State-of-The-Art Sequencing of Treatment in Patients with Castration Resistant Prostate Cancer

Michael E Hurwitz

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Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

Michael Hurwitz, MD, PhD

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Talk outline

- Biology of metastatic prostate cancer
- Androgen-directed therapy
- Other agents
- Sequencing of agents
- Novel agents and strategies

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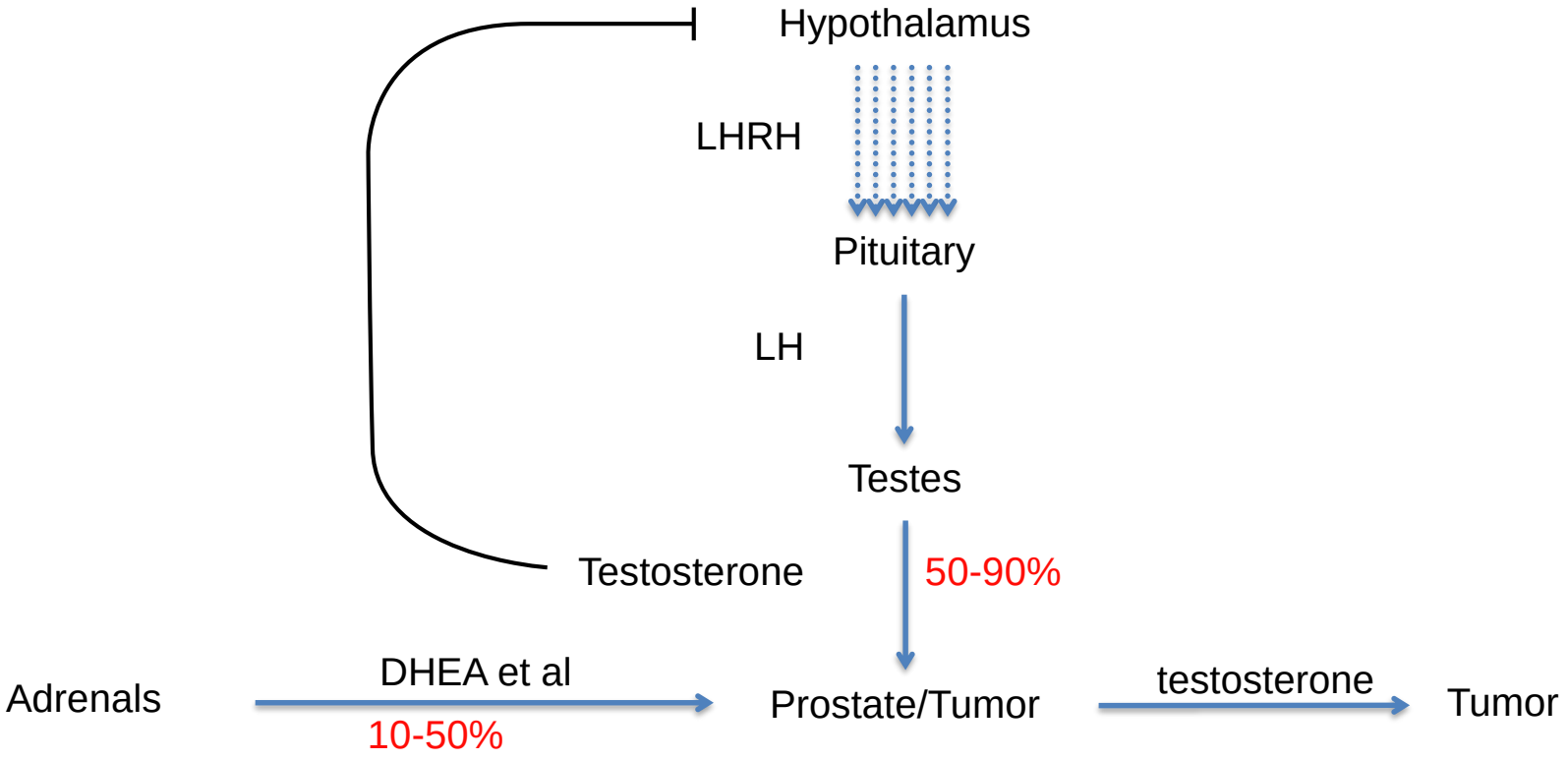
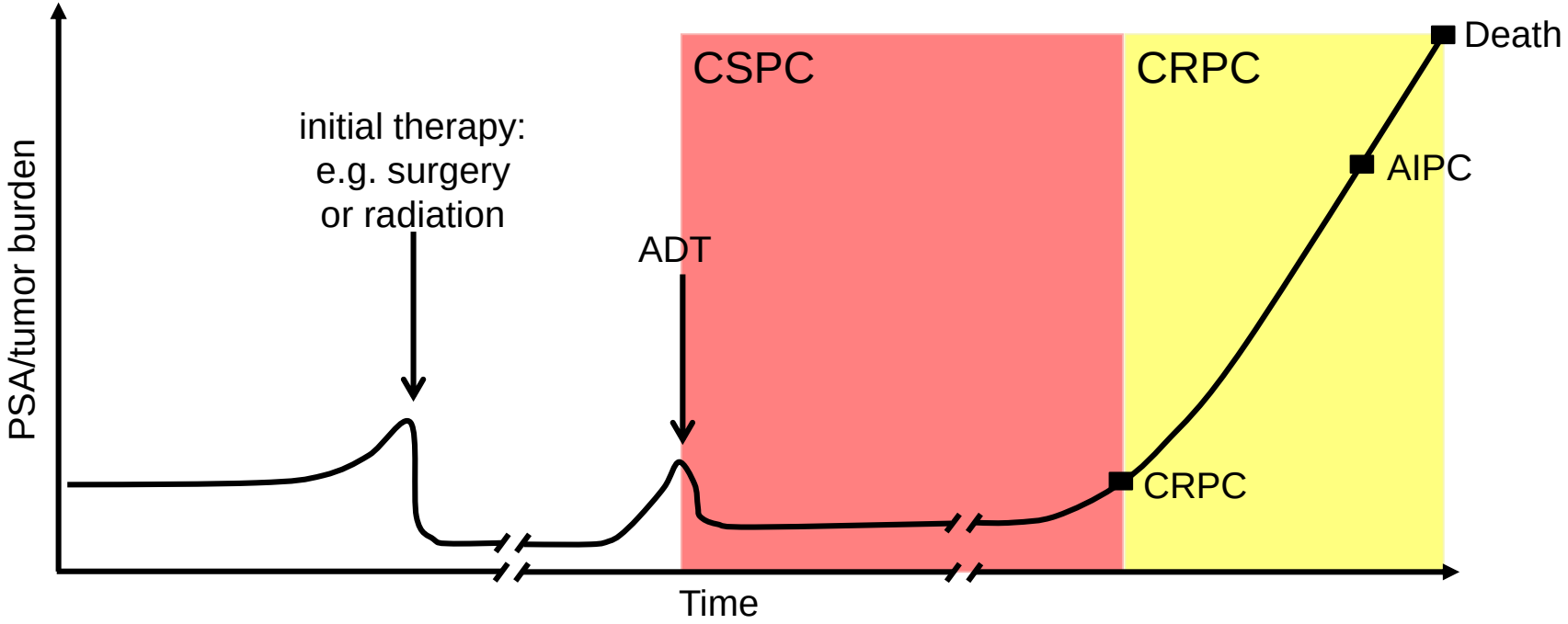
Androgen production



Natural history of prostate cancer



ADT = Androgen Deprivation Therapy
CSPC = castration-sensitive prostate cancer
CRPC = castration-resistant prostate cancer

ADT side effects

side effect	prevalence (%)
osteopenia	39 (at 2 years)
osteoporosis	53 (at 2 years)
bone fracture	15.1-19.4
metabolic-like syndrome	55
central weight gain	75
muscle loss	20.0-22.8
cardiovascular disease	poorly defined
hot flashes	44-80
gynecomastia	12.7-13.3
mastodynia	19
decreased libido	58.0-91.4
decrease in genital size	93
fatigue	poorly defined
cognitive changes	19-48
depression	13
anemia	13 (>25% decrease)

Walker et al, Clin Genitourinary Cancer 2013

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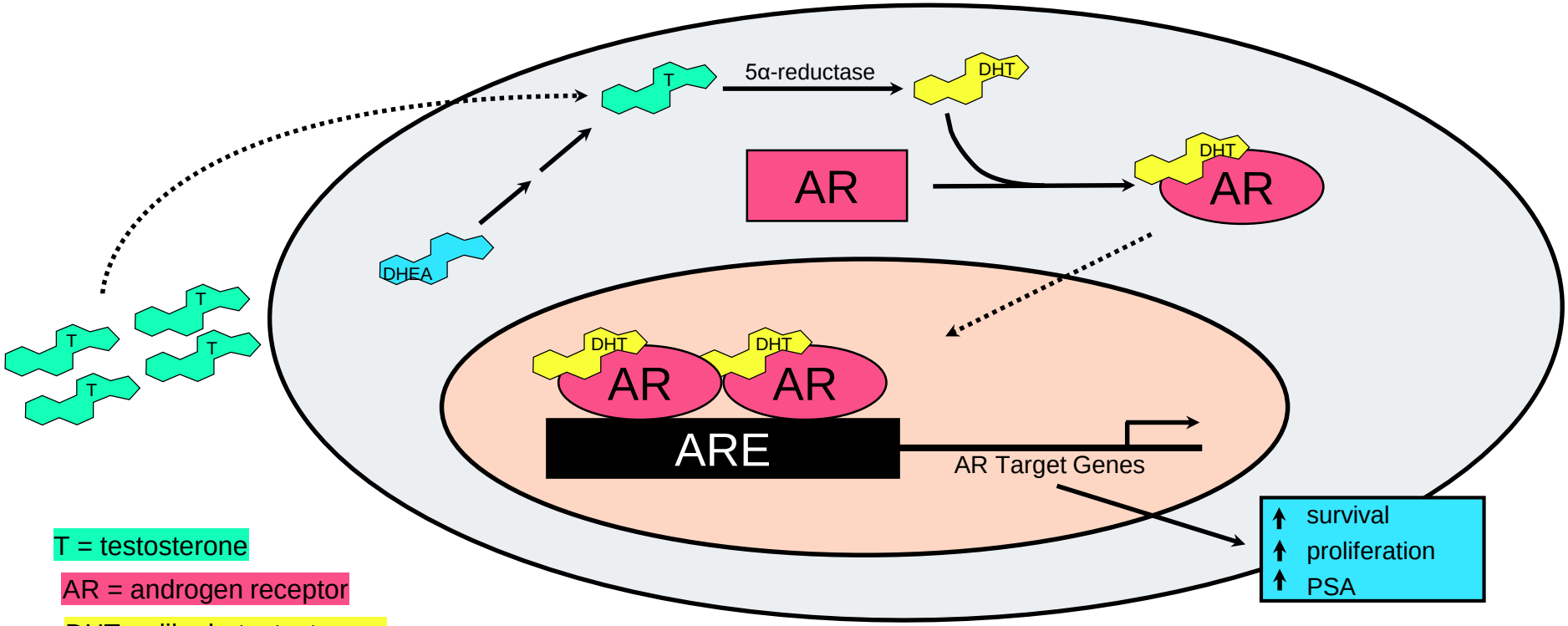
Androgen receptor signaling



T = testosterone

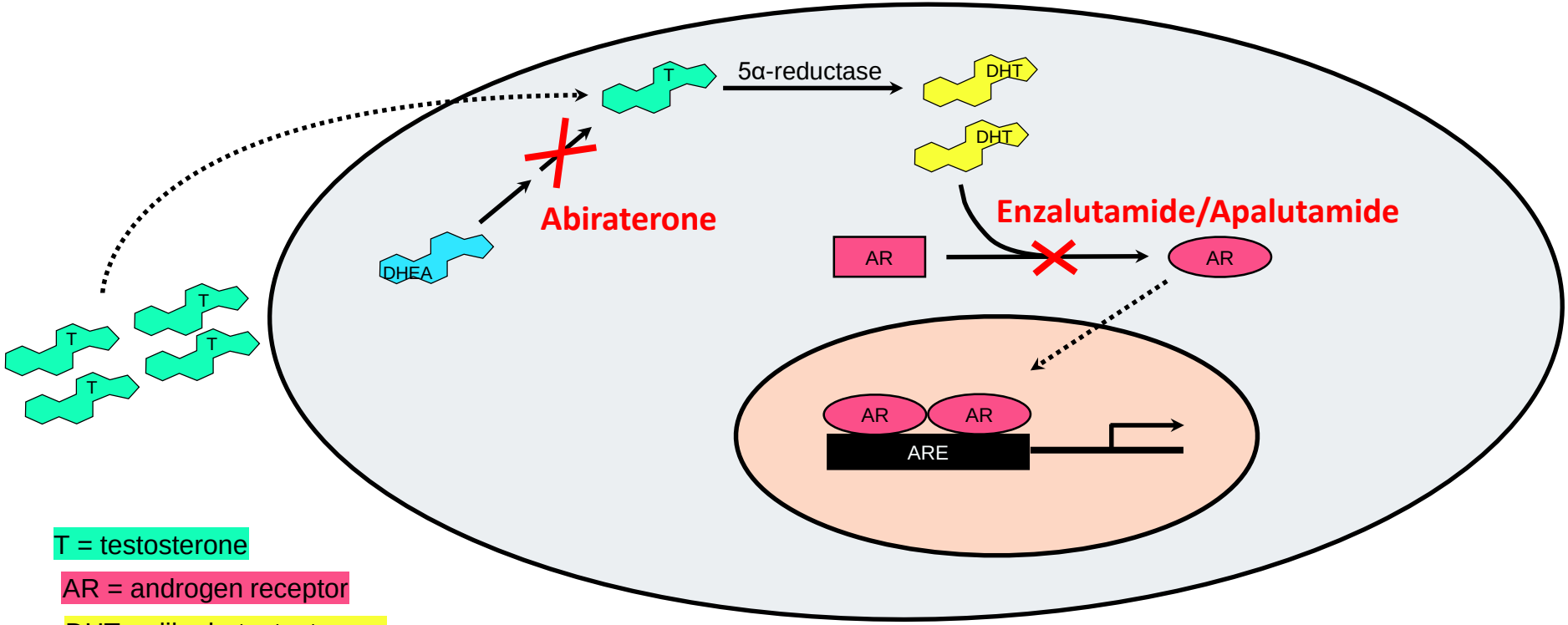
AR = androgen receptor

DHT = dihydrotestosterone

DHEA = dihydroepiandrostenedione

ARE = androgen response element

Secondary hormonal agents



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Categorizing advanced prostate cancer

	M0	M1
Castration Sensitive		
Castration Resistant		

M0 = biochemical recurrence
M1 = metastatic cancer on imaging
GnRH agonist = LHRH agonist = leuprolide, goserelin, triptorelin, (degarelix)
Anti-androgen = bicalutamide, flutamide, nilutamide

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Comparing Overall Survival Across Studies

	Median OS			3 yr OS rate	
	HR (95% CI)	Control (months)	Rx (months)	Control	Rx
LATITUDE	0.62 (0.51-0.76)	34.7 mo	NR	49%	66%
STAMPEDE	0.63	not reached (0.52 – 0.76)			
CHAARTED High Volume	0.63 (0.50-0.79)	34.4 mo	51.2 mo	~50%*	~65%*

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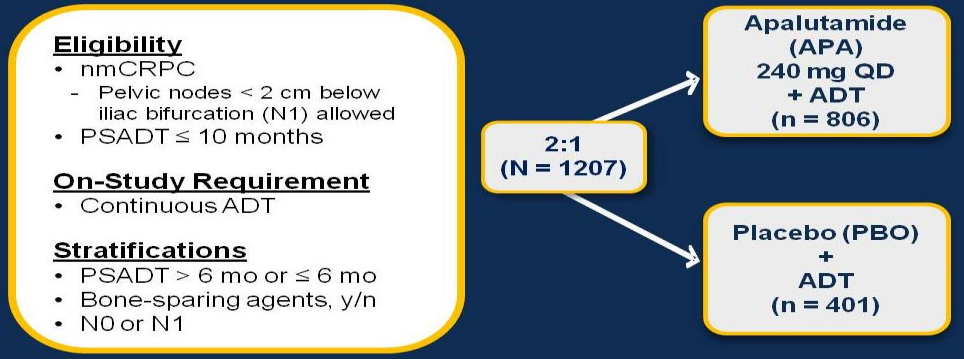
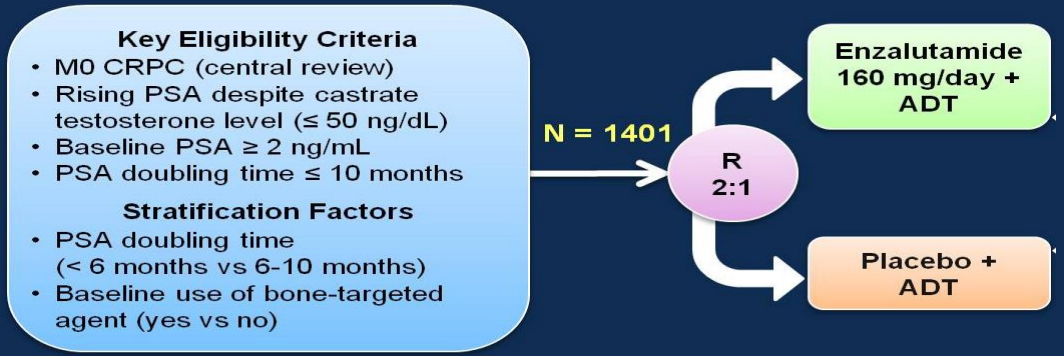
M0 disease: GnRH agonist + androgen receptor blockade

SPARTAN trial[1,2]



PROSPER trial[3]



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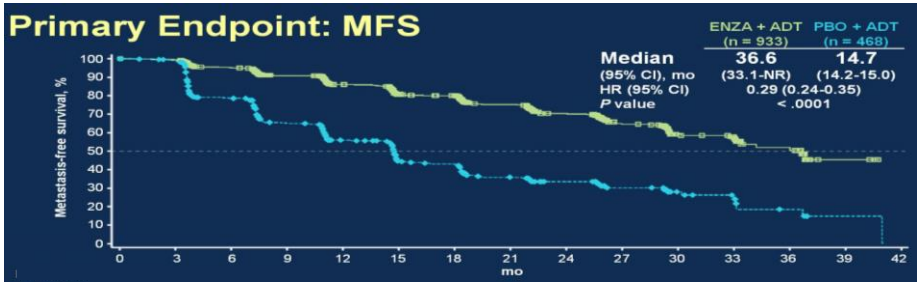
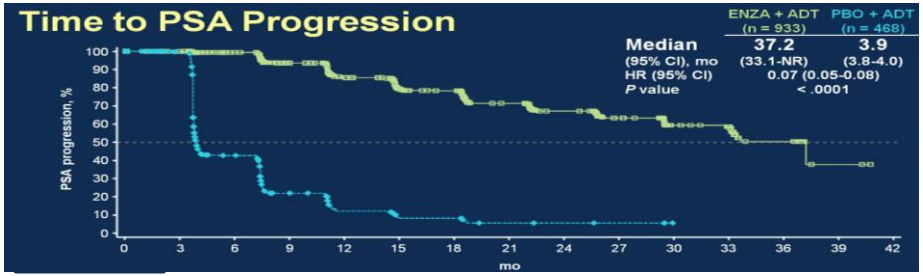
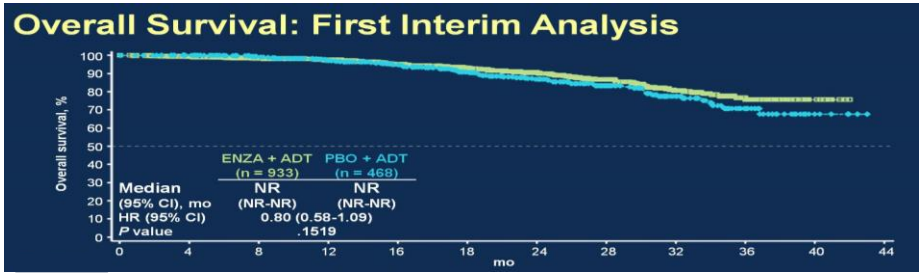
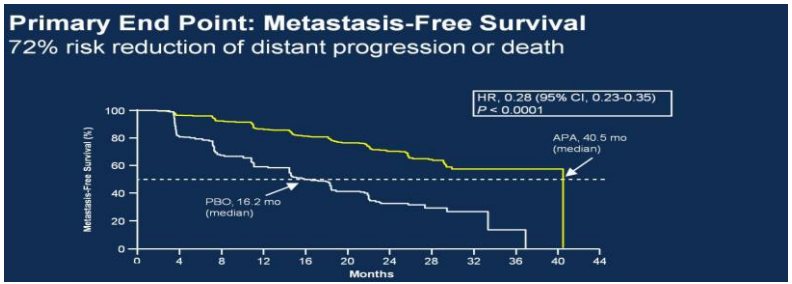
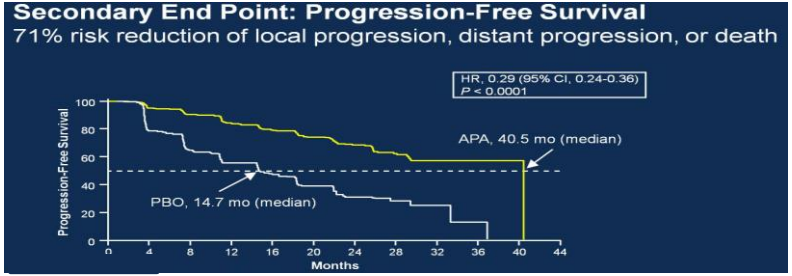


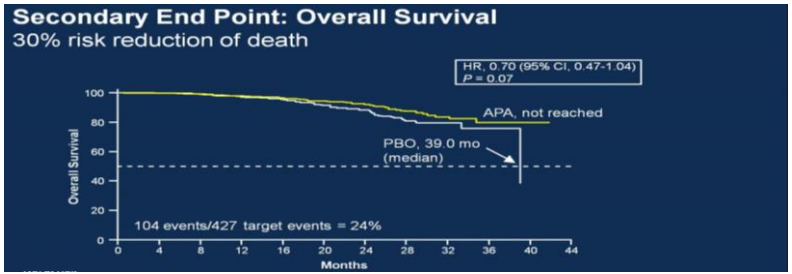




SPARTAN







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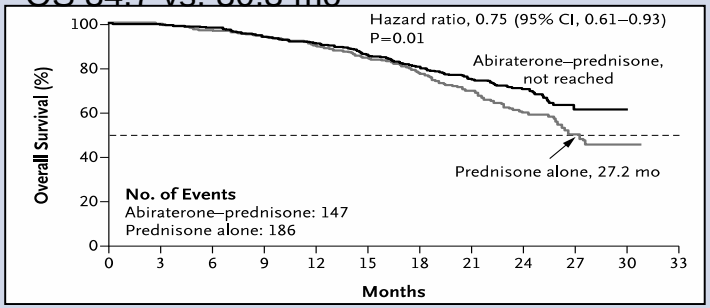
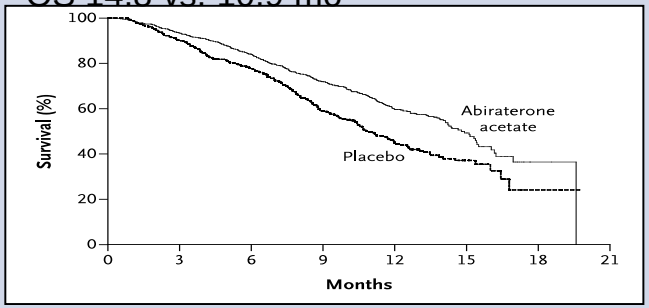
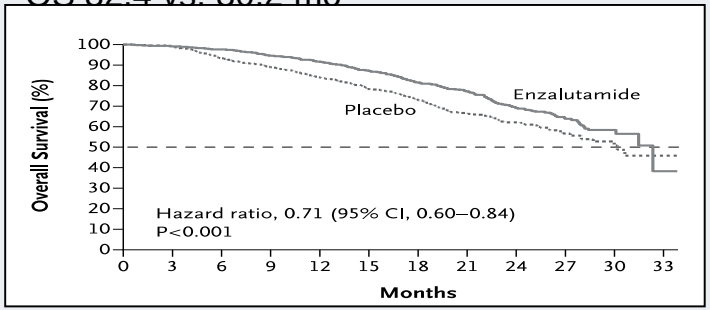
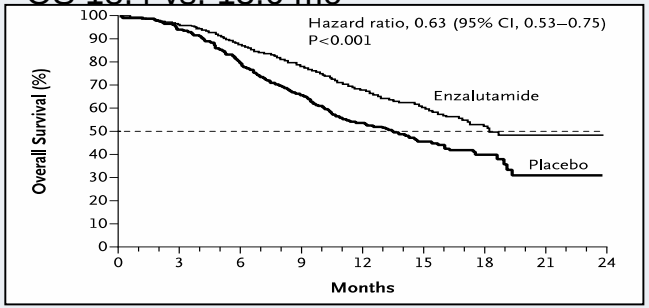
mCRPC: secondary hormonal therapy

	Pre-docetaxel	Post-docetaxel
abiraterone	OS 34.7 vs. 30.3 mo  Ryan et al., NEJM 2013	OS 14.8 vs. 10.9 mo  De Bono et al., NEJM 2011
enzalutamide	OS 32.4 vs. 30.2 mo  Beer et al., NEJM, 2014	OS 18.4 vs. 13.6 mo  Scher et al., NEJM, 2012

abiraterone acetate vs. enzalutamide

- Abiraterone:
  - Must be taken on an empty stomach
  - Requires low dose prednisone (5-10 mg daily)
- Enzalutamide:
  - Fatigue
  - Contraindicated in patients with seizure risk

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Treatment classes for mCRPC

- Blocking androgen signaling:
  - abiraterone acetate
  - enzalutamide
- Immunotherapy: Sipuleucel-T
- Bone targeting: Radium-223
- Chemotherapy
  - Docetaxel
  - Cabazitaxel
  - *mitoxantrone*
- PARP inhibition

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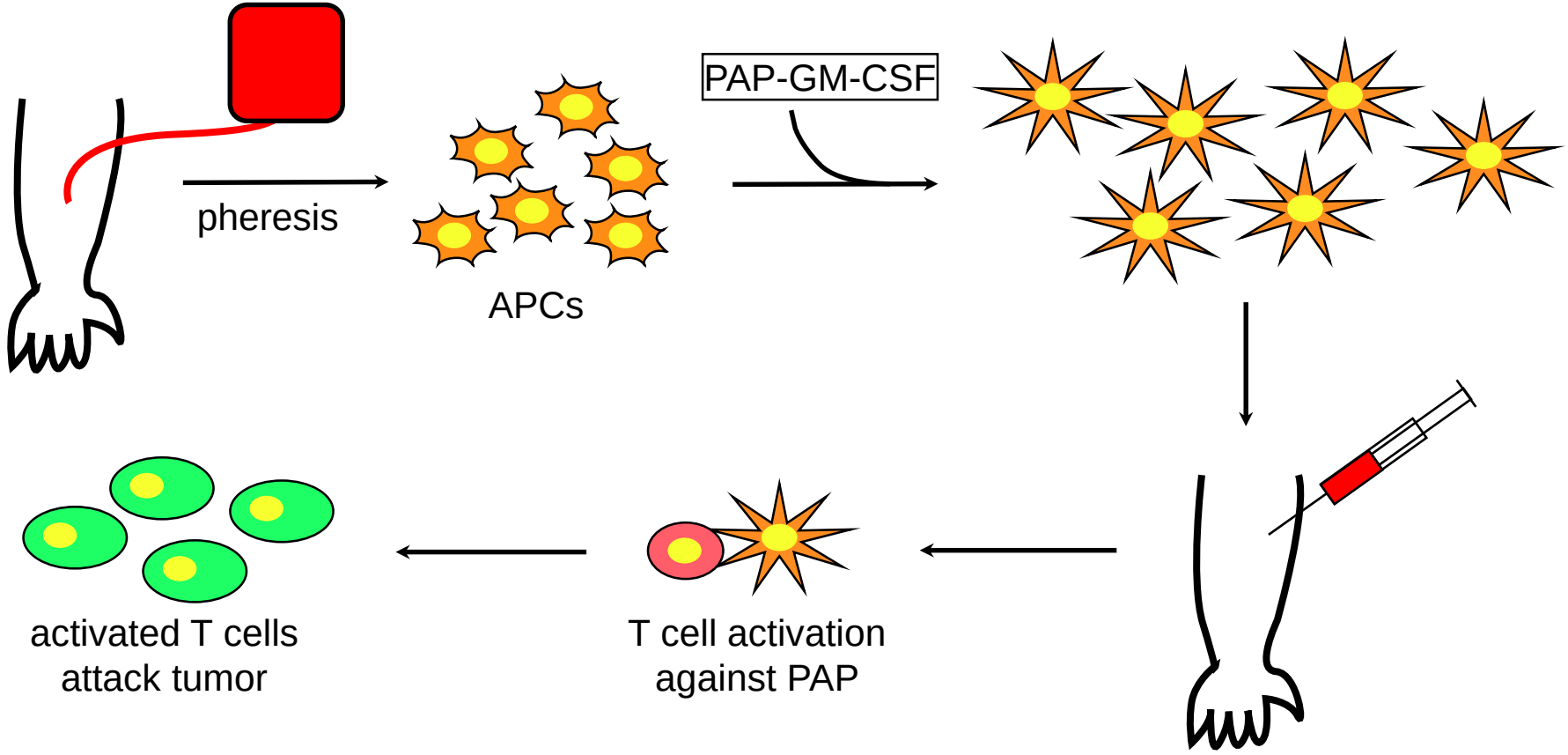
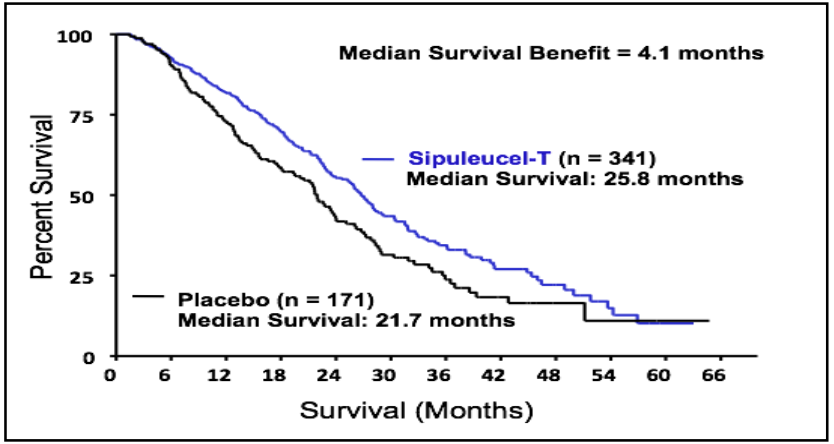
Sipuleucel-T: cellular immunotherapy

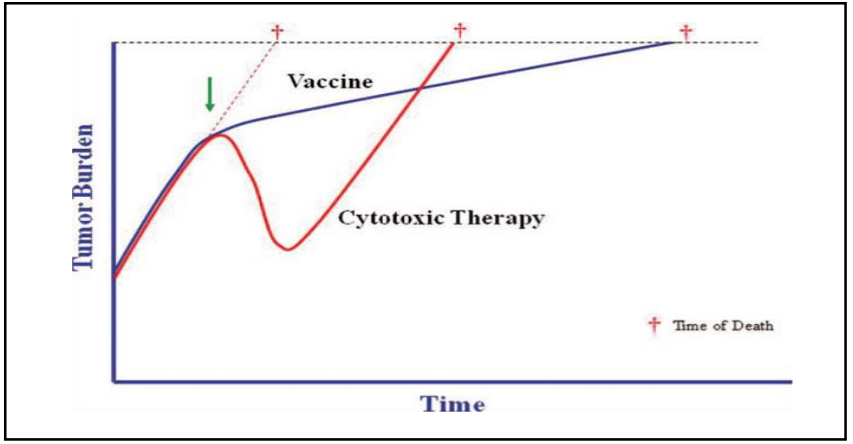


Sipuleucel-T: cellular immunotherapy

- For minimally metastatic disease: rising PSA and asymptomatic or minimally symptomatic mets
- 2-week cycles x3
- No effect on PSA or progression but OS 25.8 vs. 21.7 mo
- Few side effects



Kantoff et al., NEJM 2010



Maddan et al The Oncologist 2010

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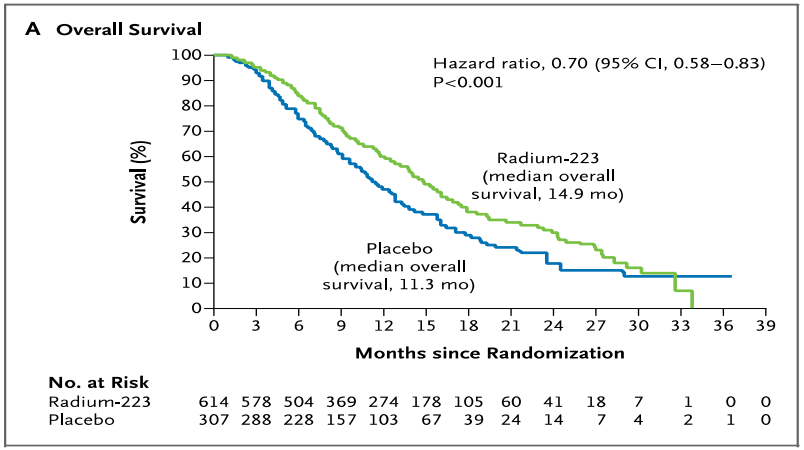
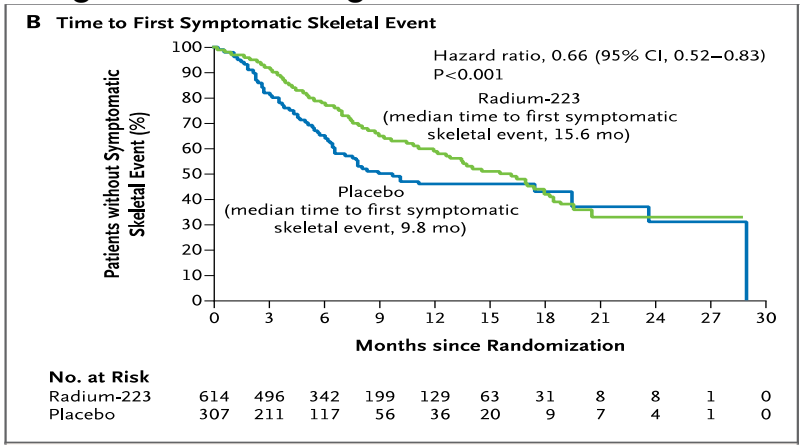
^{223}Radium dicholoride

- α-emitting isotope that targets bony lesions
- pts with symptomatic bony mets requiring analgesic medications and no visceral disease
- 3.6 mo overall survival advantage (14.9 vs. 11.3 mo)
- 5.8 mo improvement to first skeletal event
- 56% of pts will have improvement in bone pain after 2 doses
- side effects minimal, but … nausea, vomiting, anorexia, fatigue?





Parker et al., NEJM, 2013

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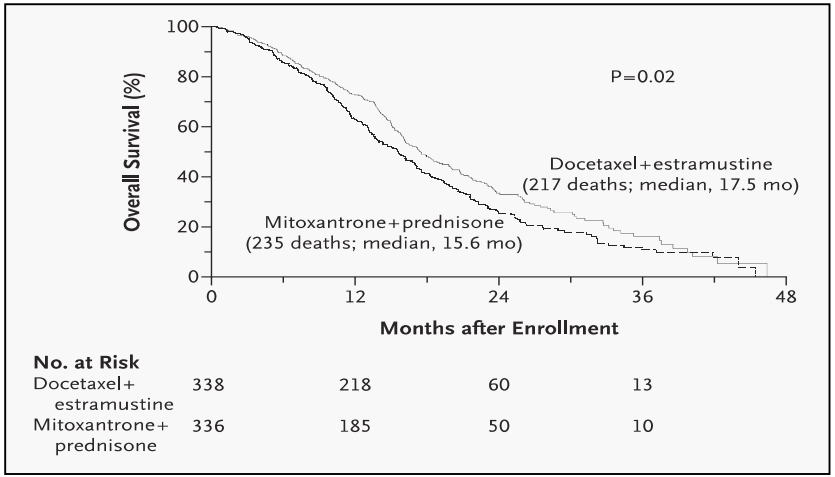
chemotherapy: docetaxel

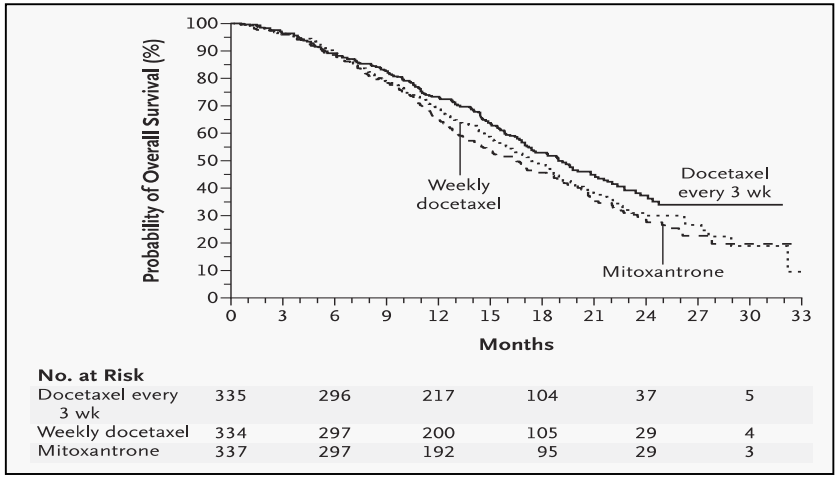
- stabilizes microtubules
- 75 mg/m^2 every 3 weeks with 10 mg prednisone daily
- side effects: fatigue, neuropathy, hair loss, nausea

SWOG 99-16:OS: 17.5 v s 15.6 mo



Petrylak et al., NEJM, 2004

TAX327:OS: 18.9 vs 16.5 mo

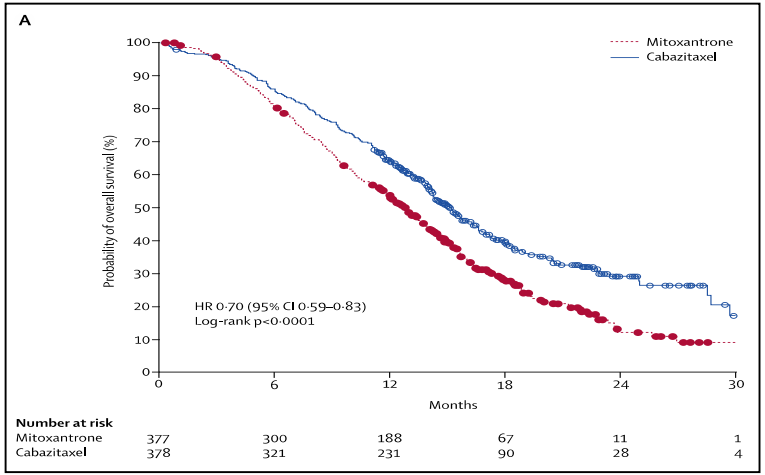


Tannock et al., NEJM, 2004

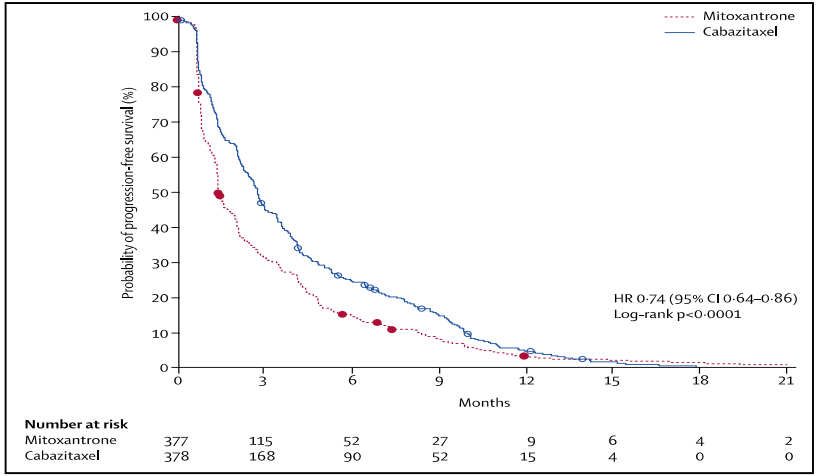
chemotherapy: cabazitaxel after docetaxel (TROPIC trial)

- decreased binding to P-glycoprotein (vs docetaxel)
- 25 mg/m^2 every 3 weeks with prednisone daily
- pegfilgrastim standard after each dose
- side effects similar to docetaxel (less neuropathy/more grade 3-4 toxicity)
- 2.4 month OS advantage (15.1 vs. 12.7 mo)

OS

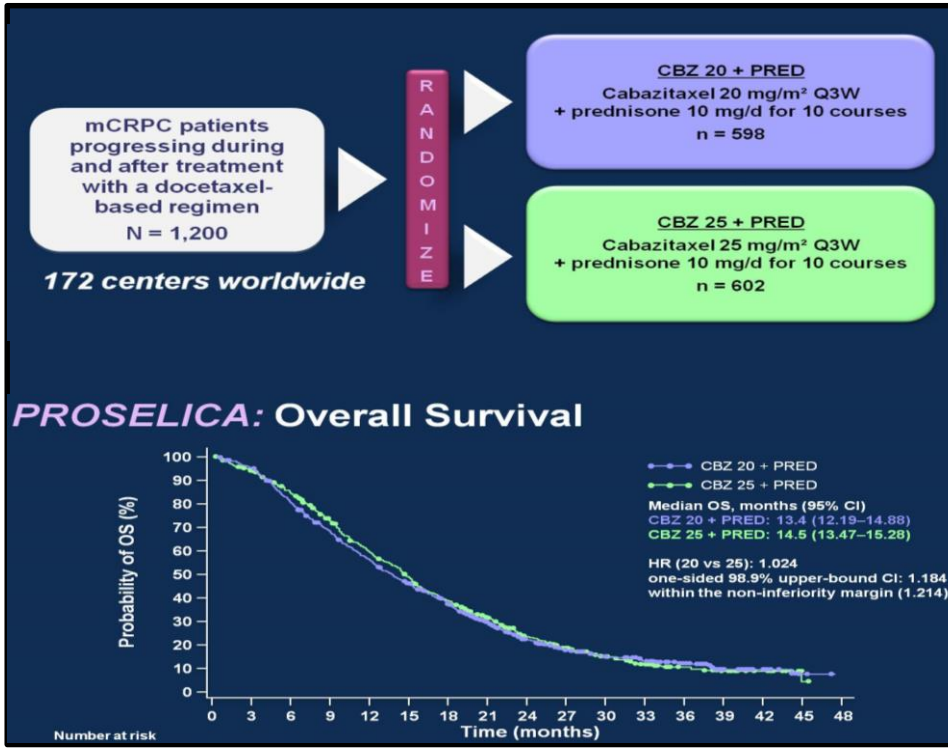


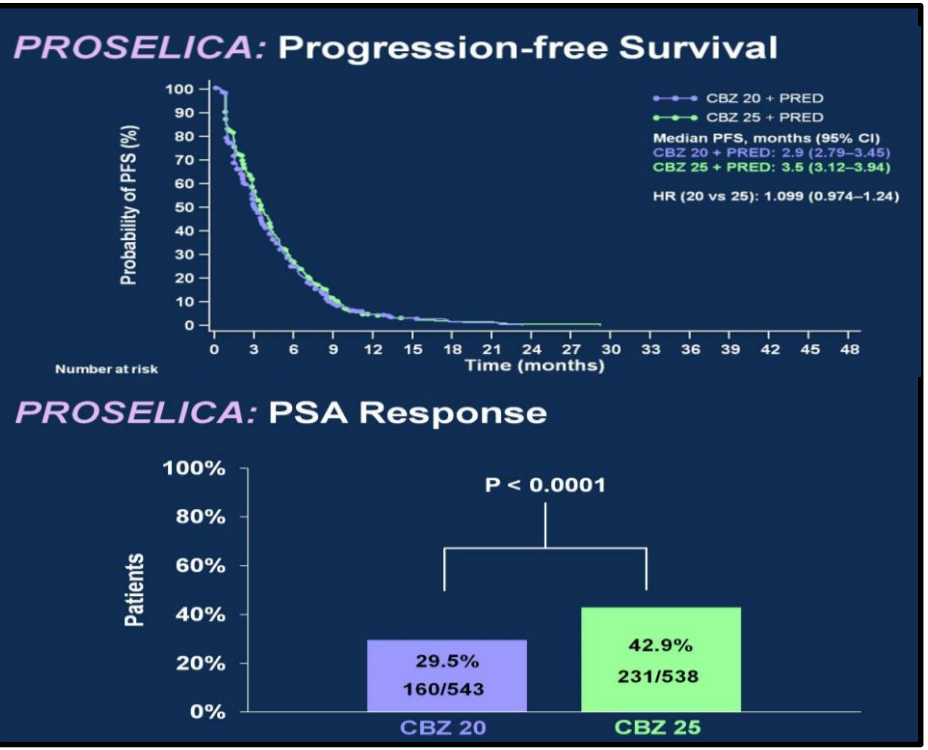
PFS



De Bono et al., Lancet, 2010

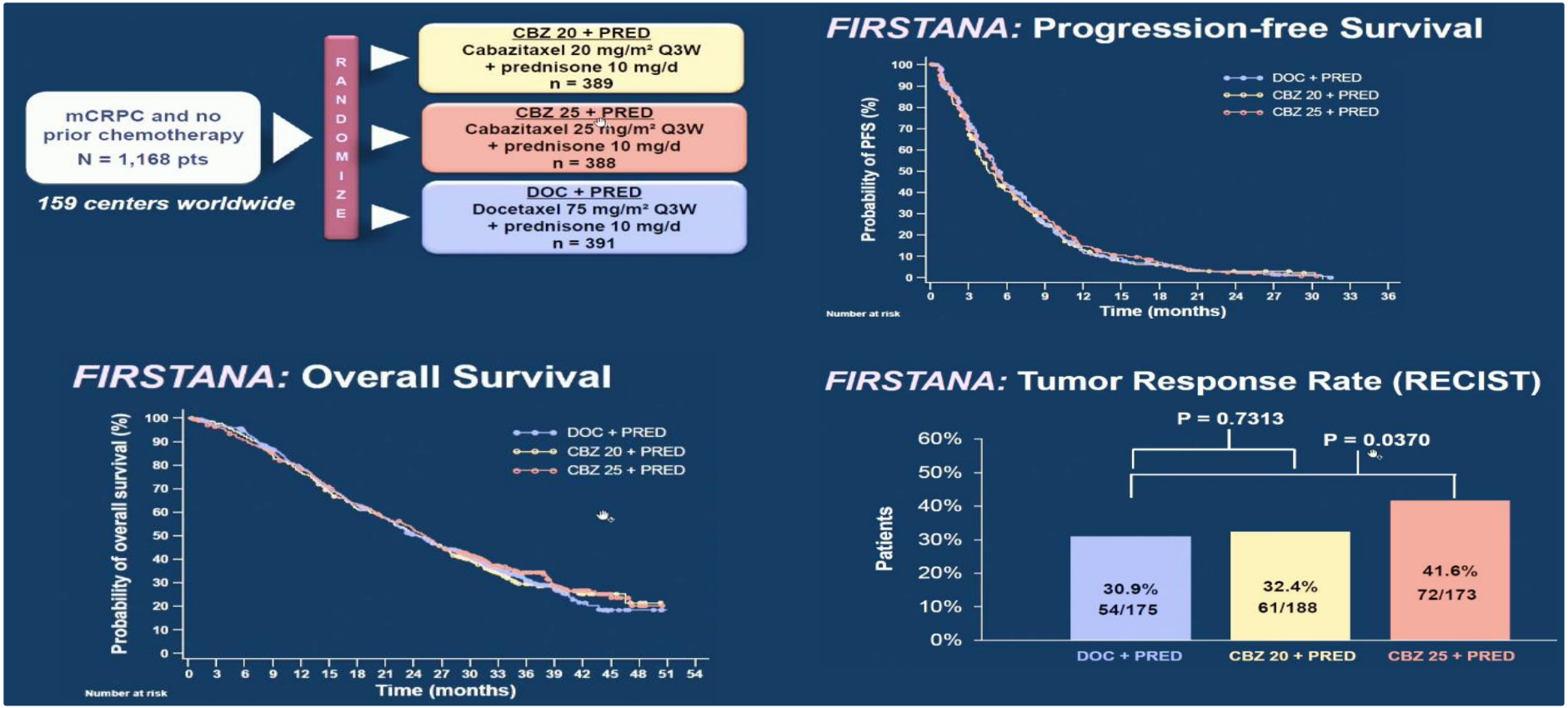
cabazitaxel 20 mg/m² vs 25 mg/m²: PROSELICA trial





De Bono et al, ASCO 2016; Eisenberger et al, JCO 2017

docetaxel vs cabazitaxel: FIRSTANA trial



Sartor et al, ASCO 2016; Oudard et al, JCO 2017

docetaxel vs cabazitaxel: side effects

FIRSTANA: TEAEs in ≥ 5% of Patients cont.

TEAEs reported in ≥ 5% of patients, n (%)	DOC + PRED N = 387		CBZ 20 + PRED N = 369		CBZ 25 + PRED N = 391	
	All Grades	Grade 3–4	All Grades	Grade 3–4	All Grades	Grade 3–4
Peripheral sensory neuropathy	97 (25.1)	8 (2.1)	43 (11.7)	1 (0.3)	48 (12.3)	0
Paresthesia	24 (6.2)	0	25 (6.8)	0	14 (3.6)	0
Muscle spasms	15 (3.9)	0	28 (7.6)	0	13 (3.3)	1 (0.3)
Arthralgia	31 (8.0)	4 (1.0)	33 (8.9)	2 (0.5)	43 (11.0)	1 (0.3)
Bone pain	25 (6.5)	6 (1.6)	31 (8.4)	8 (2.2)	30 (7.7)	4 (1.0)
Edema peripheral	79 (20.4)	6 (1.6)	36 (9.8)	0	30 (7.7)	1 (0.3)
Weight decreased	19 (4.9)	1 (0.3)	17 (4.6)	0	40 (10.2)	3 (0.8)
Alopecia	151 (39.0)	0	33 (8.9)	0	51 (13.0)	0
Nail disorder	35 (9.0)	1 (0.3)	1 (0.3)	0	3 (0.8)	0

PRESENTED AT ASCO ANNUAL MEETING '16

Presented by: Oliver Sartor

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  - abiraterone acetate
  - enzalutamide
- Immunotherapy: Sipuleucel-T
- Bone targeting: Radium-223
- Chemotherapy
  - Docetaxel
  - Cabazitaxel
  - *mitoxantrone*
- PARP inhibition

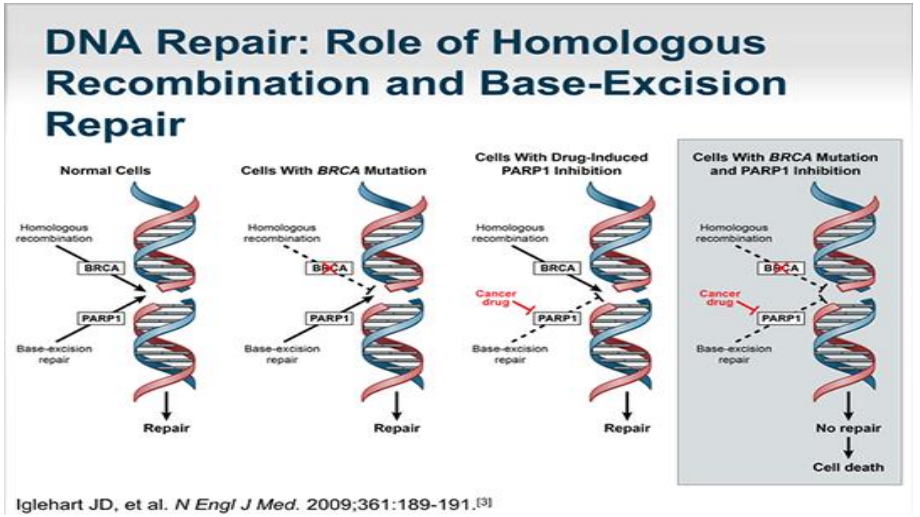
PARP inhibition in DNA-repair defective prostate cancers

- Olaparib monotherapy in heavily pretreated CRPC
- 16/49 pts had response (33%)
- 14/16 responders had defects in double-stranded DNA break repair
- Veliparib has also been studied (Feng et al, ESMO 2016, Abstract #730PD)

DNA repair defect	n	Response
-	33	6.1%
+	16	87.5%

Mateo et al, NEJM 2015

*ART = abiraterone or enzalutamide



Talk outline

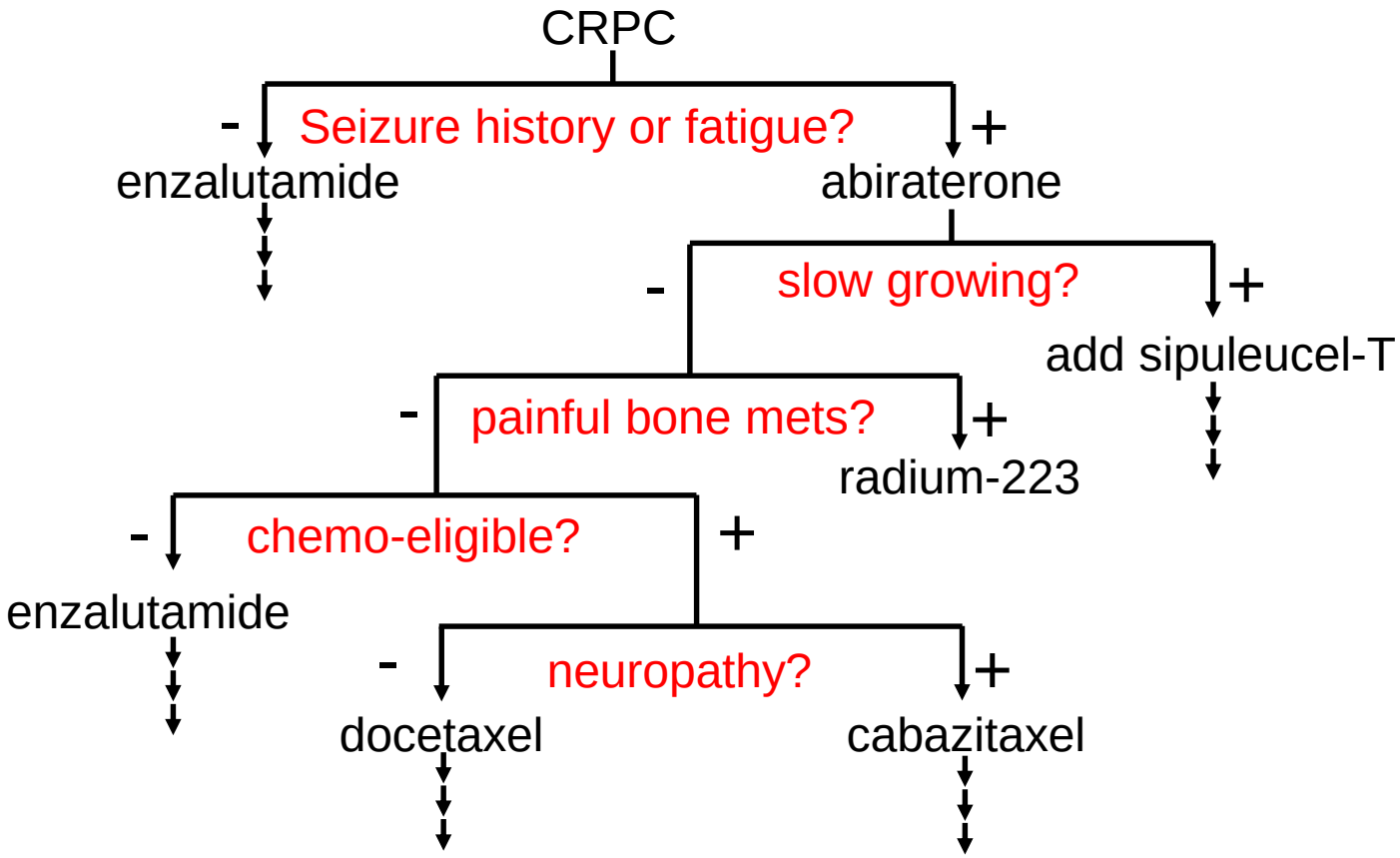
- Biology of metastatic prostate cancer
- Androgen-directed therapy
- Other agents
- Sequencing of agents
- Novel agents and strategies

Considerations for sequencing of agents

agent	eligibility	Side effects
sipuleucel-T*	Slowly growing disease Minimally symptomatic	Minimal Has little/no effect on PFS
Radium-223*	Pain requiring analgesics No visceral disease	?nausea, vomiting, anorexia, fatigue
Abiraterone acetate	requires 10 mg prednisone qd	Exacerbates ADT Steroid side effects
enzalutamide	seizure history?	Exacerbates ADT Lowers seizure threshold Fatigue
docetaxel	adequate hematologic function adequate performance status	Hematologic Alopecia Neuropathy Fatigue Nausea
cabazitaxel	adequate hematologic function adequate performance status	More toxicity, less neuropathy than docetaxel

*Can be given with abiraterone or enzalutamide safely though unknown if efficacy is equivalent in combination

Strategies for treatment: an example



abiraterone followed by enzalutamide (and vice versa)

study	PSA response rate for secondary rx	PFS (1st line)	PFS (2nd line)	ref
35 pts; D -> abi -> enza	Abi-responsive: 43.8% Abi-unresponsive: 15.8%	9 mo	4.9 mo	1
126 pts; abi -> enza or enza -> abi	1st line-responsive: 20% 1st line-unresponsive: 25%		3.6 mo	2
30 pts, enza -> abi	10% overall	41 wks	15.4 wks	3
response to D in mCRPC in pts who initially received upfront ADT alone vs ADT + D	ADT alone: 70% (n = 17) ADT+D: 0% (n = 9)		6 mo 2.5 mo	4
Retrospective 560 pts, no statistically sig OS difference	D -> C -> ART*: 37.3 mo OS D -> ART -> C: 36 mo OS ART -> D -> C: 30.1 mo OS			5
Retrospective 4070 pts, network meta-analysis; no difference in OS	Compared different agents after docetaxel			6

D = docetaxel, abi = abiraterone acetate, enza = enzalutamide, ADT = androgen deprivation therapy

1. Schrader et al, European Urology 2014; 2. Nadal et al, Prostate 2016; 3. Noonan et al, Ann Oncol 2013; 4. Lavaud et al, ESMO 2016, Abstract #761P; 5. Angelergues et al, ESMO 2016; 6. Cherubini et al, ESMO 2016

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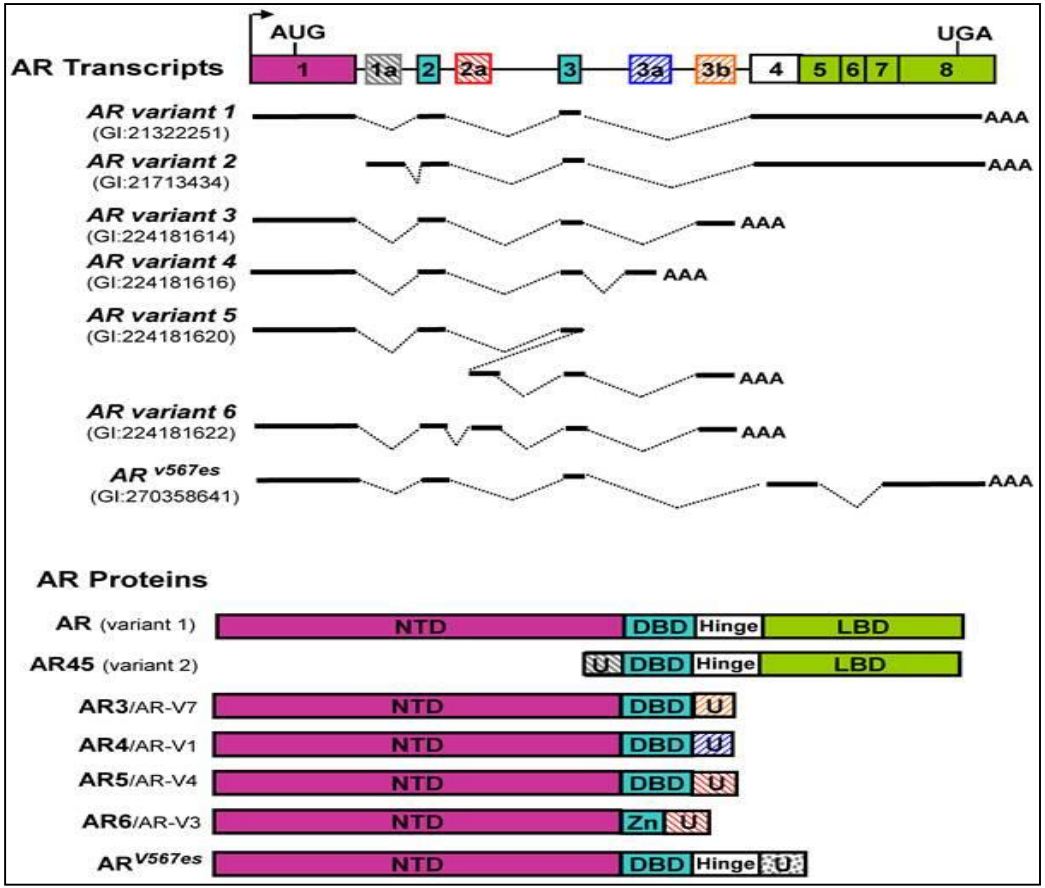
AR splice variants drive resistance to hormonal therapies

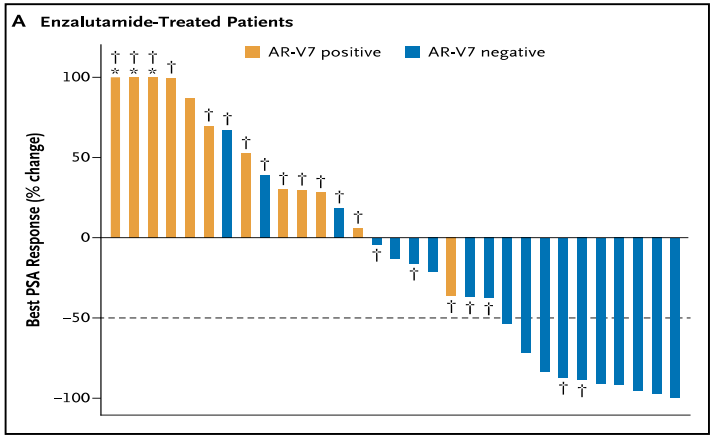


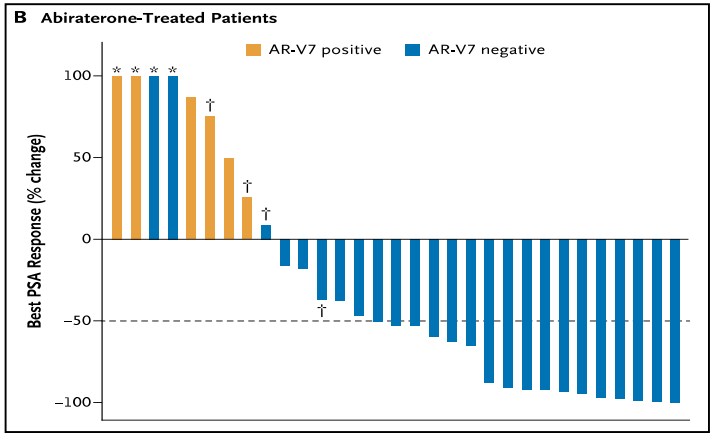
Guo and Qiu, Int J Biol Sci, 2011

*ART = abiraterone or enzalutamide

AR-V7: effects on abiraterone/enzalutamide

- Clinical study of AR-V7 testing:
  - tumor cells circulating in peripheral blood were tested for AR-V7
  - if any AR-V7 RNA present, almost no response





Antonarakis et al., NEJM, 2014

Mutations that drive resistance to hormonal therapies

mutation	Activated by:	Ref
L702H	glucocorticoids	1
V715M	Adrenal androgens (DHEA, androstenedione) and progesterone	2
H874Y	estradiol and progesterone	3
F876L	enzalutamide	4
T877A, T877S	estradiol and progesterone	3
T878A	Progesterone (3/18 pts who progressed on abi have mut)	5

1. Romanel et al, Sci Trans Med 2015; 2. Culig et al, Molec Endocrinol 1993; 3. Fenton et al, Clin Cancer Res 1997; 4. Joseph et al, Cancer Discovery 2013 and Korpal et al, Cancer Discovery 2013; 5. Chen et al, Clin Cancer Res 2015

variant prostate cancer

Features:

- Non-adenocarcinoma histology
- Exclusively visceral metastases
- Lytic bone lesions
- Bulky lymphadenopathy
- Low PSA
- Evidence of neuroendocrine differentiation
  - Synaptophysin
  - Chromogranin A
  - Malignant hypercalcemia
  - CEA
- Short time to androgen independence

Treatment:

- Platinum-containing combinations:
  - Carboplatin/docetaxel
  - Cisplatin/etoposide

*ART = abiraterone or enzalutamide

Thank you