Intermittent ADT, Quality of Life, Testosterone and other interesting developments

Scottsdale Prostate Cancer Symposium

Faculty disclosure statement: Laurence Klotz, MD

Clinical Research funding:

- Bayer/Algeta
- Ferring
- Abbott

Advisory boards:

- Amgen
- Janssen
- Ferring
- GSK
- Profound

Speaking/Honoraria:

- Sanofi-Aventis
- Ferring
- Janssen
- Tolmar
- Profound

Stock Ownership:

None

ADT: Where we have come from

1780 John Hunter castration and prostate regression

1938 Acid phosphatase

1939 Butenandt and Ruzicka, Synthesis of Testosterone (Nobel)

1940 Huggins, Orchiectomy and estrogen (Nobel)

1965 Synthetic estrogens

1977 First generation non-steroidal anti-androgens

1989 2nd generation non-steroidal AA (bicalutamide)

1985 Schally LHRH structure and LHRH agonists (Nobel)

2003 LHRH antagonist (Aberelix)

2008 Degarelix

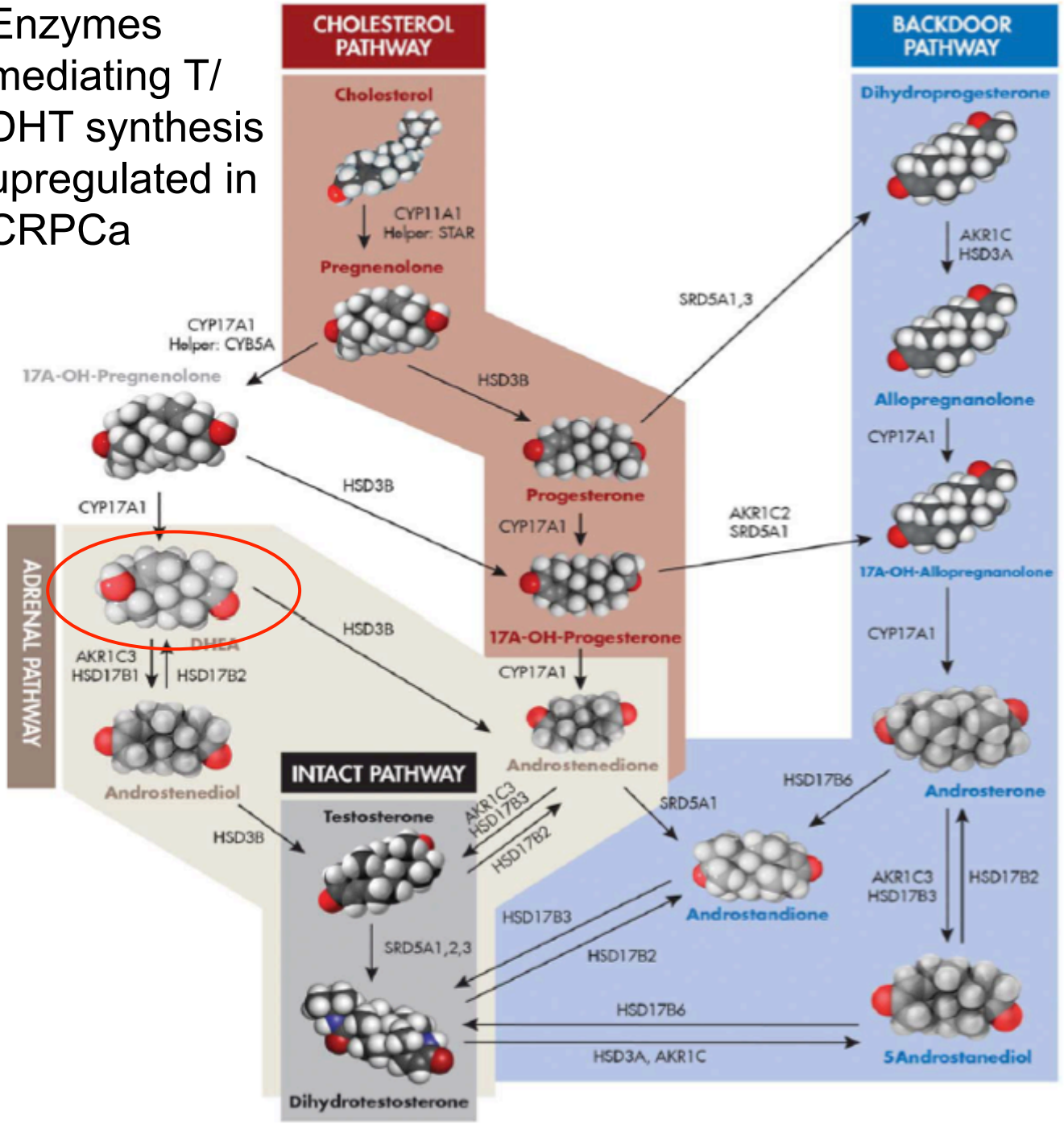
2009 Abiraterone

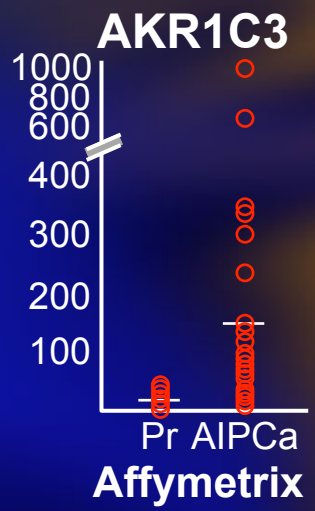
2010 Enzalutamide

Developments in last decade:

- Understanding of mechanisms of castration resistance (intracrine/autocrine synthesis of androgens, splice variants, other AR pathway alterations)
- Dynamic and heterogeneous tumour biology (treatment induced biological evolution)
- Systemic/Metabolic/CV effects of ADT
- Intermittent therapy: data from large RCTs
- Importance of testosterone levels on ADT
- LHRH antagonists
- Survival benefit in CRPC with new AR pathway targeted agents

Enzymes mediating T/ DHT synthesis upregulated in CRPCa

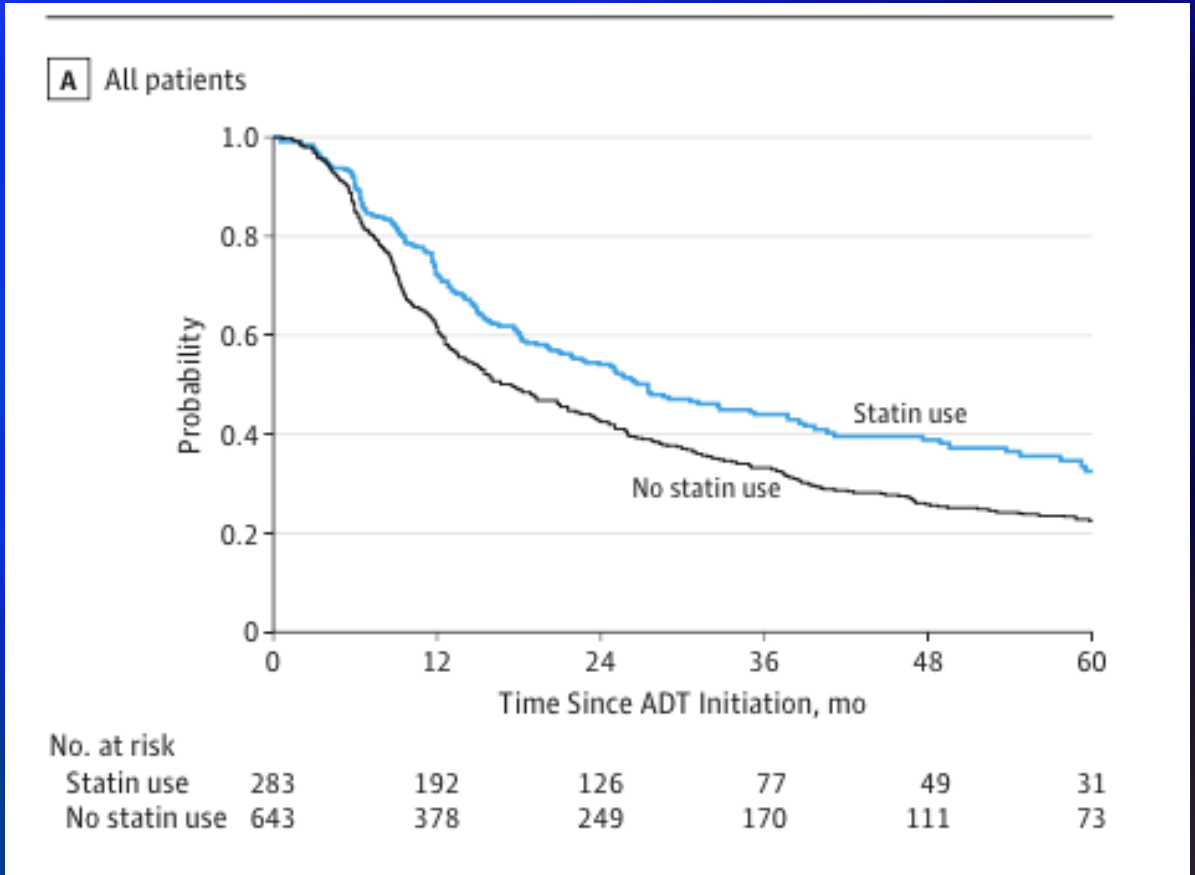




Time to progression in men on ADT: Statins

Harshman L et al *JAMA Oncol*. 2015;1(4):495-504.

- DHEA sulfate: Testosterone precursor of adrenal origin
- Dependent on transporter SLCO2B1 to enter cells
- Statins also SLCO2B1 dependent, competes with DHEAS uptake, reduces intracellular T



Intermittent therapy and on-treatment testosterone levels

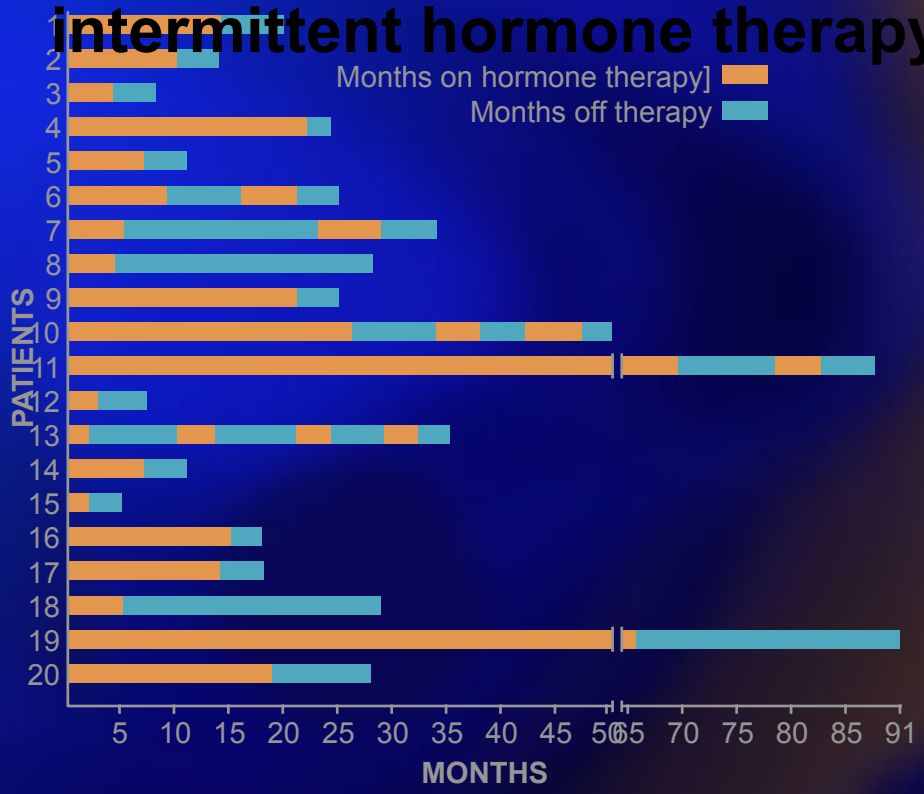
Intermittent ADT: First clinical report in 1986

- 20 D2 patients cycled on DES (pre PSA)

Results:

- Of the 10 men impotent due to endocrine therapy, nine resumed sexual activity within 3 months
- Disease progression occurred after median of 8 months

Individual patient responses to intermittent hormone therapy



Klotz L, et al. *Cancer.* 1986;58(11):2546.-.

Phase 2 Studies of Intermittent ADT

Author	Yr	N	F/U mo.	Stage	PSA nadir	Off Rx	# cycles
Klotz	‘86	20	36	D2	Pre PSA era		1-5
Higano	‘96	22	26	PSA failure + D2	<0.1	>10	1-3
Grossfield	‘98	47	24	T1c-4	0.1-4	>10	1-5
Goldenberg	‘99	87	65	A2-D2	4	10-20	1-5
Prapotnich	‘99	566	81	Advanced	<4	>10	1-12
Bouchot	‘00	44	44	D2	<4	> 20	1-2
Bracada	‘00	89	34	B-D	0	>10	1-5
Strum	‘00	52	66	T1c-D2	0	>5	1-2
Sciarra	‘00	51	48	T2-T3 rising PSA	<4		5
Pether	‘03	102	50	A2-D2	<4	10-20	1-6
De la Taille	‘03	146	46	T1-4, M1	<4	>10	1-8
Lane	‘04	75	134	All	<4	>20	1-3
Malone	‘05	95	69	All	<4	>10	1-7
Cury	‘06	39	56	T1-3	<4	>10	1-4
Bruchovsky	‘06	103	50	T1b-T3 rising PSA	<4	>10	1-5
Spry	‘06	250	30	All	<4	>20	1-2
Yu	‘10	72	76	PSA failure	<1	1-4	1-9

Phase 3 Trials of IAS

Trial	Stage	N	Results
PR7 (Canada)	PSA failure	1486	IAS Non-inferior
SWOG 9346	M1	1500	Inconclusive
SEUG (Portugal)	T3,4 or M1	914	No difference in OS
AP17/95 (Germany)	T3,4 or M1	335	No diff in TTP or OS
EC507 (Europe)	Post RP rising PSA	167	No diff TTP
Erasmus	M1	366	QOL better
FinnProstate VII	T3,4, M1	564	Pending
TULP (Netherlands)	T3,4, M1	193	Longer TTP in CAS (NS)
De Leval (Belgium)	T3,4, M1, post RP	68	TTP favoring IAS
Yamanaka	T3,4, adjuvant	188	Short f/u, no diff
Hering (Brazil)	M1	43	Trend favoring IAS, NS

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

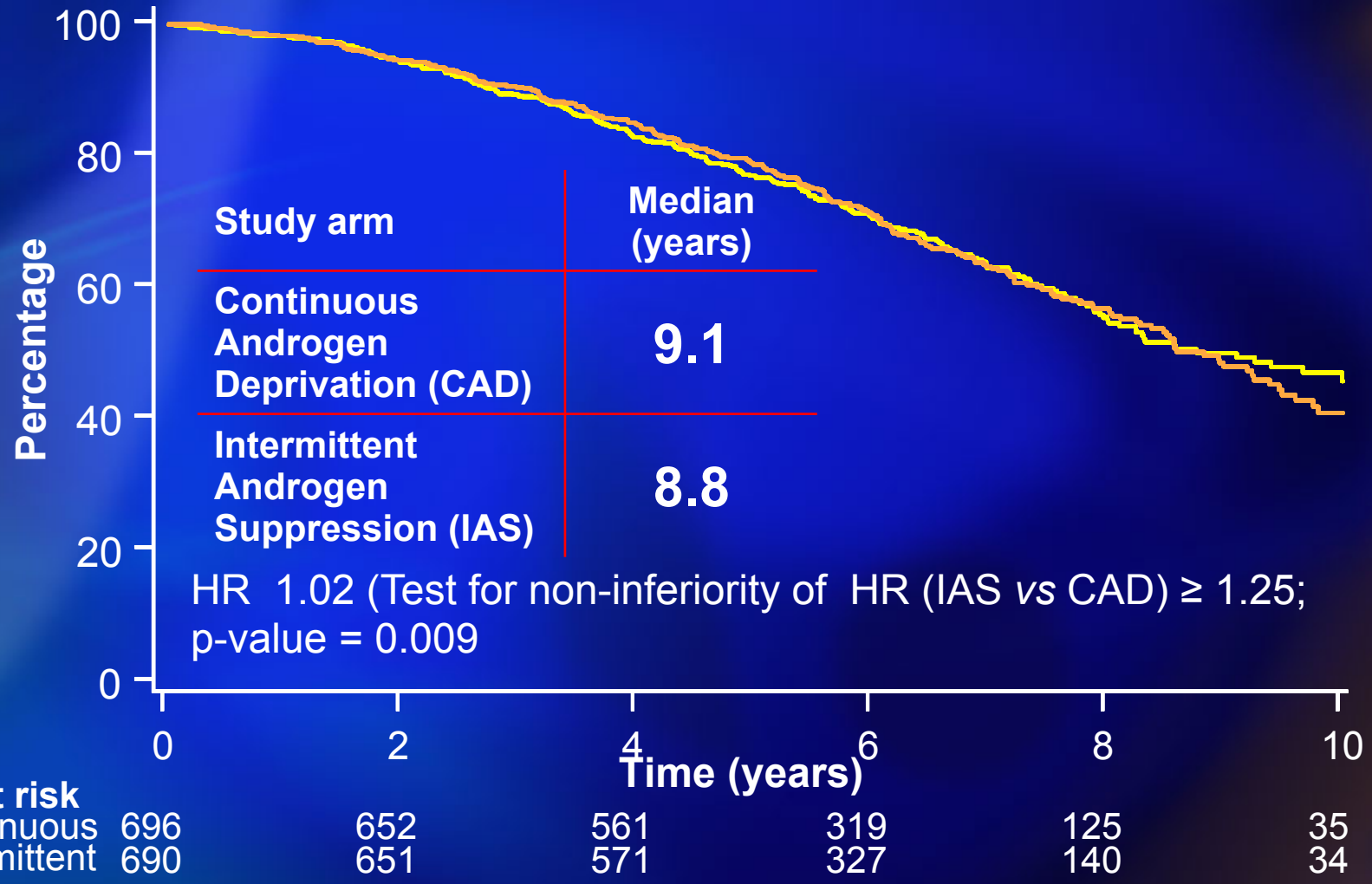
BACKGROUND

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

PR7: Overall survival (ITT)

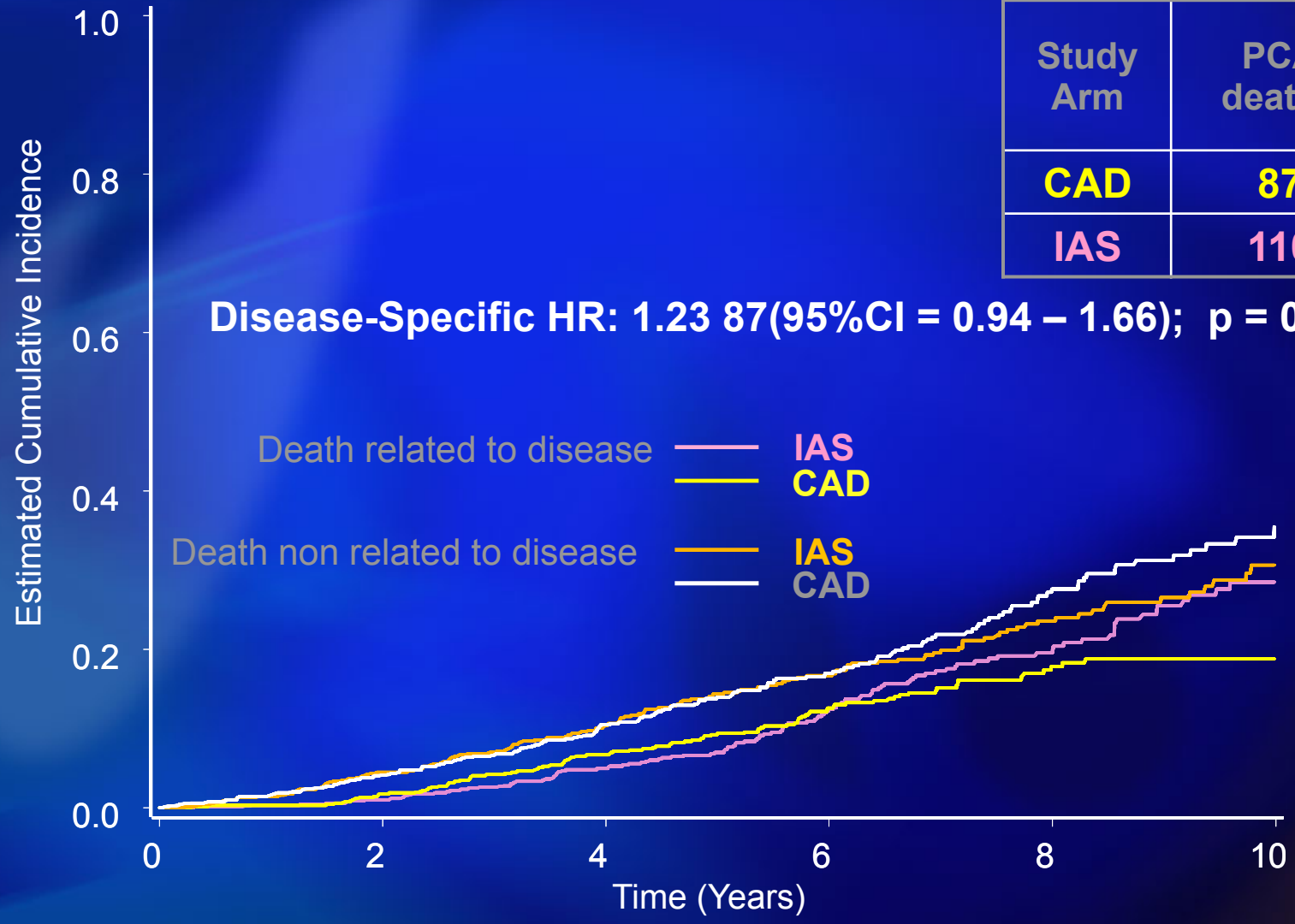
- **1486 men with PSA recurrence: cycles of 8 mo IADT induction vs continuous life long ADT**



PR7: Mortality by cause (ITT)

Study Arm	PCA deaths	CV/ Unknown cause
CAD	87	103
IAS	110	87

Disease-Specific HR: 1.23 87(95%CI = 0.94 – 1.66); p = 0.13



The NEW ENGLAND JOURNAL of MEDICINE

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

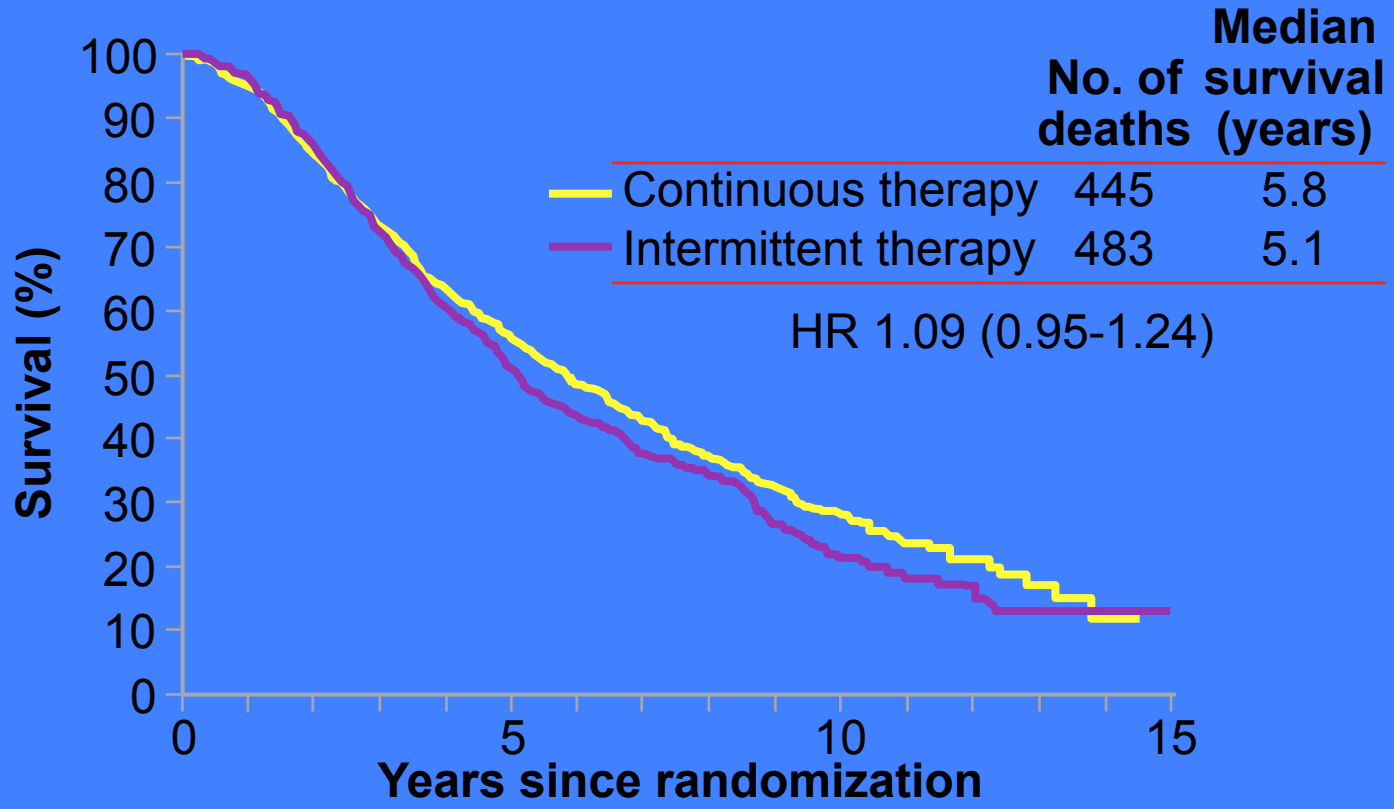
Castration resistance occurs in most patients with metastatic hormone-sensitive prostate cancer who are receiving androgen-deprivation therapy. Replacing androgens before progression of the disease is hypothesized to prolong androgen dependence.

METHODS

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

SWOG 9346 survival: M Hussain, NEJM 2013

Conclusion: 'Results inconclusive'

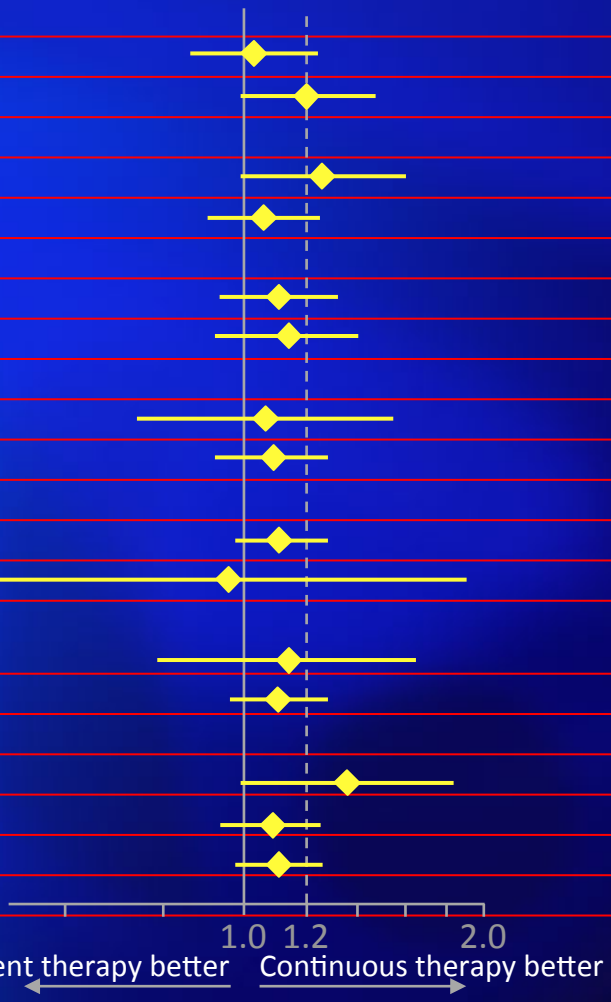


No. at risk

Continuous therapy	765	325	64
Intermittent therapy	770	291	52

PR.8: Survival by subgroups

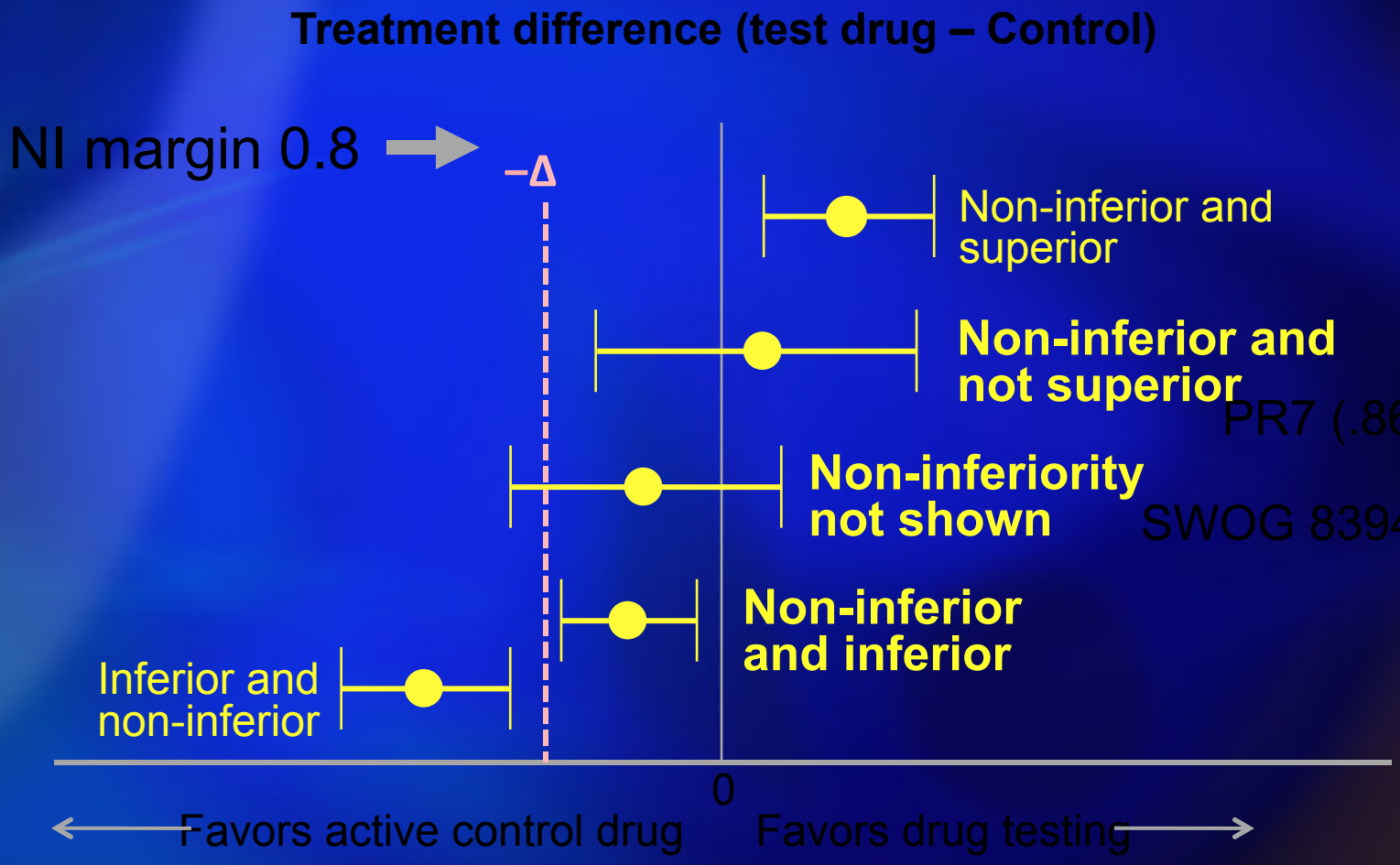
Subgroup	No. of patients	P value for interaction
Extent of disease		0.29
Extensive	743	
Minimal	792	
Bone pain		0.17
Yes	415	
No	1120	
PSA		0.61
≤ 0.2 ng/ml	995	
> 0.2–4.0 ng/ml	540	
Race		0.86
Black	189	
Not black	1066	
Performance		0.78
0 or 1	1476	
2	59	
Previous hormone therapy		0.87
Yes	186	
No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



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

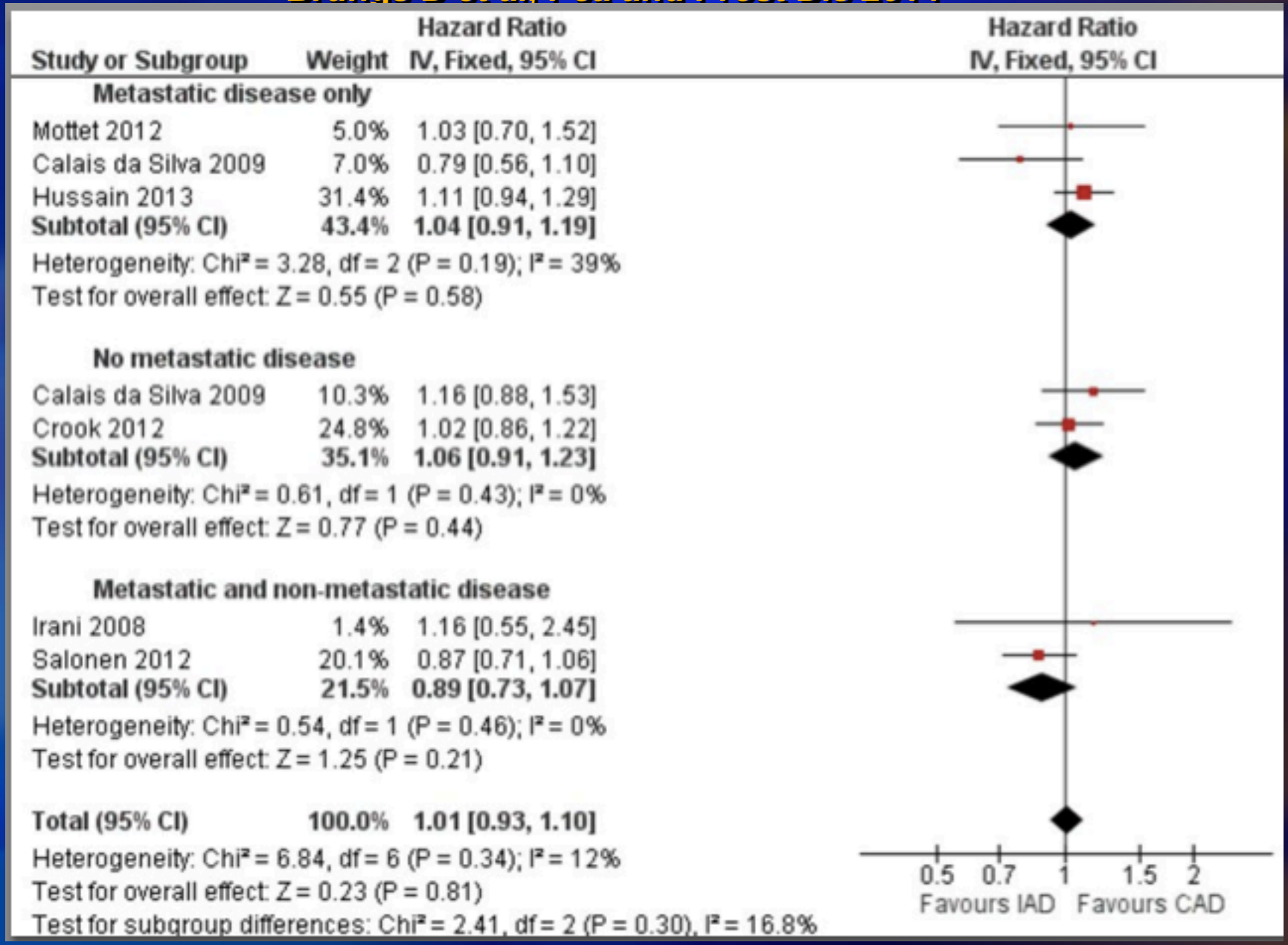
PSA, prostate specific antigen

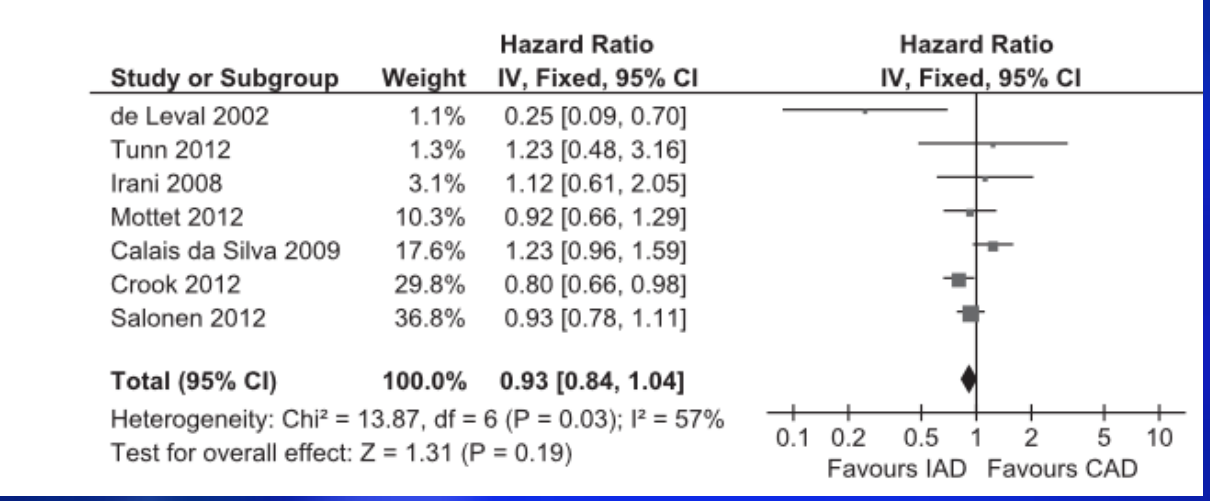
Possible outcomes of a non-inferiority trial



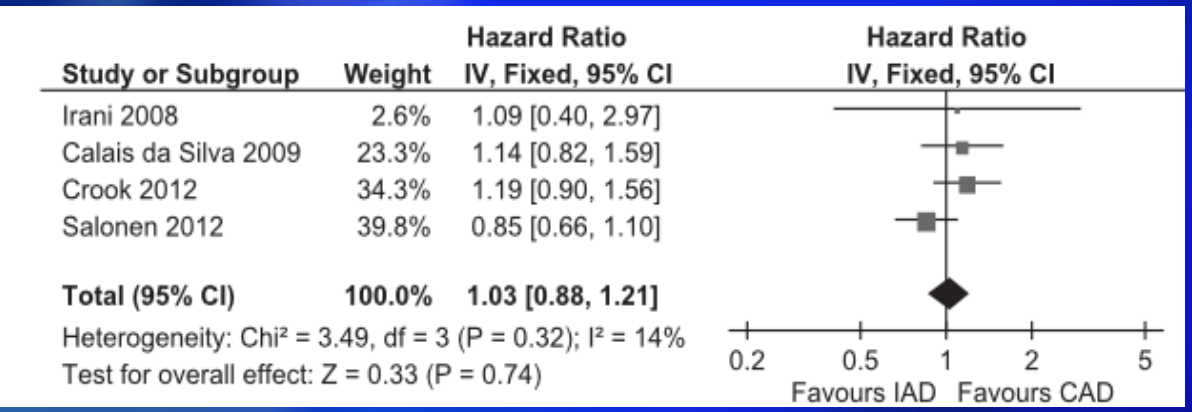
Meta-analysis of IAD studies: OS (N=5767)

Brungs D et al, Pca and Prost Dis 2014

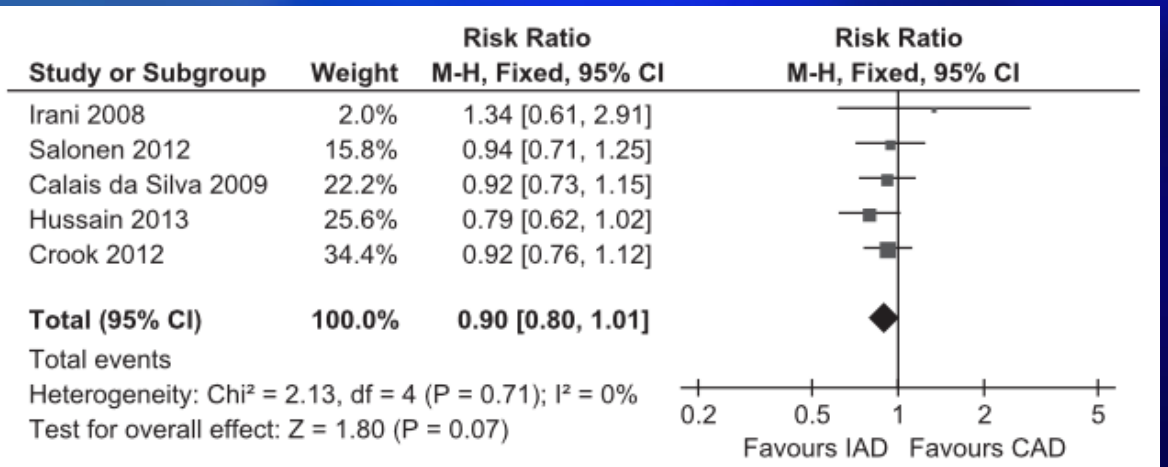




PFS: No difference

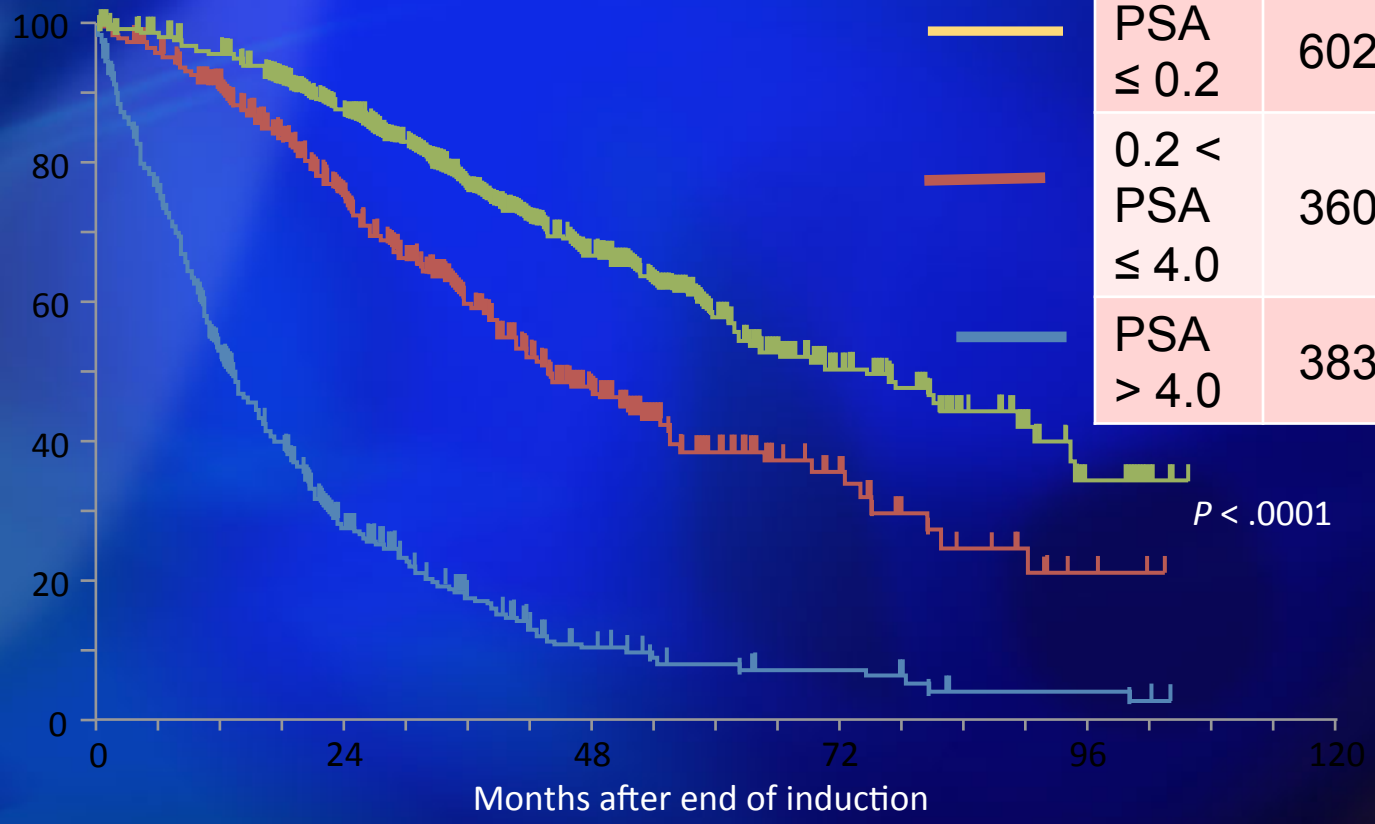


CSS: No diff.



Non pca mortality:
No diff.

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

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

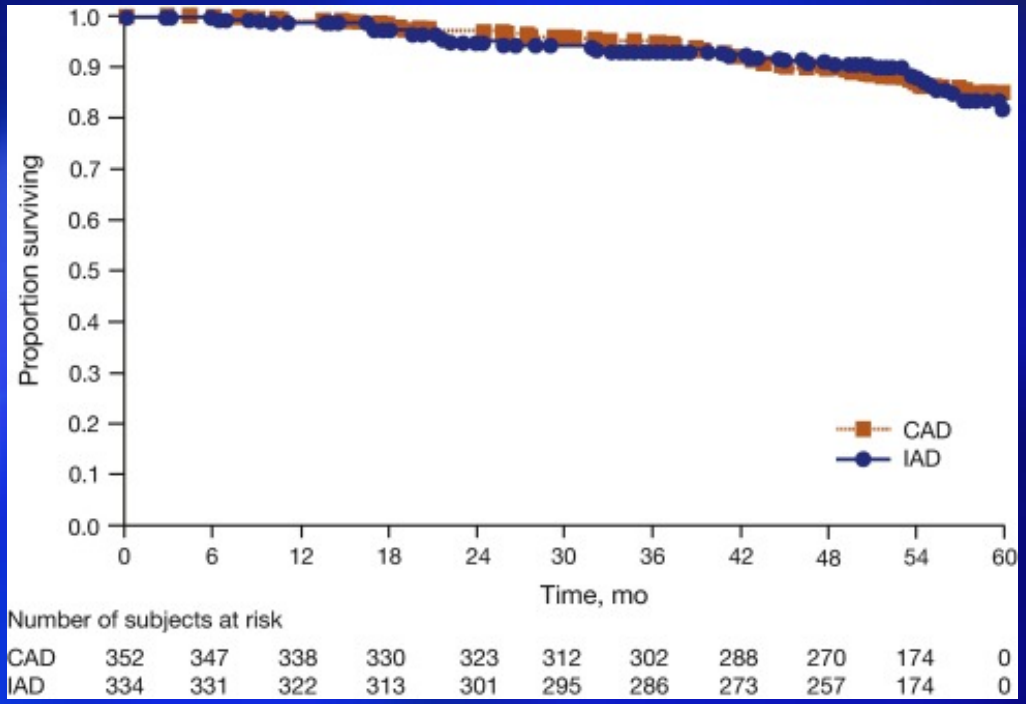


Fig. 4. Kaplan-Meier plots for time to overall survival.CAD = continuous androgen deprivation; IAD = intermittent androgen deprivation.

Claude Schulman, Erik Cornel, Vsevolod Matveev, Teuvo L. Tammela, Jan Schraml, Henri Bensadoun, Wolfgang Warnack, Raj Persad, Marek Salagierski, Francisco Gómez Veiga, Edwina Baskin-Bey, Beatriz López, Bertrand Tombal

Intermittent Versus Continuous Androgen Deprivation Therapy in Patients with Relapsing or Locally Advanced Prostate Cancer: A Phase 3b Randomised Study (ICELAND)

European Urology, Volume 69, Issue 4, 2016, 720–727

http://dx.doi.org/10.1016/j.eururo.2015.10.007

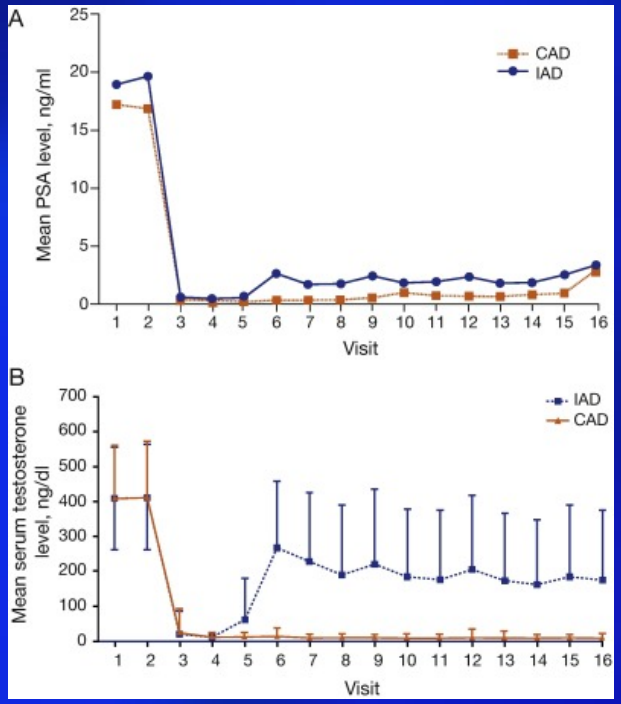


Fig. 3. (A) Mean prostate-specific antigen levels at each visit; (B) mean (standard deviation) testosterone levels at each visit.CAD = continuous androgen deprivation; IAD = intermittent androgen deprivation; PSA = prostate-specific antigen.

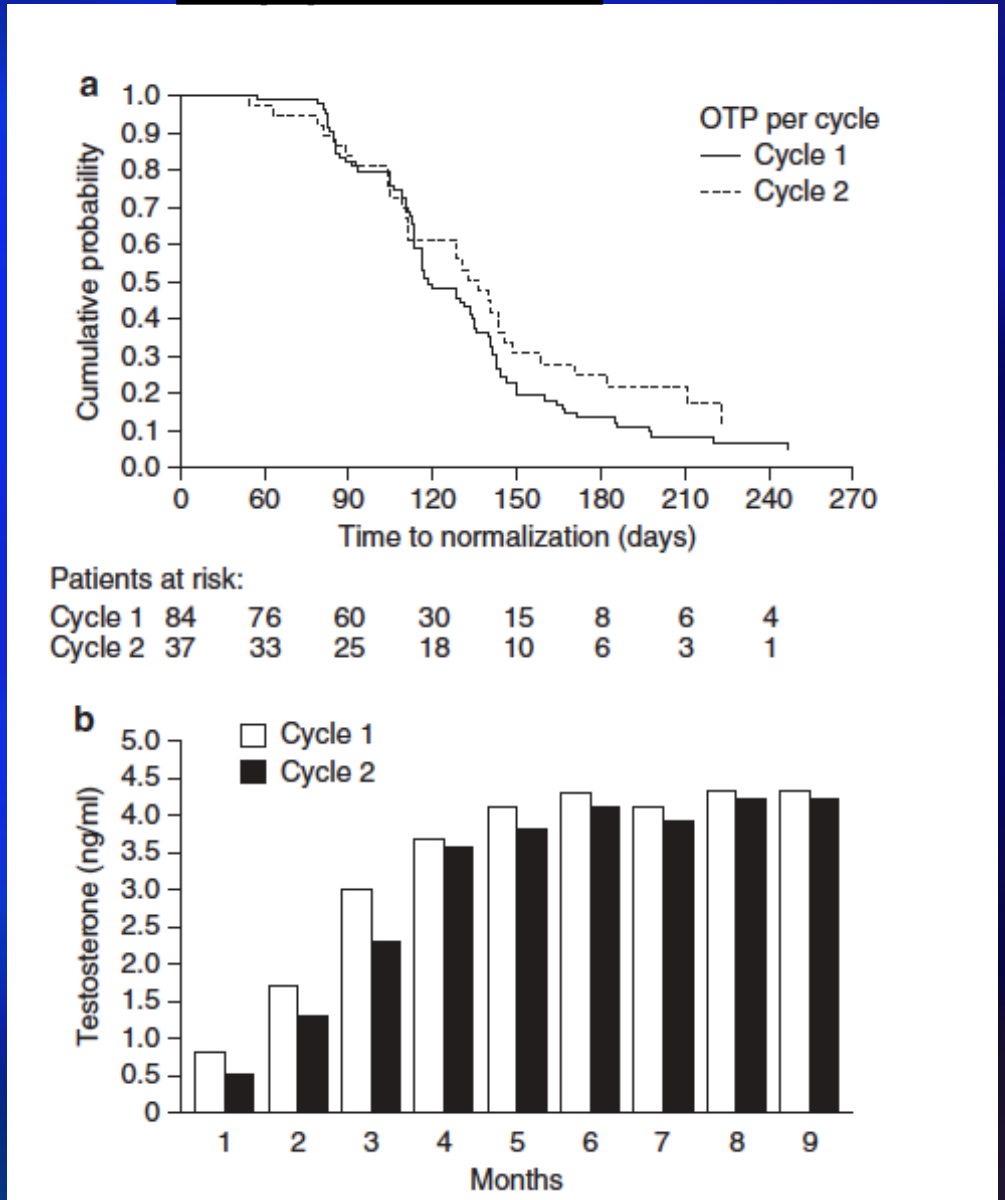
Claude Schulman, Erik Cornel, Vsevolod Matveev, Teuvo L. Tammela, Jan Schraml, Henri Bensadoun, Wolfgang Warnack, Raj Persad, Marek Salagierski, Francisco Gómez Veiga, Edwina Baskin-Bey, Beatriz López, Bertrand Tombal

Intermittent Versus Continuous Androgen Deprivation Therapy in Patients with Relapsing or Locally Advanced Prostate Cancer: A Phase 3b Randomised Study (ICELAND)

European Urology, Volume 69, Issue 4, 2016, 720–727

http://dx.doi.org/10.1016/j.eururo.2015.10.007

Testosterone recovery in patients undergoing intermittent ADT Tunn UW et al Prostate Cancer Prostatic Dis. 2012 Sep; 15(3):296-302.



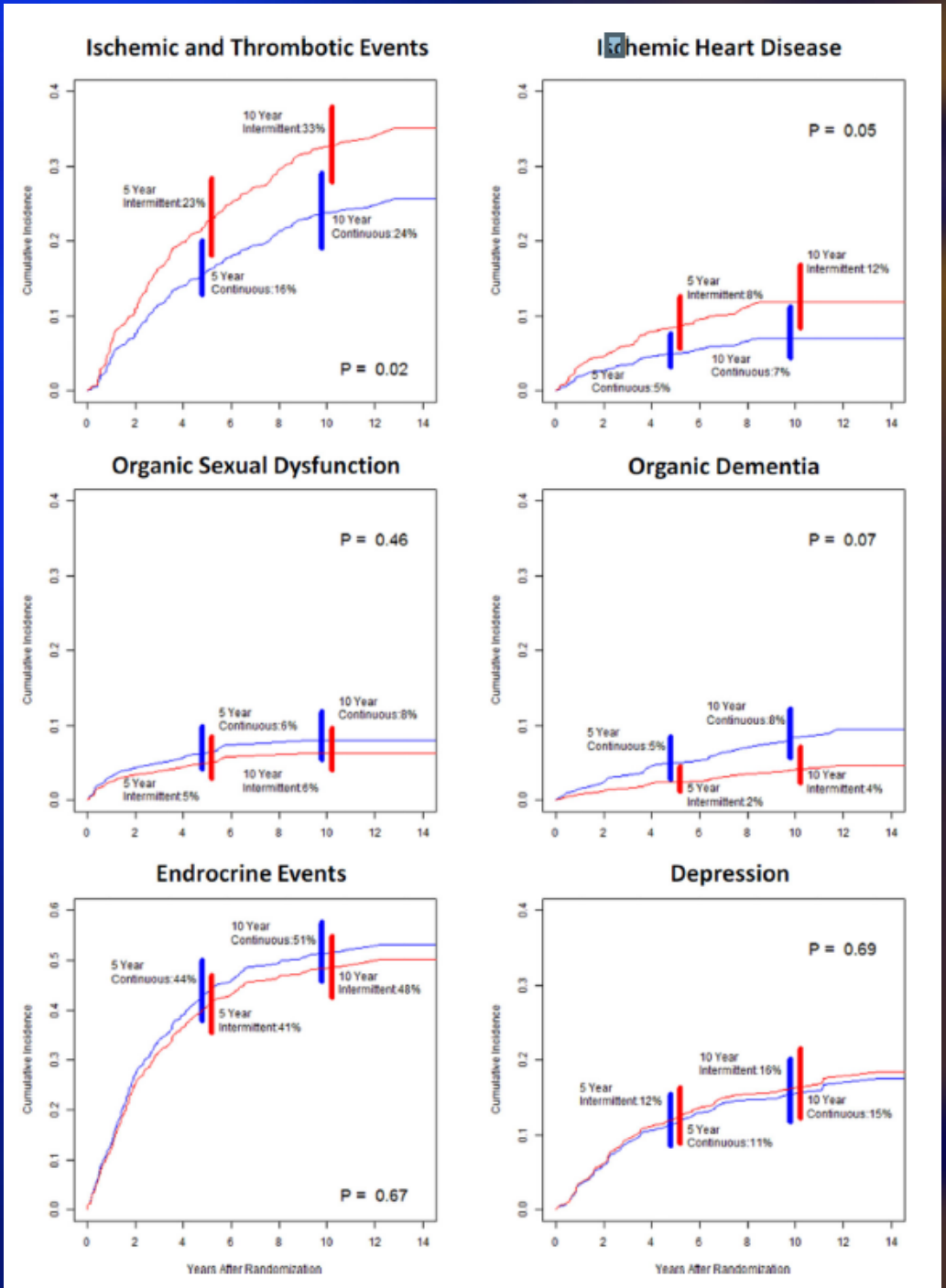
Comparative QOL benefits of Intermittent vs Continuous ADT

Author	QOL with intermittent vs continuous ADT	IAD better
Calais da Silva	Improved hot flushes, gynecomastia, ED	✔
Crook	Improved hot flushes, libido, ED, fatigue, LUTS	✔
De Leval	Improved toxicity profile	✔
Hering	Improved sexual function	✔
Hussain	Improved sexual function, mental health	✔
Irani	Improved erectile function	✔
Langenhuijsen	Improved hot flushes, nausea, gynecomastia, affect	✔
Miller	Improved overall health and sexual function	✔
Mottet	Improved side effects (headache, hot flushes)	✔
Salonen	Improved activity, physical capacity and sexual. function	✔
Verhagen	Improved physical/emotional functional domains	✔

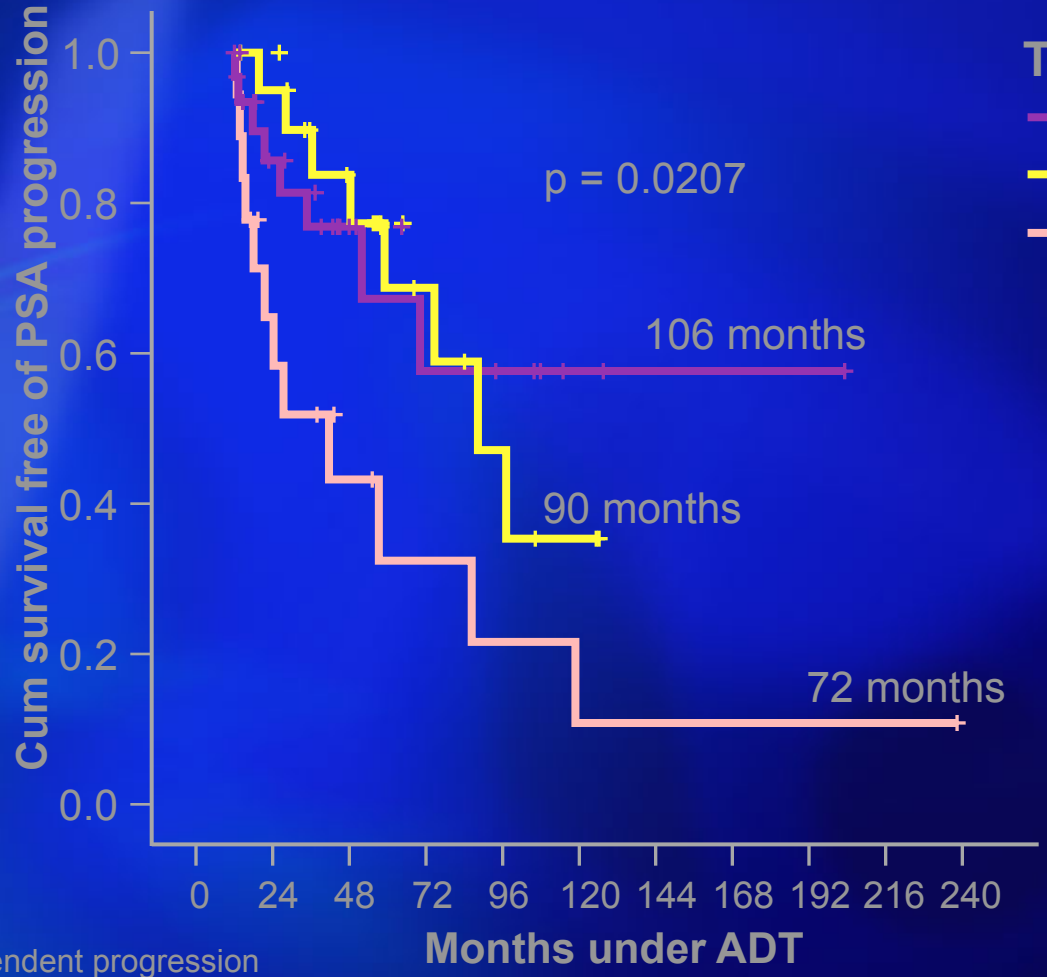
Adverse Health Events Following Intermittent and Continuous ADT in SWOG 9346.

Hershman D, Hussain M. JAMA Oncol. 2016 Apr 1;2(4):453-61

- Linked SWOG 9346 to Medicare data
- 10-year cumulative incidence of CV events:
  - 24% continuous vs 33% intermittent ADT (HR 0.69; P = .02)



Survival free of AIP according to serum testosterone on ADT N=72



AIP, Androgen independent progression

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

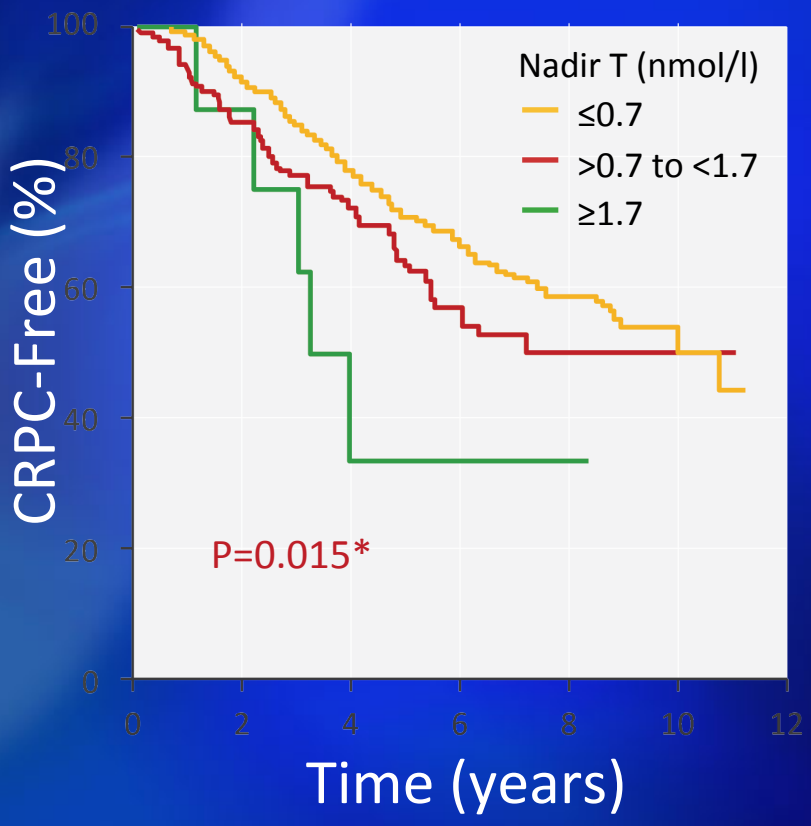
20 ng/dL = 0.7 nmol/L
50 ng/dL = 1.7 nmol/L

Prospective Analysis of PR7 Trial ADT Outcomes by T Level

- Prospective secondary analysis of the randomized, open label PR7 trial
- N=626
  - patients with biochemical progression after radical therapy
  - treated with continuous ADT*
- Hypothesis was that lower nadir testosterone in the first year would correlate with longer time to CRPC and longer CSS

Klotz L, et al. J Clin Oncol 2015;33:1151-6

PR7 Time to CRPC Relative to Nadir T Level



Nadir T (nmol/l)	Median (years)	HR [95% CI]
≤0.7	10.0	1
>0.7 to <1.7	7.21	1.62 [1.20-2.18]
≥1.7	3.62	1.90 [0.98-4.70]

Nadir testosterone level ≤0.7 nmol/l was associated with a lower risk of developing CRPC compared with higher levels (P=0.02)

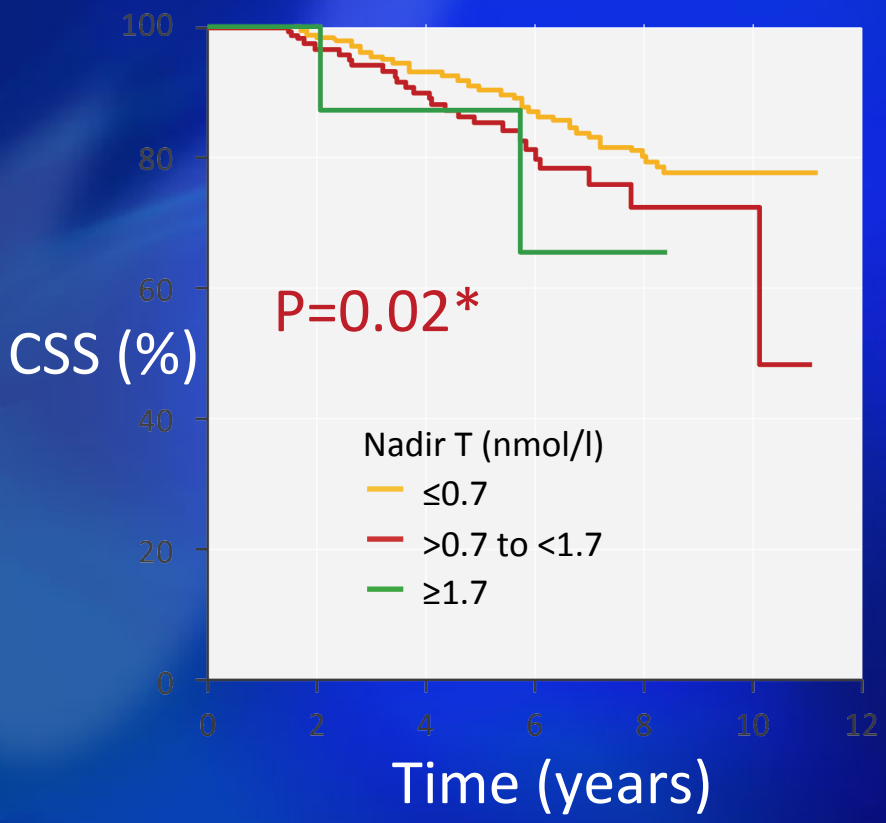
*Adjusted for multiple test based on the Hochberg method

CRPC = castration-resistant prostate cancer

T = testosterone

Klotz L, et al. J Clin Oncol 2015;33:1151-6

PR7 Cause-Specific Survival Relative to Nadir T Level



Nadir T (nmol/l)	Median (years)	HR [95% CI]
≤0.7	Not reached	1
>0.7 to <1.7	10.07	2.08 [1.28-3.38]
≥1.7	Not reached	2.93 [0.70-12.30]

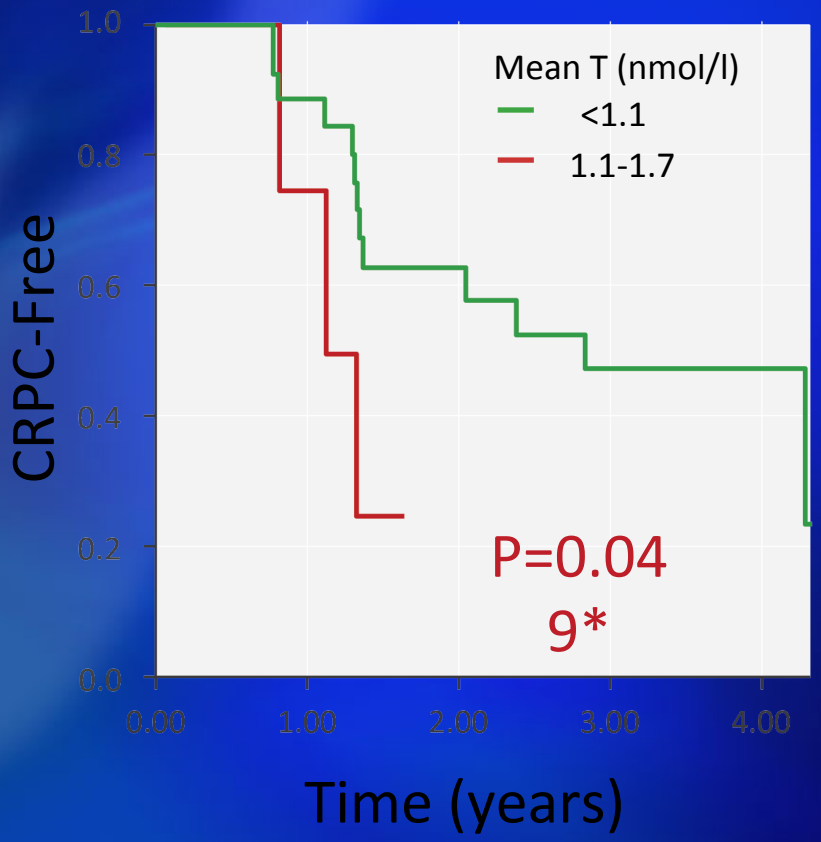
*Adjusted for multiple test based on the Hochberg method

CSS = cause-specific survival

T = testosterone

Klotz L, et al. J Clin Oncol 2015;33:1151-6

Dason et al. - Time to CRPC on ADT



Mean Testosterone Level, 1 year (nmol/l)	Median Time to CRPC (months)
<1.1	33.1
1.1-1.7	12.5

One-year mean T <1.1 nmol/l was associated with longer time to CRPC (vs 1.1-1.7 nmol/l, P=0.049)

*Log-rank p-value

ADT = androgen deprivation therapy

CRPC = castration-resistant prostate cancer; T = testosterone

Dason S, et al. Can Urol Assoc J 2013;7:E263-7

Retrospective Data on Association Between Low T and ADT Outcomes

ADT * Study	N/Setting Assay Timing	T Level	Assoc. between low T and treatment		
			PFS	OS/CSS	PSA Level
Pickles 2012 Database Review	2196/L, LA Variable	Breakthrough >1.1 or >1.7 nmol/l vs no breakthrough			✓ **p=0.008**
Kamada 2015 Multi-Center	225/L, LA & Met Multiple	Nadir: <0.7 vs ≥0.7 nmol/l	X **p=0.1163**	✓ **p<0.0014**	
Perachino 2010 Single-Center	129/Met Every 3 mo.	1.4 (6 mo. mean)		✓ **p<0.05**	
Shiota 2016 Single-Center	96/LA & Met Random, median 2x	0.1 vs 0.1-2.6 nmol/l	X **p=0.70**	✓ **p=0.014**	
Morote 2007 Single-Center	73/L, LA 3x over 6 mo.	<0.7 vs 0.7-1.7 vs >1.7 nmol/l	✓ **p=NR**		
Yasuda 2015	69/Met Every 3-6 mo.	<0.7 vs ≥0.7 nmol/l		X **OS: p=0.17** **CSS: p=0.29**	X **p=0.66****

Klotz L, et al. Can Urol Assoc J 2017

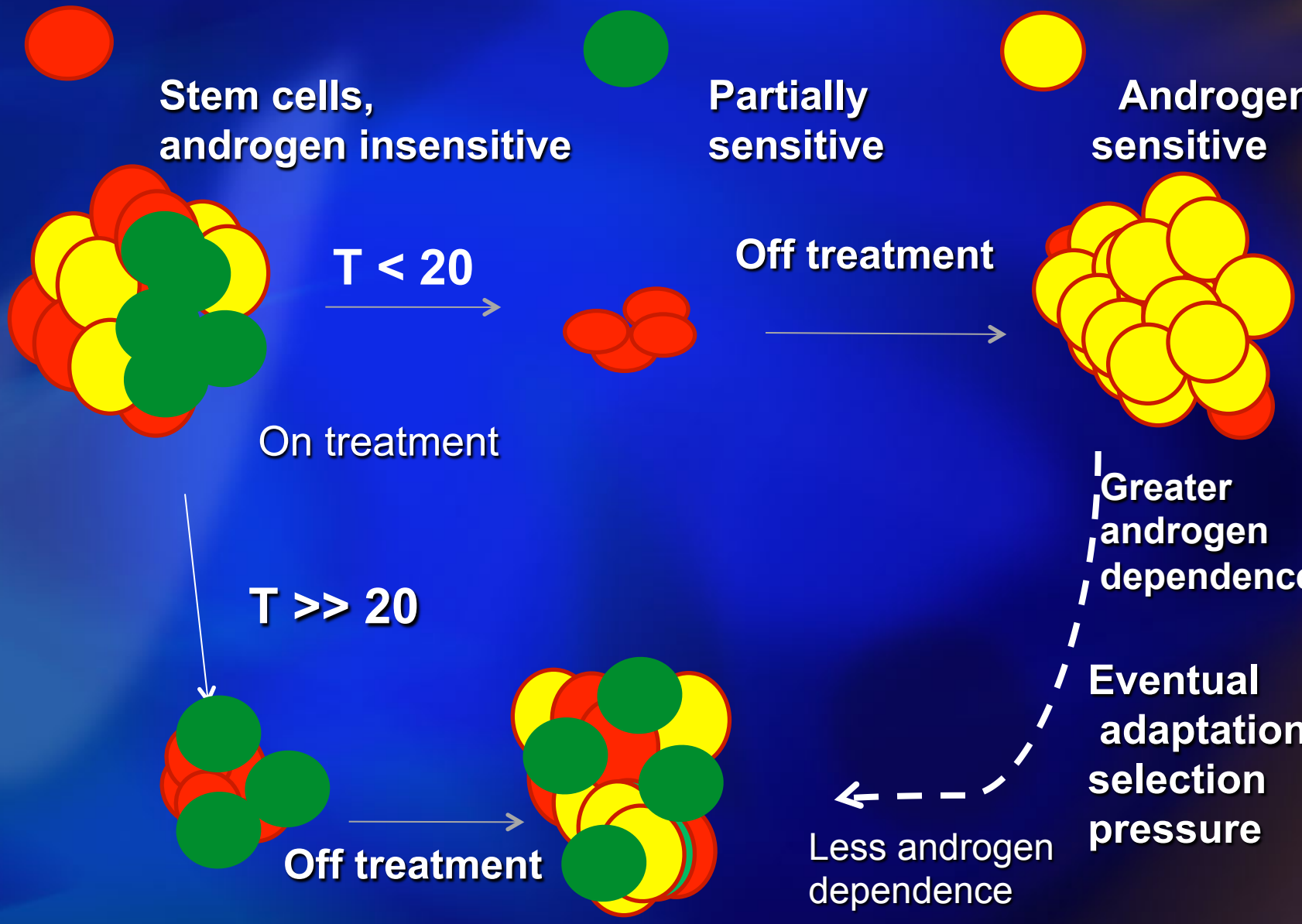
Most Data Support 0.7 nmol/l as T Threshold to Guide Treatment

Study	Clinical Outcomes by T Level Comparison
Klotz 2015, 626 patients, prospective	**Cause-specific survival,** p=0.02 **Time to CRPC,** p=0.015 (vs >0.7 to <1.7 nmol and ≥1.7 nmol/l)
Wang 2016, 206 patients, prospective	**Time to CRPC,** p=0.001 (vs >0.7 nmol/l)
Bertaglia 2013, 153 patients, prospective	**OS** (vs ≥0.7 nmol/l, p=0.020 vs >1 nmol/l, p=0.034)
Kamada 2015, 225 patients, retrospective	**OS,** p=0.0014 (vs >0.7 nmol/l)
Morote 2007, 73 patients, retrospective	**Time to CRPC** P=.03, (vs 0.7 to 1.7 nmol/l)
Yasuda 2014, 69 patients, retrospective	**OS,** p=.17 **Cause-specific survival,** p=ns (vs ≥0.7 nmol/l)

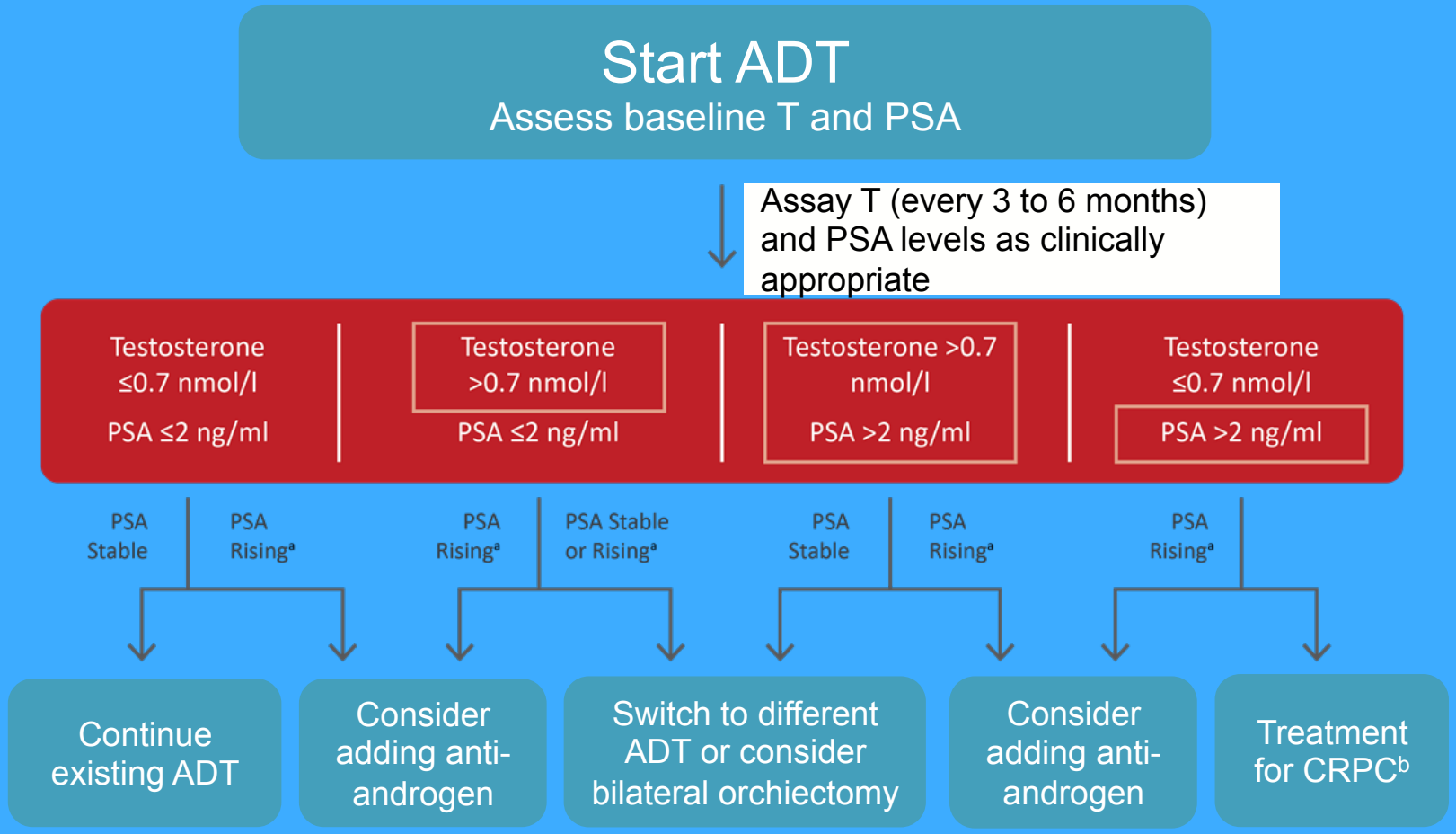
Klotz L, et al. Can Urol Assoc J 2017

How to reconcile non-inferiority of intermittent ADT with importance of low T

3 cell type model can explain conundrum



PC Management Strategies for ADT Using Testosterone Suppression Data



[a] Non-metastatic CRPC; [b] Follow CUA-CUOG guidelines for management of CRPC

ADT = androgen deprivation therapy PSA = prostate-specific antigen

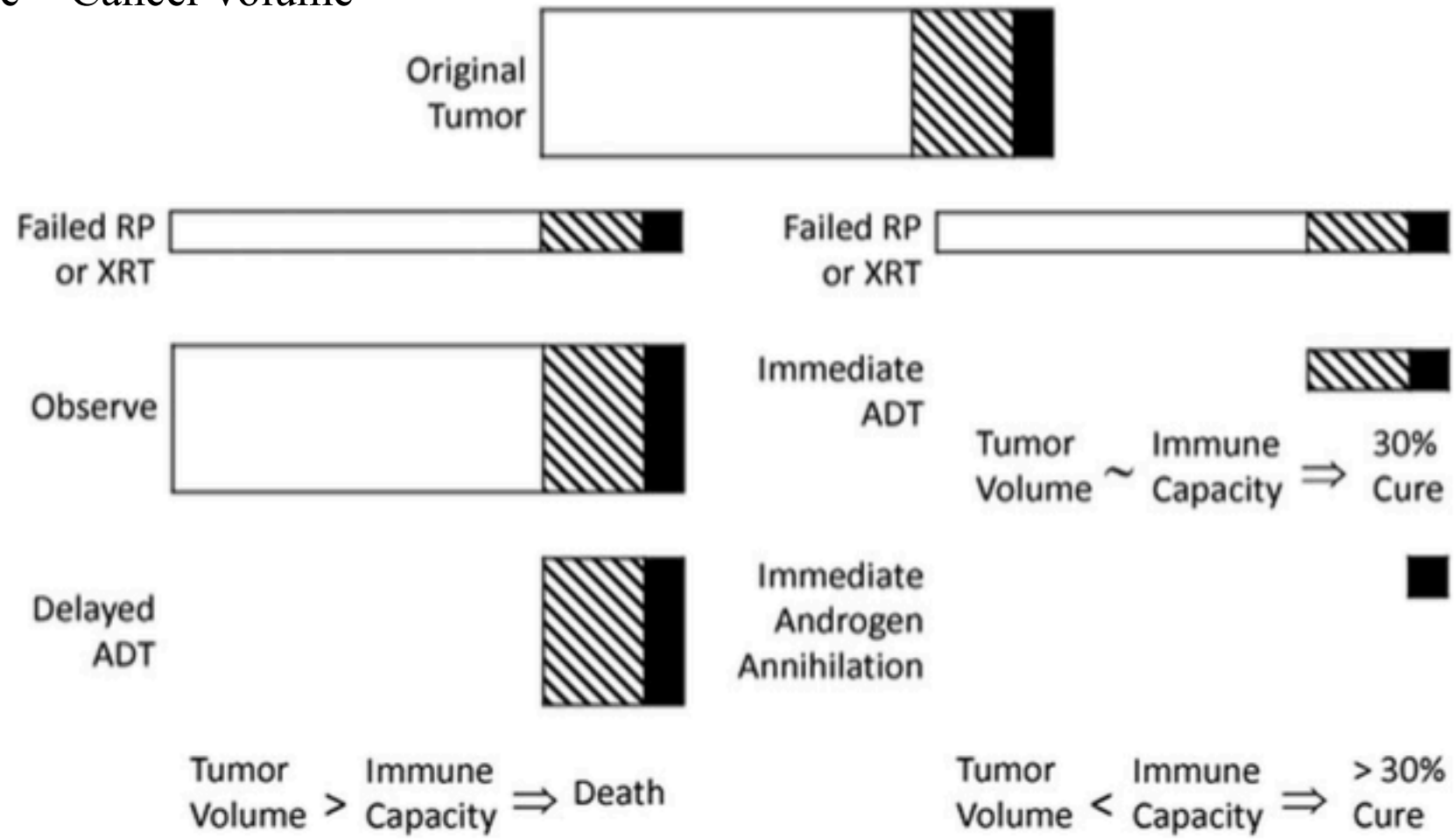
PC = prostate cancer T = testosterone

Klotz L, et al. Can Urol Assoc J 2017; *In press*

Greater response with more complete ADT

White: Androgen dependent Pca
Shaded: Androgen sensitive Pca
Solid: Androgen independent PCa

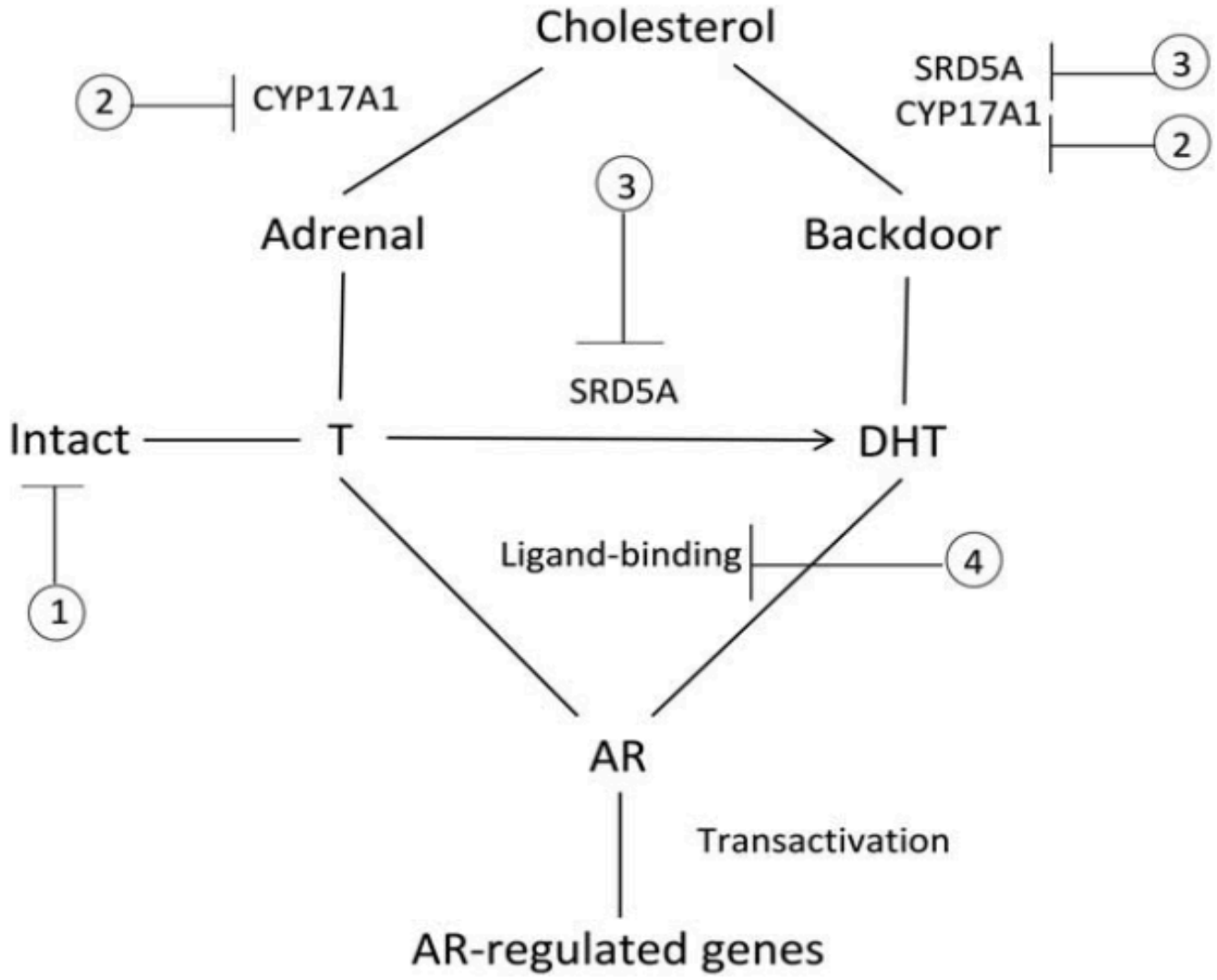
Size = Cancer volume



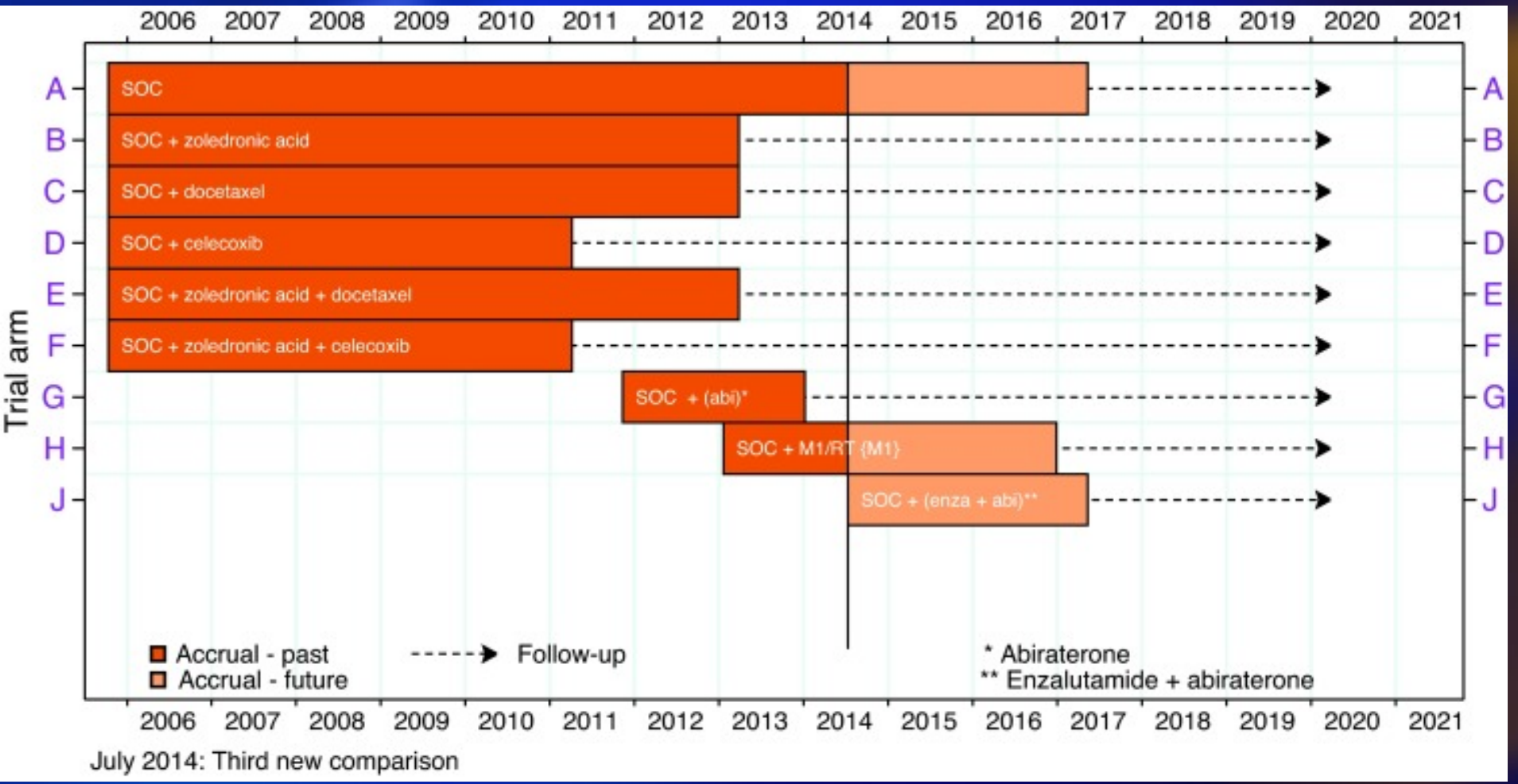
Androgen annihilation:

Mohler J Cancer. 2014 Sep 1;120(17):2628-37

1. LHRH 2. CYP 17 inhibitor 3. 5 ARI 4. AR antagonist



Combining Enzalutamide with Abiraterone, Prednisone, and Androgen Deprivation Therapy in the STAMPEDE Trial: Attard G et al, European Urology, Volume 66, Issue 5, 2014, 799–802



Conclusions re: ADT

- AR pathway complex
- Intermittent therapy for non-metastatic
- Hormone naïve metastatic:
  - Favorable risk: consider with excellent PSA response (< 1.0)
  - Unfavorable risk or poor PSA response: Chemotherapy
- Low nadir T important
  - Assay T along with PSA q 3 months
  - If consistently > 0.7, consider change in therapy