Androgen deprivation therapy: New concepts

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Faculty disclosure statement:
Laurence Klotz, MD

Clinical Research funding:

1. Bayer/Algeta
2. Ferring
3. Abbott
4. GSK
5. EMD Serono

Advisory boards:

1. Dendreon
2. Amgen
3. Janssen
4. Ferring
5. GSK
6. Profound

Speaking/Honoraria:

1. GSK
2. Sanofi-Aventis
3. Amgen
4. Ferring
5. Janssen
6. Dendreon
7. Merck
8. Sanofi-Aventis
9. Profound

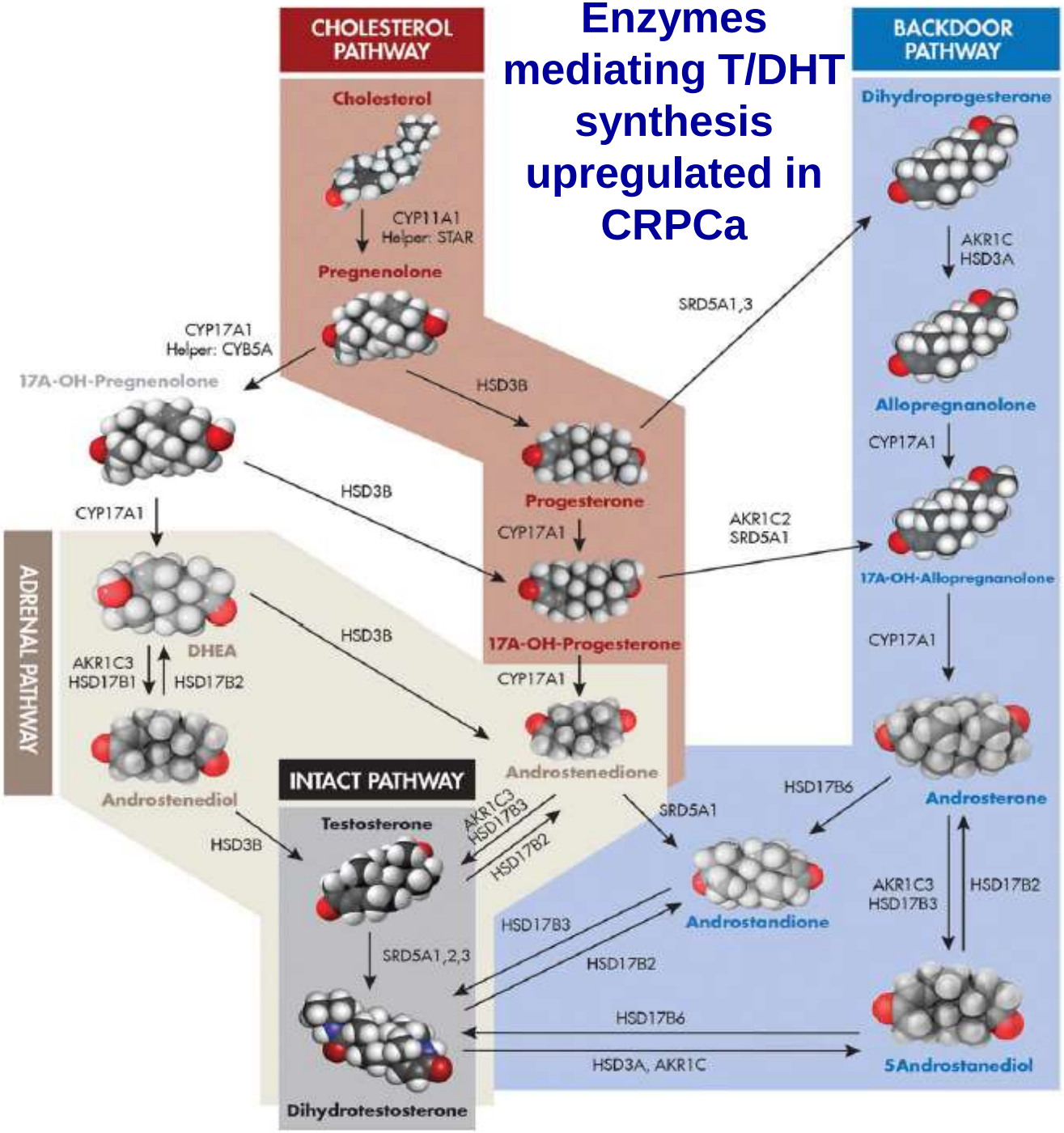
Stock Ownership:

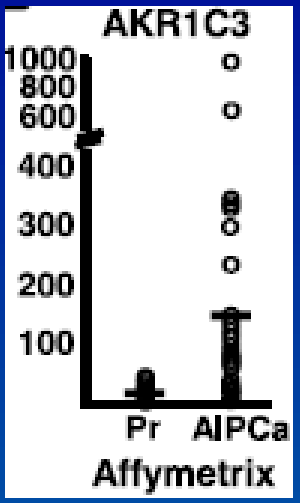
None

Developments in last decade:

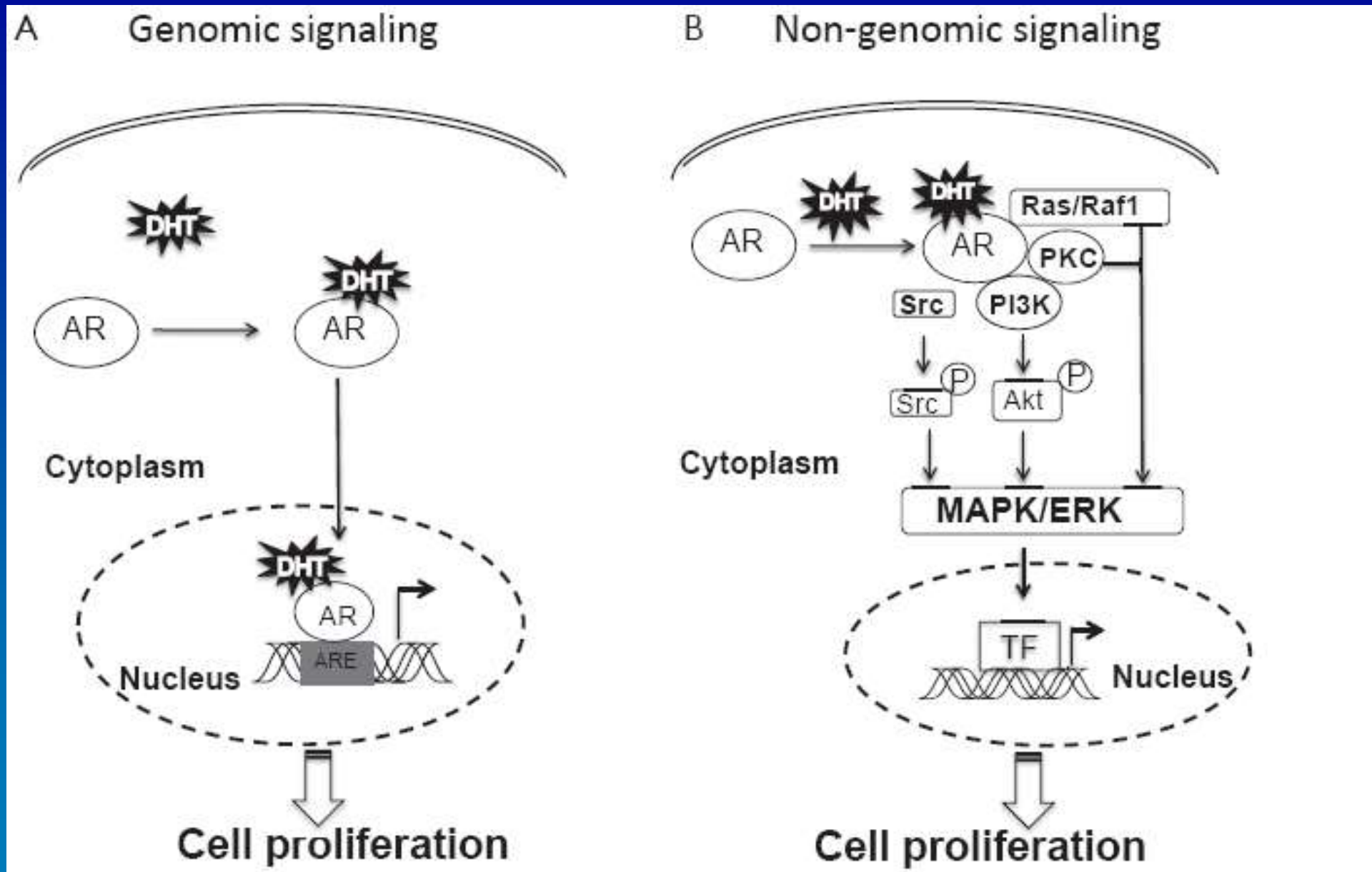
- Understanding of mechanisms of castration resistance (intracrine/autocrine synthesis of androgens, AR pathway alterations)
- Genomic vs non-genomic pathways of AR action
- Limitations of early ADT/timing
- Intermittent therapy: data from large RCTs
- Importance of testosterone levels
- Systemic/metabolic/CV effects of ADT
- LHRH antagonists
- Role of FSH, estrogen
- Survival benefit in CRPC with new AR pathway targeted agents

Enzymes mediating T/DHT synthesis upregulated in CRPCa





Androgen regulated genes (N=1500)


A
Genomic signaling
DHT
DHT
AR
AR
Cytoplasm
DHT
AR
ARE
Nucleus
Cell proliferation
B
Non-genomic signaling
DHT
DHT
AR
AR
Ras/Raf1
PKC
Src
PI3K
Src
P
Akt
P
Cytoplasm
MAPK/ERK
TF
Nucleus
Cell proliferation

A healthy 75-year-old male has a rising PSA 3 years after an RP for Gleason 4+3 pT2N0 PCa

ADT options

1. Early vs Delayed ADT
   - what PSA level?
2. LHRH agonist monotherapy
3. CAB with LHRH agonist & anti-androgen
4. Agonist/antagonist
5. 1/2/3/4/6 month depot
6. Anti-androgen monotherapy (Bicalutamide 150 mg)
7. Orchiectomy

Other options

1. Continuous vs intermittent ADT
   1. Duration of induction
   2. Trigger for re-treatment
2. CAB: flare blockade or continuous?
3. Monitor testosterone?
4. BMD assessment: When, how often
5. Bone-targeted agents for BMD protection

Intermittent therapy and on-treatment testosterone levels

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 6, 2012 VOL. 367 NO. 10

Intermittent Androgen Suppression for Rising PSA Level after Radiotherapy

Juanita M. Crook, M.D., Christopher J. O'Callaghan, D.V.M., Ph.D., Graeme Duncan, M.D., David P. Dearnaley, M.D., Celestia S. Higano, M.D., Eric M. Horwitz, M.D., Eliot Frymire, M.A., Shawn Malone, M.D., Joseph Chin, M.D., Abdenour Nabid, M.D., Padraig Warde, M.B., Thomas Corbett, M.D., Steve Angyalfi, M.D., S. Larry Goldenberg, M.D., Mary K. Gospodarowicz, M.D., Fred Saad, M.D., John P. Logue, M.R.C.P., Emma Hall, Ph.D., Paul F. Schellhammer, M.D., Keyue Ding, Ph.D., and Laurence Klotz, M.D.

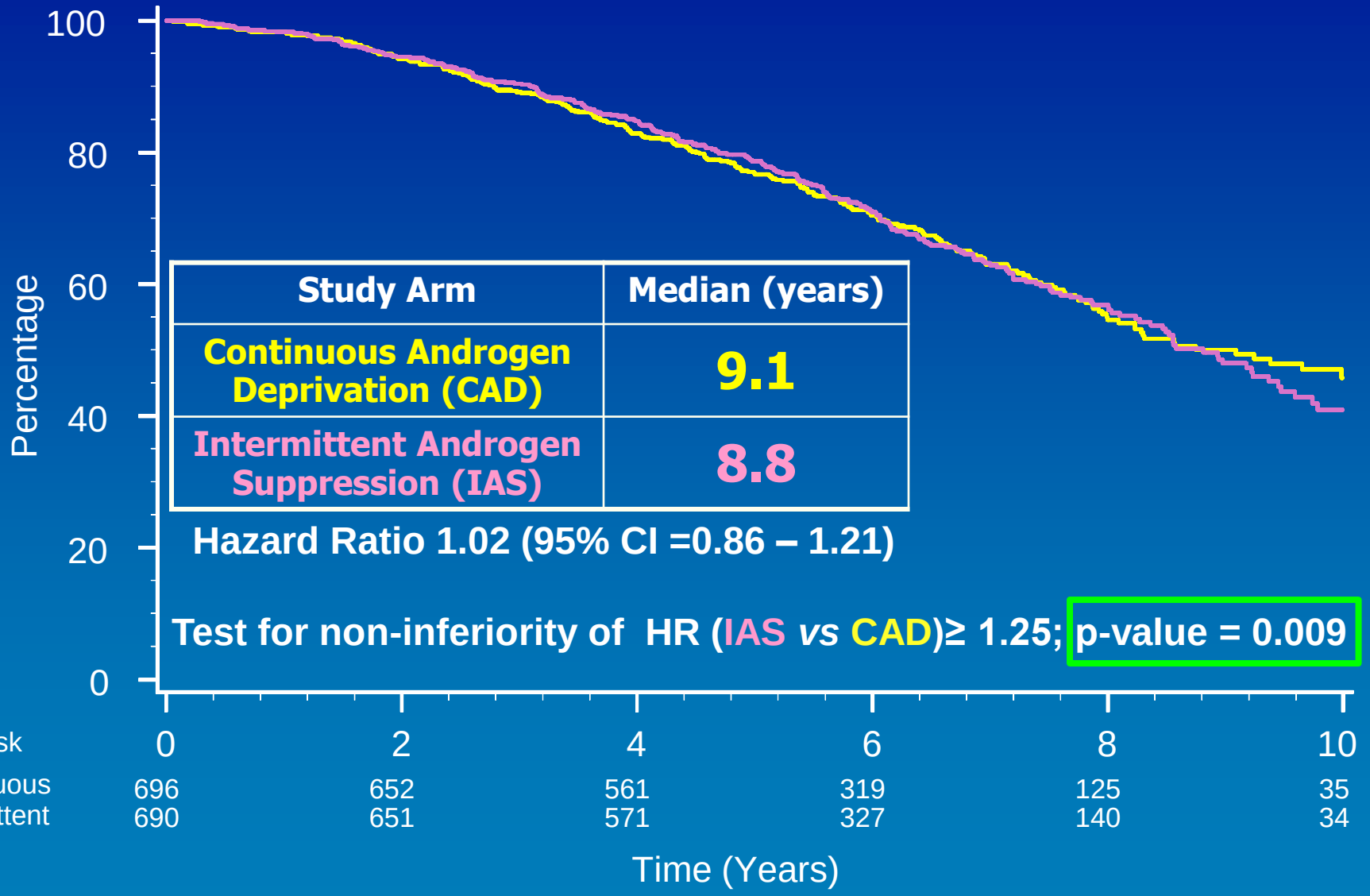
ABSTRACT

BACKGROUND

Intermittent androgen deprivation for prostate-specific antigen (PSA) elevation after radiotherapy may improve quality of life and delay hormone resistance. We assessed overall survival with intermittent versus continuous androgen deprivation in a noninferiority randomized trial.

From the British Columbia Cancer Agency, Kelowna (J.M.C., G.D.), NCIC Clinical Trials Group, Queen's University, Kingston, ON (C.J.O., E.F., K.D.), Ottawa Cancer Centre, Ottawa (S.M.), London Health Sciences

Overall Survival (ITT)



The NEW ENGLAND JOURNAL of MEDICINE

NEJM 368;14 april 4, 2013

ORIGINAL ARTICLE

Intermittent versus Continuous Androgen Deprivation in Prostate Cancer

Maha Hussain, M.D., Catherine M. Tangen, Dr.P.H., Donna L. Berry, Ph.D., R.N., Celestia S. Higano, M.D., E. David Crawford, M.D., Glenn Liu, M.D., George Wilding, M.D., Stephen Prescott, M.D., Subramanian Kanaga Sundaram, M.D., Eric Jay Small, M.D., Nancy Ann Dawson, M.D., Bryan J. Donnelly, M.D., Peter M. Venner, M.D., Ulka N. Vaishampayan, M.D., Paul F. Schellhammer, M.D., David I. Quinn, M.D., Ph.D., Derek Raghavan, M.D., Ph.D., Benjamin Ely, M.S., Carol M. Moinpour, Ph.D., Nicholas J. Vogelzang, M.D., and Ian M. Thompson, Jr., M.D.

ABSTRACT

BACKGROUND

Castration resistance occurs in most patients with metastatic hormone-sensitive prostate cancer who are receiving androgen-deprivation therapy. Replacing androgens before progression of the disease is hypothesized to prolong androgen dependence.

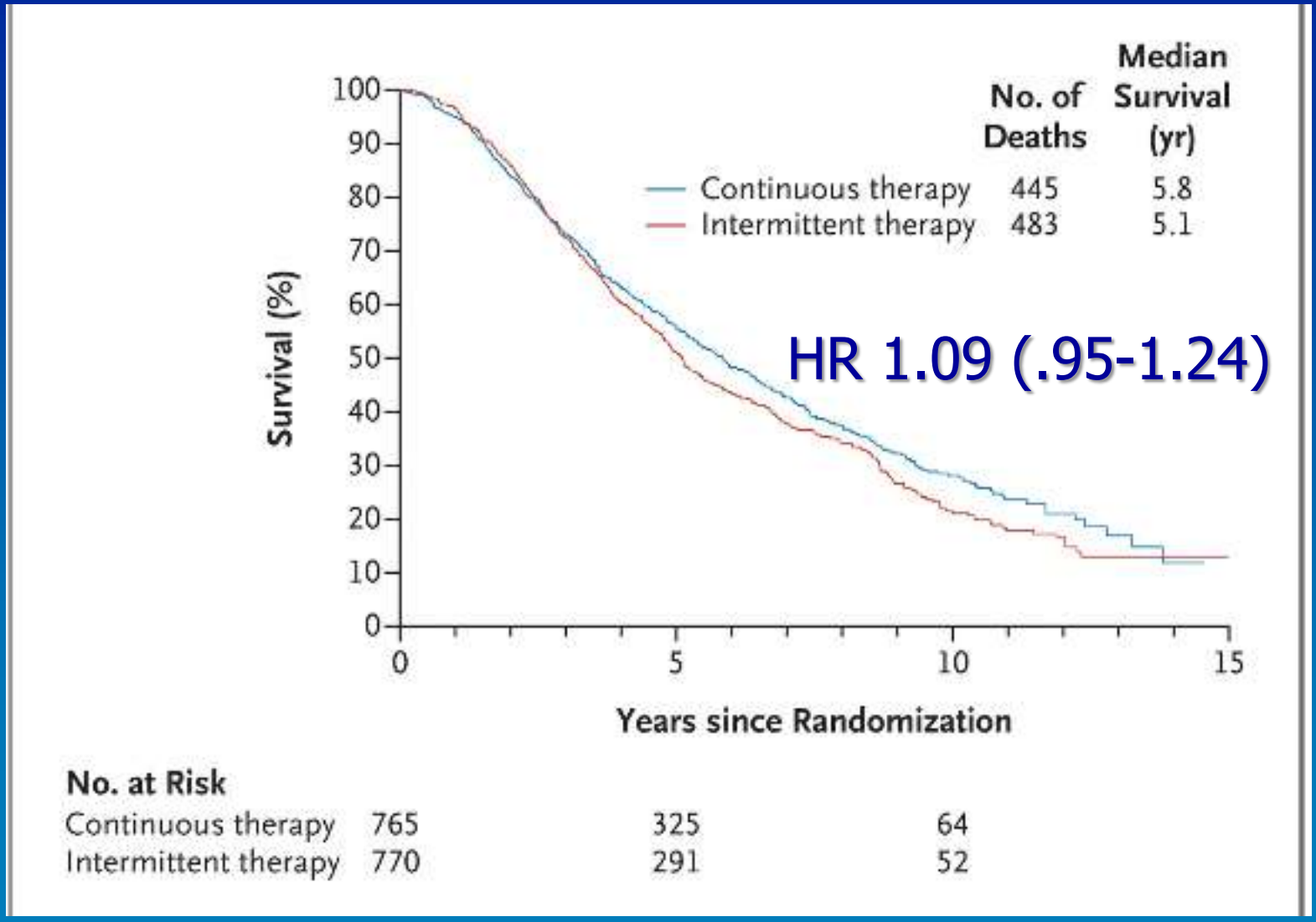
METHODS

Men with newly diagnosed, metastatic, hormone-sensitive prostate cancer, a per-

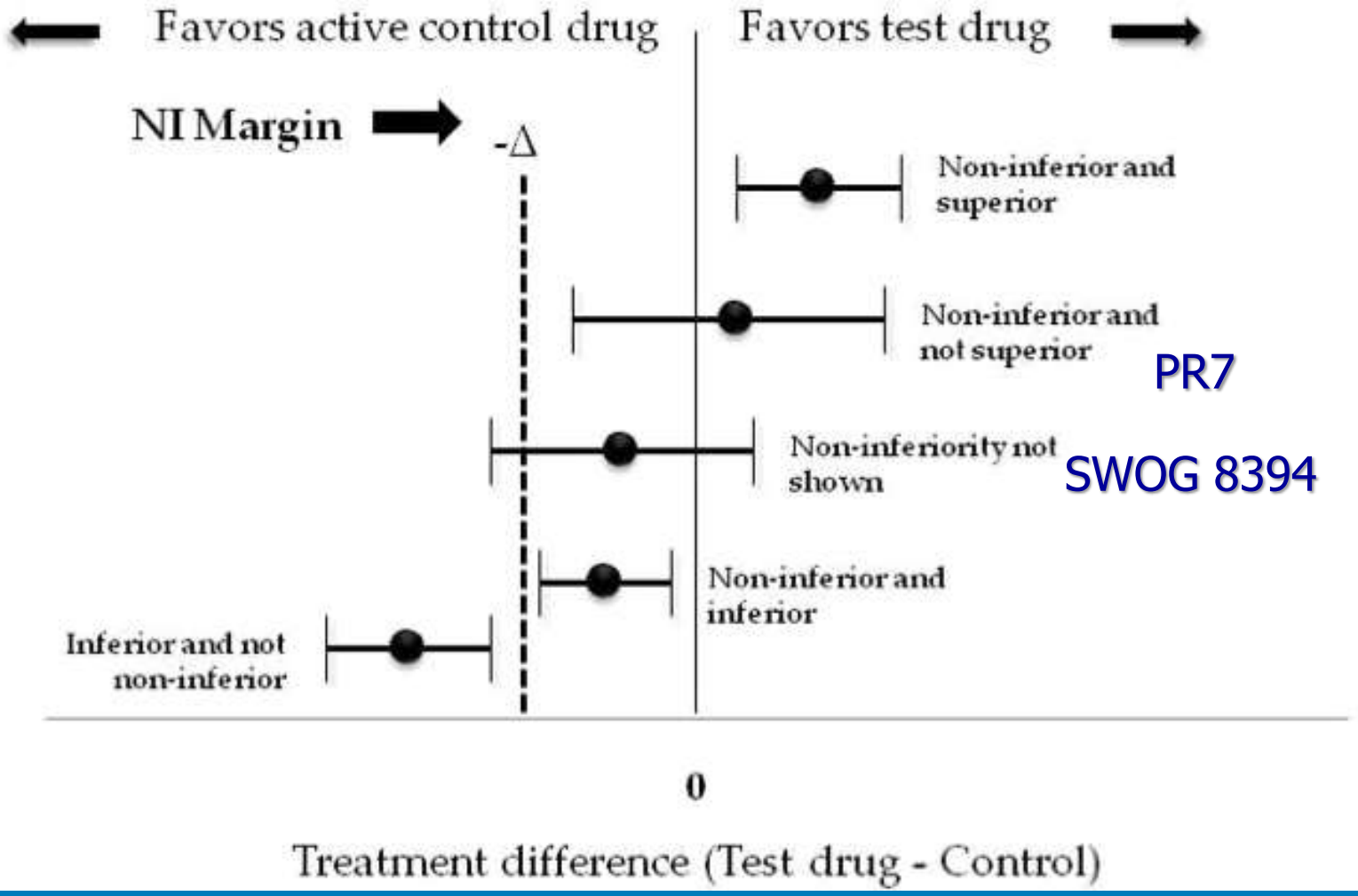
N ~ 1500 M+

Non-inferiority design; pre-defined Δ = 1.2

SWOG 9346 Survival: 'Results inconclusive'

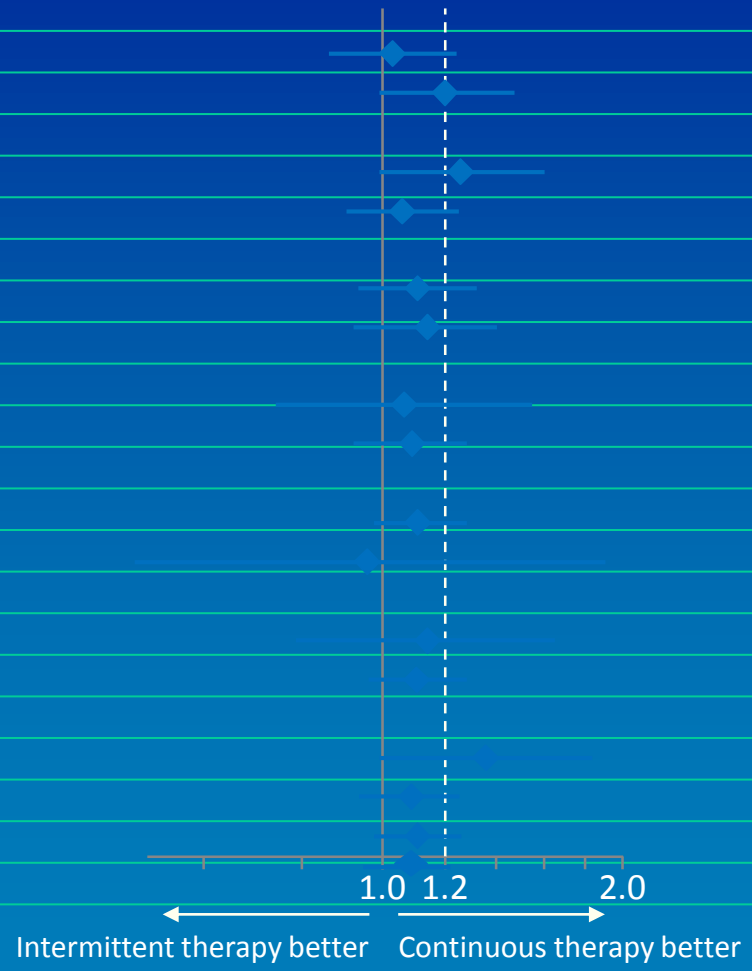


Possible outcomes of a non-inferiority trial



PR.8: Survival by Subgroups

Subgroup	No. of Patients	P Value for Interaction
Extent of disease		0.29
Extensive	743	
Minimal	792	
Bone pain		0.17
Yes	415	
No	1120	
PSA		0.61
≤ 0.2 ng/ml	995	
> 0.2–4.0 ng/ml	540	
Race		0.86
Black	189	
Not black	1066	
Performance		0.78
0 or 1	1476	
2	59	
Previous hormone therapy		0.87
Yes	186	
No	1349	
Region		0.24
Europe	280	
North America	1255	
Overall	1535	

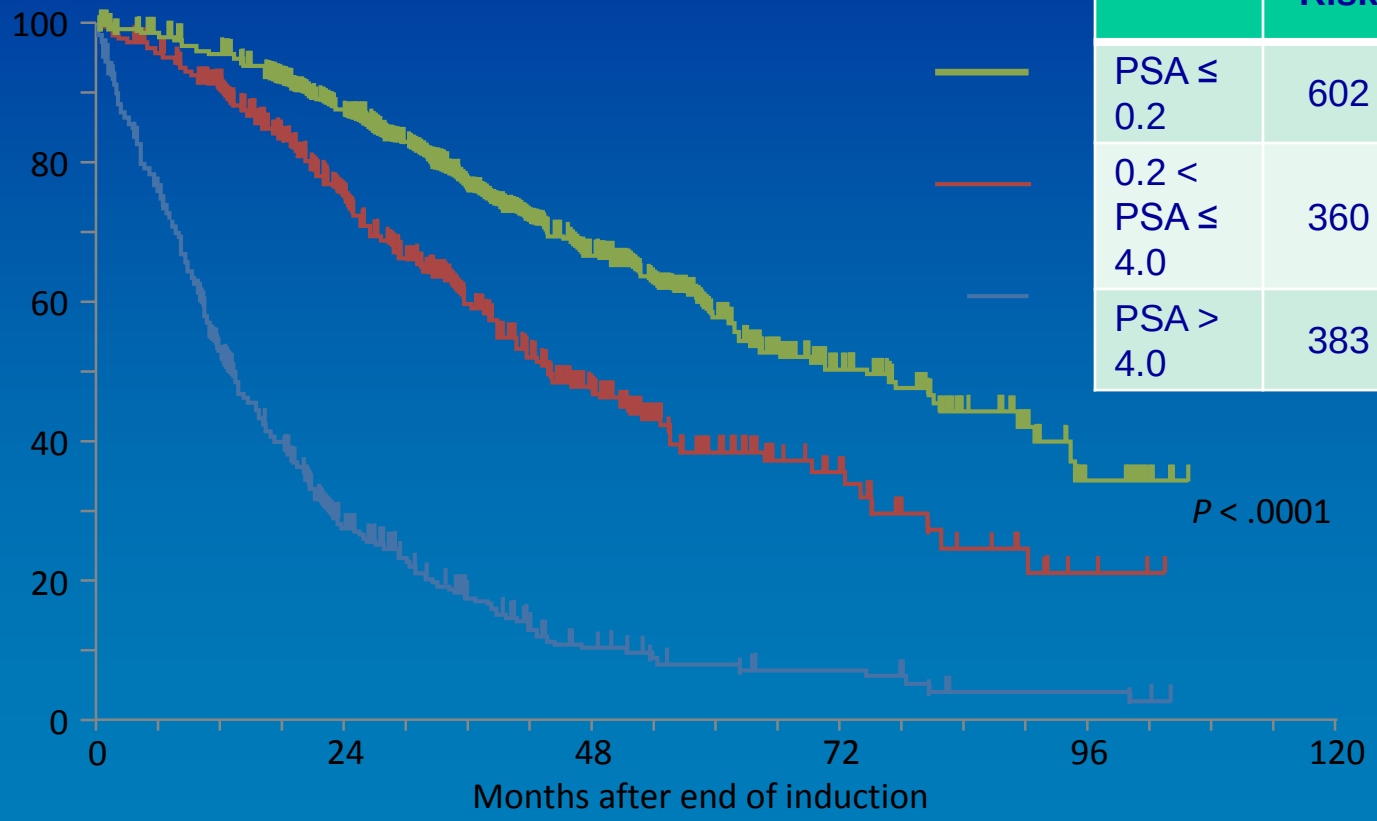


PSA, prostate specific antigen

Adapted from Hussain M, *et al. N Engl J Med* 2013;368(14):1314-25.

PSA Response is Predictive of Outcome

PSA at end of 7-month induction period and OS

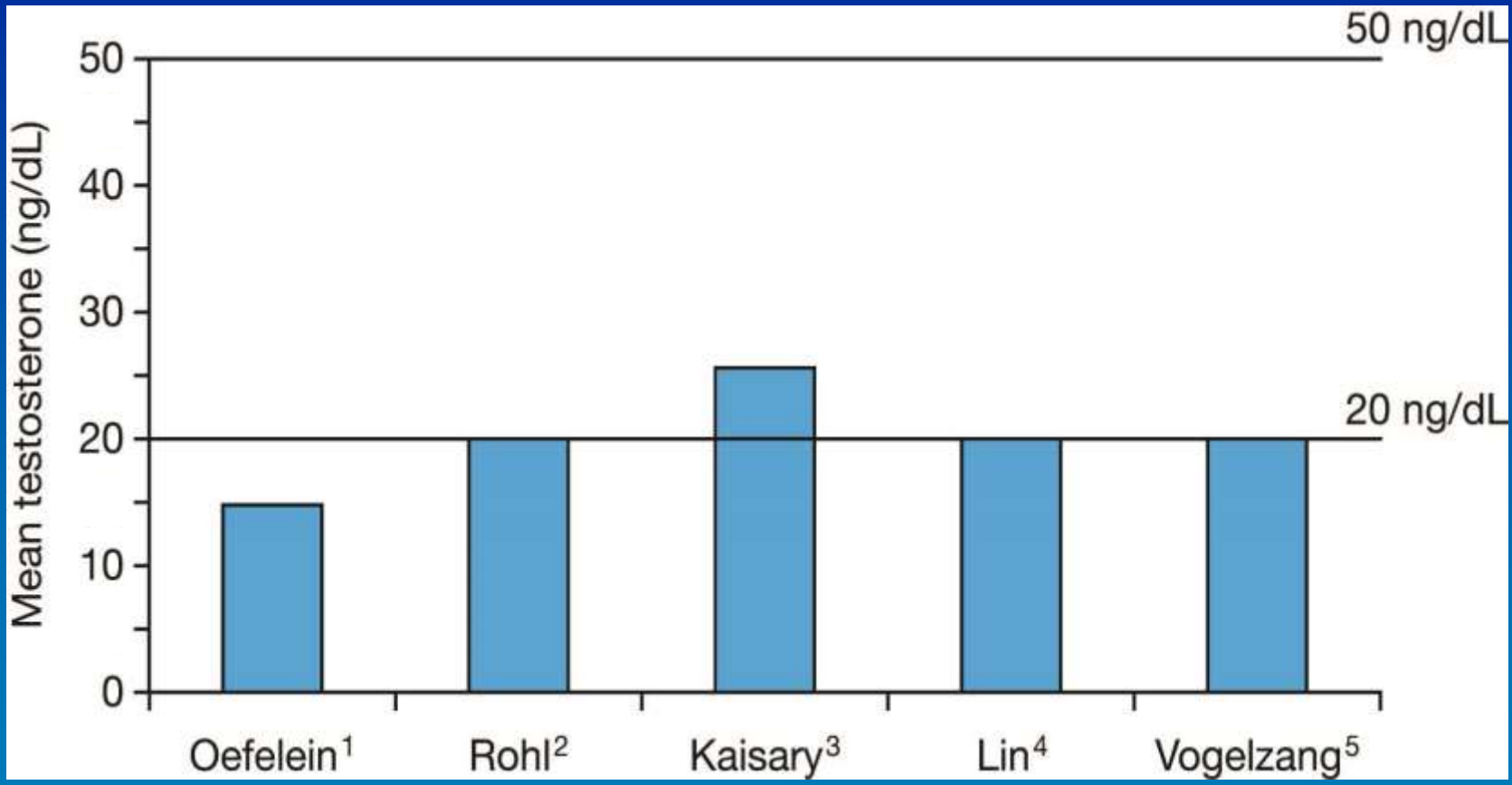


	At Risk	Deaths	Median in Months
PSA ≤ 0.2	602	199	75
0.2 < PSA ≤ 4.0	360	166	44
PSA > 4.0	383	322	13

PSA, prostate specific antigen; IAD, intermittent androgen deprivation; OS, overall survival; SWOG, Southwest Oncology Group

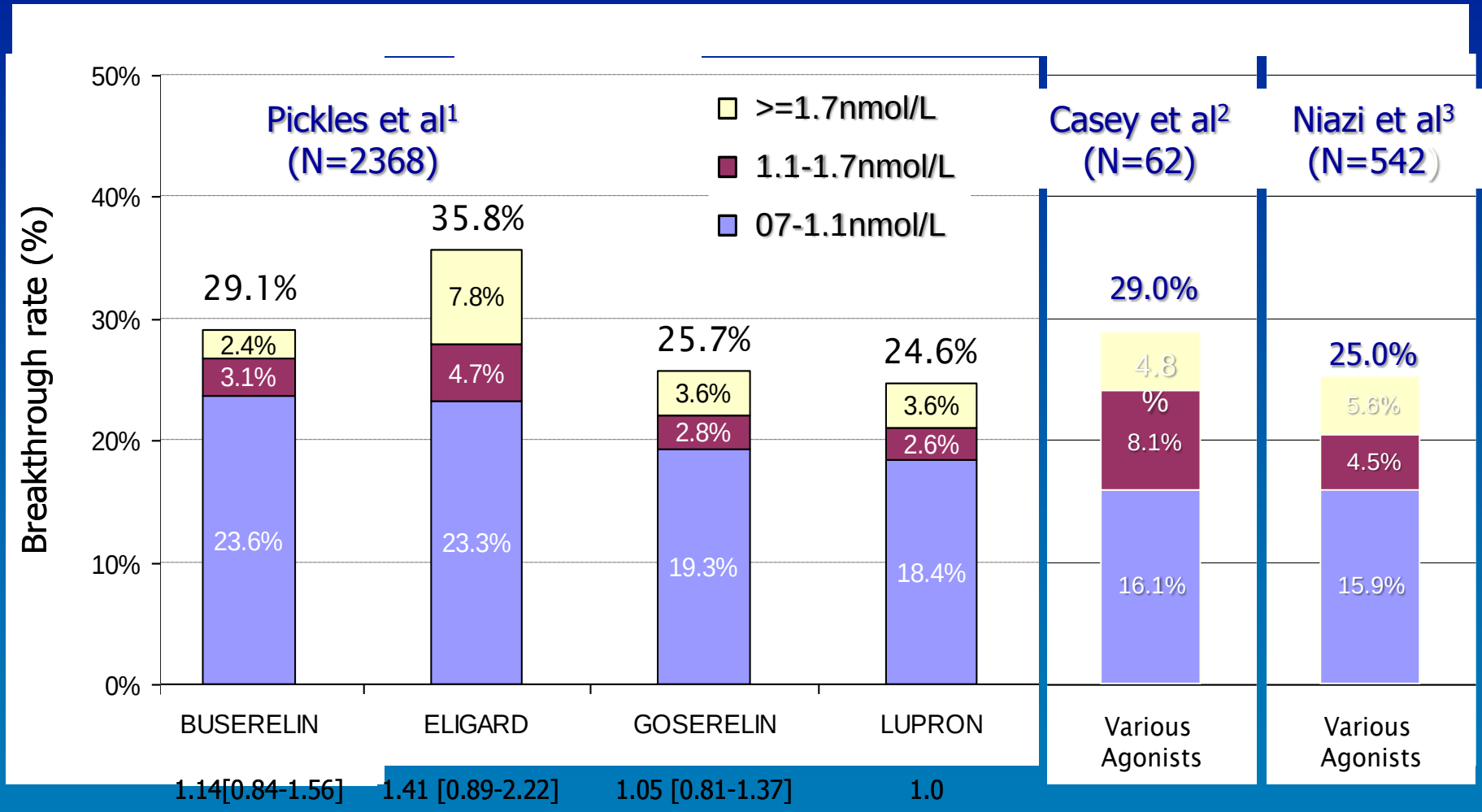
Hussain M, *et al. J Clin Oncol.* 2006;24:3984-3990.

Testosterone levels after orchiectomy



1. Oefelein, et al. Urology 2000;56:1021–4; 2. Røhl, Beuke. Scand J Urol Nephrol 1992;26:11–43; 3. Kaisary, et al. Br J Urol 1991;67:502–8; 4. Lin, et al. Urology 1994;43:834–7; 5. Vogelzang NJ et al. Urology 1995;46:220–6

Testosterone breakthrough

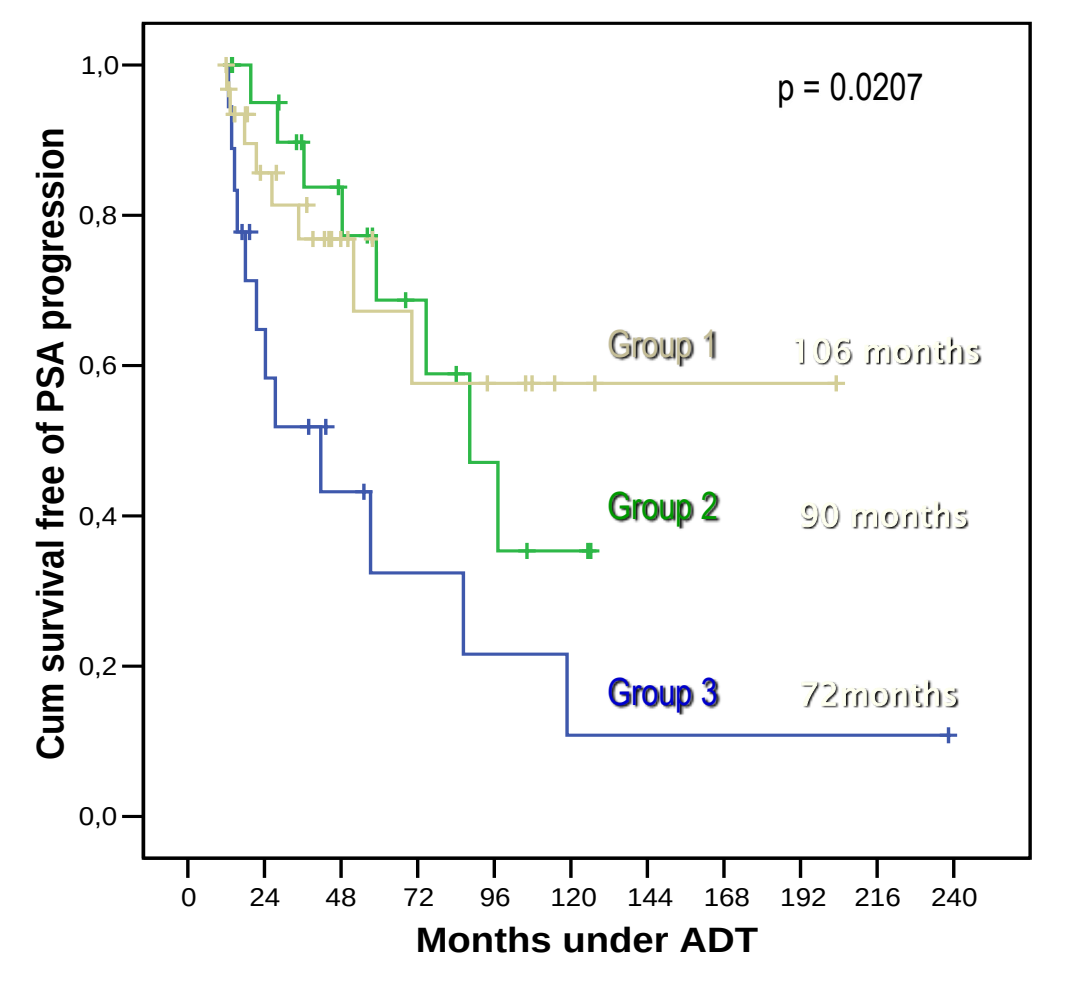


1. Casey R, Morales A, Siemens AR. CUAJ Jun 2012; Vol 6 (3Suppl1) S21
2. Pickles T et al. 2010 CARO Annual Scientific Meeting, Vancouver
3. Niazi T et al. 2013 European Cancer Congress, Amsterdam

Does the T level on ADT matter?

- 3 retrospetive studies suggested yes
  - Morote J Urol 2007: N=79
  - Parachino Euro Urol 2009: N= 129
  - Bertaglia Euro Urol 2013: 153

Survival free of AIP according to serum testosterone behaviour



Testosterone Increases

Group 1 20 ng/dL

Group 2 20–50 ng/dL

Group 3 >50 ng/dL

AIP, Androgen independent progression

Morote et al. J Urol 2007; 178: 1290-1295

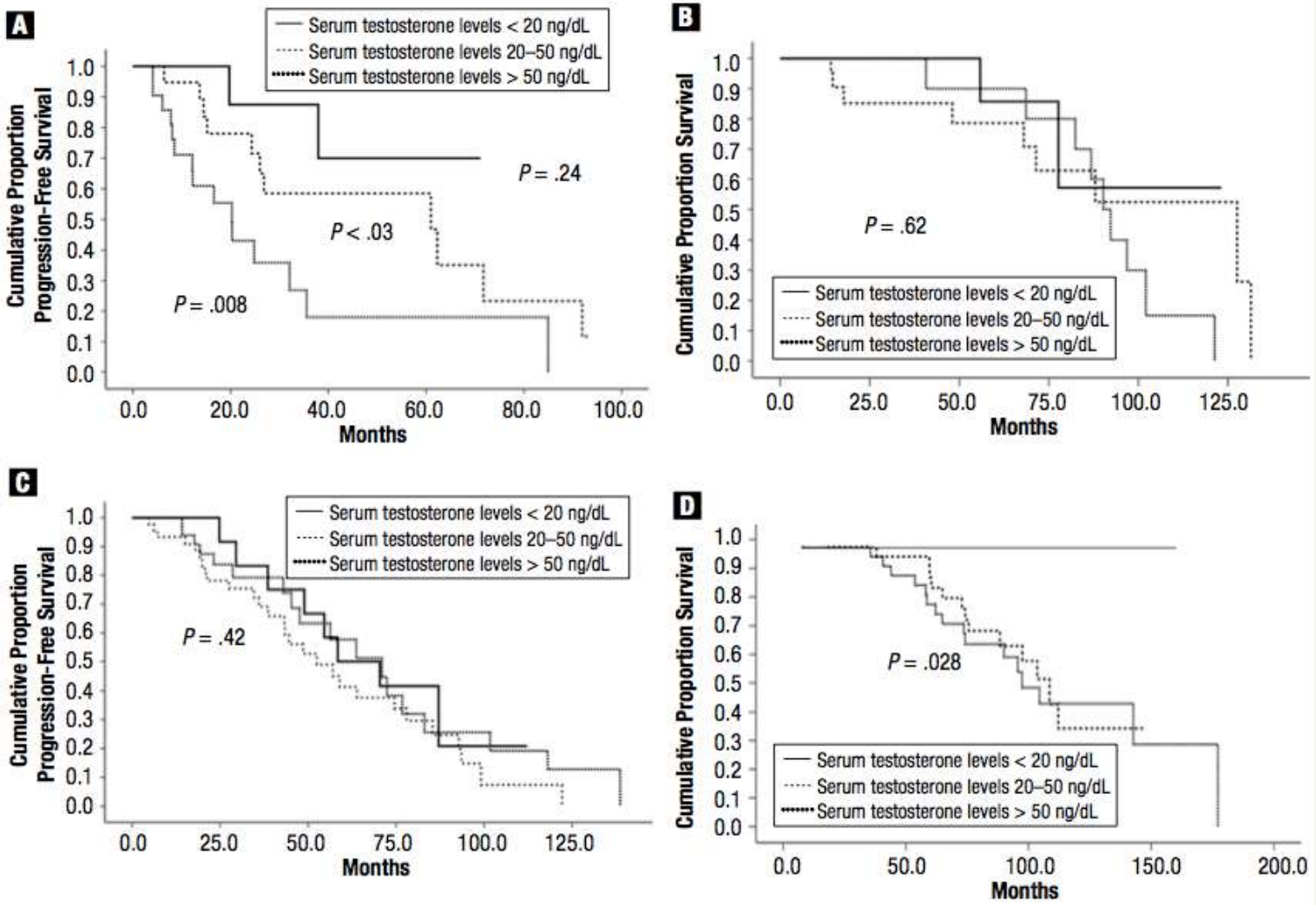
20 ng/dL = 0.7 nmol/L
50 ng/dL = 1.7 nmol/L

Testosterone Levels After 6 Months of ADT predicts PFS and OS in men with Pca Bertaglia V et al, *Clinical Genitourinary Cancer,* Vol. 11, No. 3, 325-30 20 13

N=153 men, 54 with bone mets

Whole group

99 with PSA failure

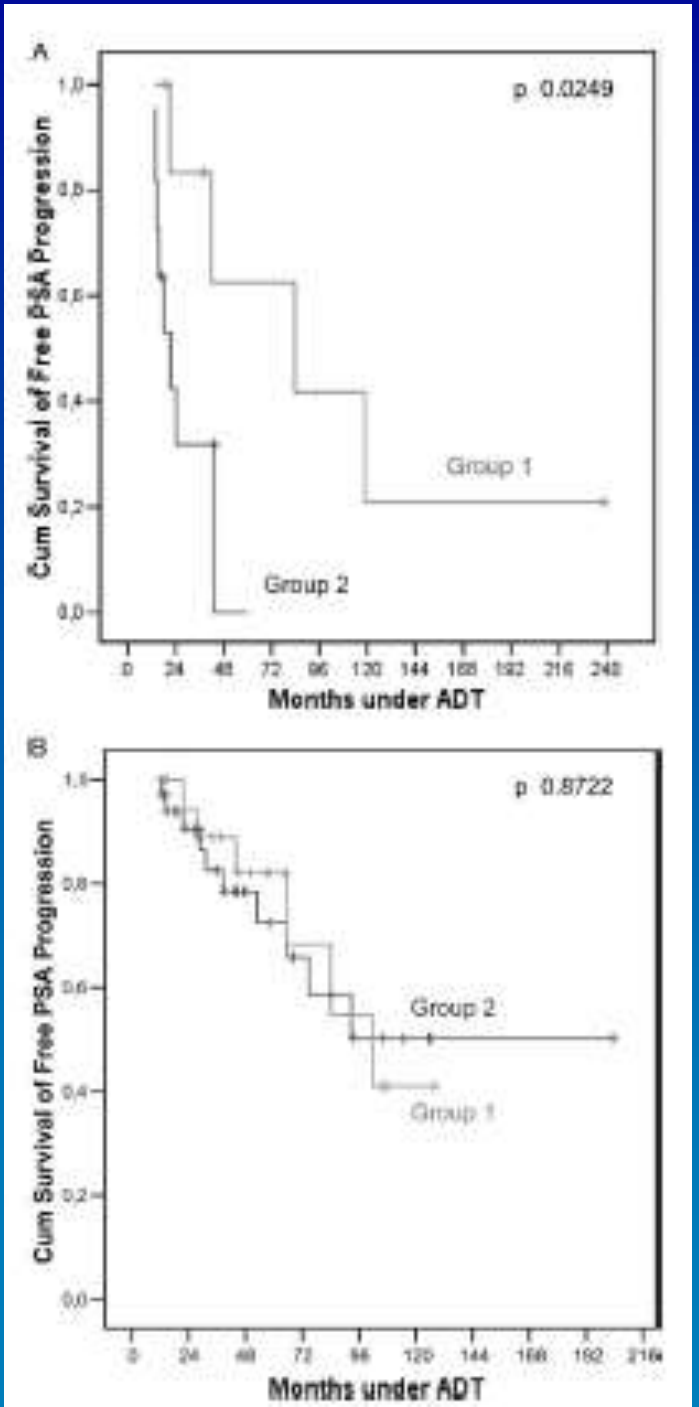


Relationship between serum T, CAB vs monotherapy with LHRH, and PFS. Morote et al. J Urol 2007; 178: 1290-1295

Group 1: CAB
Group 2: LHRH monotherapy

T > 1.7 nM

T< 1.7 nM



Conundrum: If intermittent therapy (with rising T in off treatment interval) non-inferior, how could T be important?

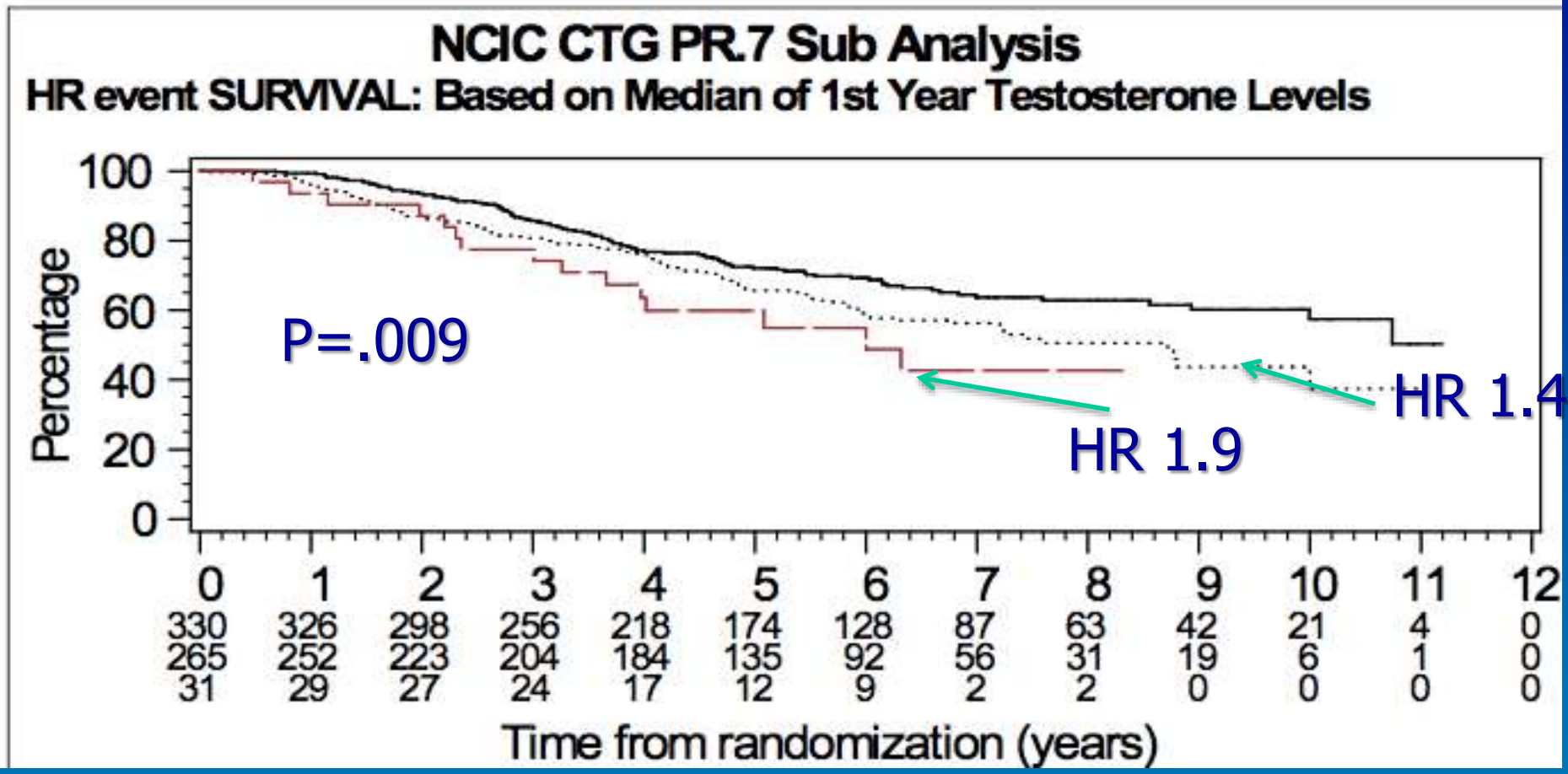
- Intracrine synthesis of androgens trhough back door pathway
- Mutations and amplification of AR, splice ligands, alteration of chaperone proteins, etc., etc.

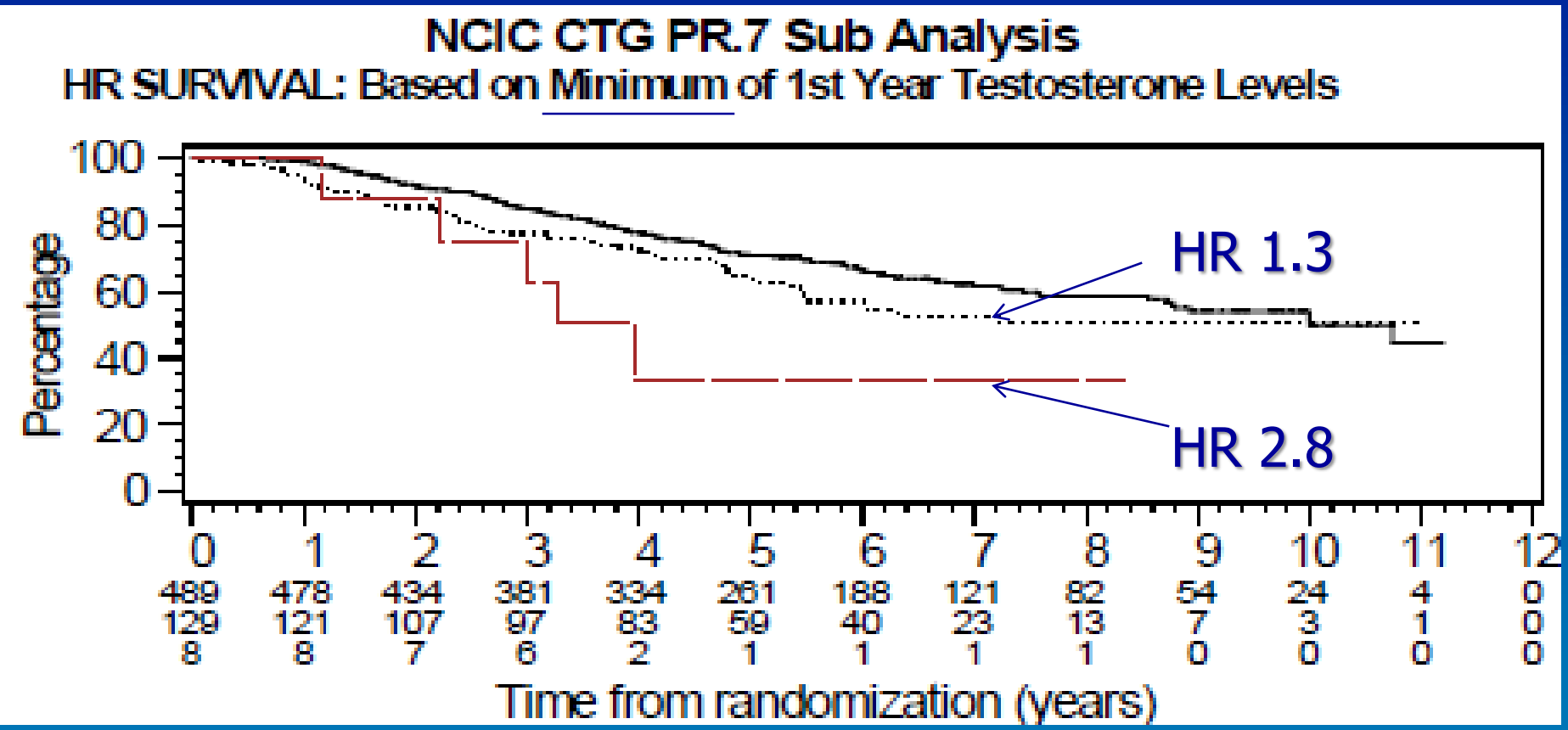
PR7 Sub-analysis: serum T on ADT in continuous arm and outcome. Klotz L et al, JCO 2015

- Analysis of the 626 patients on continuous ADT in the PR-7 trial
- Serum Testosterone measured 3 times in first year of treatment
- Examined median T and maximum T as predictor for time to CRPCa

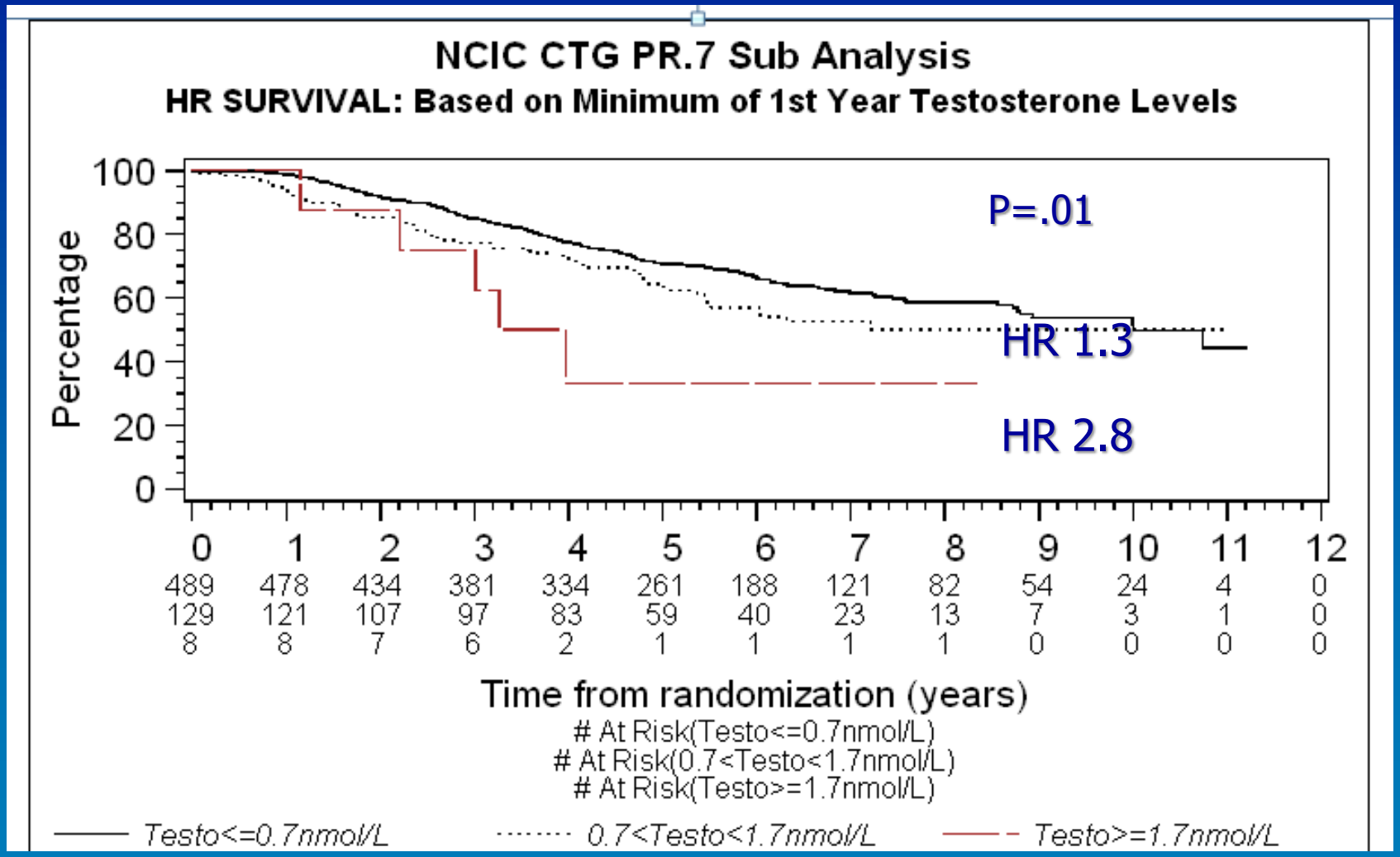
Testosterone in first year of ADT: PR7

Testosterone	≤0.7 (20)	0.7-1.7 (20-50)	≥ 1.7 (50)
Minimum T	79%	29%	1%
Median	53%	42%	5%
Maximum	27%	50%	23%


NCIC CTG PR.7 Sub Analysis
HR event SURVIVAL: Based on Median of 1st Year Testosterone Levels
Percentage
100
80
60
40
20
0
P=.009
HR 1.9
HR 1.4
0 1 2 3 4 5 6 7 8 9 10 11 12
330 326 298 256 218 174 128 87 63 42 21 4 0
265 252 223 204 184 135 92 56 31 19 6 1 0
31 29 27 24 17 12 9 2 2 0 0 0 0
Time from randomization (years)


NCIC CTG PR.7 Sub Analysis
HR SURVIVAL: Based on Minimum of 1st Year Testosterone Levels
Percentage
100
80
60
40
20
0
HR 1.3
HR 2.8
0 1 2 3 4 5 6 7 8 9 10 11 12
489 478 434 381 334 261 188 121 82 54 24 4 0
129 121 107 97 83 59 40 23 13 7 3 1 0
8 8 7 6 2 1 1 1 1 0 0 0 0
Time from randomization (years)

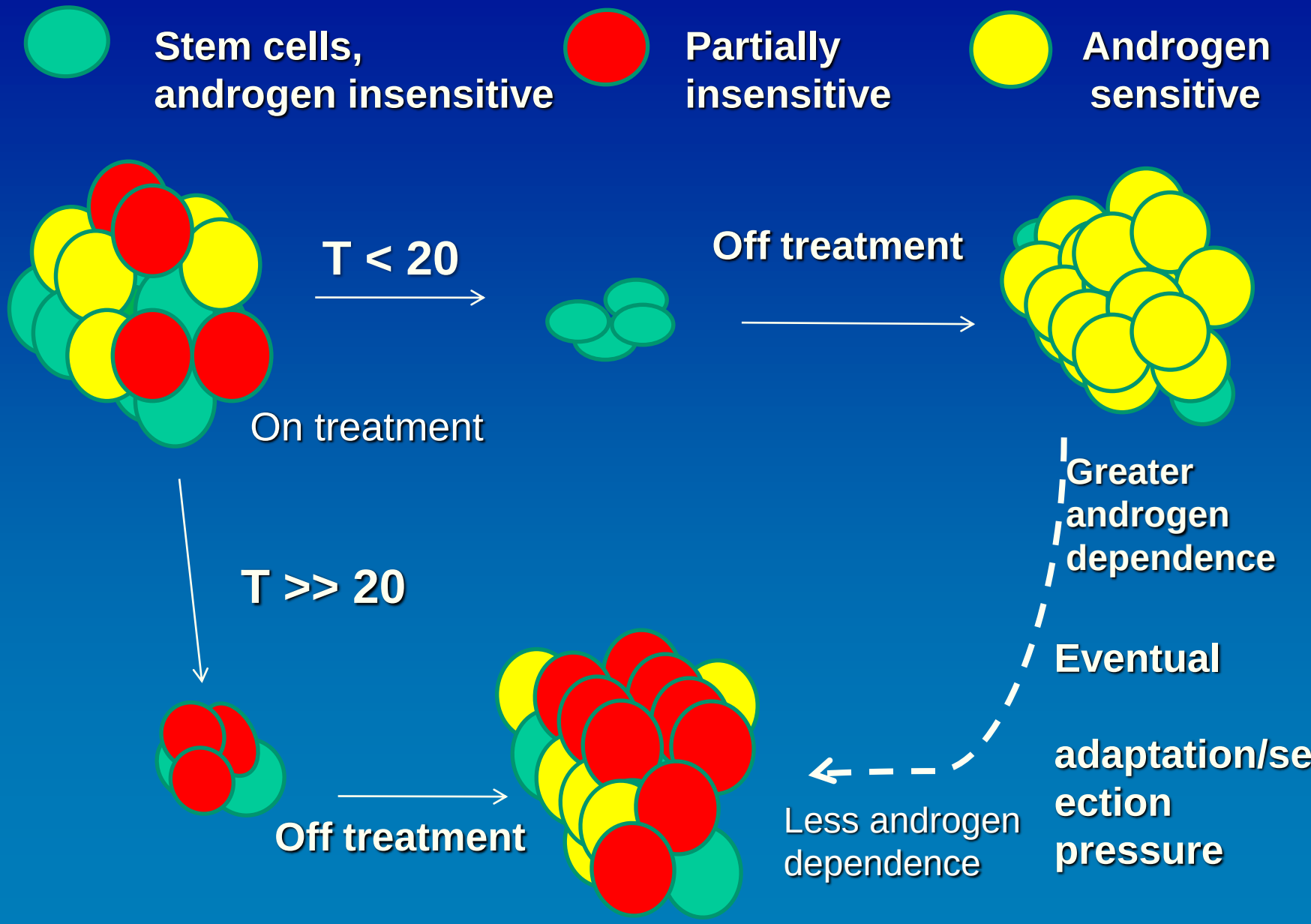
Time from hormone resistance to death by minimum T value



How to reconcile the conundrum

- Heterogeneity of prostate cancer cells response to T in vivo (demonstrated in vitro)
- Concept: Advantageous to hit cells hard in induction phase, targeting androgen sensitive and less sensitive cells
- Recovery of androgen sensitive cells in off treatment interval

3 cell type model can explain conundrum



ADT and cardiovascular risk

- Many studies, mostly population based, retrospective
- Results conflicting
- No prospective randomized studies with primary CV endpoint
- Larger trials support increased risk
- All studies suggest risk increased in men with pre-existing CV disease
- Key reference: ADT in Pca and CV risk: A Science Advisory from the AHA, AUA, ASTRO. Levine GN et al. CA Cancer J Clin. 2010;60(3):194-201
- “ADT adversely affects CV risk factors, including serum lipoproteins, insulin sensitivity, and obesity. There is a relation between ADT and an increased risk of cardiovascular disease, although different studies have and have not reported an increased risk of cardiovascular death.”

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European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by XXX on pp. x–y of this issue

Cardiovascular Morbidity Associated with Gonadotropin Releasing Hormone Agonists and an Antagonist

Peter C. Albertsen[a,*], *Laurence Klotz*[b], *Bertrand Tombal*[c], *James Grady*[a], *Tine K. Olesen*[d], *Jan Nilsson*[e]

[a] *University of Connecticut Health Center, Farmington, CT, USA;* [b] *Division of Urology, University of Toronto, ON, Canada;* [c] *University Clinics Saint Luc/Catholic University of Louvain, Brussels, Belgium;* [d] *Ferring Pharmaceuticals, Copenhagen, Denmark;* [e] *Department of Clinical Sciences, Lund University, Sweden*

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European Association of Urology

Prostate Cancer

Disease Control Outcomes from Analysis of Pooled Individual Patient Data from Five Comparative Randomised Clinical Trials of Degarelix Versus Luteinising Hormone-releasing Hormone Agonists

Laurence Klotz[a,*], *Kurt Miller*[b], *E. David Crawford*[c], *Neal Shore*[d], *Bertrand Tombal*[e], *Cathrina Karup*[f], *Anders Malmberg*[f], *Bo-Eric Persson*[g]

[a] *Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada;* [b] *Charité Universitätsmedizin Berlin, Berlin, Germany;* [c] *University of Colorado, Denver, CO, USA;* [d] *Carolina Urologic Research Center, Myrtle Beach, SC, USA;* [e] *Cliniques Universitaires Saint Luc/Université Catholique de Louvain, Brussels, Belgium;* [f] *Ferring Pharmaceuticals, Copenhagen, Denmark;* [g] *Ferring Pharmaceuticals, Saint-Prex, Switzerland*

Pooled patient population (N=2328)
707 had pre-existing CV co-morbidity

12-month phase III trials

CS21
Degarelix 240/80 mg; n=207
Degarelix 240/160 mg; n=202
Leuprolide 3.6 mg; n=201

CS35
Degarelix 240/480 mg; n=565
Goserelin 3.6/10.8 mg; n=283

CS37
Degarelix 240/80 mg; n=175*
Degarelix 240/80 mg; n=50
Leuprolide 3.6 mg; n=178

3-month phase IIIB trials

CS28
Degarelix 240/80 mg; n=27
Goserelin 3.6 mg; n=13

CS30
Degarelix 240/80 mg; n=181
Goserelin 3.6 mg; n=64

CS31
Degarelix 240/80 mg; n=83
Goserelin 3.6 mg; n=98

*Patients received 7 months of treatment

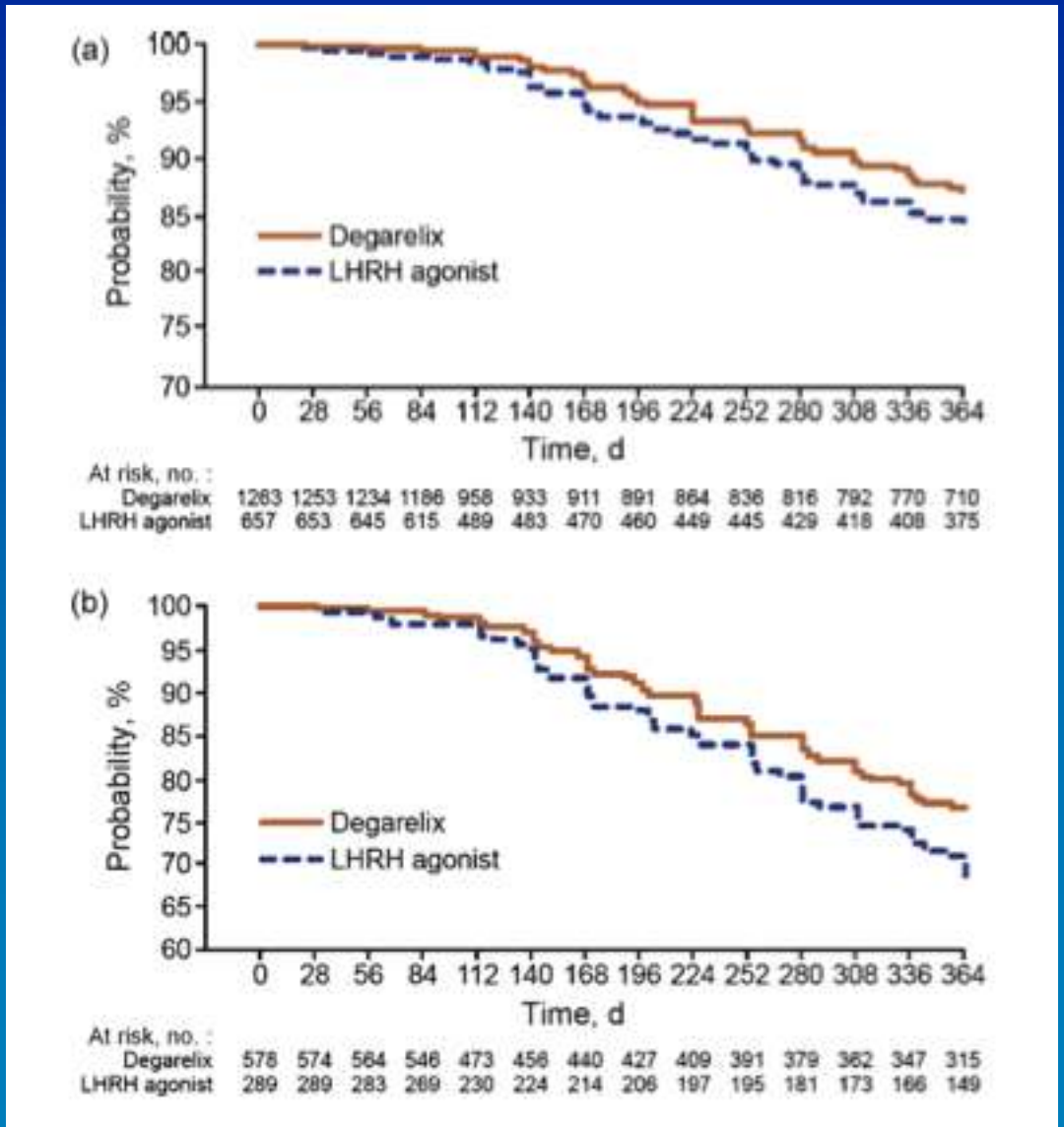
Pooled Degarelix analysis

- Strengths:
  - Increased power to detect differences
  - More adverse events
  - All studies prospective, randomized, blinded
  - Detailed information about CV co-morbidity collected during trial
- Limitations:
  - Pooled analysis
  - Short term studies (3 and 12 months)
  - Post hoc analysis
  - Hypothesis generating

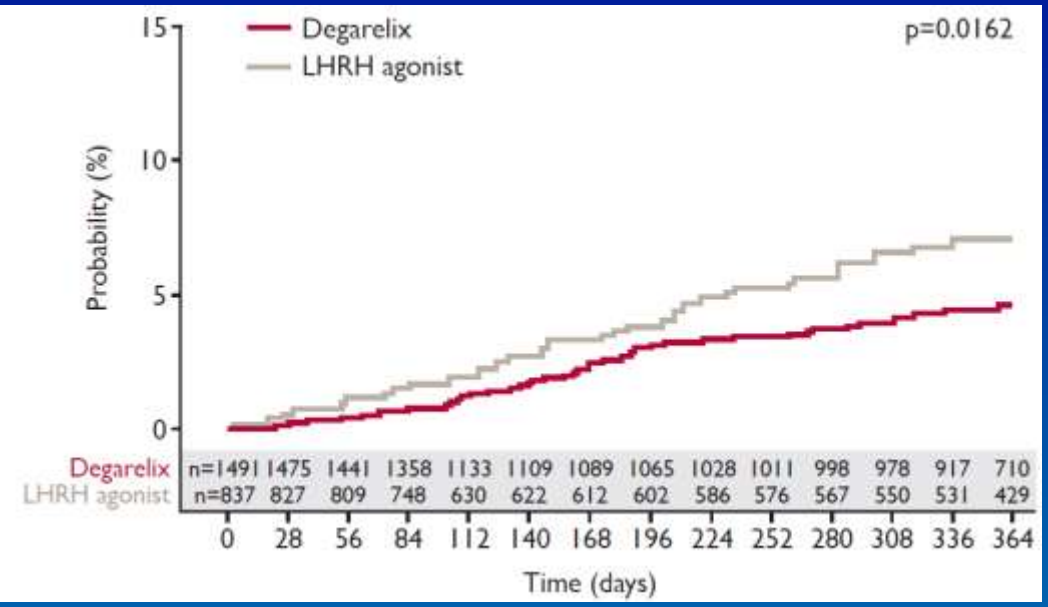
PSA progression: Pooled analysis

All patients

PSA > 20

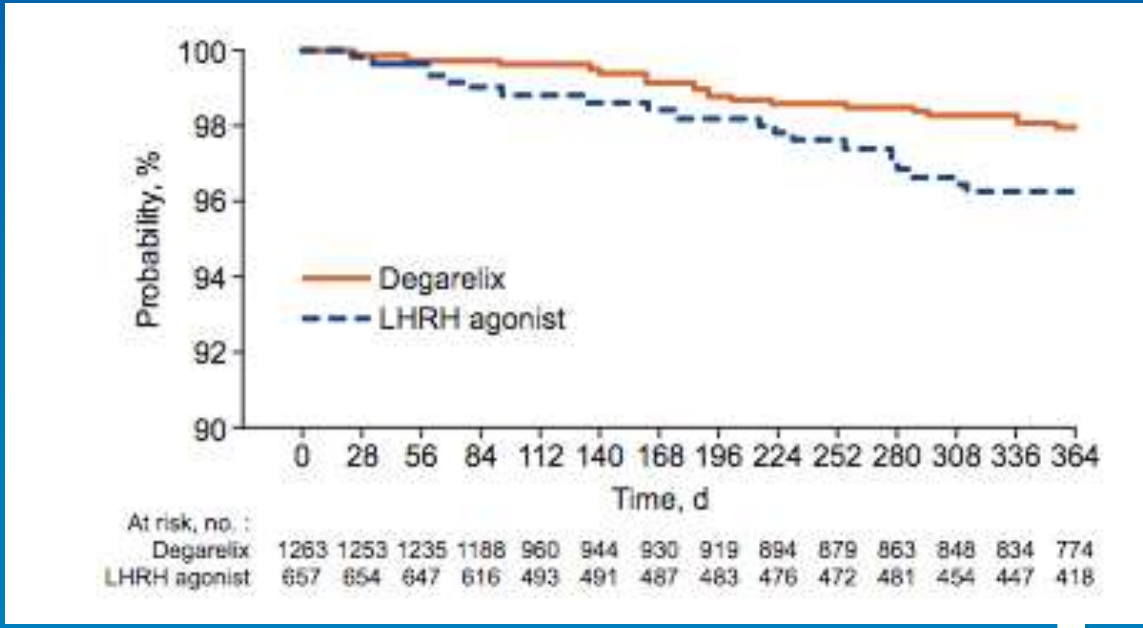


Risk of CV event and OS

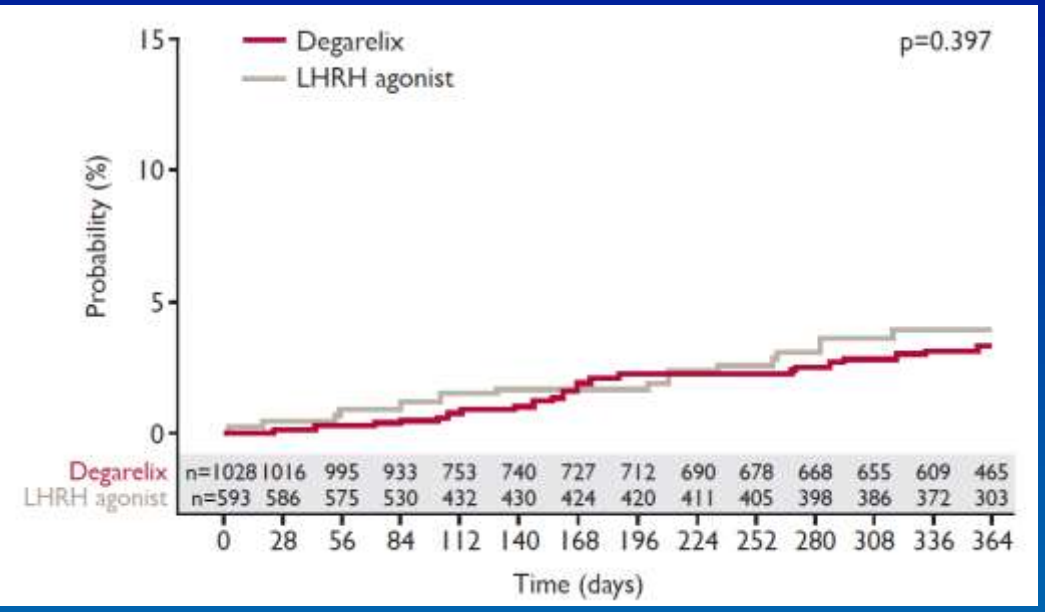


CV events

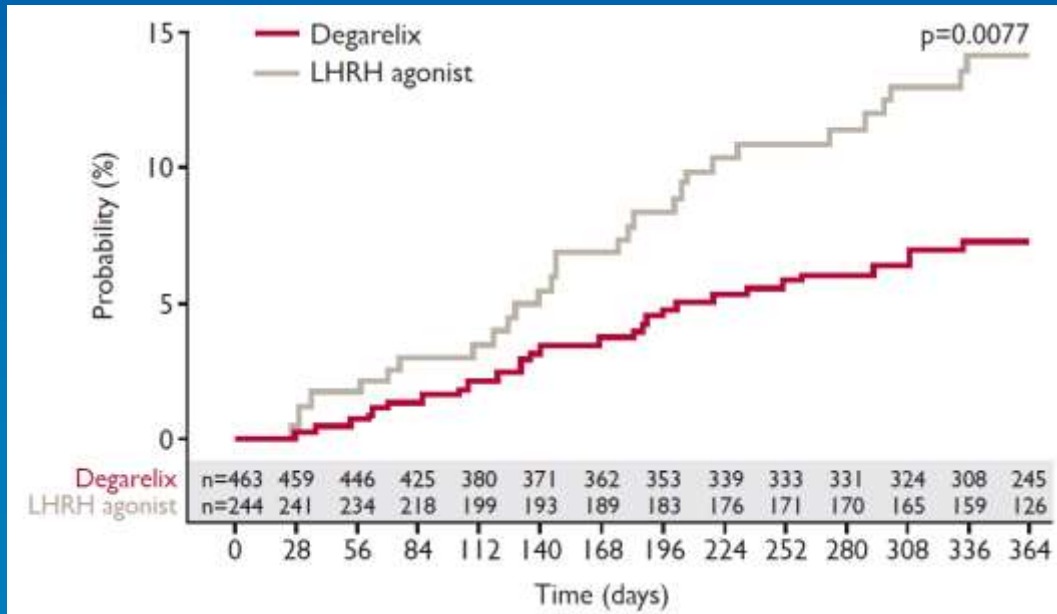
OS P=.02



Risk of CV event or death in men with and without baseline CVD

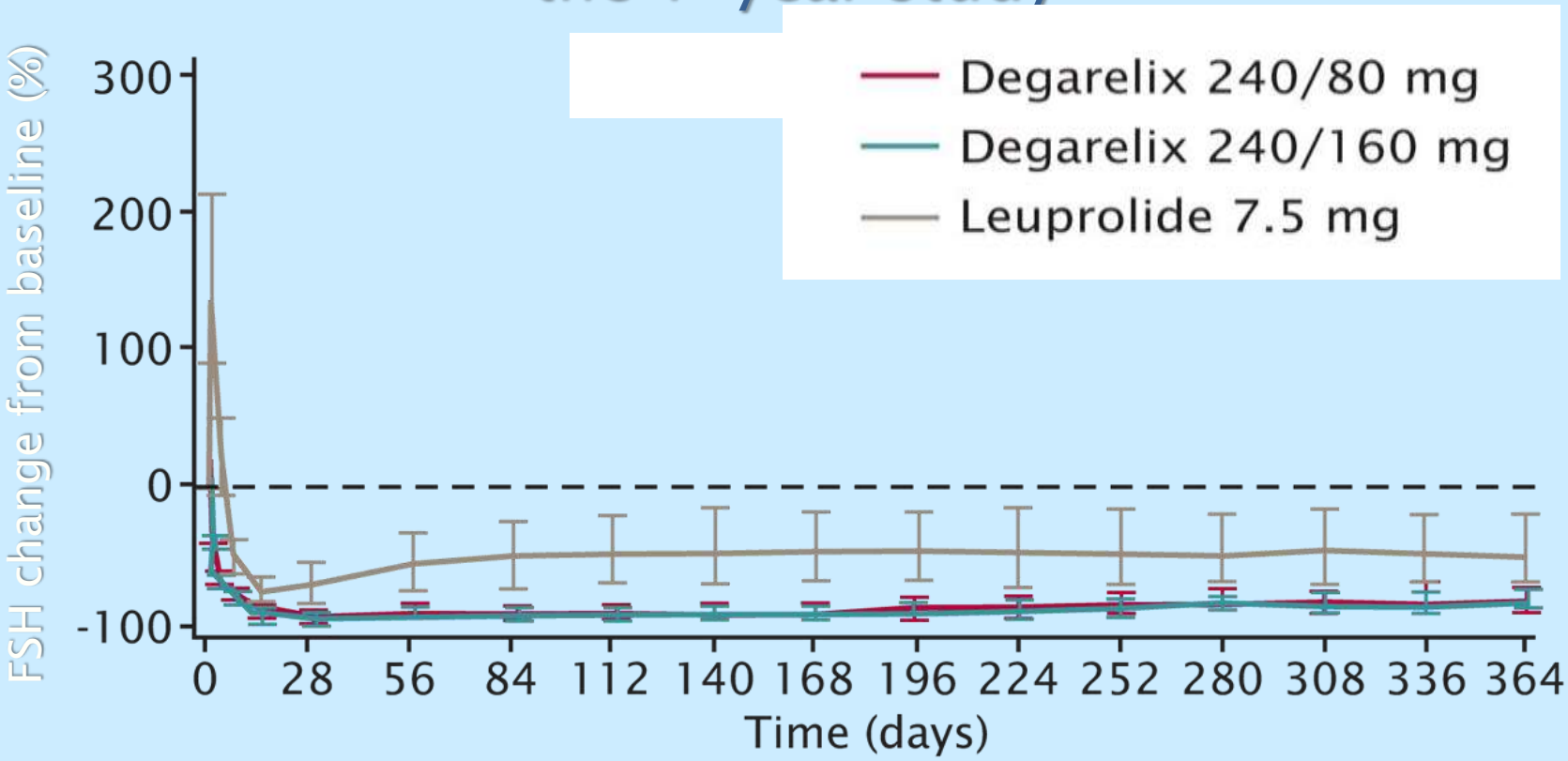


Relative risk reduction of 50%
Absolute risk reduction 7%



Degarelix -FSH

FIRMAGON rapidly decreased FSH and maintained lower levels than leuprolide during the 1-year study



Klotz L, et al. *BJU Int*. 2008;102:1531-1538.

FSH results should be interpreted with caution because the clinical relevance has not been determined.

Biologically plausibility:

- Conventional wisdom: CV events related to metabolic syndrome and other effects of androgen deprivation
- But several other explanations:
  1. FSH receptor activity in prostate cancer, endothelium, adipocytes, bone mineral density
  2. LHRH receptors in endothelial plaque macrophages and T cells

FSH and FSH-receptors in prostate cancer

FSH and FSH-receptors expressed in

- Normal prostate +
- BPH ++
- Prostate cancer +++
- Androgen refractory prostate cancer ++++

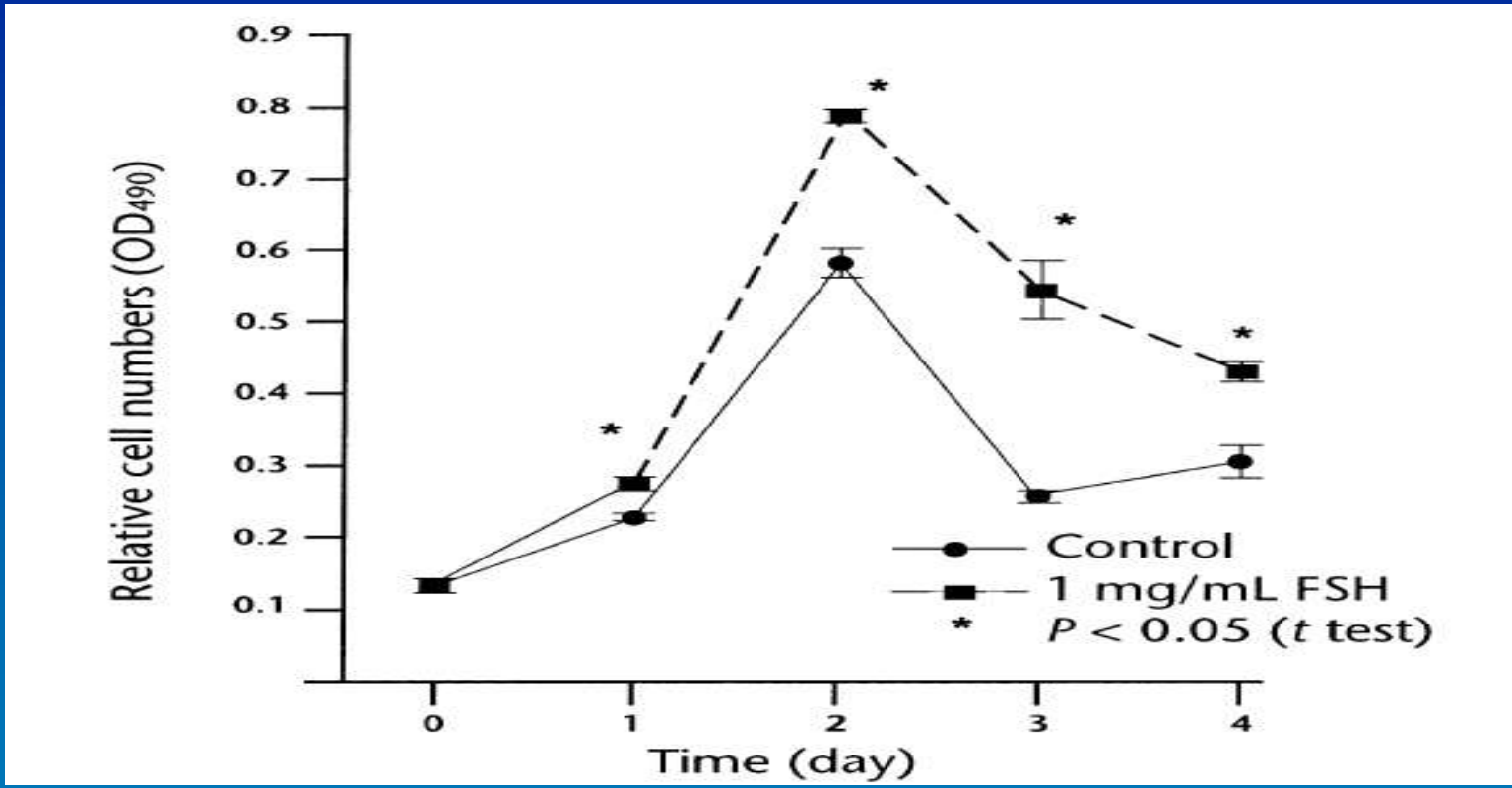
ALSO:

- Adipocytes +++
- Cardiac Myocytes +++

+ low prevalence; ++++ high prevalence

Mariani S et al. J Urol 2006; 175: 2072-2077

FSH stimulates growth of PC-3 human prostate cancer cells



PC-3 cell lines express the highest levels of FSH receptor protein

Ben – Josef E et al. J Urol 1999; 161: 970-976

Serum FSH associated with extraprostatic extension of Pca Ide H et al, Prostate Int 2013;1(3):109-112

Factors predicting for ECE

Variable	OR (95% CI)	*P*-value
Gleason score	2.04 (0.75–5.54)	0.16
Log PSA	0.65 (0.13–3.29)	0.60
Log tumor size	23.93 (1.10–521.36)	0.04
Log FSH	4.47 (1.09–18.31)	0.04

Factors prediction for tumour size

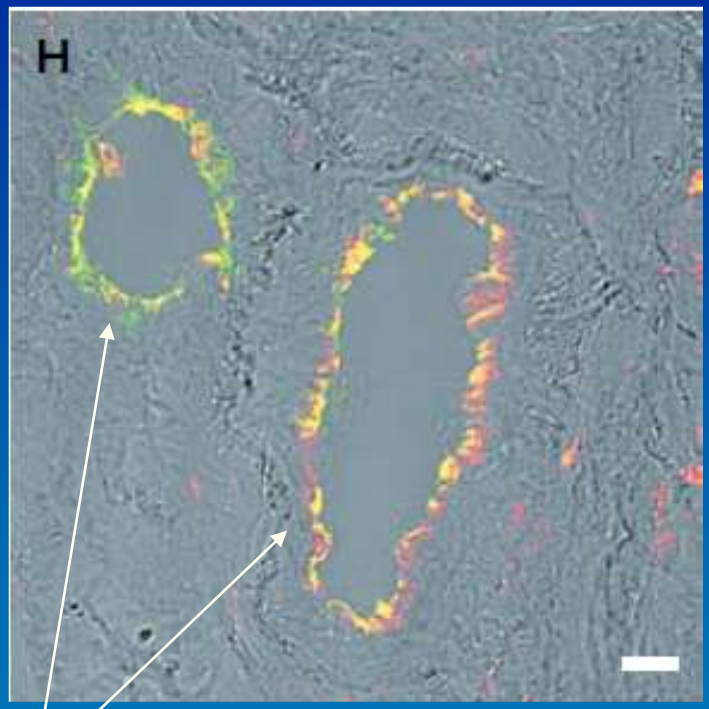
Variable	Parameter (95% CI)	*P*-value
Gleason score	1.51 (0.02–3.00)	0.050
No. of tumors	–0.17 (–0.91–0.58)	0.660
Log FSH	2.82 (0.72–4.92)	0.010
Log PSA	5.72 (3.40–8.02)	<0.001

FSH receptors identified on prostate tumour blood vessels 2010

Tumour blood vessels become resistant to therapy

FSH receptor signalling may be associated with tumour cell proliferation

Lowering FSH levels decreases proliferation of PCa cells



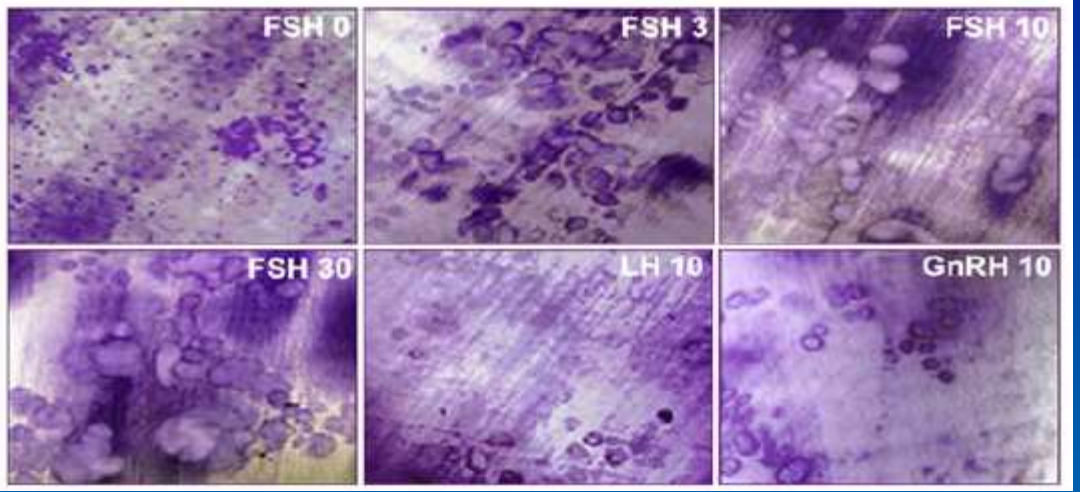
Cells expressing FSH receptors

Radu A et al. N Engl J Med 2010;363:1621-30

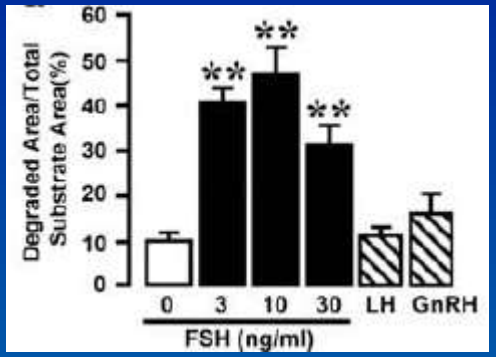
Cell

FSH Directly Regulates Bone Mass

Li Sun,[1] Yuanzhen Peng,[1] Allison C. Sharrow,[2,3] Jameel Iqbal,[1] Zhiyuan Zhang,[1] Dionysios J. Papachristou,[2,3] Samir Zaidi,[1] Ling-Ling Zhu,[1] Beatrice B. Yaroslavskiy,[2,3] Hang Zhou,[1] Alberta Zallone,[4] M. Ram Sairam,[5]



Cell 125, 247–260, April 21, 2006



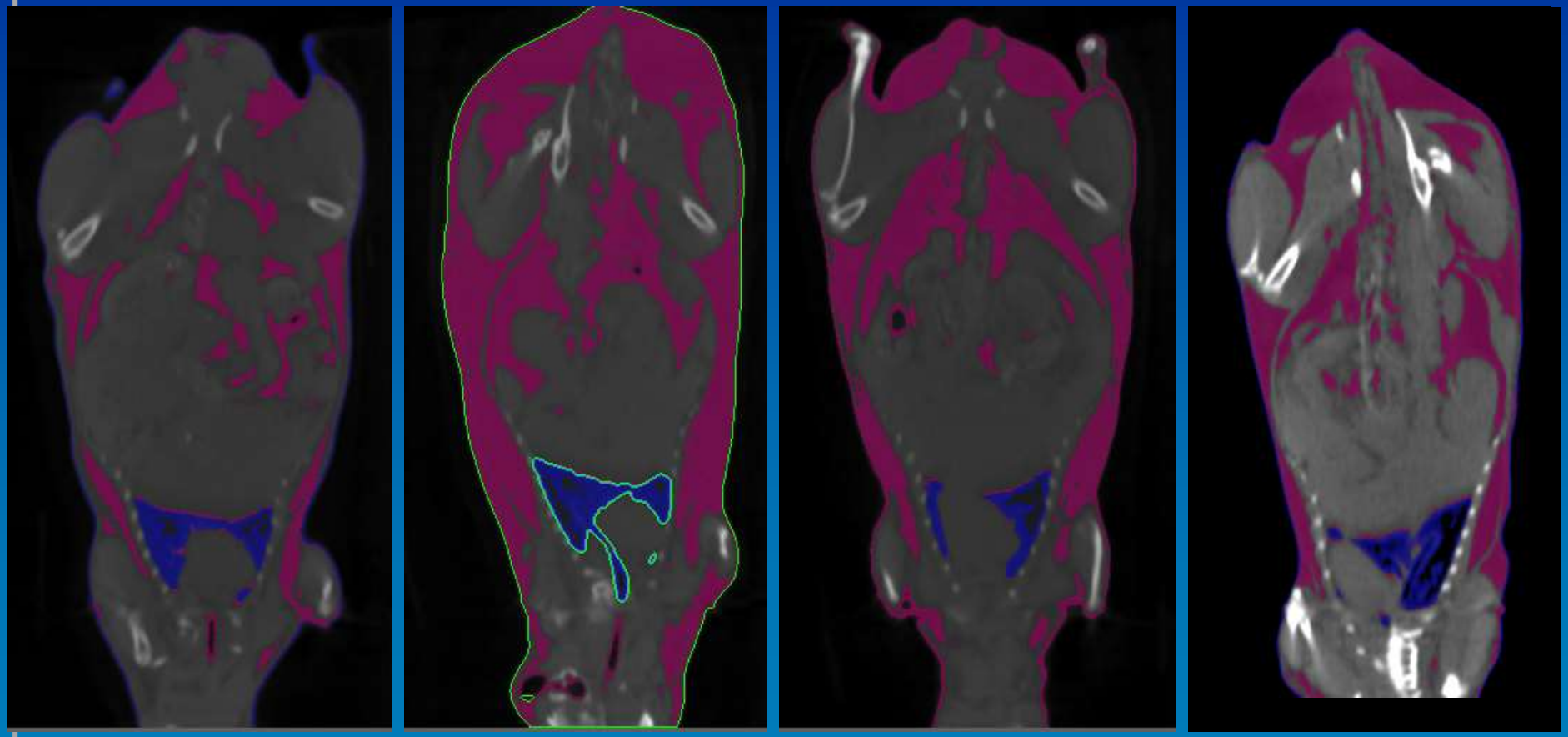
- FSH directly increases osteoclastogenesis and resorption
- Gi2a-coupled FSH receptors activate osteoclast NF-kB, and Akt resulting in enhanced osteoclast formation and function.
- High circulating FSH causes hypogonadal bone loss.

How to explain difference in CV events: T cell activation by GnRH agonists

- Most acute CV events caused by rupture of atherosclerotic plaque
- Plaque degradation by infiltrating macrophages releasing matrix-degrading proteases
- Proinflammatory T-helper 1 (Th1) lymphocytes are macrophage activators; dominant in arterial plaques
- These express GnRH receptors
- GnRH activation stimulates T-cell expansion and Th1 differentiation
- GnRH agonists could promote plaque destabilization

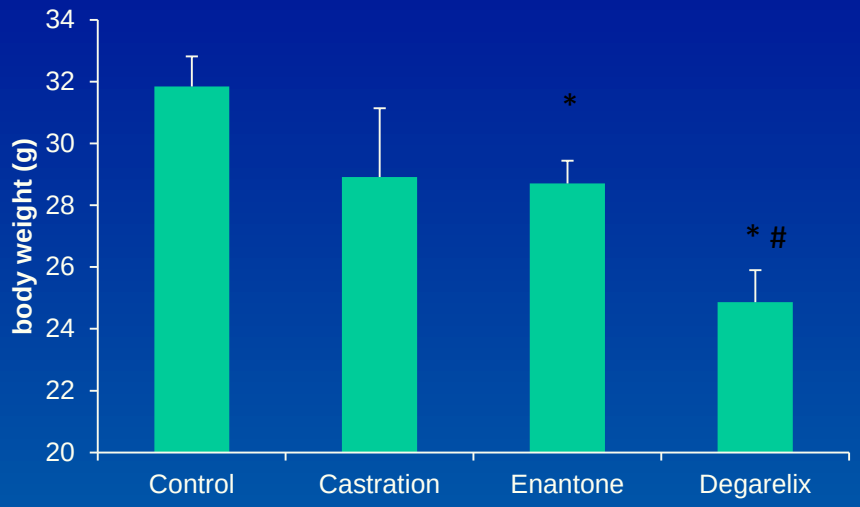
Differential adiposity between differernt types of ADT. Hopmans S, Klotz L, Pinthus J. Urol Oncol 32(8):1126-34, 2014

control castration LHRH agonist degarelix

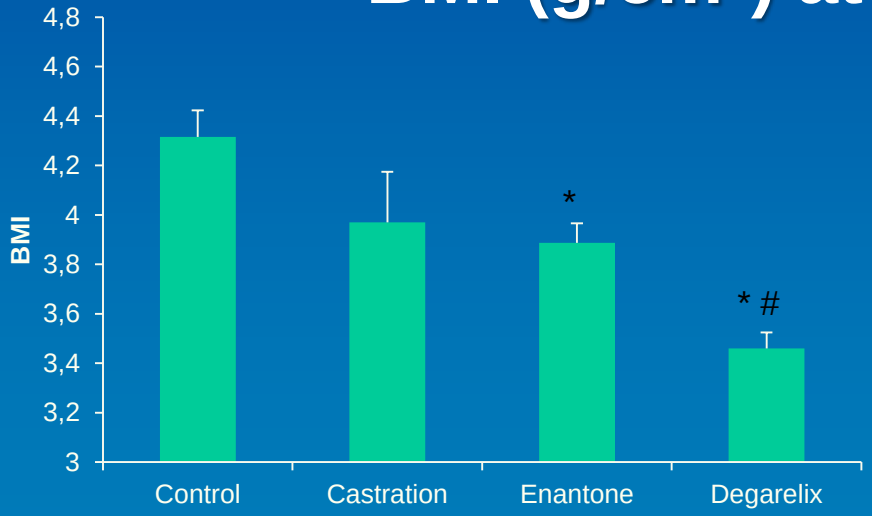


Pink: adipose tissue
Blue: Lung tissue

Total body weight (g) at 4 months



BMI (g/cm²) at 4 months

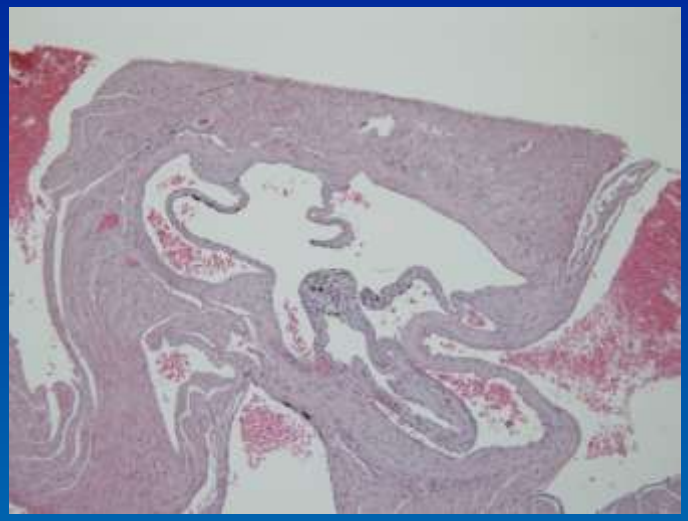


***: significantly different from control**
#: significantly different from enantone

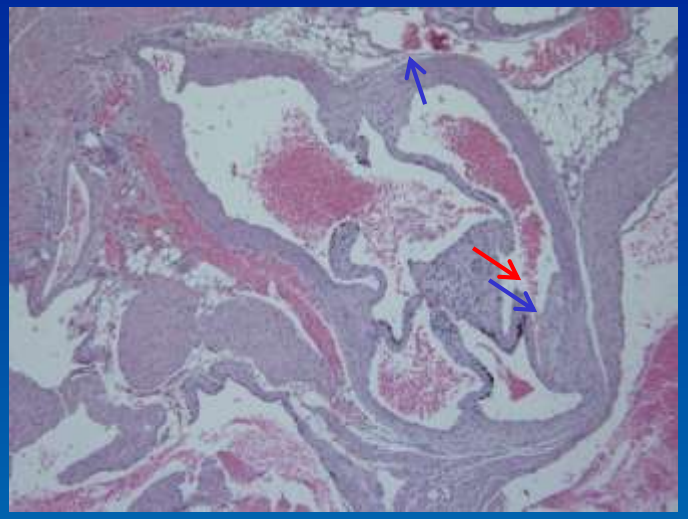
Muriune hearts on different forms of ADT: Hopmans S, Klotz L, Pinthus J. Urol Oncol 32(8): 1126-34, 2014

(normal diet, at 5 µm depth)

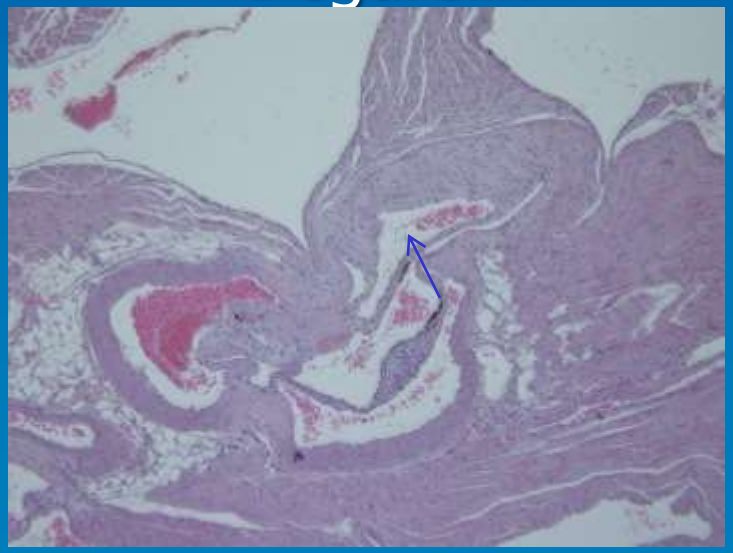
Control



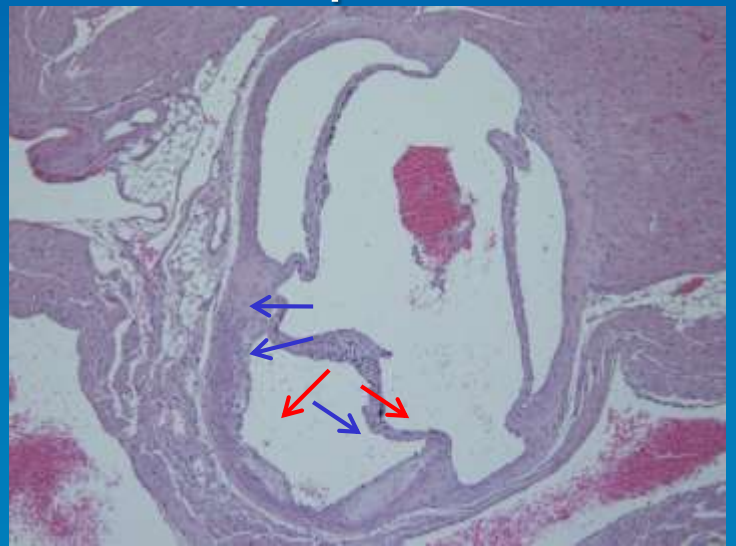
Castration



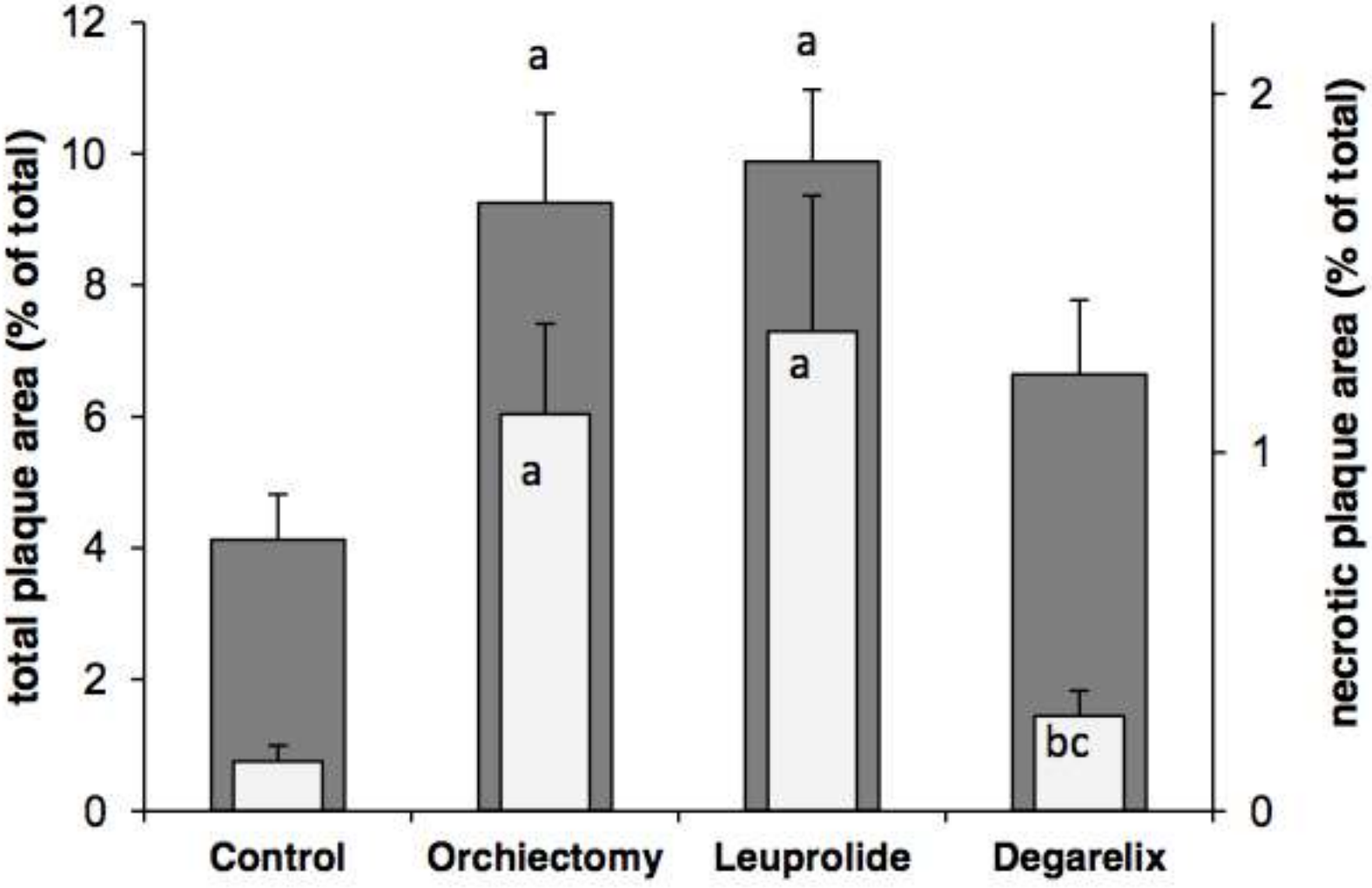
Degarelix



Leuprolide



Total plaque area and necrotic plaque area. Hopmans S et al, Urol Oncol 32(8): 1126-34, 2014



Conclusions re: ADT

- AR pathway complex
- Patients with pre-existing CV disease at increased risk for further events
  - Impact in healthy men less clear
  - Consider degarelix if patient has pre-existing CV disease
- Low nadir T important
  - Assay T along with PSA q 3 months
  - If consistently > 0.7, consider change in therapy
- Intermittent therapy for non-metastatic
- Hormone naïve metastatic:
  - Favorable risk: consider with excellent PSA response (< 1.0)
  - Unfavorable risk or poor PSA response: Chemotherapy