Treatment of Metastatic Castration Resistant Prostate Cancer

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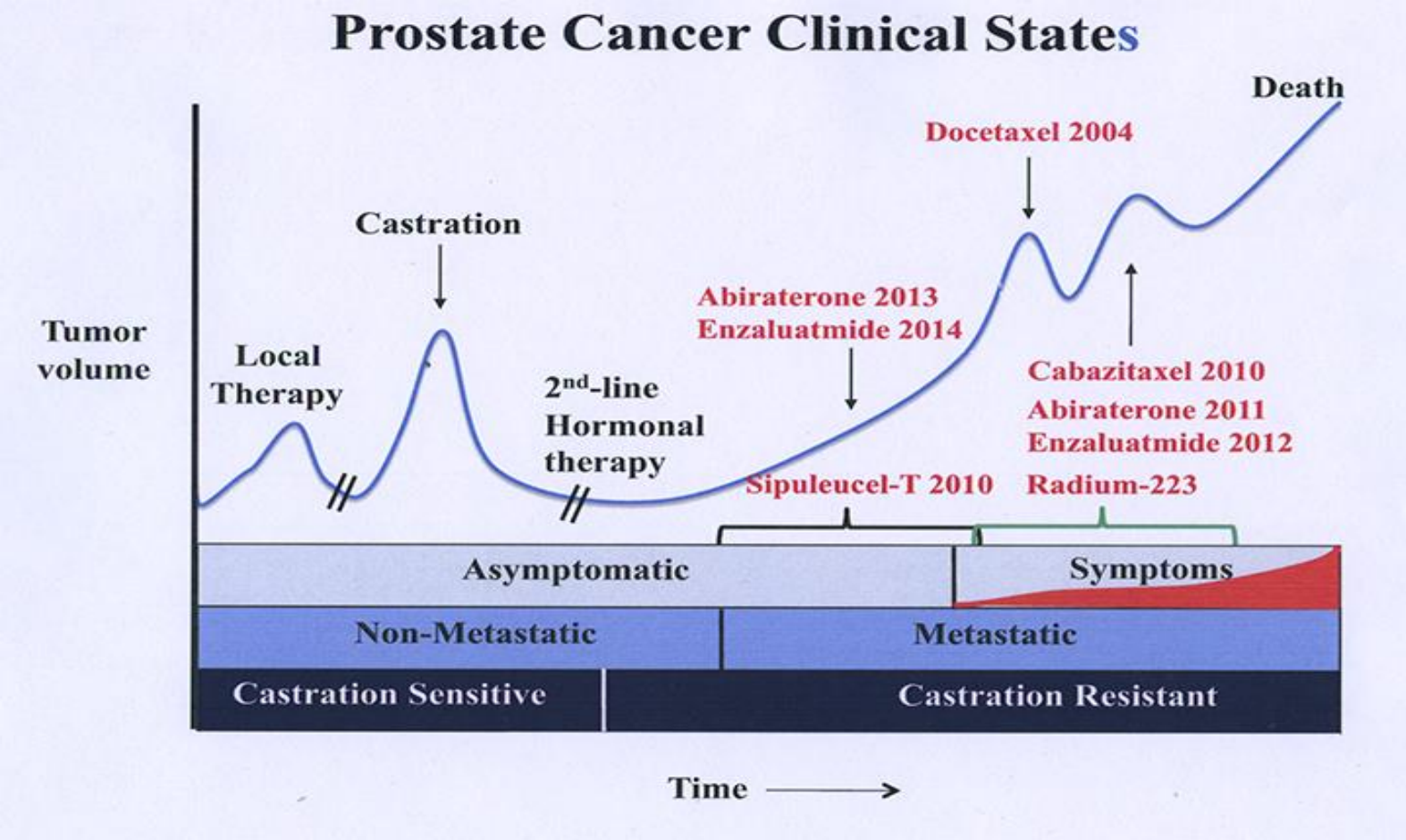
What I will not talk about today

- Treatment of primary disease
- Treatment of non-metastatic biochemically recurrent disease

What I will not talk about today

- Treatment of primary disease
  - -Surgery is curative for localized disease
  - -Radiation is curative for localized disease (with androgen deprivation for high risk
- Treatment of non-metastatic (biochemically recurrent) disease
  - -Surveillance and androgen deprivation are both options
  - -PSA doubling time is metric that can be used to evaluate pace of disease (retrospective data)

Prostate Cancer Clinical States



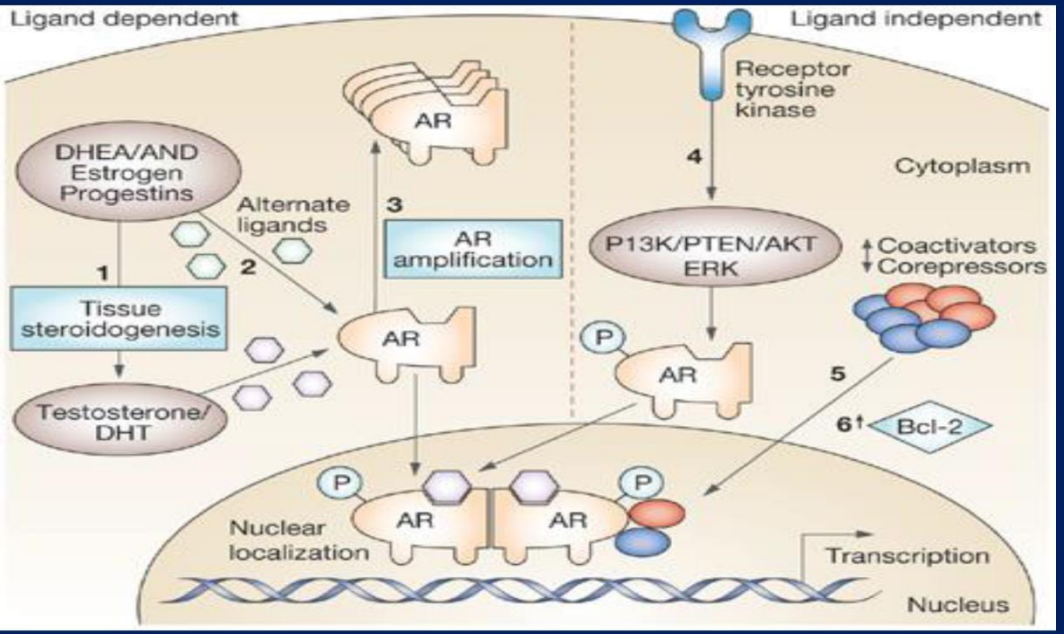
Castrate resistant prostate cancer

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?



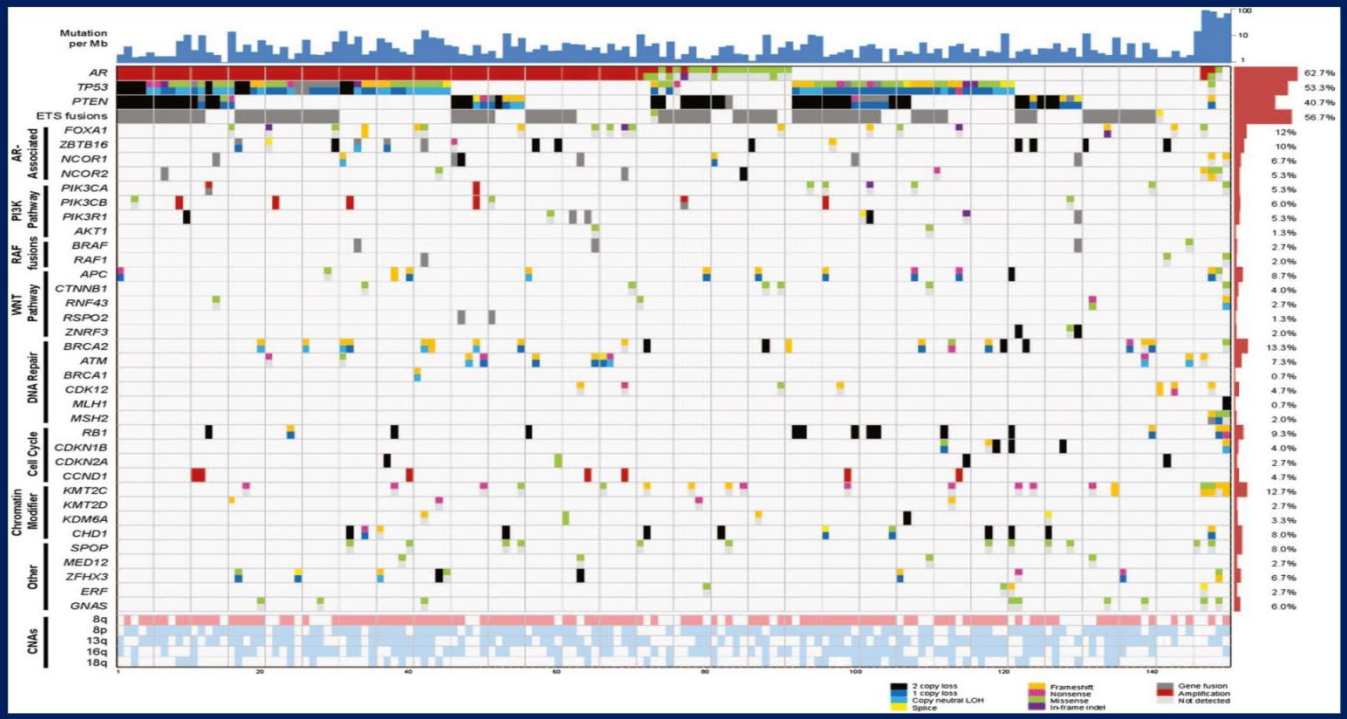
Resistance Mechanisms:

- 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?

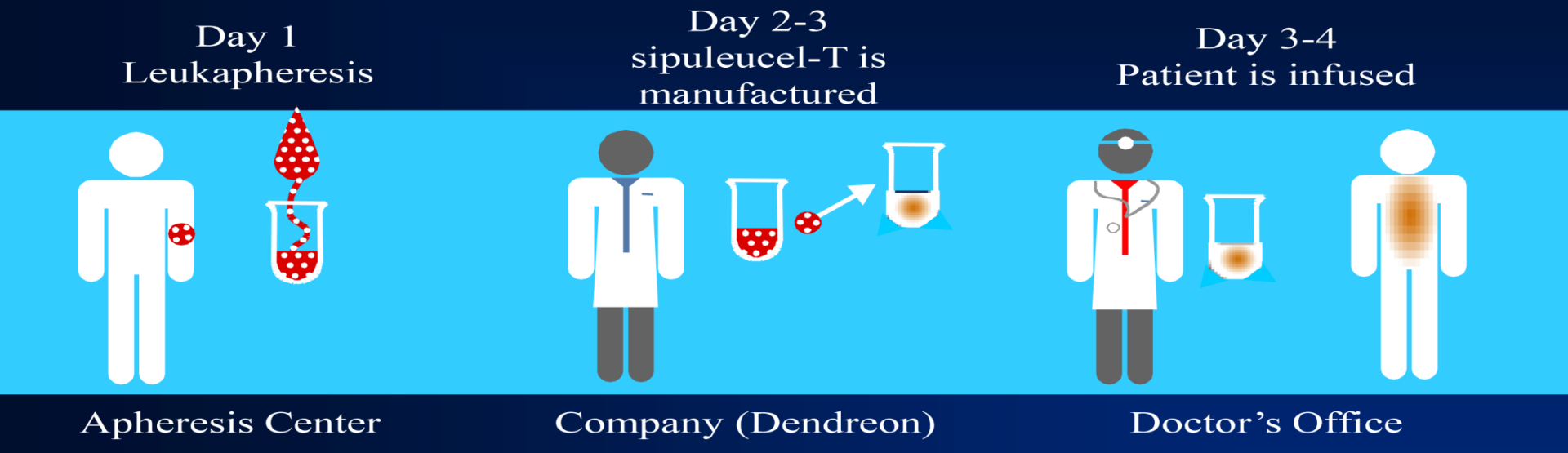
- No clear data for sequencing treatment in metastatic castration resistant prostate cancer (*mCRPC*)
- Ongoing trials will evaluate this question further
- In the absence of data I will provide ***my opinion*** on treatment selection
- Treatment decisions should be made with understanding of the following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

Prostate cancer menu

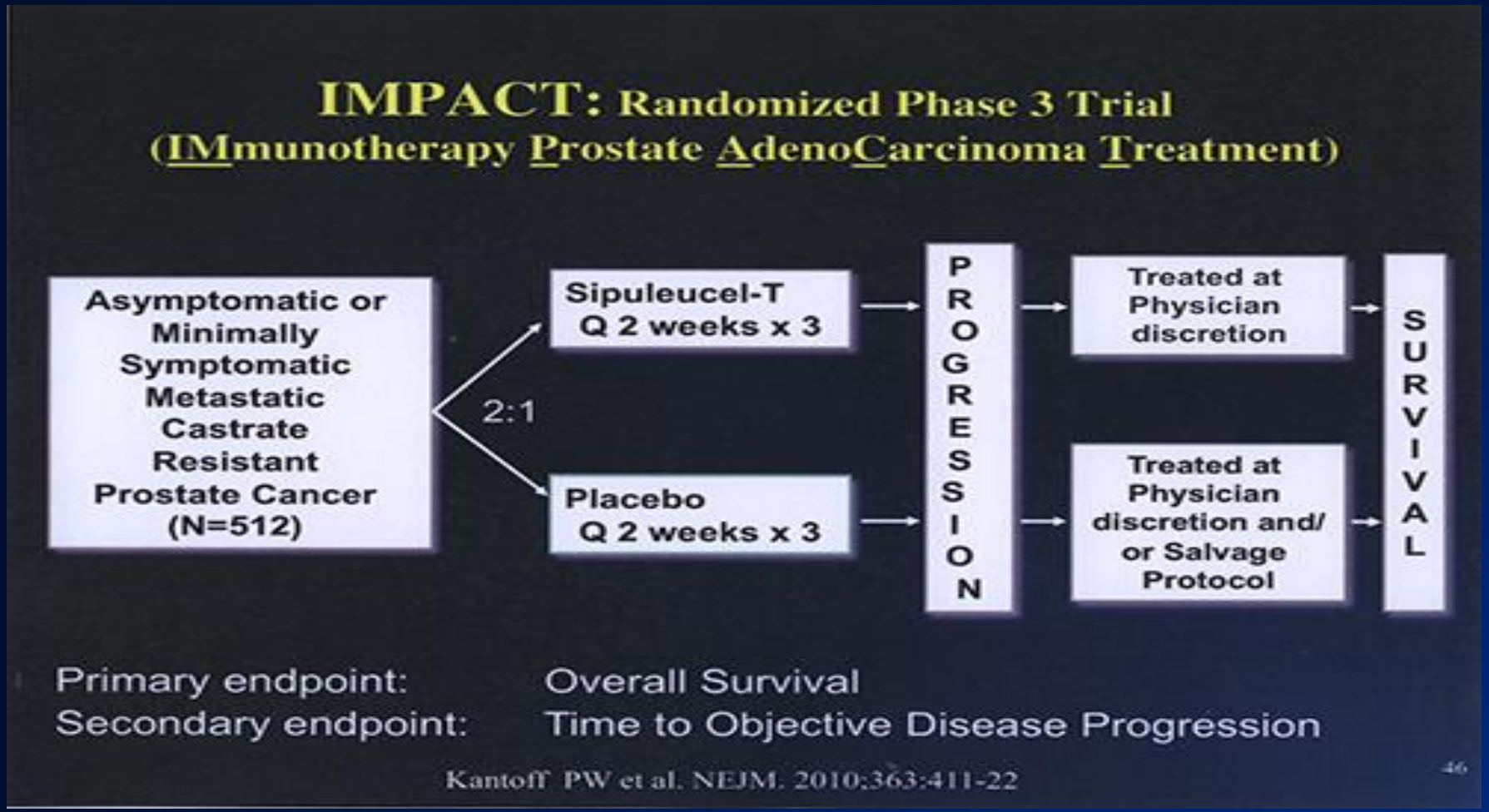
Prostate cancer appetizer

Therapeutic Cancer Vaccine: Sipuleucel-T

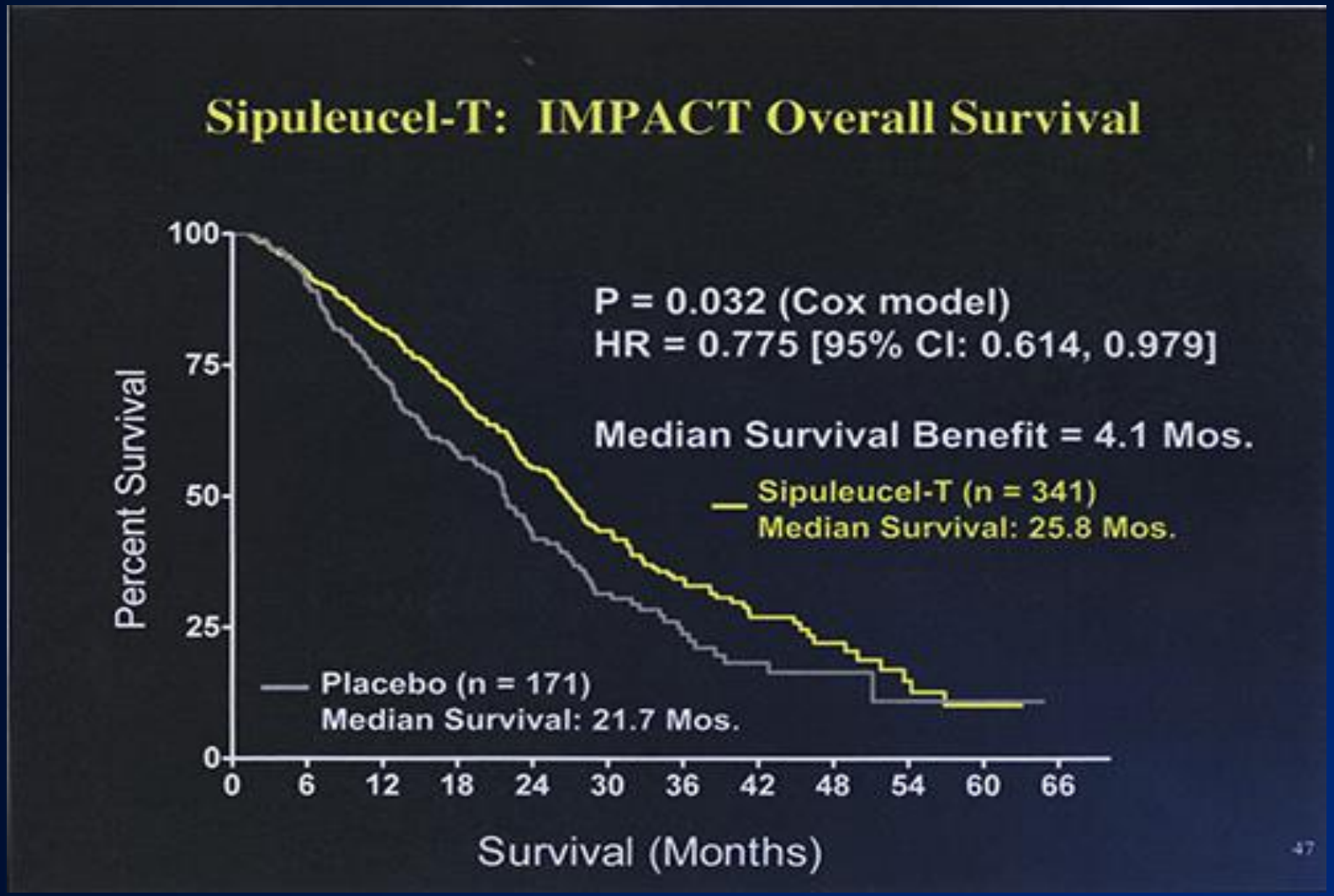
Therapeutic Cancer Vaccine: Sipuleucel-T



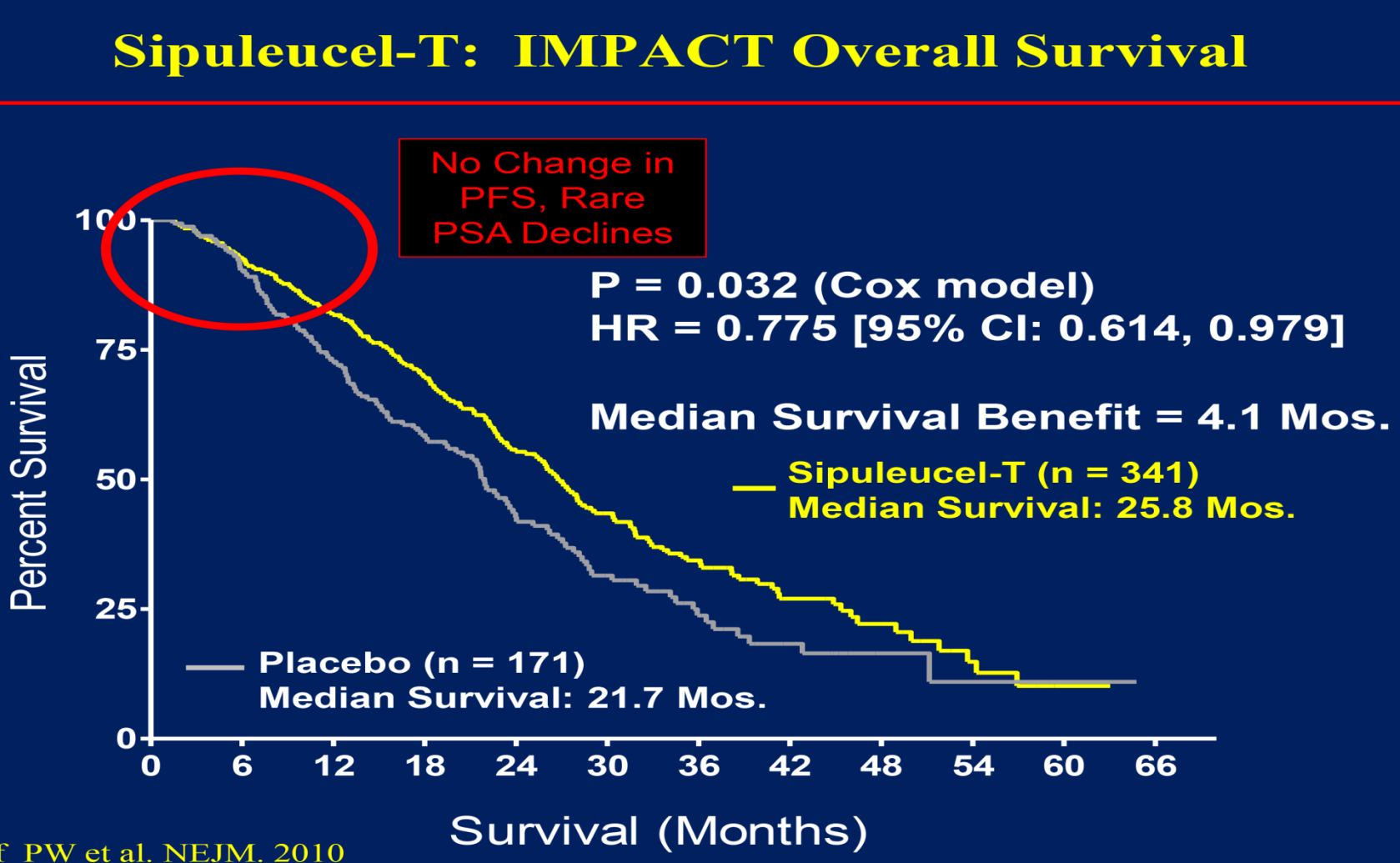
IMPACT: Randomized Phase 3 Trial



Sipuleucel-T: IMPACT Overall Survival



Sipuleucel-T



Kantoff PW et al. NEJM. 2010

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.

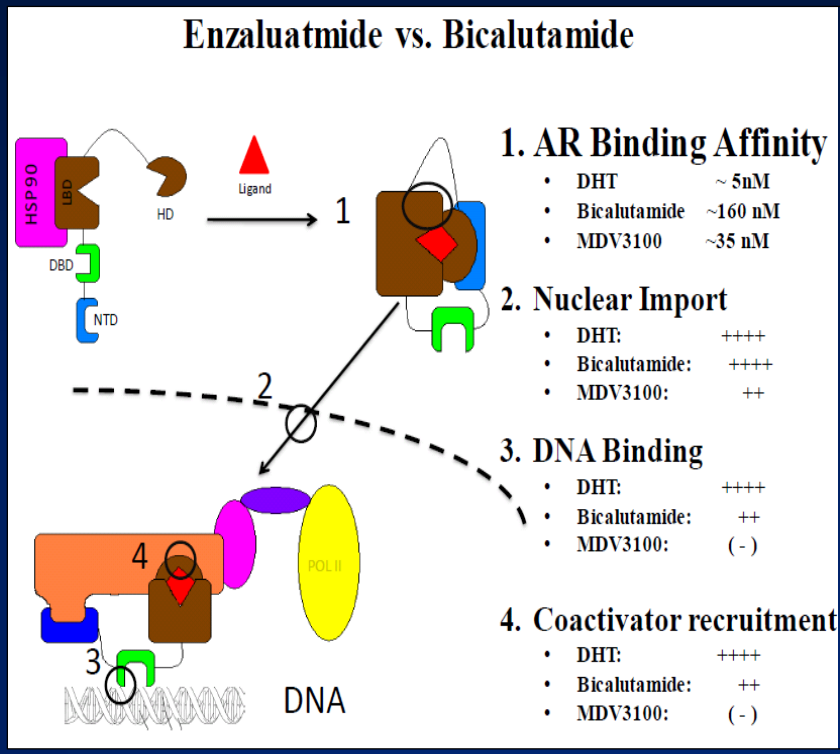
Prostate cancer first course

Enzalutamide

Enzalutamide

A small molecule AR antagonist

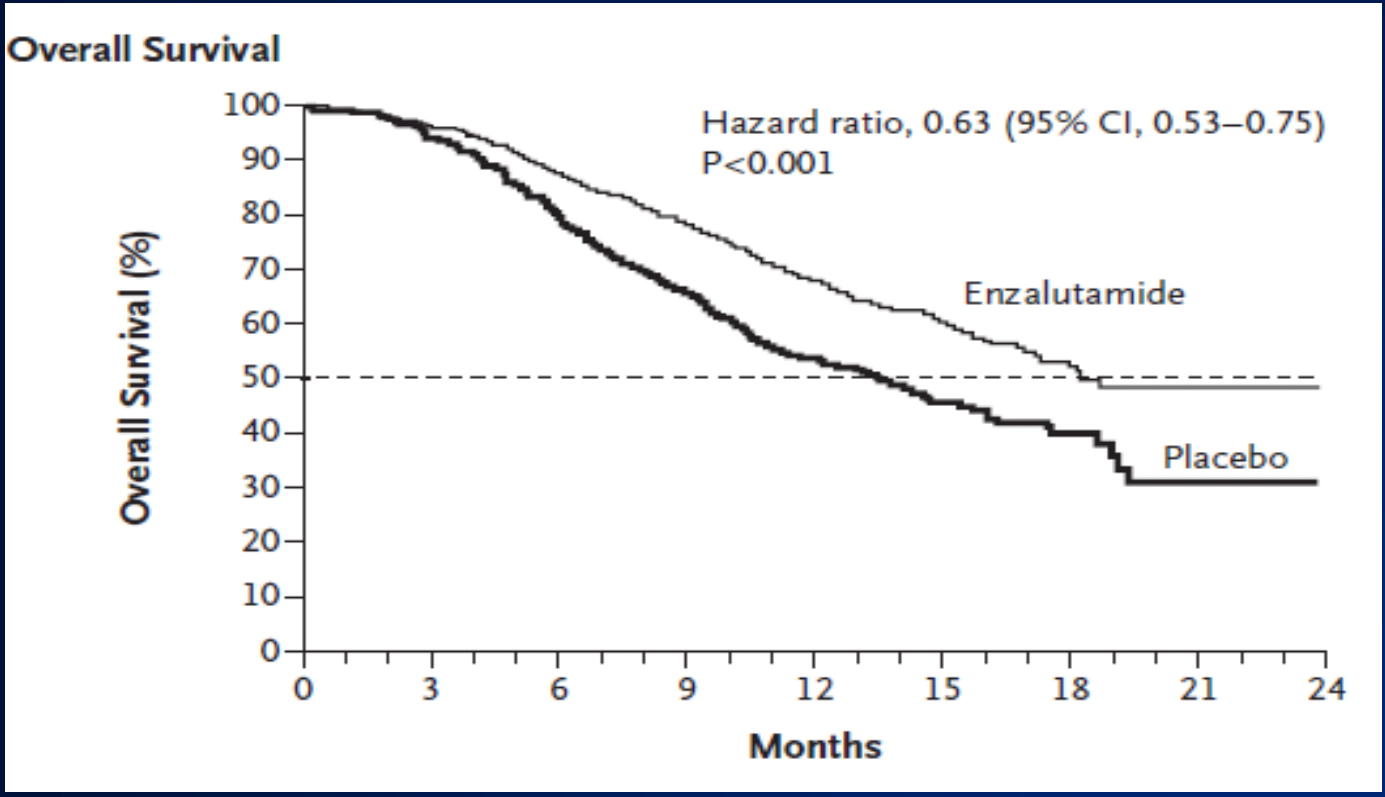
- Affinity 30 folds of bicalutamide
- Prevent nuclear translocation
- Prevents co-activator recruitment



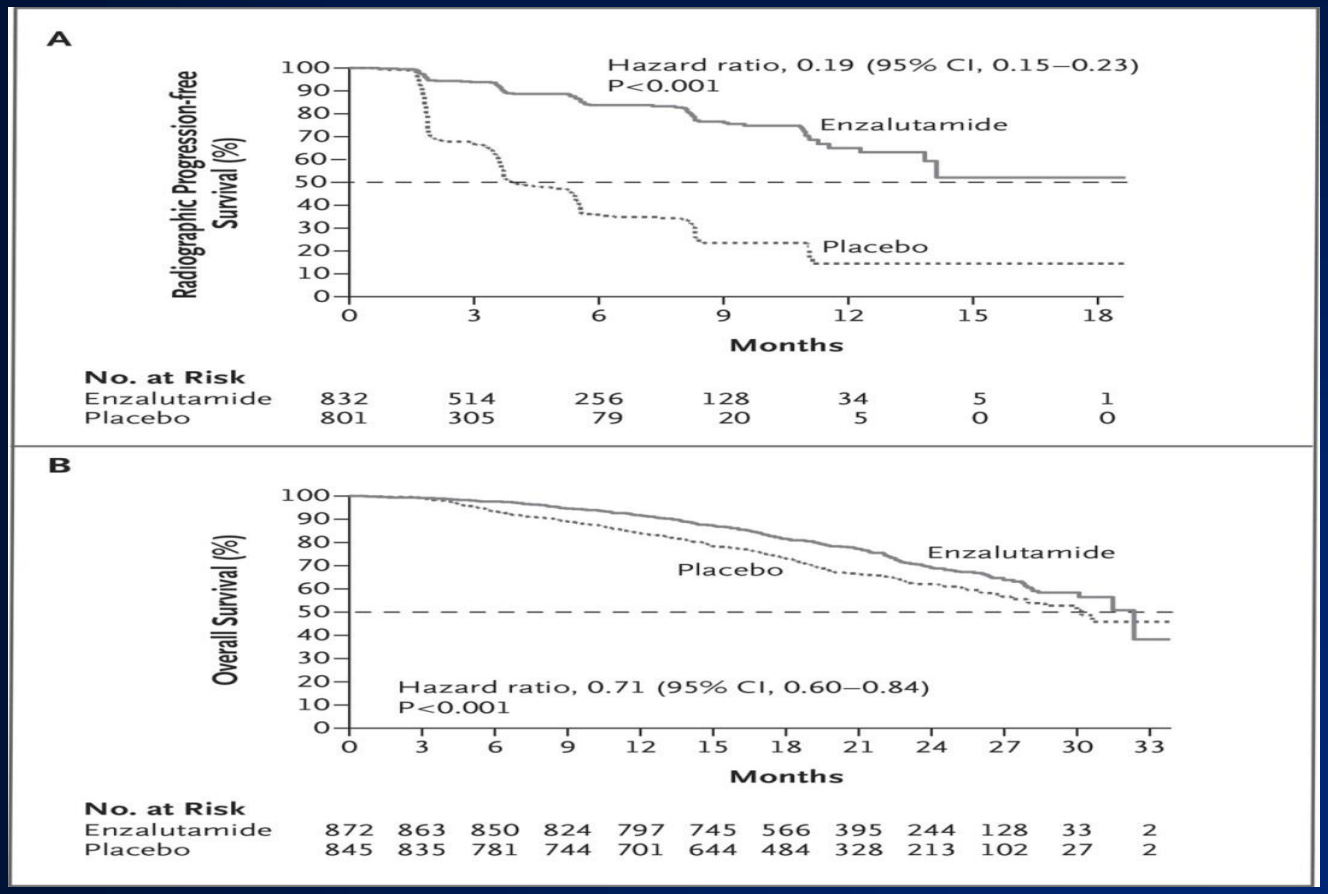
AFFIRM

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%)

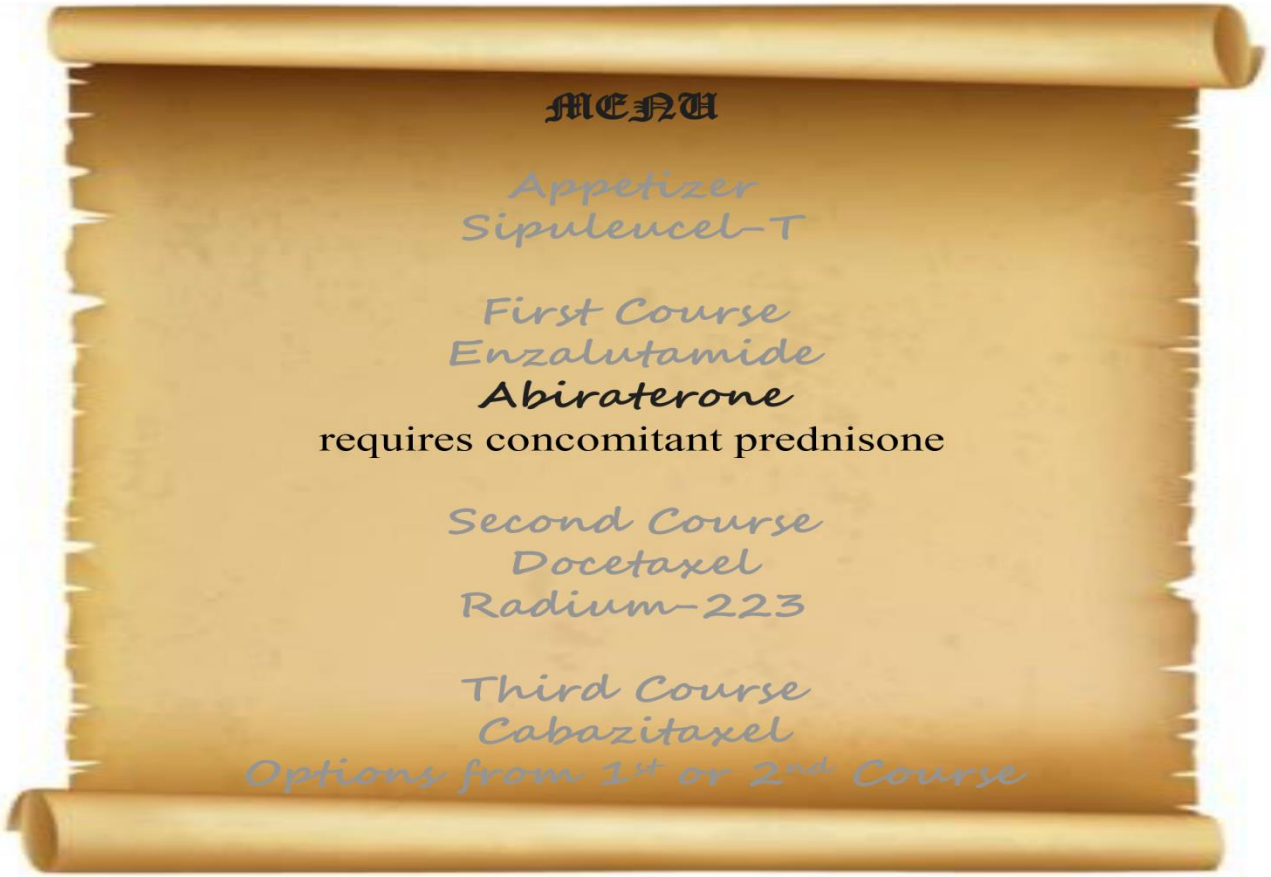
Gastrointestinal: Diarrhea (22%)

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

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

Respiratory: Upper respiratory tract infection (11%)

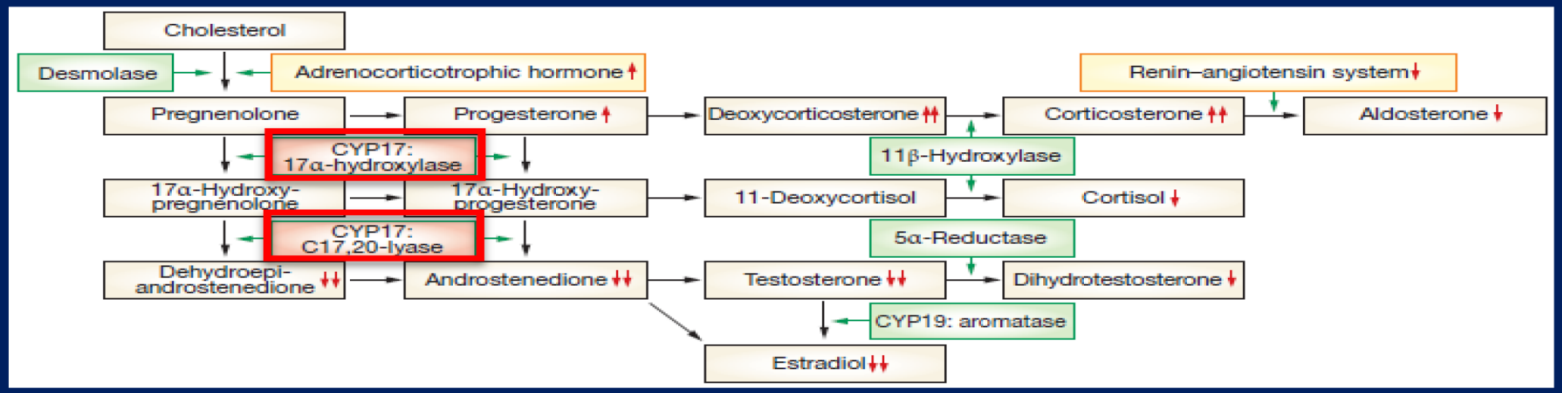
Abiraterone



Abiraterone rationale

Rationale for Abiraterone in CRPC

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

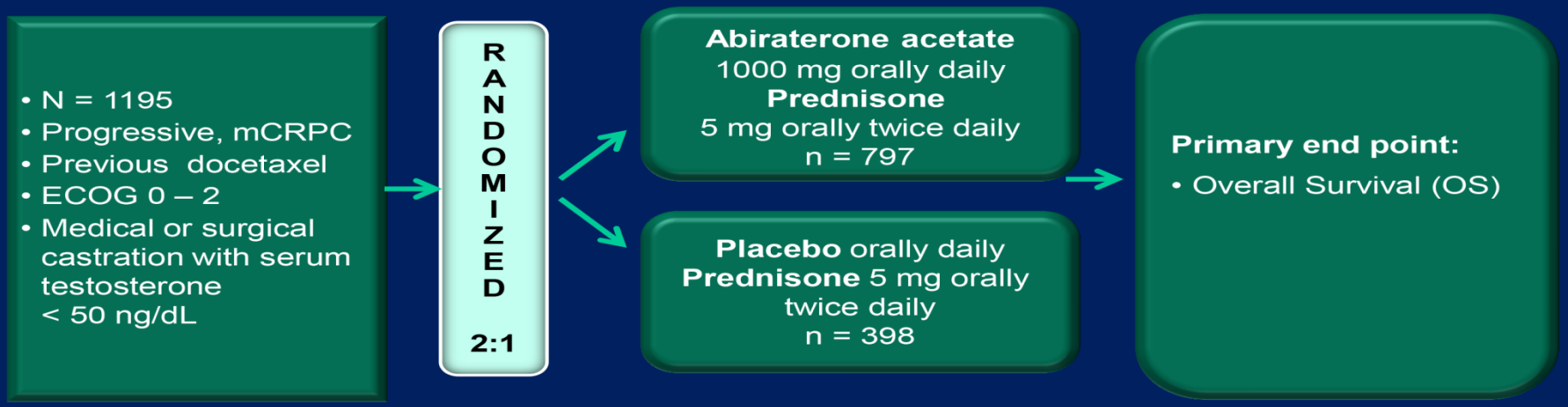


- Blocks androgen synthesis by the adrenal glands, testes and within the prostate tumor tissue

Reid et al. Nat Clin Pract Urol. 2008

Abiraterone study

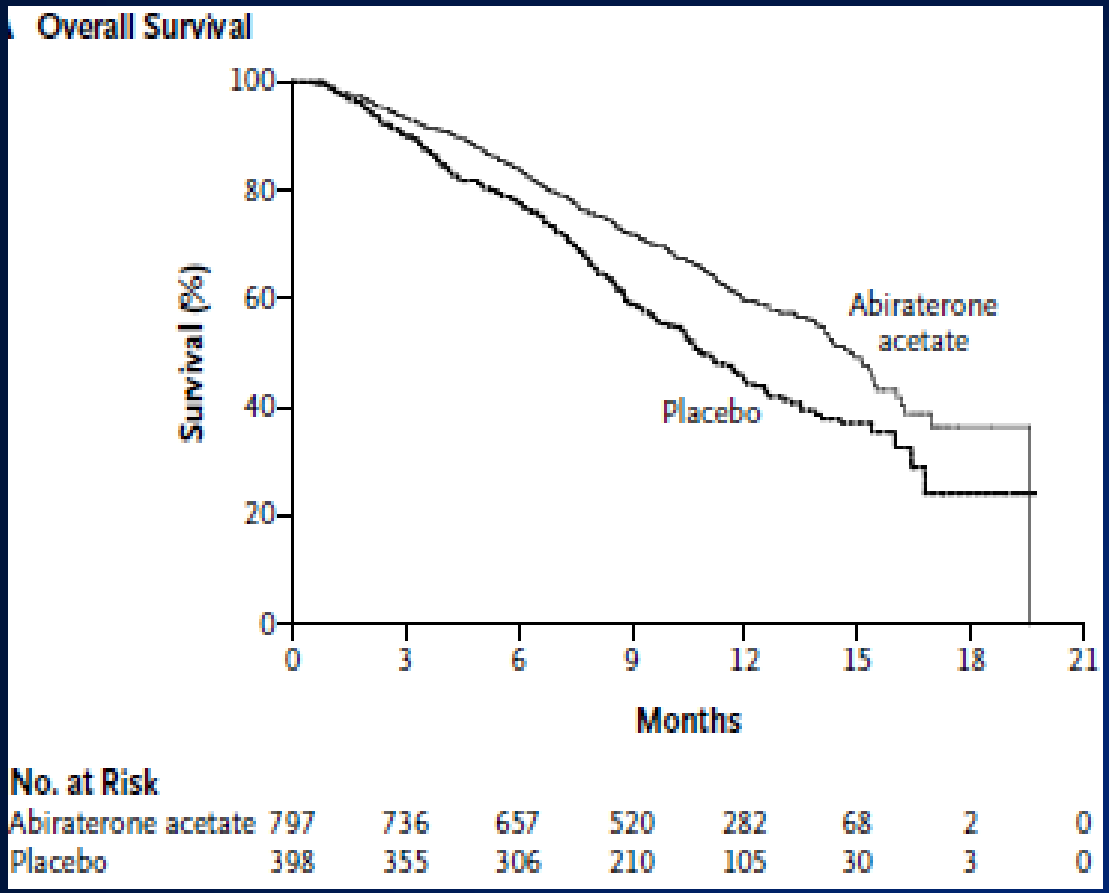
Abiraterone: COU-AA-301 Study Design



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

De Bono J, et al. NEJM 2011

Abiraterone: COU-AA-301 Trial



Abiraterone trial

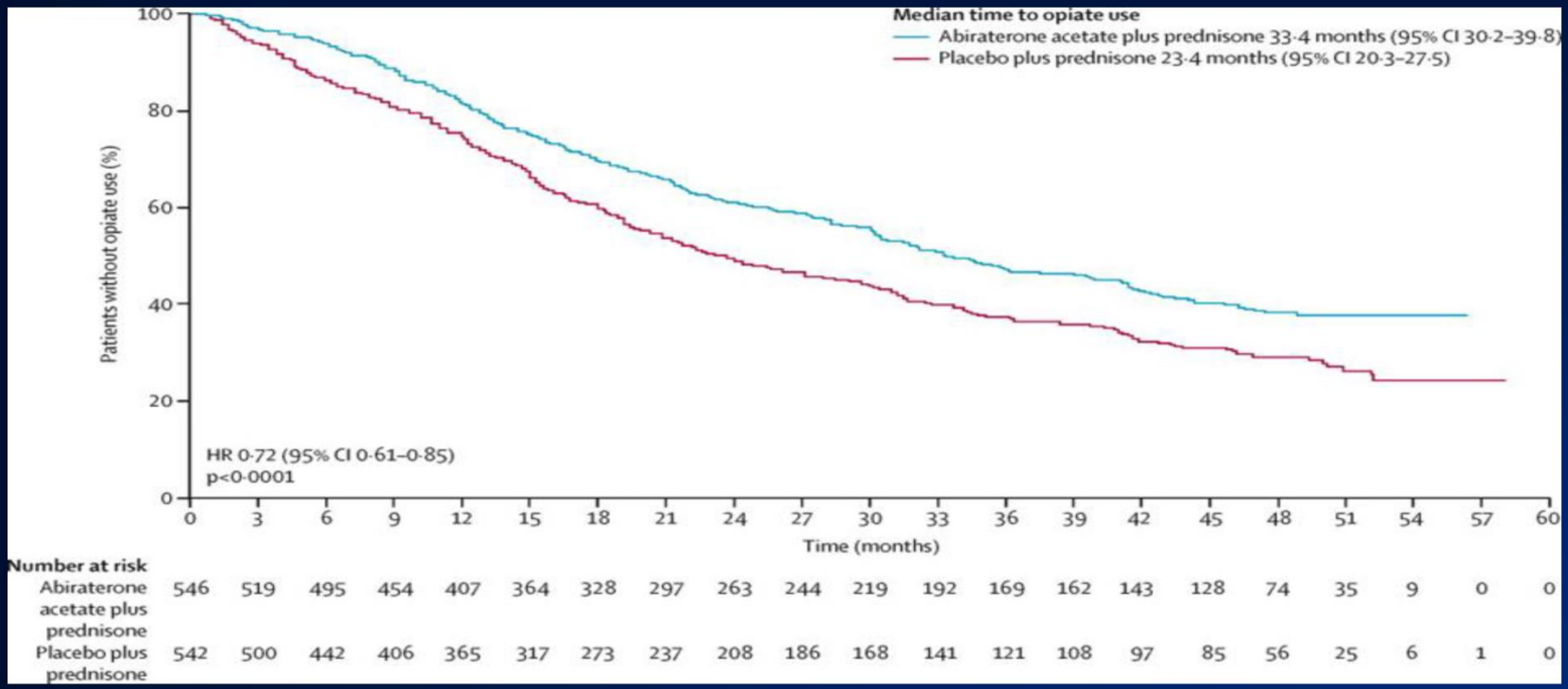
Abiraterone: COU-AA-301 Trial

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%)

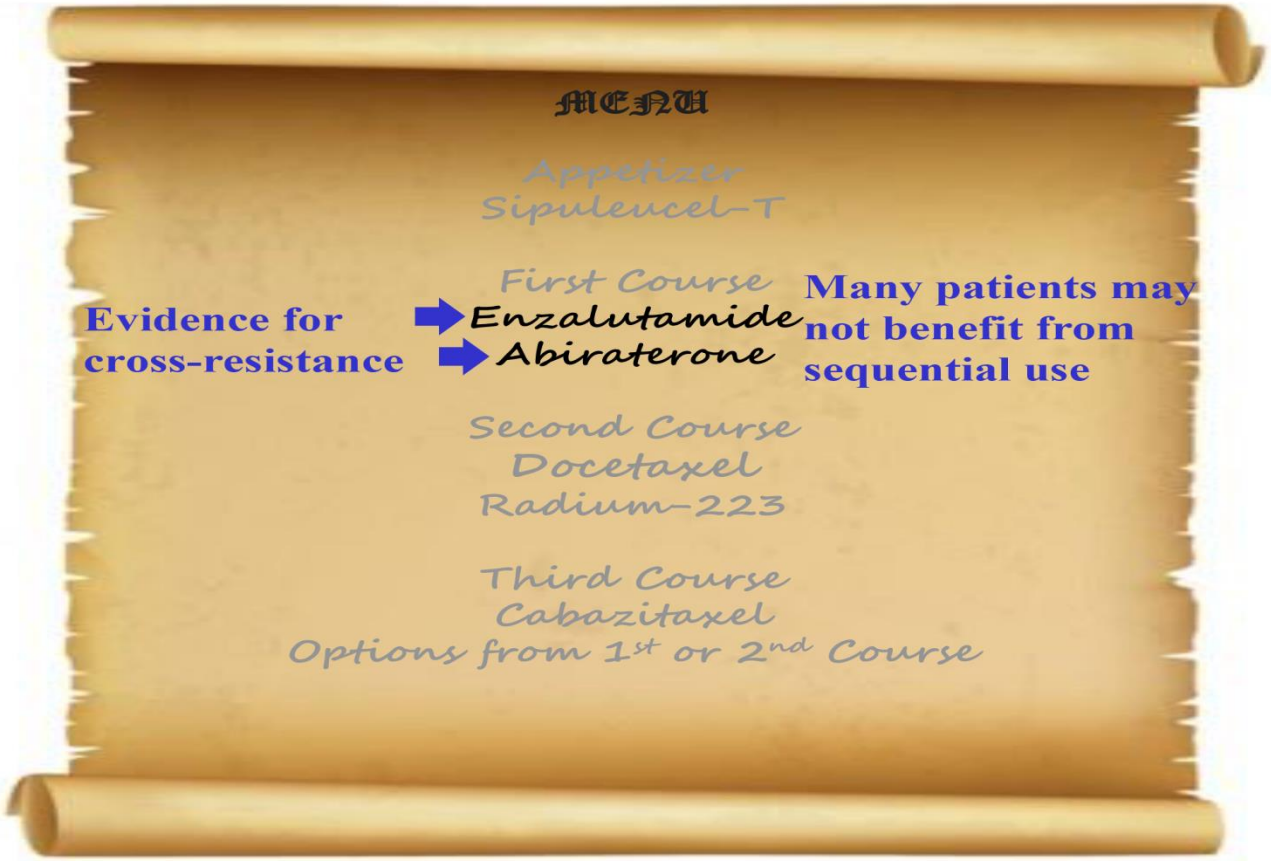
Hematologic: Lymphocytopenia (38%; grades 3/4: 9%)

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%)

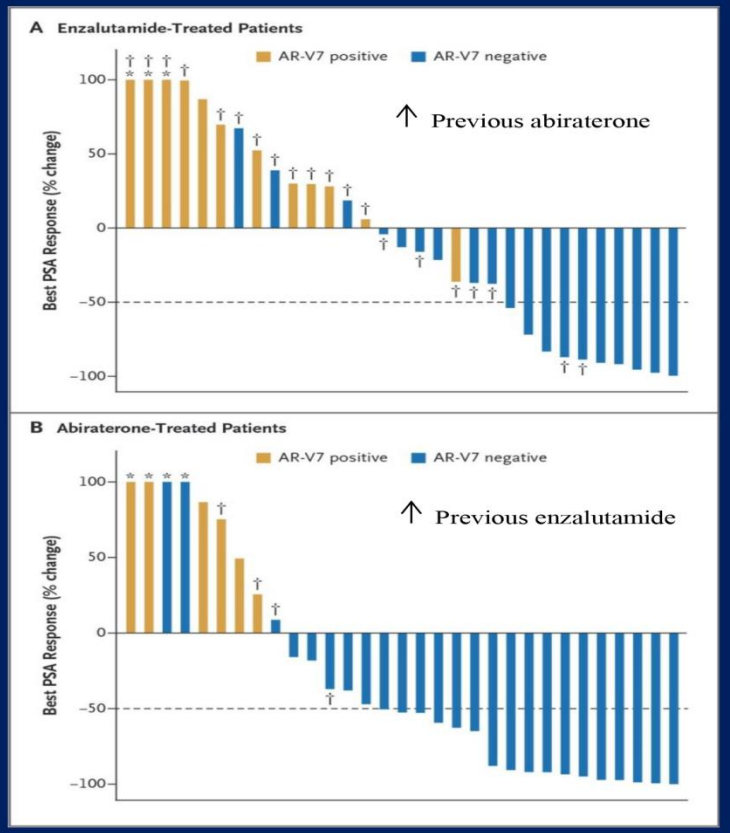
Cross resistance



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

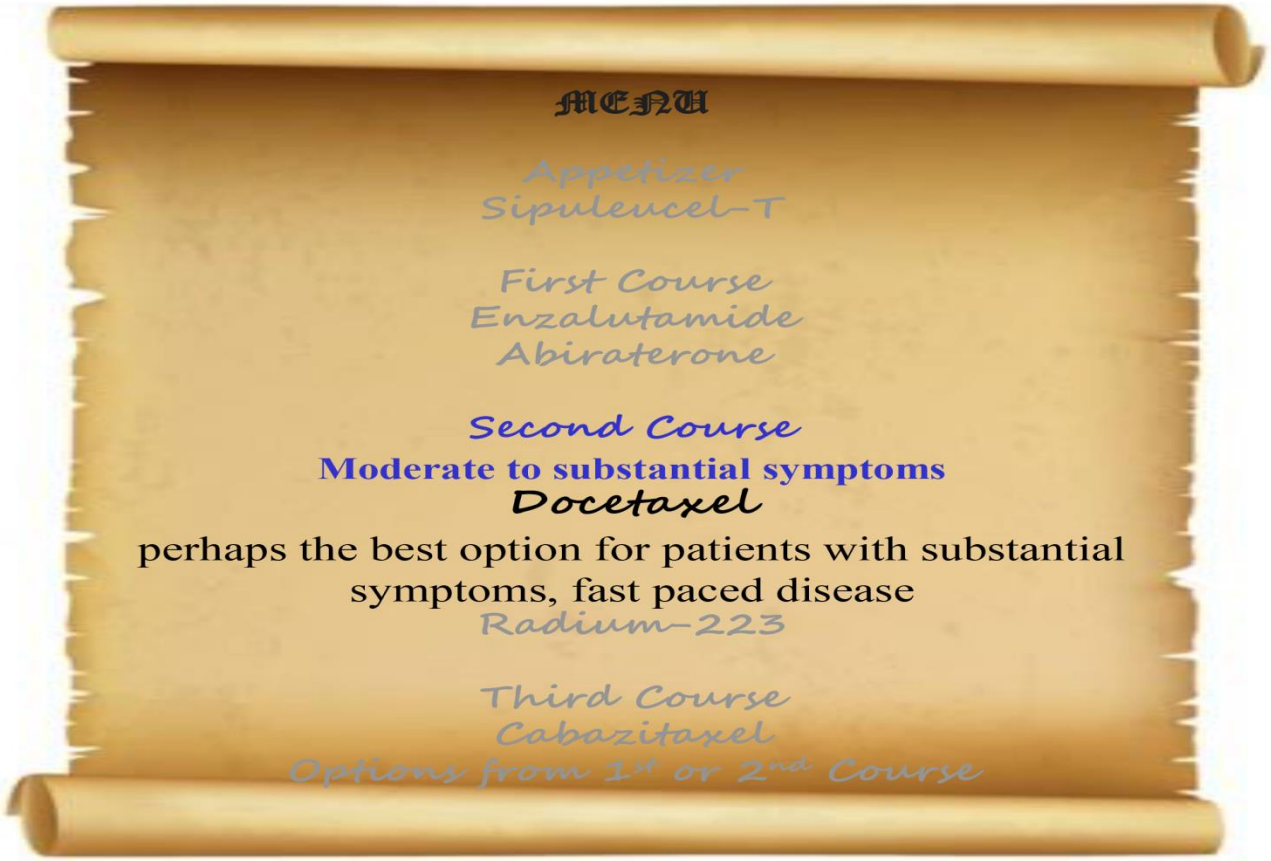


Antonarakis ES et al. NEJM, 2014.

Docetaxel


MENU
Appetizer
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



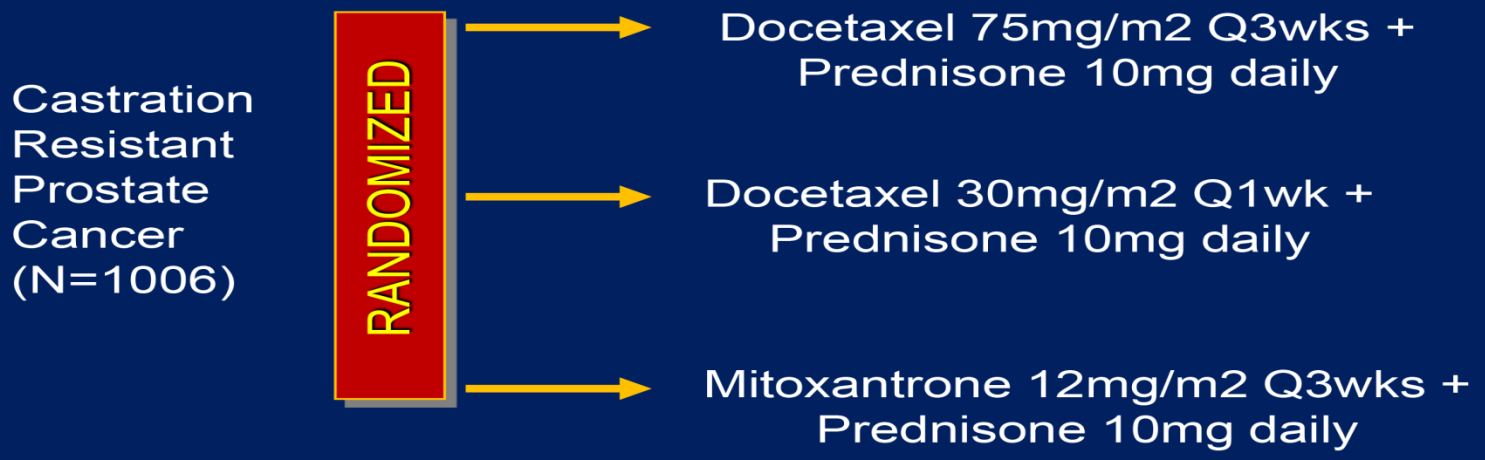
Docetaxel

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*

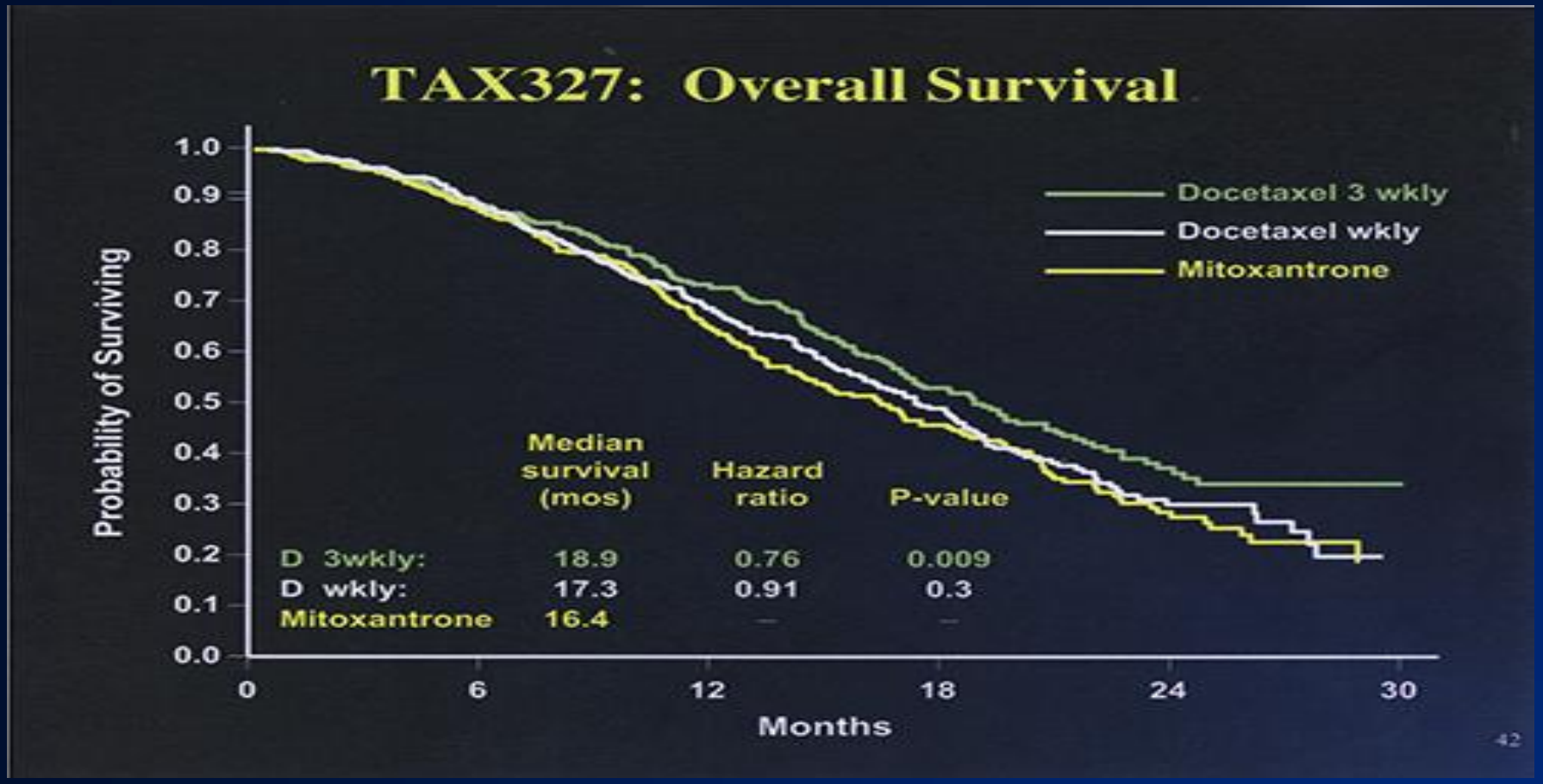
Phase III study

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%)

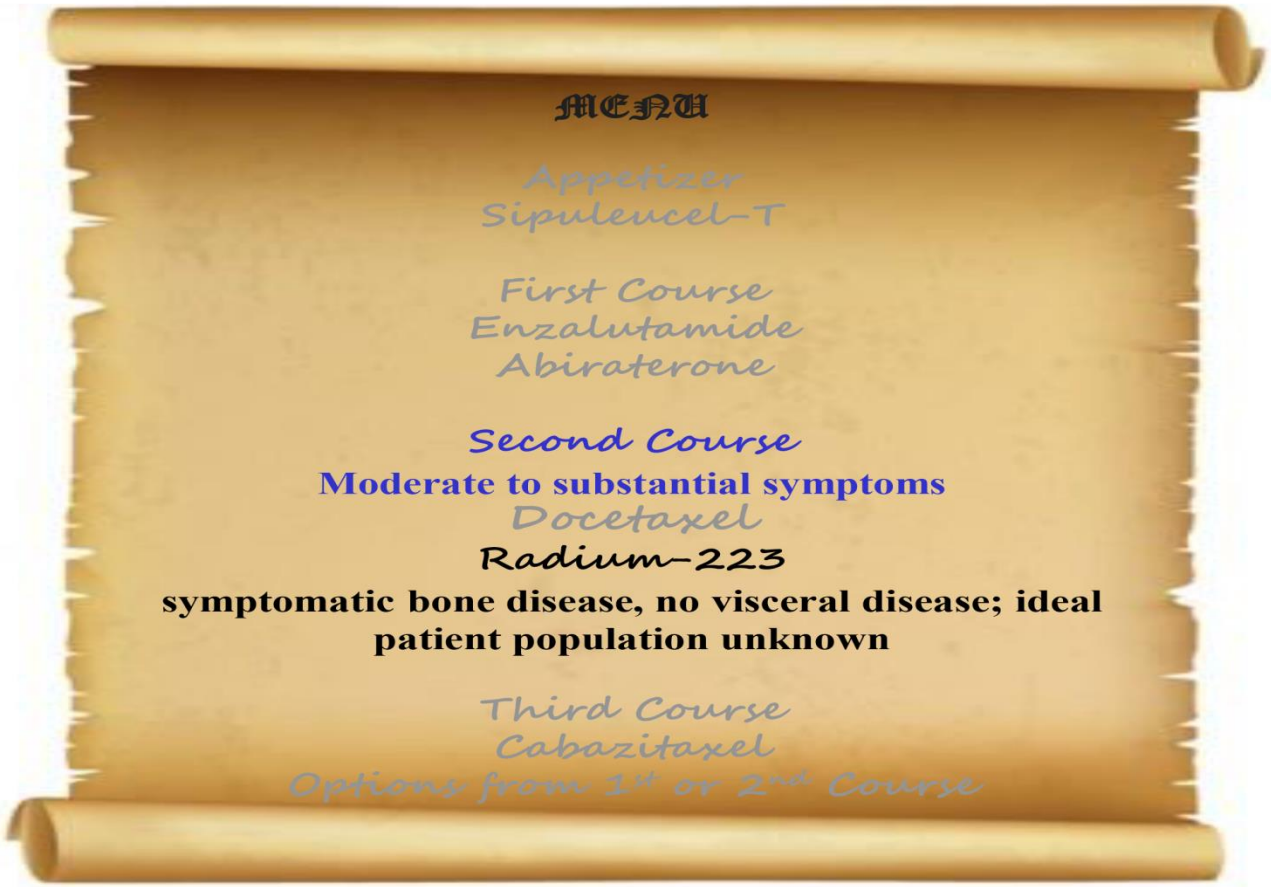
Hypersensitivity: Hypersensitivity (1% to 21%; with premedication 15%)

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%)

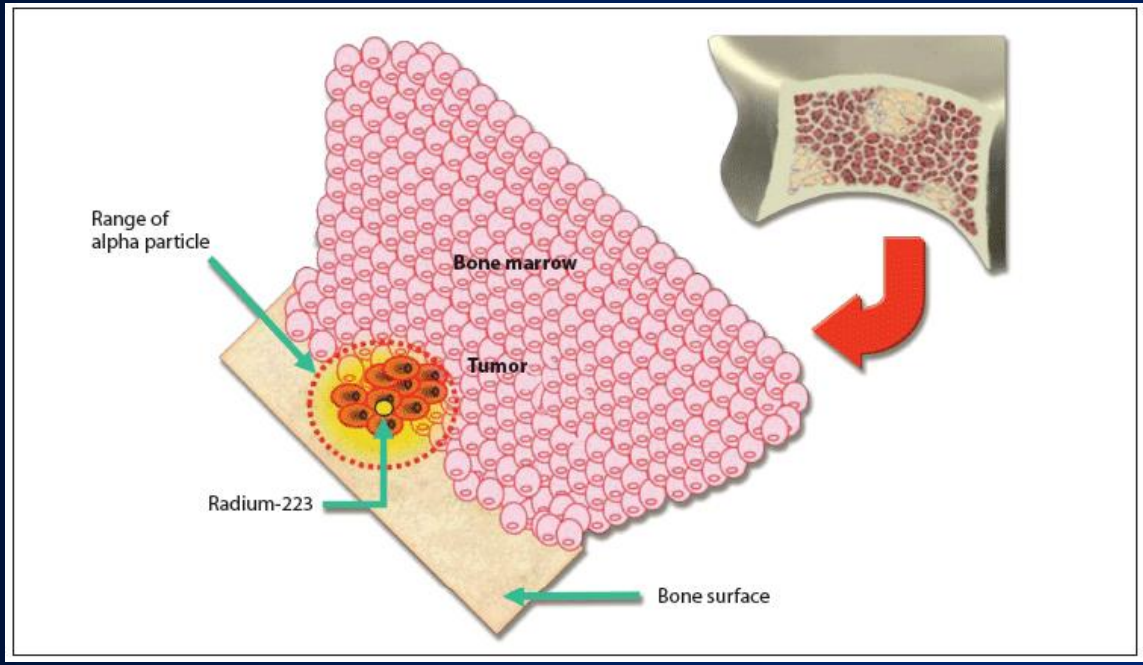
Radium


MENU
Appetizer
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
Options from 1st or 2nd Course

Radium-223 (Alpharadin)

Bone –targeting radiopharmaceutical

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

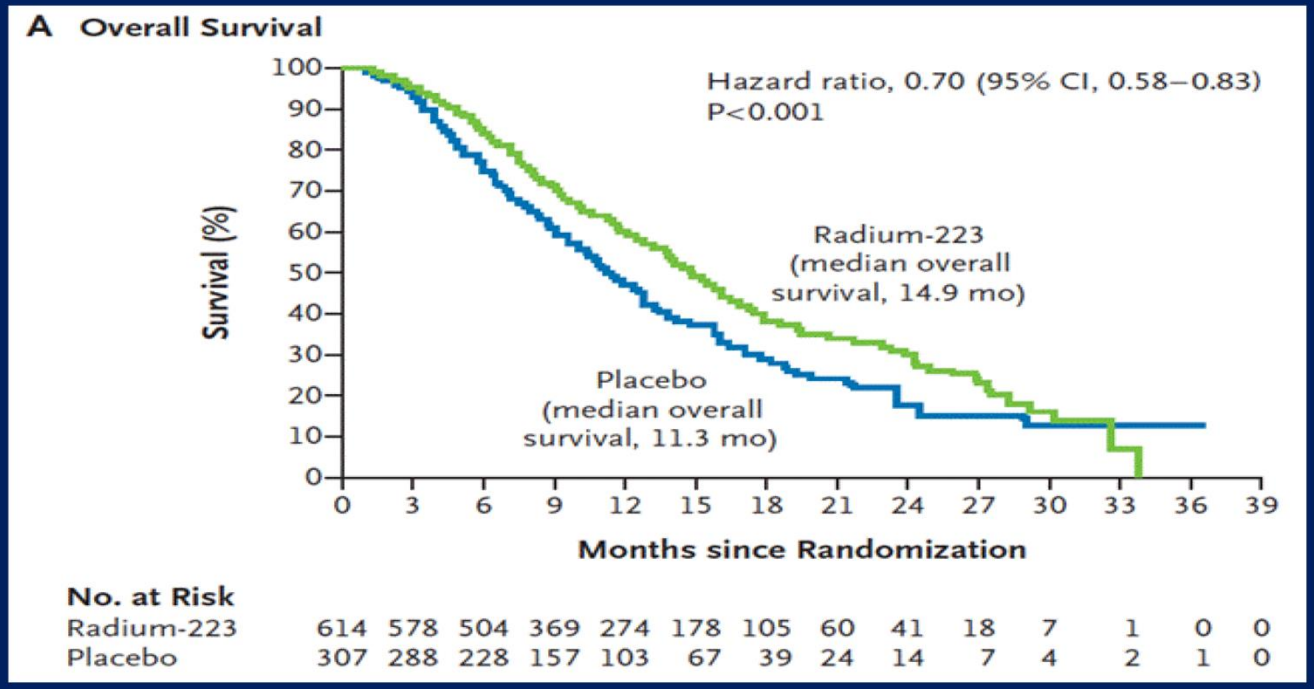


Radium trial

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

Phase III study of Radium-223

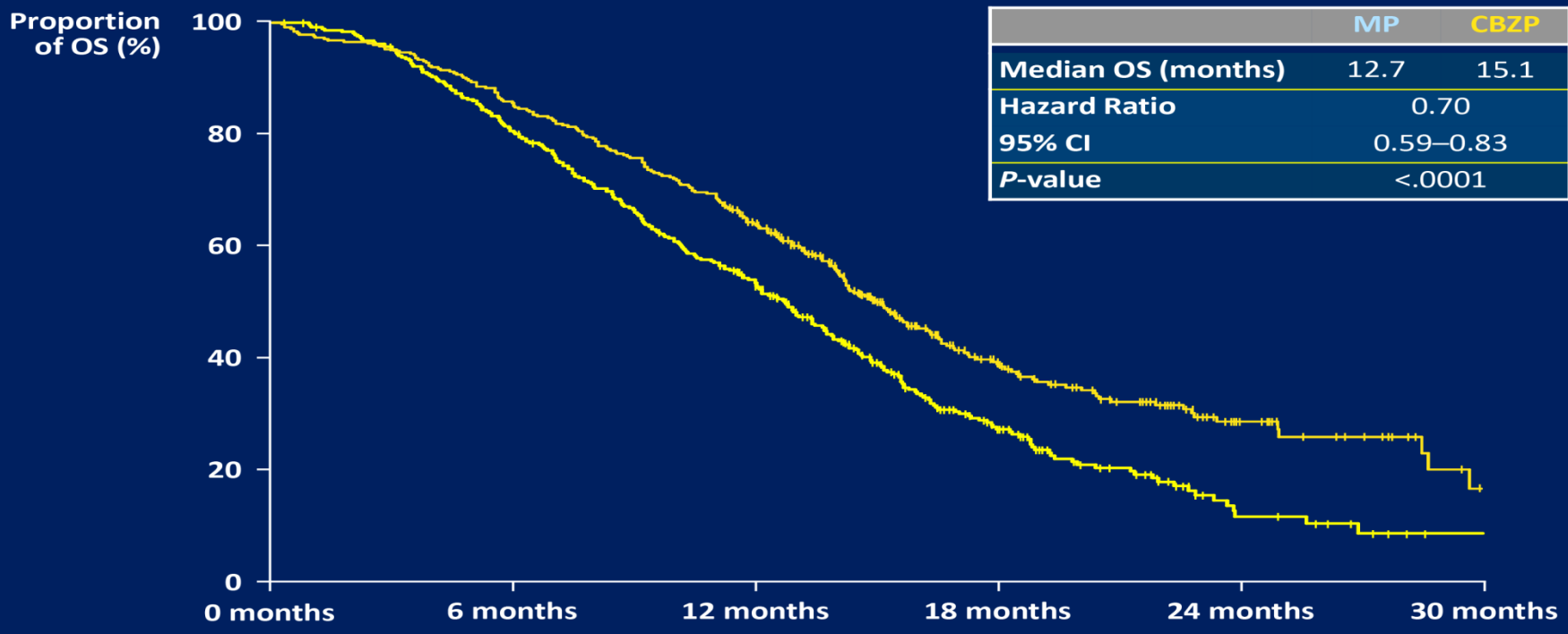
ALSYMPCA: Randomized Phase III Study of Radium-223 vs. Placebo in mCRPC with bone metastases



Parker C. et al. NEJM, 2013.

Overall survival

TROPIC: Overall Survival



	MP	CBZP
Median OS (months)	12.7	15.1
Hazard Ratio	0.70	
95% CI	0.59–0.83	
P-value	<.0001	

Number at risk						
MP	377	300	188	67	11	1
CBZP	378	321	231	90	28	4

de Bono JS. et al. Lancet. 2010

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

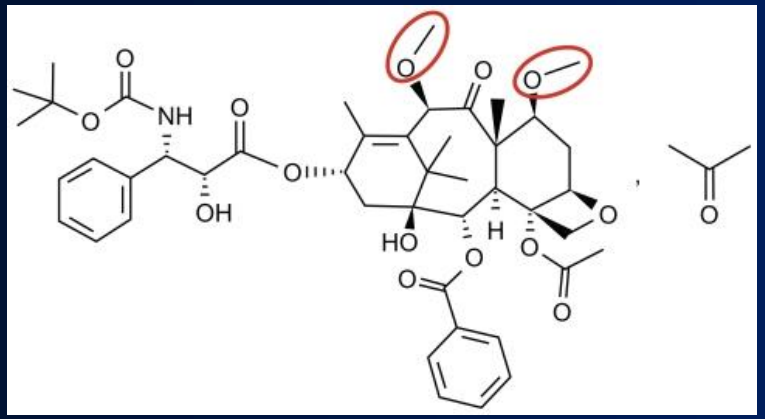
Cabazitaxel

Novel taxane active in docetaxel resistant cell lines

Less affinity for P-glycoprotein pump

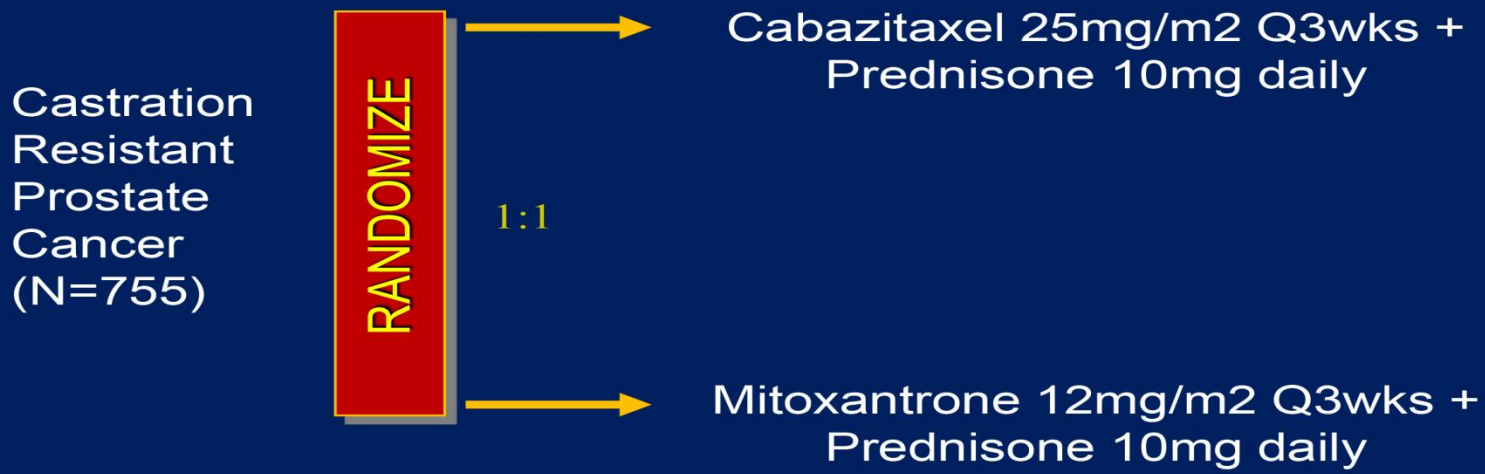
Methoxyl side chain instead of

hydroxyl groups found in docetaxel



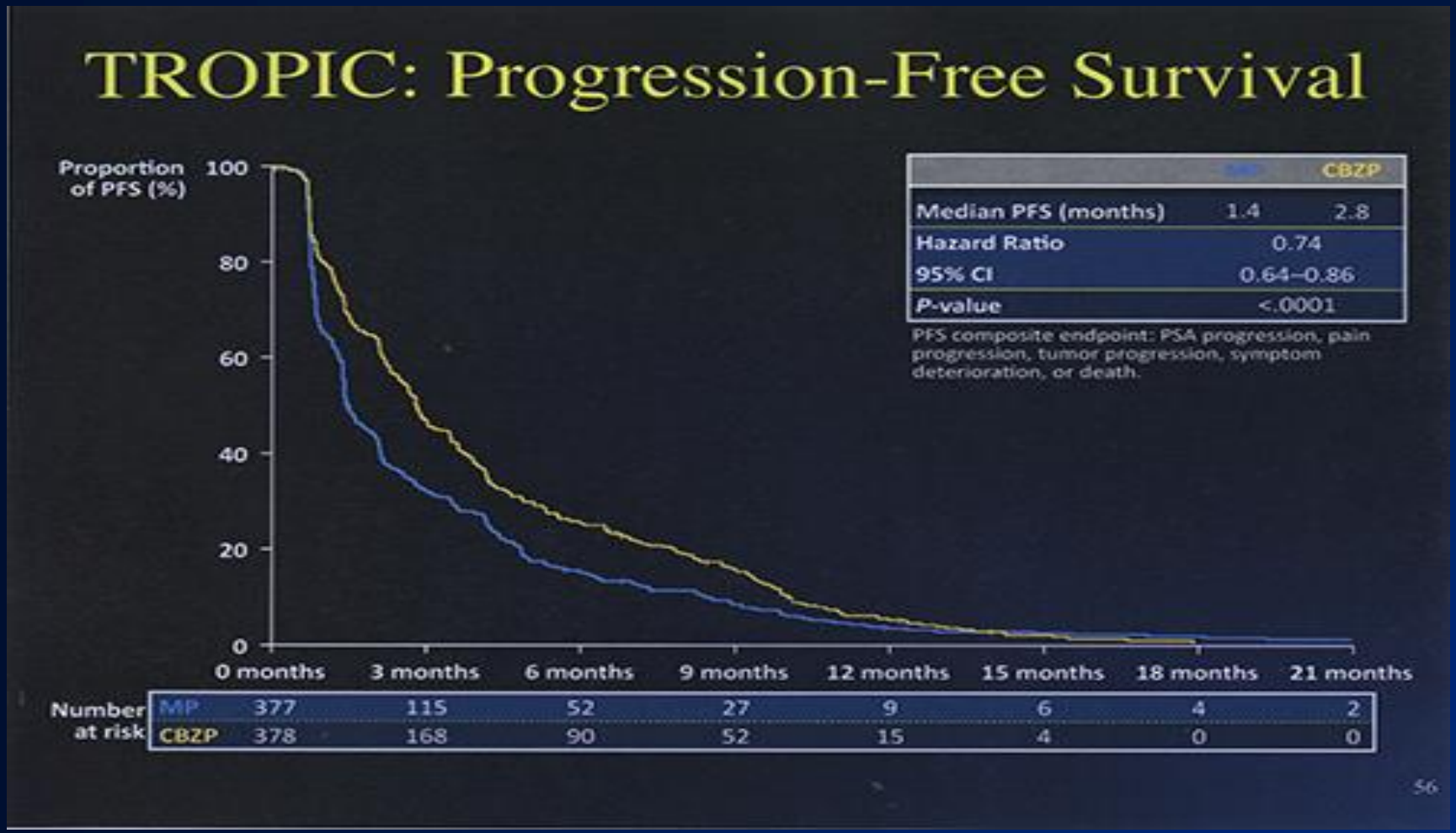
TROPIC protocol

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

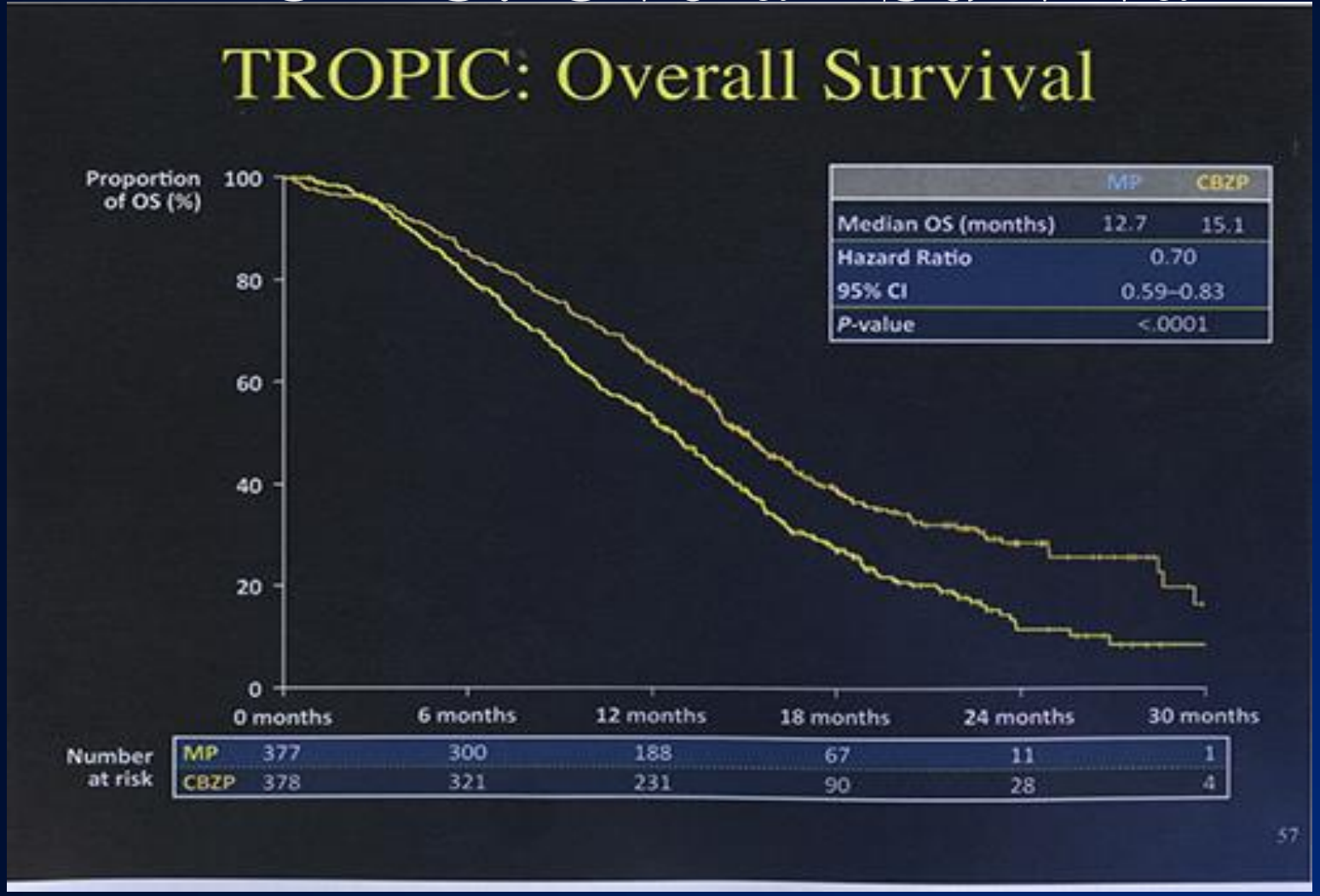


de Bono JS. et al. Lancet. 2010

TROPIC: Progression-Free Survival



TROPIC: Overall Survival



Cabazitaxel 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%)

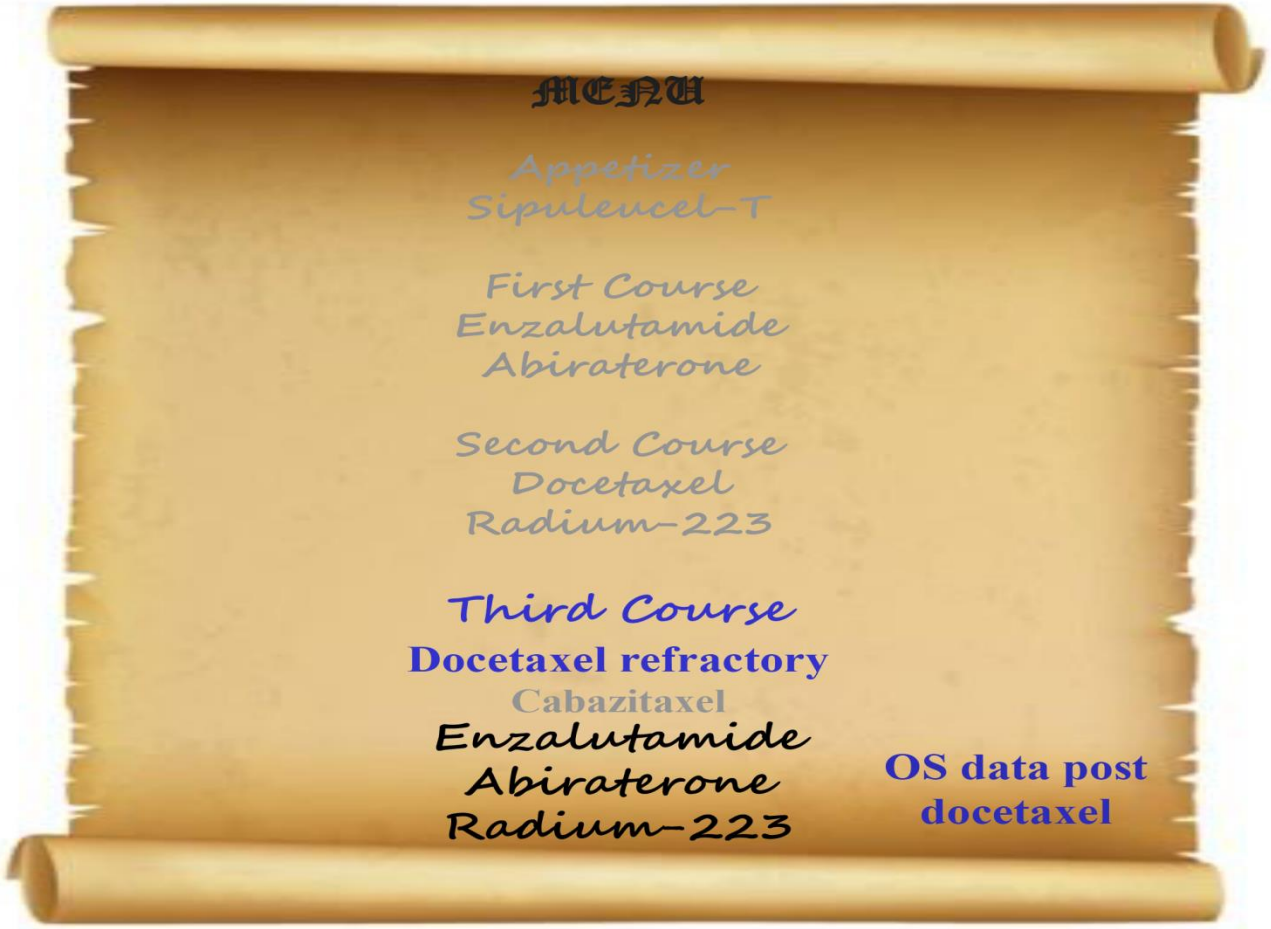
Cabazitaxel and ASCO

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

Third course



Complete menu

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

Cost of Treatments

Cost of Treatments

Table 3. Treatment Costs in Patients With CRPC for 30-Day Period (oral drugs) or One Infusion/Cycle (parenteral drugs)

Drug Name	Approval Date	Large Group Commercial Insurance Rate ($)*	Medicare Rate ($)*
Abiraterone acetate	2011	5,171.90	6,409.11
Bicalutamide	1995	Generic, 82; brand, 520	Generic, 28; brand, 527
Cabazitaxel†	2010	11,233.78	12,806.06
Degarelix	2008	445.53	536.75
Docetaxel†	1999	Brand (pregeneric), 3,006.19	Generic, 681.67
Enzalutamide	2012	‡	7,906.34
Flutamide	1989	79.65	125.80
Goserelin acetate	1995	596.00	210.32
Ketoconazole	1999	66.52	19.22
Leuprolide acetate	1998	356.00	202.84
Mitoxantrone†	1987	615.63	203.96
Nilutamide	1996	464.13	4,201.38
Prednisone	1974	3.75	6.50
Radium-223	2013	12,455.00‡	12,455.00‡
Sipuleucel-T§	2010	40,670.42	34,672.58

Bash et al, CJ et al. JCO. 2014

Cost of treatments

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Ketoconazole	1999	66.52	19.22
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Prednisone	1974	3.75	6.50
Radium-223	2013	12,455.00‡	12,455.00‡
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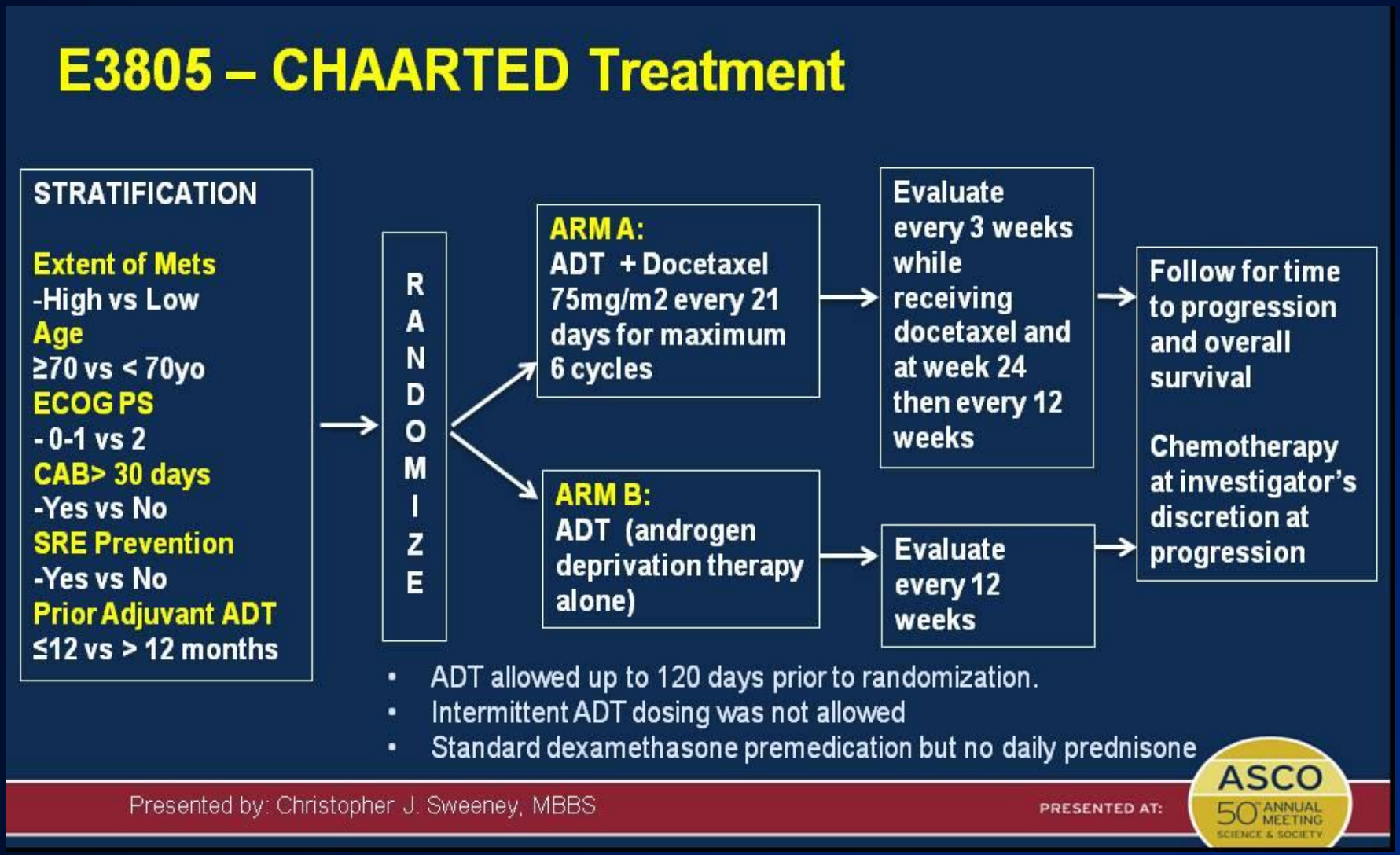
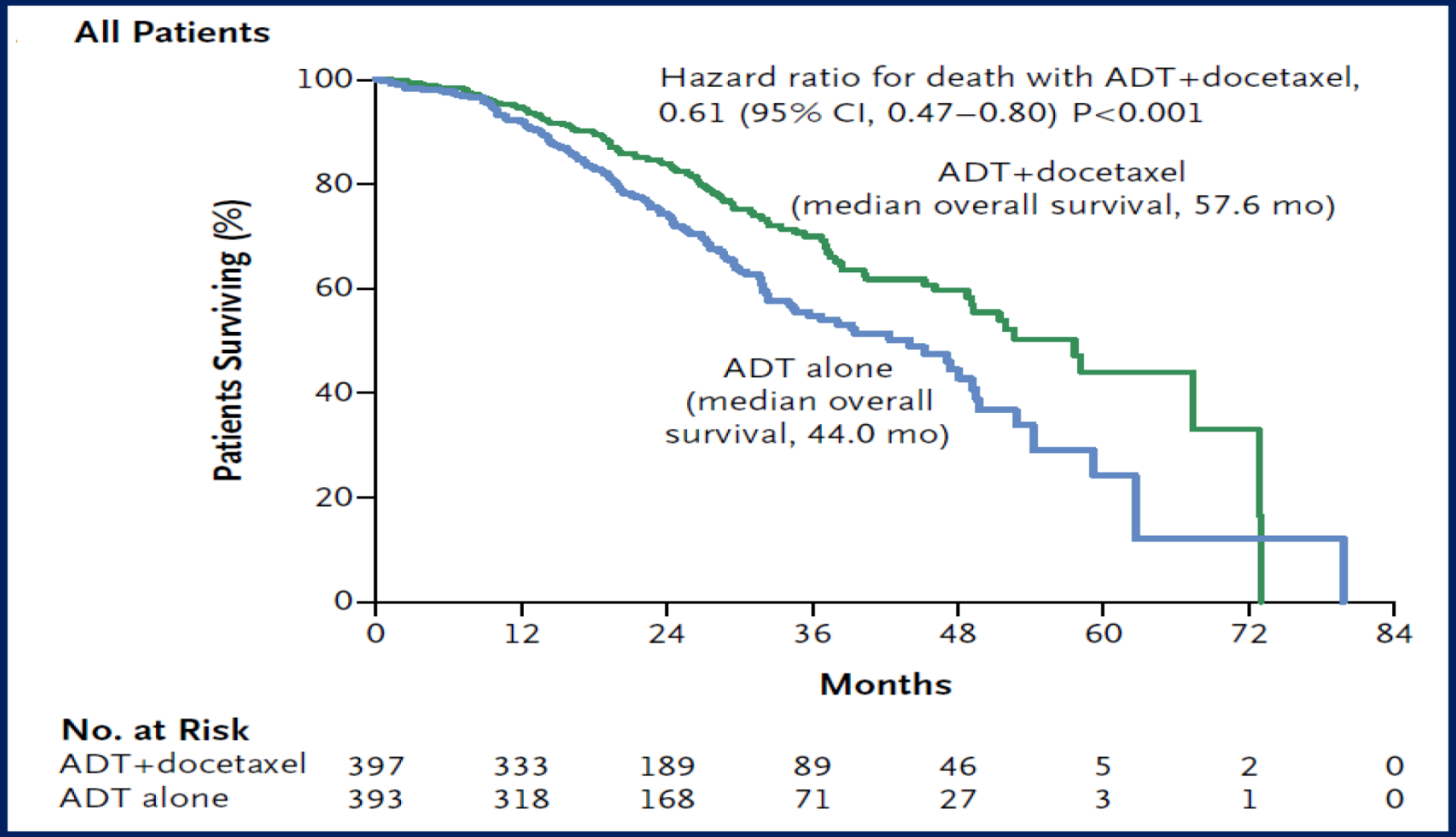
FDA-Approved for mCRPC

Bash et al, CJ et al. JCO. 2014

E3805-CHAARTED Treatment

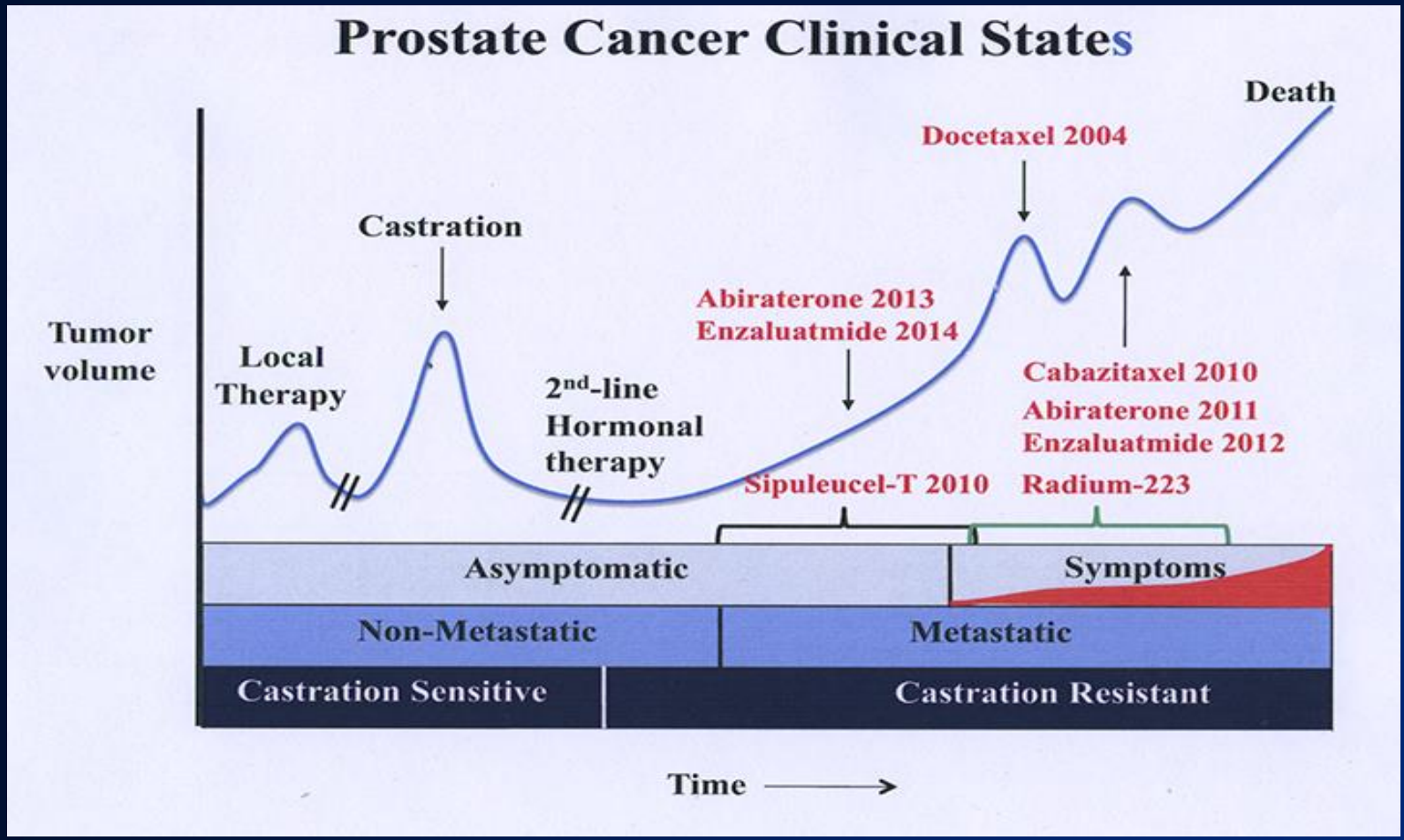


Survival curve



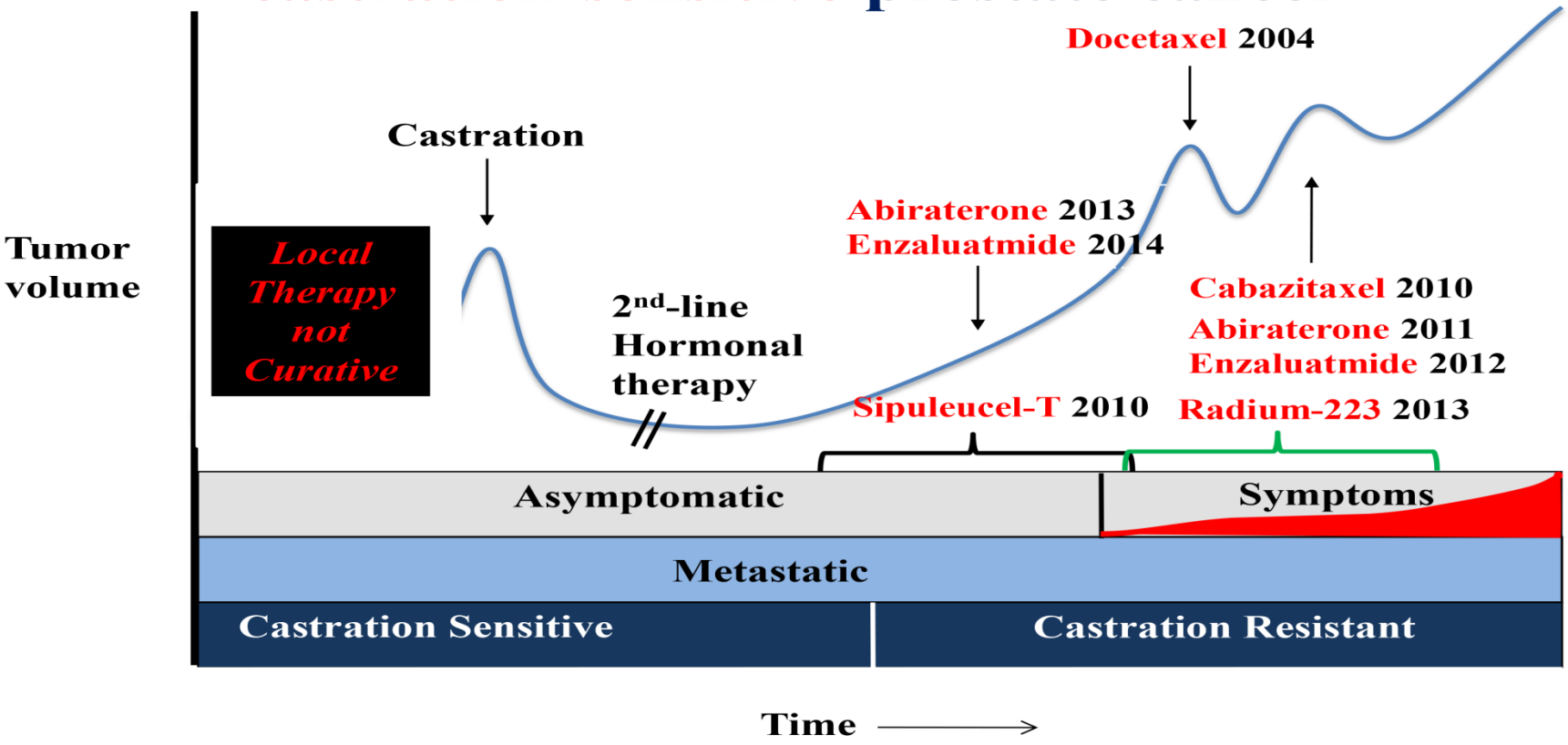
Sweeney, CJ et al. NEJM. 2015

Prostate Cancer Clinical States



Docetaxel

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



CHAARTED: Subgroup analysis

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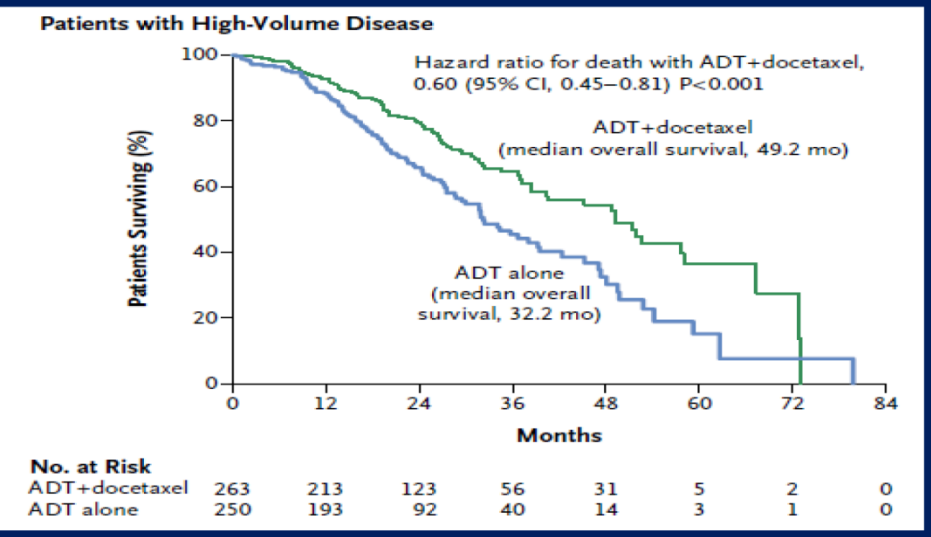
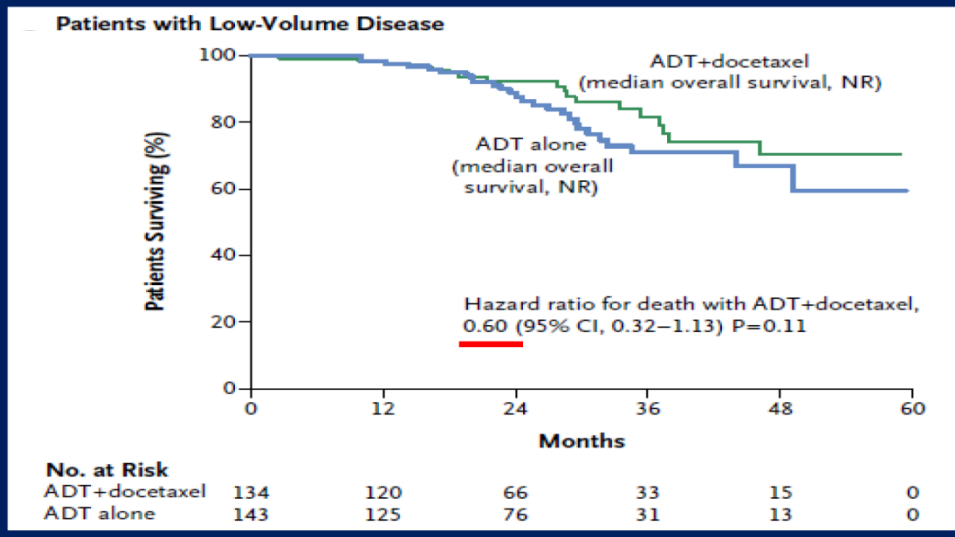
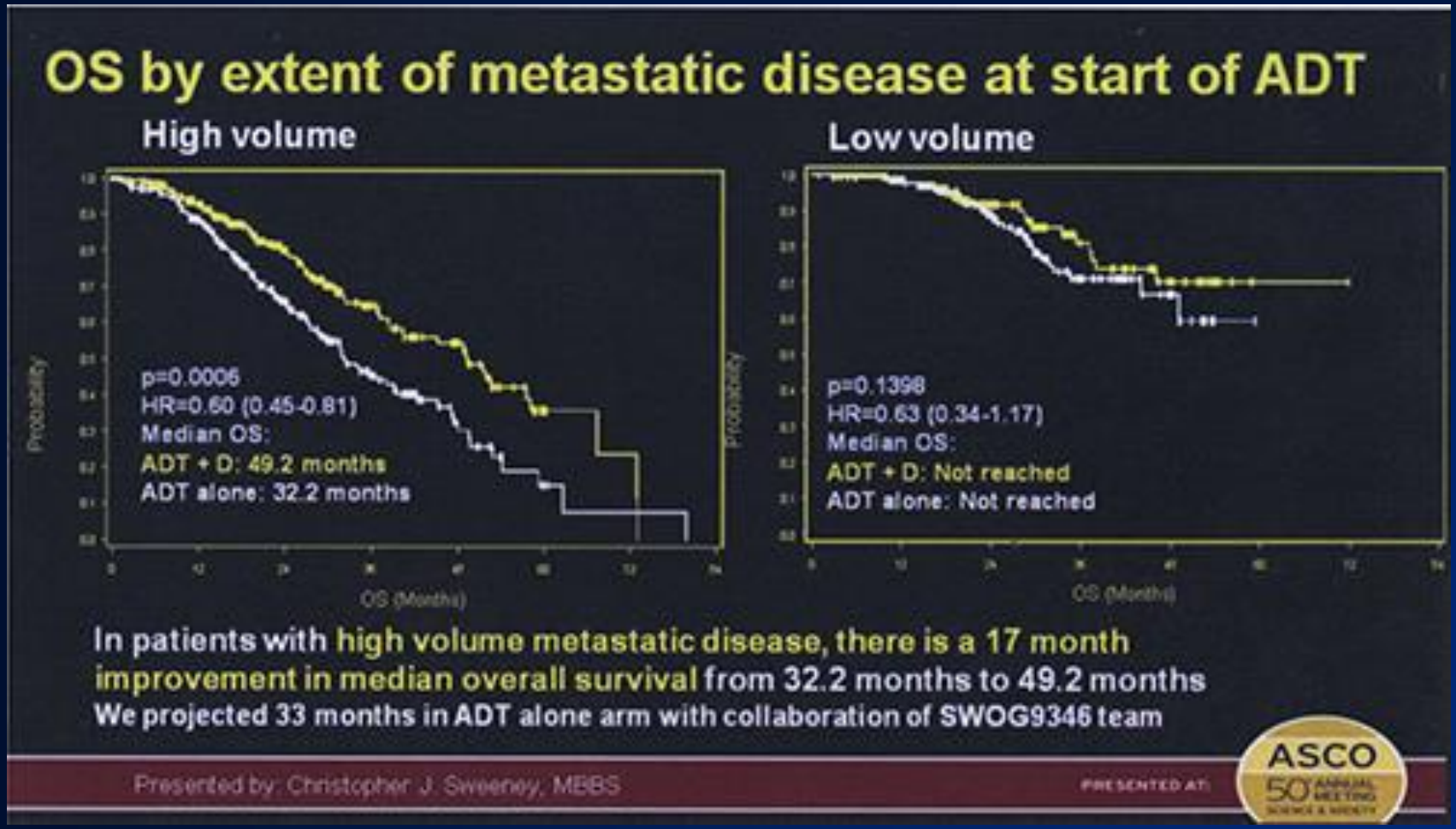




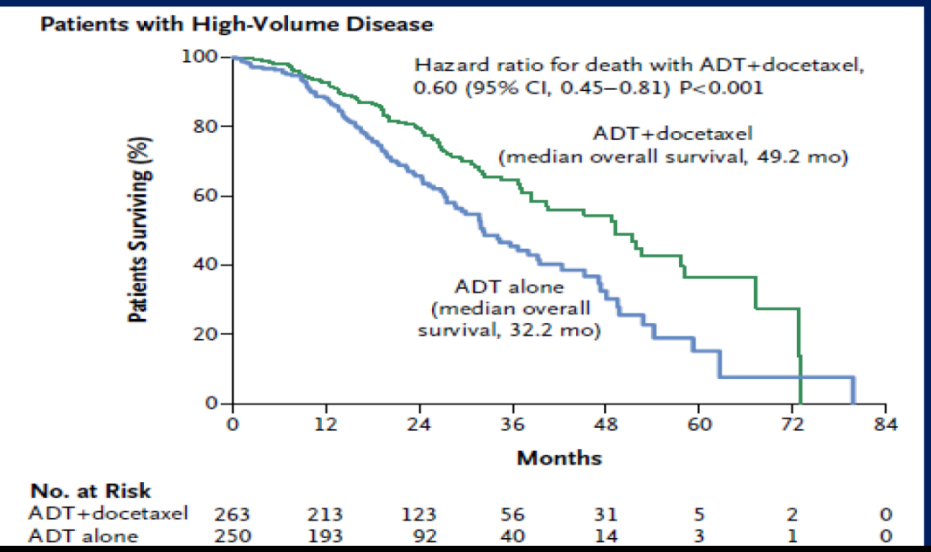
Sweeney, CJ et al. NEJM. 2015

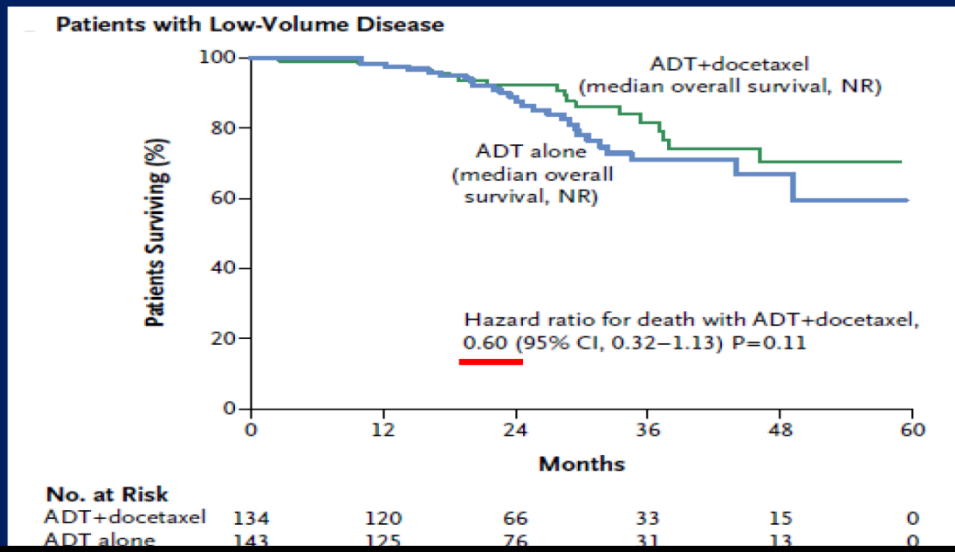
OS by extent of metastatic disease at the start of ADT



Subgroup analysis

CHAARTED: Subgroup Analysis





Should Low Volume Patients be Treated with this Regimen?

1. HR= 0.60 and curves may continue to separate

2. Study was not powered to look at subgroups

3. Toxicity and thus risks of therapy appear limited

Sweeney, CJ et al. NEJM. 2015

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
		no. of patients (%)	
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
Total	352*	

Sweeney, CJ et al. NEJM. 2015

Future Directions

Future Directions

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