New targets and drugs in prostate cancer

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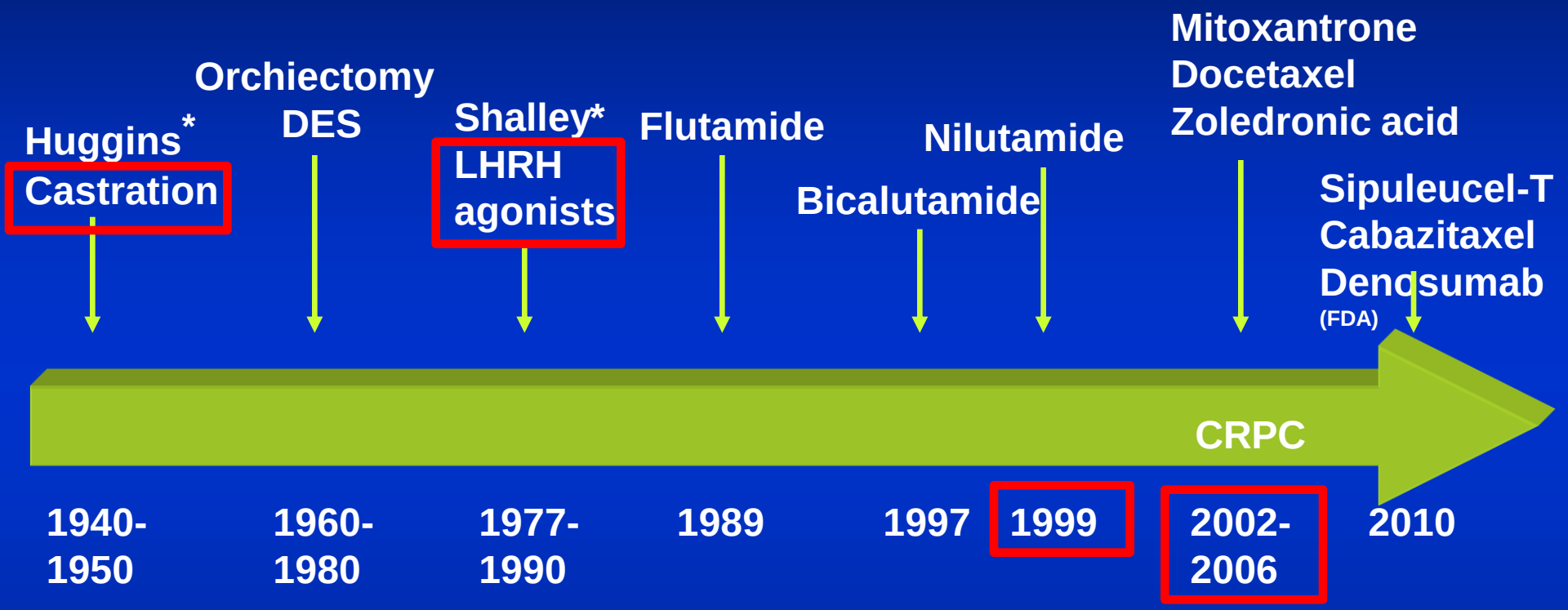
Castration Resistant Prostate Cancer (CRPC)

- Has our perception of CRPC changed with the advent of more effective therapies?
- How has our increasing knowledge about the importance of the androgen receptor (AR) in the progression of prostate cancer helped us?
- Have we commuted a death sentence into a more chronic disease that patients can learn to live with?

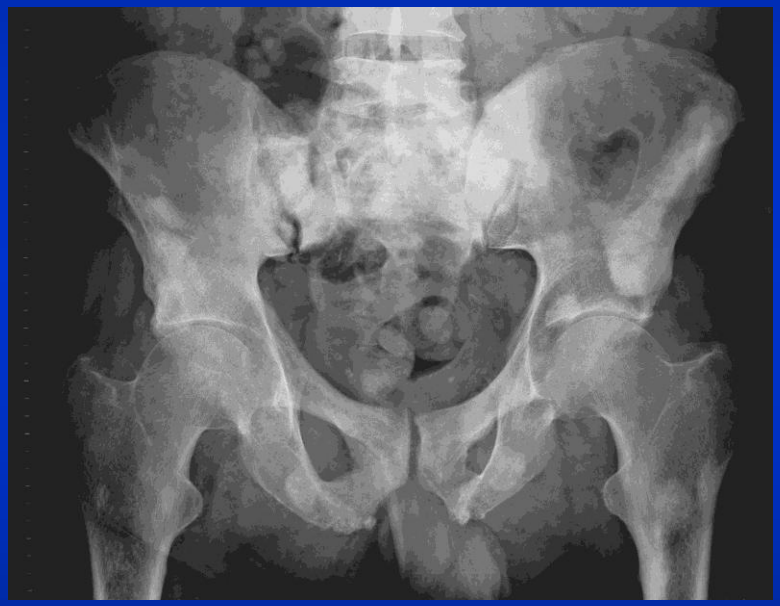
Time-line for Prostate Cancer Therapeutics

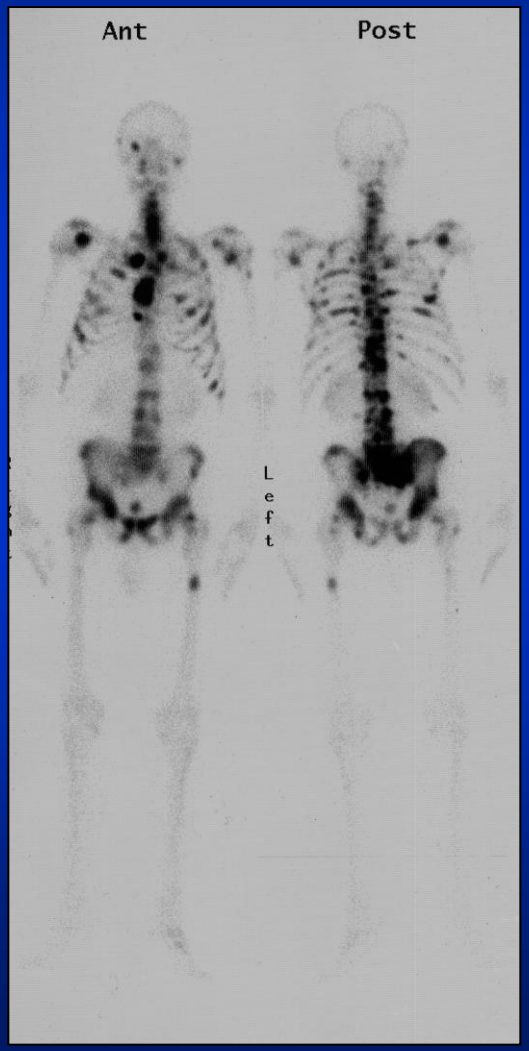


* Nobel Prize in 1966

Challenges to developing new drugs for advanced prostate cancer

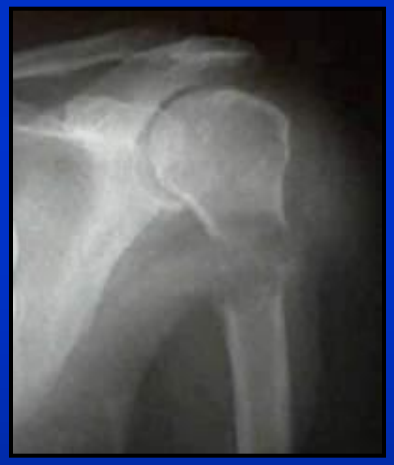
Bone metastases are difficult to evaluate





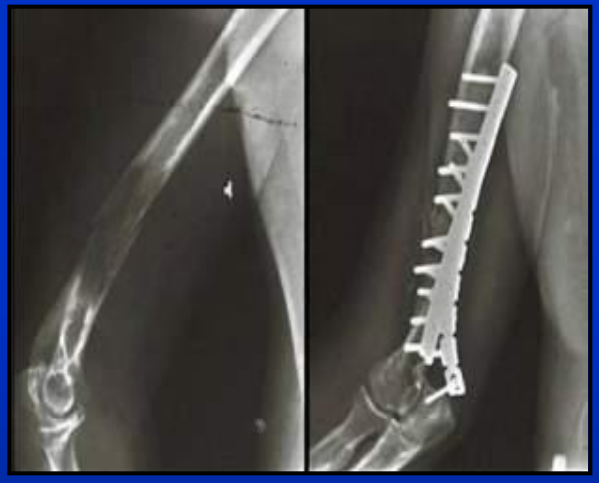
Skeletal-related events (SREs)

Pathologic Fracture

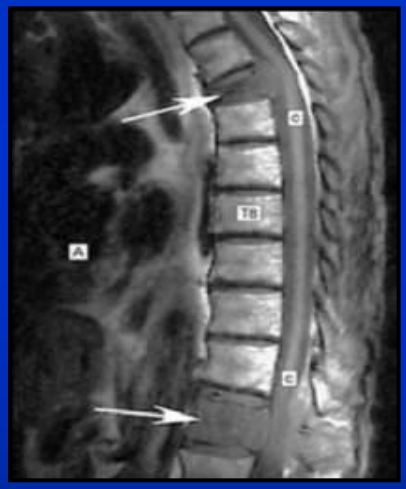


Radiotherapy to Bone

Surgery to Bone



Spinal Cord Compression



Challenges to developing new drugs for advanced prostate cancer

- Regulatory authorities: survival is the only accepted measure of outcome (no surrogate endpoints)
- Castration Resistant rather than Hormone Refractory
- Inter-patient molecular heterogeneity
  - ETS gene rearrangements (40-70%)
  - PTEN loss cancers (> 50%)
  - RAF rearrangements (~5%)
  - BRCA carrier cancers (<1%)

Most prostate trials have not selected patients on biology
Reason for late Phase III trial failure!

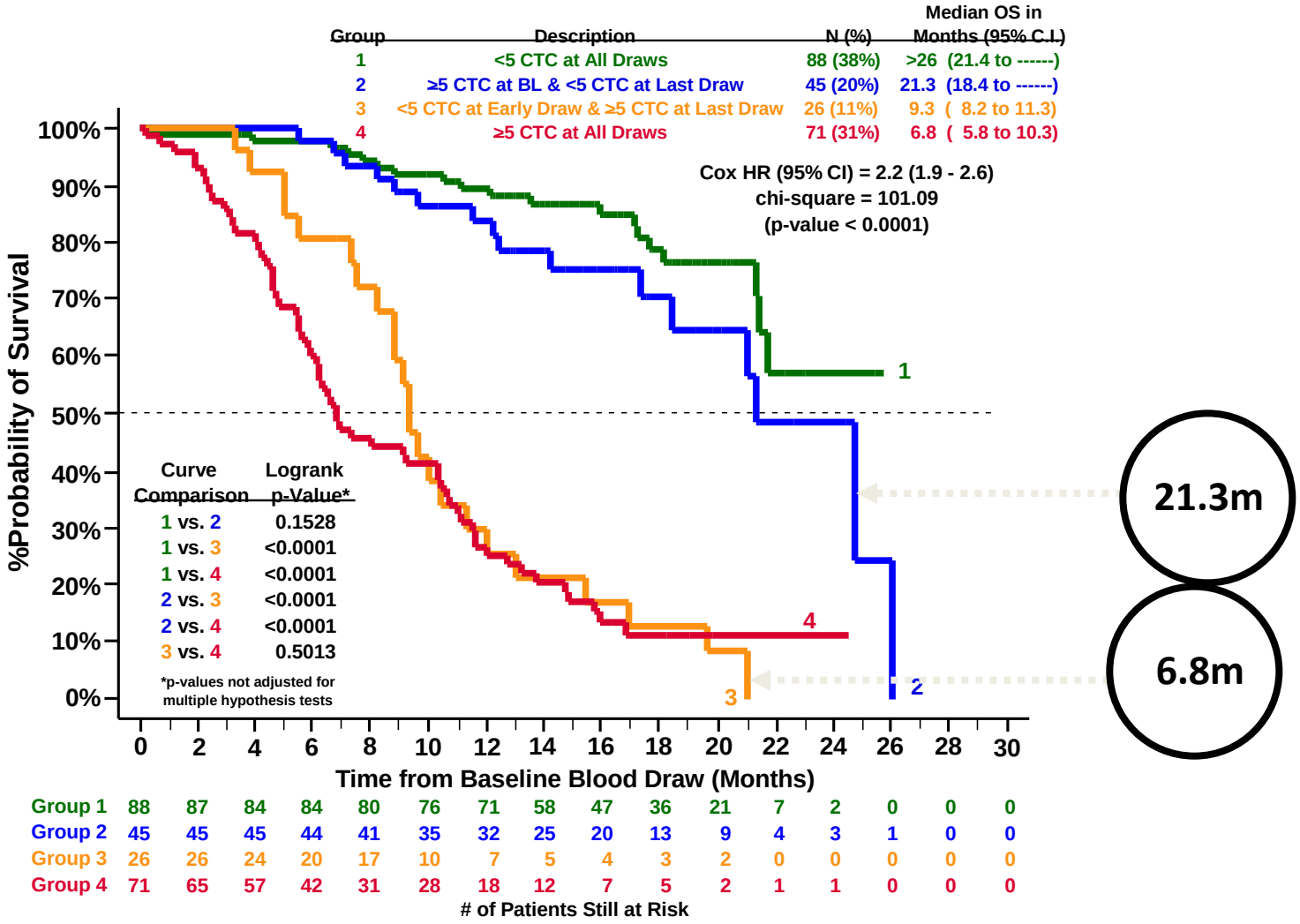
Courtesy of J. de Bono from Attard et al, Cancer Cell. 2009 Dec 8;16(6):458-62

Challenges to developing new drugs for advanced prostate cancer

- PCWG2 (Prostate Cancer Clinical Trials Working Group)
- What surrogate markers should we be measuring in the laboratory?
  - PSA
  - Circulating tumor cells

Scher HI, et al. J Clin Oncol 2008;26:1148−59

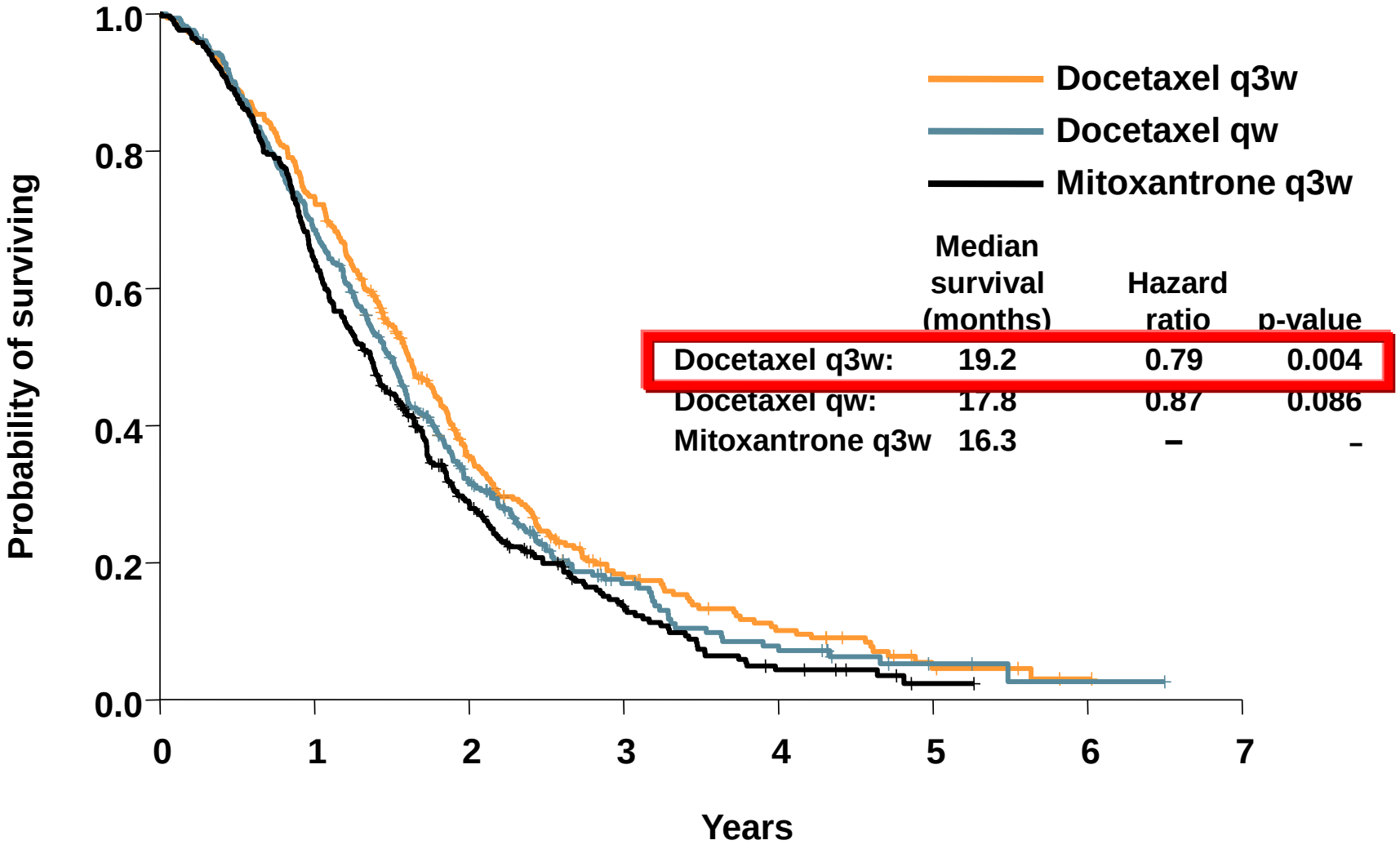
Fall in CTC count (>5 to <5) associates with improved OS



Courtesy of de Bono JS et al, Clin Cancer Res. 2008 Oct 1;14(19):6302-9

Chemotherapy

TAX 327: Updated survival analysis



	Median survival (months)	Hazard ratio	p-value
Docetaxel q3w:	19.2	0.79	0.004
Docetaxel qw:	17.8	0.87	0.086
Mitoxantrone q3w	16.3	–	–

Berthold DR, et al. J Clin Oncol 2008;26:242–245
Tannock I, N Engl J Med, 2004 Oct 7;351(15):1502-12

Metastatic CRPC 1st - line therapy Current standard of care

- Docetaxel is the standard of care in 1st-line mCRPC[1,2]
- All patients eventually progress on docetaxel-based chemotherapy
- Approximately 50% receive 2nd-line chemotherapy[3,4]
- Until recently, there has been no approved second-line therapy

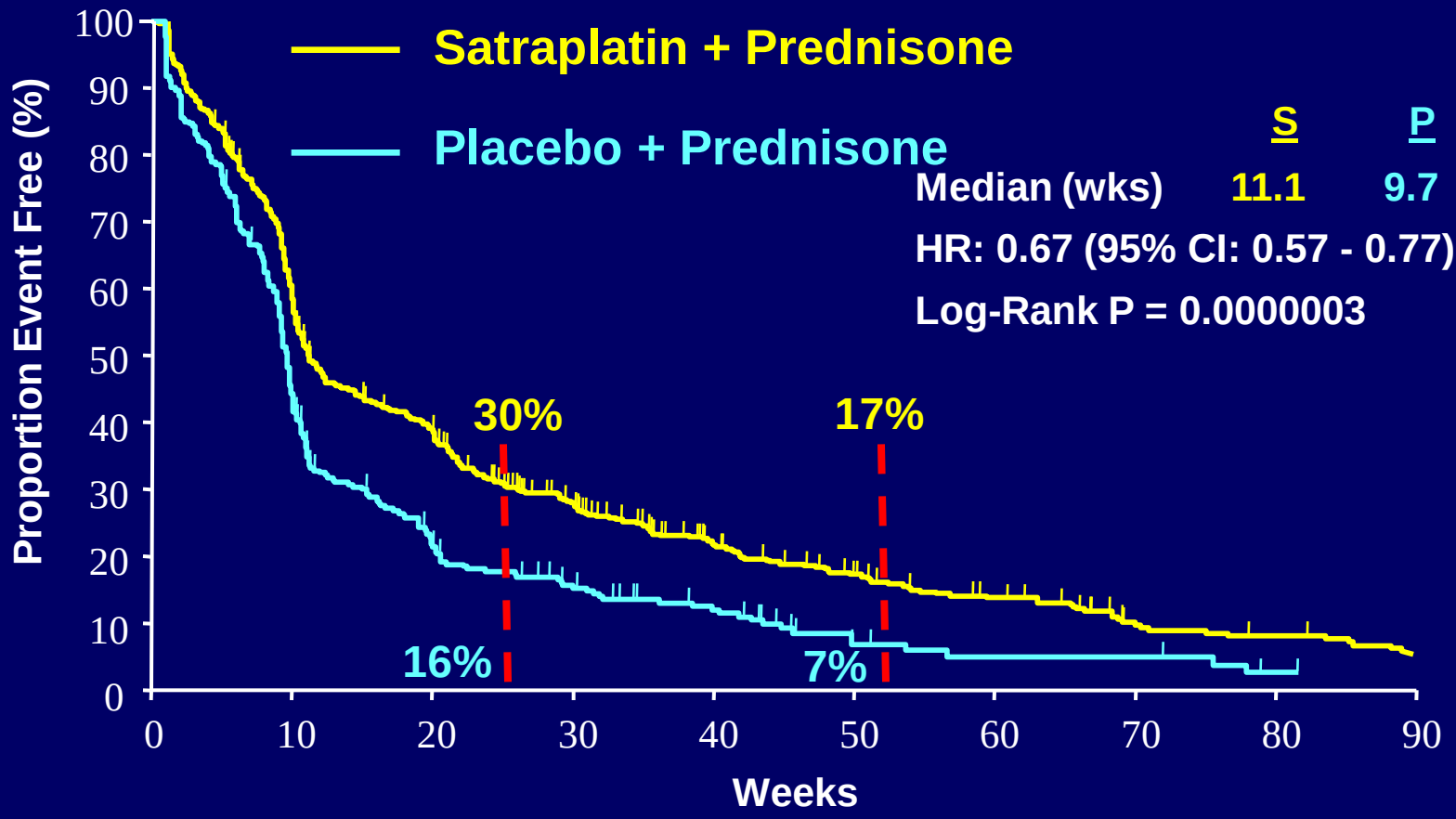
[1]Tannock IF, et al. N Engl J Med 2004;351:1502–12, [2]Berthold DR, et al. J Clin Oncol 2008;26:242–5
[3]Garmey EG, et al. Clin Adv Hematol Oncol 2008;6:118–22, 127–32, [4]Eymard JC, et al. BJU Int Mar 9, 2010 [Epub ahead of print]

Overall Survival with 2nd line chemotherapy for mCRPC

Treatment	Setting	Patients (N)	Overall survival
SPARC Satraplatin + prednisone vs Placebo + prednisone	Progression after 1 prior chemotherapy regimen	950	Median OS: 14.3 months vs 14.3 months HR = 0.98 p = 0.7999
TROPIC Cabazitaxel + prednisone vs Mitoxantrone + prednisone	Prior Docetaxel	755	Median OS: 15.1 months vs 12.7 months HR = 0.70 p<.0001

Sternberg CN, et al. J Clin Oncol 2009;27:5431−8
de Bono J, et al. Lancet. 2010 Oct 2;376(9747):1147-54

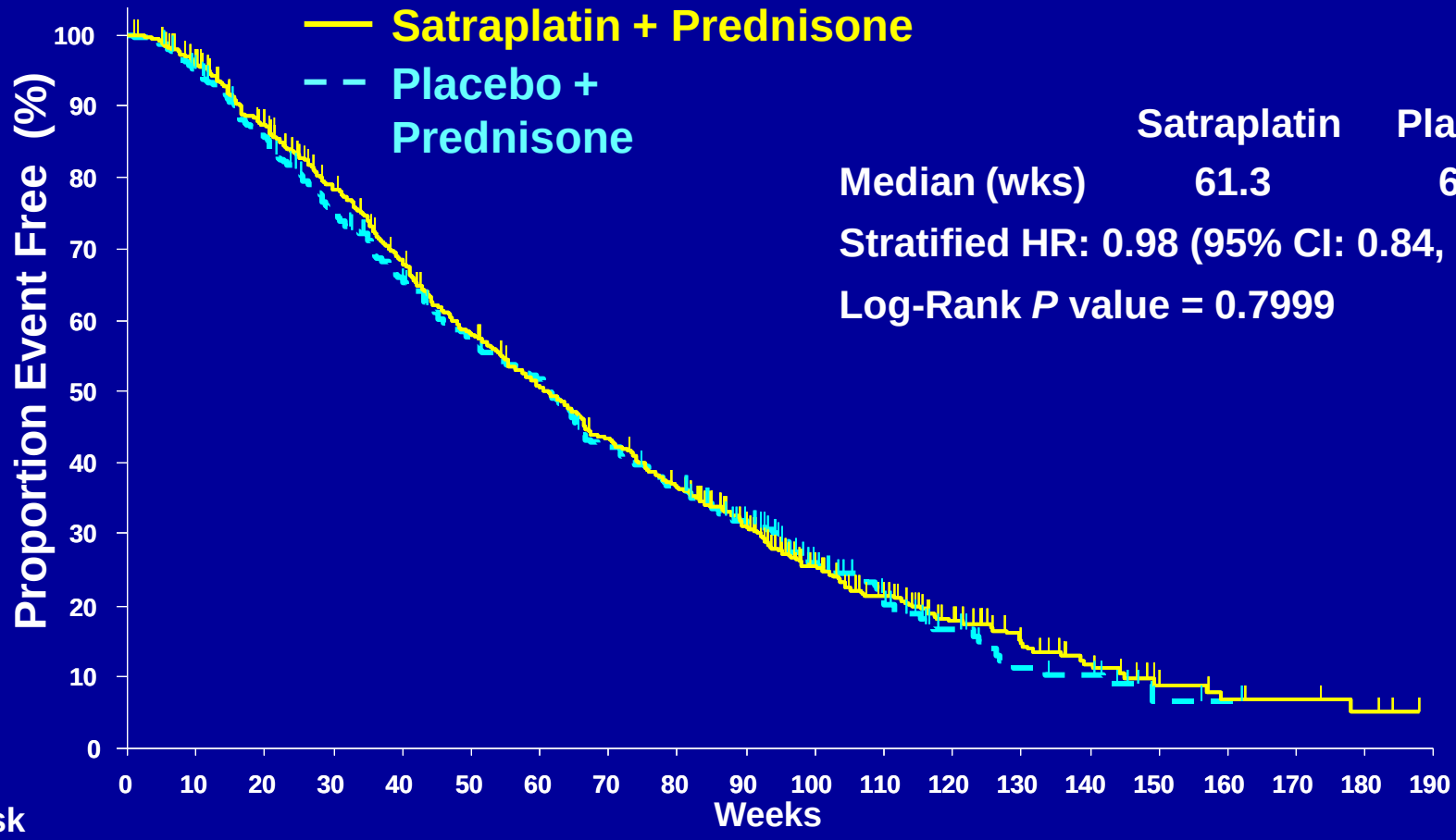
SPARC: Progression Free Survival ITT Population (per IRC)



33% Improvement in PFS

Sternberg CN, J Clin Oncol. 2009 Nov 10;27(32):5431-8

SPARC Overall Survival



	Satraplatin	Placebo
Median (wks)	61.3	61.4

Stratified HR: 0.98 (95% CI: 0.84, 1.15)

Log-Rank *P* value = 0.7999

At Risk										
Satraplatin	635	528	398	288	208	103	50	20	6	3
Placebo	315	262	194	150	105	53	21	10	1	0

Sternberg CN, J Clin Oncol. 2009 Nov 10;27(32):5431-8

Overall Survival with 2nd line chemotherapy for mCRPC

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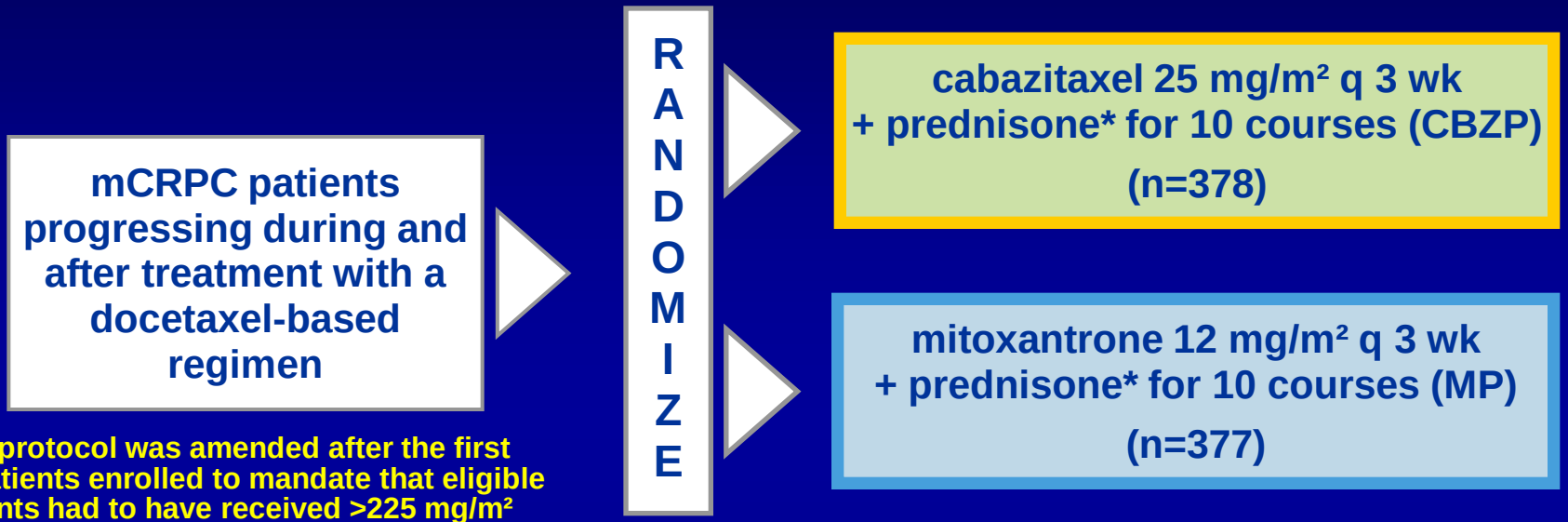
Sternberg CN, et al. J Clin Oncol 2009;27:5431−8
de Bono J, et al. Lancet. 2010 Oct 2;376(9747):1147-54

TROPIC: Randomized Phase III Trial (n=755)



***The protocol was amended after the first 59 patients enrolled to mandate that eligible patients had to have received >225 mg/m² of docetaxel**

*Oral prednisone/prednisolone: 10 mg daily

Stratification factors

- ECOG PS (0, 1 vs 2)
- Measurable vs non-measurable disease

Premedication

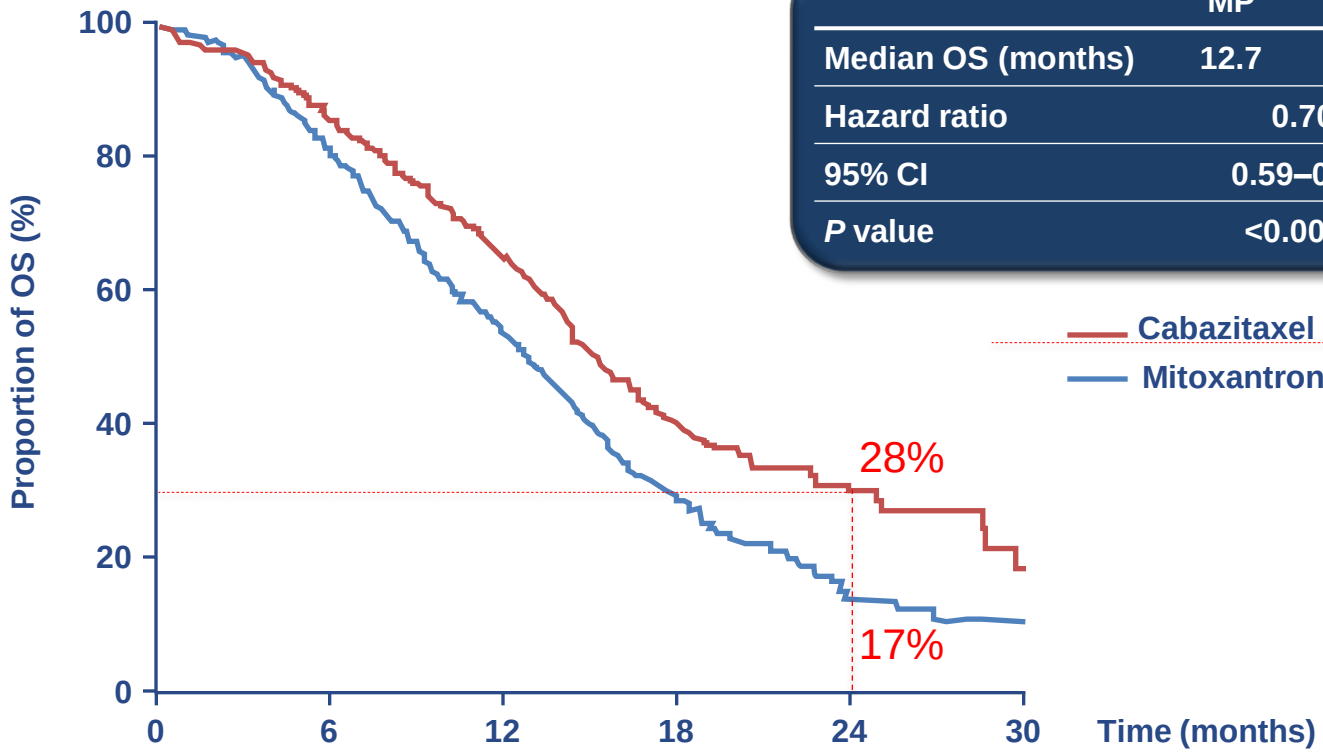
- cabazitaxel group: antihistamine, steroid, and H_2 antagonist Antiemetic prophylaxis as required

Primary objective: OS; 90% power to detect a HR of 0.75
Secondary objective: PFS

de Bono J, et al. Lancet. 2010 Oct 2;376(9747):1147-54

TROPIC – Overall survival (primary end point)

	MP	CBZP
Median OS (months)	12.7	15.1
Hazard ratio	0.70	
95% CI	0.59–0.83	
P value	<0.0001	



Number at risk							
	MP	377	300	188	67	11	1
	CBZP	378	321	231	90	28	4

30% reduction in the risk of death

de Bono J, et al. Lancet. 2010 Oct 2;376(9747):1147-54

Targeting the Androgen Receptor (AR)

Direct Measurement of Tissue Androgens Confirm The Presence of Sufficient Levels To Activate the Receptor

[CANCER RESEARCH 64, 765–771, January 15, 2004]

The Adrenal Androgen Androstenediol Is Present in Prostate Cancer Tissue after Androgen Deprivation Therapy and Activates Mutated Androgen Receptor

Atsushi Mizokami,[1] Eitetsu Koh,[1] Hiroshi Fujita[1], Yuji Maeda[1], Masayuki Egawa,[1] Kiyoshi Koshida,[1] Seiiiro Honma,[2] Evan T. Keller,[3] and Mikio Namiki[1]

Vol. 10, 440–448, January 15, 2004 Clinical Cancer Research *imal Medicine and Department*

Featured Article

The Androgen Axis in Recurrent Prostate Cancer

James L. Mohler,[1,2,6,7,8] Christopher W. Gregory,[2,5] O. Harris Ford III,[1,6] Desok Kim,[1] Catharina M. Weaver,[3] Peter Petrusz,[4] Elizabeth M. Wilson,[3,5,6] and Frank S. French[3,6]

Departments of [1]Surgery (Division of Urology), [2]Pathology and Laboratory Medicine, [3]Pediatrics (Laboratories for Reproductive Biology), [4]Cell and Developmental Biology, and [5]Biochemistry and Biophysics, and [6]University of North Carolina-Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina; [7]Department of Urology, State University of New York at Buffalo; and [8]Department of Urologic Oncology, Roswell Park Cancer Center, Buffalo, New York

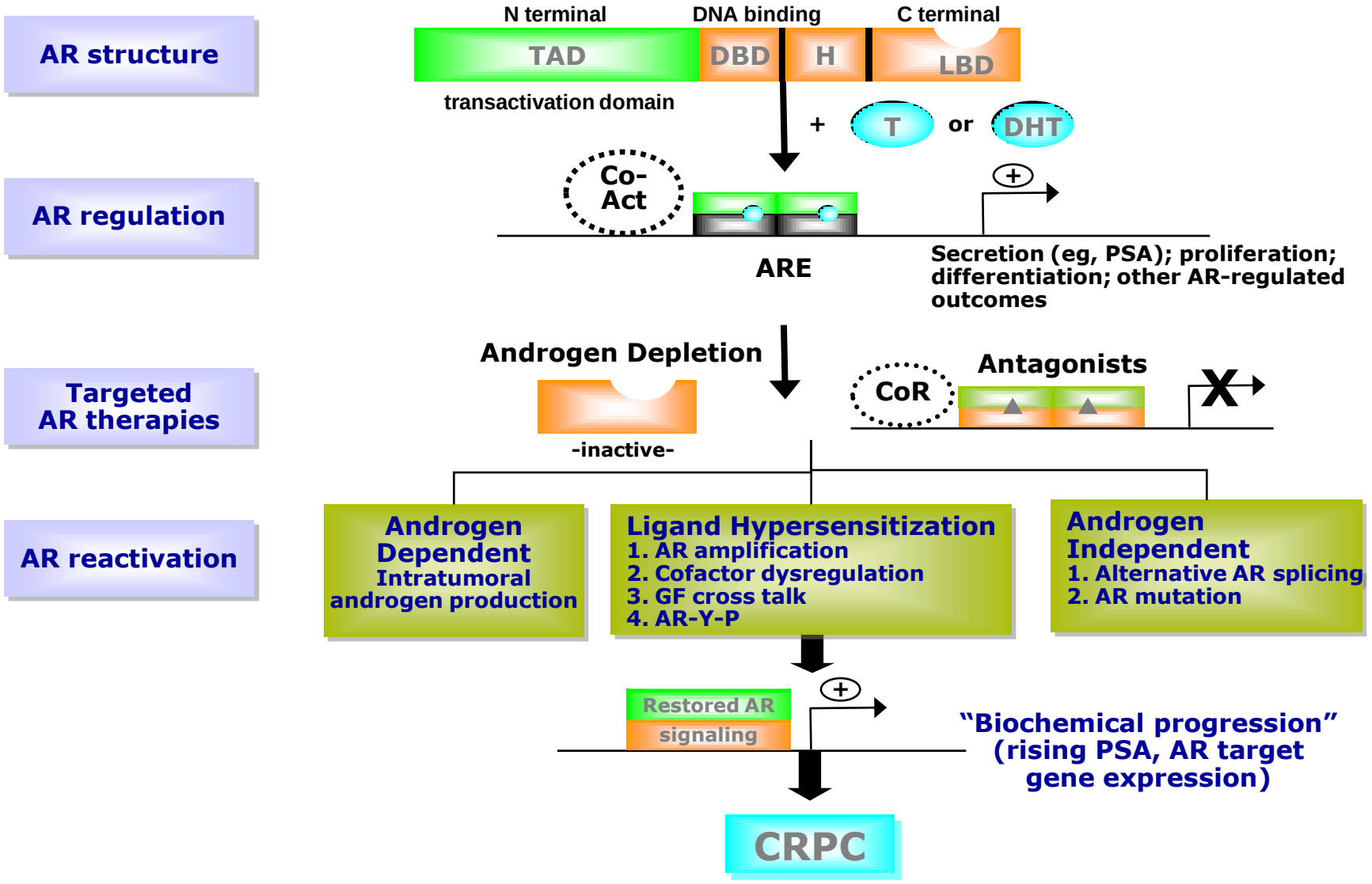
lower (Wilcoxon, $P = 0.0000068$, 0.00093, and 0.0089, respectively) in recurrent prostate cancer than in benign prostate, and mean dihydrotestosterone levels, although reduced, remained 1.45 nM. Androgen receptor activation in recurrent prostate cancer was suggested by the androgen-regulated gene product, prostate-specific antigen, at 8.80 ± 10.80 nmol/g tissue.

Conclusions. Testosterone and dihydrotestosterone occur in recurrent prostate cancer tissue at levels sufficient to activate androgen receptor. Novel therapies for recurrent prostate cancer should target androgen receptor directly and prevent the formation of androgens within prostate cancer tissue.

Intraprostatic Androgens and Androgen-Regulated Gene Expression Persist after Testosterone Suppression: Therapeutic Implications for Castration-Resistant Prostate Cancer

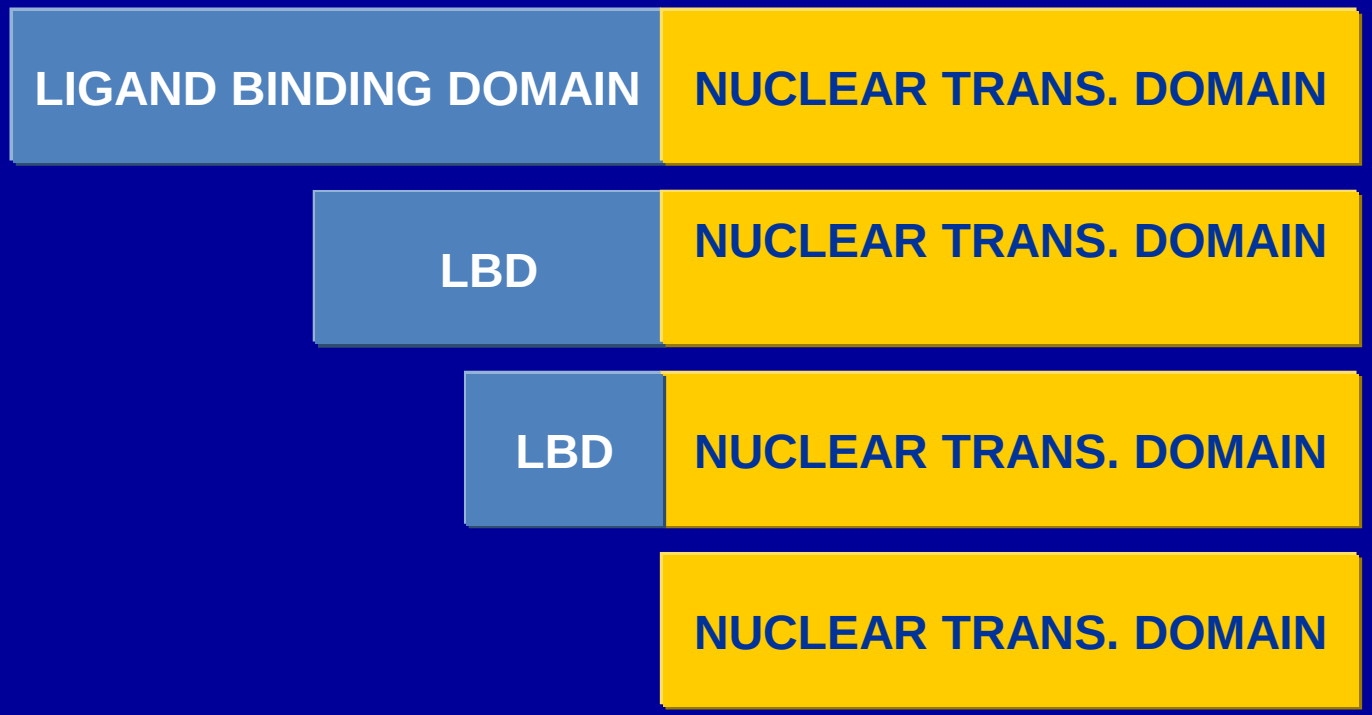
Elahe A. Mostaghel,[1,2] Stephanie T. Page,[2,5] Daniel W. Lin,[3,5] Ladan Fazli,[6] Ilsa M. Coleman,[1] Lawrence D. True,[4] Beatrice Knudsen,[1] David L. Hess,[7] Colleen C. Nelson,[6] Alvin M. Matsumoto,[2,5] William J. Bremner,[2] Martin E. Gleave,[6] and Peter S. Nelson[1]

Androgen Receptor and Reactivation



Knudsen KE, Scher HI. *Clin Cancer Res*. 2009;15:4792-4798

AR Splice Variants Offer a Clinically Important Avenue of Castration Resistance



AR splice variants lack the ligand binding domain

Sun S, Clin Invest. 2010 Aug 2;120(8):2715-30, Watson PA, PNAS, 2010 Sept 28 vol 107, no. 39; 16759-16765

Constitutively Active, Androgen Receptor Alternative Splice Variants

- Some AR splice variants are constitutively active;ligand-independent state of activation
  - ARv567es (exon skipped) vs ARfl (full length)
- Not limited to all-or-none expression, broad range of AR full length/AR variant ratios
- AR homodimers and heterodimers can form
  - ARfl-ARfl, ARfl-ARv567es, ARv567es-ARv567es

Sun S, Clin Invest. 2010 Aug 2;120(8):2715-30Watson PA, PNAS, 2010 Sept 28 vol 107, no. 39; 16759-16765

Metastases with AR splice variants are common

- Amplified cDNA from 69 metastases, derived from 13 CRPC patients

- No full-length or variant AR detected in 23 samples (neuroendocrine phenotype, non-AR dependent); of the remaining 46 metastases:
  - 80% expressed ARfl
  - 43% expressed ARv567es
  - 24% expressed ARv7es

- Metastases with AR splice variants are common:
  - 20% expressed only the ARv567es variant
  - 59% AR-positive metastases expressed one or more AR splice variants
  - **92% of patients had a minimum of at least one metastasis that was positive for at least one AR splice variant**

Sun S, Clin Invest. 2010 Aug 2;120(8):2715-30

The new antiandrogens

Abiraterone Acetate (phase III studies post and pre docetaxel)
- Potent and selective inhibitor of CYP17-α-hydroxylase and C17,20-lyase

MDV3100 (phase III studies post and pre docetaxel)
-AR antagonist, inhibits nuclear translocation and blocks DNA binding of the receptor and activation

TAK-700 (phase III studies post and pre docetaxel)
- Selective, non-steroidal, small-molecule inhibitor of 17,20-lyase

TOK- 001 (phase I/II ARMOR1)
- AR antagonist and AR degrader and a CYP17 lyase inhibitor

SARDS
- selective androgen receptor degraders (destroy the AR receptor)

ARN-509 (phase II/II)
- AR antagonist, inhibits nuclear translocation and DNA binding of the receptor

Co-factor antagonists
-Target coactivator interaction surfaces - AR antangonists

MDV3100 blocks 3 steps in testosterone signaling

Testosterone synthesis

Testosterone

Tumor death

T

T

X

AR

MDV3100

1 AR binding blocked

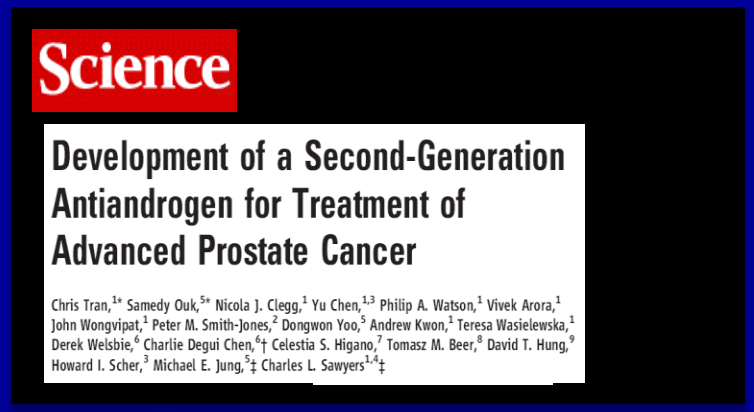
2 nuclear translocation blocked

3 DNA binding and activation blocked

X

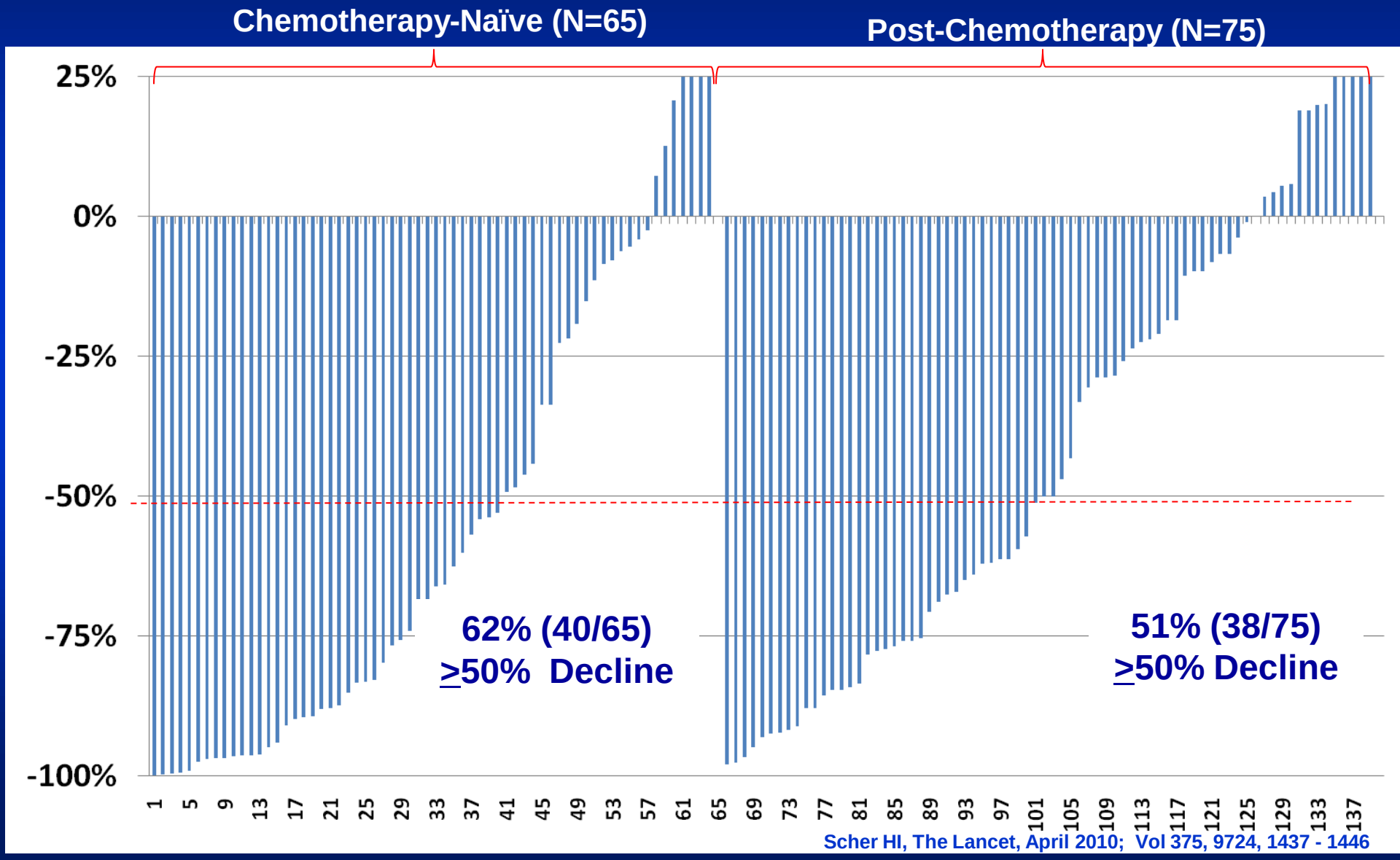
X

cell nucleus



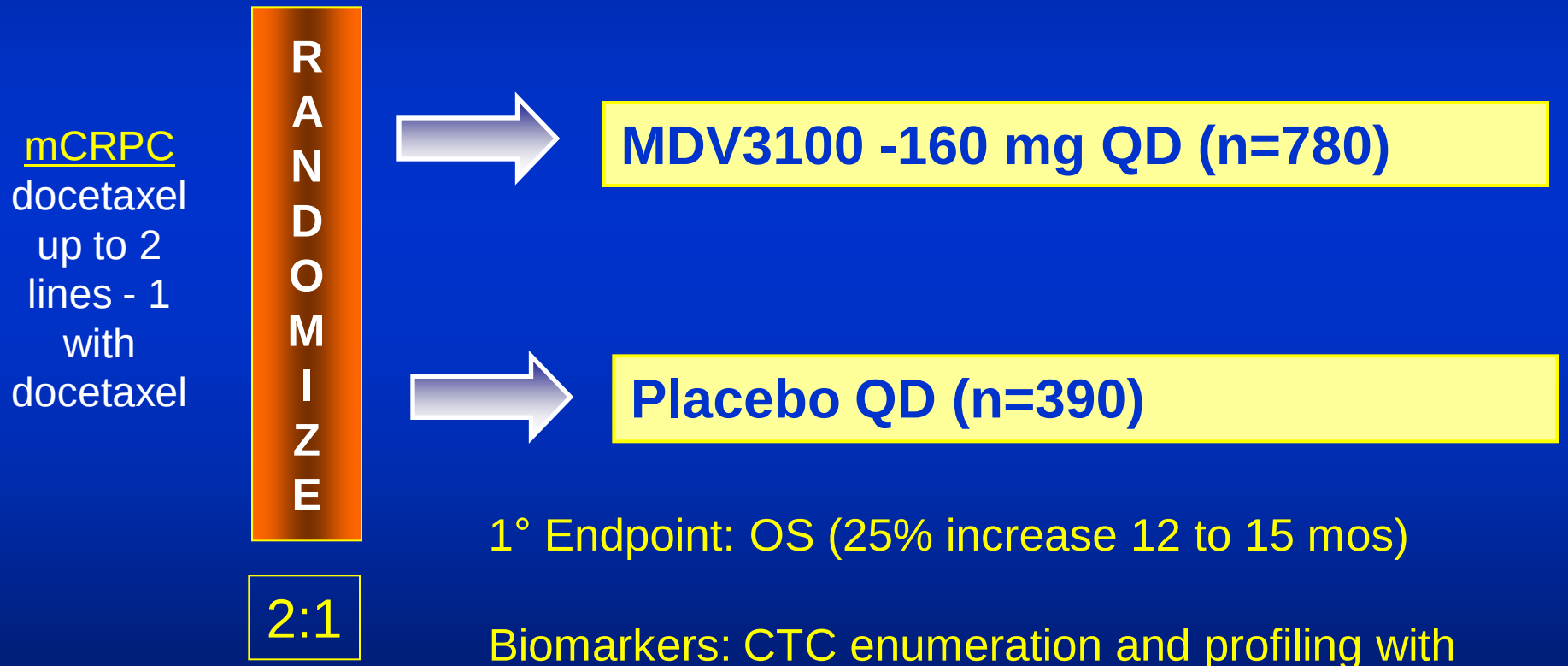
No prednisone required

Waterfall Plot of Best Percent PSA Change from Baseline



Scher HI, The Lancet, April 2010; Vol 375, 9724, 1437 - 1446

AFFIRM Phase III Trial of MDV3100 in Post-Chemotherapy CRPC (n ~1,170)



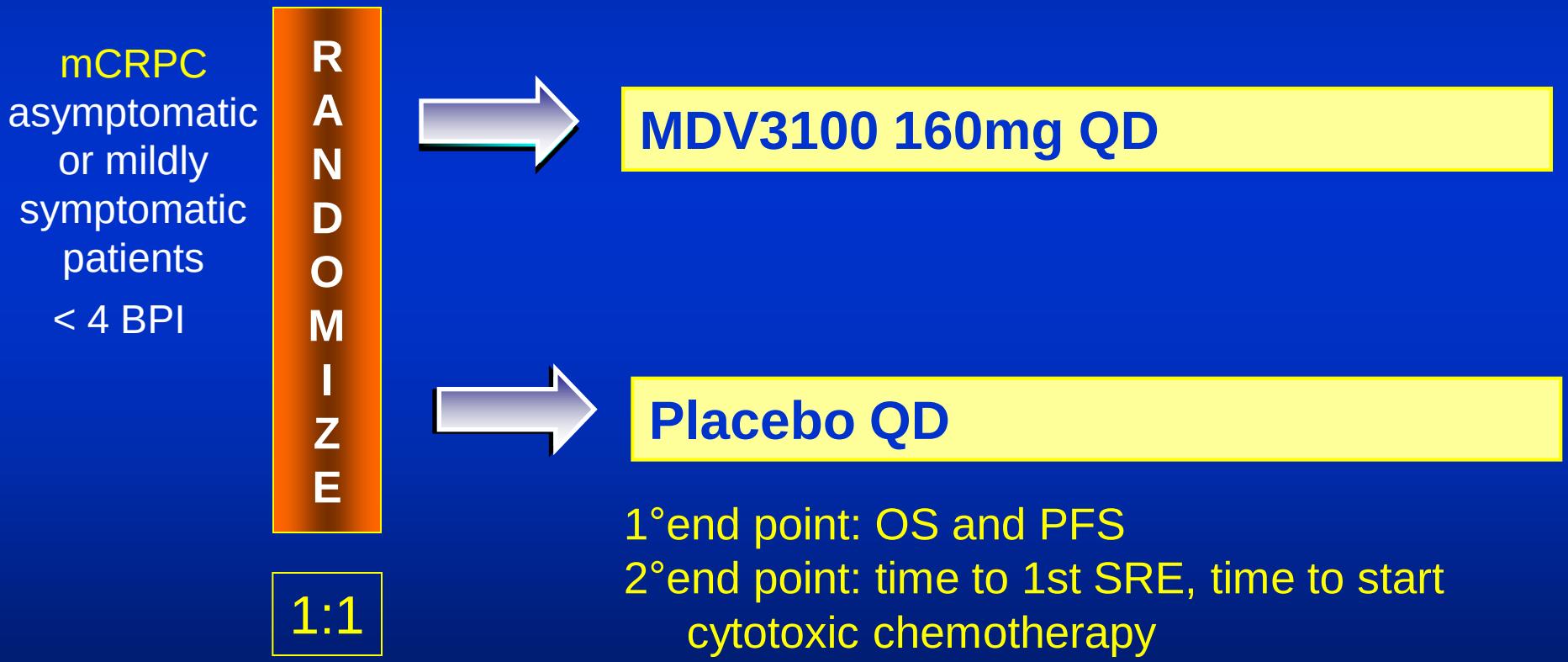
1° Endpoint: OS (25% increase 12 to 15 mos)

Biomarkers: CTC enumeration and profiling with outcome

NCT00974311

Scher HI and de Bono JS. Co-PI

PREVAIL Phase III Trial of MDV3100 in asymptomatic or mildly symptomatic mCRPC Pre Chemotherapy (n=1,680)



1°end point: OS and PFS
2°end point: time to 1st SRE, time to start cytotoxic chemotherapy

NCT01212991
1st patient enrolled Sept 29, 2010

Beer T and Tombal B, co-PI

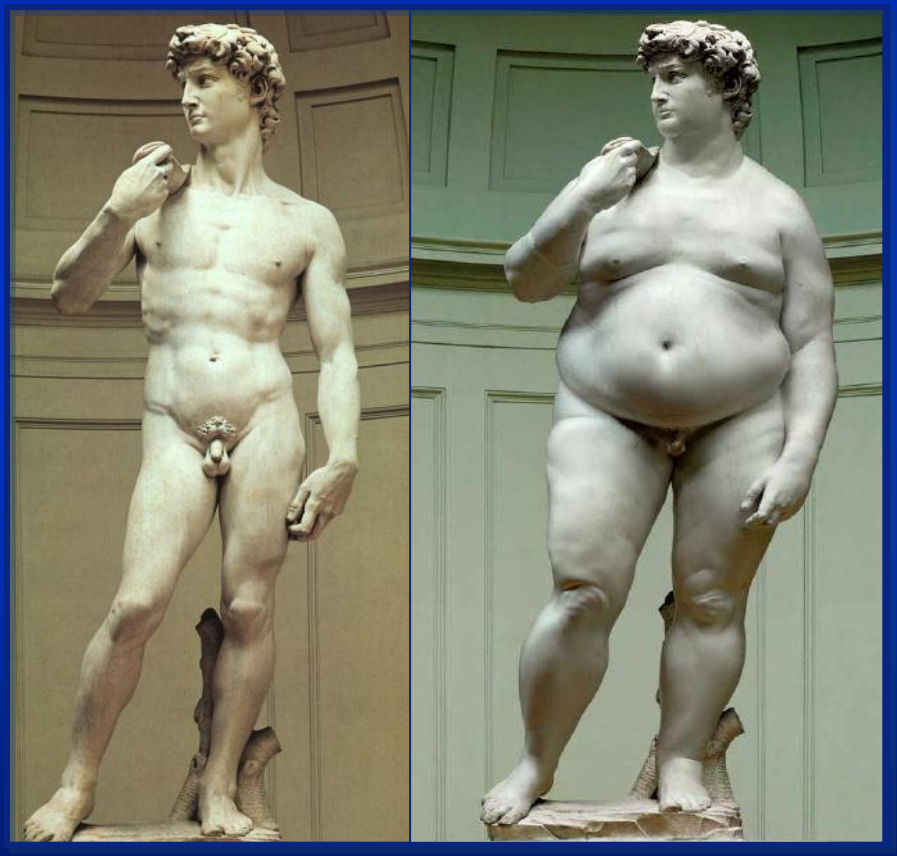
Adverse effects of androgen deprivation therapy (ADT)

- Hot flashes
- Loss of libido
- Fatigue
- Anemia
- Obesity
- Sarcopenia
- Diabetes
- Cardiovascular disease
- Osteoporosis/fracture

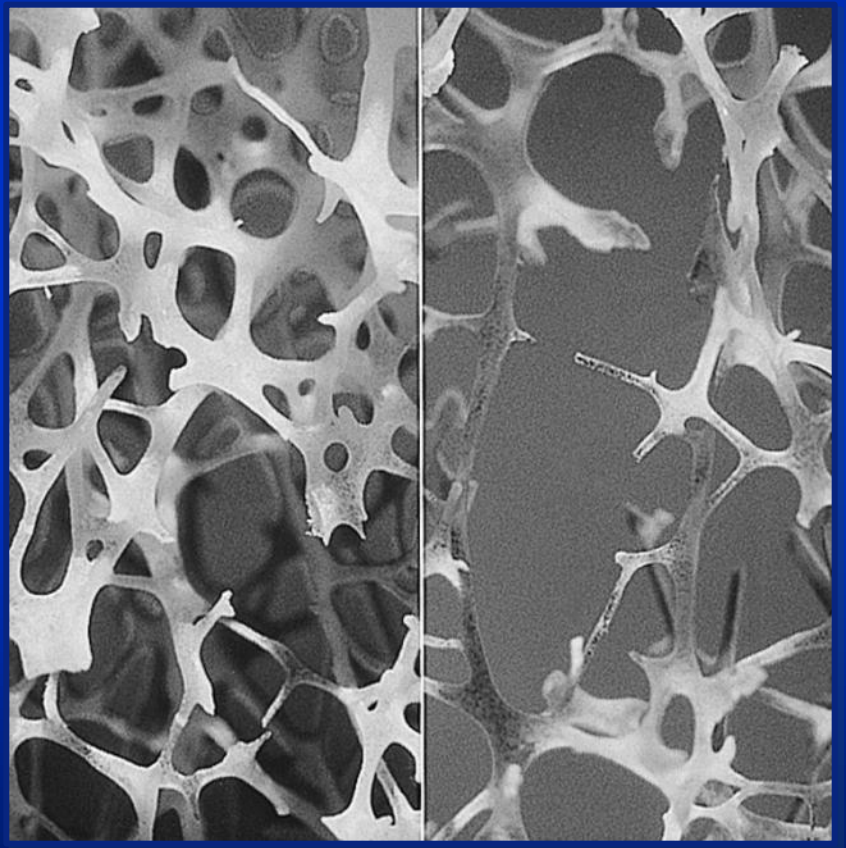
Keating NL et al, J Clin Oncol. 2006 Sep 20;24(27):4448-56
Keating NL et al, J Natl Cancer Inst. 2010 Jan 6;102(1):39-46
Taylor LG, et al. Cancer. 2009;115:2388-2399

Long-term side-effects of ADT

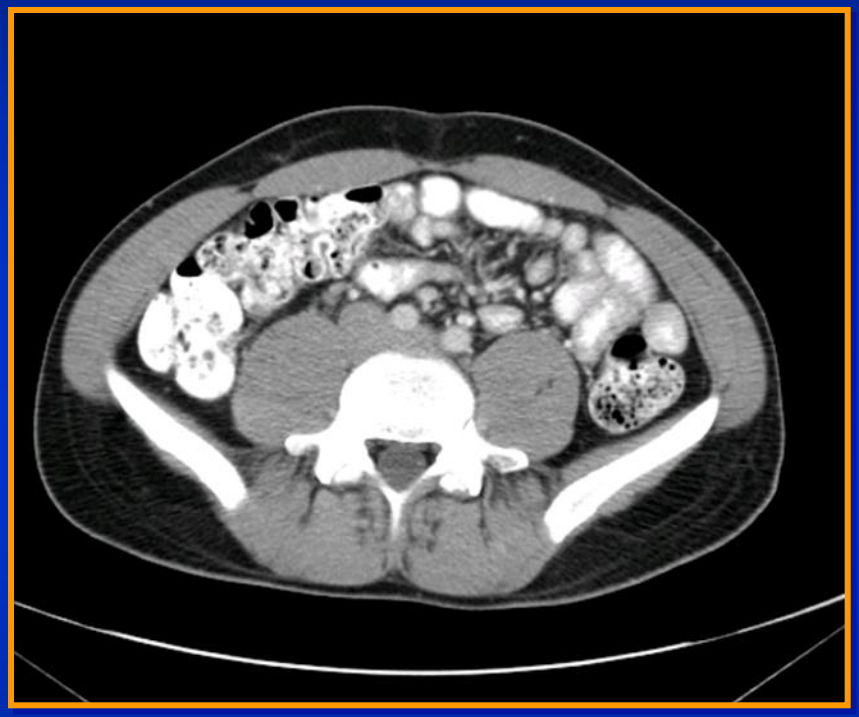
Sarcopenic obesity



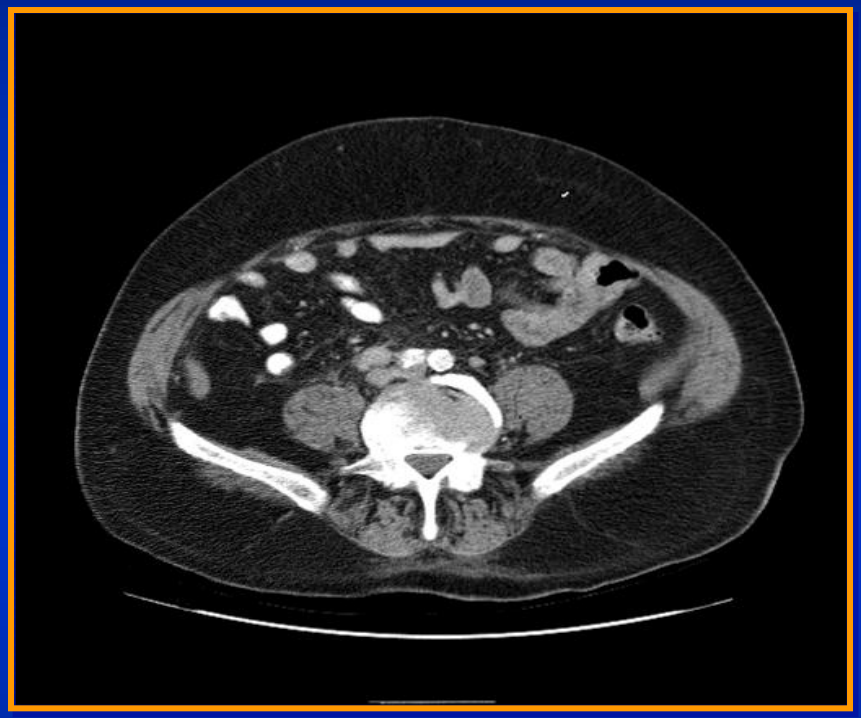
Bone loss



Abdominal obesity and sarcopenia during ADT



Eugonadal young man



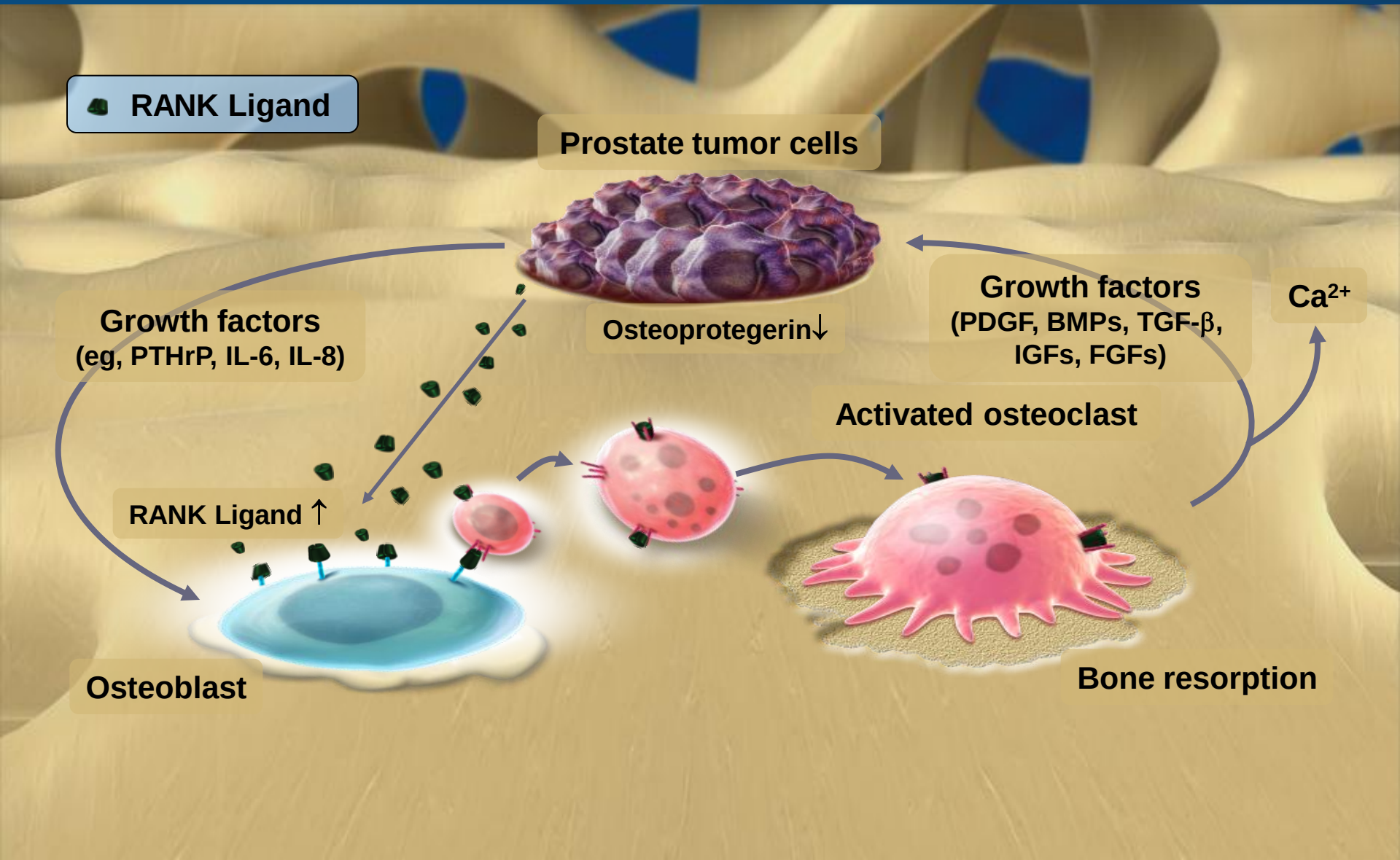
Older man on ADT

What are the long term effects of further androgen suppression?

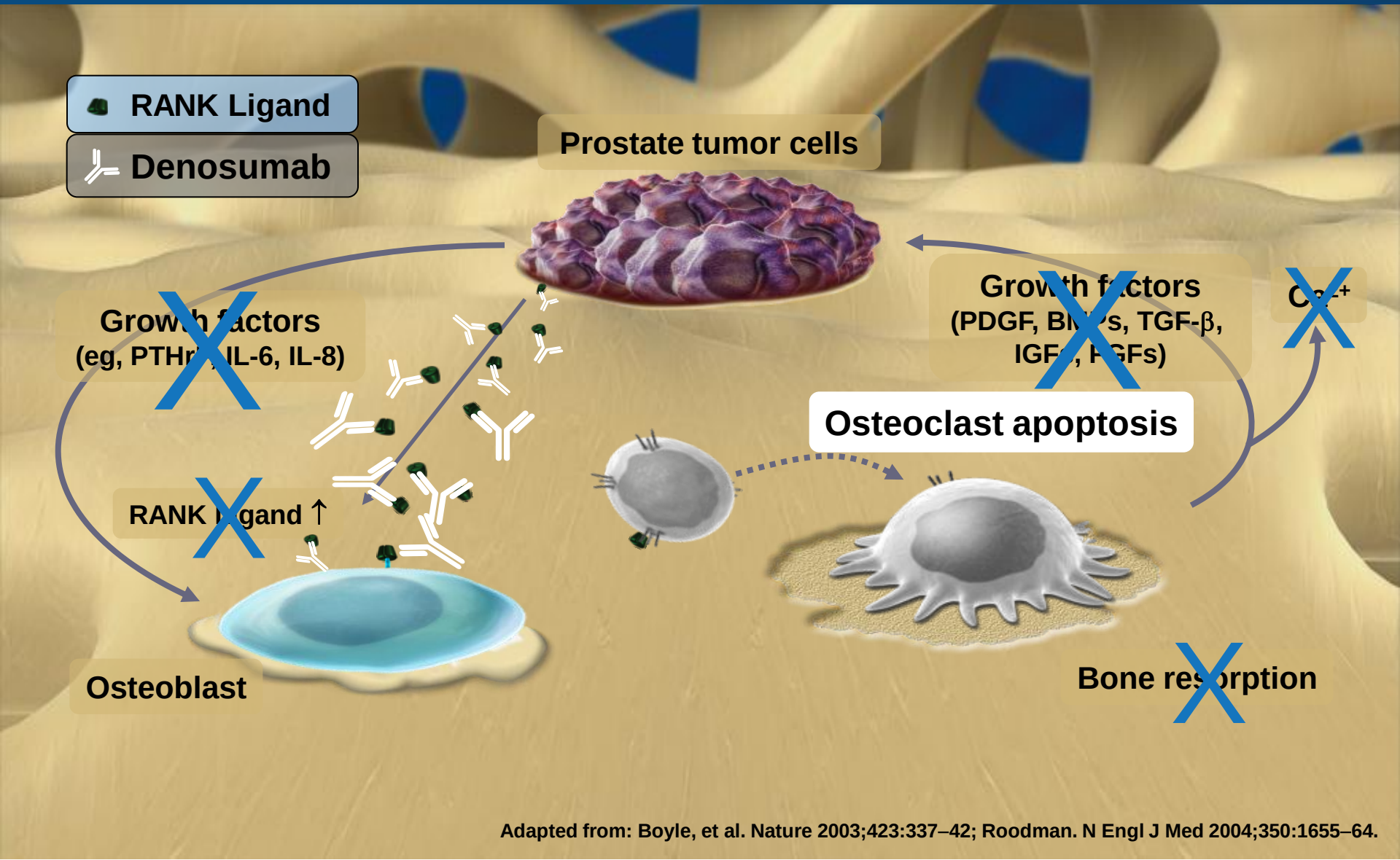
Saylor PJ, Smith MR. J Urol 2009;181:1998-2008

Targeting Bone

The ‘vicious cycle’ hypothesis of bone destruction in prostate cancer



Denosumab may interrupt the vicious cycle of bone destruction in prostate cancer



Adapted from: Boyle, et al. Nature 2003;423:337–42; Roodman. N Engl J Med 2004;350:1655–64.

Phase III randomized double-blind study of Denosumab vs Zoledronic acid for bone metastases in CRPC (n=1,904)

Eligibility:
mCRPC
No prior bisphosphonates
Stratification:
Previous SRE
PSA < or ≥ 10 ng/mL)
Current chemo

RANDOMIZE

1:1

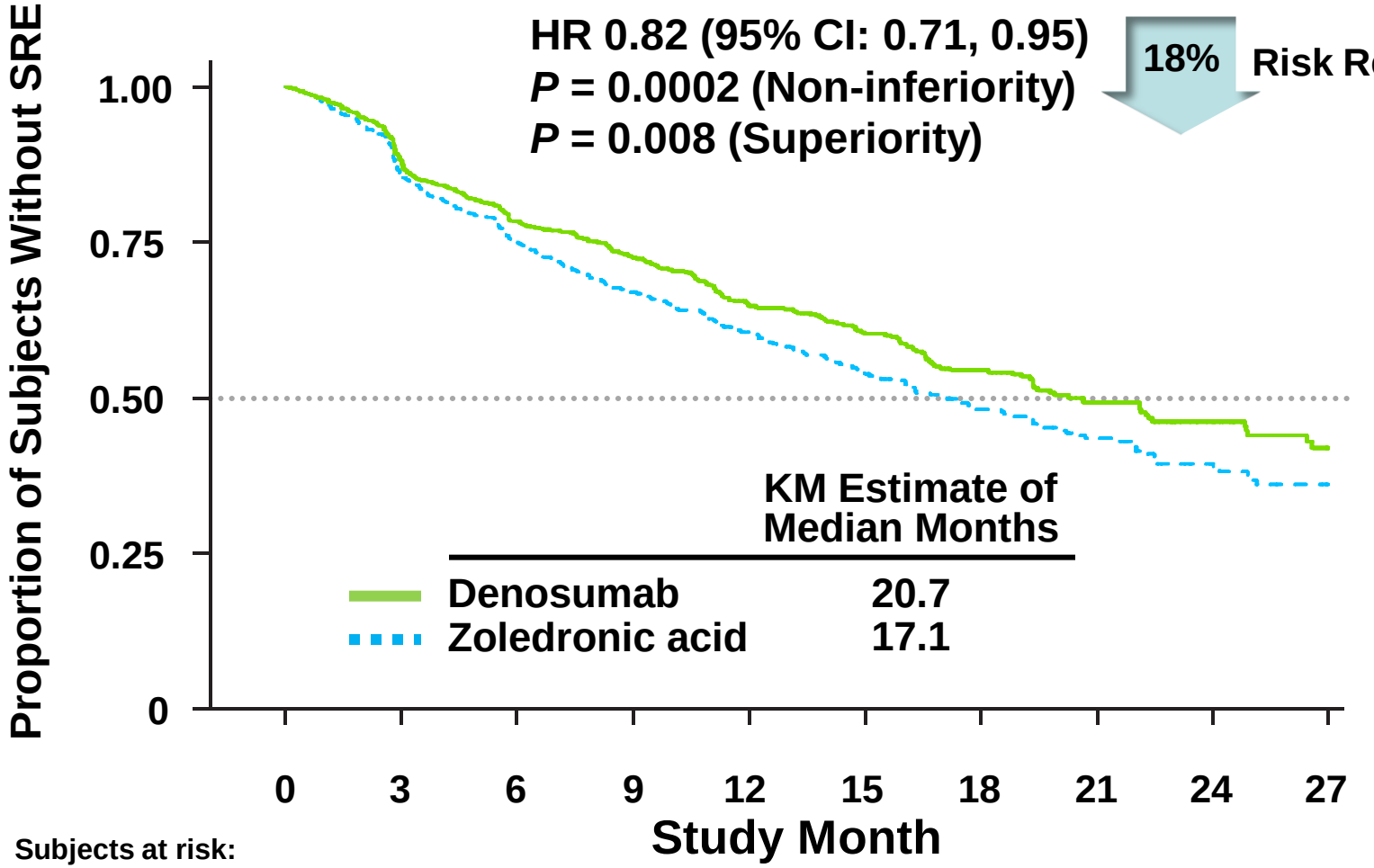
Zoledronic acid placebo IV infusion and Denosumab 120 mg SC Q4W

Zoledronic acid 4 mg IV infusion and placebo SC Q4W Q4W

Primary objective: Efficacy (non-inferiority) (SRE); Secondary objectives: Efficacy (superiority), multiple SRE analysis, safety

Fizazi K, J Clin Oncol 28:7s 2010 (suppl: abstr LBA 4507)

Denosumab vs Zoledronic acid: Time to SRE (n=1901)

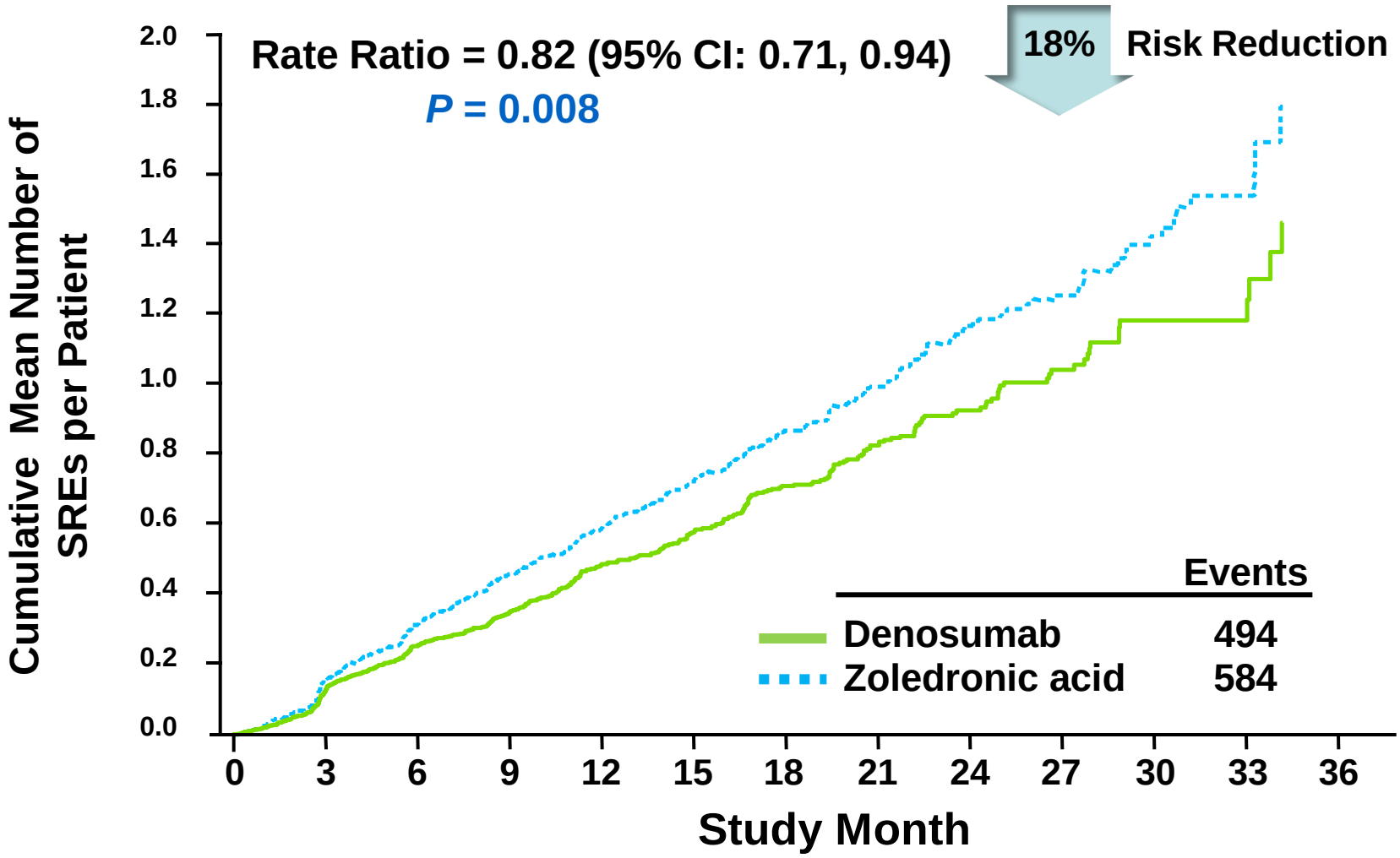


Subjects at risk:

Zoledronic Acid	951	733	544	407	299	207	140	93	64	47
Denosumab	950	758	582	472	361	259	168	115	70	39

Fizazi K, J Clin Oncol 28:18s, 2010 (suppl; abstr LBA 4507) and Lancet. 2011 Feb 24. [Epub ahead of print]

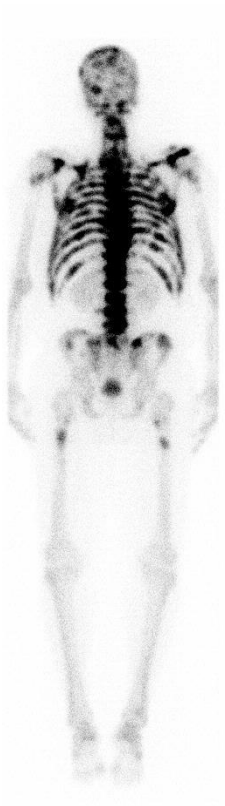
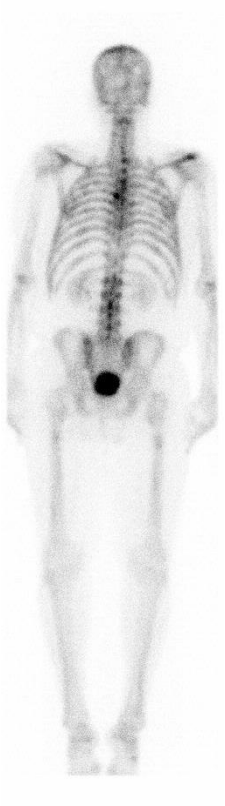
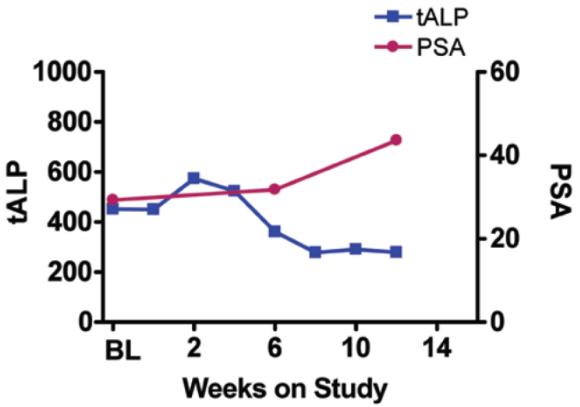
Time to First and Subsequent On-Study SRE



*Events occurring at least 21 days apart

Fizazi K, J Clin Oncol 28:18s, 2010 (suppl; abstr LBA 4507)) and Lancet. 2011 Feb 24. [Epub ahead of print]

Cabozantinib: Bone Scan Evidence of Metastasis With ≥ 1 Post-Baseline Scan

Patients With Bone Scan Resolution (Partial or Complete)[a]			
Baseline	**Week 6**	**Prior docetaxel**	Yes
		**Maximum tumor change, per mRECIST**	–14%
		Improvement in bone pain[b]	NE
		Change in tALP and PSA	
Bone scans at baseline and during therapy with cabozantinib			

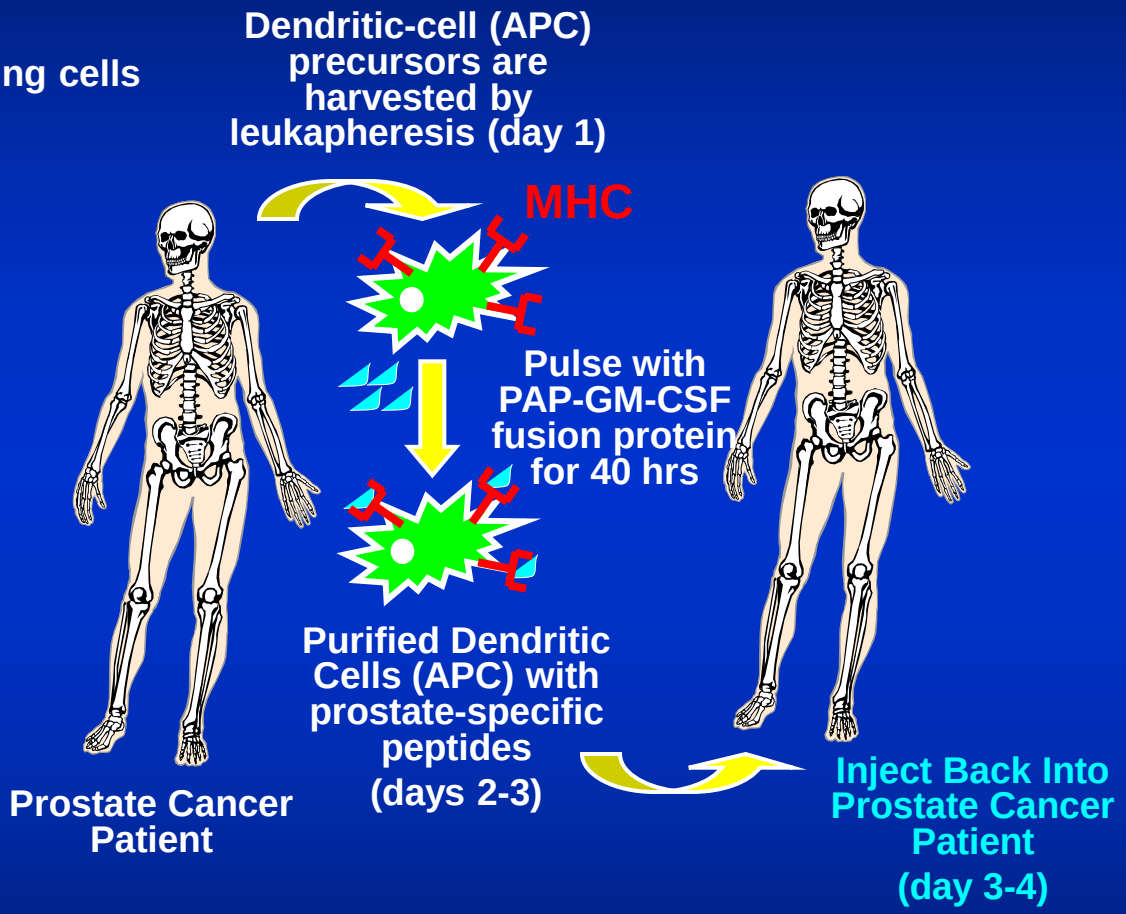
NE, not evaluated due to no pain at baseline; PSA, prostate specific antigen; BL, baseline.
[a] Independent radiologist review.
[b] Post-hoc investigator survey of whether pain improved at week 6 and/or week 12.

Smith D, J Clin Oncol 29: 2011 (suppl 7; abstr 127)

Immunotherapy

Sipuleucel -T (Provenge) Therapy with Pulsed Dendritic Cells

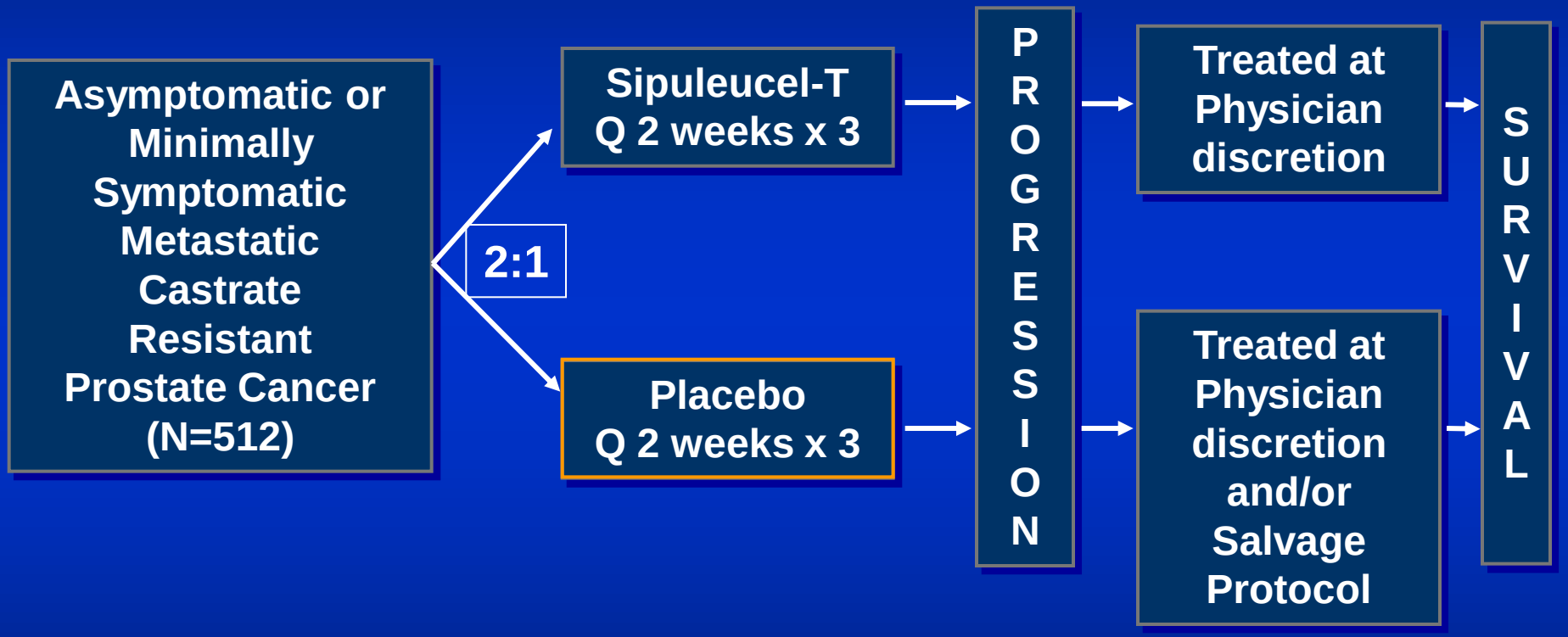
APC: Antigen presenting cells



COMPLETE COURSE OF THERAPY: Weeks 0, 2, 4

Kantoff PW et al, N Engl J Med. 2010 Jul 29;363(5):411-22

Randomized Phase III IMPACT Trial

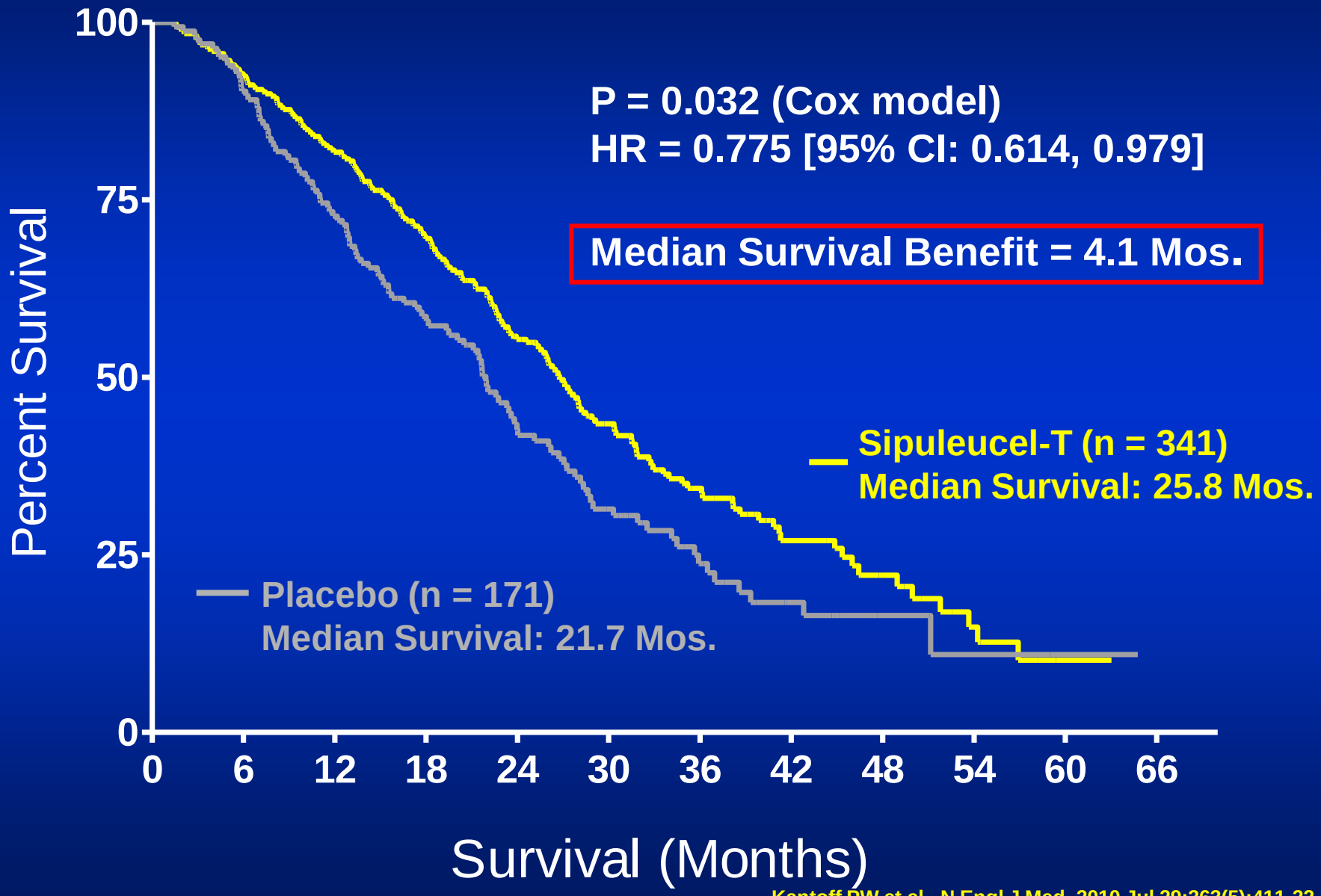


Primary endpoint: Overall Survival

Secondary endpoint: Time to Objective Disease Progression

Kantoff PW et al, N Engl J Med. 2010 Jul 29;363(5):411-22

Sipuleucel -T Immunotherapy for CRPC



Kantoff PW et al, N Engl J Med. 2010 Jul 29;363(5):411-22

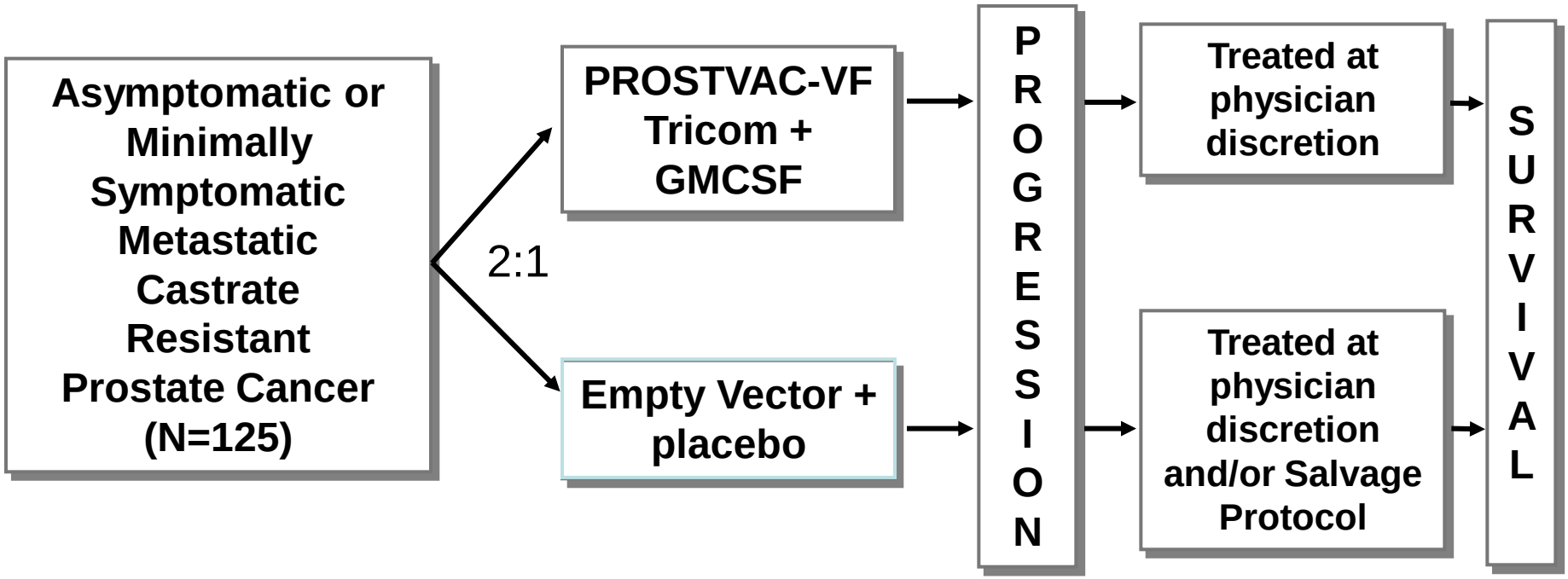
Development of PROSTVAC-VF-Tricom

- **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)

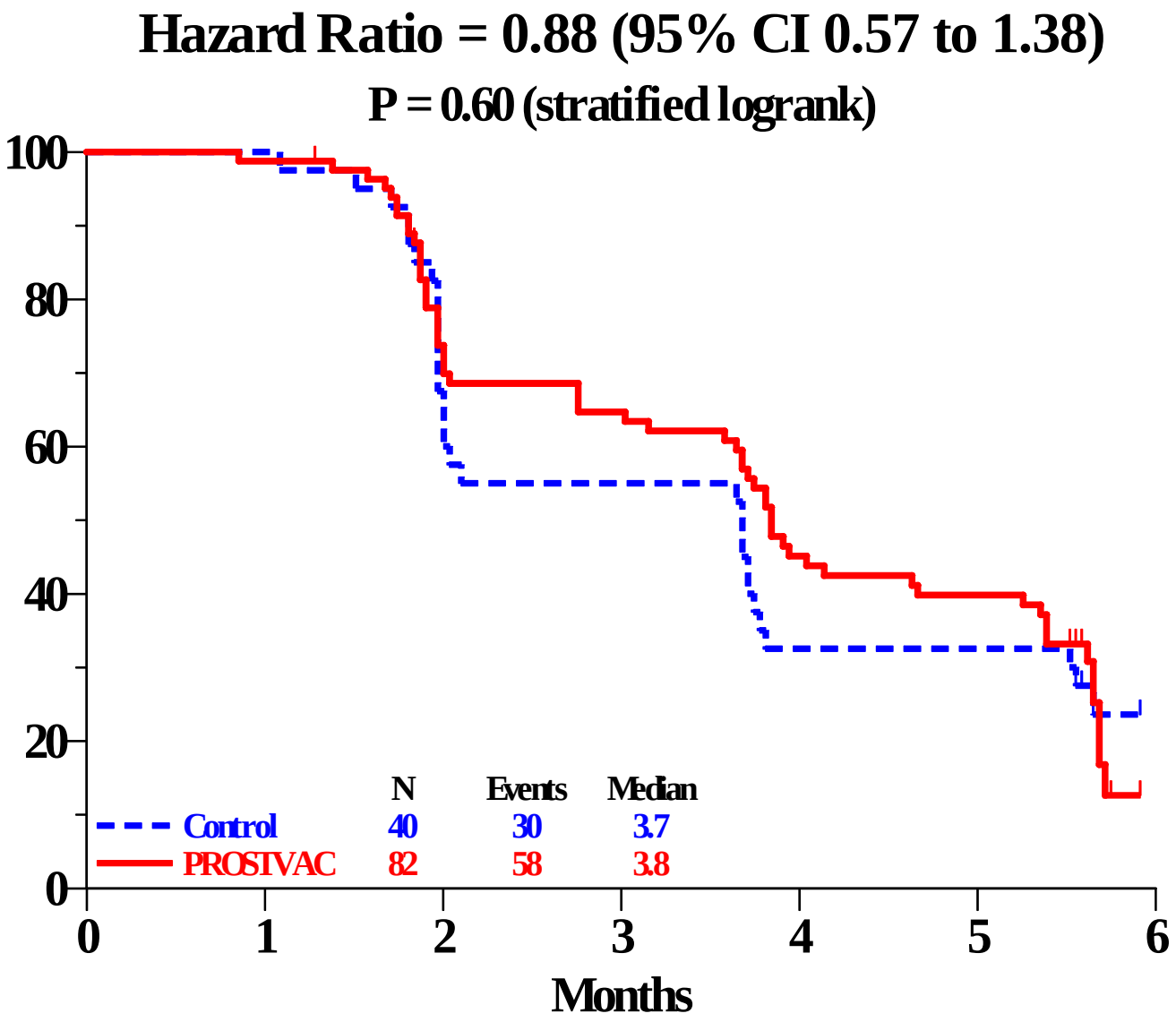
Schlom J, Exp Biol Med (Maywood). 2008 May;233(5):522-34

Randomized Phase II Study (Prostvac)



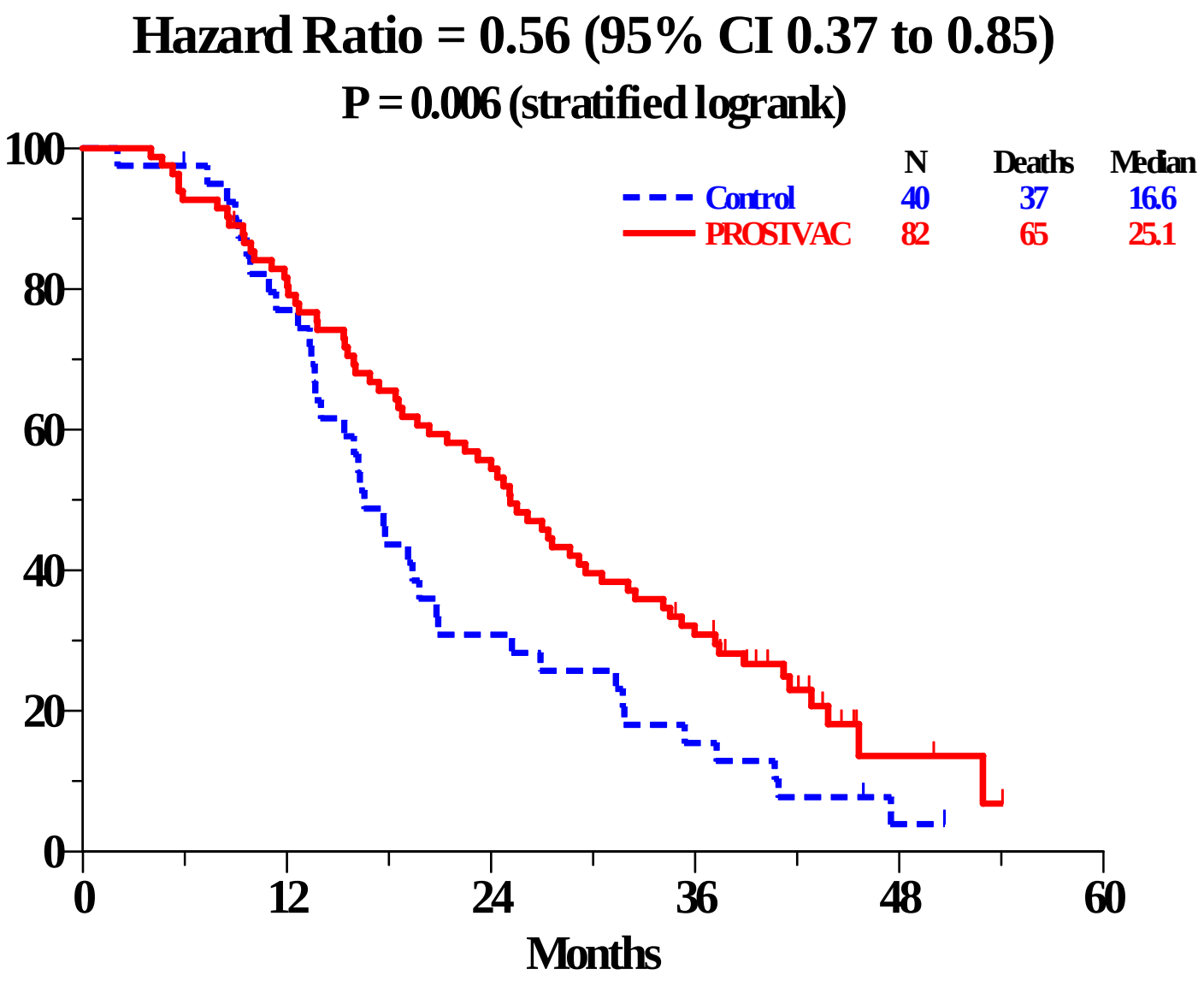
Kantoff PW, J Clin Oncol. 2010 Mar 1;28(7):1099-105

Progression-Free Survival



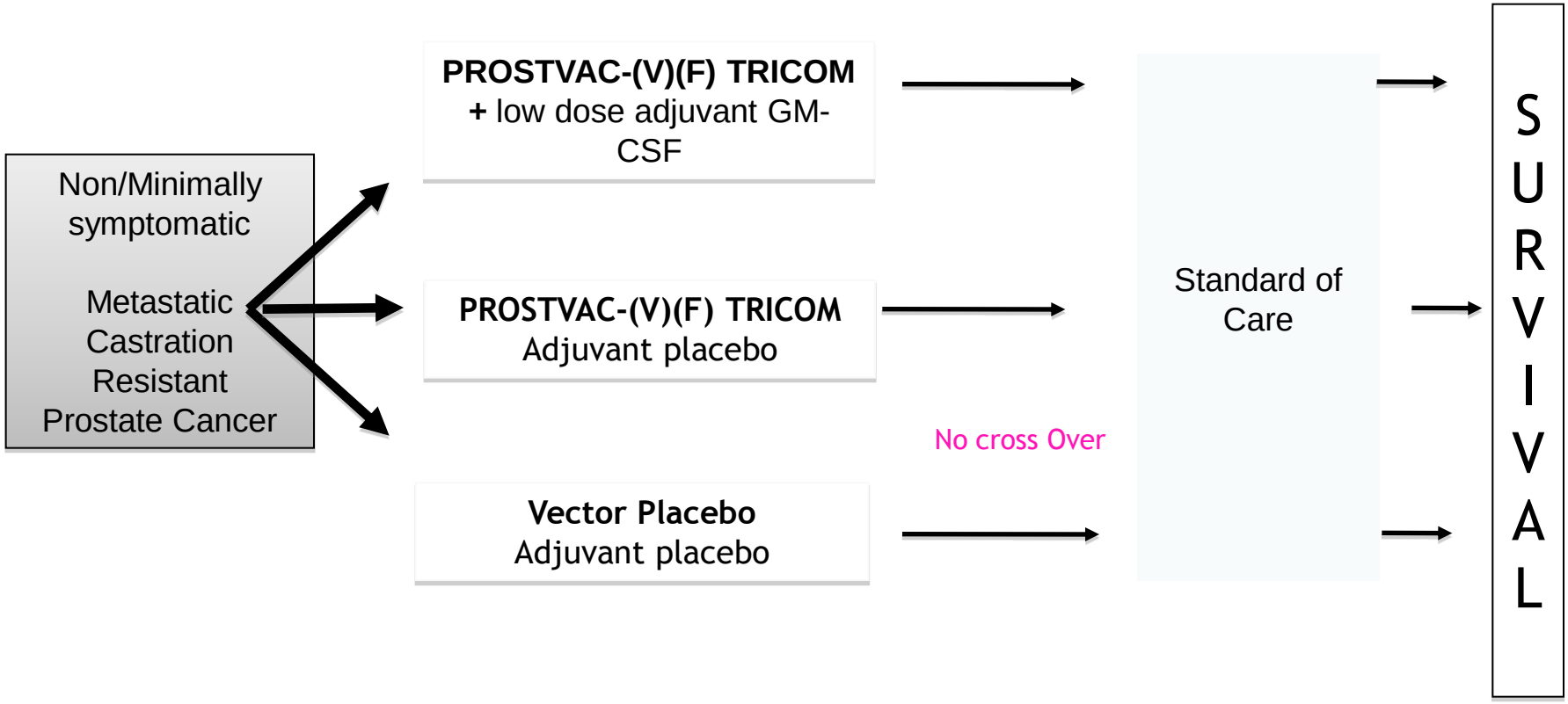
Kantoff PW, J Clin Oncol. 2010 Mar 1;28(7):1099-105

Overall Survival



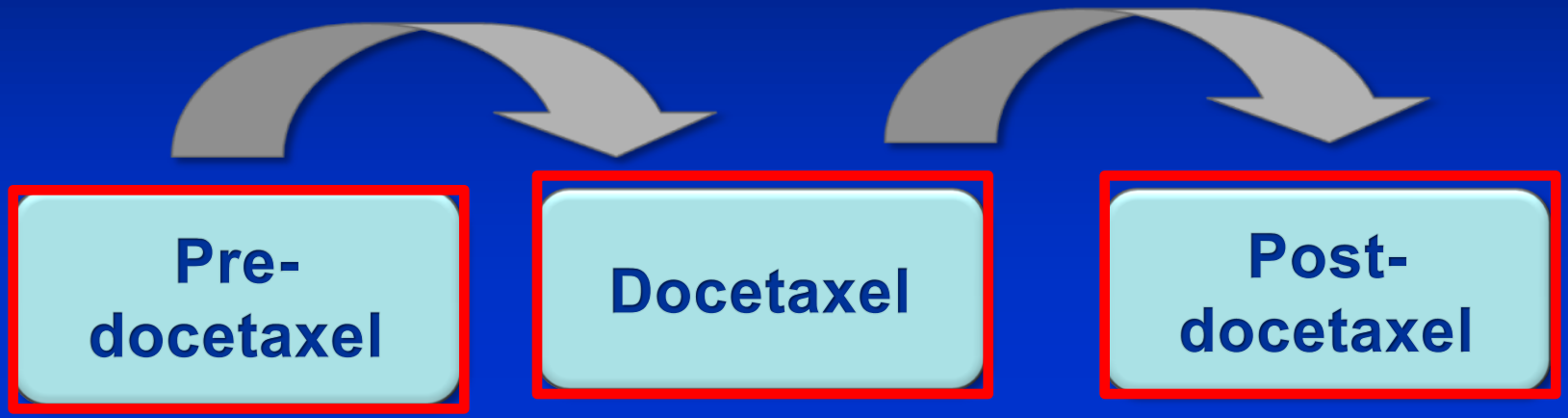
Kantoff PW, J Clin Oncol. 2010 Mar 1;28(7):1099-105

Phase III Prostvac Trial Design



PIs : James Gulley and Philip Kantoff

New Agents and Trials for CRPC

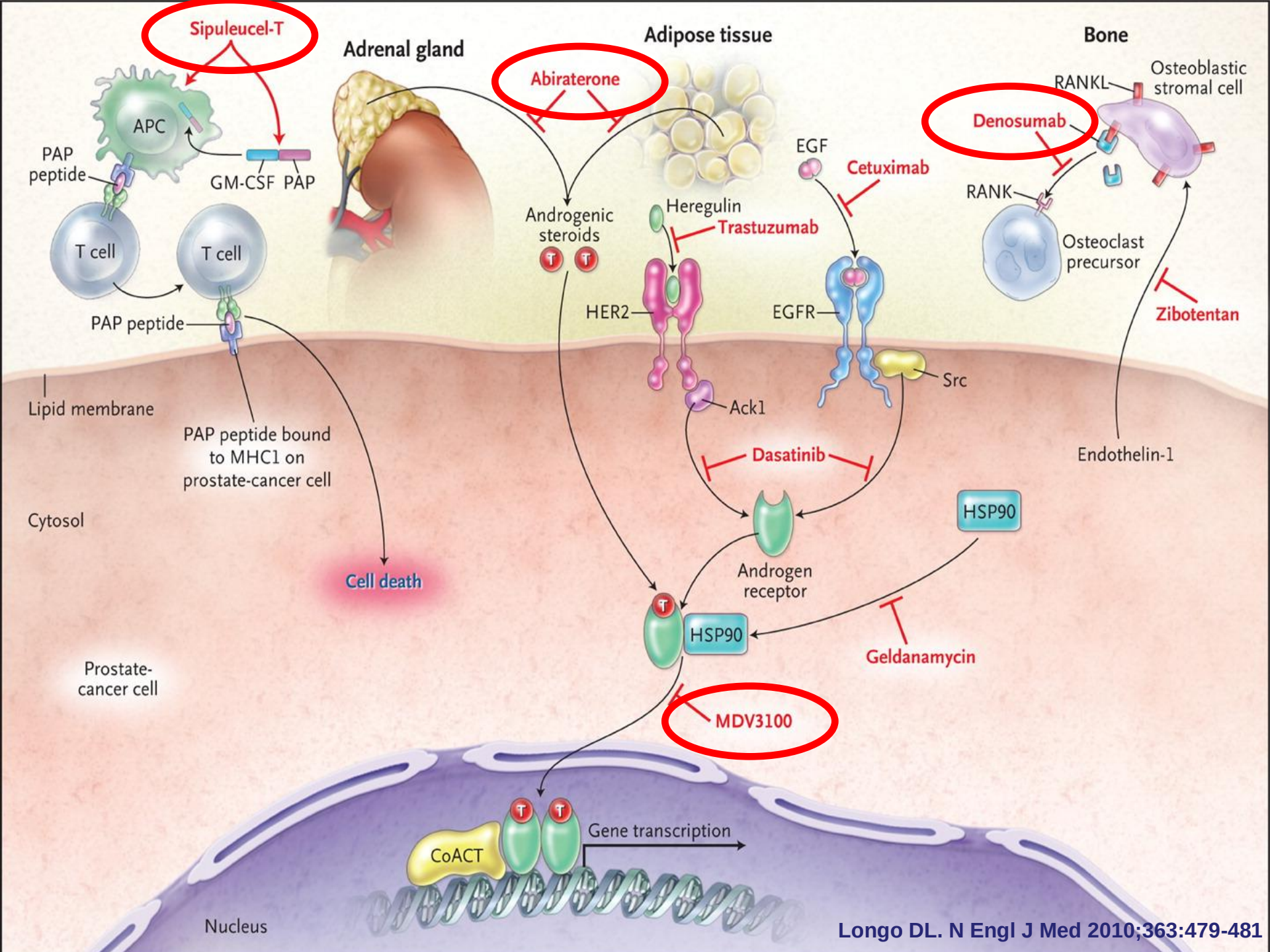


- Abiraterone
- MDV3100
- Sipuleucel-T[1]
- PROSTVAC[2]
- Zibotentan[3]
- Ipilimumab
- Tasquinimod
- TAK 700

- Dasatinib
- Atrasentan
- Zibotentan
- Aflibercept
- Lenalidomide
- OGX-011[4]

- Abiraterone[5]
- Cabazitaxel[6]
- MDV3100[7]
- Ipilimumab
- Tak-700
- Sunitinib

[1]Kantoff PW, N Engl J Med. 2010 Jul 29;363(5):411-22,[2]Kantoff PW, J Clin Oncol 2010; 28:1099–105
[3]James ND, Eur Urol 2009;55:1112–23, [4] CHi KN, J Clin Oncol; 28:4247-4254, [5]de Bono J,. NEJM (in press),
[6]de Bono J, Lancet. 2010 Oct 2;376(9747):1147-54, [7]Scher HI, The Lancet, April 2010; Vol 375, 9724, 1437 - 1446



Longo DL. N Engl J Med 2010;363:479-481

Treatment options for patients with CRPC

The near future

Abiraterone[5]

MDV3100

1 Saad F, J Natl Cancer Inst 2002;94:1458–68
2 Tannock I , N Engl J Med. 2004 Oct 7;351(15):1502-12
3 de Bono J, et al. Lancet. 2010 Oct 2;376(9747):1147-54
4 Kantoff PW, 2010 Jul 29;363(5):411-22
5 de Bono JS, NEJM (in press)
6 Fizazi K, Lancet. 2011 Feb 24

Conclusions in mCRPC

- We have unequivocal evidence of continued involvement of the AR signaling axis

- We still need to address prostate cancer heterogeneity to move the field forward

- We need further long term follow-up to evaluate cardiovascular and metabolic toxicities

- Prostate cancer is not yet a chronic disease, but we are making progress