

# Prostate Cancer

**Ravi A. Madan, MD**

**Clinical Director**

**Genitourinary Malignancies Branch**

**National Cancer Institute**

# Disclosures

- None

# Educational Objectives

By the end of this session, participants should be able to

Understand the treatment options for localized prostate cancer

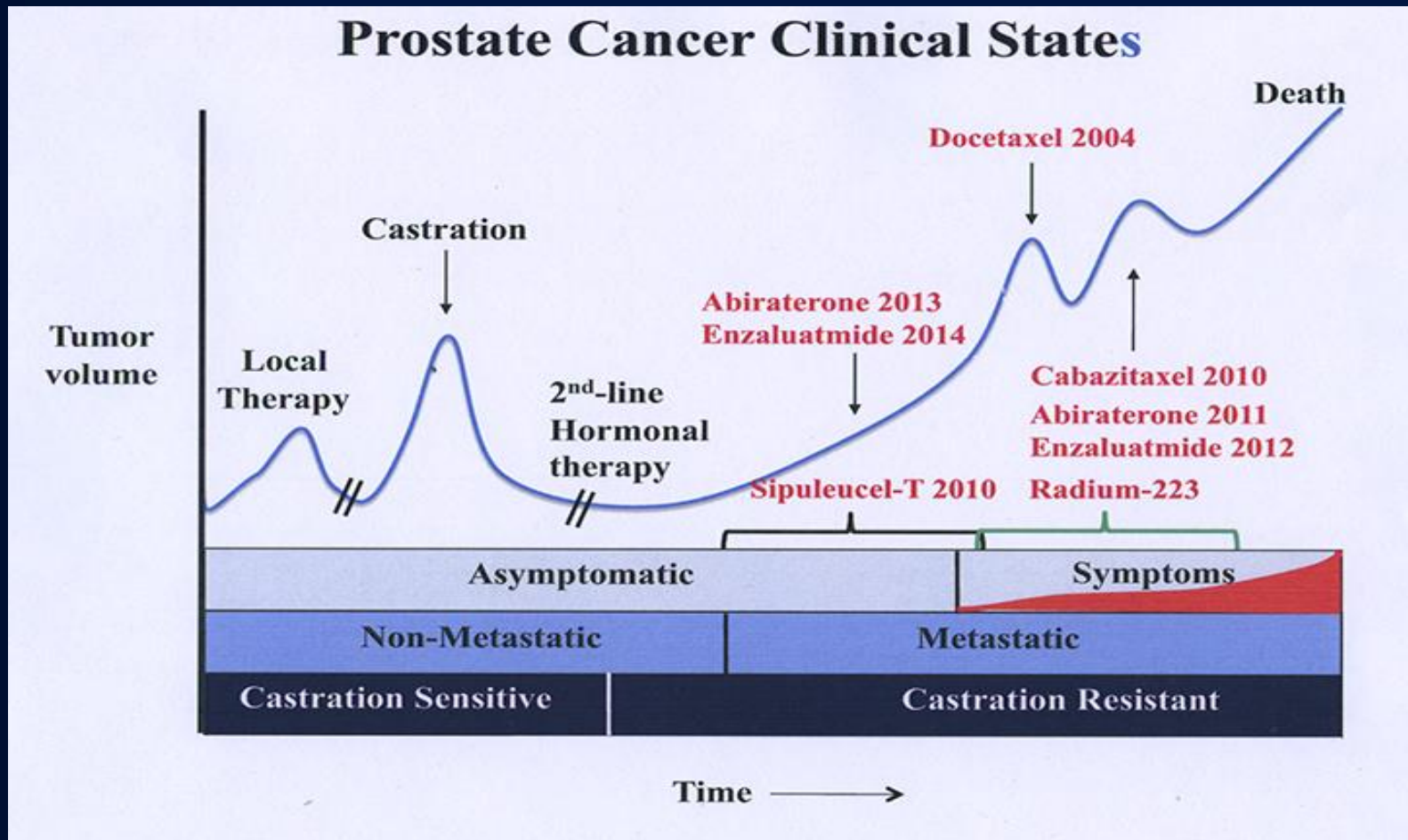
Understand the treatment options for metastatic disease

Understand emerging data on treatment resistance

# Presentation Outline

1. Prostate Cancer overview
2. Therapies for localized prostate cancer
3. Therapies for locally advanced disease
4. Systemic therapies for metastatic disease
  - a. Androgen deprivation therapy (ADT)
  - b. Chemotherapy
  - c. Immunotherapy
    - a. Radiopharmaceuticals
5. Mechanisms of Resistance
6. Future Directions


# Prostate Cancer Clinical States



# Epidemiology

- Most Common malignancy in men
- Lifetime risk of 1 in 6 men
- 2012 estimated new cases 241,740
- Estimated deaths 28,170
- 24% of men will die from their disease

Prostate	241,740	29%
Lung & bronchus	116,470	14%
Colon & rectum	73,420	9%
Urinary bladder	55,600	7%
Melanoma of the skin	44,250	5%
Kidney & renal pelvis	40,250	5%
Non-Hodgkin lymphoma	38,160	4%
Oral cavity & pharynx	28,540	3%
Leukemia	26,830	3%
Pancreas	22,090	3%
<b>All Sites</b>	<b>848,170</b>	<b>100%</b>



# Risks

Age

Family history

Genetic predisposition

HPCG

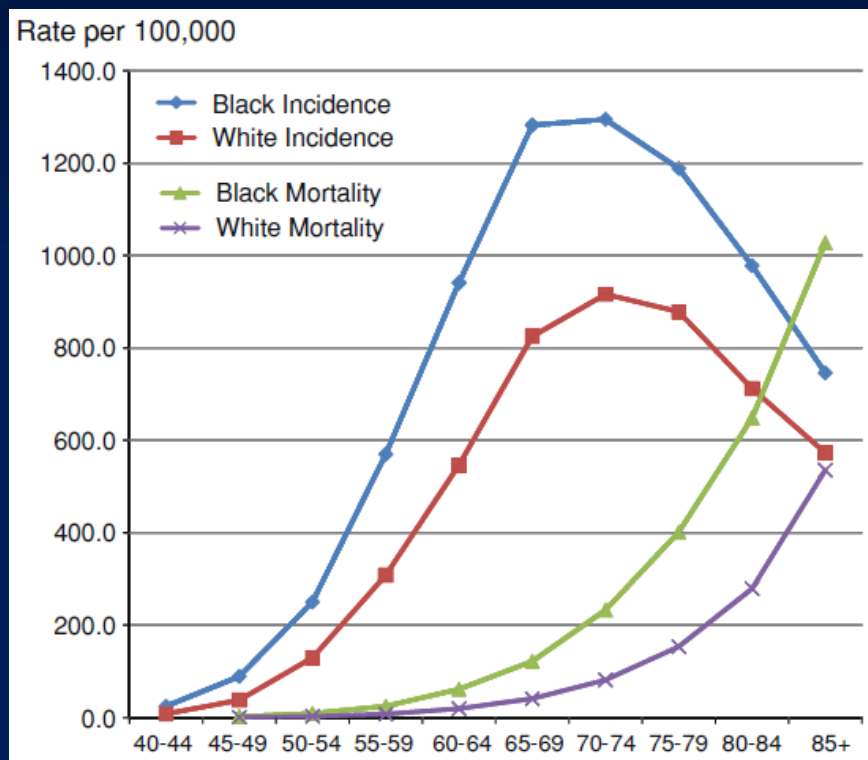
BRCA

TMPRSS2-ETS

Environmental

Obesity

Race








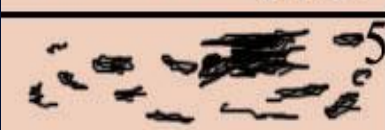
# Prevention in Prostate Cancer...

## A cautionary Tale

- 5- $\alpha$ -reductase inhibitors
  - Finasteride
    - Selective inhibitor of type II enzyme
    - Decreases DHT by about 70%
    - *Prostate Cancer Prevention Trial*
  - Dutasteride
    - Inhibits type I and II enzymes
    - Decreases DHT by >90%
    - REDUCE trial (Reduction by Dutasteride of Prostate Cancer Events)
- SELECT Trial (Vitamin E and Selenium)
  - No protective effect



# Gleason Grading

Gleason Scale		Well differentiated
	1 Small, uniform glands	
	2 More space between glands	
	3 Infiltration of cells from glands at margins	
	4 Irregular masses of cells with few glands	
	5 Lack of glands, sheets of cells	

Primary Grade

Greater 50%

Secondary Grade

<50% but  $\geq 5\%$

# Staging

## Staging

Stage	TNM	Description
I (A)	T1a (incidental)	Localized
II (B)	T1b, <i>T1c</i> , T2a,b,c (within prostate)	Locally Advanced
III (C)	T3a (through capsule) T3b (seminal vesicles)	
IV (D)	T4 (fixed, invades)	Metastatic
	N1, M1	



# Principles Guiding Therapy of Localized Prostate Cancer

Patients with a life expectancy of at least 10 are more likely to benefit

Patients older than 75 years have other competing causes of mortality

Eradication of the cancer is the goal of therapy

Low grade/stage tumors may just require active surveillance

# Watchful Waiting

Observation with palliative treatment for symptoms

No biochemical monitoring

Ideal for patients with poor life expectancy who are likely to die from causes other than prostate cancer

# Active Surveillance

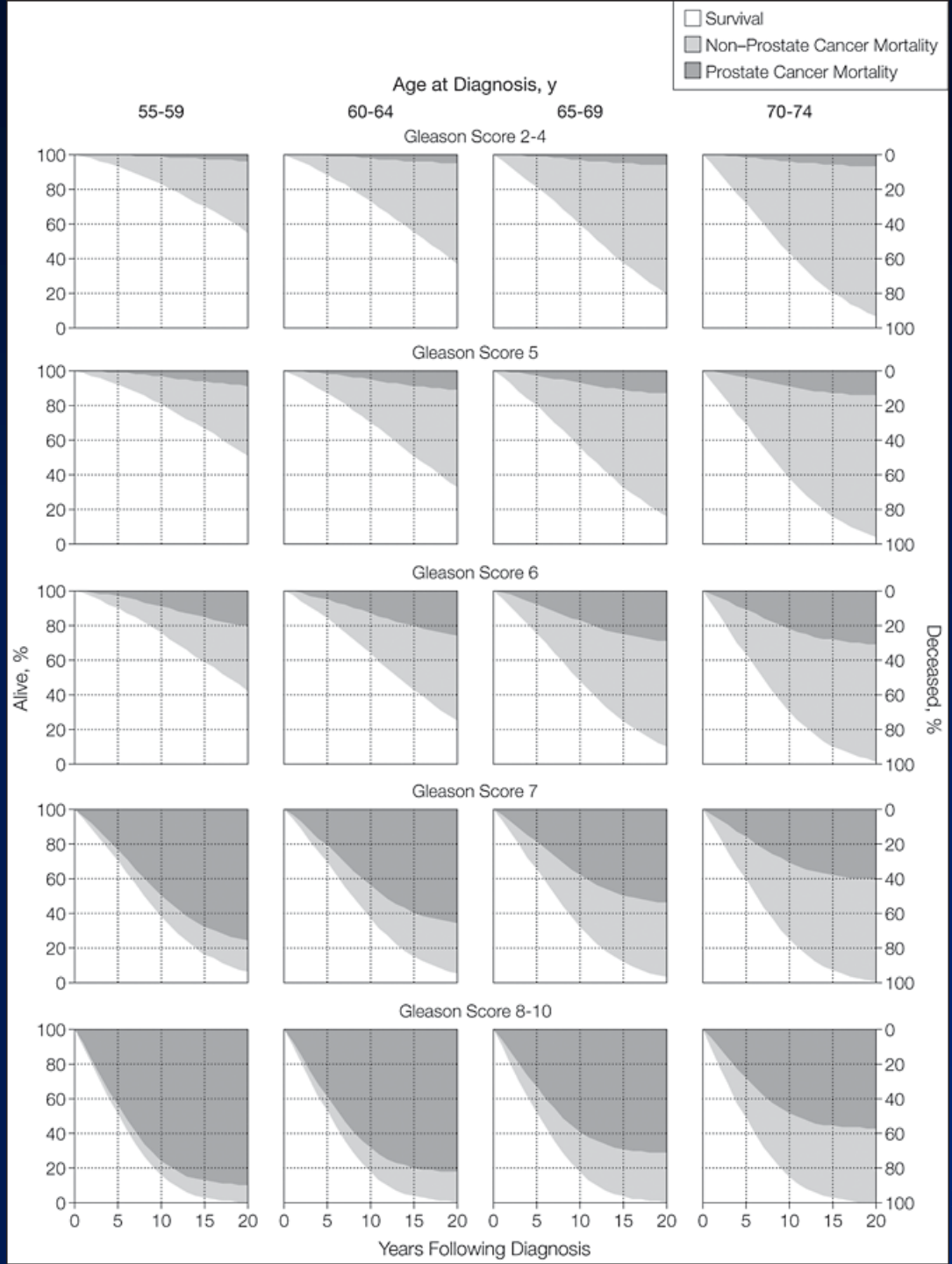
Periodic biochemical (PSA) monitoring

Annual Biopsy may be part of active surveillance

Conversion to active treatment when signs of disease progression develop

# Who is the Ideal Candidate for Watchful Waiting/Active Surveillance?

The probability of prostate cancer mortality is low with:  
 Lower Gleason score  
 Advanced age



# Randomized Trial Comparing Surgery and Watchful Waiting

Early stage prostate cancer (n=695)

Deaths at median 8.2 years of follow-up

Following prostate cancer surgery 83 died, 30 from prostate cancer

Also less metastasis

Caveats:

- More advanced clinically than current US patients

- Only 5% of men had screen detected PC

- Advantage largely in men <65 y.o.

# Radiation Therapy-External Beam

The principle is to deliver therapeutic dose of radiation to the tumor but minimize damage to adjacent structures

Modalities of external beam radiotherapy

3-dimensional conformal radiation therapy (3D-CRT)

Intensity modulated radiation therapy (IMRT)

Image-guided radiation therapy (IGRT)

Proton-beam radiation  
therapy





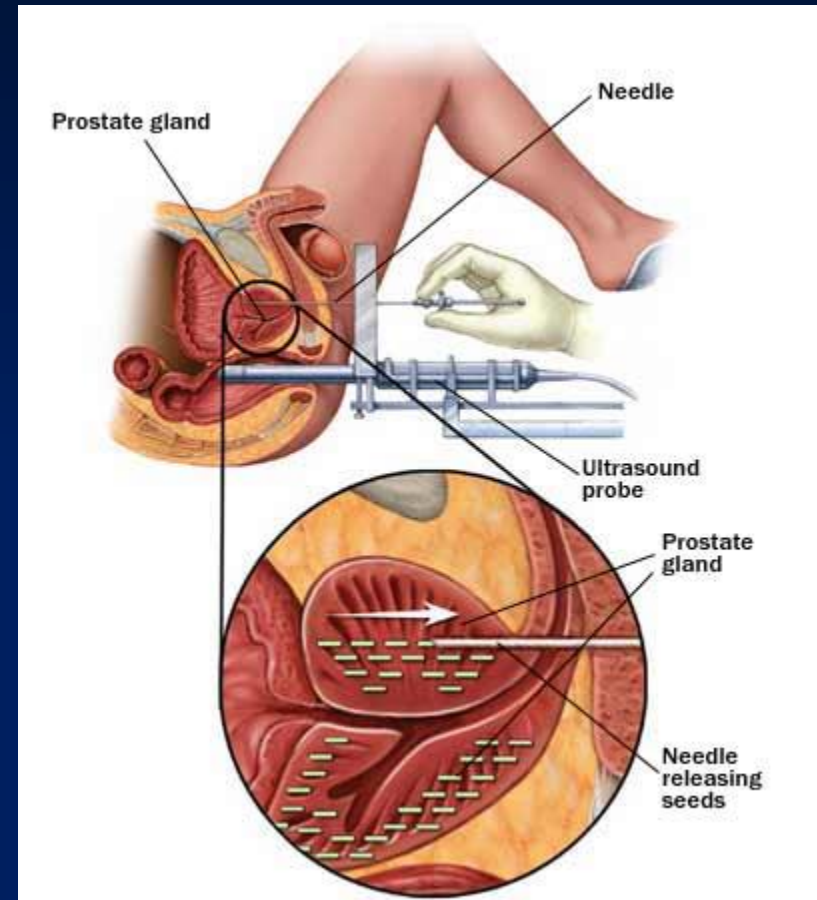
# Radiation Therapy- Brachytherapy

Direct implantation of radiation seeds

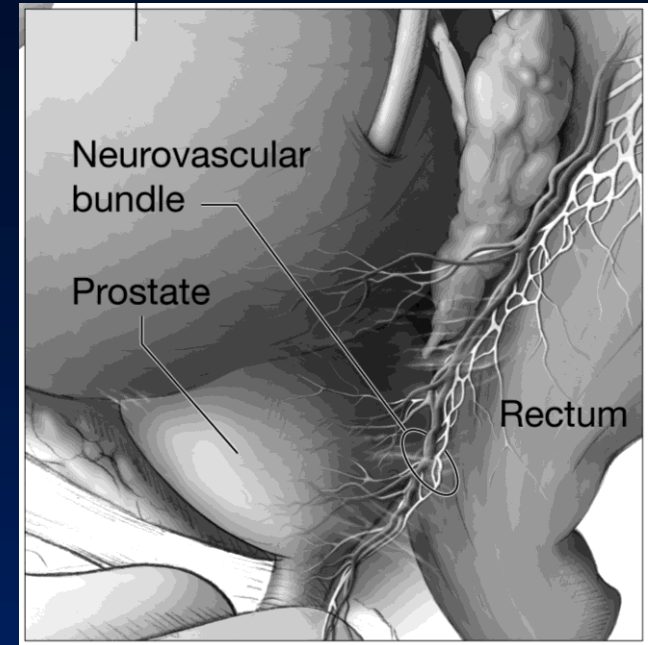
Maximizes radiotherapy to the tumor

limits damage to the surrounding structures

One time treatment



# Radiation Therapy- Complications



## Gastrointestinal

Less common with brachytherapy

## Genitourinary

Incidence of erectile dysfunction varies widely

## Secondary malignancies

Slight increase risk with bladder and to a lesser extent with rectal cancer

# Primary Androgen Deprivation Therapy

May be used in men who refused or are not candidates for definitive local therapy

EORTC Trial 30891 randomized 985 men with localized or locally advanced prostate cancer to

Immediate ADT vs. deferred ADT

Overall survival HR 1.25, in favor of immediate ADT

Prostate cancer-specific survival not different

Time to hormone refractoriness not different

# Management of Locally Advanced Prostate Cancer

Surgery with ADT

    Neoadjuvant or adjuvant

Surgery with adjuvant RT

Radiotherapy with ADT

# Neoadjuvant ADT with Surgery

149 men with T2bNxM0 prostate cancer were randomized to RP vs. RP + 3 mths of neoadjuvant leuprolide/flutamide

Neoadjuvant ADT led to

Less positive surgical margin (18% vs. 48%,  $p < 0.001$ )

5-year biochemical recurrence-free survival

64.8% vs. 67.6% ( $p = 0.663$ )

Overall survival not reported

# Adjuvant ADT with Surgery

98 men with localized **node-positive** prostate cancer randomized to

immediate ADT or deferred ADT

At 11.9 years of follow-up, immediate ADT had

Better overall survival (HR 1.84,  $p=0.04$ )

Prostate-specific survival (HR 4.09,  $p=0.0004$ )

Progression-free survival (HR 3.42,  $p<0.0001$ )

Caveat: Deferred ADT given for metastases/symptomatic recurrence, not for rising PSA

# Adjuvant RT with Surgery

SWOG study of adjuvant RT vs. observation for T<sub>3</sub>N<sub>0</sub> or positive margin (n=425)

70 in the observation group ultimately received RT

Endpoint – metastasis-free survival

Median follow-up 12.7 years

For metastasis-free survival RT = 14.7 whereas the observation = 12.9 years (p = 0.016)

For overall survival RT = 15.2 whereas the observation = 13.3 years (p = 0.023)

# Radiotherapy with ADT

EORTC 22863 randomized 415 men with high grade locally advanced prostate cancer

EBRT  $\pm$  goserelin for 3 years (cyproterone for 1 mth)

ADT group had better

10-yr disease free-survival (22.7 vs. 44.7%,  $p < 0.0001$ )

10-yr overall survival (39.8 vs. 58.1%,  $p = 0.0004$ )

10-yr disease-specific mortality (30.4 vs. 10.3%,  $p < 0.0001$ )

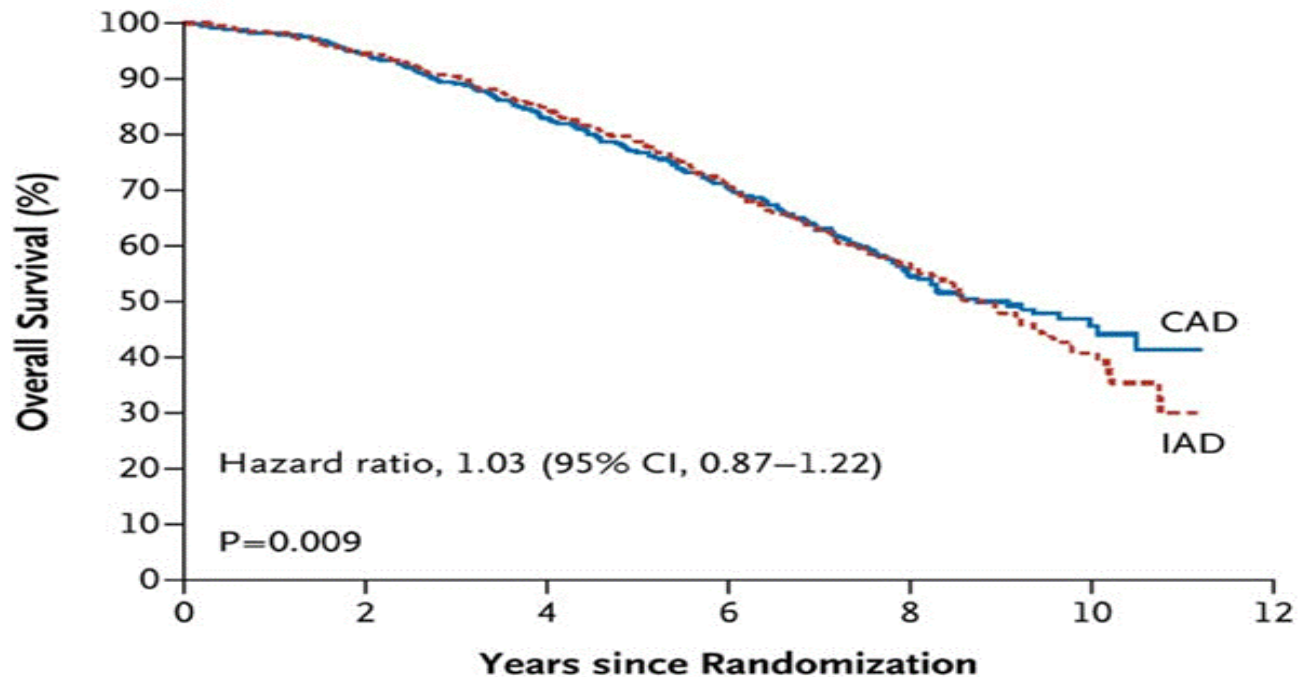


# Biochemical Recurrence after Initial Prostatectomy or RT

Rising PSA without local recurrence or metastasis

Treatment options include watchful waiting, prostatectomy, RT, and ADT

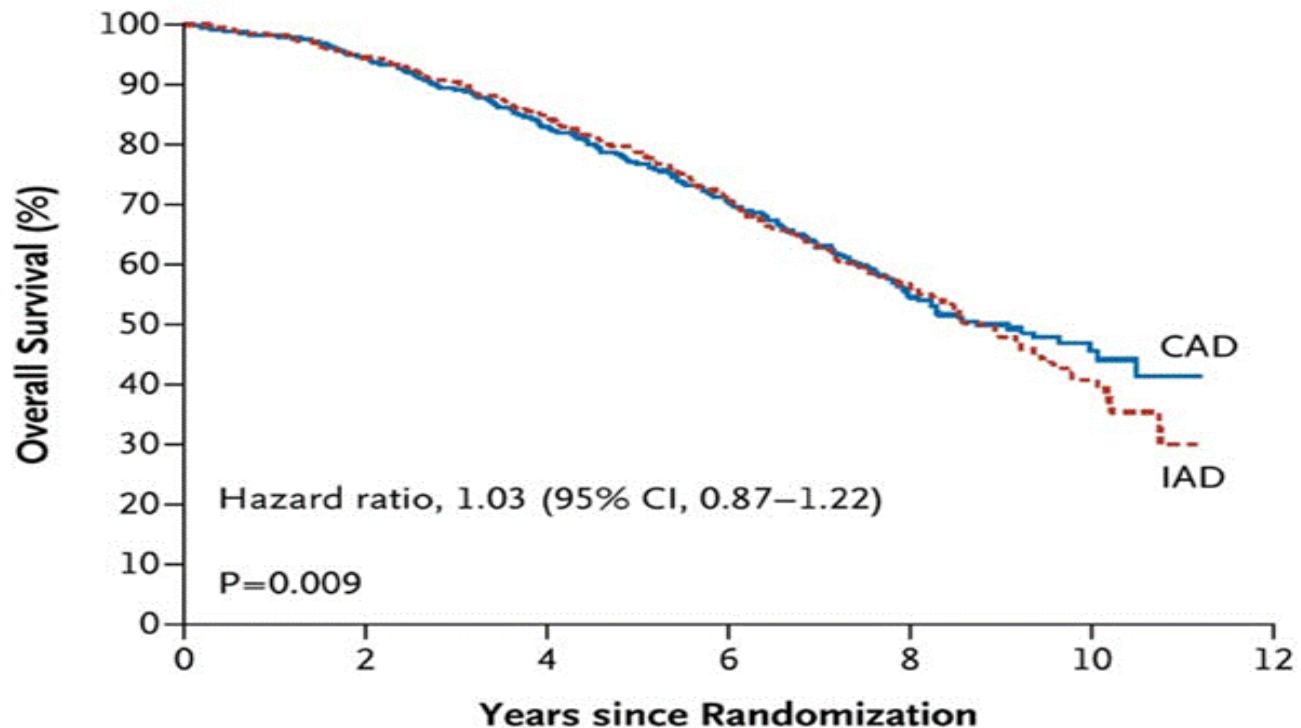
# ADT: Intermittent vs. Continuous for Non-Metastatic Castration Sensitive Disease



**No. at Risk**

CAD	696	652	561	319	125	35	0
IAD	690	651	571	327	140	34	0

# ADT: Intermittent vs. Continuous for Non-Metastatic Castration Sensitive Disease



**No. at Risk**

CAD	696	652	561	319	125	35	0
IAD	690	651	571	327	140	34	0

# Natural History of Prostate Cancer

No patients received hormonal therapy without clinically evident metastatic disease.

Median time from PSA elevation to metastatic disease was 8 years

Median time to death after metastatic disease was 5 years.

Prognostic factors predictive of outcome included the Gleason score in the surgical specimen, and PSA doubling time.

# Metastatic Prostate Cancer

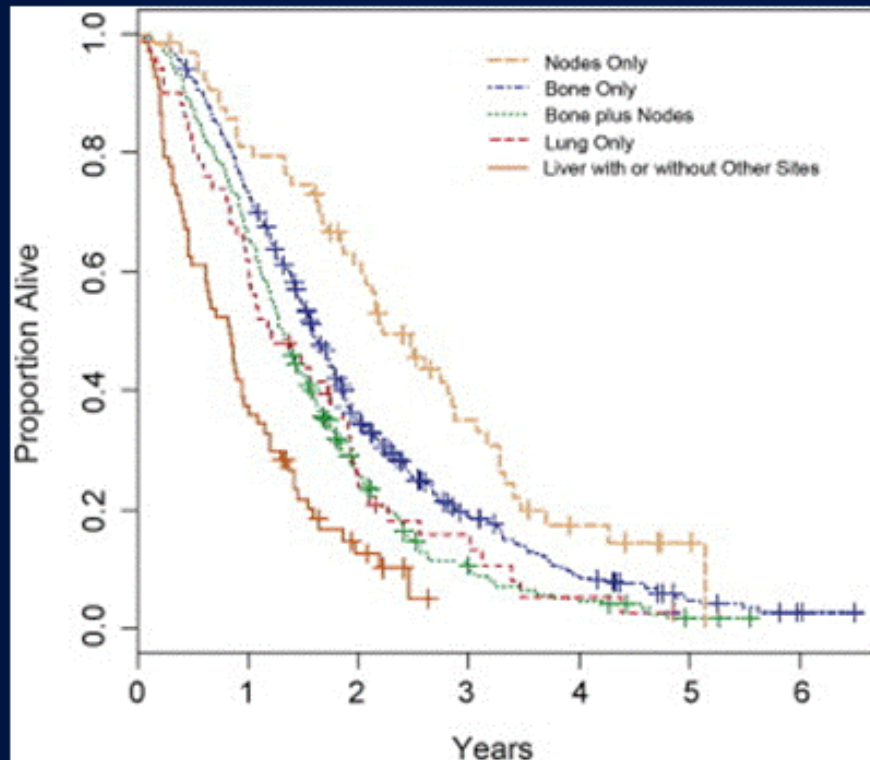
About 4% of prostate cancer have distant metastases at diagnosis

Bone metastases are most common

Metastatic disease are virtually incurable

The aim of therapy is to control the disease while maintaining quality of life

# TAX327: Influence on Metastatic Site on Survival



# ADT

Bilateral orchiectomy or surgical castration

LHRH agonist

Leuprolide acetate , goserelin, buserelin

LHRH antagonist

Abarelix, degarelix

Anti-androgens

Bicalutamide, nilutamide

# ADT

LHRH antagonists may produce an initial surge in testosterone (flare) before a decline in the levels

Orchiectomy is preferred in patients who are unlikely to comply with medical therapy or due to cost

Orchiectomy causes immediate fall in testosterone levels

LHRH antagonist do not cause the “flare”

Anti-androgen do not cause a decline in testosterone levels



# Side Effects of ADT

## Side Effects of ADT

<b>Sexual Side Effects</b>	
Decreased Libido	Erectile dysfunction
<b>Physical changes</b>	
Hot Flashes	Fatigue
Weight Gain	Gynecomastia
Decreased muscle mass	Decreased bone mineral density
Hair Changes	Decrease size of penis / testis
Breast pain	
<b>Metabolic Changes</b>	
Lipid changes (may lead to heart disease)	Anemia
Increased risk of Diabetes Mellitus	
<b>Mental Changes</b>	
Lack of Initiative	Decreased memory
Emotional lability	Decreased cognitive function

# Metastatic Castration-Resistant Prostate Cancer (CRPC)

Disease state characterized by progression despite castrate levels of testosterone

# 1<sup>st</sup> Generation Anti-Androgens

## Androgen Receptor Antagonists

Nilutamide

Flutamide

Bicalutamide

Ketokonazole (off-label, likely non-specific cyp-17 inhibition)

Limited role in treatment of non-metastatic Castration Resistant Prostate Cancer (or to prevent flare with ADT)

# Therapeutic Options in Metastatic CRPC that Improve Survival

FDA approved

Docetaxel

Sipuleucel-T

Abiraterone

Cabazitaxel (after docetaxel)

Enzalutamide

Radium-223

# Docetaxel

In 1960s, crude extract of the bark of the Pacific yew tree, *Taxus brevifolia*, was shown to have suppressive activity in preclinical tumor models.

By 1971, paclitaxel was identified as the active constituent of the bark extract.

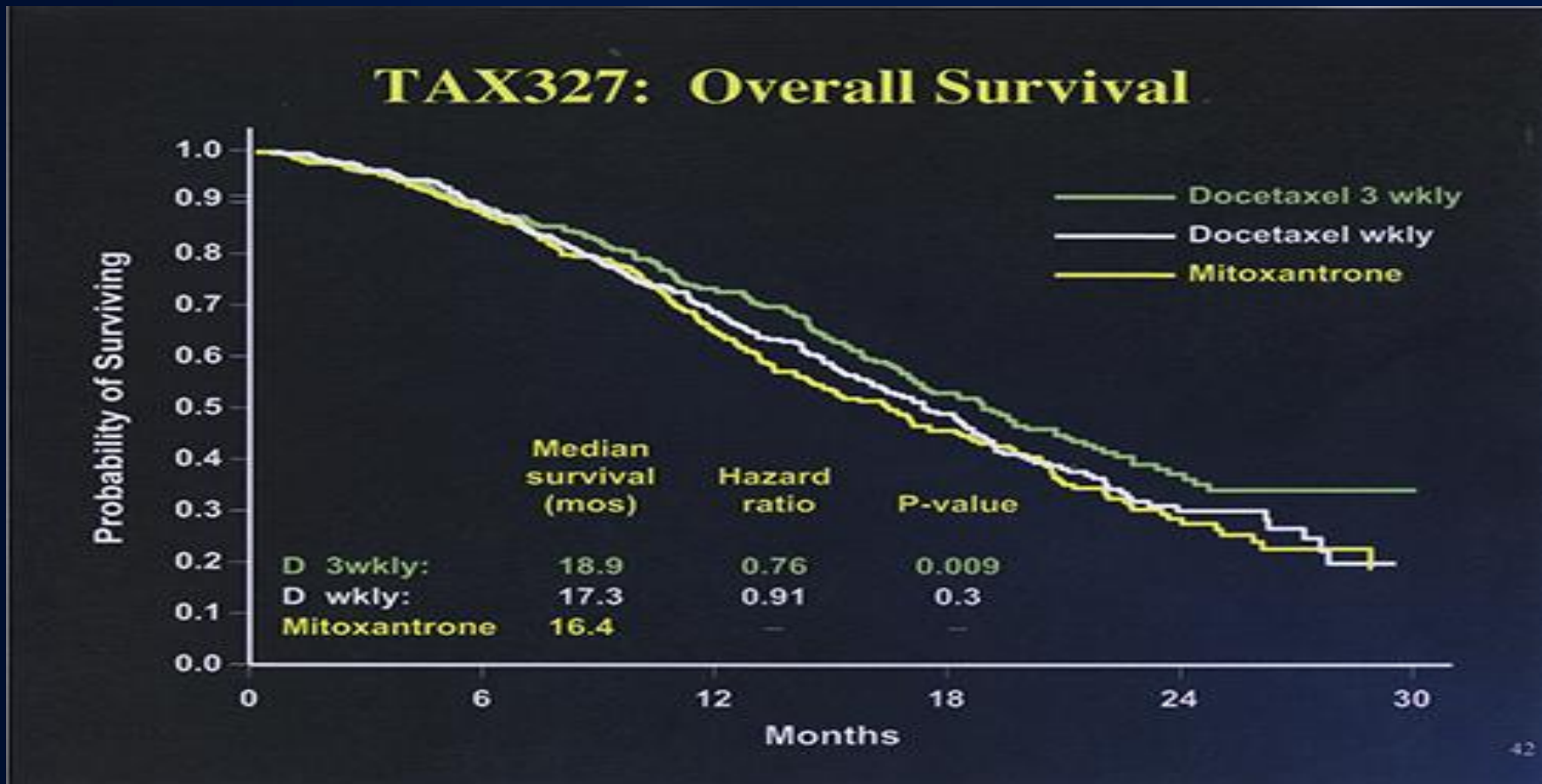
Taxanes exhibit antimicrotubule and antitumor activity

*Emerging data suggests that taxanes inhibit AR translocation via microtubules*

# TAX327

A multicenter randomized phase II study of 3 weekly Docetaxel + Prednisone vs Weekly Docetaxel + Prednisone vs Mitoxantrone + Prednisone

# TAX327: Overall Survival



# TAX327-Summary

Pain response was better with docetaxel containing regimens (35% and 31% vs. 22%)

Quality of life was better with docetaxel containing regimens (22% and 23% vs. 13%)

Is 2.5 month clinically significant?

The control arm consisted of an active agent

There was a cross-over which likely diminished the treatment effect



# Docetaxel AEs

Central nervous system: Central nervous system toxicity (20% to 58%; severe: 6%; including neuropathy)

Dermatologic: Alopecia (56% to 76%), dermatological reaction (20% to 48%; severe:  $\leq 5\%$ ), nail disease (11% to 41%)

Endocrine & metabolic: Fluid retention (13% to 60%; severe: 7% to 9%; dose dependent)

Gastrointestinal: Stomatitis (19% to 53%; severe 1% to 8%), diarrhea (23% to 43%; severe: 5% to 6%), nausea (34% to 42%), vomiting (22% to 23%)

Hematologic & oncologic: Neutropenia (84% to 99%; grade 4: 75% to 86%; nadir [median]: 7 days, duration [severe neutropenia]: 7 days; dose dependent), leukopenia (84% to 99%; grade 4: 32% to 44%), anemia (65% to 97%; dose dependent; grades 3/4: 8% to 9%), thrombocytopenia (8% to 14%; grade 4: 1%; dose dependent), febrile neutropenia (5% to 14%; dose dependent)

Hepatic: Increased serum transaminases (4% to 19%)

Hypersensitivity: Hypersensitivity (1% to 21%; with premedication 15%)

Infection: Infection (1% to 34%; dose dependent)

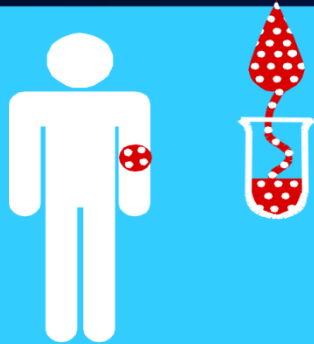
Neuromuscular & skeletal: Weakness (53% to 66%; severe 13% to 18%), myalgia (3% to 23%), neuromuscular reaction (16%)

Respiratory: Pulmonary reaction (41%)

# Therapeutic Cancer Vaccine: Sipuleucel-T

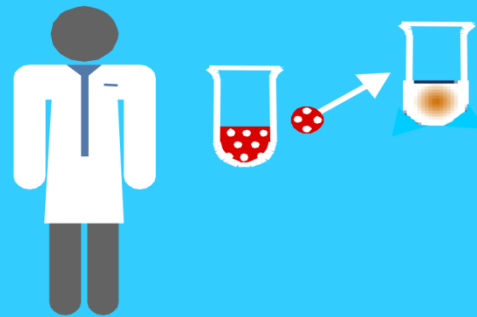
## Therapeutic Cancer Vaccine: Sipuleucel-T

Day 1  
Leukapheresis



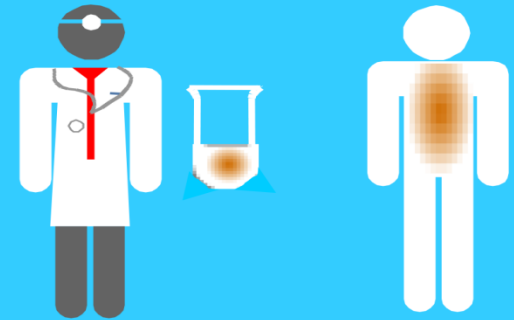
Apheresis Center

Day 2-3  
sipuleucel-T is  
manufactured



Company (Dendreon)

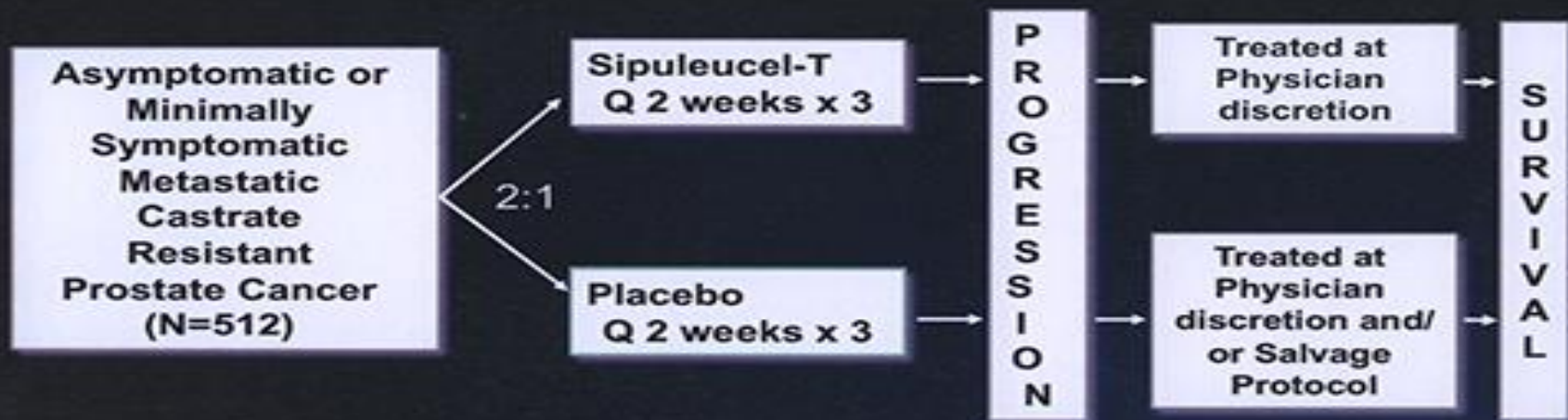
Day 3-4  
Patient is infused



Doctor's Office

# IMPACT: Randomized Phase 3 Trial

## IMPACT: Randomized Phase 3 Trial (IMmunotherapy P<sub>r</sub>ostate A<sub>d</sub>enoC<sub>a</sub>rcinoma T<sub>r</sub>eatment)



Primary endpoint:

Overall Survival

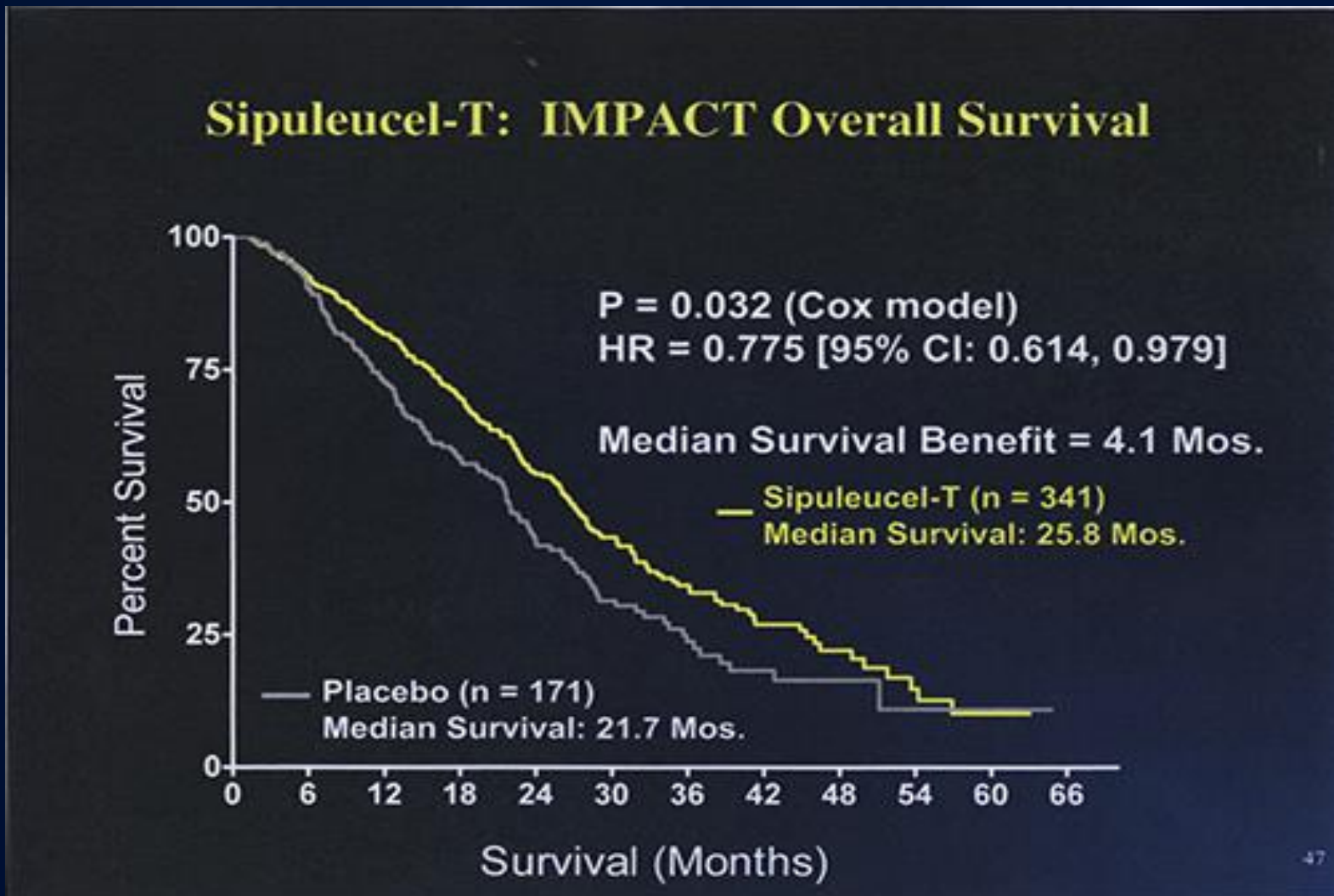
Secondary endpoint:

Time to Objective Disease Progression

Kantoff PW et al. NEJM. 2010;363:411-22

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# Sipuleucel-T: IMPACT Overall Survival



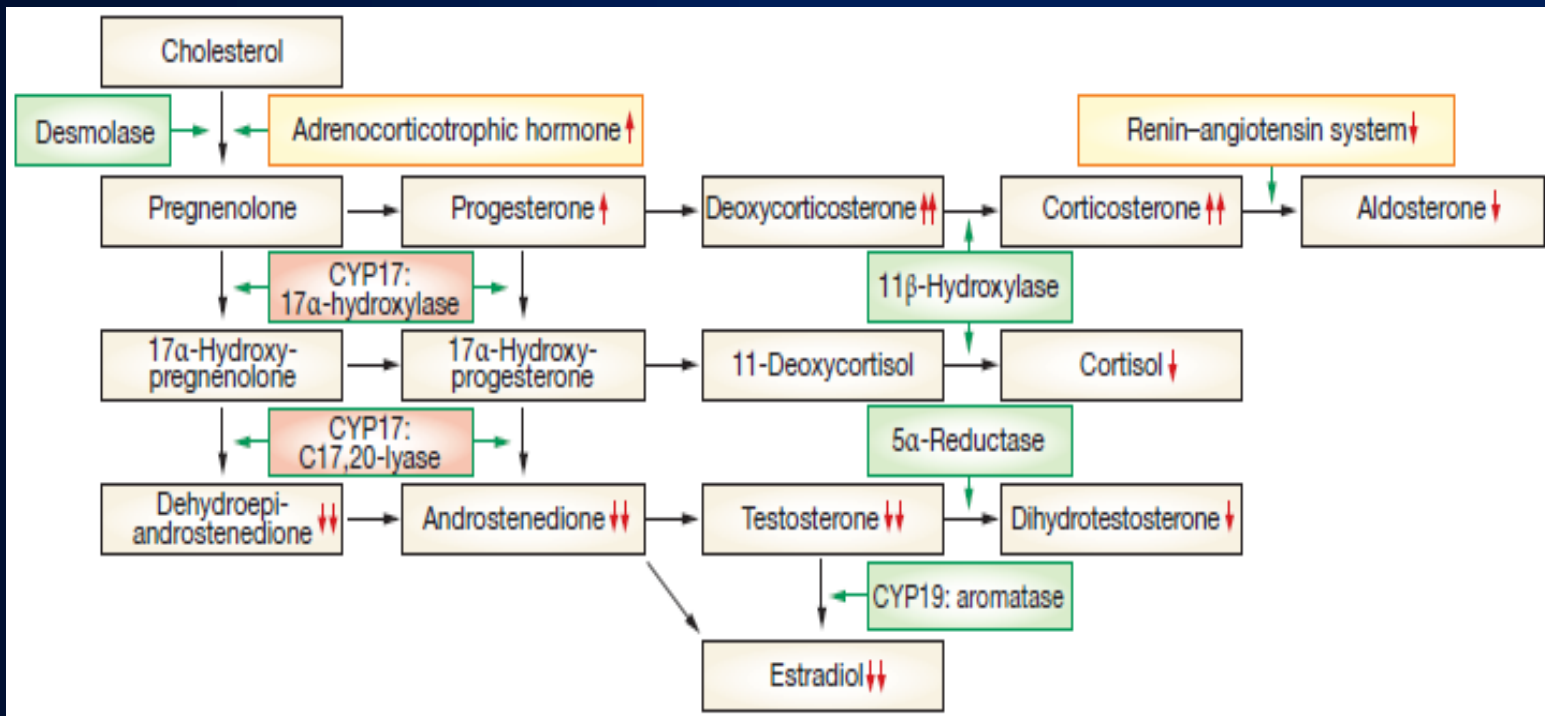
# Sipuleucel-T AEs

chills, fatigue, fever, nausea, and headache

Cerebrovascular events were reported in 3.5 percent of patients treated with sipuleucel-T patients and 2.4 percent of patients who received placebo.

# Rationale for Abiraterone in CRPC.

There is up-regulation of androgen biosynthesis enzymes in CRPC. Blocks androgen synthesis by the adrenal glands, testes and within the prostate tumor tissue



## **Abiraterone: COU-AA-301 Study Design**

**1195 prostate cancer patients were randomized and treated with Abiraterone acetate 1000 mg orally daily**

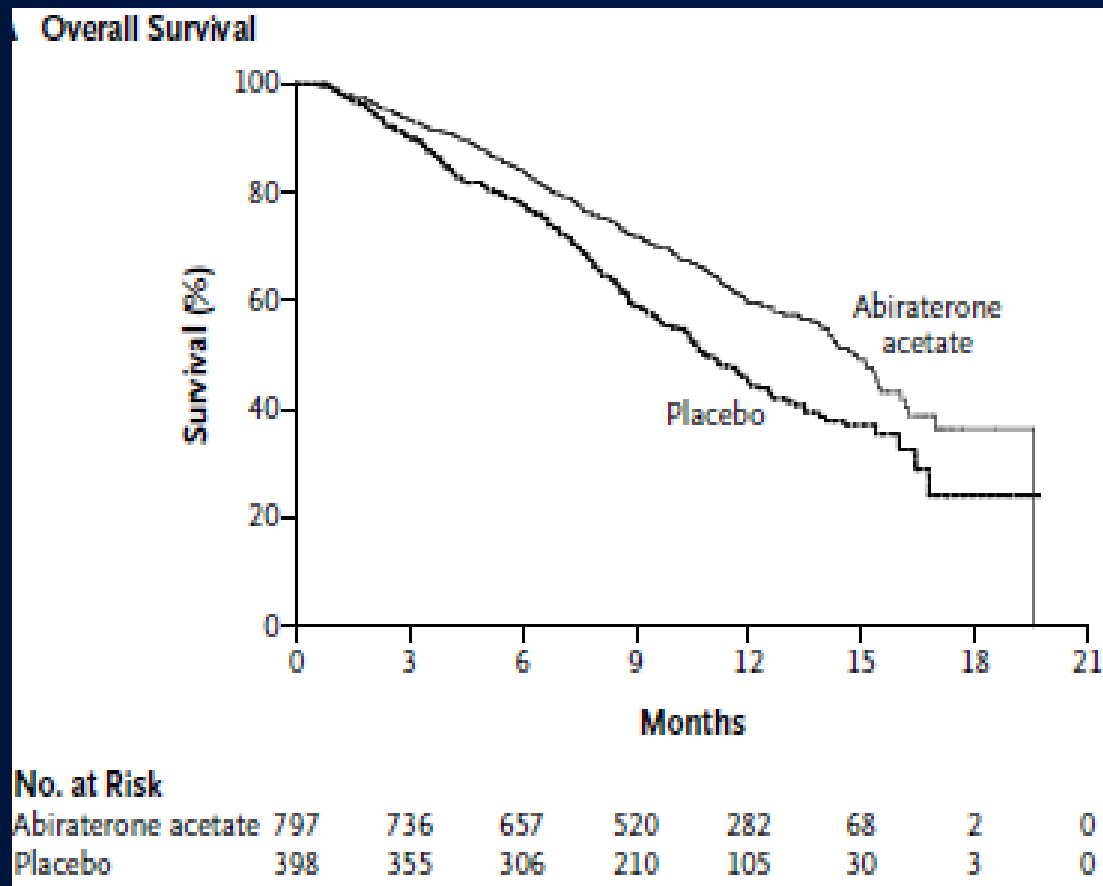
**Prednisone 5 mg orally twice daily n = 797 or Placebo orally daily Prednisone 5 mg orally twice daily n = 398.**

**The primary endpoint was overall survival.**

**This study was conducted in 147 sites in 13 countries**

**Patients were enrolled from May 2008 through July 2009**

# Abiraterone: COU-AA-301 Trial



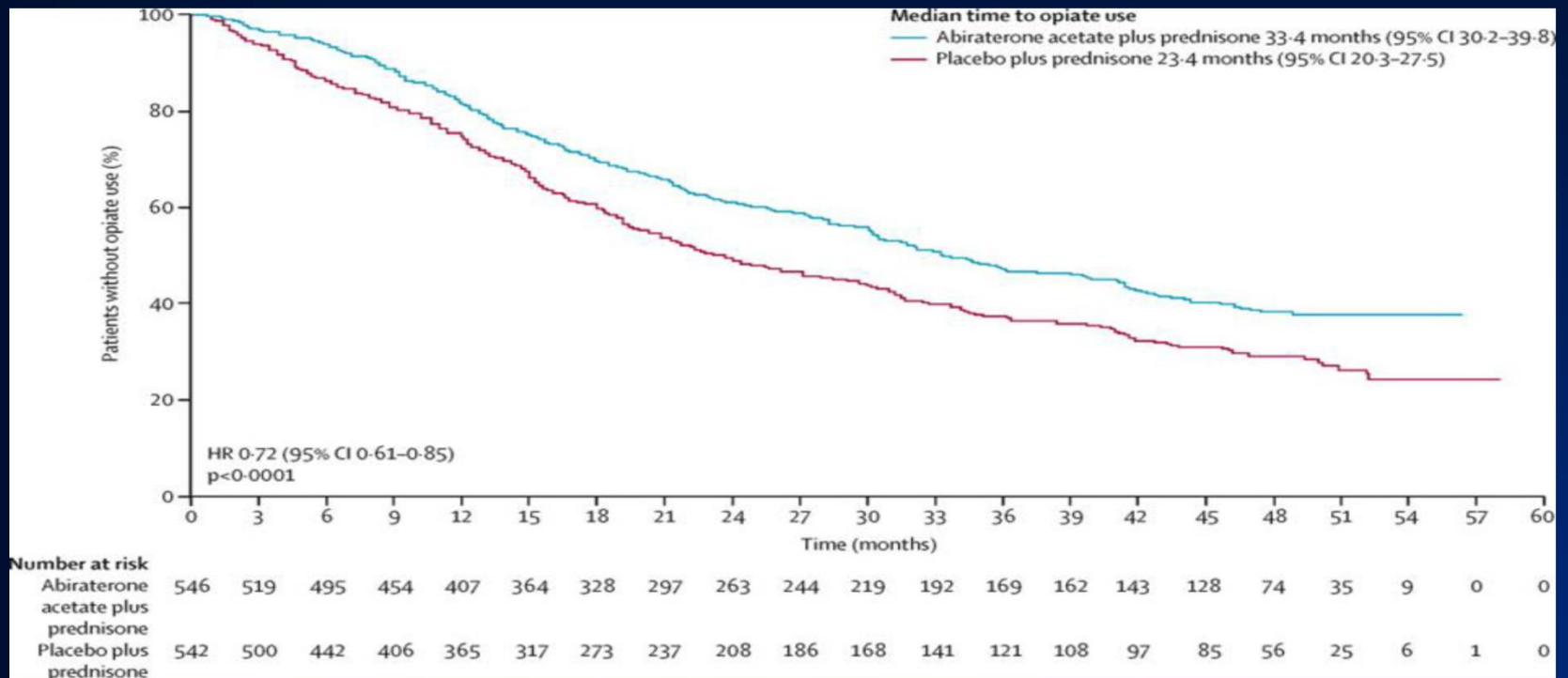


# Abiraterone: COU-AA-301 Trial

Variable	Abiraterone		Hazard Ratio (95% CI)	P Value
	Acetate (N=797)	Placebo (N=398)		
Time to PSA progression (mo)	10.2	6.6	0.58 (0.46–0.73)	<0.001
Progression-free survival according to radiographic evidence (mo)	5.6	3.6	0.67 (0.59–0.78)	<0.001
PSA response rate (%)				
Total	38.0	10.1		<0.001
Confirmed response on the basis of the PSA concentration	29.1	5.5		<0.001
Objective response on the basis of imaging studies	14.0	2.8		<0.001

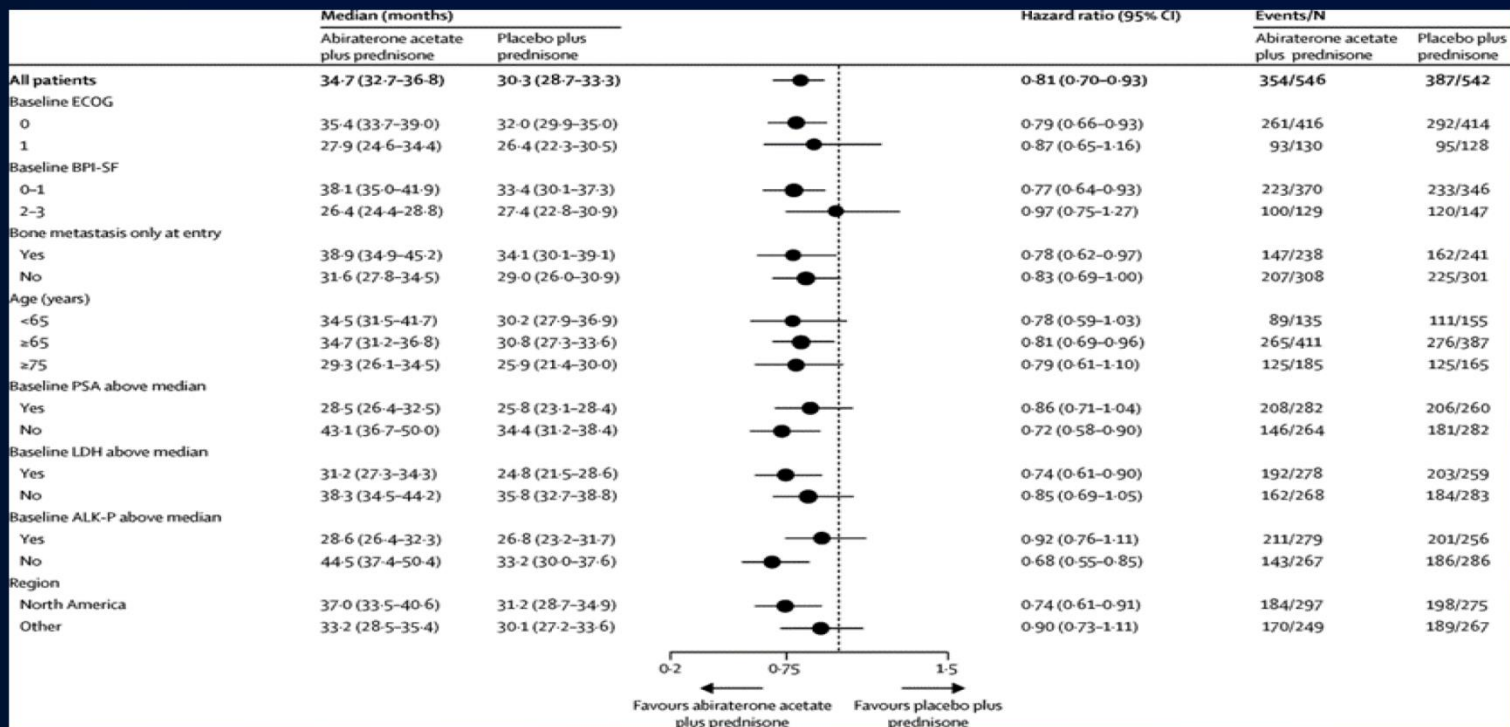
# COU-AA-302

## COU-AA-302 (chemo-naïve)



# COU-AA-302

## COU-AA-302 (chemo-naïve)



# Abiraterone AEs

Cardiovascular: Edema (25% to 27%), hypertension (9% to 22%; grades 3/4: 1% to 4%)

Central nervous system: Fatigue (39%), insomnia (14%)

Dermatologic: Bruise (13%)

Endocrine & metabolic: Increased serum triglycerides (63%), hyperglycemia (57%), hypernatremia (33%), hypokalemia (17% to 28%; grades 3/4: 3% to 5%), hypophosphatemia (24%; grades 3/4: 7%), hot flash (19% to 22%)

Gastrointestinal: Constipation (23%), diarrhea (18% to 22%), dyspepsia (6% to 11%)

Genitourinary: Urinary tract infection (12%)

Hematologic: Lymphocytopenia (38%; grades 3/4: 9%)

Hepatic: Increased serum ALT (11% to 42%; grades 3/4: 1% to 6%), increased serum AST (31% to 37%; grades 3/4: 2% to 3%)

Neuromuscular & skeletal: Joint swelling (30%, including joint discomfort), myalgia (26%)

Respiratory: Cough (11% to 17%), upper respiratory infection (5% to 13%), dyspnea (12%), nasopharyngitis (11%)

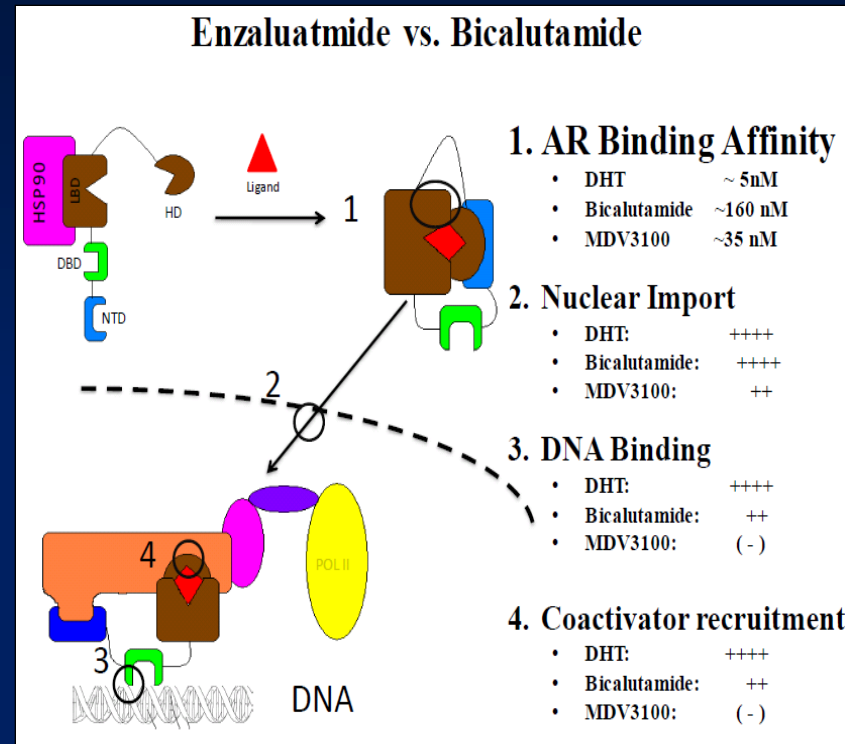
# Enzalutamide

A small molecule AR antagonist

Affinity 30 folds of  
bicalutamide

Prevent nuclear translocation

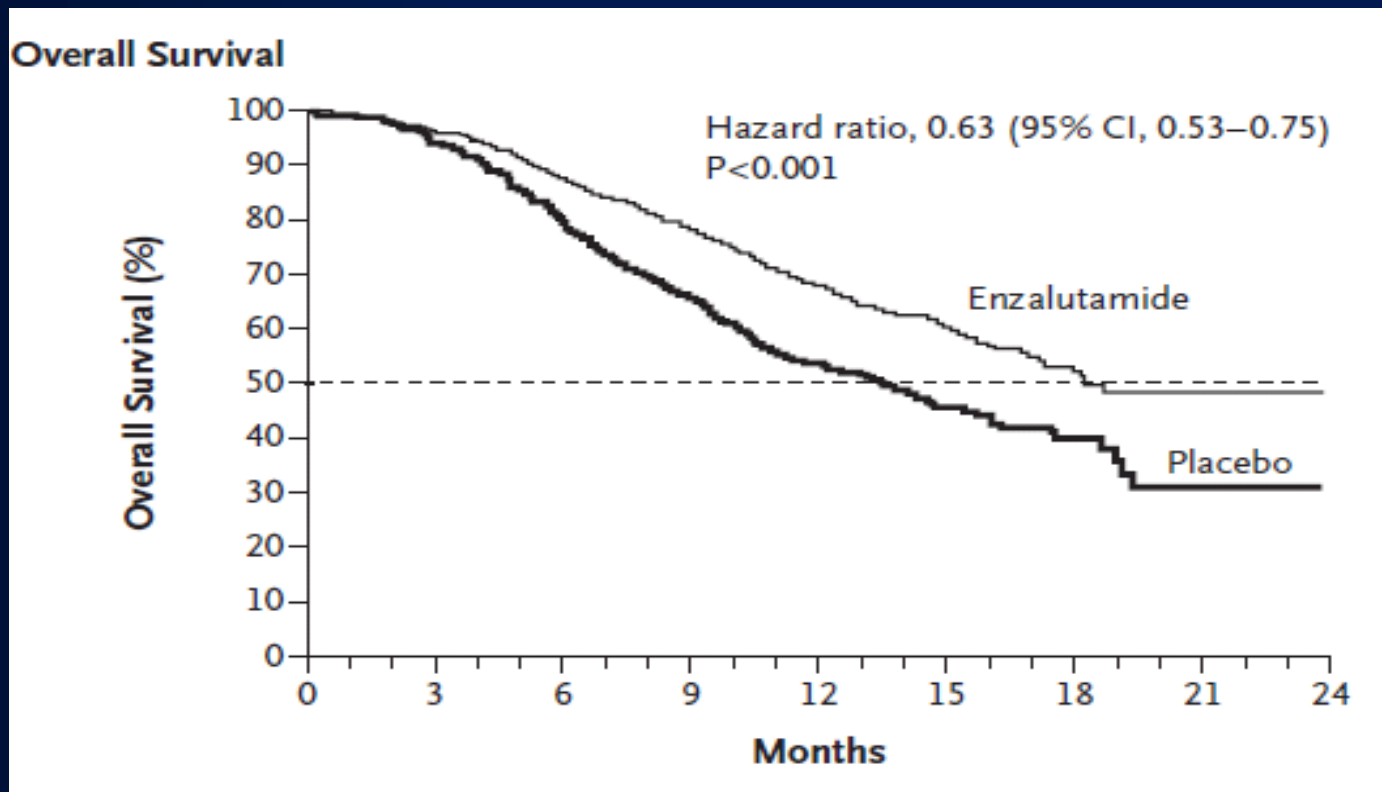
Prevents co-activator  
recruitment



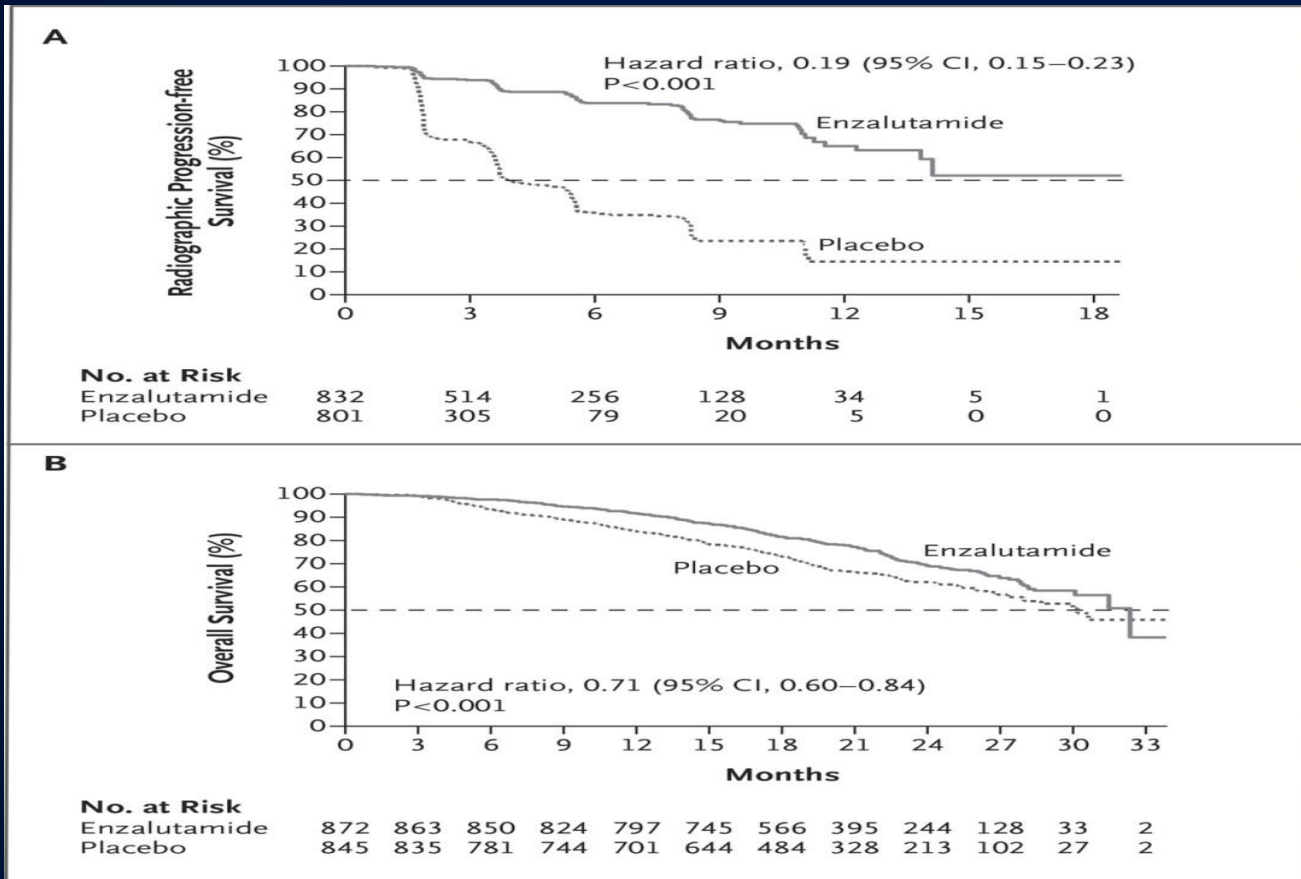
# AFFIRM:

Randomized phase III Study  
of MDV3100 vs Placebo in  
mCRPC after Progression on  
Docetaxel

**AFFIRM:** Phase III trial with 1199 patients with mCRPC Previously treated with docetaxel OS: 18.4 to 13.6 mos (HR: 0.63; P<0.001) TTP: 8.3 vs 2.9 mos (HR: 0.40; P <0.001) FDA approved on 8/31/2012



# PREVAIL: Randomized Phase III Study of Enzalutamide vs Placebo in mCRPC before chemotherapy





# Enzalutamide AEs

Cardiovascular: Peripheral edema (15%)

Central nervous system: Fatigue (51%), headache (12%)

Endocrine & metabolic: Hot flashes (20%)

Gastrointestinal: Diarrhea (22%)

Hematologic: Neutropenia (15%; grades 3/4: 1%)

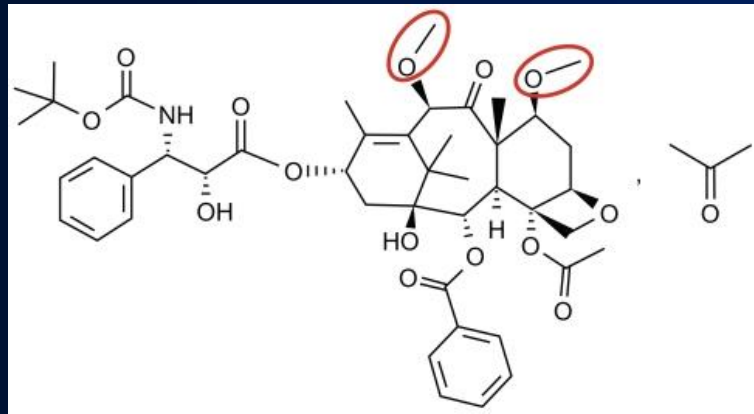
Neuromuscular & skeletal: Back pain (26%), arthralgia (21%), musculoskeletal pain (15%)

Respiratory: Upper respiratory tract infection (11%)

# Cabazitaxel

Novel taxane active in docetaxel resistant cell lines

Less affinity for P-glycoprotein pump  
Methoxyl side chain instead of hydroxyl groups found in docetaxel

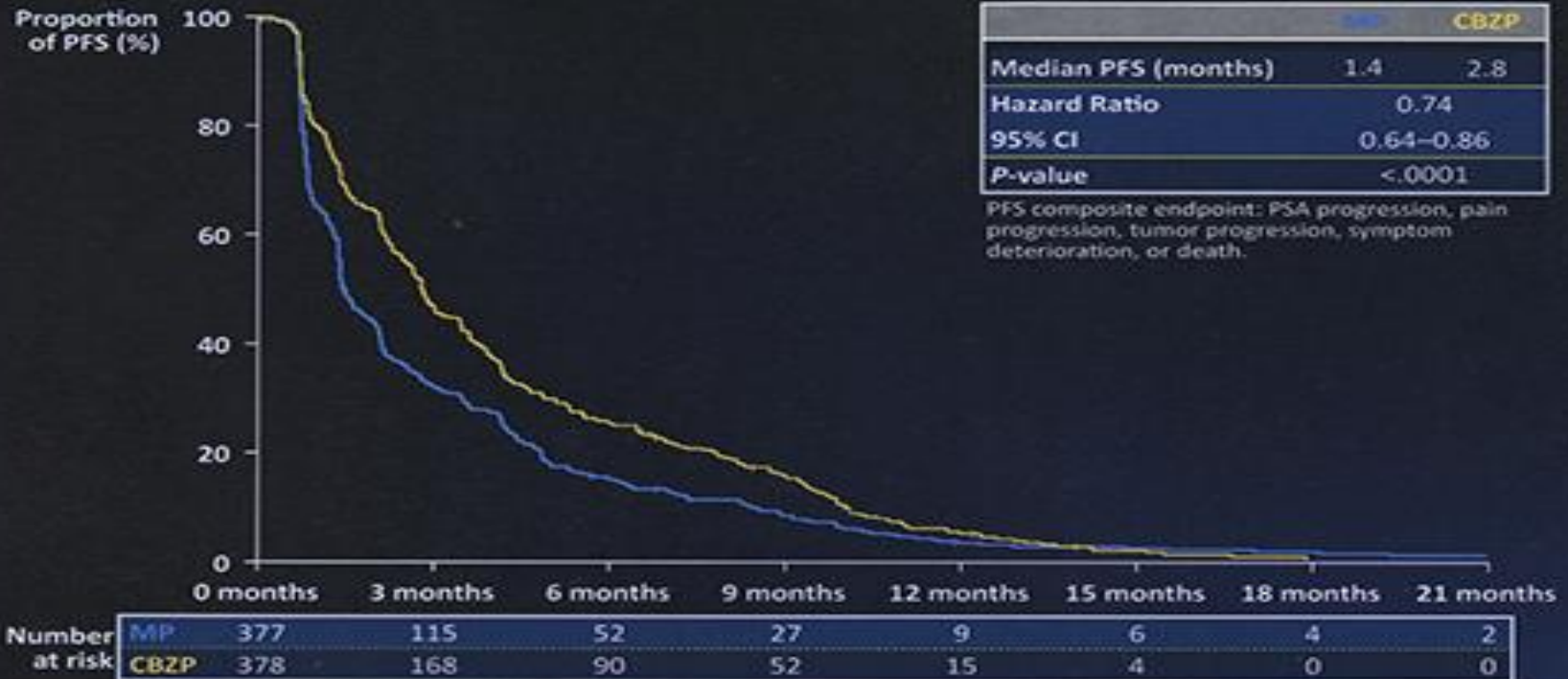


# TROPIC:

Randomized Phase III Study  
of Cabazitaxel vs Mitoxantrone  
in mCRPC after Progression on  
Docetaxel

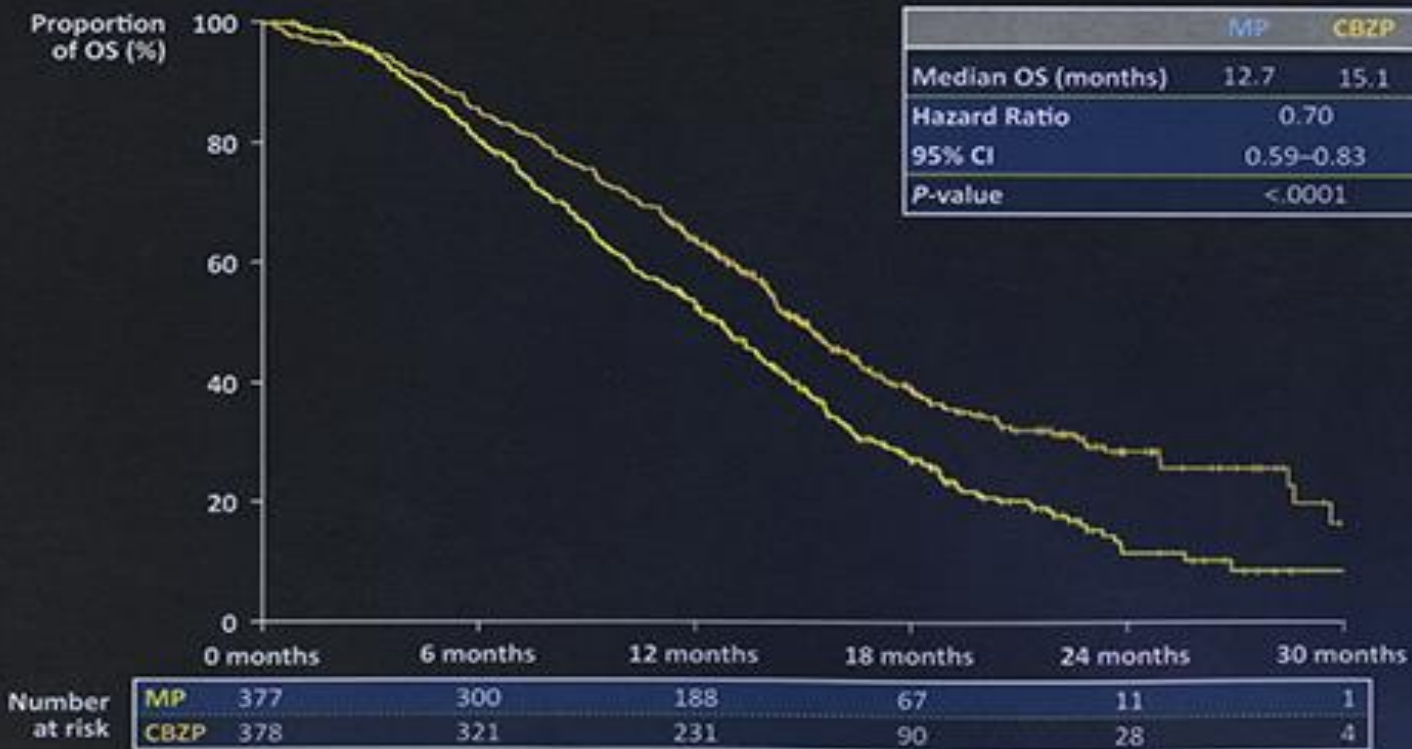
# TROPIC: Progression-Free Survival

## TROPIC: Progression-Free Survival



# TROPIC: Overall Survival

## TROPIC: Overall Survival



# Cabazitaxel AEs

Central nervous system: Fatigue (37%), fever (12%)

Gastrointestinal: Diarrhea (47%; grades 3/4: 6%), nausea (34%), vomiting (22%), constipation (20%), abdominal pain (17%), anorexia (16%), taste alteration (11%)

Hematologic: Anemia (98%; grades 3/4: 11%), leukopenia (96%; grades 3/4: 69%), neutropenia (94%; grades 3/4: 82%; nadir: 12 days [range: 4-17 days]), thrombocytopenia (48%; grades 3/4: 4%)

Neuromuscular & skeletal: Weakness (20%), back pain (16%), peripheral neuropathy (13%; grades 3/4: <1%), arthralgia (11%)

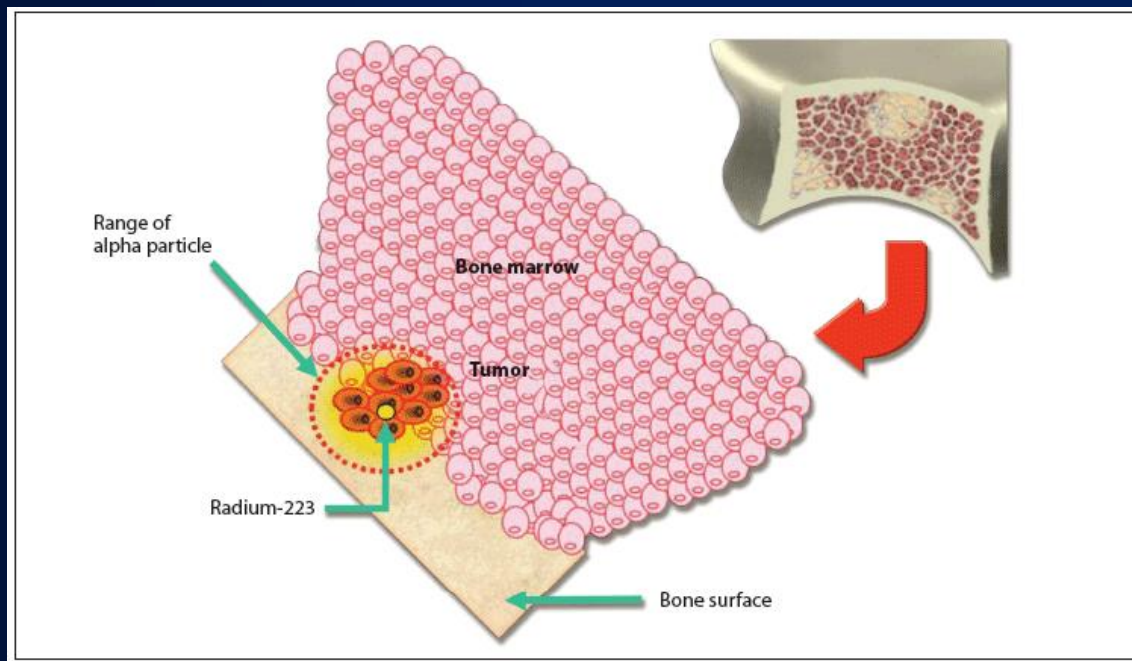
Renal: Hematuria (17%)

Respiratory: Dyspnea (12%), cough (11%)

# Radium-223 (Alpharadin)

Bone –targeting radiopharmaceutical

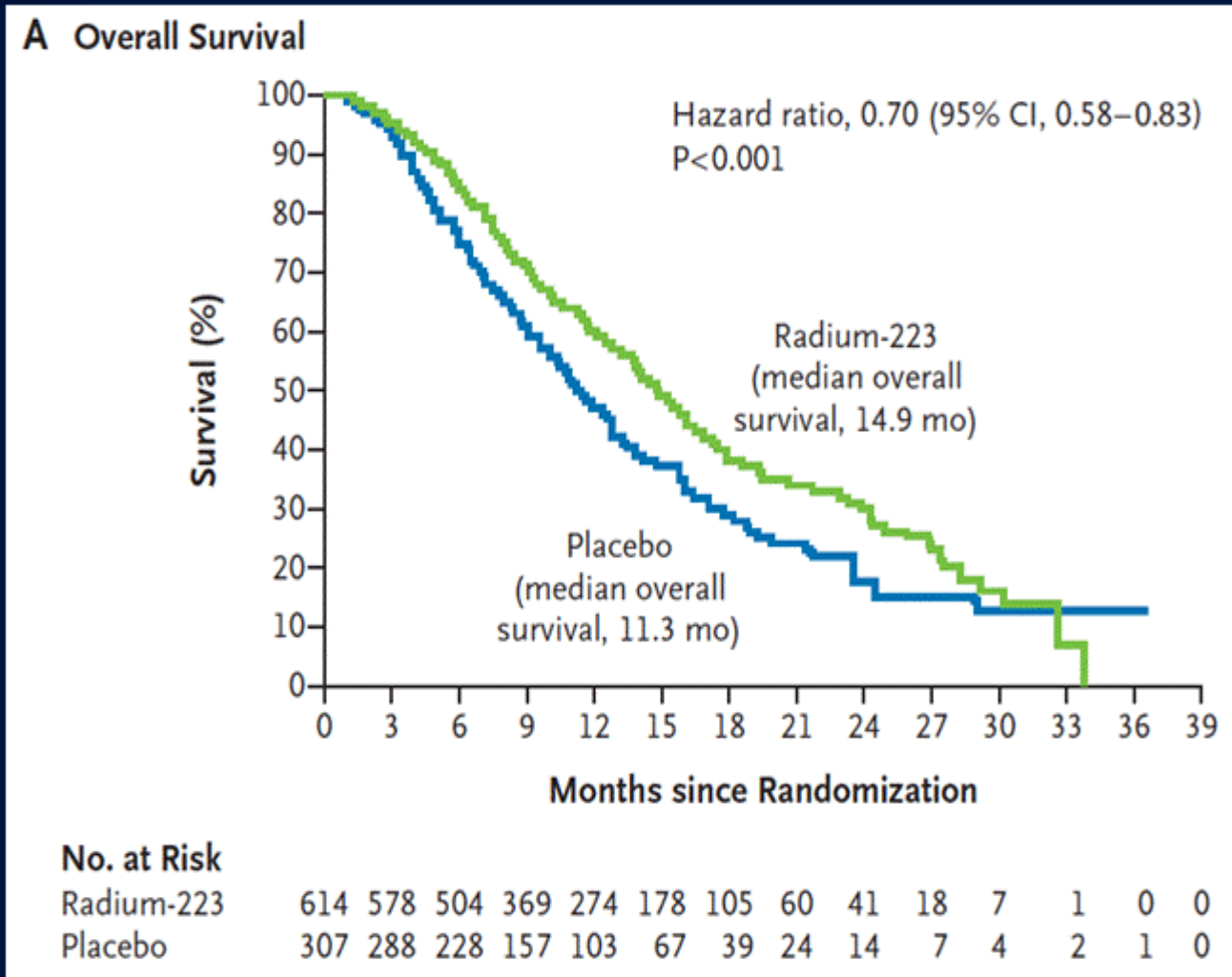
High energy alpha-particles with short range (<100 $\mu$ m) hence less bone marrow toxicity



**ALSYMPCA:** Randomized Phase III  
study of Radium-223 vs Placebo in  
mCRPC with bone metastases



# ALSYMPCA survival curve



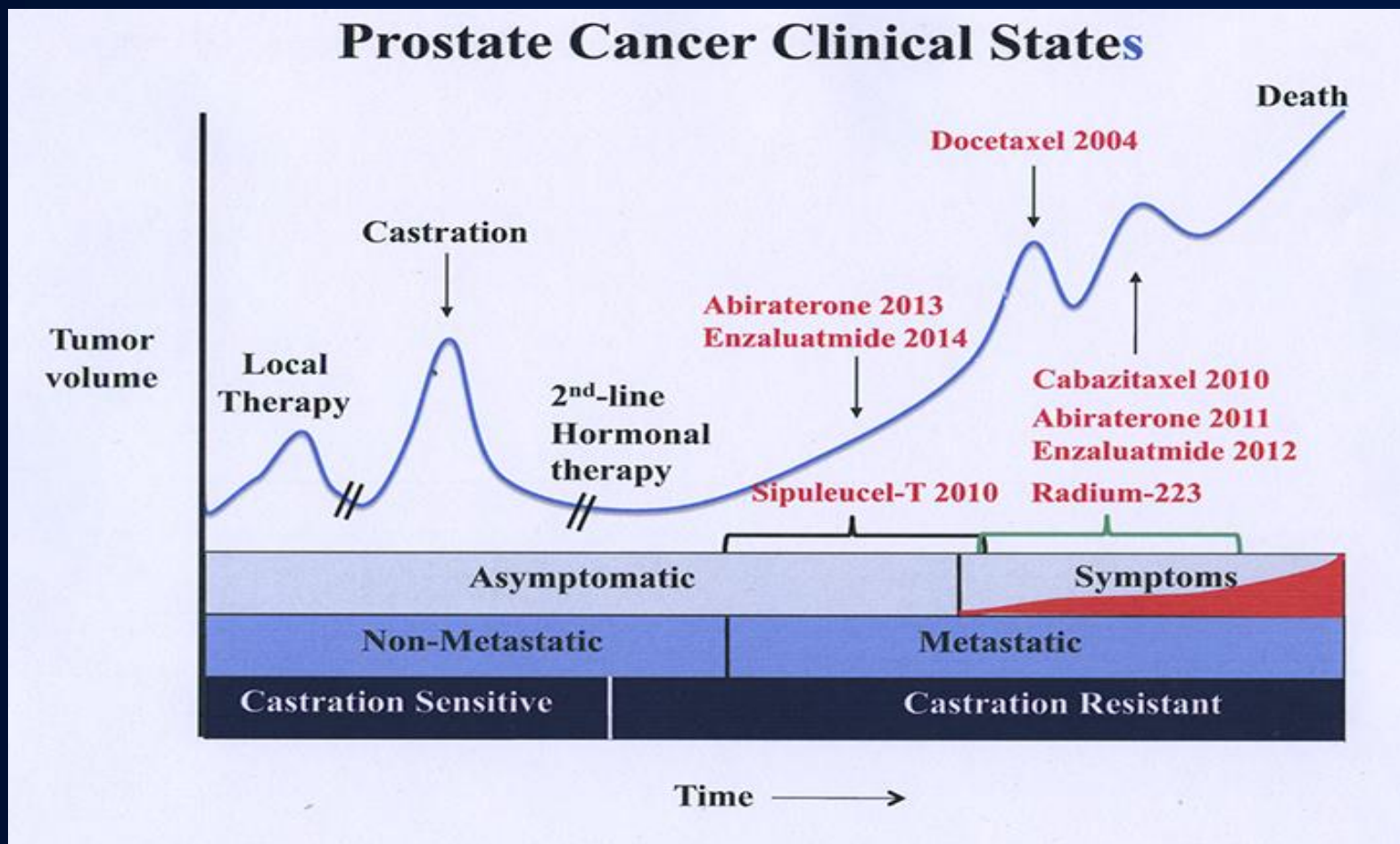
# Radium 223 AEs

Cardiovascular: Peripheral edema (13%)

Gastrointestinal: Nausea (36%), diarrhea (25%), vomiting (19%)

Hematologic & oncologic: Anemia (93%; grades 3/4: 6%), lymphocytopenia (72%; grades 3/4: 20%), leukopenia (35%; grades 3/4: 3%), thrombocytopenia (31%; grades 3/4: 1% to 6%), neutropenia (18%; grades 3/4: 1% to 3%)

# Prostate Cancer Clinical States



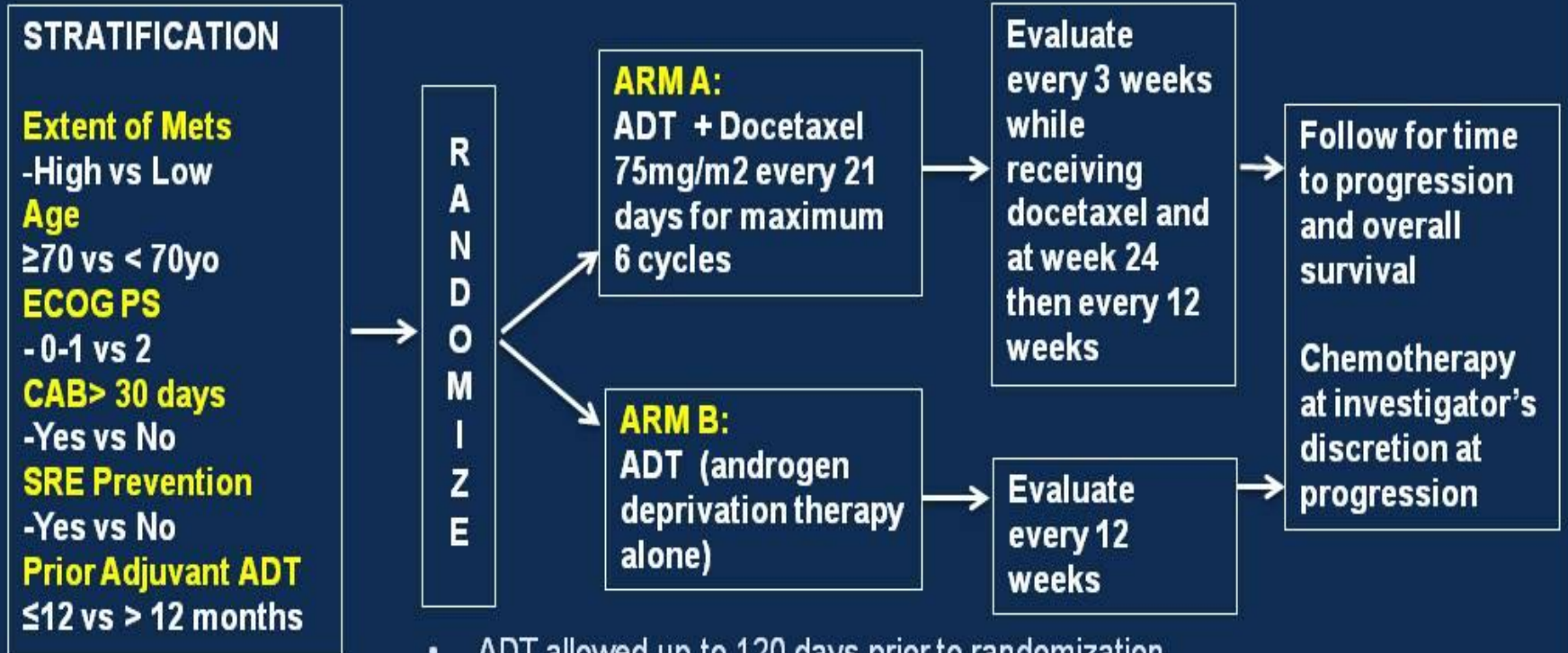
# Metastatic prostate cancer

## Metastatic Prostate Cancer

- About 4% of prostate cancer have distant metastases at diagnosis
- Bone metastases are most common
- Metastatic disease are virtually incurable
- The aim of therapy is to control the disease while maintaining quality of life

# E3805-CHAARTED Treatment

## E3805 – CHAARTED Treatment

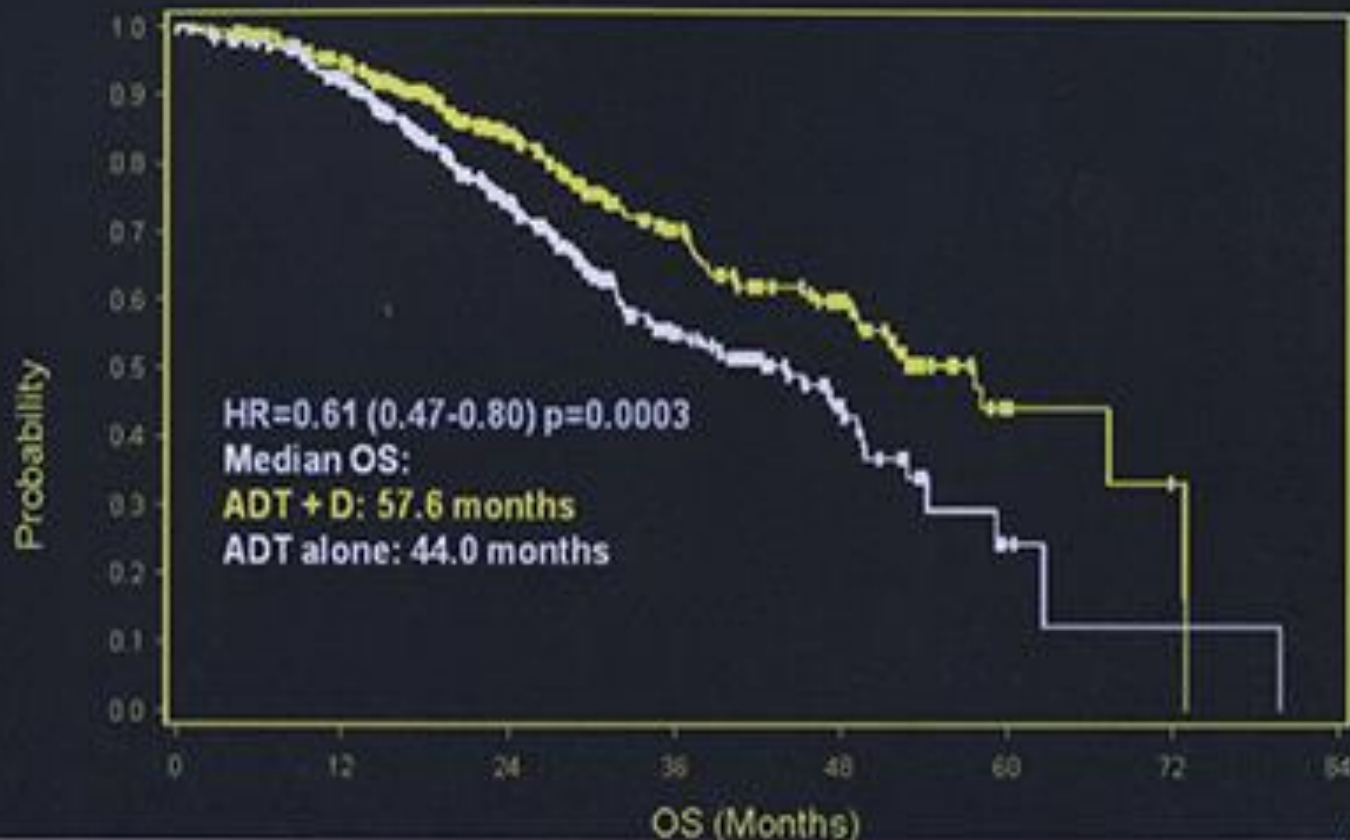


- ADT allowed up to 120 days prior to randomization.
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone

# Primary endpoint: Overall

• 1

## Primary endpoint: Overall survival



Presented by: Christopher J. Sweeney, MBBS

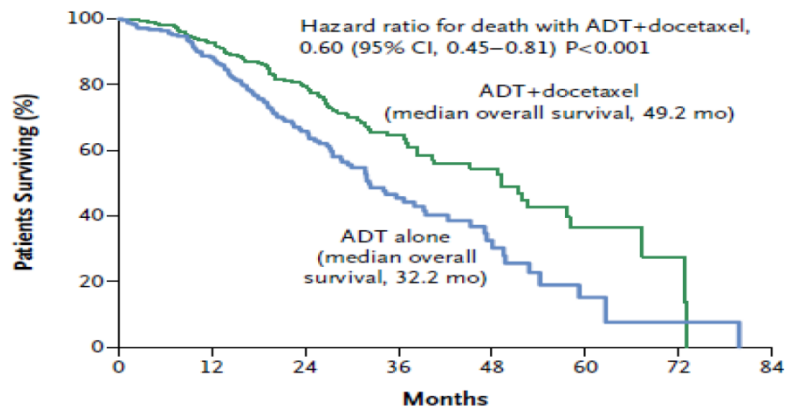
PRESENTED AT:



# CHAARTED: Subgroup analysis

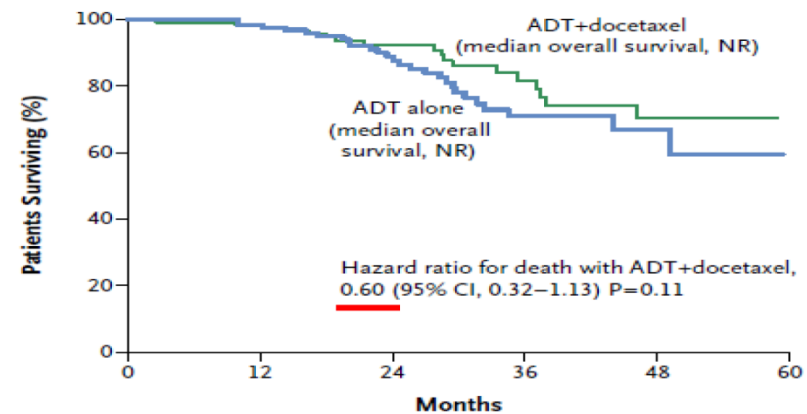
## CHAARTED: Subgroup Analysis

Patients with High-Volume Disease



No. at Risk	0	12	24	36	48	60	72	84
ADT+docetaxel	263	213	123	56	31	5	2	0
ADT alone	250	193	92	40	14	3	1	0

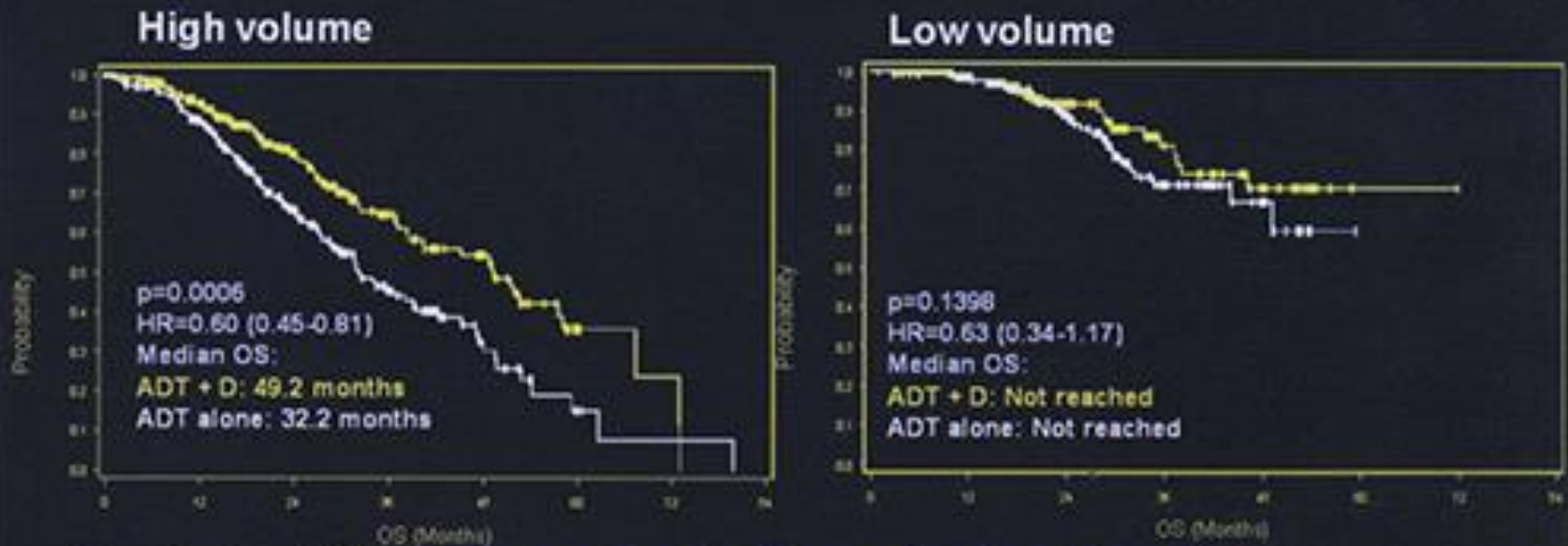
Patients with Low-Volume Disease



No. at Risk	0	12	24	36	48	60
ADT+docetaxel	134	120	66	33	15	0
ADT alone	143	125	76	31	13	0

# OS by extent of metastatic disease at the start of ADT

## OS by extent of metastatic disease at start of ADT



In patients with **high volume metastatic disease**, there is a **17 month improvement in median overall survival** from 32.2 months to 49.2 months  
We projected 33 months in ADT alone arm with collaboration of SWOG9346 team



# CHAARTED: Toxicity

## CHAARTED: Toxicity

**Table 3.** Adverse Events of Grade 3 or Higher among the 390 Patients Who Received the Docetaxel-Containing Regimen and Had Follow-up Data Available.\*

Event	Grade 3	Grade 4	Grade 5
	<i>no. of patients (%)</i>		
Allergic reaction	7 (1.8)	1 (0.3)	0
Fatigue	16 (4.1)	0	0
Diarrhea	4 (1.0)	0	0
Stomatitis	2 (0.5)	0	0
Neuropathy, motor	2 (0.5)	0	0
Neuropathy, sensory	2 (0.5)	0	0
Thromboembolism	1 (0.3)	2 (0.5)	0
Sudden death	0	0	1 (0.3)
Anemia	4 (1.0)	1 (0.3)	0
Thrombocytopenia	0	1 (0.3)	0
Neutropenia	12 (3.1)	35 (9.0)	0
Febrile neutropenia	15 (3.8)	9 (2.3)	0
Infection with neutropenia	5 (1.3)	4 (1.0)	0
Any event	65 (16.7)	49 (12.6)	1 (0.3)

## Cycles Administered

	ADT + Docetaxel (N=397)	
	Arm A	
Number of cycles	N	%
1	11	3.1
2	7	2.0
3	6	1.7
4	8	2.3
5	12	3.4
6	308	87.5
<b>Total</b>	<b>352*</b>	

# Summary

## Summary

- Localized Disease
  - RP, EBRT, Brachytherapy
- Androgen Deprivation Therapy (ADT)
  - High risk disease with EBRT
  - LN+ disease following RP
  - Metastatic disease
- Metastatic CRPC
  - Sipuleucel-T
  - Docetaxel with prednisone
  - Cabazitaxel with prednisone
  - Abiraterone with prednisone

# Future Directions

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- How to sequence the array of available and potential agents
- Multimodality therapy
- **Understanding Mechanisms of Resistance**