Prostate Cancer

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Educational Objectives

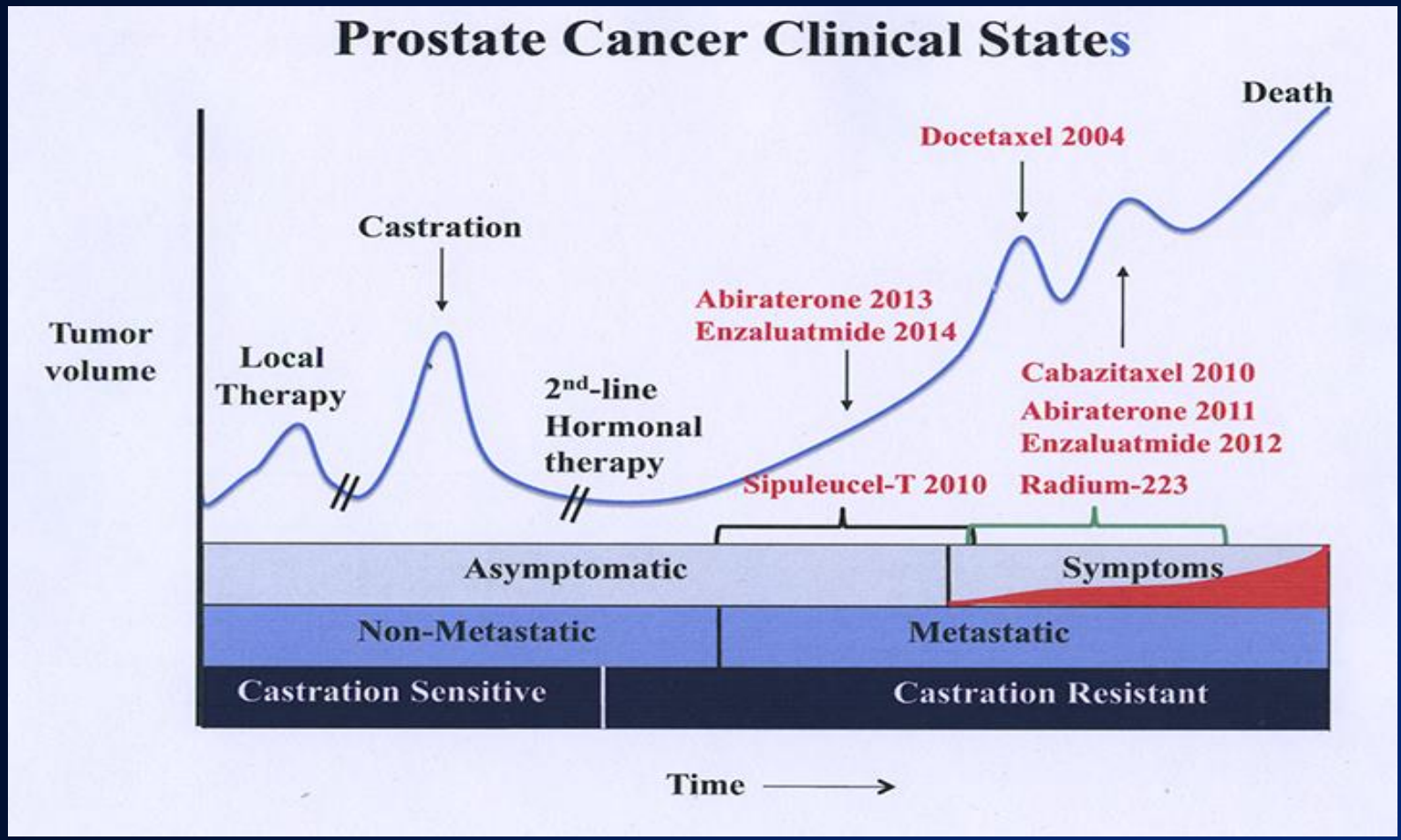
By the end of this session, participants should be able to

- 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



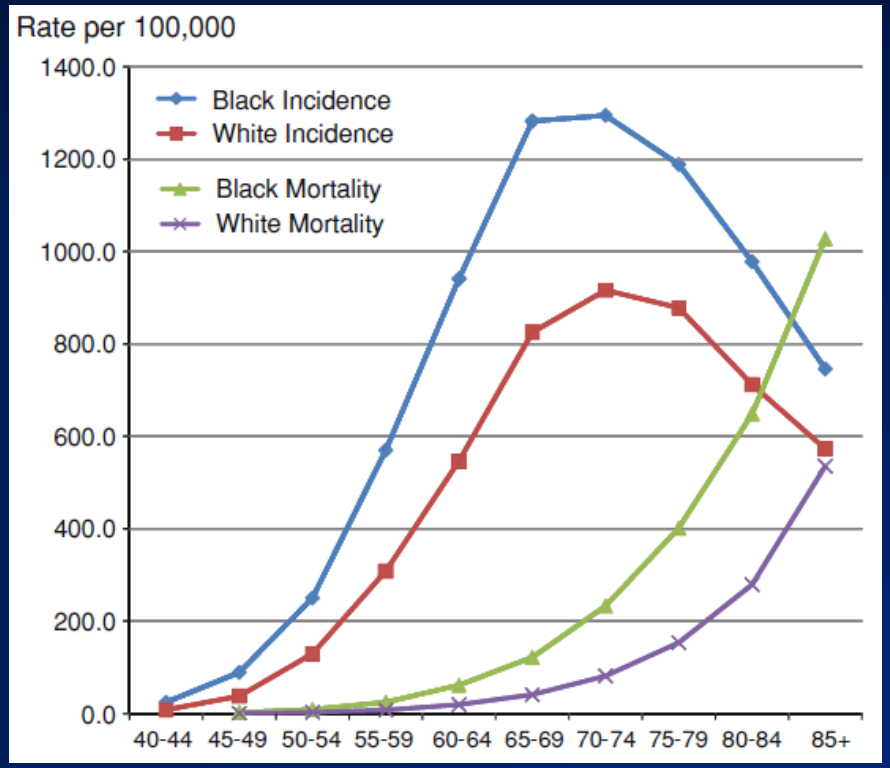
Epidemiology

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%
All Sites	**848,170**	**100%**

- 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

Risks

- Age
- Family history
- Genetic predisposition
  - HPCG
  - BRCA
  - TMPRSS2-ETS
- Environmental
- Obesity
- Race



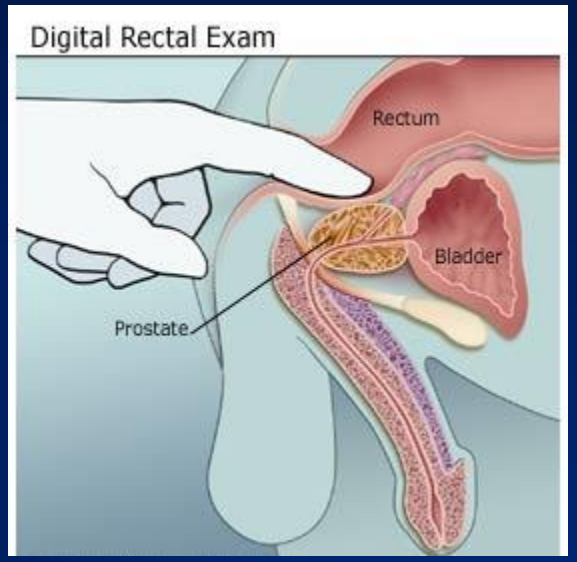
Prevention in Prostate Cancer… A cautionary Tale

- 5-α-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

Screening – Digital Rectal Exam

Digital rectal examination

- Sensitivity 53% and specificity 83%
- More advanced disease are detected

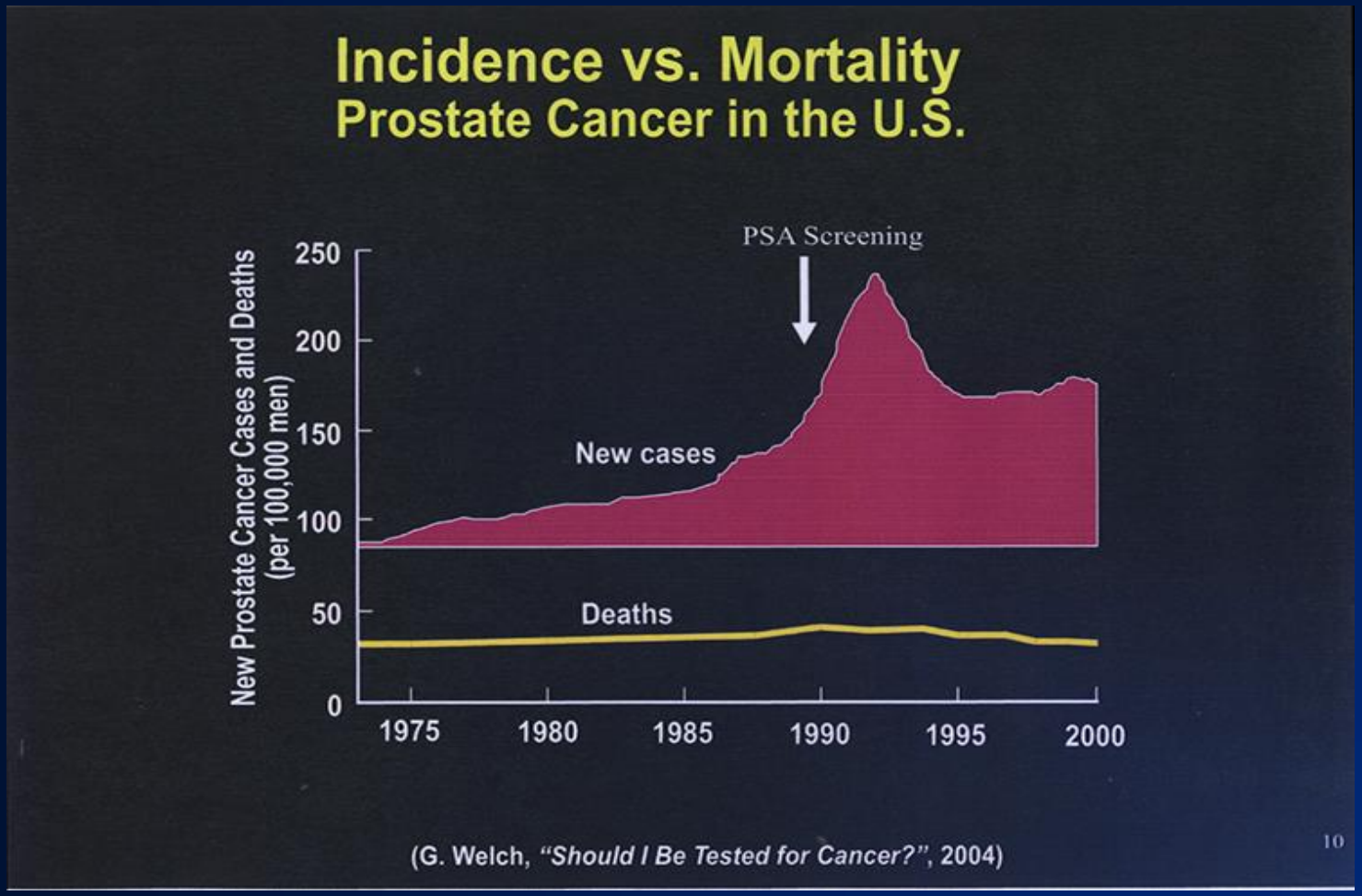


Screening - PSA

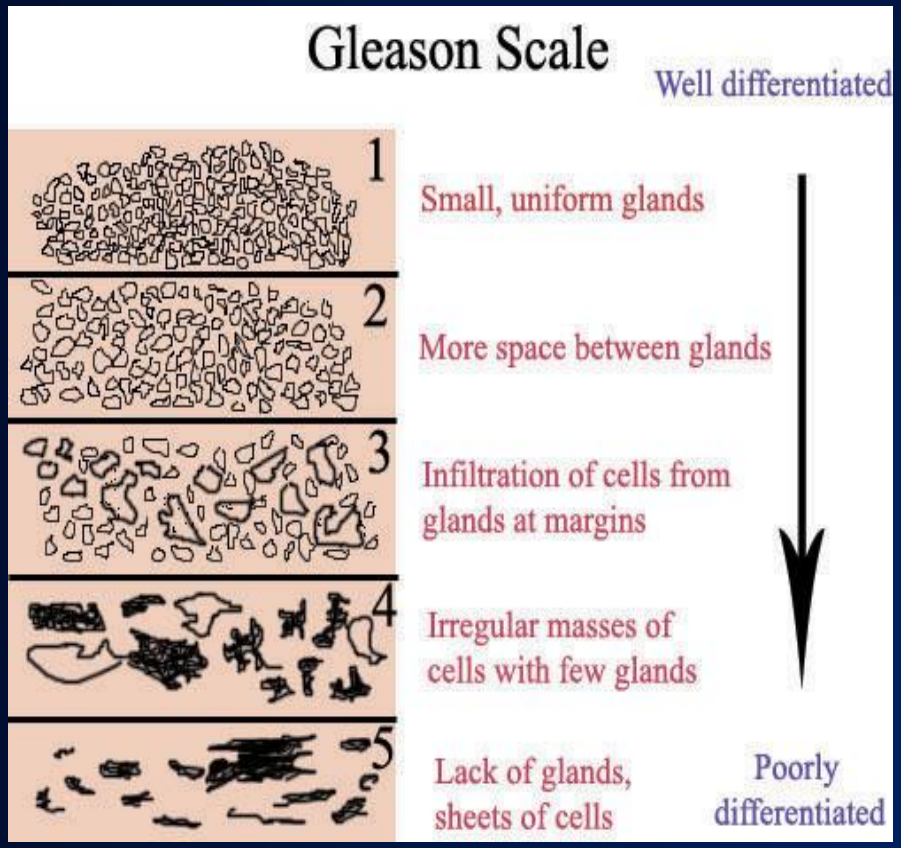
Total PSA

- At cutoff of 4.0ng/ml, sensitivity is 73% at 4 years and specificity is 91%
- “The yield of screening in terms of cancer cases detected declines rapidly with repeated annual testing. If screening were to reduce deaths, PSA screening as infrequently as every 4 years could yield as much of a benefit as annual screening” - USPSTF

Incidence versus Mortality Prostate cancer in the USA



Gleason Grading



Primary Grade

Greater 50%

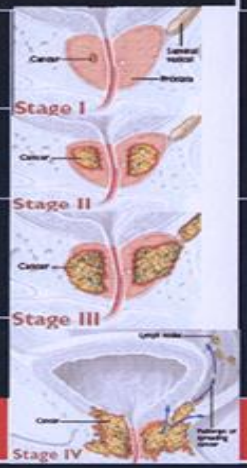
Secondary Grade

<50% but ≥5%

Staging

Staging

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



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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 surveilance

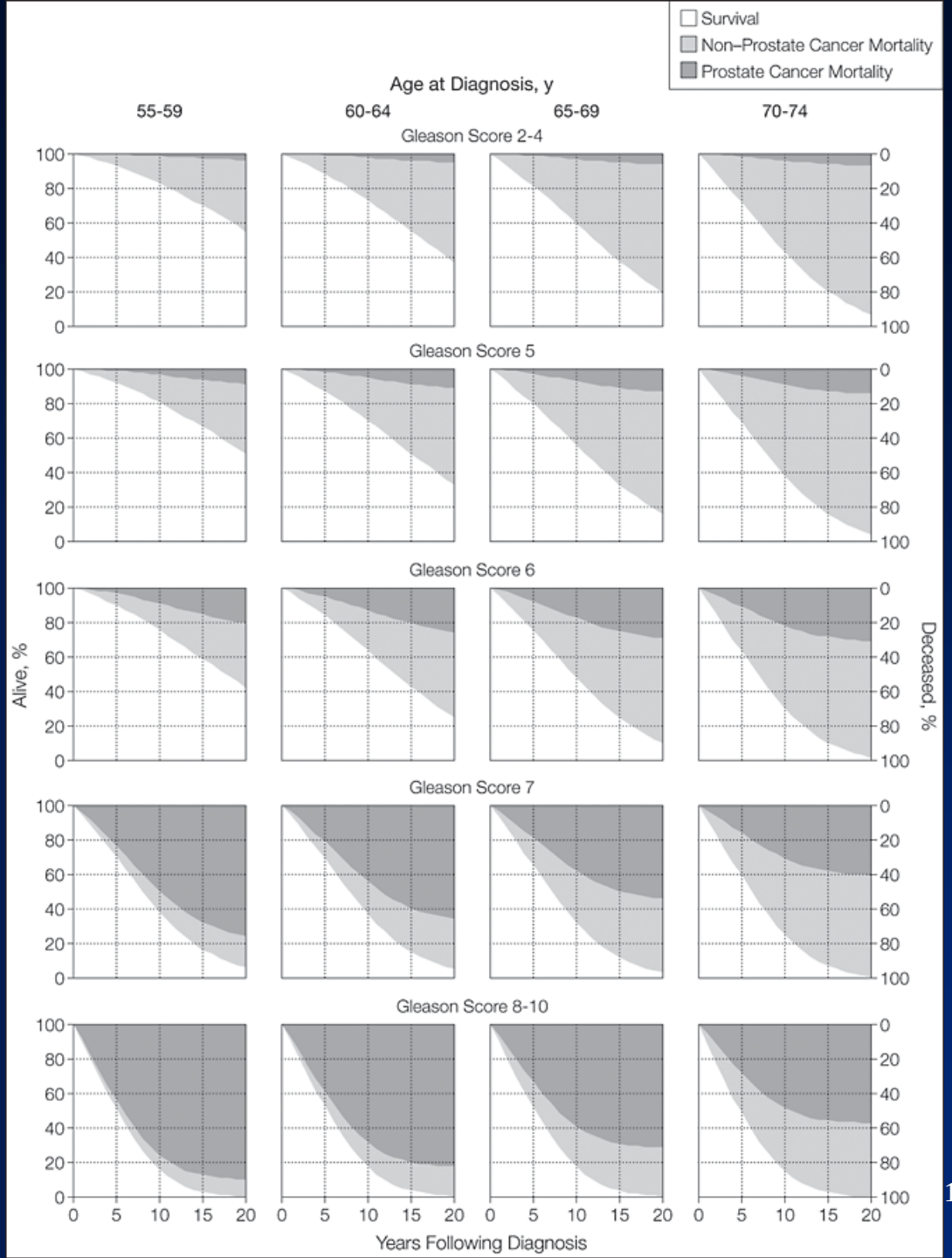
Conversion to active treatment when signs of disease progression develop

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 then current US patients
  - Only 5% of men had screen detected PC
- Advantage largely in men <65 y.o.

Surgery Complications

Incontinence

Erectile Dysfunction

Infection

Complications associated with anesthesia

Radiation Therapy-External Beam

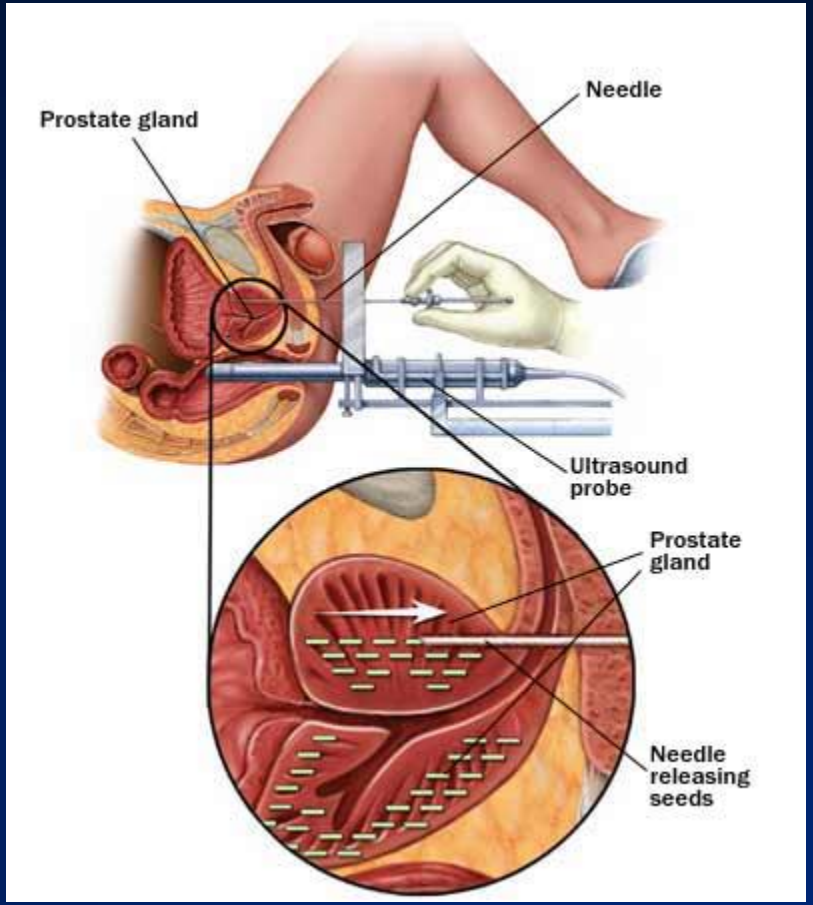
The principle is to deliver therapeutic dose of radiation to the tumor but minimize damage to adjacent structures

Modalities of external beam radiotherapy

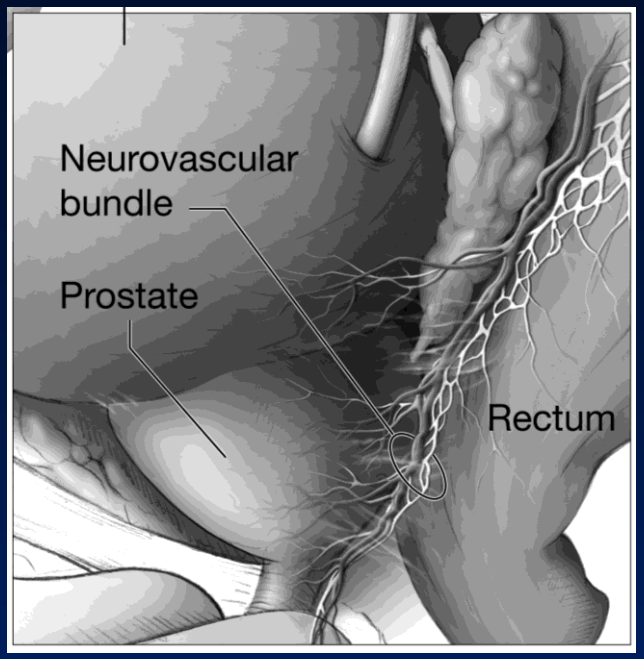
- 3-dimensional conformal radiation therapy (3D-CRT)
- Intensity modulated radiation therapy (IMRT)
- Image-guided radiation therapy (IGRT)
- Proton-beam radiation therapy

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 (HR3.42, 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_3N_0 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 ± 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%, $p=0.0004$)

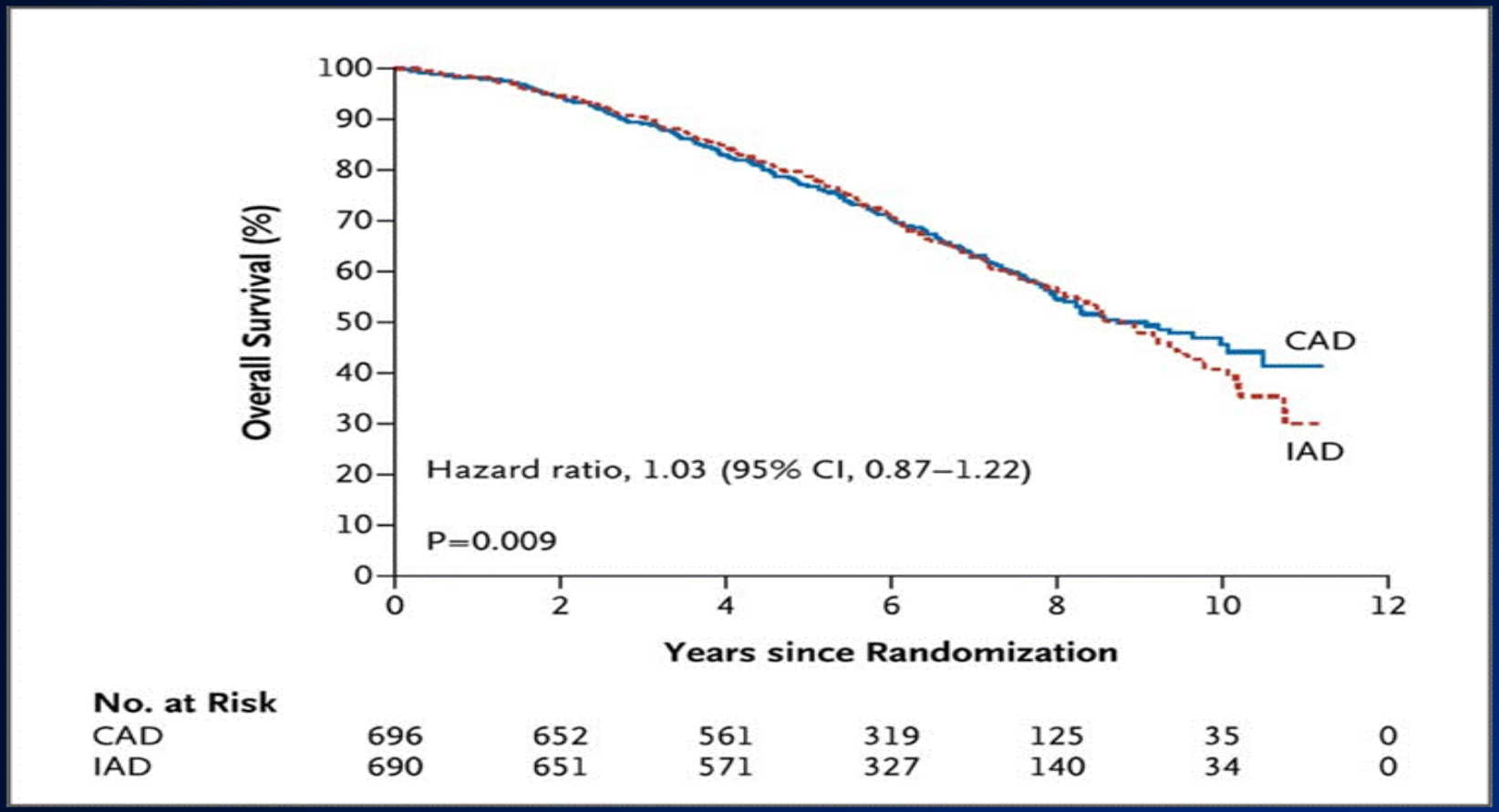
10-yr disease-specific mortality (30.4 vs. 10.3%, $p<0.0001$)

Biochemical Recurrence after Initial Prostatectomy or RT

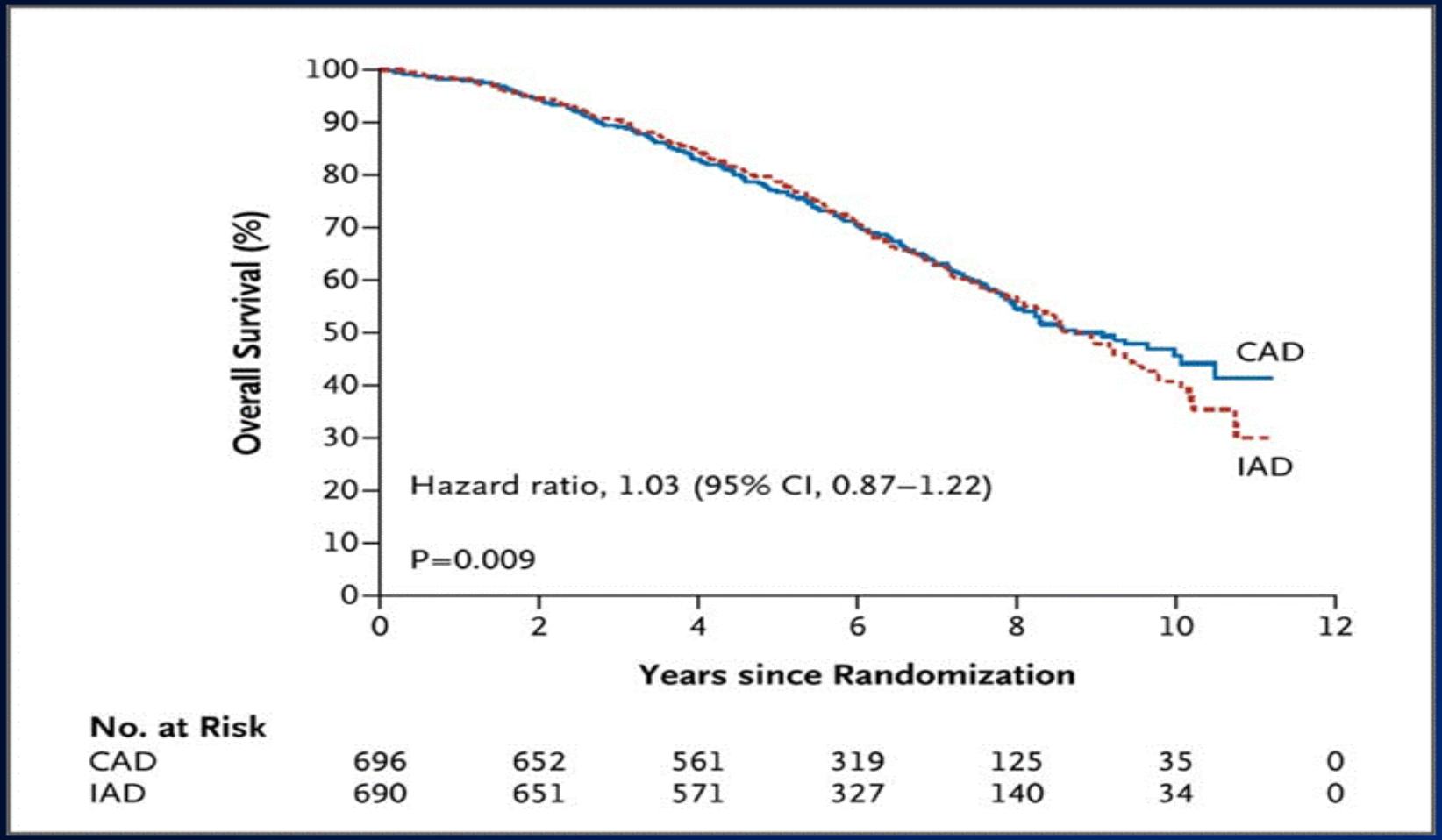
Rising PSA without local recurrence or metastasis

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

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



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

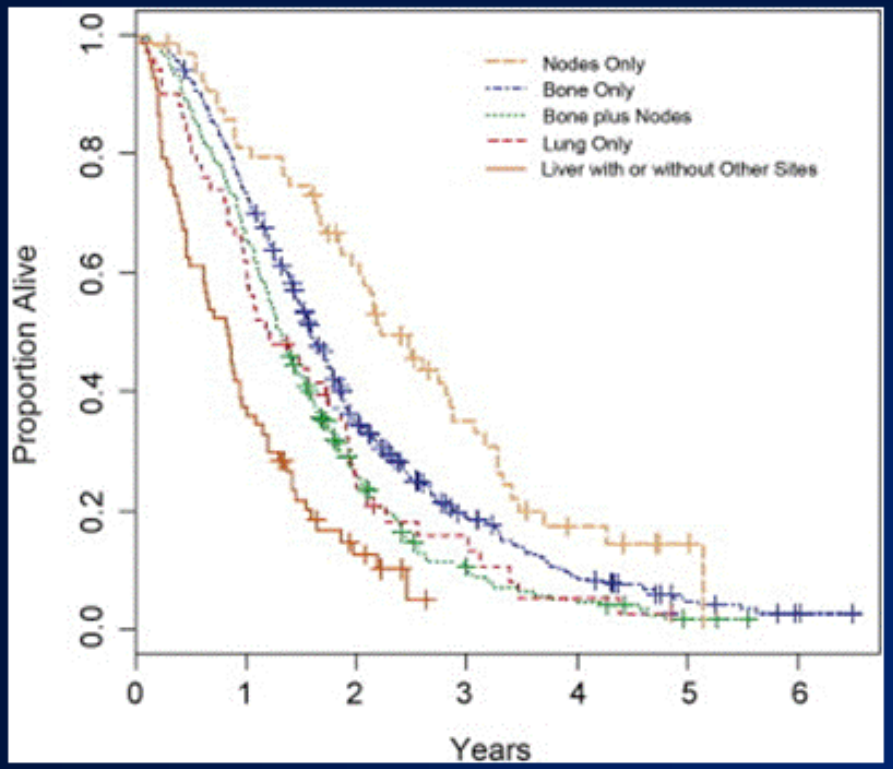
About 4% of prostate cancer have distant metastases at diagnosis

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

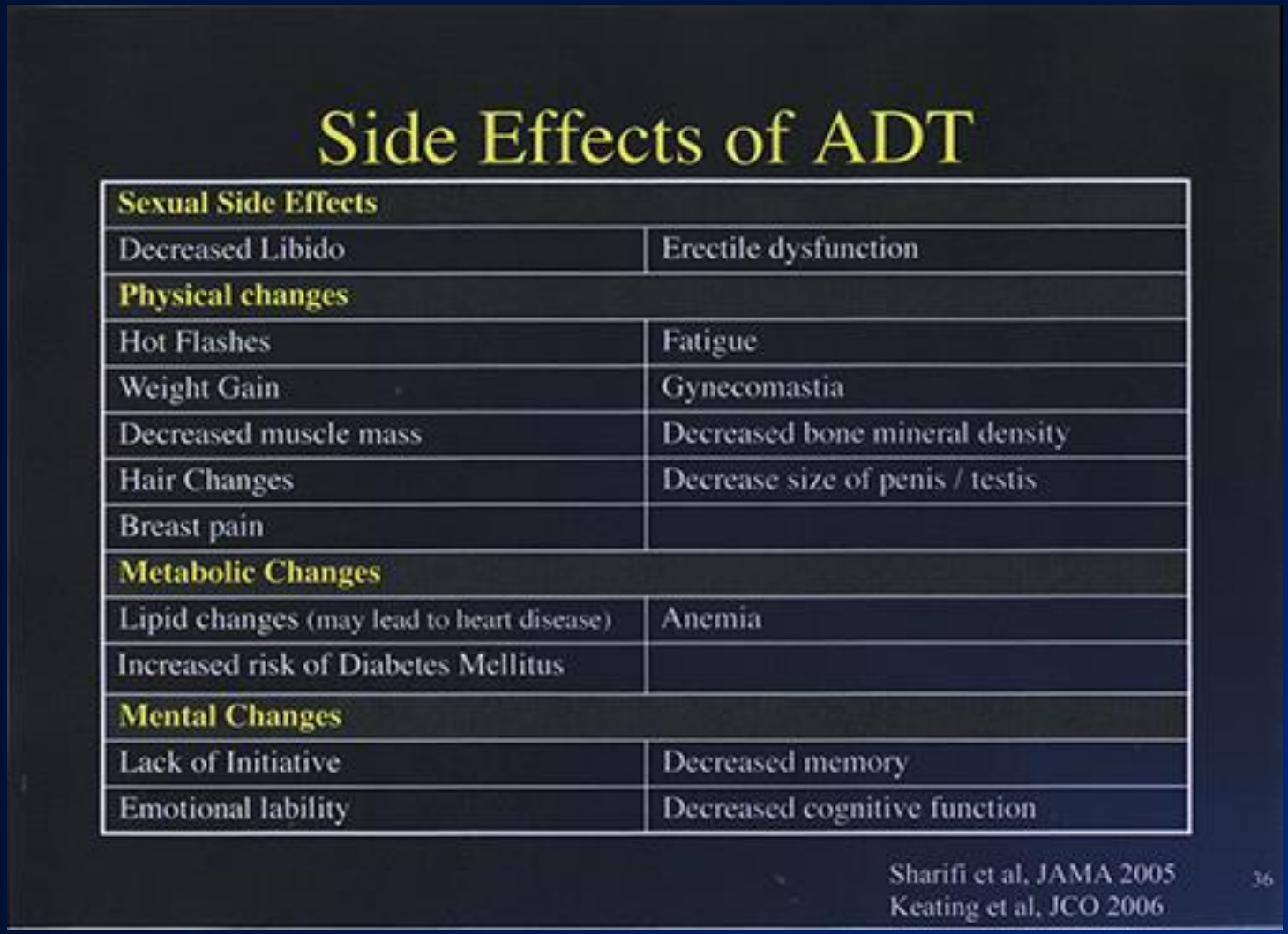
Orchiectomy is preferred in patients who are unlikely to comply with medical therapy or due to cost

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



Metastatic Castration-Resistant Prostate Cancer (CRPC)

Disease state characterized by progression despite castrate levels of testosterone

1st 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.

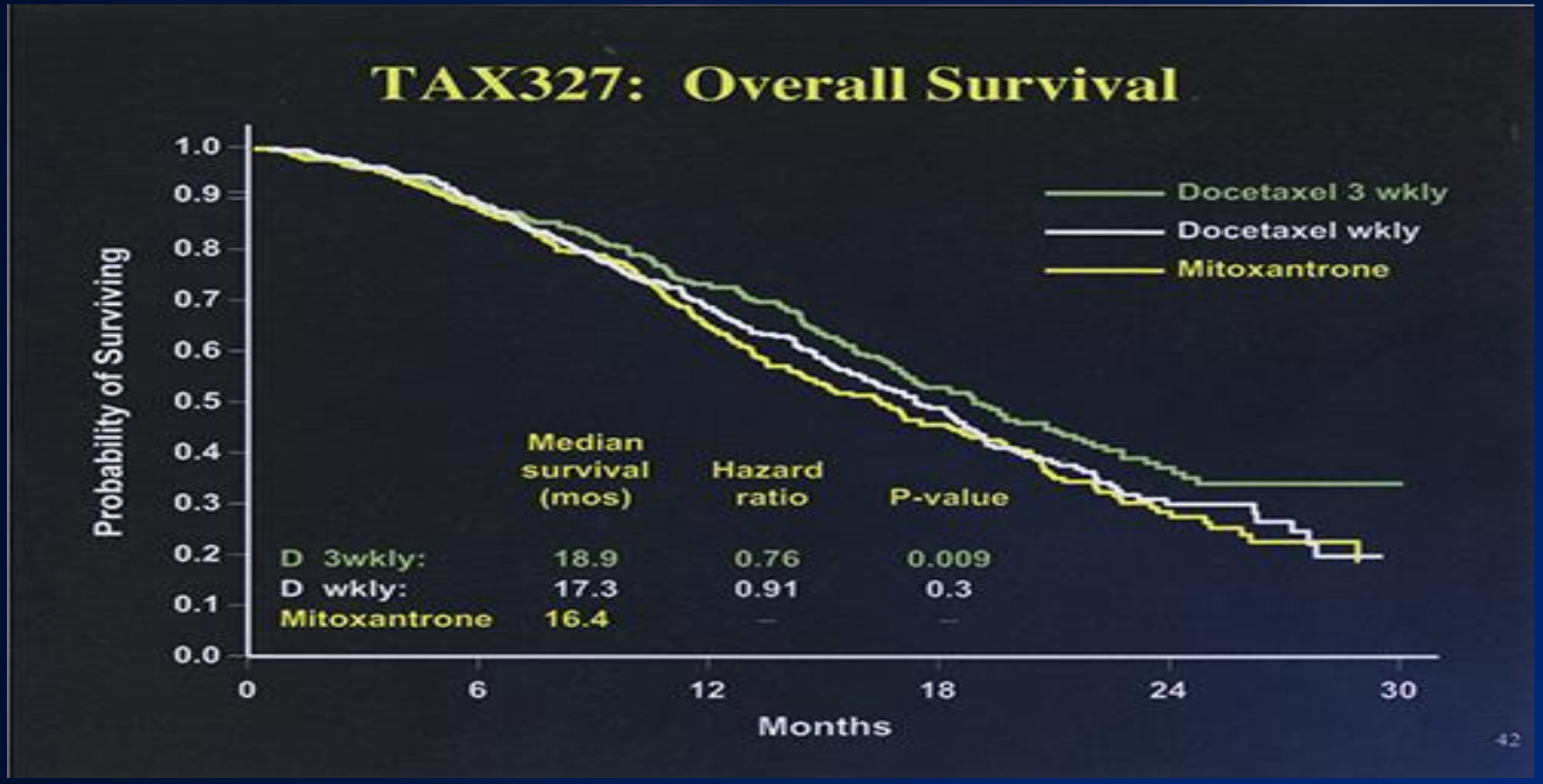
Taxanes exhibit antimicrotubule and antitumor activity

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 likley 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: ≤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%)

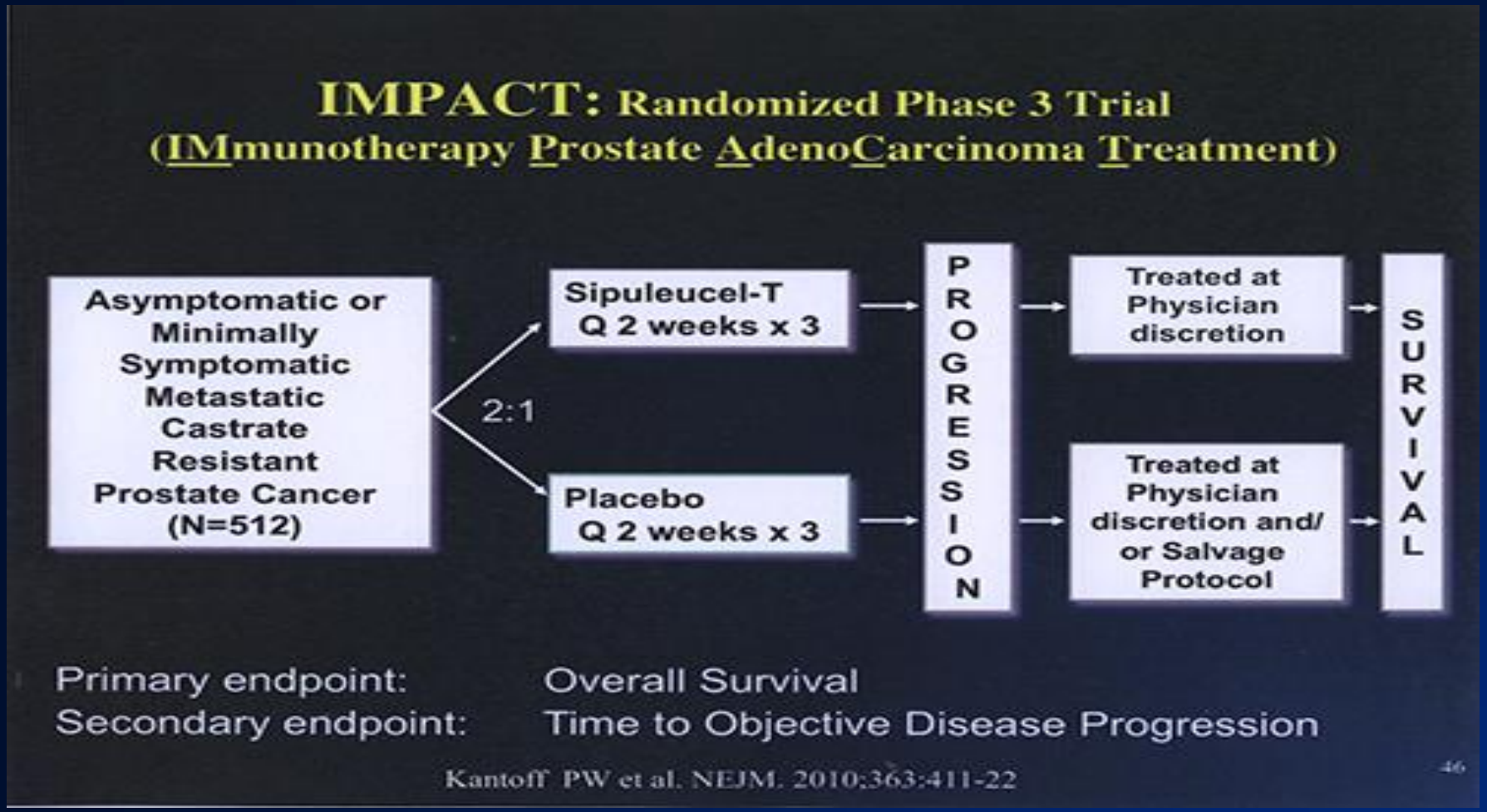
Infection: Infection (1% to 34%; dose dependent)

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

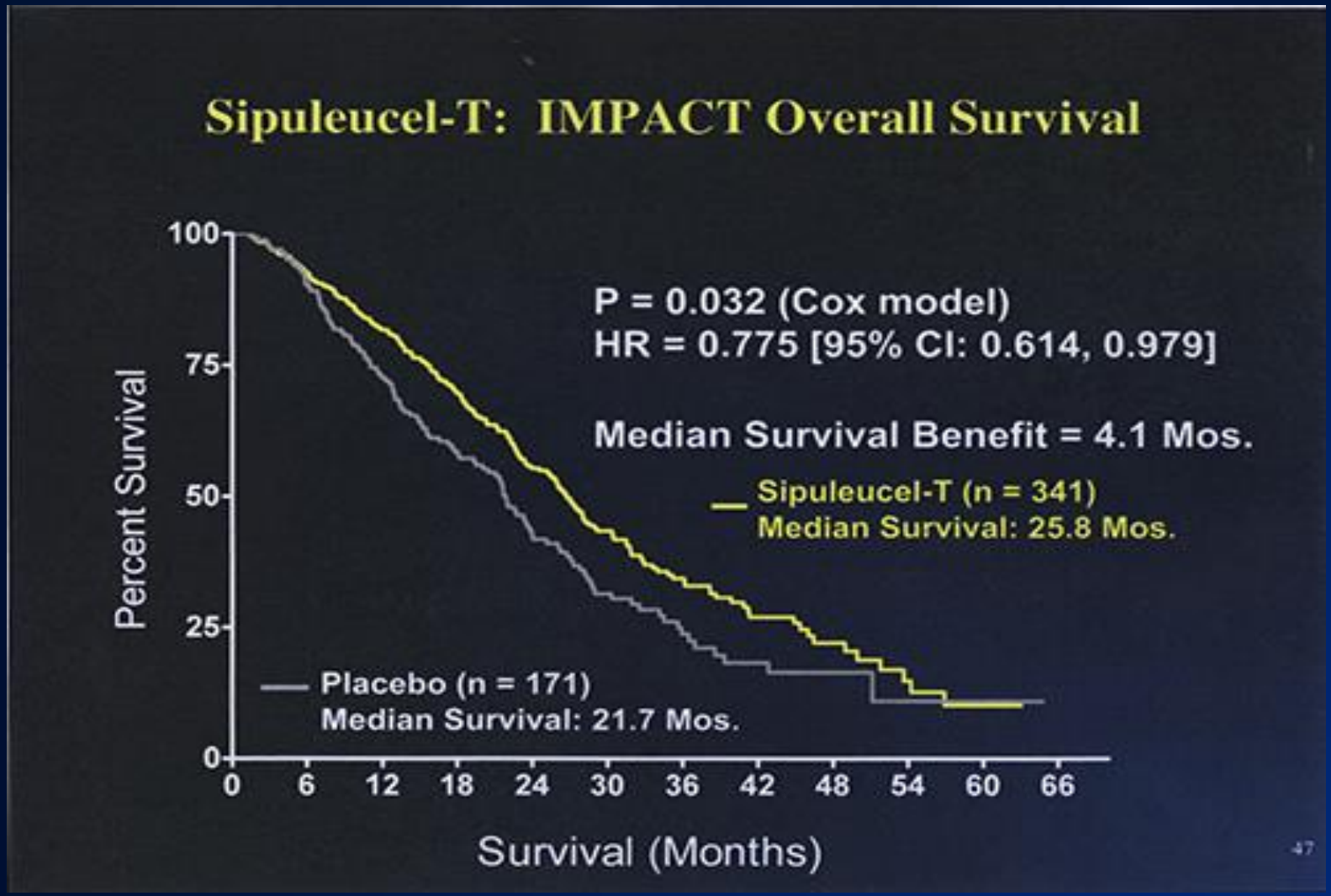
Respiratory: Pulmonary reaction (41%)

Therapeutic Cancer Vaccine:
Sipuleucel-T

IMPACT: Randomized Phase 3 Trial



Sipuleucel-T: IMPACT Overall Survival



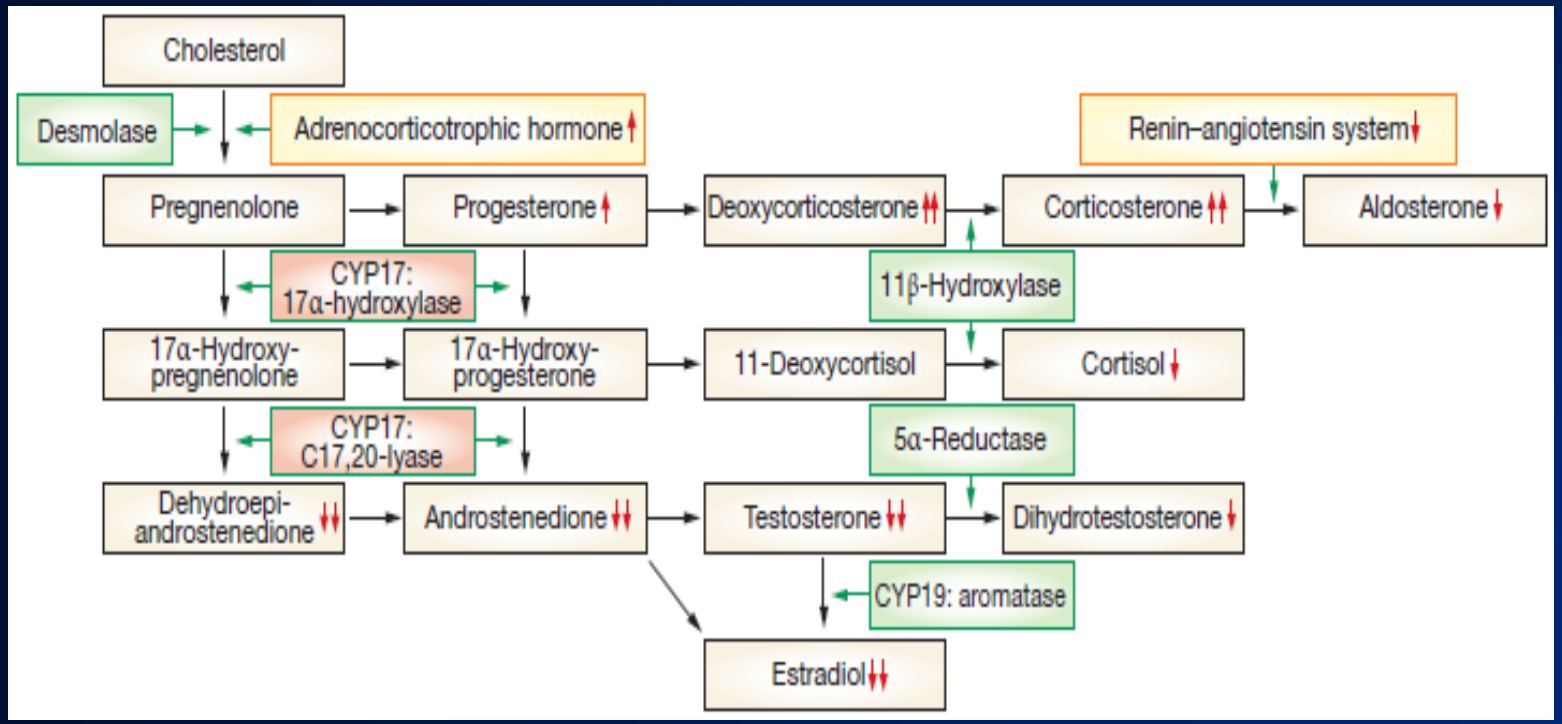
Sipuleucel-T AEs

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

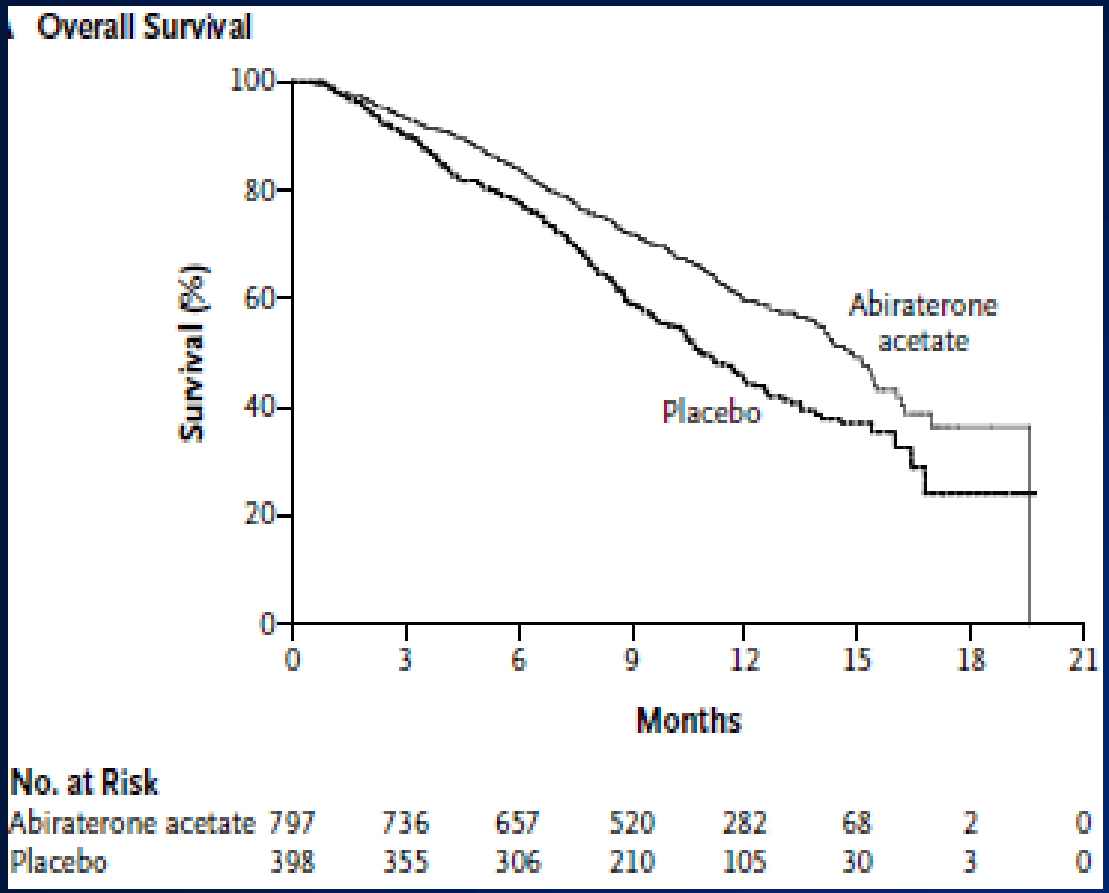
1195 prostate cancer patients were randomized and treated with Abiraterone acetate 1000 mg orally daily
Prednisone 5 mg orally twice daily n = 797 or
Placebo orally daily Prednisone 5 mg orally twice daily n = 398.

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 Acetate (N=797)	Placebo (N=398)	Hazard Ratio (95% CI)	P Value
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

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%)

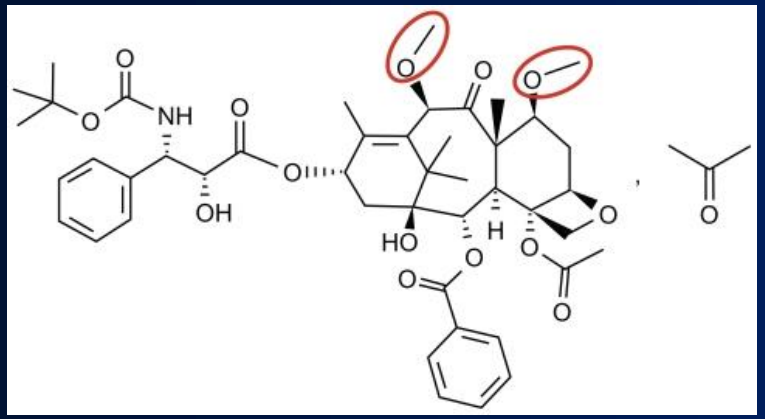
Cabazitaxel

Novel taxane active in docetaxel resistant cell lines

Less affinity for P-glycoprotein pump

Methoxyl side chain instead of

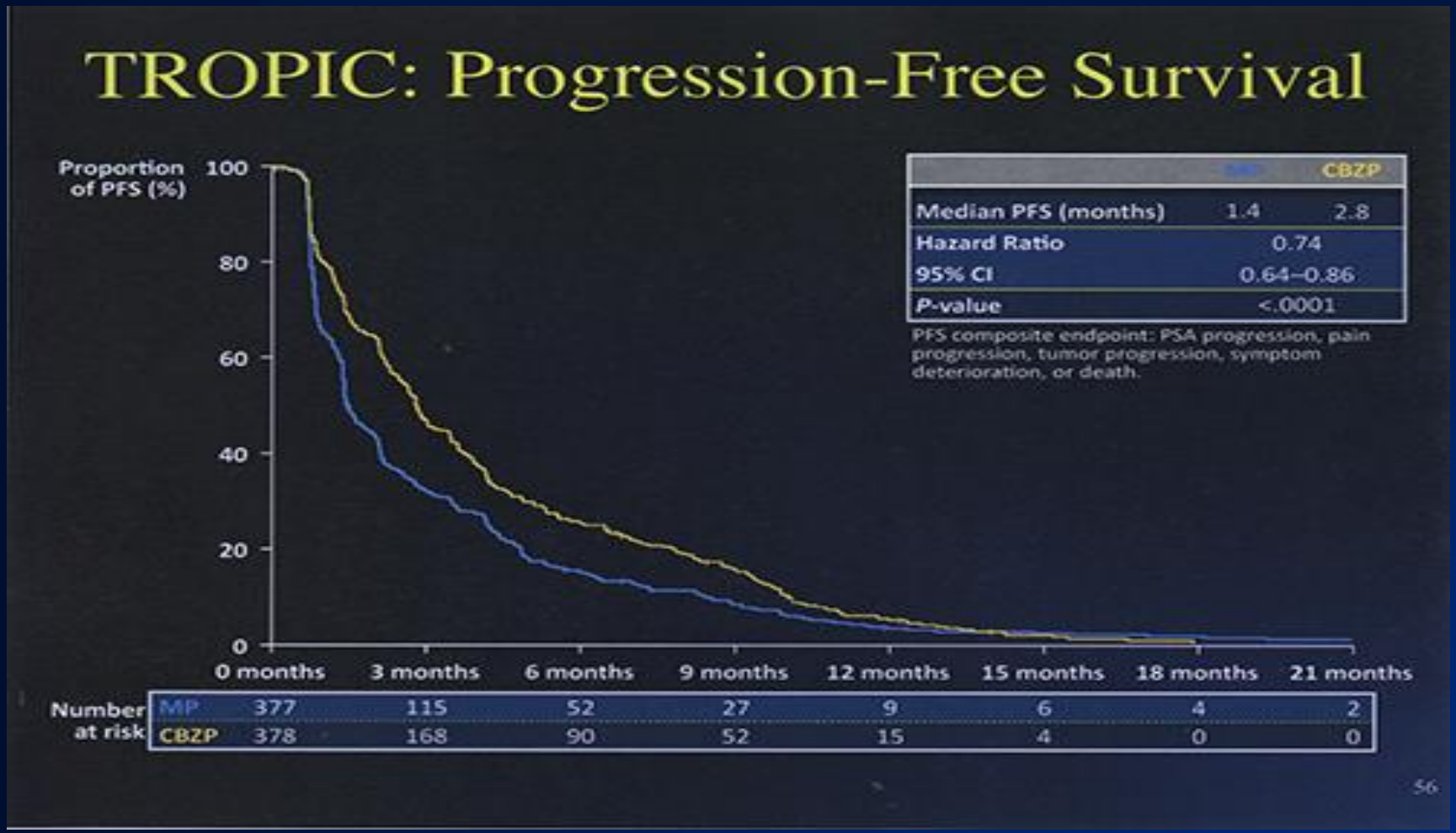
hydroxyl groups found in docetaxel



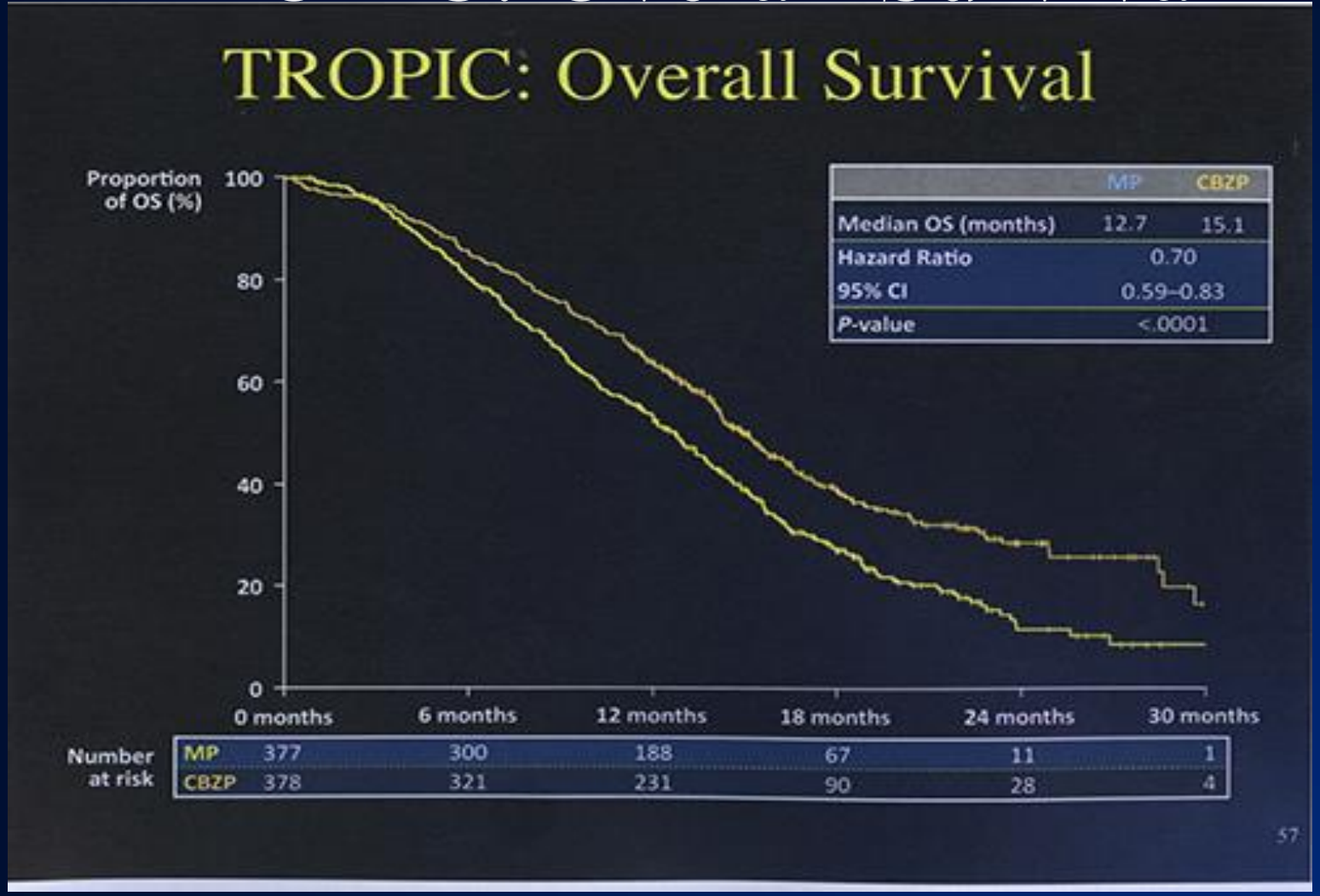
TROPIC:

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

TROPIC: Progression-Free Survival



TROPIC: 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%)

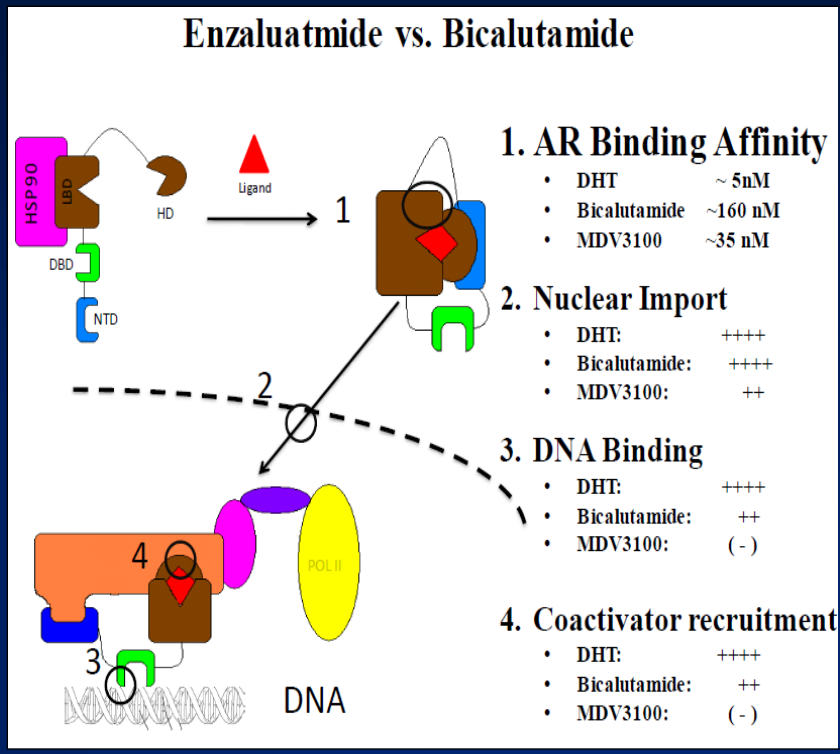
Renal: Hematuria (17%)

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

Enzalutamide

A small molecule AR antagonist

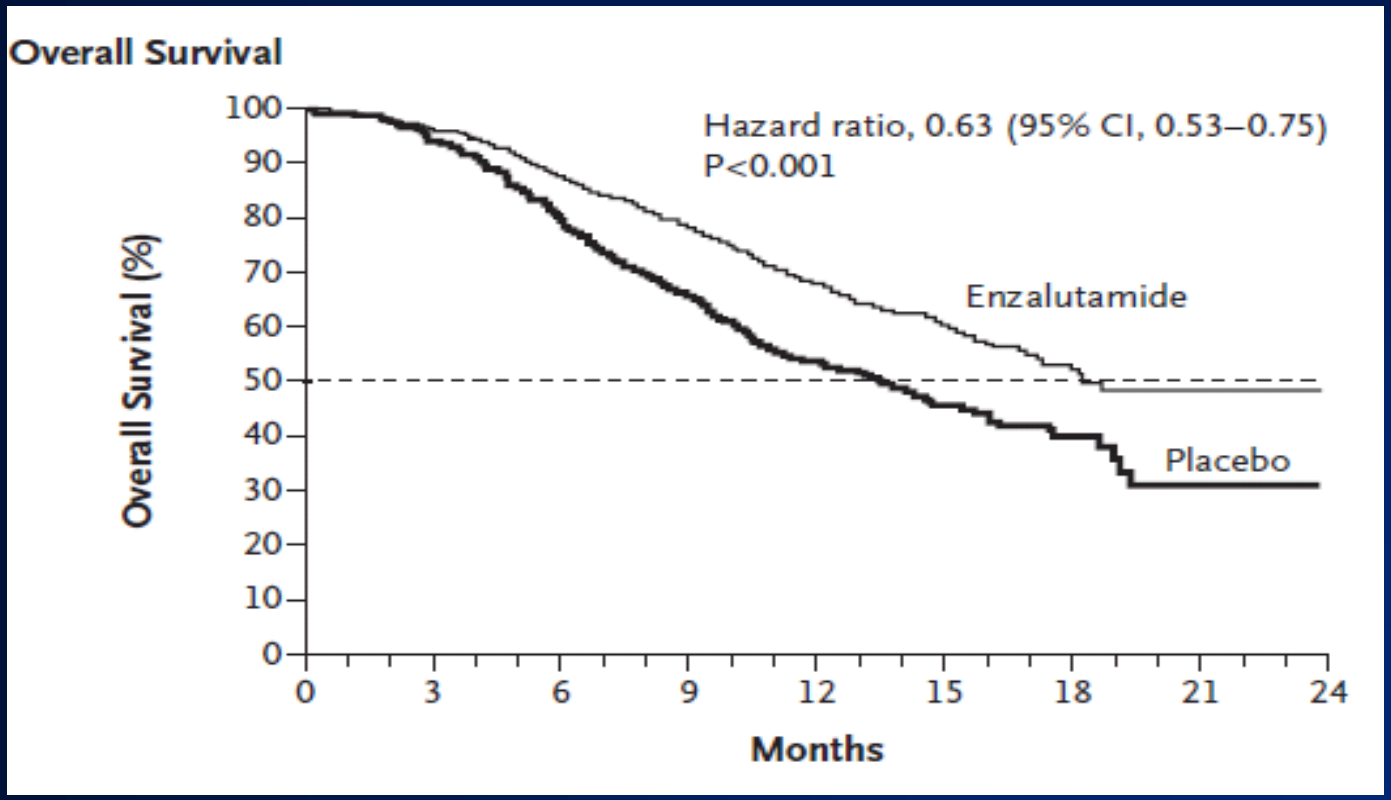
- Affinity 30 folds of bicalutamide
- Prevent nuclear translocation
- Prevents co-activator recruitment



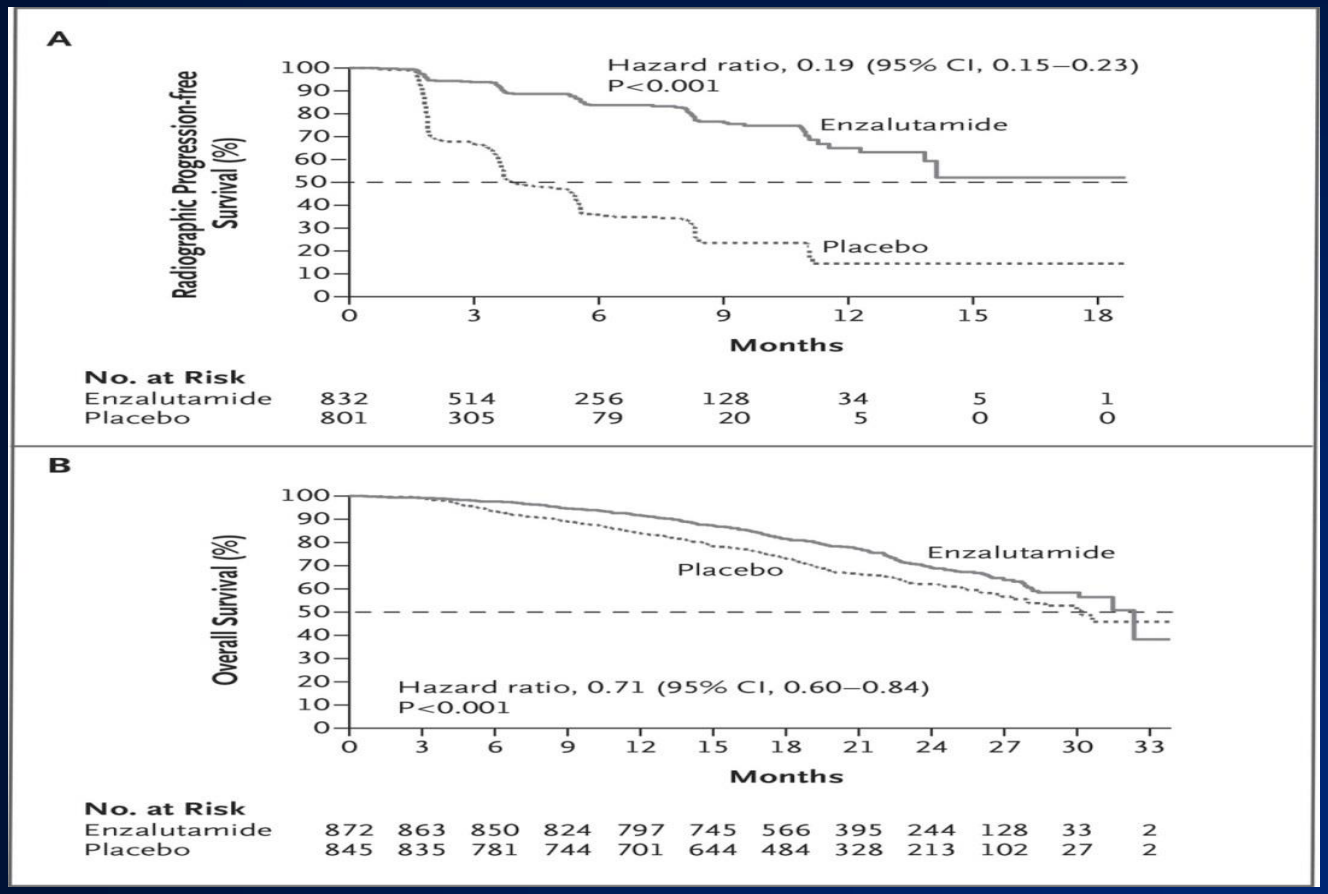
AFFIRM:

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%)

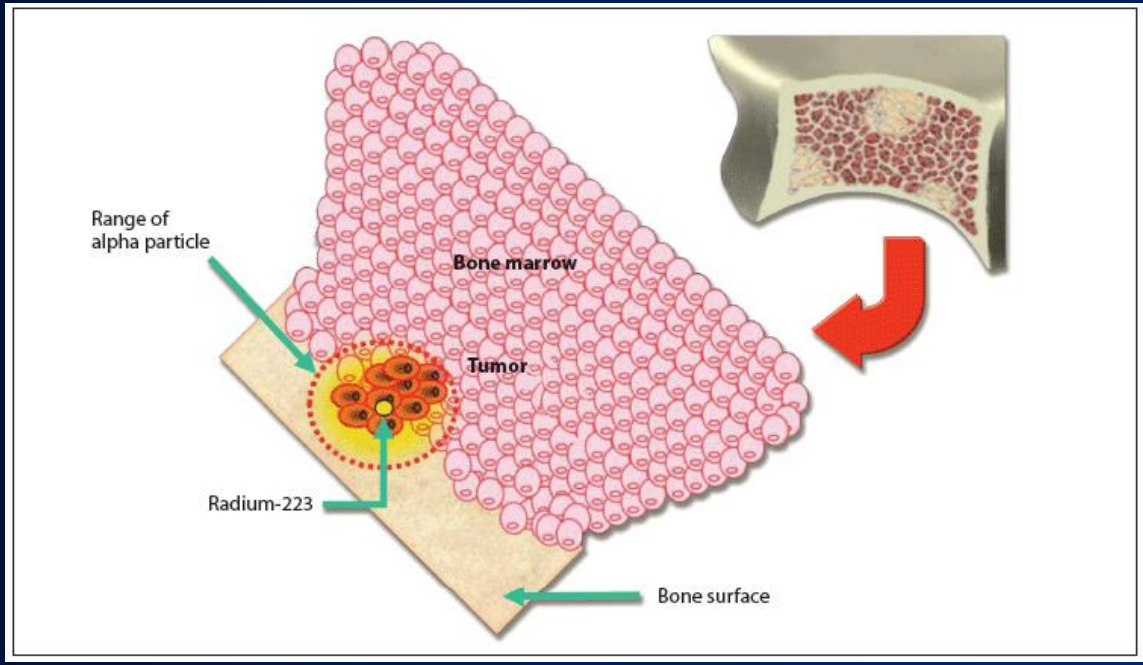
Neuromuscular & skeletal: Back pain (26%), arthralgia (21%), musculoskeletal pain (15%)

Respiratory: Upper respiratory tract infection (11%)

Radium-223 (Alpharadin)

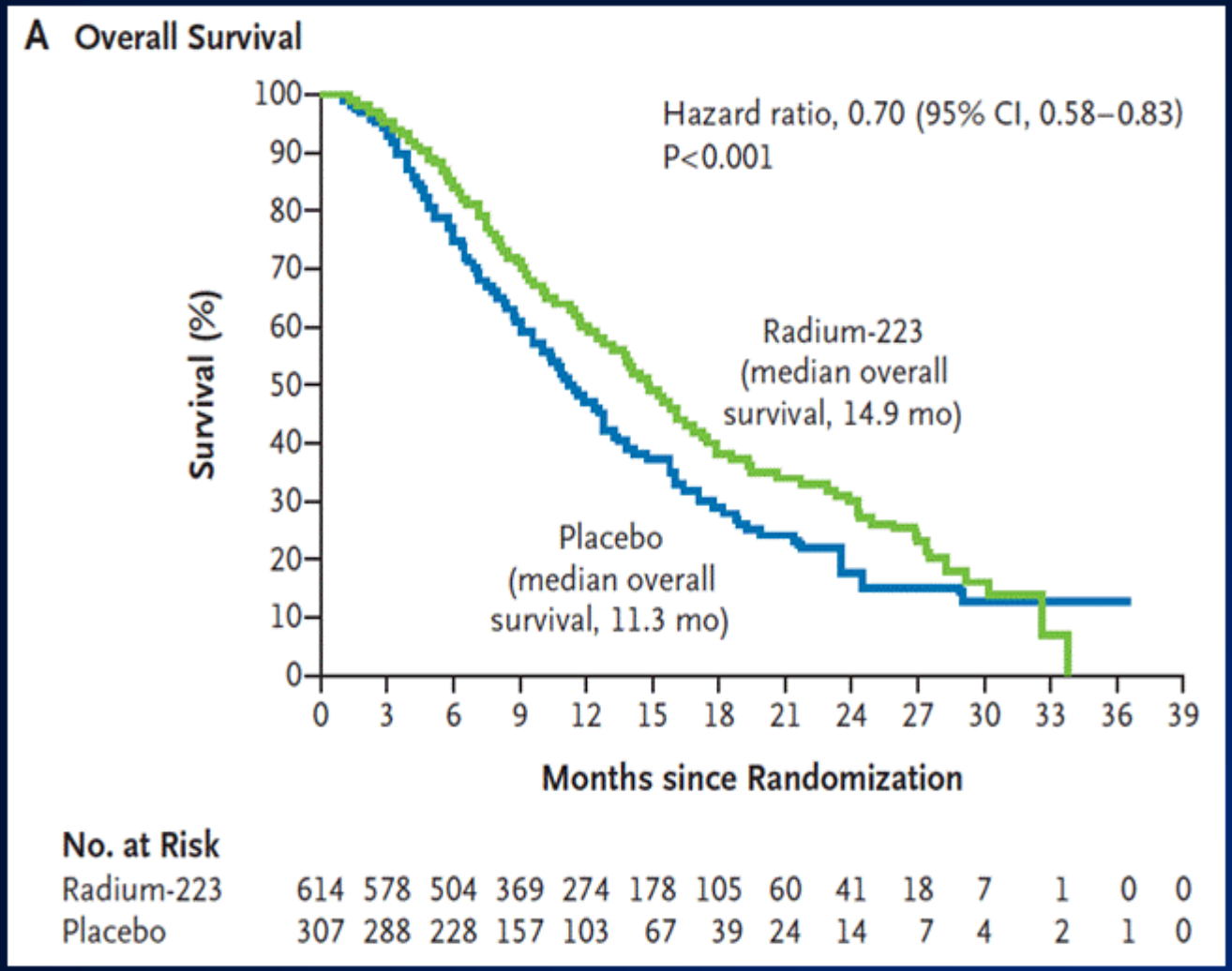
Bone –targeting radiopharmaceutical

High energy alpha-particles with short range (<100μm) hence less bone marrow toxicity



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

ALSYMPCA survival curve



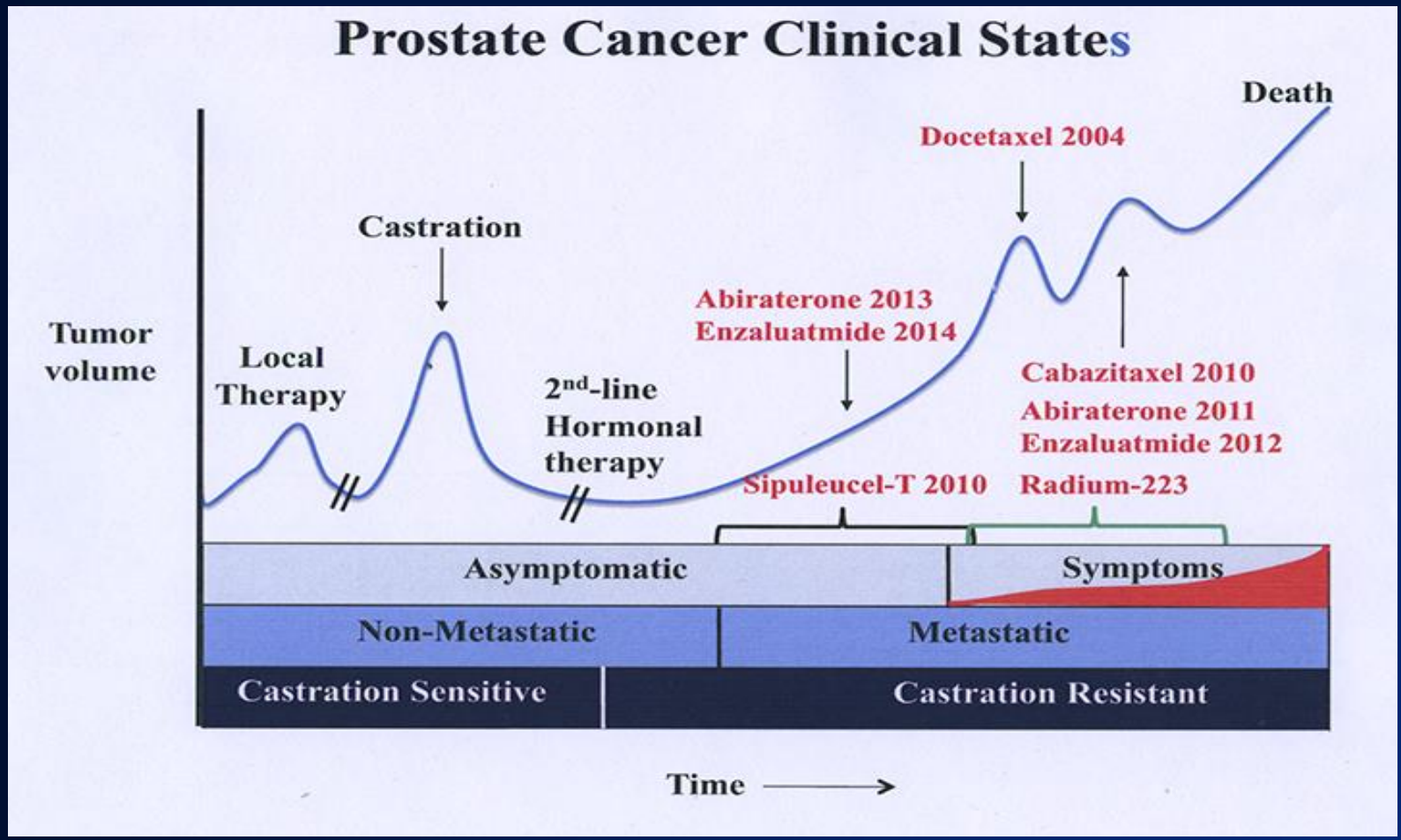
Radium 223 AEs

Cardiovascular: Peripheral edema (13%)

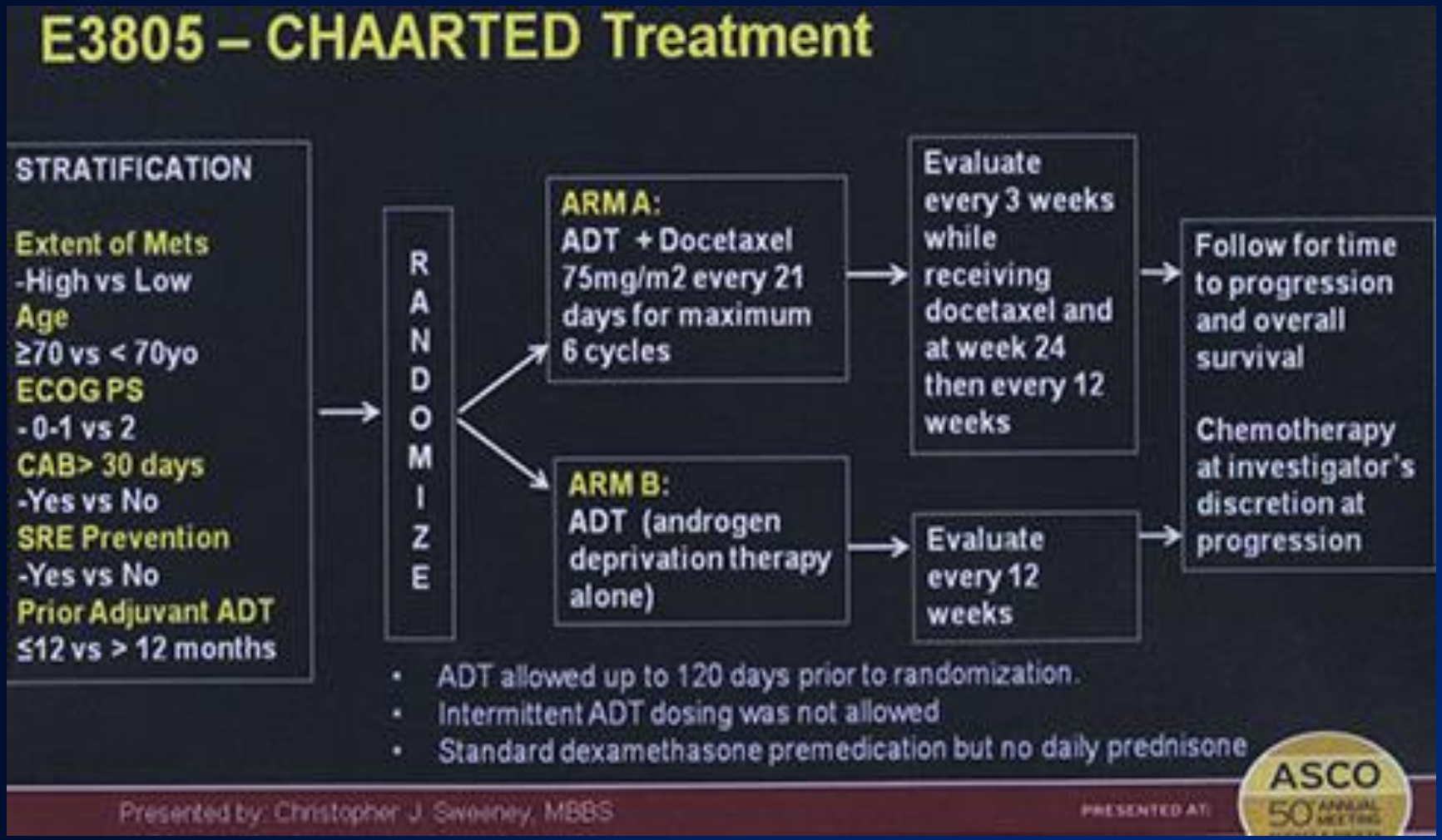
Gastrointestinal: Nausea (36%), diarrhea (25%), vomiting (19%)

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%)

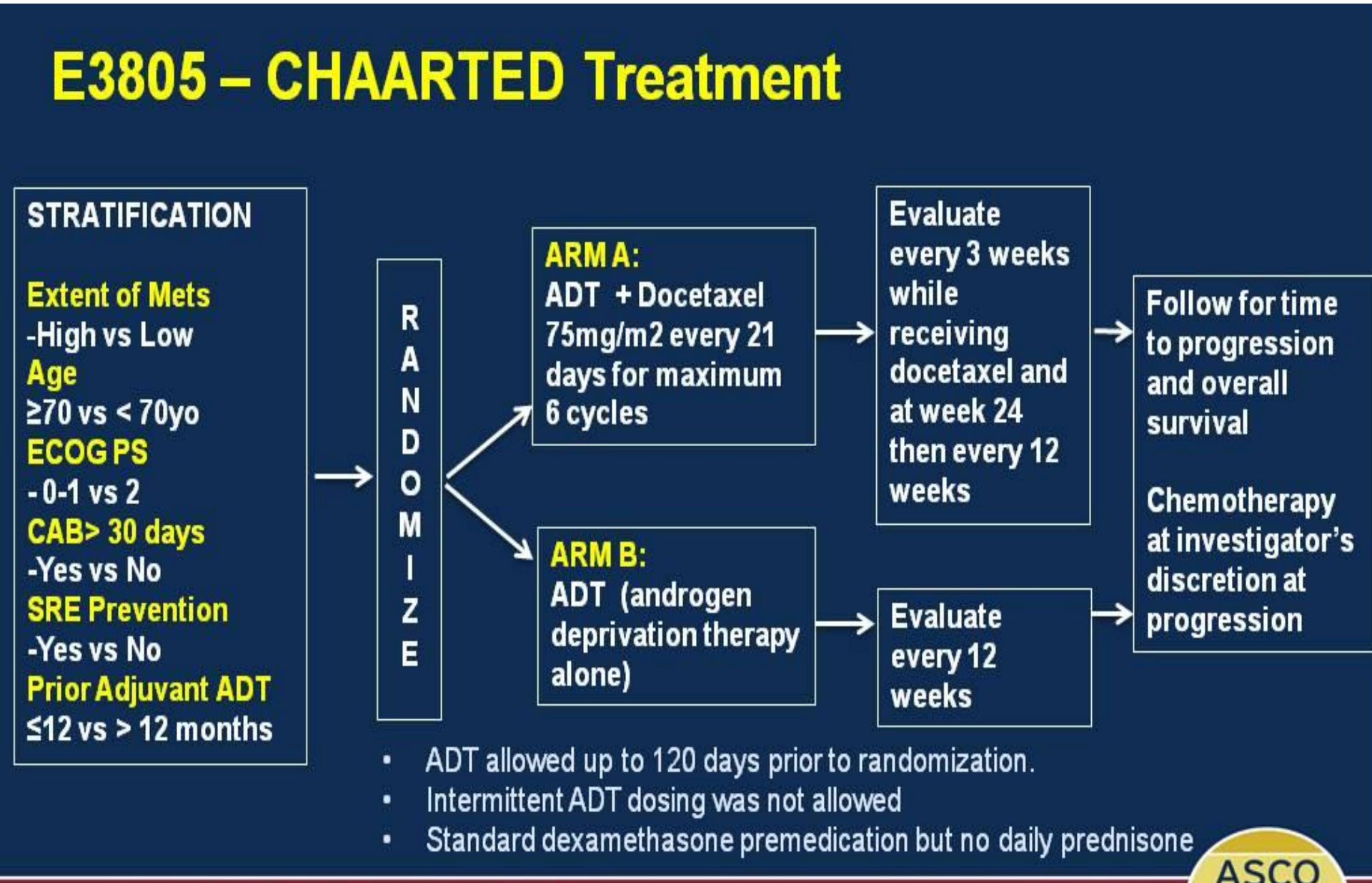
Prostate Cancer Clinical States



E3805-CHAARTED Treatment



E3805-CHAARTED Treatment



Metastatic Prostate Cancer

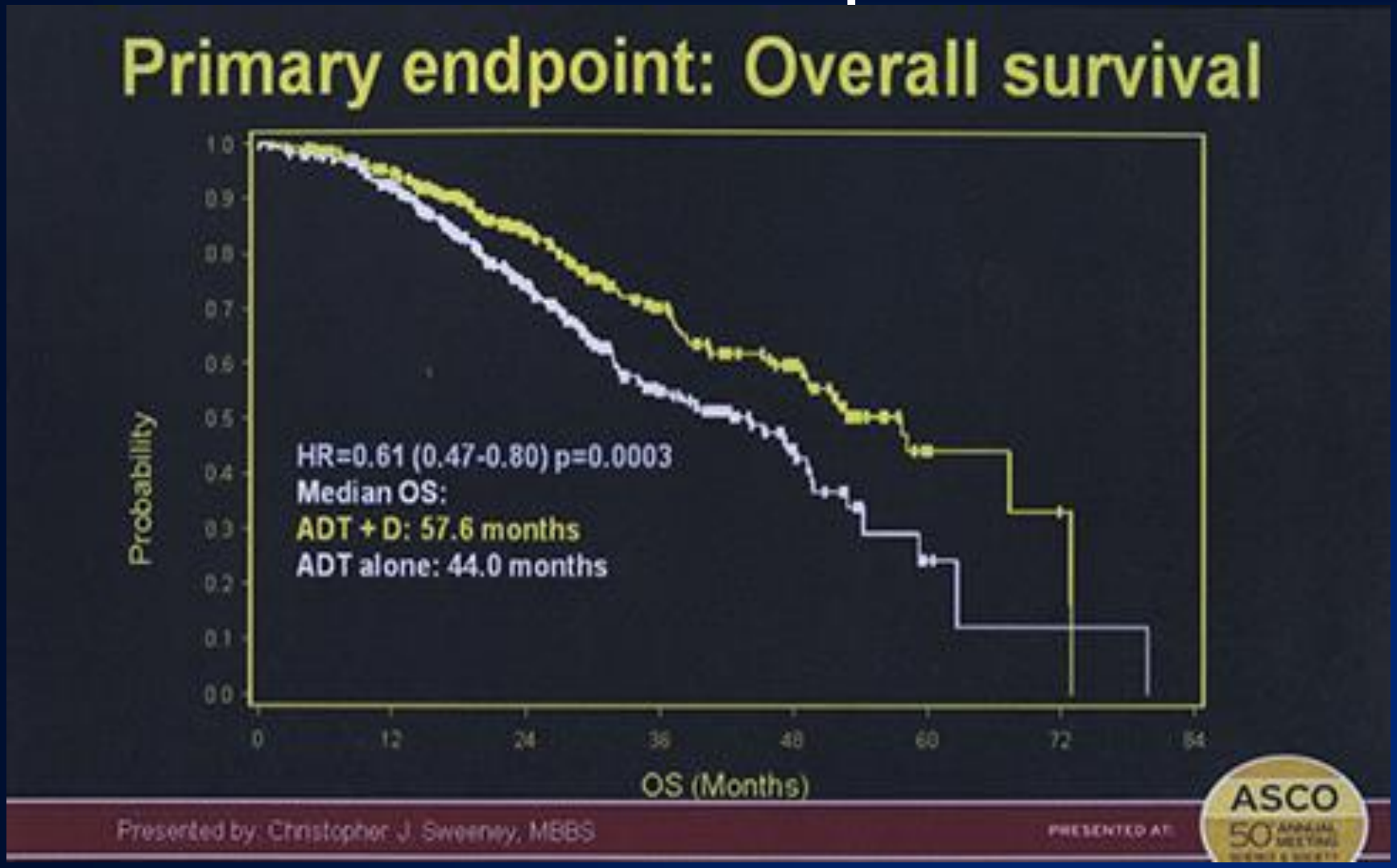
About 4% of prostate cancer have distant metastases at diagnosis

Bone metastases are most common

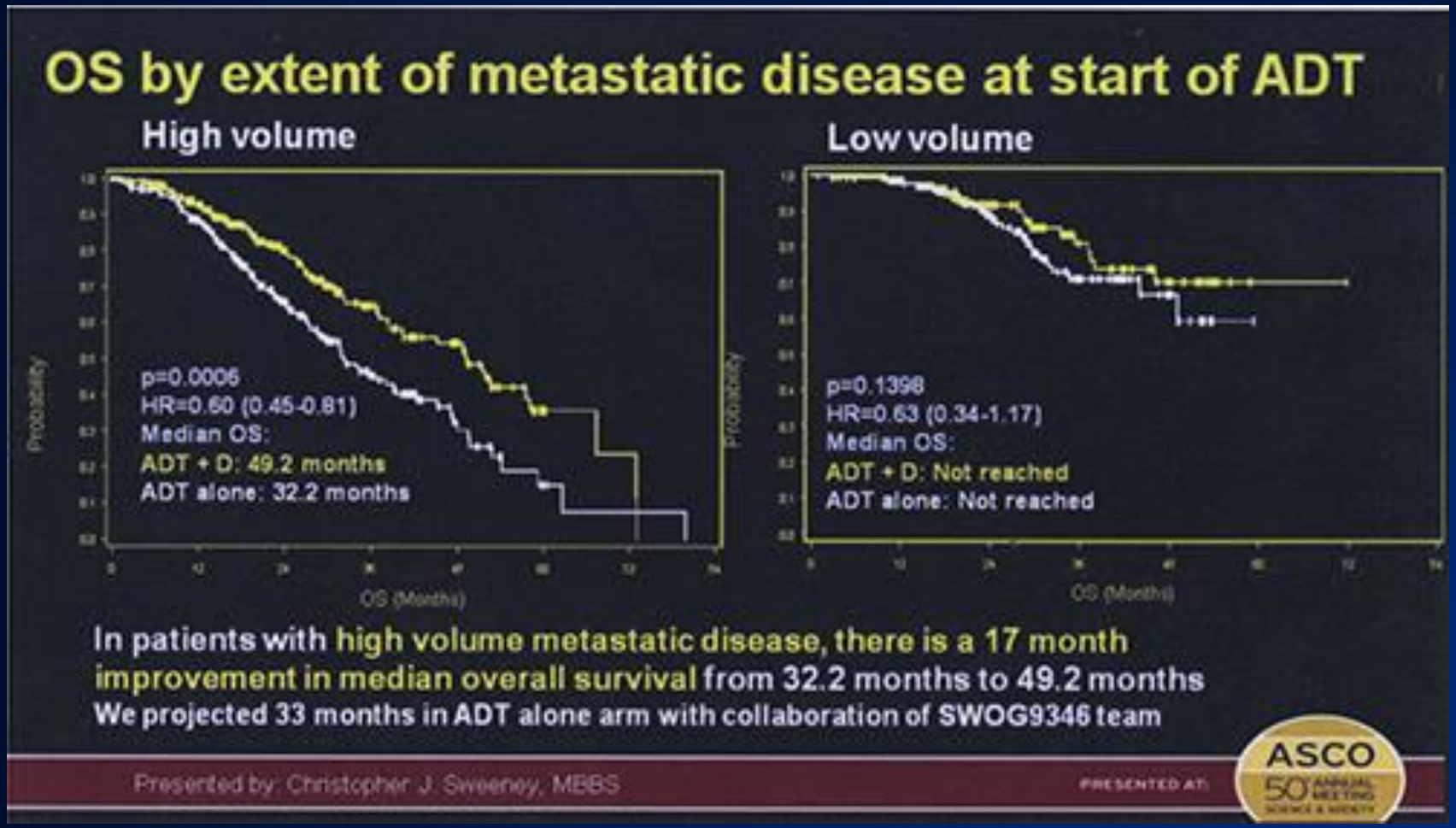
Metastatic disease are virtually incurable

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

Primary endpoint: Overall



OS by extent of metastatic disease at the start of ADT



Future Directions

How to sequence the array of available and potential agents

Multimodality therapy

Understanding Mechanisms of Resistance

Docetaxel activity after abiraterone

Mezynski et al had 35 patients with a TTP of 4.6 months and 12.5 month overall survival

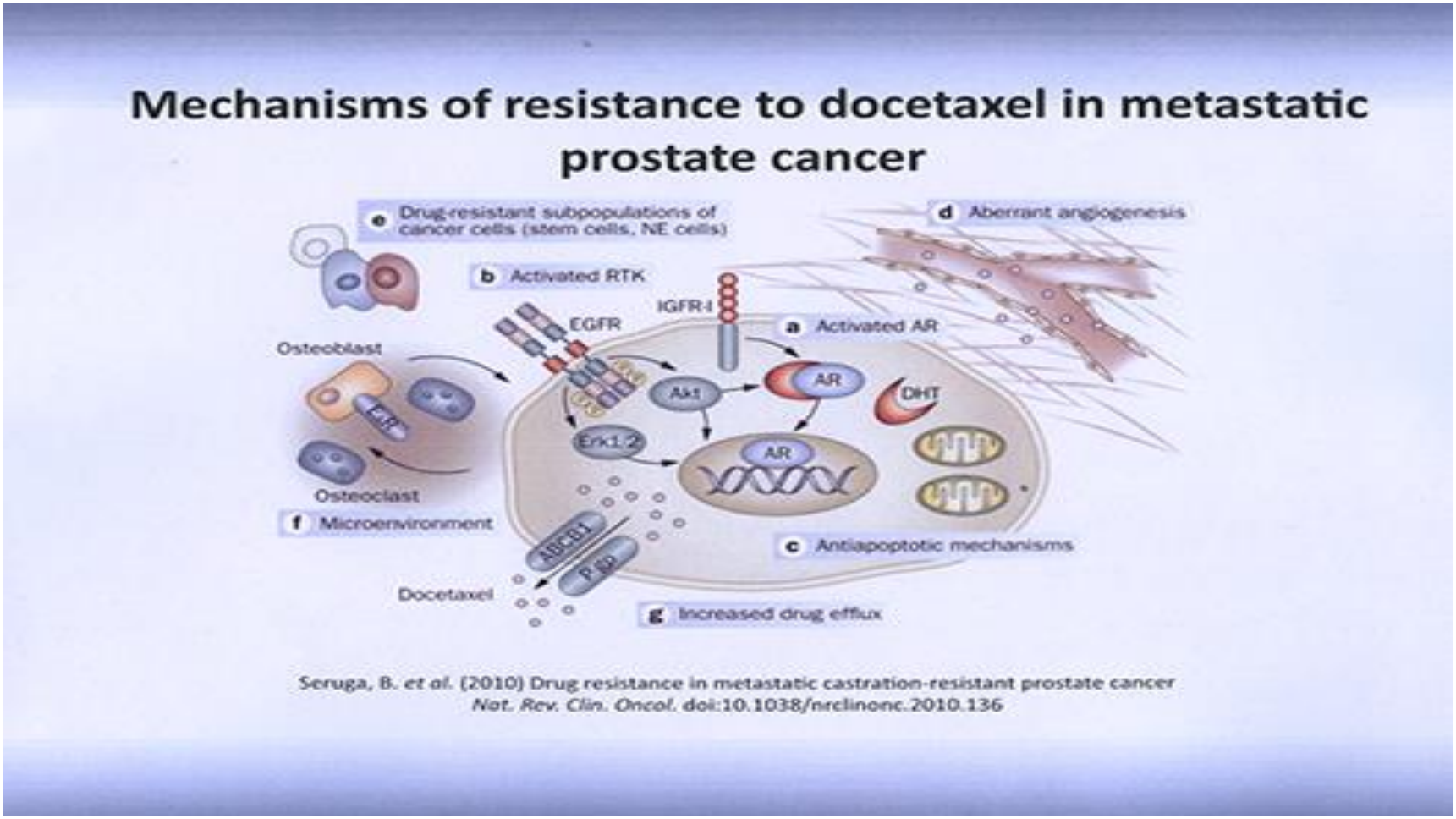
Schweizer et al had 24 patients with a TTP of 4.4 months

Aggarwal et al had 23 patients with a TTP of 4.3 months and 12.4 month overall survival

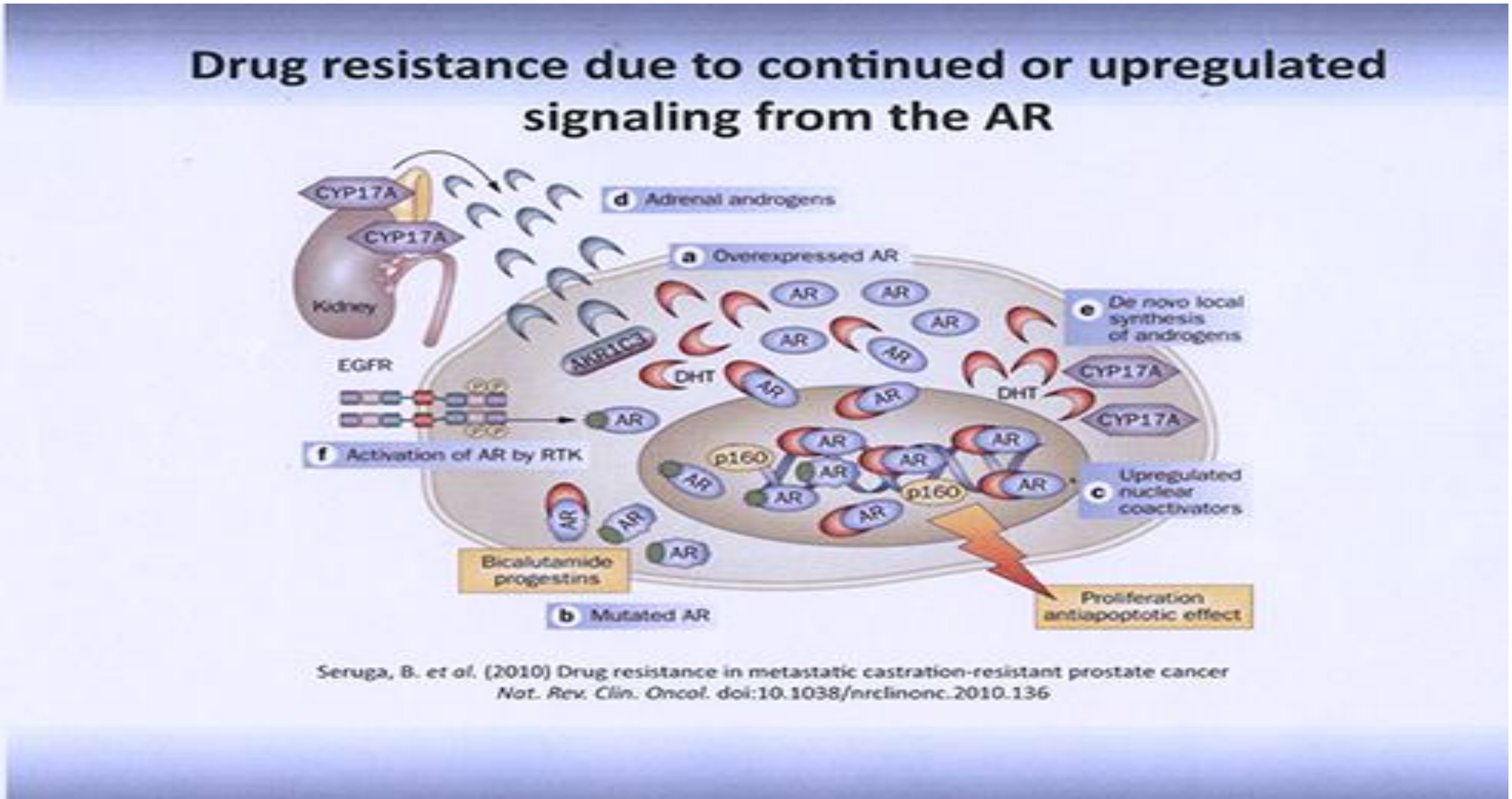
Docetaxel activity after abiraterone

Dahut et al had 13 patients with a TTP of 12.4 months

Mechanisms of resistance to docetaxel in metastatic prostate cancer



Drug resistance due to continued or upregulated signaling from the AR



Future Directions

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Can some of these therapies be moved earlier to increase the cure rate?