

Treatment Challenges in Castrate Resistant Prostate Cancer

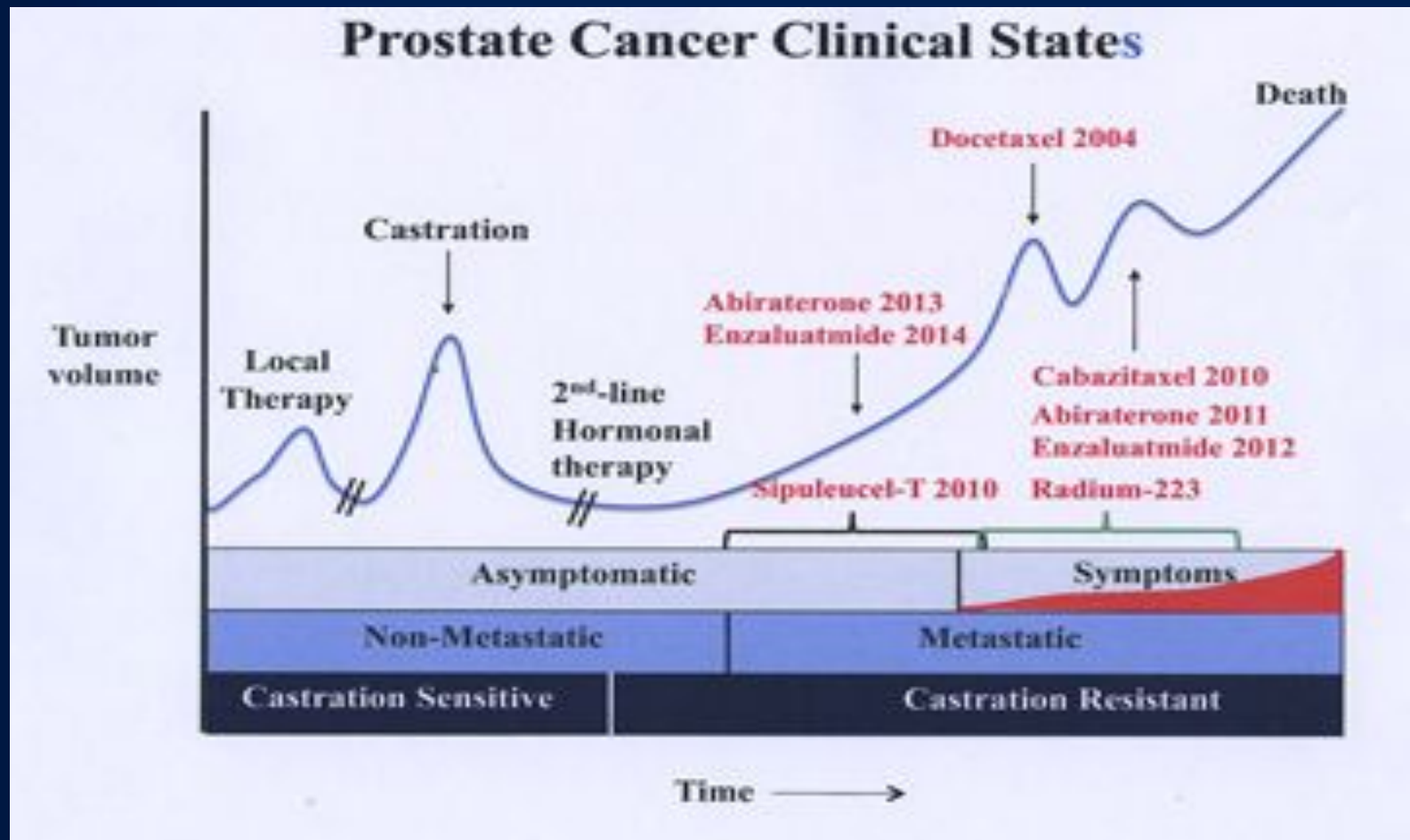
Treatment Challenges in Castrate Resistant Prostate Cancer: *Choosing and Sequencing Therapy*

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Genitourinary Malignancies Branch
National Cancer Institute
Center for Cancer Research, National Institutes of Health



@Dr_RaviMadan

Prostate Cancer Clinical States



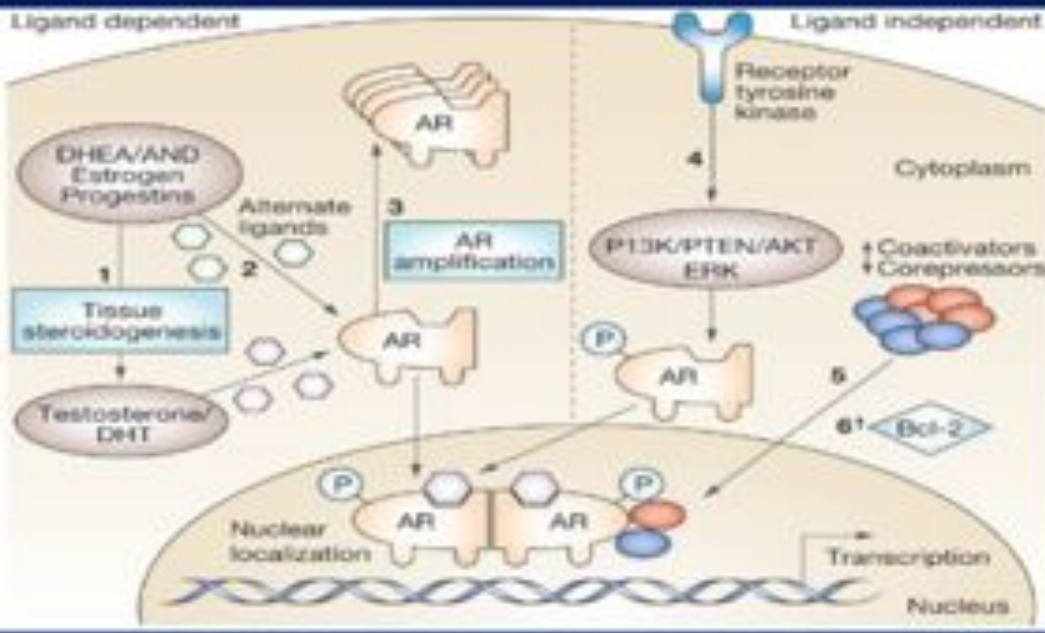
Castrate resistant prostate cancer

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?

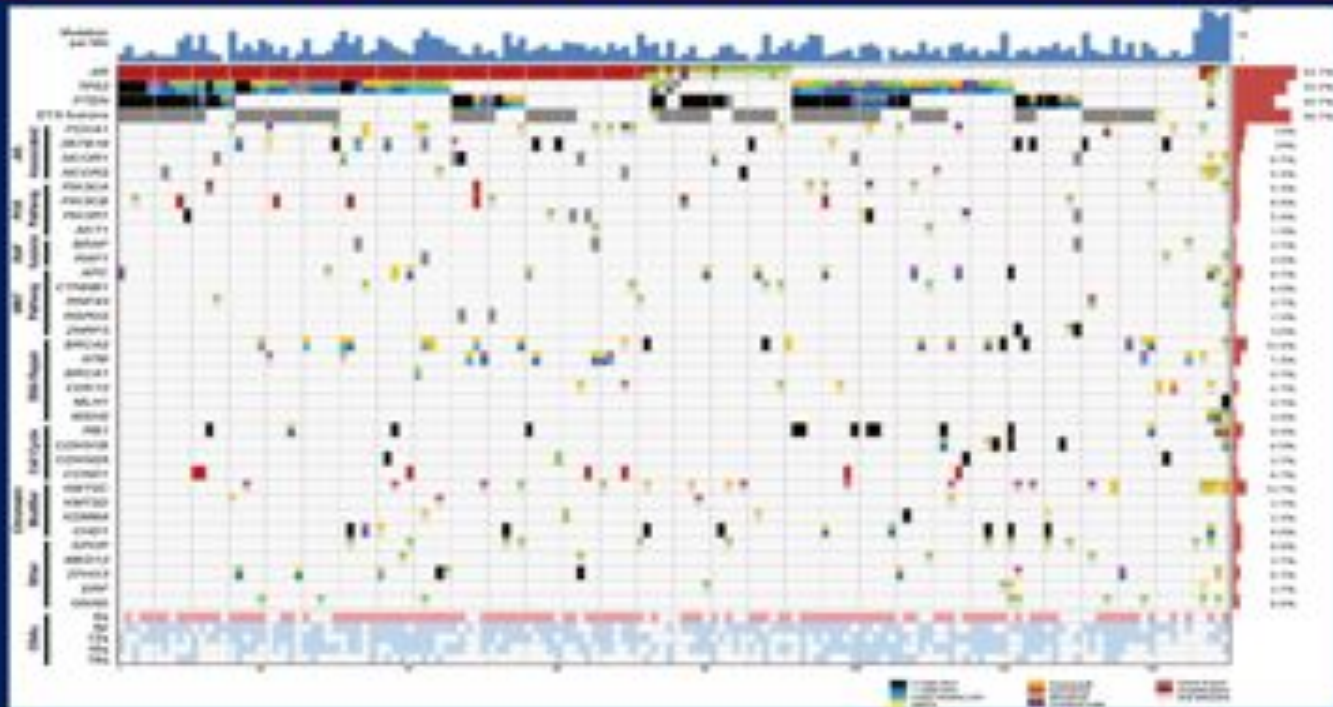


Resistance Mechanisms:

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

Integrative clinical genomics

Integrative Clinical Genomics of Advanced Prostate Cancer



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

Optimal treatment sequence

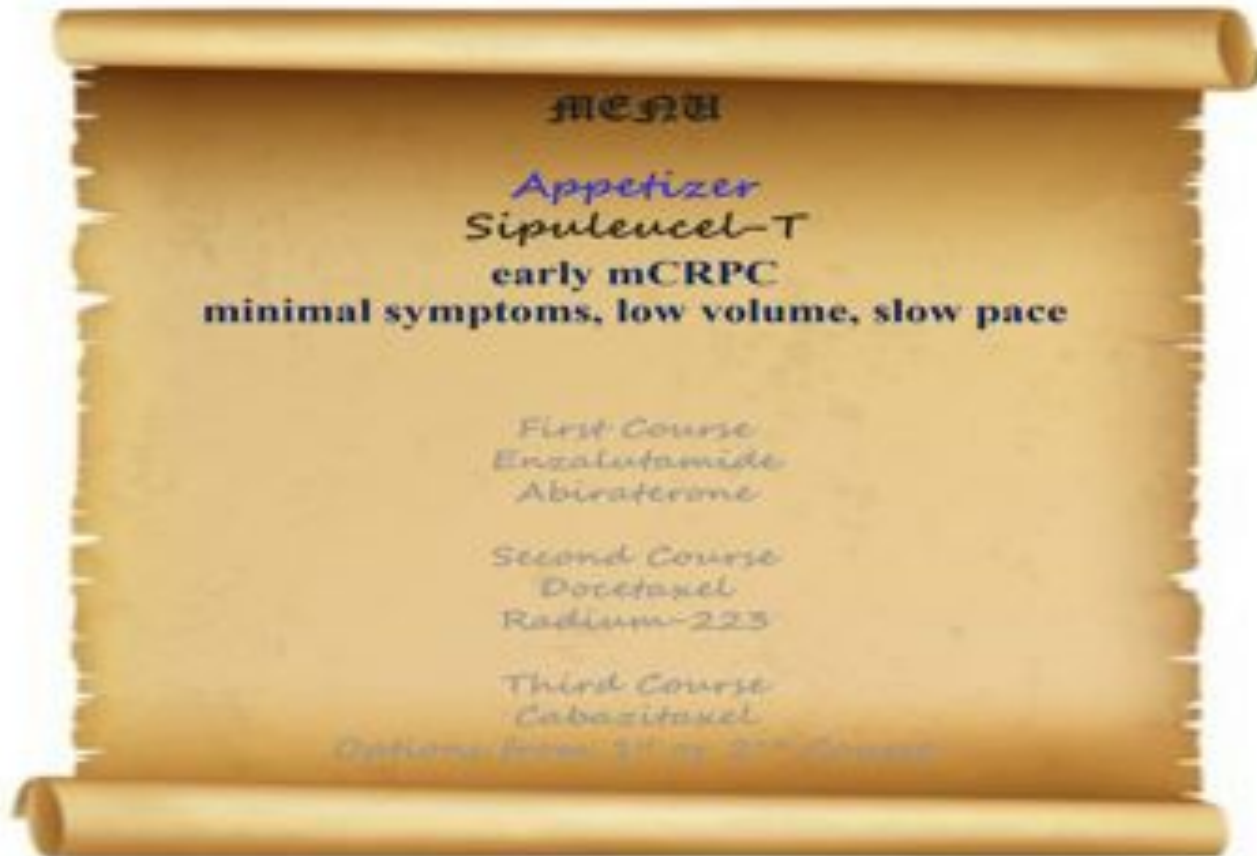
Optimal Treatment Sequence?

- 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

Therapeutic Cancer Vaccine: Sipuleucel-T

Day 1
Leukapheresis



Apheresis Center

Day 2-3
sipuleucel-T is
manufactured



Company (Dendreon)

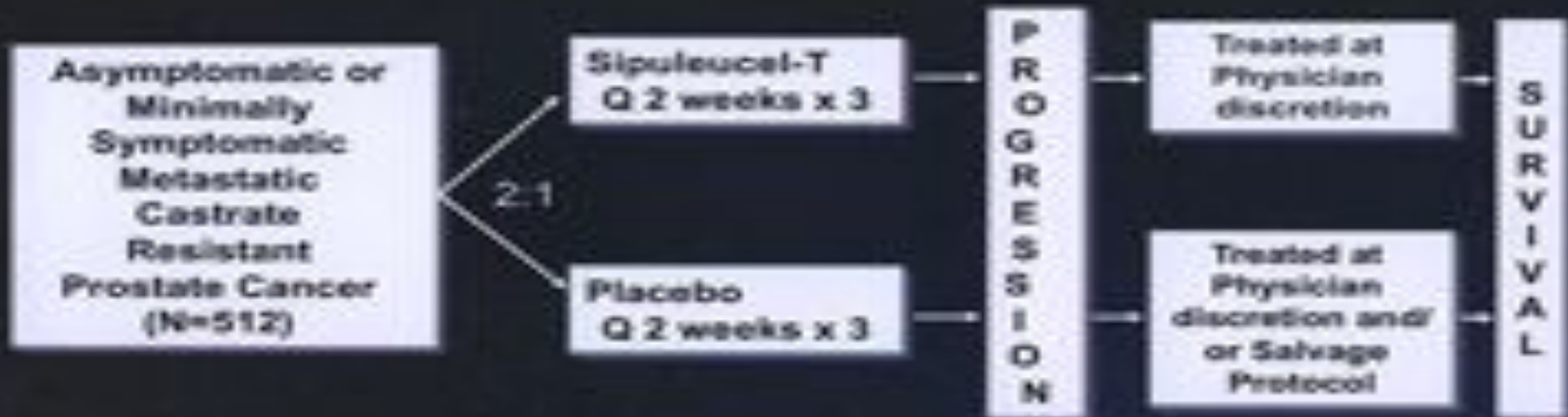
Day 3-4
Patient is infused



Doctor's Office

IMPACT: Randomized Phase 3 Trial

IMPACT: Randomized Phase 3 Trial (Immunotherapy Prostate AdenoCarcinoma Treatment)



Primary endpoint:

Overall Survival

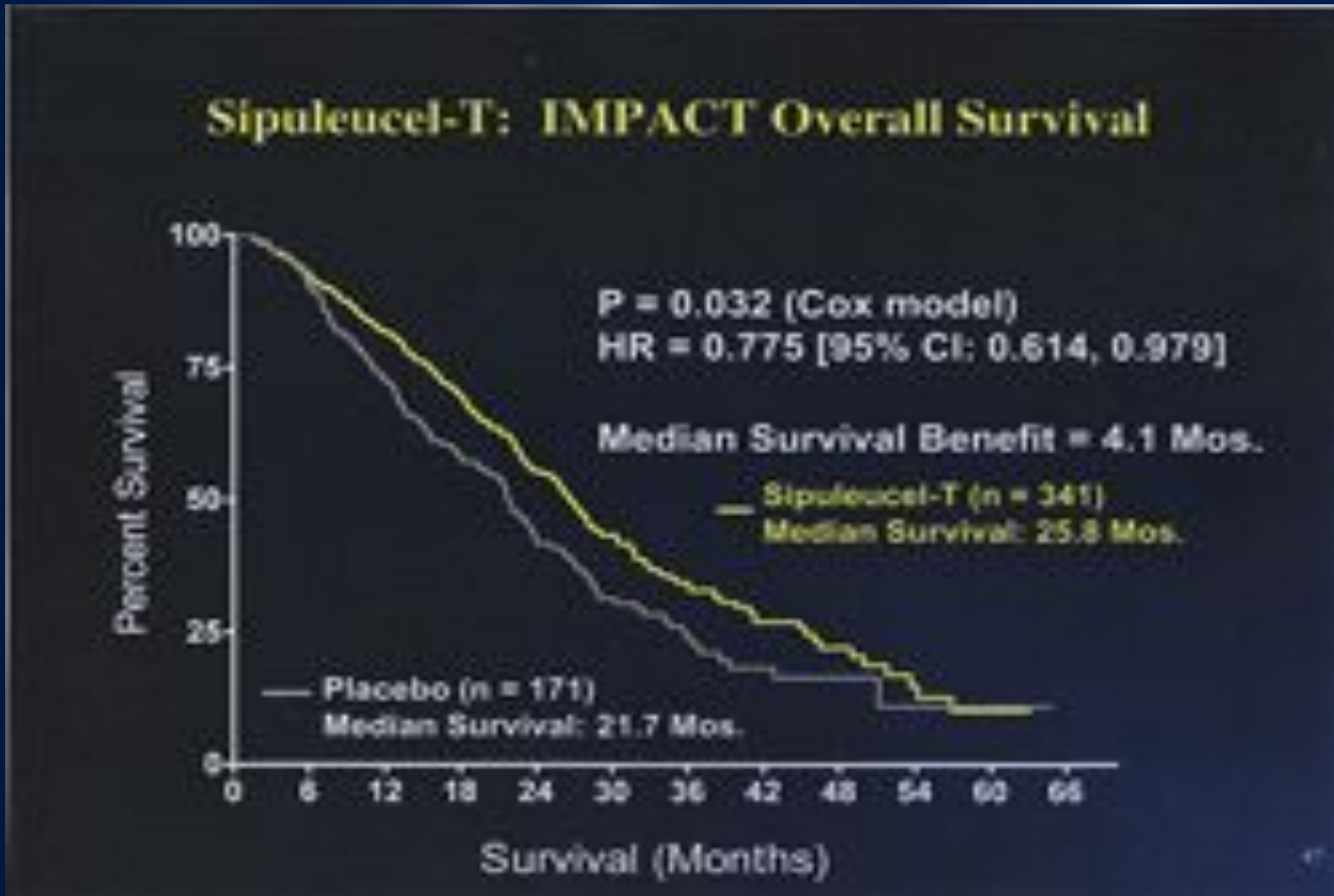
Secondary endpoint:

Time to Objective Disease Progression

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

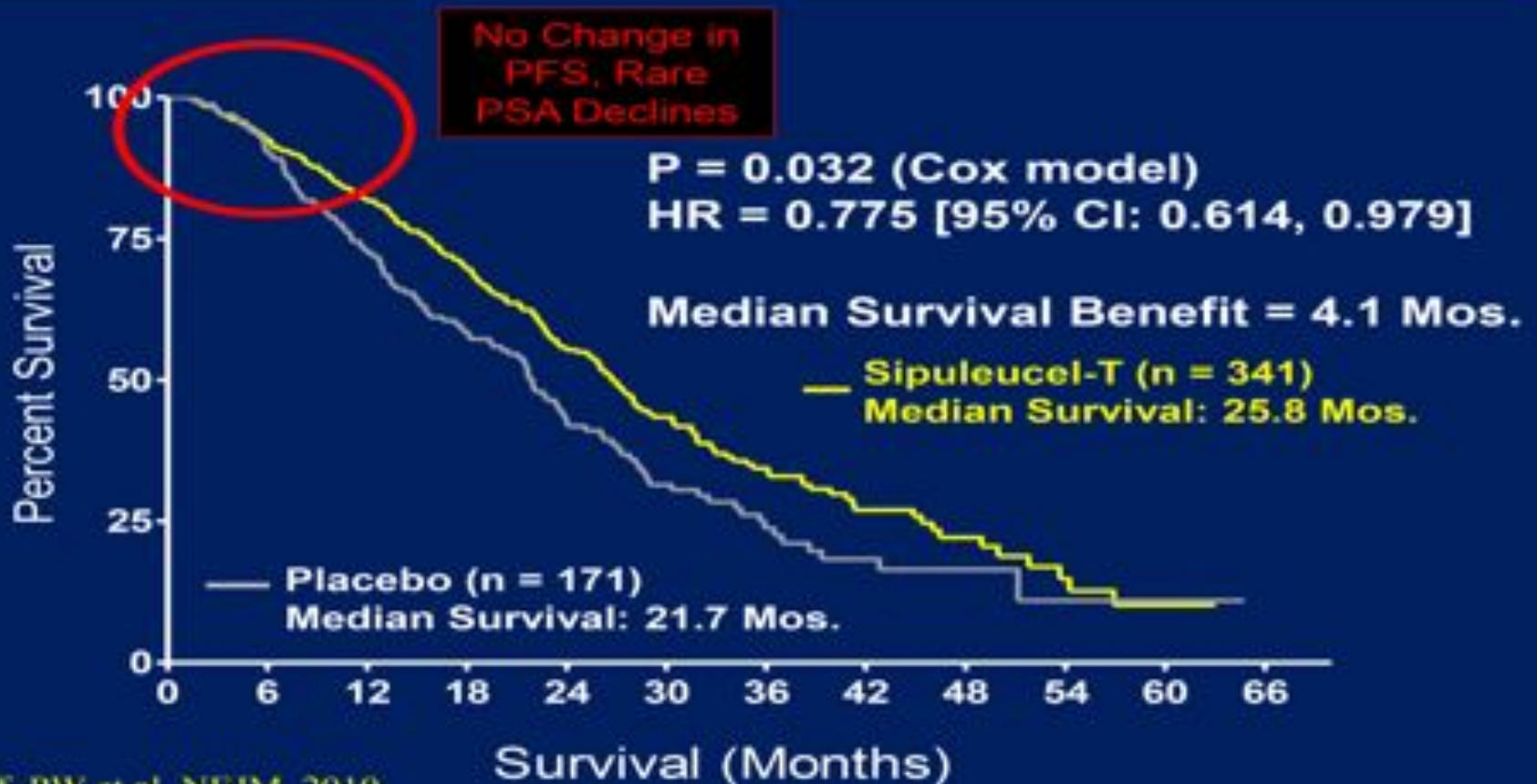


Sipuleucel-T: IMPACT Overall Survival



Sipuleucel-T

Sipuleucel-T: IMPACT Overall Survival



PSA and Sipuleucel-T

Patients with Lower PSA Had Greater OS Benefit After Sipuleucel-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

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



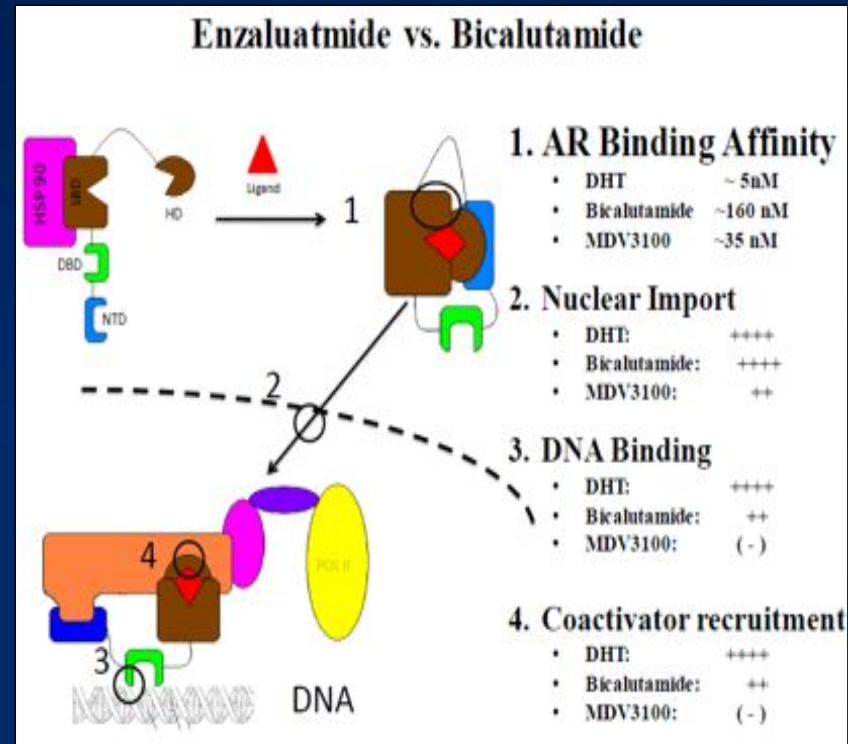
Enzalutamide

A small molecule AR antagonist

Affinity 30 folds of
bicalutamide

Prevent nuclear translocation

Prevents co-activator
recruitment

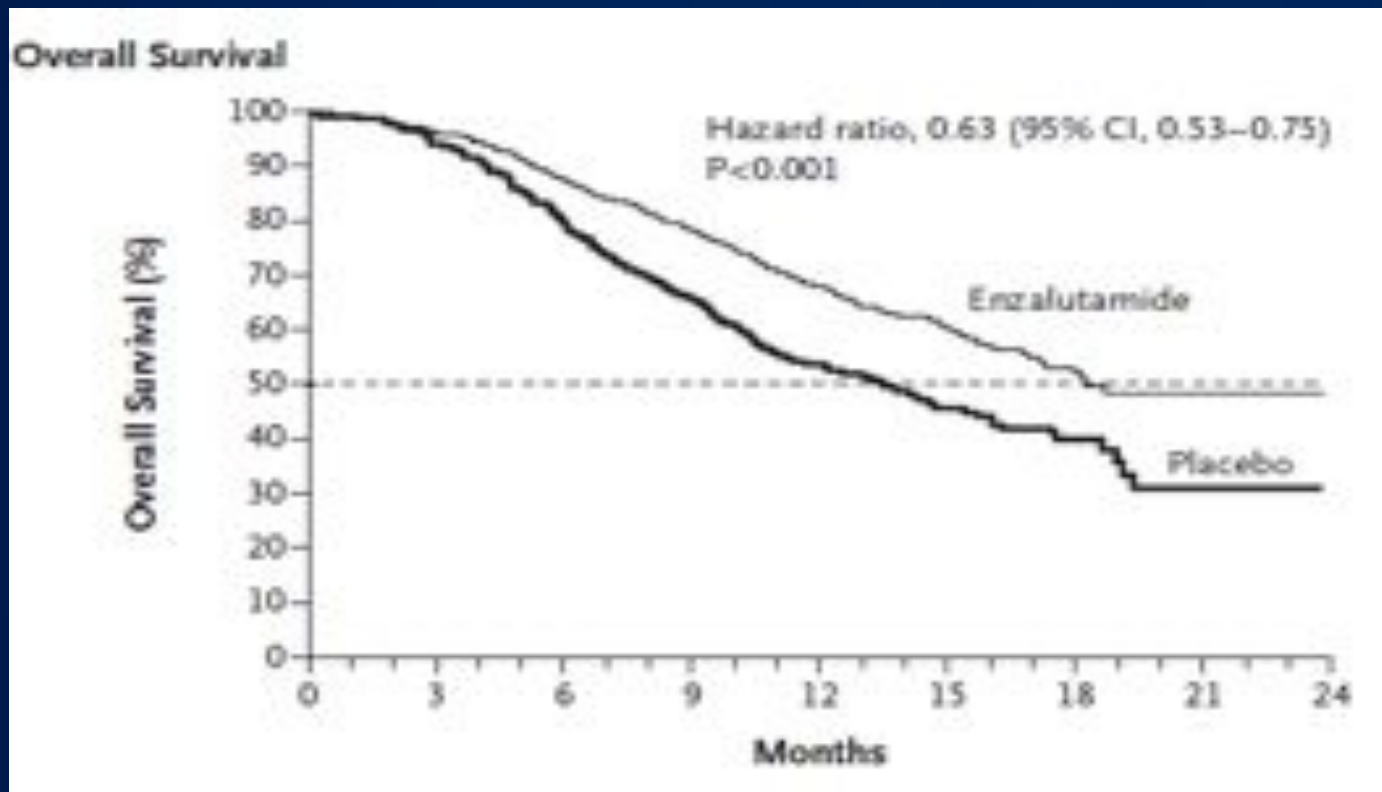


AFFIRM

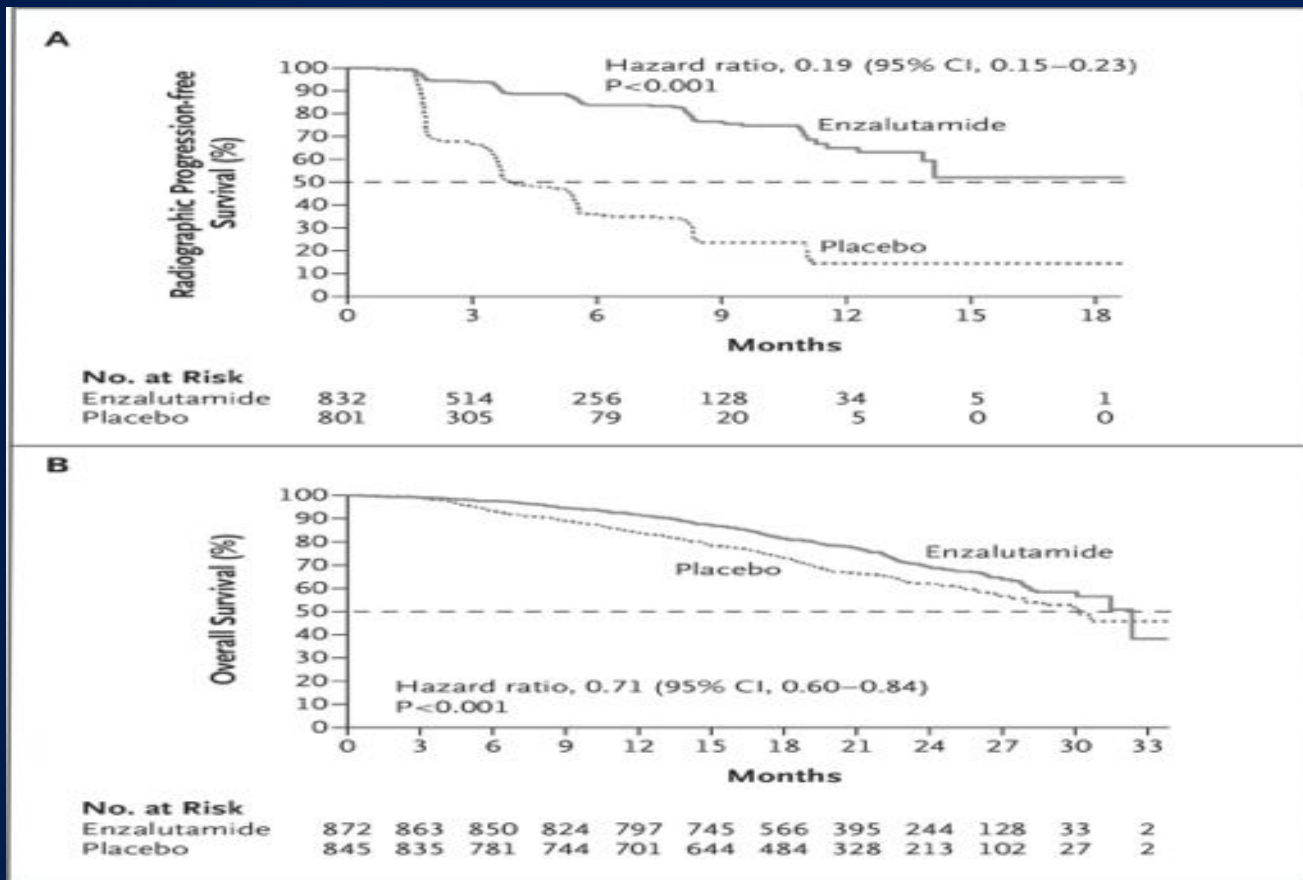
AFFIRM: Randomized Phase III Study of MDV3100 vs. Placebo in mCRPC after Progression on Docetaxel



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%)

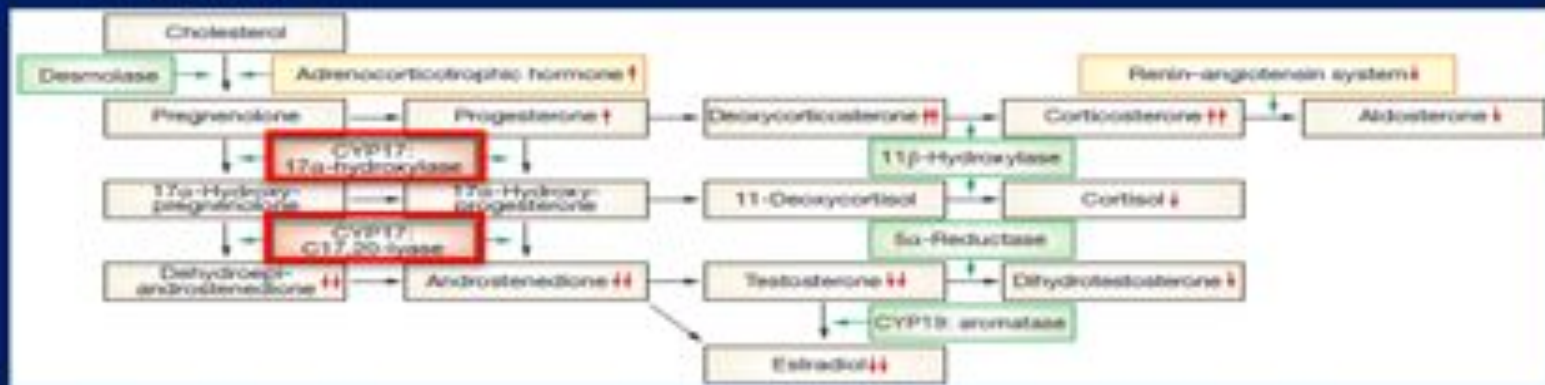
Abiraterone



Abiraterone rationale

Rationale for Abiraterone in CRPC

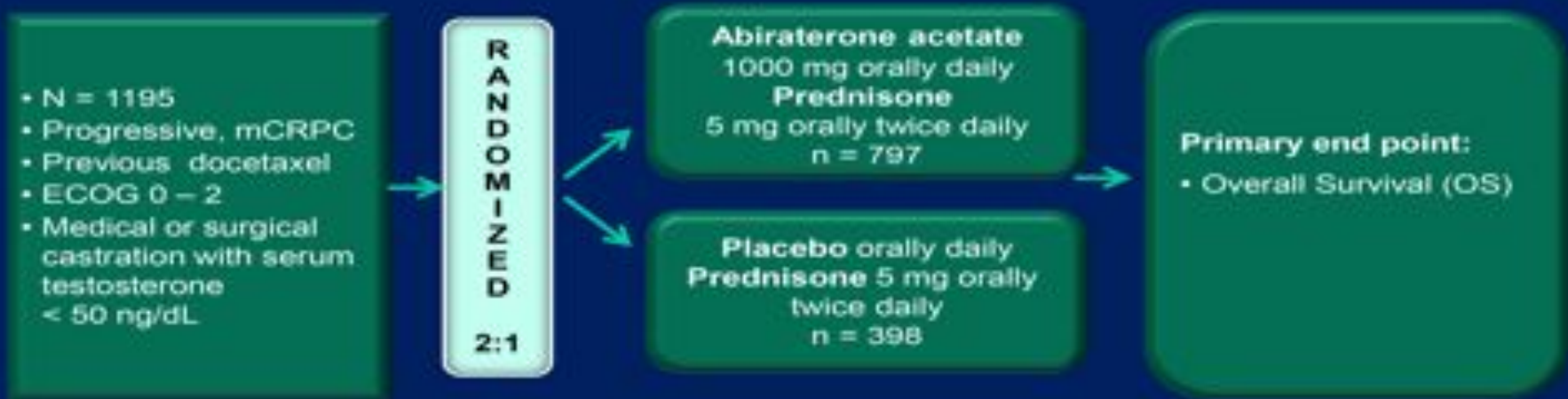
- There is up-regulation of androgen biosynthesis enzymes in CRPC



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

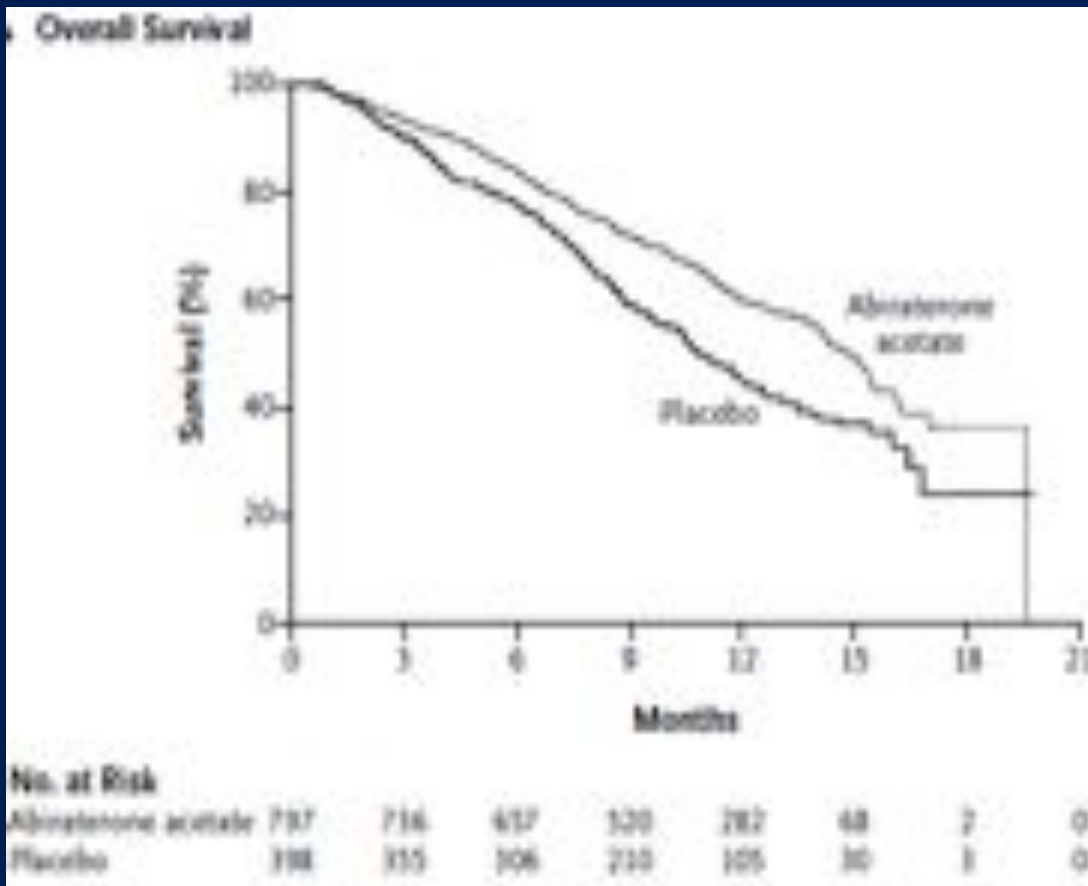
Abiraterone study

Abiraterone: COU-AA-301 Study Design



- This study was conducted in 147 sites in 13 countries
- Patients were enrolled from May 2008 through July 2009

Abiraterone: COU-AA-301 Trial



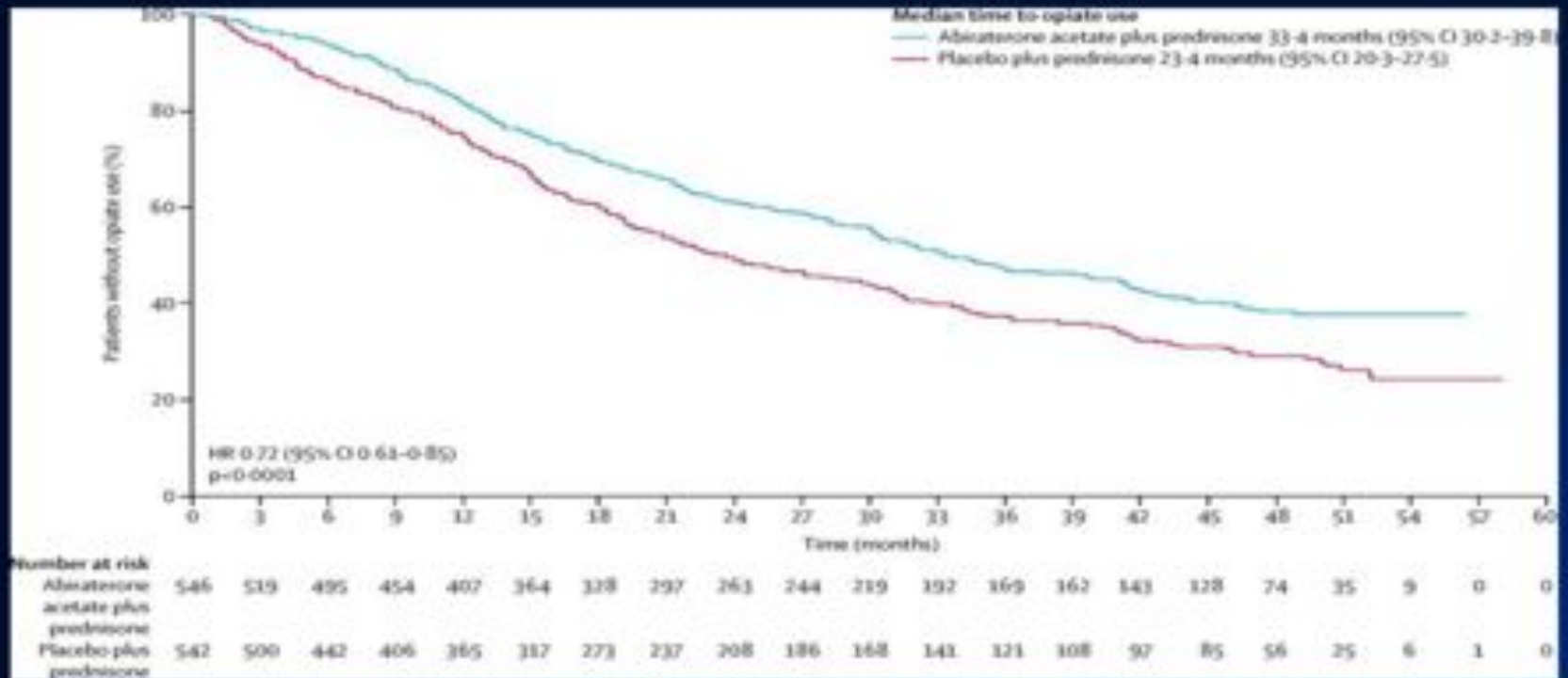
Abiraterone trial

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

COU-AA-302

COU-AA-302 (chemo-naïve)



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%)

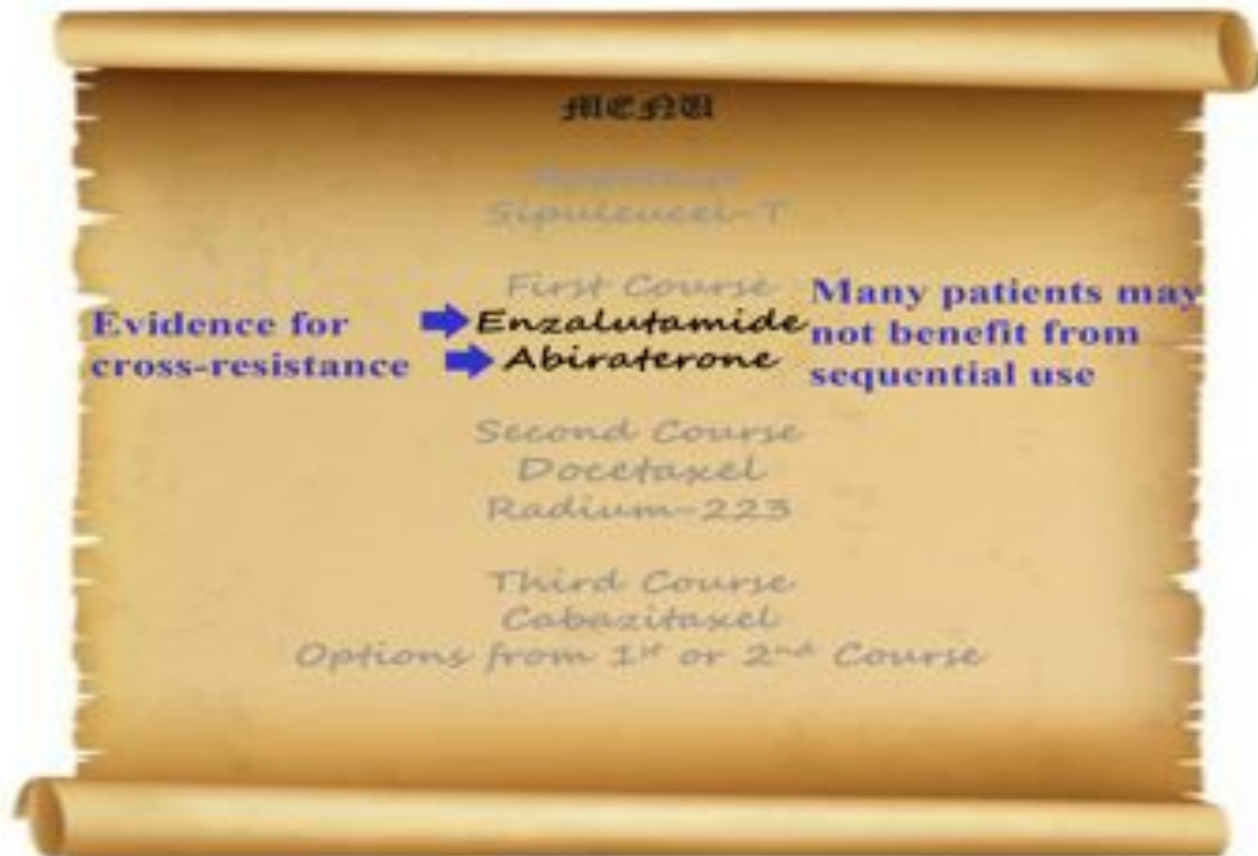
Hematologic: Lymphocytopenia (38%; grades 3/4: 9%)

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%)

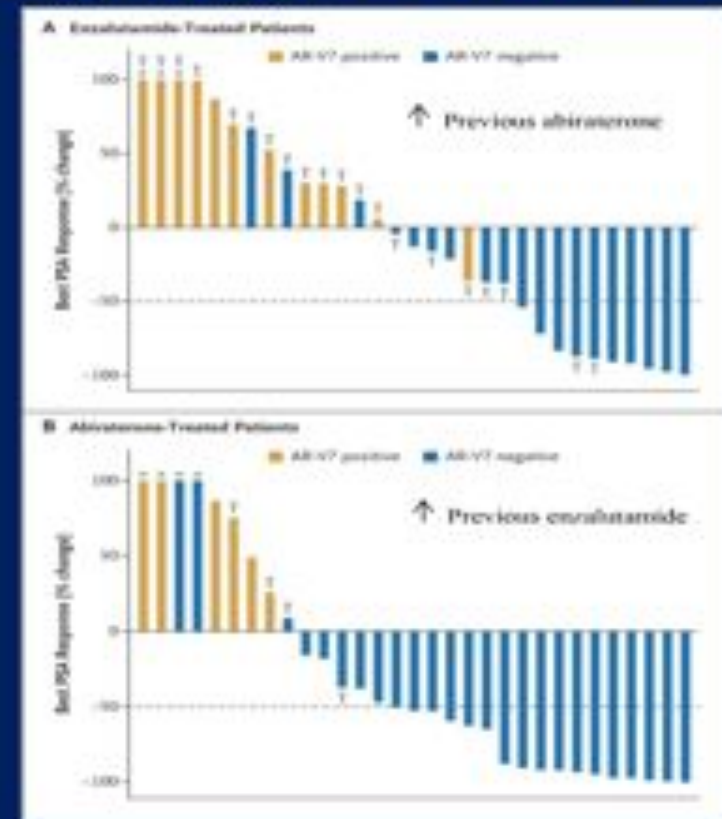
Cross resistance



Overlapping resistance

Overlapping Resistance: Androgen Receptor Splice Variants

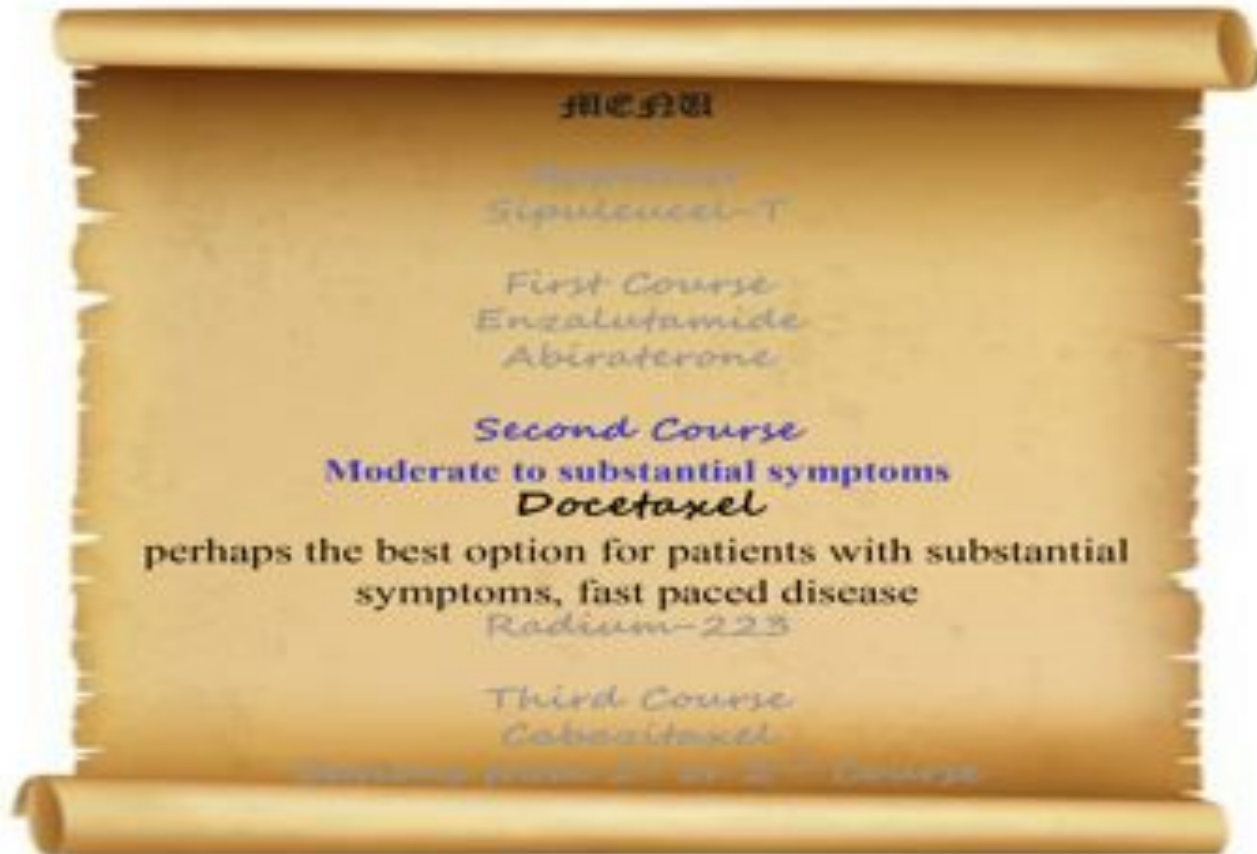
- Variable splicing of AR mRNA can lead to resistance mechanisms to anti-androgen therapy
- ARV-7 has been investigated extensively, lacks a ligand binding domain and is constitutently active
- Increases in ARV-7 seen after treatment with Abiraterone/Enzalutamide, likely contributing to cross-resistance.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



Docetaxel



For fast paced disease



Docetaxel

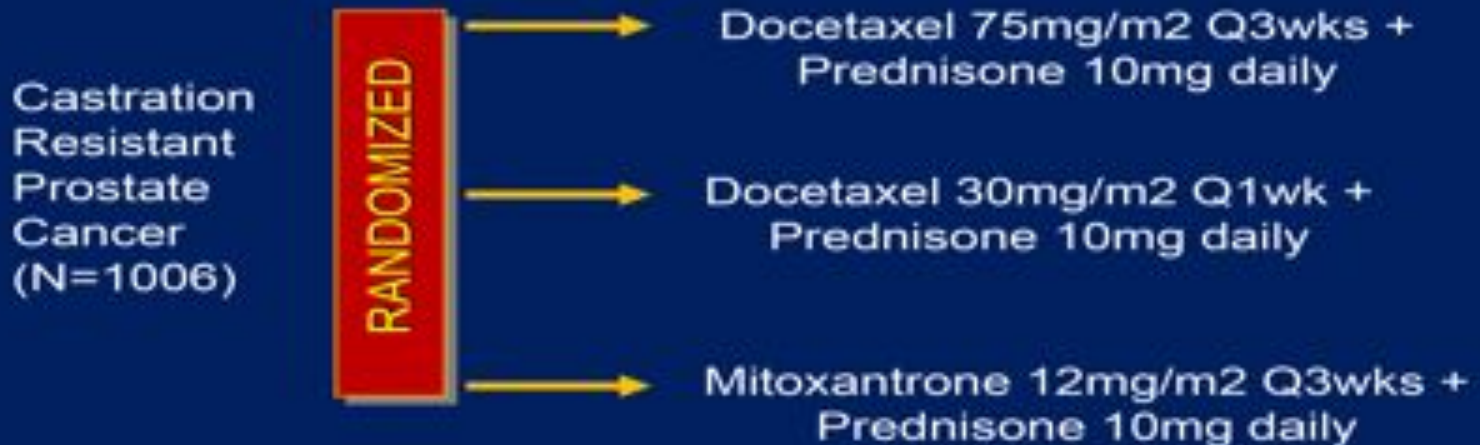
Docetaxel

- 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*

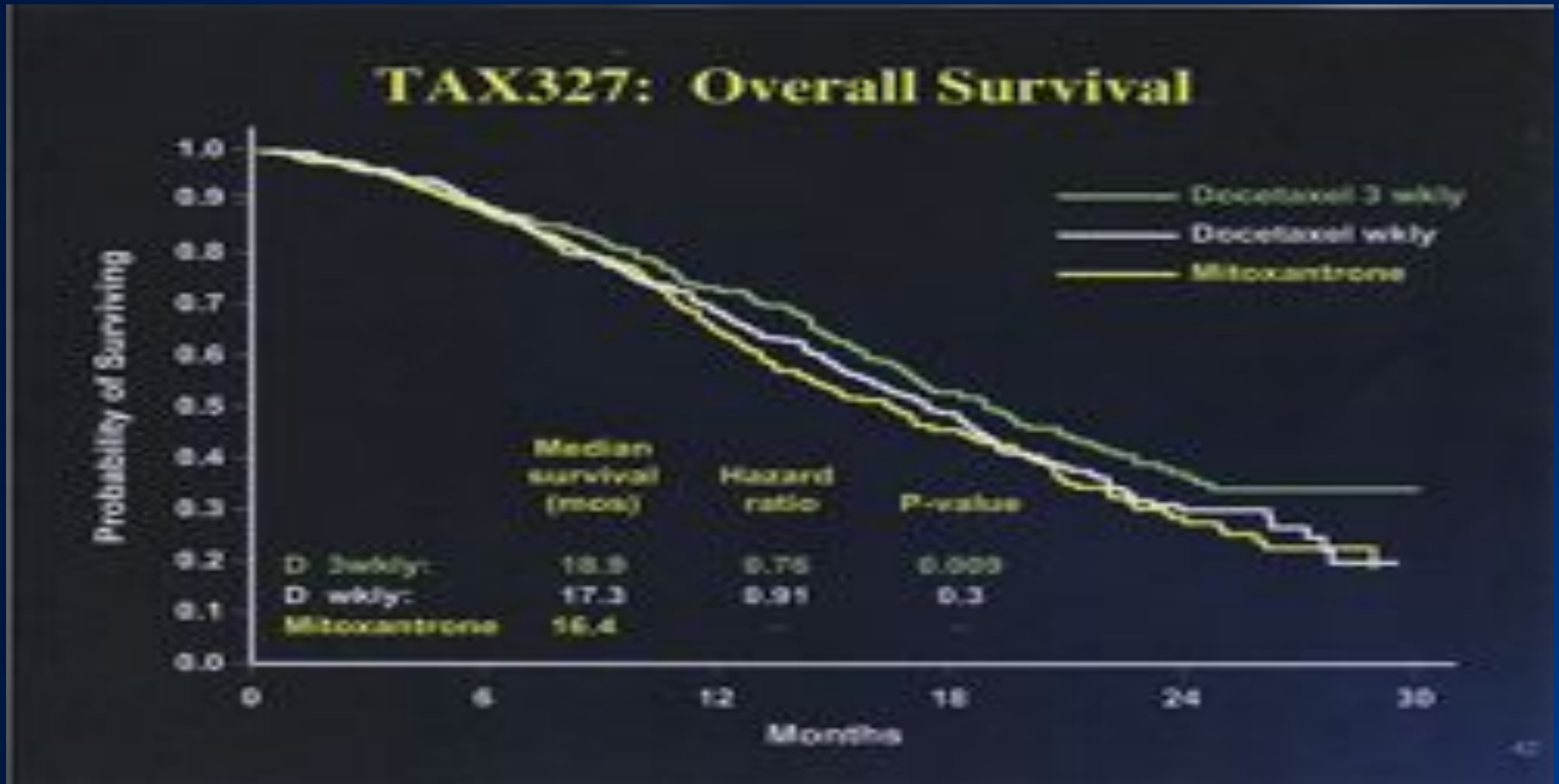


Phase III study

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



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: $\leq 5\%$), 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%)

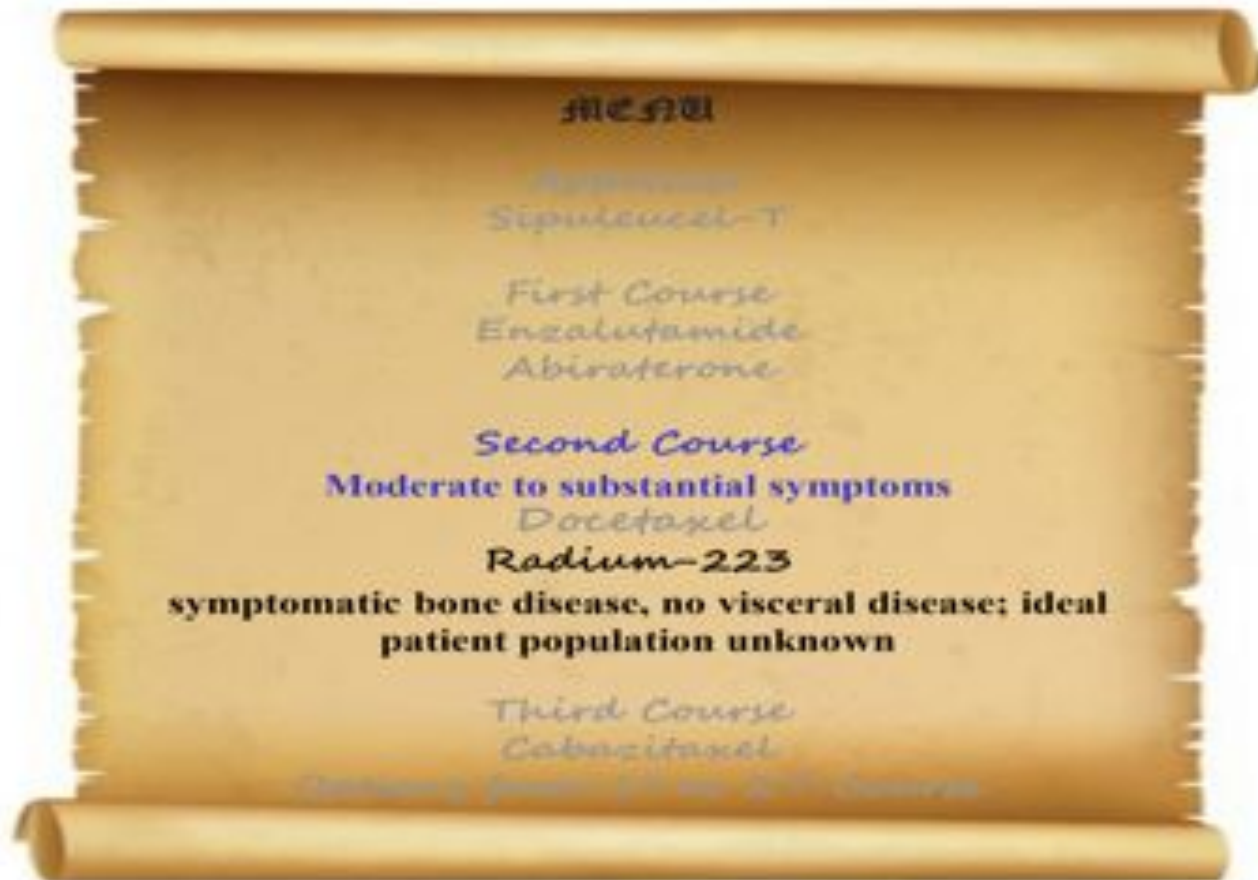
Hypersensitivity: Hypersensitivity (1% to 21%; with premedication 15%)

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%)

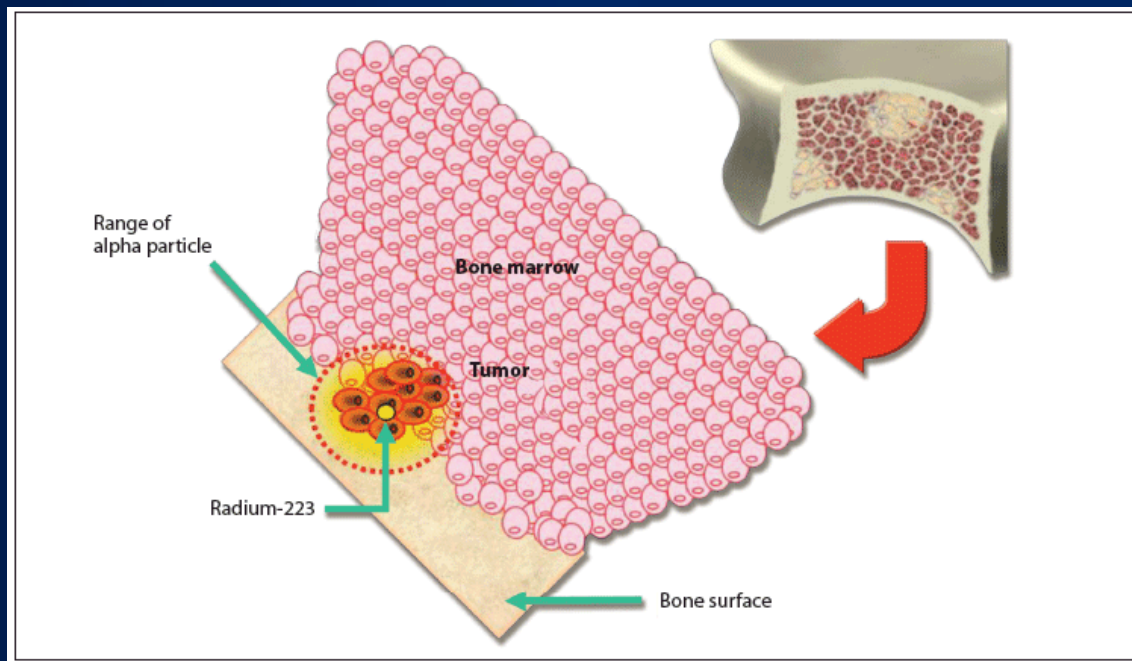
Radium



Radium-223 (Alpharadin)

Bone –targeting radiopharmaceutical

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



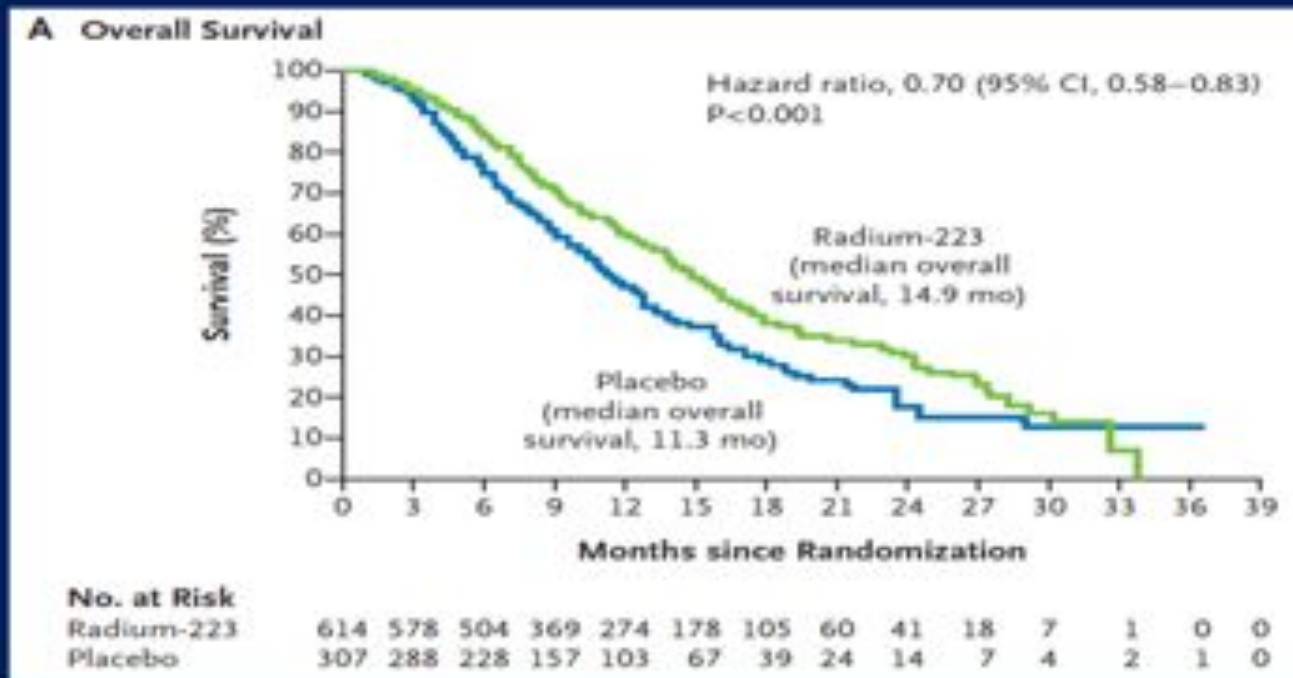
Radium trial

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



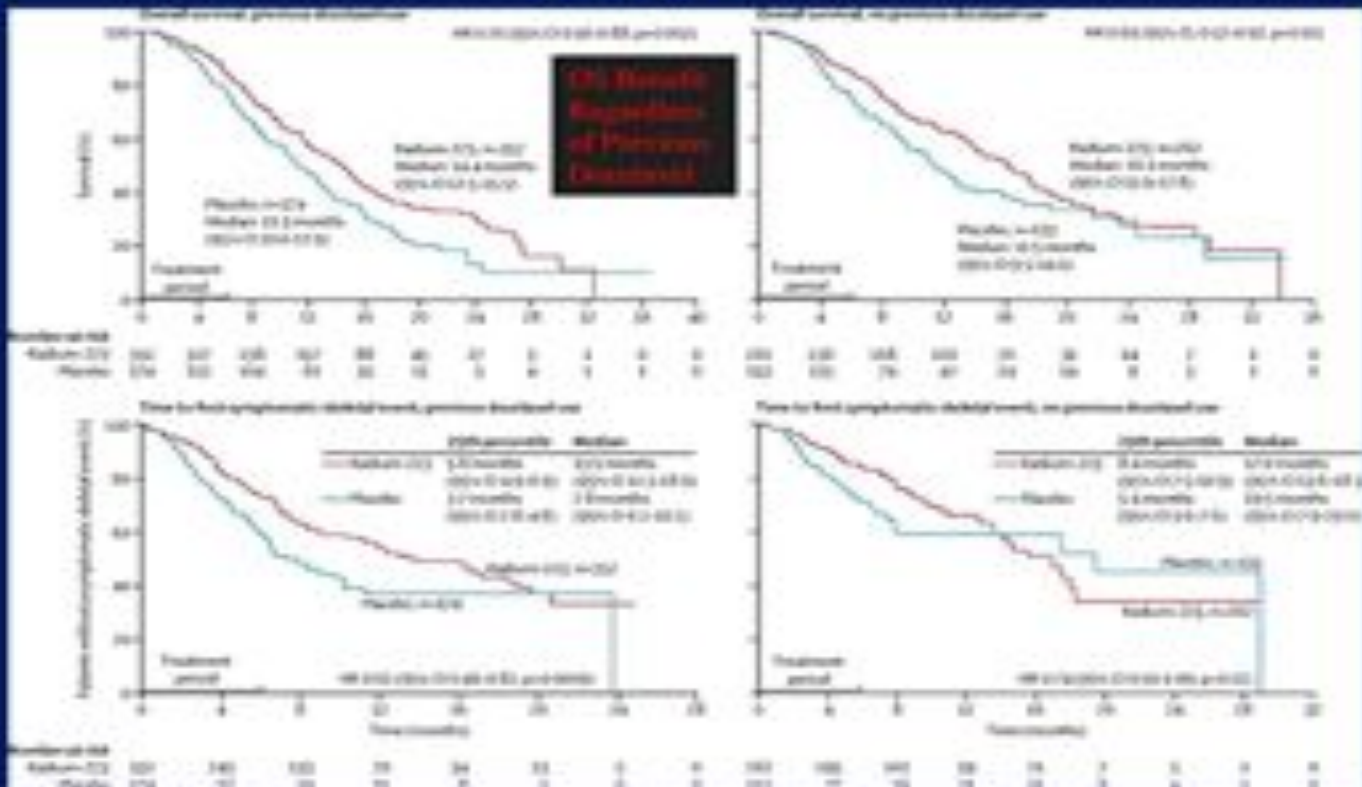
Phase III study of Radium-223

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



Survival curves

ALSYMPCA: Subgroup Analysis based on Previous Docetaxel



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%)

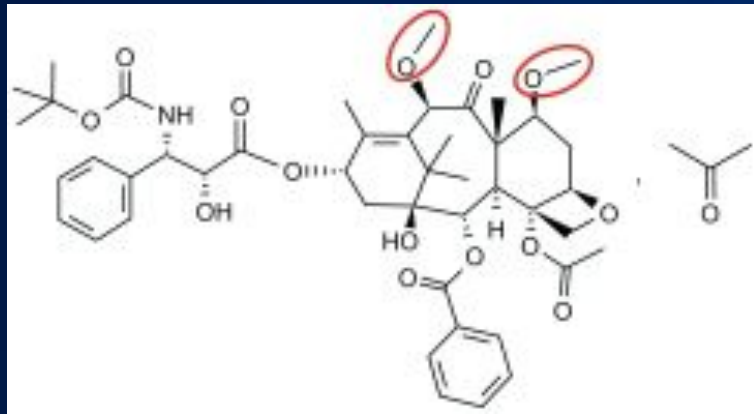
Third course



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



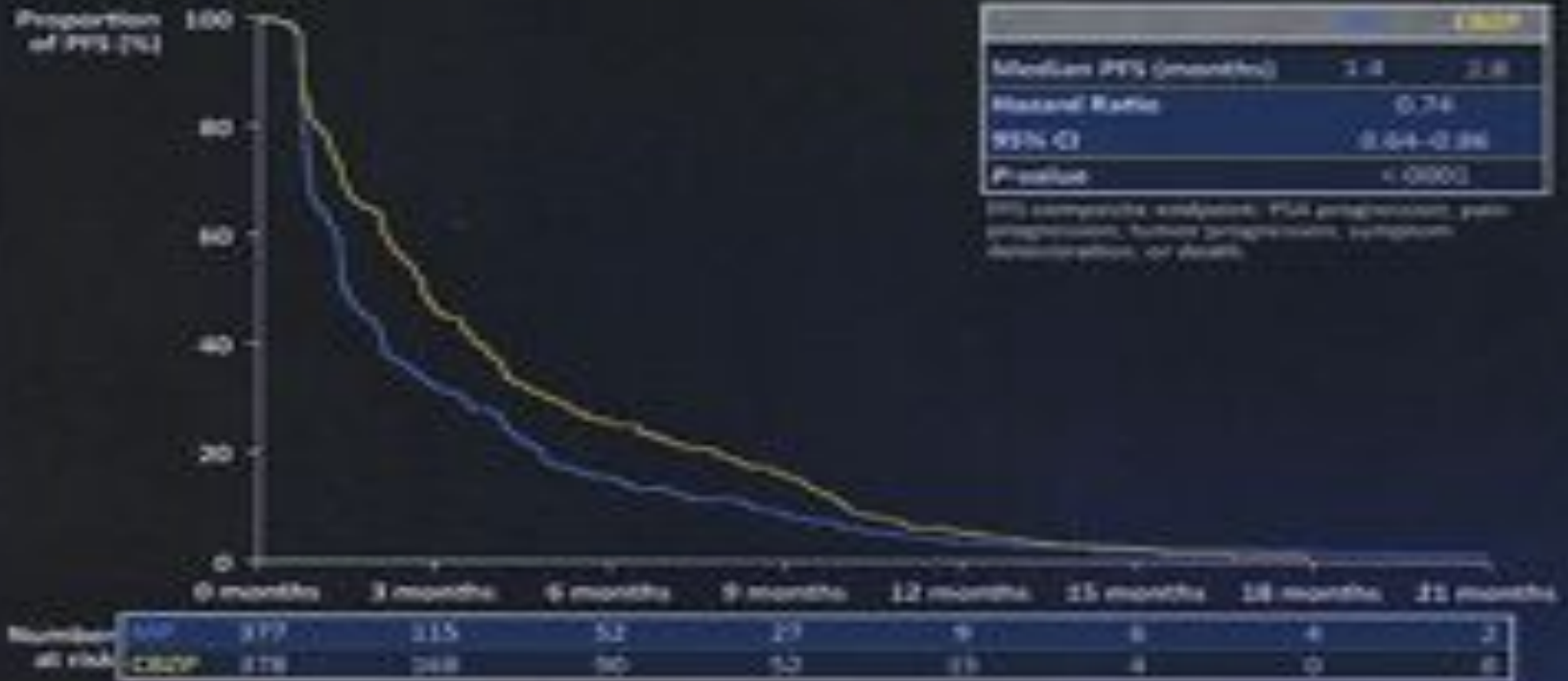
TROPIC protocol

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



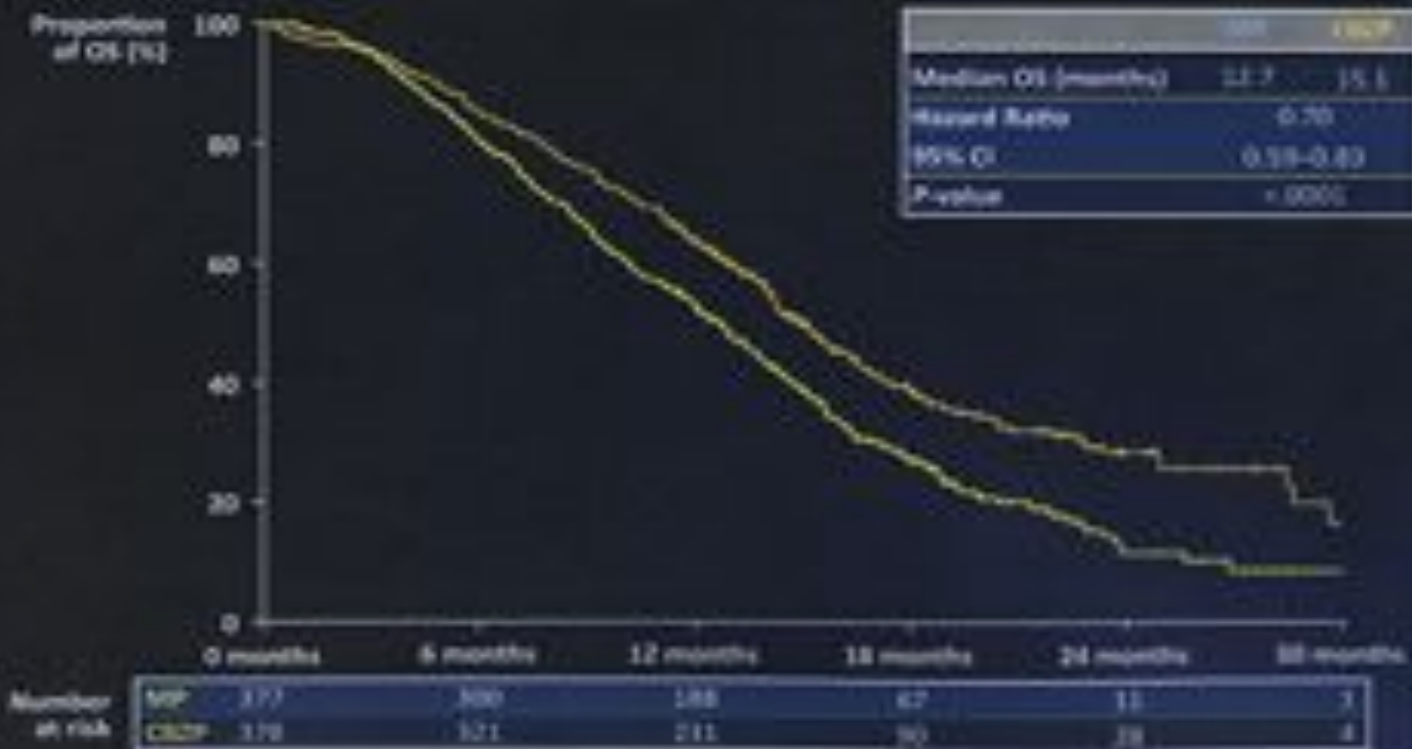
TROPIC: Progression-Free Survival

TROPIC: Progression-Free Survival



TROPIC: Overall 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

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%)

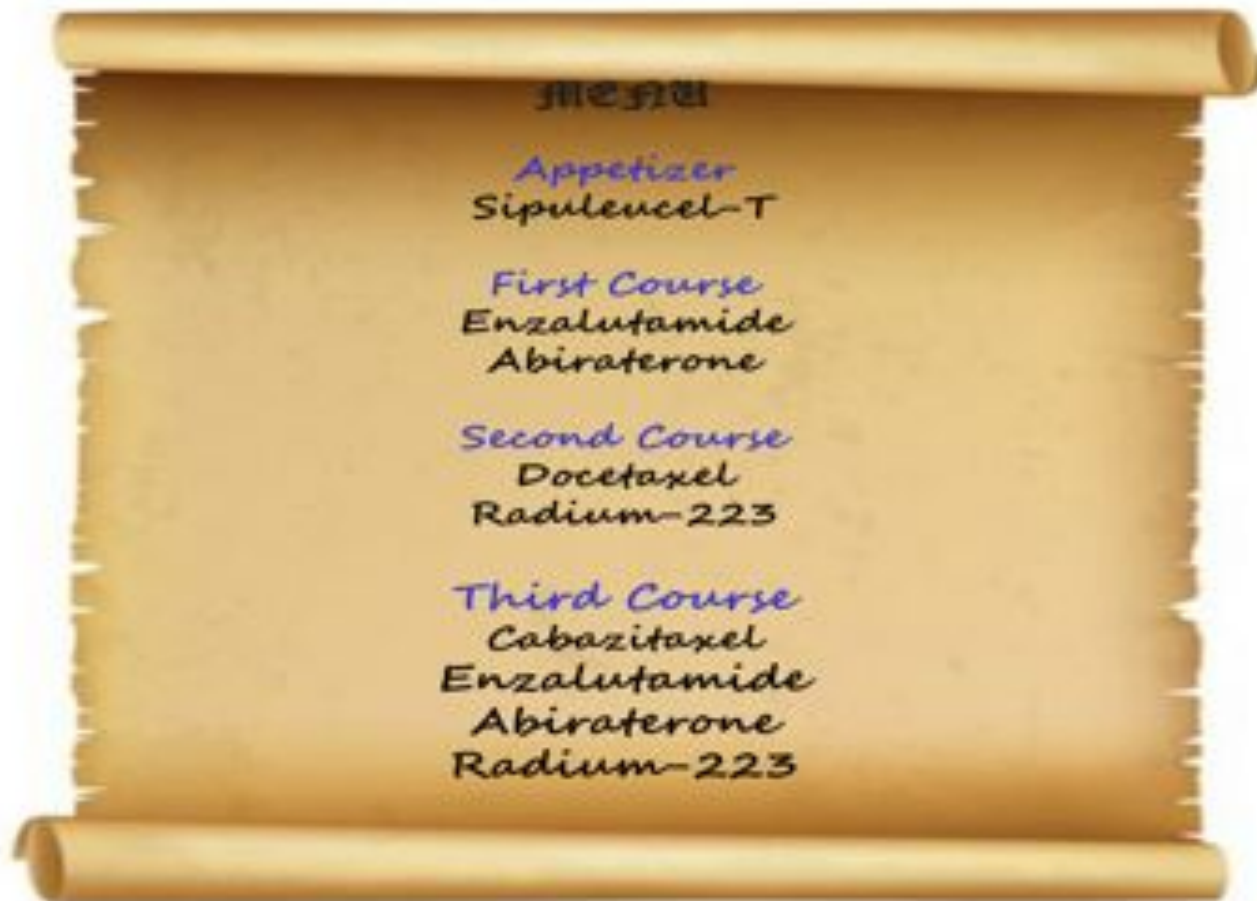
Renal: Hematuria (17%)

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

Specials



PARP Inhibitor

PARP Inhibitor – Breakthrough Status

- 50 patients treated with a olaparib
- 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**

ESTABLISHED 1827

VOLUME 365, 2012

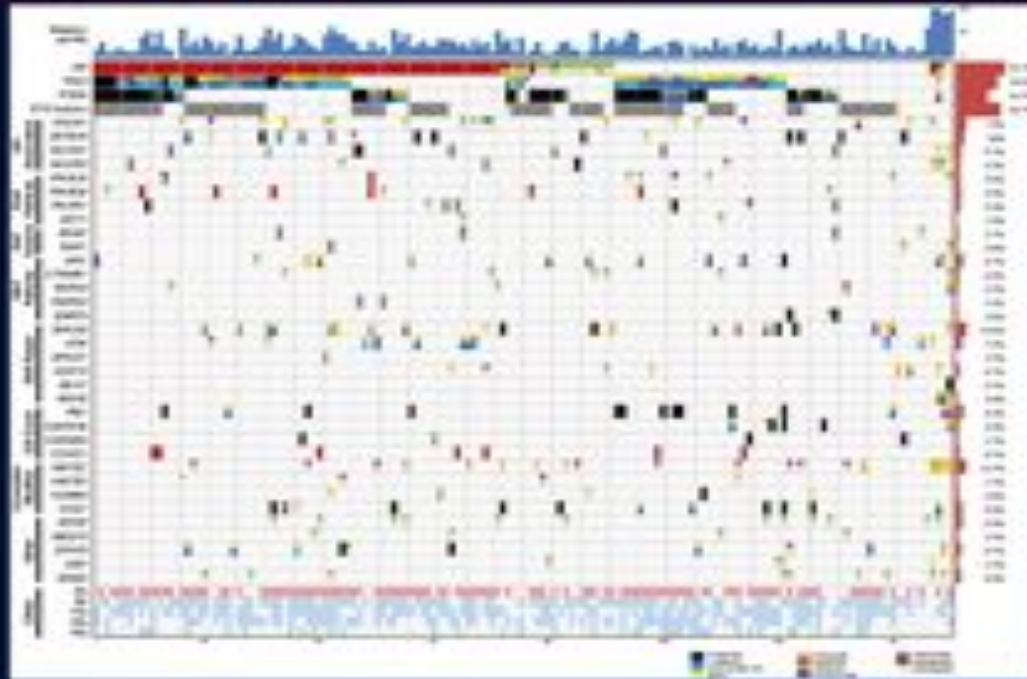
ISSN 0028-2752

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

J. Mani, S. Carreira, S. Cauffman, S. Miranda, M. Mavrouk, B. Pines, S. Pines, M. Nava Rodriguez, D. Robinson, M. Quinn, M. Tumber, G. Bazyar, M. Park, P. Fisher, A. Gillman, J. Figueroa, C. Fong, G. S. Li, S. J. Lee, C. D. Kelly, A. Pritchard, S. Hunsberger, B. J. Goldstein, T. Elliott, D. McGovern, D. B. Skonecny, J. G. Hodge, C. Zujewski, C. C. Williams, M. K. Karim, B. S. Ghossein, B. P. D'Amico, G. P. Jarman, G. S. Li, M. Nava, Y. M. Wu, R. C. Chen, B. Bruggen, M. P. Goetz, R. A. Miller, A. S. Dearn, L. P. Kavanagh, K. T. Kelly, G. Alford, C. J. Lamb, A. Schmitt, M. A. Rubin, R. E. Kluwe, F. Y. Feng, A. M. Chinnaiyan, E. Hall, and J. S. de Bono

Clinical genomics

Integrative Clinical Genomics of Advanced Prostate Cancer



E3805 CHAARTED Treatment

E3805 – CHAARTED Treatment

STRATIFICATION

Extent of Mets

-High vs Low

Age

≥70 vs < 70yo

ECOG PS

-0-1 vs 2

CAS > 30 days

-Yes vs No

SRE Prevention

-Yes vs No

Prior Adjuvant ADT

≤12 vs > 12 months

R
A
N
D
O
M
I
Z
E

ARM A:
ADT + Docetaxel
75mg/m² every 21
days for maximum
6 cycles

ARM B:
ADT (androgen
deprivation therapy
alone)

Evaluate
every 3 weeks
while
receiving
docetaxel and
at week 24
then every 12
weeks

Evaluate
every 12
weeks

Follow for time
to progression
and overall
survival

Chemotherapy
at investigator's
discretion at
progression

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

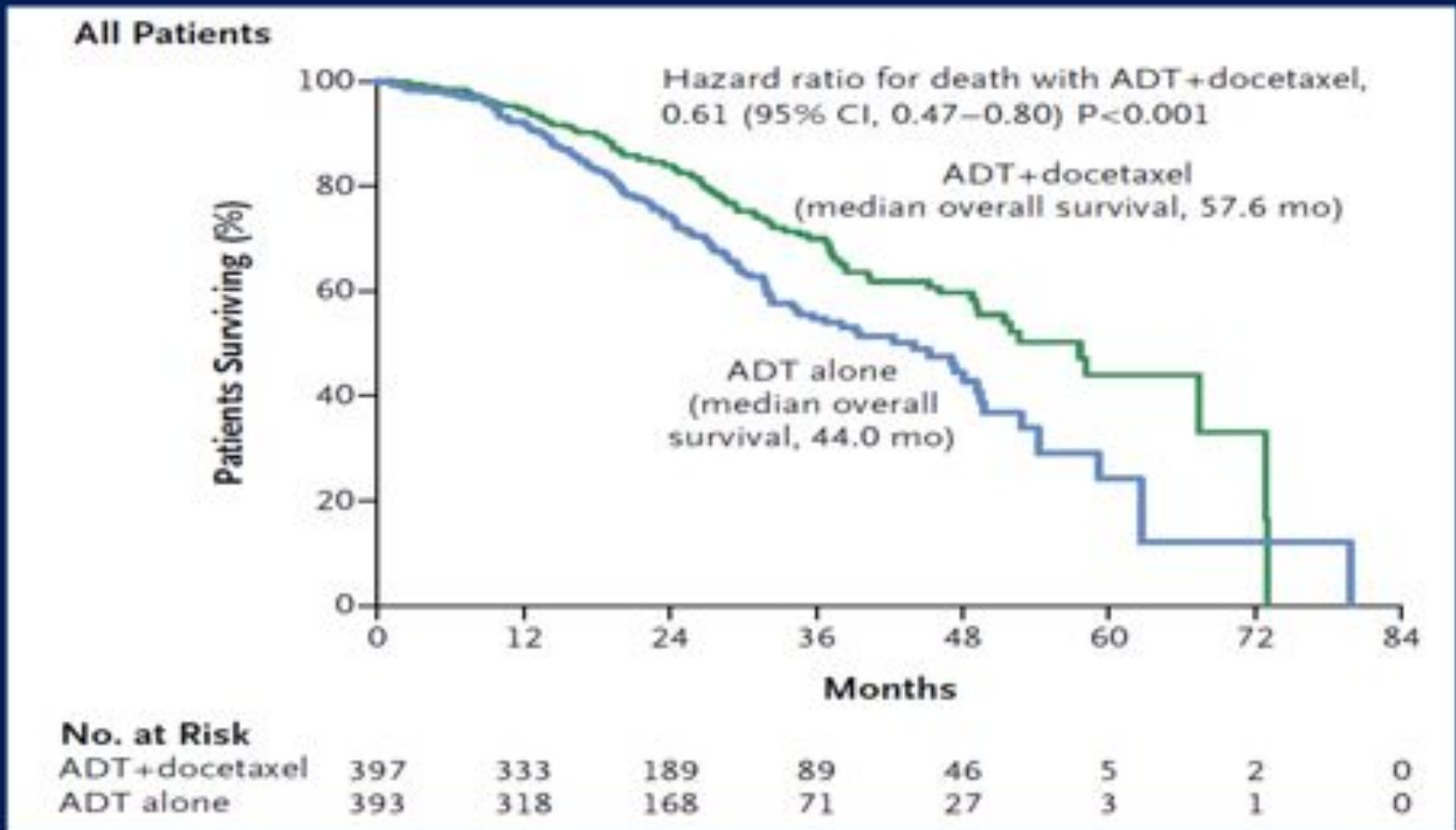
Presented by: Christopher J. Sweeney, MD, PhD

ASCO 2014

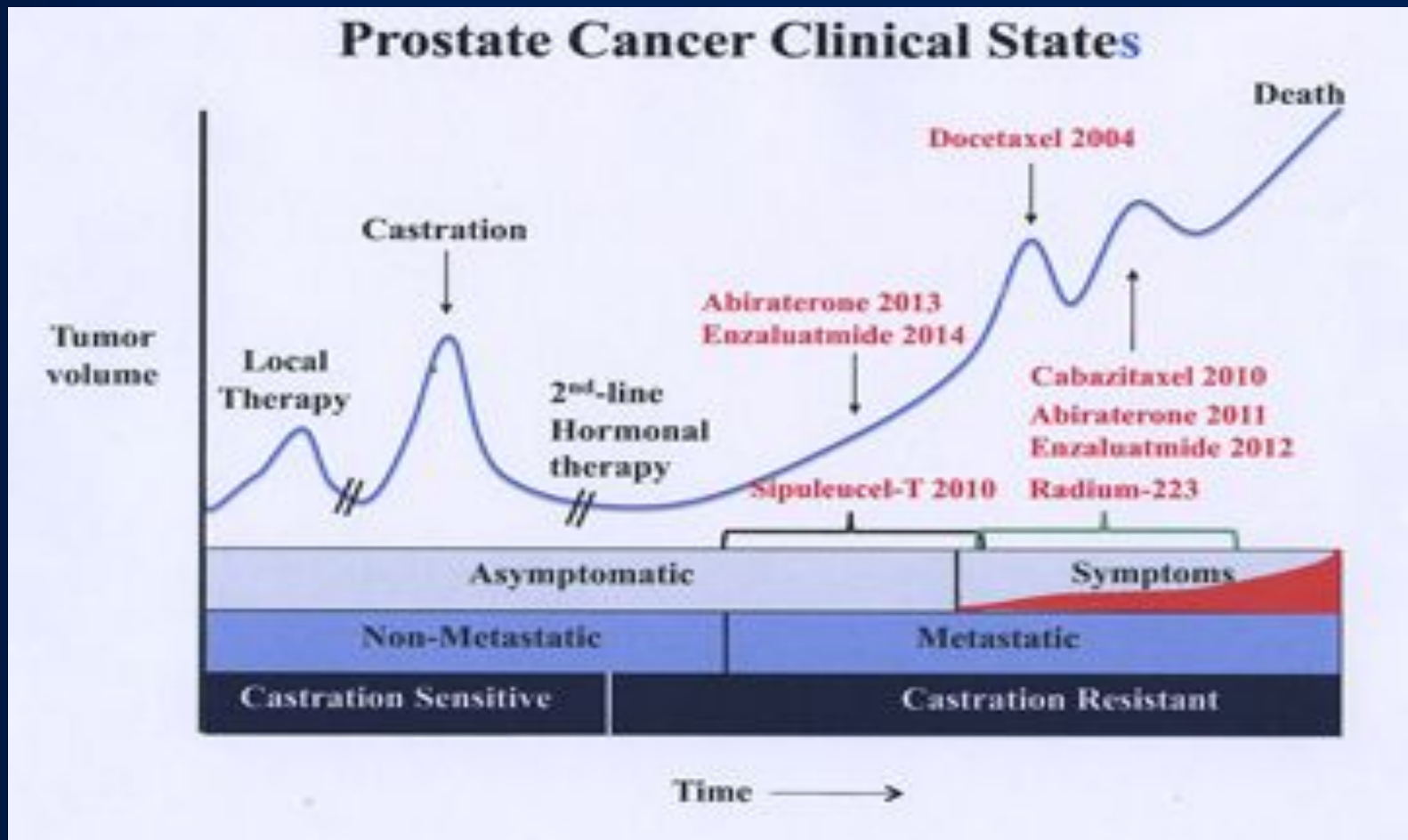


Presented By Christopher Sweeney at 2014 ASCO Annual Meeting

Survival curve

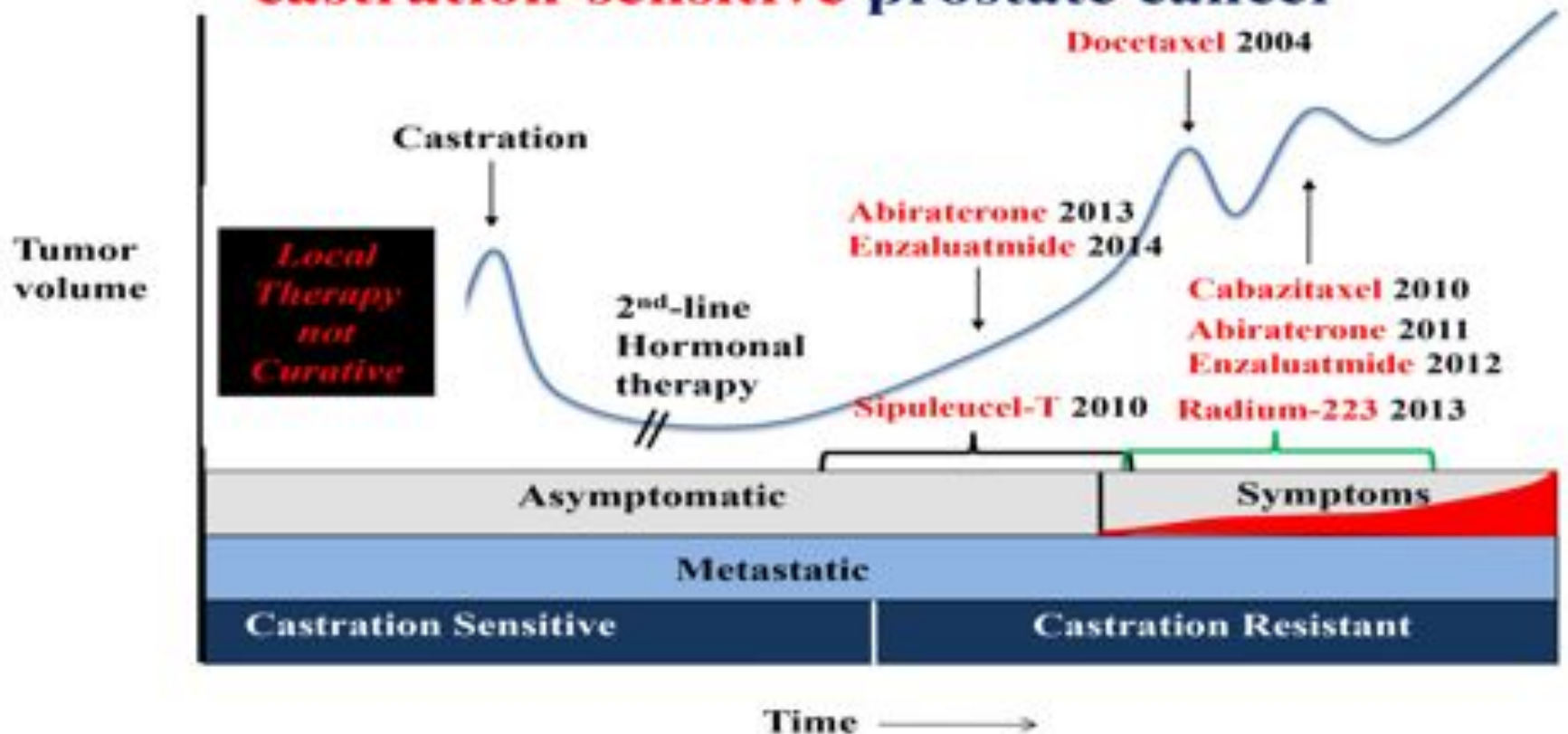


Prostate Cancer Clinical States



Docetaxel

CHAARTED/ E3805 supports docetaxel in metastatic castration-sensitive prostate cancer



LATITUDE study

Overall study design of LATITUDE



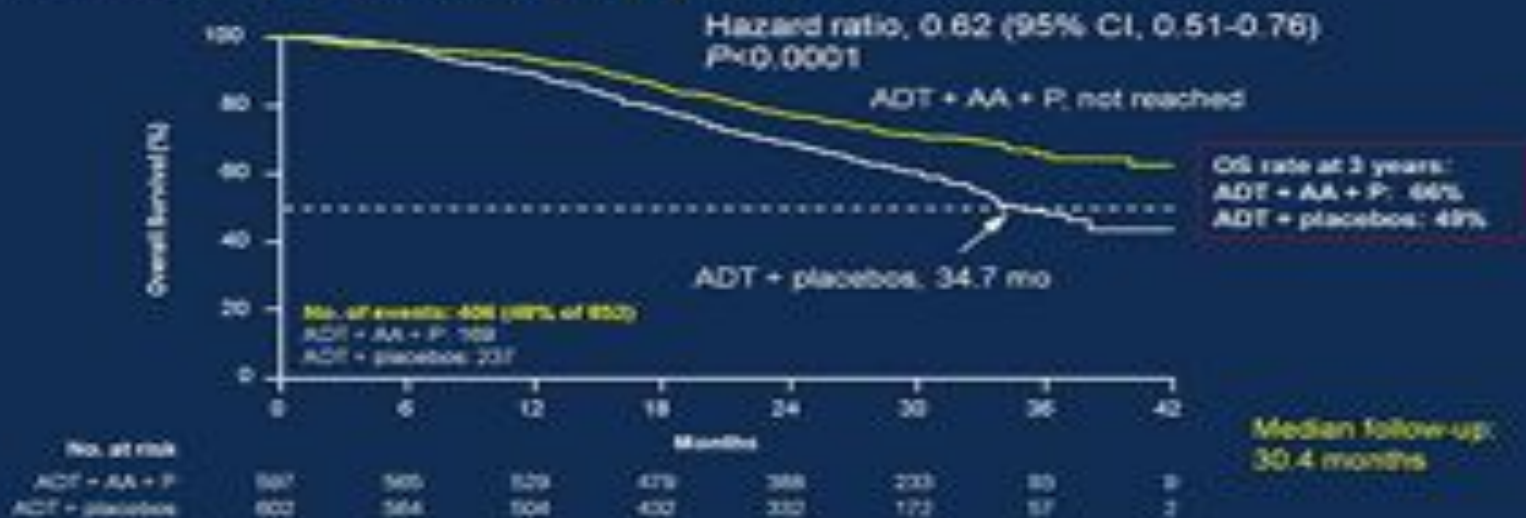
- Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada
- Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results

Presented at ASCO ANNUAL MEETING '17 #ASCO17

Presented by: Karim Fizazi

Survival curve

Statistically significant **38%** risk reduction of death



Summary



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

Third course



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

Carbazitaxel vs. Docetaxel

Cabazitaxel vs. Docetaxel

- 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

78

Dilemmas in treatment

Dilemmas in Treating Metastatic Castration
Sensitive Prostate Cancer

Dilemmas in Treatment

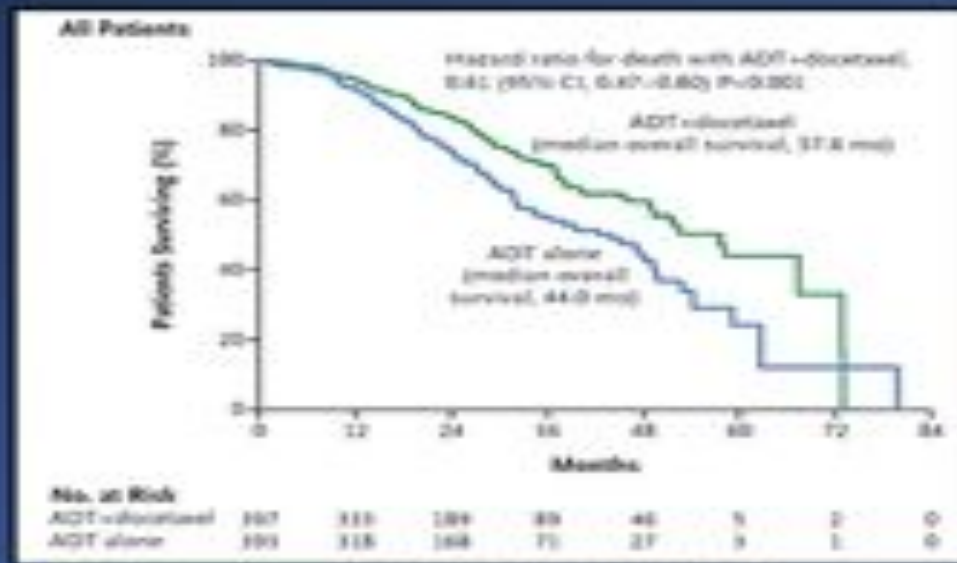
Dilemmas in Treating Metastatic Castration Sensitive Prostate Cancer

- What is Metastatic Castration Sensitive Prostate Cancer?
 - Newly diagnosed patients who have metastatic disease
 - Patients who had been previously treated with definitive surgery or radiation but then develop metastasis
 - All patients have **NORMAL Testosterone**

CHAARTED Treatment



Survival curve



Shewchuk, C.J. et al. *NCLM*, 2016

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 Tolerability

Docetaxel Tolerability

Table 2. Adverse Events of Grade 1 or Higher among the 107 Patients who Received the Treatment/Controling Regimen and the Follow-up Data Available*

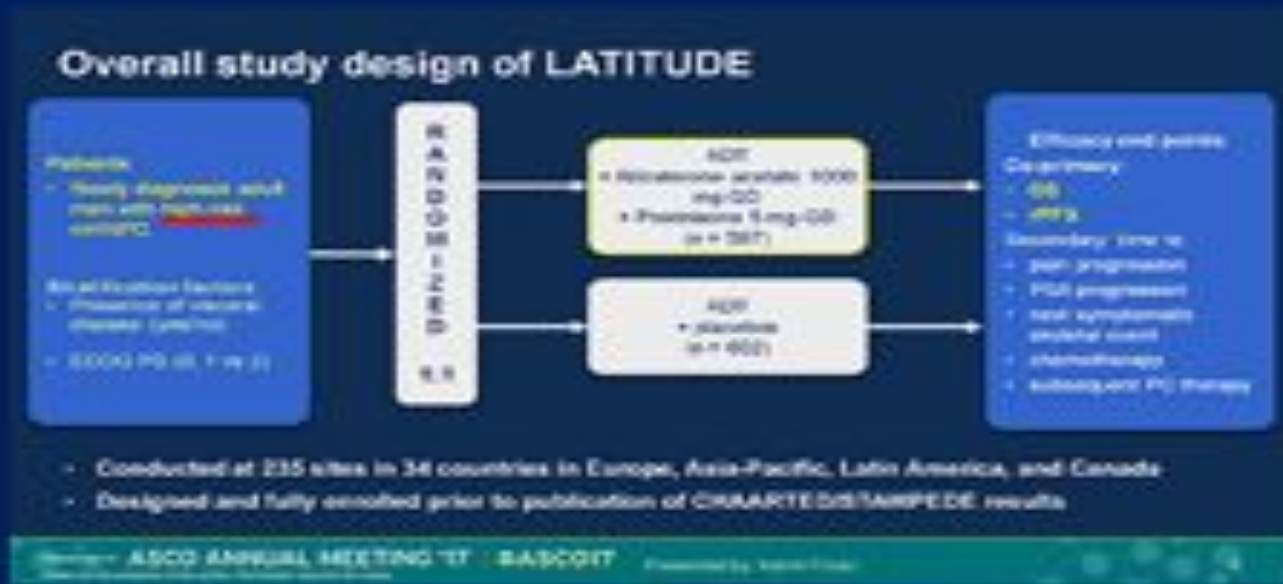
Event	Grade 1	Grade 2	Grade 3
n = 107 (100%)			
Allergic reaction	7 (6.6)	1 (0.9)	0
Asympt	36 (33.7)	0	0
Diarrhea	4 (3.7)	0	0
Dizziness	2 (1.9)	0	0
Hypotension	2 (1.9)	0	0
Neutropenia	2 (1.9)	0	0
Peripheral neuropathy	0	0	1 (0.9)
Rhinitis	4 (3.7)	1 (0.9)	0
Thrombocytopenia	0	1 (0.9)	0
Weight gain	5 (4.7)	2 (1.9)	0
Adverse unexplained	21 (19.6)	4 (3.7)	0
Adverse with unexplained	7 (6.6)	4 (3.7)	0
All event	67 (62.6)	10 (9.4)	1 (0.9)

Deming, Co et al. NCLM 2015

Cycles Administered

Number of cycles	RCT + Docetaxel (N=227)	
	n	%
1	191	84.1
2	7	3.1
3	6	2.7
4	8	3.5
5	10	4.4
6	208	92.5
Total	227	

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.

Abiraterone outcomes

Abiraterone: Outcomes in Metastatic Castration Sensitive Prostate Cancer

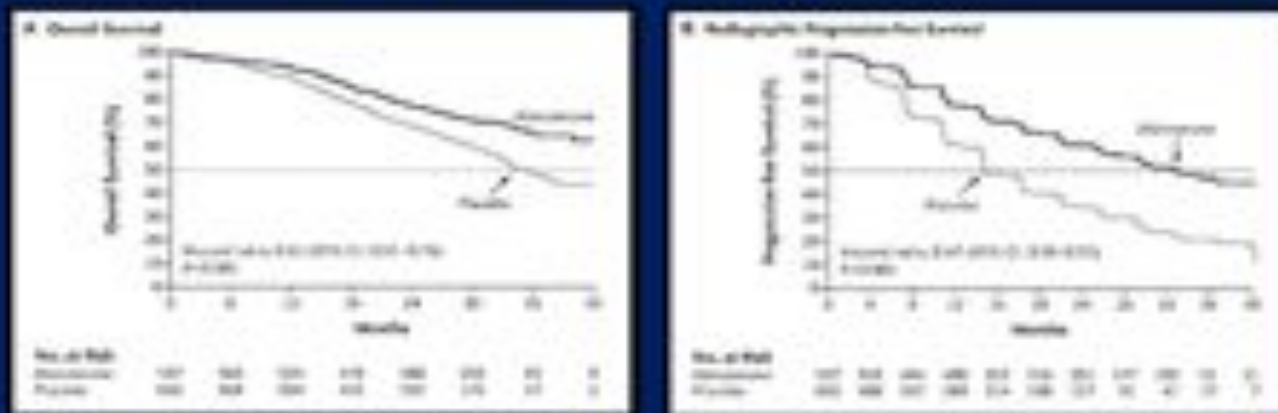


Figure 4. *n* = 200. *N Engl J Med*. 2017.

Abiraterone toxicity

Toxicity
Abiraterone in
metastatic
Castration
Sensitive Prostate
Cancer

Table 1. Adverse Events

Adverse Event	Abiraterone group		Placebo group		P-value
	n (%)	n (%)	n (%)	n (%)	
All adverse events	148 (85)	148 (85)	148 (85)	148 (85)	
Grade 1-2 adverse events	148 (85)	148 (85)	148 (85)	148 (85)	
Grade 3-4 adverse events	148 (85)	148 (85)	148 (85)	148 (85)	
Adverse events leading to death	148 (85)	148 (85)	148 (85)	148 (85)	
Systemic adverse events					
Headache	148 (85)	148 (85)	148 (85)	148 (85)	0.001
Diarrhea	148 (85)	148 (85)	148 (85)	148 (85)	0.001
Constipation	148 (85)	148 (85)	148 (85)	148 (85)	0.001
Abdominal pain	148 (85)	148 (85)	148 (85)	148 (85)	0.001
Back pain	148 (85)	148 (85)	148 (85)	148 (85)	0.001
Local adverse events					
Itch	148 (85)	148 (85)	148 (85)	148 (85)	0.001
Rash	148 (85)	148 (85)	148 (85)	148 (85)	0.001
Swelling	148 (85)	148 (85)	148 (85)	148 (85)	0.001
Redness	148 (85)	148 (85)	148 (85)	148 (85)	0.001
Stinging	148 (85)	148 (85)	148 (85)	148 (85)	0.001
Open wound/ulcer	148 (85)	148 (85)	148 (85)	148 (85)	0.001

NOTE: All adverse events were defined as any event that occurred during the study, with a minimum frequency of 1% in either group. The most common adverse events were headache, diarrhea, constipation, abdominal pain, back pain, and rash. The most common local adverse events were itch, redness, and stinging. The most common systemic adverse events were headache, diarrhea, constipation, abdominal pain, and back pain. The most common local adverse events were itch, redness, and stinging. The most common systemic adverse events were headache, diarrhea, constipation, abdominal pain, and back pain.

Figure 1. N. Engl. J. Med. 2017

Abiraterone

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

Supplementary Table 1A. Individual Life-prolonging Effects for Primary Events.

Event	Abiraterone Group (n=952)	Placebo Group (n=952)
	n(%)	
Death	47 (5%)	47 (5%)
Progression to castrate-resistant prostate cancer	25 (3%)	33 (3%)
Worsening of prostate cancer	11 (1%)	16 (2%)
Death due to prostate cancer	10 (1%)	17 (2%)
Death due to cause other than prostate cancer	37 (4%)	30 (3%)
Death due to unknown cause	11 (1%)	27 (3%)

Horos R, et al. NEJM, 2017

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 retreat with docetaxel if you give 6 cycles of docetaxel?
- High volume vs. Low volume – should they be treated differently?

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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-orchectomy
 - In addition, sequential anti-androgens could be used (bicalutamide, flutamide, nilutamide, ketoconazole)

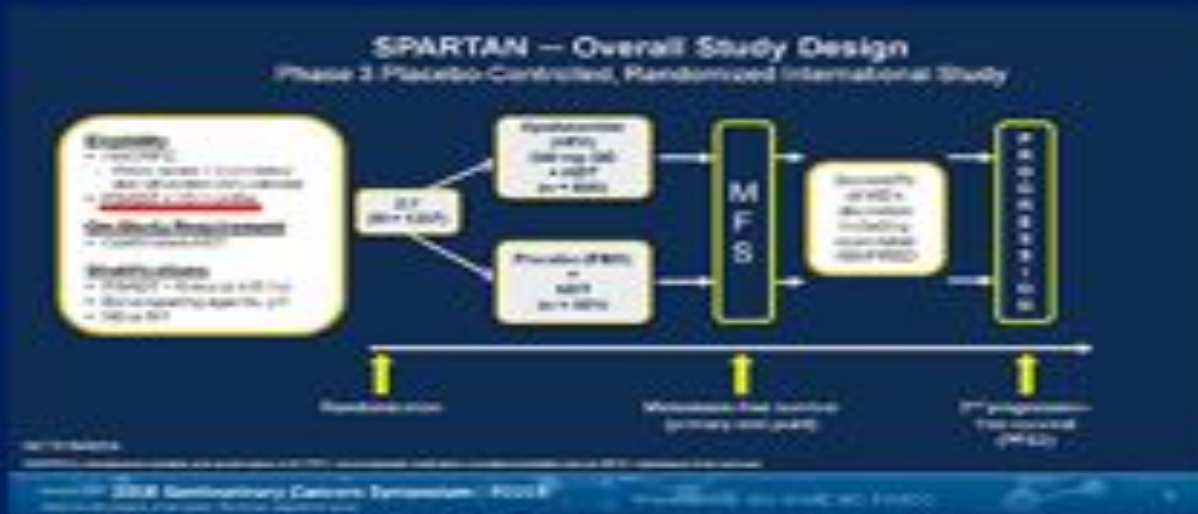
Apalutamide

Apalutamide

- Nonsteroidal antiandrogen
- Binds to the ligand-binding domain of the androgen receptor (AR)
- Limits androgen-receptor translocation to the nucleus
- Limits DNA binding of the AR in the nucleus
- Limits androgen-receptor-mediated transcription

© 2014, J. H. Kim et al. NEJM 2014

SPARTAN



Patient characteristics

Patient Baseline Characteristics

Apalutamide in M0 prostate cancer

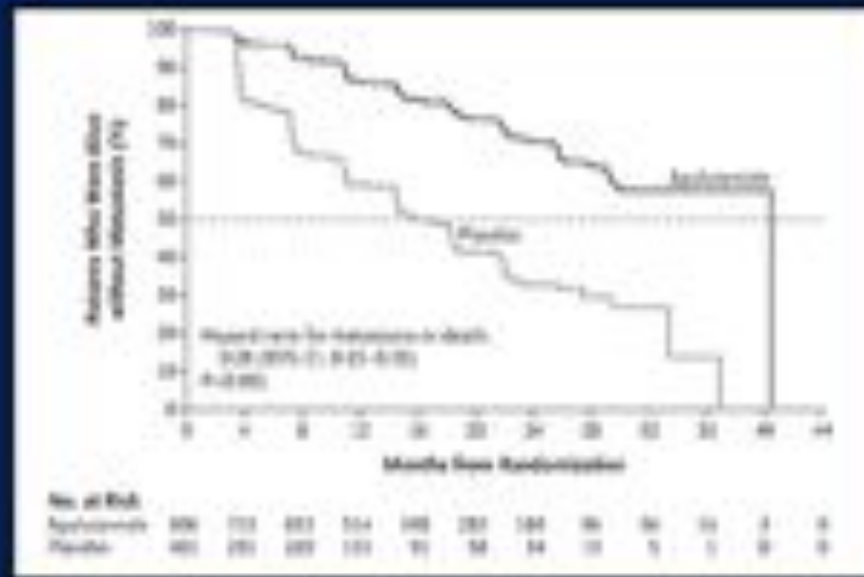
Table 2 Demographic and Disease Characteristics at Baseline^a

Characteristic	Apalutamide (N=488)	Placebo (N=488)
Age (yr)		
Mean	70	70
Range	48-91	50-91
Prostate-specific antigen (ng/mL) at baseline	7.10	7.20
Median (range)	4.40 (0.1-20.0)	4.30 (0.1-20.0)
< 4.0 (n, %)	179 (36.7)	184 (37.5)
≥ 4.0 (n, %)	309 (63.3)	304 (62.5)
< 10.0 (n, %)	381 (77.9)	381 (77.9)
≥ 10.0 (n, %)	107 (22.1)	107 (22.1)
< 15.0 (n, %)	374 (76.6)	374 (76.6)
≥ 15.0 (n, %)	114 (23.4)	114 (23.4)
< 20.0 (n, %)	370 (75.8)	370 (75.8)
≥ 20.0 (n, %)	118 (24.2)	118 (24.2)
< 25.0 (n, %)	367 (75.0)	367 (75.0)
≥ 25.0 (n, %)	121 (25.0)	121 (25.0)
< 30.0 (n, %)	363 (74.4)	363 (74.4)
≥ 30.0 (n, %)	125 (25.6)	125 (25.6)
< 35.0 (n, %)	359 (73.6)	359 (73.6)
≥ 35.0 (n, %)	129 (26.4)	129 (26.4)

^aThere were no significant differences between groups in the demographic and disease characteristics at baseline (comparing apalutamide versus placebo) for age, prostate-specific antigen, and race/ethnicity.

Apalutamide

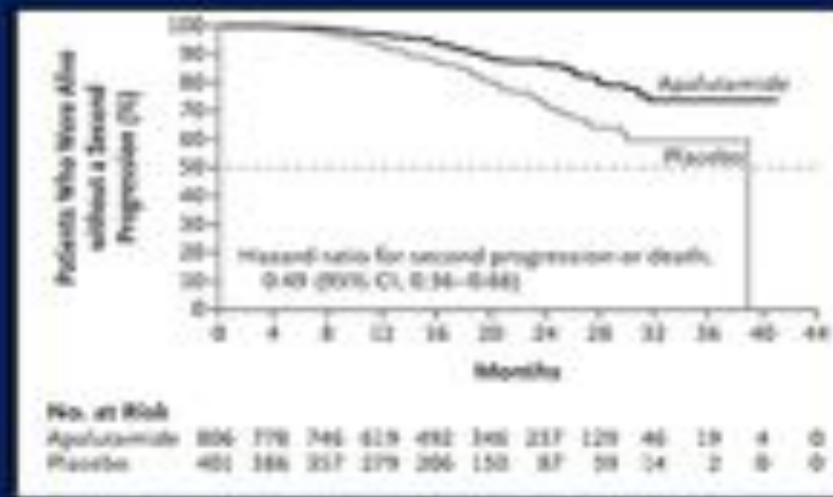
Apalutamide Improves Metastasis-Free Survival



SWOG S1808 (NCT01967553)

Secondary Progression

Secondary Progression for Patients Who were Subsequently Treated with Abiraterone



Simon, JRM et al. NEJM 2018

Abiraterone administration

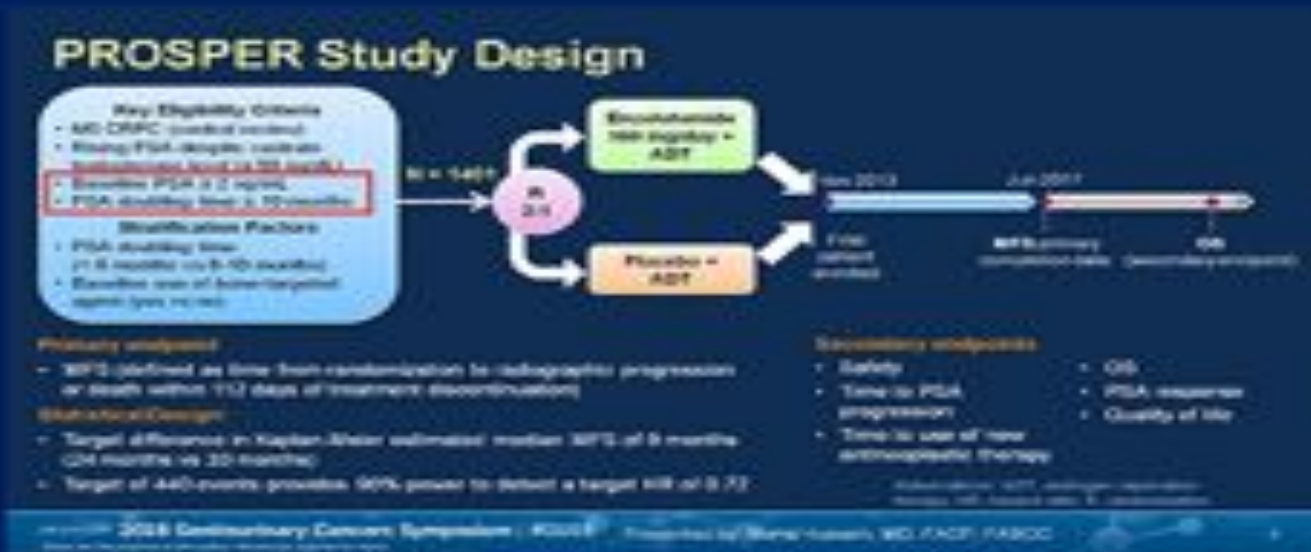
Toxicity

Abiraterone in
metastatic
Castration
Sensitive Prostate
Cancer

Adverse Event	Metastatic Capecitabine (n=100)			Metastatic Enzalutamide (n=100)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Headache	100/100	100/100	100/100	100/100	100/100	100/100
Diarrhea	100/100	100/100	100/100	100/100	100/100	100/100
Constipation	100/100	100/100	100/100	100/100	100/100	100/100
Abdominal pain	100/100	100/100	100/100	100/100	100/100	100/100
Back pain	100/100	100/100	100/100	100/100	100/100	100/100
Arthralgia	100/100	100/100	100/100	100/100	100/100	100/100
Myalgia	100/100	100/100	100/100	100/100	100/100	100/100
Fatigue	100/100	100/100	100/100	100/100	100/100	100/100
Weight loss	100/100	100/100	100/100	100/100	100/100	100/100
Hot flashes	100/100	100/100	100/100	100/100	100/100	100/100
Decreased libido	100/100	100/100	100/100	100/100	100/100	100/100
Sexual dysfunction	100/100	100/100	100/100	100/100	100/100	100/100

Source: X. et al. JCO, 2017

Prosper Study Design



Patient characteristics

Baseline Patient Characteristics (N = 1401)

Characteristic	Enzalutamide + ADT (n = 933)	Placebo + ADT (n = 468)
Median age (range), y	74 (50-95)	73 (50-92)
ECOG PS, no. (%)		
0	747 (80%)	362 (80%)
1	185 (20%)	95 (20%)
Median serum PSA (range), ng/mL	11.1 (0.3-1071.5)	10.2 (0.2-407.5)
Median PSA doubling time (range), mo	3.8 (0.4-37.4)	3.8 (0.5-71.8)
PSA doubling time category, no. (%)		
< 6 mo	718 (77%)	363 (77%)
≥ 6 mo	217 (23%)	107 (23%)
Baseline use of bone-targeting agent, no. (%)		
No	828 (89%)	420 (90%)
Yes	105 (11%)	48 (10%)

- Median duration of therapy was 15.4 (range, 0-41.3*) months for enzalutamide and 15.1 (range, 0-42.3*) months for placebo.
- Patients on treatment as of 28 June 2017 (study date): 434 patients (46%) on enzalutamide and 178 patients (38%) on placebo.

Adverse events

Adverse Events of Special Interest*

Any Grade Event, No. (%)	Enzalutamide + ADT (n = 820)	Placebo + ADT (n = 493)
Hypertension†	114 (12%)	25 (5%)
Major adverse cardiovascular event†	48 (5%)	13 (3%)
Blurred vision/visual disorders†	48 (5%)	9 (2%)
Hepatic impairment	15 (1%)	9 (2%)
Neutropenia	9 (1%)	1 (< 1%)
Convulsion	3 (< 1%)	0
Posterior reversible encephalopathy syndrome	0	0

In both arms the incidence of major adverse cardiovascular events was higher in patients with:

- Baseline history of cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia, or age ≥ 75 years

*Adverse events were defined as: 1) Any adverse event of grade 1 or higher; 2) Hypertension, blurred vision/visual disorders.

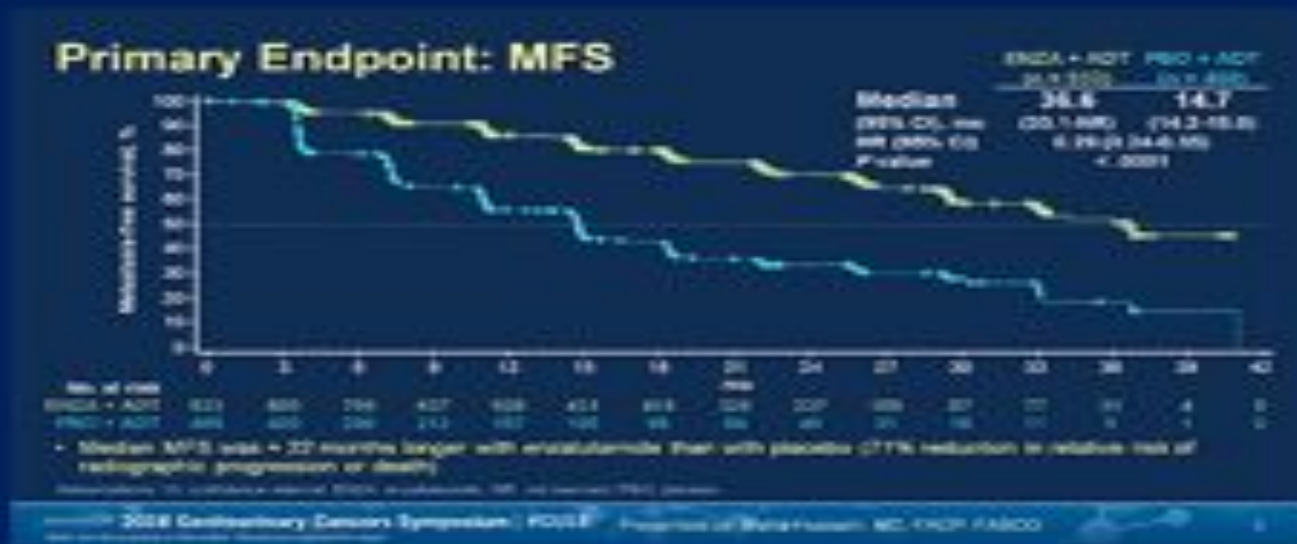
†Includes events of grade 1 or higher.

‡Includes events of grade 1 or higher, including cardiovascular conditions, serious noncardiovascular conditions, and death from

any cause. ††Includes events of grade 1 or higher, including laboratory abnormalities, serious noncardiovascular conditions, serious noncardiovascular conditions, and death from

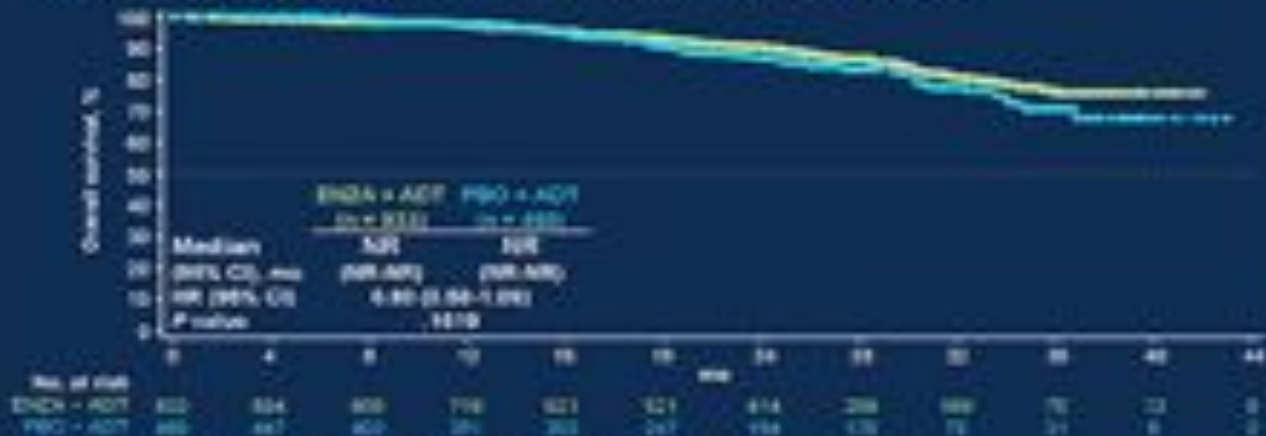
any cause.

Primary endpoint



Overall survival

Overall Survival: First Interim Analysis



- Median follow-up time was ~ 22 months for each treatment arm
- There was a 20% reduction in the relative risk of death with enzalutamide vs placebo

Progression event

Progression Event by Type

Event, No. (%)	Enzalutamide + ADT (n = 832)	Placebo + ADT (n = 868)
All progression events¹	219 (27%)	326 (40%)
Radiographic progression ²	187 (23%)	224 (26%)
New bone metastases	71 (9%)	79 (9%)
New soft-tissue metastases	109 (13%)	132 (15%)
Concurrent new bone and soft-tissue metastases	7 (1%)	13 (2%)
Death without documented radiographic progression within 112 days of study treatment discontinuation ³	32 (4%)	4 (1%)

* The proportion of progression events in the enzalutamide arm was 50% less than that of the placebo arm

¹Metastases are based on the number of patients randomized to each arm (enzalutamide + ADT, n = 832; placebo + ADT, n = 868).
²Percent of each percentage are based on total number of events in each arm (enzalutamide + ADT, n = 219; placebo + ADT, n = 326).

Treating M0 Prostate Cancer

My Thoughts on Treating M0 Prostate Cancer

- Consider the eligibility of the trial
 - PSA Doubling Time less than 10 months
 - Minimum PSA Value
- Risk vs. Benefit in an elderly population
- We still do not know if earlier Enzalutamide or Apalutamide is better (I.e. M0 vs. at mCRPC)
- OS benefit still unclear (with either treatment or head to head)
- Personally, I may still consider an older agent (I.e. bicalutamide) first, but apalutamide/enzalutamide will be a good for a subset of patients

Future Investigations

Future Investigations

- Identify best **sequence** of therapy
- **Biomarkers** to select best therapy
- Are **combinations** better than sequence
- How will more sensitive **imaging** change the disease
- Can you cure **oligometastatic** disease
- How does **immunotherapy** fit in the treatment of prostate cancer