Intermittent Therapy: When To Start, or Restart, and the Role of Imaging

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Why Intermittent Androgen Suppression ?

- Androgen Deprivation Therapy (ADT) is associated with adverse events:

  - Short-term: hot flushes, loss of libido, ED, fatigue
  - Long-term: bone demineralization, anemia, muscle wasting, metabolic syndrome, depression
  - development of hormone resistance

Holzbeierlein JM Urol Clin NA 2006,33:181-90; Spry NA et al BJUI (2009) Epub; Gomella, et al Urology. 2009 May;73:S28-35

- Intermittent Androgen Deprivation (IAD) / Intermittent Hormonal Therapy (IHT) goals:

  - Minimize adverse events
  - Maximize quality of life (QoL)
  - Delay development hormone resistant prostate cancer (HRPC)
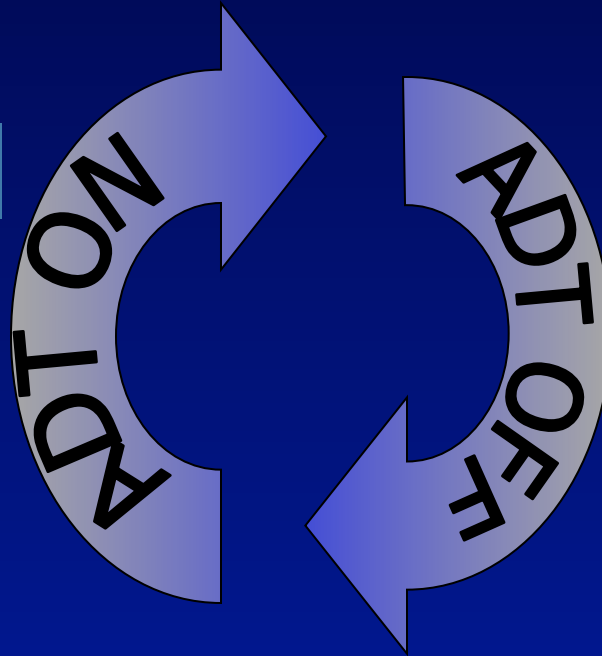 - Reduction of non-oncologic morbidity/mortality and cost of care

Tunn U. BJU Int 2007;99 (Suppl 1):19-22; Boccon-Gibod L et al. BJU Int 2007;100:738-43; Gleave M et al Urol Oncol 2009,27:81-86

What is Intermittent Androgen Suppression Therapy (IHT/IAD) ?

Cyclic ADT therapy

On-treatment:

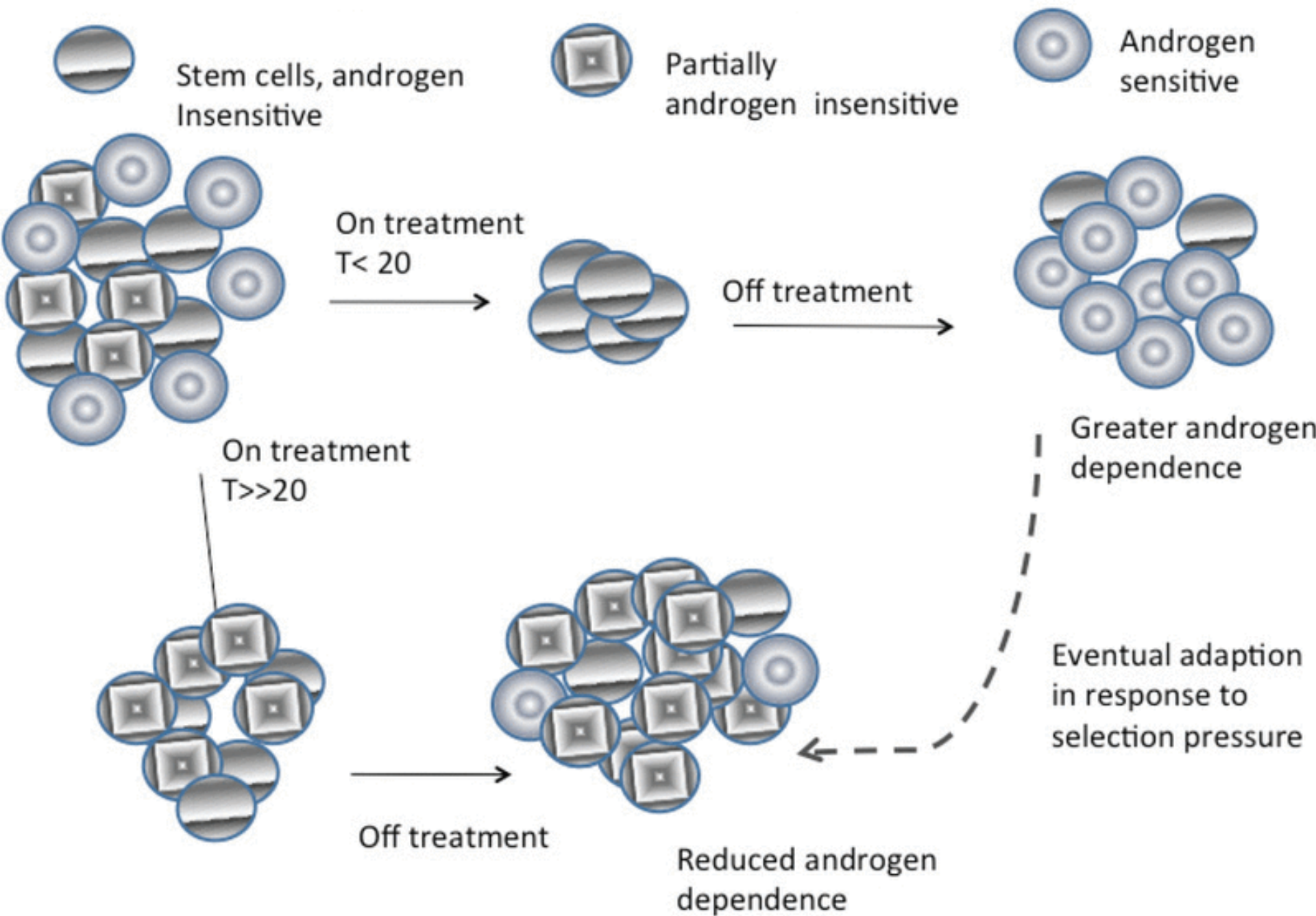-**Fixed period:**
 -6-9 months
 -or until PSA nadir
  is reached

ADT ON

ADT OFF

Off-treatment:

-**Variable period**
-Depending on PSA-rising

Tunn U. BJU Int 2007;99 (Suppl 1):19-22; Boccon-Gibod L et al. BJU Int 2007;100:738-43

Metastatic Prostate Cancer: Continuous vs Intermittent ADT (CHT/IHT)

- **Rationale**
  - Hypothesized to delay time to AIPC
    - Shinogi Model, LNCaP cell line
    - Randomized clinical trial
      - ⬇Neuroendocrine markers with IHT versus continuous
  - Preservation of QOL
    - Time off therapy
  - ⬇ Health care costs
- First described in 1986 (pre PSA era)

Bruchovsky et al. Cancer Res 50:2275,1990   Sato et al J Steroid Biochem Mol Biol 58: 139, 1996
Sciarra et al Prostate 55: 168, 2003   Sciarra et al. Eur Urol 64: 722, 2013
Klotz Nature Reviews Urology 10, 372-374 (July 2013)

Stem cells, androgen Insensitive

Partially androgen insensitive

Androgen sensitive

On treatment T< 20

Off treatment

On treatment T>>20

Off treatment

Greater androgen dependence

Eventual adaption in response to selection pressure

Reduced androgen dependence

Where have we been with IHT?

IHT Early Reports

- 47 pts (stages A2-D2)

- Treated with CPA and DES and/or LHRH analogs x 6 months

- Therapy d/c after 6 months and PSA nadir $\leq$ 4 ng/ml

- Therapy restarted when PSA between 10-20 ng/ml

- Mean % time off therapy was 41-45%

- Lower stage pts: faster decline to nadir and longer off therapy

- Pts cycled for 1-5 times before becoming AI ranging from 15-57 months

- Improved QOL, sexual potency, libido

Phase II IHT Trials 1995 – 2009 (n=23, >2600 patients)

- Good acceptance and feasibility

- Improved QoL during off-treatment

- Reduced toxicity

- IIHT did not appear to affect time to progression or   survival negatively

- Differences in treatment protocols and results demonstrated the need for Phase-III trials

Summary of Phase II studies

- Heterogeneous designs- feasibility\tolerability studies
- Wide range of patients form localized to metastatic ds
- PSA cutoff: ranged from 0-4 ng/ml
- Re-treatment initiated PSA between 10-20 ng/ml
- Cycle lengths: Mean 2-3 per patient (range 1-12)
- Testosterone Recovery: 70-80% normalized post 1 cycle- Close relationship btw serum T and PSA
- Development of CRPC: 181/1446 (12.5%) with max FU of 197 months (Shaw et al, BJU 2007;99:1056-65.)

Percentage Time off Therapy per cycle with IHT
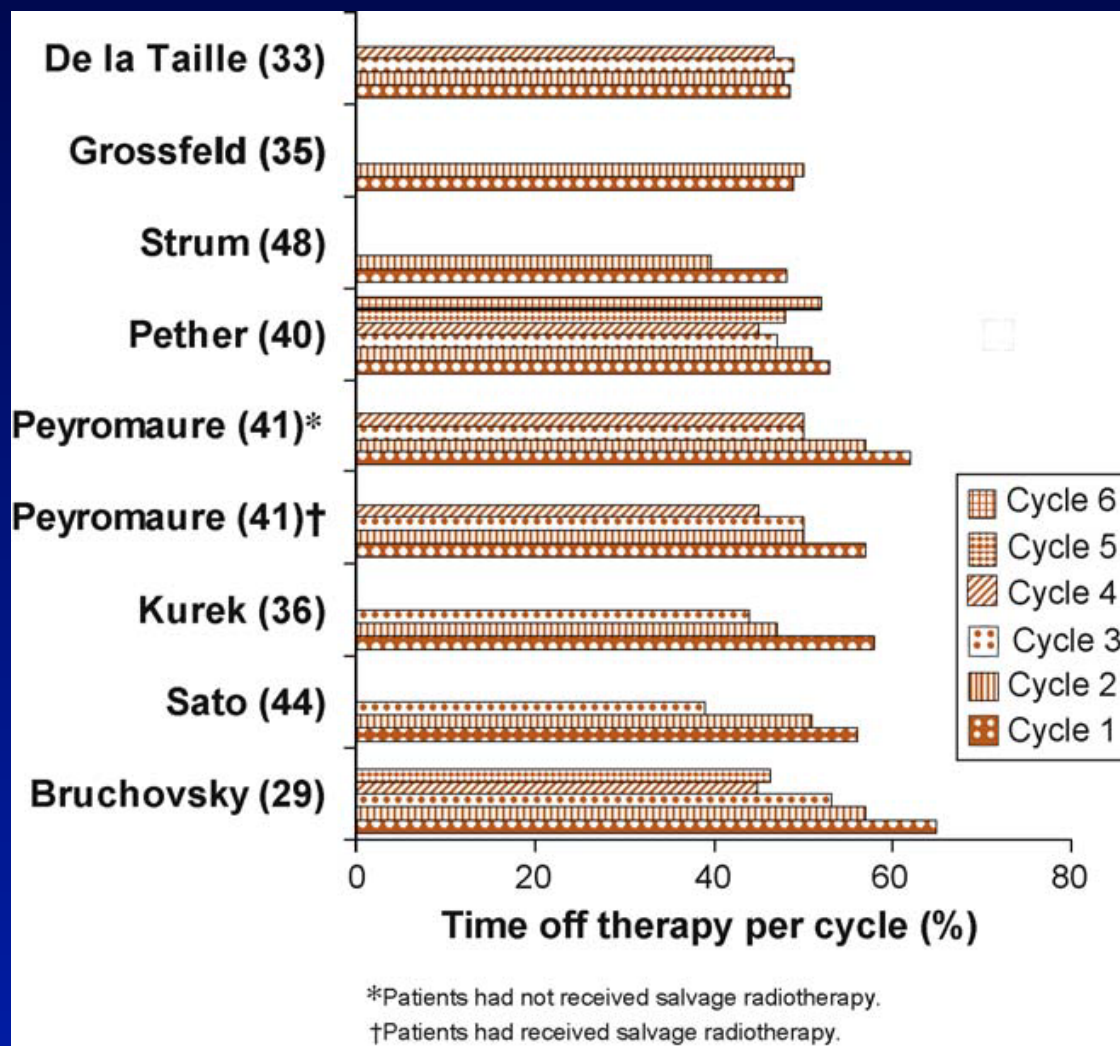
Percentage of patients with testosterone levels 17.5 nmol/l (505 ng/dL) following interruption of ADT in men with PSAR after RT
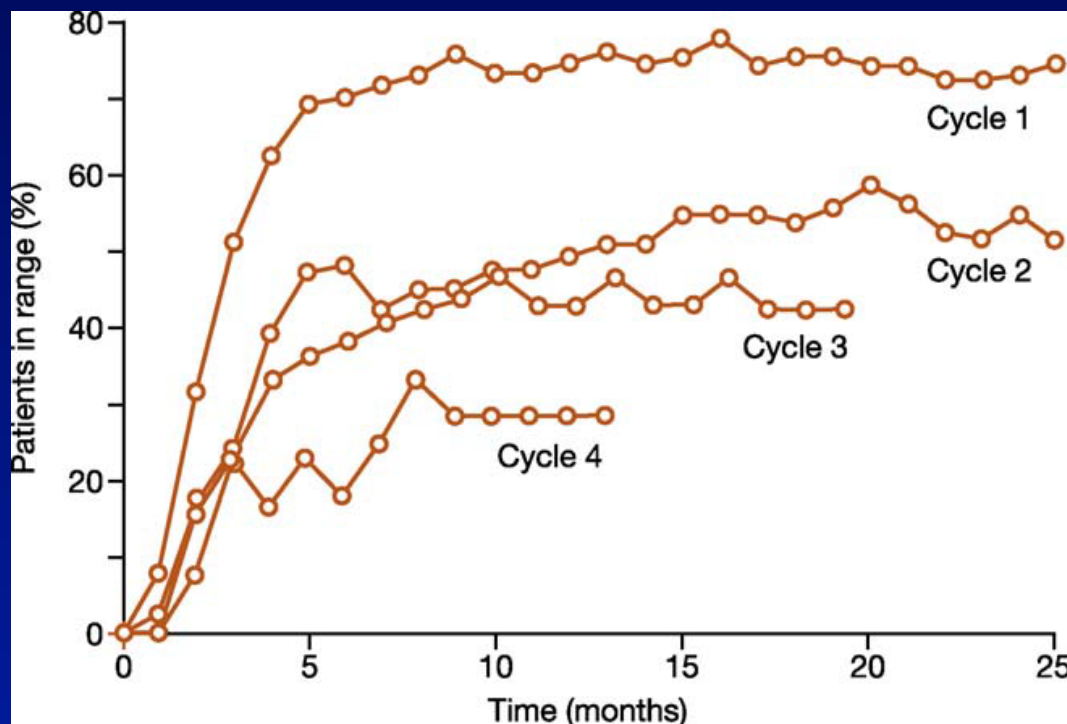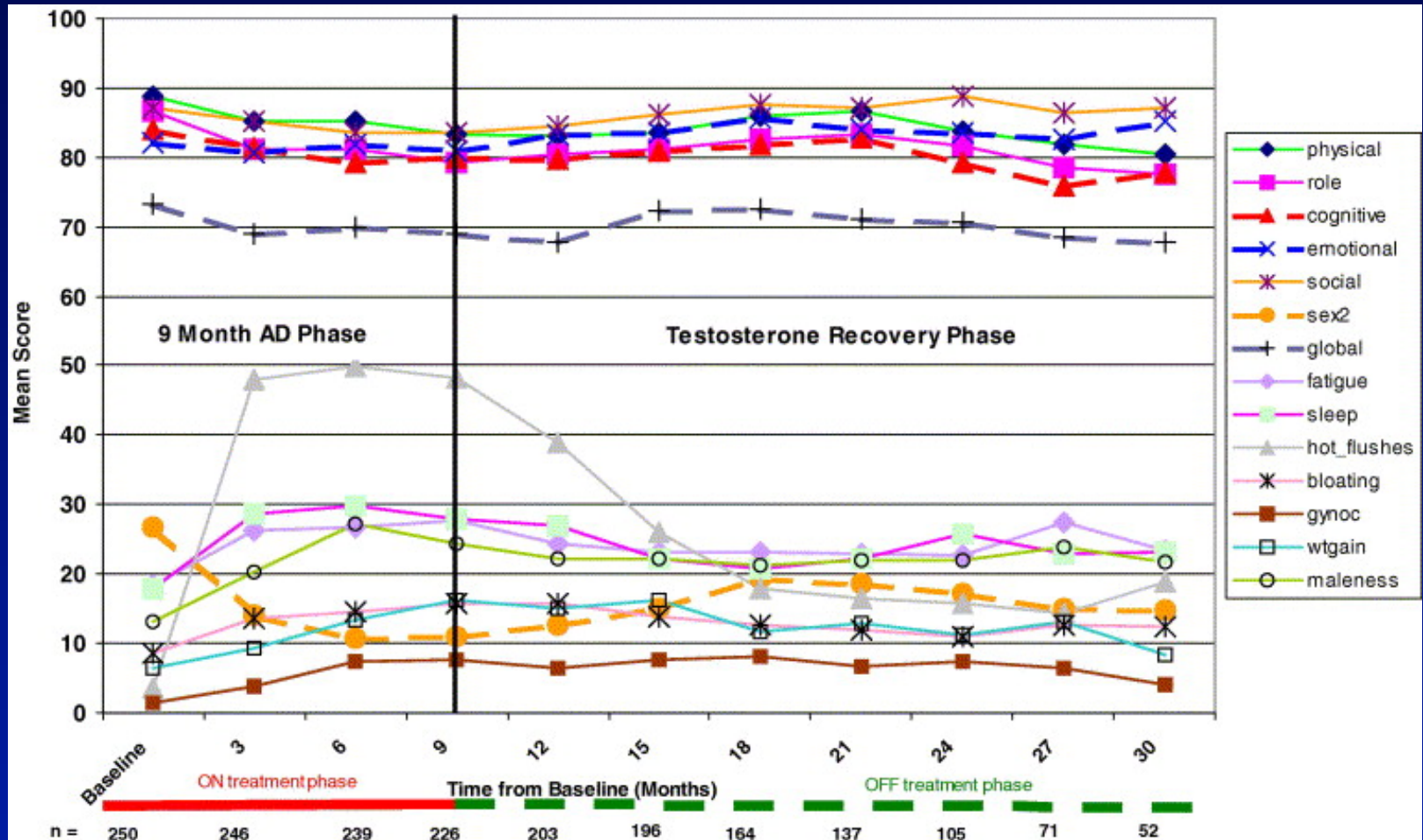

Factors delaying androgen recovery
- Advanced age
- Low baseline T
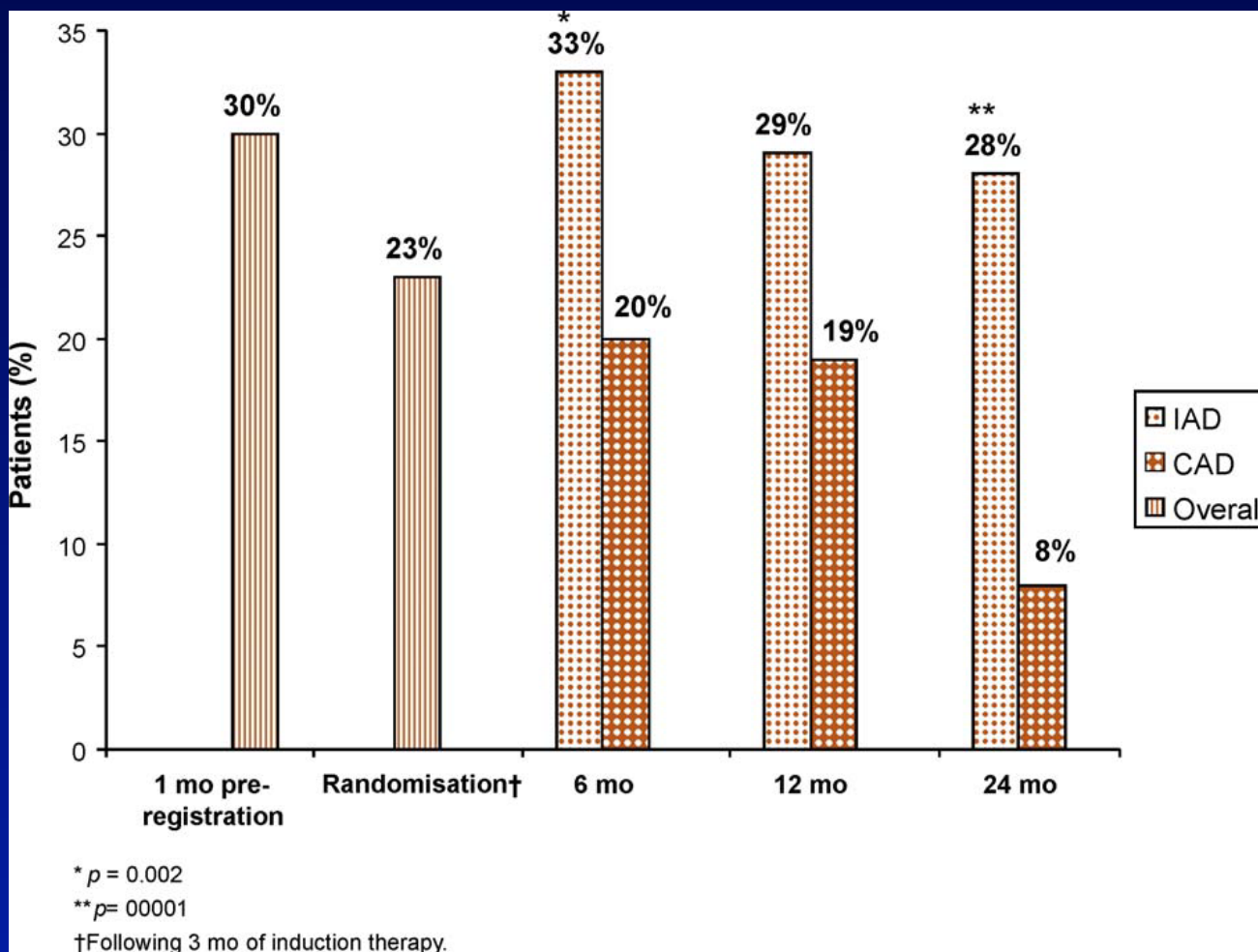- Duration of ADT

IHT:
Improved Tolerability and Quality of Life

- Improved anemia

- Normalization of weight gain

- Dissipation of hot flashes

- Overall improvement in physical and psychological well being

- Improvement in sexual activity

Adverse QOL can recover with IHT

Comparison of sexual activity: IHT vs CHT in a phase 3 trial.

Who can be considered for IHT?

- Patients responding to ADT with a decline of PSA to "normal" values:

Previously untreated	< 4 ng/mL
PSA relapse after radiotherapy	
PSA relapse after surgery	< 0.5 ng/mL

When to Restart ADT?

The Retreatment PSA triggers:

| CaP patients	PSA [ng/ml]
Without previous treatment	M_0: 6 – 15
	M_+: 10 – 20
PSA relapse after RP	> 3 ng/mL
PSA relapse after RT	> 6 – 10 ng/mL

All thresholds are empirically chosen (in RCTs)

2007 International study on the use IHT: Meta-analysis of 1446 patients

Conclusions

1. Patients spent 39% of the time off therapy
2. Initial PSA, PSA nadir, type of treatment and PSA threshold for re-starting treatment predicts outcome with IAS
3. The duration of treatment was not a predictor of outcome in patients without mets
   - Pts. with good PSA < 4 months –safe to curtail treatment
   - Longer Treatment for pts. with Mets (≥ 8 months)
4. Restarting treatment when the PSA level approaches 15 ng/ml is associated with improved survival in patients with Metastatic disease
5. MAB or LHRH analogue should be used as the standard for patients treated with IAS

Duration of First Off-Treatment Interval Is Prognostic for Time to Castration Resistance and Death in Men With Biochemical Relapse of Prostate Cancer Treated on a Prospective Trial of Intermittent Androgen Deprivation
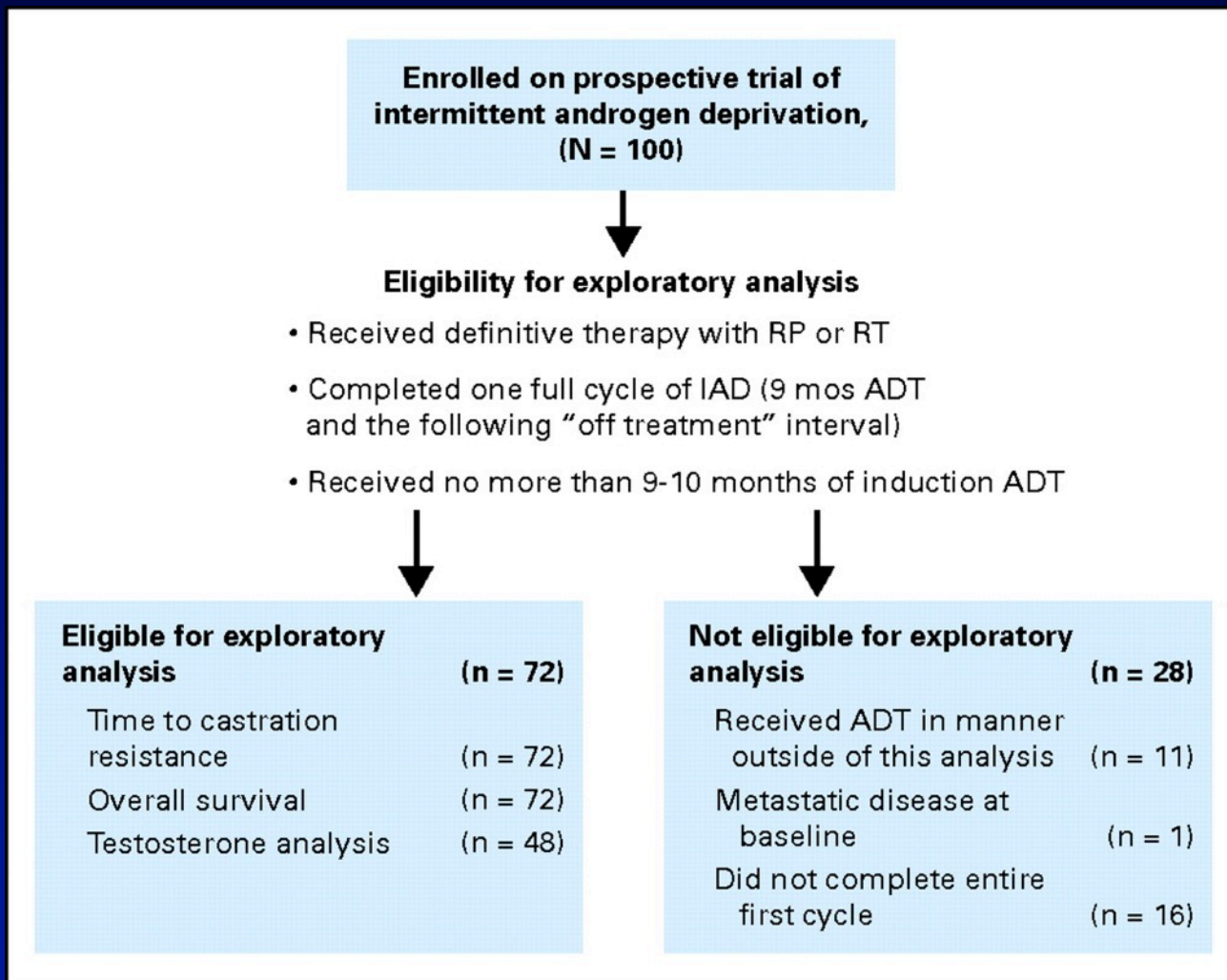
Yu E Y et al. JCO 2010;28:2668-2673

Duration of First Off-Treatment Interval Is Prognostic for Time to CRPC and death in Men With BCR Treated on a IHT Trial
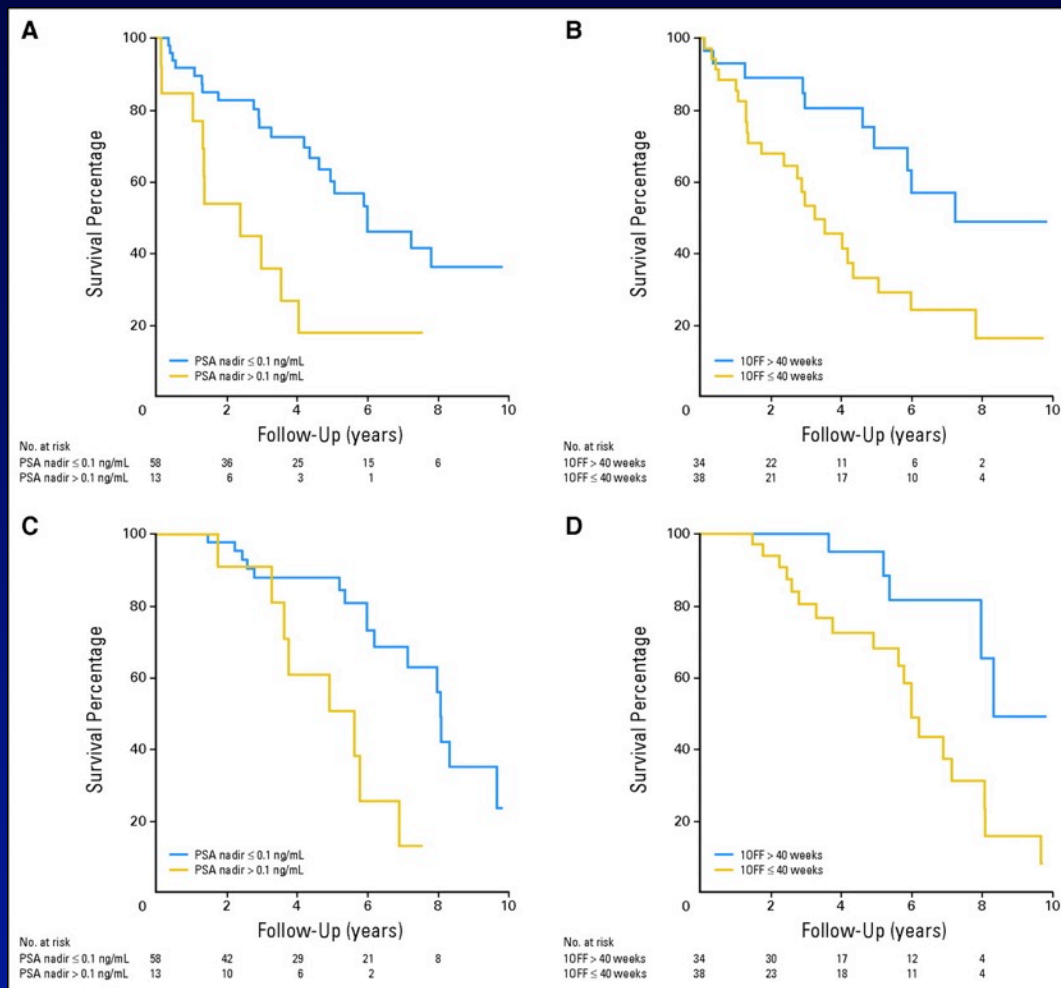
Kaplan-Meier survival curves for years to (A, B) CRPC and (C, D) death stratified by (A, C) on-treatment PSA nadir ≤ or more than 0.1 ng/mL and (B, D) off-treatment (1OFF) duration ≤ or more than 4.
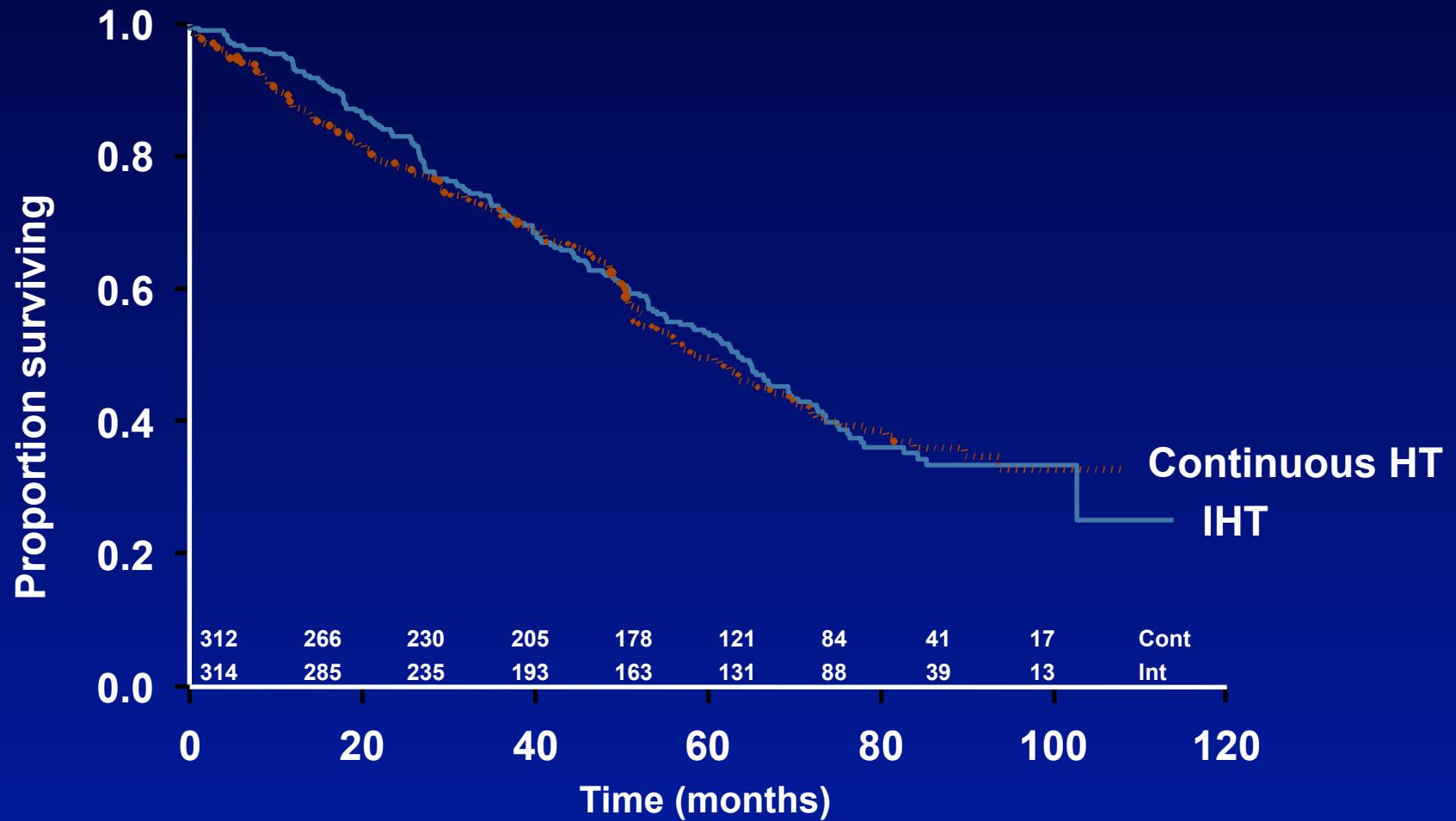
Yu E Y et al. JCO 2010;28:2668-2673

IHT Major Phase III trials

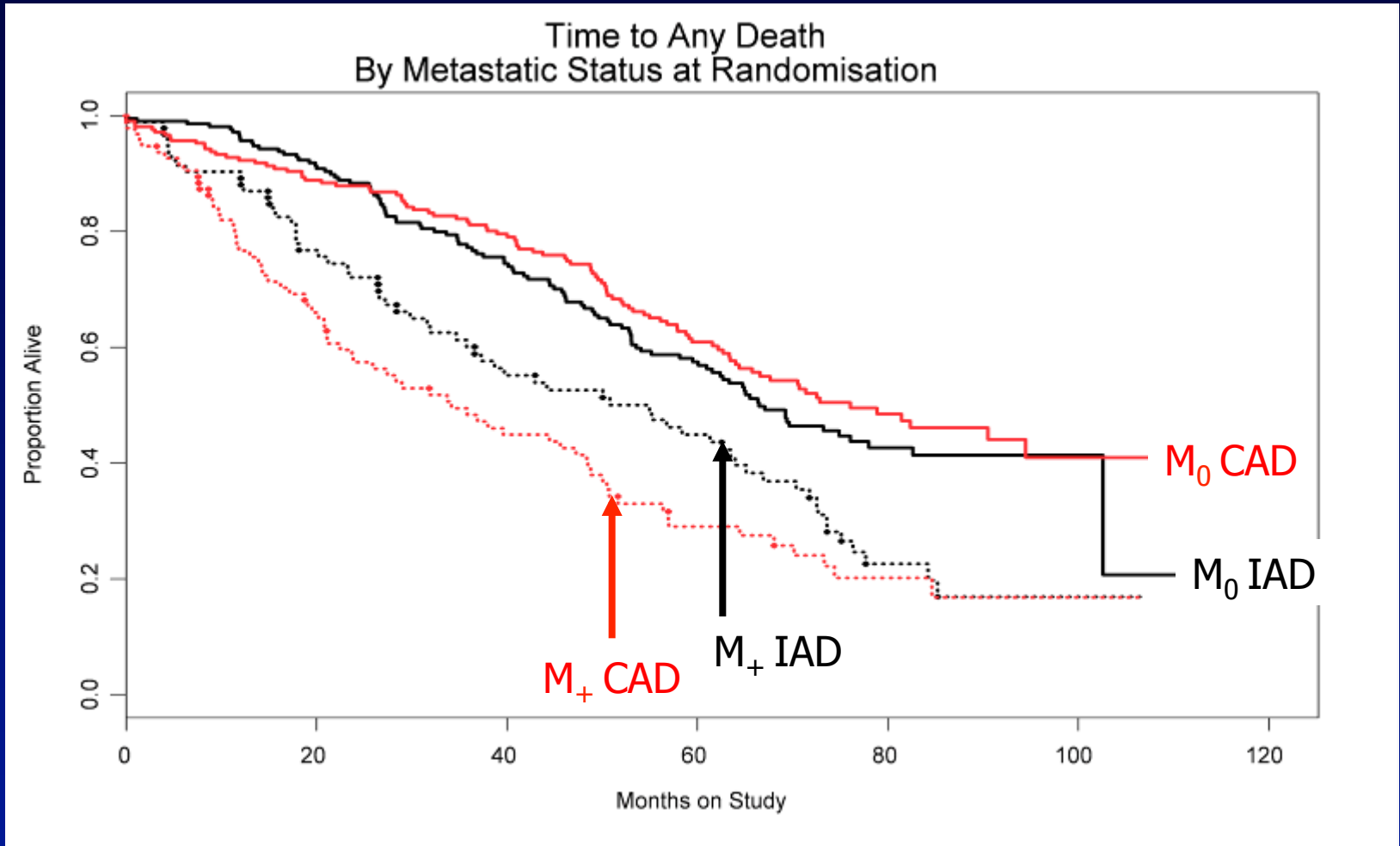| Trial	Population	No. of pts	Status
NCIC/PR7	PSA relapse after RT	1340	closed
EC 507	PSA relapse after RP	201	closed
ICELAND	PSA relapse/locally advanced	700	closed
Japan	Locally advanced	300	closed
SEUG	Advanced PCa	766	closed
AP 17/95	Advanced PCa and M +	325	closed
SWOG 9346	M+ PCa (PSA > 5 ng/mL)	1500	closed
EC 210	M+ PCa (PSA > 20 ng/mL)	387	closed

SEUG

- South European Urological Group, phase III trial

- 626 pts (T_{3-4} M_{0-1} PCa with no previous treatment) randomised to continuous HT vs. IHT

- 54.4 % of patients died

Da Silva F Eur.Urol. (2009) Epub

SEUG : no difference in OS

Da Silva F Eur.Urol. (2009) Epub

SEUG Survival curves

Time to Any Death
By Metastatic Status at Randomisation

- No difference in OS and subj./obj. Progression
- IHT fewer side effects

A Phase III Randomized Trial Comparing Intermittent Versus Continuous Androgen Suppression for Patients with PSA Progression After Radical Therapy

NCIC CTG PR.7

SWOG JPR.7
CTSU JPR.7
UK Intercontinental Trial CRUKE/01/013

L. Klotz, C. J. O'Callaghan, K. Ding, D. P. Dearnaley, C. S. Higano, E. M. Horwitz, S. Malone, S. L. Goldenberg, M. K. Gospodarowicz, J. M. Crook

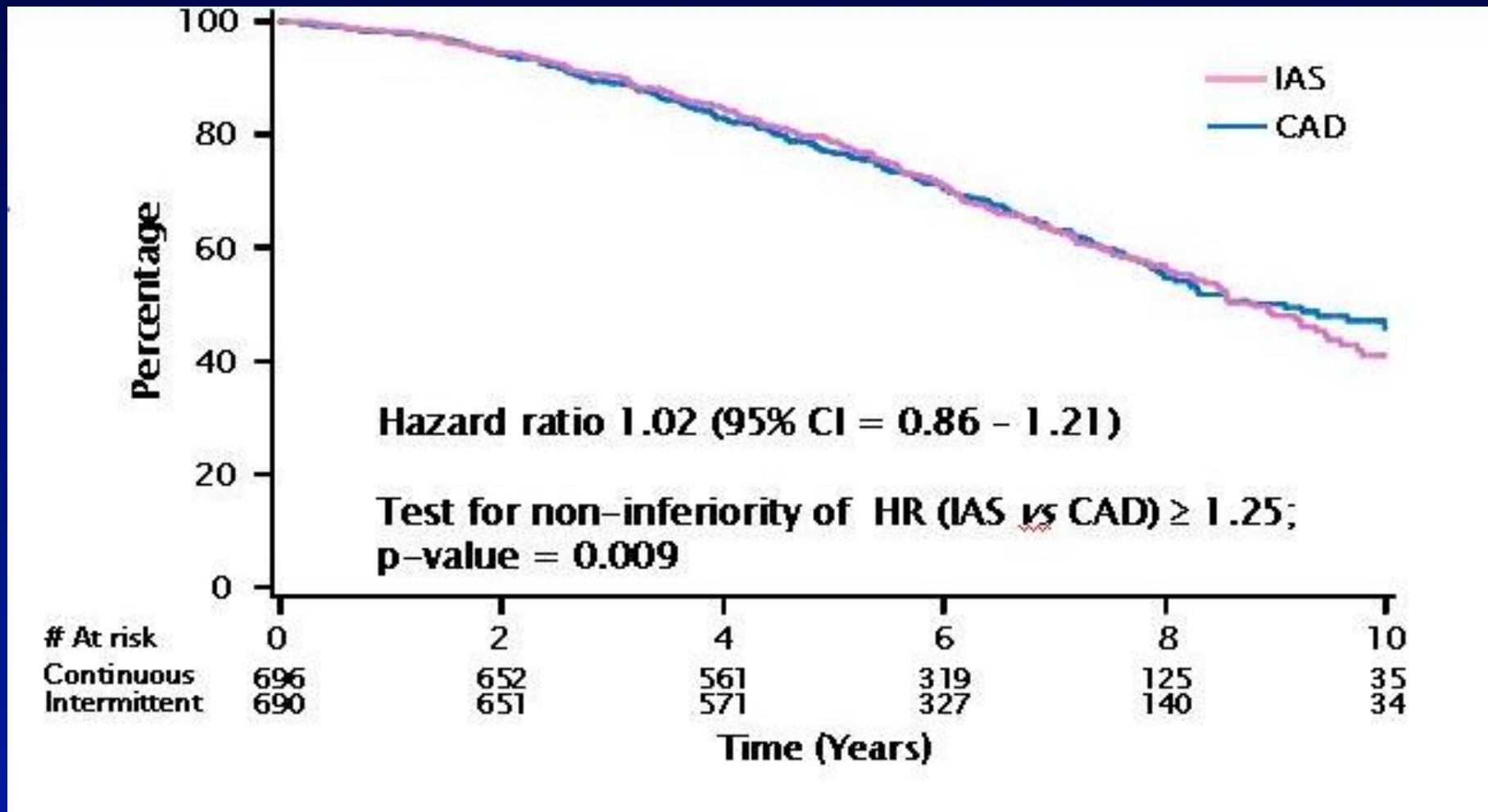# Key PR-7 Eligibility Criteria

- Previous XRT for PCa, either as primary management or post prostatectomy

- Serum PSA > 3 ng/ml (3 μg/L) and rising

- Serum testosterone > 5 nmol/L (145 ng/dl)

- No metastatic disease

- Maximum of 12 months of adjuvant / neoadjuvant ADT completed at least 1 year prior to randomization.
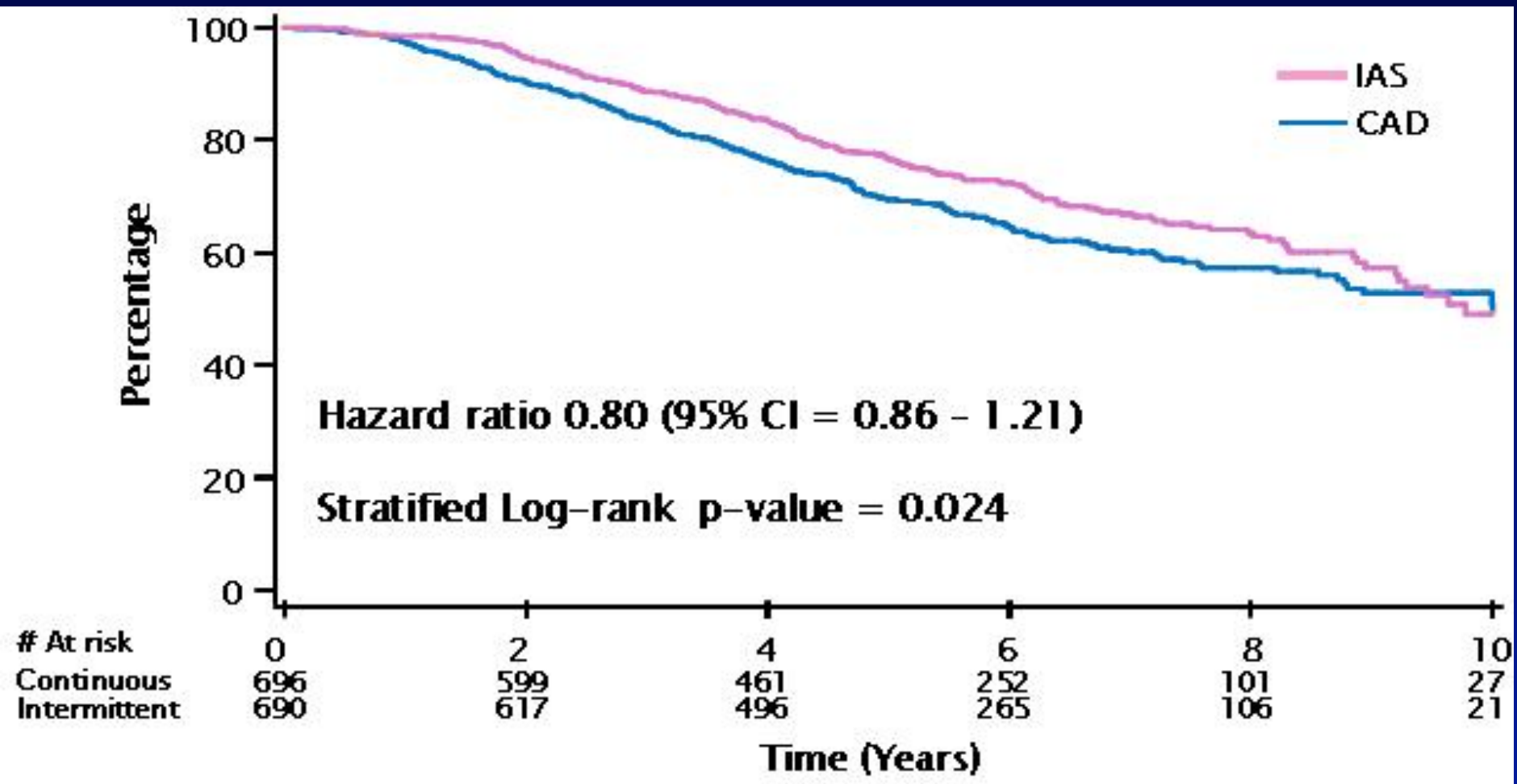
- ECOG 0 or 1

Indications for Resuming ADT for IHT Patients in Non-Treatment Interval

- PSA and testosterone q 2 months
- When PSA > 10 ng/ml:
  - 8 months of ADT
- Continuous therapy if clinical or PSA progression

PR-7 Overall Survival (ITT)

Klotz L et al. ASCO GU Conf 2011

Time to Castration Resistance (ITT)

Klotz L et al. ASCO GU Conf 2011

Disease-Specific Mortality (ITT)

Study Arm	7 year disease specific deaths
CAD	15%
IAS	18%

Disease-specific HR: 1.18 (95%CI = 0.90 - 1.55); p = 0.24

Death related to disease — IAS / CAD

Death non related to disease — IAS / CAD

Klotz L et al. ASCO GU Conf 2011
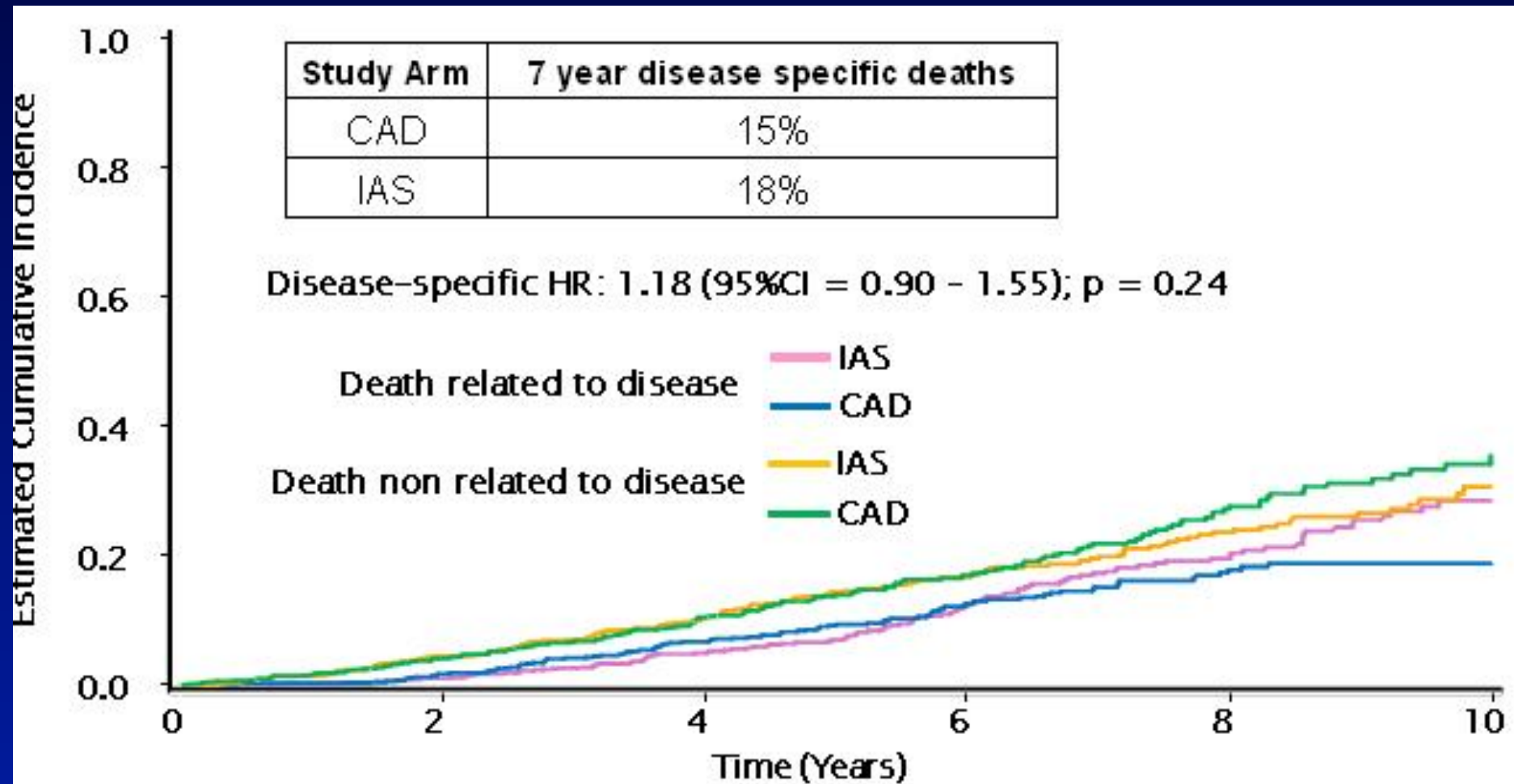
PR.7 Conclusions

- IHT non-inferior to CHT with respect to OS.
- Improved time to castration resistance with IHT
  - but design bias in favour of intermittent
- 9% more PCa deaths on IHT and 8% more non-PCa deaths CHT
- Adverse events similar between arms (except fewer hot flashes on IHT)
- IHT should be the standard of care for most patients with PSA recurrence after XRT (+/- prior RP) initiating ADT

PSA Progression Predicts Overall Survival in Patients With Metastatic Prostate Cancer: Southwest Oncology Group Trials 9346 (Intergroup Study 0162)

Hussain M et al. JCO 2009;27:2450-2456
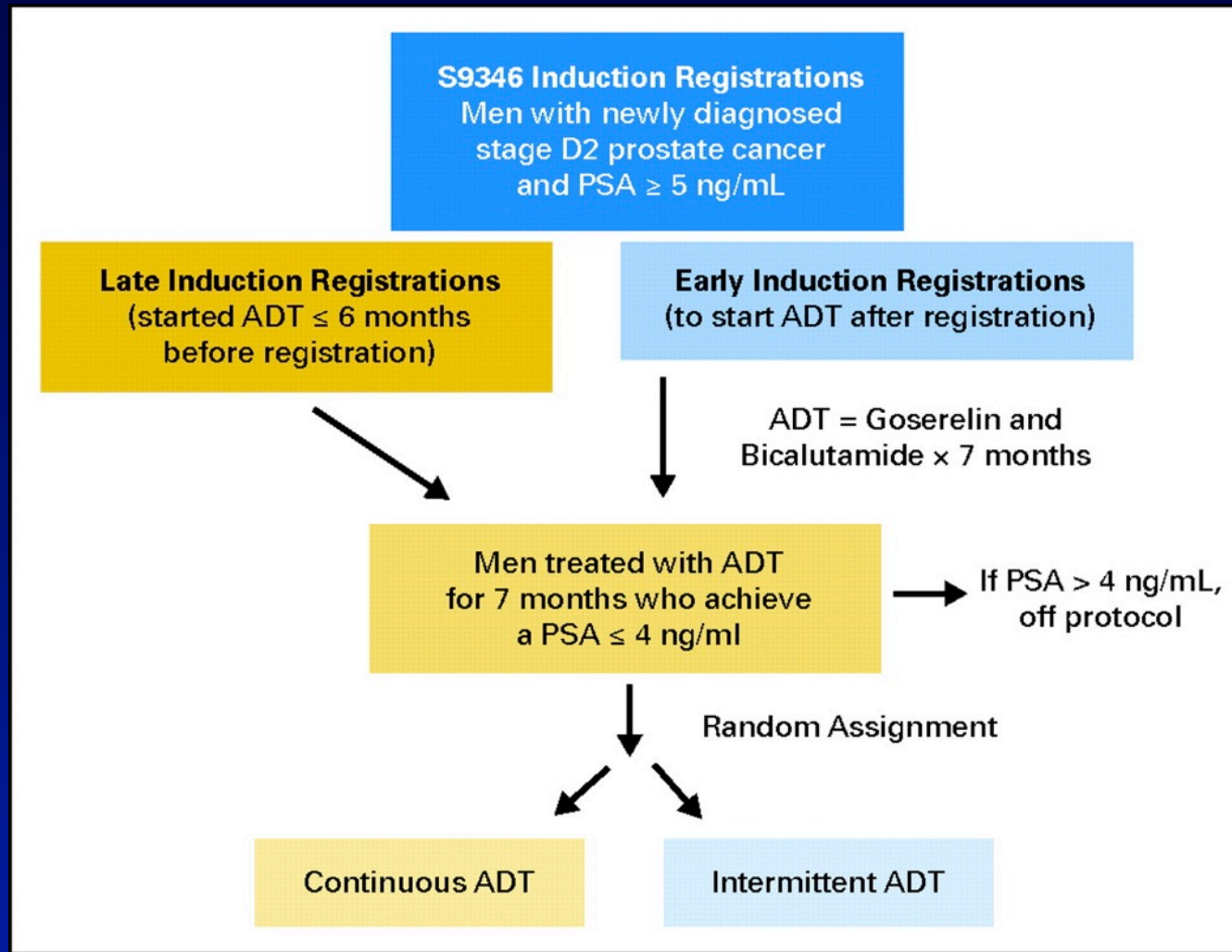
Intermittent versus Continuous Androgen Deprivation in Prostate Cancer

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.

SWOG 9346

- Newly diagnosed hormone sensitive metastatic PCa
  - ➢ Performance Status 0-2
  - ➢ Serum PSA ≥ 5ng/ml
  - ➢ Goserelin & Bicalutamide for 7 mos
- Randomized patients
  - ➢ Achieved PSA nadir ≤ 4ng/ml
  - ➢ IAD versus continuous (CAD)
- Non randomized patients
  - ➢ Followed on continuous ADT
- Co-Primary Endpoints
  - ➢ Noninferiority IAD compared with CAD
    - ❖ Upper limit of Hazard at 1.20
  - ➢ QOL @ 3 mos post randomization

SWOG 9346: CAD Versus IAD

Figure 1. Median Survival from Randomization in the Two Treatment Groups.
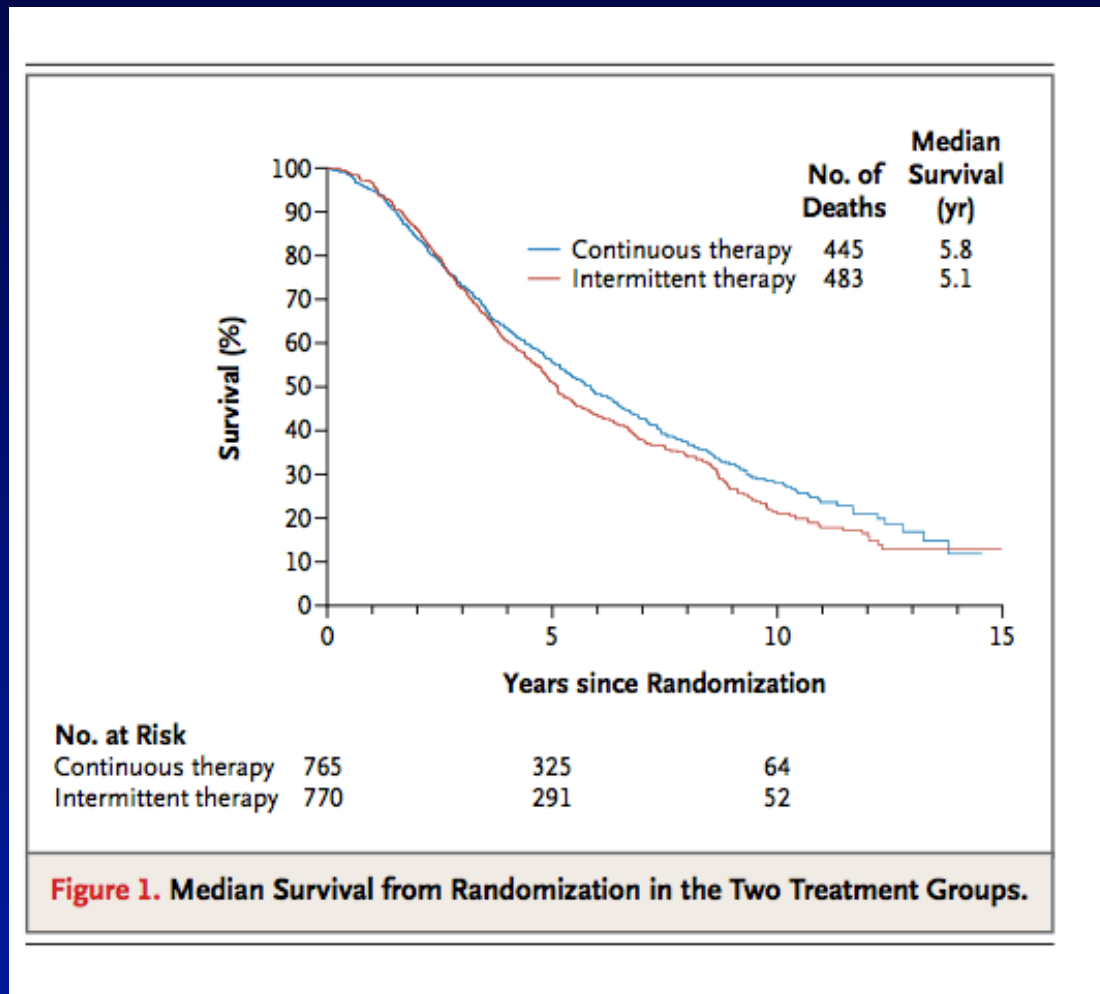
HR for IAD 1.10 (0.99-1.23)

PSA Progression Predicts Overall Survival in Patients With Metastatic Prostate Cancer: SWOG 9346 (Intergroup Study 0162)

Hussain, M. et al. J Clin Oncol; 24:3984-3990 2006
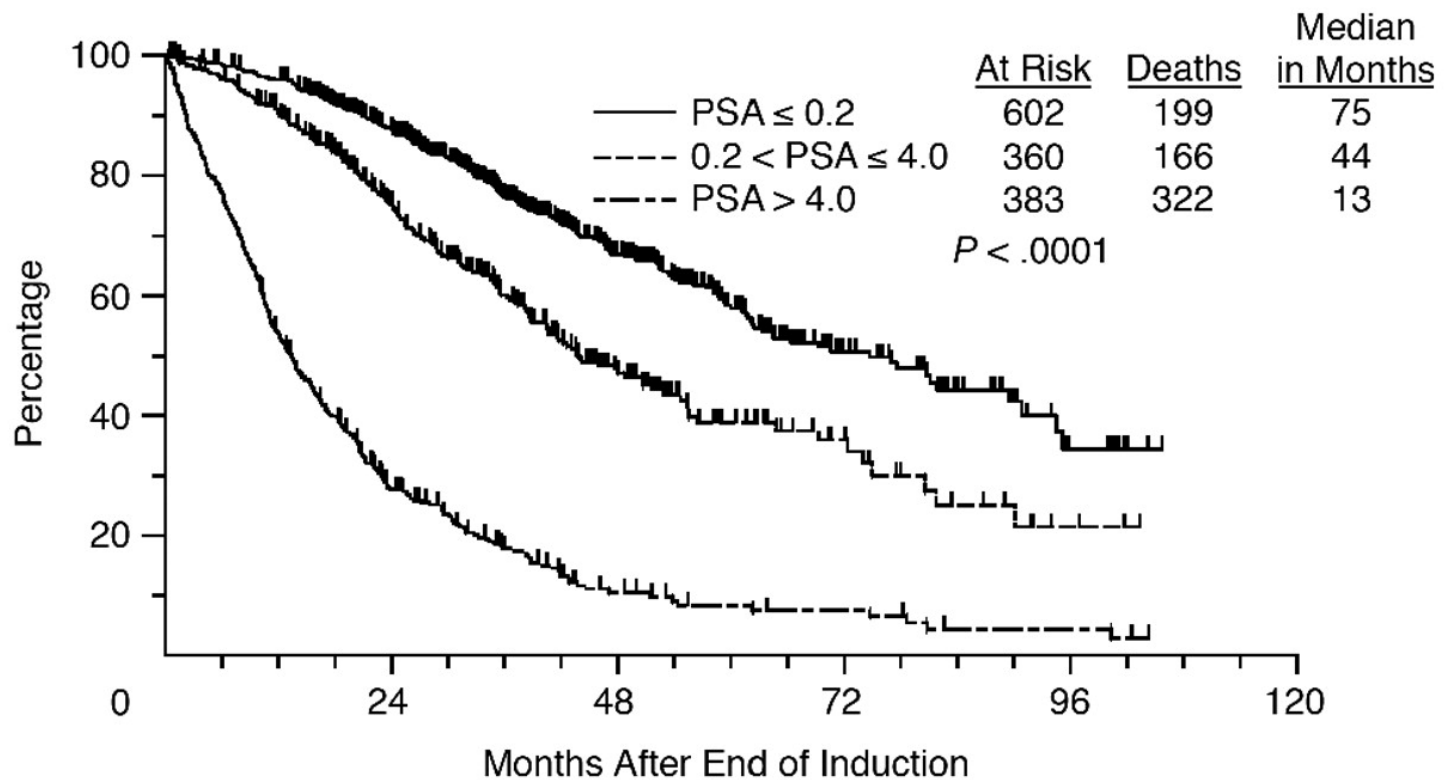
SWOG 9346 Median Survival

PSA after ADT-Induction	Survival (mo)	Risk of Death
>4	13	
0.2 – 4	44	< one third (p< .001)
<0.2	75	< one fifth (p< .001)

➔ PSA of 4 ng/ml or less after inductive ADT is a strong predictor of survival

……and Introducing "Bipolar Androgen Therapy"

- Rapid cycling from supraphysiologic to near-castrate serum T: bipolar androgen therapy (BAT).
- 16 CRPC: testosterone cypionate (400 mg IM); day 1 of 28) and etoposide (100 mg/d; days 1-14
- After three cycles, those with a declining PSA continued on IHT (monotherapy).
- 4 men > 1 year therapy
- 10/10 had PSA reductions w/IHT after BAT
  – BAT may also restore sensitivity to ADTs

RADAR Imaging Recommendations

GOAL: EARLY IDENTIFICATION OF METASTATIC DISEASE

Newly Diagnosed Patients

Scan high-risk patient and intermediate-risk patient with at least 2 of the following criteria positive:

- PSA level >10 ng/mL
- Gleason score = 7
- Palpable disease (≥T2b)

Biochemical Recurrent Patients

- 1st scan when PSA level between 5 and 10 ng/mL
- Imaging frequency if negative for previous scan: 2nd scanning when PSA=20 ng/mL and every doubling of PSA level thereafter (based on PSA testing every 3 months)

M0 Castrate-Resistant Patients

- 1st scan when PSA level ≥2 ng/mL
- Imaging frequency if negative for previous scan: 2nd scanning when PSA=5 ng/mL and every doubling of PSA level thereafter (based on PSA testing every 3 months)

Crawford, et al Urology. 2014 Mar;83(3):664-9

What we have learned about IHT

- Level I evidence supports the oncologic equivalence of IHT compared with continuous androgen blockade in men with biochemical failure.

- Compared with CHT, IHT demonstrates improved QOL and fewer side effects.

- Patient selection for IHT is important to maintain good oncologic results.

- Monitoring of PSA response and duration of off-treatment intervals allow for stratification of patients by risk of progression.

Klotz and Toren Current Oncology 19:2012

What we have learned about IHT

- Both SWOG 9346 and PR7 were non-inferiority trials. The non-inferiority result of the PR7 trial showed < 8% survival difference

- The SWOG 9346 produced an statistically inconclusive result (HR: 1.1; CI: 0.99-1.23), with the upper limit being above the pre-specified 90% upper limit of 1.2.

- Other Benefits: Bone protection, protection against metabolic syndrome, decrease in treatment costs.

EAU Prostate cancer guidelines 2012
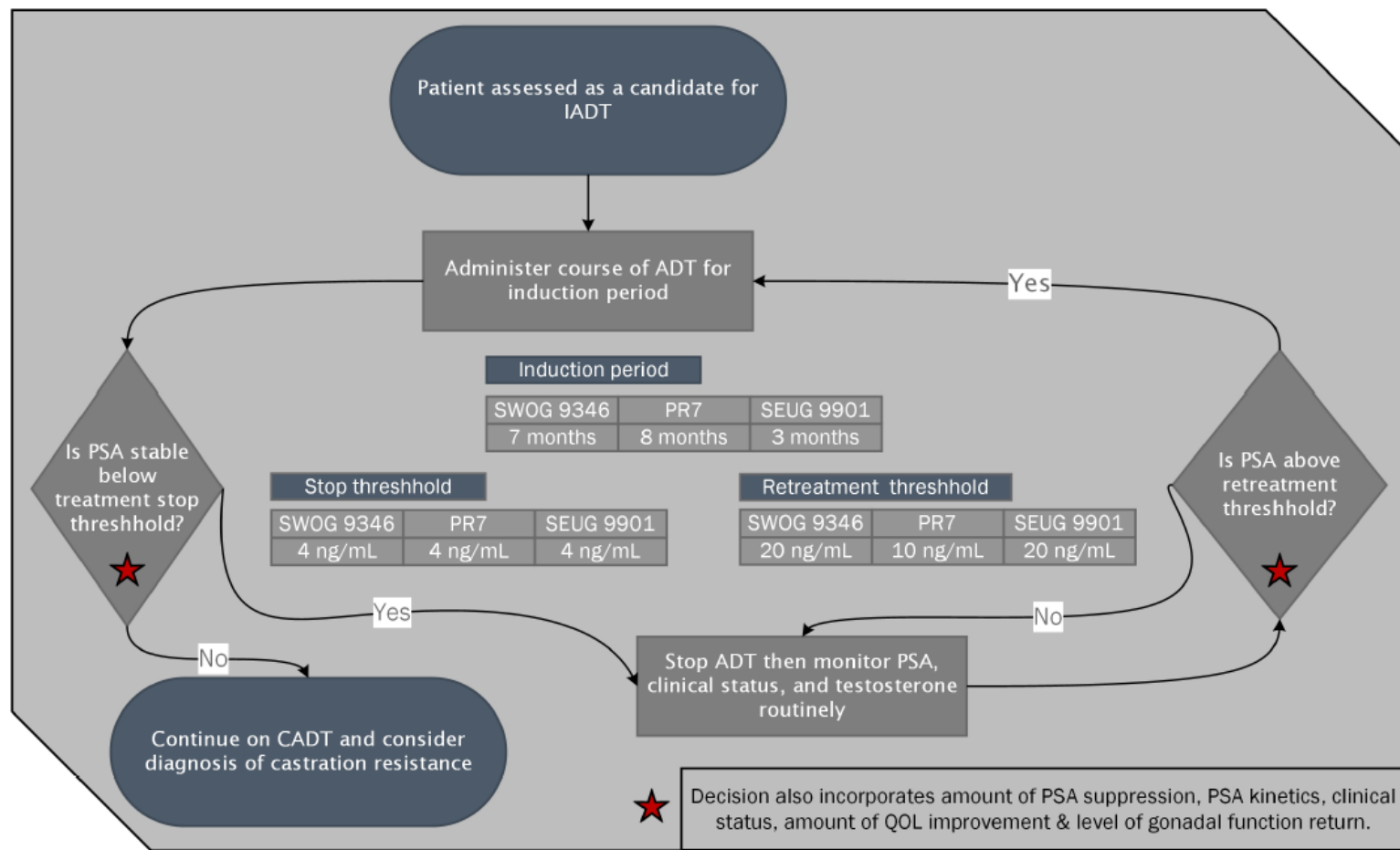
Where are we today with IHT?

Figure 2 – Clinical protocol for IADT administration. ADT – androgen deprivation therapy, IADT – intermittent ADT, CADT – continuous ADT, PSA – prostate specific antigen. SWOG 9346, PR7 and SEUG 9901 are the 3 largest phase 3 trials comparison IADT and CADT.

After Dason S., et al CJU February 2014

2015 IHT Major Review

- References: 10,510
- Published: 2000 to 2013
- 22 articles from15 trials (6856 patients)
- No significant difference between IHT and CHT
  - overall survival
  - cancer-specific survival
  - progression-free survival
- Minimal difference in self-reported QOL
- Most trials observed improved physical and sexual functioning with IHT

A Overall survival

Source	Log HR (SE)	HR (95% CI)	Favors IAD	Favors CAD	Weight, %
Irani et al,[31] 2008	0.5128 (0.3950)	1.67 (0.77-3.62)			1.2
Calais da Silva et al,[27] 2009	0.0392 (0.0870)	1.04 (0.88-1.23)			17.7
Crook et al,[13] 2012	0.0198 (0.0871)	1.02 (0.86-1.21)			17.6
Mottet et al,[36] 2012	0.2070 (0.2069)	1.23 (0.82-1.85)			4.2
Hussain et al,[14] 2013	0.0953 (0.0641)	1.10 (0.97-1.25)			25.9
Organ et al,[37] 2012	0.3293 (0.3800)	1.39 (0.66-2.93)			1.3
Salonen et al,[38,39] 2008	-0.1393 (0.1008)	0.87 (0.71-1.06)			14.3
Calais da Silva et al,[15] 2013	-0.1054 (0.0863)	0.90 (0.76-1.07)			17.9
Total		1.02 (0.93-1.11)			100
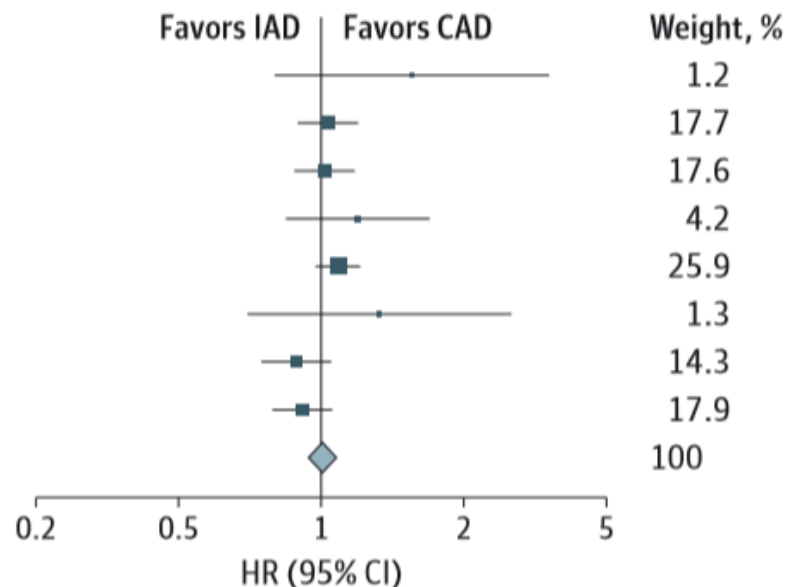
HR (95% CI)

B Cancer-specific survival

Source	Log HR (SE)	HR (95% CI)	Favors IAD	Favors CAD	Weight, %
Irani et al,[31] 2008	0.5108 (0.5004)	1.67 (0.63-4.44)			2.5
Calais da Silva et al,[27] 2009	0.1275 (0.1707)	1.14 (0.81-1.59)			18.8
Salonen et al,[38,39] 2008	-0.1570 (0.1304)	0.85 (0.66-1.10)			29.3
Crook et al,[13] 2012	0.1655 (0.1382)	1.18 (0.90-1.55)			26.7
Calais da Silva et al,[15] 2013	-0.0726 (0.1523)	0.93 (0.69-1.25)			22.8
Total		1.02 (0.87-1.19)			100

HR (95% CI)

JAMAOncol.2015;1(9):1261-1269
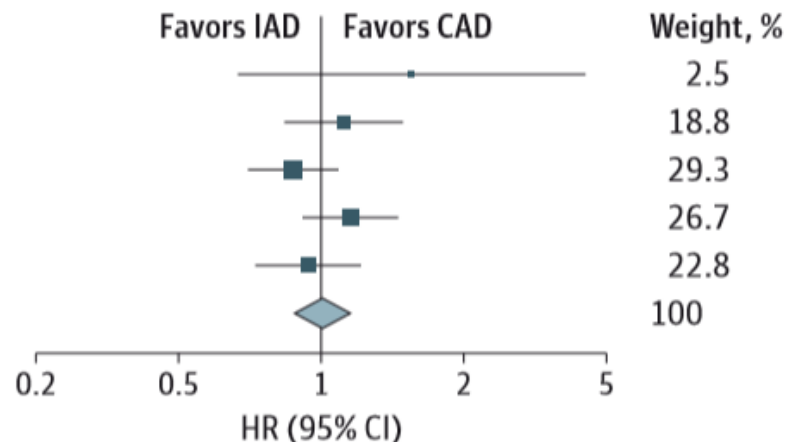
EAU-Guidelines 2012

13.4.3. Intermittent Androgen Blockade

… The best population to consider for IAD <u>has still to be fully characterized.</u> However, the most important factor seems to be the patient's response to the first cycle of IAD, e.g. the PSA level response.
… should be the standard of care for those relapsing after radiotherapy

Heidenreich A.et al : European Urology 53 (2008) 75

Metastatic Prostate Cancer: CHT versus IHT

<u>EAU 2015-</u> Is now "positive" on IHT

➢ Not investigational despite empirical cut points

- IHT used only with castration agents; motivated pt
    - LHRH antagonists "might be valid"; CAB is standard
- Initial induction must be at least 6-7 months
    - IHT ok if PSA<4 in metastatic
- Defined threshold for re-start: 10-20 for metastatic
- Strict follow up every 3-6 months, T/PSA same lab

Metastatic Prostate Cancer: CCHT versus IHT

ESMO 2015- Mixed

➤ "Continuous ADT is recommended as first-line treatment of metastatic, hormone-naïve disease"

➤ IHT "recommended for men with biochemical relapse after radical RT starting ADT"

Metastatic Prostate Cancer: CHT versus IHT

<u>NCCN 2016</u> - positive

- ➢ **Can consider for M0/M1 to reduce toxicity (NEW)**
- ➢ **3 meta analysis failed to show any survival difference**
- ➢ **IHT not inferior**
  - ➢ Study demonstrating increased death in IHT balanced by more non prostate cancer deaths in CHT arm
- ➢ **Unplanned analysis GI 8-10 longer OS with CHT (8y vs 6.8y): Consider CHT**
- ➢ **QOL better with IHT**

NCCN 2016
IHT Strategy

- Initial Induction with standard ADT for 7 mos
- Risk Stratify based on Serum PSA after 7 mos
  - Low =PSA <0.2ng/ml (Med survival =75mos.)
  - Intermed= PSA 0.2-4 ng/ml (Med survival=44 mos)
  - High = PSA>4ng/ml (Med survival =13 mos)
- Asymptomatic patients after 7 mos of ADT
  - Remain on CAB
- Symptoms related to ADT
  - Low-Intermediate risk-Consider IAD

IHT: 2016 Bottom Line

- **Individual studies can be confusing**
- **Option after RT failure**
- **Option in selected M1 patients after ADT induction (good PSA response)**
- **Use in M0 less clear but accepted**
- **No data yet on IHT after up front chemo (CHARRTED Trial)**
- **Comprehensive metaanalysis of 15 trials**
  - **No difference in OS/CSS/PFS**
  - **QOL may be better**

You can become a tree when you die. There's a biodegradable urn that contains a tree seed and absorbs the nutrients in your ashes.

- Intermittent hormonal therapy on and off treatment cycles are primarily determined by which of the following:
- 1. Testosterone recovery
- 2. Side effect resolution
- 3. Imaging
- 4. PSA levels

- Choose the correct statement concerning IHT
- 1.   Major metaanalysis has shown no significant difference between IHT and CHT in physical and sexual functioning
- 2.   Major metaanalysis has shown no significant difference between IHT and CHT in overall survival and cancer specific survival
- 3.   All major guidelines now support the use of IHT for all patients wih advance disease (ESMO/NCCN/EAU)
- 4.   ECOG/SWOG 9346 and the Canadian PR7 trials showed that IHT was inferior to CHT