

# **Androgen deprivation therapy: New concepts**

**Laurence Klotz**

**Professor of Surgery**

**Sunnybrook HSC**

**University of Toronto**

# 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

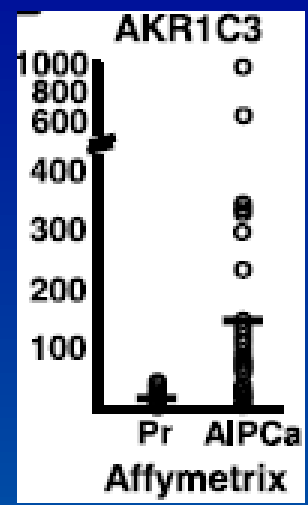
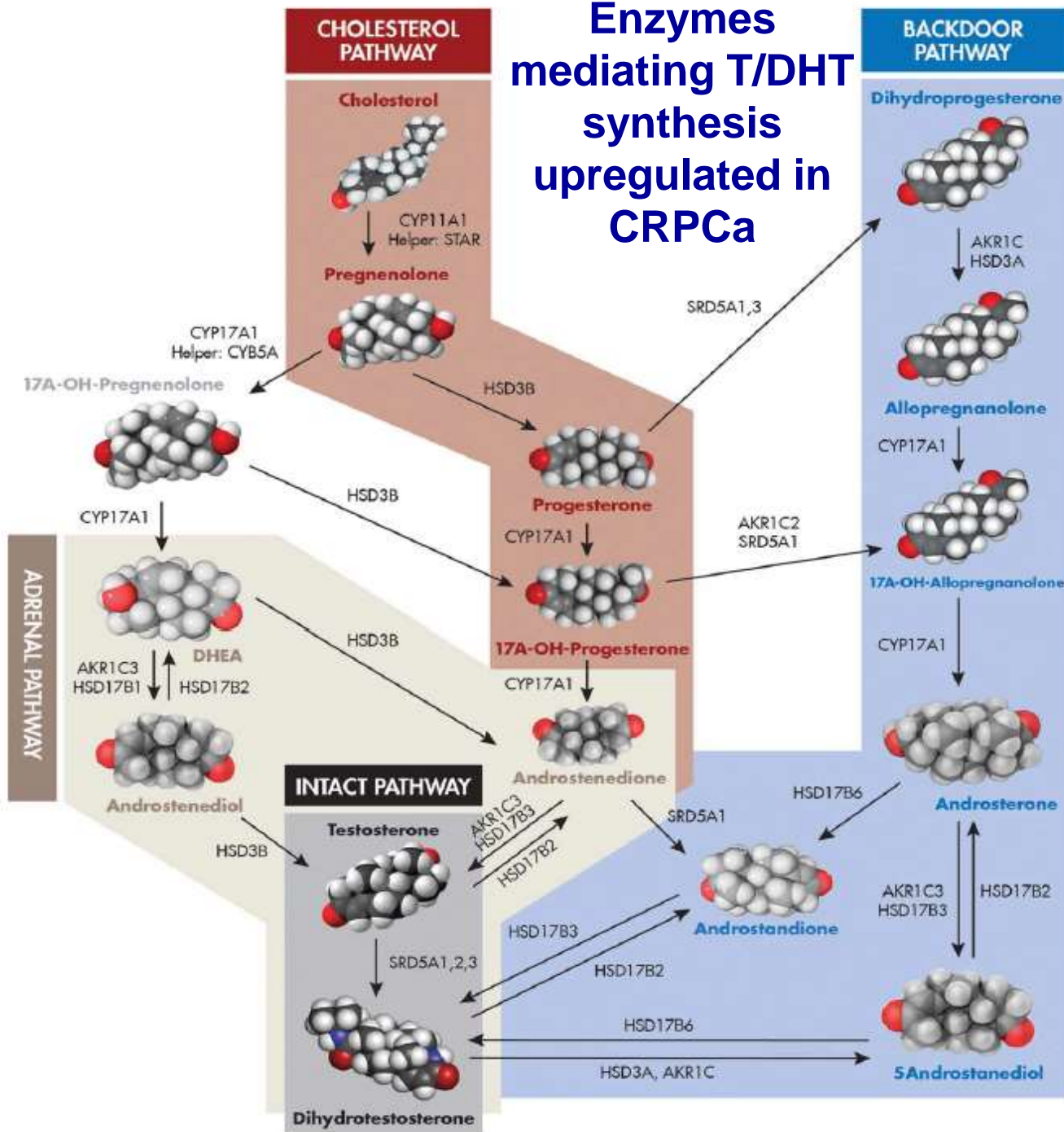
### Stock Ownership:

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)

DHCR24, LIFR, NDRG1, DDX, MMP16, CTBP1, FKBP5, KLK3, APPBP2, DDC, ALDH1A3, KRT8, ELL2, HEPIC3, TPO52, SEC24D, CDK4, BICHE, ABHD2, ICH1, DNAB39, MERTK, SORD, ABCO4, DDC1, PKOR3, PTPRR, KLK2, GATA2, BARD1, TMPPSS2, SGK, IQGAP2, FN1

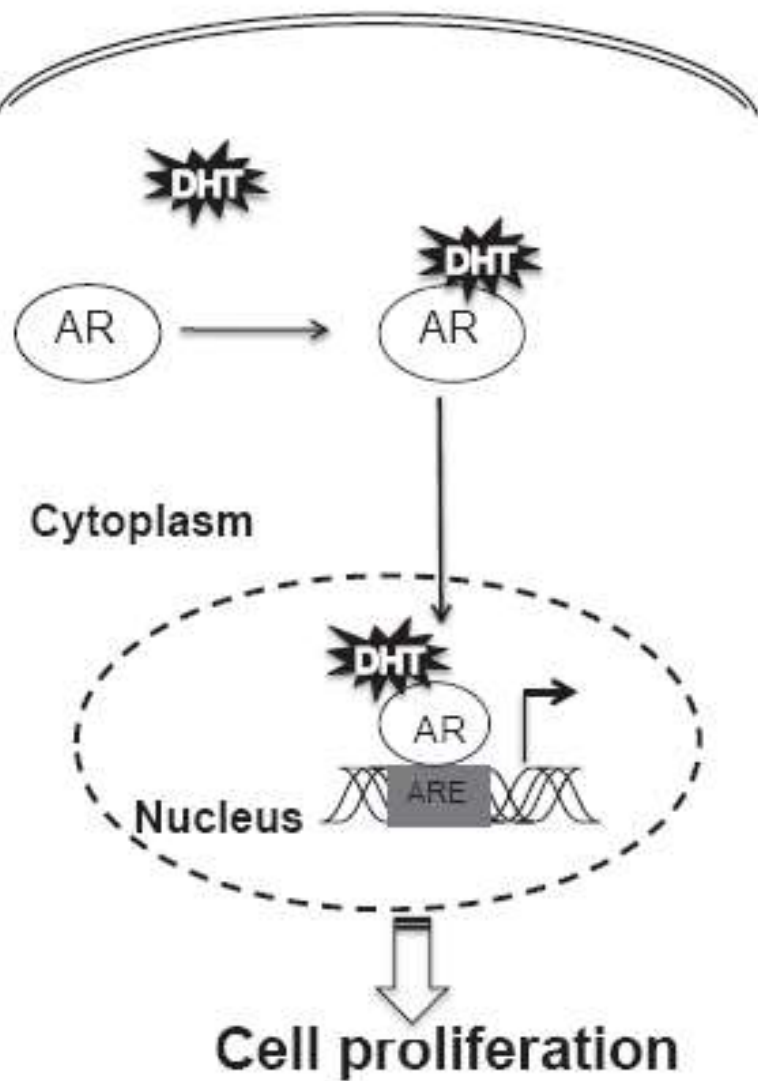
SMARCC3, DPVSL2, TSC22D1, MAPK6, ACSL3, SEPP1, ATAD2, ANK1, PEA15, GHR, PLA2G2A, FOUH1, NKX3-1, ORF1, CALU, UGT2B15, PPAP2A, PRKD1, BAMB1, SNO25, PPF1CB, OPRK1, PK8, NCAPD3, MPH0SPH8, SLC35F2, LCP1, TBRG1, TMEPAI, CAMKK2, RAB7A, ABCO1, HMGC31, DNMT1, CENPN, LONRF1, ST7, PGM3, SPMAR, TXNIP, COLEC12, MTMR9, ATP2B1, LMAN1, CXCR7, B2M, MYC, FURA, CALD1, ADD3, ZBTB16, PGM5, UBE2G1

KCNMA1, DDEF2, PTPRR, SLC15A2, LRRN1, SASH1, ACAD8, SLC35A7, NAPI1L3, HOMER2, ADAMTS1, MANEA, RHOL1, SERPINE1, BTG1, THYN1, HS3ST1, NR4A1, SMAD1, PTPN21, WPI1, PPM1K, CBLL1, AKAP12, SPDEF, AZGP1, SEC61G, DGG31, ABHD3, SYTL2, KRT18, PECL, MDI1, BCAF29, SDC52, SPCS3, CEBPD, LRRFP2, WDR41, WWCI, NEDD4L, ARMET, PGC, KCNA2, SMAD7, SEPP1, MAK, EDH1, FDF1, SQLE, PFBP1, PCTP, UBE2J1, GARNL3, TMFP2, KDELR2, HSD17B, TRB1, MAP2K4, KCTD3, TRPS1, ERN1, MLPH, CYBP2, MAP7D1, TWIST1, TRIM36, KCTD9, SELENBP1, STRK17B, SL, UTX, S5BP2, TNBP1, VGLL4, ABLIM1, STK39, ST6GALNAC1, ANGPT2, AFF3, PKOXP1, C10orf91, KLF4, LDLR, MKN1, SMS, VEGFA, SESN1, RAB4A, PKOR1, BTD, NFKBIA, SCAP, IL1R1, SAT1, ARF4, NDFIP2, SLC7A2, INPP4B, CEBPG, MBOAT2, PAK2, IMPDH2, TMEM78, PICALM, MYH1, PEX1, NET1, GFB1, LRIG1, FUT6, ZCCHC3, ARFGAP3, NFKB1, ERGIC2, ATP1B1, H0X813, C10orf21, SLC44A1, TULP4, LAMC1, YCL

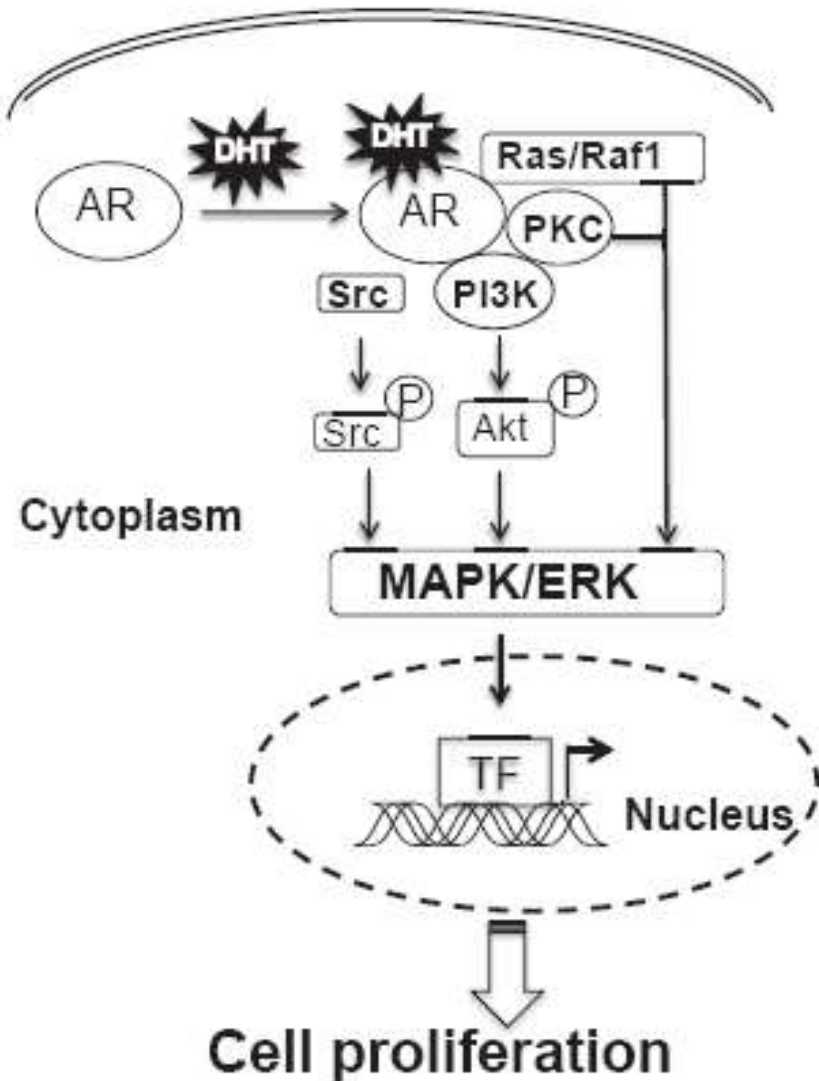
PGM2, CREB3L2, CXOR4, RLN2, PELD, GDF15, GRB10, IGF, NIPSNAP3A, SERPINE5, CLON, TMEM39A, PLDN, ARHGAP18, KIAA0247, FAM105A, GMPFB, ABCG1, SDC8R, GLUC2, SLC16A6, NUP93, OCLN, LOC400451, NFB, SEC24B, LRRIC16, RAB38, ALDH1A1, TNFRSF1TRK3, CPEB3, PART1, SLC43A1, GNM1, KLF5, CDK2AP2, TNFAIP8, GPR177, SLC25A20, SRA1L2, C5orf30, TNFRSF10B, EXTL2, ST5, GSR2, NUP1, SLC12A2, TMEM144, SMPD2, MAPRE2, C14orf4, ADORA2B, VAPA, ANXA9, MRPS18A, TMEM140, STEAP4, LRIG3, C5orf32, MAFK2, GPR126, CAAMK2B, PEX10, CADPS2, TMEM79, VLDLR, TBC1D8, ZNF482, PRKCH, ANTXR1, IMPDH1, FZD3, ITR10, GFM1, KLK4, ENO1, MAN1A, STK3, TGM3, TRM1, SALL3, MAK, CABLE1, NFAT5, HPGD, PAK1P1, GLI3, TMEFF2, PPAPC1B, GPR160, TNFAIP3, NANS, CBLN2, FXD3, INSG1, KCN53, HEBP2, PPM1D, CRFB3L4, LOC81891, MDCC2, EBF2C4, SEMA6A, EAF2, AGR2, STCH, PMS2, GRAMD1C, DNAJC10, THRASP, SORL1, PSCD3, C5orf13, C10orf18, PCSK6, RBM6, AP251, CA12, C14orf24, GSR, FAM3C, PFKFB2, MAPKAPK3, PACS1, FZD6, ERBB2, USP33, HIST1H2AC, SLC28A2, ATP2B4, ID2, DDX21, C21orf33, ICAM3, JUP, SLC41A1, GTF2E2, NFN1, IFRD2, CHPT1, GLRX2, BCL3, DSC2, SRR3, SLC36A2, TME65, BHP44, FRAP1, ACPI, CAMK2N1, SRP19, LASP1, CUL1, CLDN12, CDYL2, GRK1, ENPP5, ZBTB1, PSAT1, TBC1D1, ENDOD1, IGF1R, CAPRN2, SHROCK5, HMGL1, ASNS, FRK, CHD4, PRAME, RELN, C10orf116, GOLGA4, RAB7A, HIF, ELOVL5, ZIC2, POLR1E, TRAM1, SMOAL, ATP1A1, RALGPS1, SEC63, PSMD8, LRBA, LLZP2, RCN1, SREBF2, WWP1, GFTT1, PLCB4, PYGB, HIST2H4B, ARPC1B, SNRK, SSR1, F5, GLUDP5, OBFC2A, ERF11, SEC61B, PBD2, CAP2B, KIAA0247, PACSIN2, BIK, FASN, ST3GAL1, ARNT, HIST1H3B, DSG2, JAG1, DNAJC3, ELOVL7, ZBTB43, CDCA7L, MTHFD2, EPRS, CTH, SEMA3B, CSNK1A1, CHKA, TBC1D4, SS18, SESN3, HIST1H4H, LRDD, HERRFUD1, CAPRN1, MB, REEP5, RHOB, KPA, EP4K1, SFRP8, MRPS27, PCCA, SLC45A3, C5orf76, BMP1B, TLL1, SNAI2, AMD1

PHLE01, PMAA1, PKNOX2, KLHL13, TMEM34, C10orf78, CYP39A1, STYK1, APPI, MALTI, SEC23E, H0X13, COTL1, GSC, GADD45G, CERK, NOSTRIN, ZNF365, POOLCE, TMEM118, PCYT2, NUDT9, RXR5, OFPN, PCDH11Y, HGD, KLHL1, GPR137B, COL3A2, SMAD3, GFTT2, RTMAR, MYLK, C5orf81, ROR2, MADA, CORO2A, H0X9, GREB1, EMP2, ALG2, AFRM1, ABCA1, SLC26A3, BB5A, KIAA1324, DUSP5, COL18A1, SLC12A6, EHD1, PPAP2C, C14orf132, HK2, GEPD, THR1B, C19orf48, CPNE3, CDC42EP3, RPS27A, DGAT2, STRBP, FGD4, HCF2, SFRS5, TNFRSF21, TSC2, RASSF5, ACAA1, SEC11C, ARSG, MYNN, GLDC, ZBTB10, TTC18, SUS4, SAT, MAP1, FBXW2, LRRC31, NPPC, MESP1, JAUJ02, SEC14L2, IL1RN, IFO3, IFIT2, C5orf81, PKA, NAB1, APCDD1, PRAC, PPM1M, SOX9, TM4SF1, TM5F3, TTN, MAP3K8, LOK, FGF13, C13orf1, TRIM45, COL5A2, ARHGEP17, C6orf158, DIO1, GDC, C14orf143, CHG1, RGS10, HYPE, TRIM48, CASO1, MCFD2, NEK1, ORMD2, ENO2, ITPR1, EDN2, CDC42EP2, FBXO38, TCF15, CDK3, KLF13, GALNT7, FLJ22594, PDKL, ASRG1, CTNNA2, MTP18, APC, CSMD1, LAMA1, FZD4, PER3, DLX1, SEPT6, AUTS2, MMP10, C10orf33, PHLD62, ARHGEP10, LIN7B, FB, MGC14376, S100A11, EFHC2, DNAS, PDE4A, SMAD6, GALNT10, DRCSL, ADCY1, ARNT2, C10orf47, DHRS2, FSTL1, MMP2, GPR98, BTG2, TUB1, PFKF, C10orf5, FAM134B, RDN10, HIST1H4J, TRB3, COPS7A, EFNB1, C11orf2, C19orf10, ABR, DUSP4, UFM1, EBF1, RFX3, CRELD2, GCLM, GMPRA, SNX19, SEC14L1, ID1, PKC3B, CDC42BP4, LRRC8A, MYO5C, SARF, EML3, PRDX4, ATF7, KIAA1196, NFIL3, GCA, GLO1, XPC, ZNF350, SORBS2, GLYT1L2, LMO4, SKAP2, HIST1H4L, OCT4, GRHL1, RPN1, CPD, HIST1H4L, HIST1H4E, TARSL2, TNFRSF1A, PHGDH, AGER, PAPP4, SLC35B1, IGFBP2, DNAJC1, NR102, RNF43, PHF12, SETBP1, MAST4, CCDC14, SPTLC3, PHYH, LAMA3, RALB, TESK1, EBR, TDP1, HIST1H4B, GTFE2, NLGN4X, C5orf72, HACL1, CBR4, ADCYAP1, AGRN, TLE3, SPRY1, CDON, NETO1, SKN2L2, ZIIG, LRRC49, SMARCA4, TMEM3, PPT2R2A, PLEKH41, TRB31, ABCO5, SNAPC5, MOCS9, SLC3A5, RBM5, NCL, HIST1H3C, CLON3, CANN1, C5orf66, GRAM, BRE, THRA, SNAPC2, PEG3, CRP1, ARG2, JARD1A, LRCH1, C3orf58, EDG7, HIST1H3D, C10orf118, SMO, HIST1H4H, PUF6, SHRF1, GPRK3, MICAL1, SLC27A2, DDO, SEPT11, SDF2L1, IGFBP3, PSMA6, TERF1, EBF3, CYB5A, NCOA7, HIST1H1C, ABCA5, DNAJB14, WRB, HIST1H4A, HIST1H3J, MT2A, ROR1, ADAM2, FAM13A1, NR1D1, SORHA, UGT2B28, HVAL1, DNASE2B, MYB, ANKRD37, XRO2, SLC44A4, KIAA1712, COX5A, SMARCC2, HIST2H4, CD4, GTF2E1, SFPQ, RGS16, DIAPH2, PSMA1, BMP1A, C5orf192, RALY, DGR4, HTR2C, CACNB3, CCDC141, RBBP9, PLEKH81, MRPL33, FAS, CNKSR3, MRPL12, MGAT1, GOLPH3, CLK2, HSD17B11, RAMP1, BAGALT1, SELS, PDXK, PRMT2, COX17, PRKAA1, MTF1, FLOT2, MAPK1, CDKN2D, HPR, ZFRK4, TSPY12, EBF25, SMPD1, VIM, LDHA, PDK2, MPZL1, ADAM9, FNGR2, CAP1, PKP4, GGN5L2, CDX7, RBS1, HIST1H3G, POLR2E, RBL2, RCAN3, FOSD2, FPM, VARS2, HCAF2, MGF1, ELMOD2, KDELR3, MGMT, SUTRK6, ACHE, KRT6A, HIST1H4K, CDC2, CLK1, GLYT1L1, ALSICR13, L1CAM, RGS2, PTMA, KIAA1324L, GMAP2, SFRS2, CLSTN1, HSP90B1, EPHA3, PTPH1, PCDH1, CYP14Z, MGAT2, NUCB2, NUBP1, HIST1H2BG, NFK, AKAP1, CCDC3, ERBB3, FROX1, AGRWT2, TP53NP1, RNF144B, CLU, RRM2, COG5, NCBP2, EFN62, NLGN1, NAV1, POLR1D, LRRC29, DNDC9, MAP2, NOS3, RBL, GSTM2, XBP1, BPH1, OTUD7B, HIST4H, CAP2, DSEL, SLC29A2, RBM4, HPK2, GPER, EIF4A2, CLDN8, NDUFA9, ZNF77, PRAGD, STC2, AMT, DSS3L, CTSH, TMEM2, AHNK2, VTA1, CRISPLD2, NRP1, CEP57, HIST1H4F, ZNF133, TFF3, SUOX, S1A11, NPC1, INPP5A, PTPN8, TRAF1, BTG3, APP, KLHL24, SPOCK1, KOL2, MUM1L1, TACC2, PDHA1, TKT, PAK1, CYCS, GYS1, SLC33A1, TMCC3, SLC16A1, RAB39, UGT2B17, HIST1H4E, STY1, C5orf5, FADG1, ERS, HSD11B2, ROK1, DDB2, HECTD2, KIAA431, QDPR, MAPK12, RIN2, HYOUT, TPCN1, CDH15, DDX39, C12orf44, PTMS, PPK2B, RGL1, ABO, PLD1, WDR6, ZCCHC9, NEEL, C16orf22, GARS, NEMO, IL1RL2, PFK, CHAF1A, FTH1, CTSH, NFRK3, SEC13, WDR91, ITGB1, ZNF177, EPS15, CBX1, PRAS, SURF4, DEPDC6, C10orf1, ANAPC1, PIPN14, RBM3, ZKSCAN1, CRAT, ZWNT, DERL2, SLC7A11, SLC14A2, SPW42, TNDX2, PTPN6, CREM, PTDG8A, SSFA2, TEAD4, EEF1A2, MED, CBNL1, D4S234E, RAB9, EFNAS, PALM, FLJ4580, PPF3C8, TLN2, C10orf26, GADD45A, AASS, PSCN1, KRT6C, TRMS2, HIST1H4D, FAM15A, TCEB1, ARL6IP5, IARS, SFRP4, ADV1, C5orf3, STP1, HESPE1, RALGPS2, GUSB, COPS3, PHLD2, COL16A1, ST3GAL4, PHF8, KRT19, SBDS, GABRD, NDC1, TGF1, ANKRD13A, YARS, ADAM17, CTNND1, PPR1P11, CPS1, AGR25, WDR68, PPK, ETRF, MDD1, RAB1A, C2orf9, ADPGK, IDE, LPM1, FAM111B, GALNT1, SNRPC, ARCN1, SEC3A, SGK, NAT1, ME1, SRRM2, EDEM5, LARPS, HVAL3, RFX5, HLF, ZBTB34, SORDL, ARL1, PROM2, NRP1, FAM129A, RAB3GAP1, CRLS1, CYP2U1, AFD3, CALM4, TELL6, KLHL33, HLA-E, YEATS2, AFRO3A, KIF5B, HSD17B4, ELF3, RAPIGAP, MEF2A, PDKL2, RAI14, NRP7, ARHGEP2, ARF1, ECOP, PSCD1, HSPAAL, CRY1, MAP2K6, SNAPC4, CDK6, SNAP25, RAG1AP1, NAF6, IDWD1, WARS, PPF2CB, CYC1, KYNU, CYBASC3, STARD3NL, LPA, CDH6, ACD1, C10orf28, CD46, C17orf48, PNPLA8, ILF3, ADRM1, PEX8, MCEE, TNDX16, IQCB1, ATFA, TBTX15, COA5Y, VPR2, SELH, EIF4B, TAX1BP1, OGT, RARA, ANKRD16, PML, TLE1, PRM1, ACAD3B, IGF2, ETPDH, SNAP23, M01, GSTK1, YFF1, GALK2, HES6, SAP18, LIMCH1, MM4A, CDKN1, ACAT2, TROVE2, ELOVL6, MDK, KHDRBS3, COL14A1, ADK, HIST1H4F, CRY2, UBAP2L, SLC25A33, RPS51, TRIM32, CYP51A1, CORG, MGATA4, PPAPDC2, SNR, RAVR2, PFBP2, SROGAP3, ZNF137, RPL13A, DYE, SCRN1A, C16orf61, PLD3, UPP1, SC3DL, SMARCA2, UBP1, LGALS5, DOR1, KLF10, NME3, HIST1H5A, PRM2, ANXA4, ATR, PRKCA, SLC2, RPSK3, RAB5A

# A Genomic signaling



# B Non-genomic signaling



# 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.

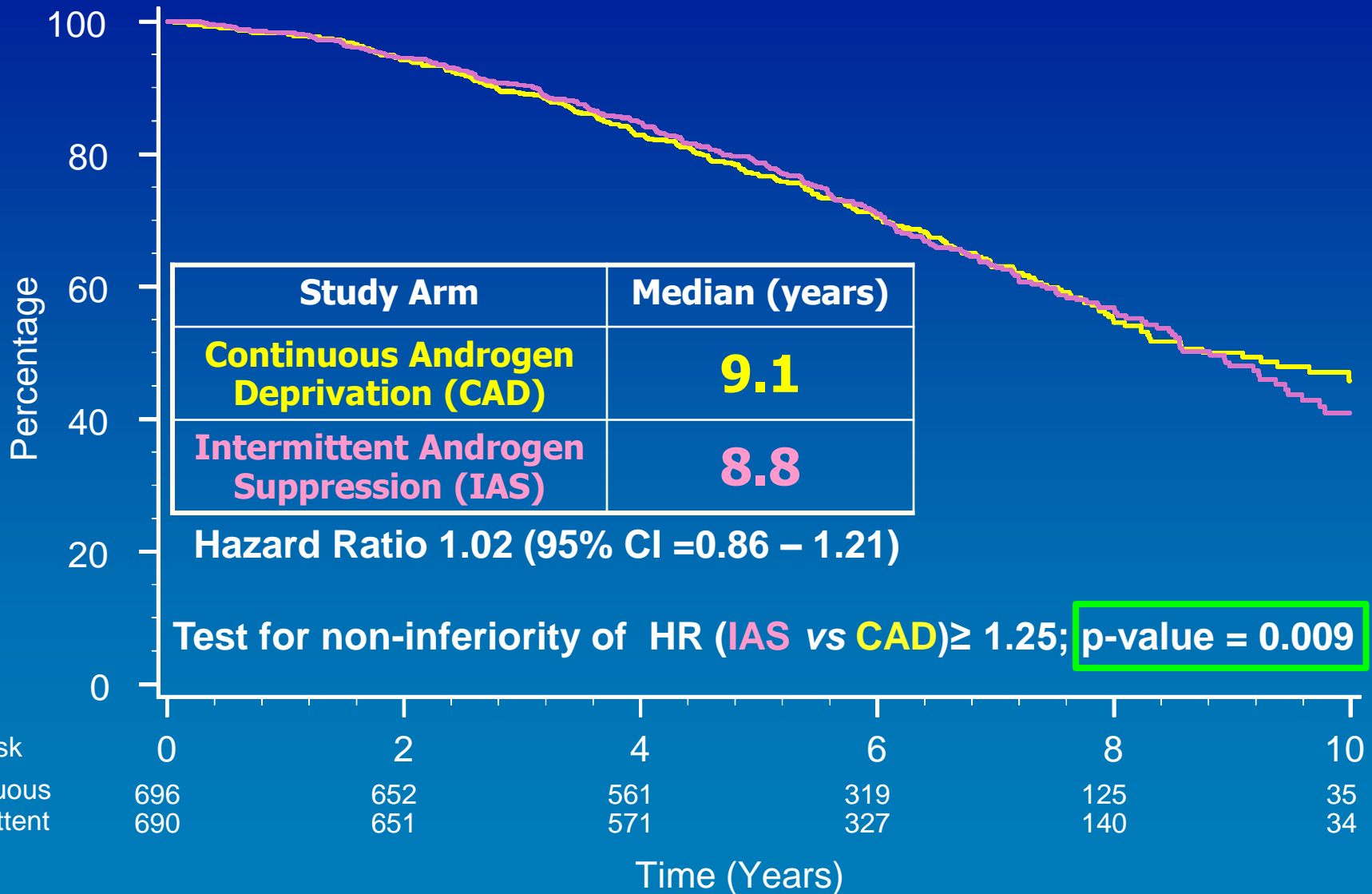
### ABSTRACT

#### 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)



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.

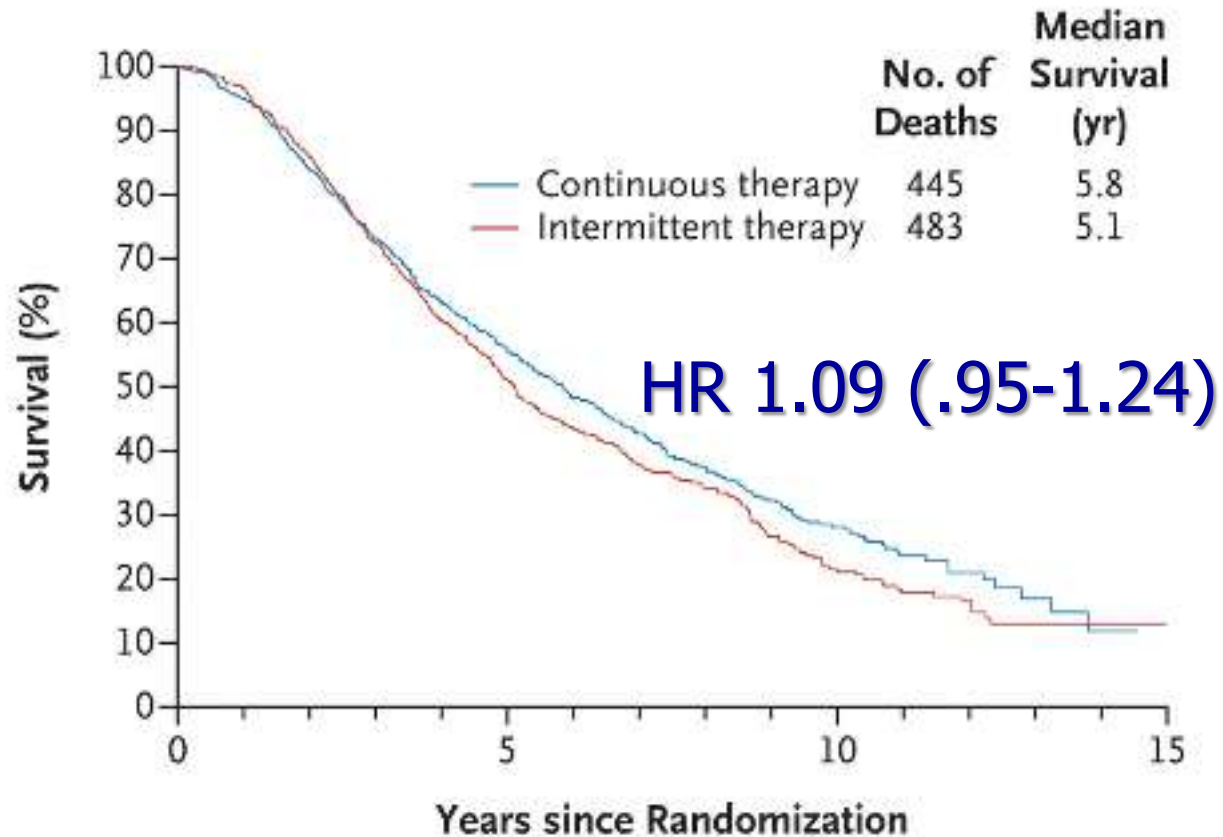
#### METHODS

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

**N ~ 1500 M+**

**Non-inferiority design; pre-defined  $\Delta = 1.2$**

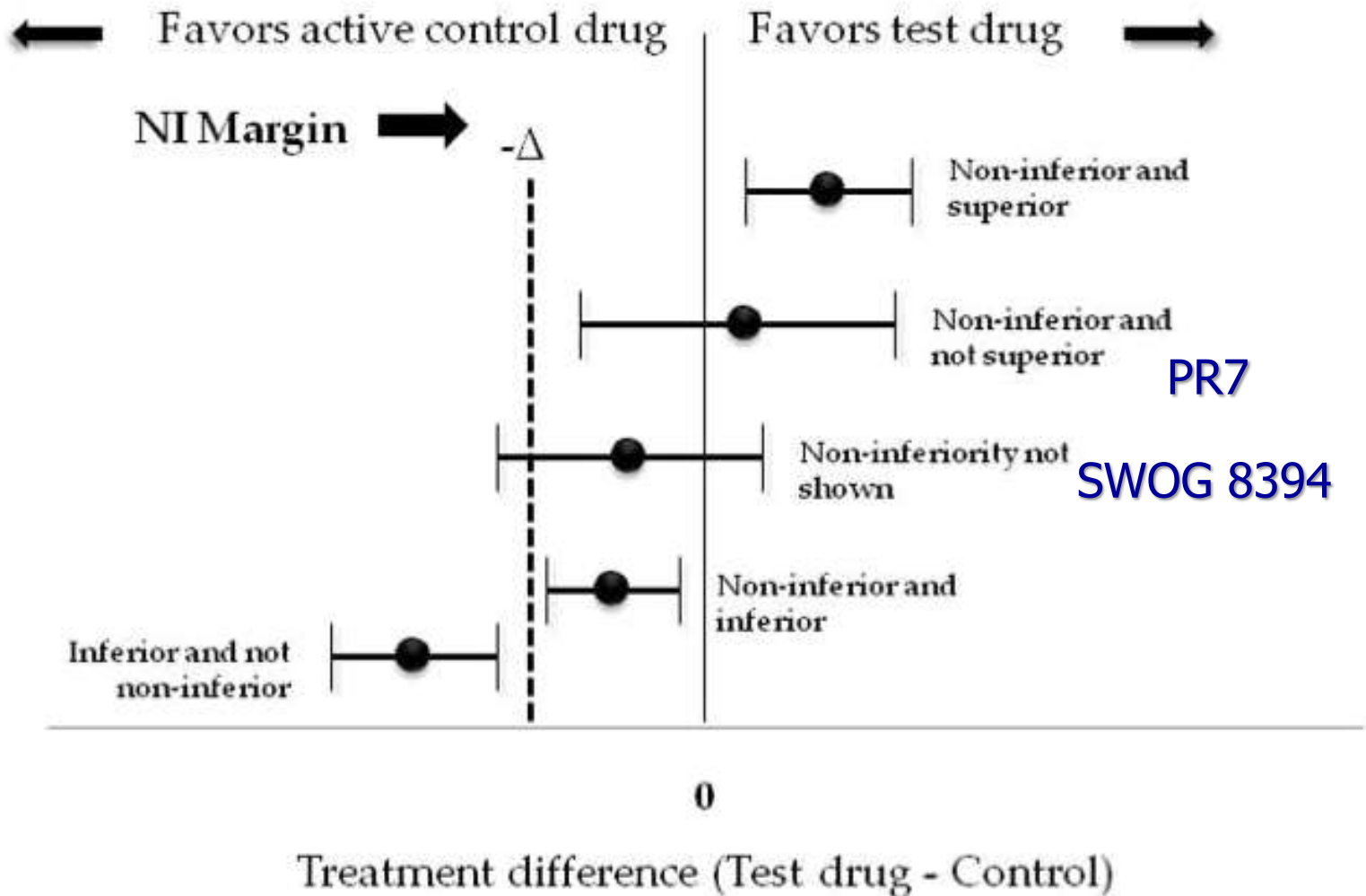
# SWOG 9346 Survival: 'Results inconclusive'



## No. at Risk

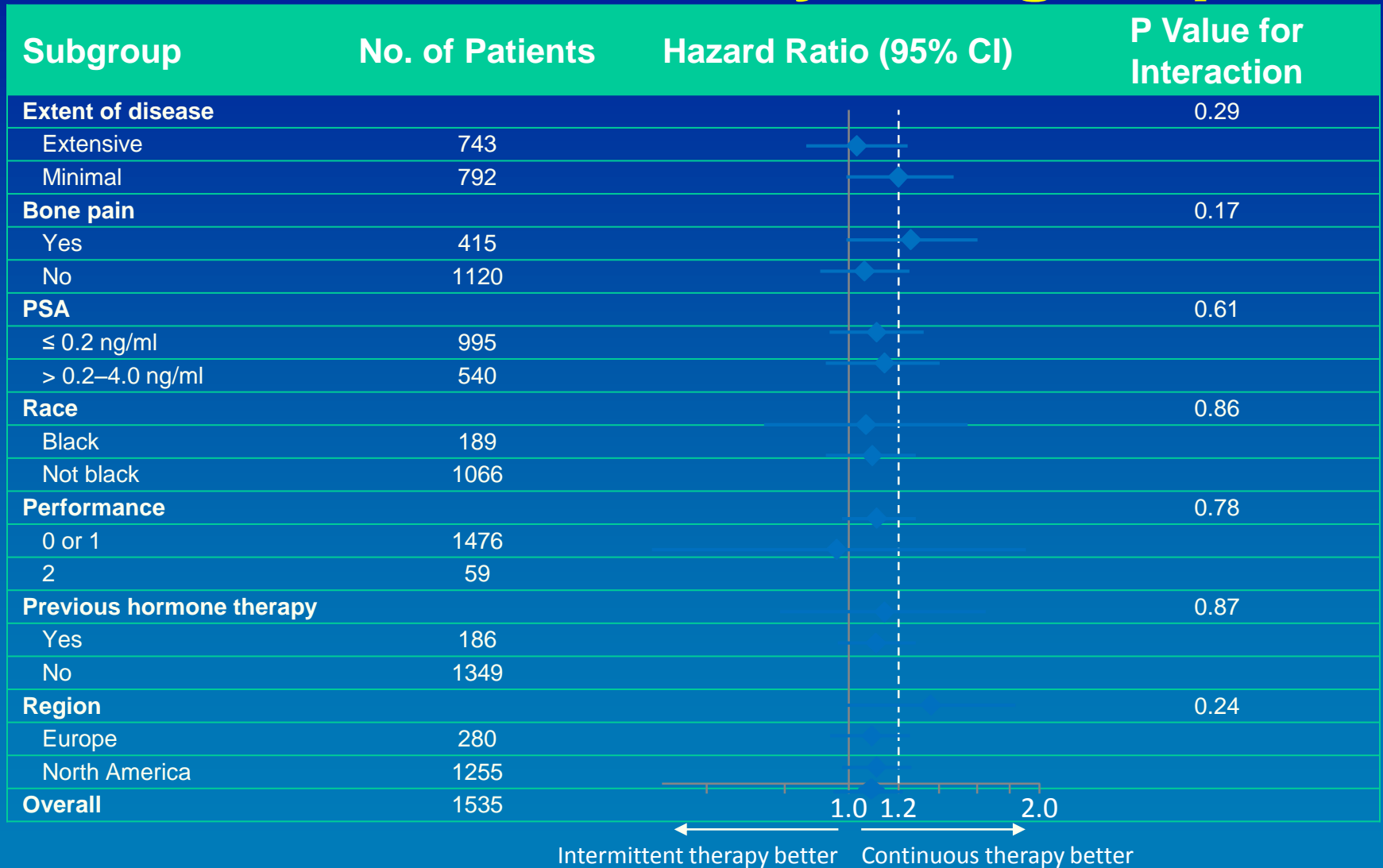
Continuous therapy	765	325	64
Intermittent therapy	770	291	52

# Possible outcomes of a non-inferiority trial



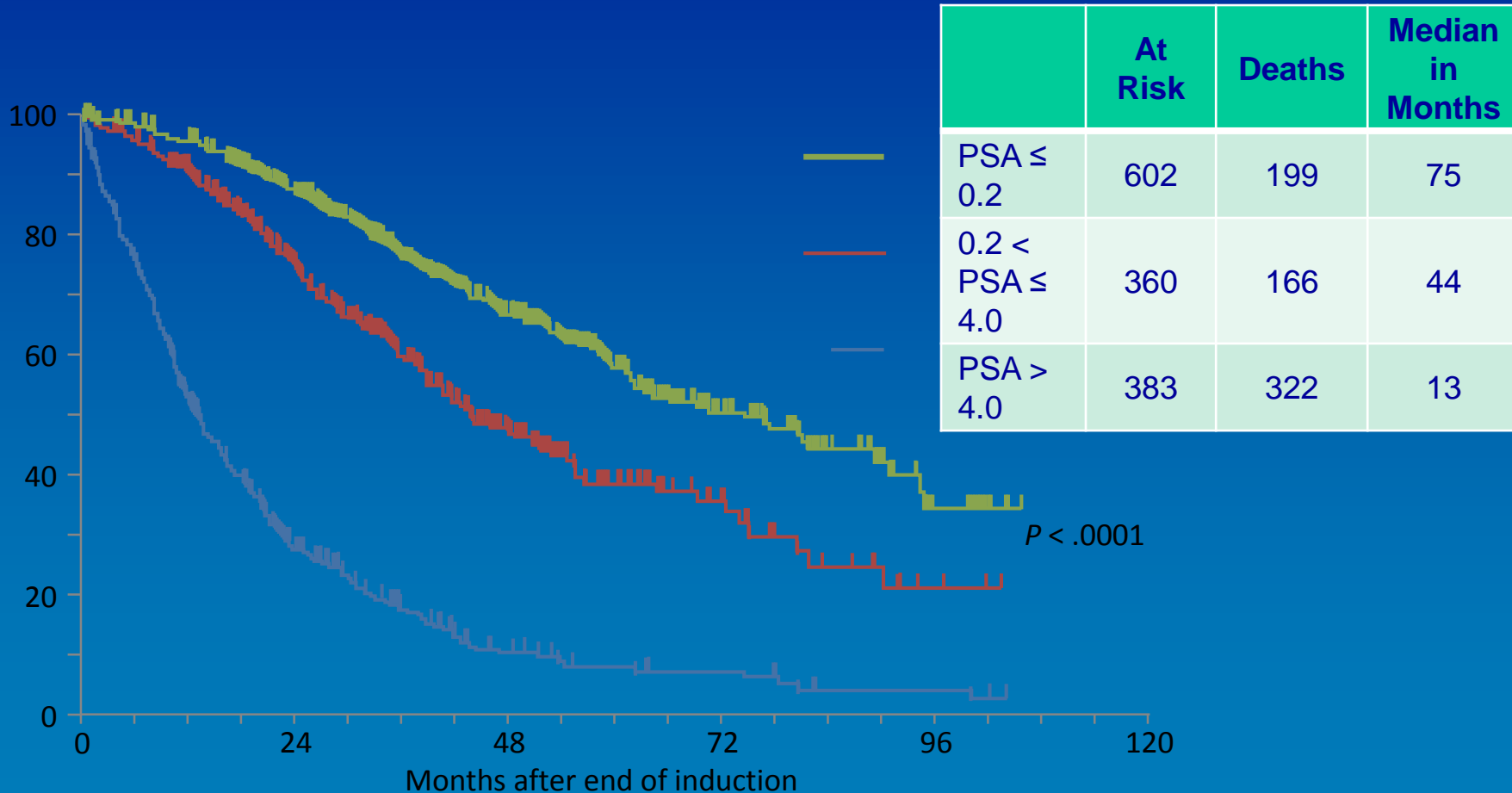


# PR.8: Survival by Subgroups

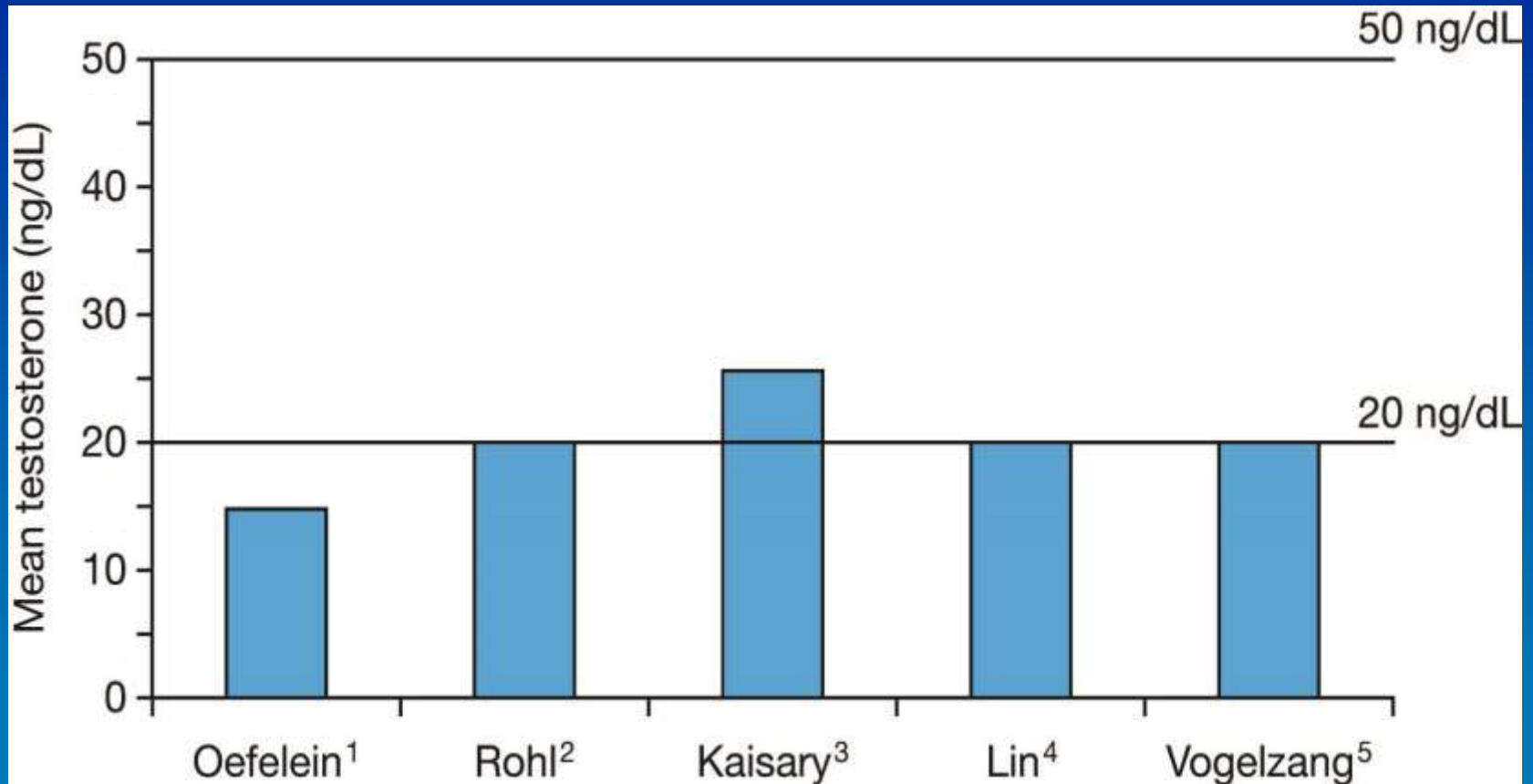


# PSA Response is Predictive of Outcome

PSA at end of 7-month induction period and OS

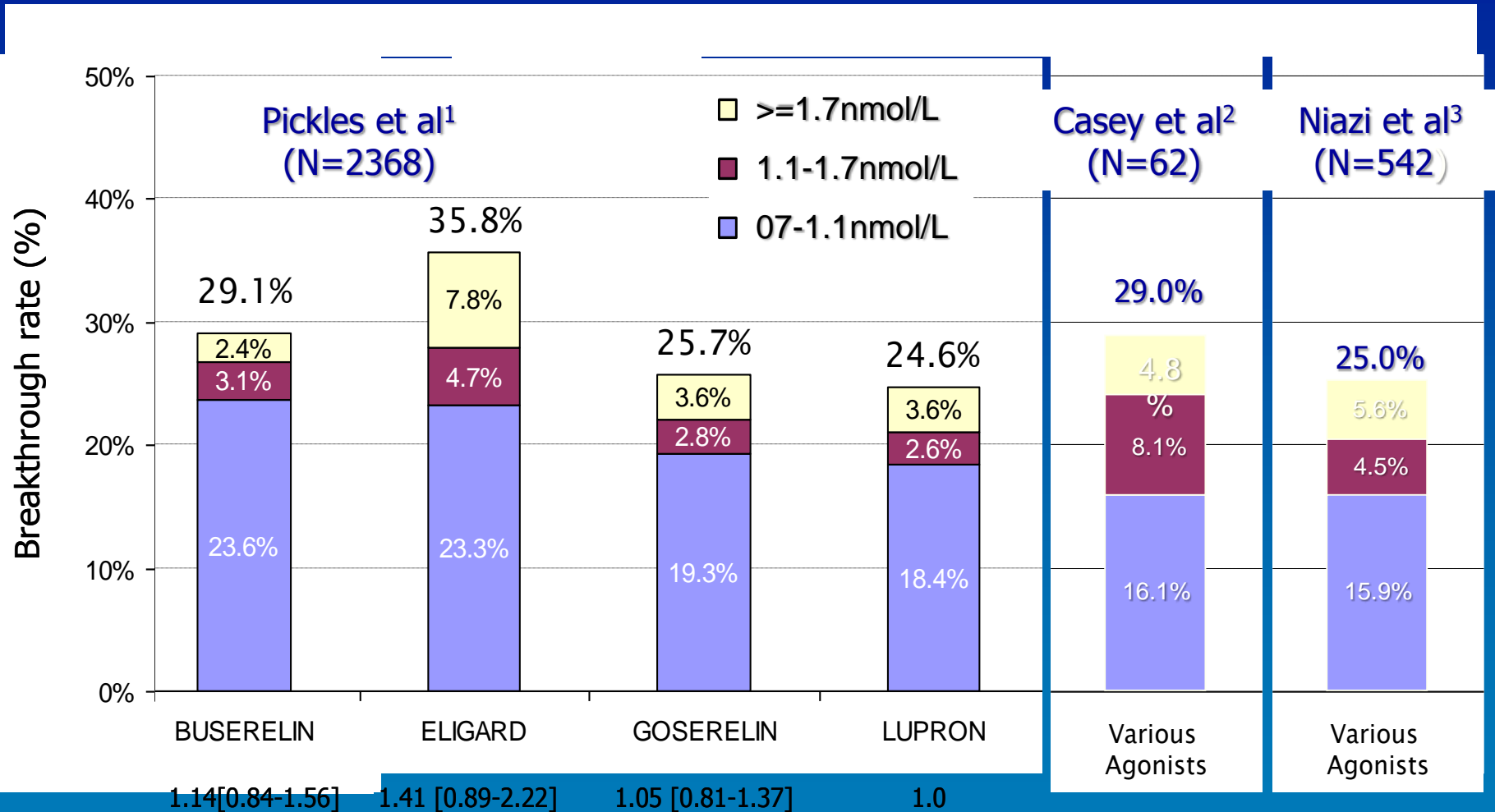


# Testosterone levels after orchiectomy



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



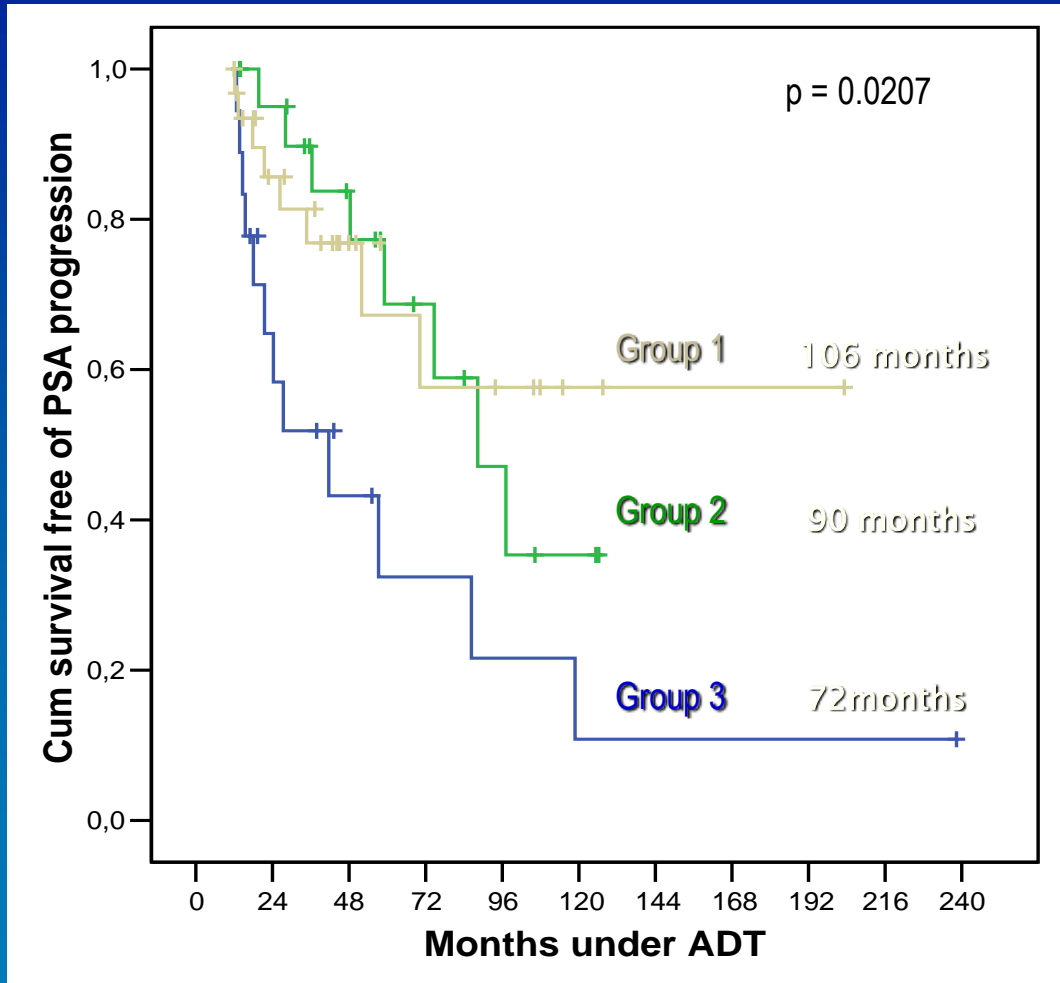
1. Casey R, Morales A, Siemens AR. CUAJ Jun 2012; Vol 6 (3Suppl1) S21
2. Pickles T et al. 2010 CARO Annual Scientific Meeting, Vancouver
3. Niazi T et al. 2013 European Cancer Congress, Amsterdam

# Does the T level on ADT matter?

- 3 retrospective 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

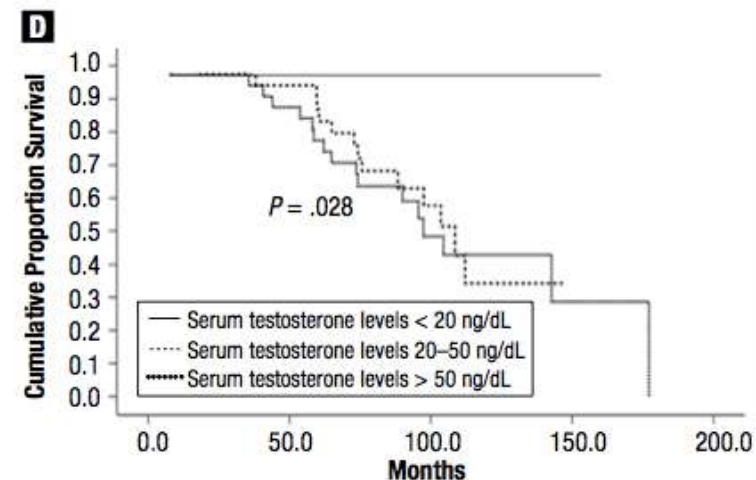
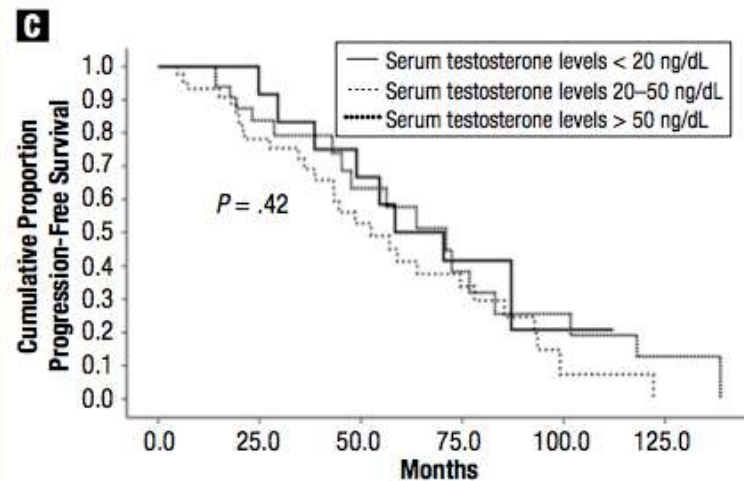
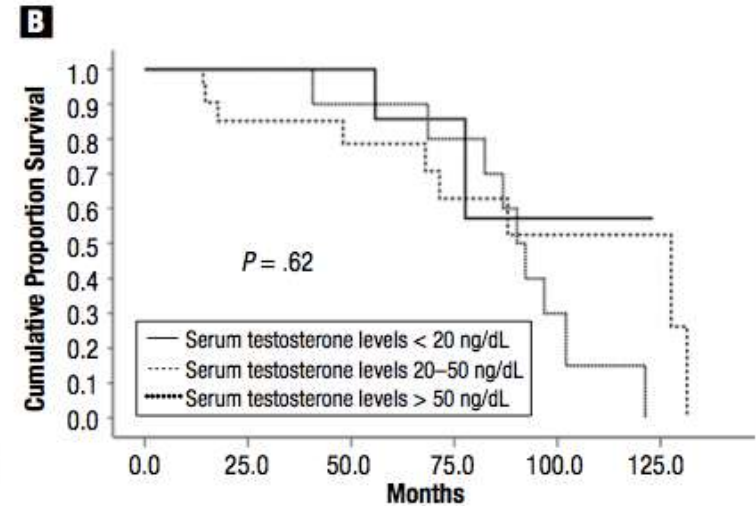
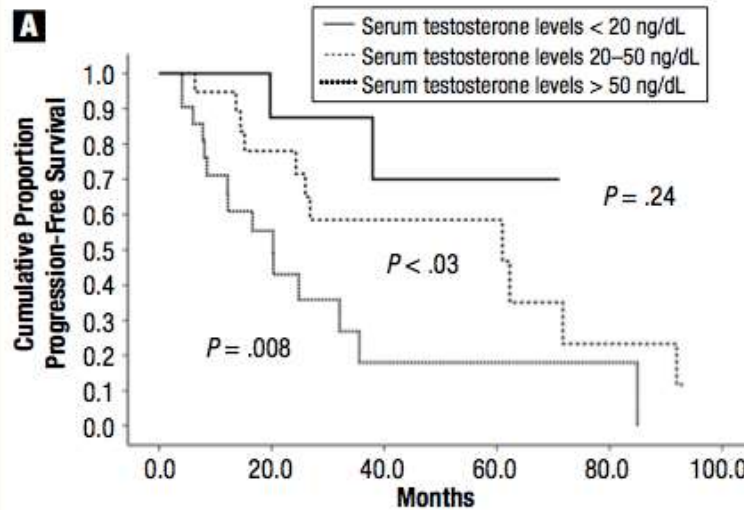
AIP, Androgen independent progression  
Morote et al. J Urol 2007; 178: 1290-1295

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



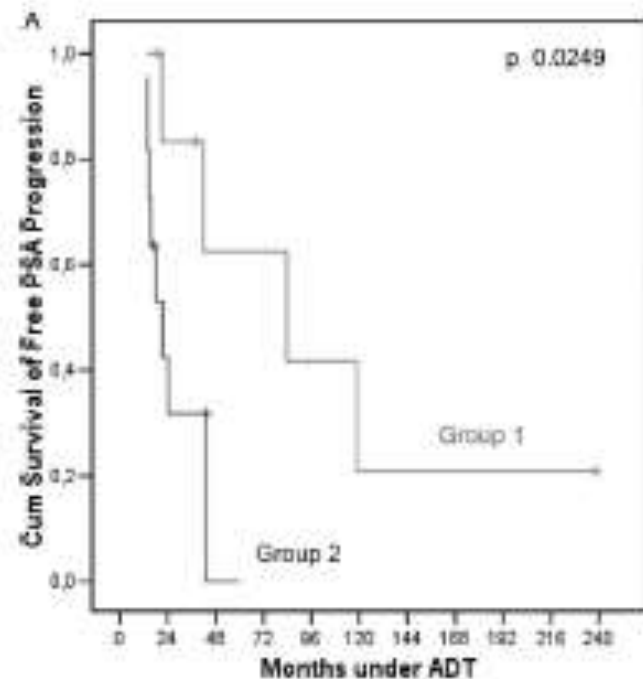
99 with PSA failure

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

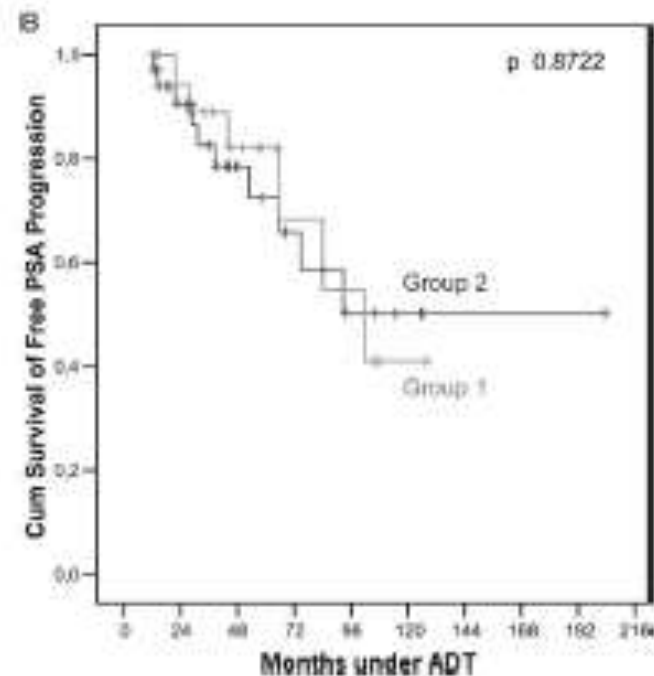
Group 1: CAB

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 through 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

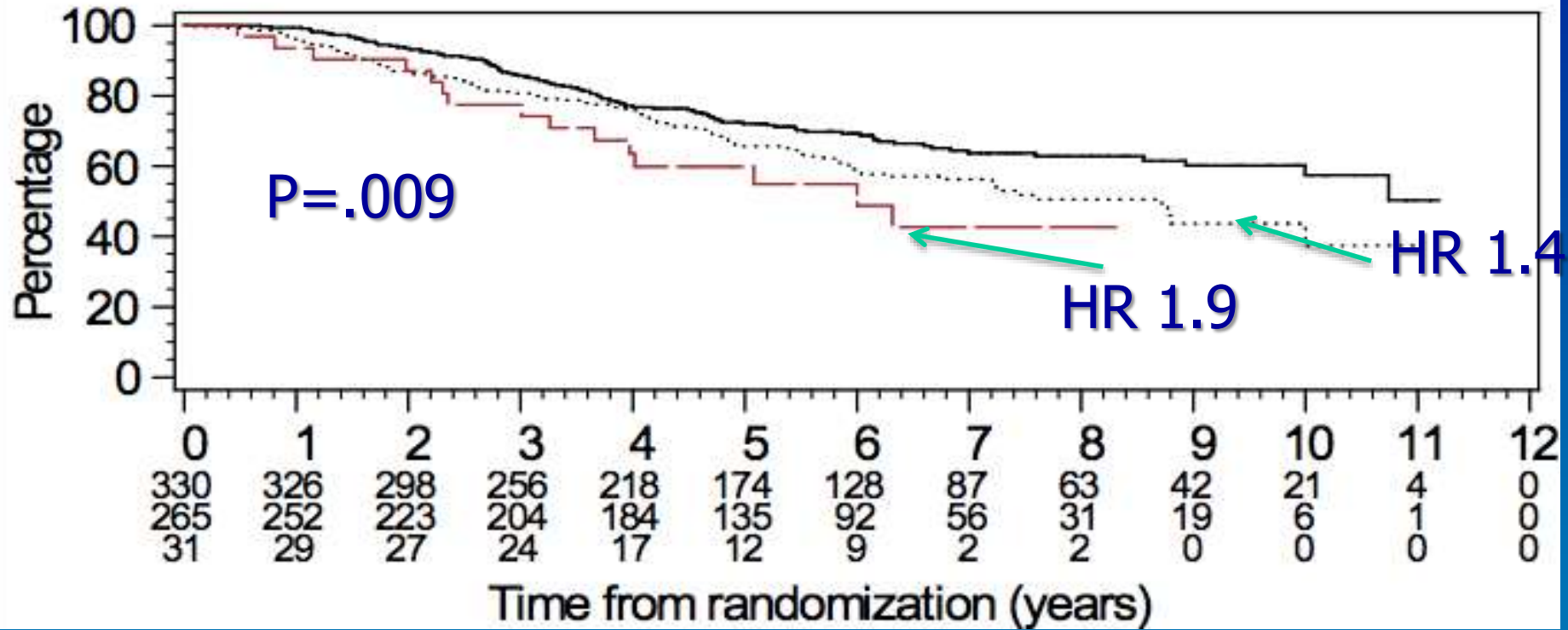


# Testosterone in first year of ADT: PR7

Testosterone	$\leq 0.7$ (20)	0.7-1.7 (20-50)	$\geq 1.7$ (50)
Minimum T	79%	29%	1%
Median	53%	42%	5%
Maximum	27%	50%	23%

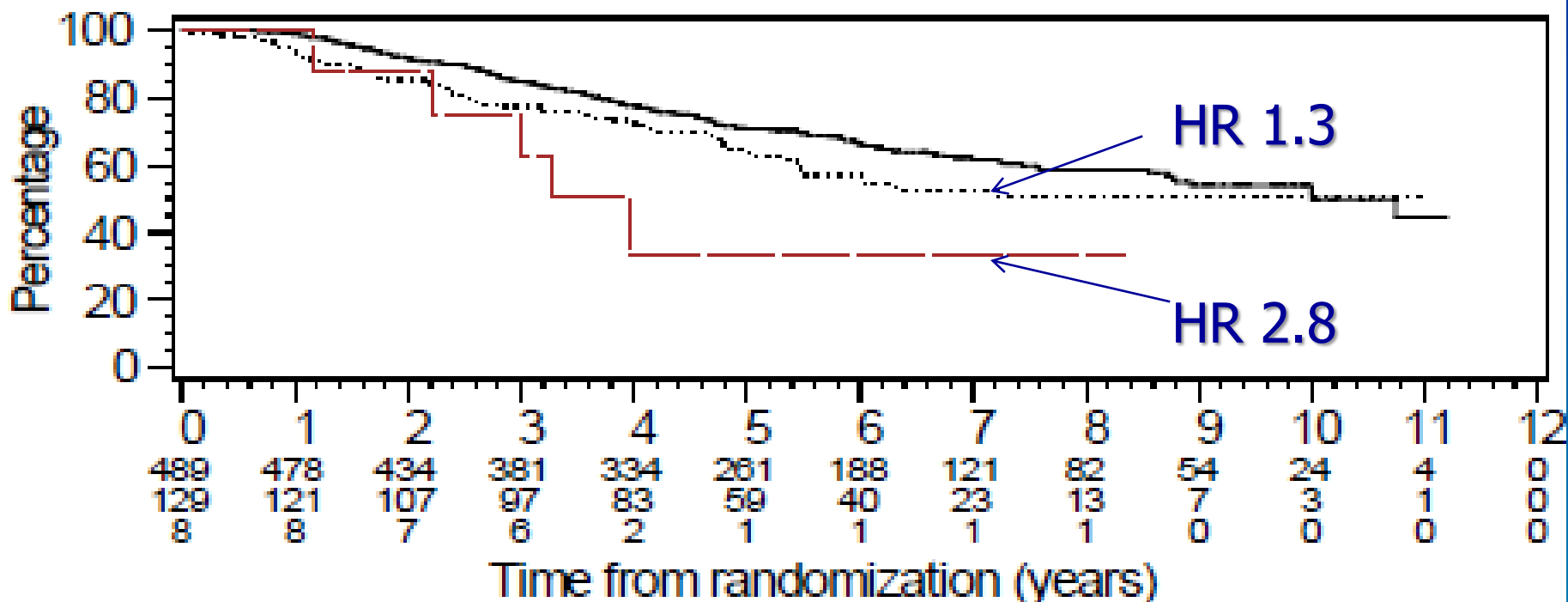
# NCIC CTG PR.7 Sub Analysis

HR event SURVIVAL: Based on Median of 1st Year Testosterone Levels

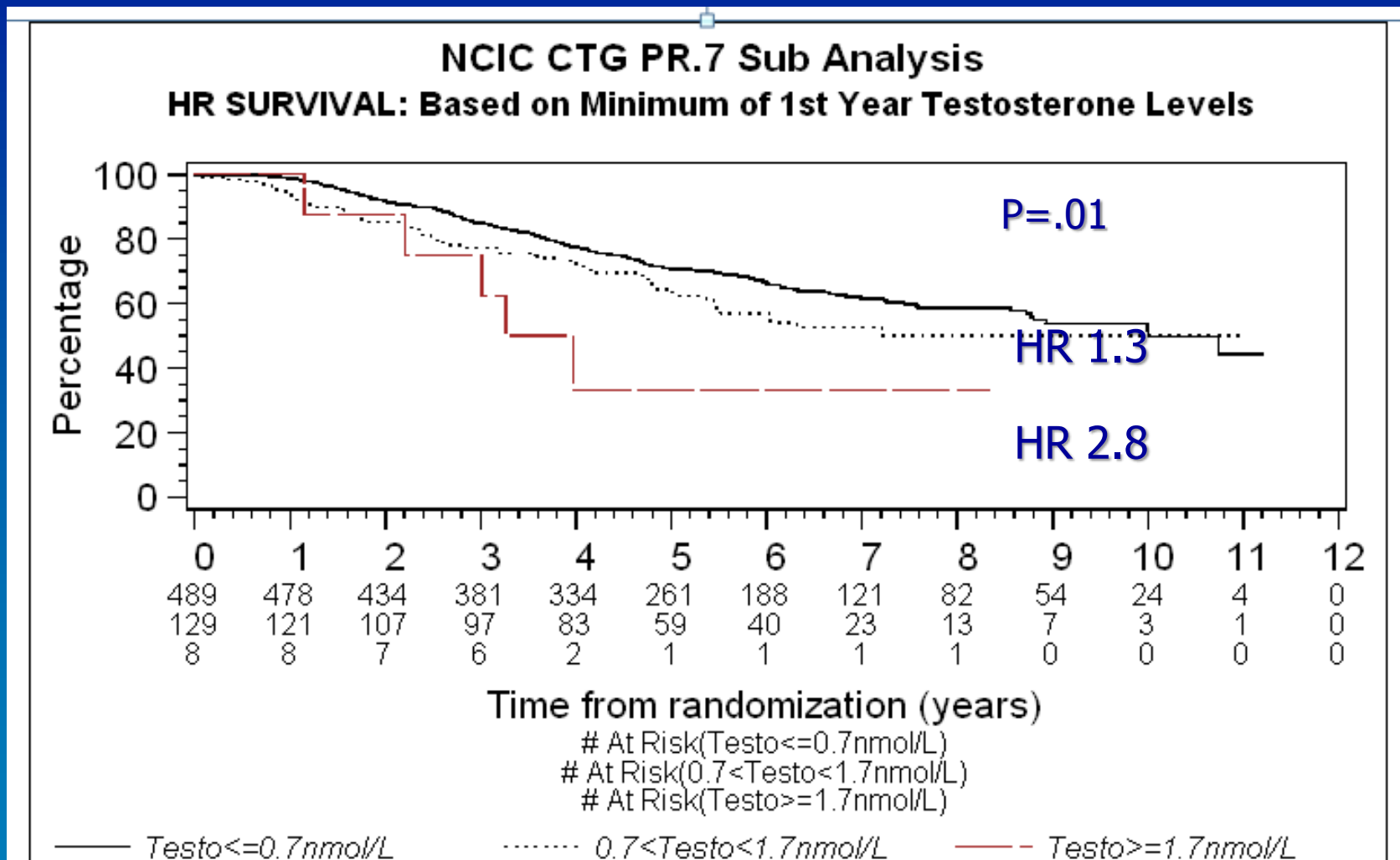


## NCIC CTG PR.7 Sub Analysis

HR SURVIVAL: Based on Minimum of 1st Year Testosterone Levels



# Time from hormone resistance to death by minimum T value

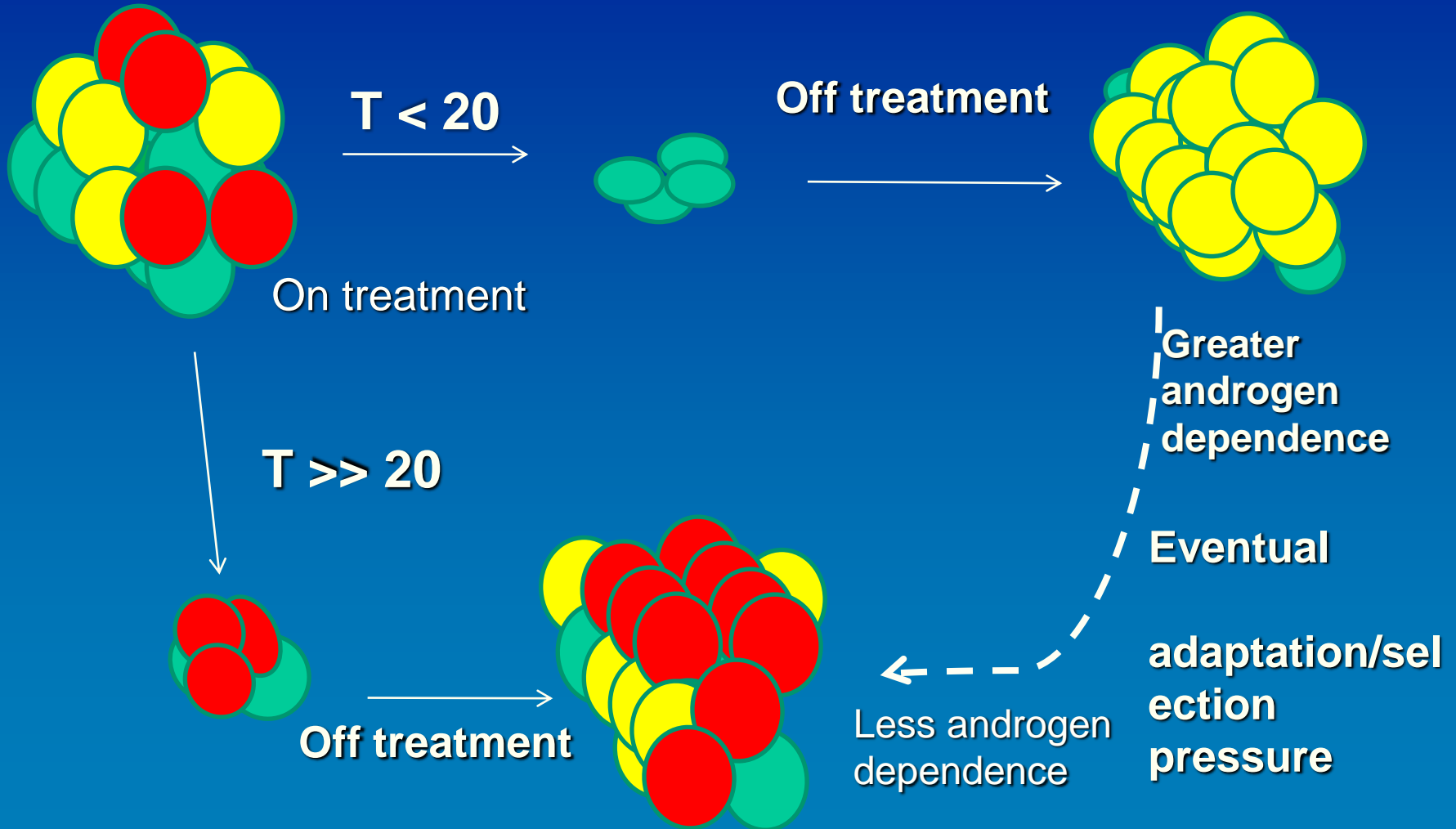


# How to reconcile the conundrum

- 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.”



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<sup>a,\*</sup>, Laurence Klotz<sup>b</sup>, Bertrand Tombal<sup>c</sup>, James Grady<sup>a</sup>,  
Tine K. Olesen<sup>d</sup>, Jan Nilsson<sup>e</sup>

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



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<sup>a,\*</sup>, Kurt Miller<sup>b</sup>, E. David Crawford<sup>c</sup>, Neal Shore<sup>d</sup>, Bertrand Tombal<sup>e</sup>,  
Cathrina Karup<sup>f</sup>, Anders Malmberg<sup>f</sup>, Bo-Eric Persson<sup>g</sup>

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

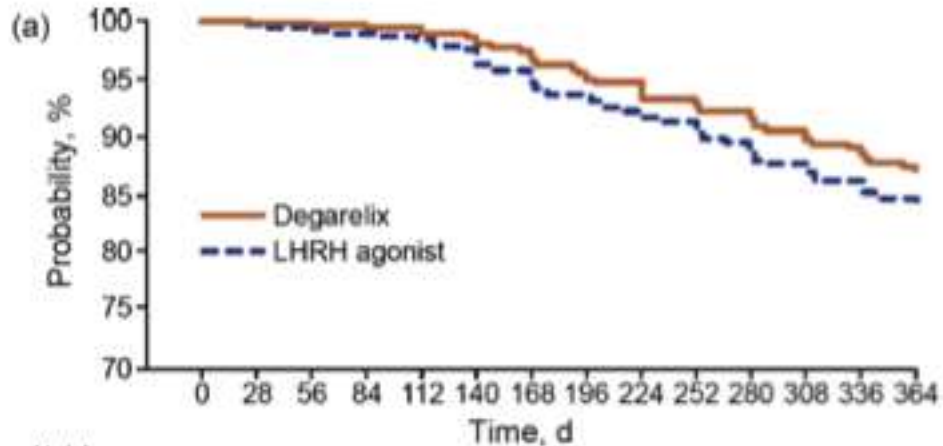
\*Patients received 7 months of treatment

# 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

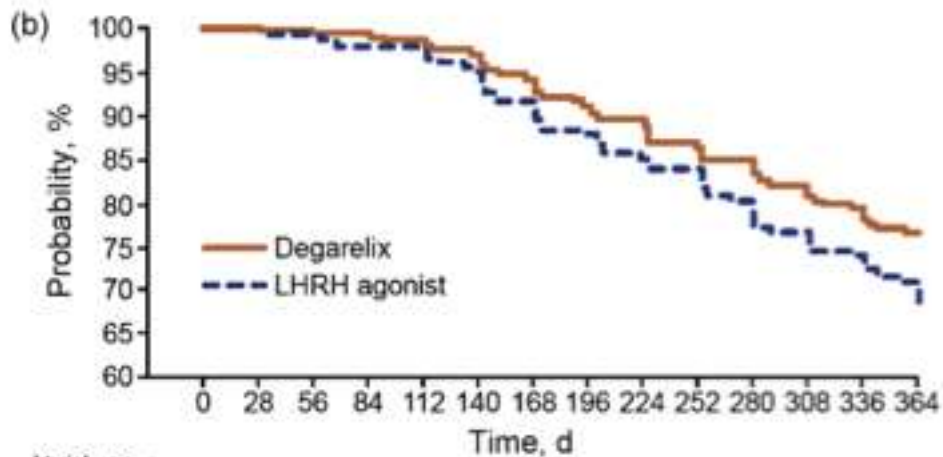
All patients



At risk, no. :

Degarelix	1283	1253	1234	1186	958	933	911	891	864	836	816	792	770	710
LHRH agonist	657	653	645	615	489	483	470	460	449	445	429	418	408	375

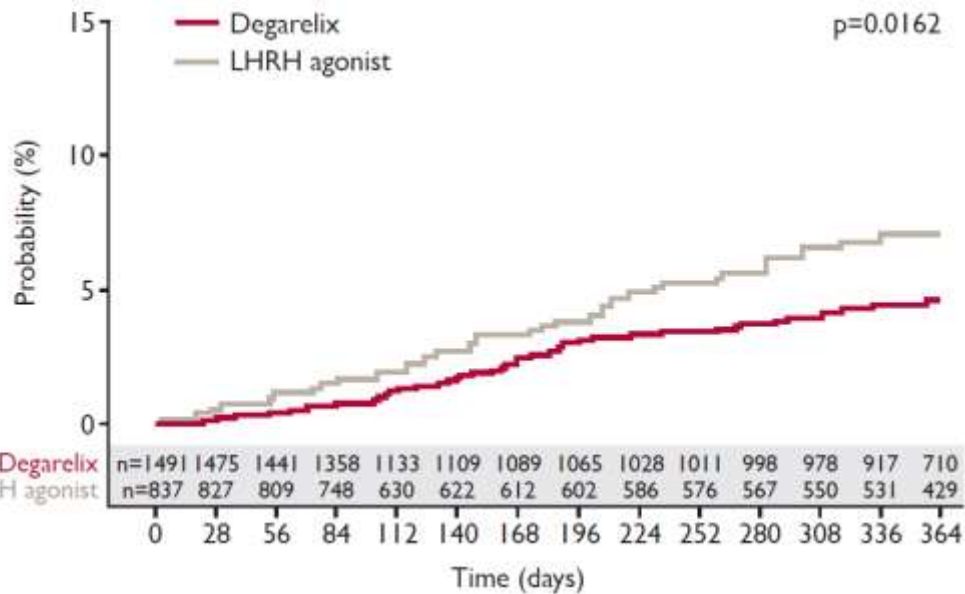
PSA > 20



At risk, no. :

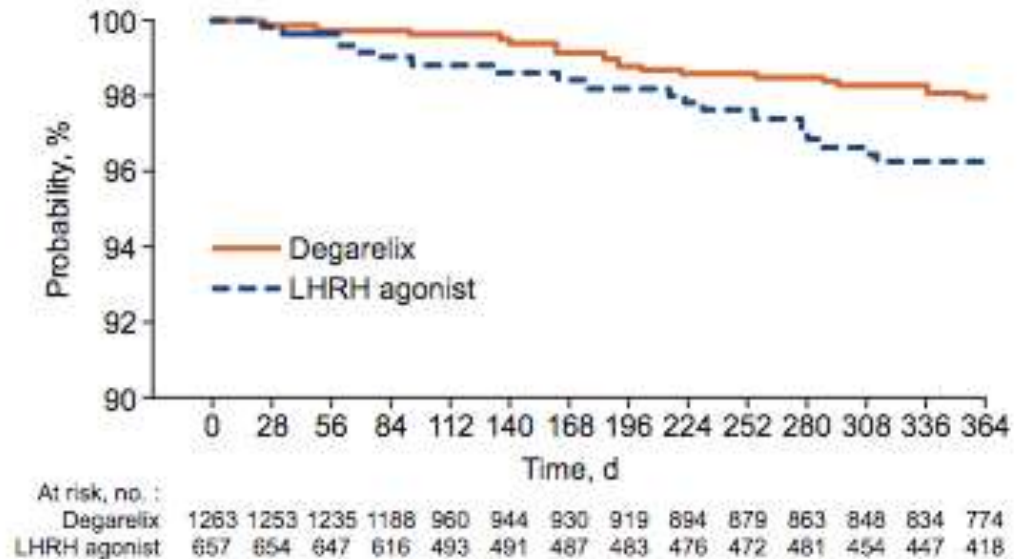
Degarelix	578	574	564	546	473	456	440	427	409	391	379	362	347	315
LHRH agonist	289	289	283	269	230	224	214	206	197	195	181	173	166	149

# Risk of CV event and OS



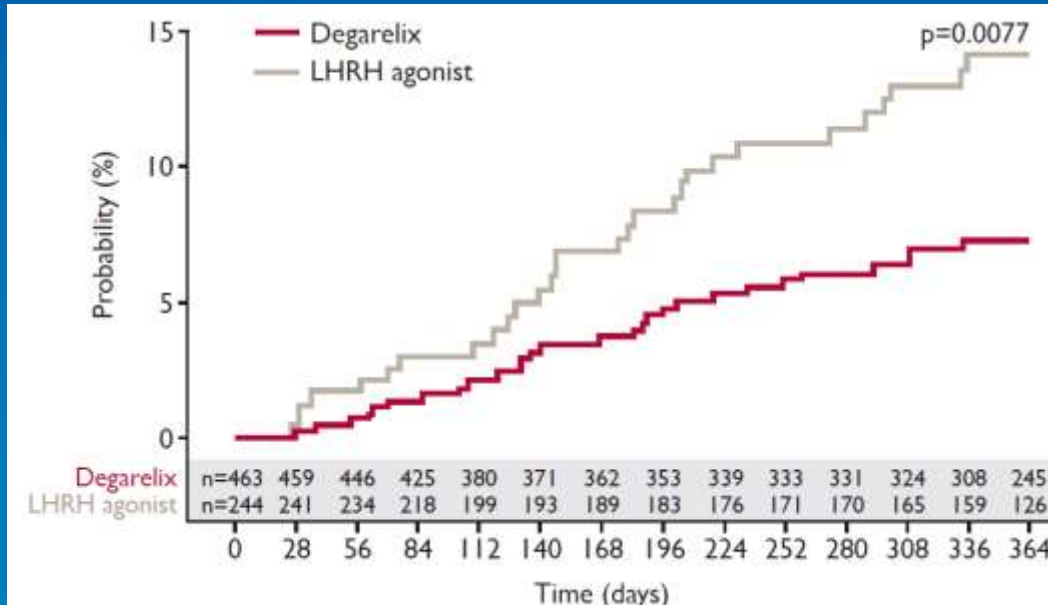
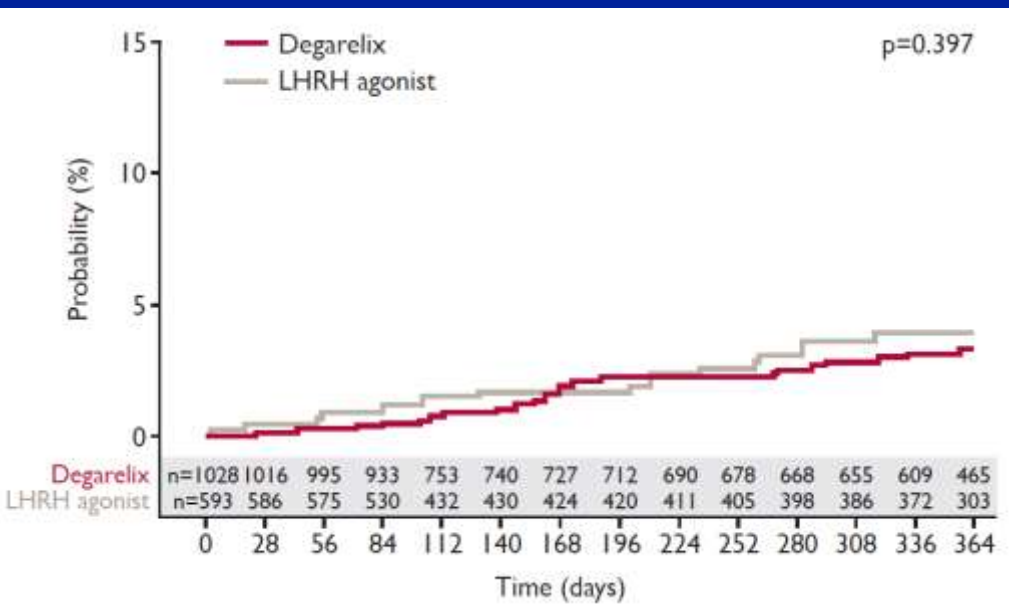
CV events

OS P=.02





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

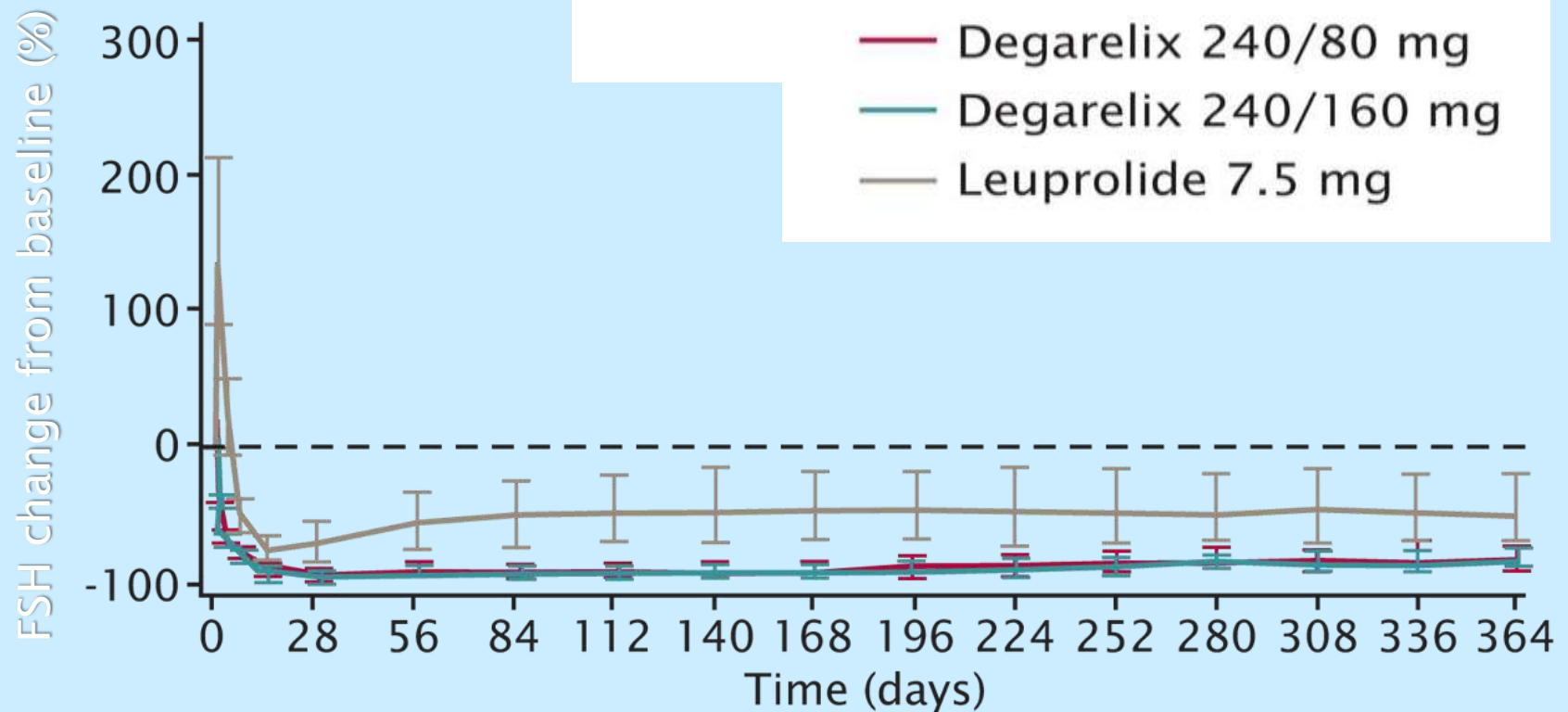


Relative risk reduction of 50%  
Absolute risk reduction 7%



# 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

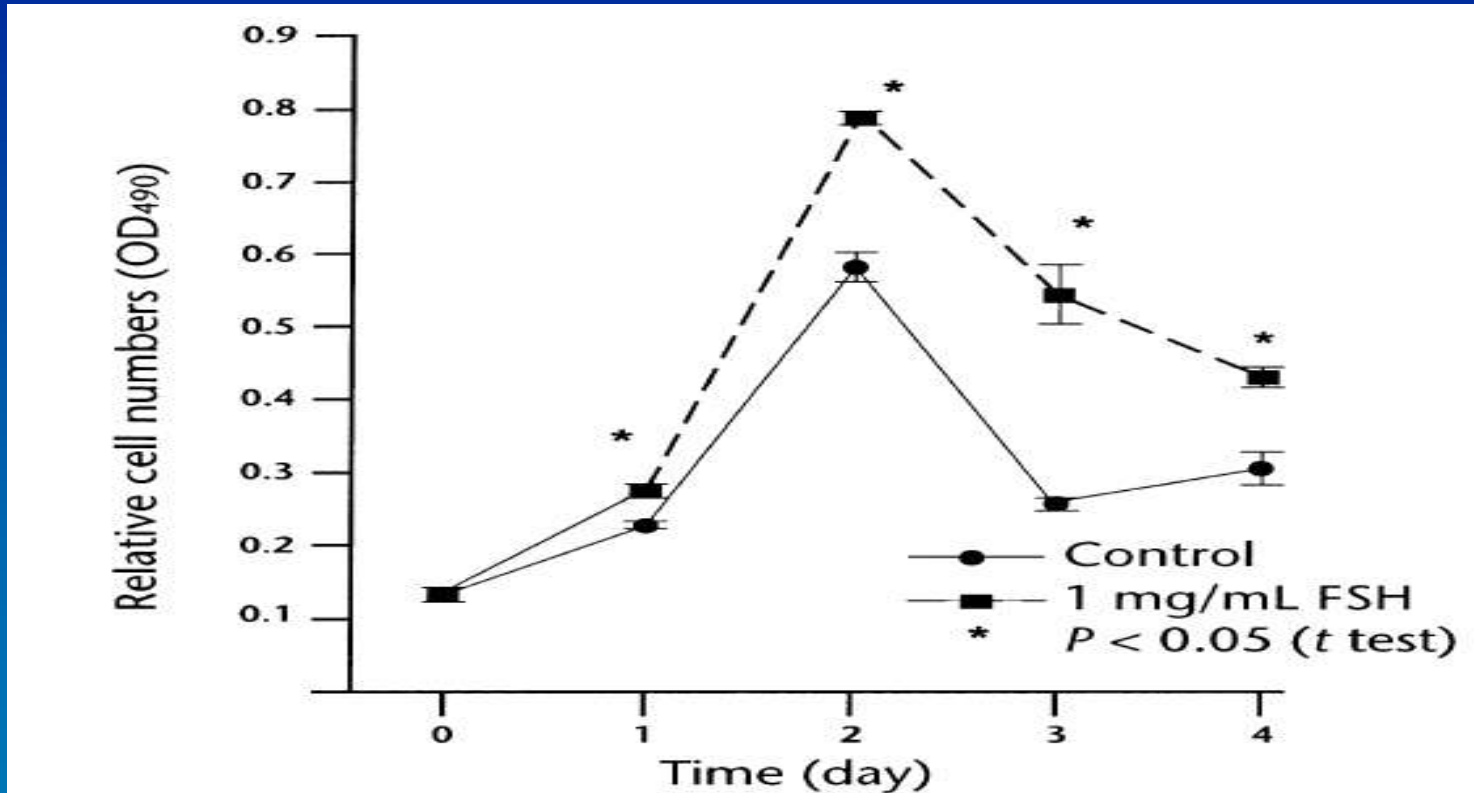
## FSH and FSH-receptors expressed in

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

## ALSO:

- Adipocytes +++  
+ low prevalence; +++++ high prevalence
- Cardiac Myocytes +++

# FSH stimulates growth of PC-3 human prostate cancer cells



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

# 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

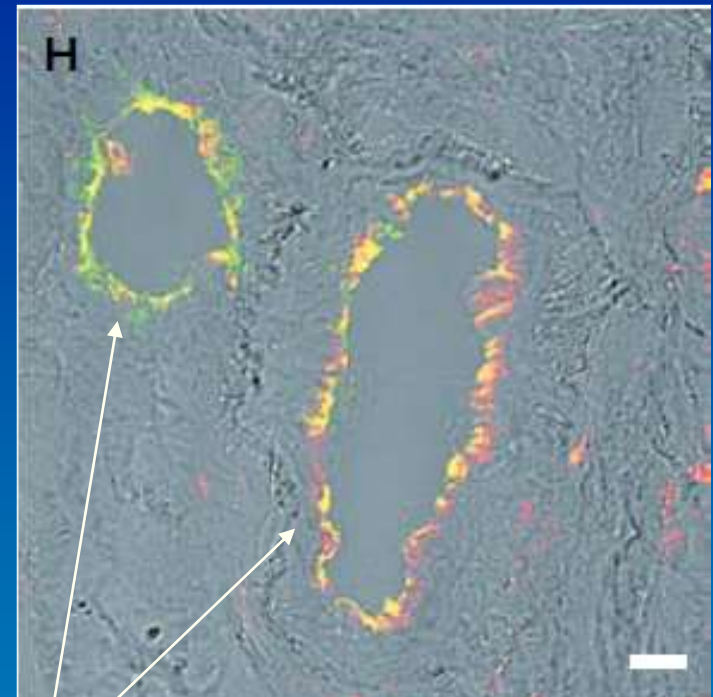
2010



**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**

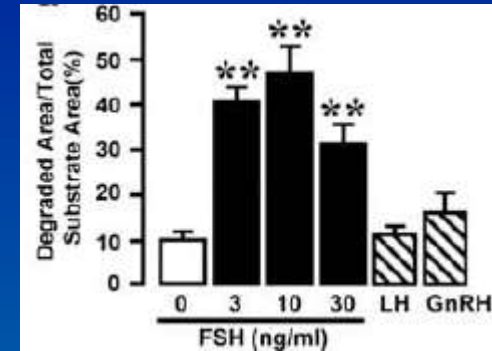
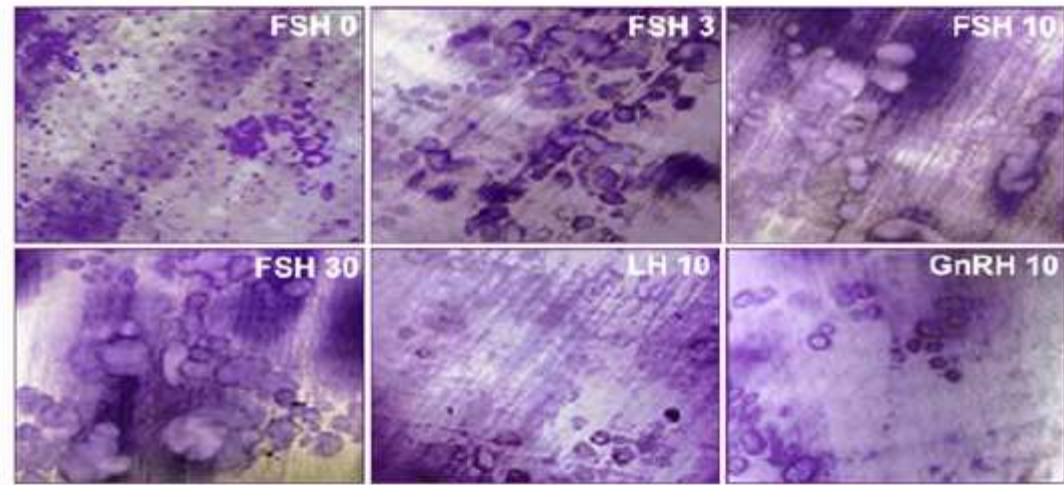


Cells expressing FSH receptors

# FSH Directly Regulates Bone Mass

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

Cell 125, 247–260, April 21, 2006



- FSH directly increases osteoclastogenesis and resorption
- Gi2a-coupled FSH receptors activate osteoclast NF- $\kappa$ B, 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



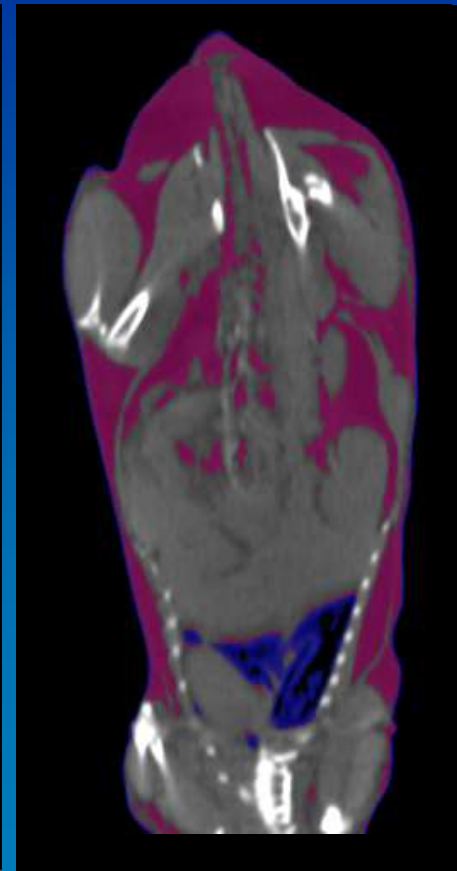
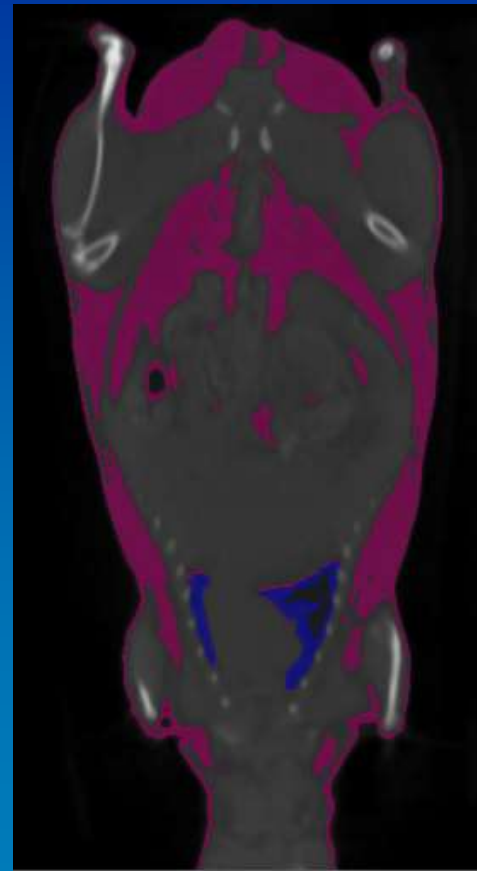
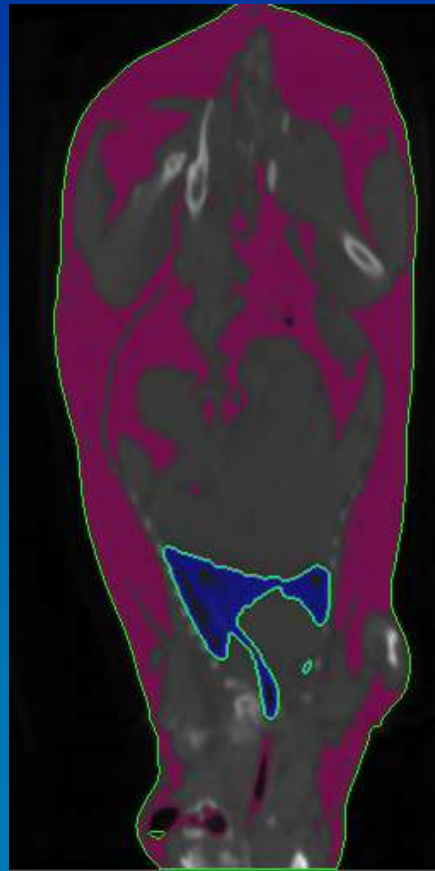
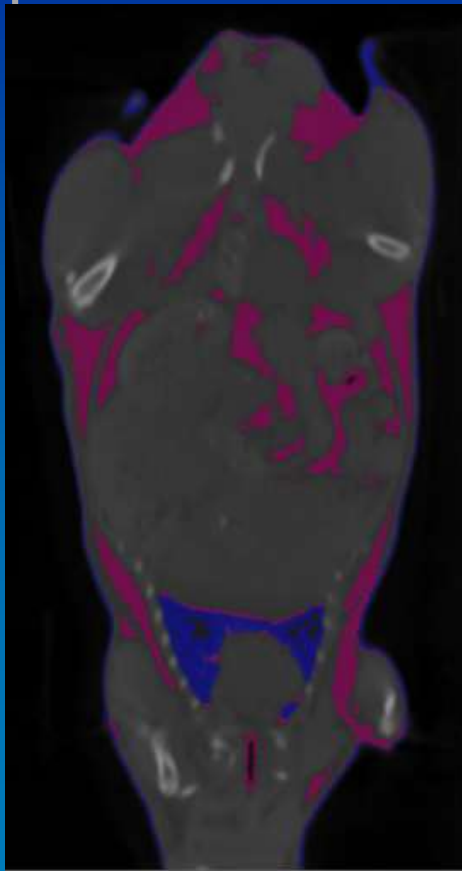
# Differential adiposity between different types of ADT. Hopmans S, Klotz L, Pinthus J. Urol Oncol 32(8):1126-34, 2014

control

castration

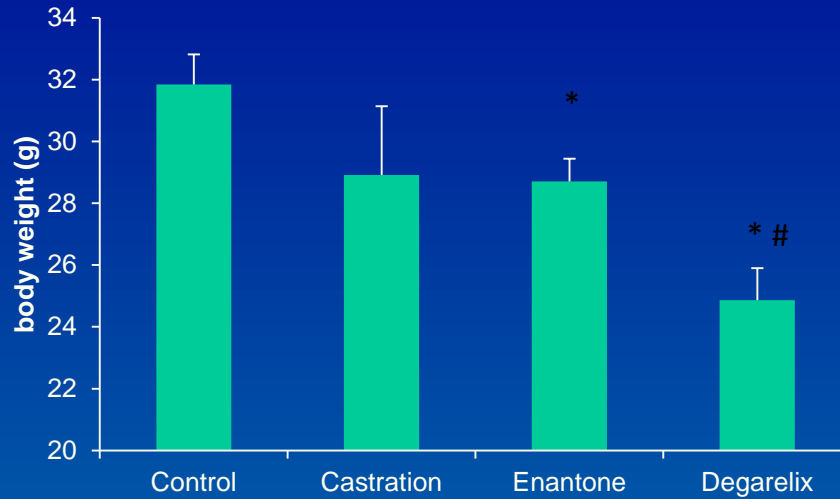
LHRH agonist

degarelix

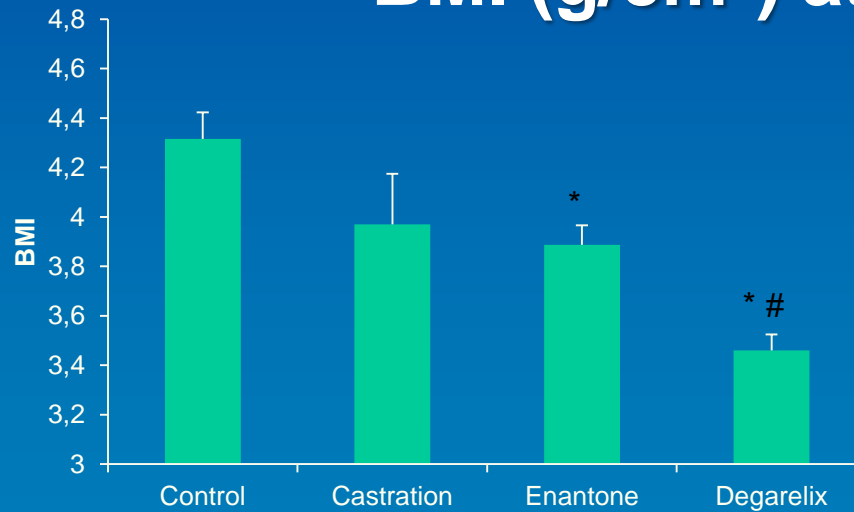


Pink: adipose tissue  
Blue: Lung tissue

# Total body weight (g) at 4 months



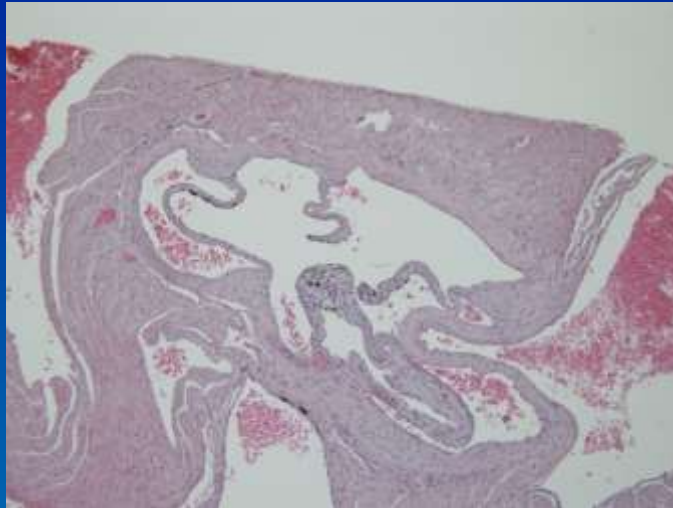
# BMI (g/cm<sup>2</sup>) at 4 months



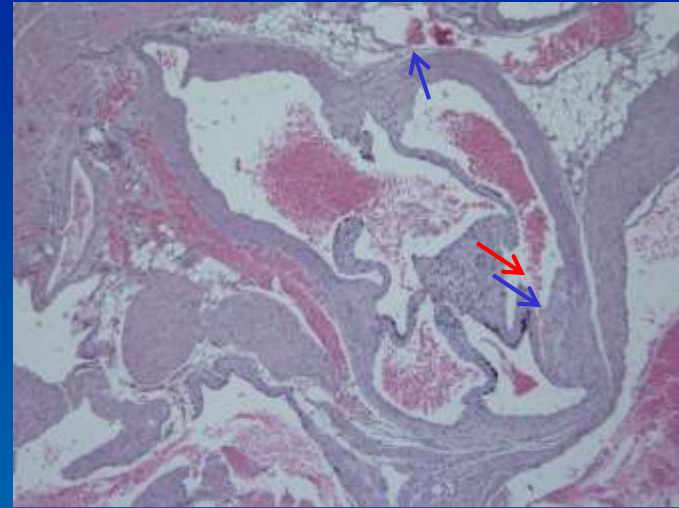
\*: significantly different from control  
#: significantly different from enantone

# 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)

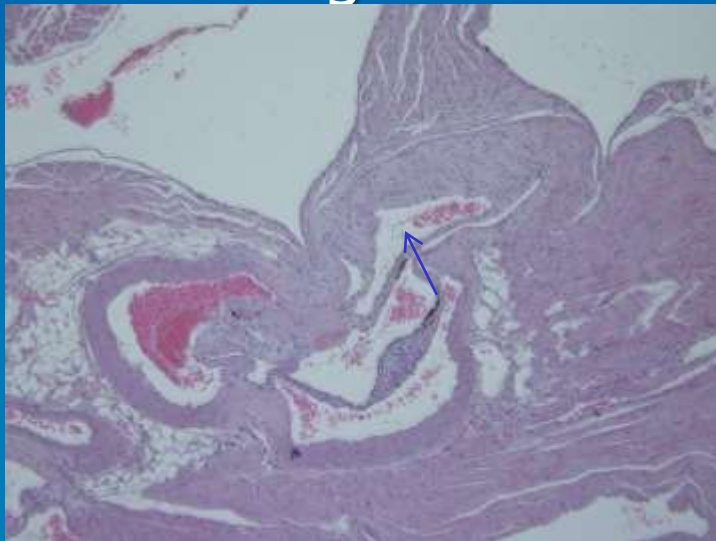
Control



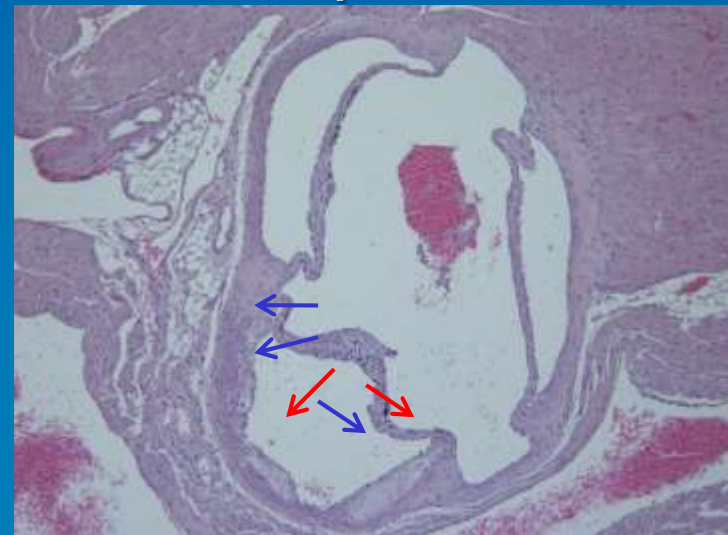
Castration



Degarelix

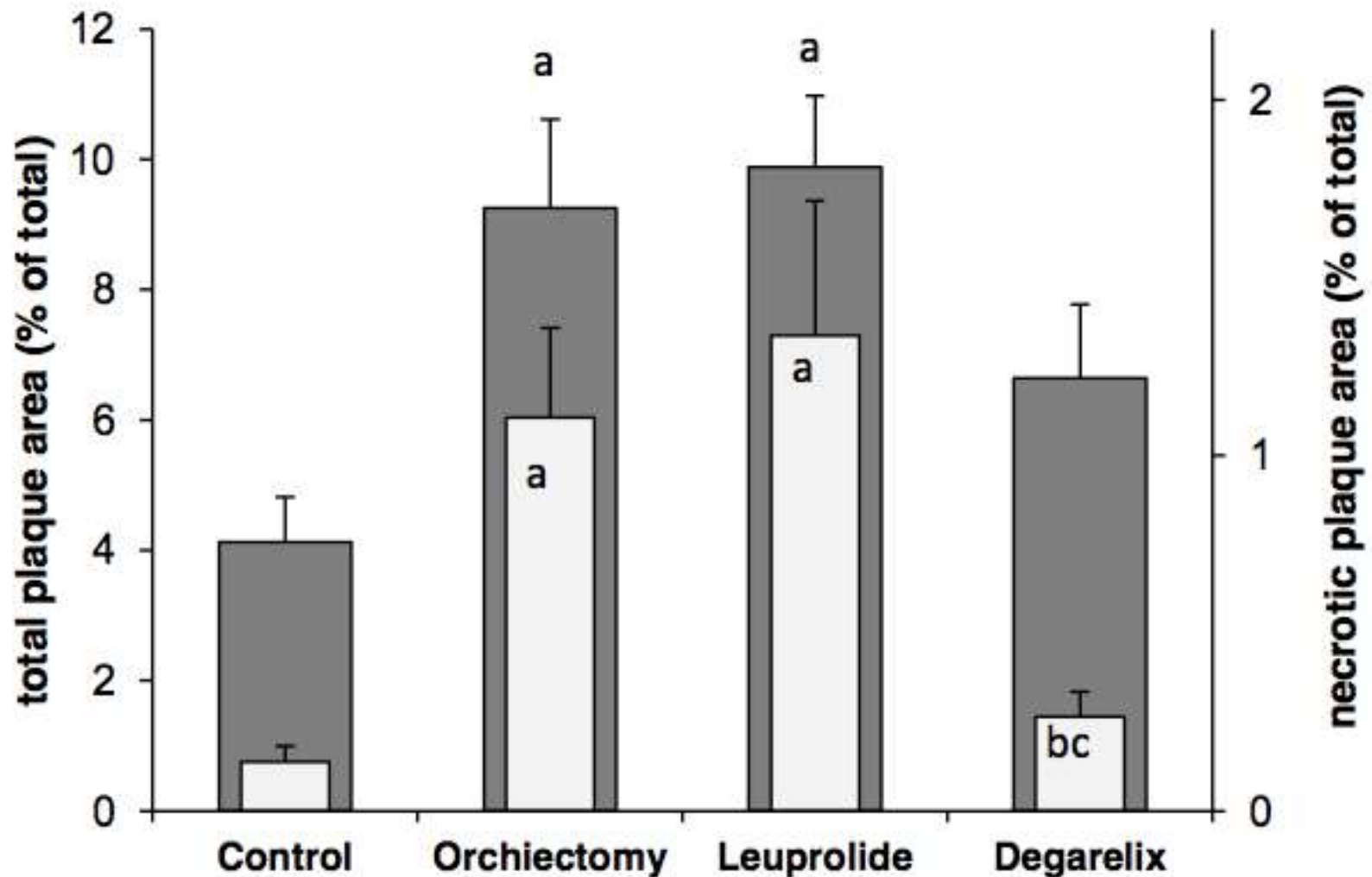


Leuprolide



# 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