Development and Features of Non-Metastatic Castration Resistant Prostate Cancer

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Department of Urology

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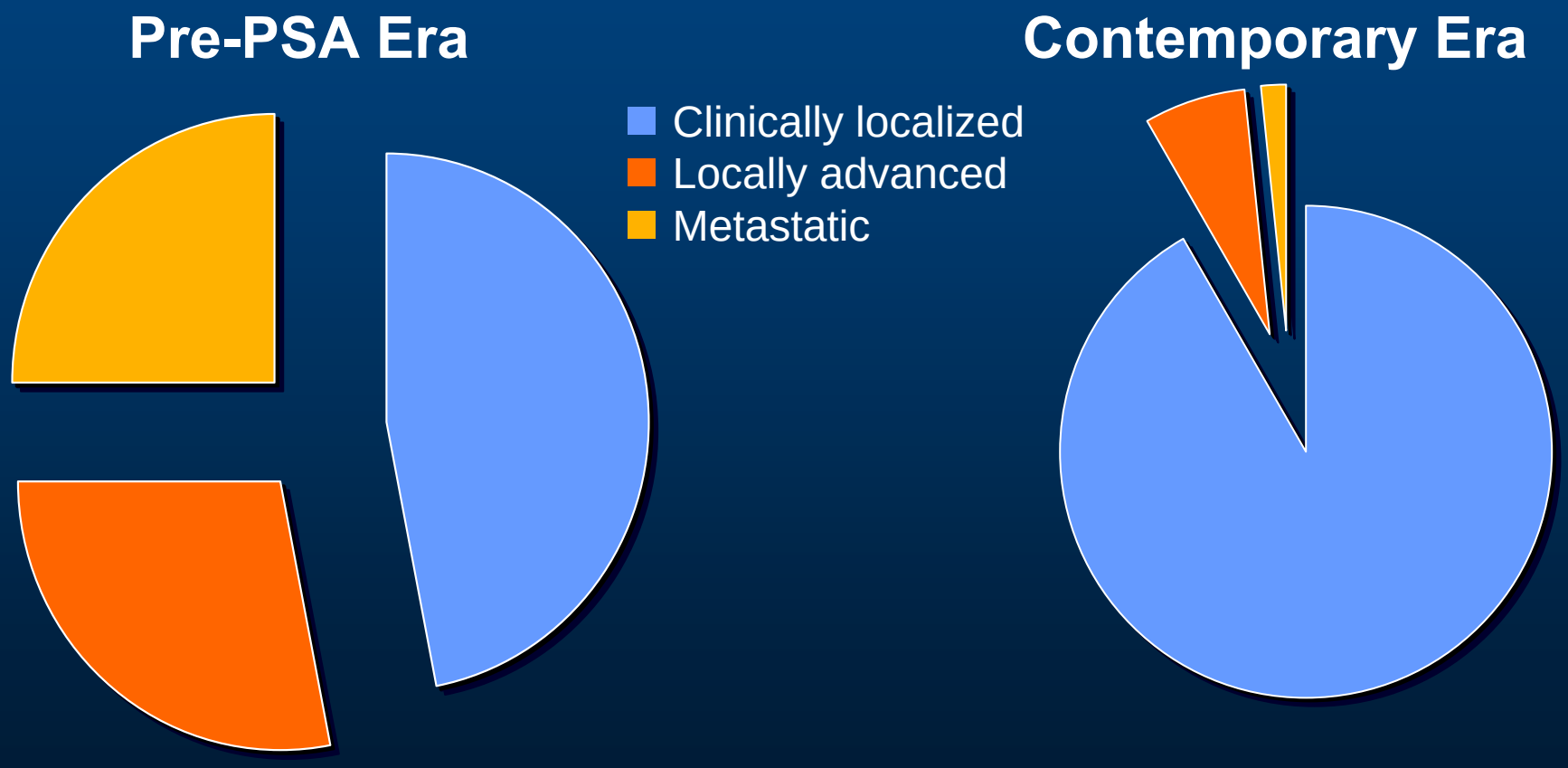
Change in Clinical Stage of Prostate Cancer at Initial Presentation



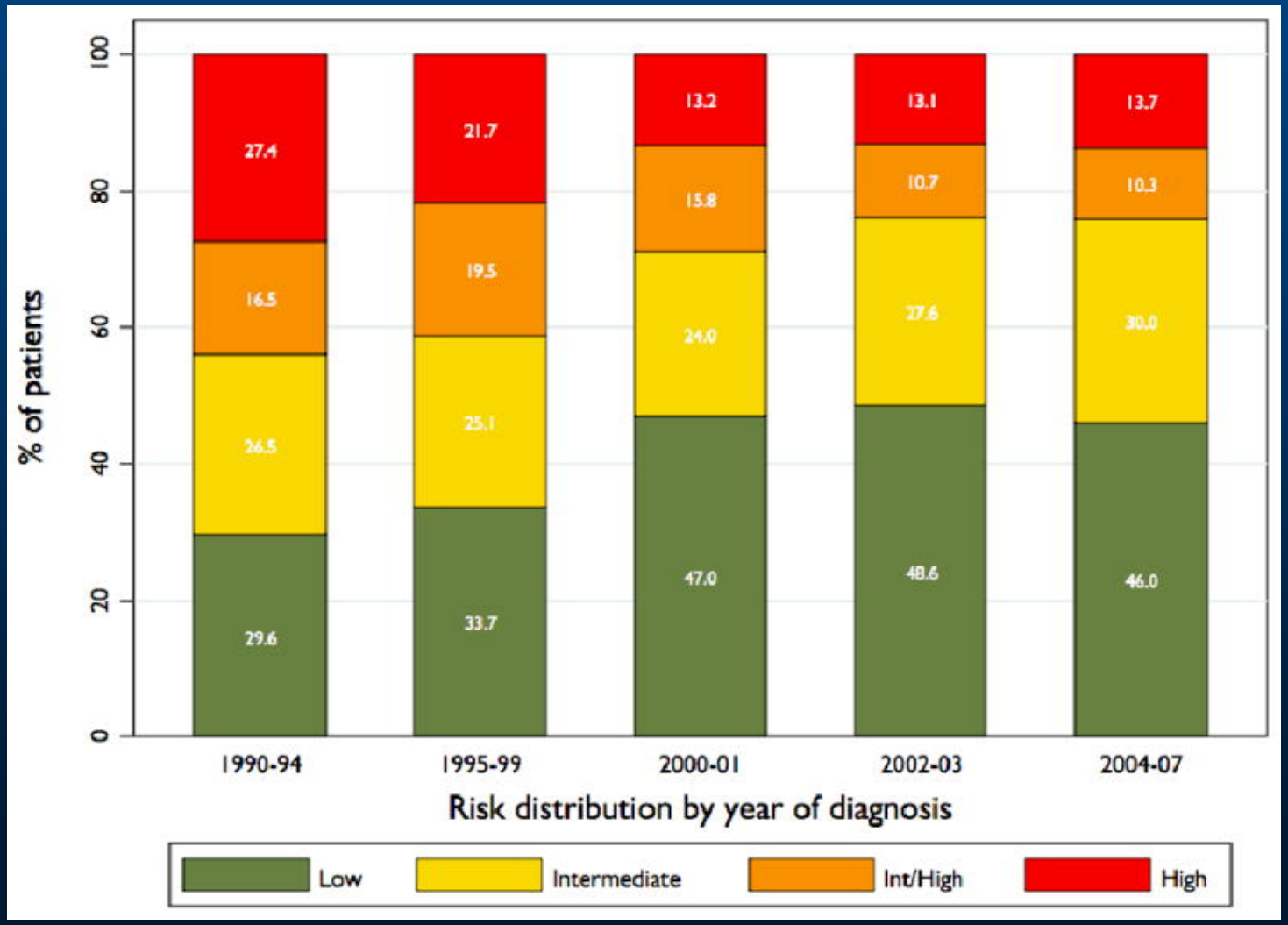
Johansson JE, et al. Lancet. 1989;333:799-803. Cooperberg M, et al. J Urol. 2003;170:S21-S25.
Ryan CJ, et al. Urol Oncol. 2006;24:396-402.

Tools to Assess Prostate Cancer Risk

Tool	Description	Pro / Con
Risk Categories **D'Amico Risk Groups**	**PSA *and/or*** **Gleason *and/or*** **T Stage**	**Easy to apply /** **Imprecise**
Probability Tables **Partin Tables**	**PSA, Stage, Biopsy Gleason**	**Snapshot /** **Pertinence ?**
Risk Scores **UCSF-CAPRA**	**Adds Age,** **% of Pos Cores**	**1-10 Score /** **Cumbersome**
Nomograms **Kattan MSKCC**	**Continuous and Categorical Input**	**Individualized /** **Need computer**

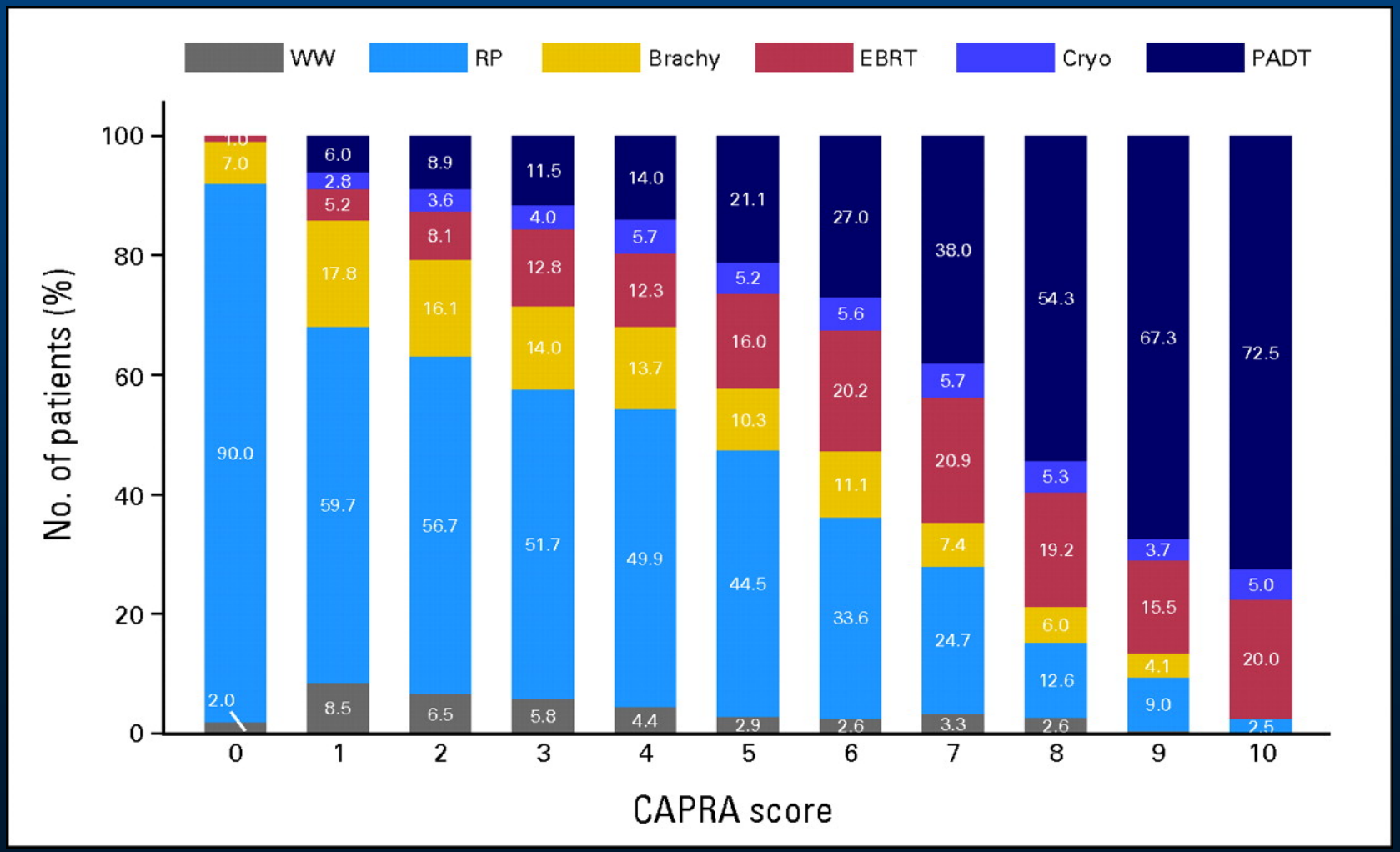
D'Amico AV et al: JAMA 280:969-974, 1998 Makarov DV, et al: Urology 69:1095-1101, 2007
Cooperberg MR, et al: J Urol 173:1938-1942, 2005 Kattan MW et al: JNCI 90:766-771, 1998

Change in Clinical Stage of Prostate Cancer at Initial Presentation



Cooperberg MR, et al; World J Urol 26:211-18, 2008

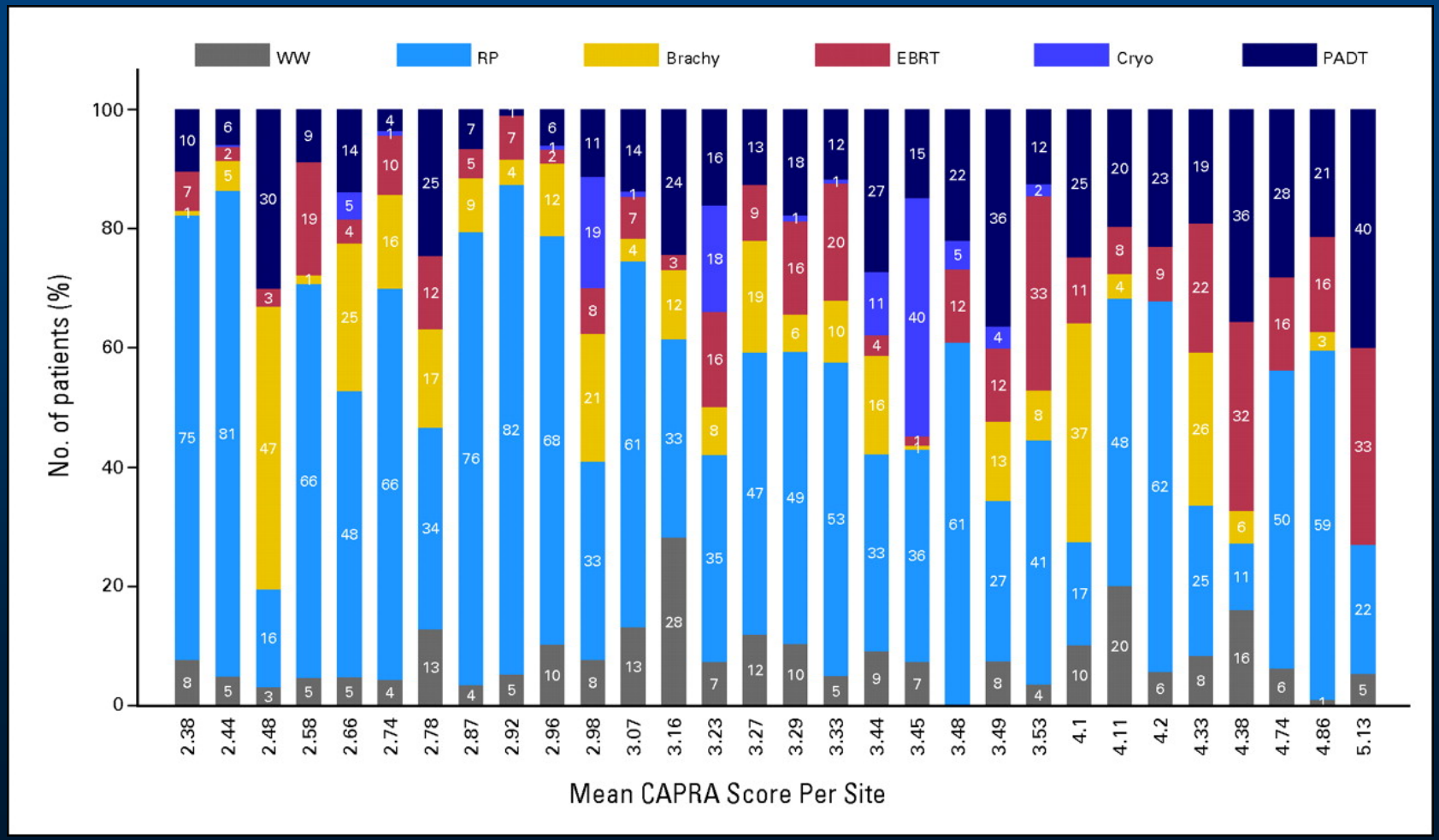
Management of Primary Prostate Cancer Based on Risk



Cooperberg, M. R. et al. J Clin Oncol; 28:1117-1123 2010

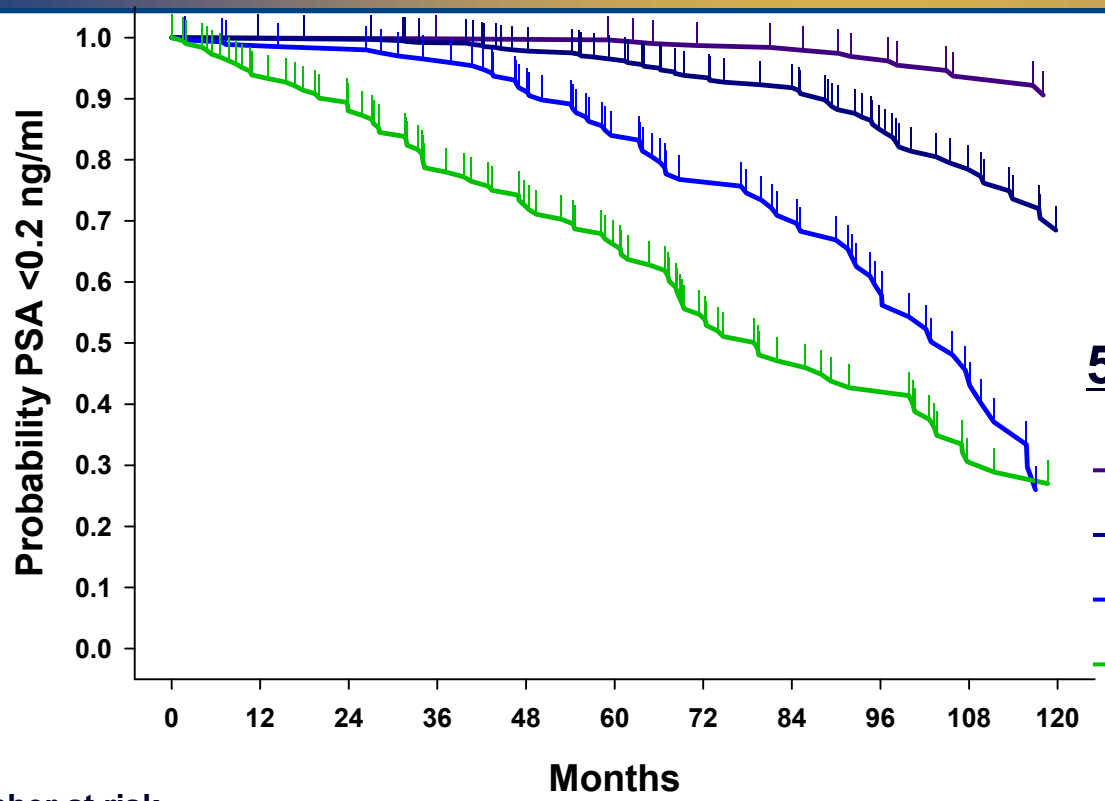
JOURNAL OF CLINICAL ONCOLOGY

Variability of Primary Prostate Cancer Management by Site of Care



Cooperberg, M. R. et al. J Clin Oncol; 28:1117-1123 2010

Biochemical Recurrence after RP



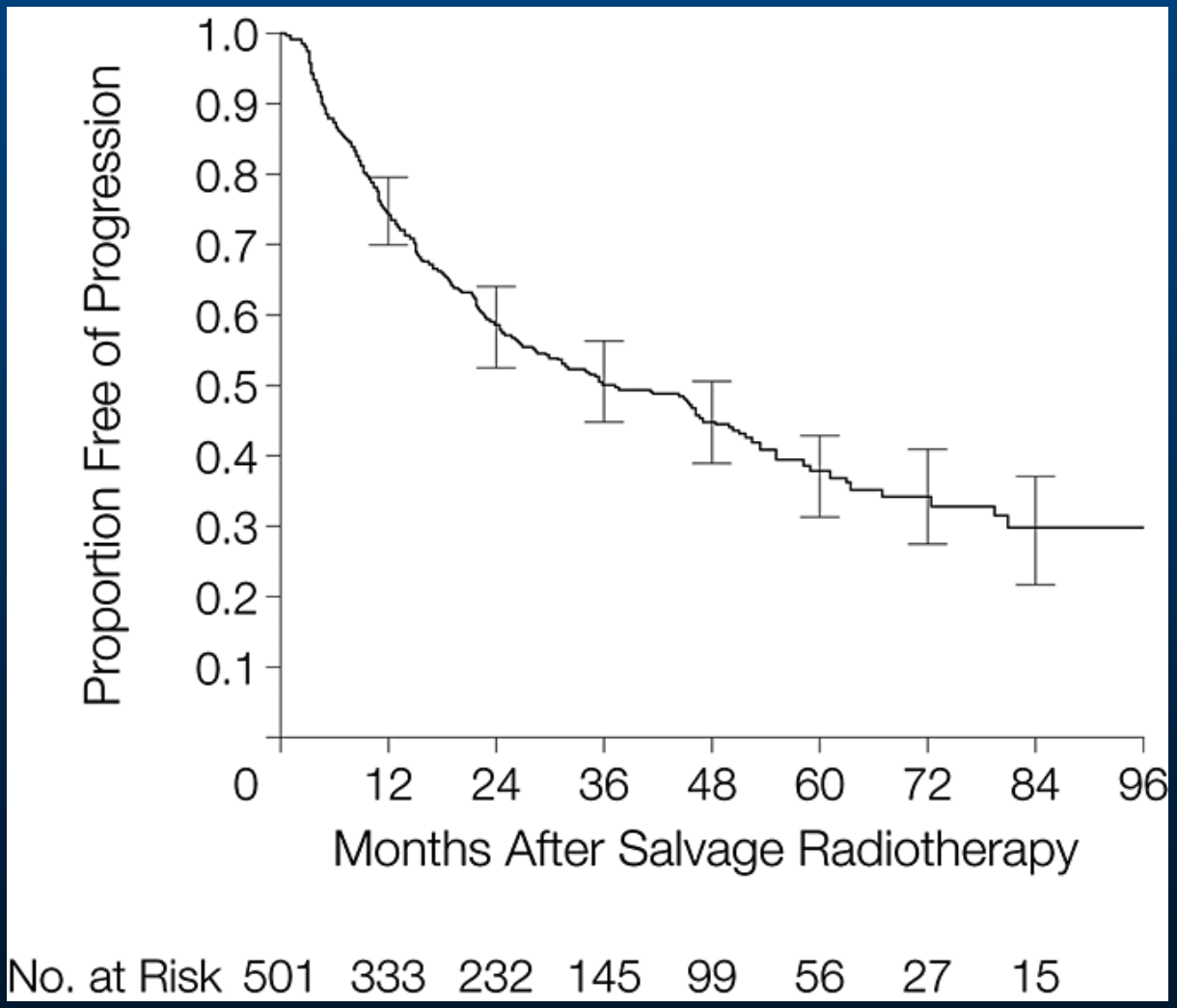
5 Yrs PSA < 0.2, % (95% CI)

3+3=6	99.6 (99-100)
3+4=7	96.5 (95-98)
4+3=7	84 (79-89)
8-10	66 (57-75)

Number at risk

3+3=6	732	664	585	474	520	399	320	241	153	94	44
3+4=7	1166	953	799	626	457	341	265	196	127	75	34
4+3=7	293	241	209	178	140	103	76	56	36	18	7
8-10	200	157	127	106	94	79	60	46	35	21	14

Salvage Radiotherapy for Recurrence

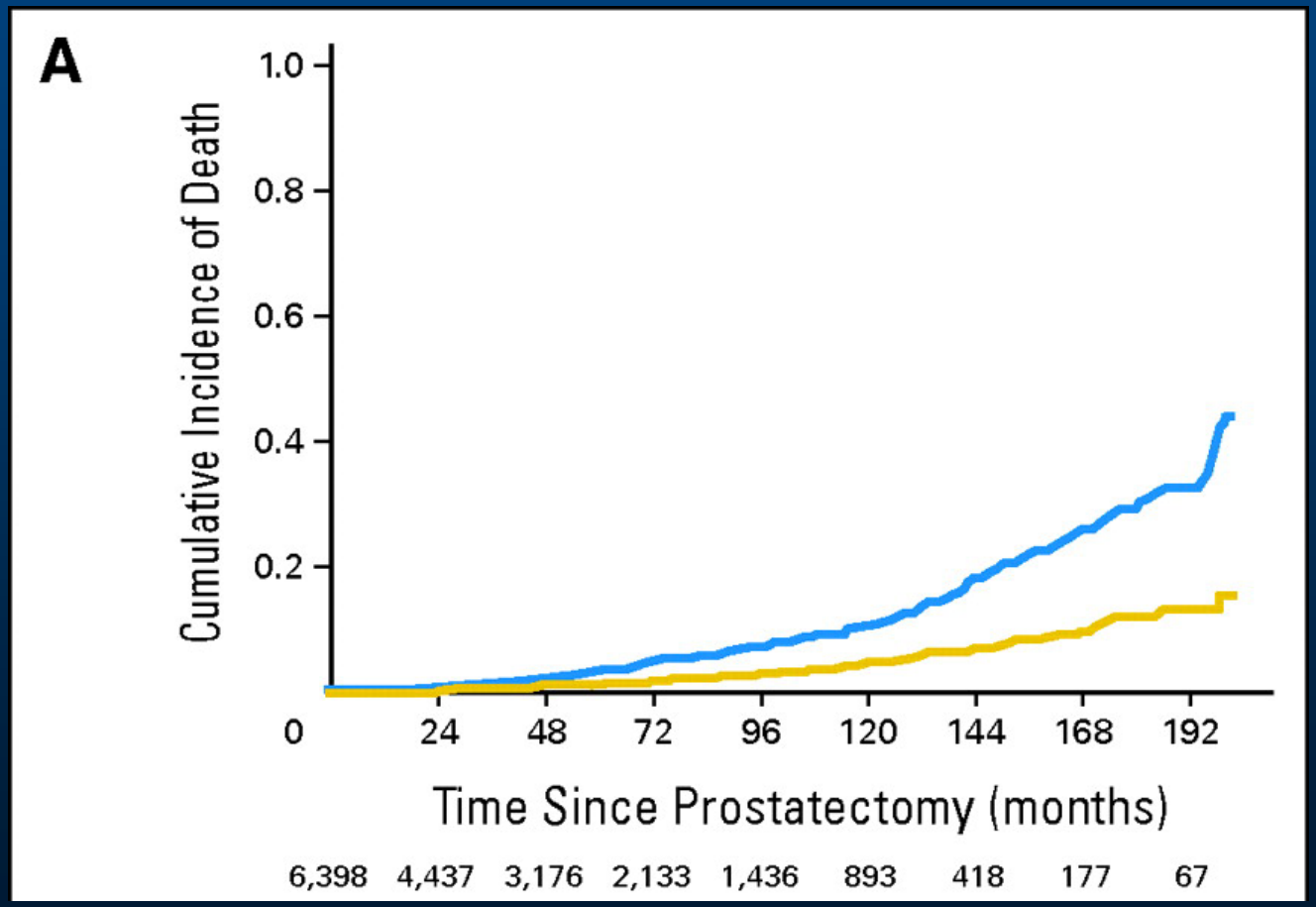


Predictors of failure

- Gleason 8-10
- PreRT PSA > 2 ng/ml
- Negative surgical margins
- PSADT < 10 months
- Seminal vesicle invasion

Stephenson, A. J. et al. JAMA 2004;291:1325-1332

Prostate Cancer-Specific Mortality After Radical Prostatectomy



NonPCSM

PCSM

Stephenson AJ, et al: JCO 27:4300-4305, 2009

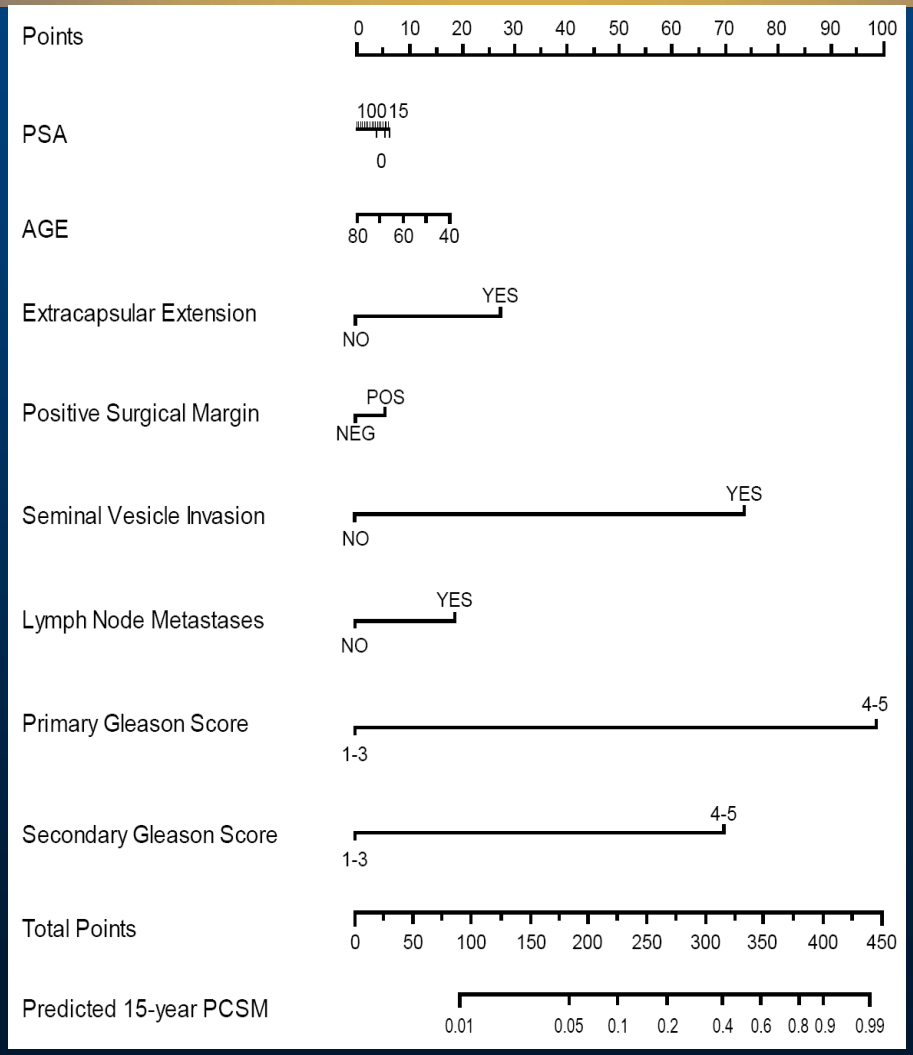
Prostate Cancer-Specific Mortality After Radical Prostatectomy

Variable	15 yr PCSM	% Pts
Gleason 8-10	34%	6%
T3	38%	2%
PSA 20-50	22%	6%
"High Risk"	19%	17%

Adverse clinical features are rare and most patients do not die of PCa

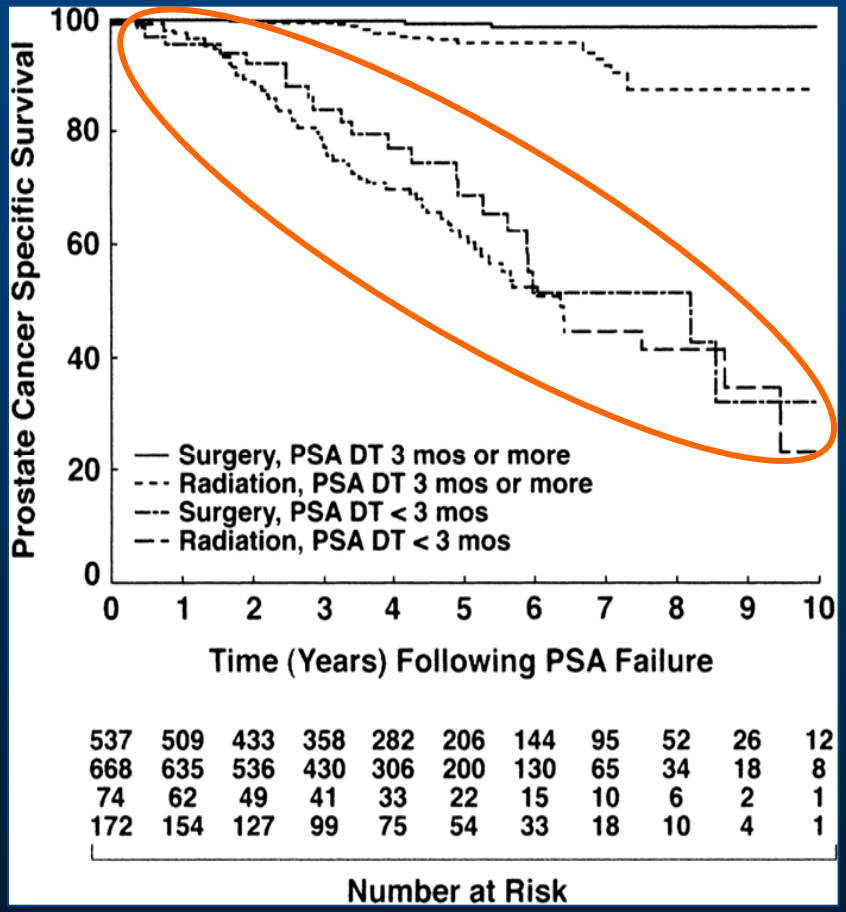
Stephenson AJ, et al: JCO 27:4300-4305, 2009

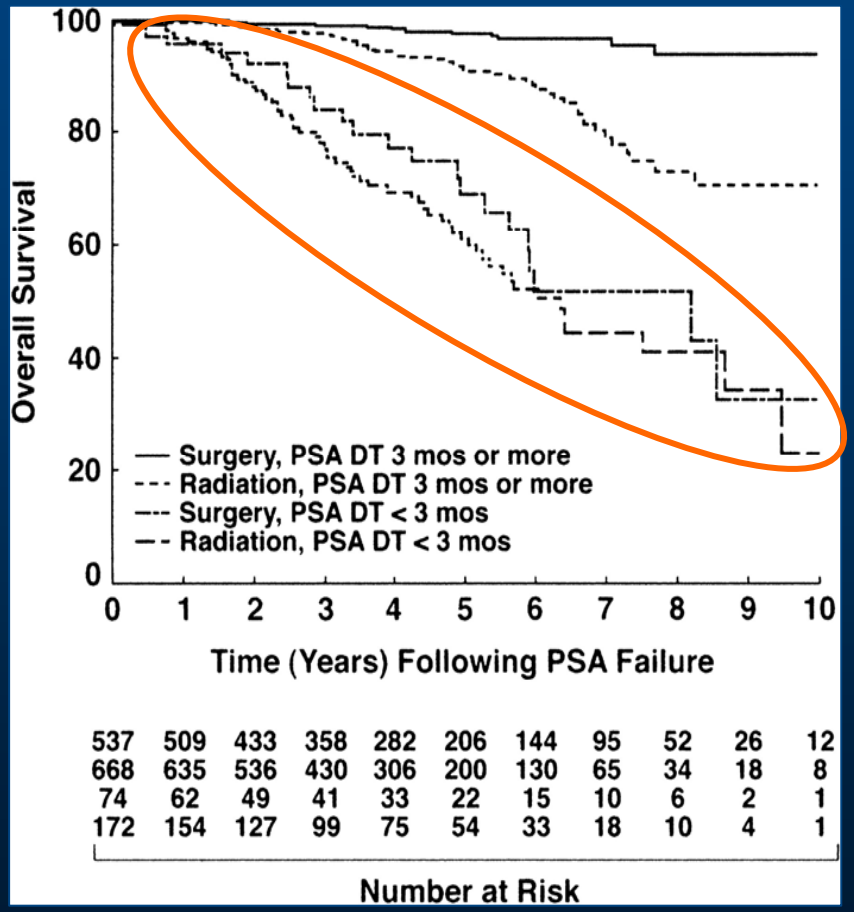
Nomogram for 15-year PCSM after RP



Eggener SE, et al: J Urol 185:869-75, 2011

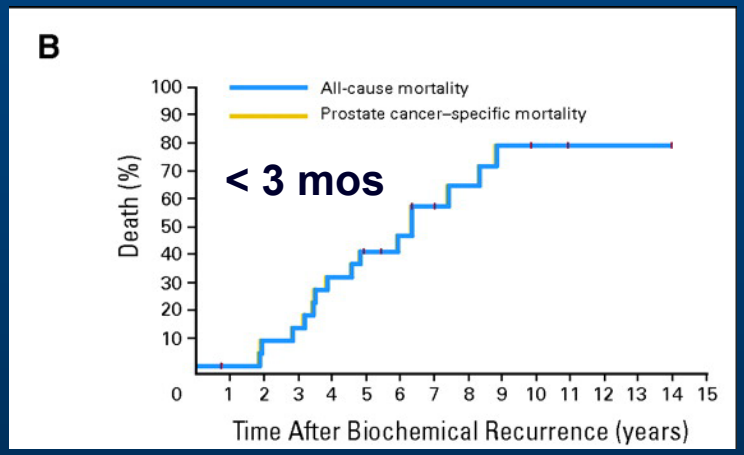
PSA kinetics (PSADT) are predictive PCSM

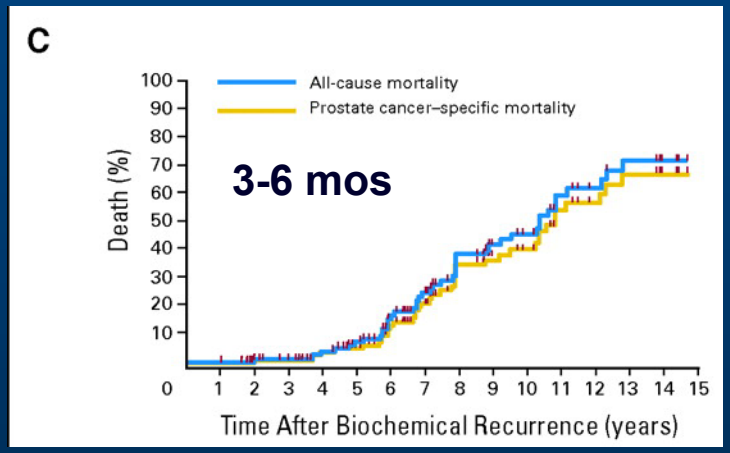


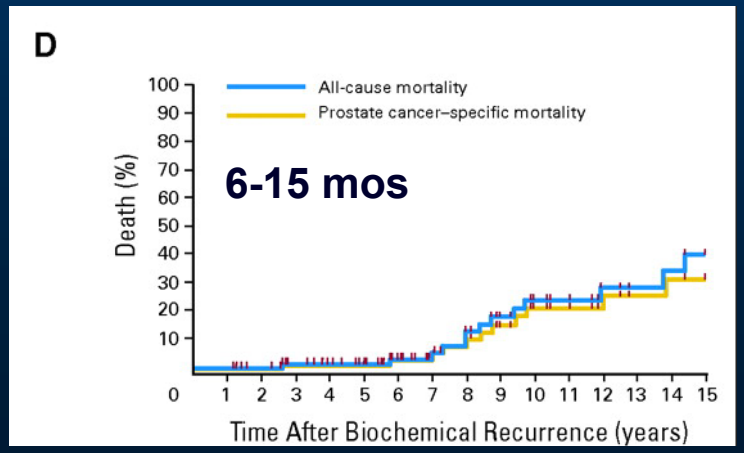


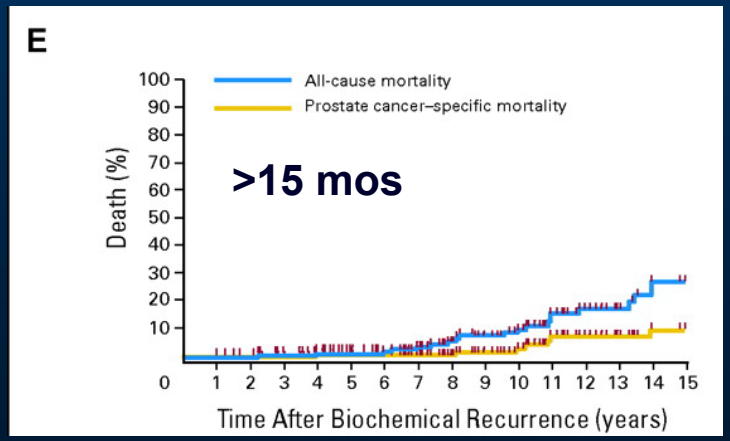
D'Amico AV, et al: JNCI 95:1376, 2003

Shorter PSADT: Increased PCSM



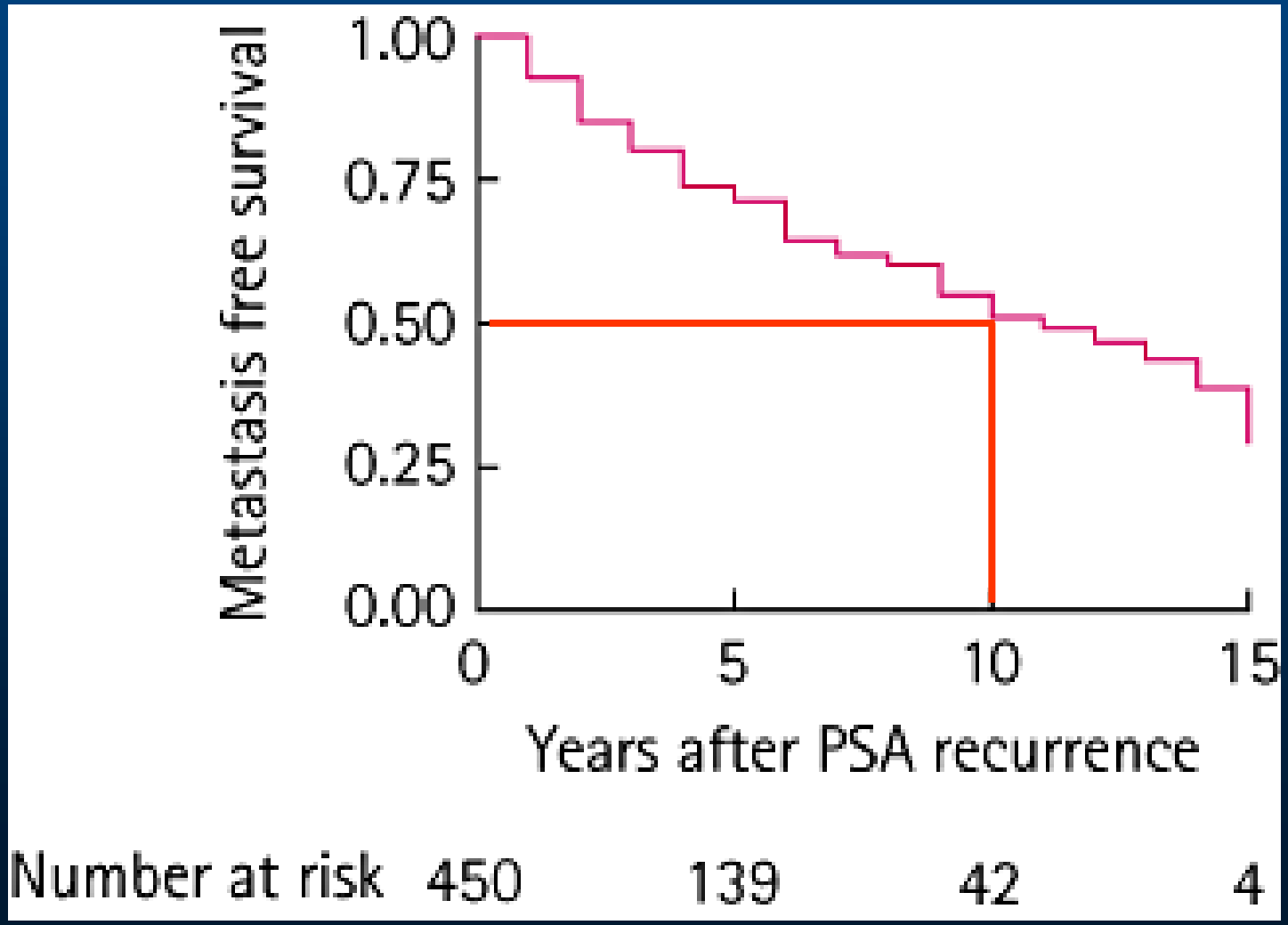






Freedland, S. J. et al. J Clin Oncol; 25:1765-1771 2007

Metastasis Free Survival in Untreated Biochemical Recurrence after RP



Antonarakis ES et al; BJU Int 2011 doi:10.1111/j.1464-410X.2011.10422.x.

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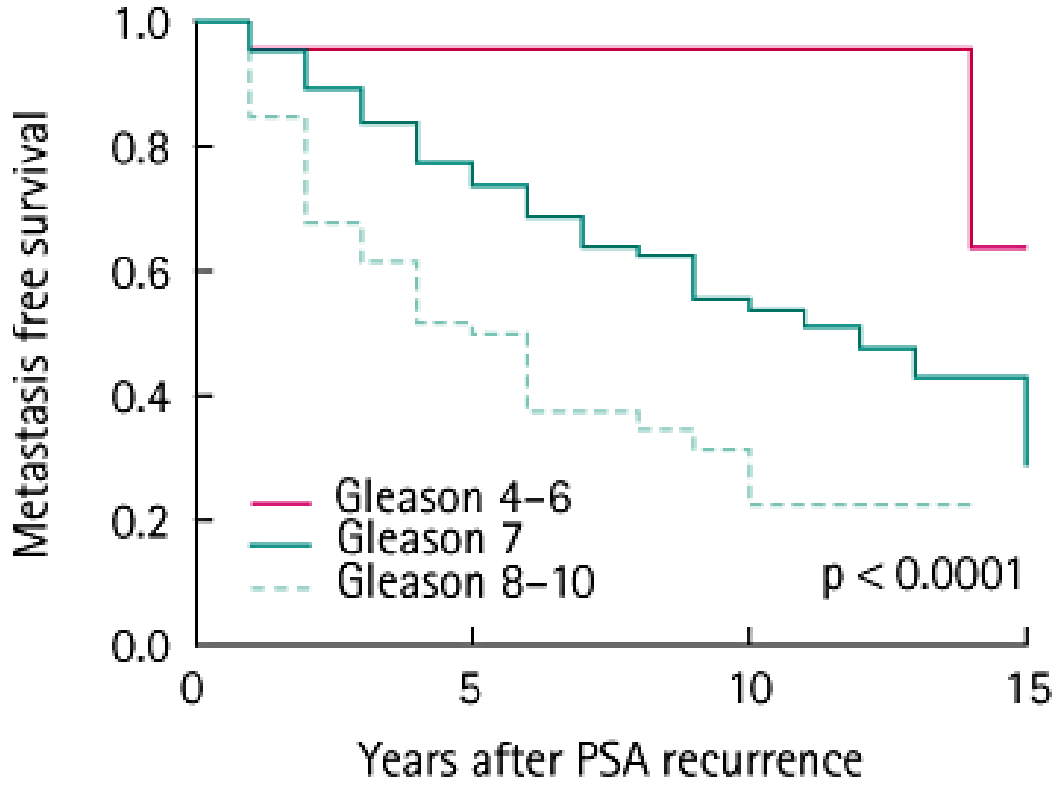


Number at risk

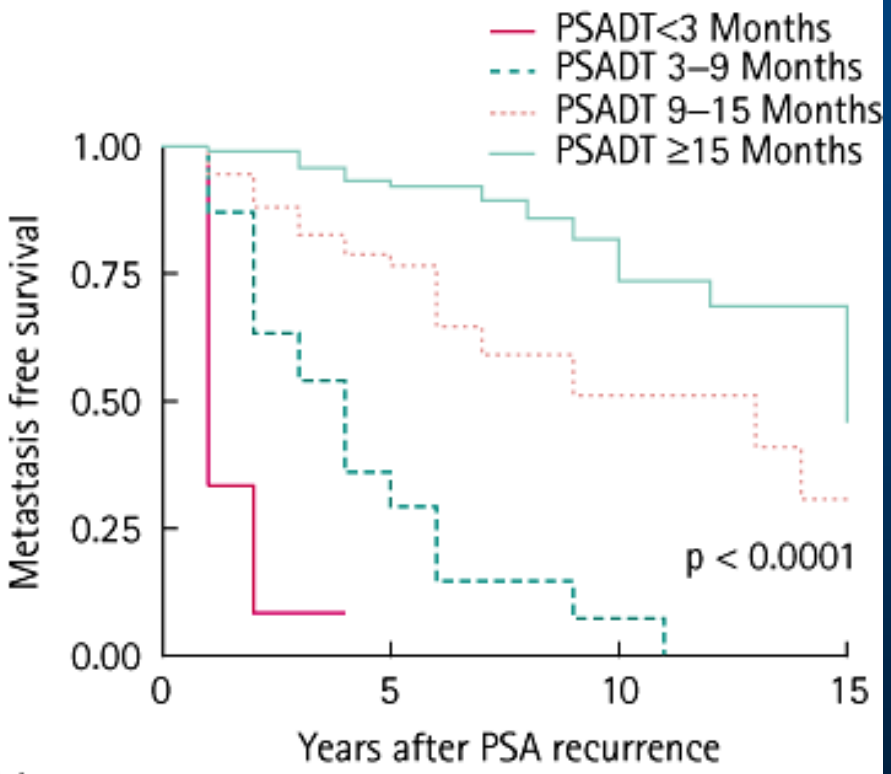
Gleason score 4–6	88	26	6	1
Gleason score 7	239	85	29	3
Gleason score 8–10	123	28	7	0

Median MFS Years

Gleason 4–6	>15
Gleason 7	11
Gleason 8–10	4

Antonarakis ES et al: BJU Int 2011 doi:10.1111/j.1464-410X.2011.10422.x.

Metastasis Free Survival in Untreated Biochemical Recurrence after RP



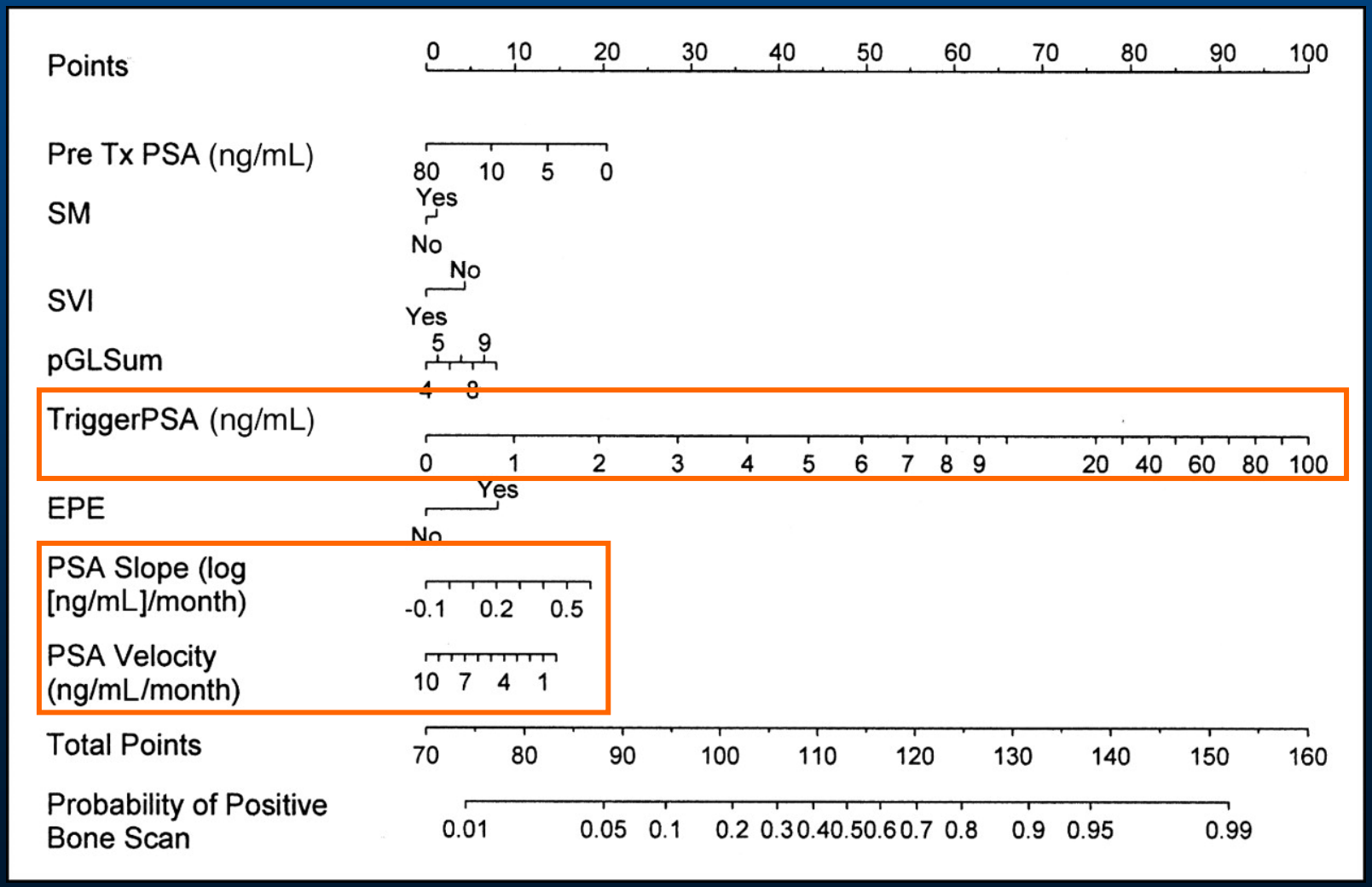
Number at risk

PSADT <3 Month	46	0	0	0
PSADT 3–9 Month	106	16	2	0
PSADT 9–15 Month	86	37	11	1
PSADT ≥15 Month	212	86	30	3

	Median MFS Years
PSADT<3 Months	1
PSADT 3–9 Months	4
PSADT 9–15 Months	13
PSADT ≥15 Months	15

Antonarakis ES et al: BJU Int 2011 doi:10.1111/j.1464-410X.2011.10422.x.

Probability of Positive Bone Scan in ADT-Naïve Men with Biochemical Recurrence after RP



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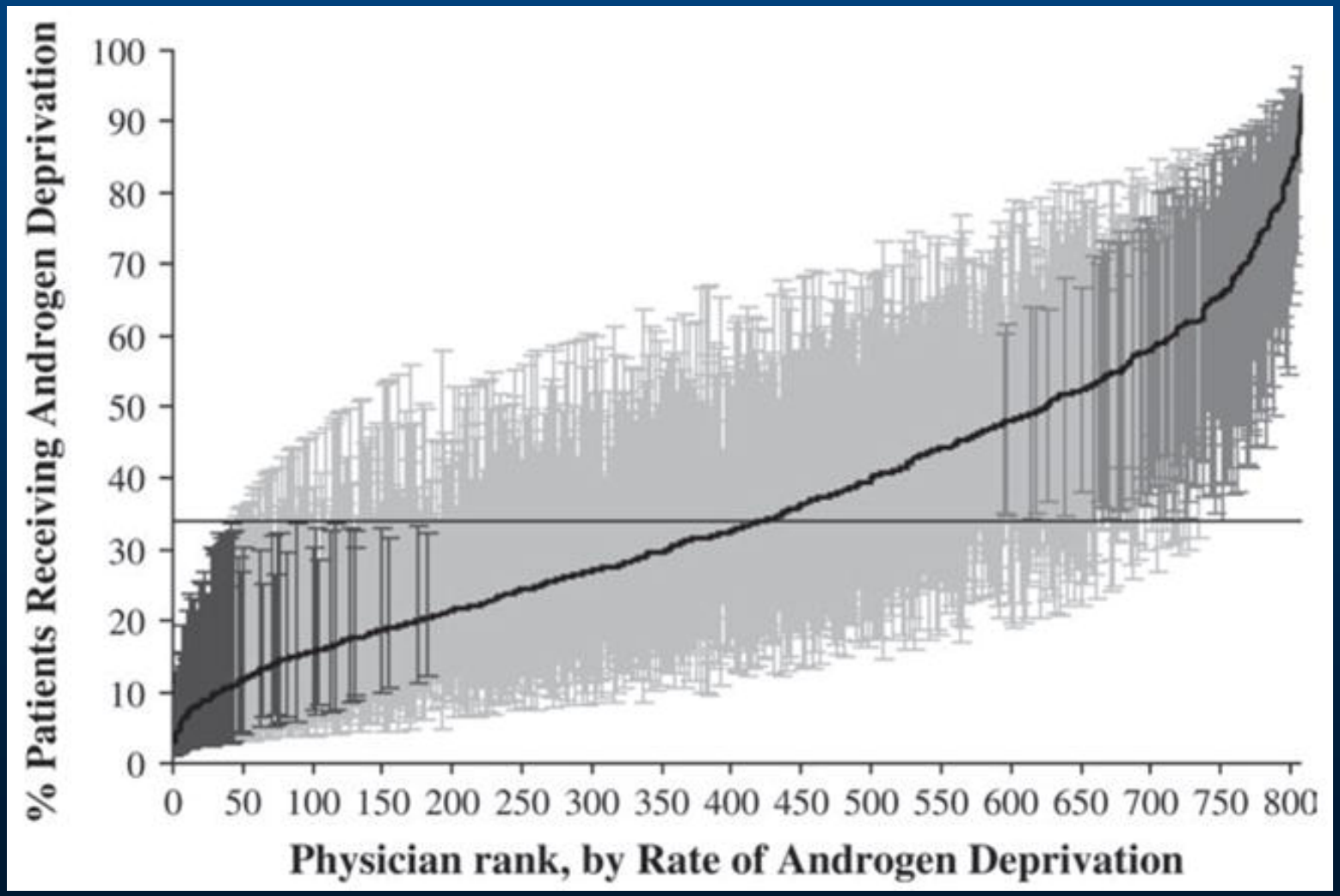
Dotan Z A et al. JCO 2005;23:1962-1968

Heterogeneous Use of ADT for PCa

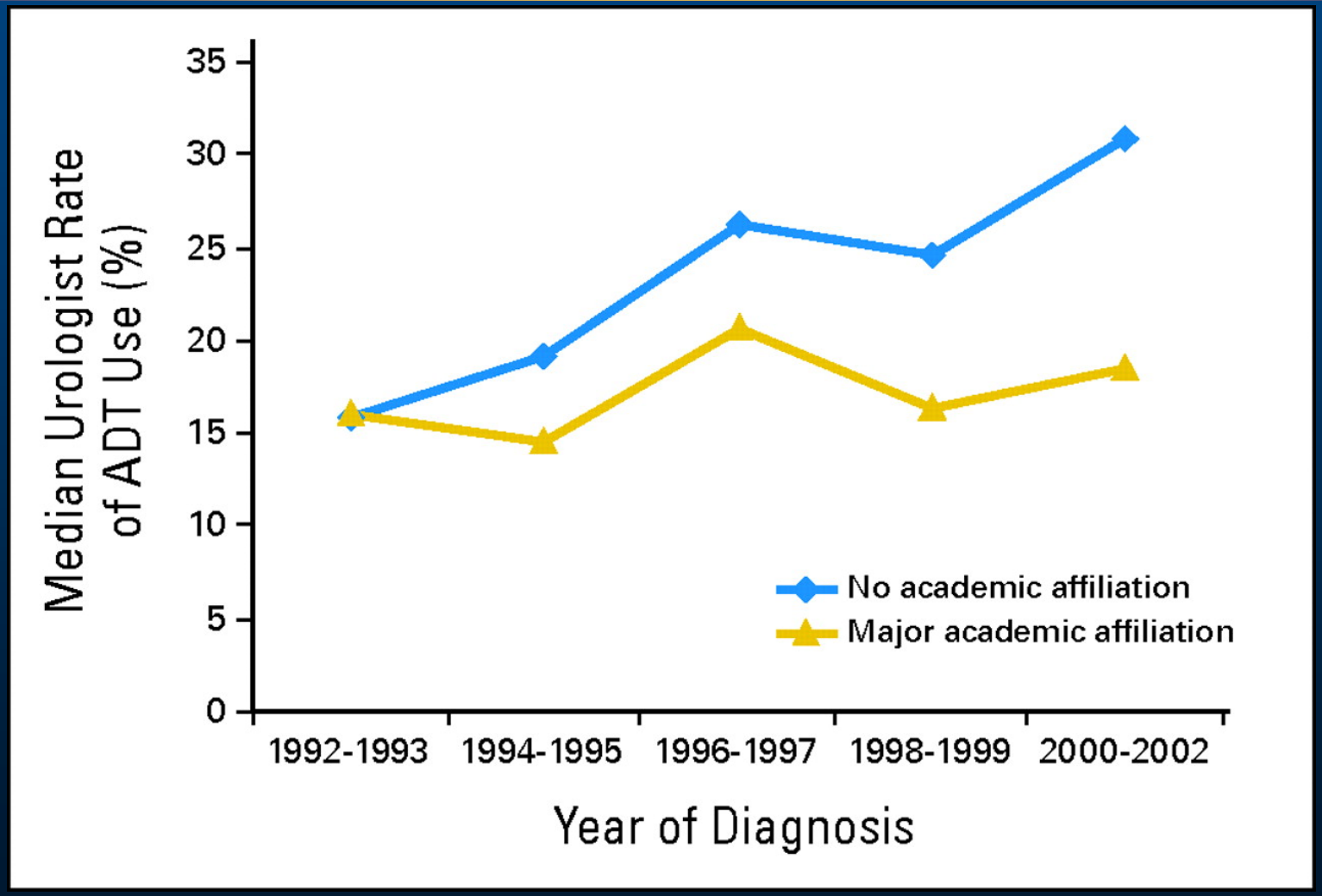
- Inappropriate use
  - Primary use in low grade, localized disease
    - No evidence of efficacy in clinical trials
- Appropriate use
  - In combination with RT for locally advanced and/or high grade disease
  - Node positive disease with RP
  - Distant metastases
  - High-risk biochemical recurrence?
    - Short PSADT

Variability in Uncertain-Benefit Use of Androgen Deprivation



Sharinian VB et al: JNCI 98:839-45, 2006

Uncertain-Benefit Use of Androgen Deprivation by Urologist Characteristics



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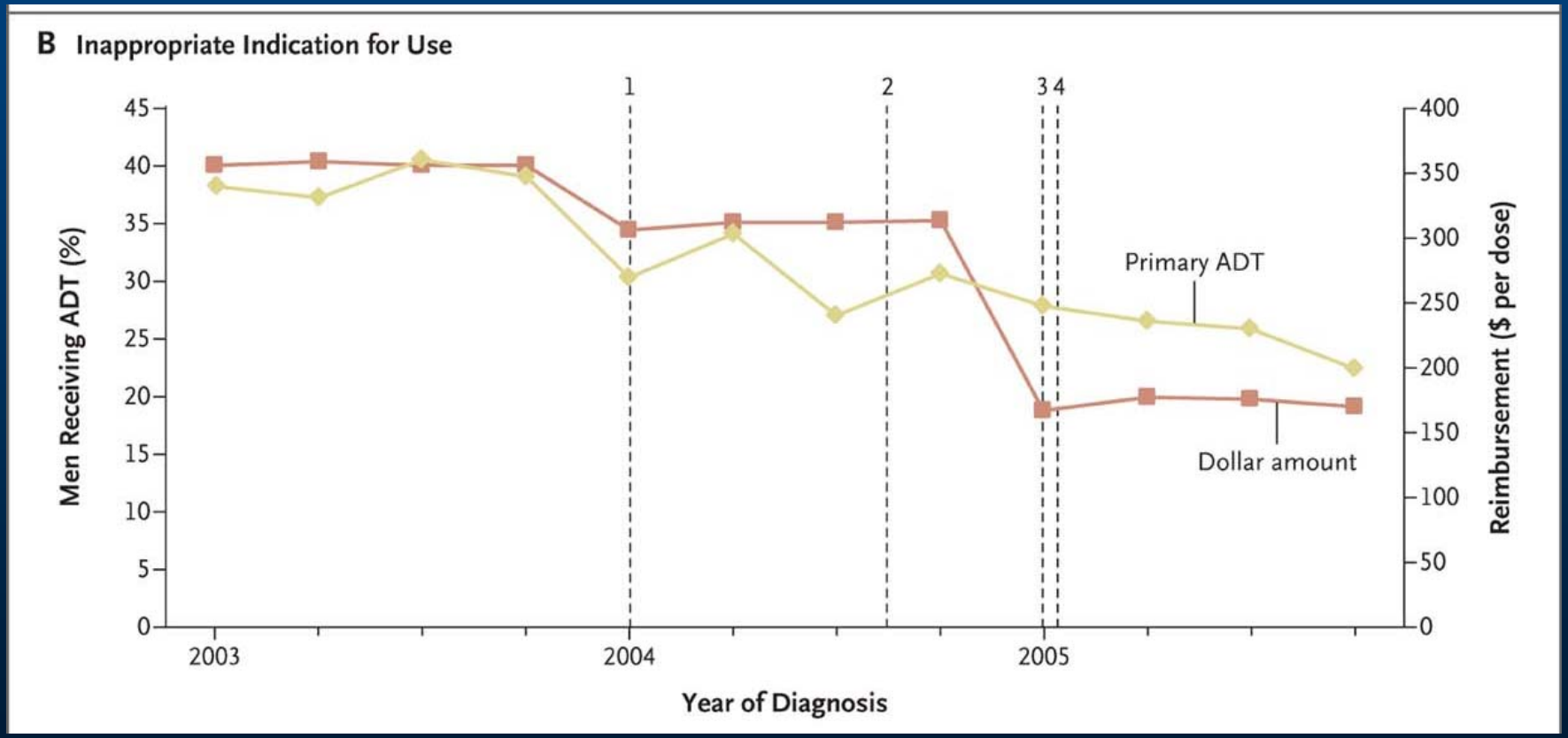
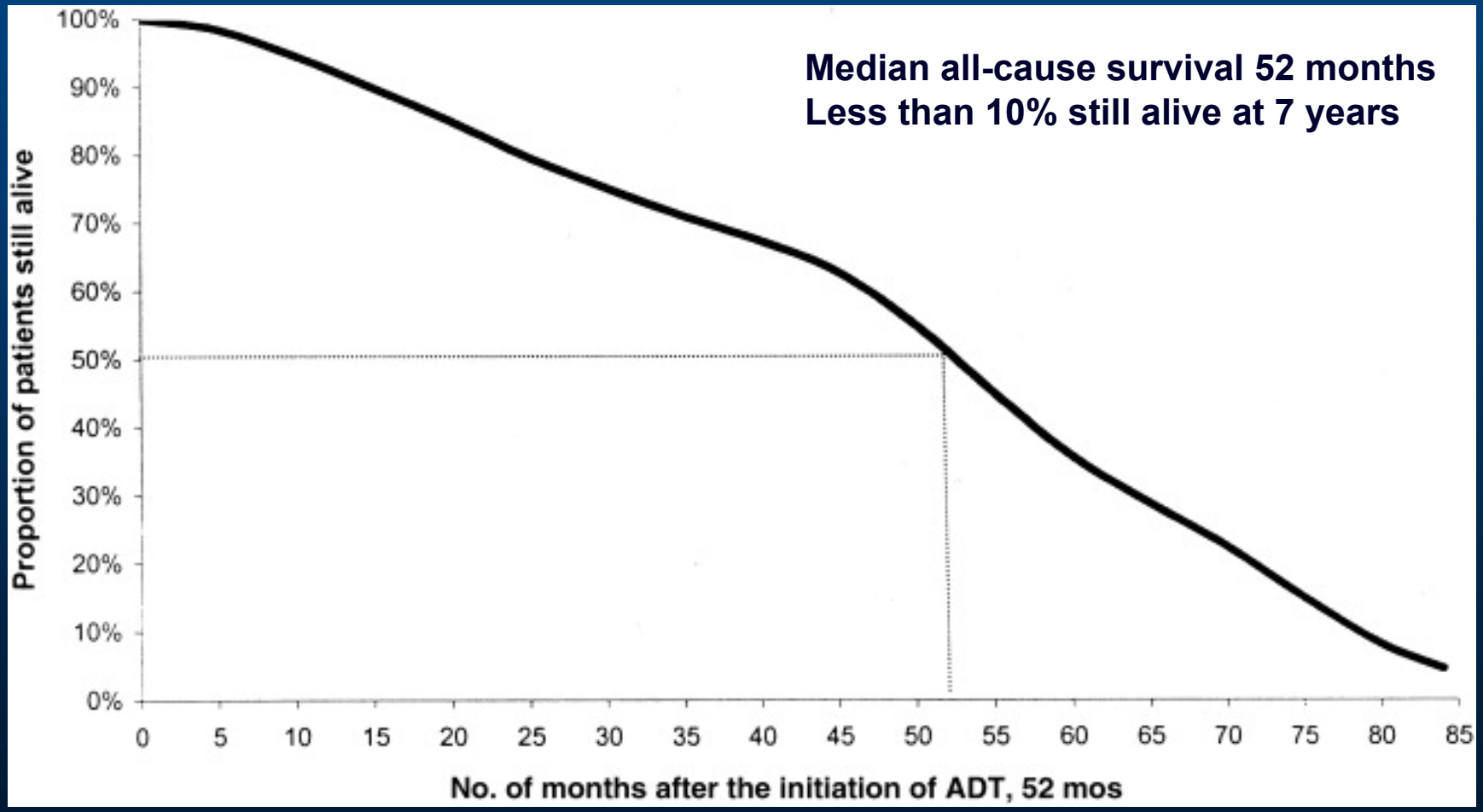
Shahinian V B et al. JCO 2007;25:5359-5365

Use of Inappropriate ADT within 6 months of Diagnosis by Reimbursement



Shahinian VB et al. N Engl J Med 2010;363:1822-1832

Inevitability of Death after Initiating ADT



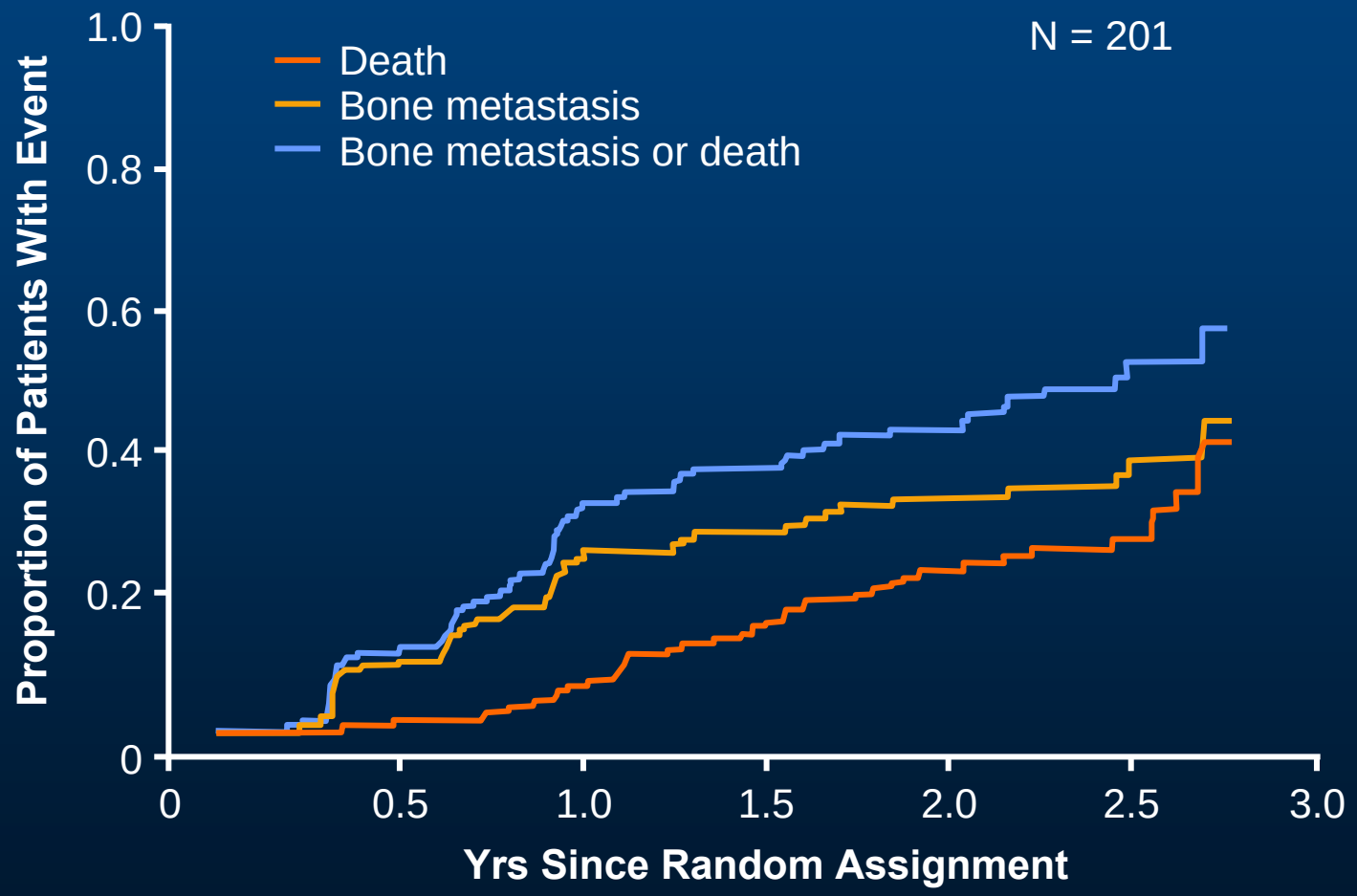
Krupski TL, et al: Cancer 101:541-549, 2004

Challenges of Clinical Trials in M0 Disease

- Long natural history of CRPC M0 to M+
  - Analysis of 201 patients with non-metastatic prostate cancer and rising PSA despite ADT
  - At 2 yrs, only 33% had developed bone metastases
  - Median time to first bone metastasis not reached by 30 mos

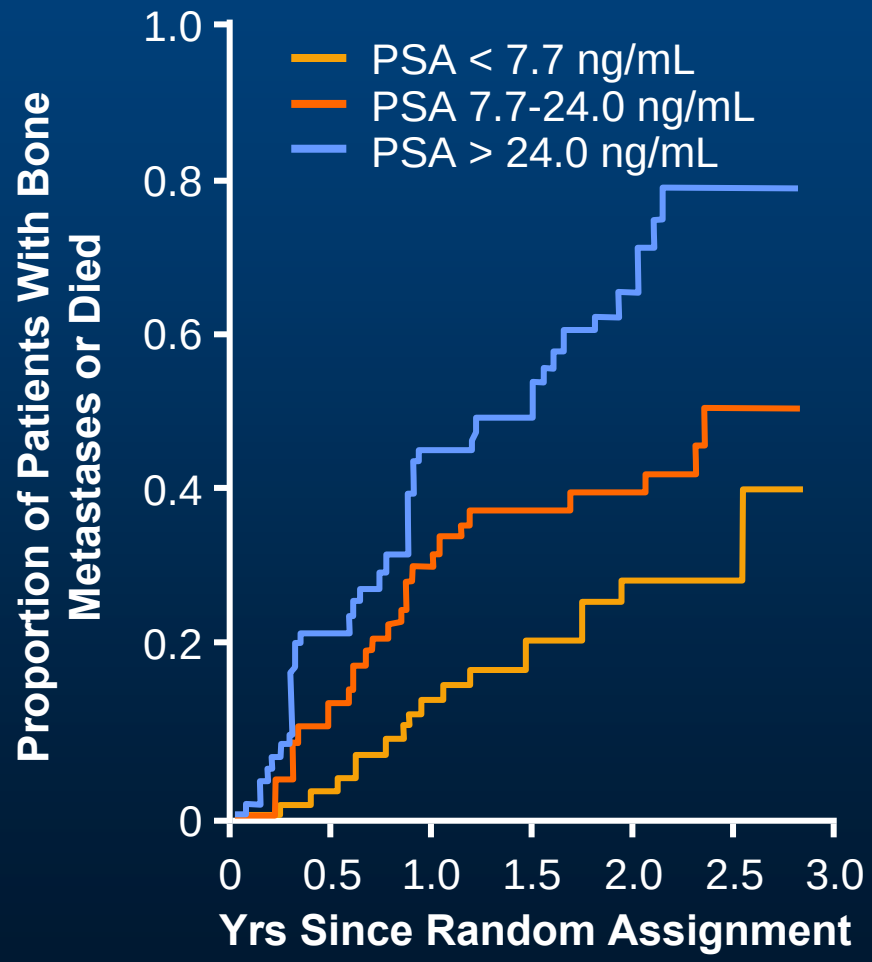
Smith MR, et al. J Clin Oncol. 2005;72:2918-2925.

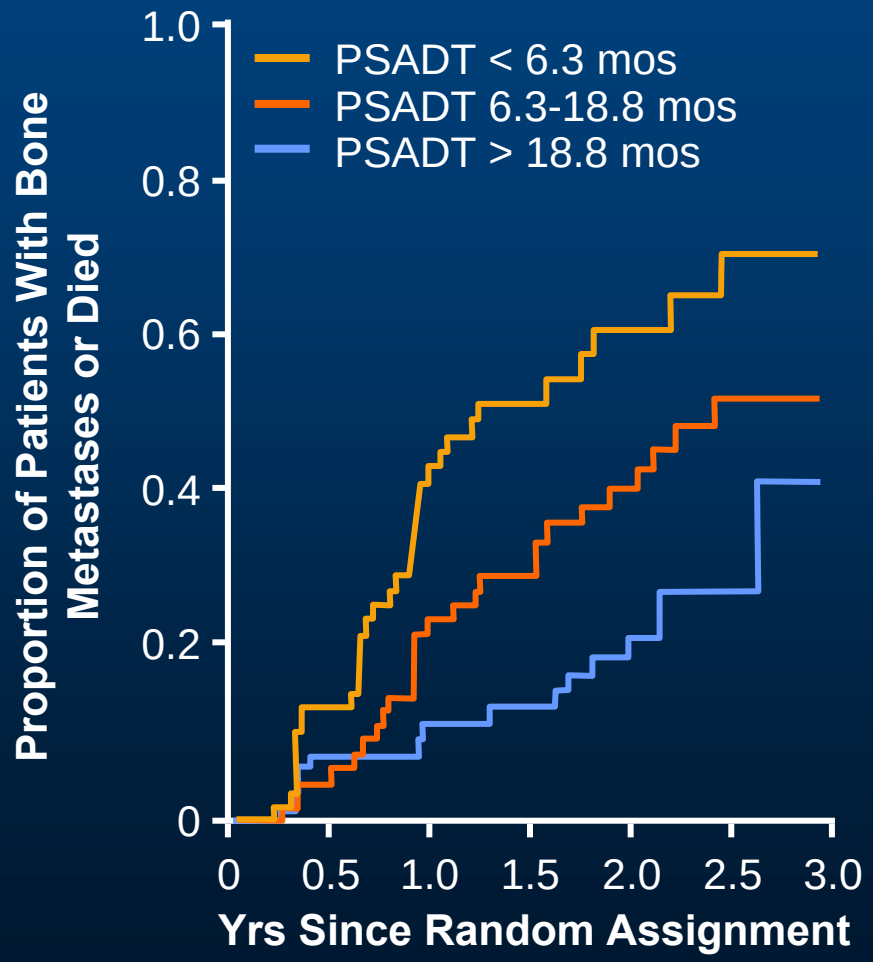
Time to Bone Metastasis and/or Death in Nonmetastatic HRPC



Smith MR, et al. J Clin Oncol. 2005;72:2918-2925.

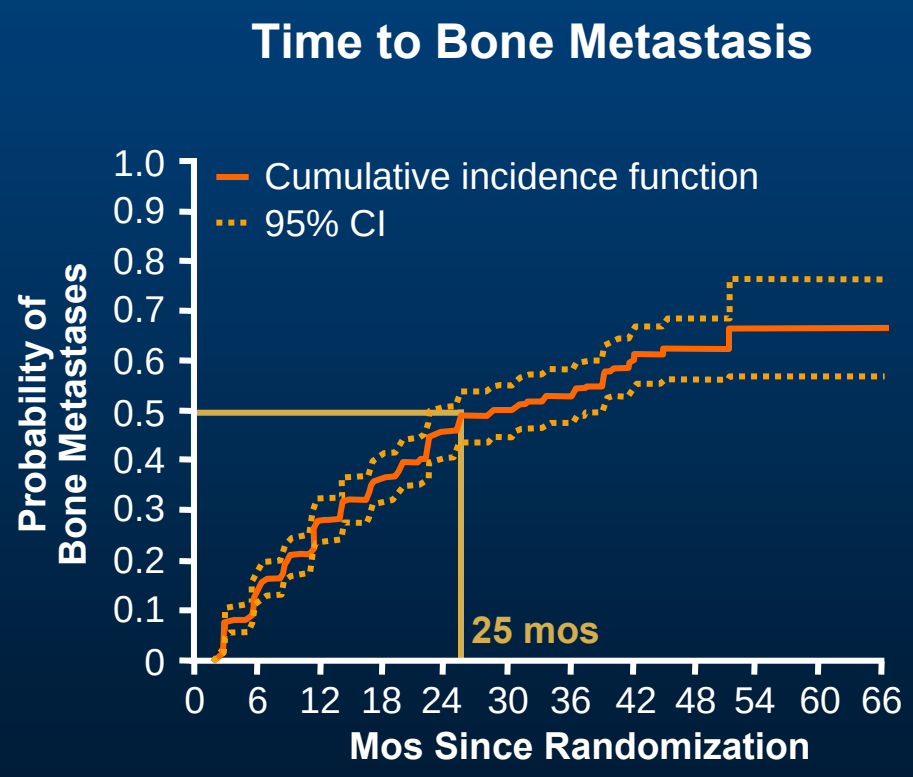
PSA Level and Doubling Time Define Shift From M0 to M+ in CRPC

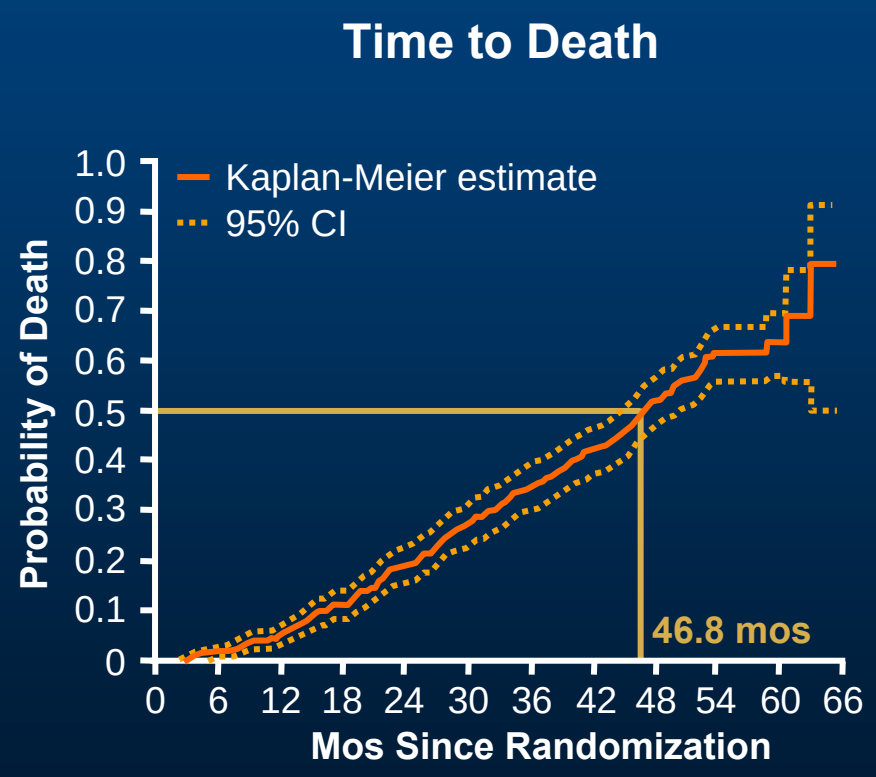




Smith MR, et al. J Clin Oncol. 2005;72:2918-2925.

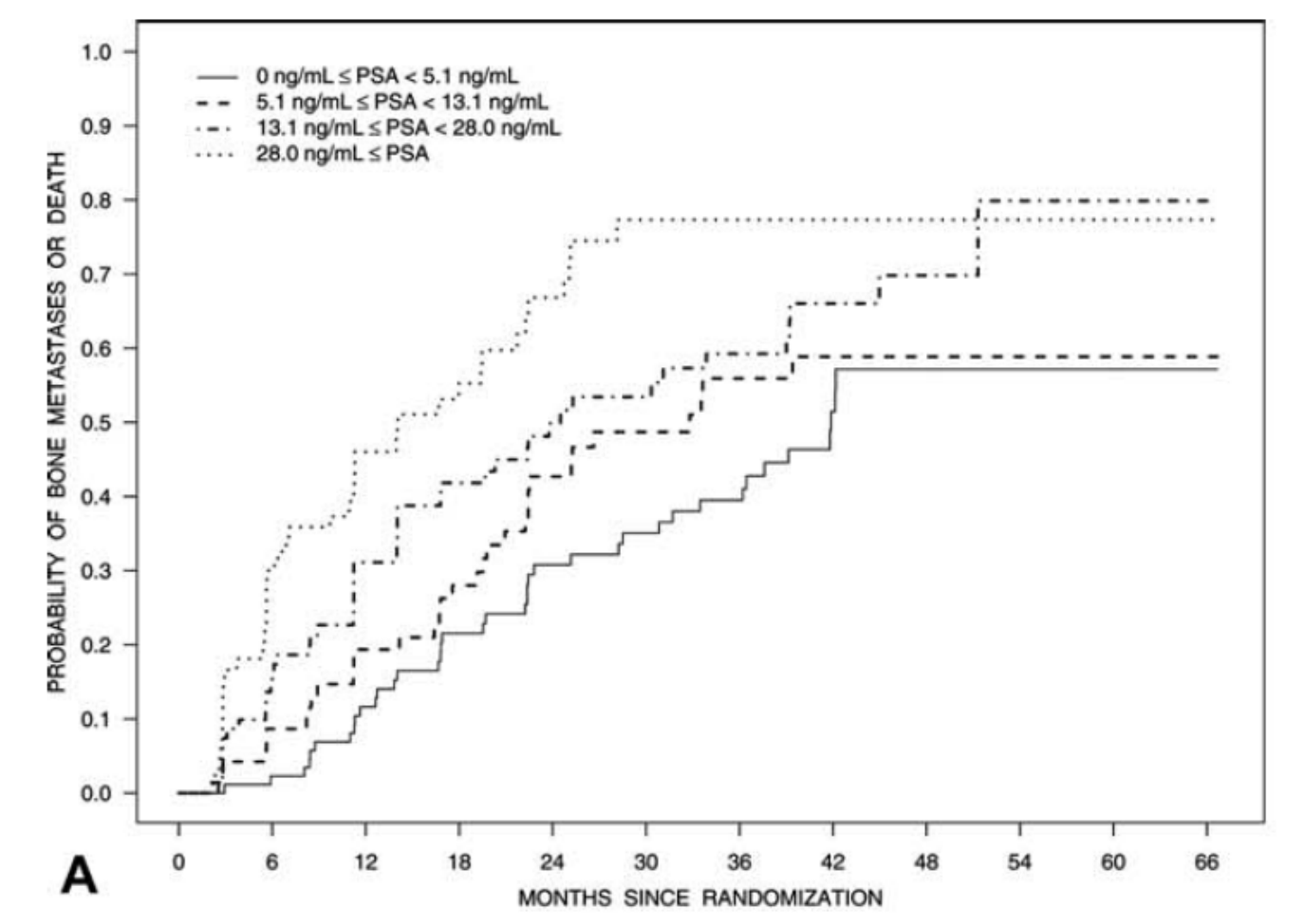
Time of M0 to M1 and Death in Progressive, Non-metastatic CRPC





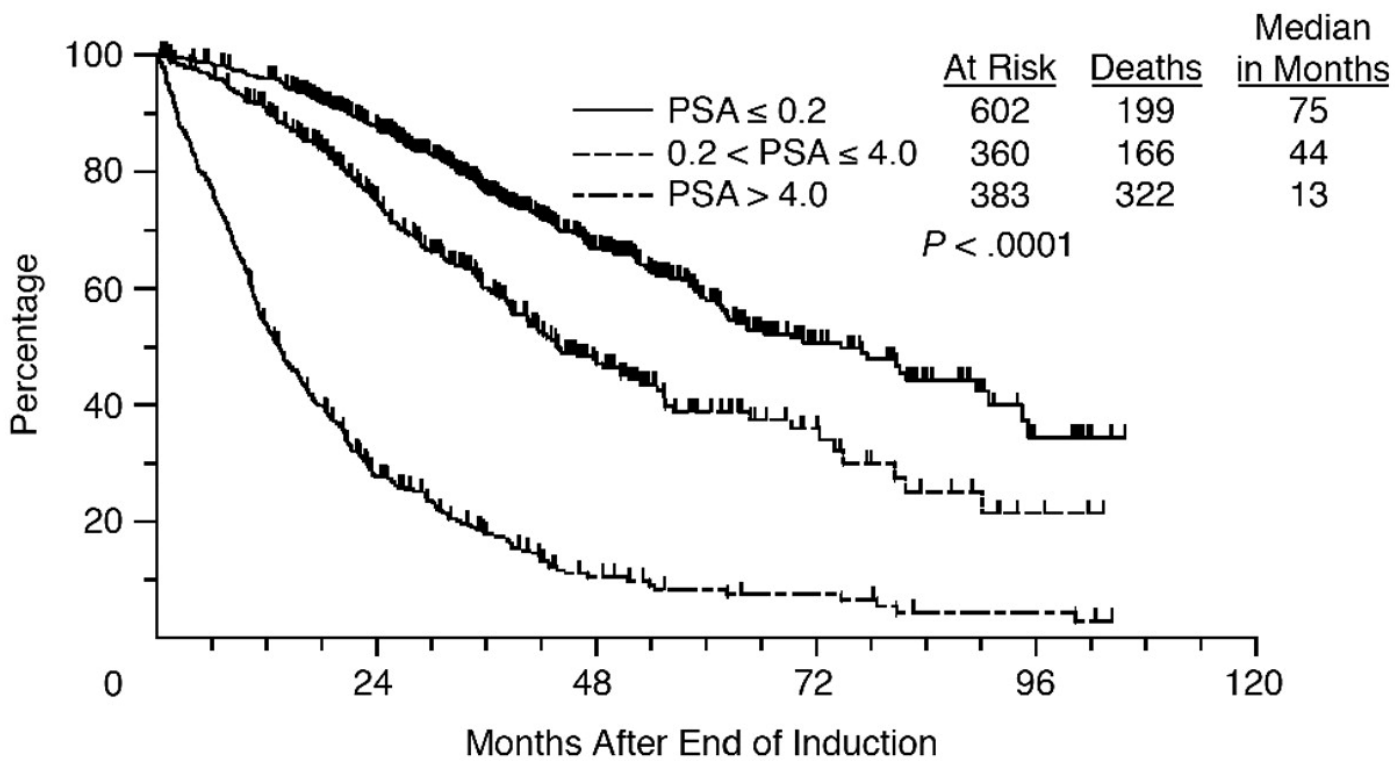
Smith MR, et al. Cancer. 2010;117:2077-2085

Time of M0 to M1 and Death in Progressive, Nonmetastatic CRPC by PSA



Smith MR, et al. Cancer. 2010;117:2077-2085

M+:PSA Response to Initial ADT Predicts OS

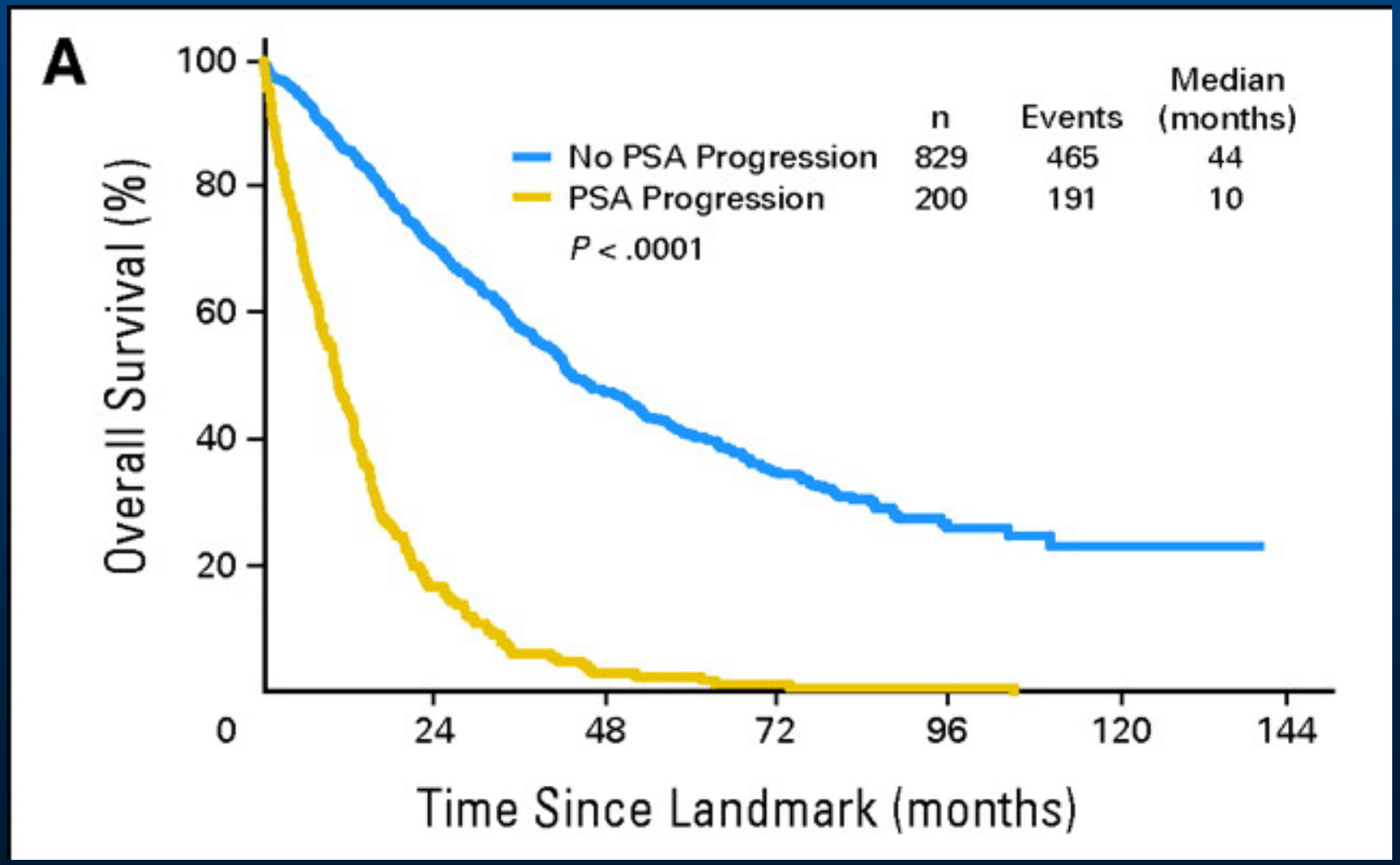


At risk:

PSA ≤ 0.2 ng/mL	453	210	63
0.2 < PSA ≤ 4.0	219	77	20
PSA > 4.0	92	17	7

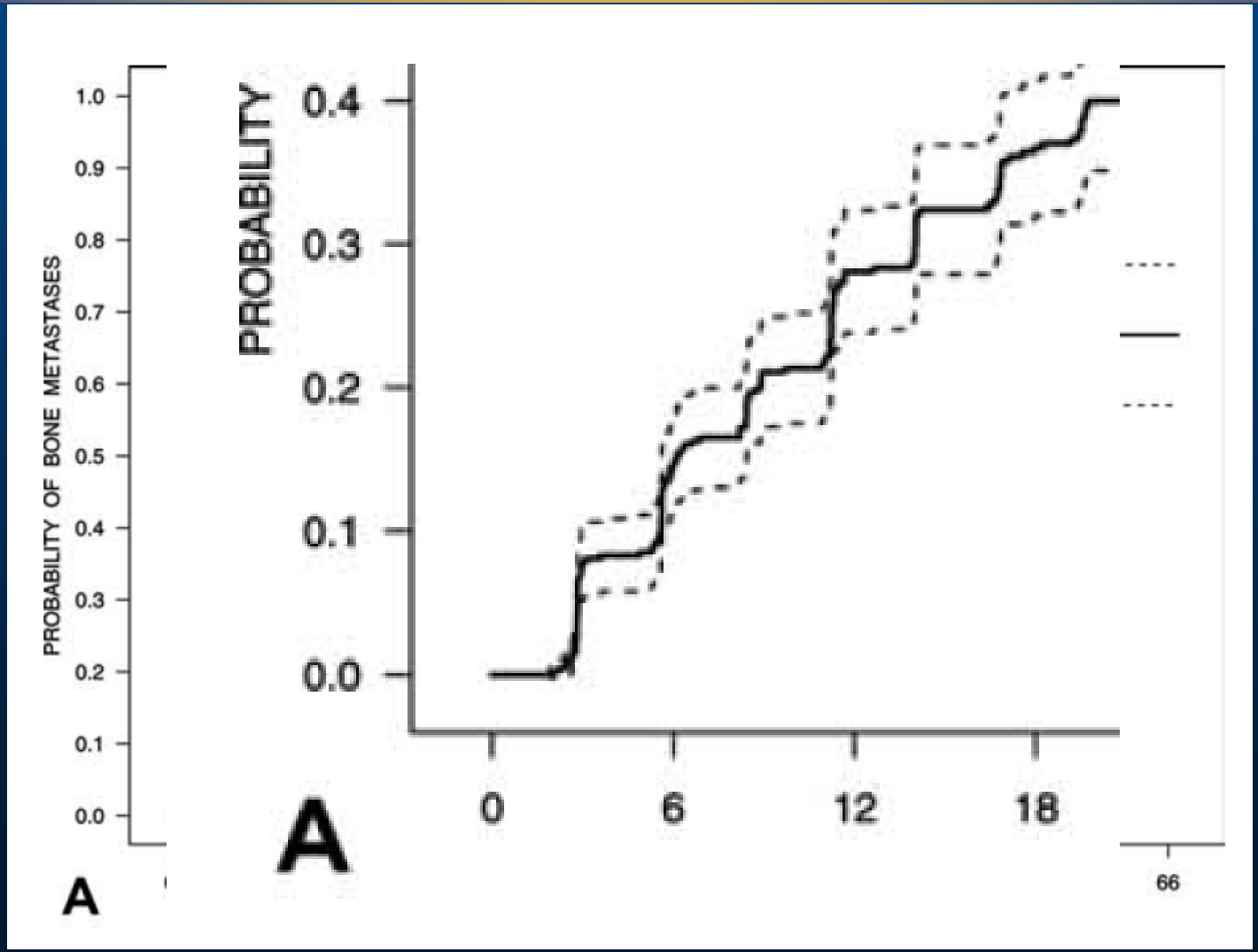
Hussain M et al. JCO 2006;24:3984-3990

M+: PSA Progression (≥25% increase and ≥ 2 ng/ml) after Initiating ADT Predicts OS



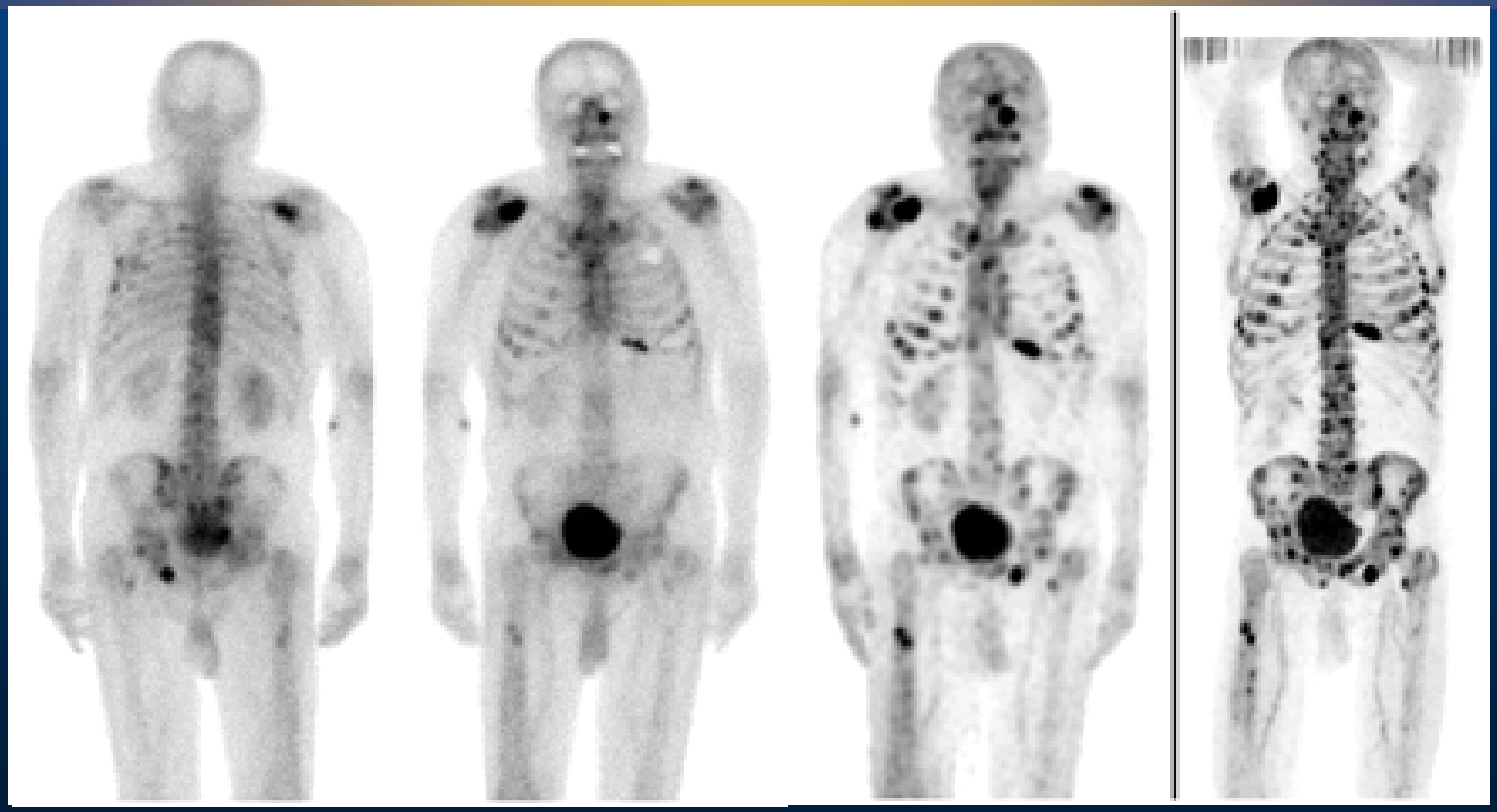
Hussain M et al. JCO 2009;27:2450-2456

The Challenge of Detecting Bone Metastases



Smith MR, et al. Cancer. 2010;117:2077-2085

Improving Detection of Bone Metastases

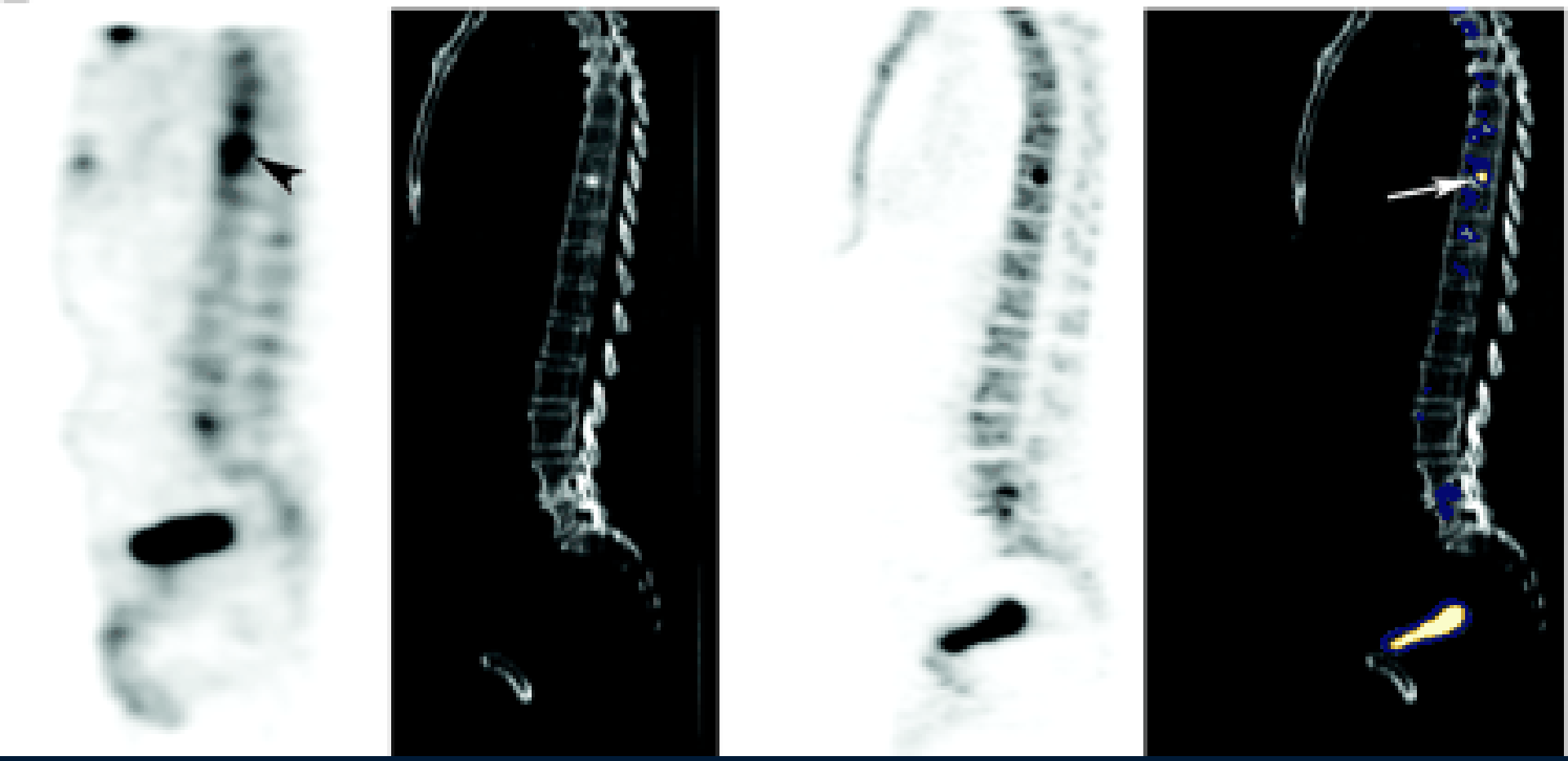


Posterior Anterior

^{99m}Tc-MDP Planar Bone Scan Multi-FOV SPECT ^{18}F-Fluoride PET

Grant FD, et al: J Nucl Med 49:68-78, 2008

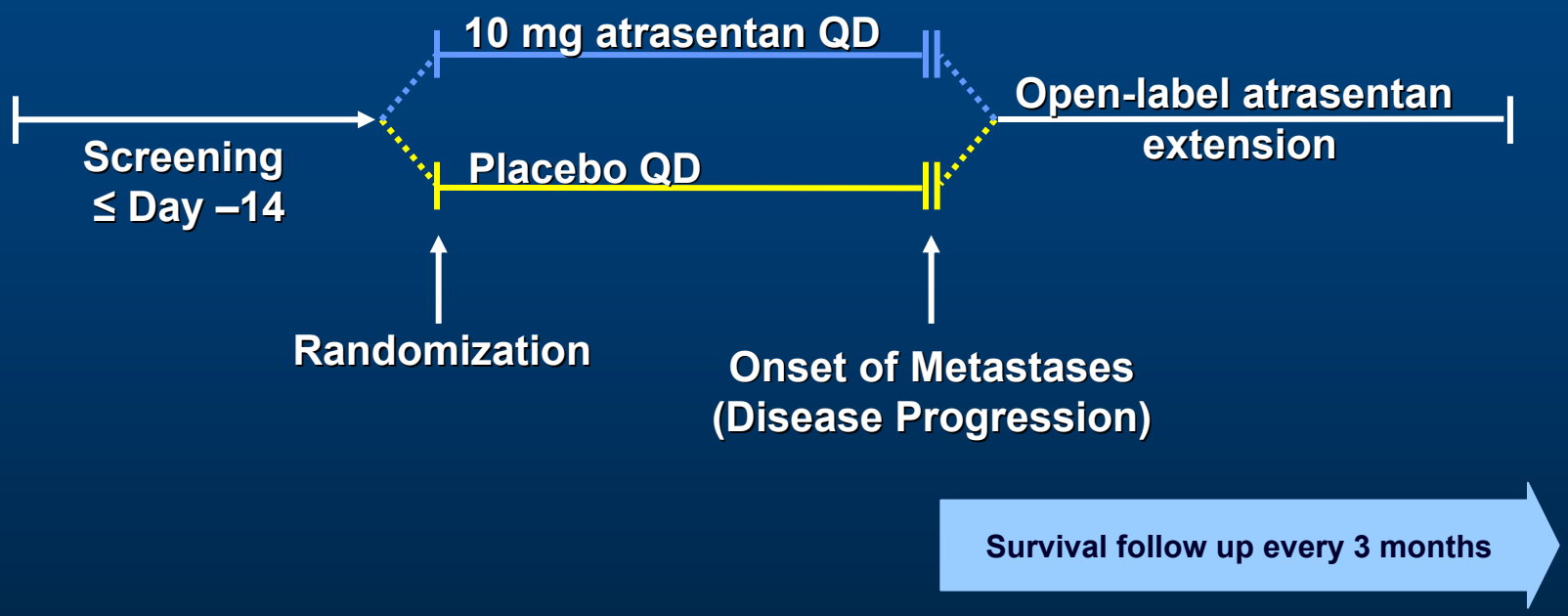
Improving Detection of Bone Metastases



SPECT | CT | ^{18}F-Fluoride PET | Fused PET/CT

Even-Sapir E, et al; J Nucl Med 47:287-97, 2006

Phase 3 Study: Atrasentan to Delay Disease Progression in M0

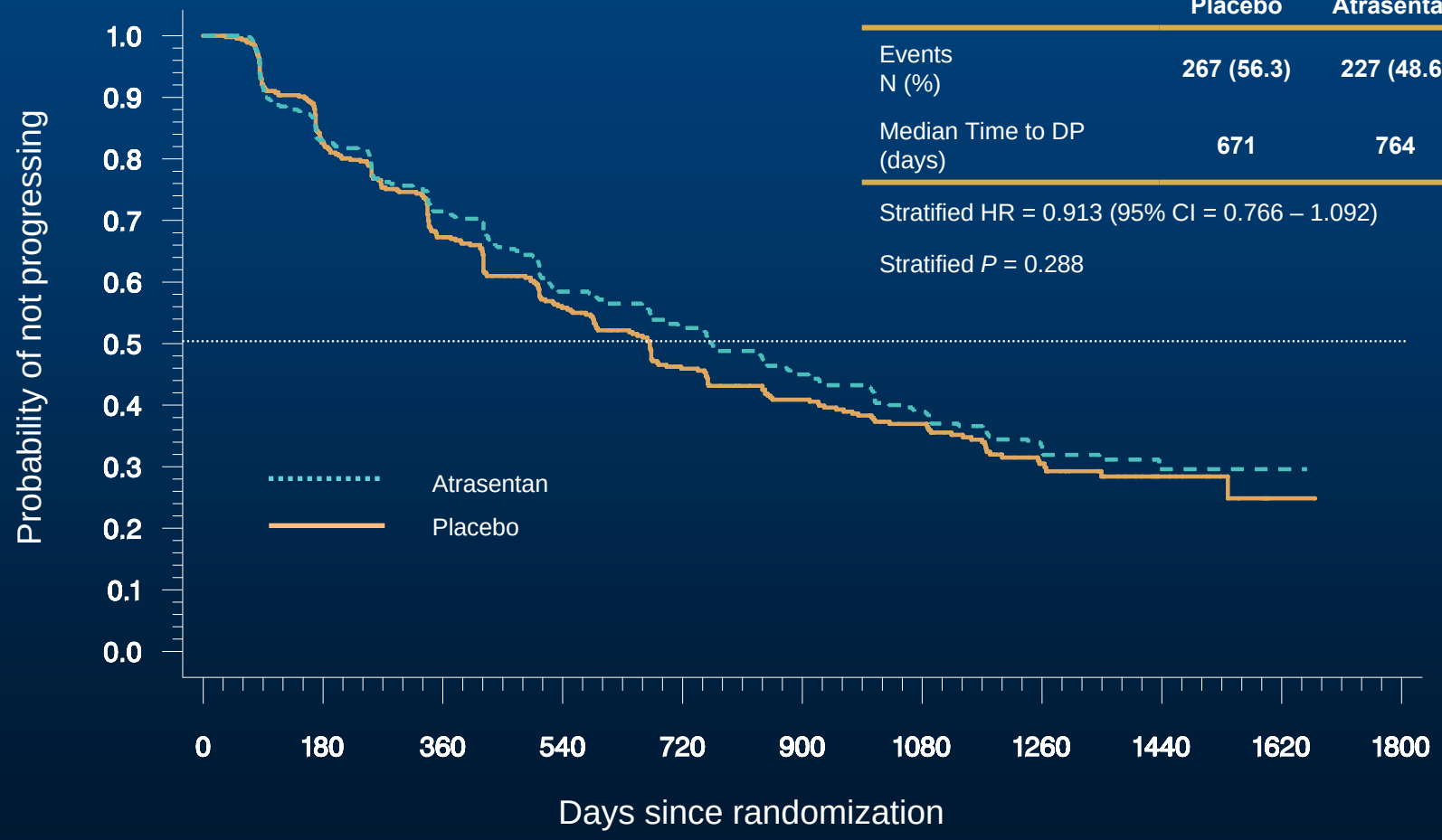


- 941 patients with non-metastatic CRPC

Nelson JB, et al: Cancer 113:2478-87, 2008

Time to Disease Progression

M0: Atrasentan ITT



	Placebo	Atrasentan
Events N (%)	267 (56.3)	227 (48.6)
Median Time to DP (days)	671	764

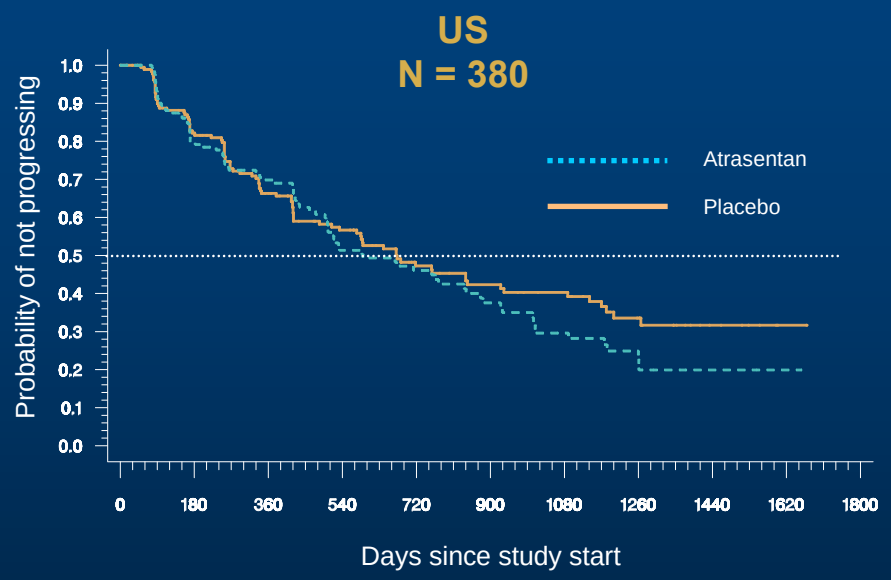
Stratified HR = 0.913 (95% CI = 0.766 – 1.092)

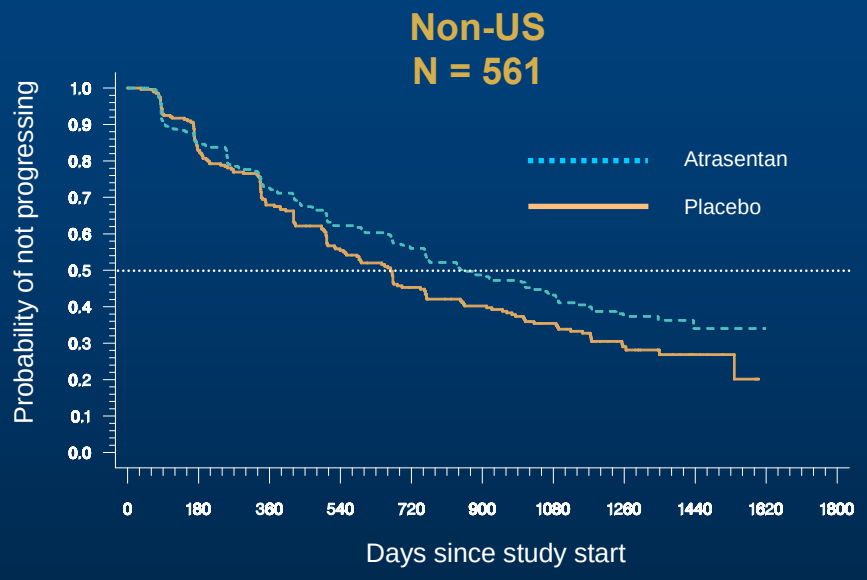
Stratified *P* = 0.288

Nelson JB, et al: Cancer 113:2478-87, 2008

Time to Disease Progression by Region

M0 Atrasentan ITT





US	Placebo	Atrasentan
Median Time to DP (days)	671	590

HR = 1.154 (95% CI = 0.862 – 1.545)

P = 0.177

P values are exploratory.

Non-US	Placebo	Atrasentan
Median Time to DP (days)	667	847

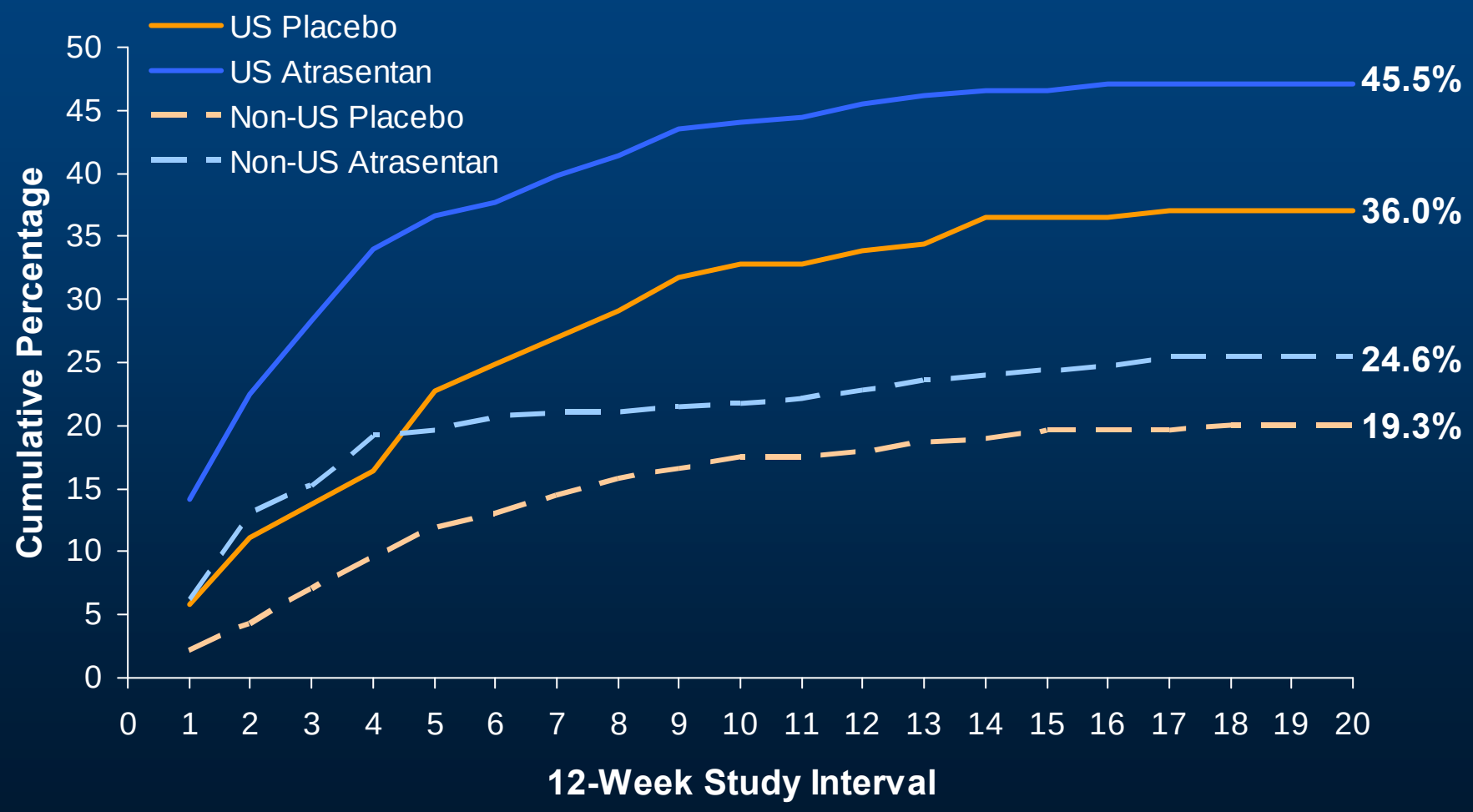
HR = 0.800 (95% CI = 0.639 – 1.000)

P = 0.021

Nelson JB, et al: Cancer 113:2478-87, 2008

Cumulative Discontinuations by Region

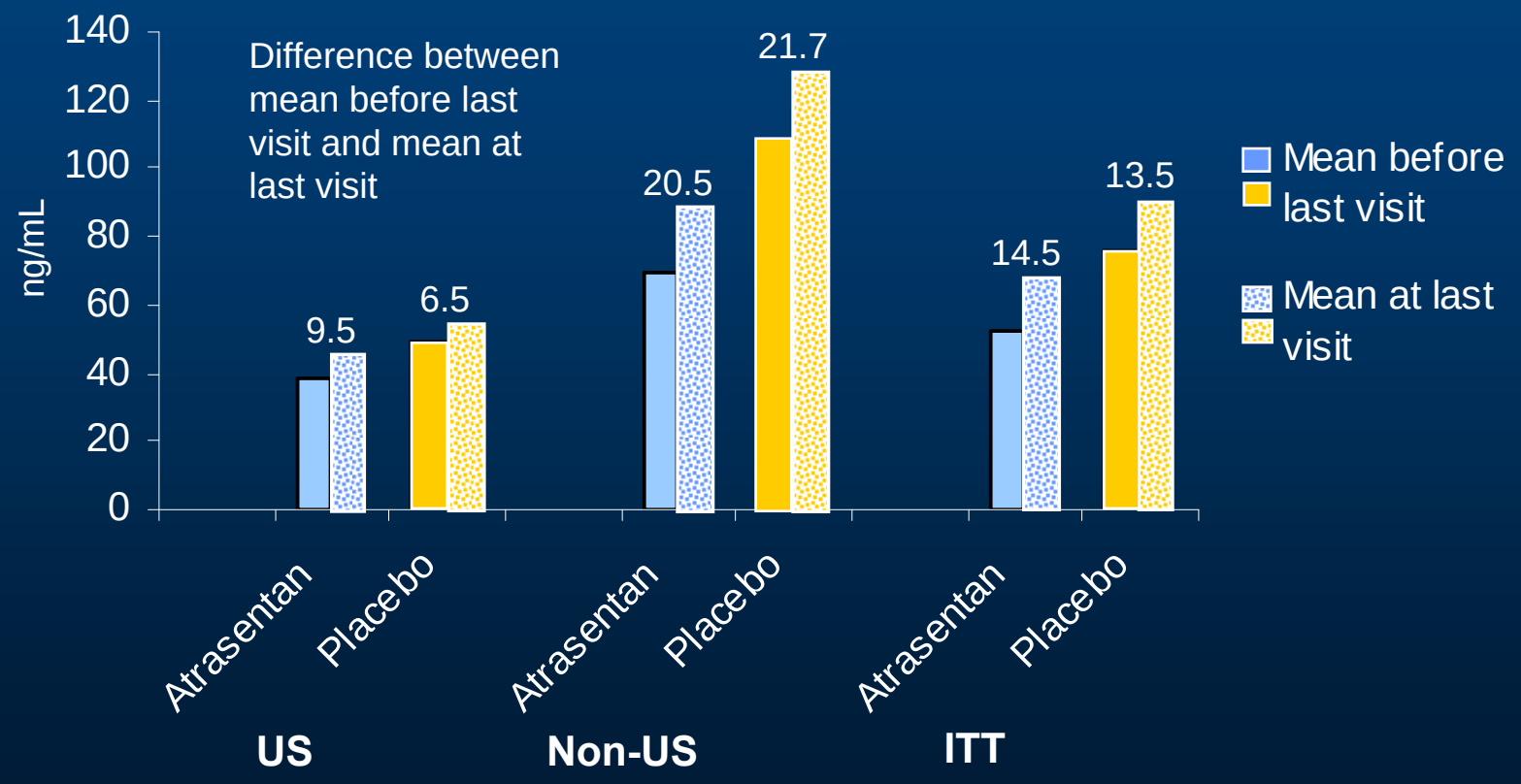
M0 Atrasentan ITT



Nelson JB, et al: Cancer 113:2478-87, 2008

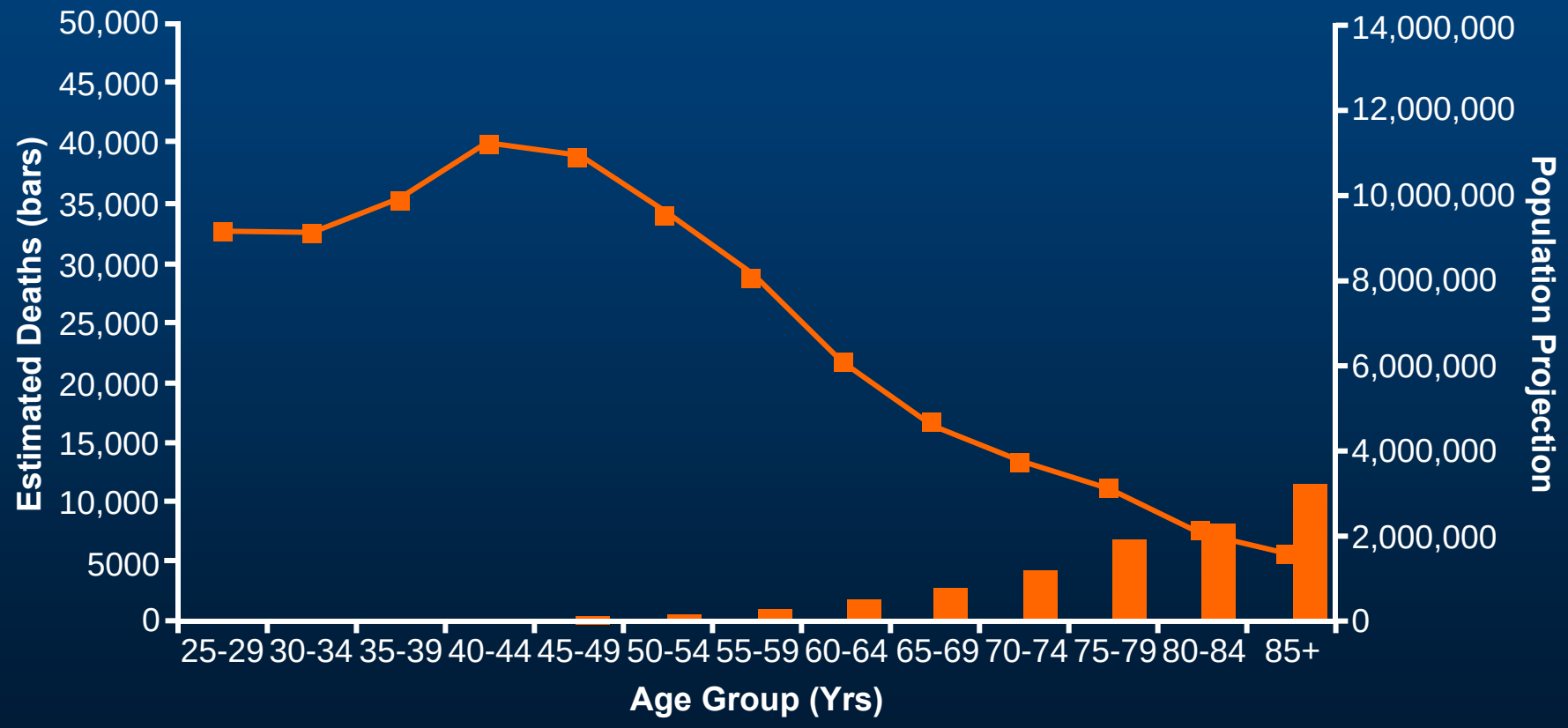
PSA Change in Patients Who Discontinued

M0 Atrasentan ITT



Nelson JB, et al: Cancer 113:2478-2487, 2008

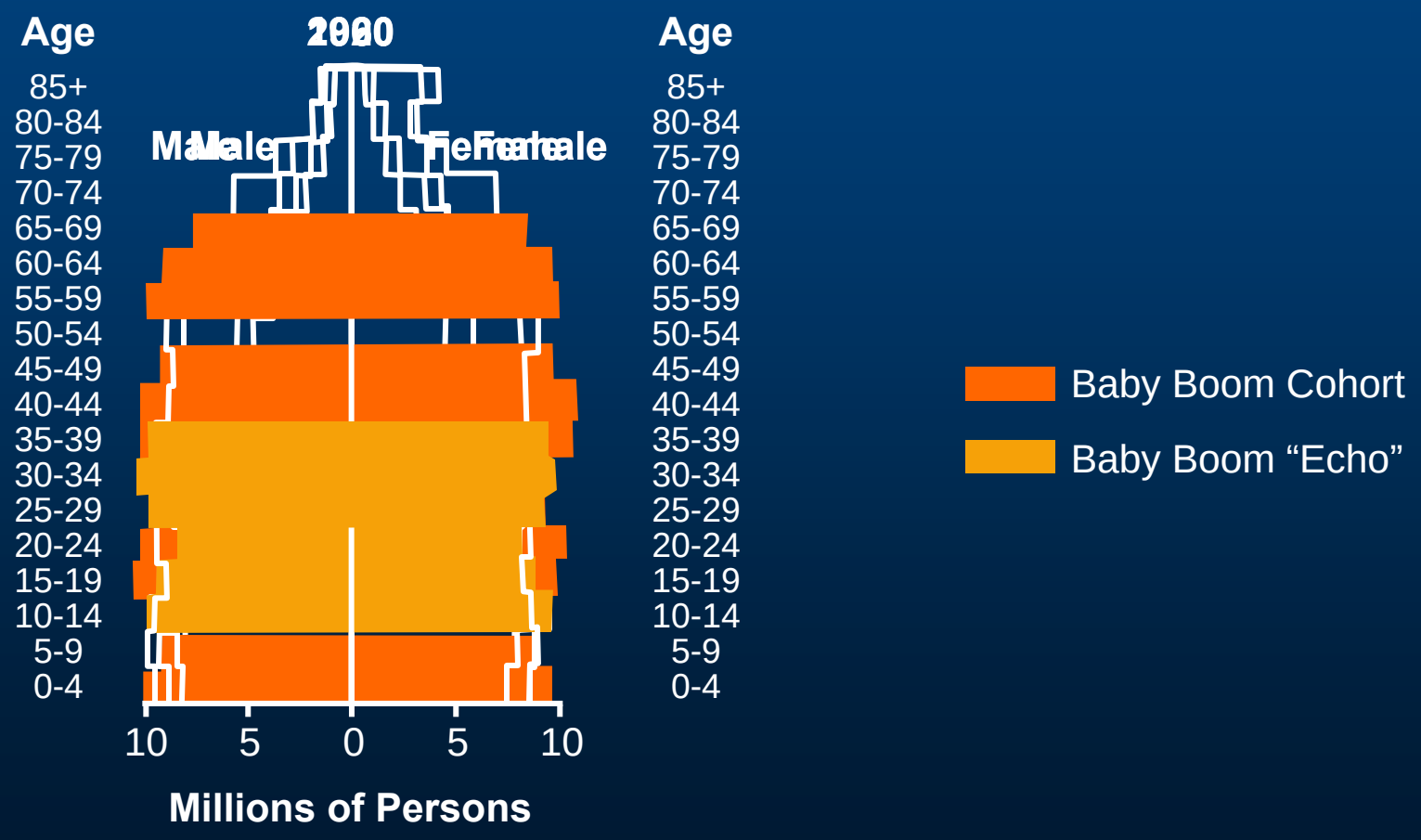
2005 Projected Male Population and Prostate Cancer Deaths



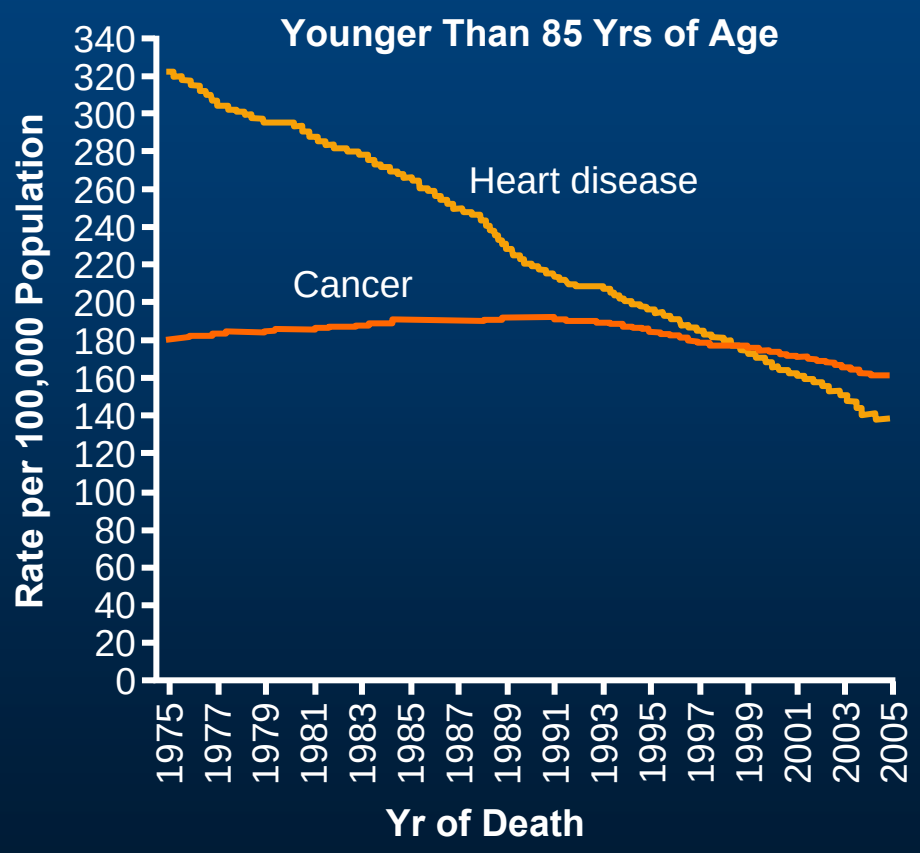
Chan JM, et al. J Urol. 2004;172:S13-S17.

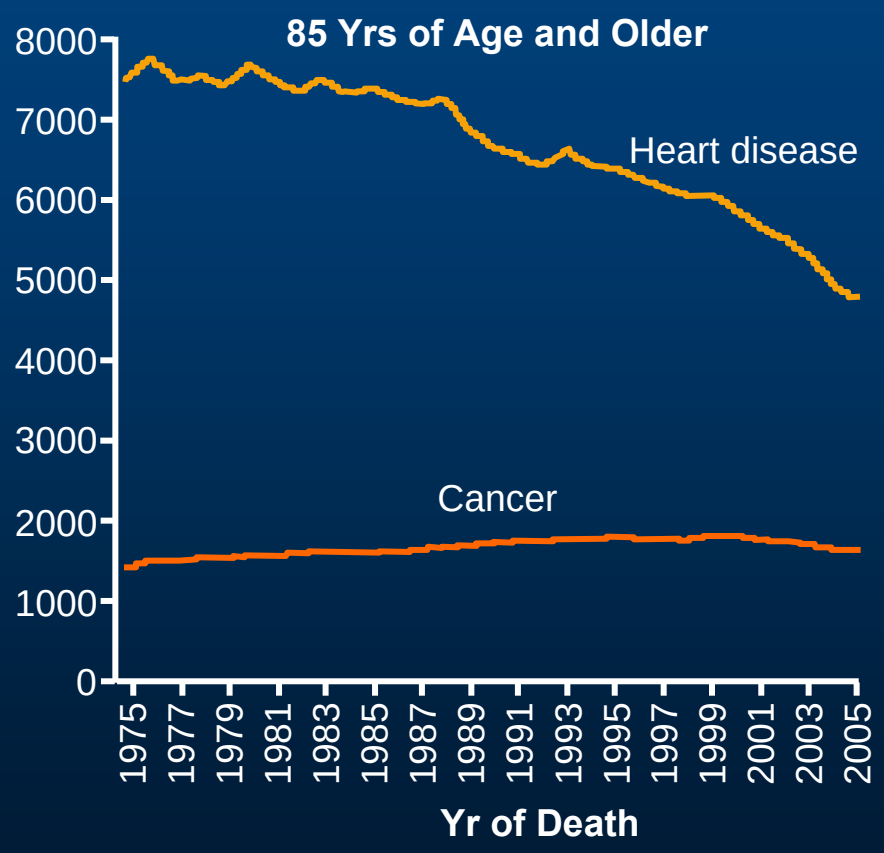
CHEMICAL BANK & TRUST

The Baby Boomers Are Aging



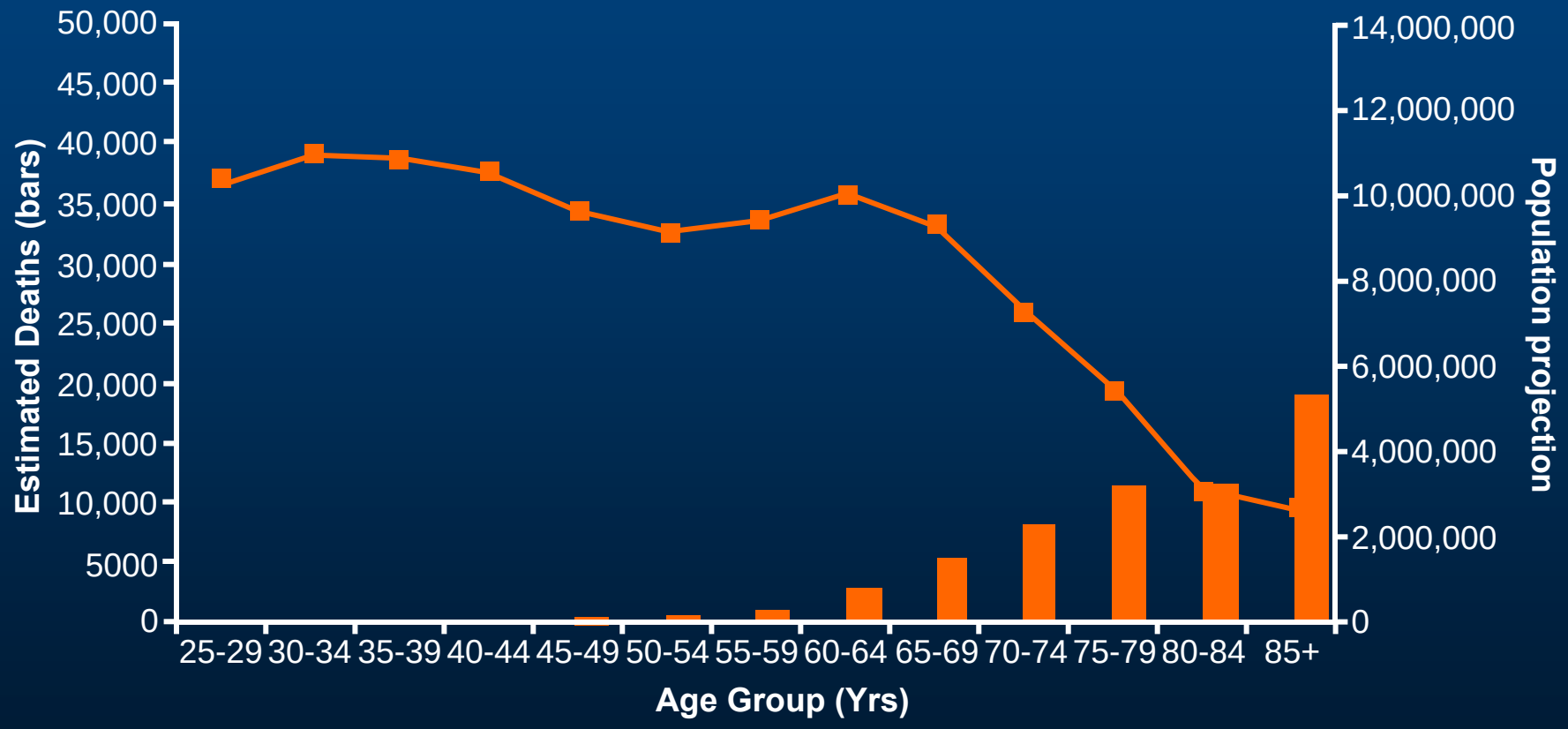
Death From Heart Disease Is Plummeting





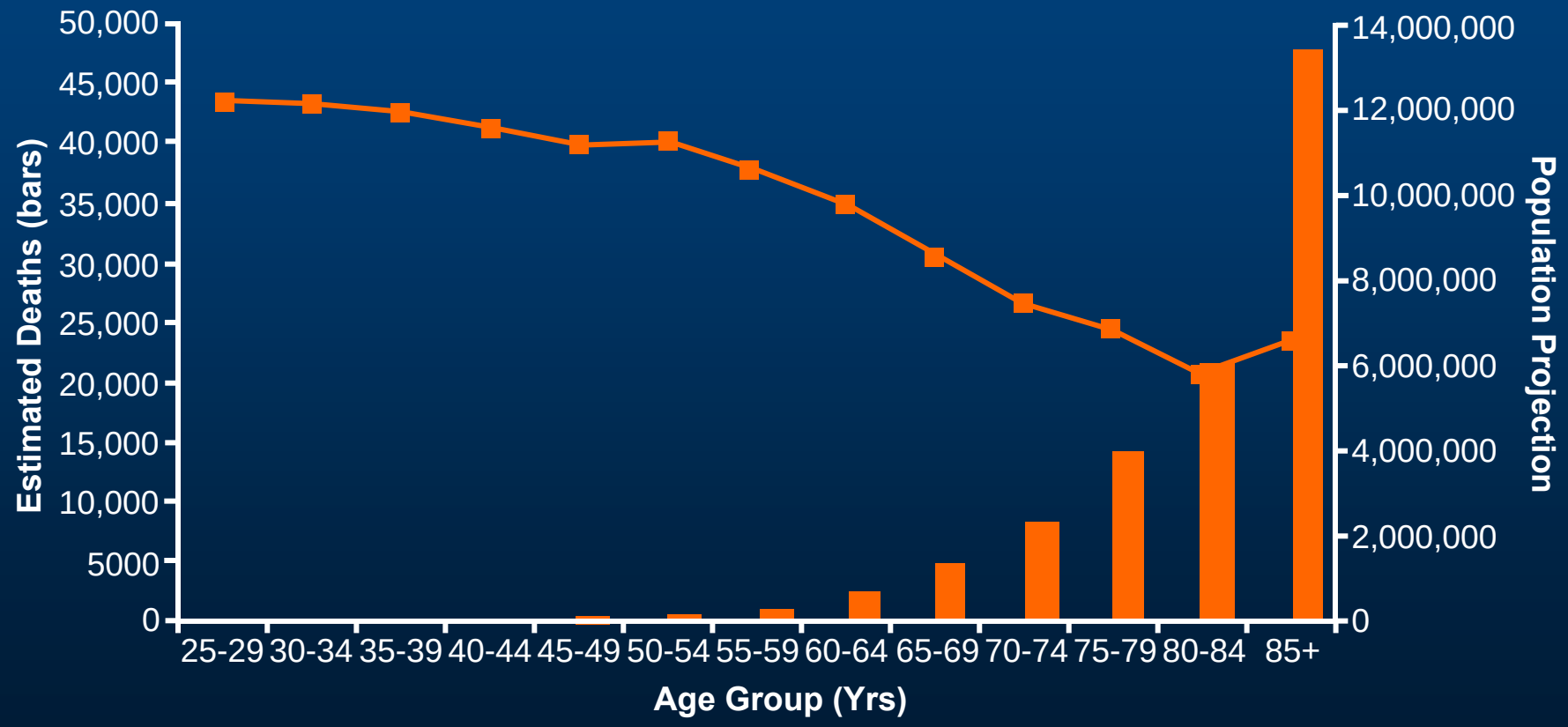
Jemal A, et al. CA Cancer J Clin. 2010;60:277-230.
National Center for Health Statistics, Centers for Disease Control and Prevention

2025 Projected Male Population and Prostate Cancer Deaths



Chan JM, et al. J Urol. 2004;172:S13-S17.

2045 Projected Male Population and Prostate Cancer Deaths



Chan JM, et al. J Urol. 2004;172:S13-S17.

Conclusions

- Clinical features of primary tumor predict biochemical recurrence
- PSA kinetics at recurrence predict metastases and death
- ADT use is often not evidence based
- Progression of non-metastatic CRPC is diverse
  - Challenges clinical trial design and patients
- CRPC will be an increasing clinical problem

Trials in the Non-Metastatic Rising PSA Castrate State: Realities of Implementation and Completion

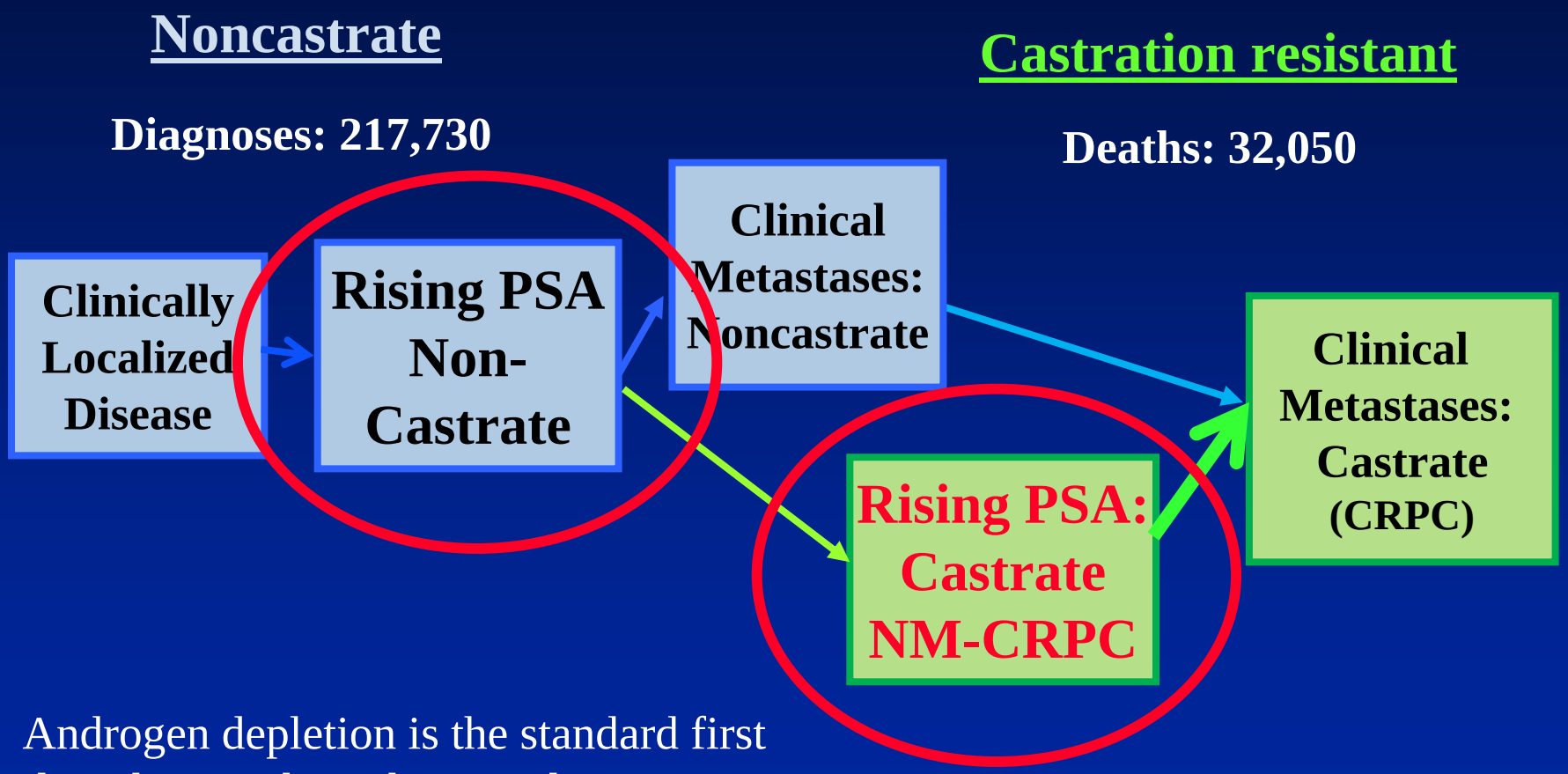
FDA ODAC

Howard I. Scher, M.D.
D. Wayne Calloway Chair in Urologic Oncology
Chief, Genitourinary Oncology Service
Memorial Sloan-Kettering Cancer Center
September 14, 2011

Trials in Non-Metastatic Castration Resistant Prostate Cancer (NM-CRPC)

1. A disease framework.
2. Patient population.
3. Trial designs.
4. Outcomes.

A Range of Prognoses Across States and Within States: Metastatic Castration-Resistant Disease (CRPC) Represents The Lethal Phenotype of the Illness



Androgen depletion is the standard first line therapy, but when to administer it is controversial.

Modified from Scher and Heller. *Urology*. 2000.

The Prostate-Specific Antigen Working Group Addressed Trial Issues For the *Rising PSA Non-Castrate State* When There Was No Systemic Therapy Approved for Survival

VOLUME 22 · NUMBER 3 · FEBRUARY 1 2004

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Eligibility and Outcomes Reporting Guidelines for Clinical Trials for Patients in the State of a Rising Prostate-Specific Antigen: Recommendations From the Prostate-Specific Antigen Working Group

Howard I. Scher, Mario Eisenberger, Anthony V. D'Amico, Susan Halabi, Eric J. Small, Michael Morris, Michael W. Kattan, Mack Roach, Philip Kantoff, Kenneth J. Pienta, Michael A. Carducci, David Agus, Susan F. Slovin, Glenn Heller, William Kevin Kelly, Paul H. Lange, Daniel Petrylak, William Berg, Celestra Higano, George Wilding, Judd W. Moul, Alan N. Partin, Christopher Logothetis, and Howard R. Soule

Hypothesis: Trials in this population should not be conducted because ….

1. The prognosis is not well defined.

2. Post-therapy PSA changes may not inform whether or not a patient is benefitting from a treatment.

3. Patients will not remain on treatment (placebo) if PSA levels rise until a radiographic or clinical endpoint (symptoms) is reached.

4. The Group advised not to begin drug development in this state.

Prostate-Specific Antigen Working Group Questions

1. How to define the clinical significance of a **rising PSA with non- castrate** levels of testosterone?

2. How should outcomes be assessed?

3. Can trial designs be standardized?

4. How can we prove that a treatment has favorably altered the untreated history of the disease and at what cost?

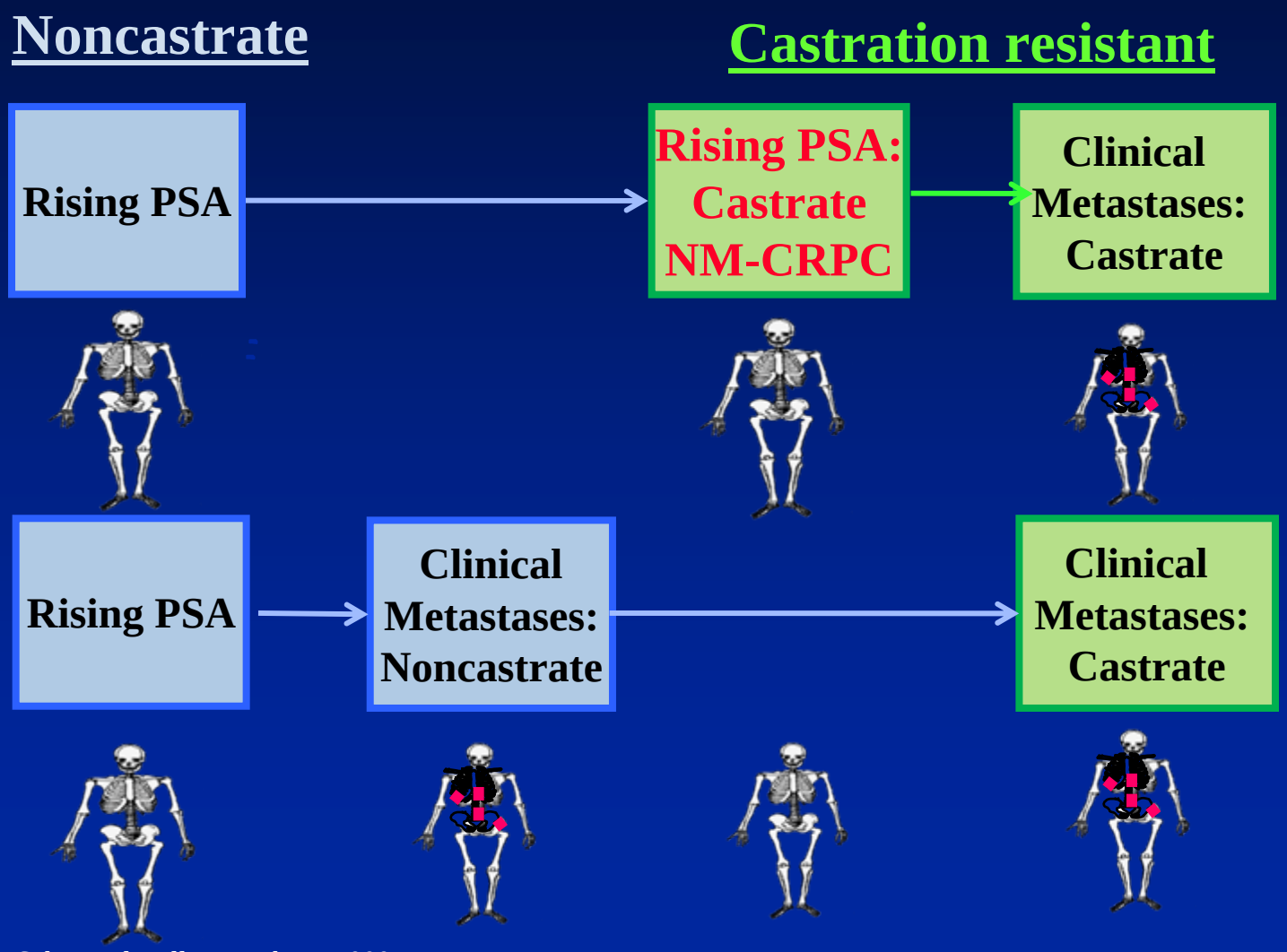
Clinical Trials Are Conducted With Therapeutic Intent And Include Several Components

1. **Therapeutic goals:**	Objectives / potential indication
	Unmet need
2. **Patient population:**	Entry criteria
3. **Intervention:**	Drug or agent; disease assessments
4. **Outcome measures:**	Endpoints
5. **Statistics:**	Go – No go
6. **Conclusions:**	Decision on further testing

PATIENT POPULATION

The *Rising PSA Castrate State* Includes Men Who Did Not and Do Not Have Detectable Disease on an Imaging Study:

No Therapy is FDA Approved in this Disease State



Modified from Scher and Heller. *Urology*. 2000.

The Modalities Used To Detect Disease and Determine NM-CRPC Status Varies Between Trials

1. Plain radiographs.
2. Bone scan.
3. Computerize tomography.
4. Magnetic resonance imaging: bone marrow
5. Antibody scans.
6. Circulating tumor cell detection.
7. Molecular detection of disseminated tumor cells in the bone marrow.

Measurements must be analytically valid, and associated with clinical outcomes.

Question #1: Does Treatment of Patients with NM-CRPC Represent an Unmet Medical Need**?**

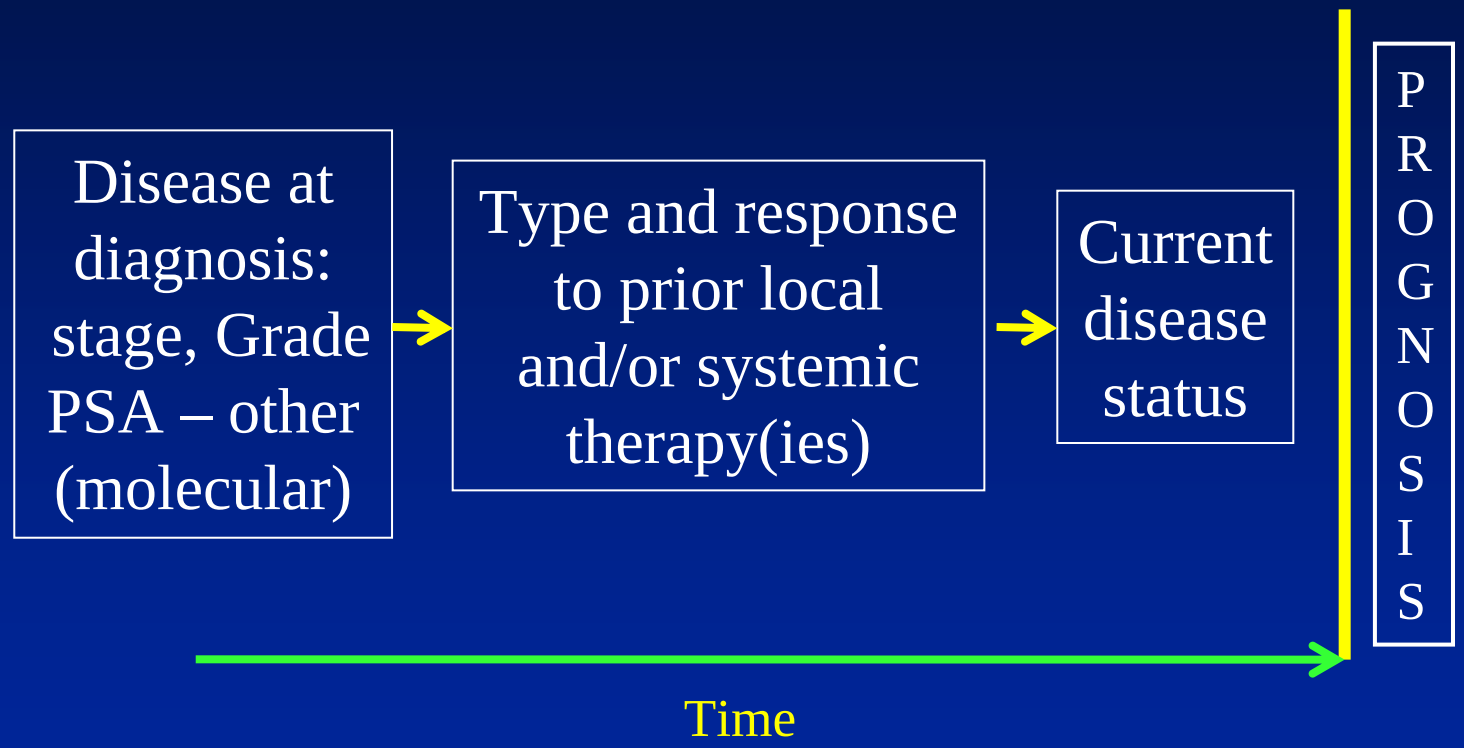
Trial conduct in this state is challenging, but these patients do exist and management has to be addressed.

Variability in practice patterns makes it difficult to estimate the frequency of this state.

Analyses of patients randomized to the “control arms” of prospective trials has enabled risk profiles to be estimated.

Based on prognosis, an important therapeutic option for some patients, is no immediate treatment.

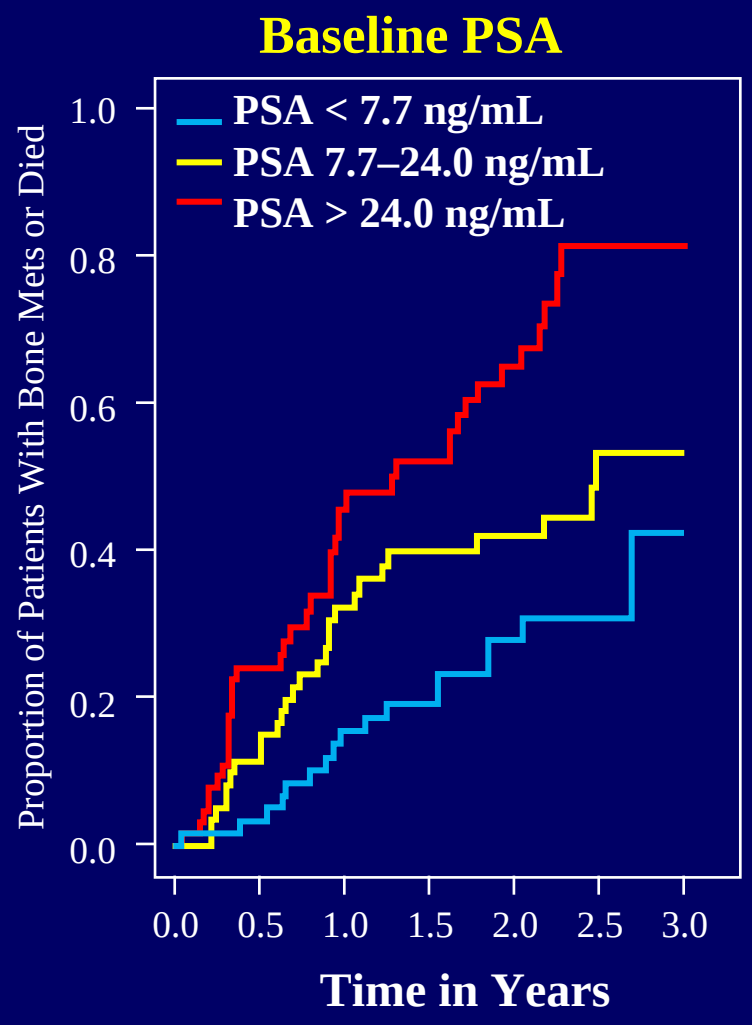
Treatment Objectives are Determined by a Patient's Prognosis Based on Current Disease Manifestations And Prior Treatment History

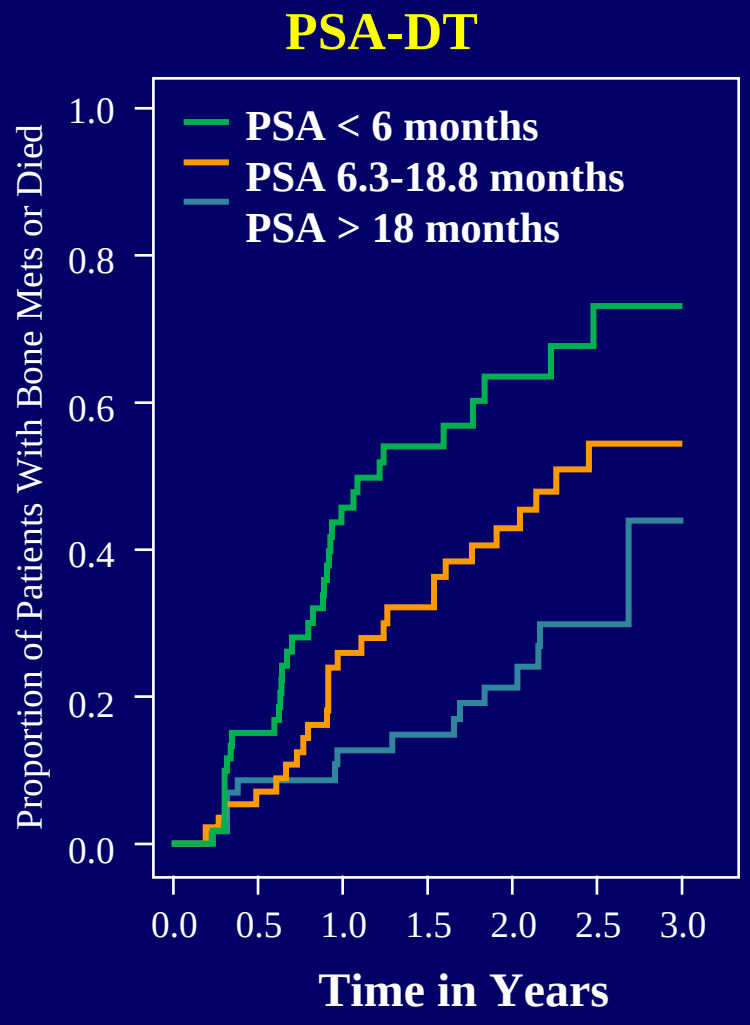


The decision to offer treatment depends on the risk/reward ratio of the therapy.

Modified from Scher and Heller. *Urology*. 2000.

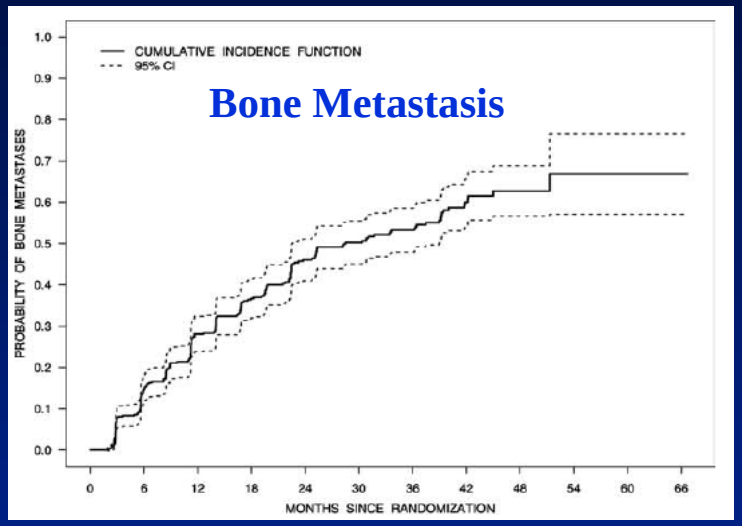
Baseline PSA and PSA Doubling Time (PSA-DT) Of Patients Randomized to Control Treatment Were Were Used to Develop Risk Strata from NM-CRPC

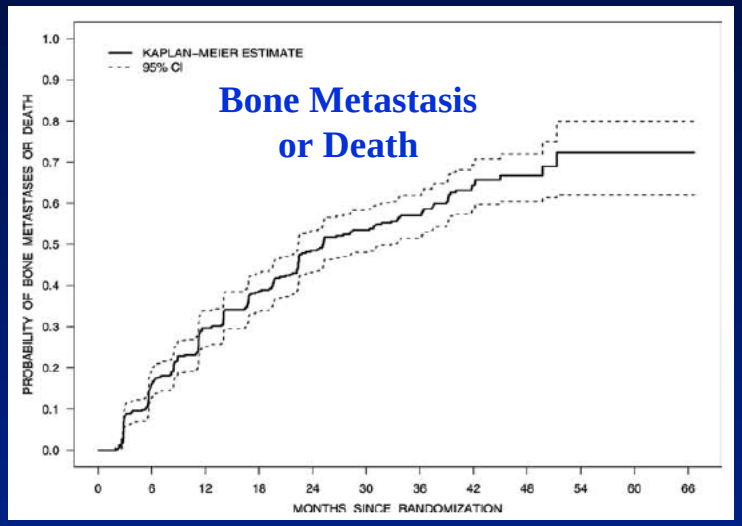


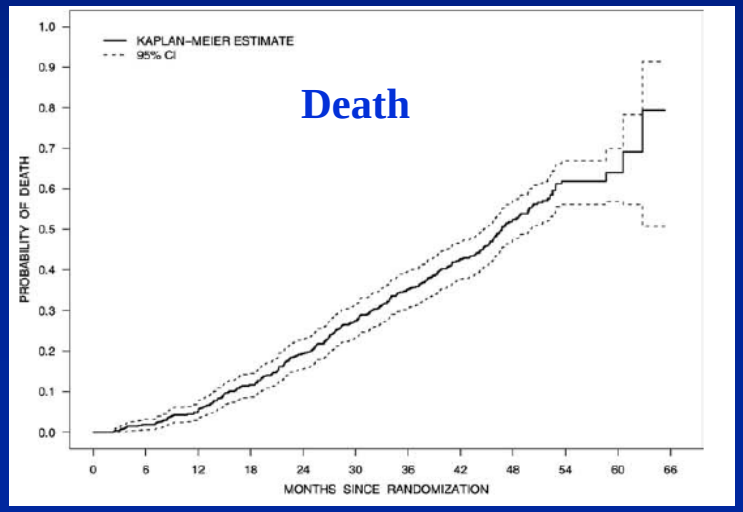


Smith et al., JCO 23: 2319, 2005

A Similar Analysis of a Control Group From a Second Randomized Trial Assessed Probability of Metastases, Metastasis Free Survival, and Overall Survival



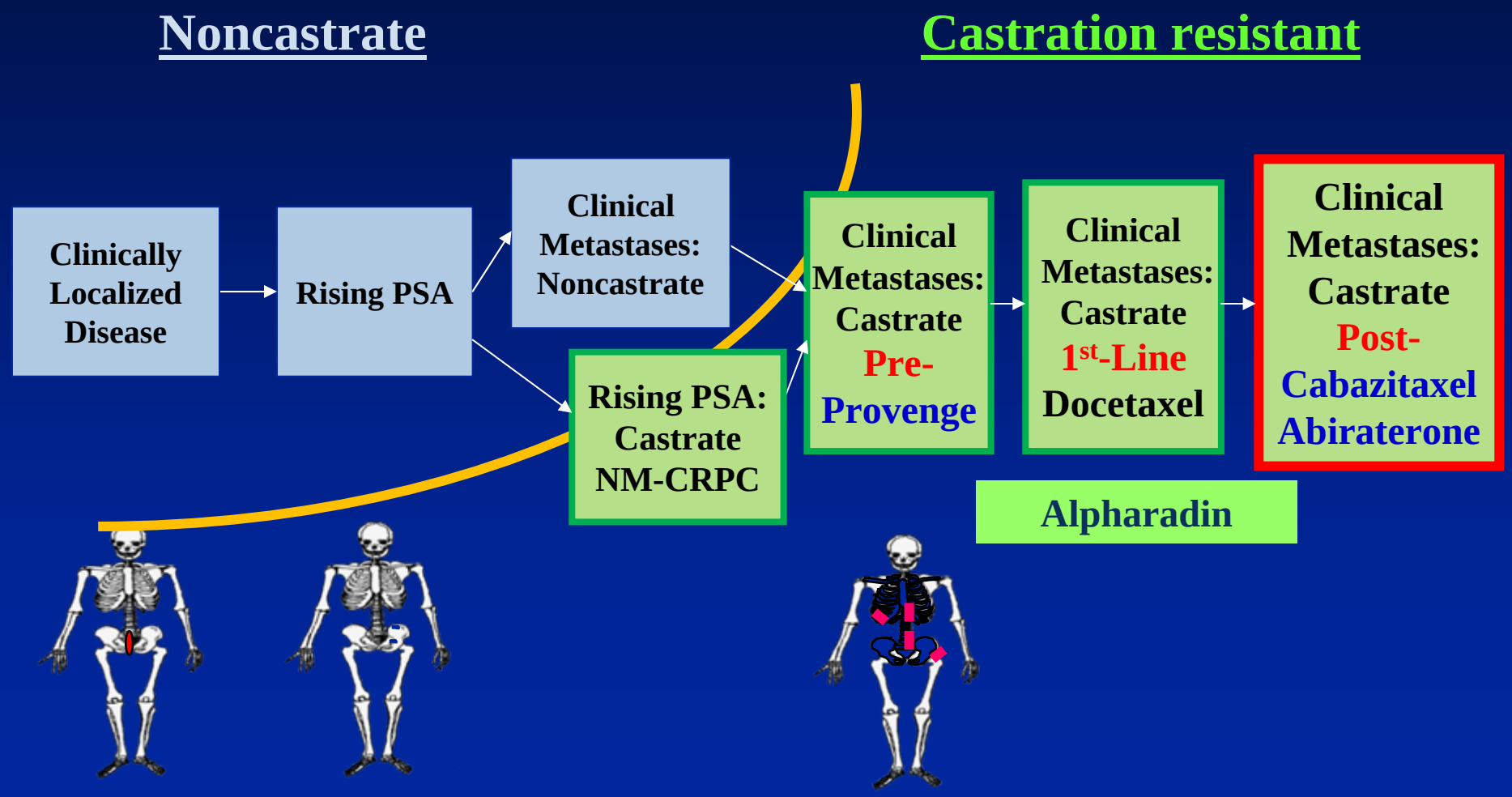




Smith et al. Cancer 117:2077, 2011

Interest in this state has increased because treatments effective in advanced disease may be more effective if used in the setting of lesser tumor burdens.

Prostate Cancer Clinical States: A Rapidly Changing Landscape After 4 Diverse Therapies Were Shown to Prolong Life in CRPC and 3 Were FDA Approved



Modified from Scher and Heller. *Urology*. 2000.

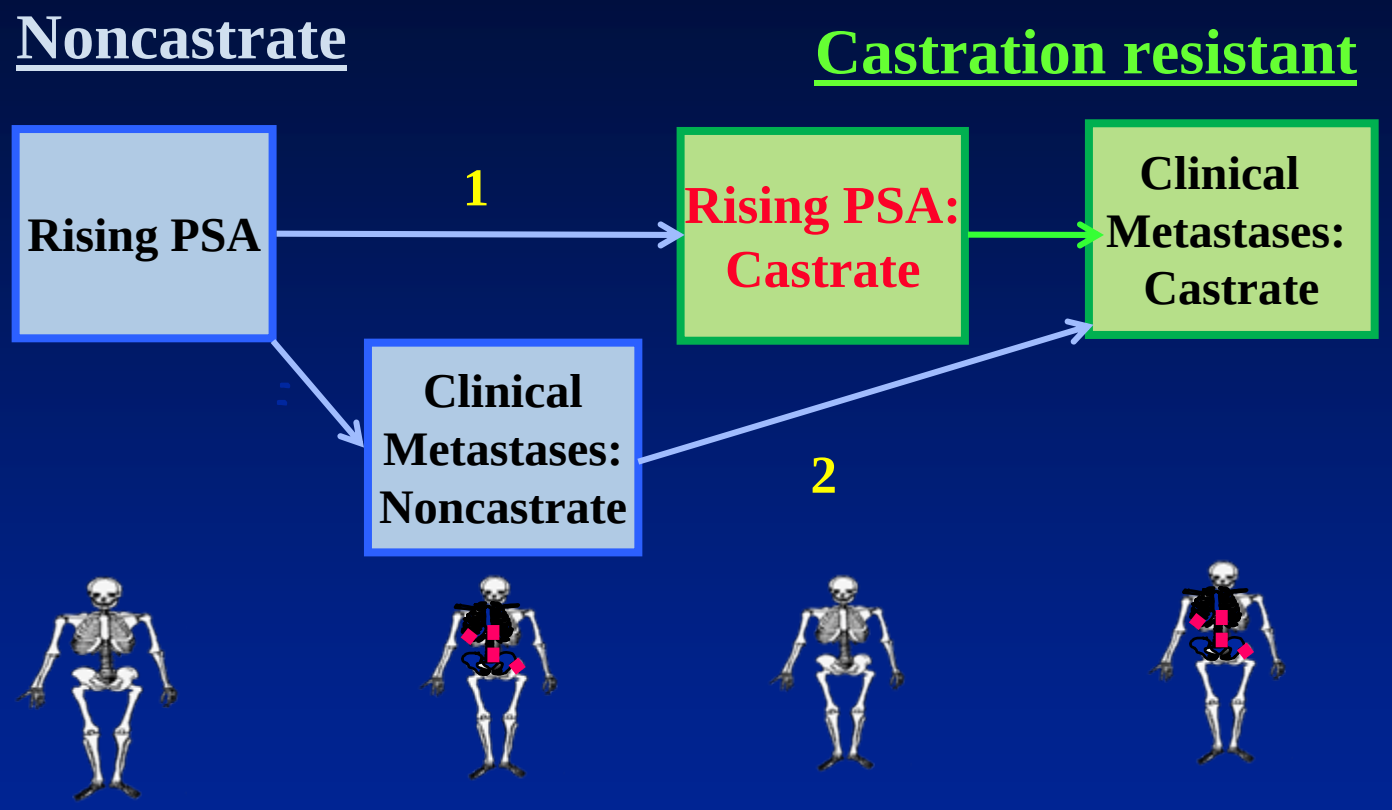
Question #2:

With the hypothesis that earlier use of a therapy proven to be effective in late state disease will be more effective if used in a minimal tumor burden setting, the Agency questions whether approval of a product would encourage the use of unproven and off label ADT.

Independent questions that have trade-offs.

No.

The Trade Offs Of Early Versus Delayed Therapy Using Androgen Depletion as an Example



1. **EARLY: ADT given in the Rising PSA State will reduce frequency of metastases but increase the risk for treatment related adverse events.**

2. **LATE: Deferred treatment may increase risk of SRE, while reducing risk of ADT related complications.**

Modified from Scher and Heller. *Urology*. 2000.

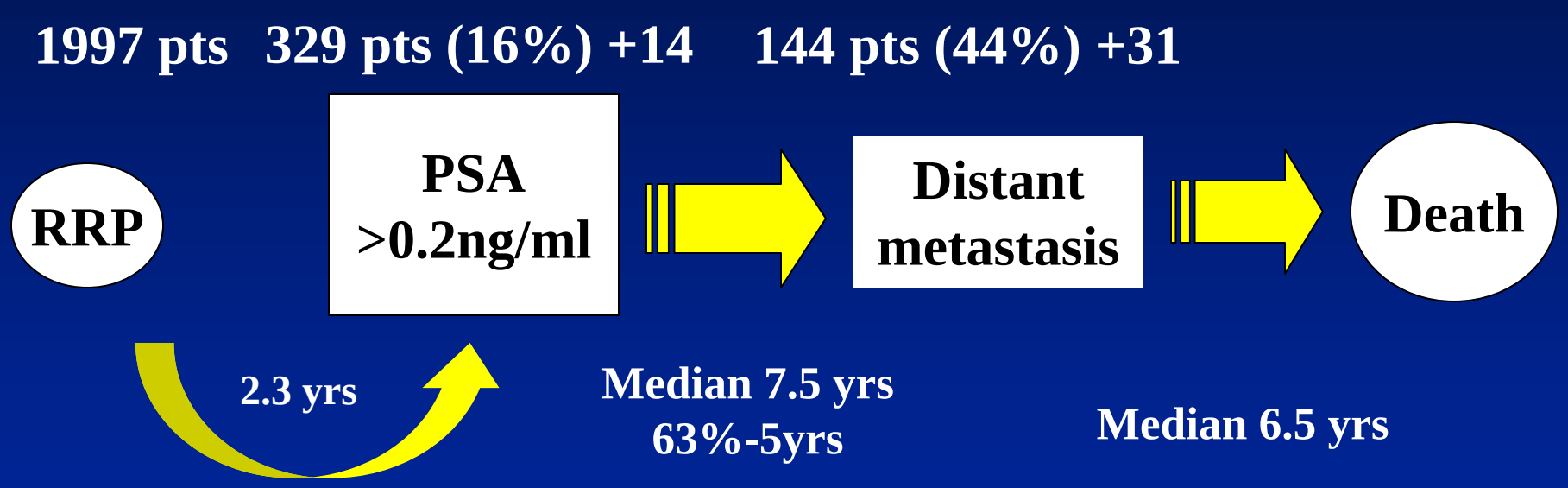
Question #2A:

Would it be more appropriate to conduct such trials in patients in the Rising PSA – Non-Castrate State after definitive primary treatment of prostate cancer?

This is an option but represents a different design.

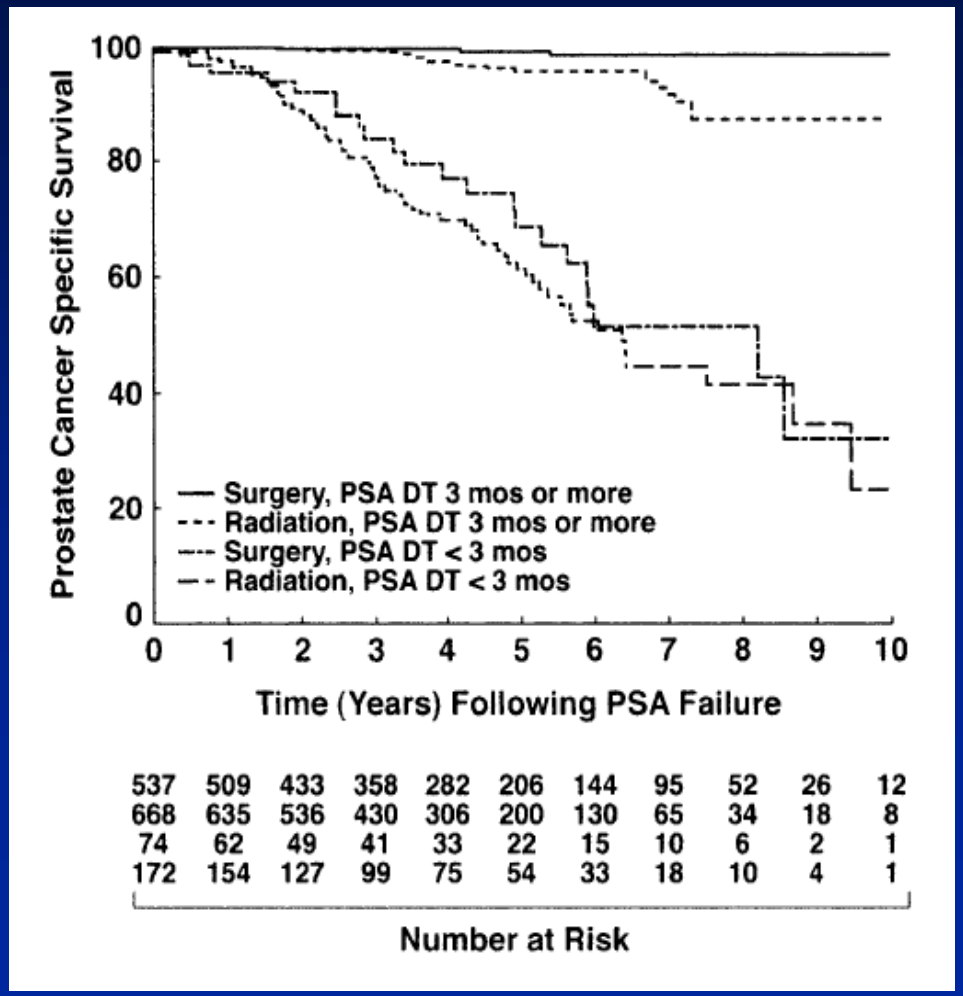
Groups at a high risk for metastasis and death have been identified.

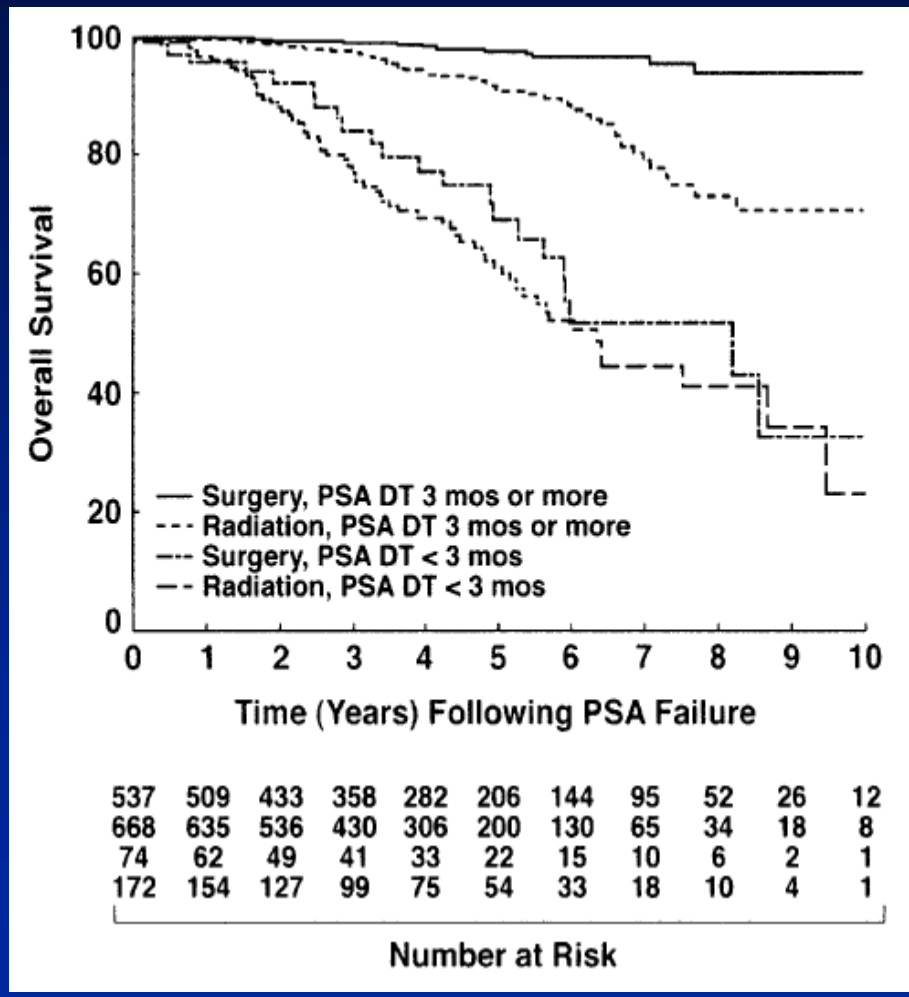
For the Rising PSA: Non-Castrate State as a Whole The Median Time From PSA Recurrence to Death from Cancer was 14 years



Pound et al. JAMA 281: 1592, 1999; updated 2003.

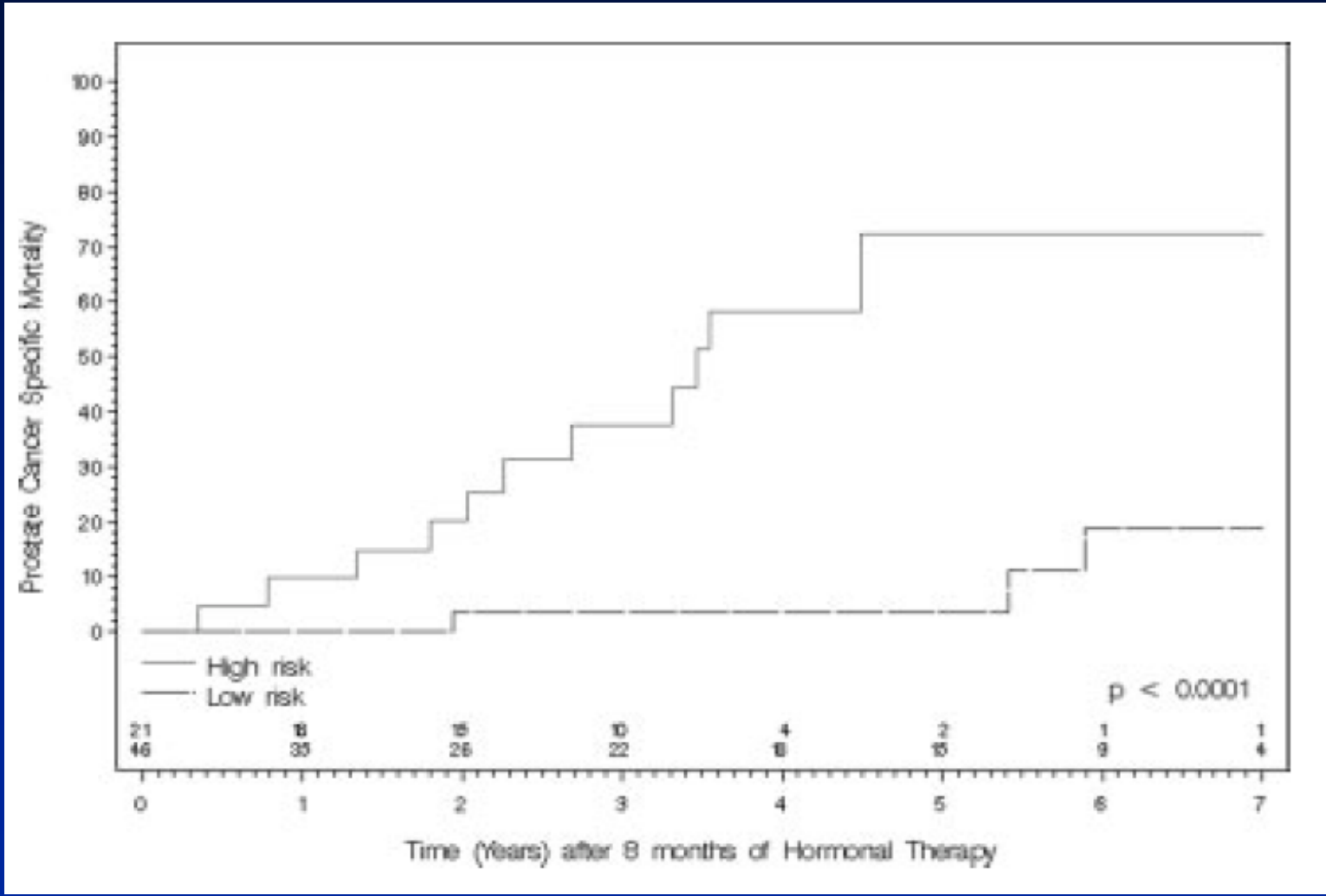
A PSA Doubling Time of 3 Months of Less (22% of the Population) Was Associated With the Highest Risk of Death and Prostate Cancer Specific Mortality





D'Amico et al. JNCI 95:1976, 2003

Patients in the Rising PSA-Non Castrate States Who do Not Achieve a PSA Nadir of 0.2 or Less (23% of the Population) Are Also At a High Risk of a Prostate Cancer Specific Death



D'Amico et al. Cancer 107:514, 2006

Question #3:

Given the indolent course in some patients, should trials be enriched for those at risk for prostate cancer specific morbidity and mortality?

Treatment effects will be the same in different cohorts, but benefit will be seen more rapidly in an enriched cohort .

Potential adverse events may be more acceptable for a higher risk patient group.

Question #4:
How would you define high risk?

Will vary in a trial context vs. a clinical practice context and what a drug might offer.

More informative prognostic models are needed to better assess the risk / reward ratio.

In general, a risk of developing bone metastasis of 30-40% or more in a 2 year period seems reasonable.

TRIAL DESIGN

Prostate Cancer Clinical Trial Design: The Question Dictates The Outcomes

1. What is the objective? Why is it being offered or tested?
2. What are the disease manifestations of the patient group (state) receiving it?
3. What changes in disease manifestations of the patient group (state) will be used to assess treatment effects?
4. How do we determine that it worked and at what cost (clinical benefit)?

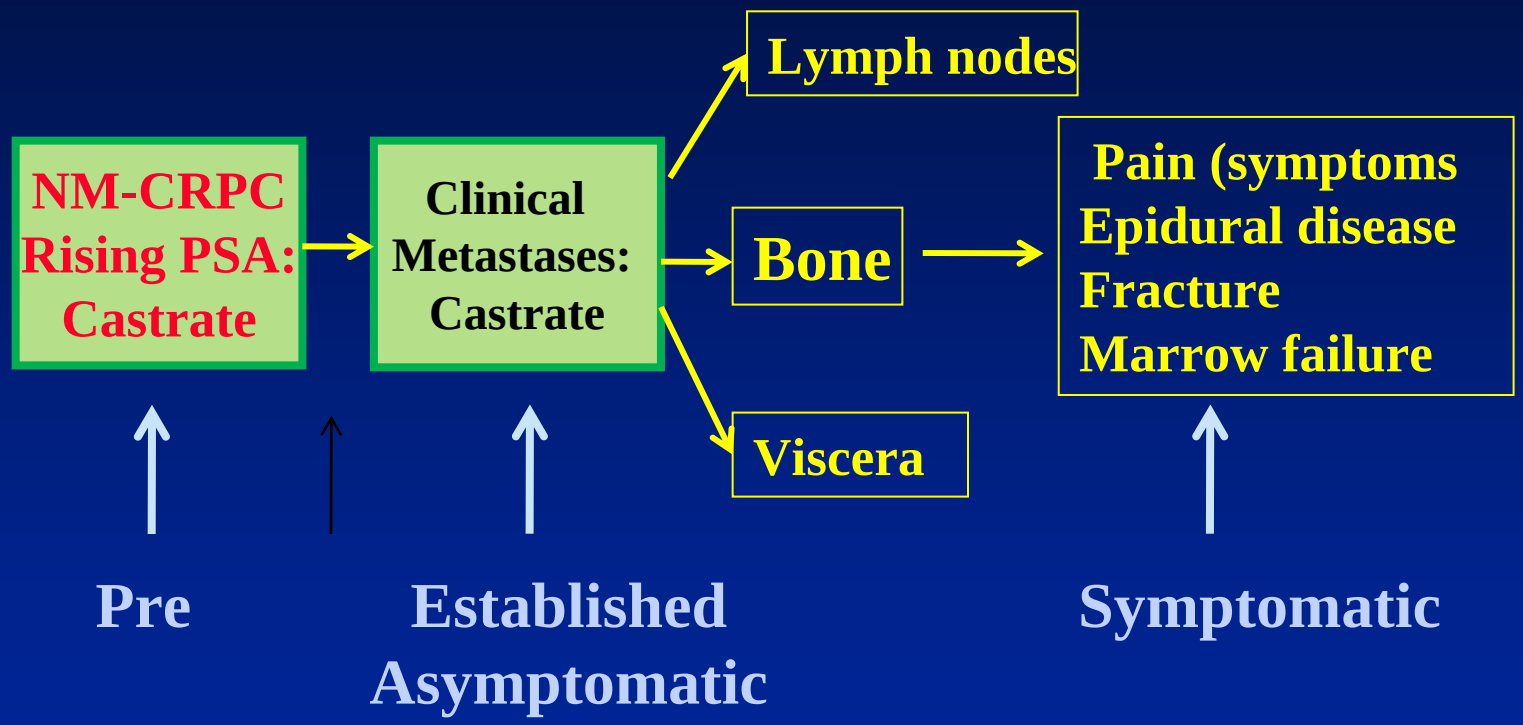
In Metastatic CRPC The APPROVED Drugs SUPPORT a Paradigm of Control Eliminate/Relieve – Delay/Prevent Objectives and Outcomes

Survival is one, but not the only measure of clinical benefit.

Control, Relieve, Eliminate: "Response"	Delay /Prevent: "Time to Event"
Control/Relief/Elimination of Pain: • Radiopharmaceuticals • Mitoxantrone + prednisone	***Delay/Prevent SREs*** •Zoledronic acid •Denosumab
No approvals based on PSA changes or tumor regressions	***Delay/Prevent Death from Disease*** • Docetaxel • Sipuleucal-T •Cabazitaxel • Abiraterone

Scher et al., JCO 26:1128, 2008, JCO [Epub 2011].

Left Untreated, NM-CRPC Will Progress to Lymph Nodes, Bone and/or Viscera: The Question is in What Time Frame and When is it Best to Intervene?



Bone metastases produce some of the most feared and debilitating complications of the disease.

Delaying or preventing bone metastases is a clinical benefit to patients.

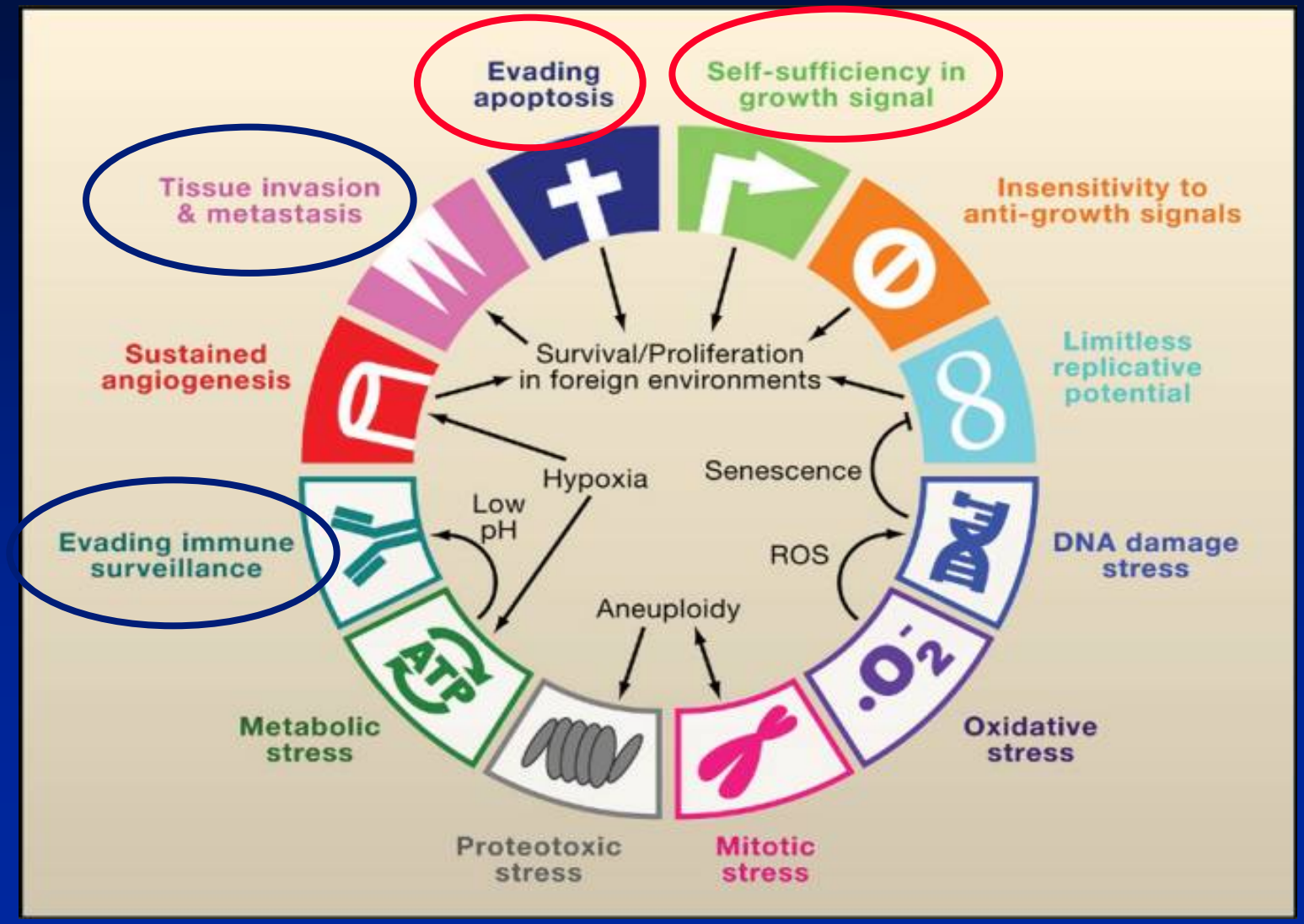
Each Outcome Should Be Assessed and Reported Independently

We do not know the clinical significance of a solitary bone scan finding – when it might cause symptoms.

A bone targeting agent will not affect the development or spread of extraosseous disease.

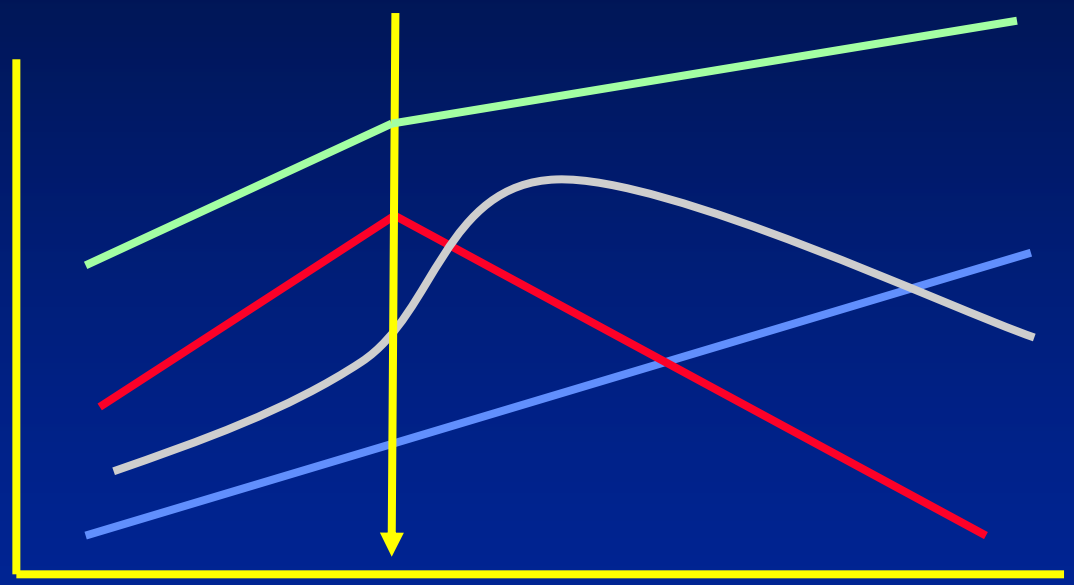
Some agents may treat both bone and soft-tissue.

We Are Moving Beyond Standard Hormones and Cytotoxics To Target The Malignant Process



Luo et al, Cell 2009

PSA Changes Are Not Stand Alone Criterion: A Continued Rise Does Not Exclude Clinical Benefit: Bone Targeting, Anti-metastatic or Anti-Angiogenic Drugs



DESIGN #1: A Head to Head Comparison In NM-CRPC of a Product With Proven Efficacy in Metastatic CRPC: Focusing on Delay / Prevent – Time to Event Endpoints

Eligibility

- NM-CRPC
- Risk to be determined
- Record prior therapy and baseline factors

→ **RANDOMIZED 1:1**

→ **Approved Therapy "X"** →

→ **Placebo** →

Efficacy end points (ITT)

Primary end point:

Metastasis free survival

Secondary end points:

- Time to bone metastases
- SRE
- Time to new treatment
- Symptoms
- Survival

N=1200

Option to continue therapy in either arm.

ITT: Intent to treat: SRE: Skeletal related events

Disease Assessments Should Be Standardized by Modality Performed at Predetermined Intervals

	Baseline	Month 4	Month 7	Month 10	Month X + 3	Off Study
PSA	X	X	X	X	X	X
Bone markers	X	X	X	X	X	X
Bone Scan	X	X	X	X	X	X
Computerized Tomography	X	X	X	X	X	X
Magnetic Resonance Imaging	X	X	X	X	X	X

Symptoms and adverse events recorded at each visit.

Record Outcomes for Each Manifestation Separately and By Modality With Option to Continue Therapy if Change "Not Clinically Significant"

1. Bone: New lesions, growth of existing lesions

2. Soft tissue: Lymph nodes: new of > 2 cm
   Visceral : new

3. Markers: Bone Tumor

4. Symptoms: Disease vs. therapy

Time to Event Studies Require Standardization

1. In most trials, disease assessments are stopped after a patient "progresses" or comes off treatment.

2. Given that the "significance" of the different outcome measures varies or is uncertain, longer follow-up and continued disease assessments at fixed intervals are needed.

3. Subsequent treatment and the response to the treatment should also be monitored.

4. This is particularly important given that a number of treatments have been shown to prolong life.

Endpoints

1. **TTFM:** Time to first metastasis

2. **MFS:** Metastasis free survival (includes death from disease)

3. Should symptoms or SRE be the primary endpoint?

   Will be difficult to continue treatment in setting of new metastases.

   Endpoint may be confounded by new effective treatment.

4. Overall survival: Important but not the only measure of clinical benefit.

Use of the PCWG2 CRPC Guidelines To Define Bone Progression May Enable a Better Understanding of the Natural History of a "New Lesion" on Scan

1. The documentation of a new lesion on scan should be confirmed on a second scan performed 6 or more weeks later.

   Progression requires the documentation of an additional new lesion on the follow-up scan.

2. Quantitative methods to image bone are under development.

Scher et al., JCO 26: 1128, 2008.

Recording Key Trial Metrics Provides Insights into Patient Tolerance and Overall Outcomes: Hypothetical Proportions For Therapy A and B

	A	**B**
Withdrew Consent	15%	7%
Non-bone progression	8%	3%
Adverse Events	**23%**	5%
Disease related symptoms	**20%**	8%

TRIAL DESIGN (2)

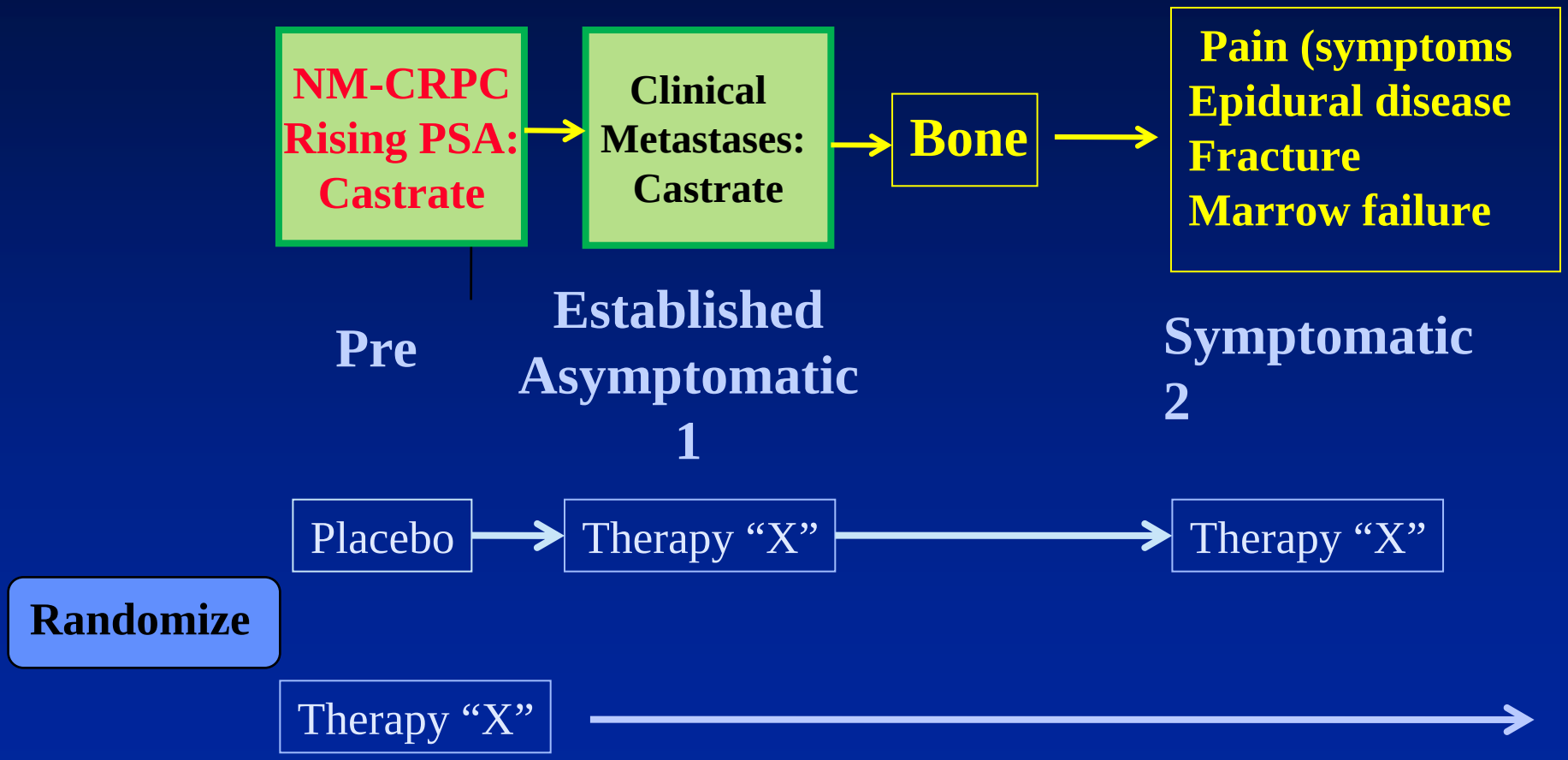
1. Early vs. delayed therapy using a product already proven in late state disease.

2. Discuss potential triggers to initiate therapy in the deferred arm:

   PSA, new lesions or symptoms

Early vs. Delayed Therapy for Patients With NM-CRPC Using a Drug Shown to be Effective in Metastatic CRPC:

? When To Add Therapy "X" to Placebo Patients



What is the Trigger to Initiate Treatment?

Triggers

1. Should not be PSA based.

2. PCWG2: Detection of metastasis confirmed by a second scan (new lesion or enlarging lesion).

3. Extraosseous spread: Anticipated for bone targeting agent.

4. **Symptoms (SRE):** Preferred.

Reality is that it will be difficult to withhold other treatments known to prolong life, or to dictate one vs. another which may affect the survival endpoint.

TRIAL DESIGN (3):

Is there an Opportunity for Cure In a Minimal Disease Setting?

Establishing a Cure Paradigm Using an Undetectable PSA Endpoint

A Clean Endpoint:

1. Potentially acceptable as evidence of being disease free
2. A tangible benefit: no equivocation over the meaning of stable but low PSAs
3. No debate over "meaningful" post-treatment PSA declines and "response"
4. Binary value

Although survival is a "gold standard" primary endpoint in clinical trials, biochemical recurrence indicates treatment failure when the objective is disease eradication.

A Head to Head Comparison In NM-CRPC of a Product With Proven Efficacy in Metastatic CRPC:

Eligibility

- NM-CRPC
- Risk to be determined
- Record prior therapy and baseline factors

→ **RANDOMIZED 1:1**

→ **Approved Therapy "X"**

→ **Placebo**

→ **Efficacy end points (ITT)**

Primary end point:

Undetectable PSA with non-castrate levels of testosterone (150 ng/dl) - at a fixed time point

Secondary end points:

Proportion achieving an undetectable PSA

Time to PSA failure

Option to continue therapy in either arm.

ITT: Intent to treat: SRE: Skeletal related events

Agency Position

1. Drug development in the non-metastatic psa recurrence population (NM-CRPC and particularly NM-hormone naive), should focus on patient populations at higher risk for cancer-related morbidity or mortality (trial population enrichment).

2. The preferred endpoint of clinical benefit is prostate cancer-specific survival.

3. A survival endpoint is feasible for patients with a high risk of prostate cancer-specific death in non-metastatic castration resistant prostate cancer.

4. Ignores the issue of multiple effective therapies.

***