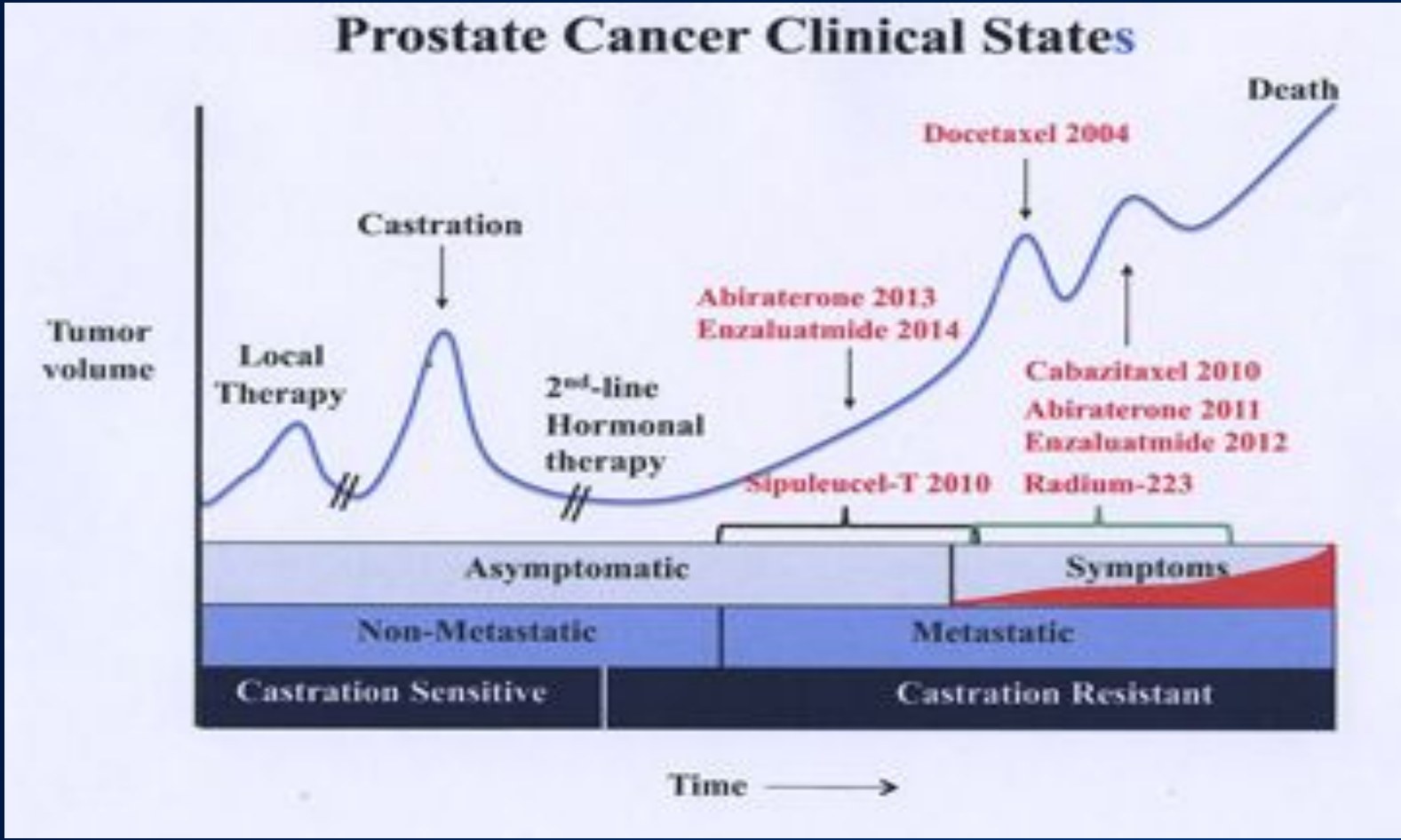
Treatment Challenges in Castrate Resistant Prostate Cancer

Prostate Cancer Clinical States



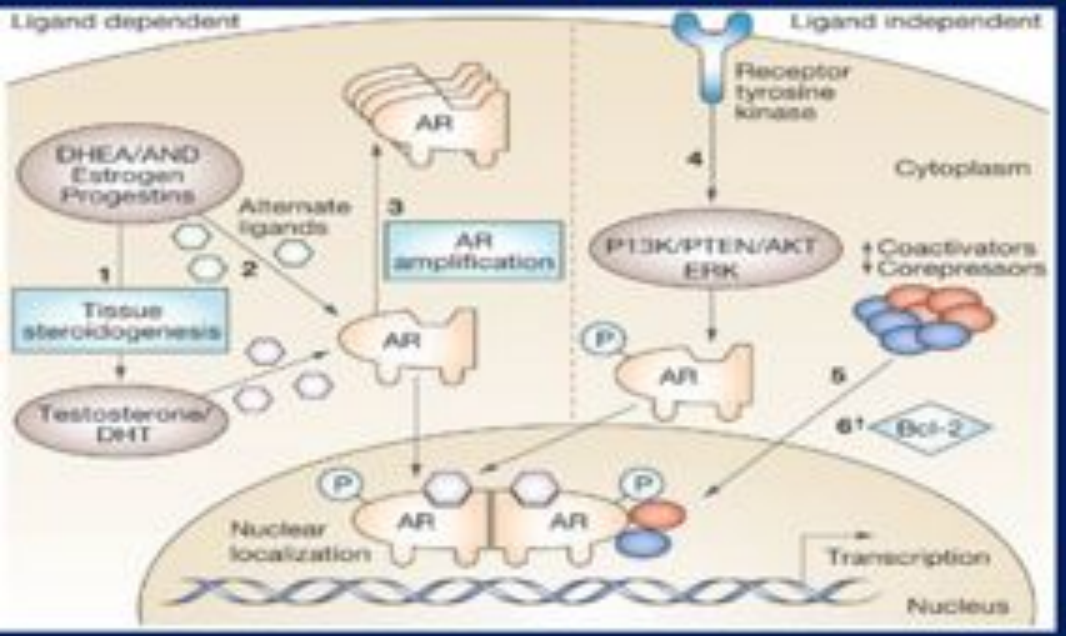
Castrate resistant prostate cancer

What is Castration Resistance Prostate Cancer?

- Progressive disease despite castration levels of testosterone (50 ng/dL)
- Progression could be PSA or Imaging
- The androgen receptor drives prostate cancer growth
  - Depriving the tumor of testosterone is the primary therapy for metastatic disease

Anti-androgen therapy

So why do we use Anti-Androgen therapy in CRPC?



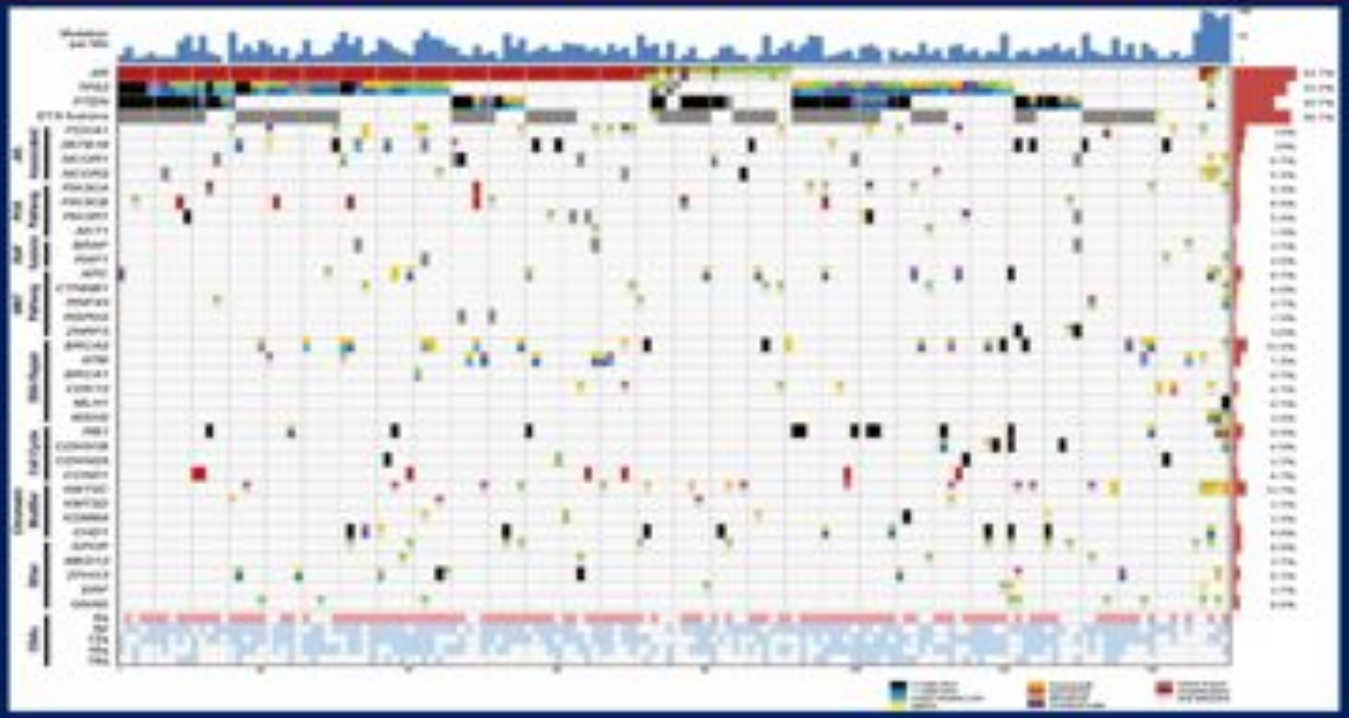
Resistance Mechanisms:

- AR Amplification
- Secondary androgen production
- Ligand independent growth
- Intranuclear changes

Harris W P *et al. Nat Clin Pract Urol, 2009*

Integrative clinical genomics

Integrative Clinical Genomics of Advanced Prostate Cancer



Robinson D *et al. Cell, 2015*

Prostate cancer rules

Rules of the Game: Prostate Cancer Working Group

- PSA is **NOT** the primary measure of progression in mCRPC
- Radiographic imaging is the primary objective measure
- Patient symptoms and treatment tolerability also paramount

Scher, HI et al J. Clin Oncol, 2008

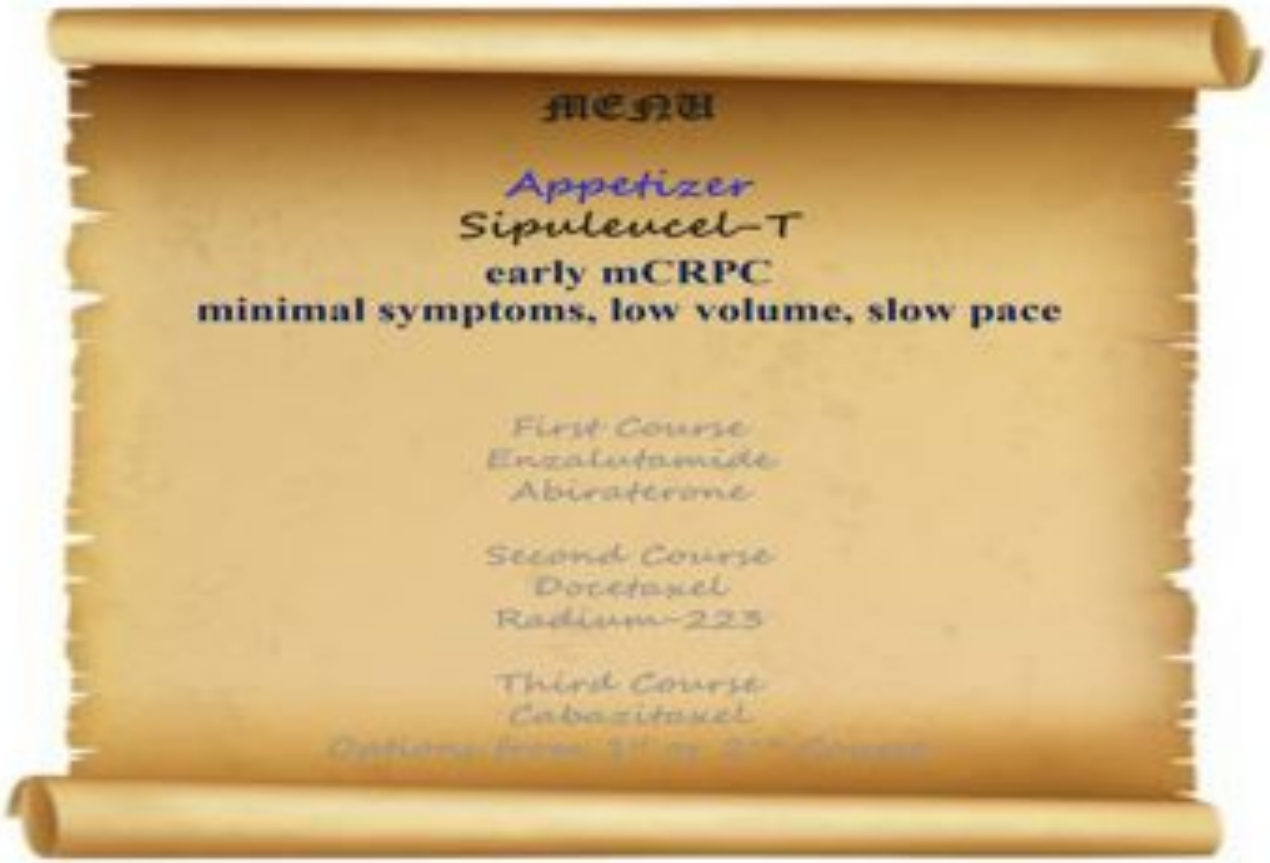
Optimal treatment sequence

Optimal Treatment Sequence?

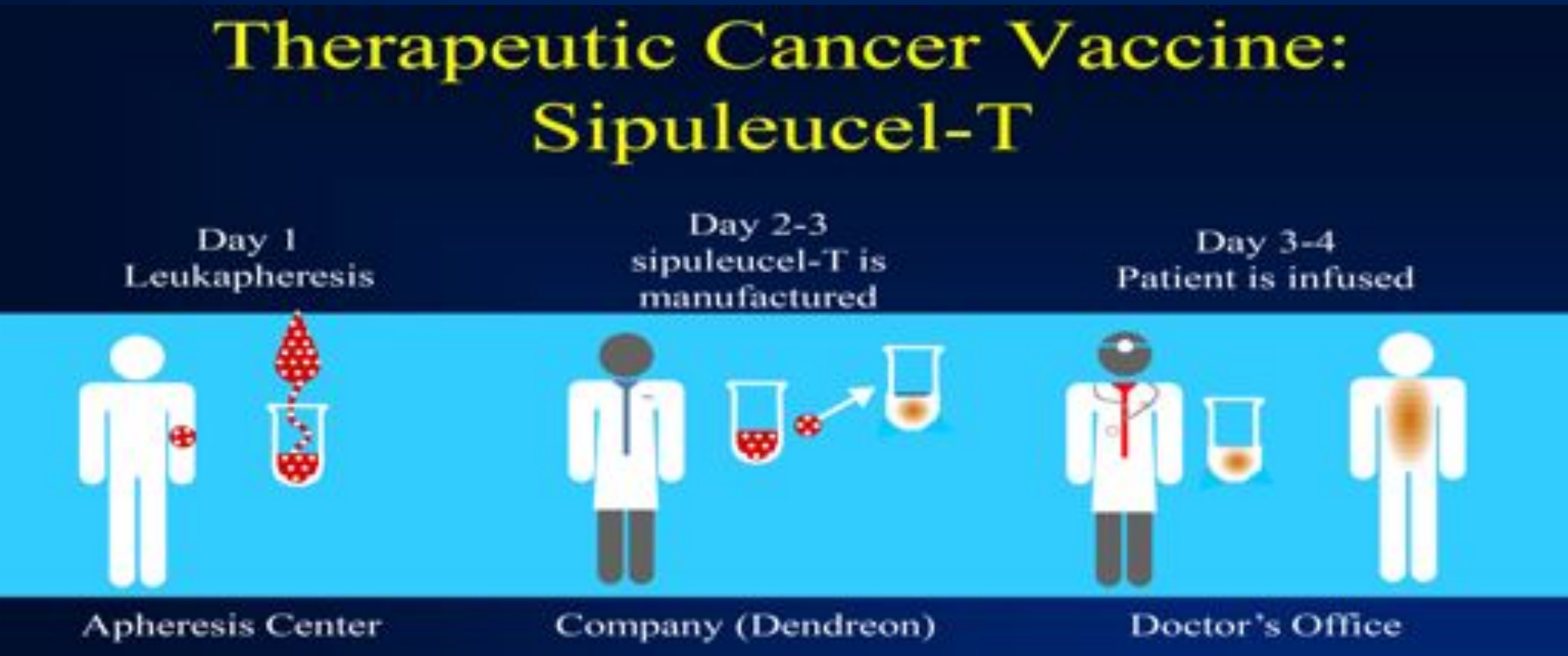
- No clear data for sequencing treatment in metastatic castration resistant prostate cancer (*mCRPC*)
- Ongoing trials will evaluate this question further
- In the absence of data I will provide ***my opinion*** on treatment selection
- Treatment decisions should be made with understanding of the following factors
  - Treatment side effects
  - Patient co-morbidities
  - Patient symptoms
  - Pace of disease

Prostate cancer menu

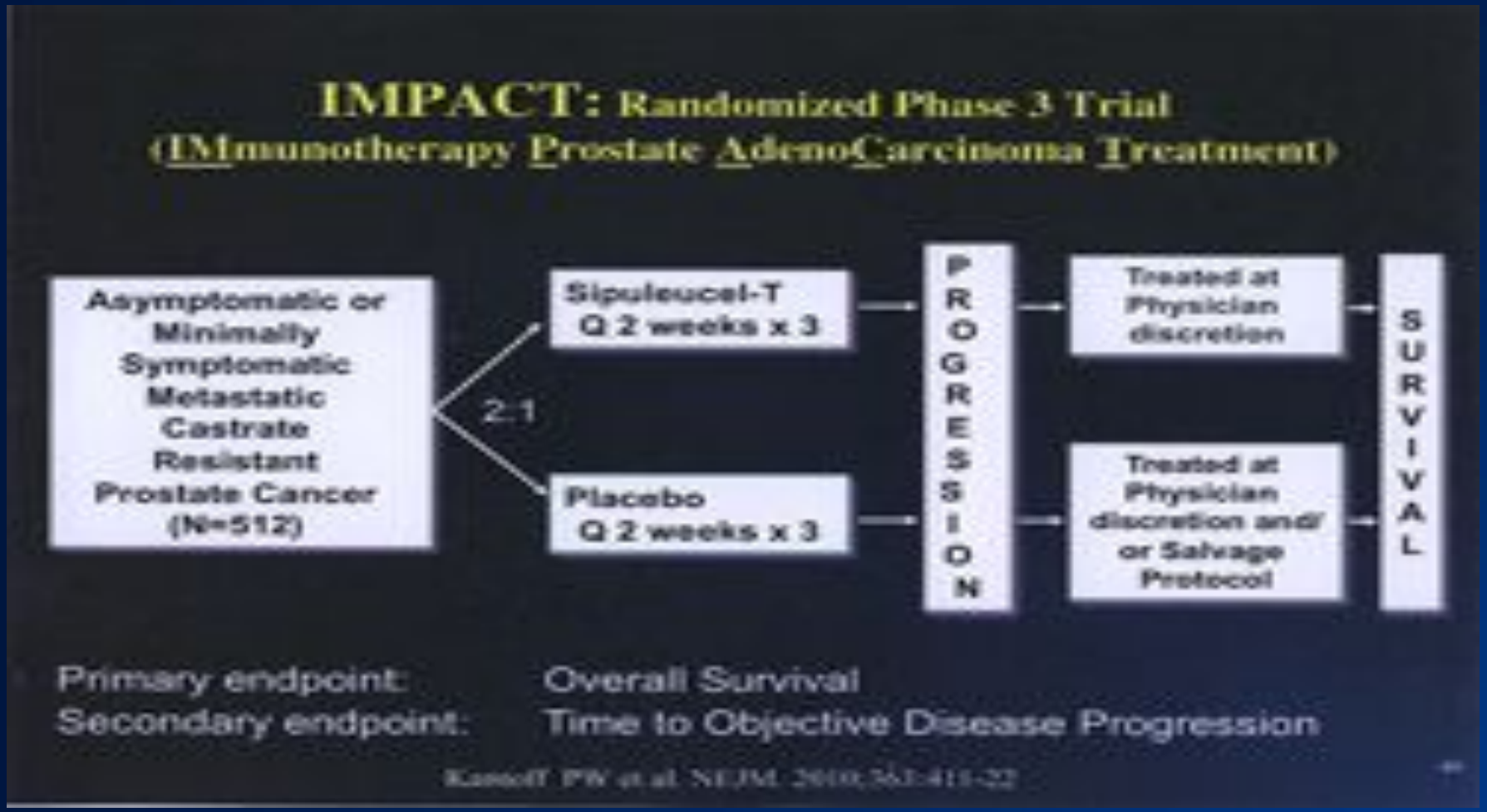
Prostate cancer appetizer



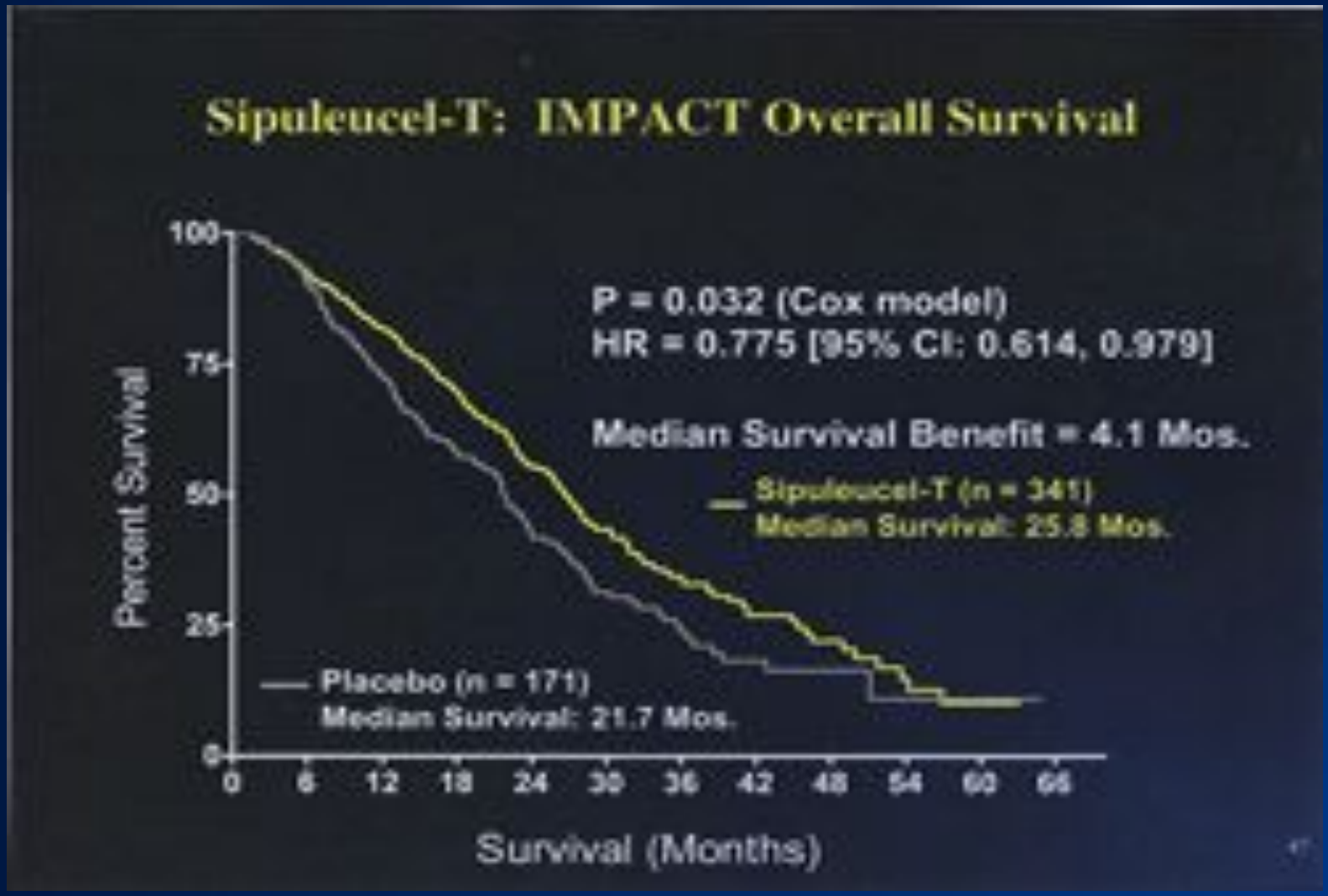
Therapeutic Cancer Vaccine: Sipuleucel-T



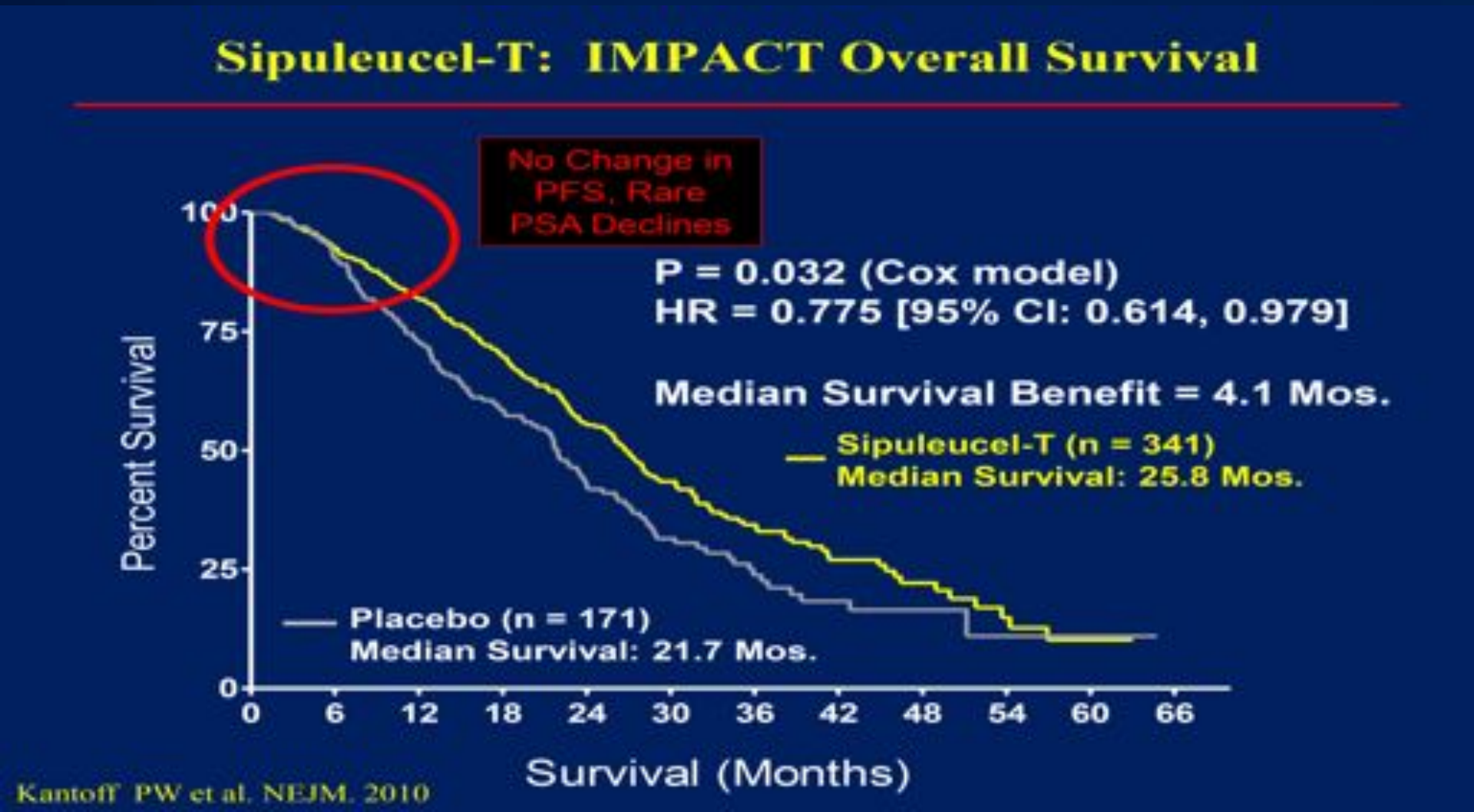
IMPACT: Randomized Phase 3 Trial



Sipuleucel-T: IMPACT Overall Survival



Sipuleucel-T



PSA and Sipuleucel-T

Patients with Lower PSA Had Greater OS Benefit After Sipuleucl-T

	Baseline PSA (ng/ml)			
	<22 (n=188)	22-50 (n=128)	50-134 (n=128)	>134
Median OS (mos)				
Sipuleucel-T	41.3	27.1	20.4	18.4
Control	28.3	20.1	15.0	15.6
Difference	13.0	7.0	5.4	2.8
HR	0.51	0.74	0.81	0.84

Schellhammer PF et al. Urol. 2013

Sipuleucel-T Toxicity

- 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.

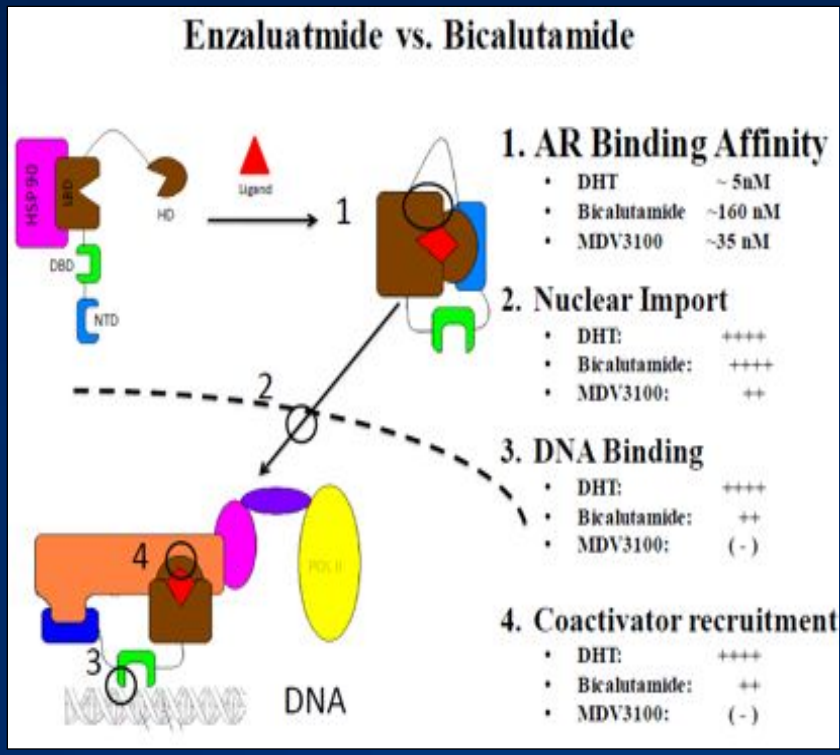
Prostate cancer first course

Enzalutamide

Enzalutamide

A small molecule AR antagonist

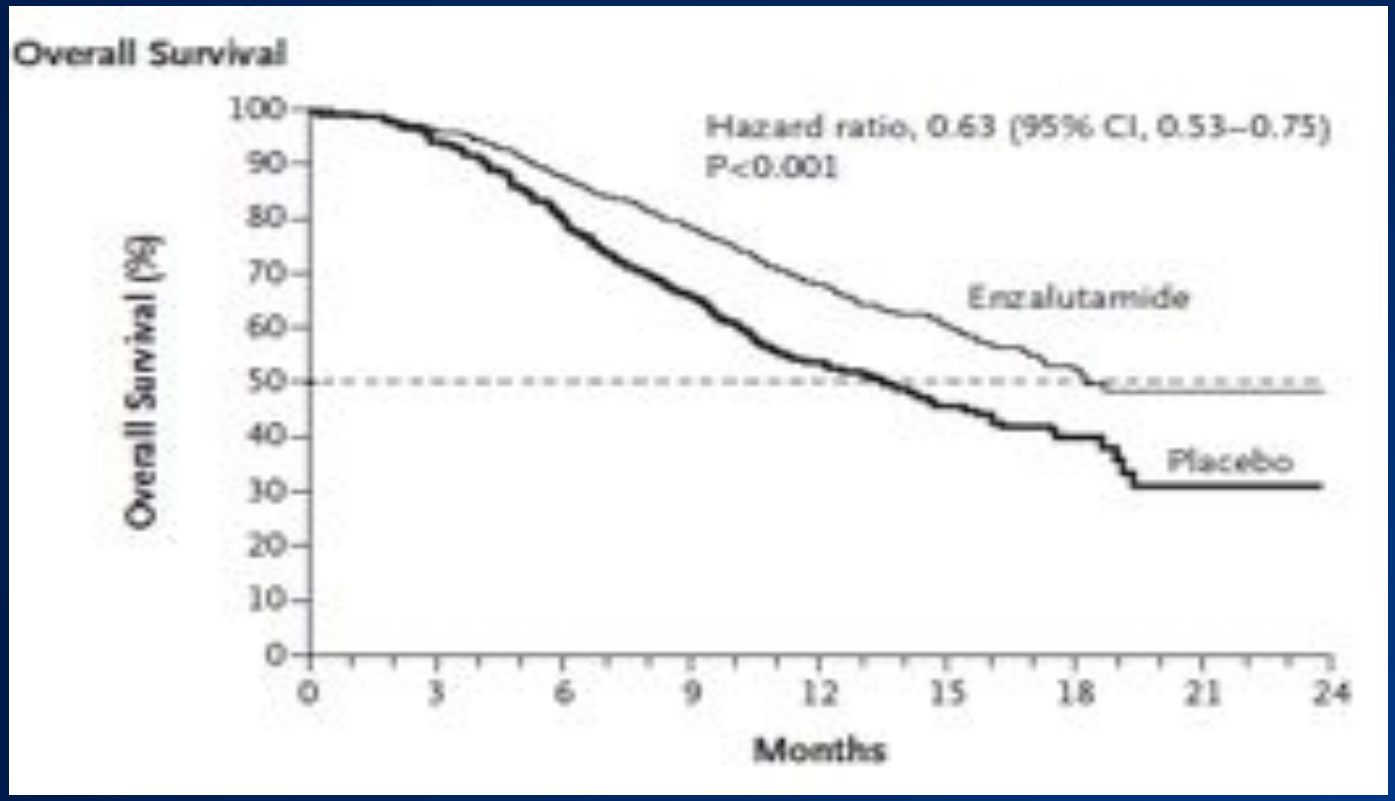
- Affinity 30 folds of bicalutamide
- Prevent nuclear translocation
- Prevents co-activator recruitment



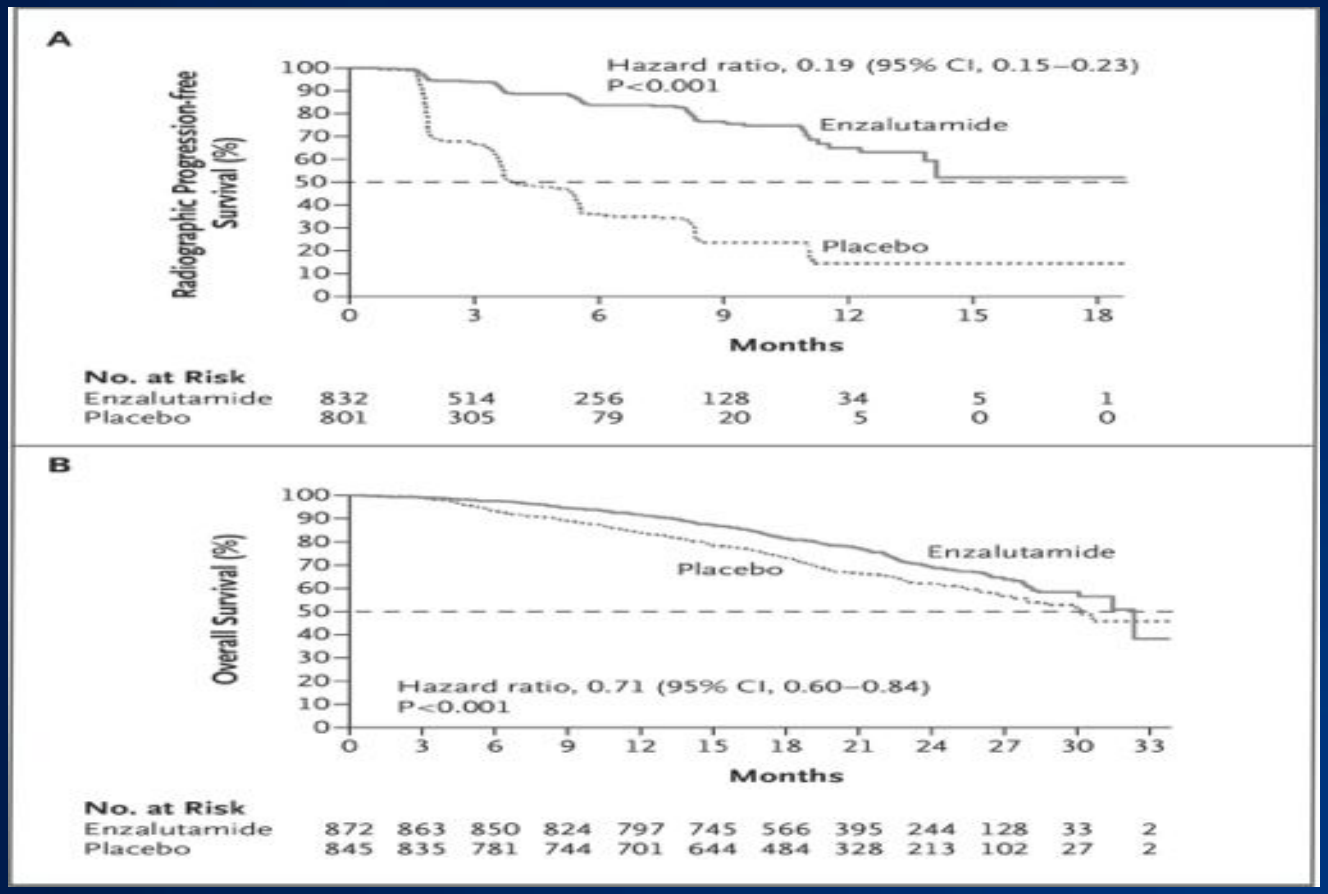
AFFIRM

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 Toxicity

Cardiovascular: Peripheral edema (15%)

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

Endocrine & metabolic: Hot flashes (20%)

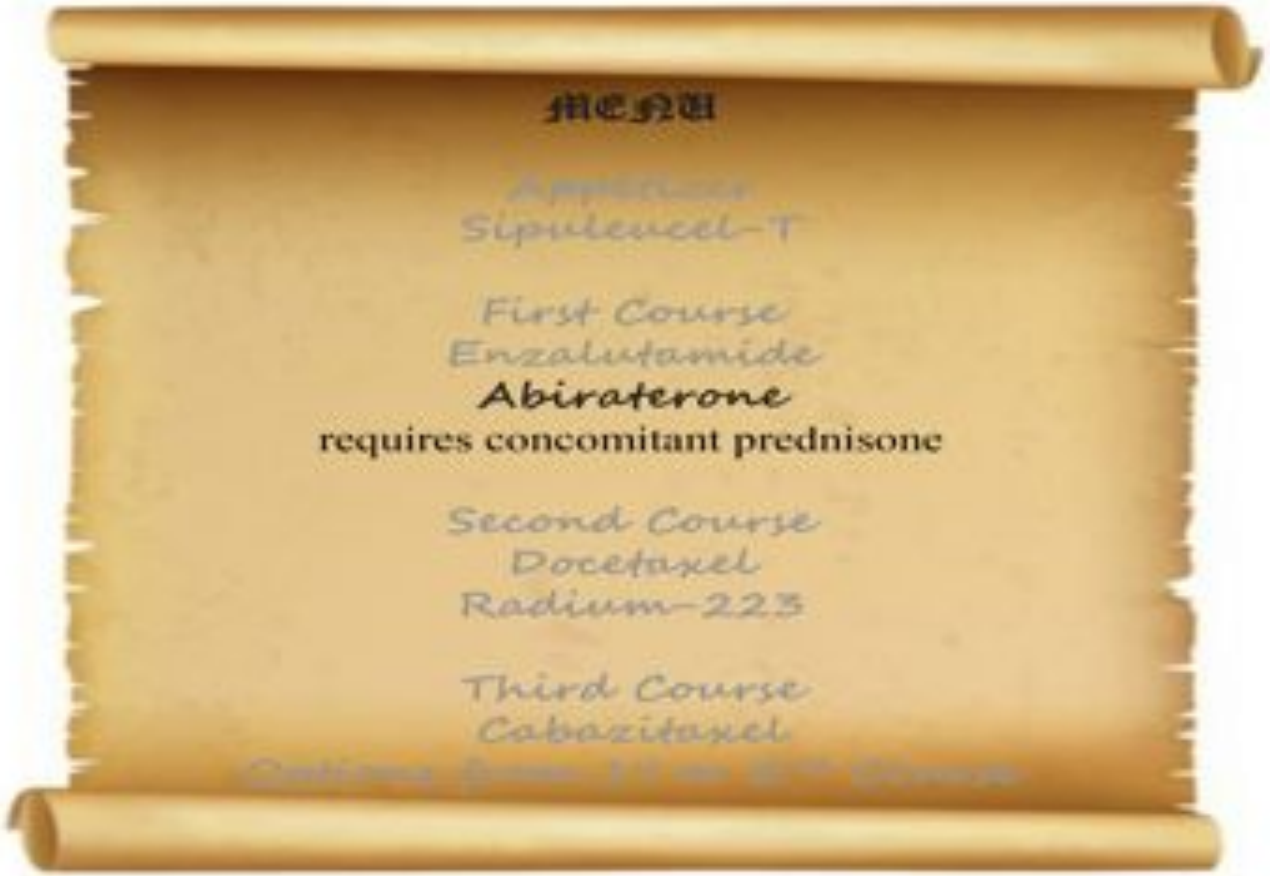
Gastrointestinal: Diarrhea (22%)

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

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

Respiratory: Upper respiratory tract infection (11%)

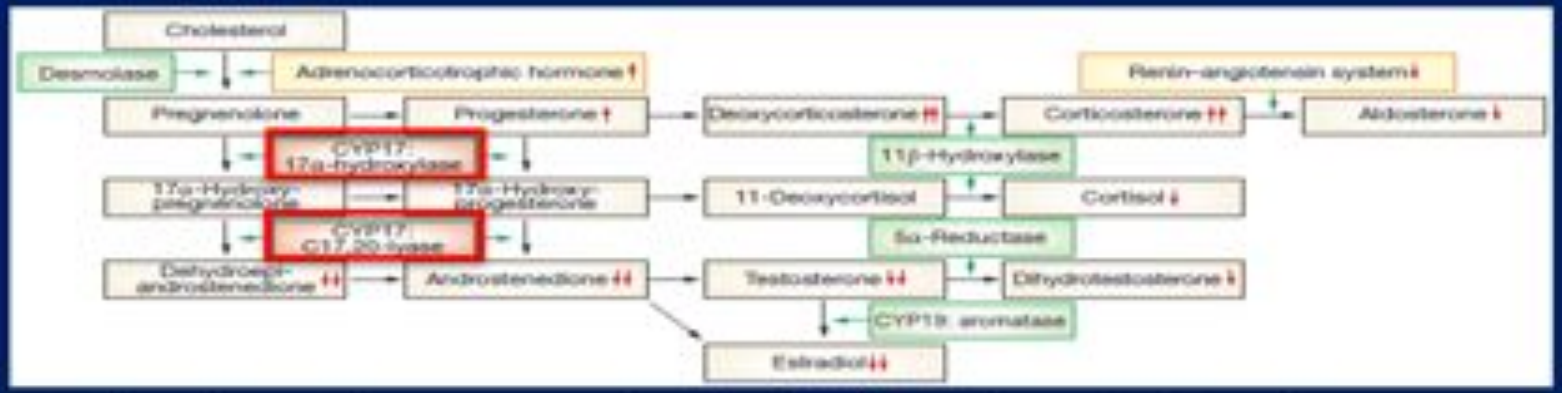
Abiraterone



Abiraterone rationale

Rationale for Abiraterone in CRPC

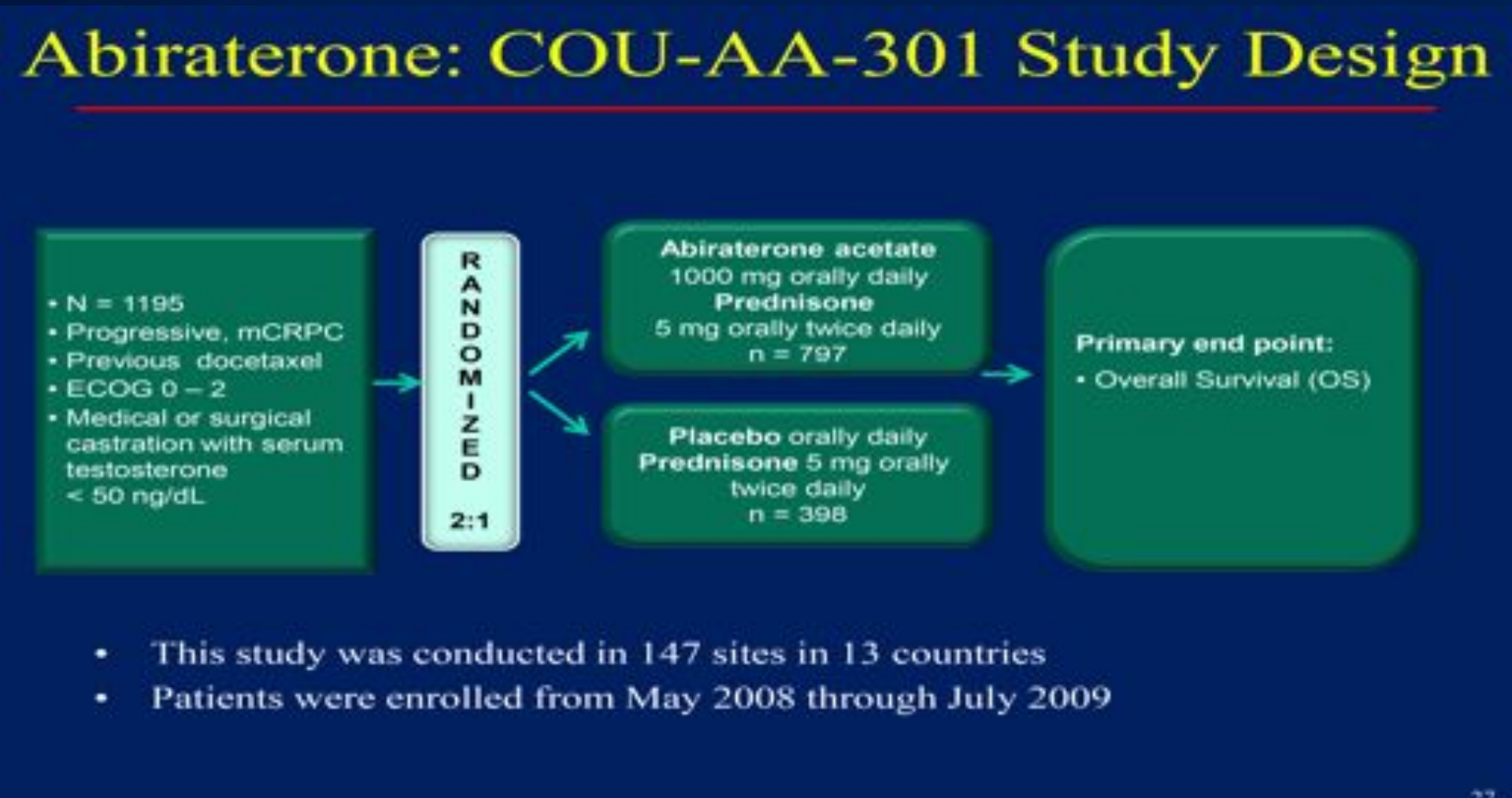
- There is up-regulation of androgen biosynthesis enzymes in CRPC



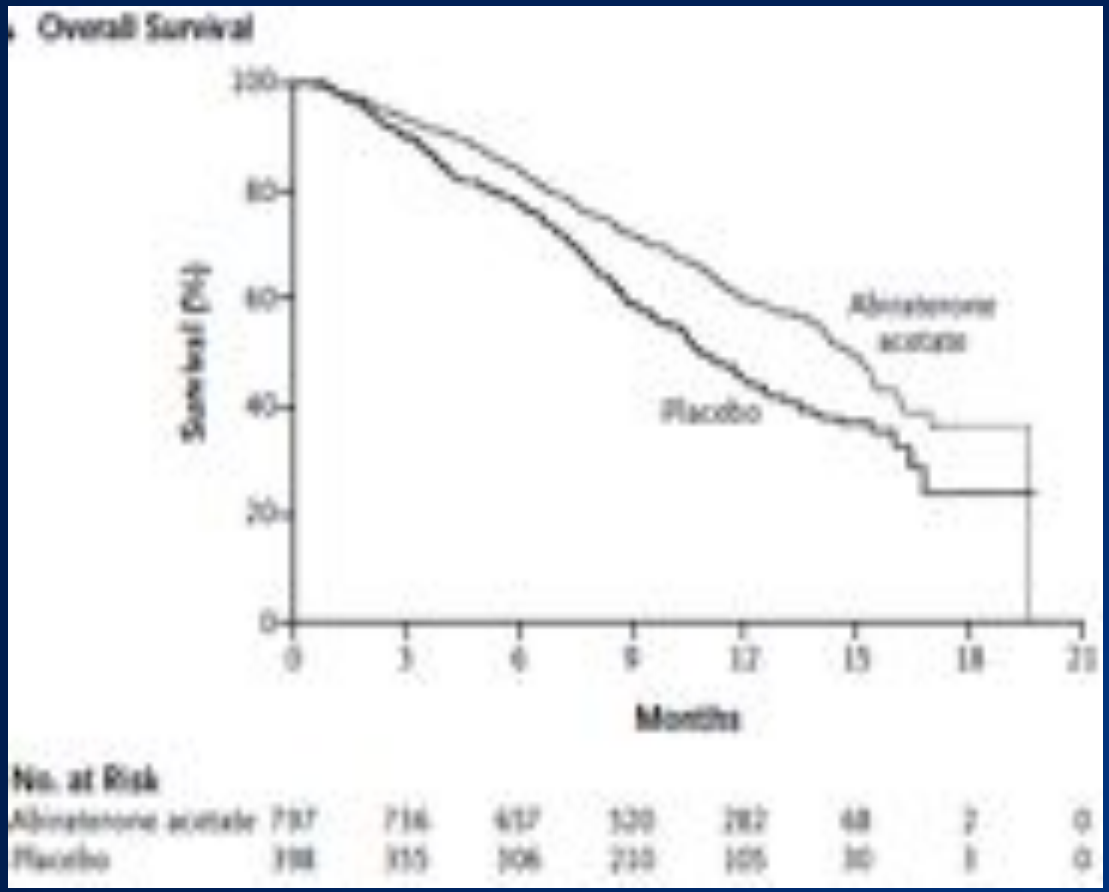
- Blocks androgen synthesis by the adrenal glands, testes and within the prostate tumor tissue

Reid et al. Nat Clin Pract Urol. 2008

Abiraterone study



Abiraterone: COU-AA-301 Trial



Abiraterone trial

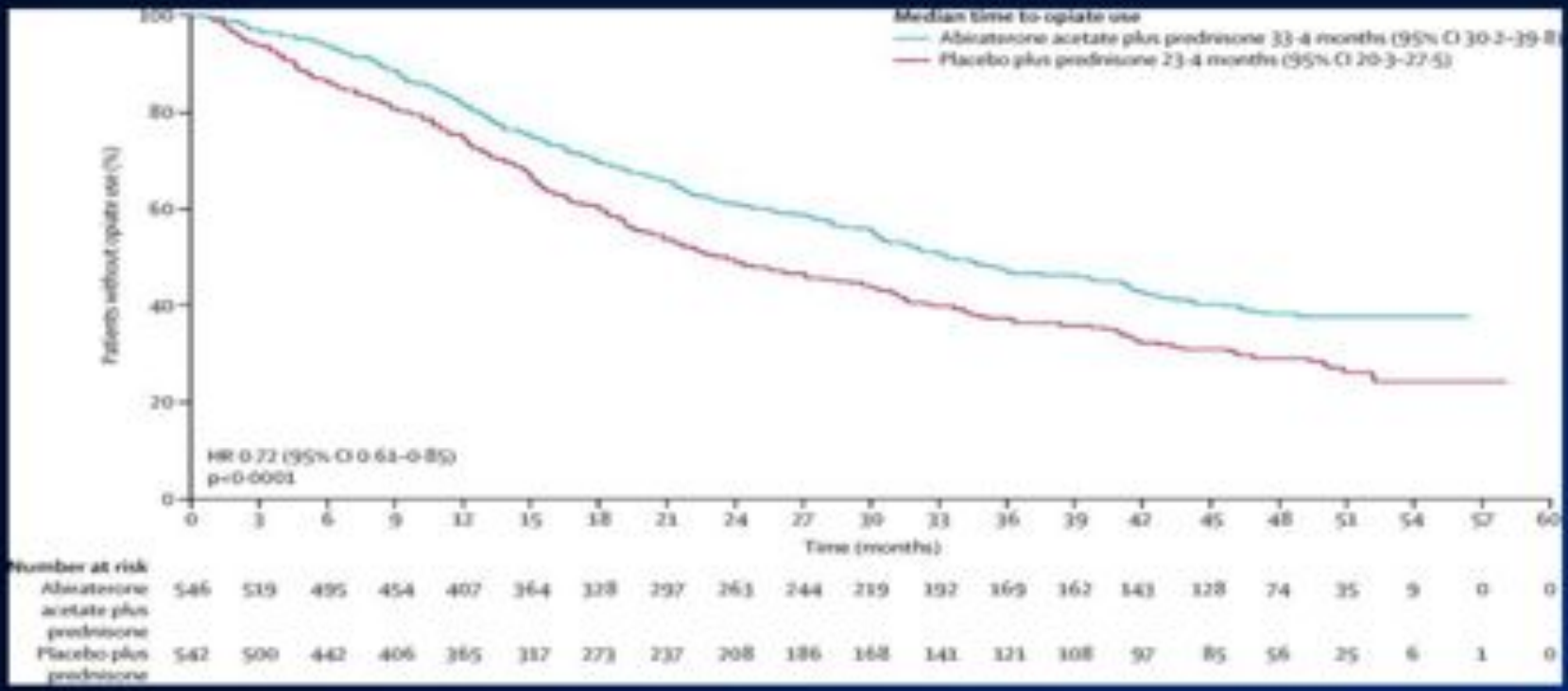
Abiraterone: COU-AA-301 Trial

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

de Bono JS et al. NEJM 2011

COU-AA-302

COU-AA-302 (chemo-naïve)



Ryan CJ, Lancet Oncol, 2015

Abiraterone Toxicity

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%)

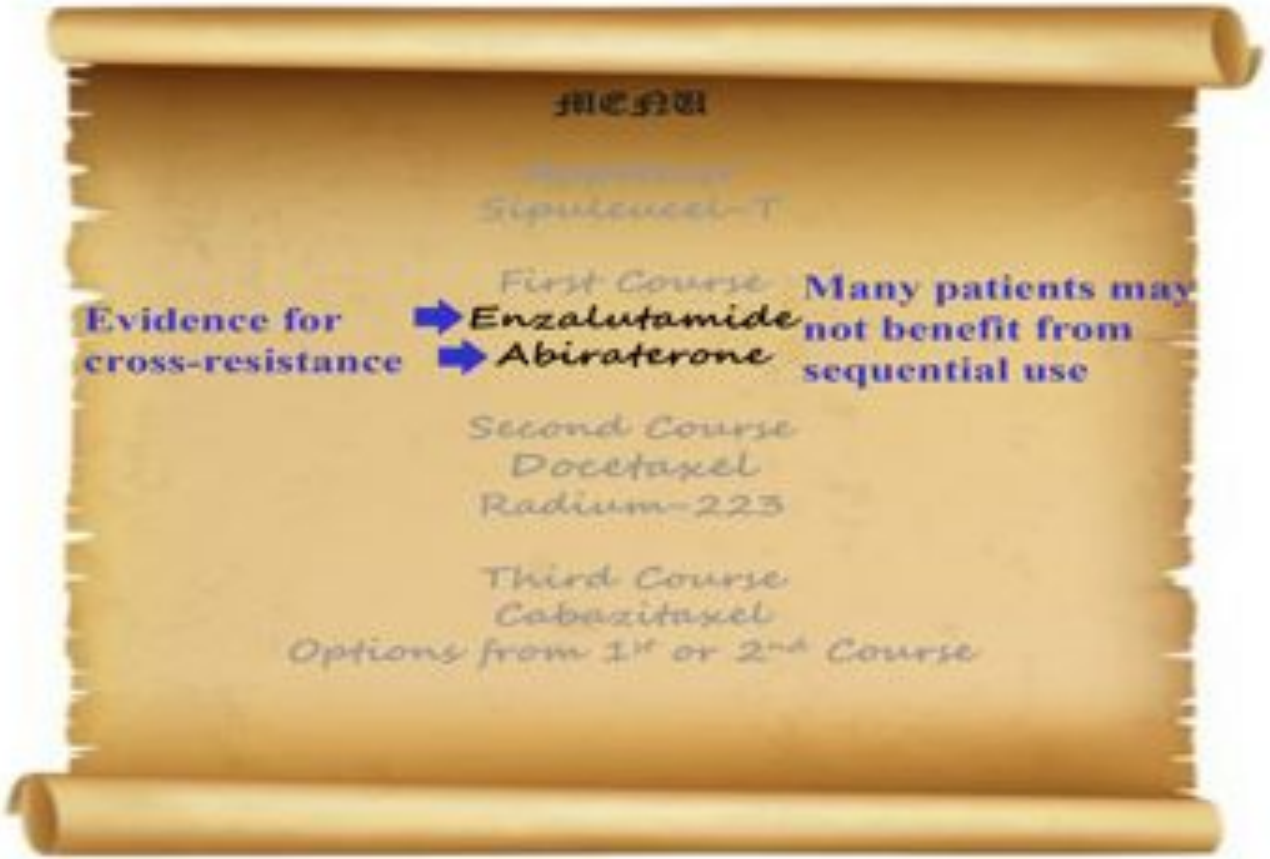
Hematologic: Lymphocytopenia (38%; grades 3/4: 9%)

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%)

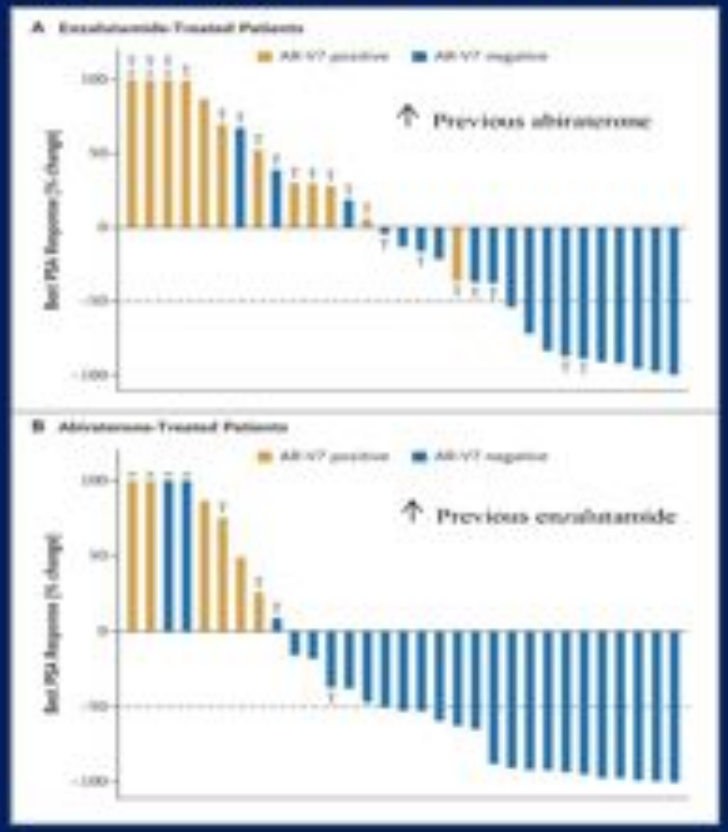
Cross resistance



Overlapping resistance

Overlapping Resistance: Androgen Receptor Splice Variants

- Variable splicing of AR mRNA can lead to resistance mechanisms to anti-androgen therapy
- ARV-7 has been investigated extensively, lacks a ligand binding domain and is constituently active
- Increases in ARV-7 seen after treatment with Abiraterone/Enzalutamide, likely contributing to cross-resistance.
- Thus sequential abiraterone and enzalutamide use may not have additive benefits

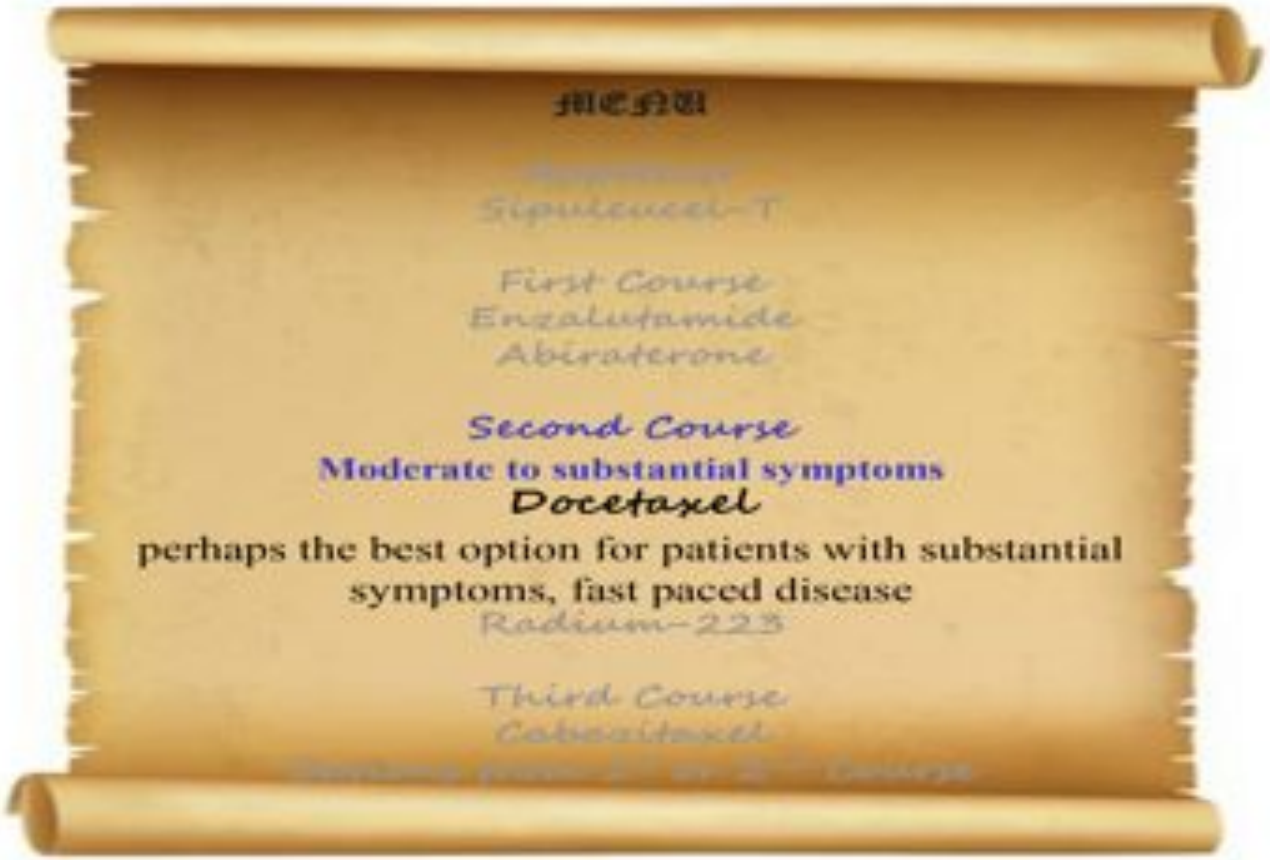


Antonarakis ES et al. NEJM, 2014.

Docetaxel


MENU
Sipuleucel-T
First Course
Enzalutamide
Abiraterone
Second Course
Moderate to substantial symptoms
Docetaxel
Radium-223
Third Course
Cabazitaxel
Options from 1st or 2nd Course

For fast paced disease



Docetaxel

Docetaxel

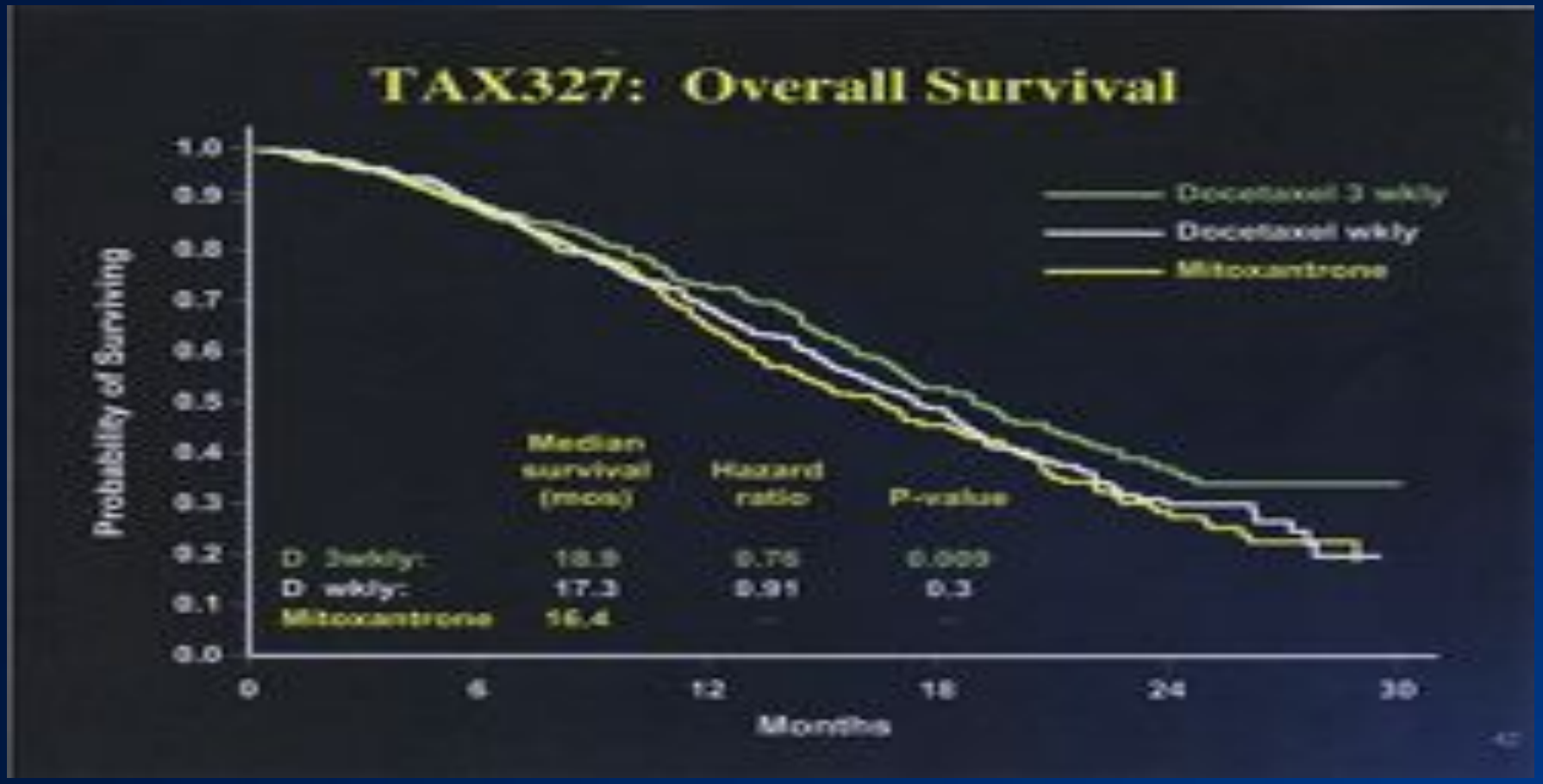
- In 1960s, crude extract of the bark of the Pacific yew tree, Taxus brevifolia, was shown to have suppressive activity in preclinical tumor models.
- By 1971, paclitaxel was identified as the active constituent of the bark extract.
- Taxanes exhibit antimicrotubule and antitumor activity
- *Emerging data suggests that taxanes inhibit AR translocation via microtubules*

Phase III study

TAX327: A Multicenter, Randomized Phase III Study of 3 weekly Docetaxel + Prednisone vs. Weekly Docetaxel + Prednisone vs. Mitoxantrone + Prednisone

Tannock IF et al. NEJM. 2004.

TAX327: Overall Survival



Docetaxel Toxicity

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%)

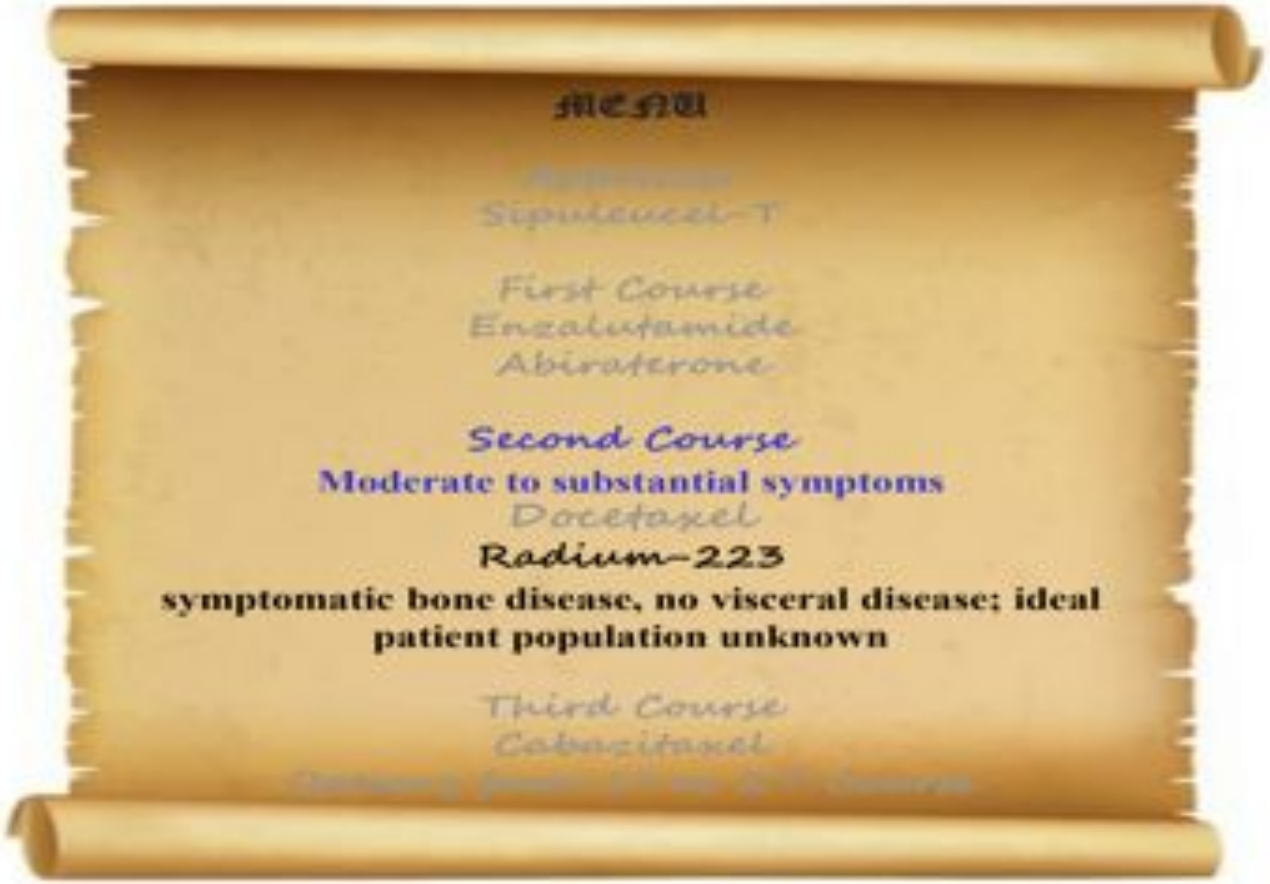
Hypersensitivity: Hypersensitivity (1% to 21%; with premedication 15%)

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%)

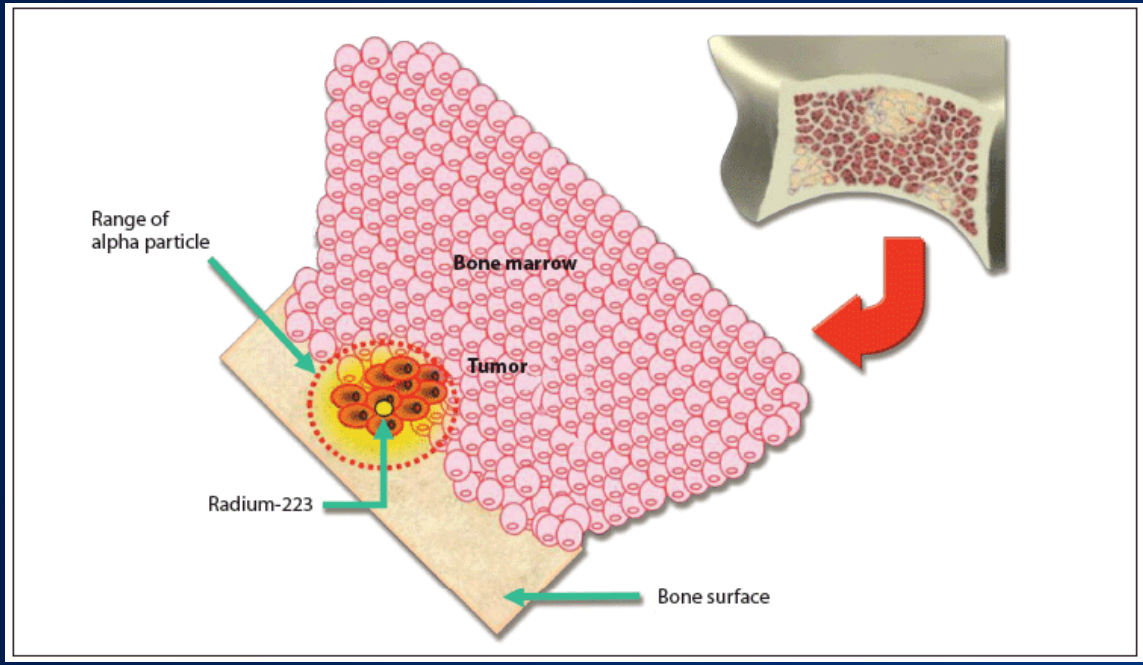
Radium


Menu
Sipuleucel-T
First Course
Enzalutamide
Abiraterone
Second Course
Moderate to substantial symptoms
Docetaxel
Radium-223
symptomatic bone disease, no visceral disease; ideal patient population unknown
Third Course
Cabazitaxel

Radium-223 (Alpharadin)

Bone –targeting radiopharmaceutical

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

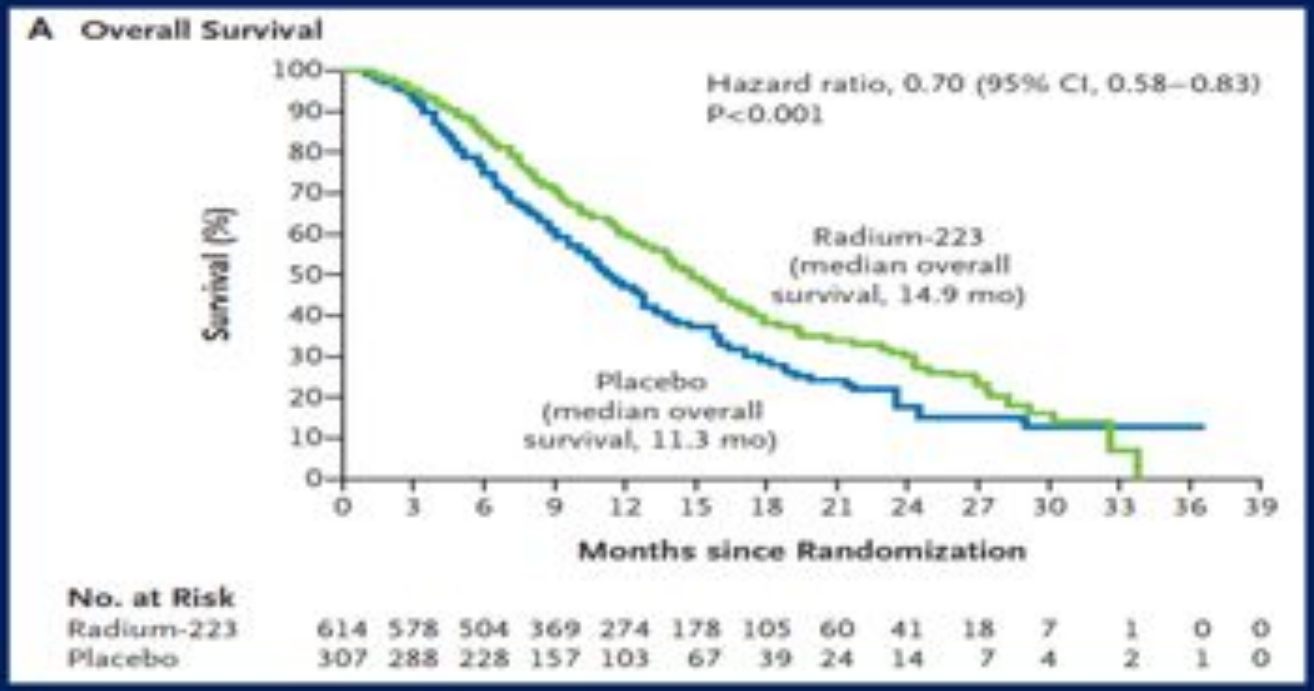


Radium trial

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

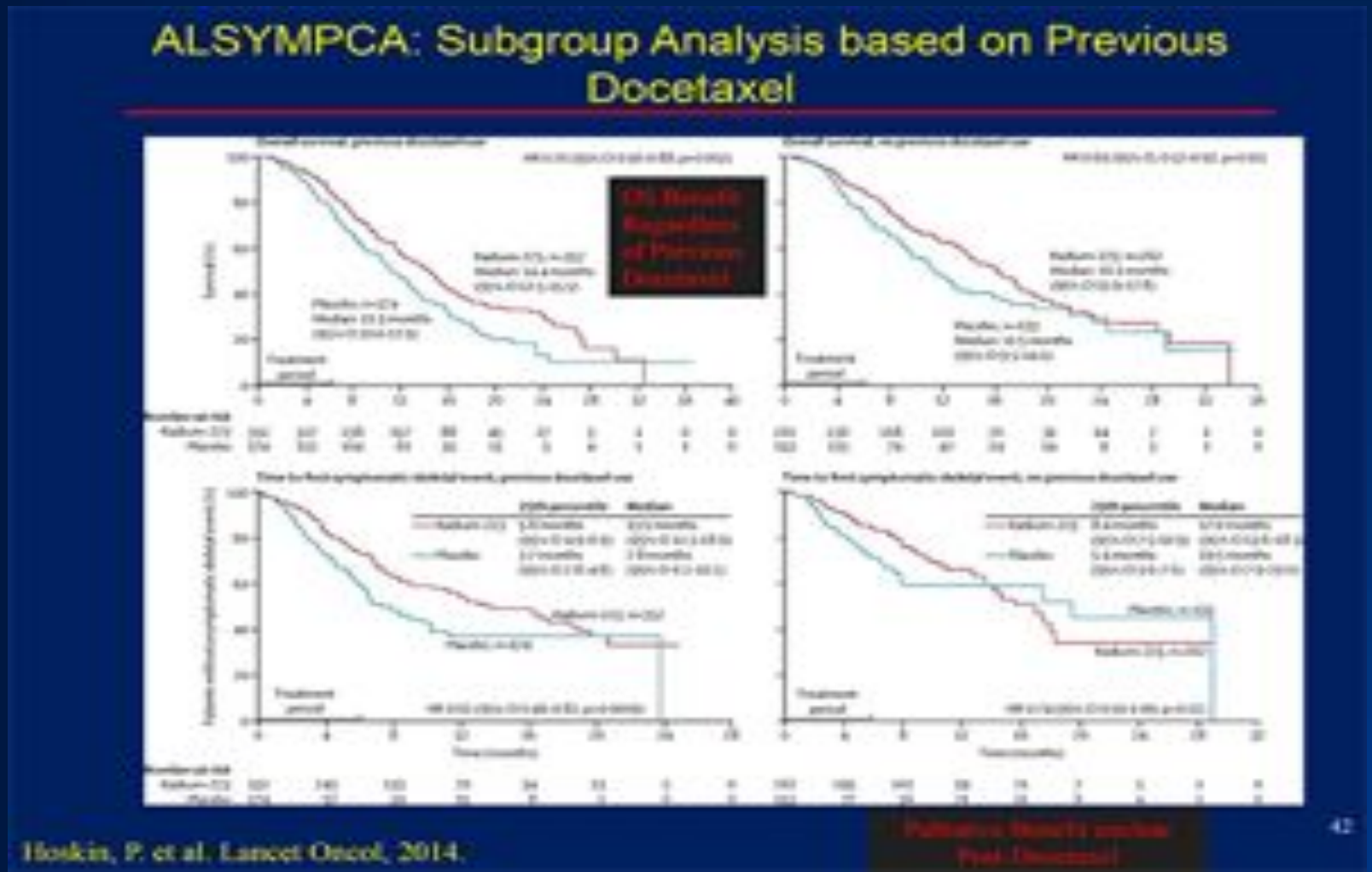
Phase III study of Radium-223

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



Parker C. et al. NEJM, 2013.

Survival curves



Radium toxicity

Radium 223 AEs

- Cardiovascular: Peripheral edema (13%)
- Gastrointestinal: Nausea (36%), diarrhea (25%), vomiting (19%)
- Hematologic: 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%)

Third course

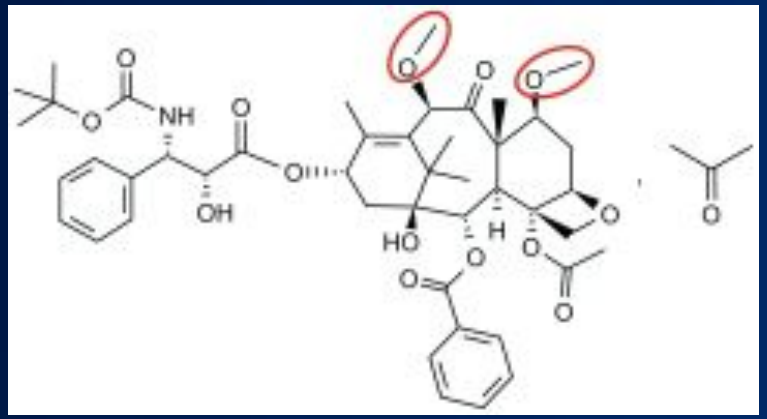
Cabazitaxel

Novel taxane active in docetaxel resistant cell lines

Less affinity for P-glycoprotein pump

Methoxyl side chain instead of

hydroxyl groups found in docetaxel

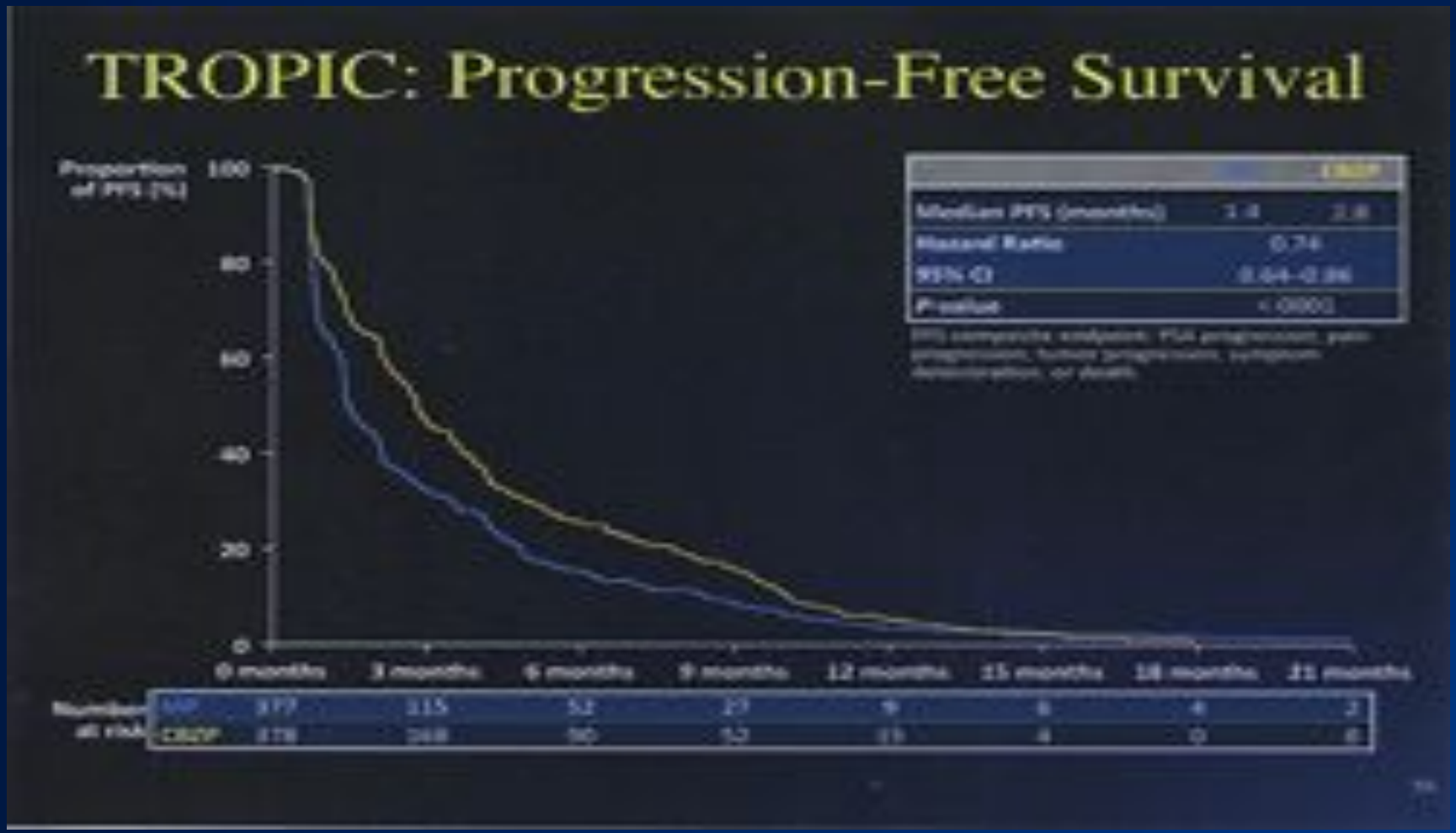


TROPIC protocol

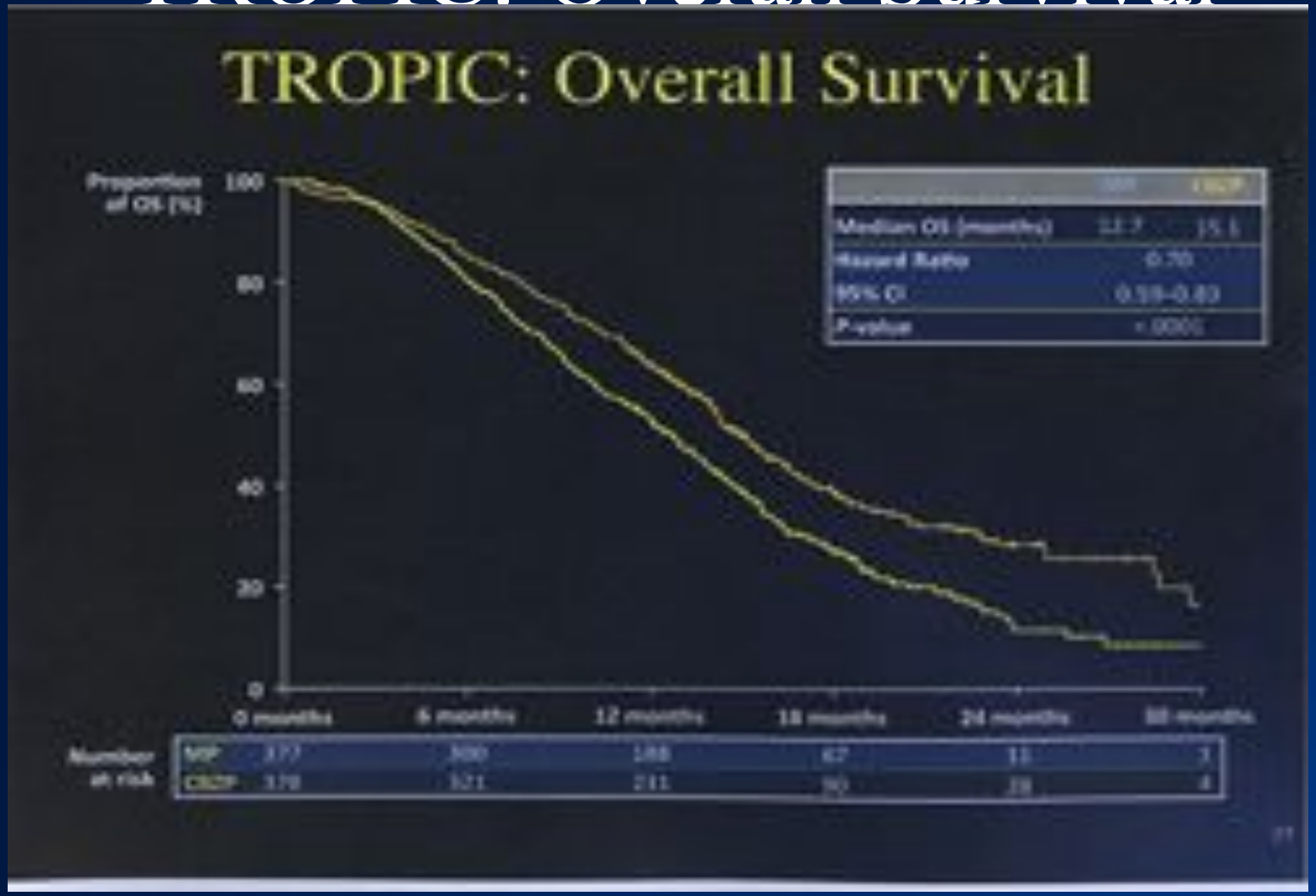
TROPIC: Randomized Phase III Study of Cabazitaxel vs. Mitoxantrone in mCRPC after Progression on Docetaxel

de Bono JS, et al. Lancet. 2010

TROPIC: Progression-Free Survival



TROPIC: Overall Survival



Cabazitaxel and ASCO

Cabazitaxel at ASCO 2016

- Cabazitaxel was not superior to docetaxel in front-line chemotherapy setting
- Cabazitaxel at 20 mg has same long term outcomes as Cabazitaxel at 25 mg

Sartor OA et al. ASCO 2016

Cabazitaxel Toxicity

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%)

Third course

Complete menu

Ultimate Goal: Use as many items on the menu while also maximizing quality of life

Specials

PARP Inhibitor

PARP Inhibitor – Breakthrough Status

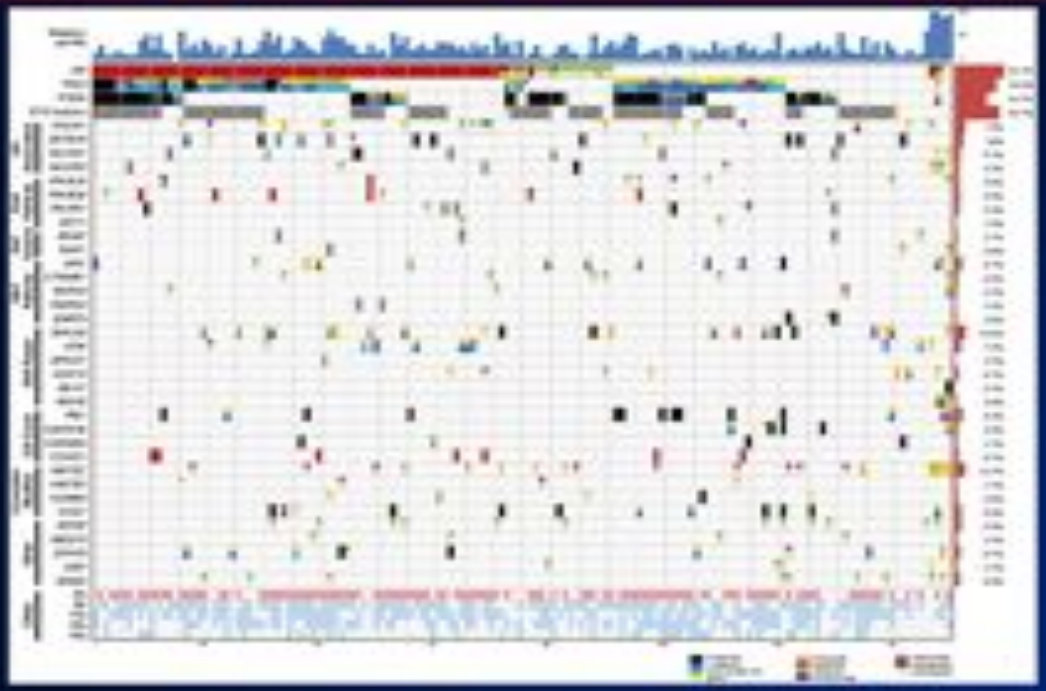
- 50 patients treated with a olparib
- 16 patients had "responses"
- 14 of the 16 had DNA damage repair defects
- Total of 16 patients overall had DNA damage repair defects


The NEW ENGLAND JOURNAL of MEDICINE

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

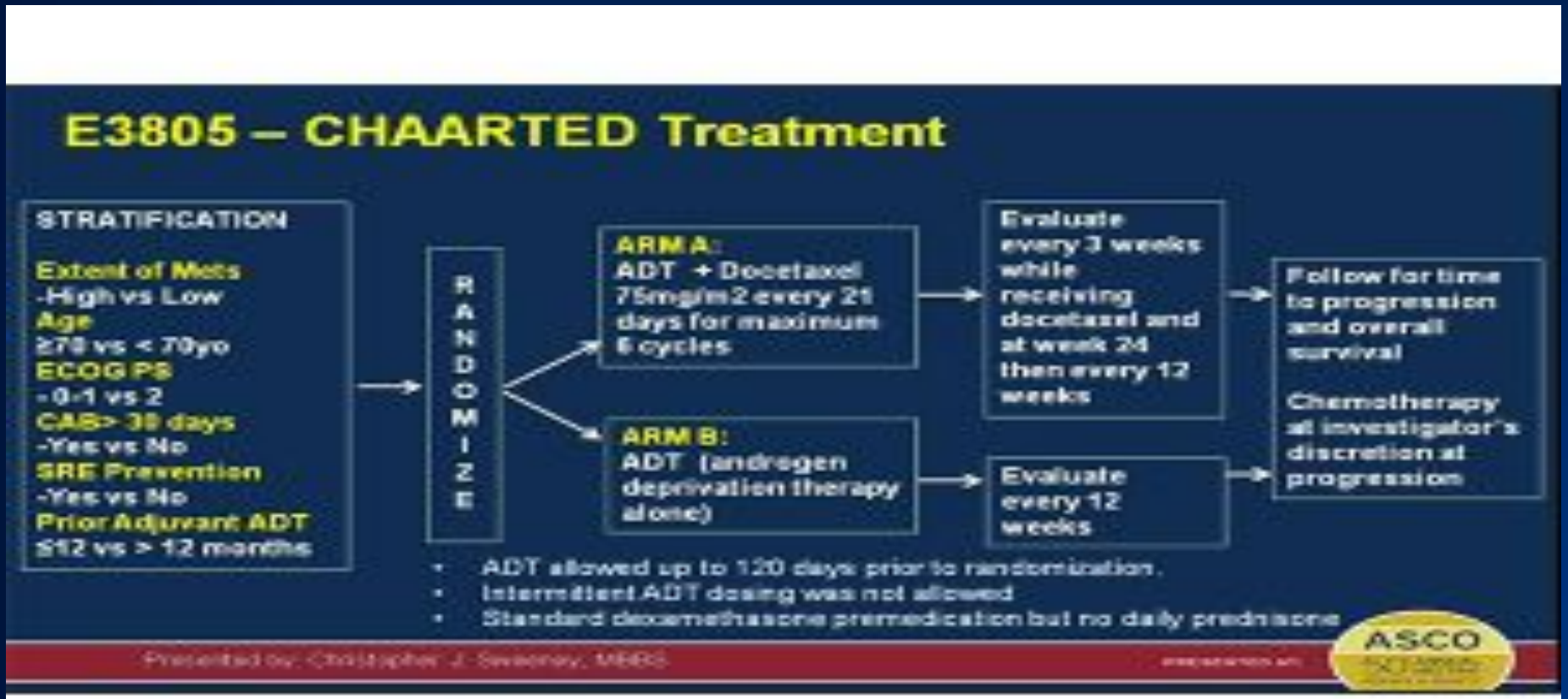
Clinical genomics

Integrative Clinical Genomics of Advanced Prostate Cancer



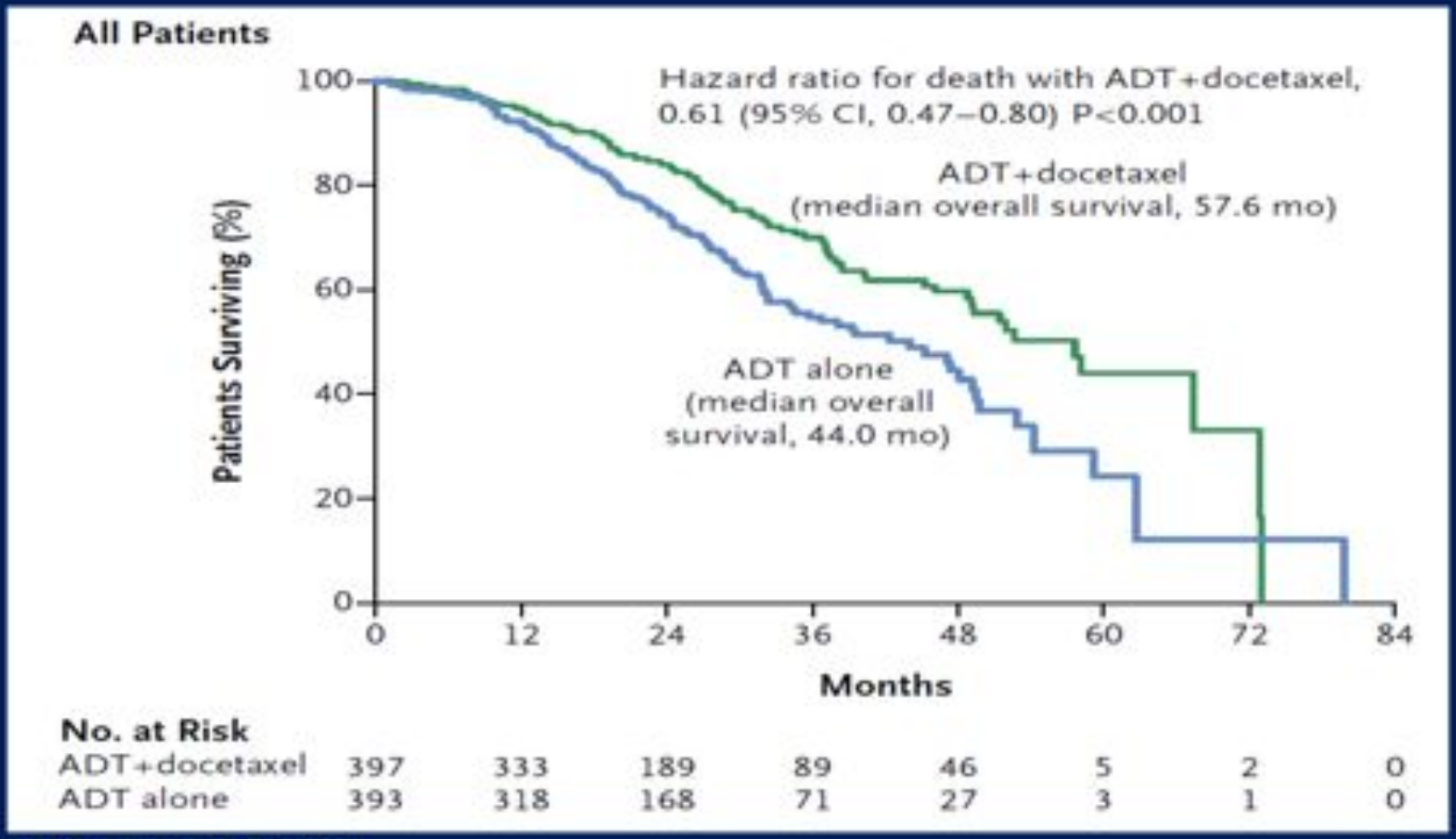
Robinson D *et al. Cell, 2015*

E3805 CHAARTED Treatment



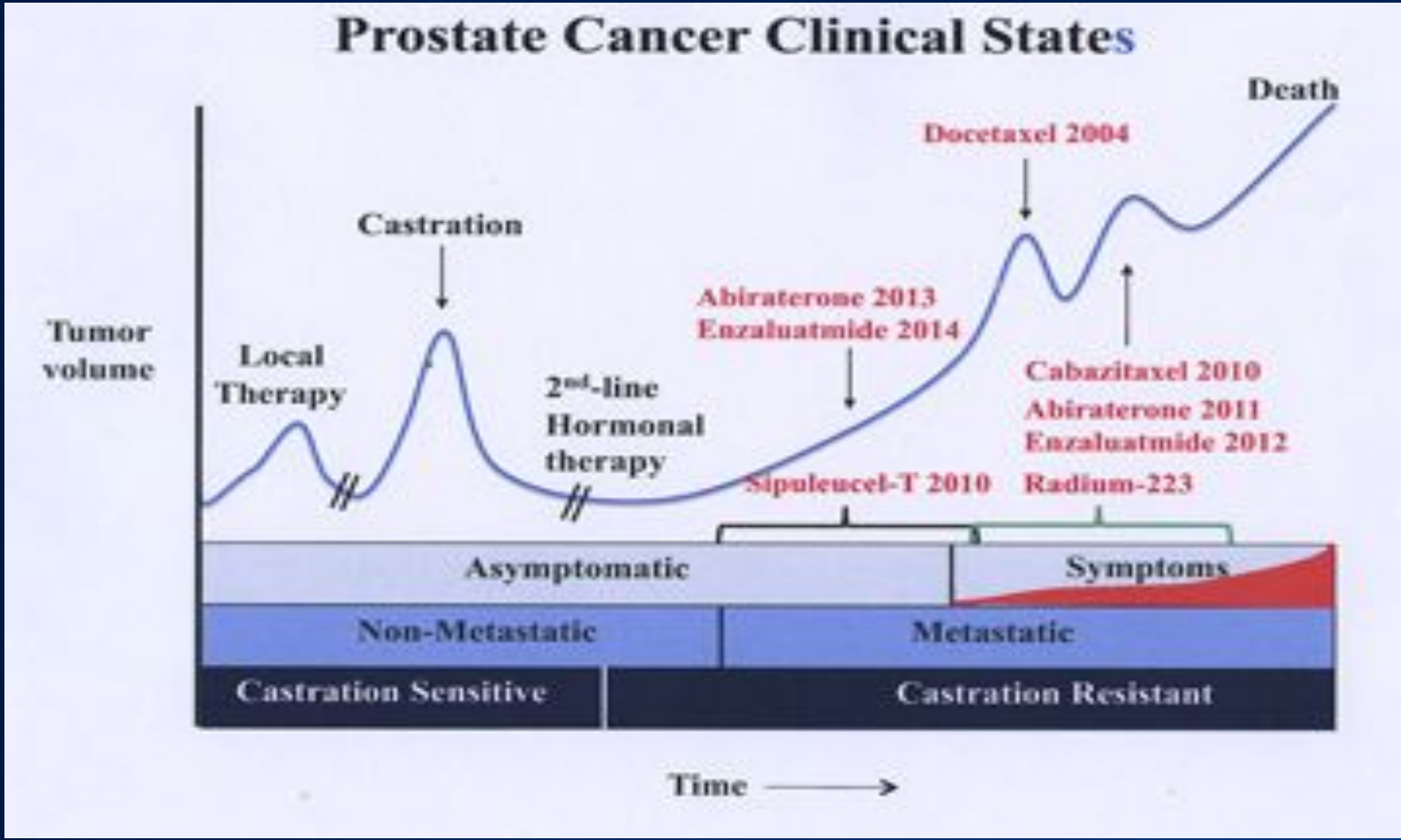
Presented By Christopher Sweeney at 2014 ASCO Annual Meeting

Survival curve

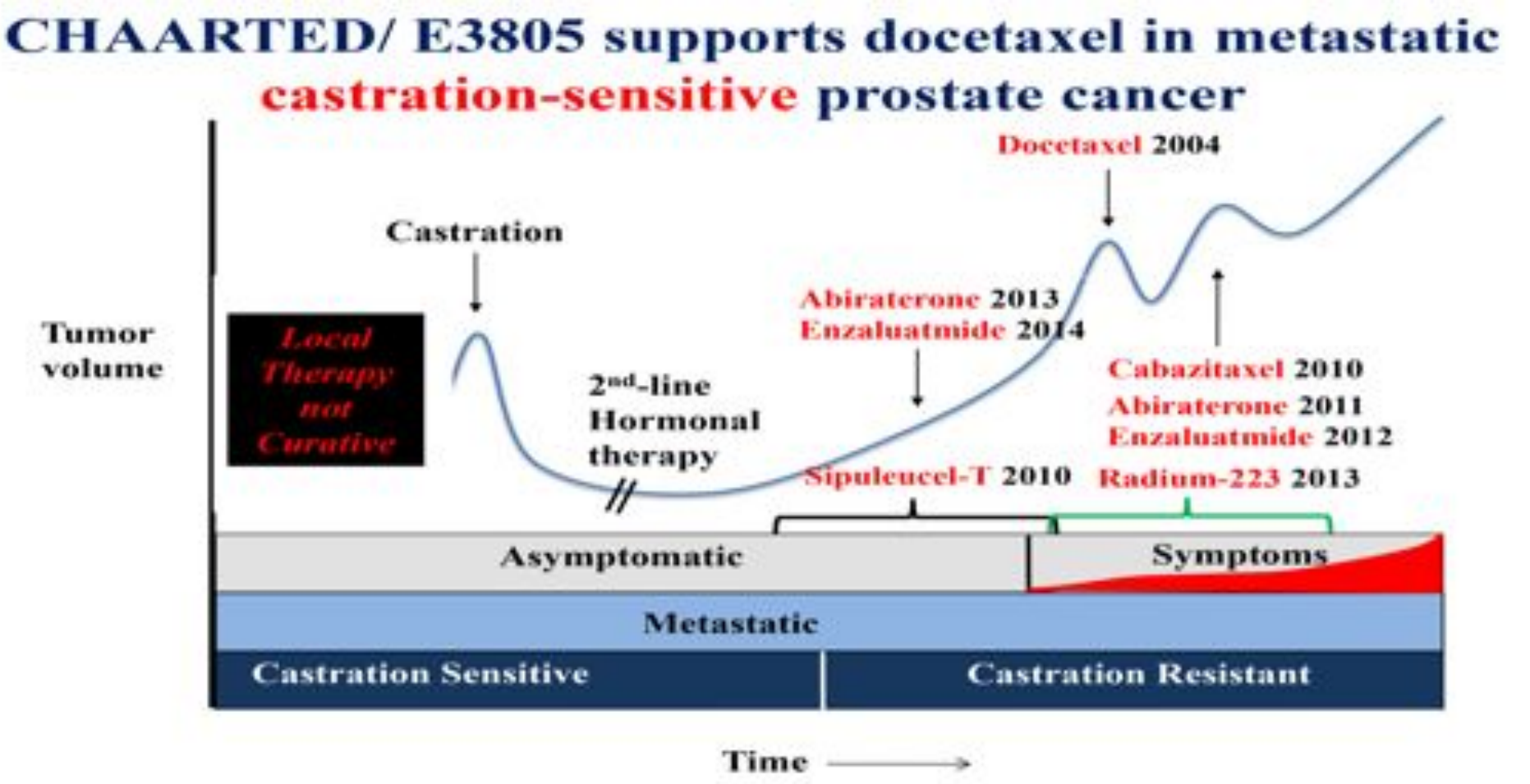


Sweeney, CJ et al. NEJM. 2015

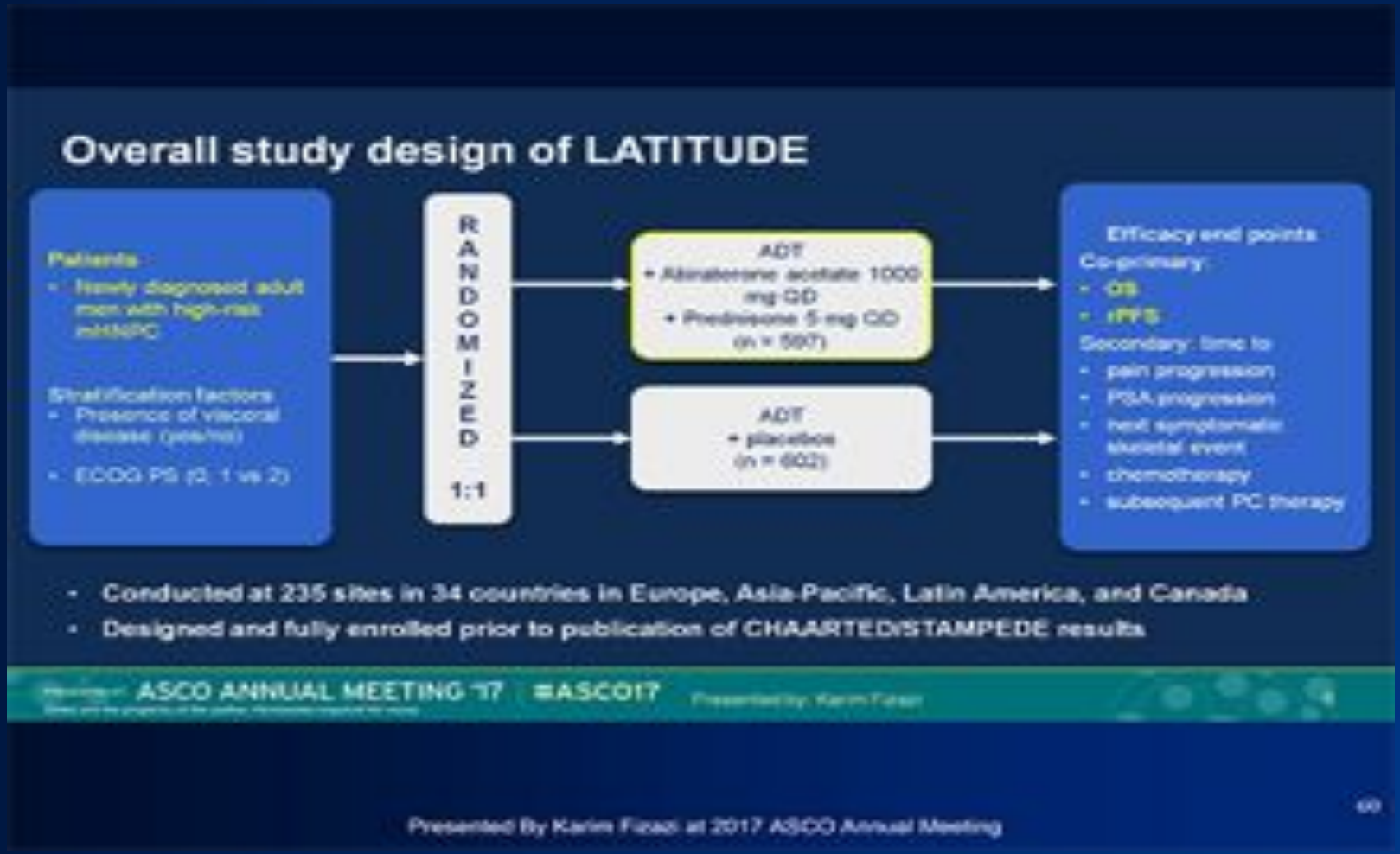
Prostate Cancer Clinical States



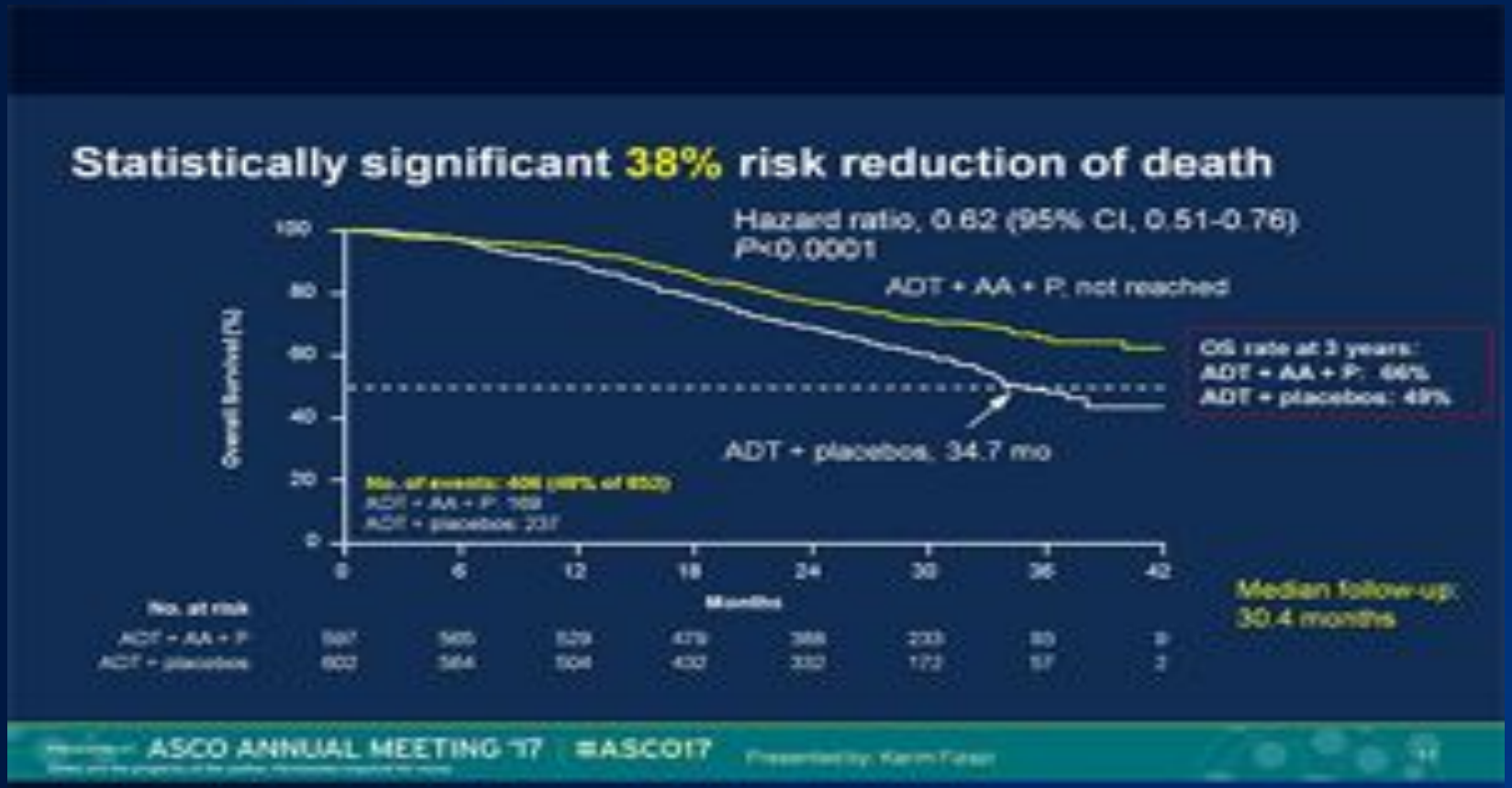
Docetaxel


CHAARTED/ E3805 supports docetaxel in metastatic castration-sensitive prostate cancer
Docetaxel 2004
Castration
Abiraterone 2013
Enzaluatmide 2014
Tumor volume
Local Therapy not Curative
2nd-line Hormonal therapy
Cabazitaxel 2010
Abiraterone 2011
Enzaluatmide 2012
Sipuleucel-T 2010
Radium-223 2013
Asymptomatic
Symptoms
Metastatic
Castration Sensitive
Castration Resistant
Time

LATITUDE study



Survival curve

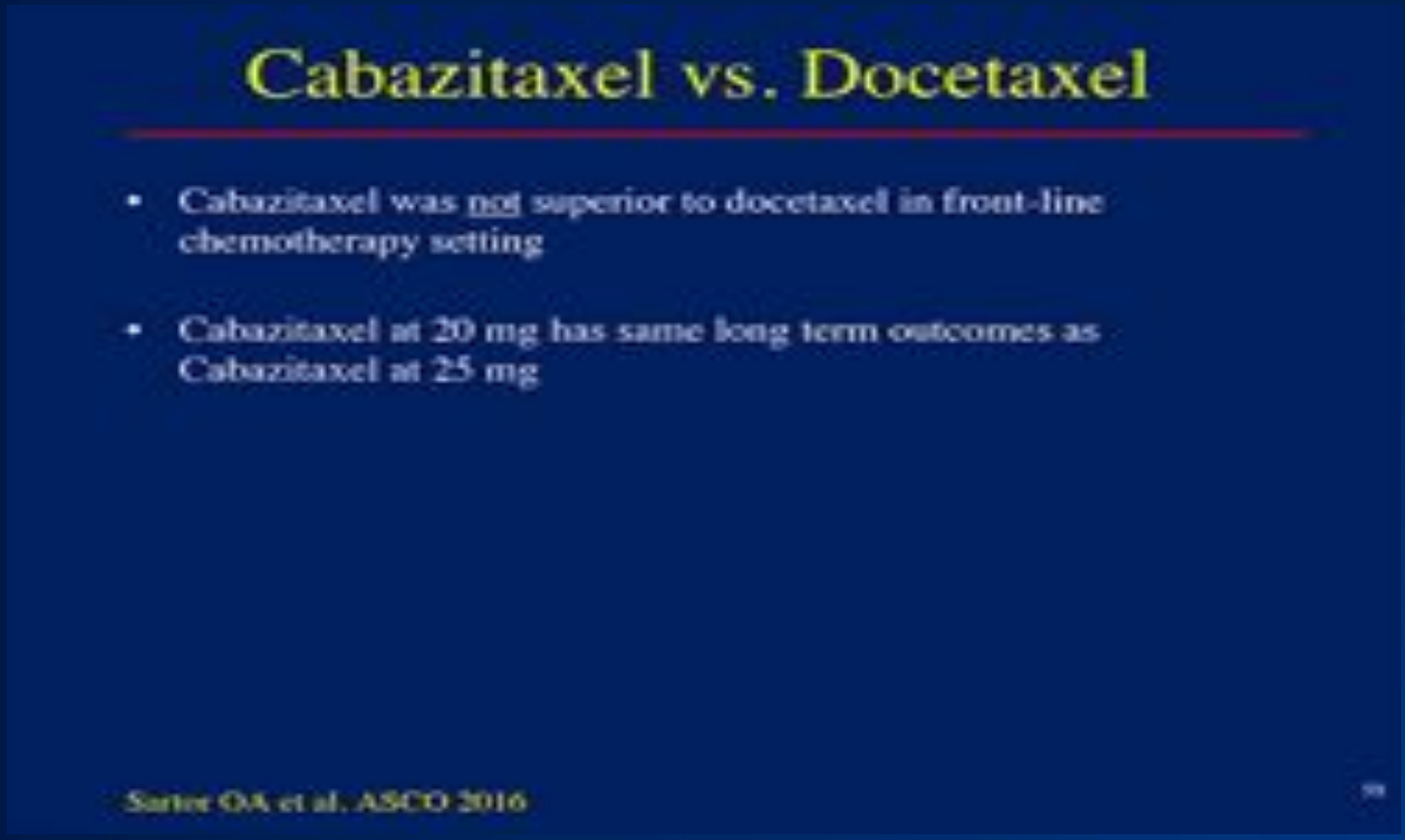


Summary

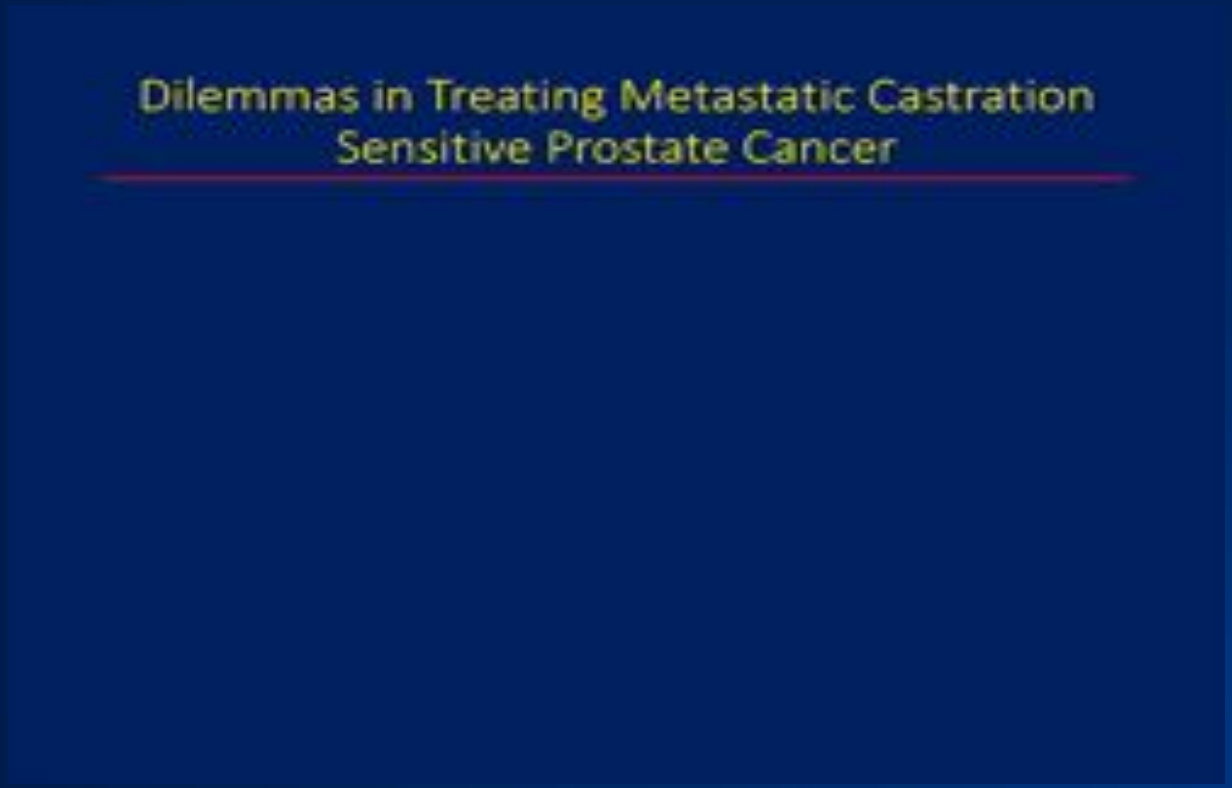

Appetizer
Sipuleucel-T
First Course
Enzalutamide
Abiraterone
Second Course
Docetaxel
Radium-223
Third Course
Cabazitaxel
Enzalutamide
Abiraterone
Radium-223
Ultimate Goal: Use as many items on the menu while also maximizing quality of life

Third course

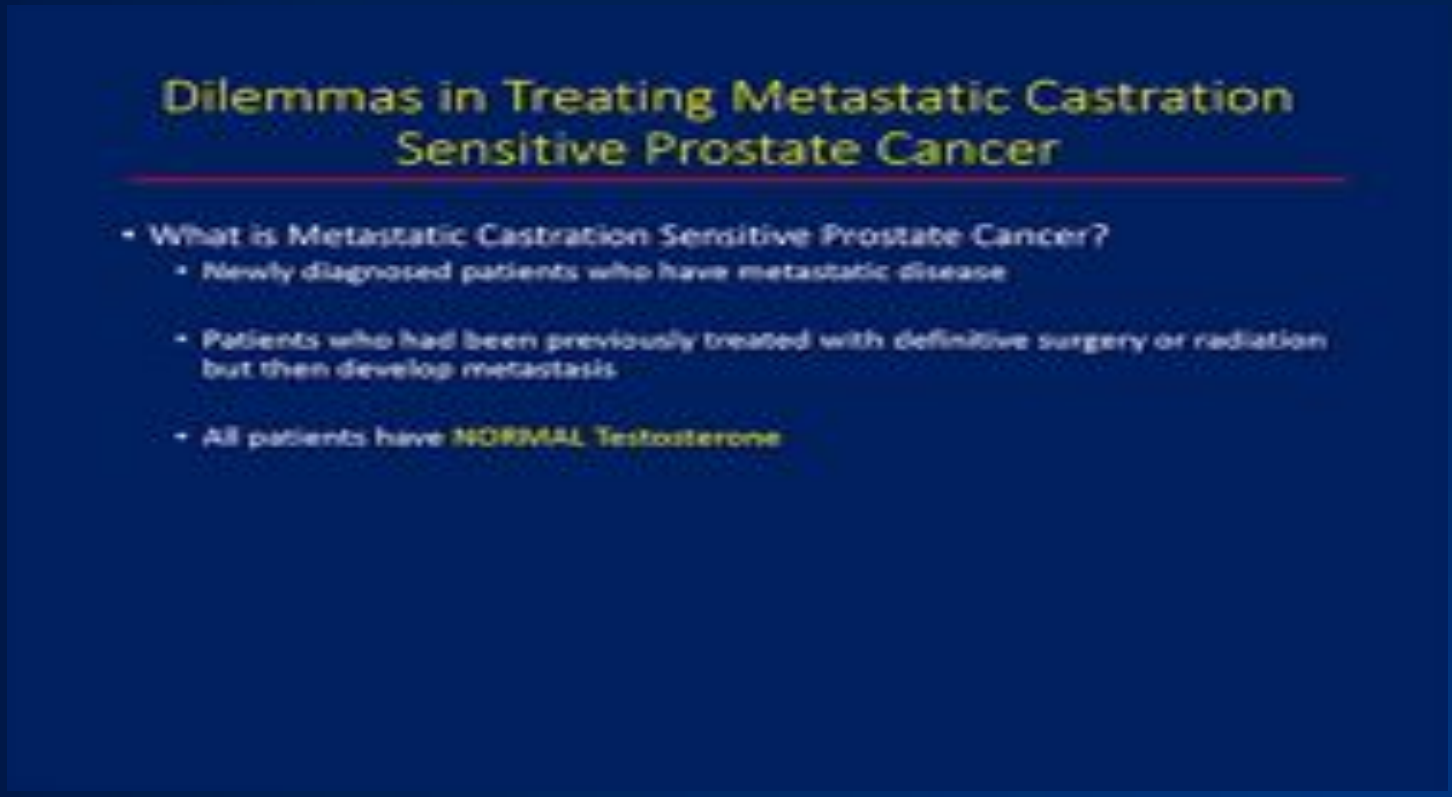
Carbazitaxel vs. Docetaxel



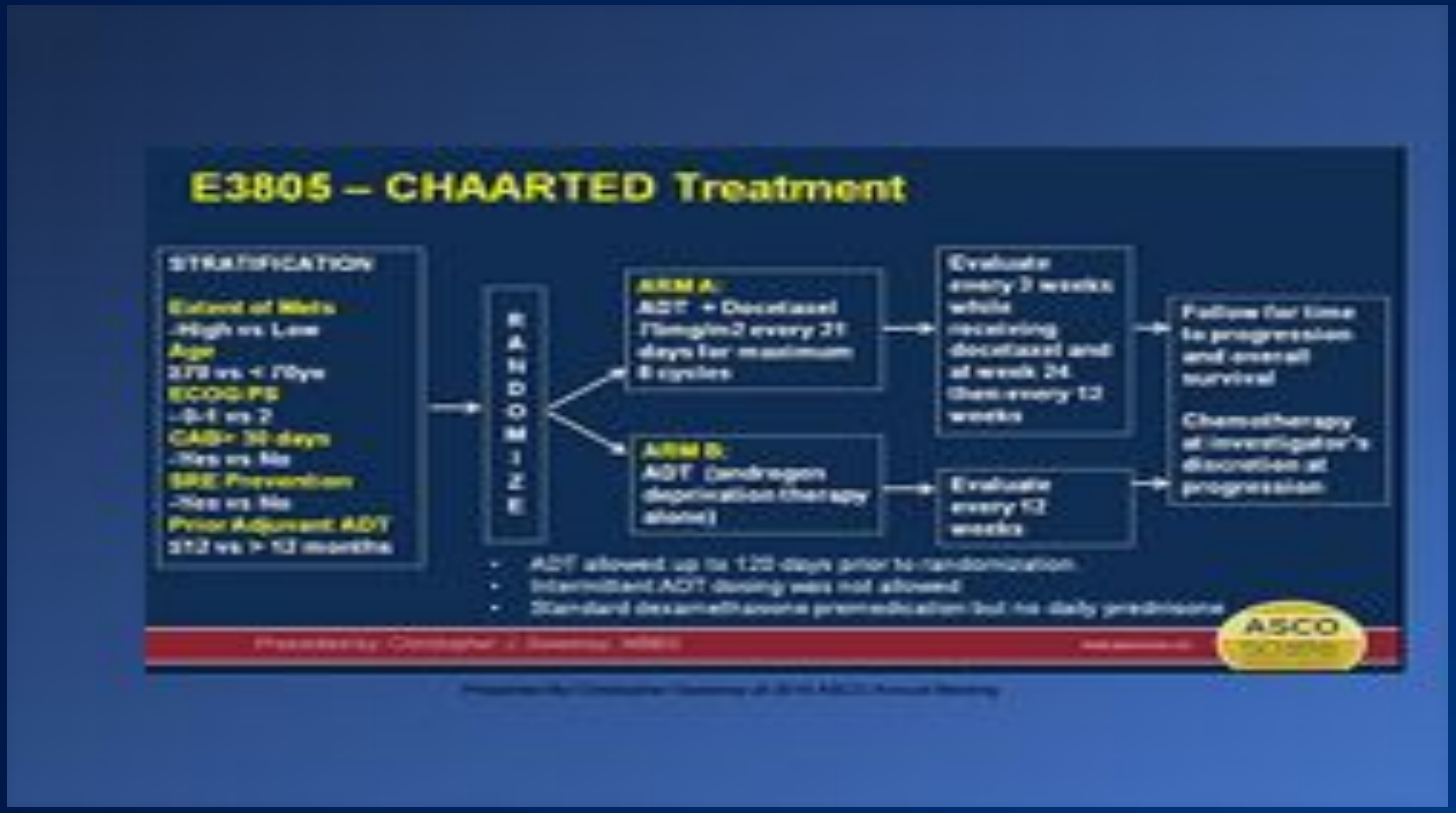
Dilemmas in treatment



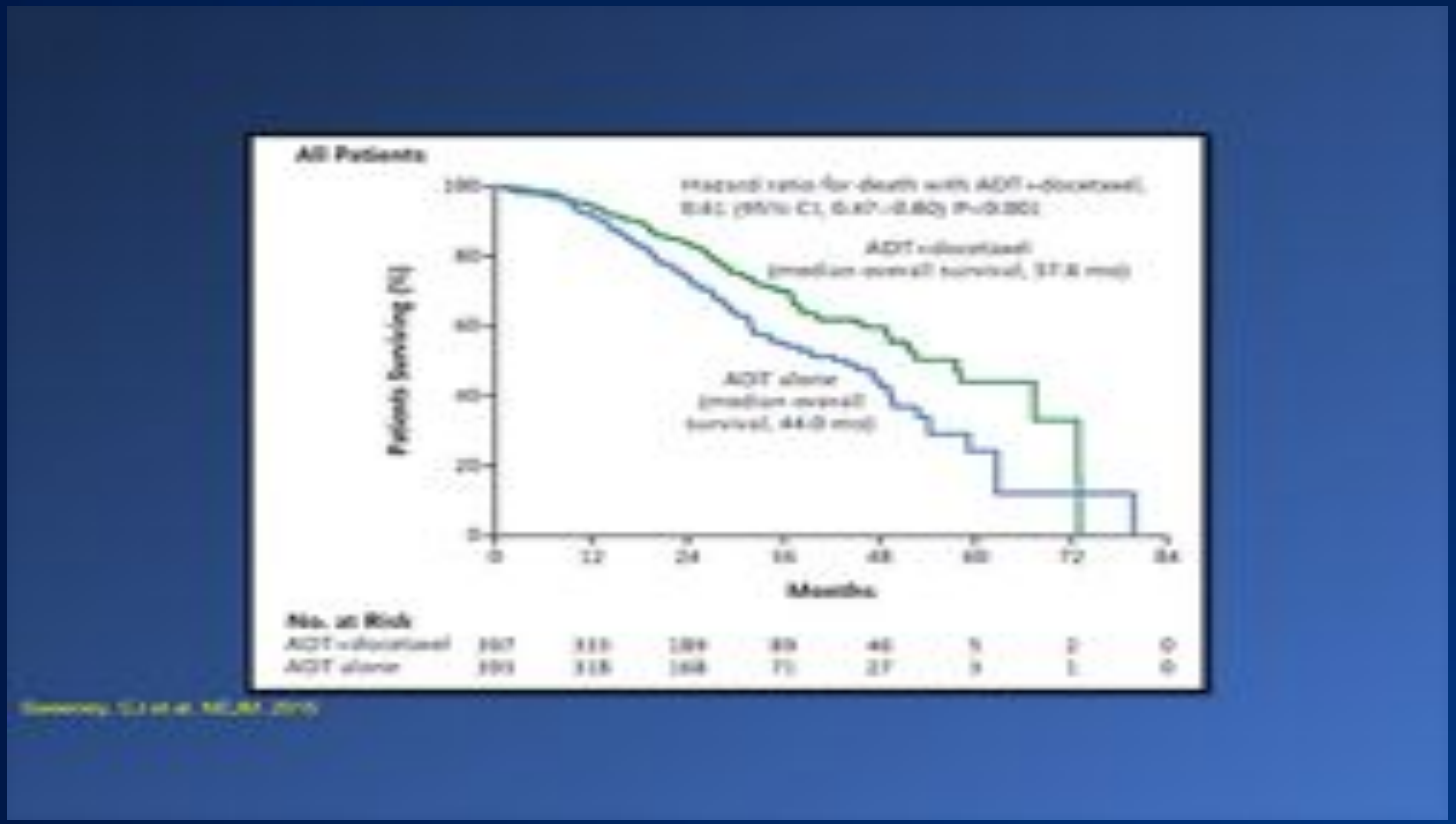
Dilemmas in Treatment



CHAARTED Treatment



Survival curve



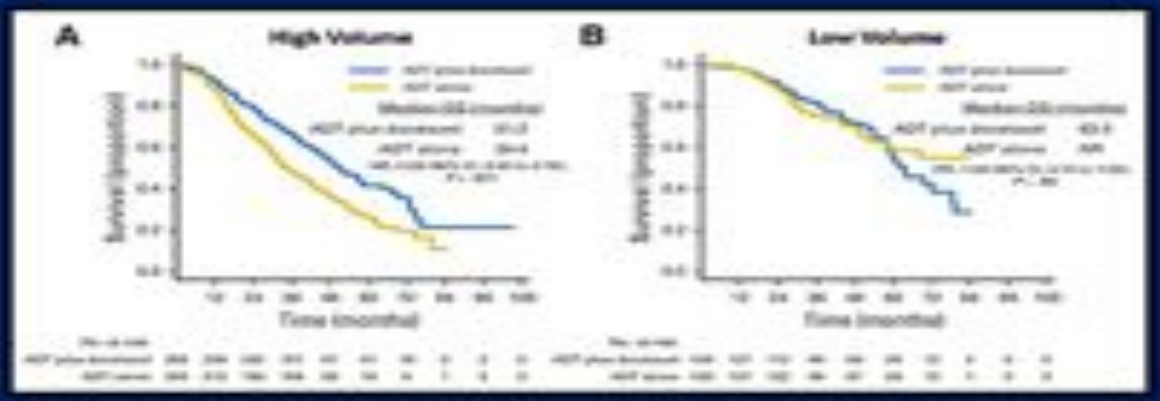
Docetaxel overall survival

Docetaxel OS based on Volume of Disease

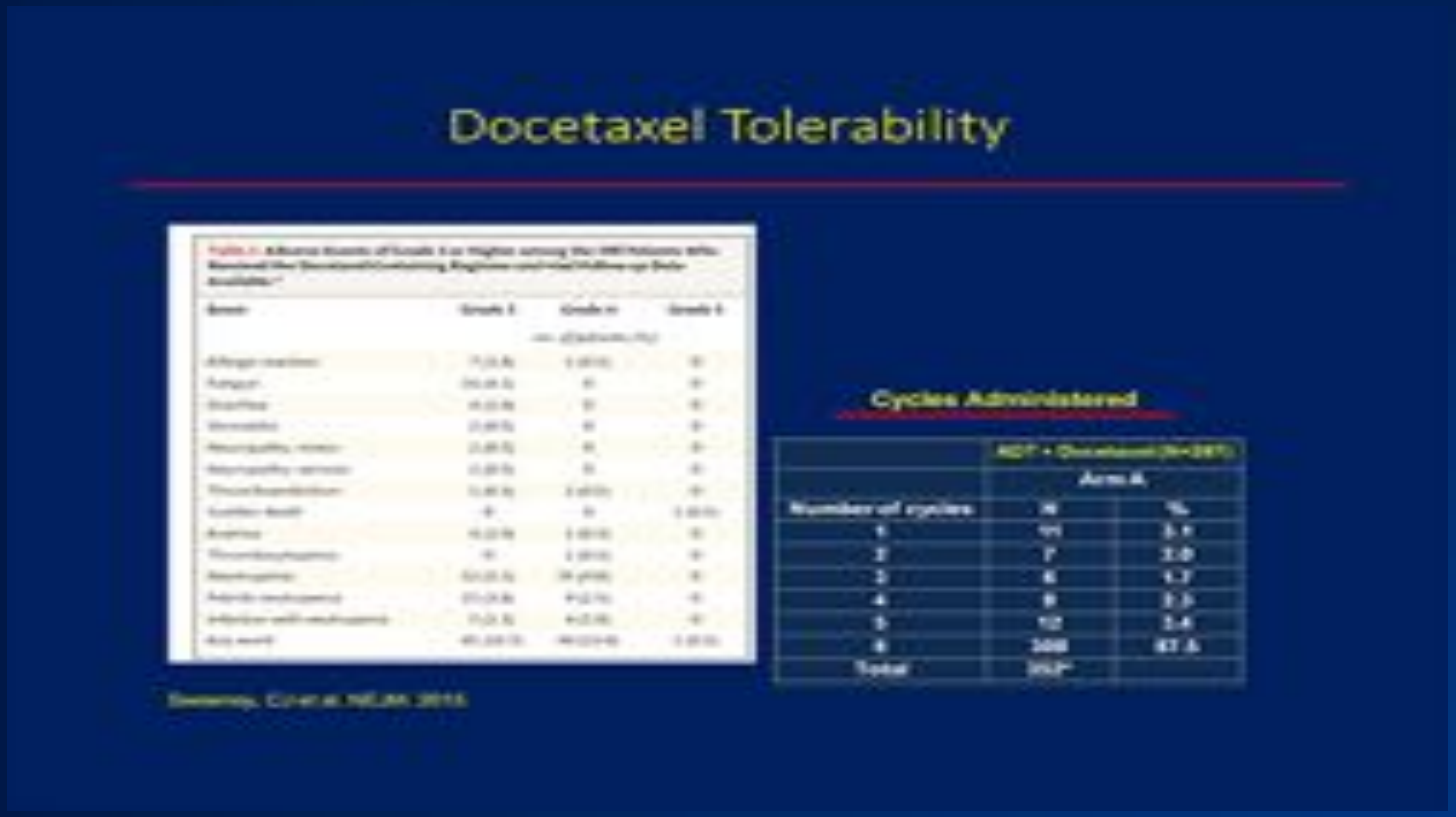
- Pre-defined categories
- High Volume – more than 4 bone lesions (1 of which must be beyond the spine/pelvis)
  - or any visceral disease
- Low Volume – disease confined to the axial skeleton (spine and pelvis)
  - or less than 3 lesions
  - no visceral disease
- Lymph node disease is not factored in

Docetaxel overall survival

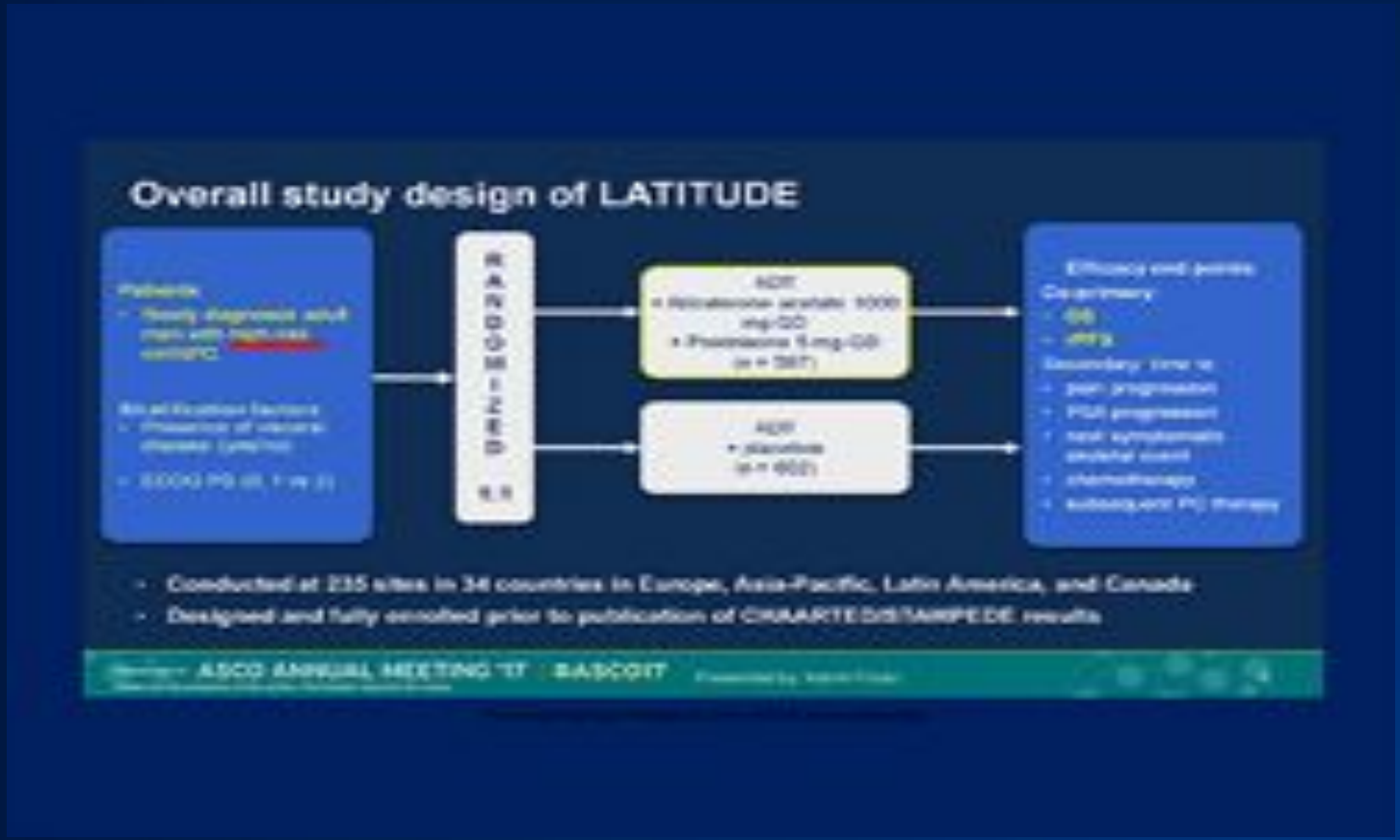
Docetaxel OS based on Volume of Disease



Docetaxel Tolerability



Study design

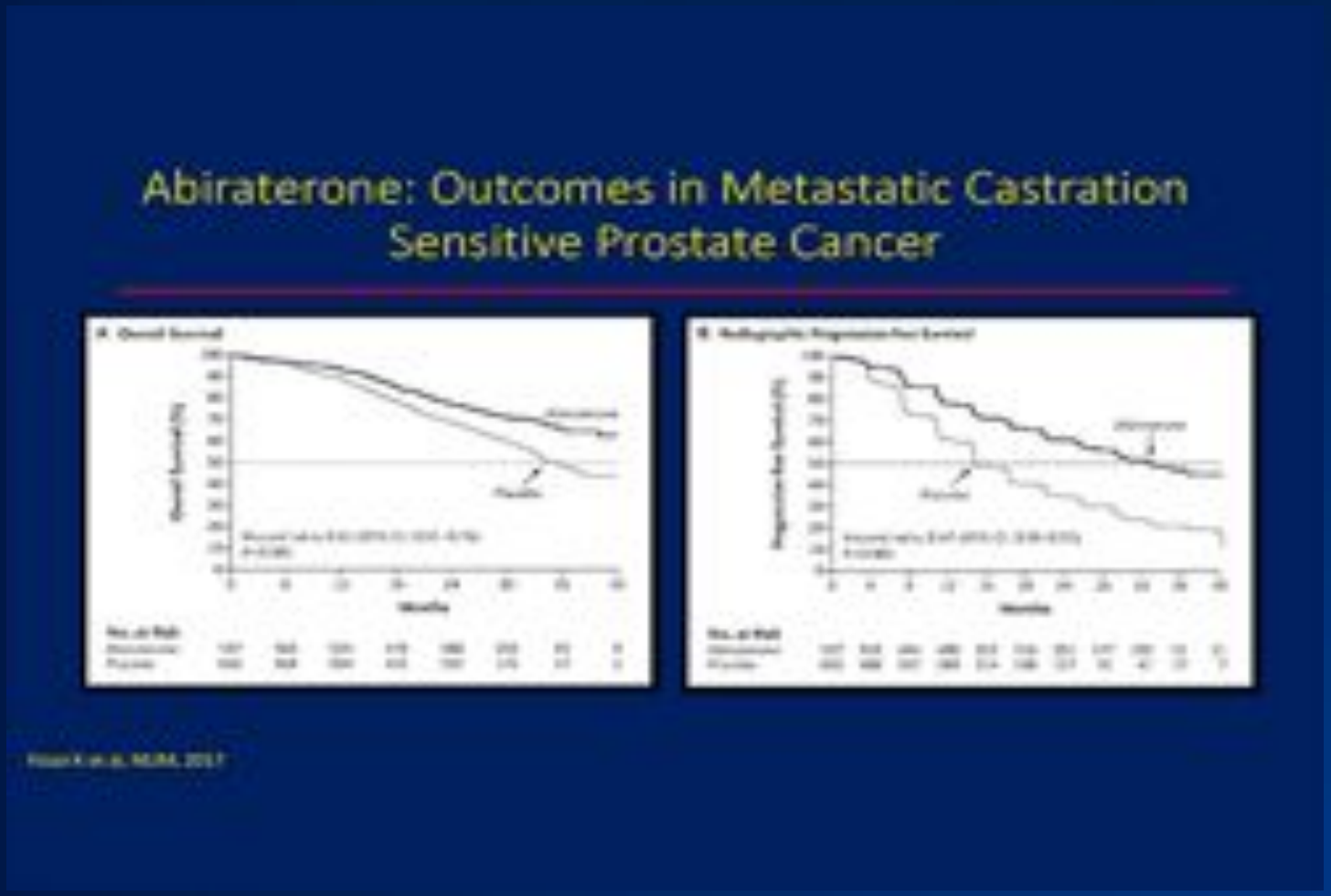


Patient Eligibility

Patient Eligibility: "Defining High Risk" In LATITUDE

- Different than docetaxel study
- At least 2 of the following 3 were required:
  - Gleason 8 or higher
  - More than 3 bone lesions (sites unspecified)
  - Visceral disease.

Abiratenone outcomes



Abiraterone toxicity

Toxicity

Abiraterone in metastatic Castration Sensitive Prostate Cancer

Abiraterone

This was NOT a Study of Early Abiraterone vs. Late Abiraterone (at mCRPC)

Dilemmas

Dilemmas in Treating Metastatic Castration Sensitive Prostate Cancer

- Abiraterone (indefinitely) vs 6 infusions of docetaxel
- ADT is continued indefinitely with both options
- Risk benefit discussion with the patient
- Can you retreate with docetaxel if you give 6 cycles of docetaxel?
- High volume vs. Low volume – should they be treated differently?

Dilemmas

Dilemmas in Treating Metastatic Castration Sensitive Prostate Cancer

- Abiraterone (indefinitely) vs 6 infusions of docetaxel
- ADT is continued indefinitely with both options
- Risk benefit discussion with the patient
- Can you retreate with docetaxel if you give 6 cycles of docetaxel?
- High volume vs. Low volume – should they be treated differently?

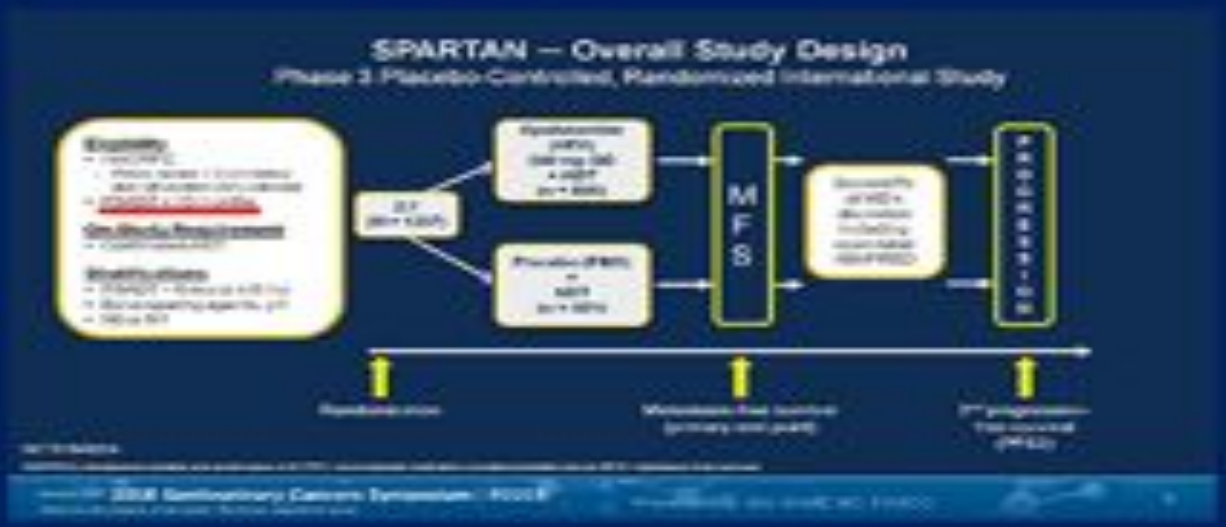
New Treatments

New Treatments for M0 Prostate Cancer

- What is M0 prostate cancer
  - Rising PSA despite castrate levels of testosterone
  - No evidence of metastasis on conventional imaging (CT and bone scan)
  - Metastatic castration sensitive prostate cancer
- What were the previous "standard approaches"
  - All patients are on androgen deprivation therapy (ADT) or post-orchiectomy
  - In addition, sequential anti-androgens could be used (bicalutamide, flutamide, nilutamide, ketoconazole)

Apalutamide

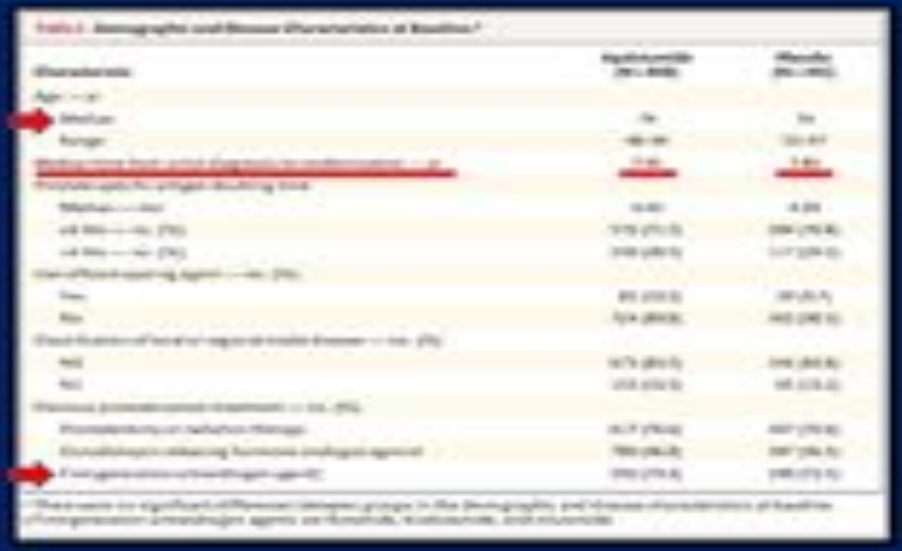
SPARTAN


SPARTAN — Overall Study Design
Phase 3 Placebo-Controlled, Randomized International Study
M
F
S

Patient characteristics

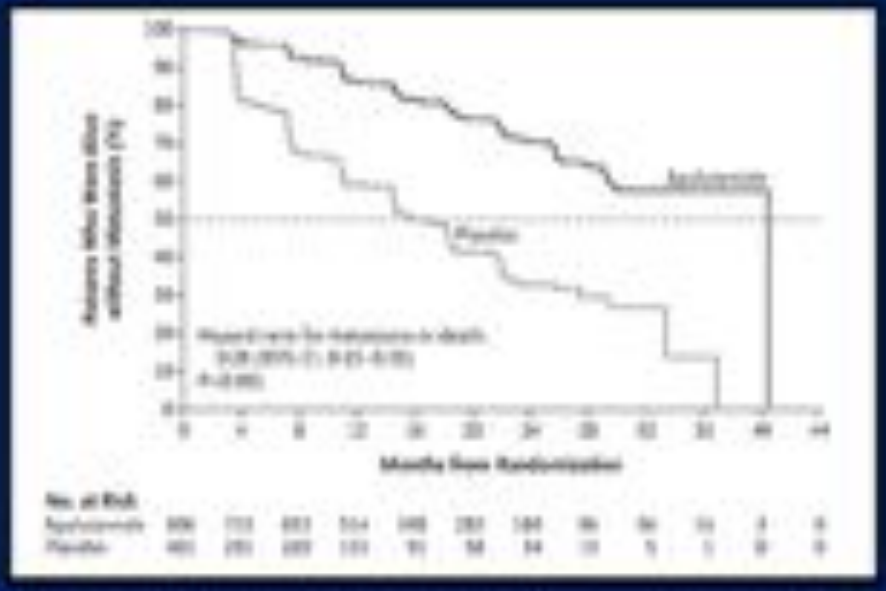
Patient Baseline Characteristics

Apalutamide in M0 prostate cancer



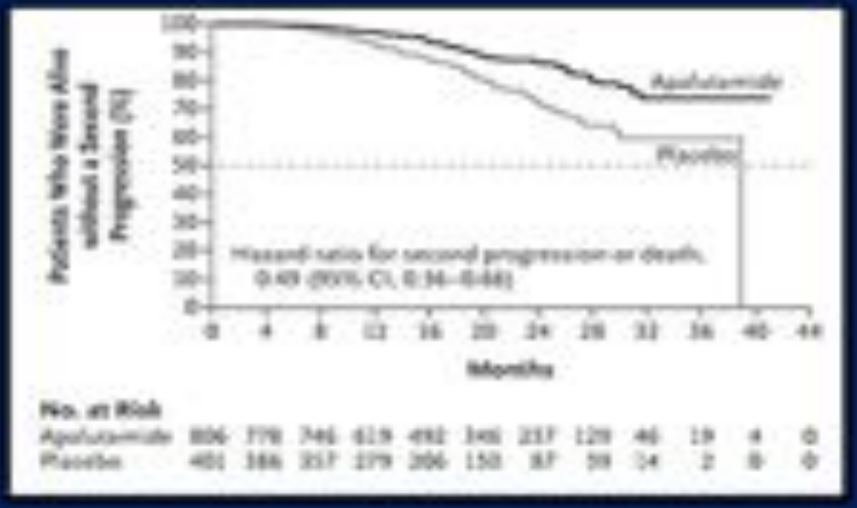
Apalutamide

Apalutamide Improves Metastasis-Free Survival



Secondary Progression

Secondary Progression for Patients Who were Subsequently Treated with Abiraterone

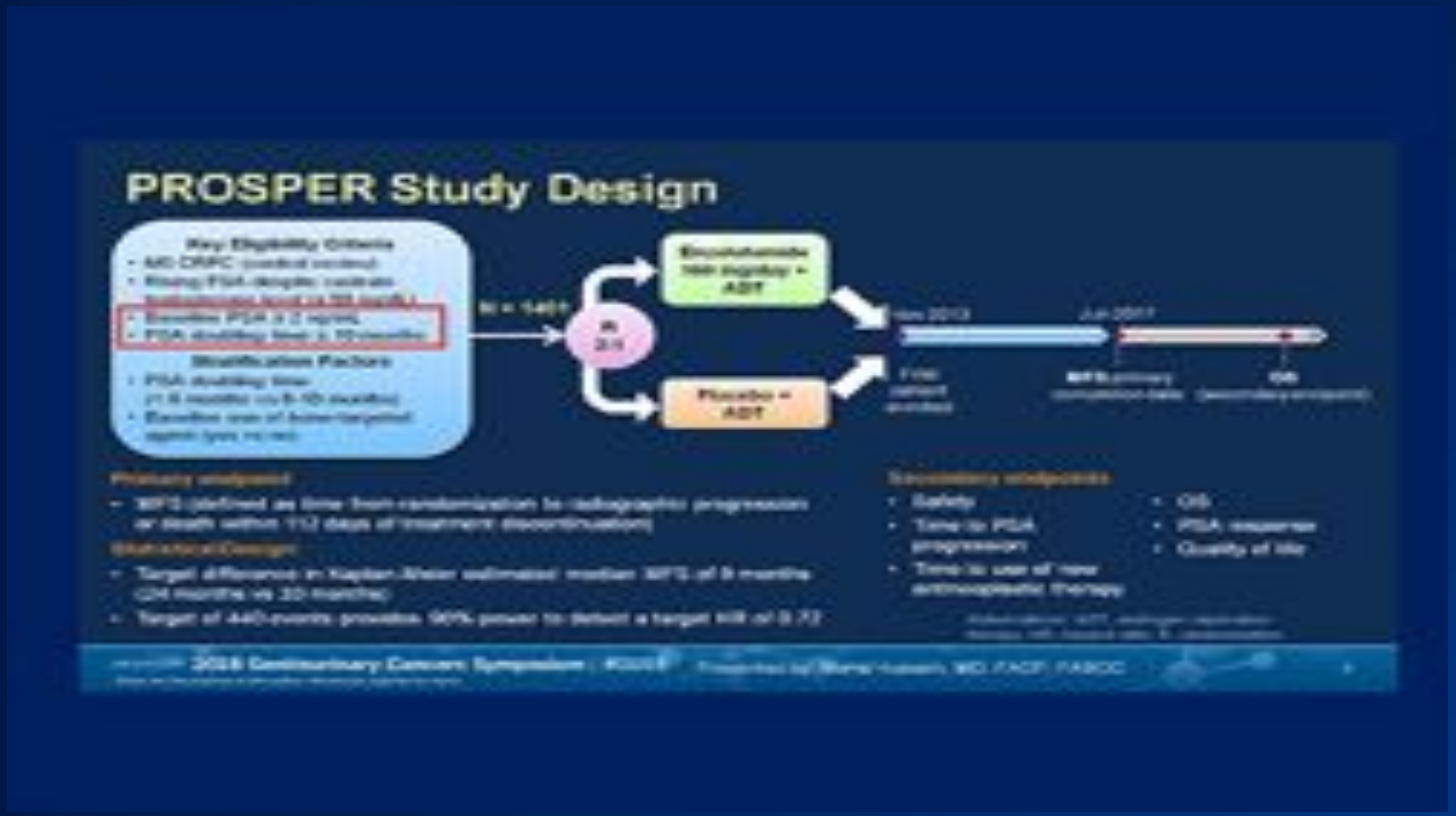


Abiraterone administration

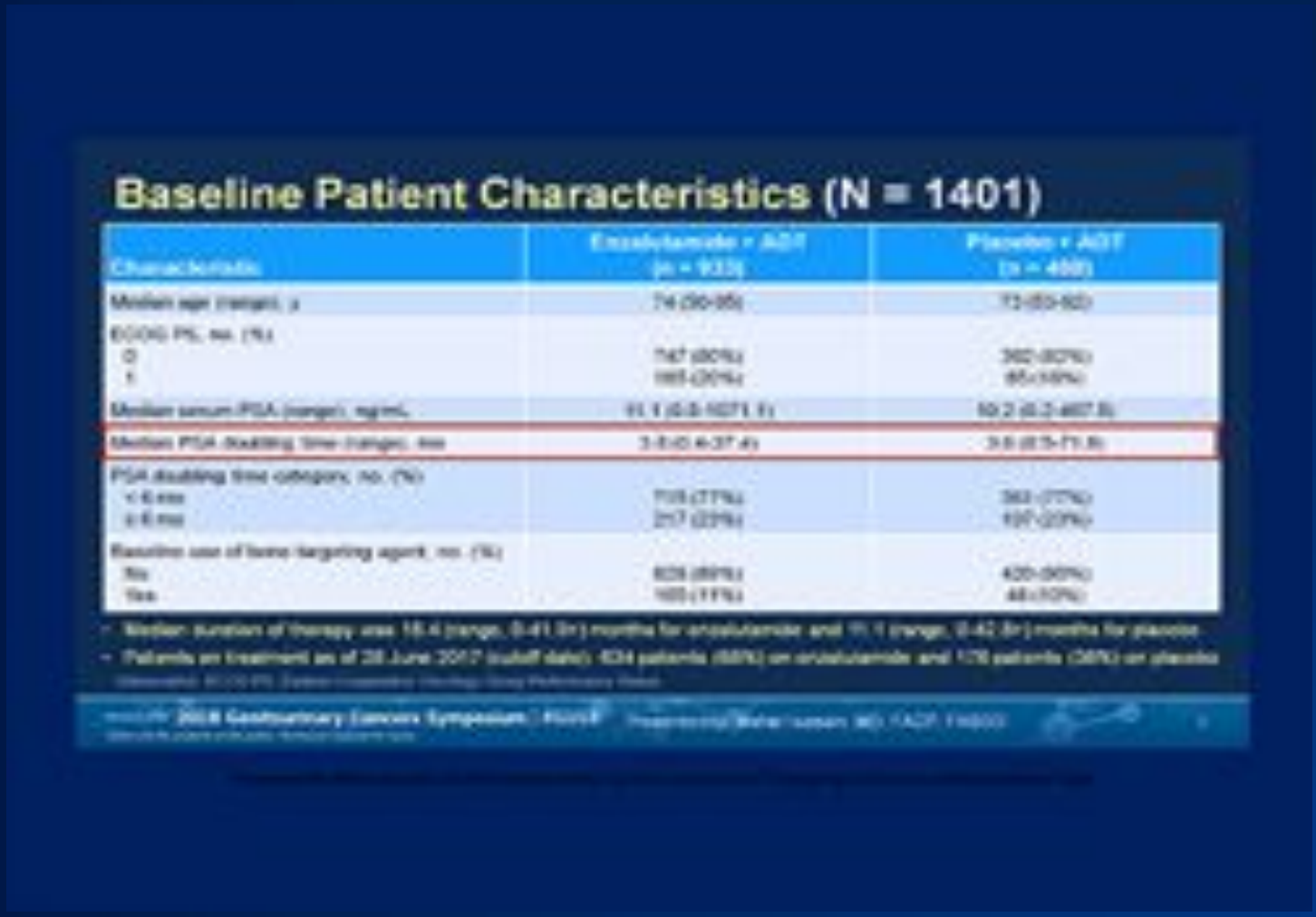
Toxicity

Abiraterone in metastatic Castration Sensitive Prostate Cancer

Prosper Study Design

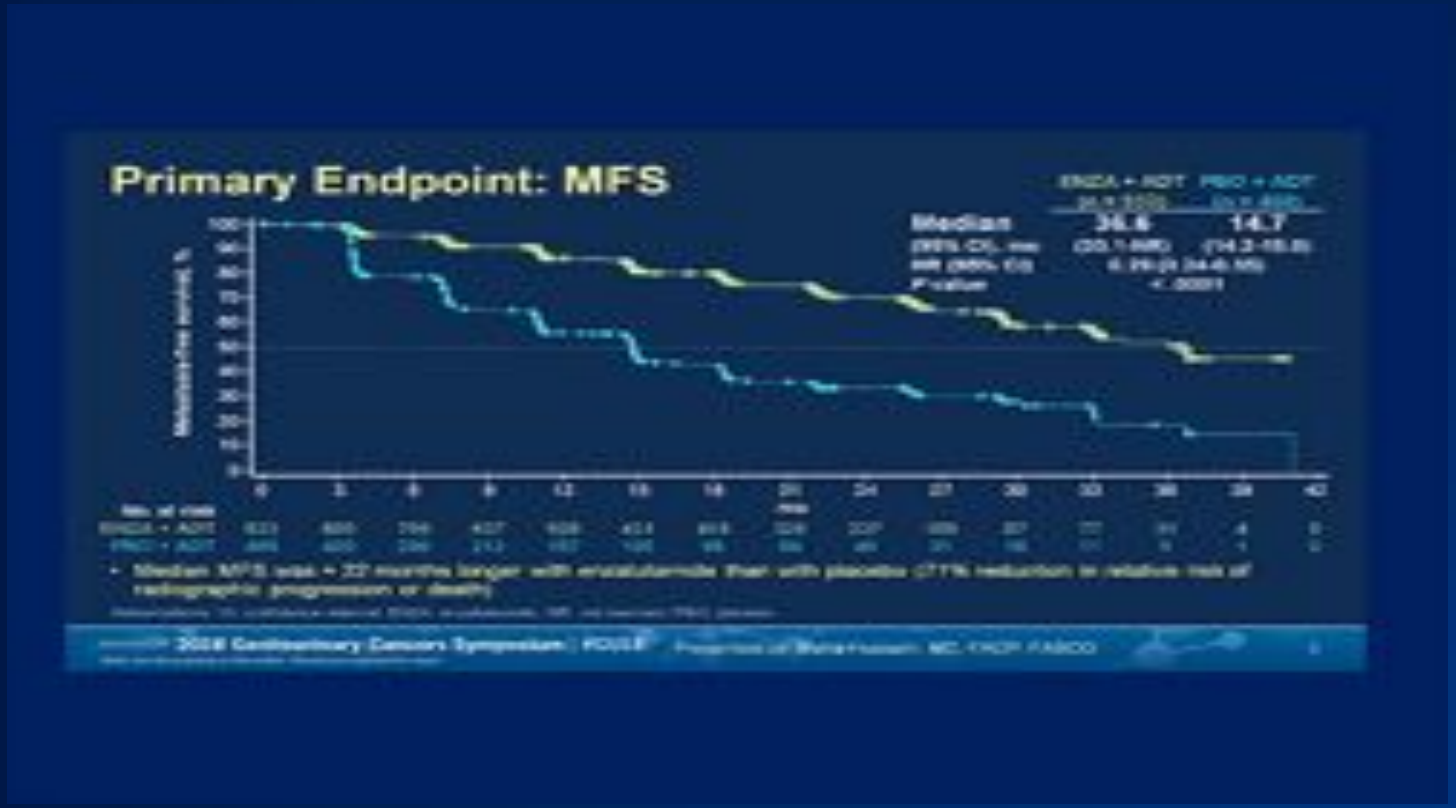


Patient characteristics

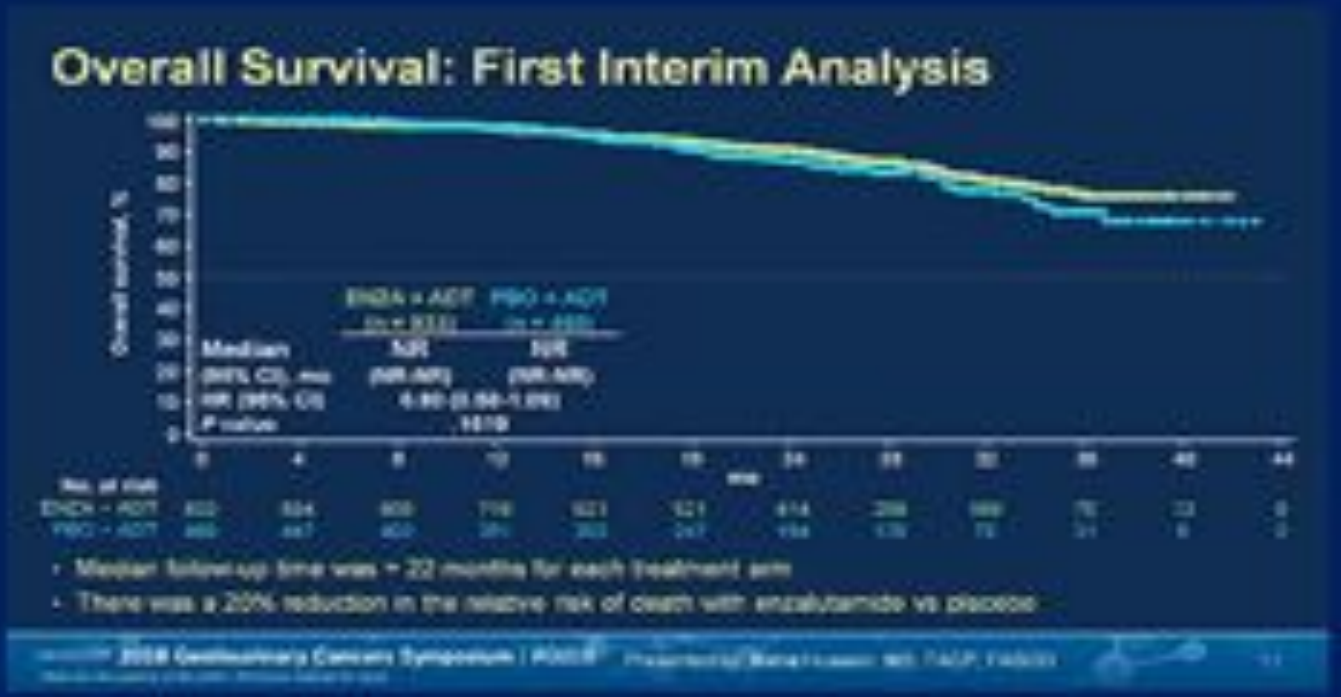


Adverse events

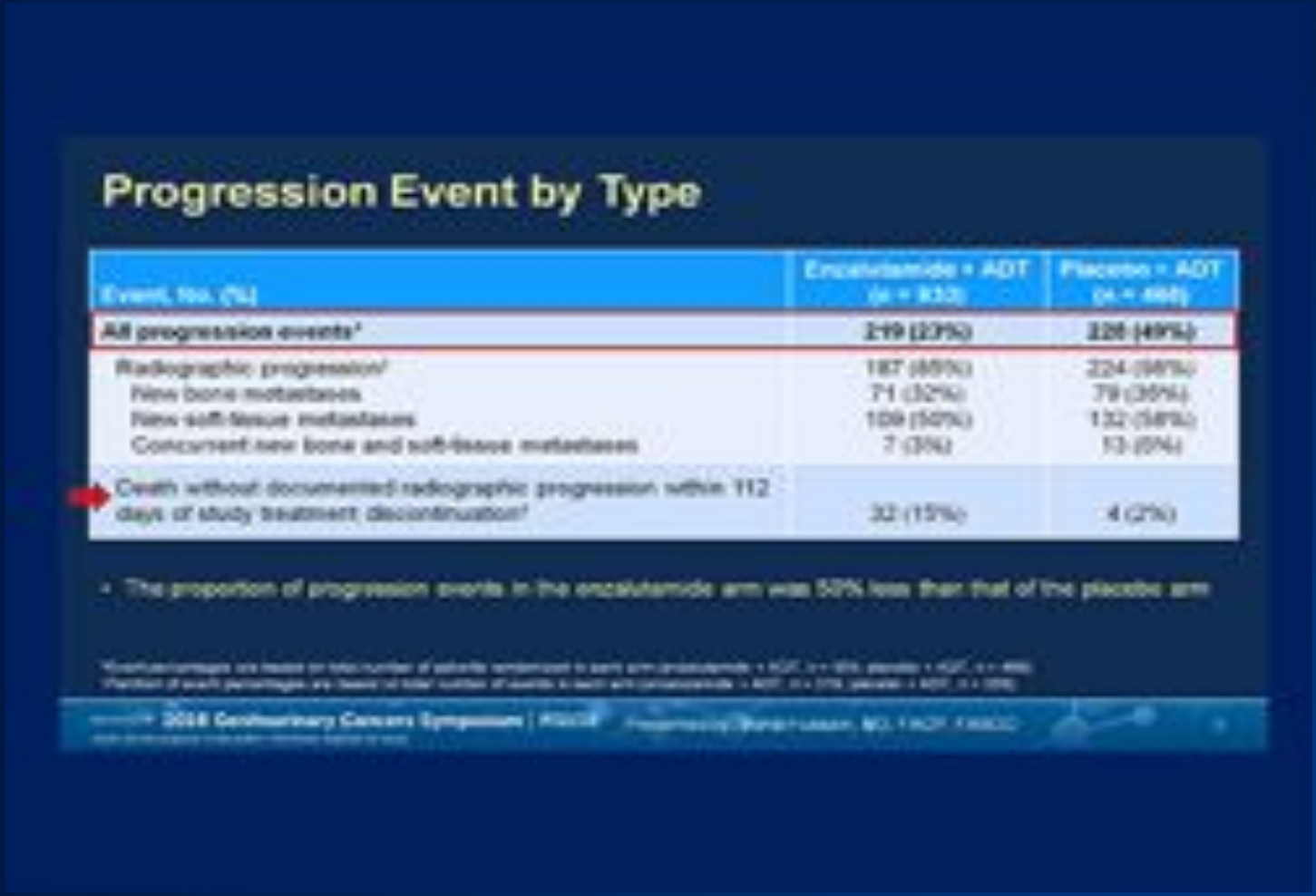
Primary endpoint



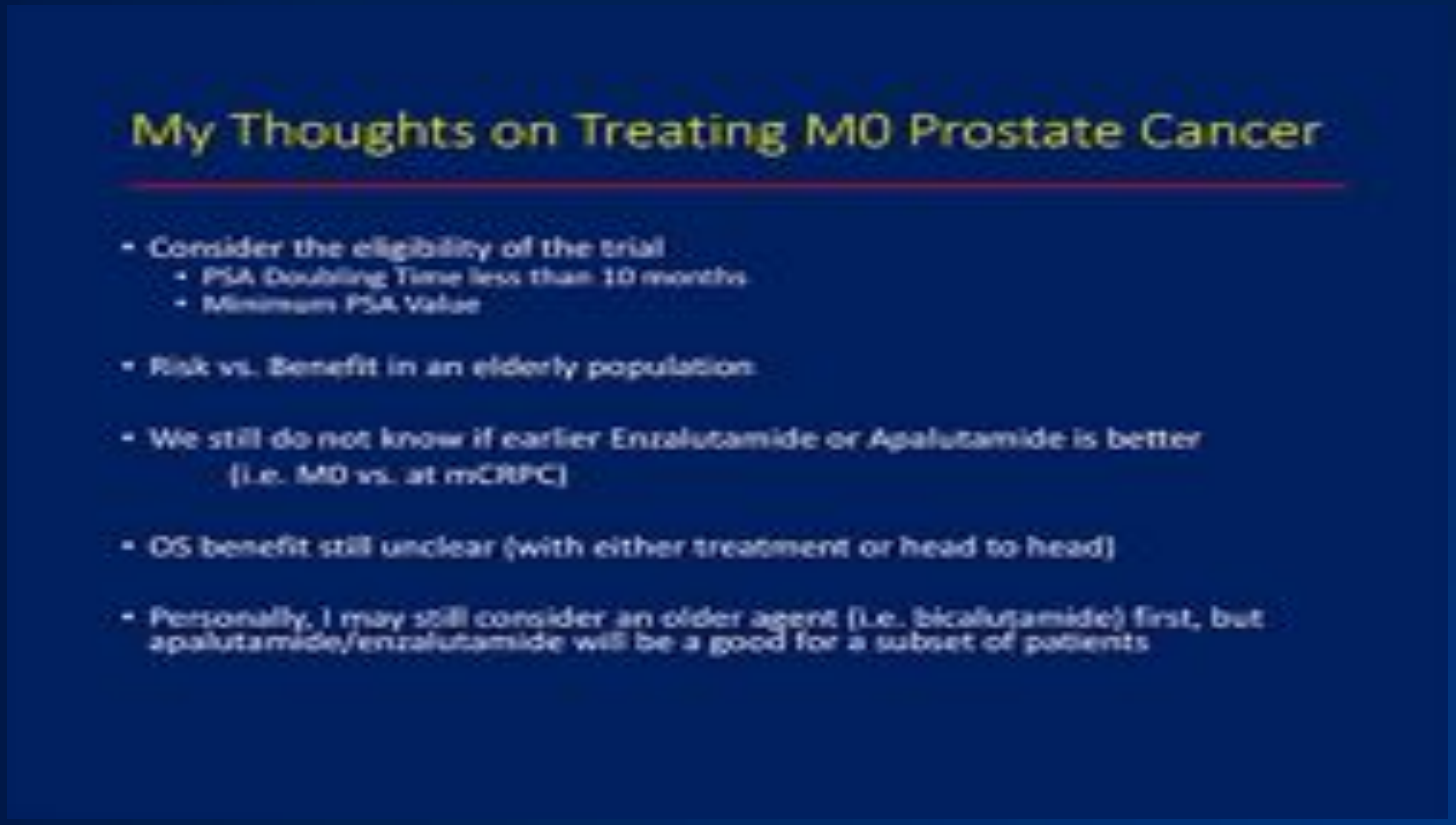
Overall survival



Progression event



Treating MO Prostate Cancer



Future Investigations