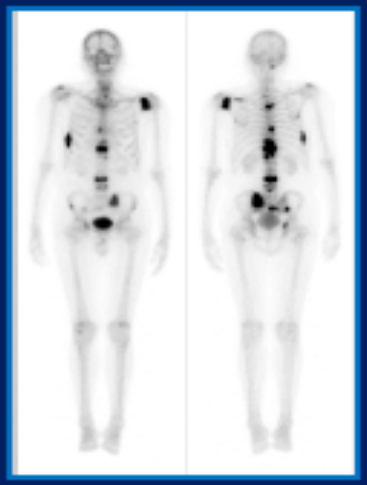
Castration-resistant prostate cancer

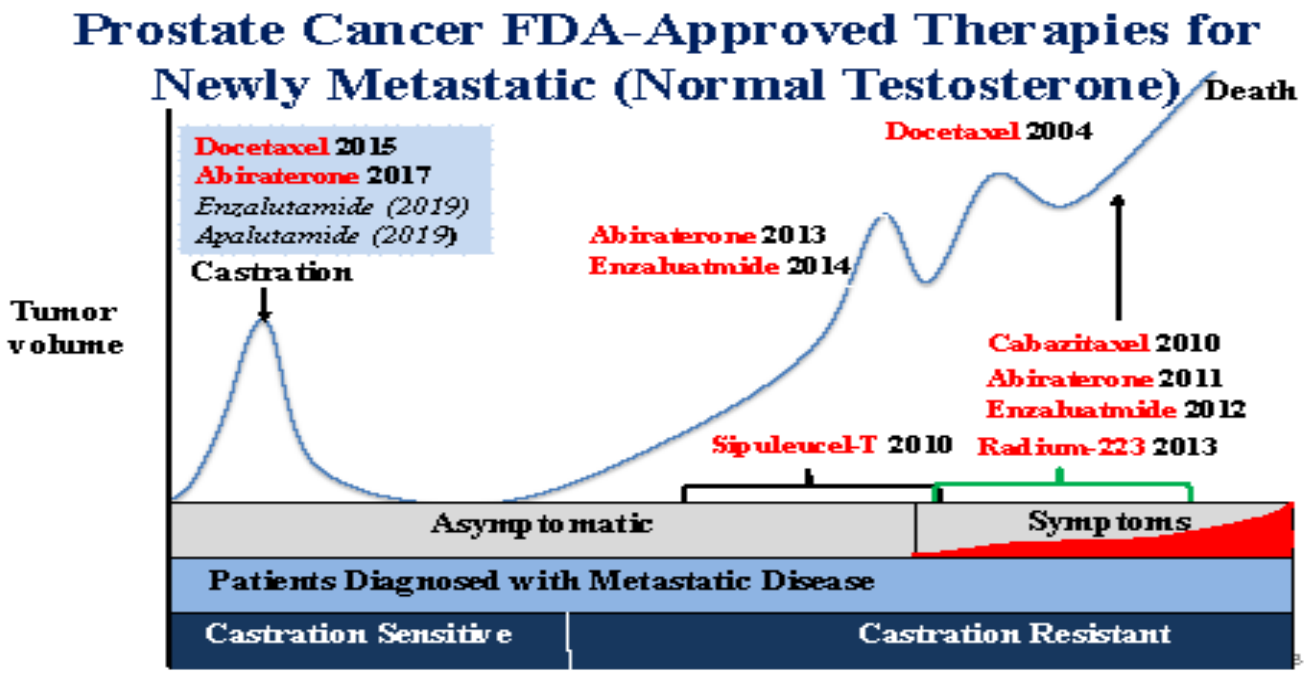
Castration-Resistant Prostate Cancer: Current Approach



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

@Dr_RaviMadan

FDA approved therapies



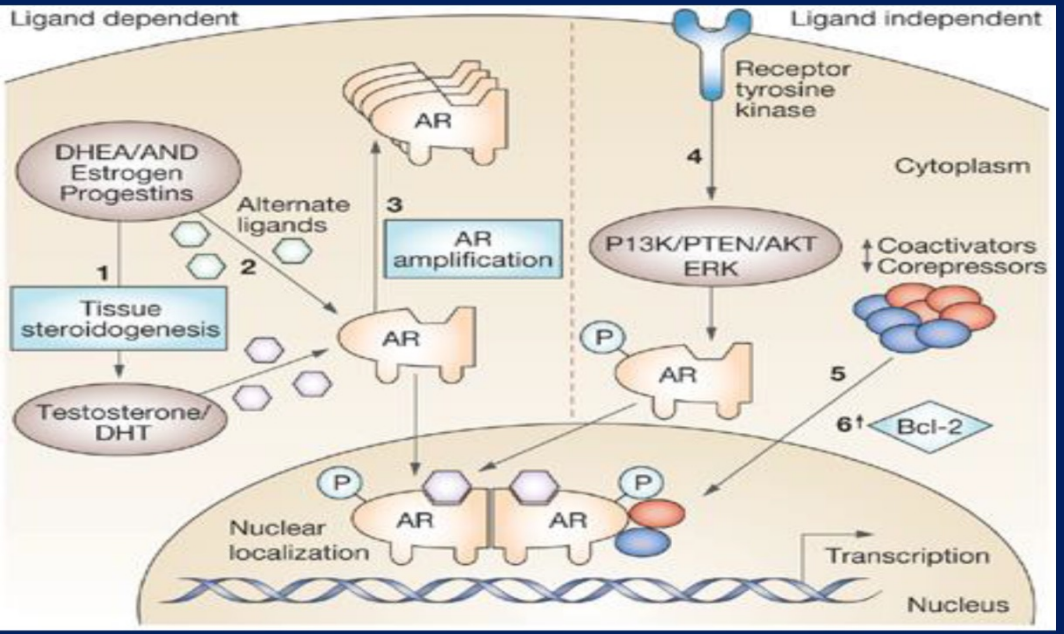
Castrate resistant prostate cancer

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

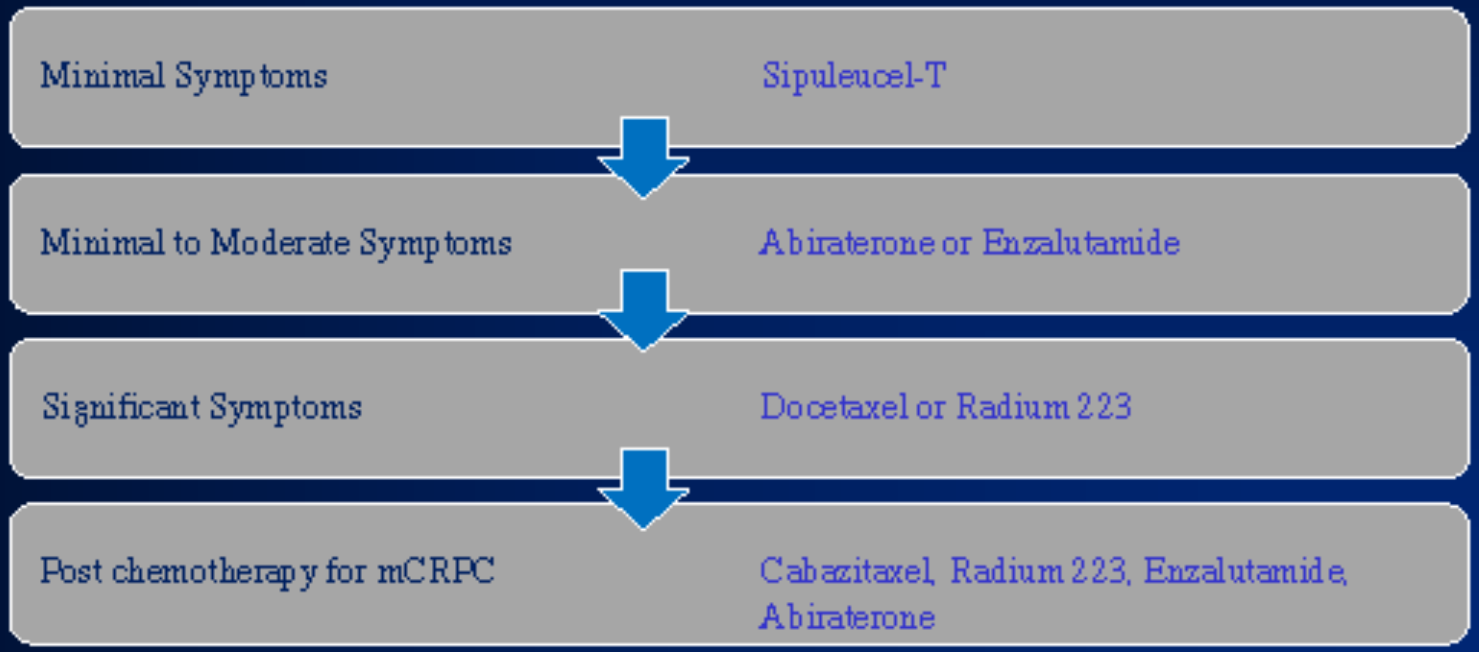
Key disease questions:

- 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

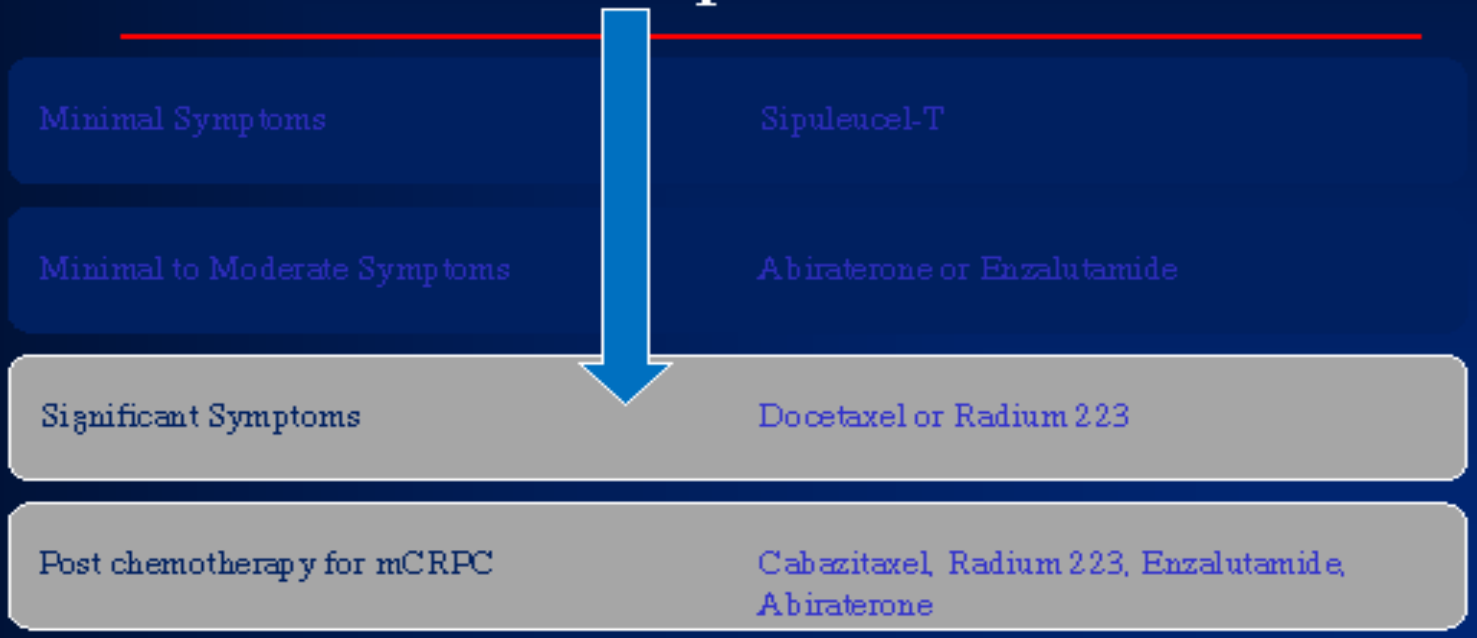
One Possible Decision Algorithm for Treatment of mCRPC: Normal Pace of Disease*



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

Algorithm

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



*Initial response to ADT short (e.g less than 1 year) or
*Metastasis on scans shows rapid progression

Decision algorithm

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

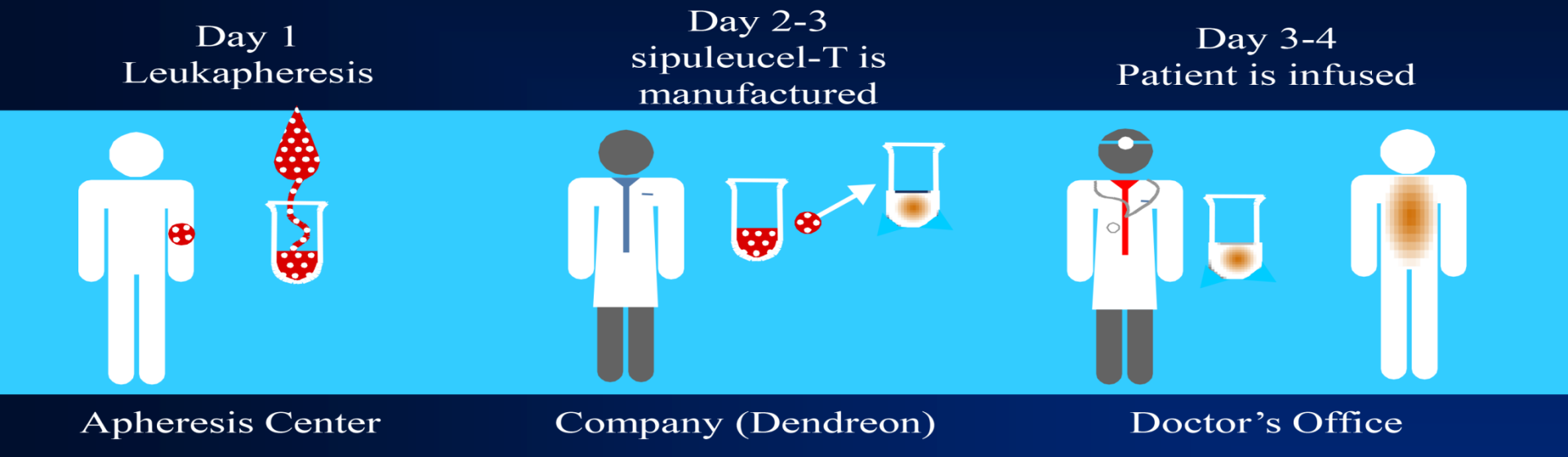
Minimal Symptoms	Sipuleucel-T

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

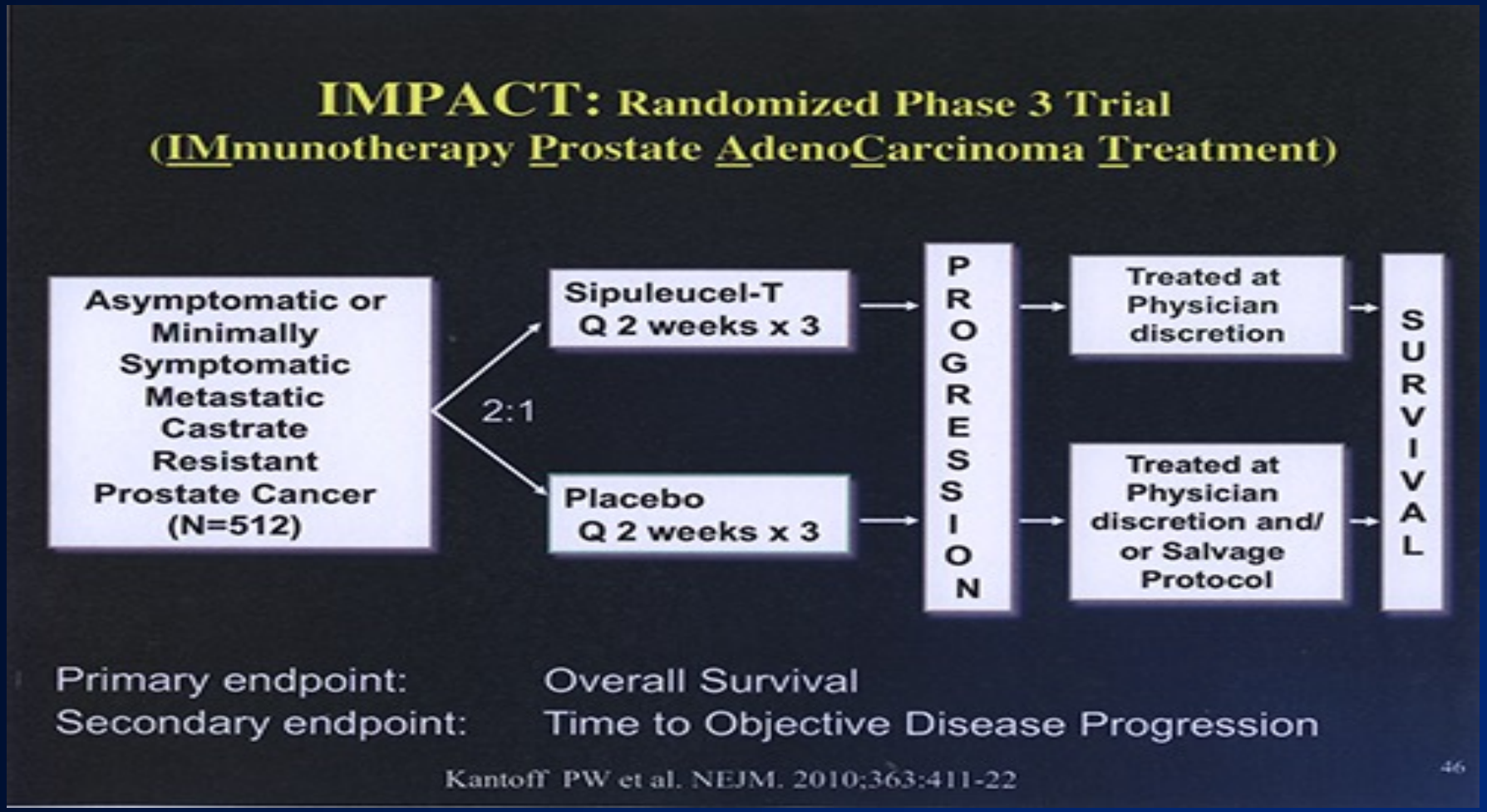
11

Therapeutic Cancer Vaccine: Sipuleucel-T

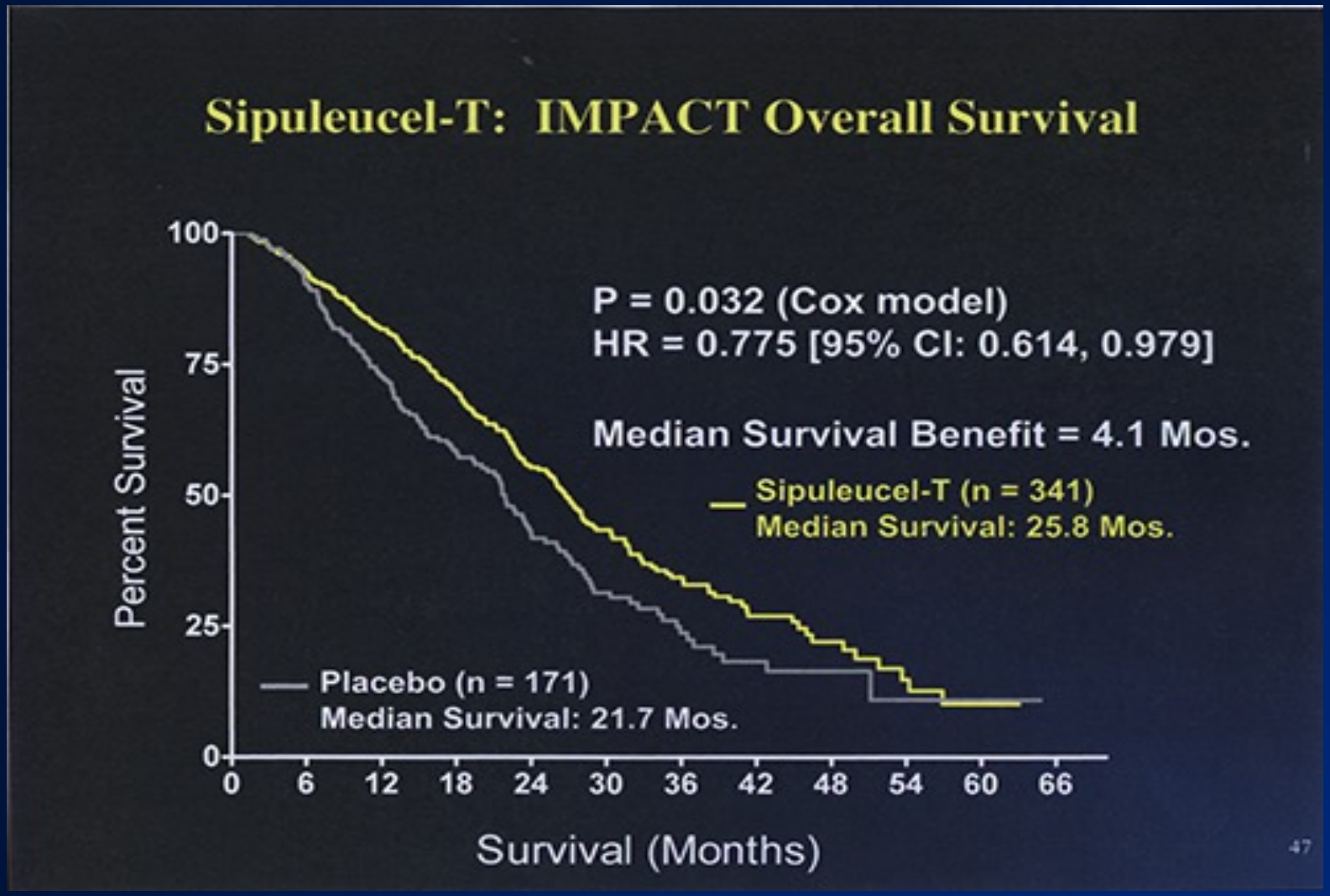
Therapeutic Cancer Vaccine: Sipuleucel-T



IMPACT: Randomized Phase 3 Trial

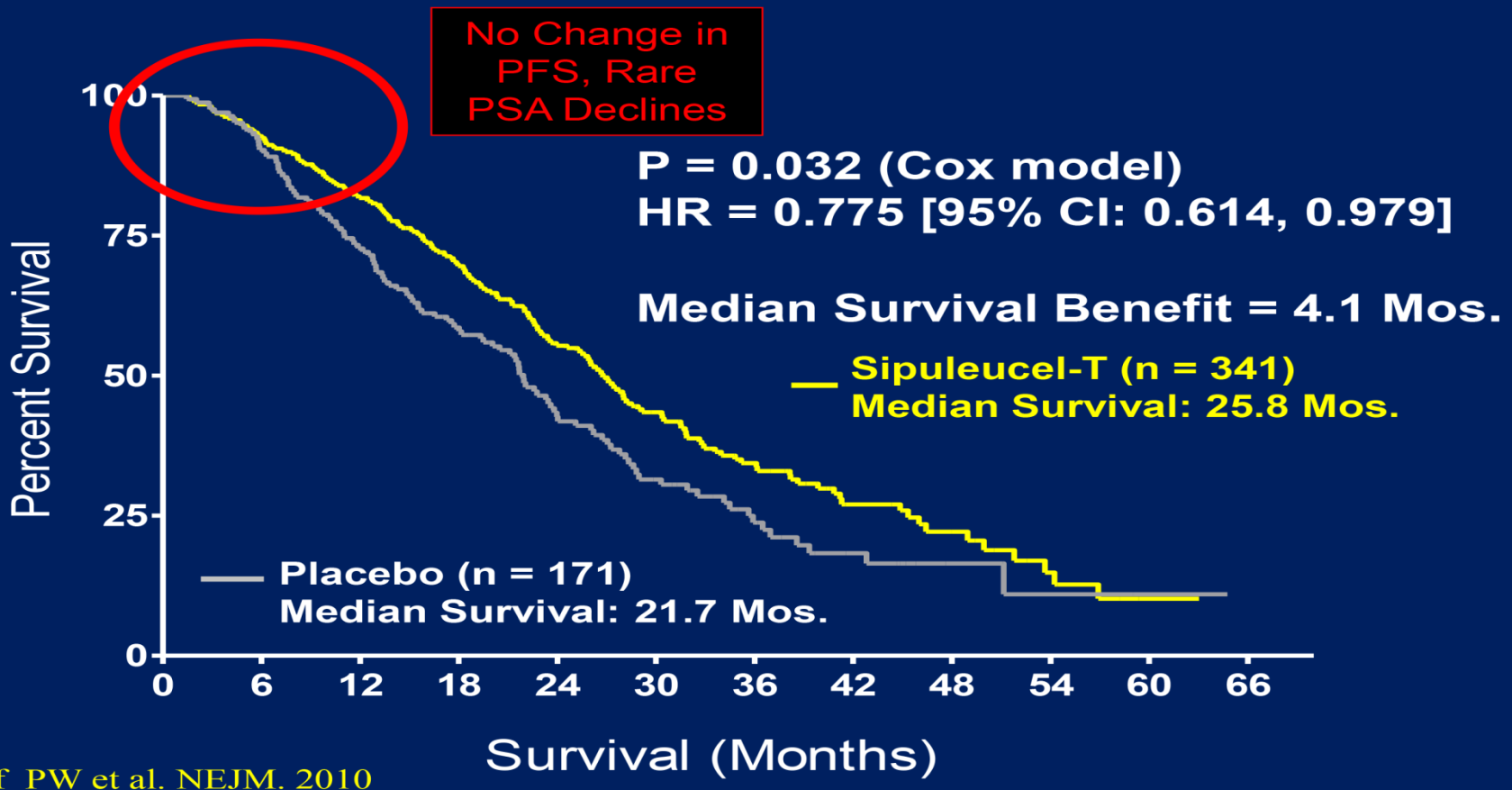


Sipuleucel-T: IMPACT Overall Survival



Sipuleucel-T

Sipuleucel-T: IMPACT Overall Survival



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

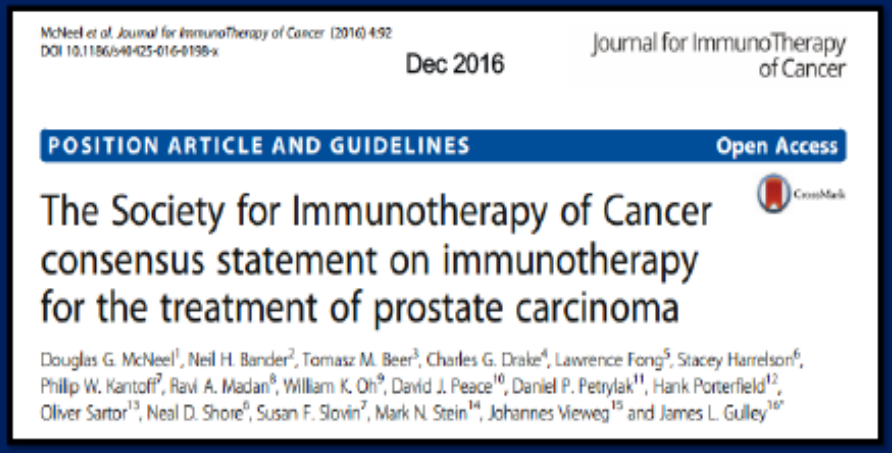
Sipuleucel-T Toxicity

- 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.

Sipuleucel-T

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 Harrelson[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*]

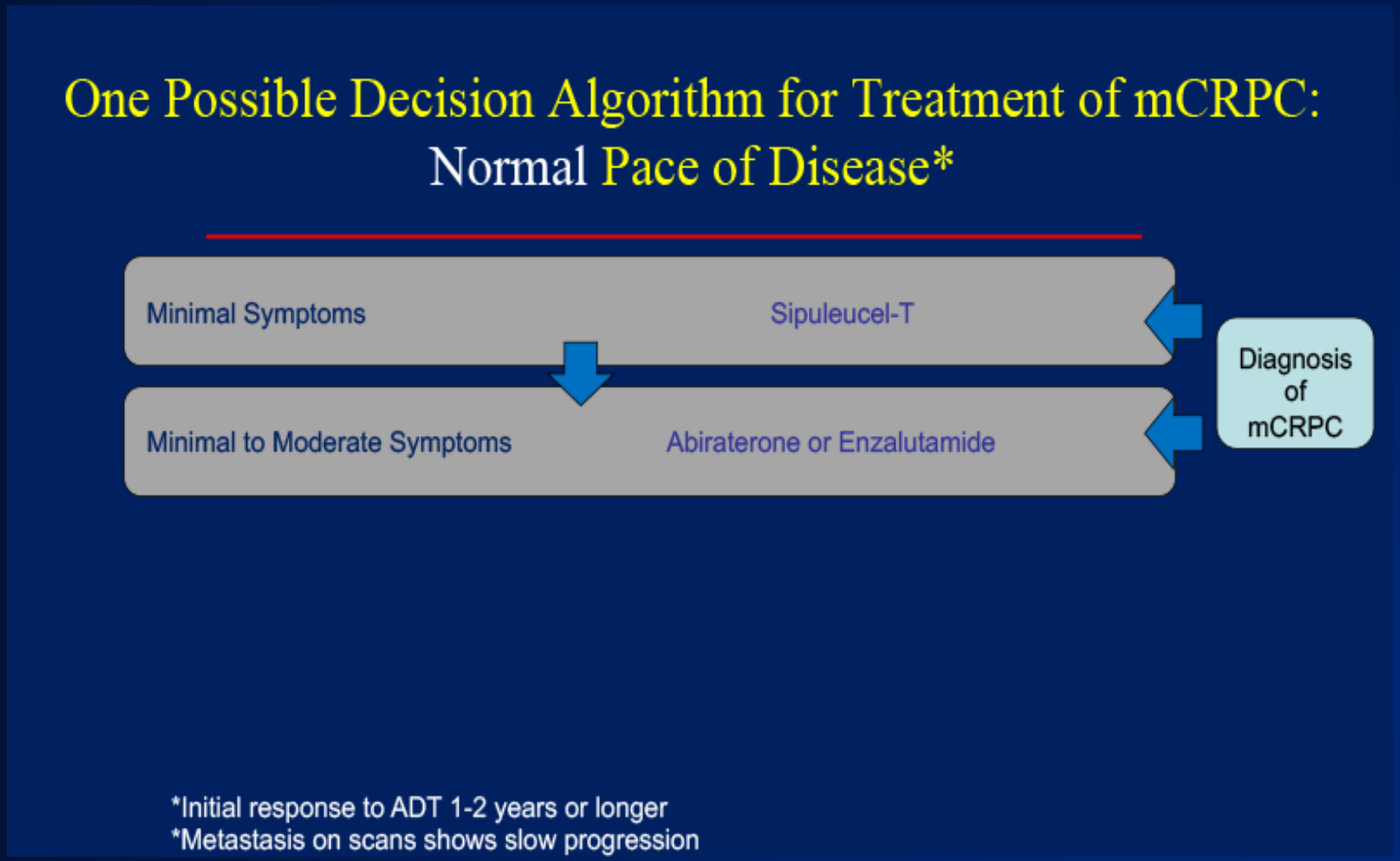
Sipuleucel-T

-Don't expect PSA decrease

-Use early, in less aggressive disease

My recommendation:
Treat and move on to the next therapy

Algorithm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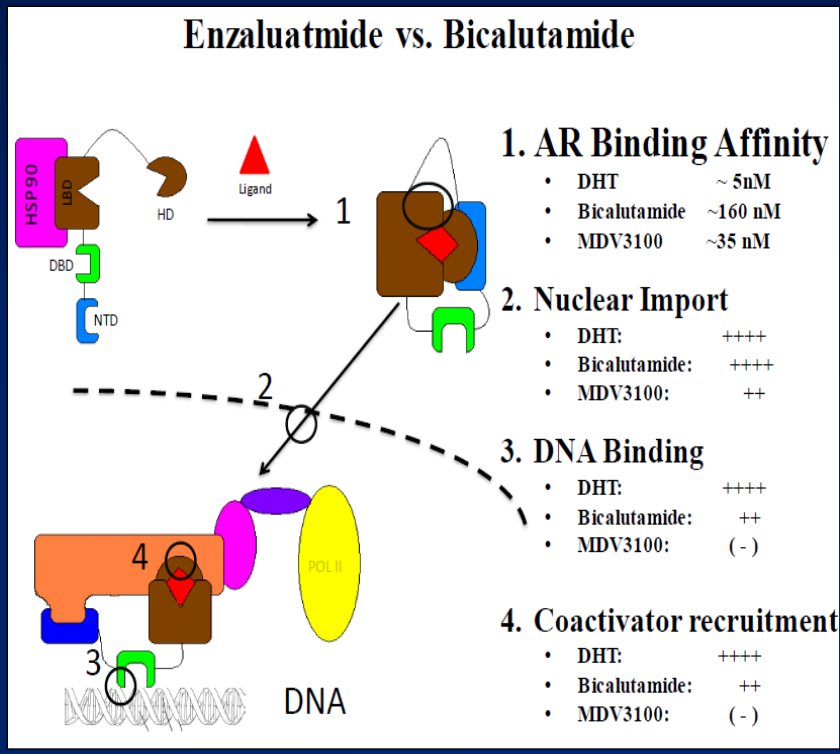
Normal Pace of Disease*
Minimal Symptoms
Sipuleucel-T
Minimal to Moderate Symptoms
Abiraterone or Enzalutamide
Diagnosis of mCRPC
*Initial response to ADT 1-2 years or longer
*Metastasis on scans shows slow progression

Enzalutamide

A small molecule AR antagonist

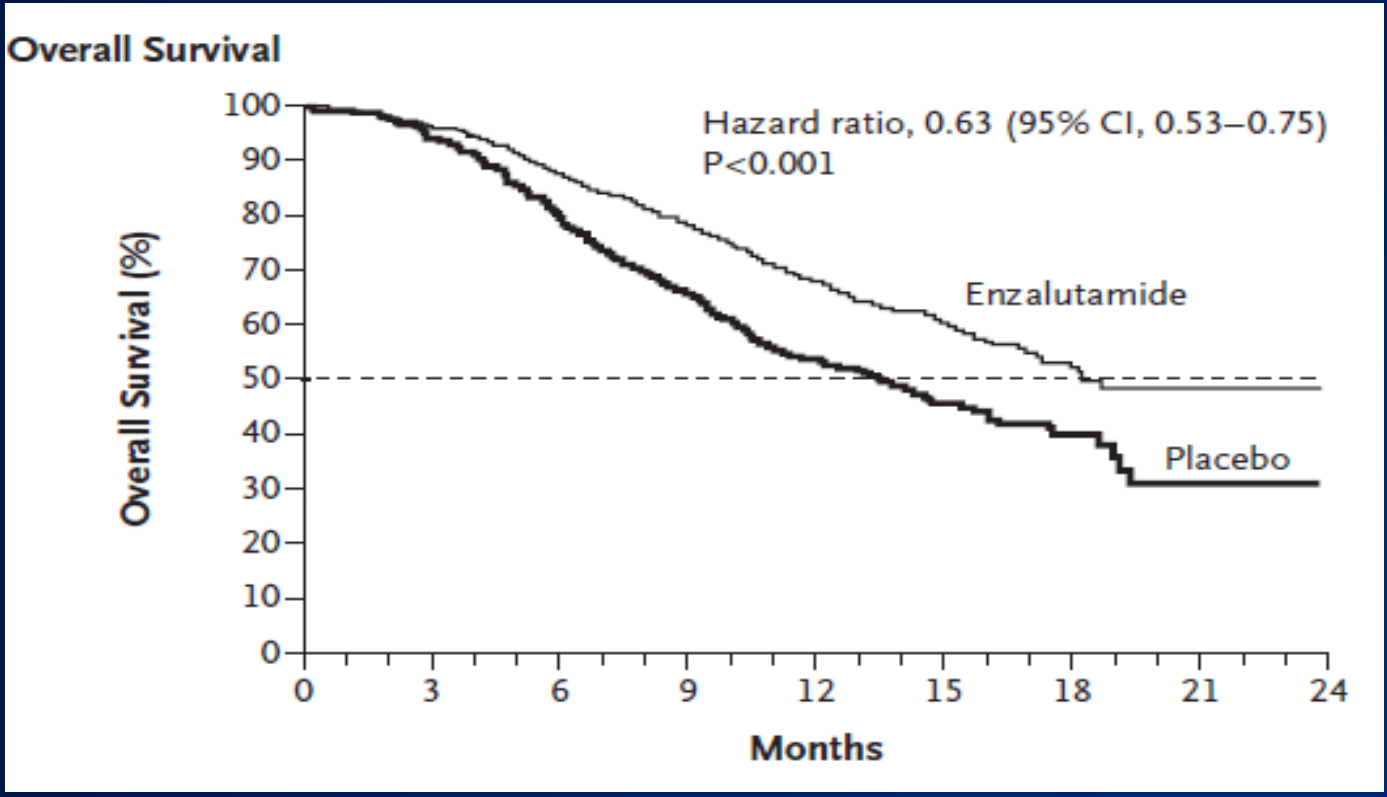
- Affinity 30 folds of bicalutamide
- Prevent nuclear translocation
- Prevents co-activator recruitment



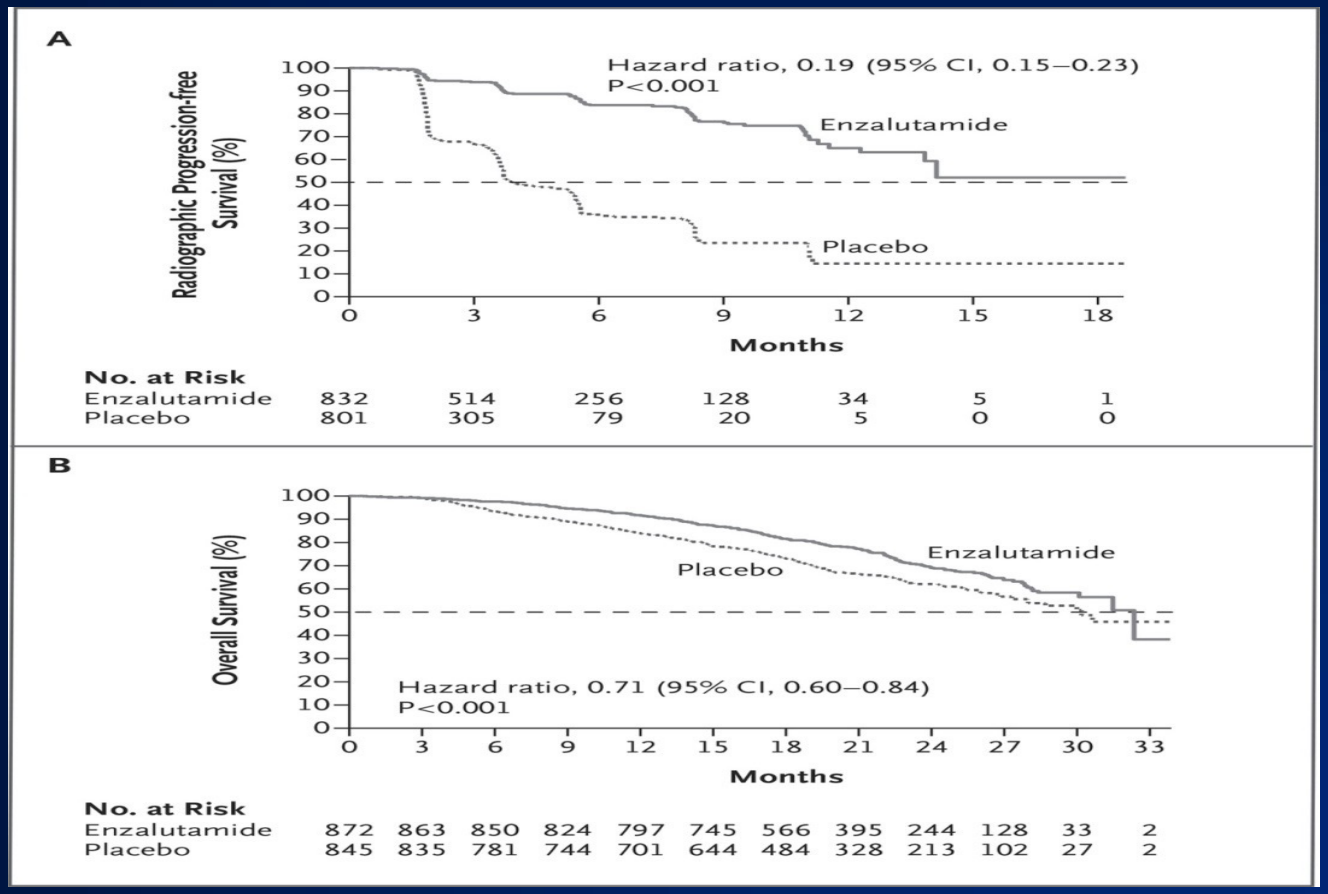
AFFIRM

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%)

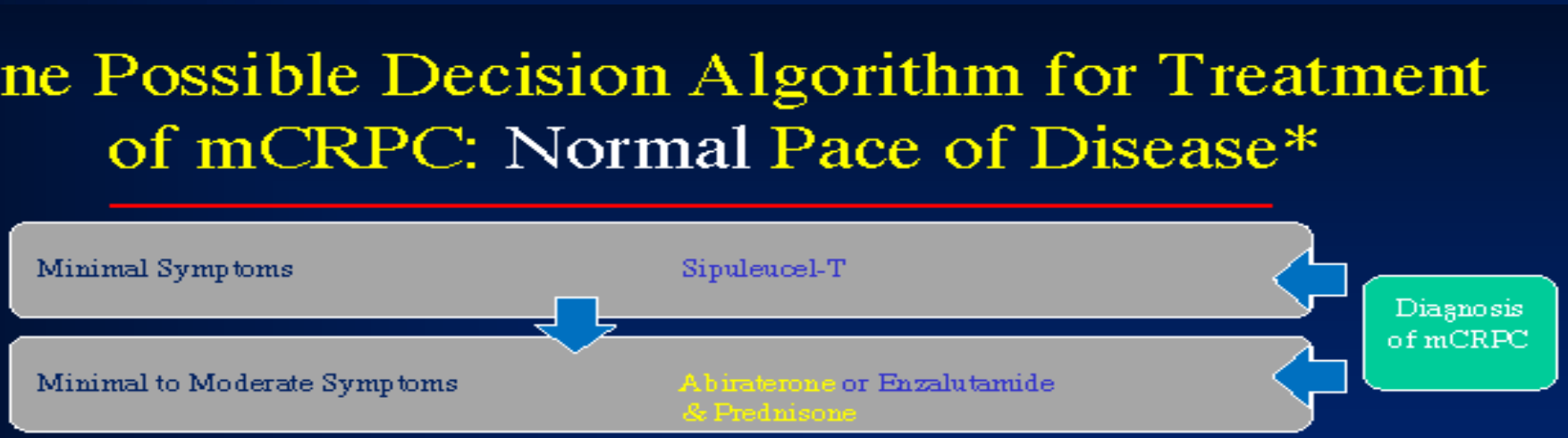
Gastrointestinal: Diarrhea (22%)

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
*Metastasis on scans shows slow progression

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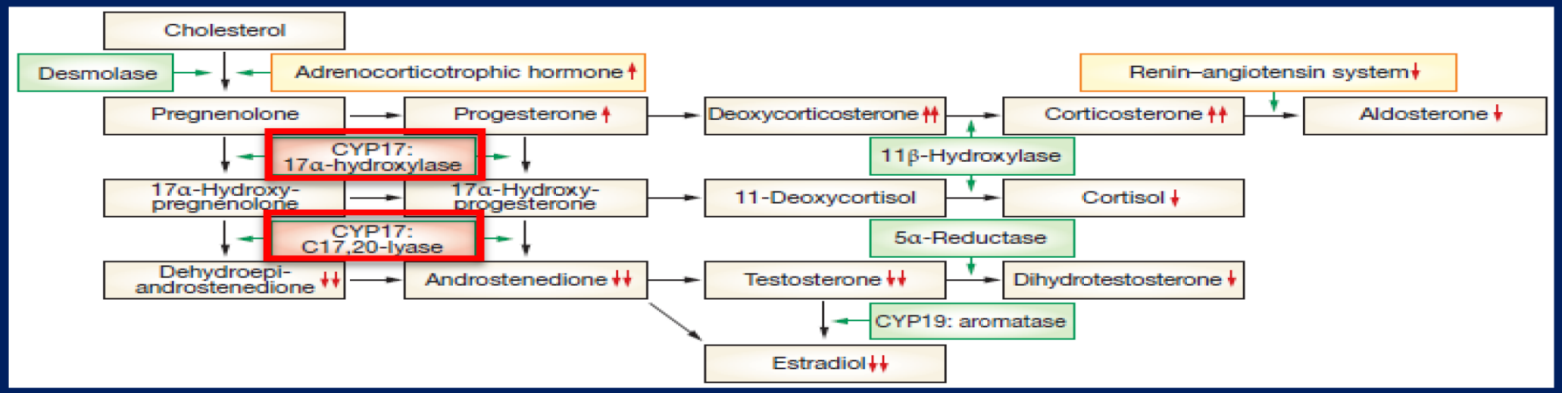
Abiraterone rationale

Rationale for Abiraterone in CRPC

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

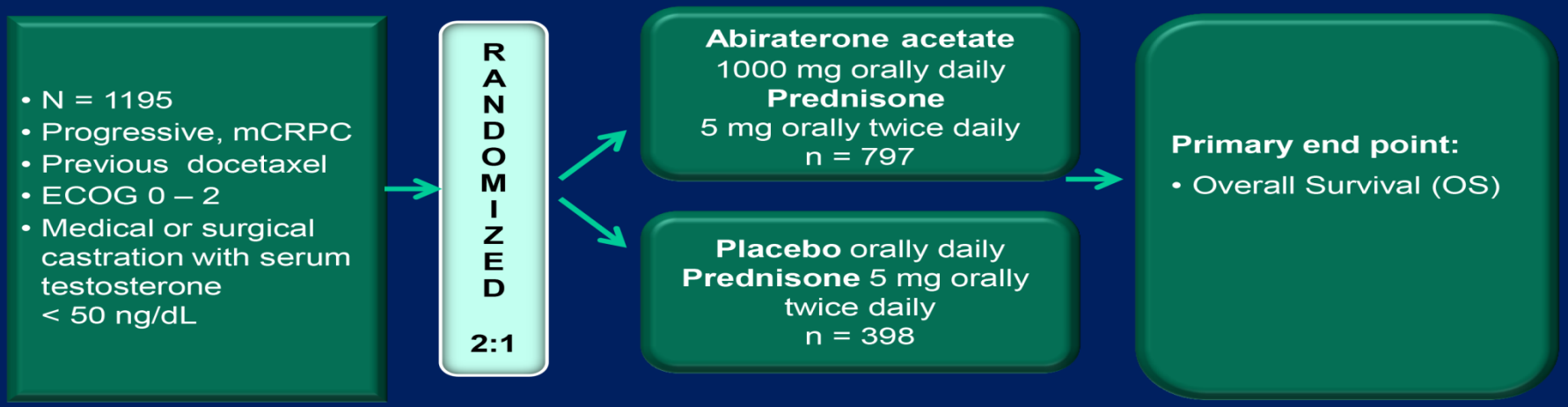


- Blocks androgen synthesis by the adrenal glands, testes and within the prostate tumor tissue

Reid et al. Nat Clin Pract Urol. 2008

Abiraterone study

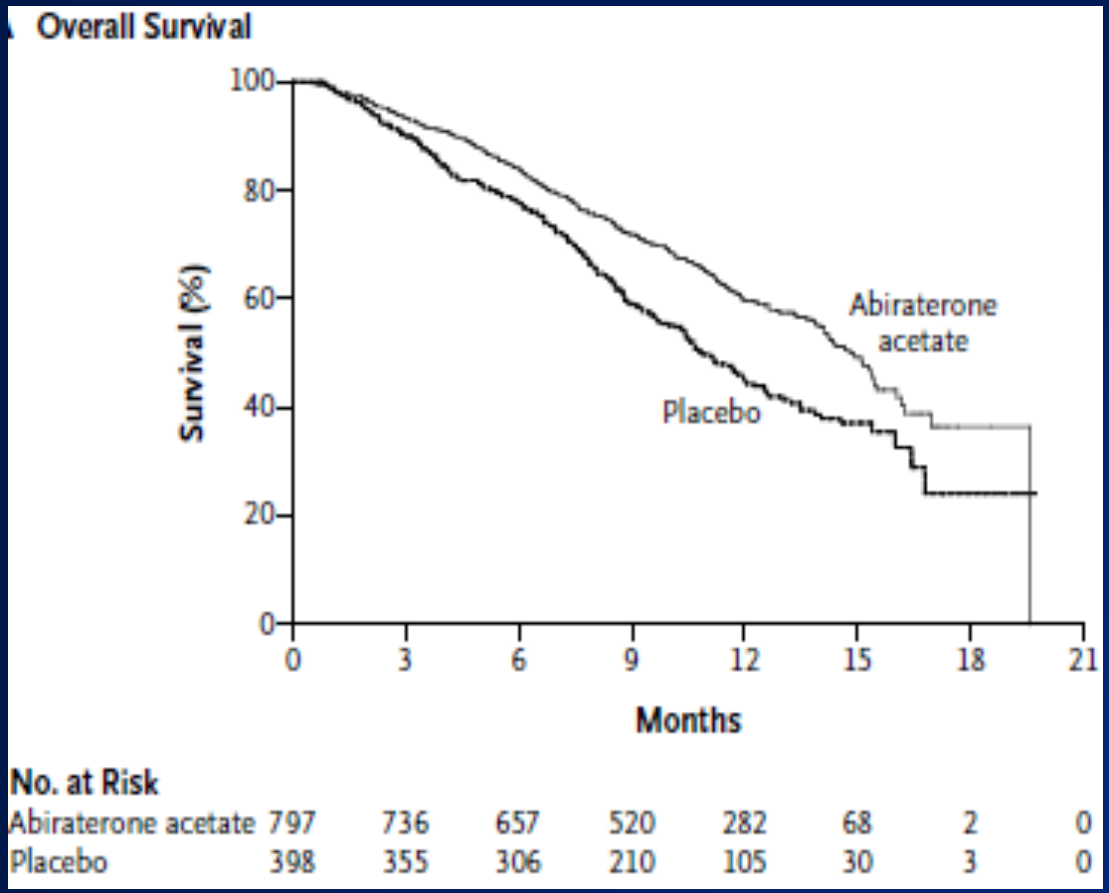
Abiraterone: COU-AA-301 Study Design



- 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

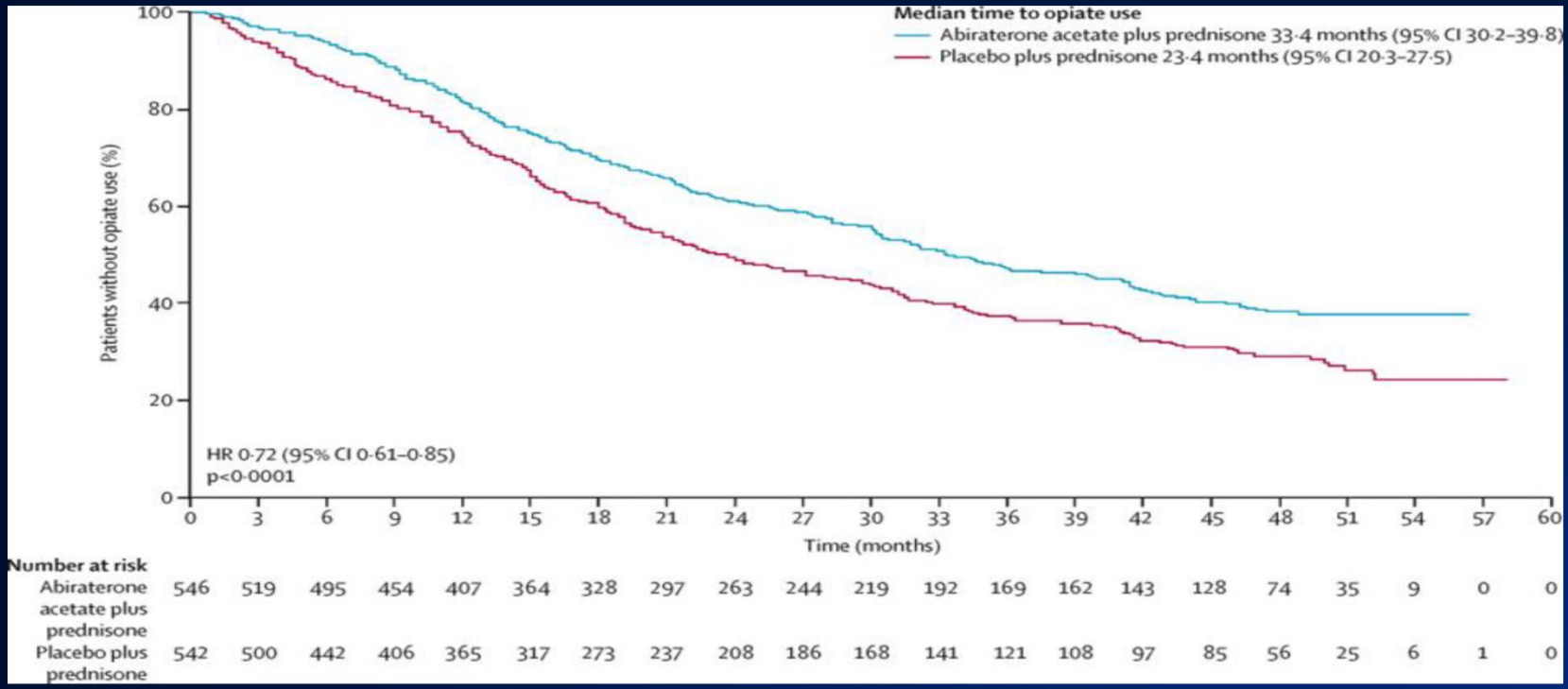
Abiraterone: COU-AA-301 Trial

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%)

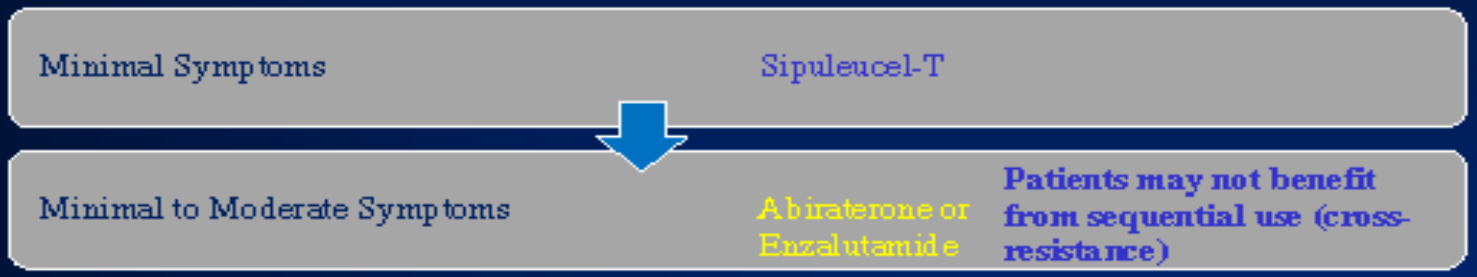
Hepatic: Increased serum ALT (11% to 42%; grades 3/4: 1% to 6%), increased serum AST (31% to 37%; grades 3/4: 2% to 3%)

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

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

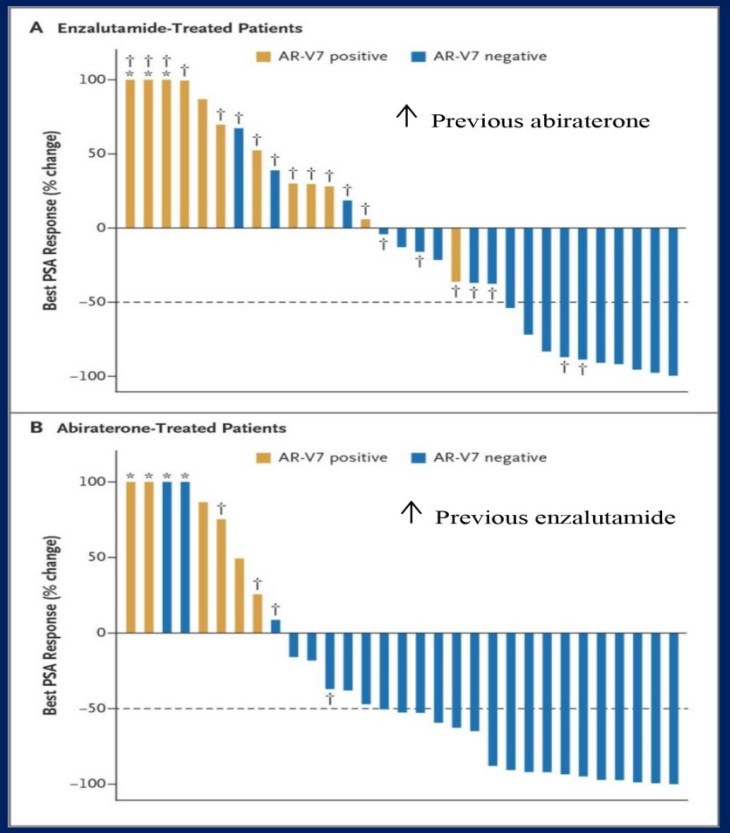


*Initial response to ADT 1-2 years or longer
*Metastasis on scans shows slow progression

Overlapping resistance

Overlapping Resistance: Androgen Receptor Splice Variants

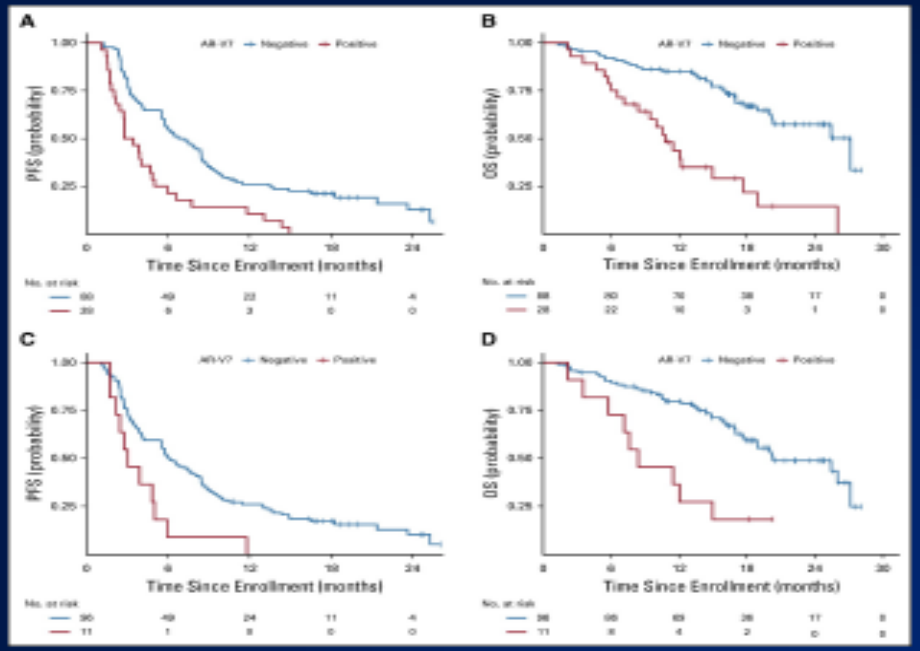
- Variable splicing of AR mRNA can lead to resistance mechanisms to anti-androgen therapy
- ARV-7 has been investigated extensively, lacks a ligand binding domain and is constituently active
- Increases in ARV-7 seen after treatment with Abiraterone/Enzalutamide, likely contributing to cross-resistance.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



Antonarakis ES et al. NEJM, 2014.

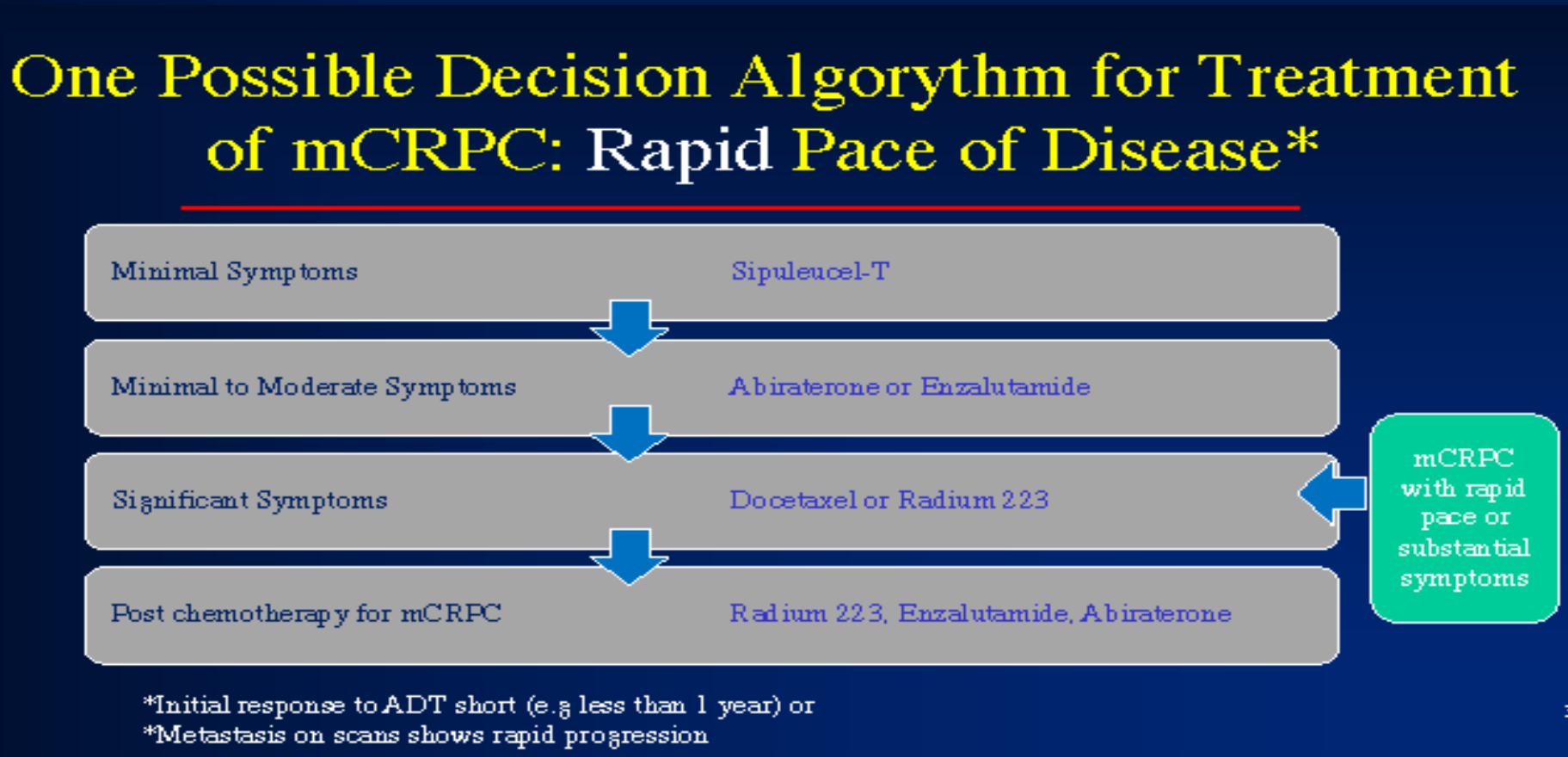
PROPHECY

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



Armstrong AJ et al. JCO, 2019

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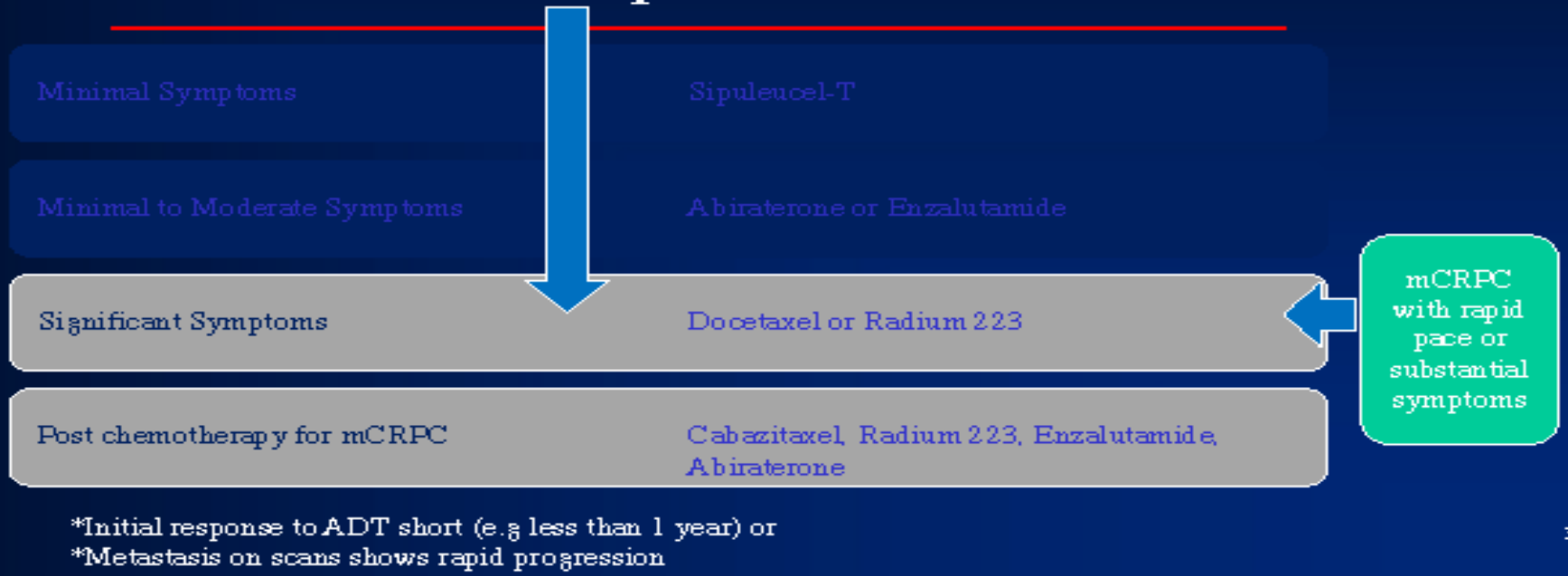
Minimal Symptoms
Sipuleucel-T
Minimal to Moderate Symptoms
Abiraterone or Enzalutamide
Significant Symptoms
Docetaxel or Radium 223
Post chemotherapy for mCRPC
Radium 223, Enzalutamide, Abiraterone
mCRPC with rapid pace or substantial symptoms
*Initial response to ADT short (e.g less than 1 year) or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

Algorithm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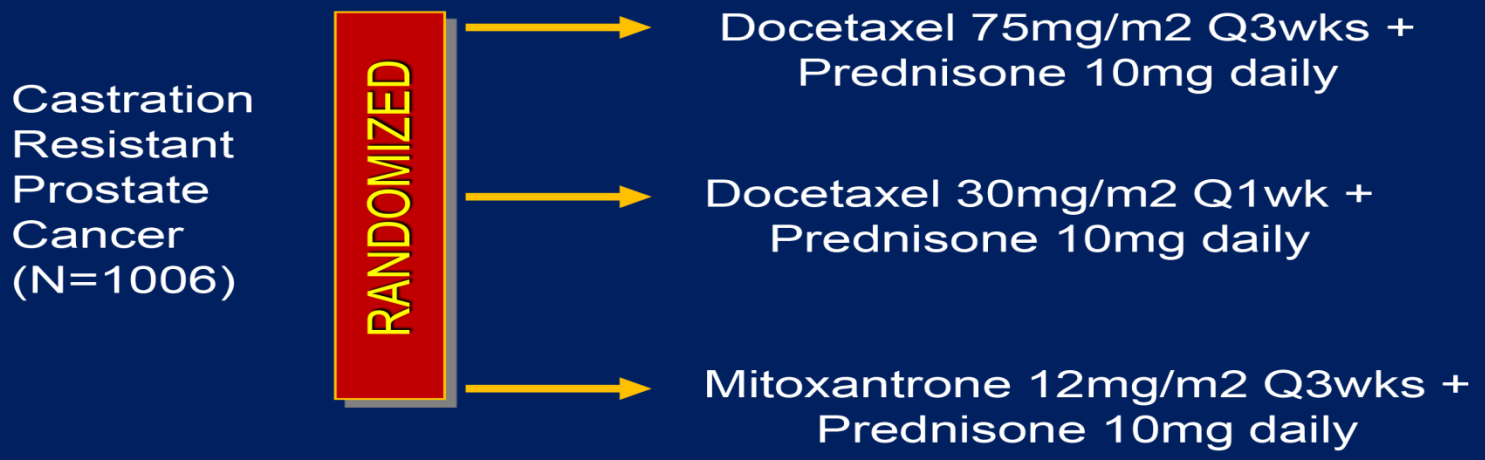
Docetaxel

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*

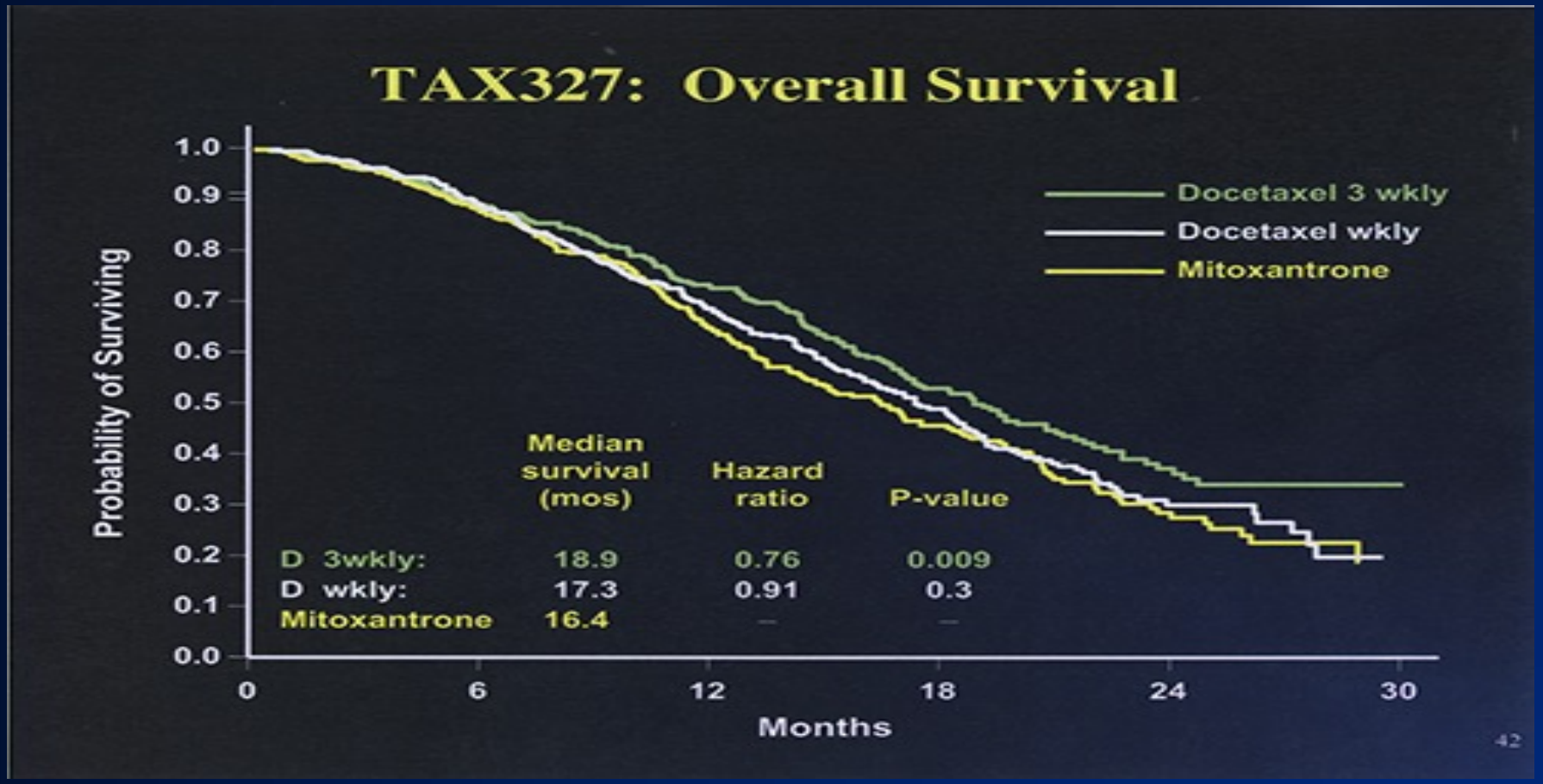
Phase III study

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%)

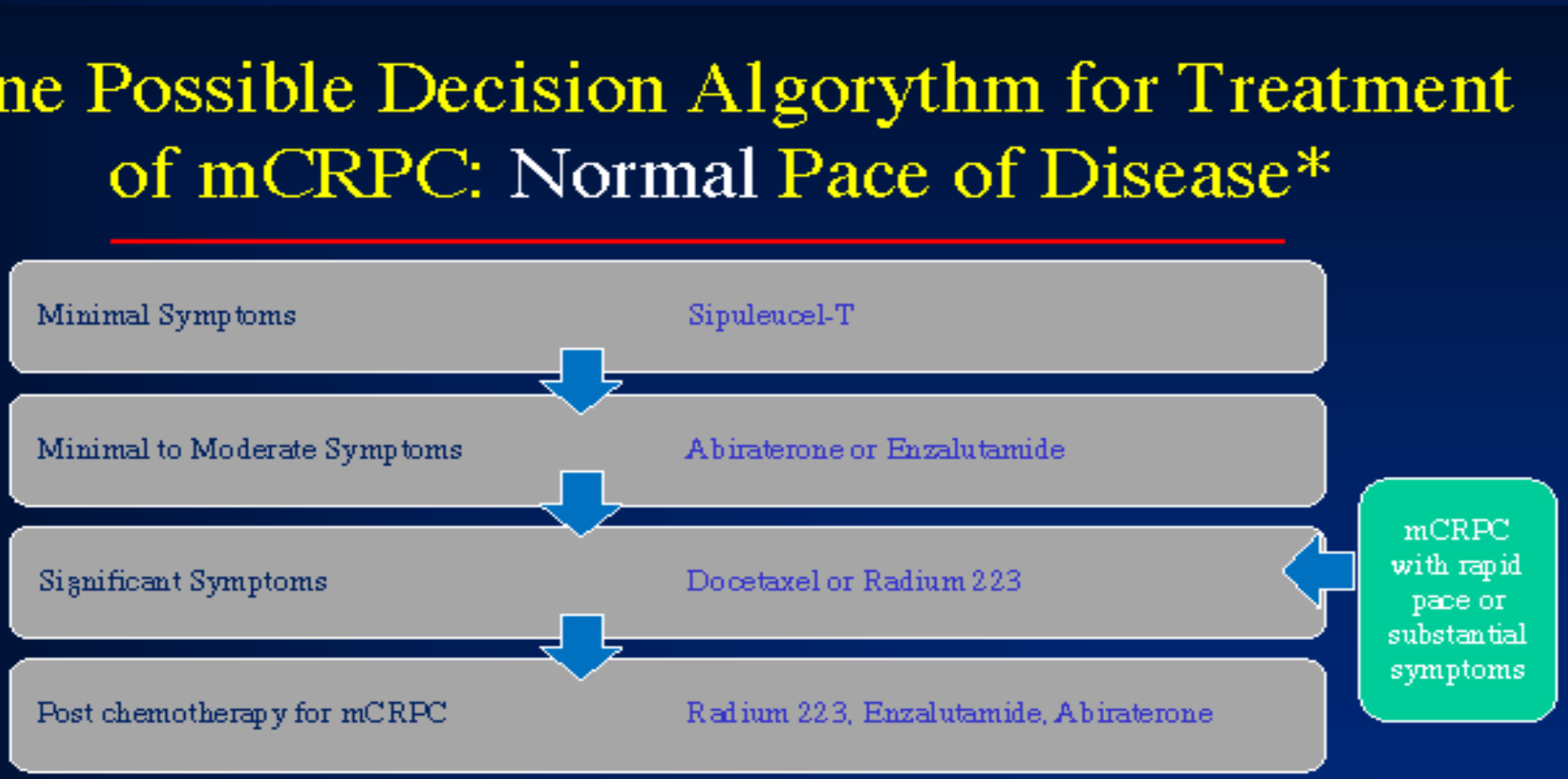
Hypersensitivity: Hypersensitivity (1% to 21%; with premedication 15%)

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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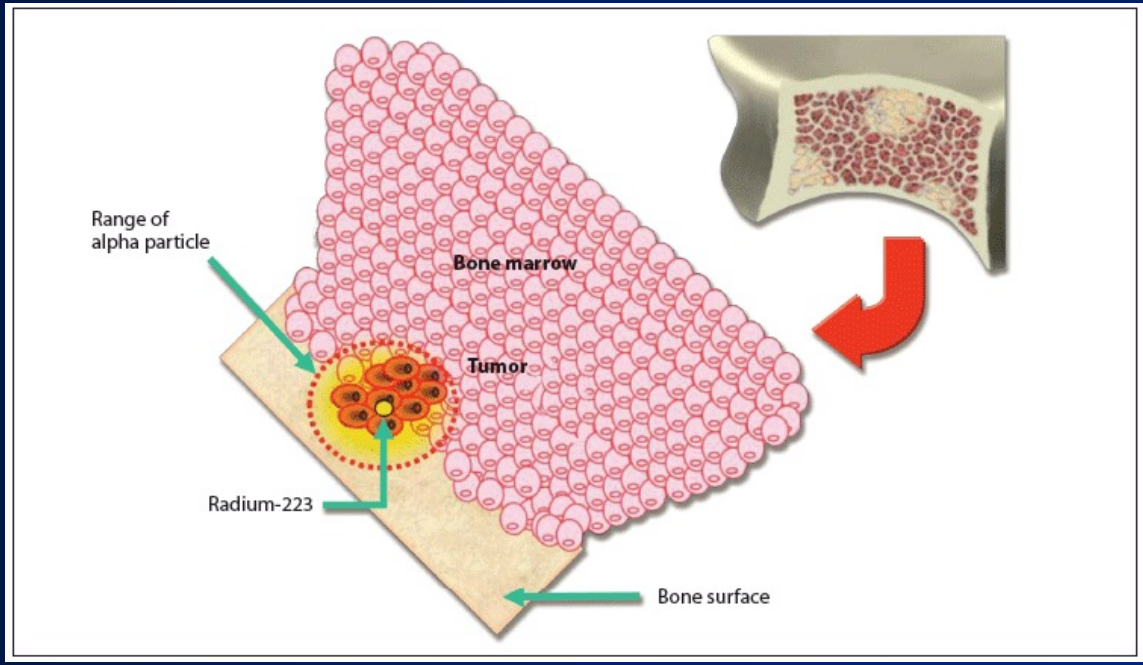
Radium-223 (Alpharadin)

Bone –targeting radiopharmaceutical

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

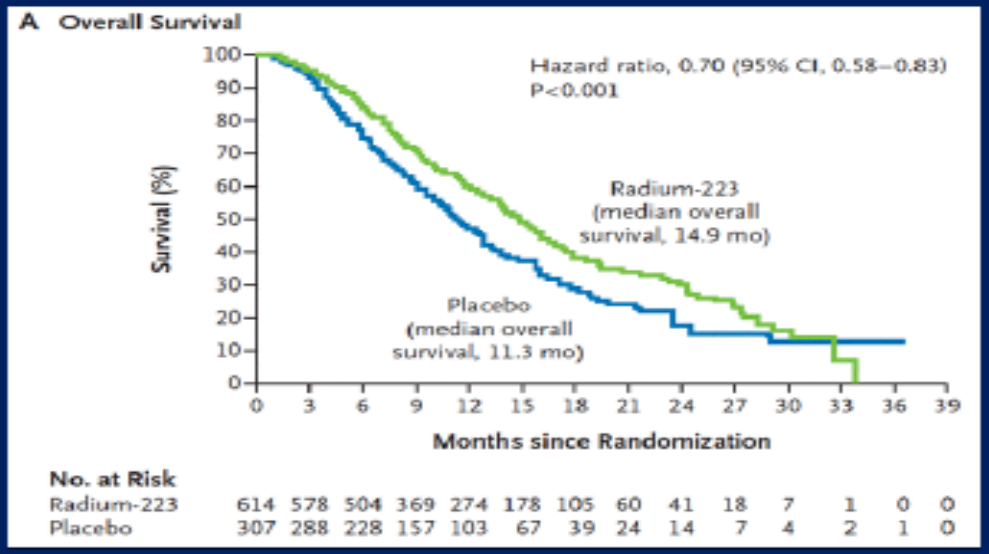


Radium trial

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

ALSYMPCA trial

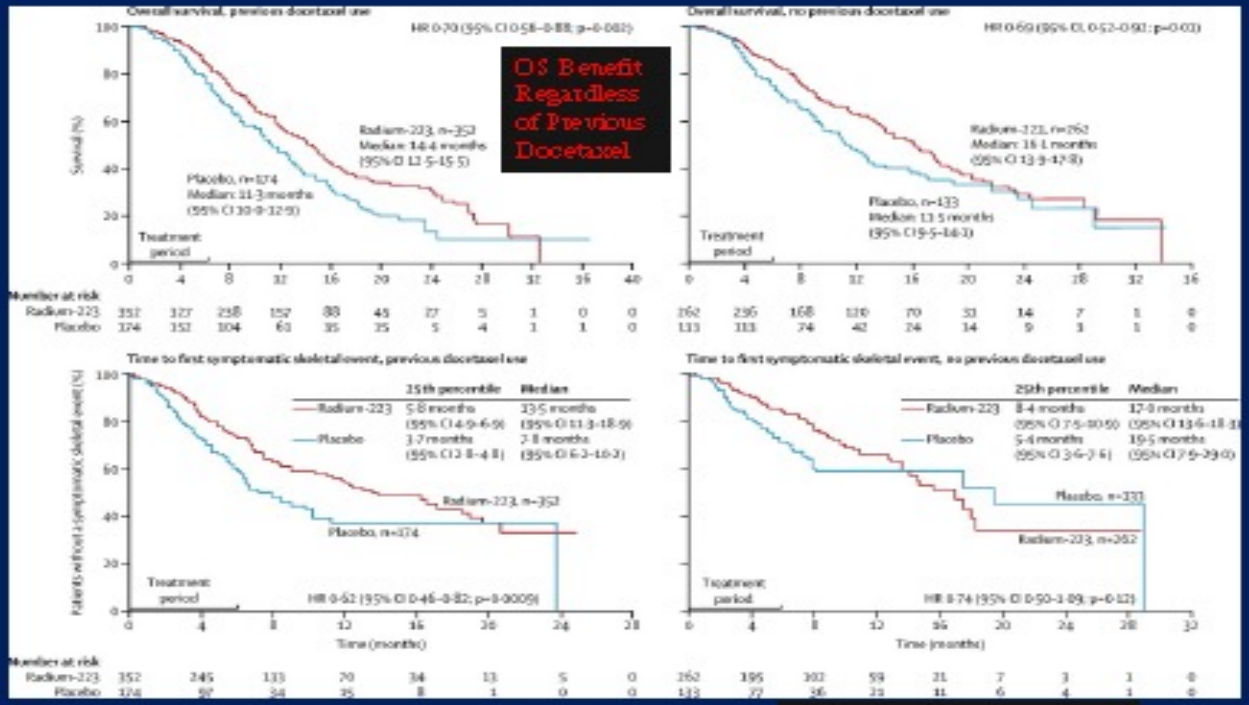
ALSYMPCA: Randomized Phase III Study of Radium-223 vs. Placebo in mCRPC with bone metastases



Parker C. et al. NEJM, 2013.

Survival curve

ALSYMPCA: Subgroup Analysis based on Previous Docetaxel



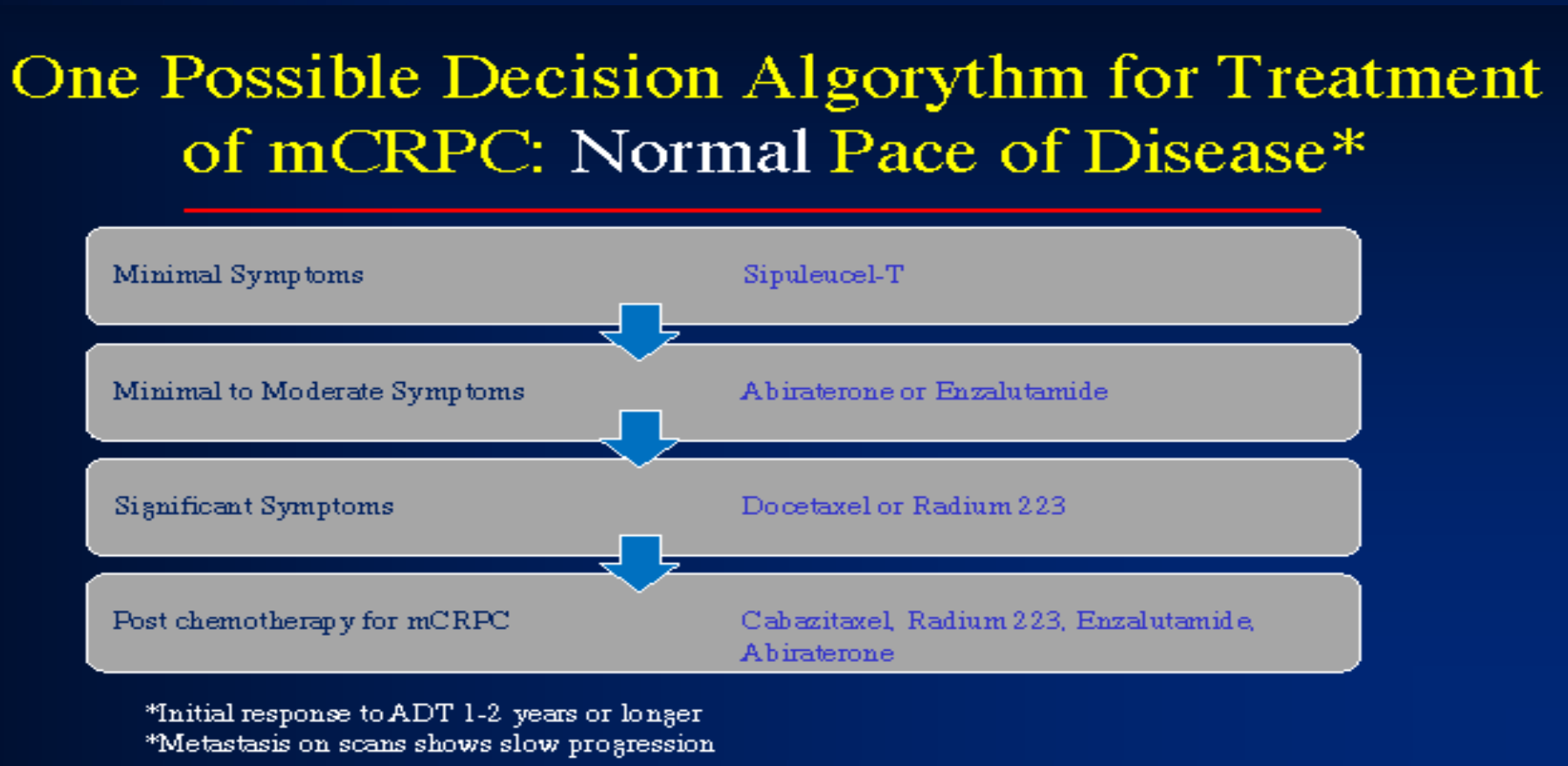
Hoskin, P. et al. Lancet Oncol, 2014.

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, Radium 223, Enzalutamide, Abiraterone
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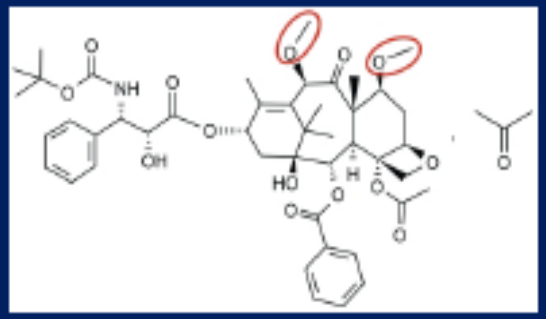
Cabazitaxel

Cabazitaxel

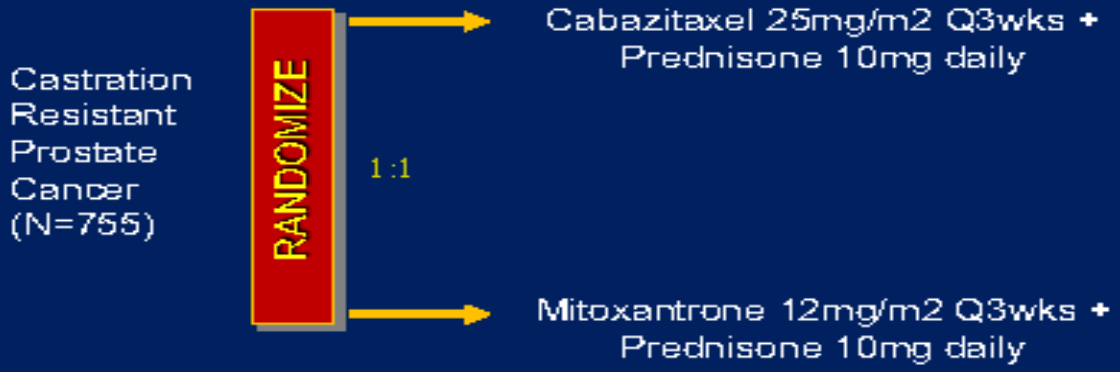
- Novel taxane active in docetaxel resistant cell lines
  - Less affinity for P-glycoprotein pump



Methoxyl side chain instead of hydroxyl groups found in docetaxel

Phase III study

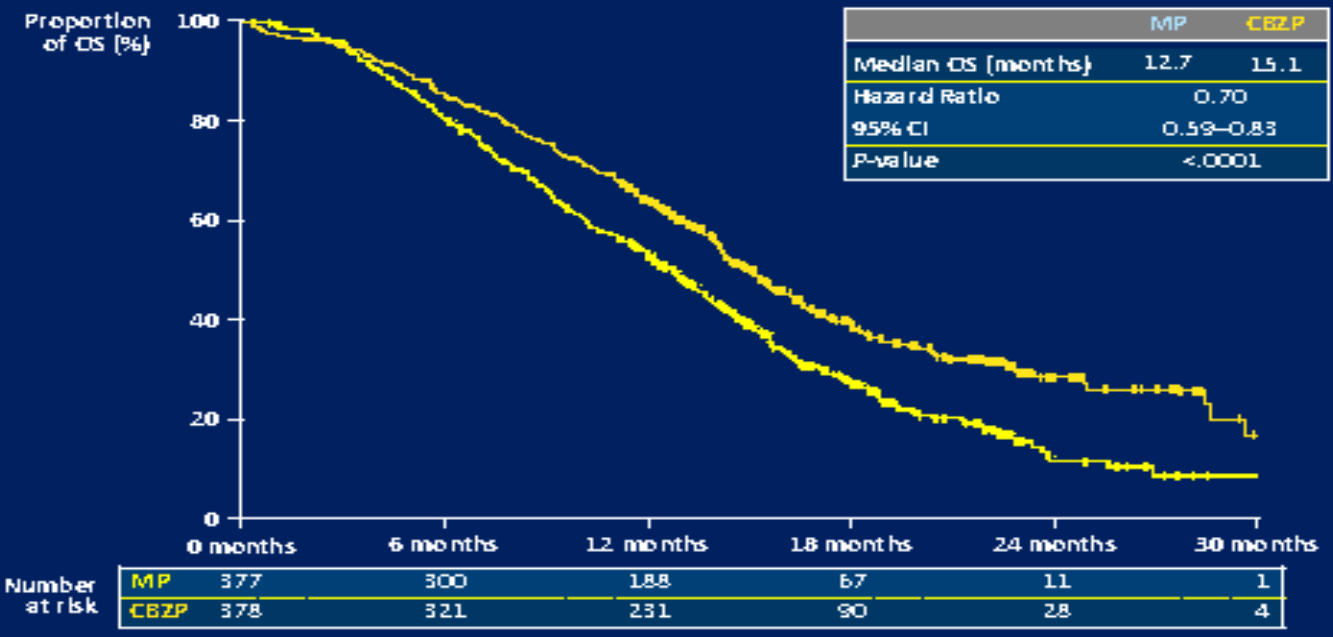
TROPIC: Randomized Phase III Study of Cabazitaxel vs. Mitoxantrone in mCRPC after Progression on Docetaxel



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%)

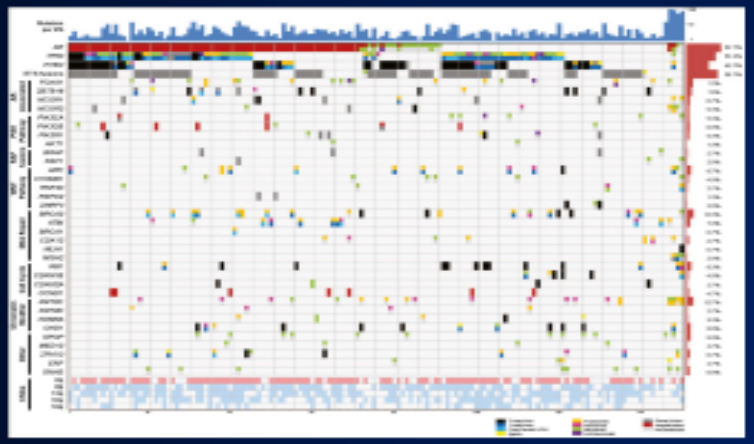
Should strongly consider the use of growth factor

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

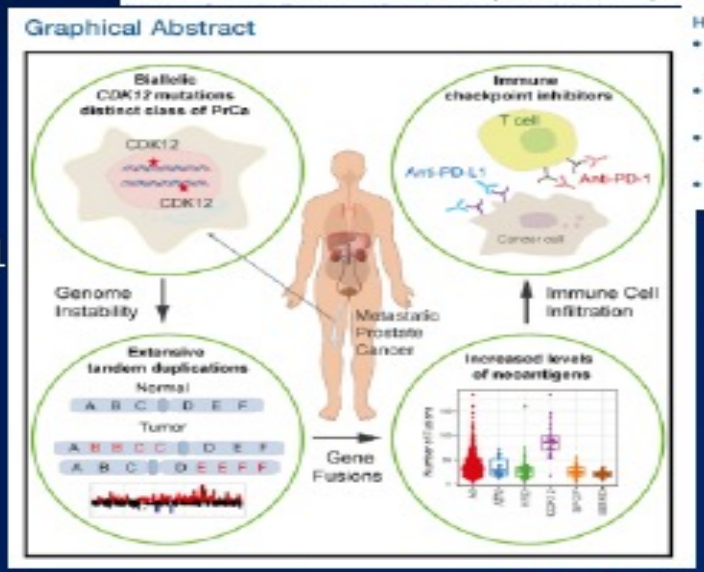
Incidence

- 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, Marcin Cieślik, Robert J. Lonigro, Pankaj Vats, Melissa A. Reimers, Xuhong Cao, Yu Ning, Lisha Wang, Lakshmi P. Kunju, Navonil de Sarkar, Elisabeth I. Heath, Jonathan Chou, Felix Y. Feng, Peter S. Nelson, Johann S. de Bono, Weiping Zou, Bruce Montgomery, Ajjai Alva, PCF/SU2C International Prostate Cancer Dream Team, Dan R. Robinson, and Arul M. Chinnaiyan



Highlights

- *CDK12* biallelic inactivating mutations define a distinct subtype of prostate cancer
- *CDK12* loss is associated with genomic instability and focal 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*

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New therapies

MSI High Prostate Cancer

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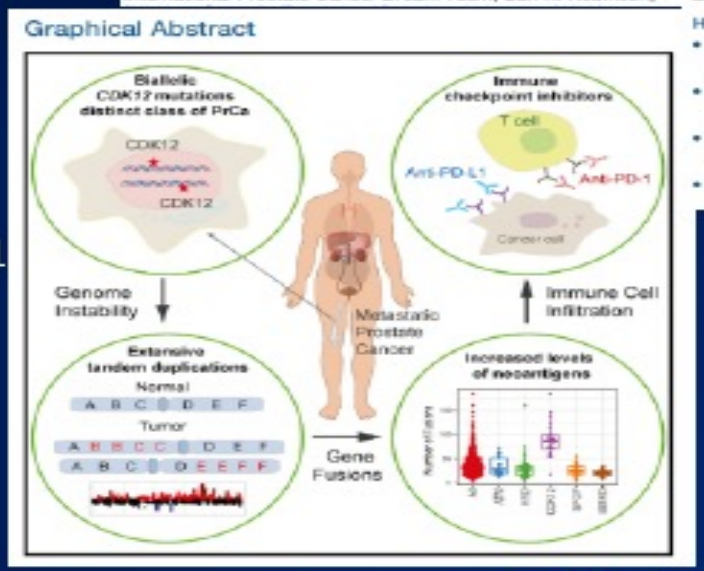

Wu YM *et al. Cell, 2018*

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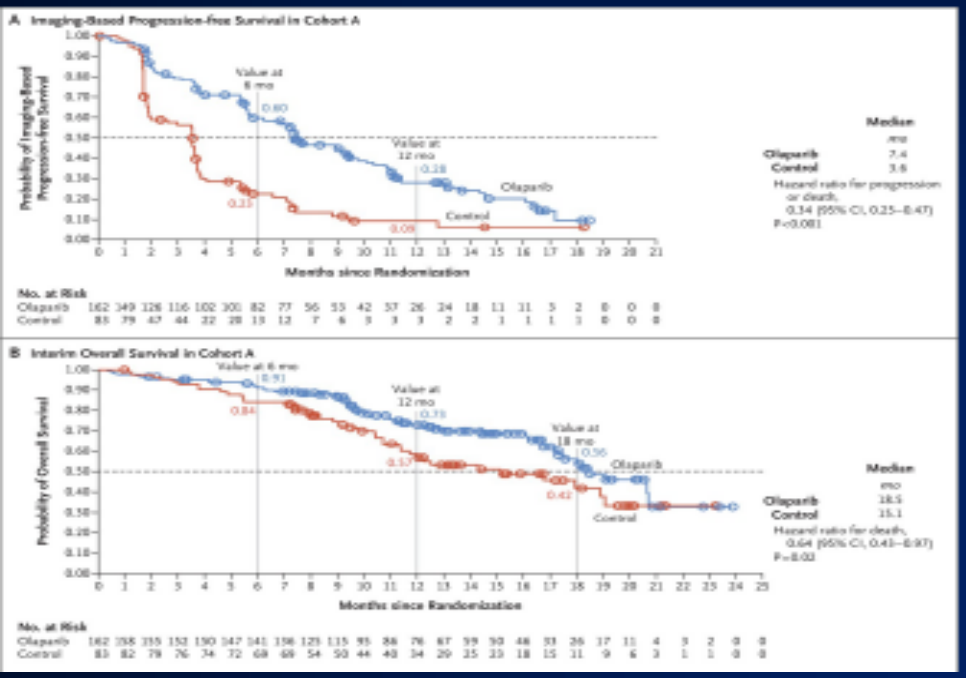
Olaparib

Olaparib for mCRPC (chemo-naïve)



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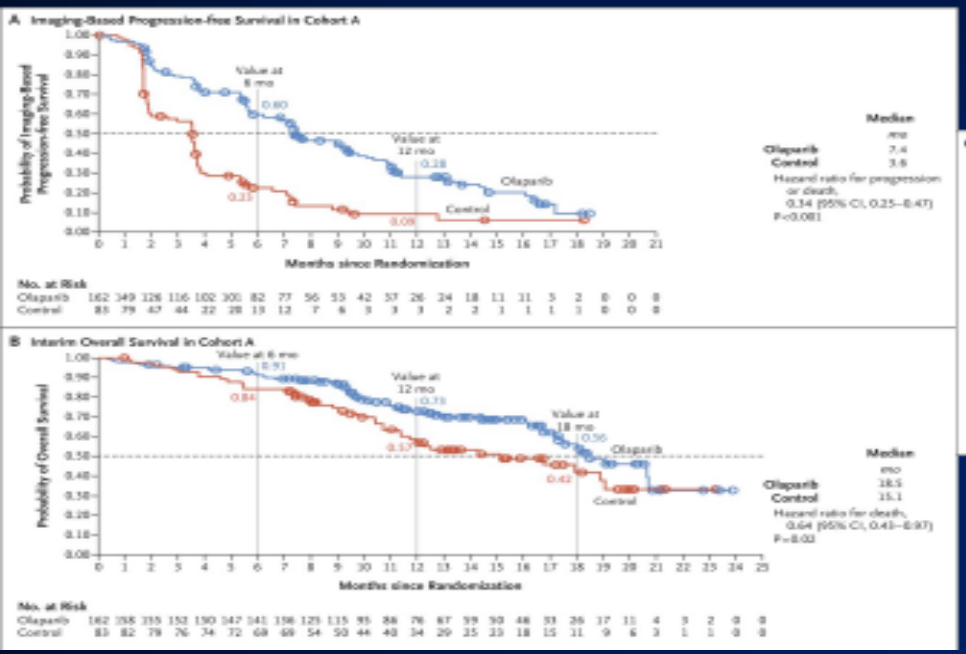
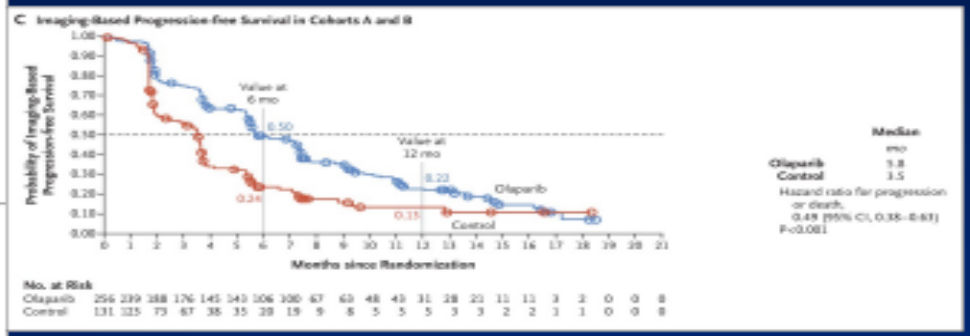
de Bono J. et al. N Engl J Med 2020

Olaparib

Olaparib for mCRPC (chemo-naïve)

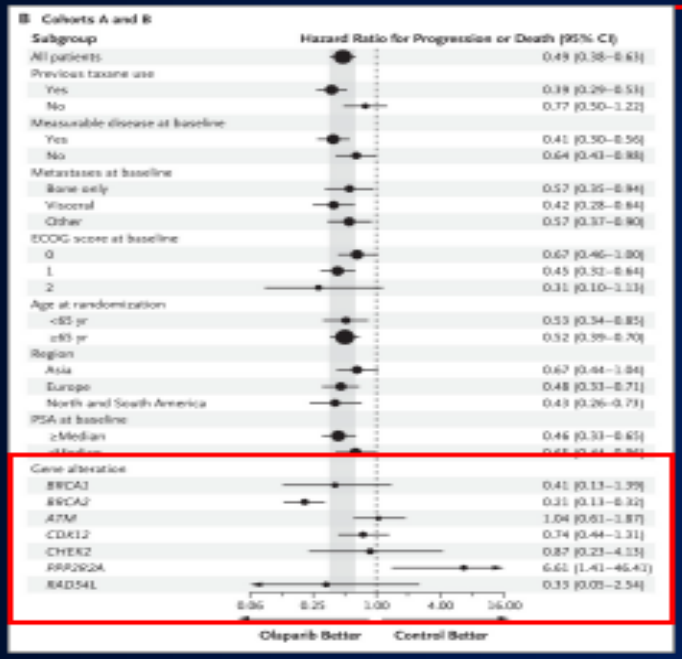


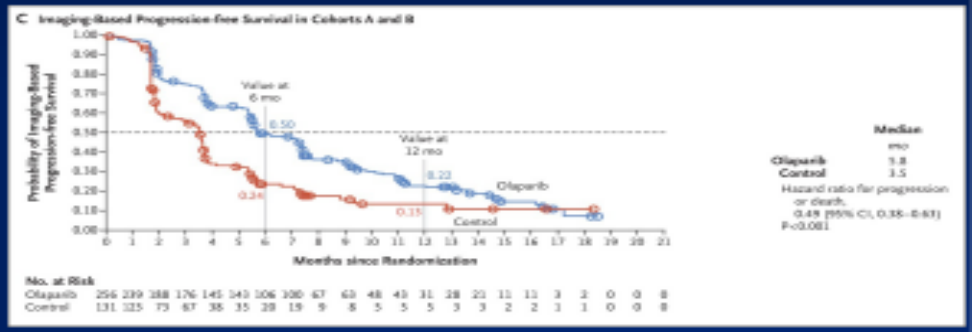


de Bono J et al. N Engl J Med 2020

Olaparib for mCRPC

Olaparib for mCRPC (chemo-naïve)





de Bono J et al. N Engl J Med 2020

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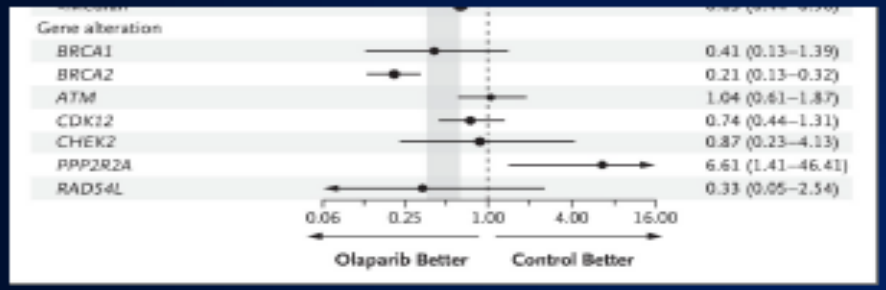
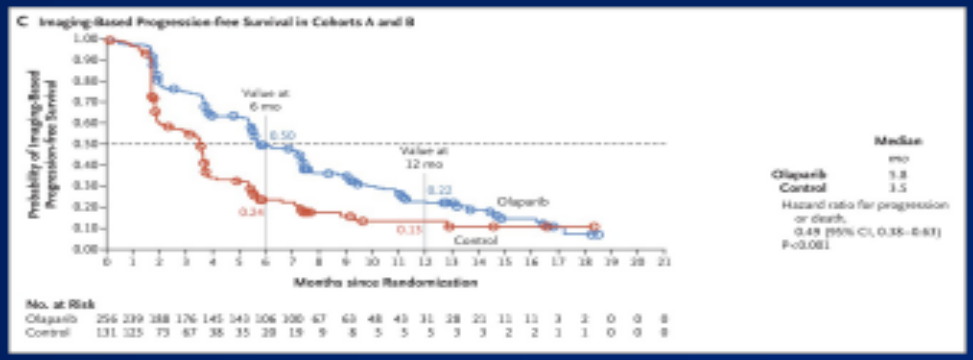
Chemo-naive

Olaparib for mCRPC (chemo-naïve)



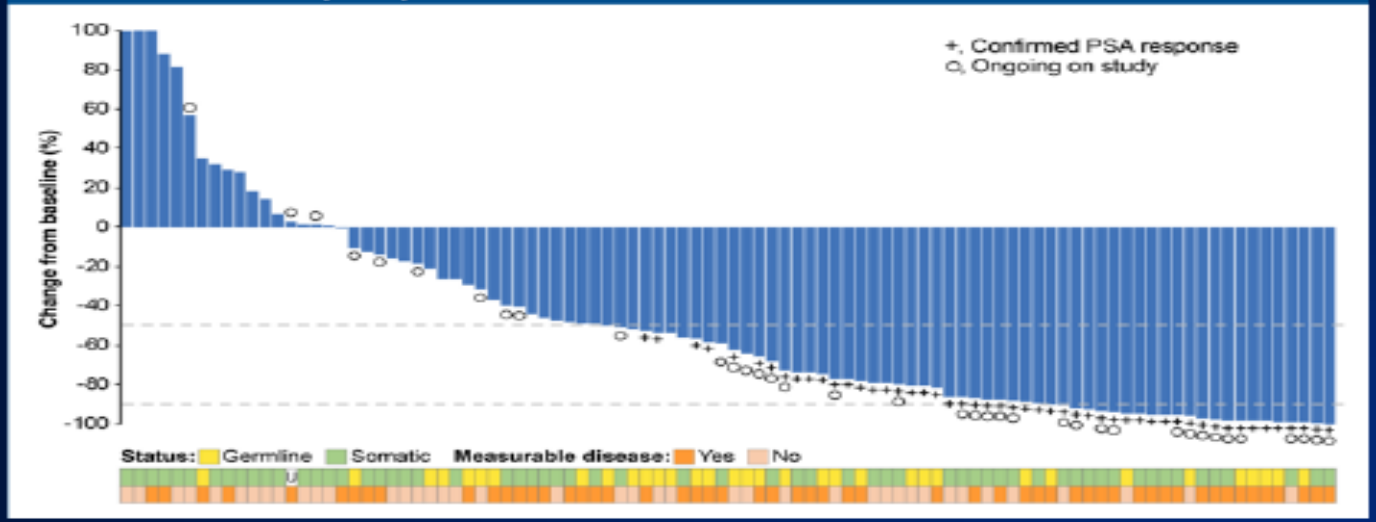


de Bono J et al. N Engl J Med 2020

Rucaparib

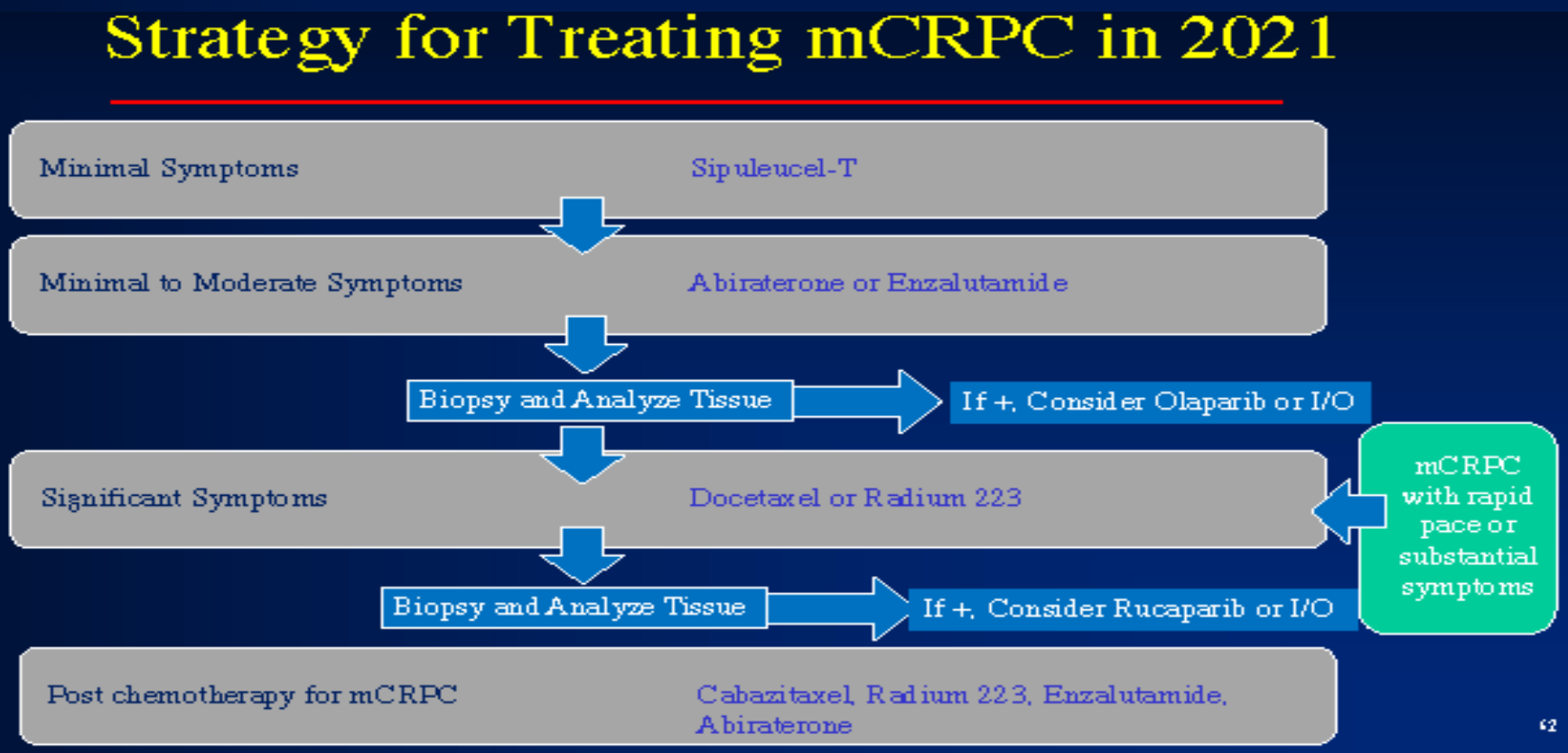
Rucaparib mCRPC (chemo-refractory)

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



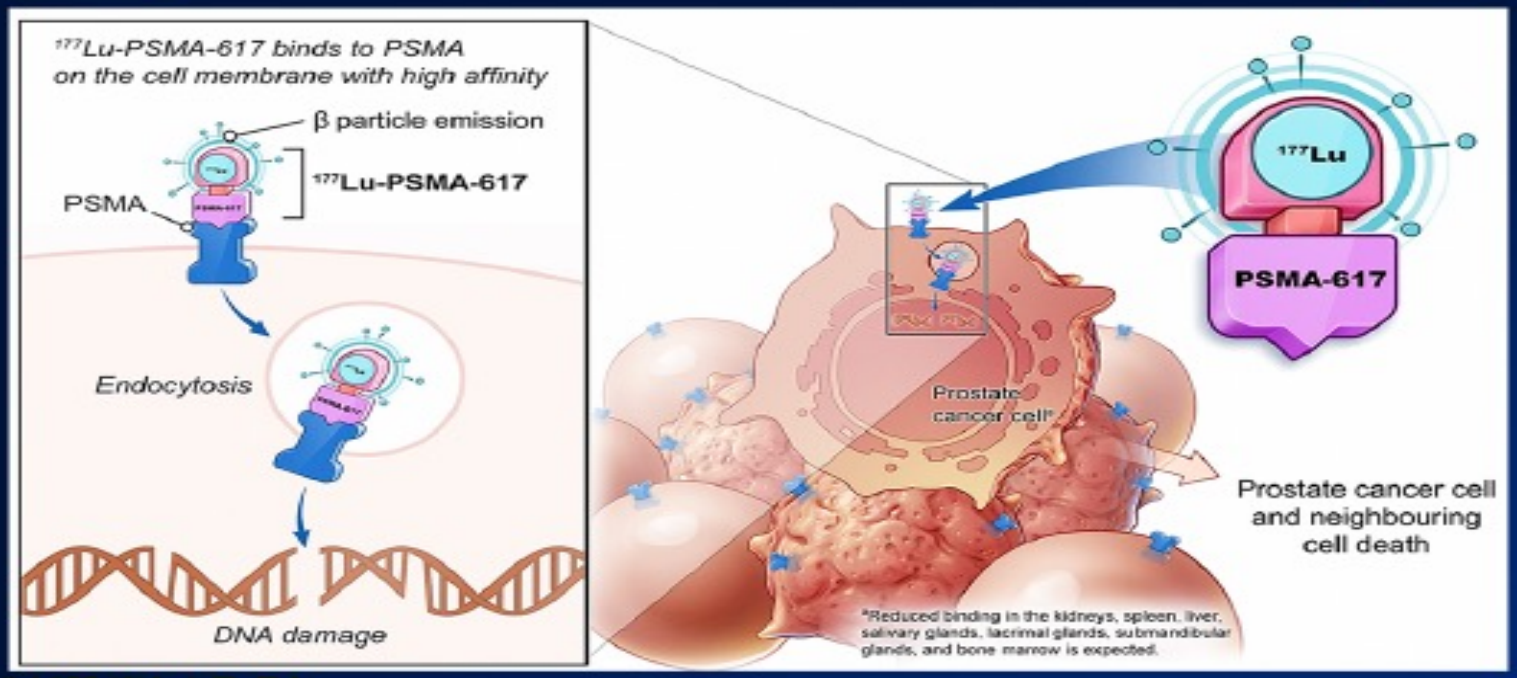
Abida W et al. ESMO 2020

Treatment strategy



Lu-177-PMSA

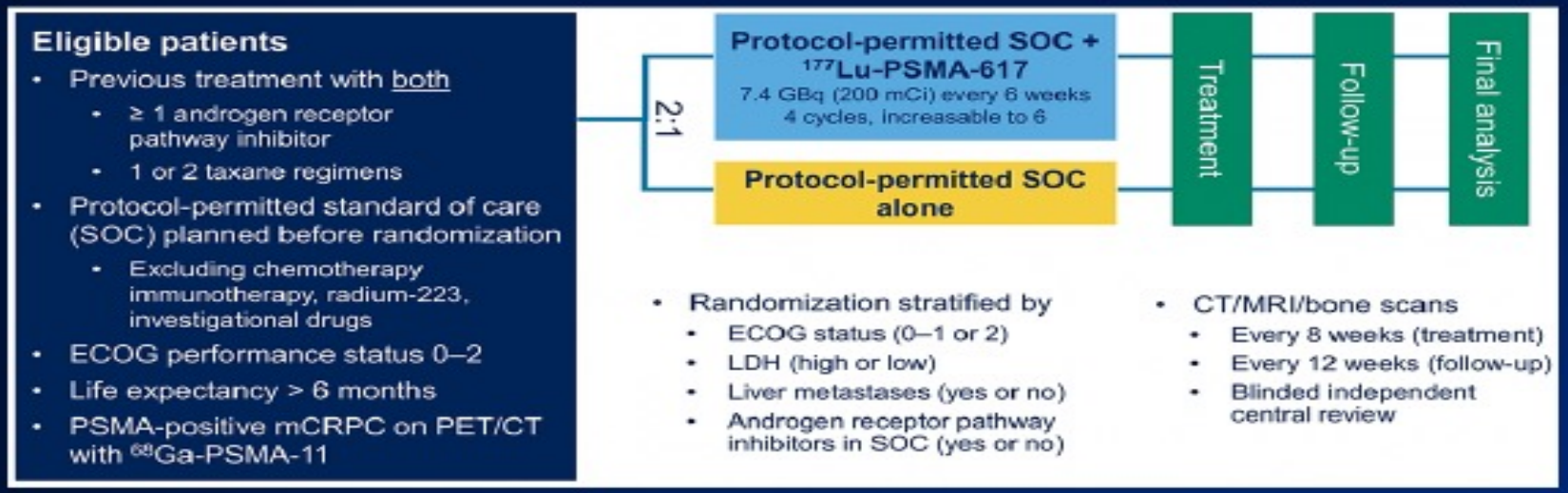
2021 Update: Lu-177-PSMA



Morris, MJ et al, ASCO 2021 via UroToday

Phase 3 Trial

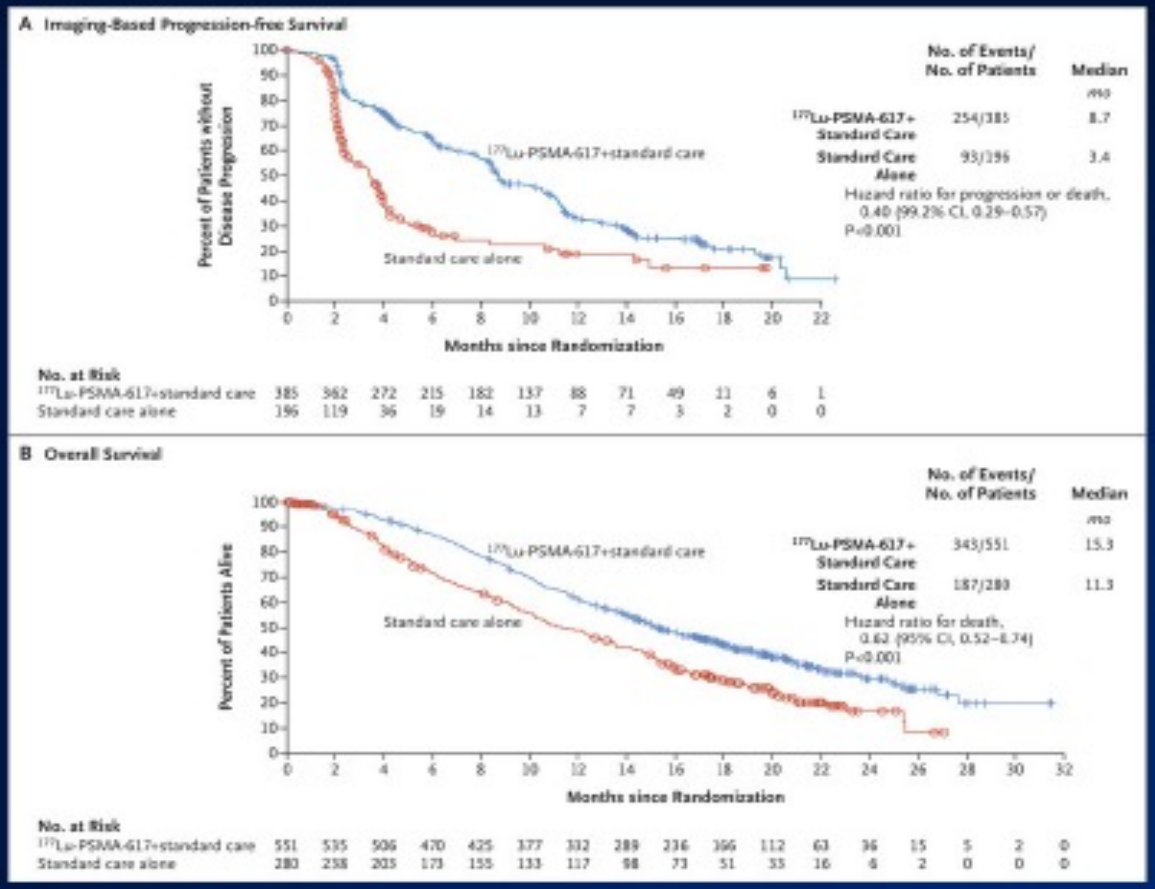
Lu-177-PSMA Phase 3 Trial (post docetaxel)



Morris, MJ et al, ASCO 2021 via UroToday

Survival curve

Lu-177-PSMA

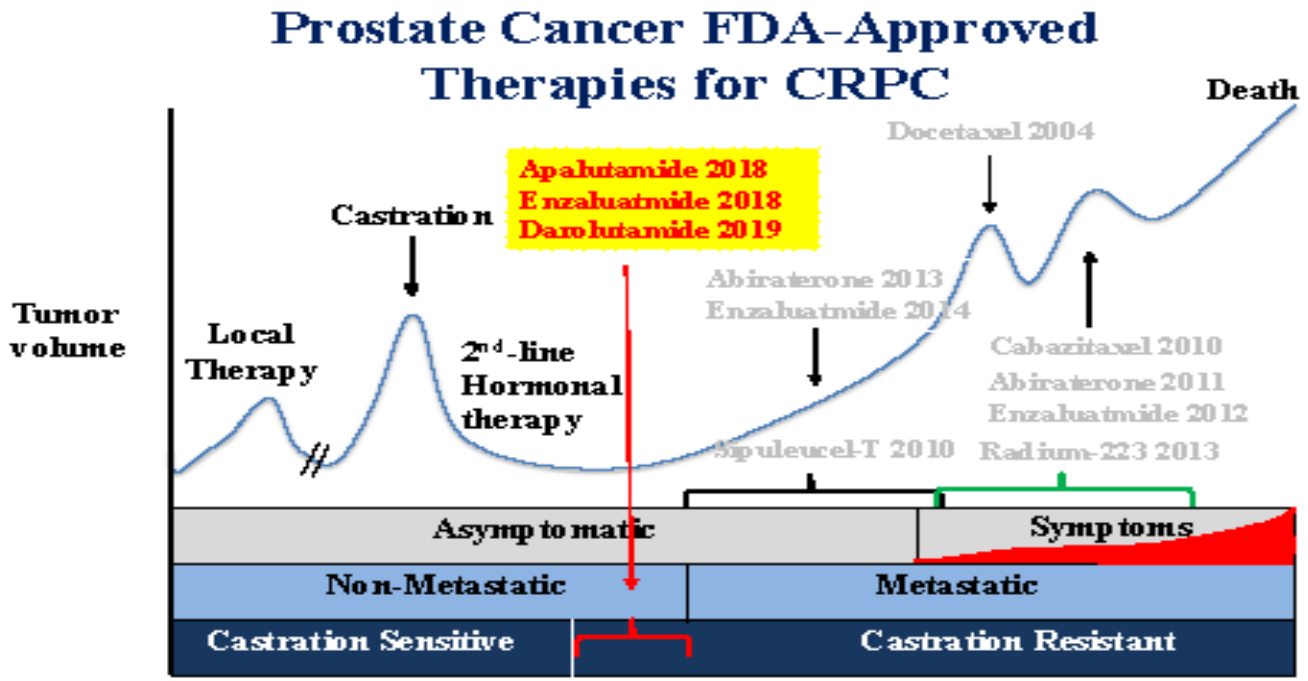


Sartor, O et al. NEJM, 2021

Prostate cancer

Non-Metastatic Castration Resistant Prostate Cancer

Approved therapies. My thoughts



Castration sensitive prostate cancer

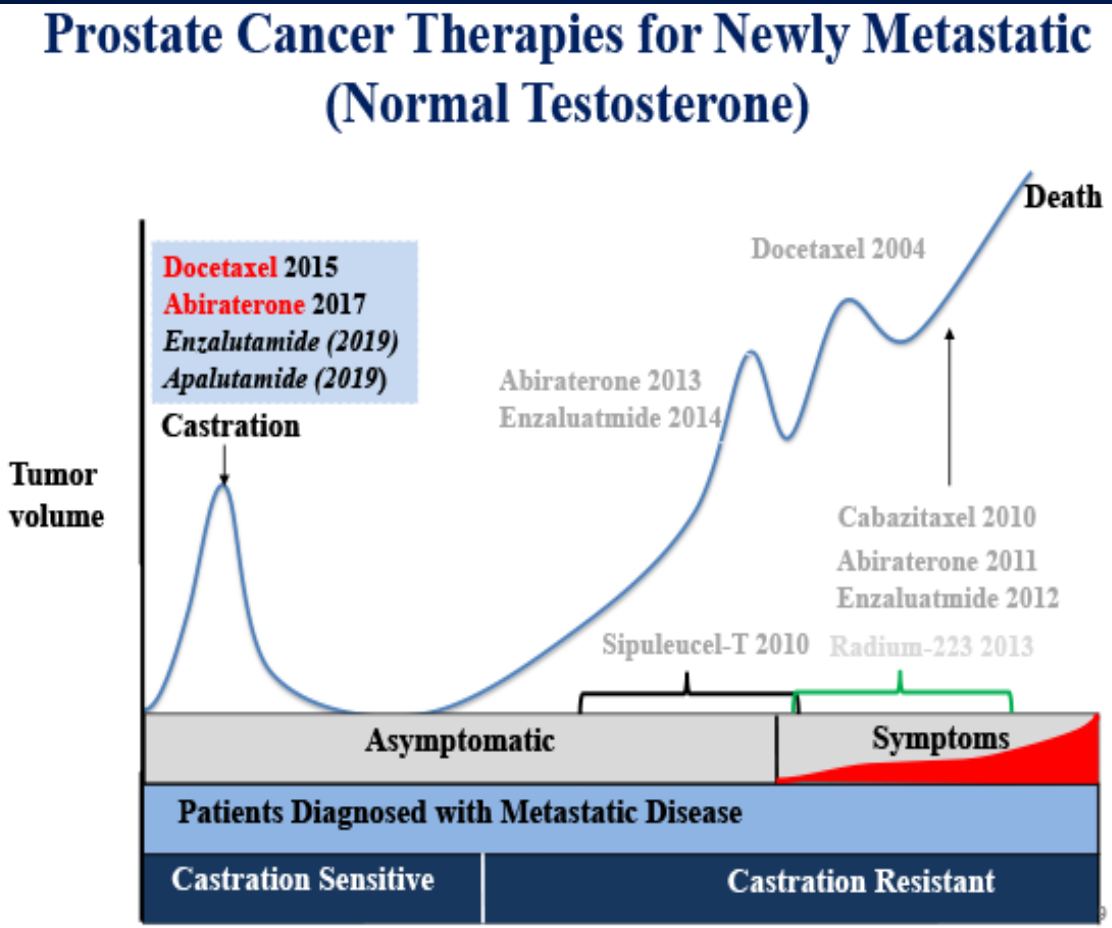
Metastatic Castration *Sensitive* Prostate Cancer

- Newly diagnosed with metastatic disease

or

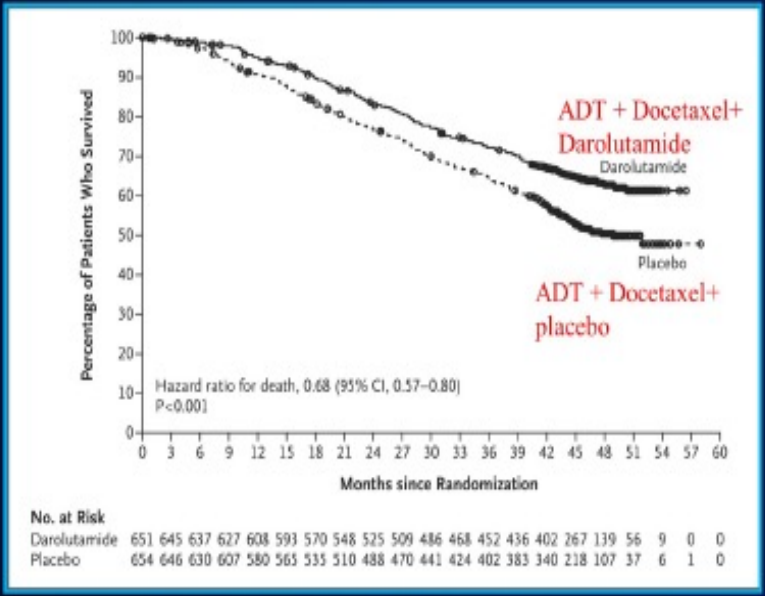
- Recurrent disease that presents with metastasis

Therapies

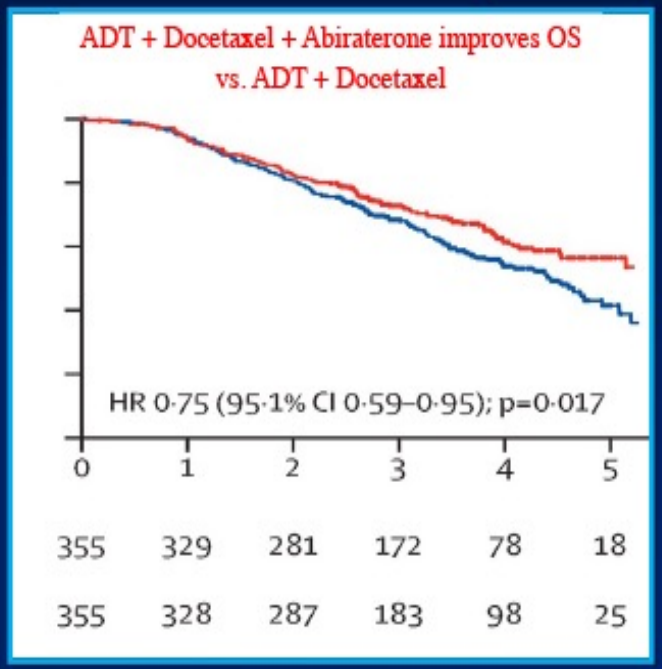

Prostate Cancer Therapies for Newly Metastatic (Normal Testosterone)
Death
Docetaxel 2004
Docetaxel 2015
Abiraterone 2017
Enzalutamide (2019)
Apalutamide (2019)
Castration
Abiraterone 2013
Enzaluatmide 2014
Tumor volume
Cabazitaxel 2010
Abiraterone 2011
Enzaluatmide 2012
Sipuleucel-T 2010
Radium-223 2013
Asymptomatic
Symptoms
Patients Diagnosed with Metastatic Disease
Castration Sensitive
Castration Resistant

Treatment intensification

Treatment Intensification for Metastatic Castration *Sensitive* Prostate Cancer *(High Volume)*



ARASENS: Smith, MR et al NEJM, 2022



PEACE-1 Fizazi, K et al. Lancet, 2022

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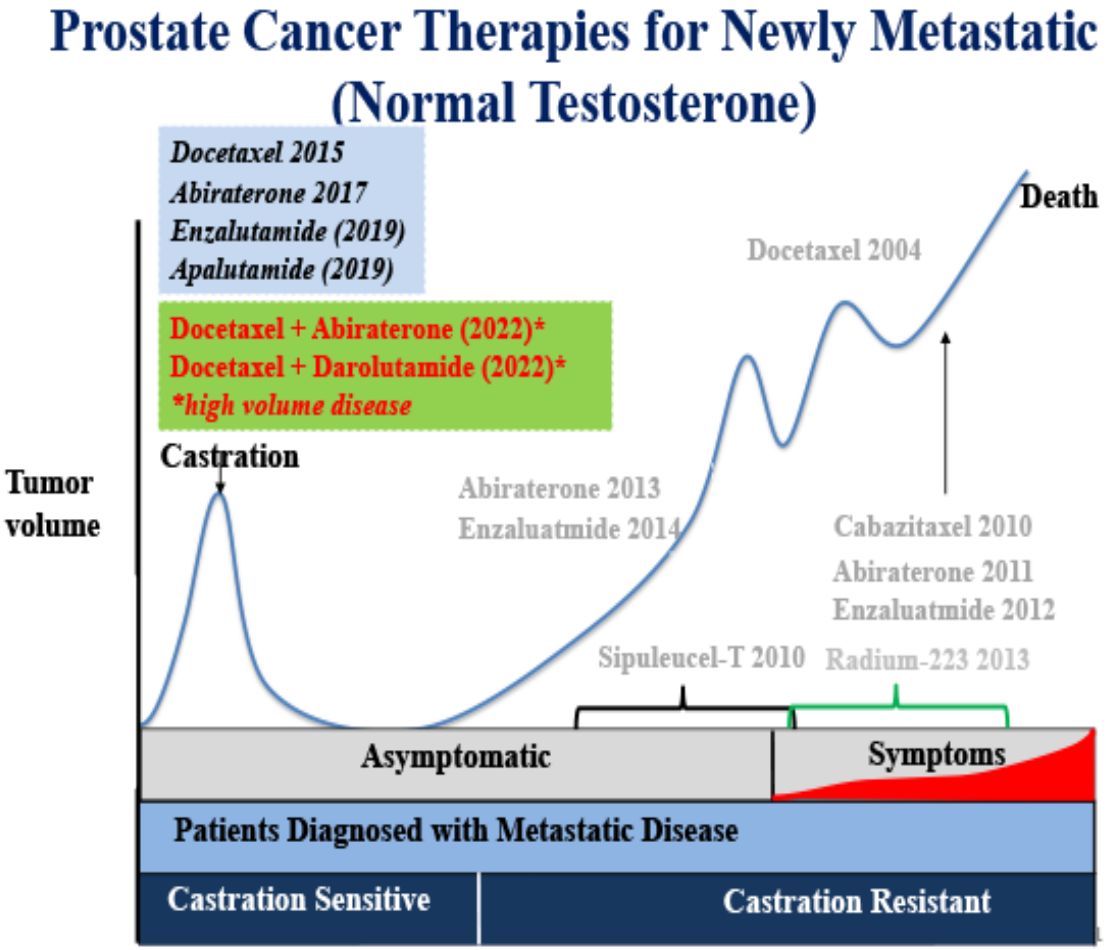
Therapies


Prostate Cancer Therapies for Newly Metastatic (Normal Testosterone)
Docetaxel 2015
Abiraterone 2017
Enzalutamide (2019)
Apalutamide (2019)
Docetaxel + Abiraterone (2022)*
Docetaxel + Darolutamide (2022)*
*high volume disease
Tumor volume
Castration
Death
Docetaxel 2004
Abiraterone 2013
Enzaluatmide 2014
Cabazitaxel 2010
Abiraterone 2011
Enzaluatmide 2012
Sipuleucel-T 2010
Radium-223 2013
Asymptomatic
Symptoms
Patients Diagnosed with Metastatic Disease
Castration Sensitive
Castration Resistant

Conclusions

Conclusions

- The treatment landscape for mCRPC is expanding, extending survival of patients
- Targeting DNA-damage repair mutations in mCRPC increase the need to biopsy late-stage patients and/or consider germline testing
- Future efforts will be made to advances Lu-PSMA to earlier stage patients
- With many treatments now available in mCRPC, treatment options must be tailored to individual patients