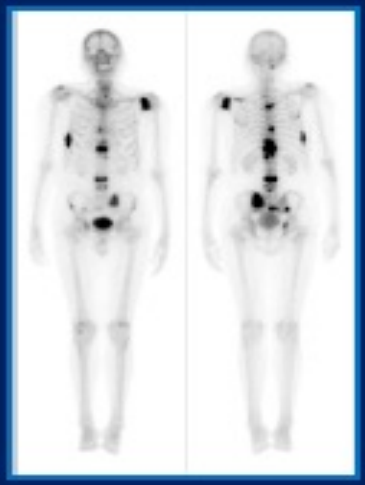
Castration-resistant prostate cancer

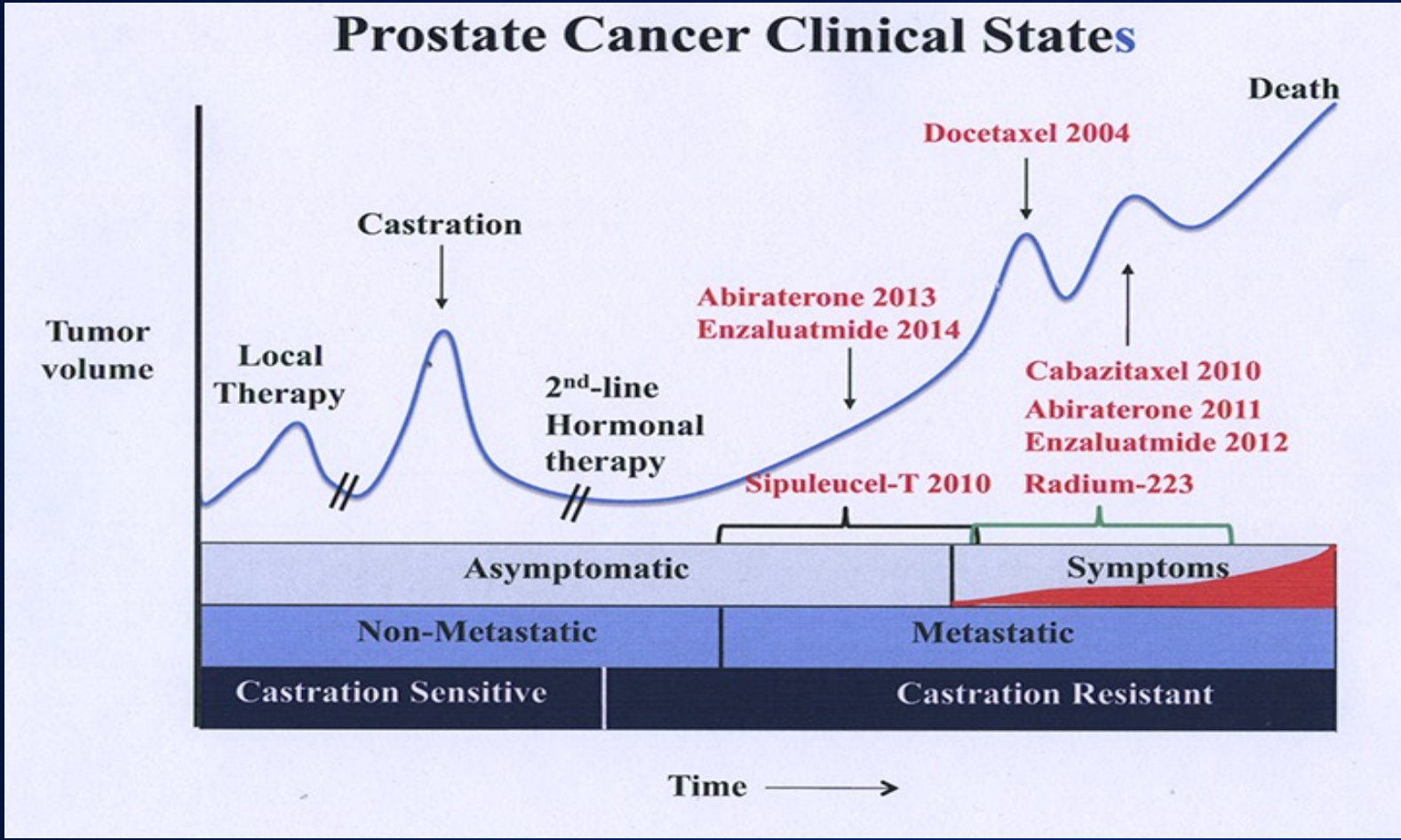
Castration-Resistant Prostate Cancer: Current Approach



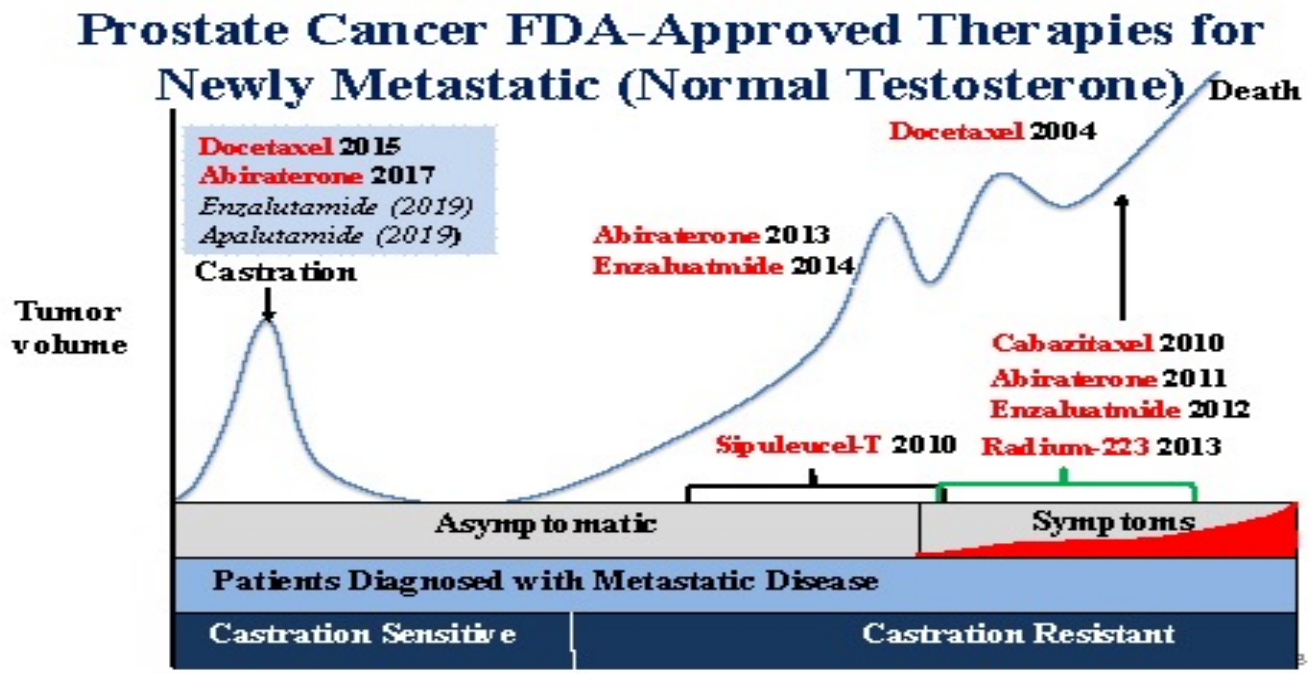
Ravi A. Madan, M.D.
Clinical Director
Genitourinary Malignancies Branch
Center for Cancer Research, NCI, NIH

@Dr_RaviMadan

Prostate Cancer Clinical States



FDA approved therapies



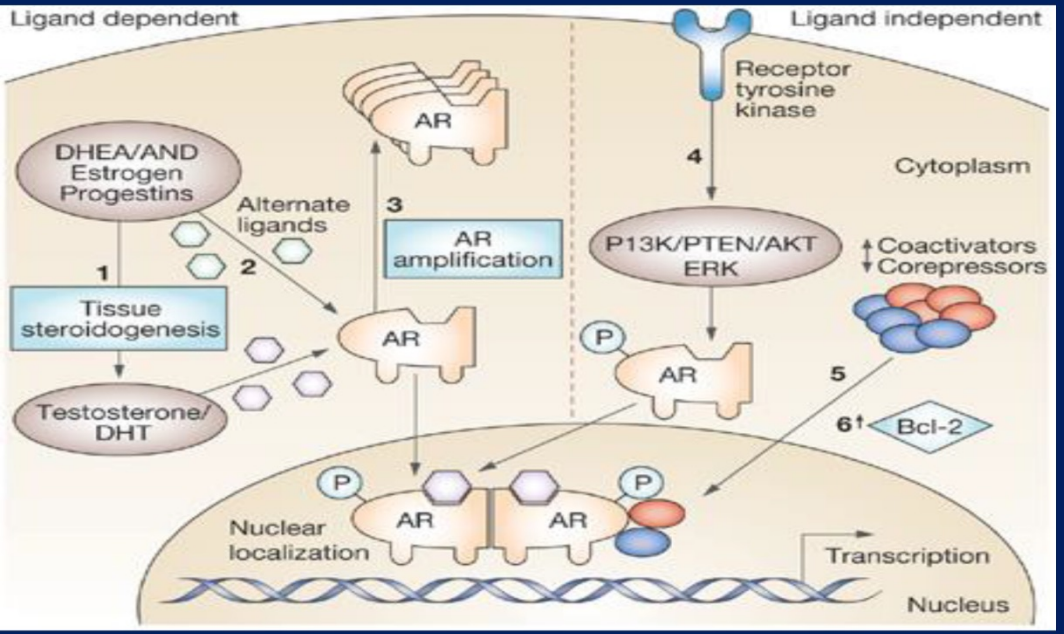
Castrate resistant prostate cancer

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*

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

mCRPC treatment considerations

Considerations for the Treatment of mCRPC

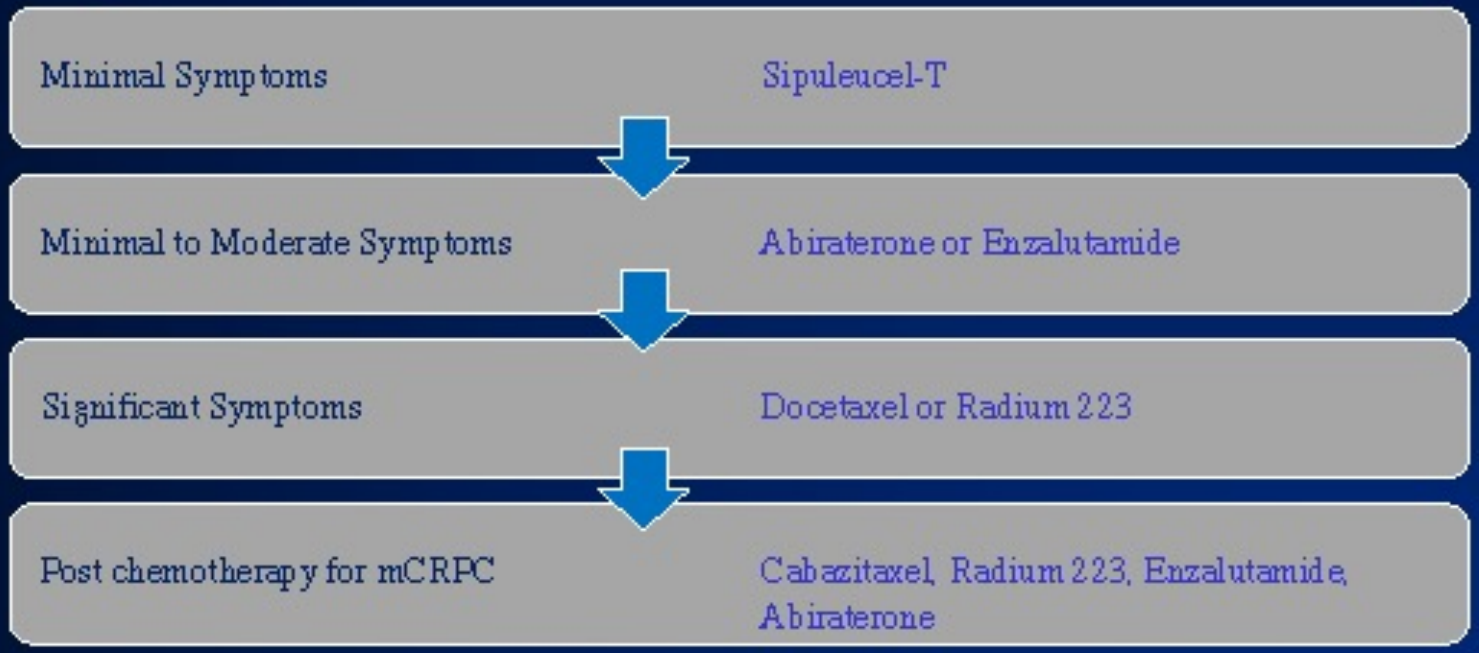
Key disease questions:

- Previous therapies
- Pace of disease (e.g. time of progression on ADT, pace of mets)
- Symptoms (none, moderate or significant)

Key patient characteristics:

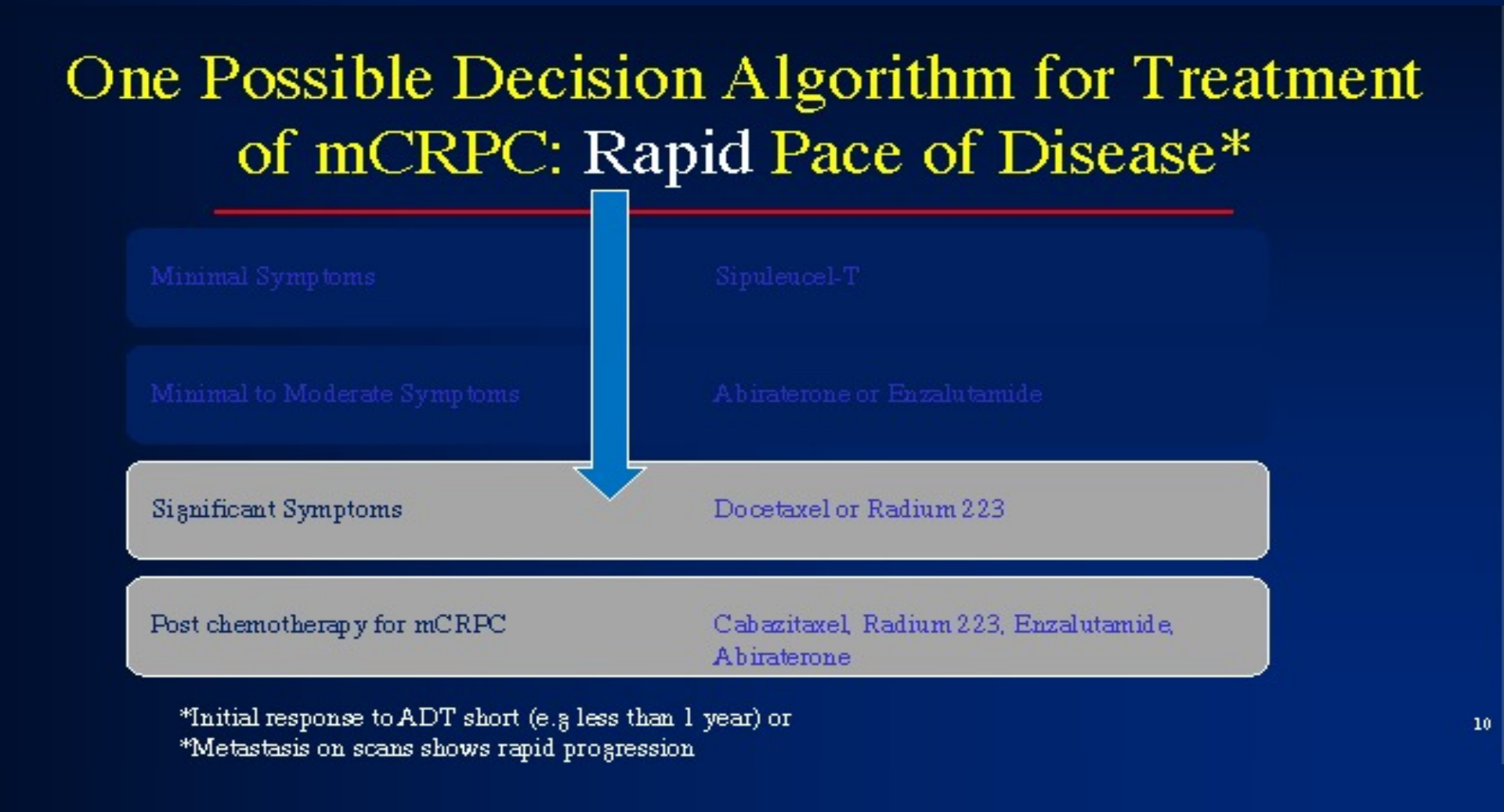
- Age
- Comorbidities
- Quality of life preferences
- Treatment logistics

One Possible Decision Algorithm for Treatment of mCRPC: Normal Pace of Disease*



*Initial response to ADT 1-2 years or longer
*Metastasis on scans shows slow progression

Algorithym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Sipuleucel-T
Minimal to Moderate Symptoms
Abiraterone or Enzalutamide
Significant Symptoms
Docetaxel or Radium 223
Post chemotherapy for mCRPC
Cabazitaxel, Radium 223, Enzalutamide, Abiraterone
*Initial response to ADT short (e.g less than 1 year) or
*Metastasis on scans shows rapid progression

Decision algorythm

One Possible Decision Algorythm for Treatment of mCRPC: Normal Pace of Disease*

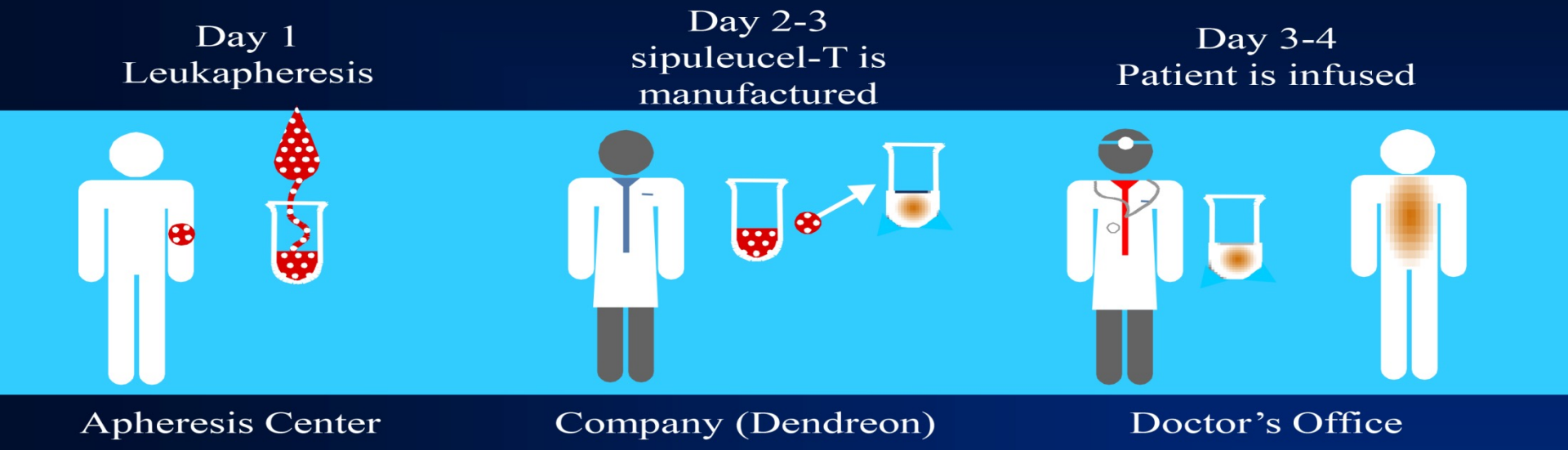
Minimal Symptoms — Sipuleucel-T

*Initial response to ADT 1-2 years or longer
*Metastasis on scans shows slow progression

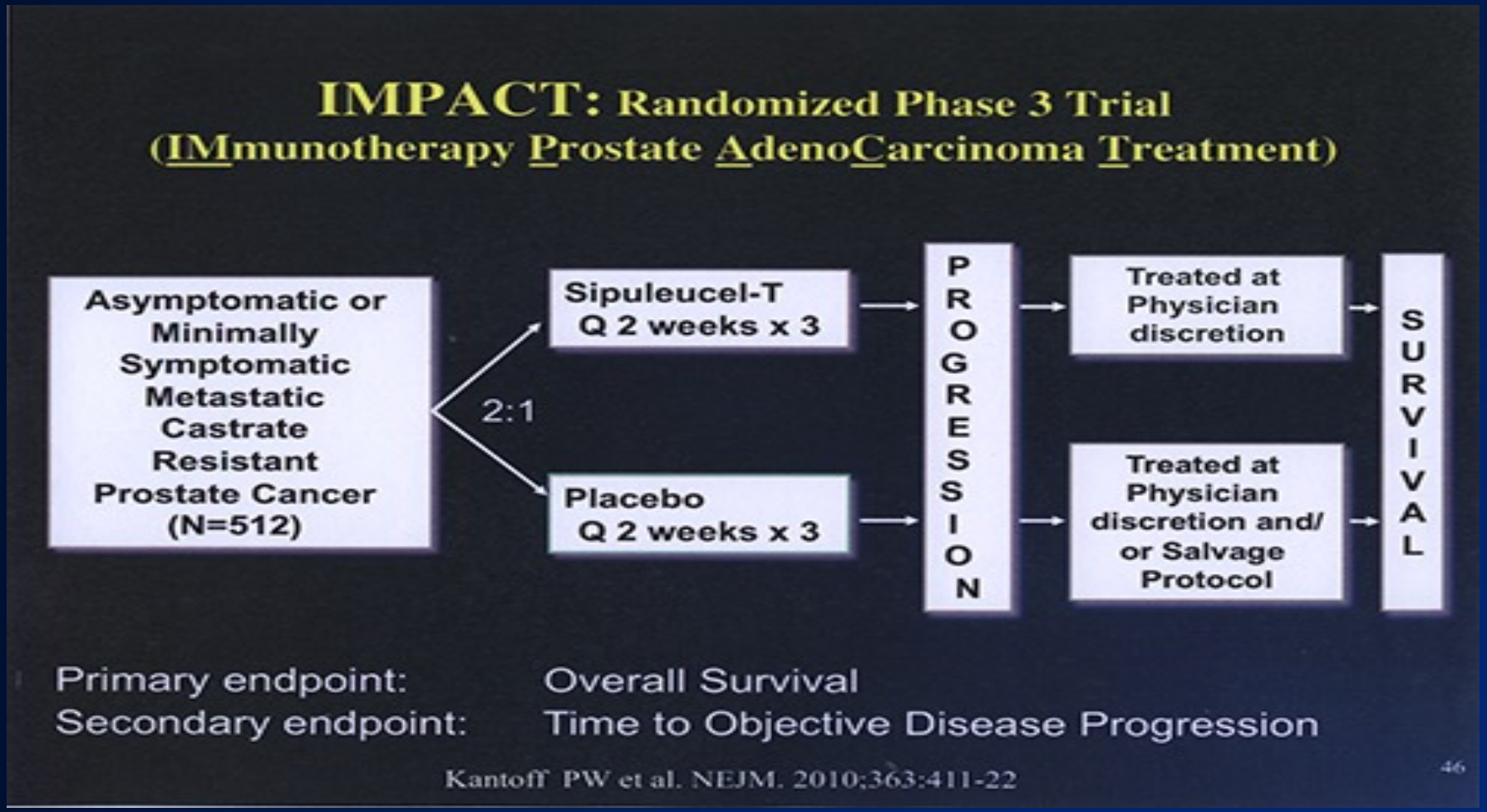
11

Therapeutic Cancer Vaccine: Sipuleucel-T

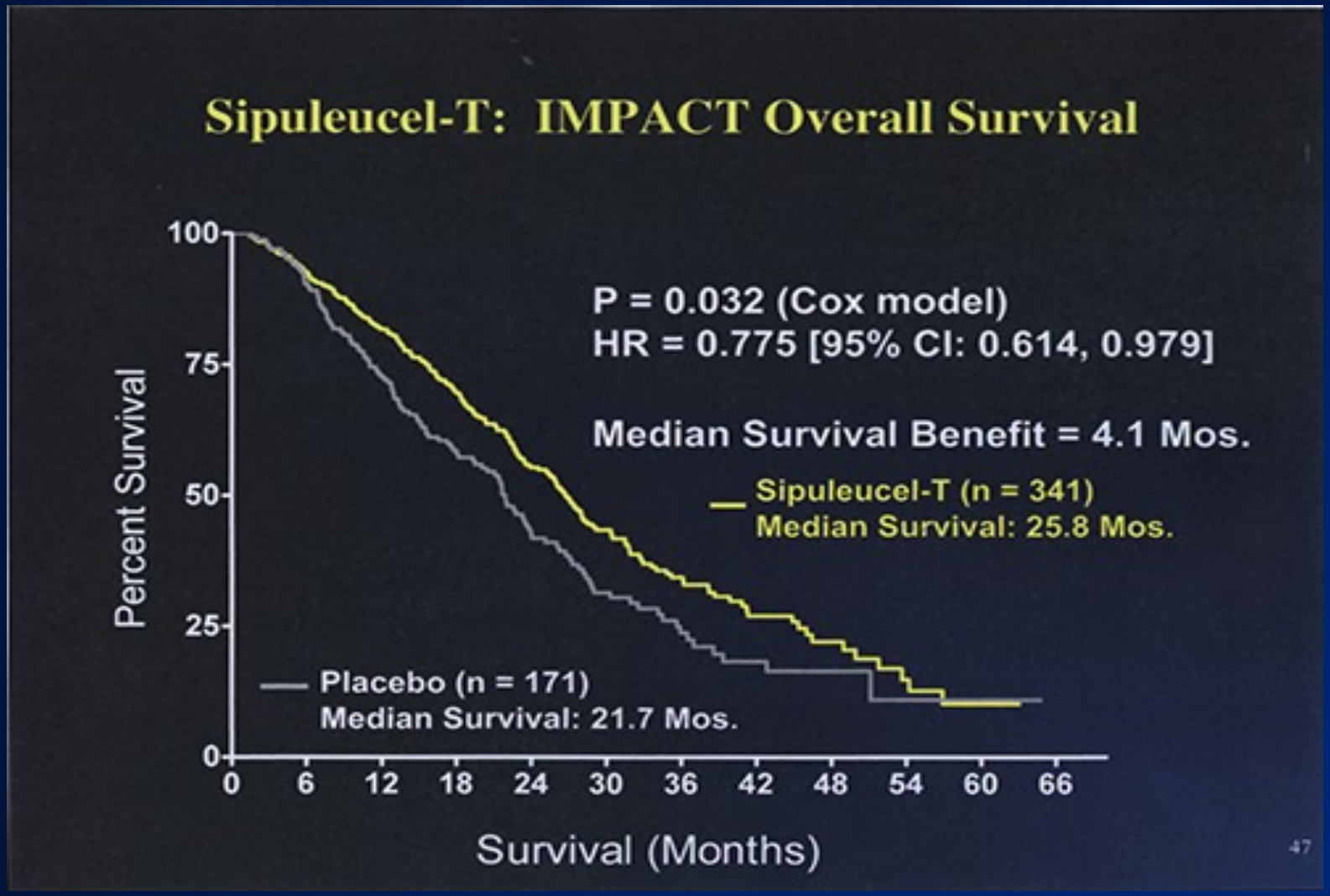
Therapeutic Cancer Vaccine: Sipuleucel-T



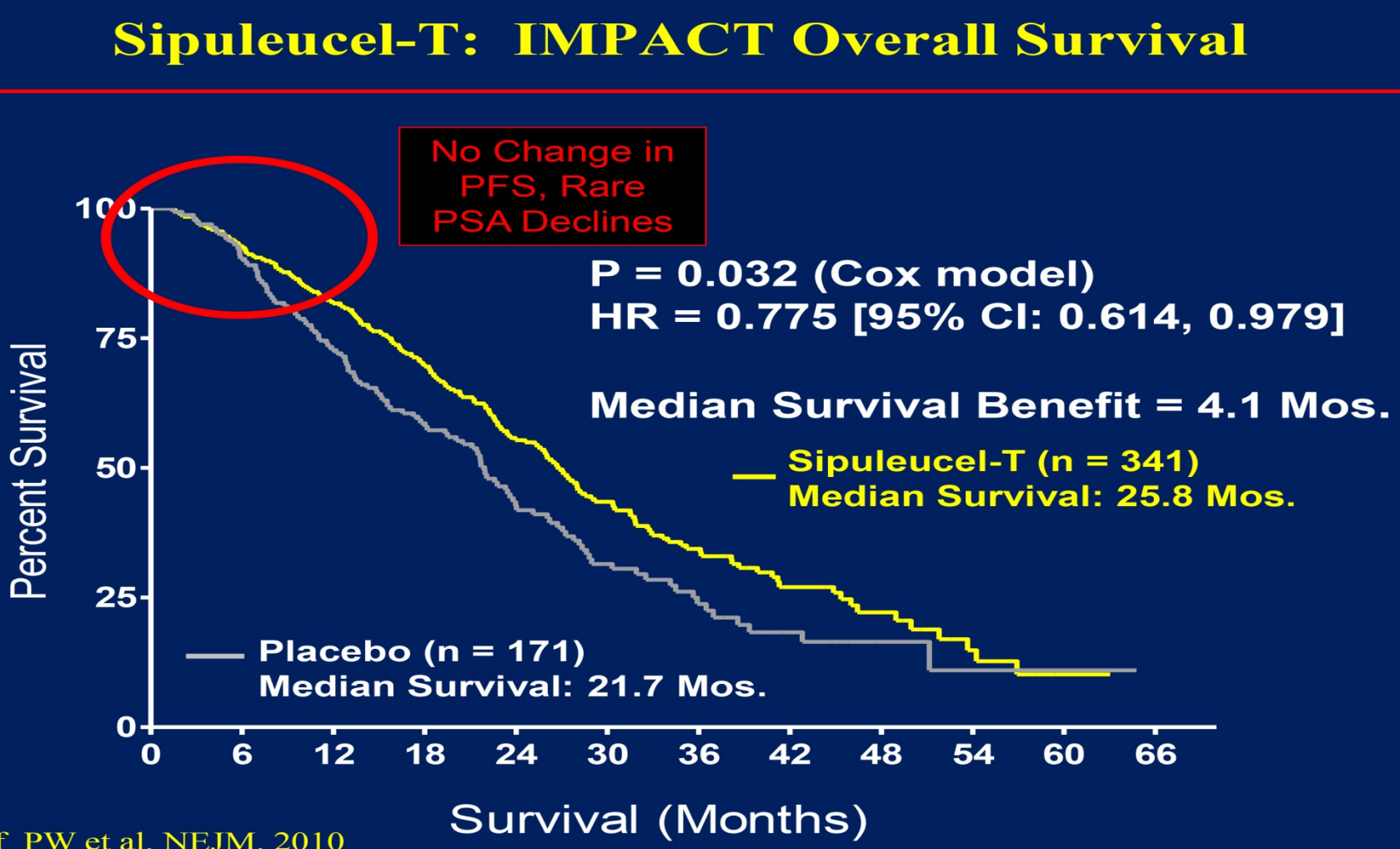
IMPACT: Randomized Phase 3 Trial



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-Y recommendations

Society of Immunotherapy of Cancer (SITC) Recommendations for Sipuleucel-T

McNeel et al. Journal for ImmunoTherapy of Cancer (2016) 4:92
DOI 10.1186/s40425-016-0198-x

Dec 2016

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES — Open Access

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of prostate carcinoma

Douglas G. McNeel[1], Neil H. Bander[2], Tomasz M. Beer[3], Charles G. Drake[4], Lawrence Fong[5], Stacey Hamelson[6], Philip W. Kantoff[7], Ravi A. Madan[8], William K. Oh[9], David J. Peace[10], Daniel P. Petrylak[11], Hank Porterfield[12], Oliver Sartor[13], Neal D. Shore[6], Susan F. Slovin[7], Mark N. Stein[14], Johannes Vieweg[15] and James L. Gulley[16*]

Sipuleucel-T

-Don't expect PSA decrease

-Use early, in less aggressive disease

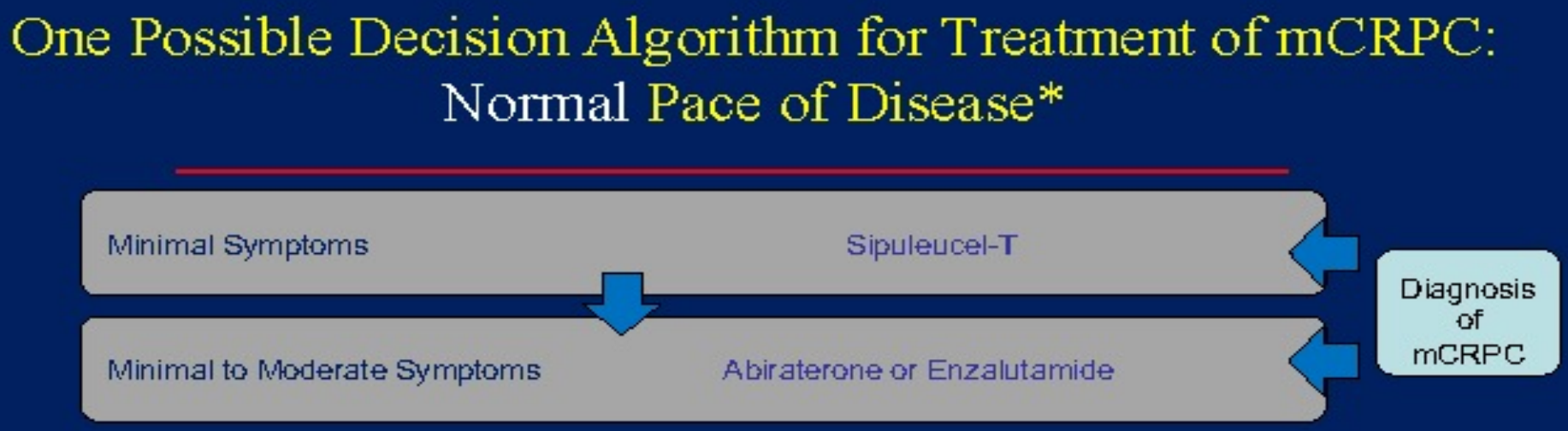
My recommendation:
Treat and move on to the next therapy

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.

Algorithm



*Initial response to ADT 1-2 years or longer
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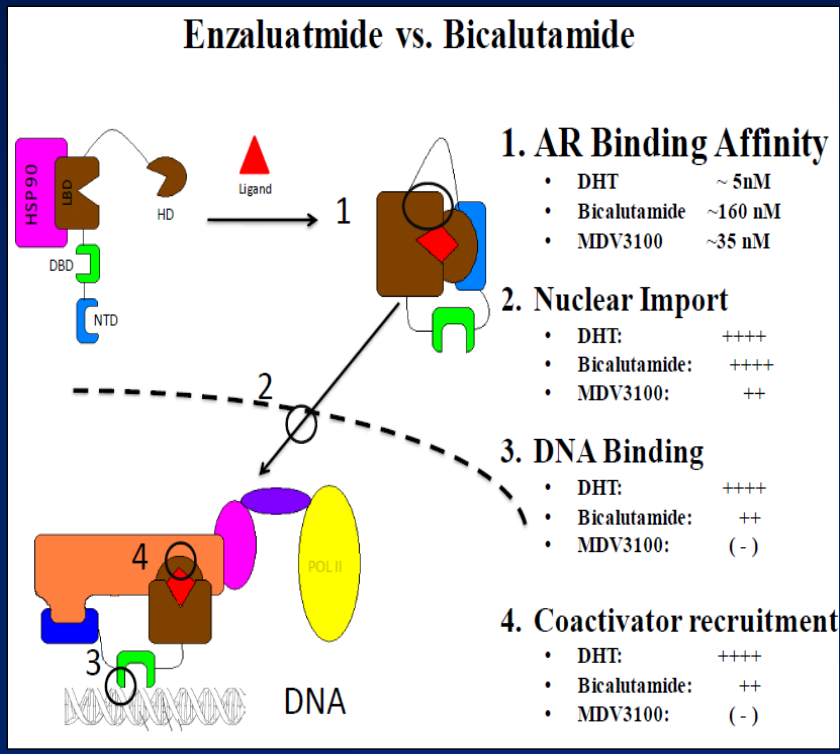
Enzalutamide

A small molecule AR antagonist

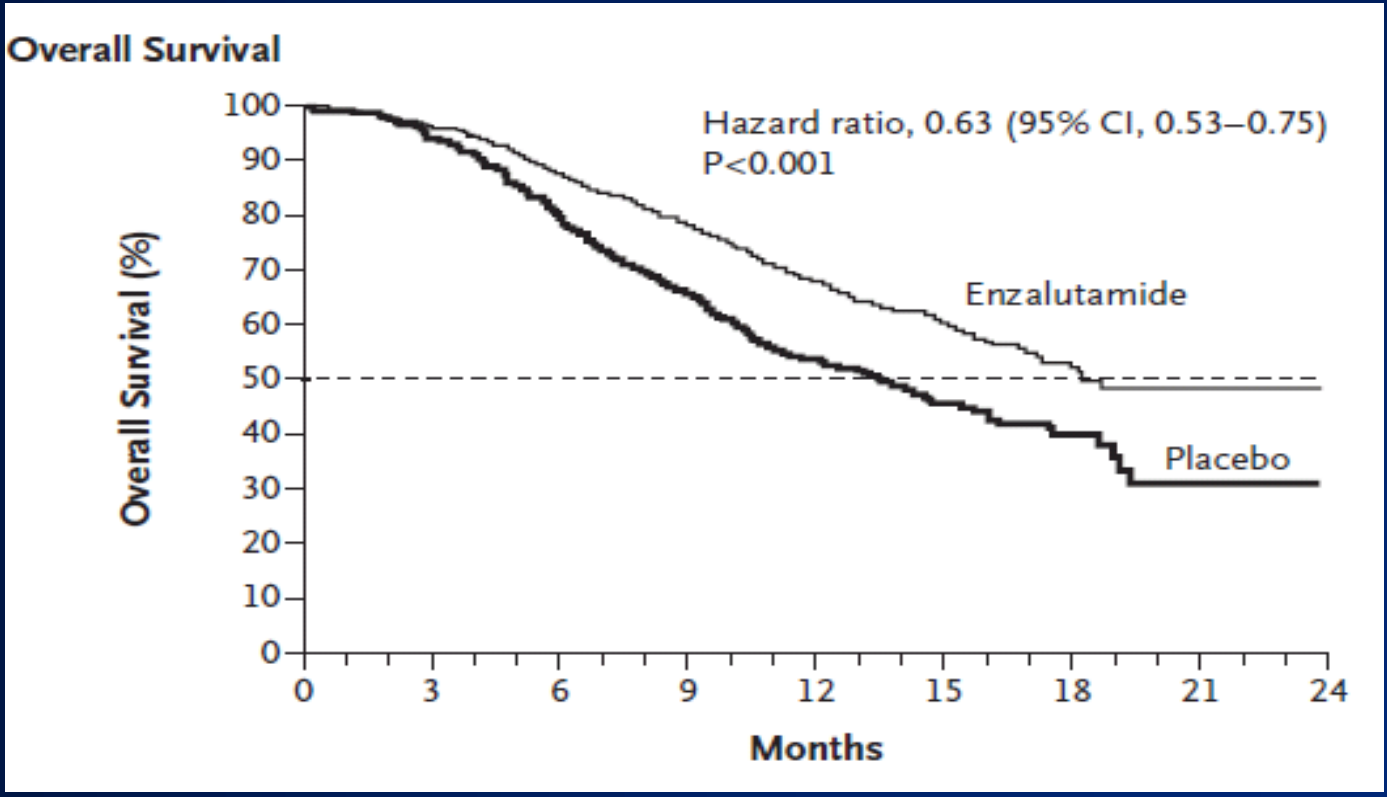
- Affinity 30 folds of bicalutamide
- Prevent nuclear translocation
- Prevents co-activator recruitment



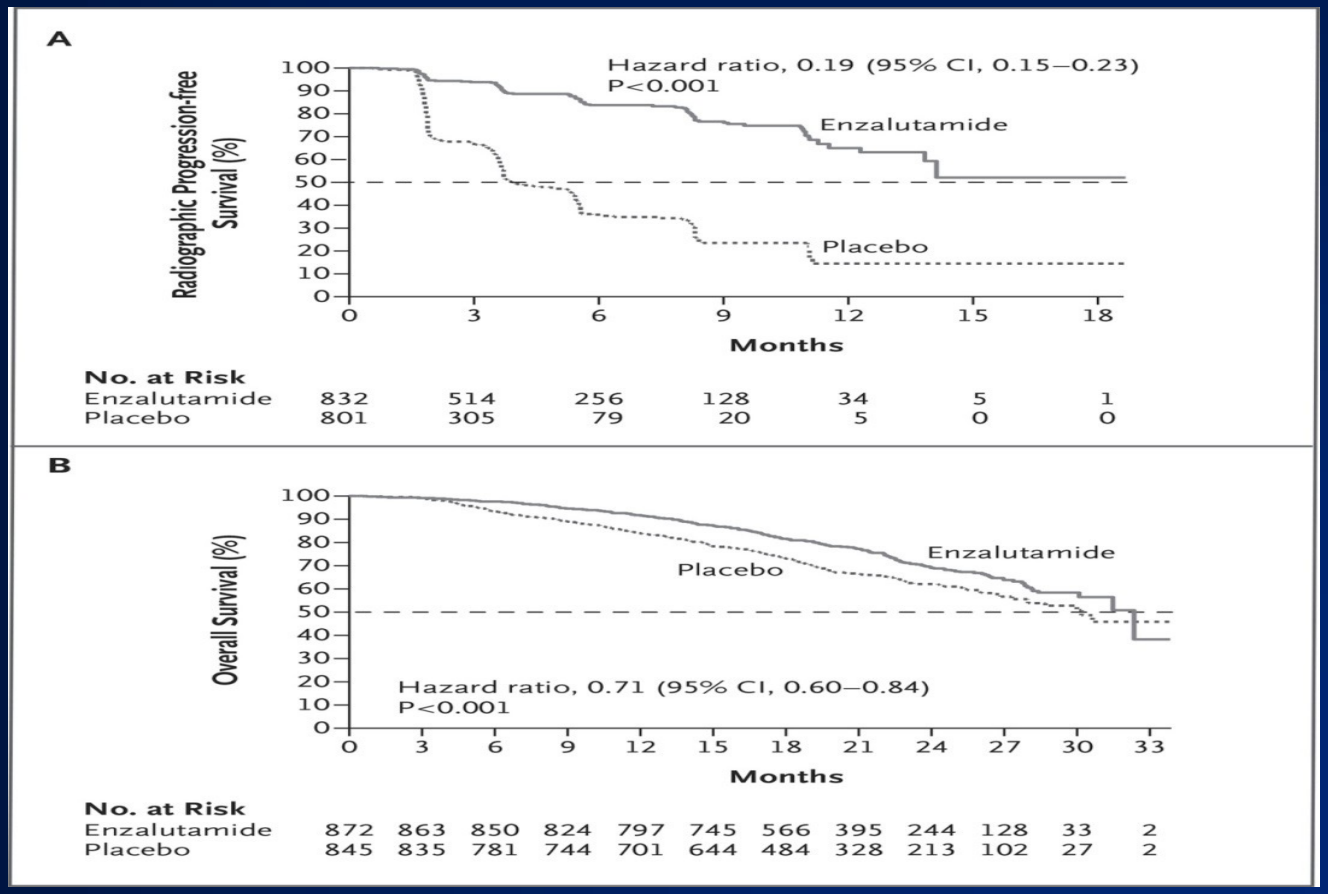
AFFIRM

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%)

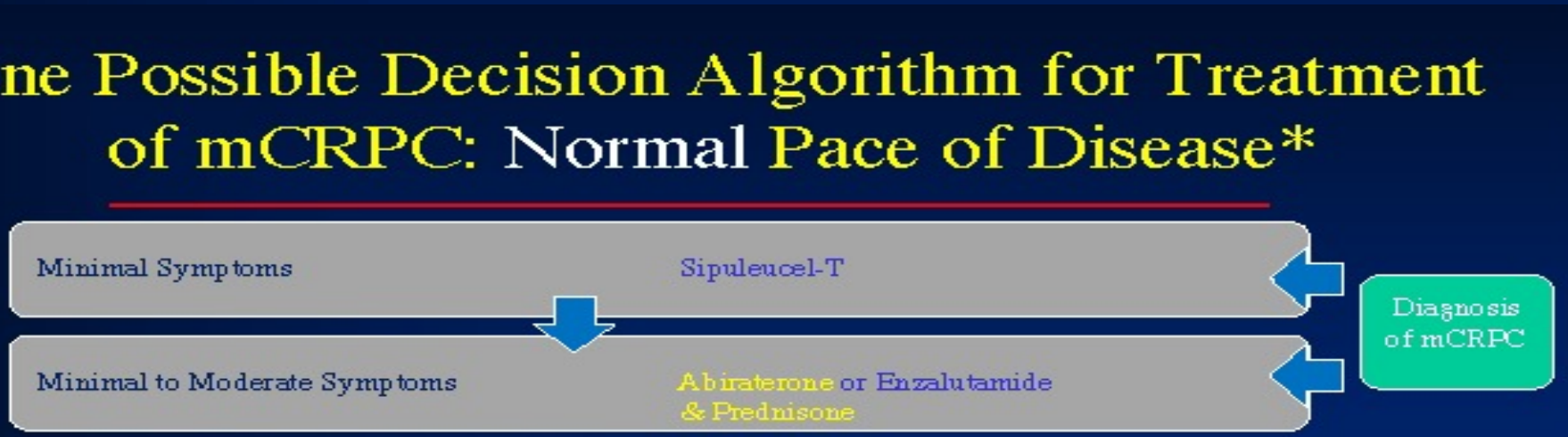
Gastrointestinal: Diarrhea (22%)

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

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

Respiratory: Upper respiratory tract infection (11%)

Algorithm



*Initial response to ADT 1-2 years or longer
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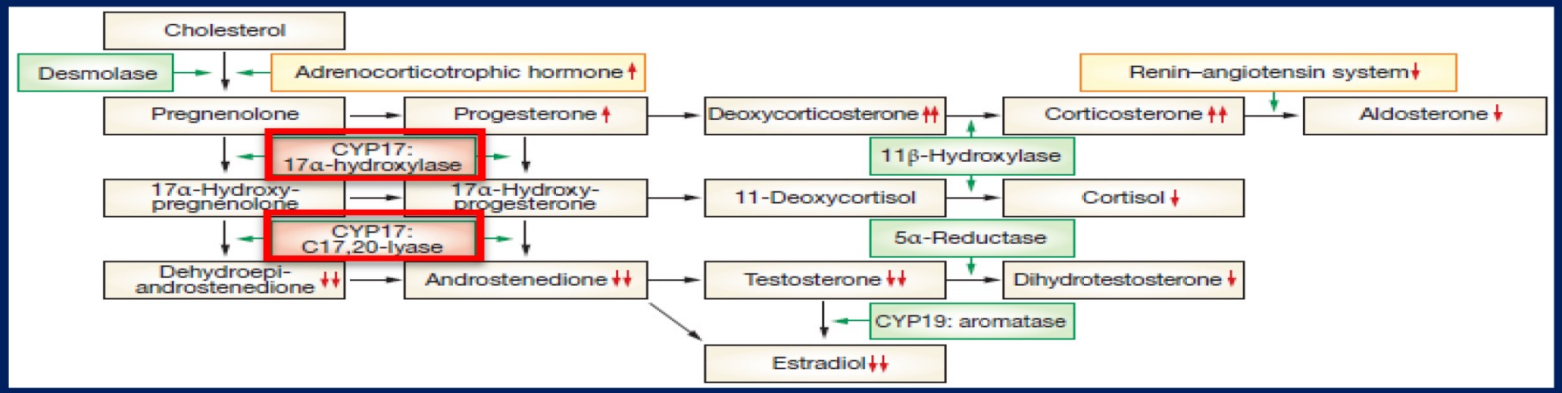
Abiraterone rationale

Rationale for Abiraterone in CRPC

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

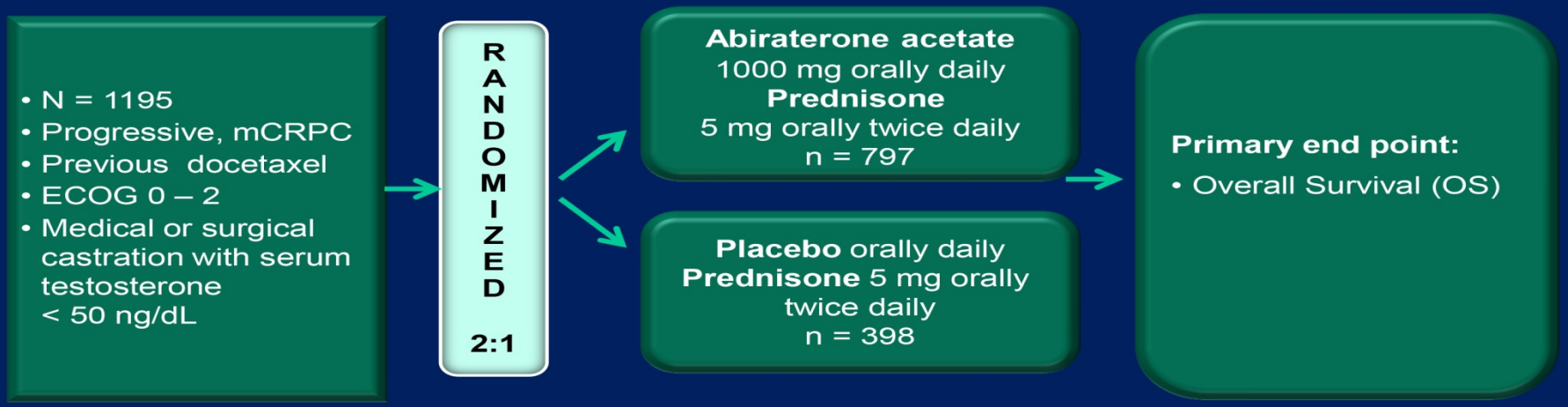


- Blocks androgen synthesis by the adrenal glands, testes and within the prostate tumor tissue

Reid et al. Nat Clin Pract Urol. 2008

Abiraterone study

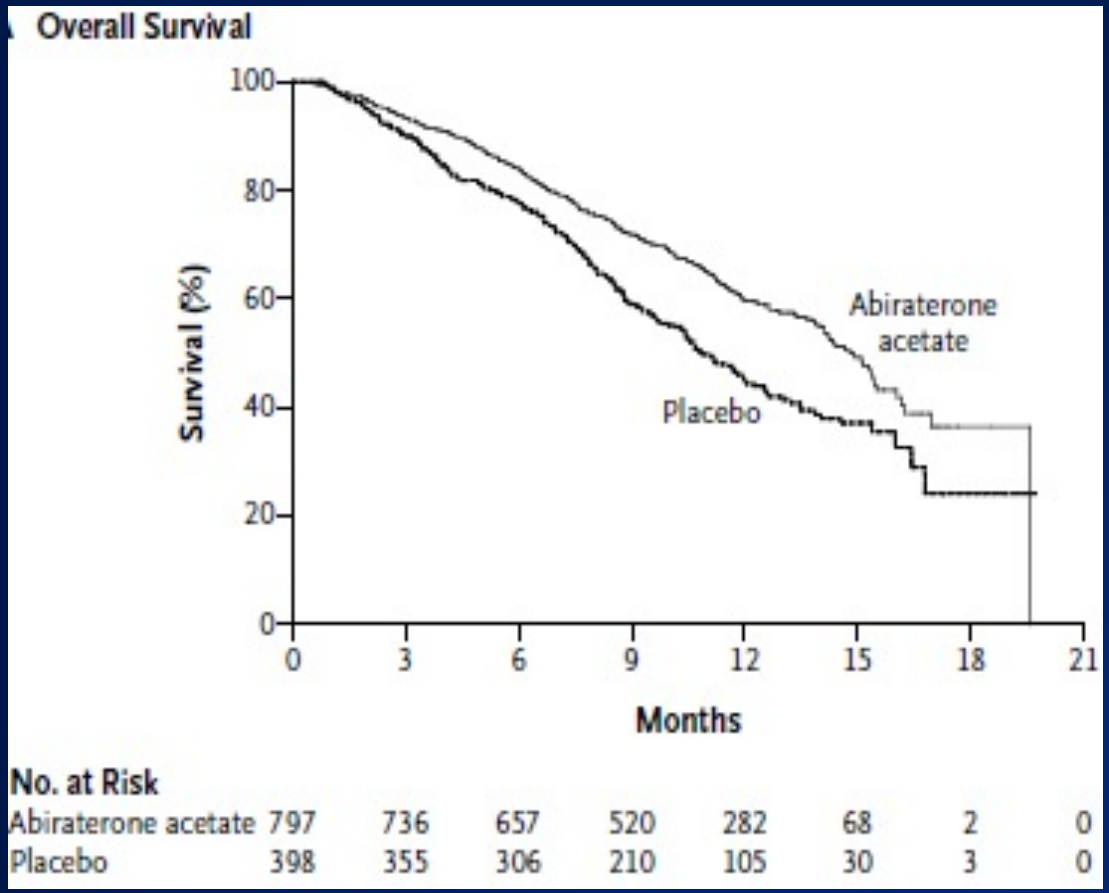
Abiraterone: COU-AA-301 Study Design



- 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

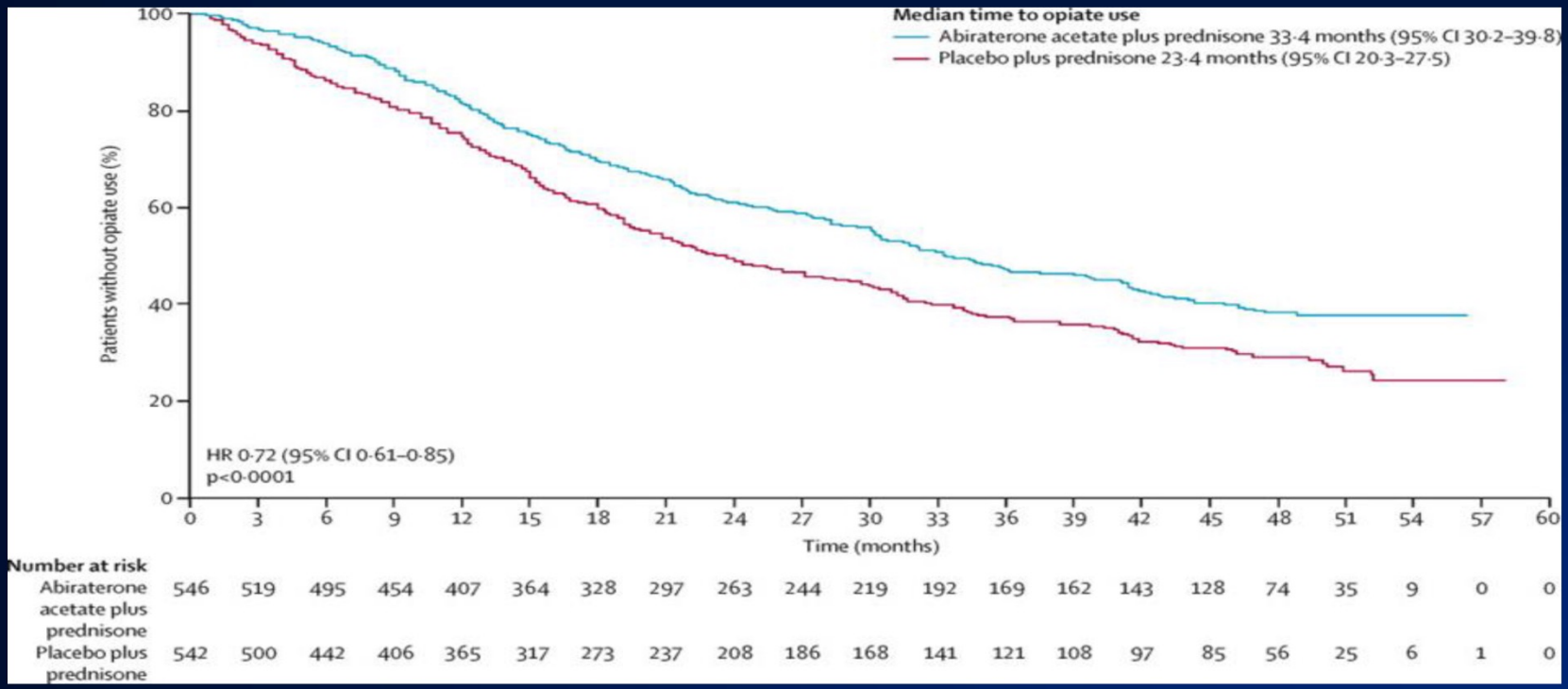
Abiraterone: COU-AA-301 Trial

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%)

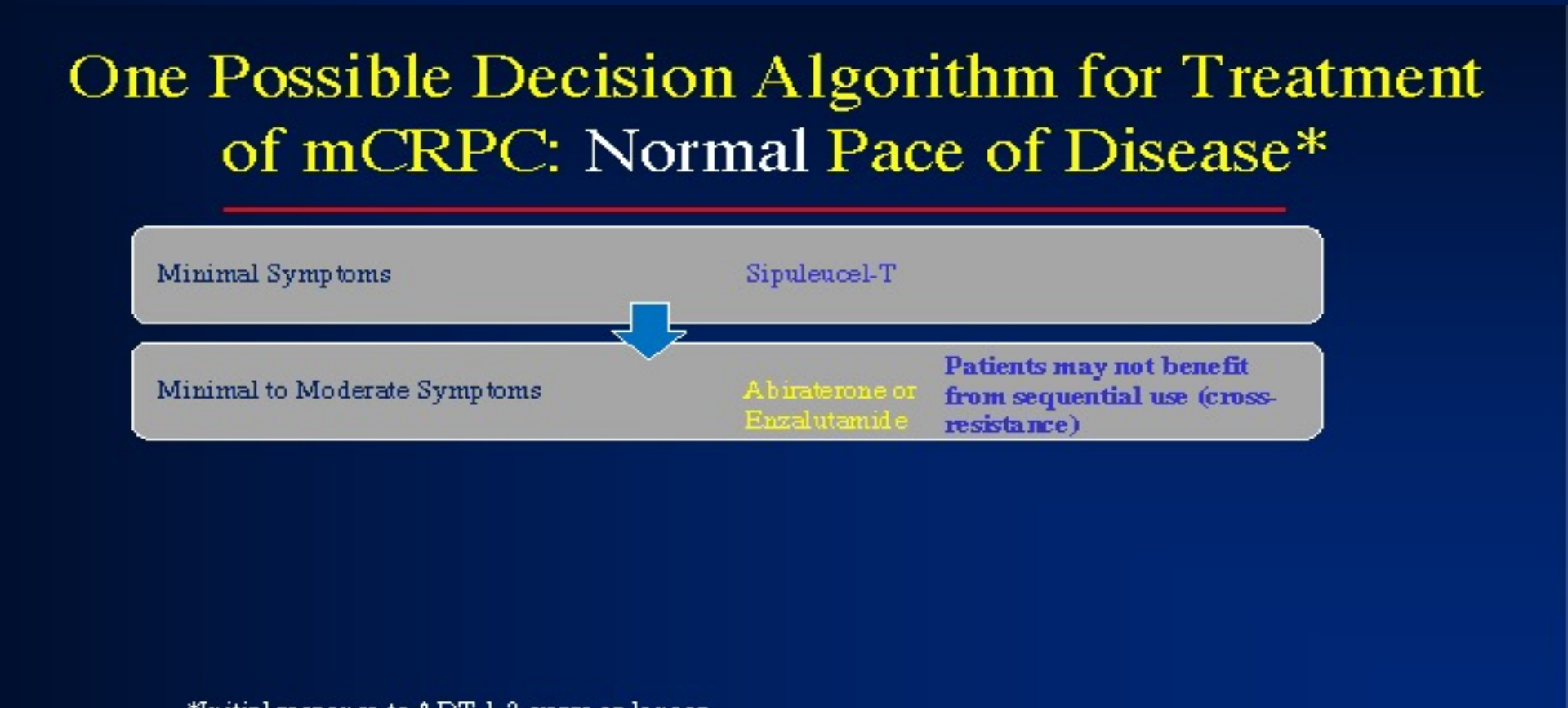
Hematologic: Lymphocytopenia (38%; grades 3/4: 9%)

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%)

Normal pace of disease



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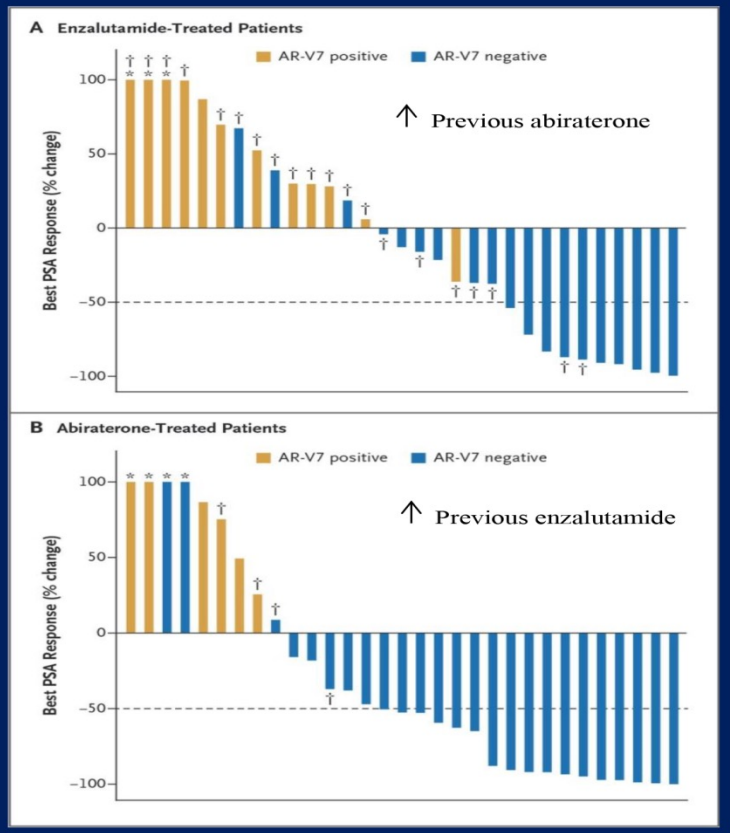
Overlapping resistance

Overlapping Resistance: Androgen Receptor Splice Variants

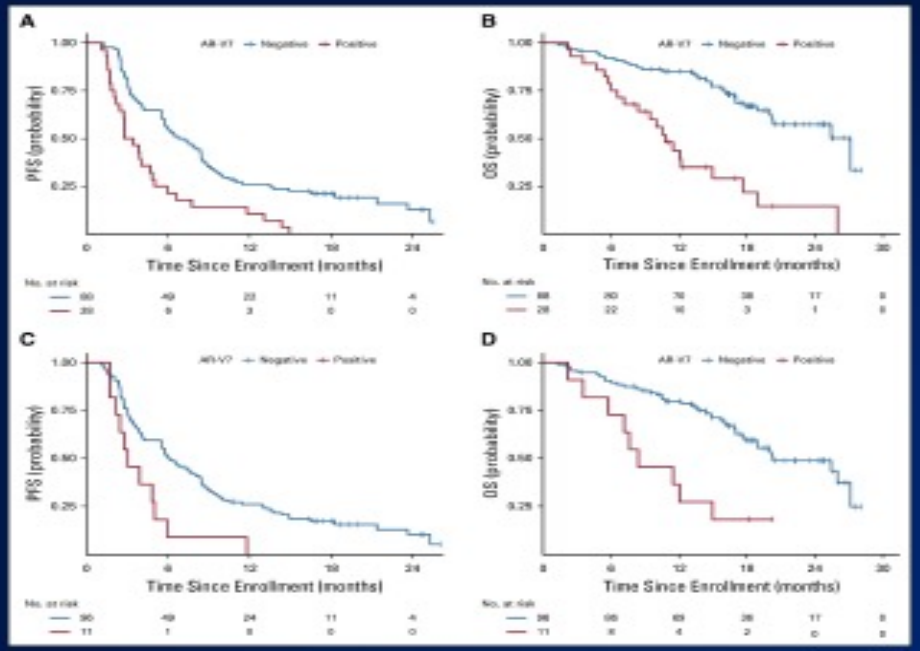
- Variable splicing of AR mRNA can lead to resistance mechanisms to anti-androgen therapy
- ARV-7 has been investigated extensively, lacks a ligand binding domain and is constituently active
- Increases in ARV-7 seen after treatment with Abiraterone/Enzalutamide, likely contributing to cross-resistance.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



Antonarakis ES et al. NEJM, 2014.

PROPHECY

PROPHECY: Regardless of Platform, Patients with Splice Variant AR-V7 had Worse Outcomes



Armstrong AJ et al. JCO, 2019

34

PROPHECY

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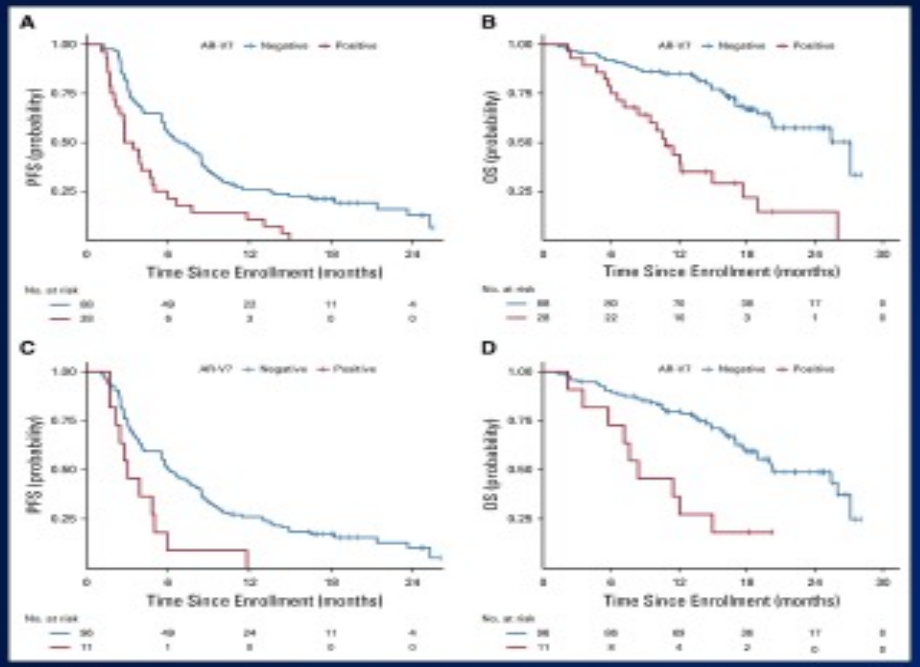
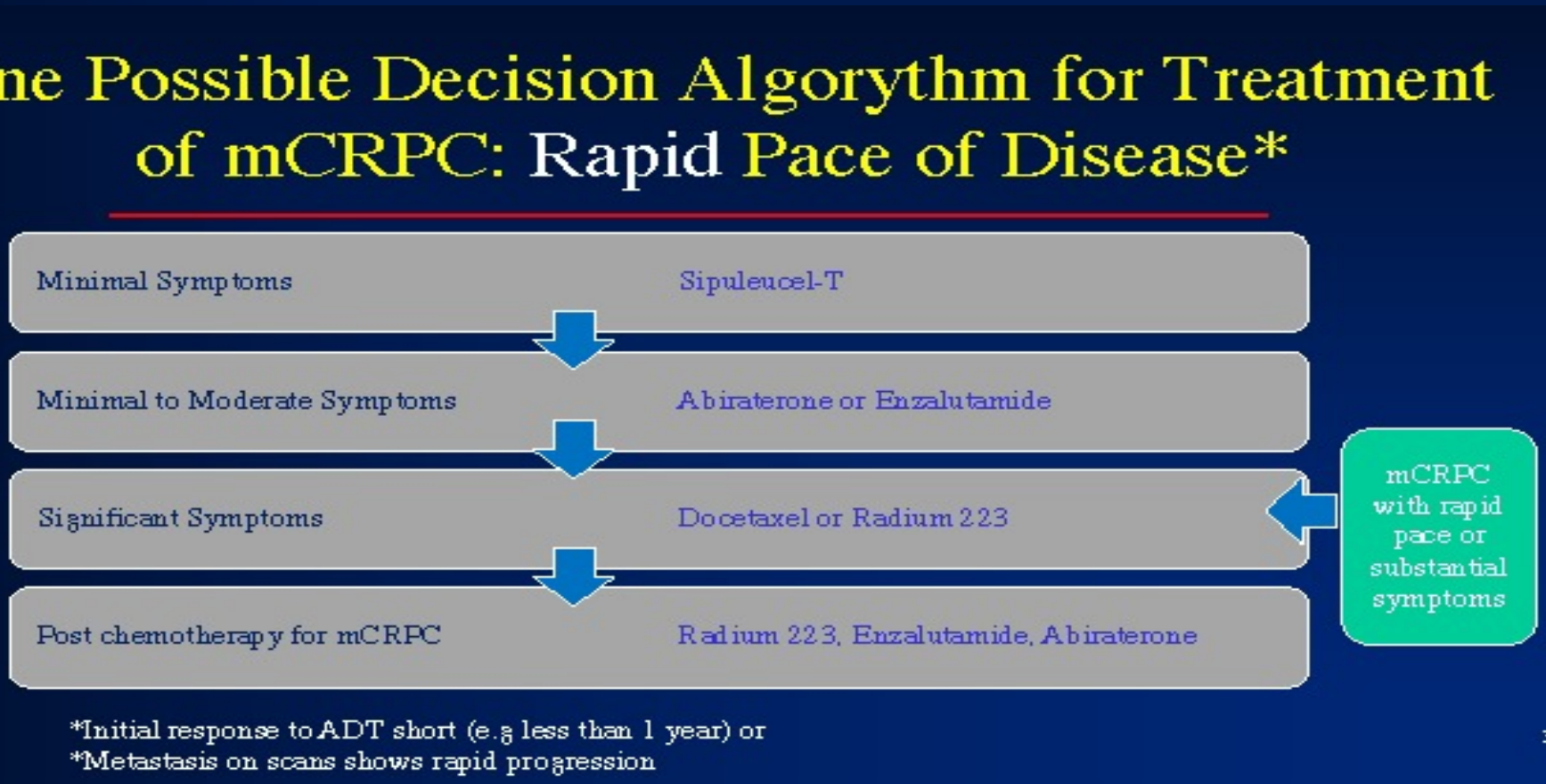


Armstrong AJ et al. JCO. 2019

Algorithm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Significant Symptoms
Docetaxel or Radium 223
Post chemotherapy for mCRPC
Radium 223, Enzalutamide, Abiraterone
mCRPC with rapid pace or substantial symptoms
*Initial response to ADT short (e.g less than 1 year) or
*Metastasis on scans shows rapid progression

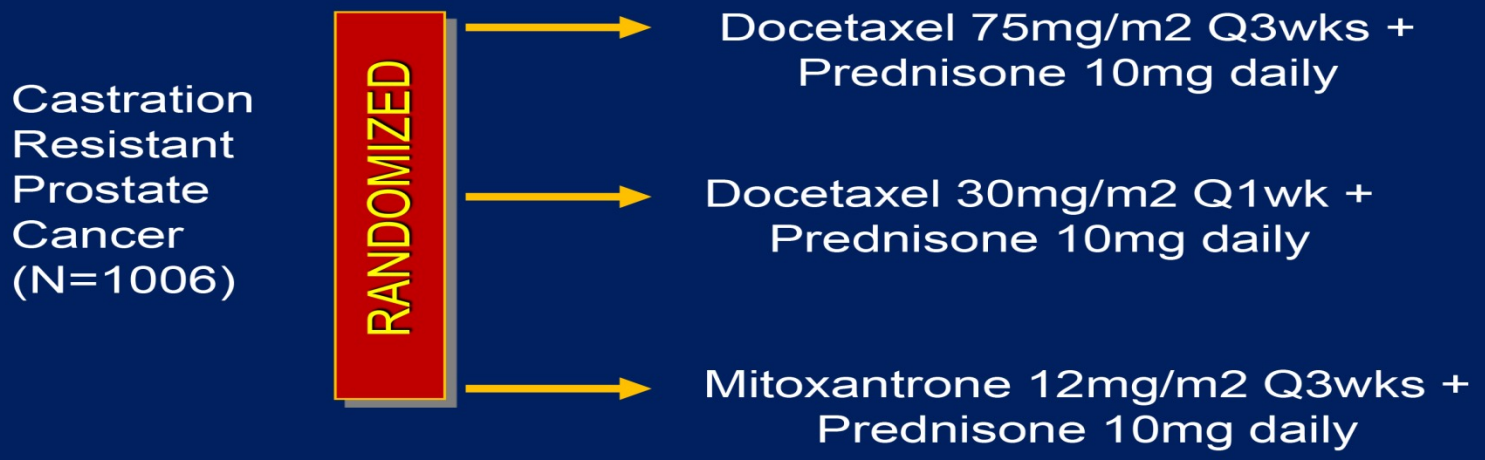
Docetaxel

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*

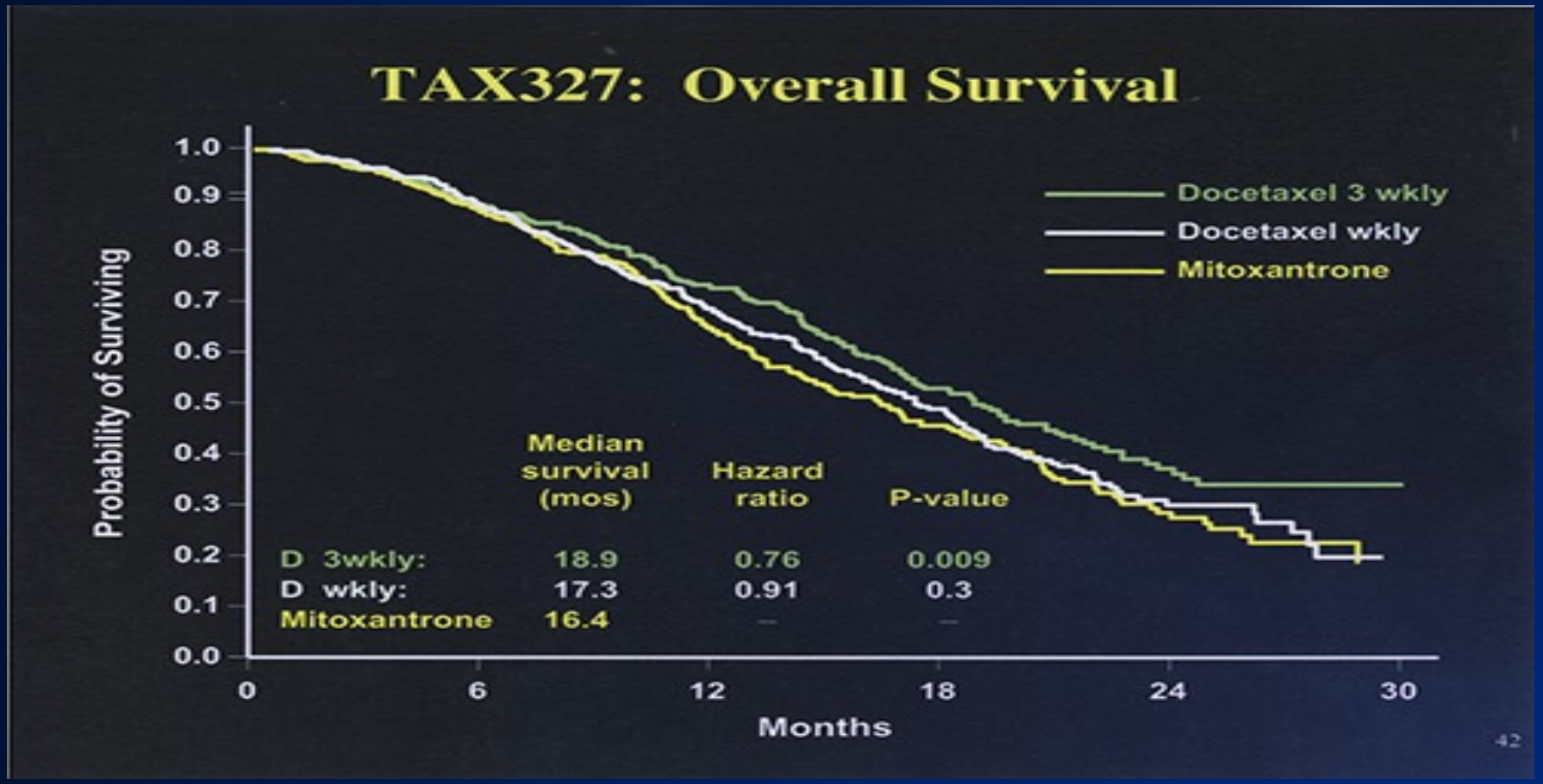
Phase III study

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%)

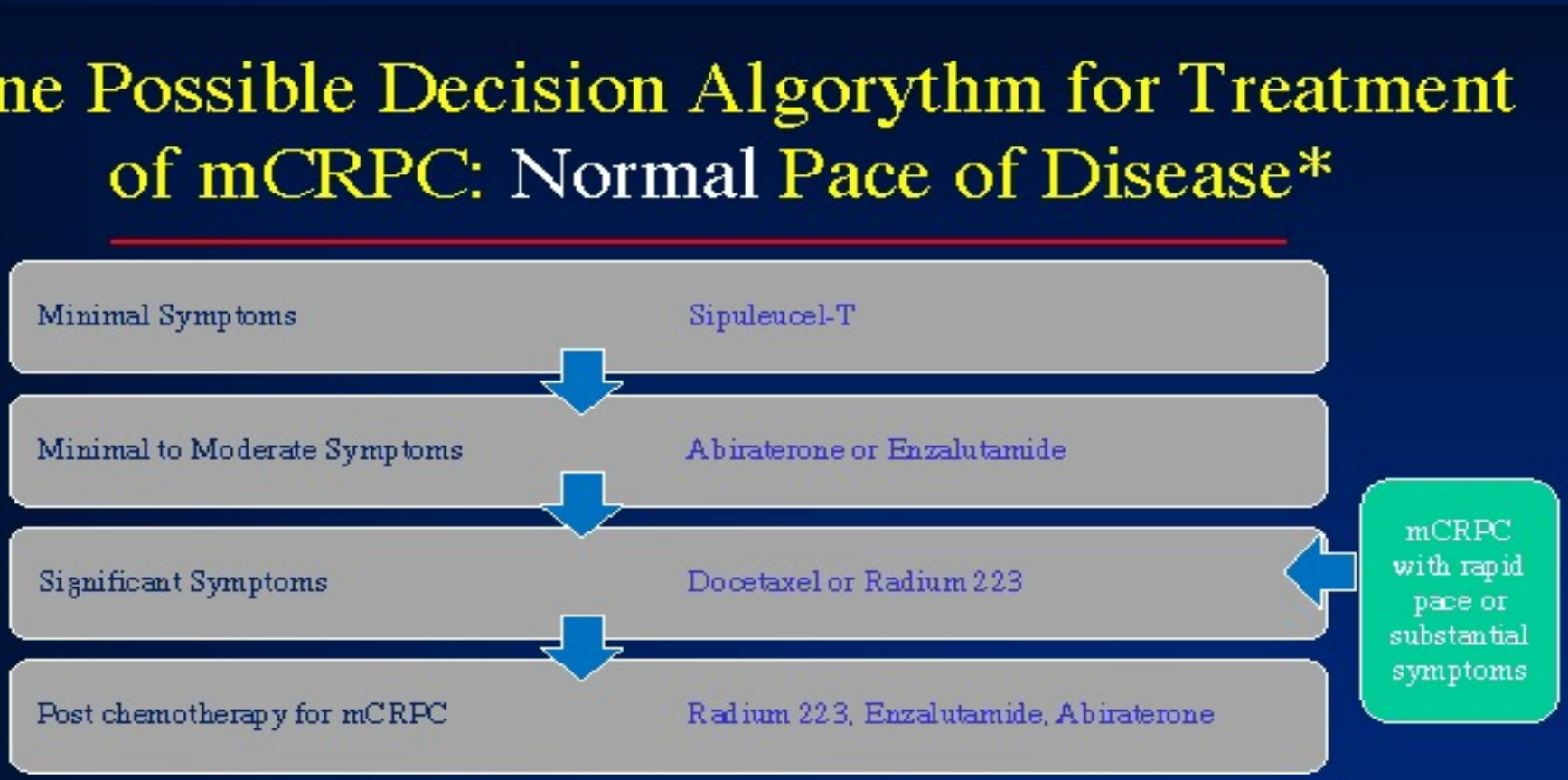
Hypersensitivity: Hypersensitivity (1% to 21%; with premedication 15%)

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%)

Algorithm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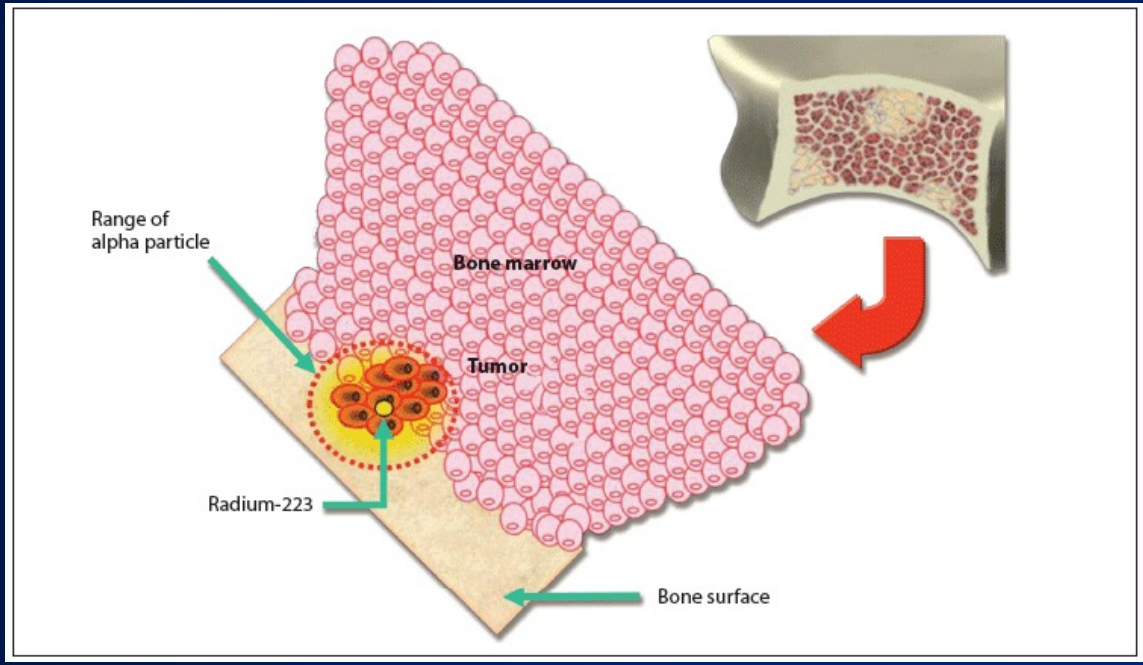
Radium-223 (Alpharadin)

Bone –targeting radiopharmaceutical

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

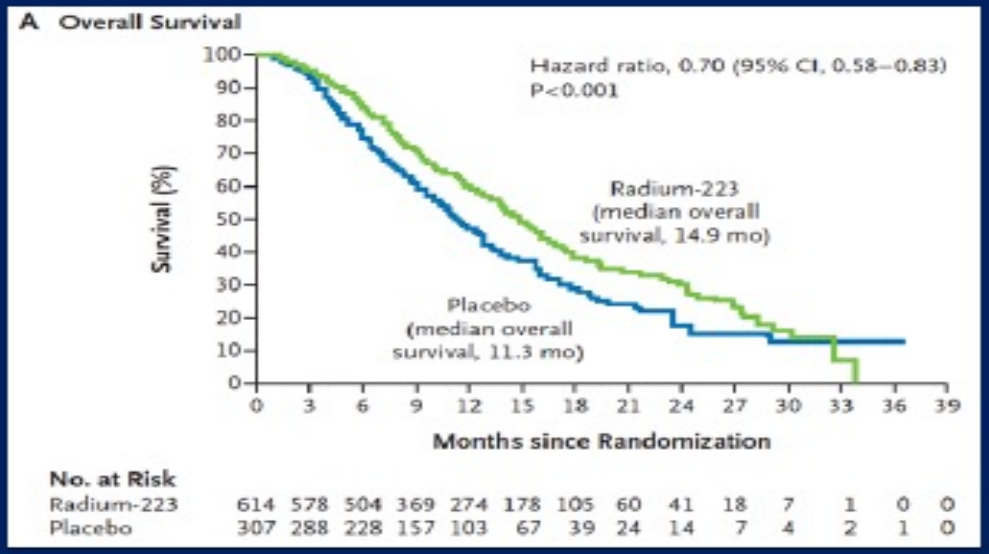


Radium trial

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

ALSYMPCA trial

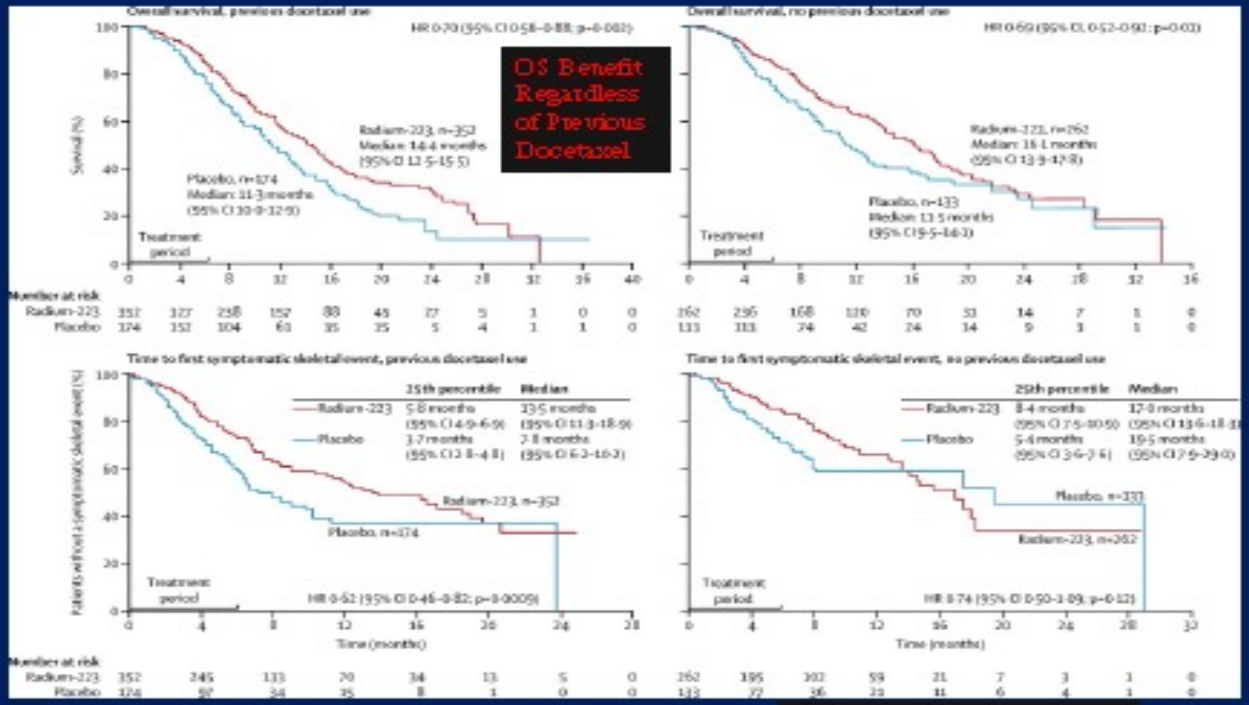
ALSYMPCA: Randomized Phase III Study of Radium-223 vs. Placebo in mCRPC with bone metastases



Parker C. et al. NEJM, 2013.

Survival curve

ALSYMPCA: Subgroup Analysis based on Previous Docetaxel



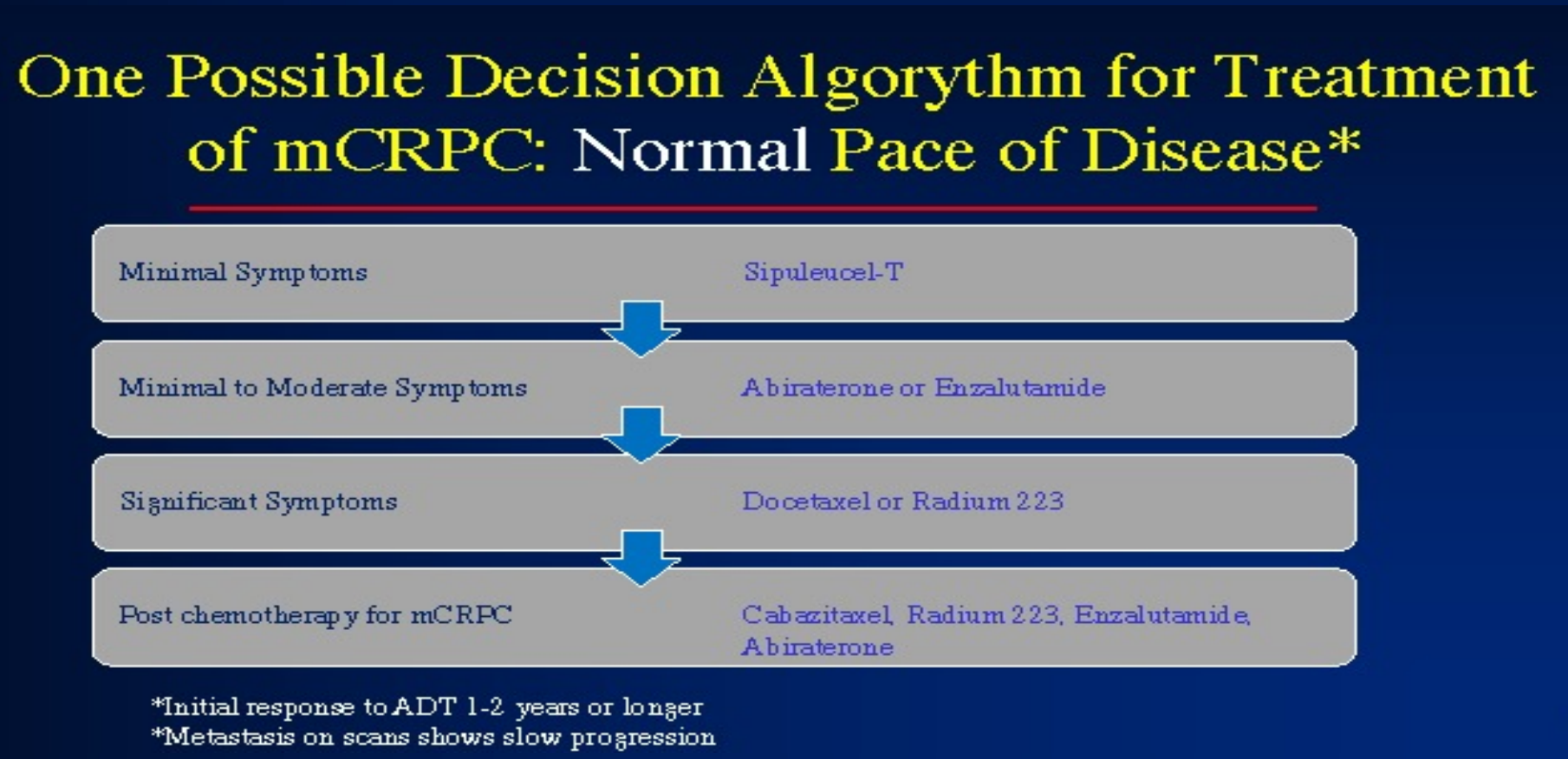
Hoskin, P. et al. Lancet Oncol, 2014.

Radium 223 AEs

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%)

Algorithm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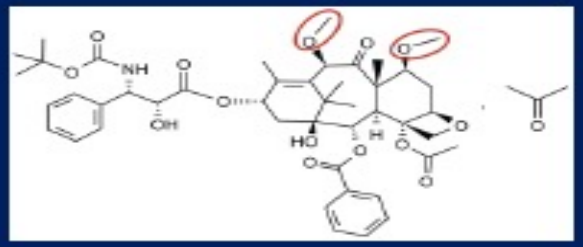
Cabazitaxel

Cabazitaxel

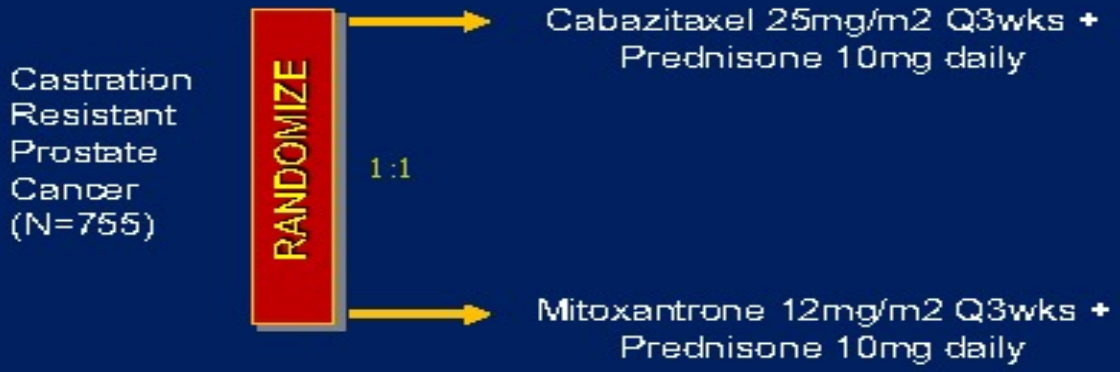
- Novel taxane active in docetaxel resistant cell lines
  - Less affinity for P-glycoprotein pump



Methoxyl side chain instead of hydroxyl groups found in docetaxel

Phase III study

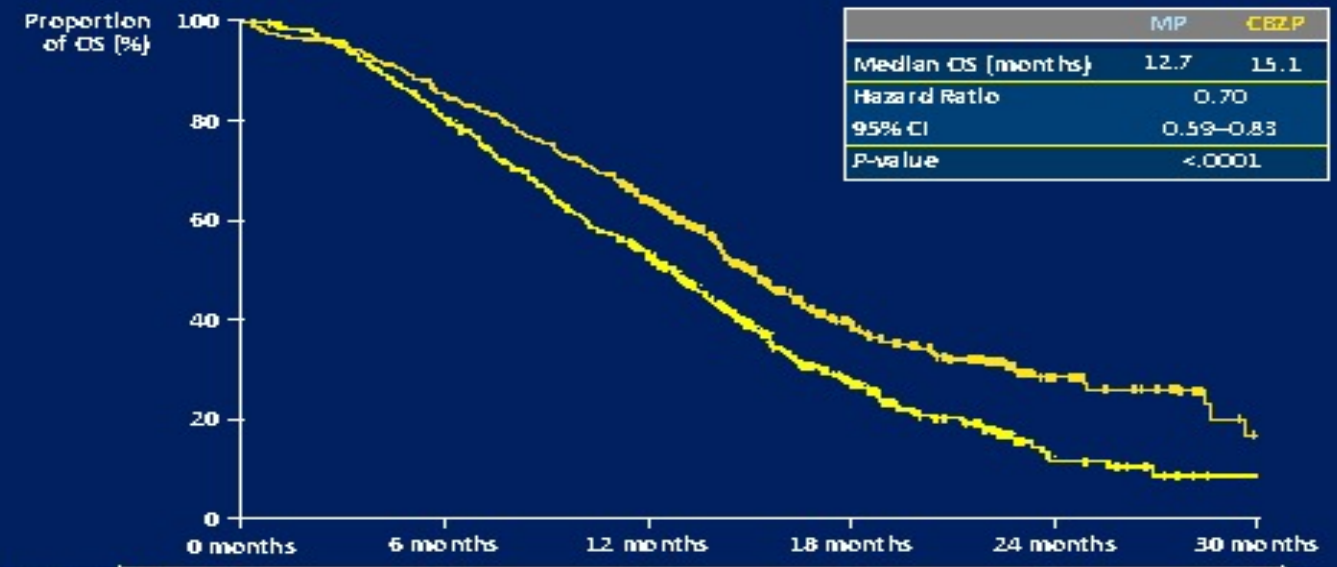
TROPIC: Randomized Phase III Study of Cabazitaxel vs. Mitoxantrone in mCRPC after Progression on Docetaxel



de Bono JS. et al. Lancet 2010

TROPIC

TROPIC: Overall Survival



de Bono JS. et al. Lancet 2010

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Cabazitaxel 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

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Cabazitaxel toxicity

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%)

Should strongly consider the use of growth factor

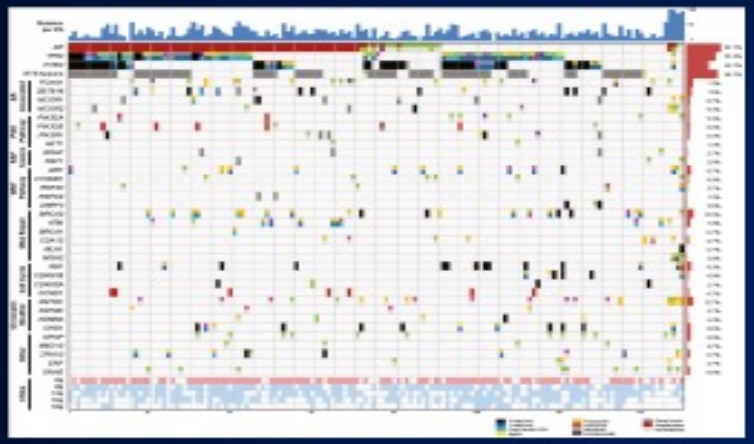
32

Metastatic disease

Biopsy Metastatic Disease?
Why?
When?

PARP inhibitor

PARP Inhibitor – Breakthrough Status



Robinson D *et al. Cell, 2015*

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

The NEW ENGLAND JOURNAL of MEDICINE

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

MSI high prostate cancer

MSI High Prostate Cancer

Approval of pembrolizumab

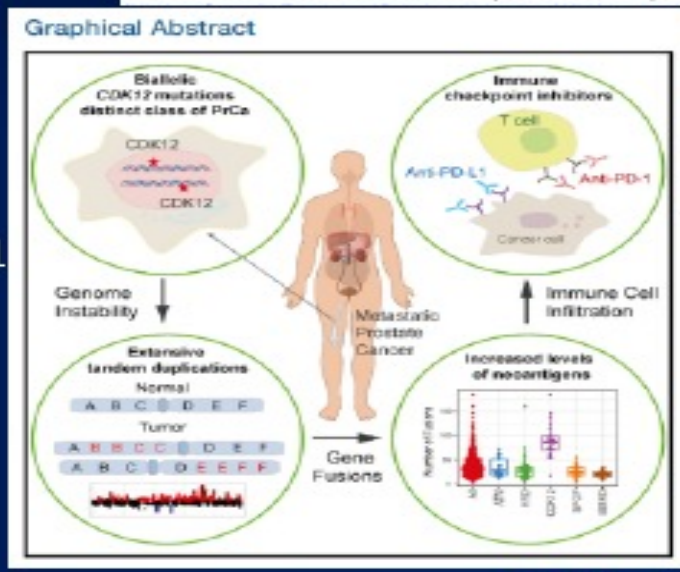
Incidence

- Localized PC ~2%
- Autopsy series of mCRPC ~12%
  - Pritchard et al., *Nature Com* 201
- Ongoing testing suggests 5-6% of mCRPC

Lemery et al., *NEJM* 2017

Inactivation of *CDK12* Delineates a Distinct Immunogenic Class of Advanced Prostate Cancer

Yi-Mi Wu,[1,2,20] Marcin Cieślik,[1,2,20] Robert J. Lonigro,[1] Pankaj Vats,[1] Melissa A. Reimers,[3] Xuhong Cao,[1] Yu Ning,[1] Lisha Wang,[1] Lakshmi P. Kunju,[1,2,4] Navonil de Sarkar,[5] Elisabeth I. Heath,[6,7] Jonathan Chou,[5] Felix Y. Feng,[8,9,10,11] Peter S. Nelson,[5,12,13] Johann S. de Bono,[14,15] Weiping Zou,[1,2,16] Bruce Montgomery,[12,17] Ajjai Alva,[1,2] PCF/SU2C International Prostate Cancer Dream Team, Dan R. Robinson,[1,2,*] and Arul M. Chinnaiyan[1,2,4,18,19,21,*]



Highlights

- *CDK12* biallelic inactivating mutations define a distinct subtype of prostate cancer
- *CDK12* loss is associated with genomic instability and local tandem duplications
- *CDK12* loss leads to increased gene fusions, neoantigen burden, and T cell infiltration
- Patients with *CDK12* mutant tumors may benefit from immune checkpoint inhibition

Wu YM *et al. Cell, 2018*

55

New therapies

MSI High Prostate Cancer

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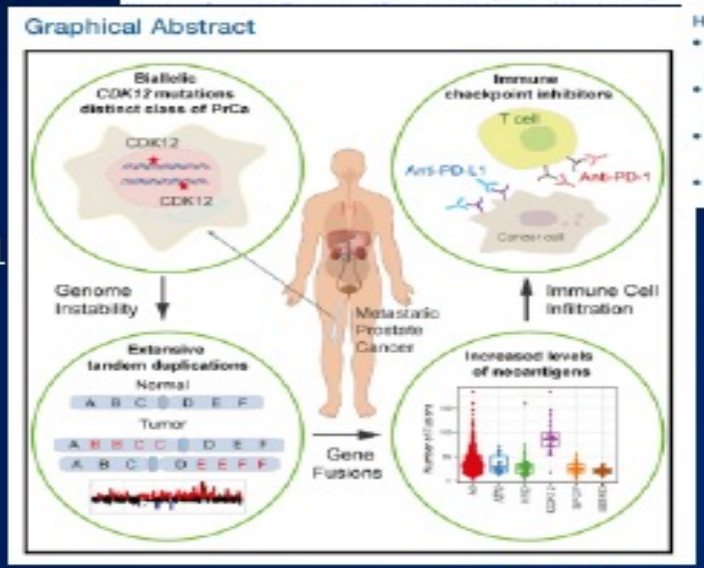

Wu YM *et al. Cell, 2018*

55

MSI

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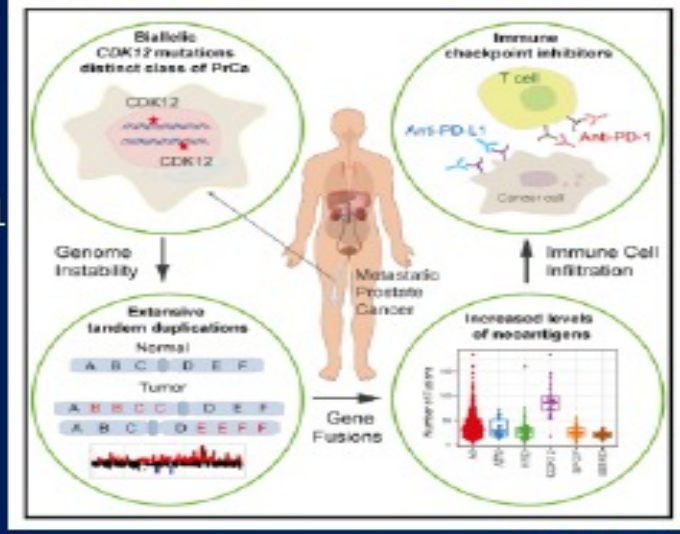

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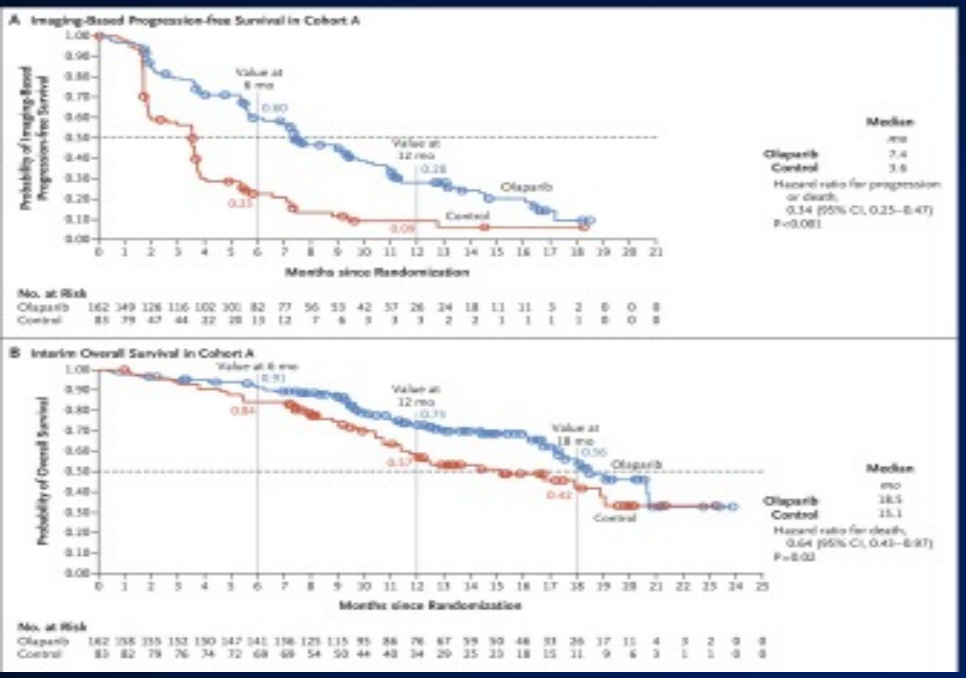
Wu YM et al. Cell, 2018

55

Olaparib

Olaparib for mCRPC (chemo-naïve)



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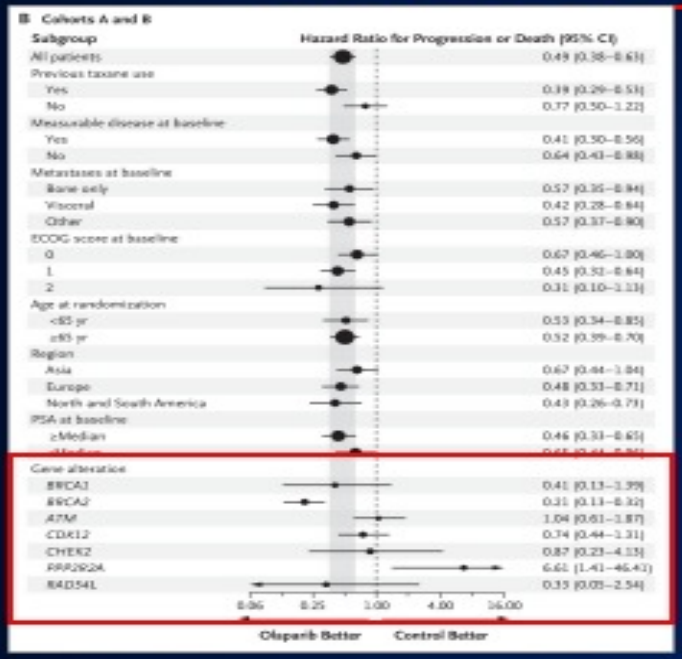
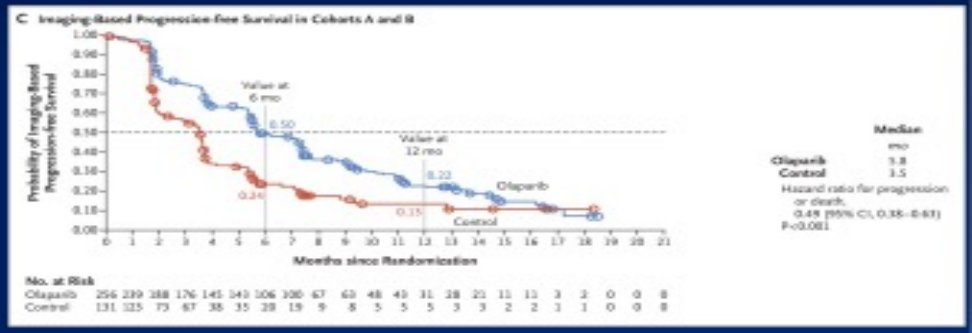
de Bono et al. N Engl J Med 2020

Olaparib for mCRPC

Olaparib for mCRPC (chemo-naïve)





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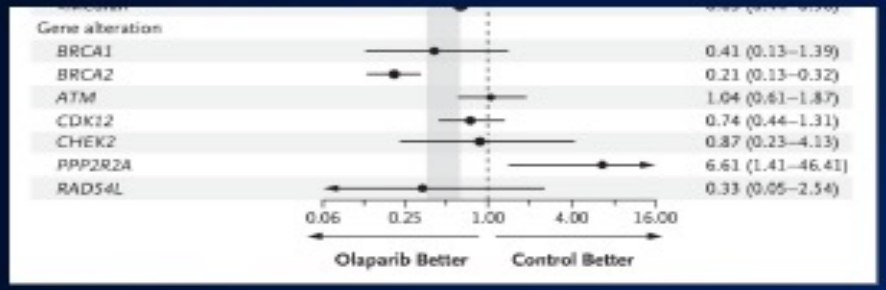
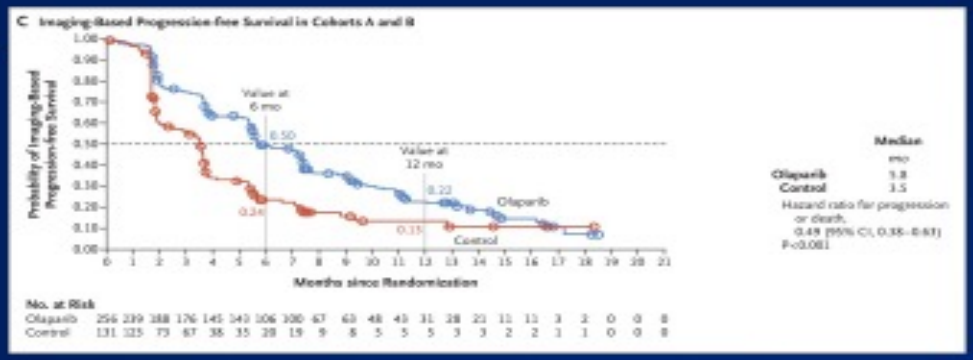
de Bono J. et al. N Engl J Med 2020

Chemo-naive

Olaparib for mCRPC (chemo-naïve)



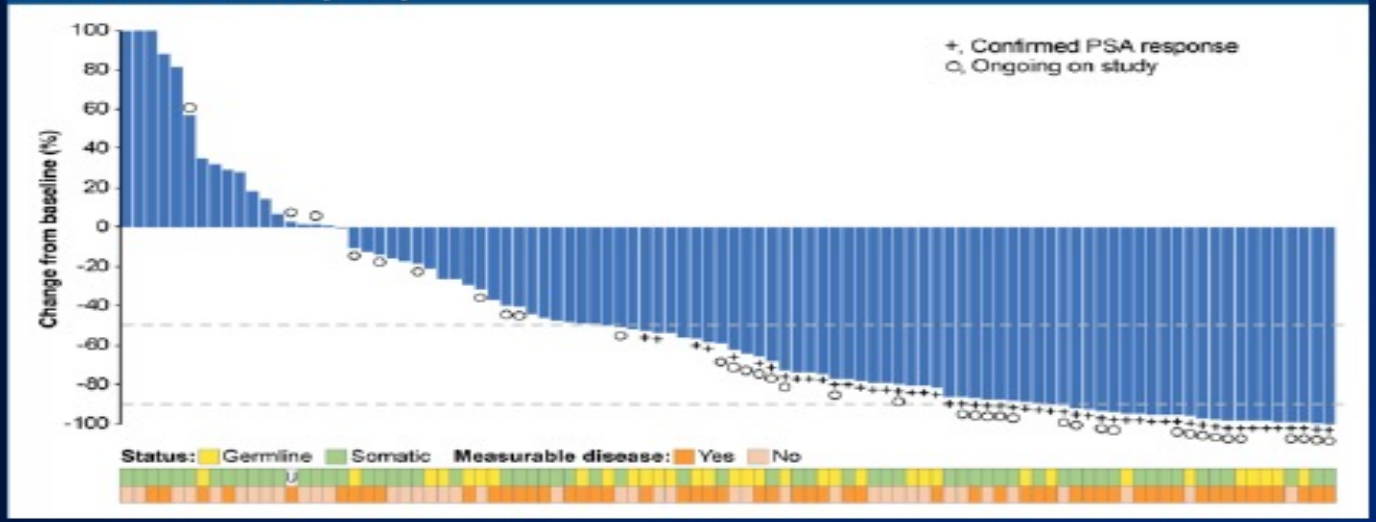


de Bono et al. N Engl J Med 2020

Rucaparib

Rucaparib mCRPC (chemo-refractory)

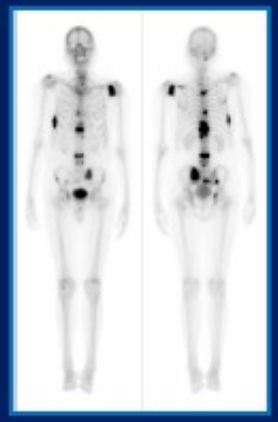
Figure 4. Best Change from Baseline in PSA in Rucaparib-Treated Patients with a *BRCA1/2* Alteration (n=96)



Abida W et al. ESMO 2020

Current approach

Castration-Resistant Prostate Cancer: Current Approach



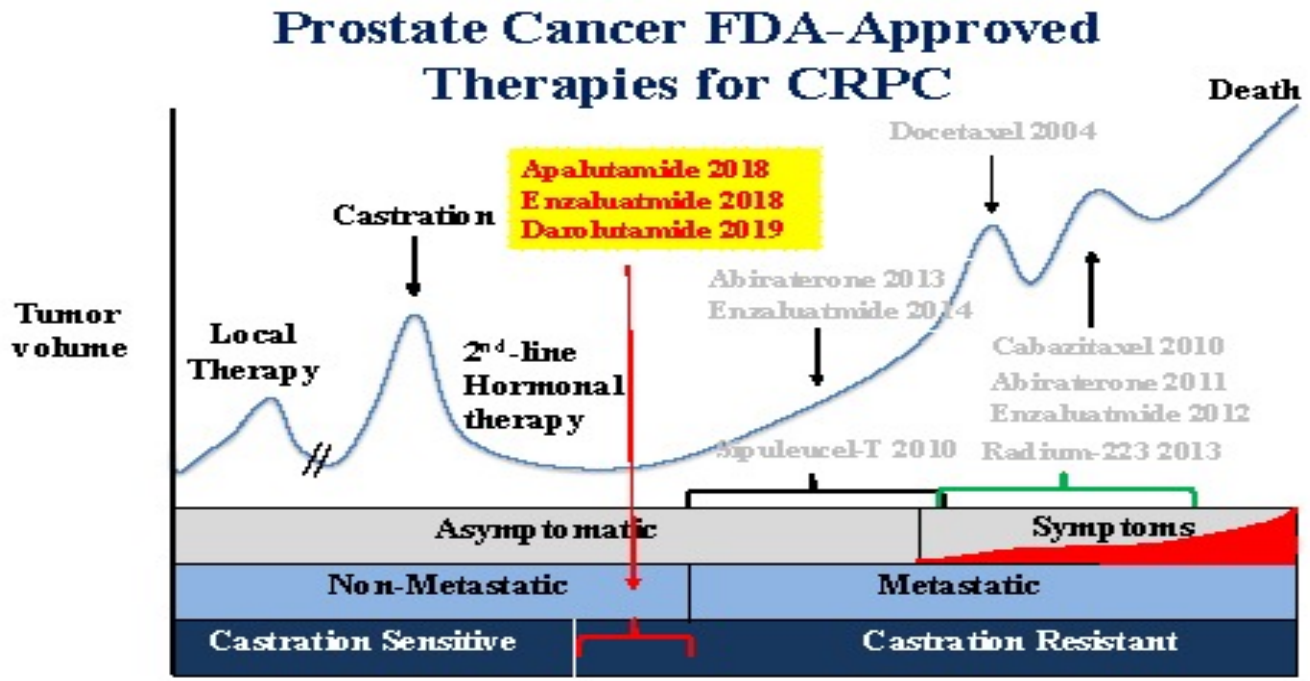
Ravi A. Madan, M.D.
Clinical Director
Genitourinary Malignancies Branch
Center for Cancer Research, NCI, NIH

@Dr_RaviMadan

Prostate cancer

Non-Metastatic Castration Resistant Prostate Cancer

Approved therapies



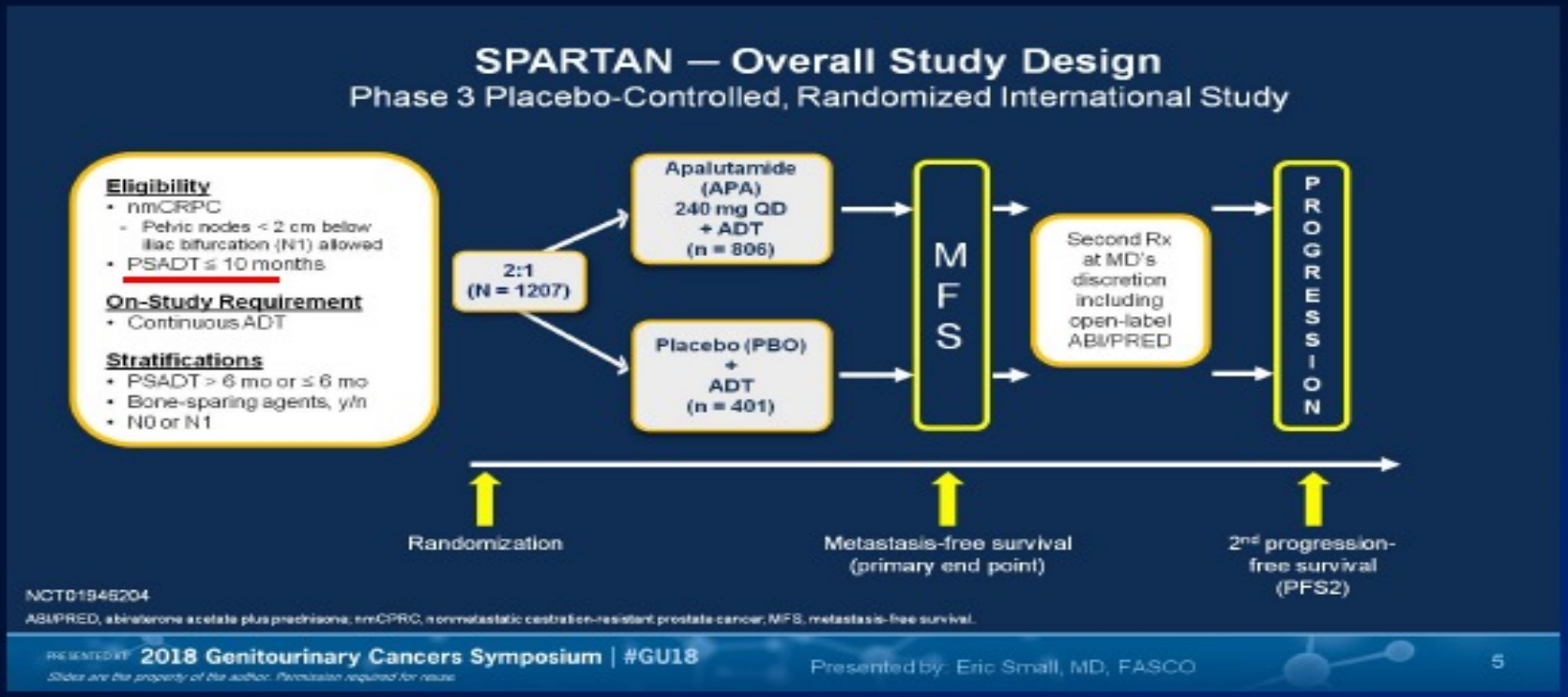
Apalutamide

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

Smith, M R et al , NEJM, 2018

SPARTAN


SPARTAN — Overall Study Design
Phase 3 Placebo-Controlled, Randomized International Study
Eligibility
• nmCRPC
- Pelvic nodes < 2 cm below iliac bifurcation (N1) allowed
• PSADT ≤ 10 months
On-Study Requirement
• Continuous ADT
Stratifications
• PSADT > 6 mo or ≤ 6 mo
• Bone-sparing agents, y/n
• N0 or N1
2:1
(N = 1207)
Apalutamide (APA) 240 mg QD + ADT (n = 806)
Placebo (PBO) + ADT (n = 401)
MFS
Second Rx at MD's discretion including open-label ABI/PRED
PROGRESSION
Randomization
Metastasis-free survival (primary end point)
2nd progression-free survival (PFS2)
NCT01946204
ABI/PRED, abiraterone acetate plus prednisone; nmCPRC, nonmetastatic castration-resistant prostate cancer; MFS, metastasis-free survival.
PRESENTED AT 2018 Genitourinary Cancers Symposium | #GU18
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Presented by: Eric Small, MD, FASCO
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Apalutamide

Apalutamide in nmCRPC

Patient Baseline Characteristics

Apalutamide in M0 prostate cancer

Table 1. Demographic and Disease Characteristics at Baseline.*

Characteristic	Apalutamide (N = 806)	Placebo (N = 401)
Age — yr		
Median	74	74
Range	48–94	52–97
Median time from initial diagnosis to randomization — yr	7.95	7.85
Prostate-specific antigen doubling time		
Median — mo	4.40	4.50
≤6 Mo — no. (%)	576 (71.5)	284 (70.8)
>6 Mo — no. (%)	230 (28.5)	117 (29.2)
Use of bone-sparing agent — no. (%)		
Yes	82 (10.2)	39 (9.7)
No	724 (89.8)	362 (90.3)
Classification of local or regional nodal disease — no. (%)		
N0	673 (83.5)	336 (83.8)
N1	133 (16.5)	65 (16.2)
Previous prostate-cancer treatment — no. (%)		
Prostatectomy or radiation therapy	617 (76.6)	307 (76.6)
Gonadotropin-releasing hormone analogue agonist	780 (96.8)	387 (96.5)
First-generation antiandrogen agent†	592 (73.4)	290 (72.3)

* There were no significant differences between groups in the demographic and disease characteristics at baseline.
† First-generation antiandrogen agents are flutamide, bicalutamide, and nilutamide.

Smith, MR et al, NEJM, 2018

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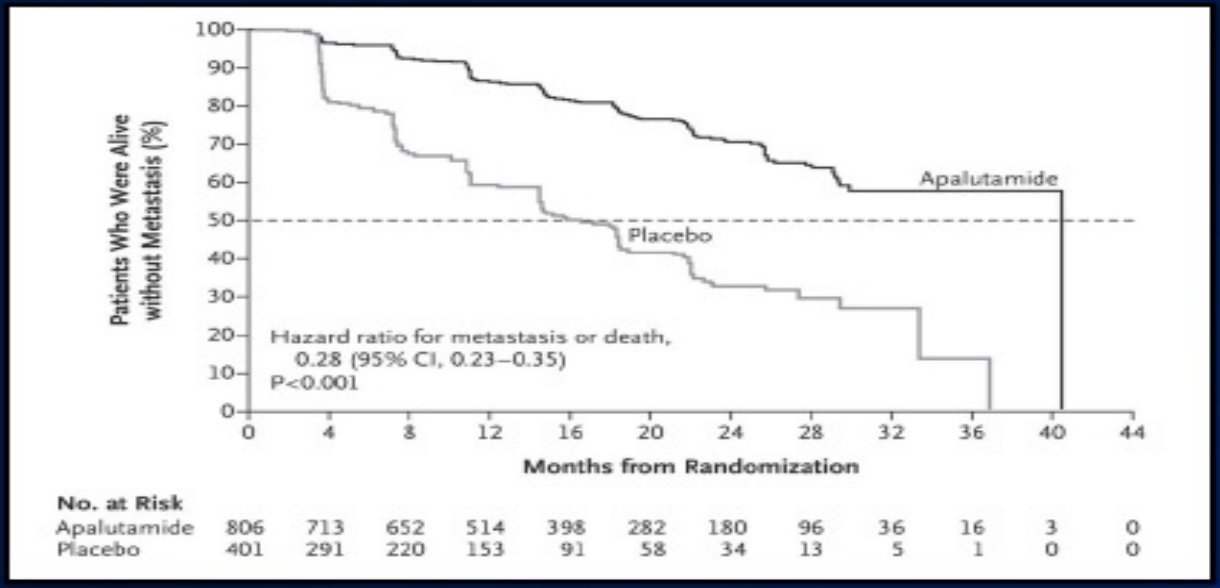
Metastasis-free survival

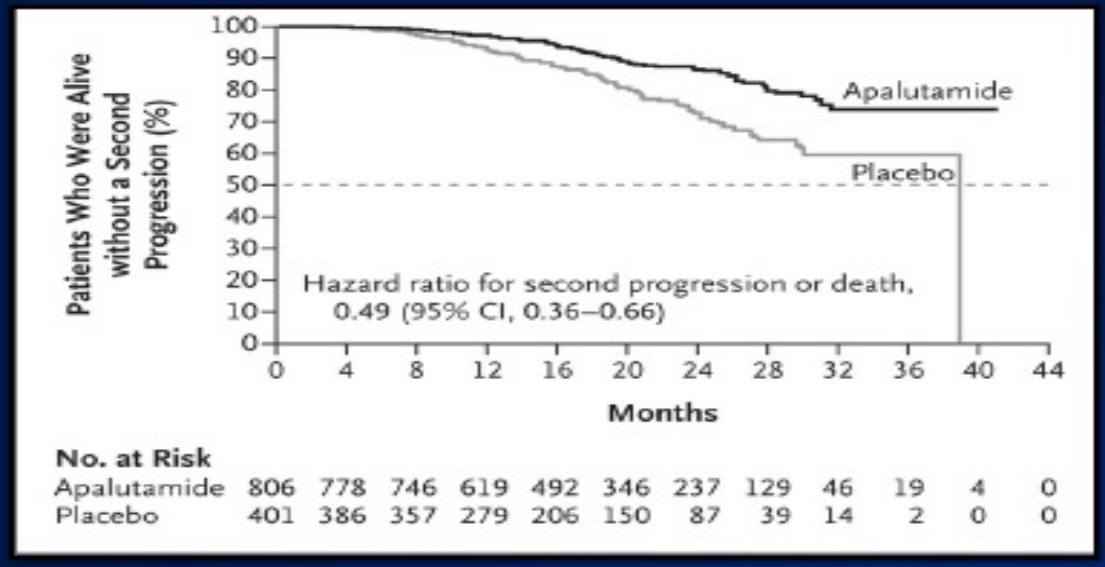
Apalutamide Improves Metastasis-Free Survival



Smith, M R et al, NEJM, 2018

Secondary progression

Secondary Progression for Patients Who were Subsequently Treated with Abiraterone



Smith, MR et al, NEJM, 2018

Apalutamide

Apalutamide in nmCRPC

Toxicity

Apalutamide in MO Prostate Cancer

Table 3. Adverse Events.

Adverse Event*	Apalutamide (N=806)		Placebo (N=398)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	no. of patients (%)			
Any adverse event	775 (96.5)	362 (45.1)	371 (93.2)	136 (34.2)
Serious adverse event	199 (24.8)	—	92 (23.1)	—
Adverse event leading to discontinuation of the trial regimen	85 (10.6)	—	28 (7.0)	—
Adverse event associated with death	10 (1.2)	—	1 (0.3)	—
Adverse events that occurred in ≥15% of patients in either group†				
Fatigue‡	244 (30.4)	7 (0.9)	84 (21.1)	1 (0.3)
Hypertension	199 (24.8)	115 (14.3)	79 (19.8)	47 (11.8)
Rash‡	191 (23.8)	42 (5.2)	22 (5.5)	1 (0.3)
Diarrhea	163 (20.3)	8 (1.0)	60 (15.1)	2 (0.5)
Nausea	145 (18.1)	0	63 (15.8)	0
Weight loss	129 (16.1)	9 (1.1)	25 (6.3)	1 (0.3)
Arthralgia	128 (15.9)	0	30 (7.5)	0
Fall‡	125 (15.6)	14 (1.7)	36 (9.0)	3 (0.8)
Other adverse events of interest				
Fracture‡	94 (11.7)	22 (2.7)	26 (6.5)	3 (0.8)
Dizziness	75 (9.3)	5 (0.6)	25 (6.3)	0
Hypothyroidism‡	65 (8.1)	0	8 (2.0)	0
Mental-impairment disorder‖	41 (5.1)	0	12 (3.0)	0
Seizure‡	2 (0.2)	0	0	0

Smith, MR et al, NEJM, 2018

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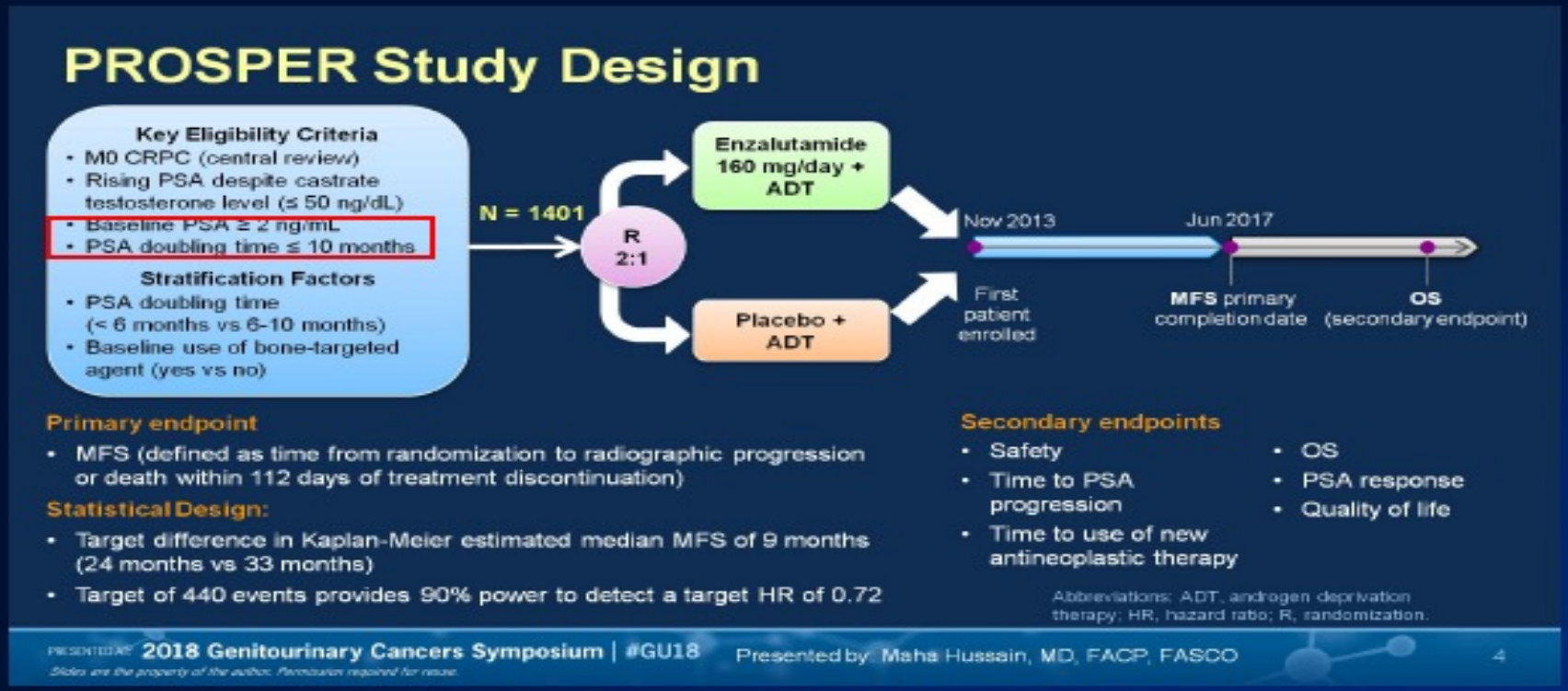
PROSPER


PROSPER Study Design
Key Eligibility Criteria
• M0 CRPC (central review)
• Rising PSA despite castrate testosterone level (≤ 50 ng/dL)
• Baseline PSA ≥ 2 ng/mL
• PSA doubling time ≤ 10 months
Stratification Factors
• PSA doubling time (< 6 months vs 6-10 months)
• Baseline use of bone-targeted agent (yes vs no)
N = 1401
R 2:1
Enzalutamide 160 mg/day + ADT
Placebo + ADT
Nov 2013
Jun 2017
First patient enrolled
MFS primary completion date
OS (secondary endpoint)
Primary endpoint
• MFS (defined as time from randomization to radiographic progression or death within 112 days of treatment discontinuation)
Statistical Design:
• Target difference in Kaplan-Meier estimated median MFS of 9 months (24 months vs 33 months)
• Target of 440 events provides 90% power to detect a target HR of 0.72
Secondary endpoints
• Safety
• Time to PSA progression
• Time to use of new antineoplastic therapy
• OS
• PSA response
• Quality of life
Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; R, randomization.
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Presented by: Maha Hussain, MD, FACP, FASCO
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Enzalutamide

Enzalutamide in M0/nmCRPC: The Patients

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Enzalutamide Group (N=933)	Placebo Group (N=468)
Age — yr		
Median	74	73
Range	50–95	53–92
ECOG performance-status score — no. (%)†		
0	747 (80)	382 (82)
1	185 (20)	85 (18)
Missing data	1 (<1)	1 (<1)
Serum PSA value — ng/ml		
Median	11.1	10.2
Range	0.8–3071.1	0.2–467.5
PSA doubling time		
Median — mo	3.8	3.6
Range — mo	0.4–37.4	0.5–71.8
Distribution — no. (%)		
<6 mo	715 (77)	361 (77)
≥6 mo	217 (23)	107 (23)
Missing data	1 (<1)	0
Use of bone-targeting agent — no. (%)		
No	828 (89)	420 (90)
Yes	105 (11)	48 (10)

* There were no significant between-group differences in these characteristics at baseline. Percentages may not total 100 because of rounding. PSA denotes prostate-specific antigen.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores are on a scale from 0 to 5, with higher scores indicating greater disability and a score of 5 indicating death.

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Mets free survival

Enzalutamide in M0/nmCRPC: Mets Free Survival

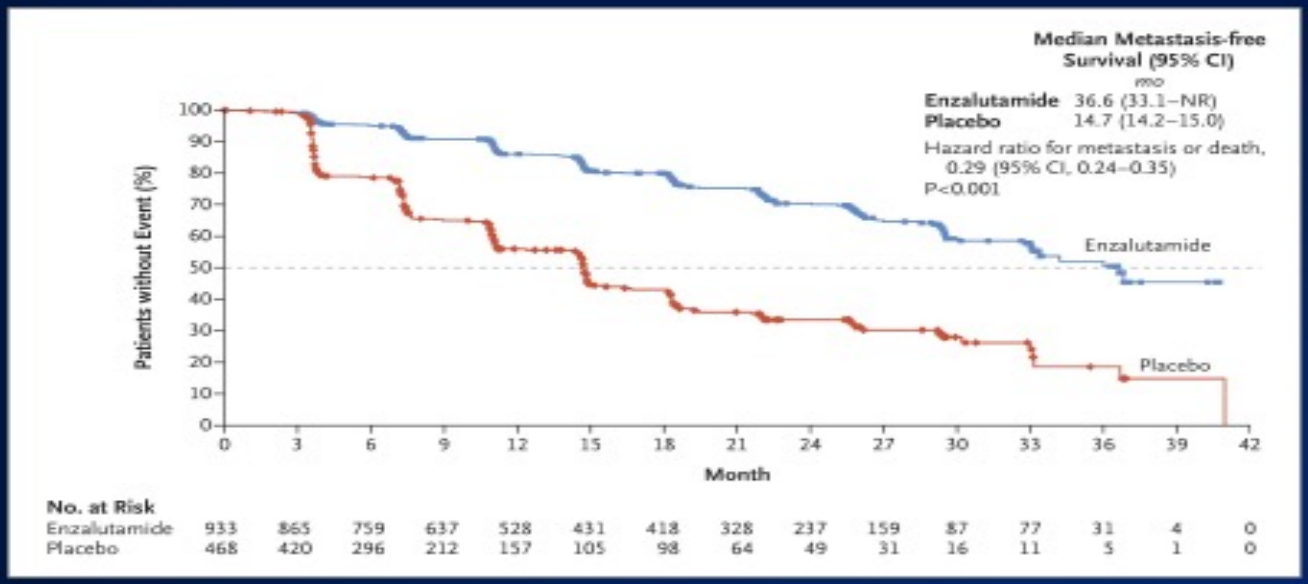
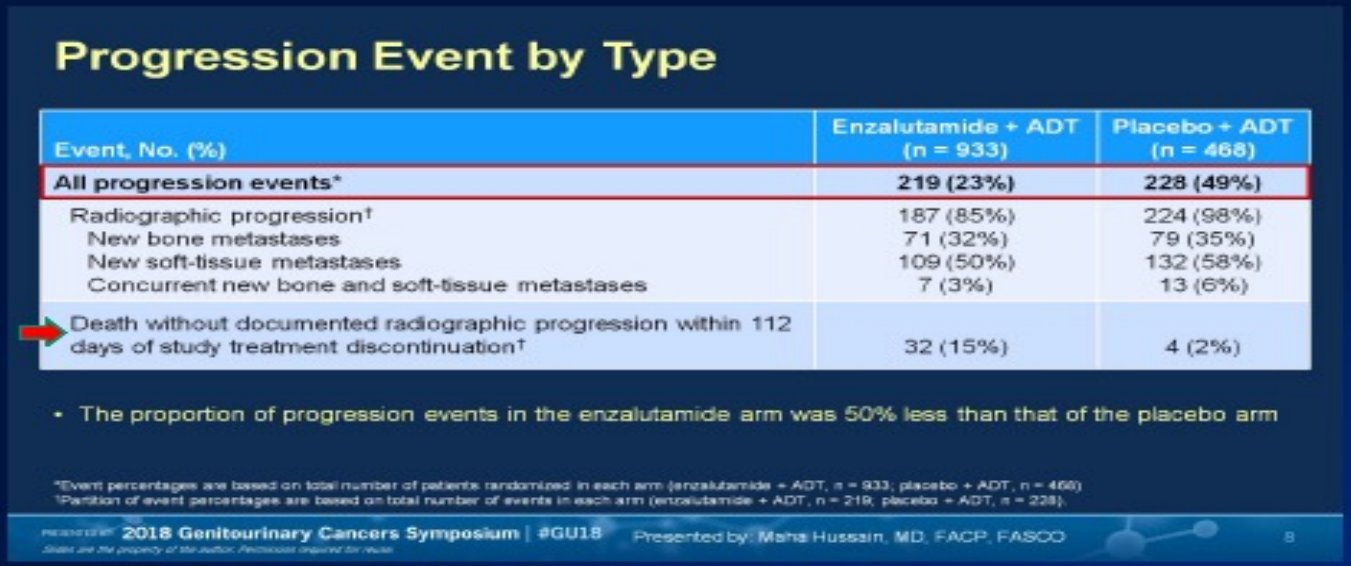


Table 3. Adverse Events.

Event	Enzalutamide Group (N = 930)		Placebo Group (N = 465)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any adverse event	808 (87)	292 (31)	360 (77)	109 (23)
Any serious adverse event*	226 (24)	—	85 (18)	—
Adverse event leading to discontinuation of trial regimen	87 (9)	—	28 (6)	—
Adverse event leading to death	32 (3)	—	3 (1)	—
Most common adverse events, occurring in ≥5% of patients†				
Fatigue	303 (33)	27 (3)	64 (14)	3 (1)
Hot flush	121 (13)	1 (<1)	36 (8)	0
Nausea	106 (11)	3 (<1)	40 (9)	0
Diarrhea	91 (10)	3 (<1)	45 (10)	2 (<1)
Hypertension	111 (12)	43 (5)	24 (5)	10 (2)
Fall	106 (11)	12 (1)	19 (4)	3 (1)
Constipation	85 (9)	2 (<1)	32 (7)	2 (<1)
Dizziness	91 (10)	4 (<1)	20 (4)	0
Arthralgia	78 (8)	1 (<1)	32 (7)	1 (<1)
Asthenia	82 (9)	11 (1)	28 (6)	1 (<1)
Decreased appetite	89 (10)	2 (<1)	18 (4)	1 (<1)
Back pain	73 (8)	2 (<1)	33 (7)	1 (<1)
Headache	85 (9)	2 (<1)	21 (5)	0
Hematuria	62 (7)	16 (2)	36 (8)	13 (3)
Urinary tract infection	38 (4)	7 (1)	30 (6)	3 (1)
Weight loss	55 (6)	2 (<1)	7 (2)	0
Urinary retention	20 (2)	4 (<1)	28 (6)	5 (1)
Adverse events of special interest				
Hypertension‡	114 (12)	43 (5)	25 (5)	11 (2)
Major adverse cardiovascular event§	48 (5)	34 (4)	13 (3)	8 (2)
Mental impairment disorders¶	48 (5)	1 (<1)	9 (2)	0
Hepatic impairment	11 (1)	5 (1)	9 (2)	2 (<1)
Neutropenia	9 (1)	5 (1)	1 (<1)	1 (<1)
Convulsion	3 (<1)	2 (<1)	0	0
Posterior reversible encephalopathy syndrome	0	0	0	0

Progression



Progression Event by Type

Event, No. (%)	Enzalutamide + ADT (n = 933)	Placebo + ADT (n = 468)
All progression events*	**219 (23%)**	**228 (49%)**
Radiographic progression†	187 (85%)	224 (98%)
New bone metastases	71 (32%)	79 (35%)
New soft-tissue metastases	109 (50%)	132 (58%)
Concurrent new bone and soft-tissue metastases	7 (3%)	13 (6%)
Death without documented radiographic progression within 112 days of study treatment discontinuation†	32 (15%)	4 (2%)

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

*Event percentages are based on total number of patients randomized in each arm (enzalutamide + ADT, n = 933; placebo + ADT, n = 468).
†Partition of event percentages are based on total number of events in each arm (enzalutamide + ADT, n = 219; placebo + ADT, n = 228).

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Updated data

Most Updated Data in nmCRPC

Comparison of phase III trials investigating enzalutamide, apalutamide and darolutamide in patients with non-metastatic castration resistant prostate cancer.

	PROSPER [4, 5]	SPARTAN [2, 7]	ARAMIS [3, 8]
Total number of patients			1509
Investigational drug (N) vs placebo (N)			Darolutamide (955) vs. placebo (554)
Median MFS in months (HR for metastasis or death; 95% CI, p-value)			40.4 vs. 18.4 (0.41; 0.34 - 0.50; $p < 0.001$)
Median time to PSA progression in months (HR of PSA progression or death; 95% CI, p-value)			33.2 vs. 7.3 (0.13; 0.11 to 0.16; $p < 0.001$)
Median overall survival in months (HR, 95% CI; p-value)			NR vs NR (0.69, 0.53 – 0.88; $p = 0.003$)
Duration of treatment in months; Subsequent Therapy (%)			NR; NR
Time to first pain progression in months (HR, 95% CI, p-value)			40.3 vs 25.4 (0.65, 0.53 – 0.79; $p < 0.001$)
Time to subsequent antineoplastic therapy months (HR, 95% CI, p-value)			NR vs NR (0.33, 0.23–0.47; $p < 0.001$)
Time to first cytotoxic chemotherapy in months (HR, 95% CI, p-value)			NR vs NR (0.58, 0.44 – 0.76; $p < 0.001$)

N: numbers; MFS: Metastasis-free survival; NR: Not reported;.
HR: Hazards ratio; CI: Confidence Interval.

Sekani , Jeha , Cancer Treatment and Research Communications, 2020

nmCRPC data

Most Updated Data in nmCRPC

Comparison of phase III trials investigating enzalutamide, apalutamide and darolutamide in patients with non-metastatic castration resistant prostate cancer.

	PROSPER [4, 5]	SPARTAN [2, 7]	ARAMIS [3, 8]
Total number of patients	1401	1207	1509
Investigational drug (N) vs placebo (N)	Enzalutamide (933) vs. placebo (468)	Apalutamide (806) vs. placebo (401)	Darolutamide (955) vs. placebo (554)
Median MFS in months (HR for metastasis or death; 95% CI, p-value)	36.6 vs. 14.7 (0.29; 0.24 - 0.35; $p<0.001$)	40.5 vs. 16.2 (0.28; 0.23 to 0.35; $p<0.001$)	40.4 vs. 18.4 (0.41; 0.34 - 0.50; $p<0.001$)
Median time to PSA progression in months (HR of PSA progression or death; 95% CI, p-value)	37.2 vs. 3.9 (0.07; 0.05–0.08, $p<0.001$)	NR vs. 3.7 (0.06; 0.05–0.08; p-value NR)	33.2 vs. 7.3 (0.13; 0.11 to 0.16; $p<0.001$)
Median overall survival in months (HR, 95% CI; p-value)	67 vs. 56.3 (0.73, 0.61 – 0.89; $p = 0.0011$) with median 48 months follow-up	73.9 vs. 59.9 (0.784, N/A, $p = 0.0161$) with median 52 months follow-up	NR vs NR (0.69, 0.53 – 0.88; $p = 0.003$)
Duration of treatment in months; Subsequent Therapy (%)	33.9 vs 14.2; 33% vs. 65%	32.9 vs 11.5; NR	NR; NR
Time to first pain progression in months (HR, 95% CI, p-value)	NR	NR	40.3 vs 25.4 (0.65, 0.53 – 0.79; $p < 0.001$)
Time to subsequent antineoplastic therapy months (HR, 95% CI, p-value)	39.6 vs. 17.7 (0.21; 0.17–0.26; $p<0.001$)	NR	NR vs NR (0.33; 0.23–0.47; $p<0.001$)
Time to first cytotoxic chemotherapy in months (HR, 95% CI, p-value)	N/A	NR vs NR (0.629, N/A; $p = 0.0002$)	NR vs NR (0.58, 0.44 – 0.76; $p < 0.001$)

N: numbers; MFS: Metastasis-free survival; NR: Not reported;.
HR: Hazards ratio; CI: Confidence Interval.

Sekhoacha M, et al. Cancer Treatment and Research Communications. 2020

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My thoughts

My Thoughts on Treating M0 Prostate Cancer/nmCRPC

- Consider the eligibility of the trials
  - PSA Doubling Time less than 10 months
  - Minimum PSA Value (i.e. 2)
- Risk vs. Benefit in an elderly population
- Personally, I may still consider an older agent (i.e. bicalutamide) first, but apalutamide/enzalutamide will be a good for a subset of patients
- Unknown how PET imaging will impact these populations

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