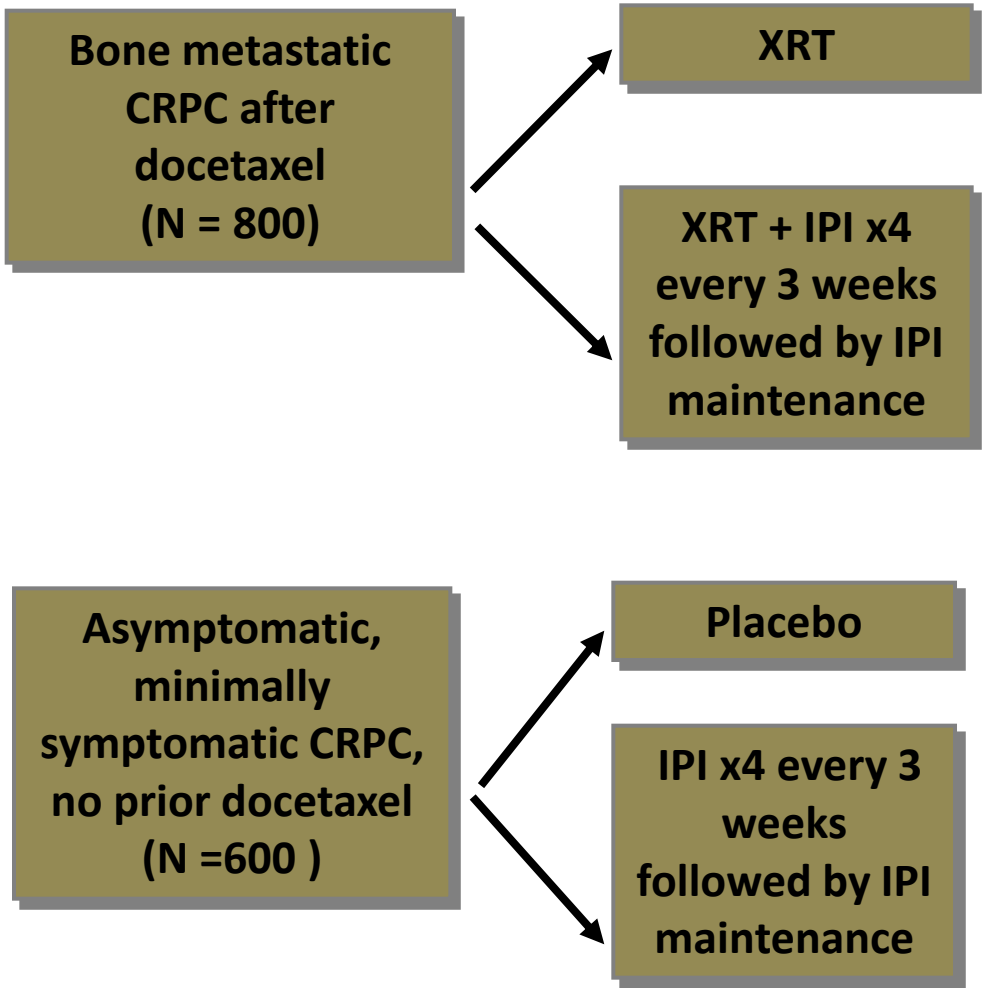

OS

Conclusions on Immunotherapy Approaches

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- Proof of concept that immunotherapy provides clinical benefit in prostate cancer
  - Sipuleucel-T in prostate cancer
- Potential for further advances in prostate cancer in next few years
  - PROSTVAC VF-Tricom
  - Ipilimumab
  - Combination therapies