Intermittent versus Continuous Androgen Deprivation in Hormone Sensitive Metastatic Prostate Cancer Patients: Results of SWOG 9346 (INT-0162) an International Phase III Trial

Hussain M, Tangen CM, Higano CS, Crawford ED, Liu G, Wilding G, Prescott S, Akdas A, Small EJ, Dawson NA, Donnelly BJ, Venner P, Vaishampayan UN, Schellhammer PF, Quinn DI, Raghavan D, Vogelzang NJ, Thompson Jr, IM

Univ. of Michigan, Ann Arbor, MI; SWOG Statistical Center, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA; University of Colorado Health Science Center, Aurora, CO; University of Wisconsin Carbone Cancer Center, Madison, WI; St. James University Hopsital, Leeds, UK; Marmara University, Istanbul, Turkey; University of California, San Francisco, San Francisco, CA; Georgetown University Hospital Lombardi Comprehensive Cancer Center, Washington, DC; Prostate Cancer Institute, Calgary, Alberta, Canada, Calgary, AB; Cross Cancer Institute, Edmonton, AB; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Urology of Virginia, Norfolk, VA; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Levine Cancer Institute, Carolinas HealthCare System, Charlotte NC; US Oncology Research, LLC, McKesson Specialty Health, The Woodlands, TX, and Comprehensive Cancer Centers of Nevada, Las Vegas, NV; University of Texas Health Science Center at San Antonio, San Antonio, TX

Background

- Continuous androgen deprivation (CAD) is the standard for patients with metastatic hormone sensitive prostate cancer.
- Despite a high response rate most patients will progress to castration resistance.
- The historic median survival is 2.5-3 years.[1,2]
- Scientific data indicate that progression to castration resistance is an adaptive process secondary to AD via androgen receptor dependent and independent mechanisms. [3]

1. Crawford ED et al. N Engl J Med 1989, 2. Eisenberger M et al. N Engl J Med 1998,
3. Debes J, Tindall D. N Engl J Med 2004;351:1488–90

Background & Rational for Intermittent Therapy

- Preclinical data in an androgen-dependent tumor model:
  - Progression on AD was associated with a 500-fold increase in the proportion of androgen-independent stem cells.[1]
  - Apoptosis could be re-induced with intermittent androgen deprivation (IAD). [2]
  - IAD prolonged (almost tripled) the mean time to androgen-independence. [2]

- Early clinical trials indicated that IAD is feasible and may be associated with improvement in quality of life. [3-6]

1. Bruchovsky Cancer Research 1990, 2. Akakura Cancer 1993, 3. Bruchovsky Prostate 1996, 4. Goldenberg Urology 1995, 5. Higano Urology 1996, 6. Bhandari, J Clin Oncol 2005

S9346 (INT-0162): Objectives

Primary

- Determine if survival with IAD is Not Inferior to survival with CAD.
- QOL*: To compare 3 treatment-specific symptoms (Impotence, Libido, Energy/Vitality) and physical and emotional functioning between arms

Secondary:

-More general QOL measures
-PSA dynamics between arms, and correlations with other endpoints

******Moinpour et-al, Abstract # 4571 describes results for QOL***

Step 1: Induction Registration
Key Eligibility Criteria

- Newly diagnosed metastatic prostate cancer.
- PSA $\geq$ 5 ng/ml prior to initiation of AD.
- Prior neoadjuvant or adjuvant hormone therapy or prior finasteride was allowed with some restrictions.
- SWOG performance status of 0-2.
- Signed IRB approved informed consent.

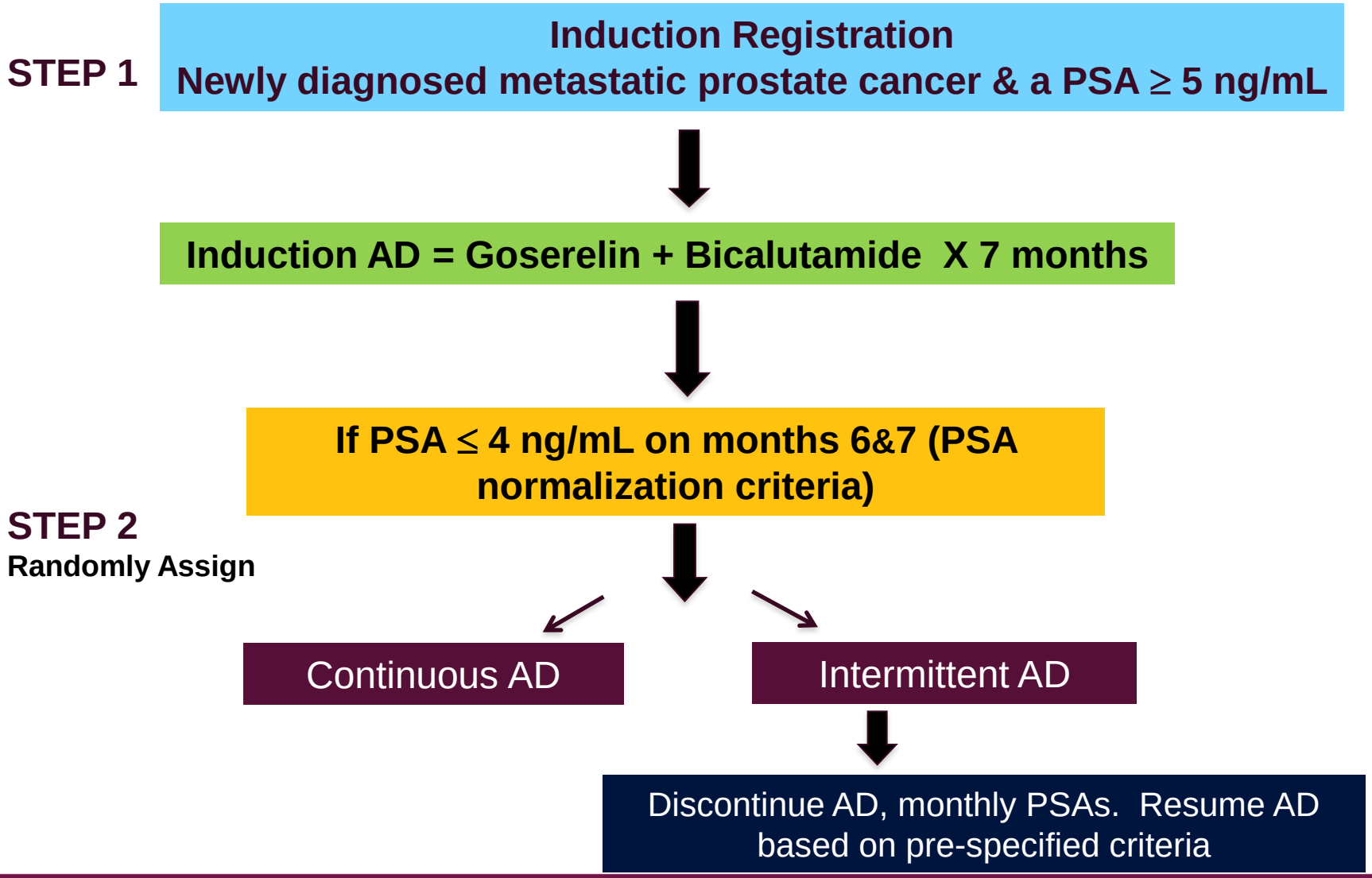
Stratification factors:

- Performance Status: 0 - 1 vs. 2
- Extent of Disease:
  - Minimal: Spine, pelvis &/or Lymph nodes

  vs.
  - Extensive: Ribs, long bones and / or visceral organs (Liver, lung)

- Prior hormone therapy:
  - Neoadjuvant therapy vs. finasteride vs. neither

Study Design



IAD Arm: Subsequent Therapy Cycles

- Therapy was reinitiated when PSA increased to 20 ng/ml (or returned to baseline for patients who had pre-registration baseline value < 20 ng/ml) or for symptoms.

- If the PSA after another 7 months induction course met the PSA normalization criterion then the patients started another observation period.

- If the PSA at either months 6 or 7th of an induction course was greater than 4 ng/ml then the patients received continuous therapy until progression.

Statistical Methods

- **Primary outcome:** Survival post-randomization
  - Hypothesis: "**IAD is NOT inferior to CAD**"

- **Design specifications:**
  - **Survival with IAD is not inferior if the 95% confidence interval for the hazard ratio (IAD vs. CAD) excludes 1.2,** α=0.05, power=90%, adjusting for stratification factors in proportional hazards model.

- **Assumptions:** post-randomization median survival for CAD = 3 years:
  - Sample size: 1500 eligible, randomized patients
  - accrual: 6.25 yrs. + 2 additional yrs. of follow-up.

S9346 Study Information

Activated: 5/15/1995 **Closed**: 9/1/2008

Step 1: Induction Registrations:
3040 pts *(90 ineligible)*

Step 2: Randomization to CAD vs. IAD:
1535 eligible pts
(projected 50% randomized)

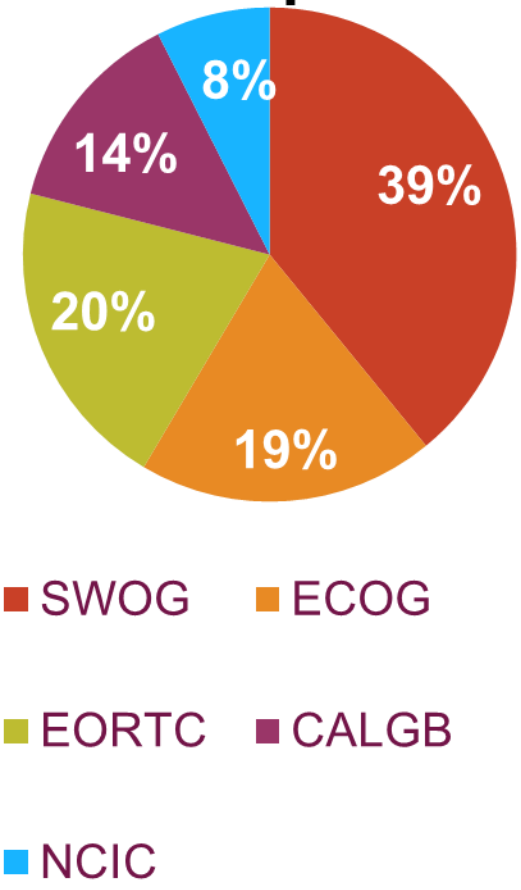
IAD
770 eligible patients

CAD
765 eligible patients

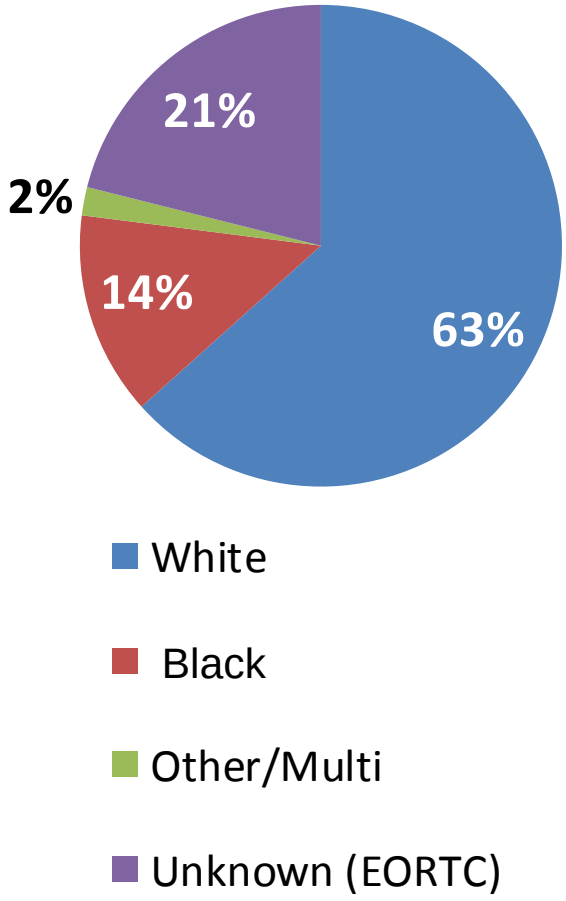
S9346 Study Information

N=3040

Accrual by Cooperative Group



Race



Patients Characteristics at Randomization (Step 2)

		IAD (N=770)	CAD (N=765)
Age (yrs)	median (range)	70 (39, 97)	70 (39, 92)
PSA (ng/ml) at Randomization			
	≤ 0.2	35.4%	34.9%
	0.3 – 4.0	64.6%	65.1%
Performance Status:	0-1 vs. 2	96%, 4%	96%, 4%
Disease Extent:	Extensive	49%	47%
	Minimal	51%	53%
Visceral Disease:	Any	7.1%	6.3%
Prior hormone therapy:	None	87%	88%
	Neoadjuvant, Finasteride	12%, 1%	11%, 1%
Bone Pain:	present	28%	26%
Gleason score:	≤ 6	23%	25%
	7	50%	48%
(31% missing)	8-10	27%	27%

IAD Arm: Time on Study & Receiving Treatment (Only Patients Who are Off Protocol Treatment)

	Time on Study*	% of time "on study" patient is receiving CAD	
All Patients median (25%,75%) (N=618)	**19** (10,38) months	**47%**	**(23%, 69%)**
Extensive Disease median (25%,75%) (N=319)	**17** (10,34) months	**51%**	**(25%, 73%)**
Minimal Disease median (25%,75%) (N=299)	**21** (9, 38) months	**47%**	**(22%, 64%)**

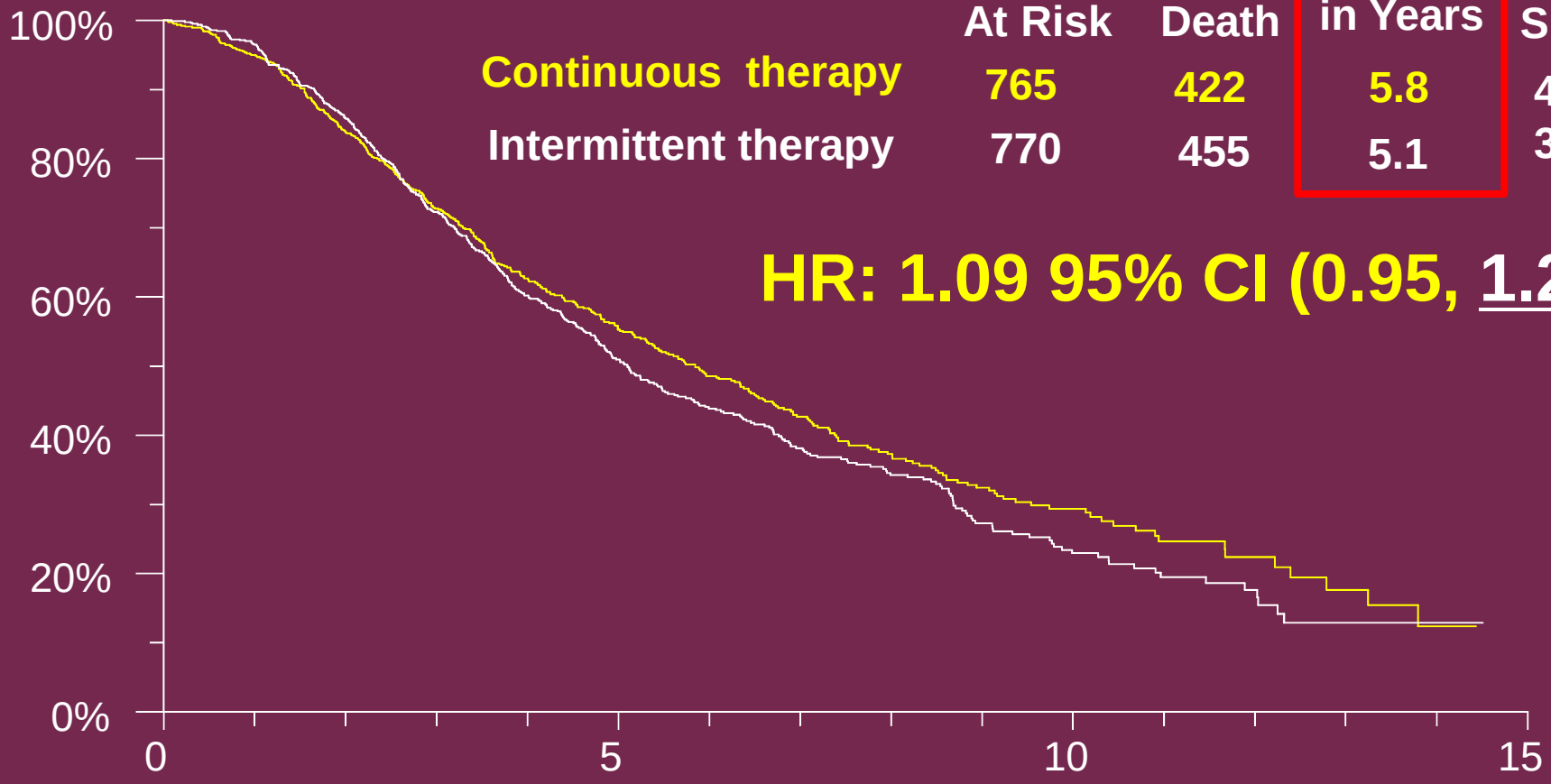
*** Time on study: from randomization to "Off Study" notification**

Adverse Events with a Grade 4 Reported*

	IAD (N=703)		CAD (N=731)	
AE Category	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Cardiovascular	8	3	10	5
Flu-like Symptoms	18	2	26	2
Gastrointestinal	4	0	6	3
Hemorrhage	0	1	3	0
Liver	7	0	3	1
Lung	9	2	12	1
Musculoskeletal	1	1	2	1
Neurologic	15	1	15	2
Pain	26	1	30	2
Renal/Bladder	11	0	4	1
Max Grade Any AE	**203**	**11**	**224**	**15**

*** Treatment attribution: possible, probable, or definite, No Grade 5 reported**

Overall Survival: Intermittent Therapy is Inferior Compared to Continuous Therapy



	At Risk	Death	Median in Years	7 yr Survival
Continuous therapy	765	422	5.8	42%
Intermittent therapy	770	455	5.1	38%

HR: 1.09 95% CI (0.95, 1.24)

At risk		
Intermittent	267	47
Continuous	301	53

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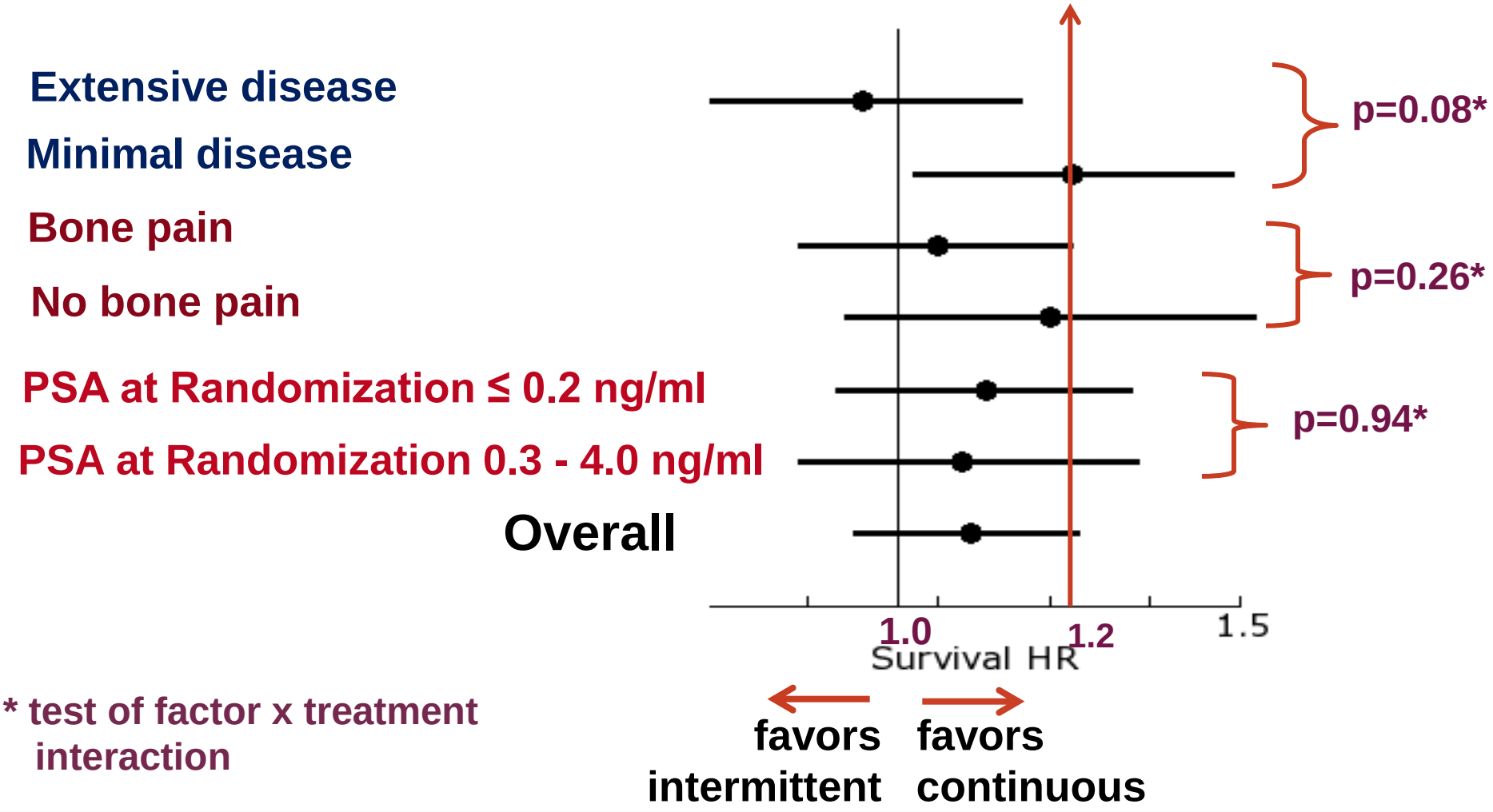
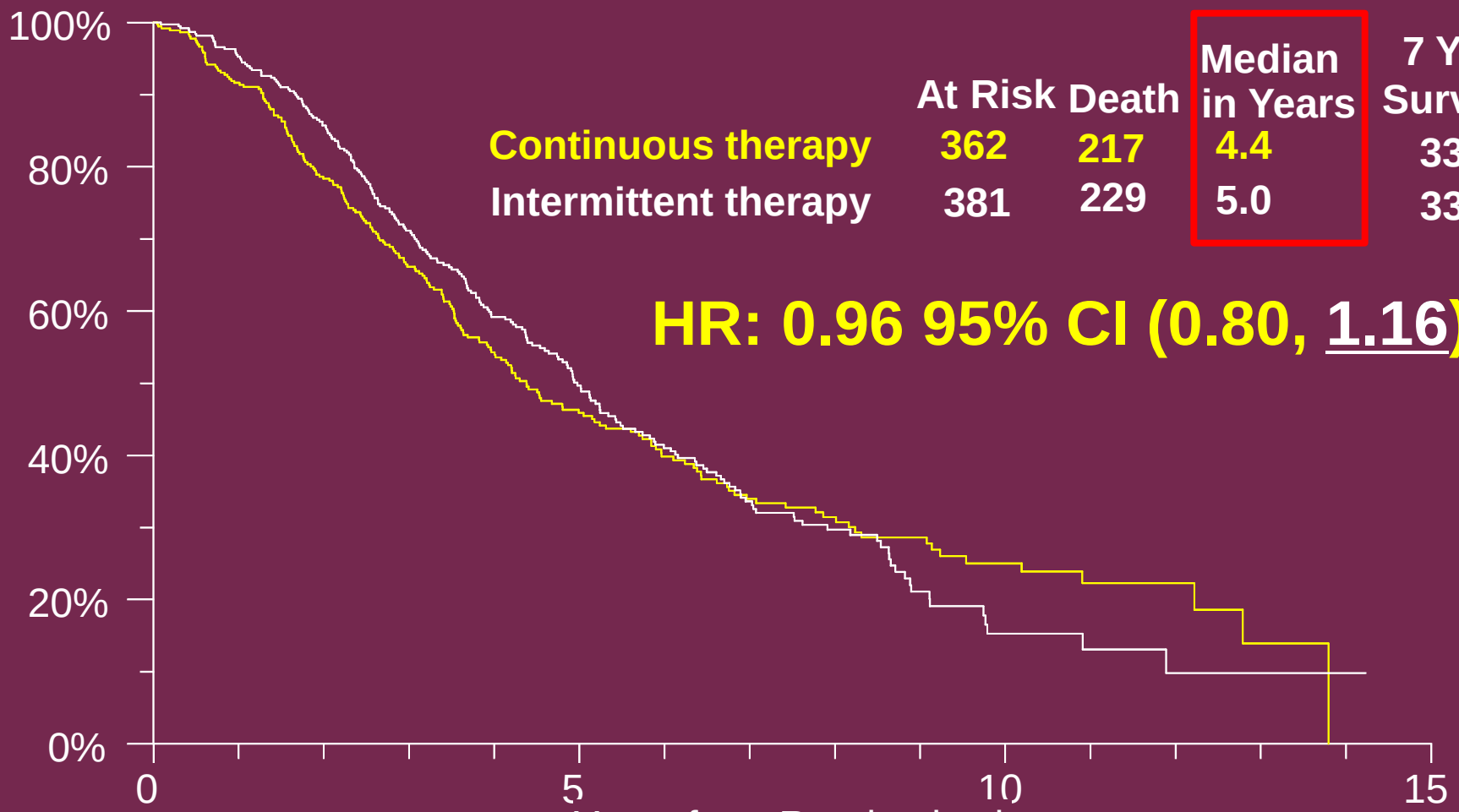
Evaluating Homogeneity of Treatment Effect Across Subsets of Patients



* test of factor x treatment interaction

Overall Survival for Patients with Extensive Disease by Treatment Arm



	At Risk	Death	Median in Years	7 Year Survival
Continuous therapy	362	217	4.4	33%
Intermittent therapy	381	229	5.0	33%

HR: 0.96 95% CI (0.80, 1.16)

At risk		
Intermittent	119	11
Continuous	106	22

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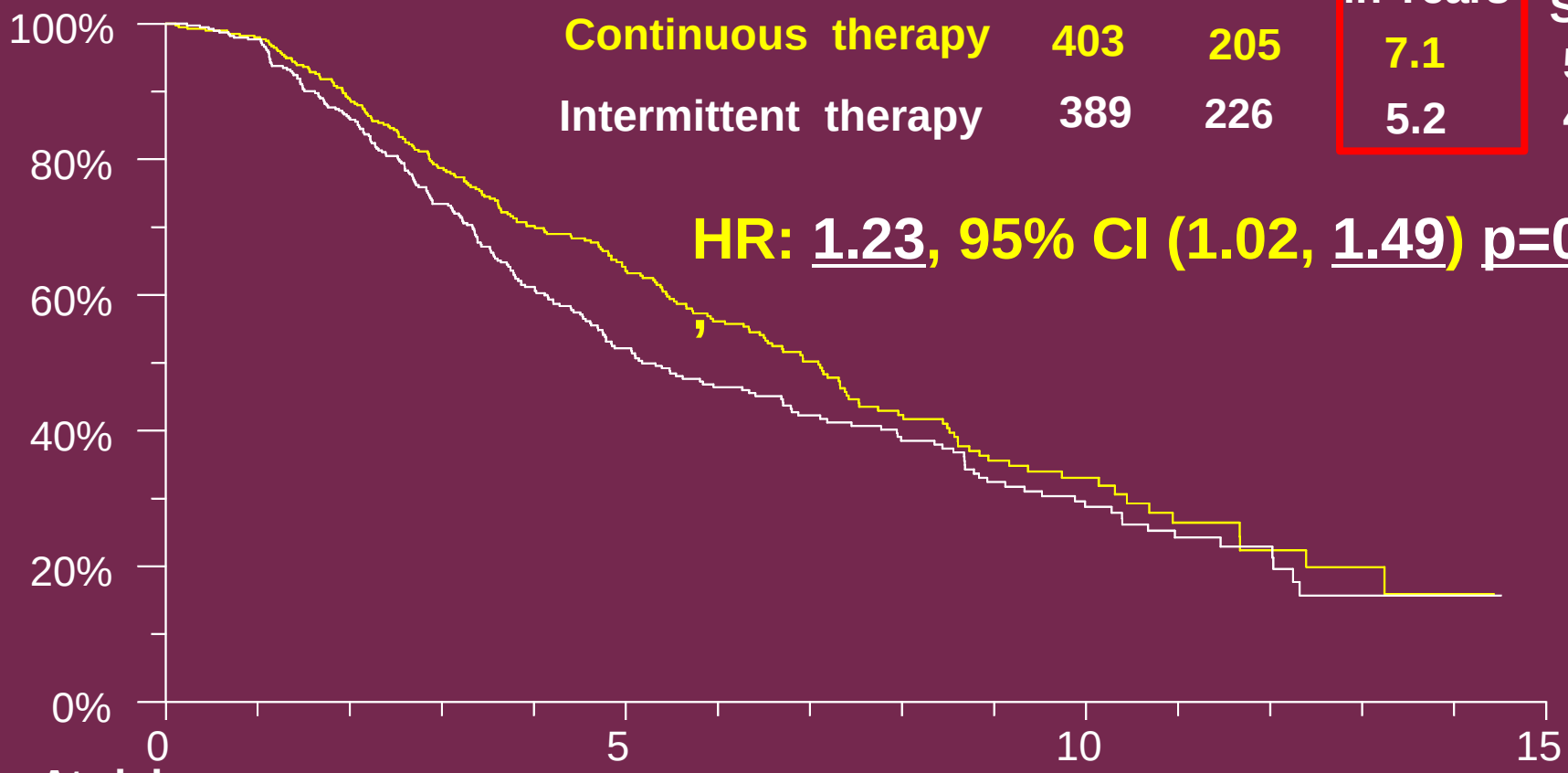
Overall Survival for Patients with Minimal Disease by Treatment Arm



	At Risk	Death	Median in Years	7 yr. Survival
Continuous therapy	403	205	7.1	50%
Intermittent therapy	389	226	5.2	42%

HR: 1.23, 95% CI (1.02, 1.49) p=0.034

At risk		
Intermittent	143	35
Continuous	194	30

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Conclusions

In this international phase III trial in patients with metastatic hormone sensitive prostate cancer :

1. IAD was inferior to CAD based on our pre-specified definition of survival comparability [HR: 1.09, 95% CI (0.95, 1.24)]. Therefore, CAD continues to be the standard of care.
2. In a secondary analysis:
   - IAD was not-inferior to CAD in patients with extensive disease. [HR: 0.96 95% CI (0.80, 1.16)].
   - IAD was inferior in patients with minimal disease & CAD was statistically significantly superior [HR: 1.23, 95% CI (1.02, 1.49), p=0.034].
   - These observations suggest inherent biological differences and warrant further mechanistic evaluation.

Acknowledgments

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