

Advanced Prostate Cancer: Role of Clinical Trials

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Faculty/Presenter Disclosure

Faculty/Presenter: **Dr. Pawel Zalewski**

Relationship with commercial interests:

- Grants/Research Supports:
- Speaker bureau/Honoraria:
- Consulting Fees:
- Clinical trials: Participates in trials sponsored by various pharmaceutical companies without receiving direct payment

The DRCC Research Program: Historical & Current Activity

- Oncology Clinical Trials Unit formed in mid 1990s with a focus on breast, CRC, and lung
- 1st Clinical Trial conducted in 1994 (NCIC MA.12):
 - *Double-blind randomized trial of Tamoxifen vs. PLA in patients with node + or high risk node – Bca*
- Over the last decade clinical trials have been extended to all cancer types within Medical & Radiation Oncology
- From 1994 until present, 255 studies have been conducted
- Currently 57 active clinical trials (prostate, breast, lung, GI, GU, melanoma, hematology, radiation)

DRCC Research Team

- 2 Clinical Trials Medical Leads & 25+ Investigators who conduct clinical trials in medical and radiation oncology
- Research Director & Oncology Research Coordinator
- RNs, RPNs, Radiation Coordinator
- Ethics Associate, Admin Assistant & Clinical Research Assistant



Prostate Cancer Research

Plethora of Targets & Agents



Pathway	Target	Agents
Angiogenesis	PDGF receptor	Olaratumab
	Unknown	Tasquinimod
	VEGF	Aflibercept
Androgen signaling*	VEGF receptor	Ramucirumab
	Androgen receptor	ARN-509, Enzalutamide
	CYP17	Abiraterone , Orteronel
Apoptosis	BCL-2	AT-101
	Clusterin, MDM2	Custirsen, MI-773
Cell cycle*	Microtubules	Docetaxel, Cabazitaxel , Eribulin
DNA repair	PARP	Veliparib
Bone*	Osteoclast, RANKL, Integrins	Radium-223, Zoledronic Acid, Denosumab , EMD 525797
	Vaccine, CTLA-4 Multiple	Sipuleucel-T , Ipilimumab Lenalidomide
Other Pathways	HSP27, IGF-1R, Src MET +/-VEGFR2	OGX-427, Cixutumumab Cabozantinib, LY2875358 PAM4983g

Metastatic Castration-Resistant Prostate Cancer: 13 Positive Trials → 12 FDA Approvals Since 1996

- **Survival Improvement**

- Docetaxel
- Sipuleucel-T
- Cabazitaxel
- Abiraterone X 2
- Enzalutamide X 1
- Radium-223

(Since 2004)

- **Pain**

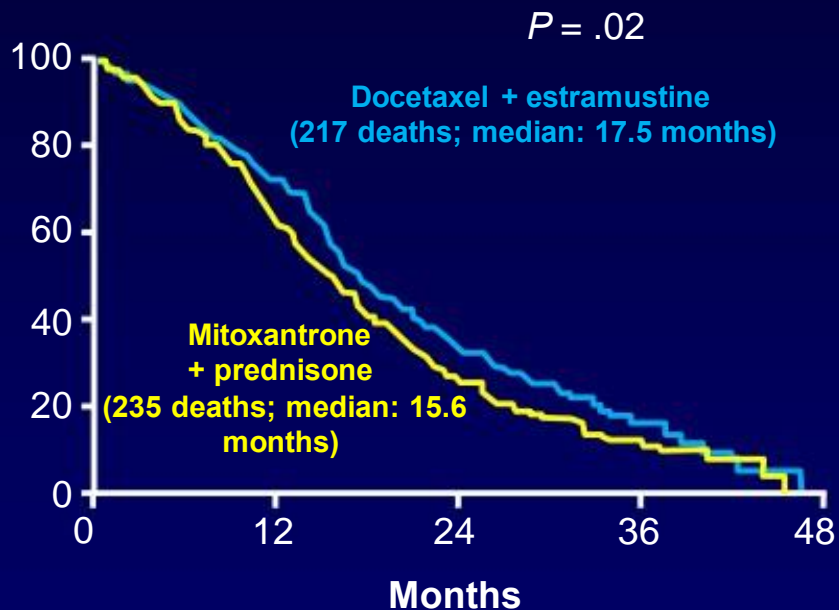
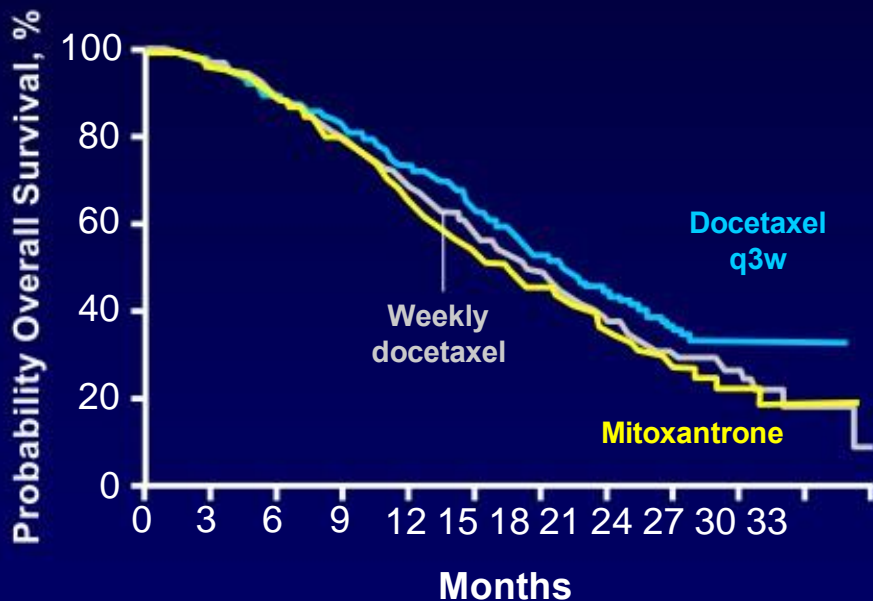
- *Mitoxantrone, Strontium, Samarium*

- **Skeletal-related events**

- *Zoledronic acid, Denosumab*

Docetaxel + Prednisone or Mitoxantrone + Prednisone for Castration-Resistant Prostate Cancer

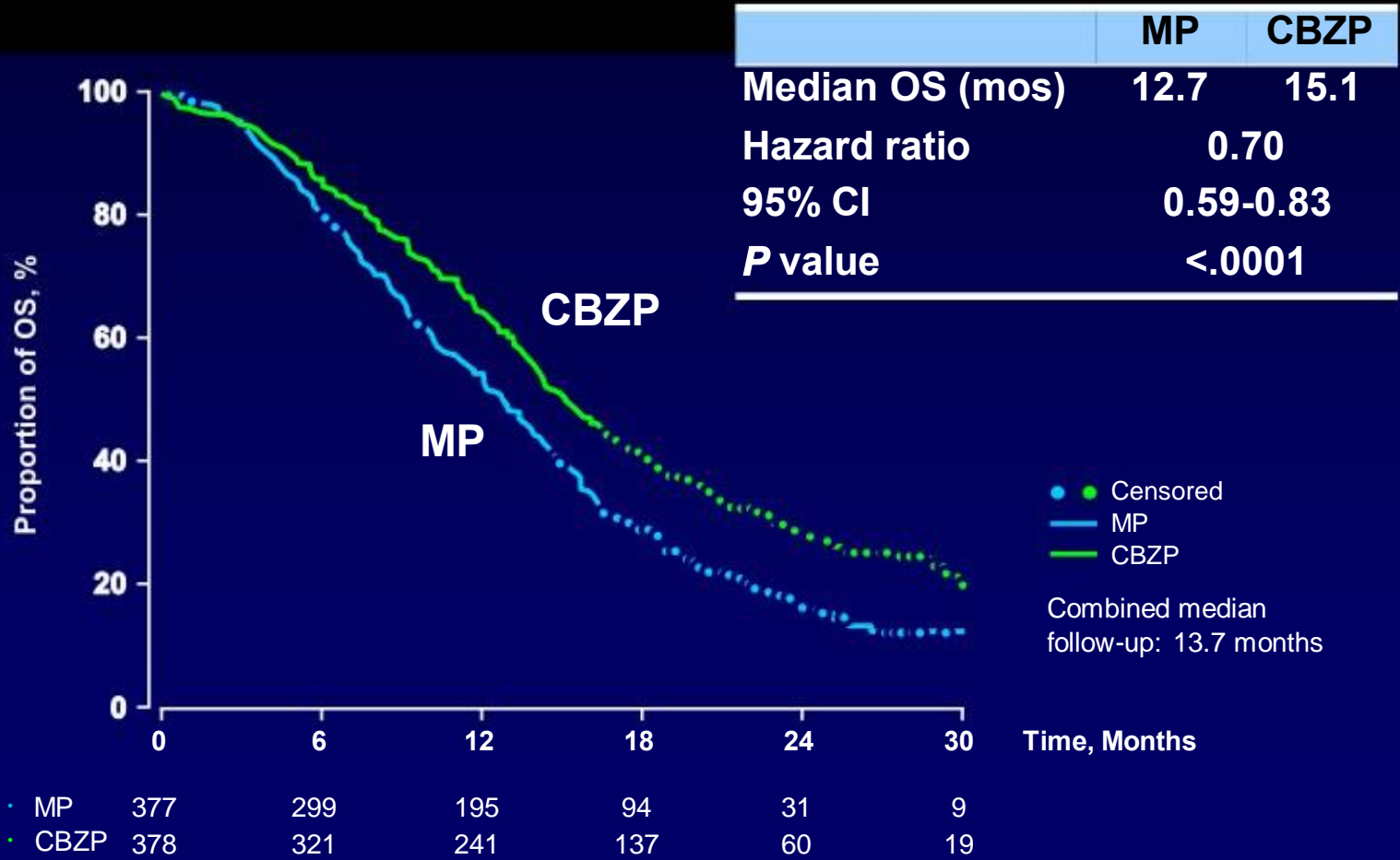
Overall Survival



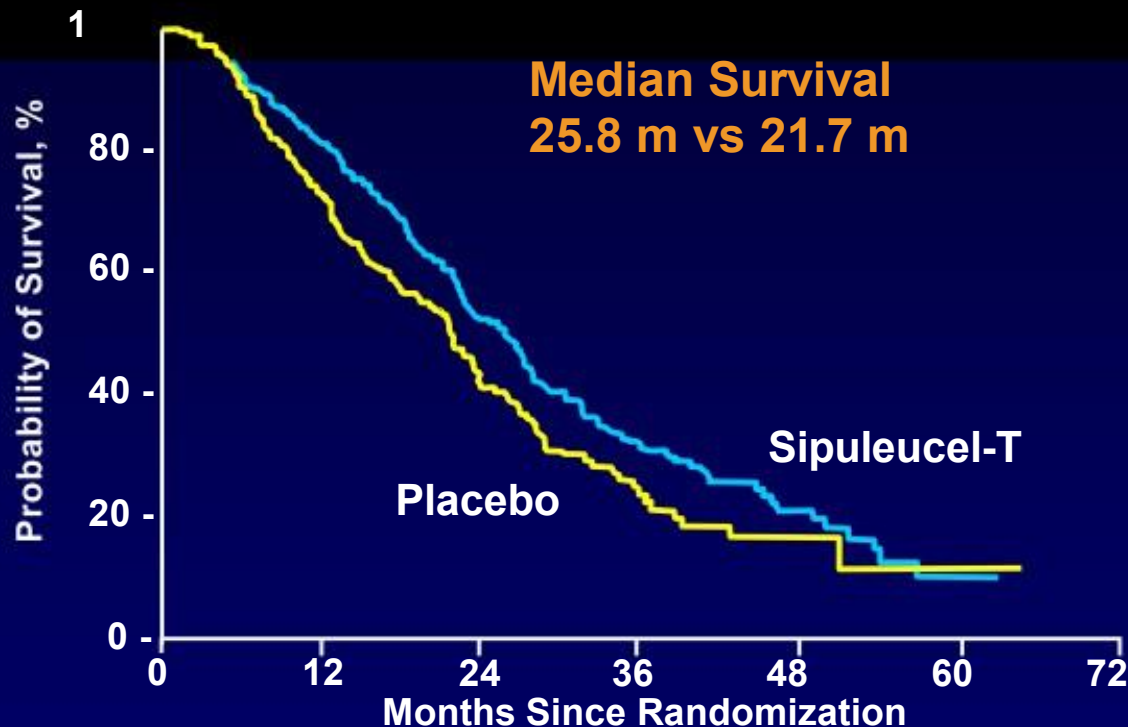
No at Risk	0	3	6	9	12	15	18	21	24	27	30	33
Docetaxel every 3 wk	335	296	217	104	37	5						
Wkly docetaxel	334	297	200	105	29	4						
Mitoxantrone	337	297	192	95	29	3						

No at Risk	0	12	24	36	48
Docetaxel + estramustine	338	218	60	13	
Mitoxantrone + prednisone	336	185	50	10	

Post Docetaxel: Cabazitaxel/Prednisone vs Mitoxantrone/Prednisone Overall Survival



Pre Docetaxel: Sipuleucel-T vs Placebo Overall Survival



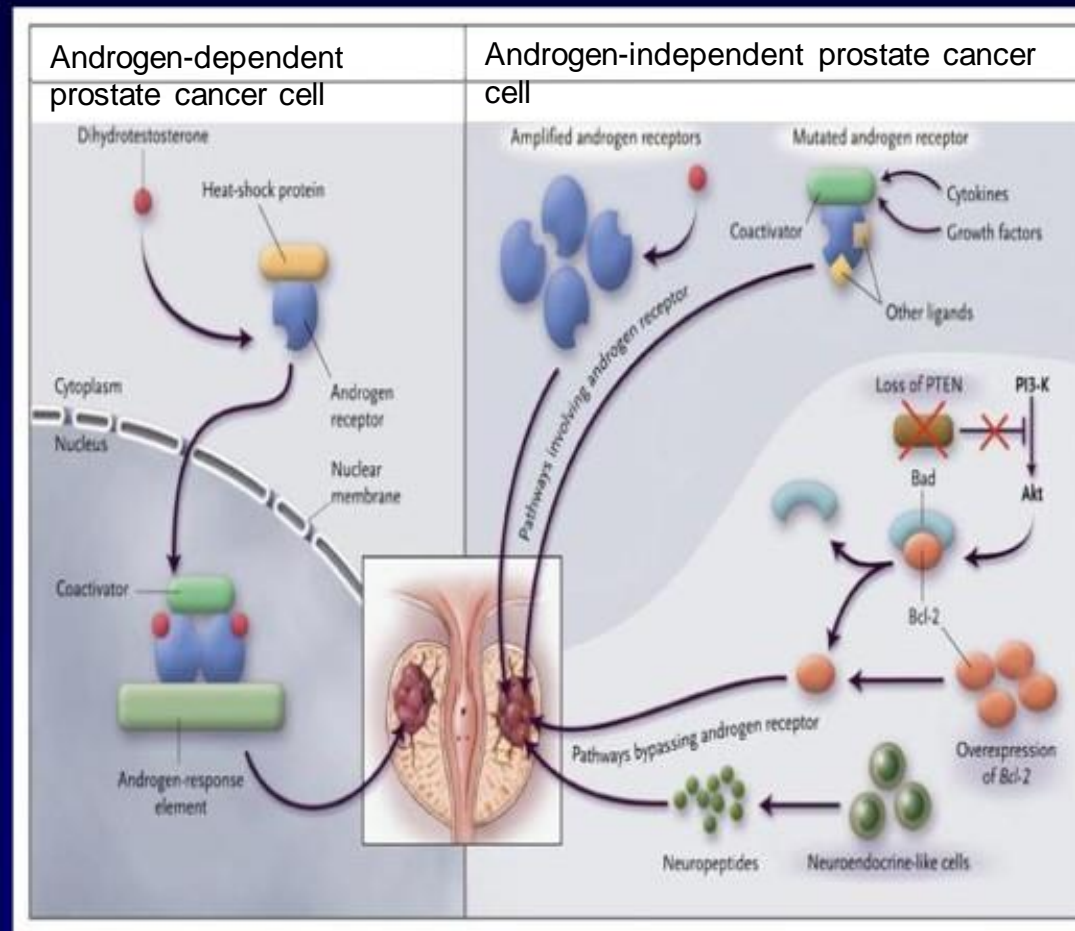
No at Risk	0	12	24	36	48	60	72
Sipuleucel-T	341	274	129	49	14	1	
Placebo	171	123	55	19	4	1	

	Sipuleucel-T (n = 341)	Placebo (n = 171)	P Value
Median Survival	25.8 ms	21.7 ms	.032
Time to Progression	3.7 ms	3.6 ms	.630
≥50% PSA Reduction	2.6%	1.3%	

Progression to Castration Resistance

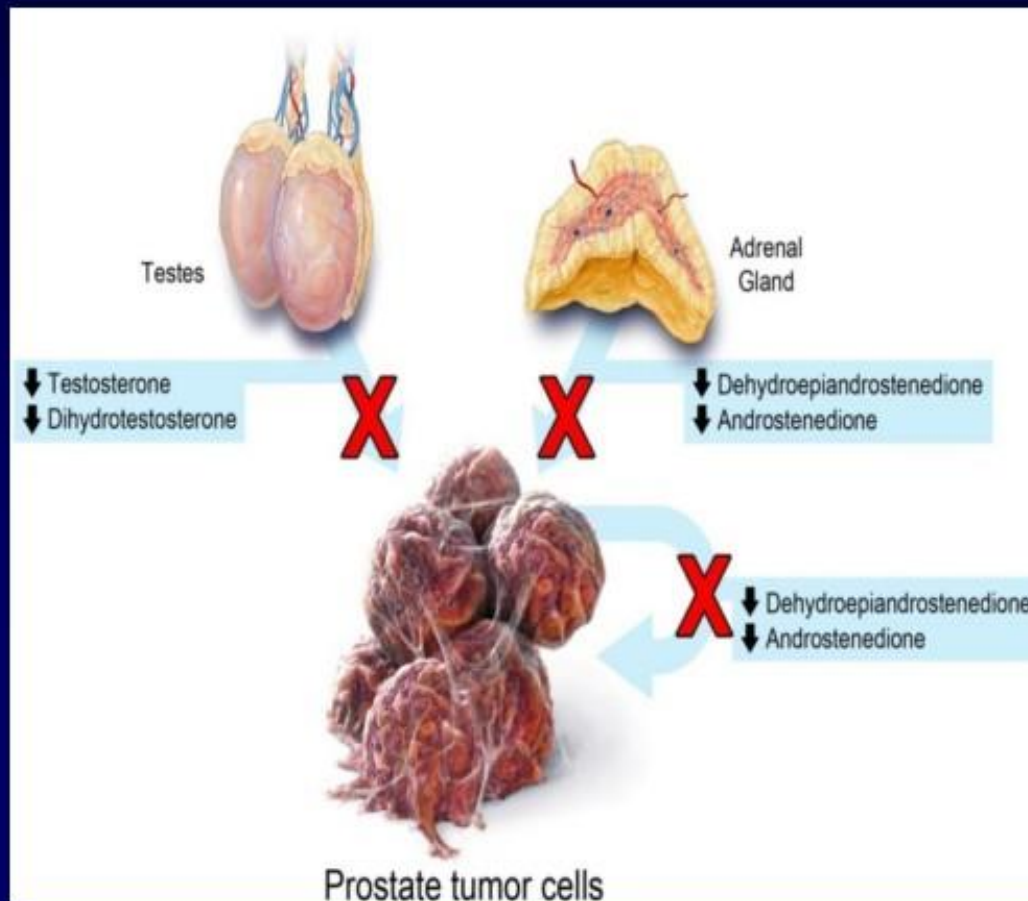
Progression to castration resistance is an adaptive process secondary to AD via androgen receptor (AR)-dependent & independent mechanisms.

- Androgen receptor
 - Gene amplification
 - Mutations
- Alteration in survival pathways bypassing AR



Progression to Castration Resistance

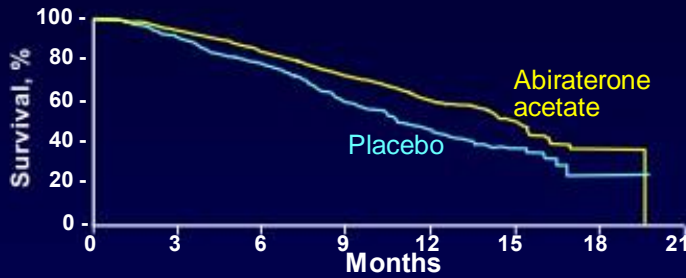
“Castration Resistant” vs “Hormone Refractory”
AR Signaling Still Matters



AR Signalling Still Matters

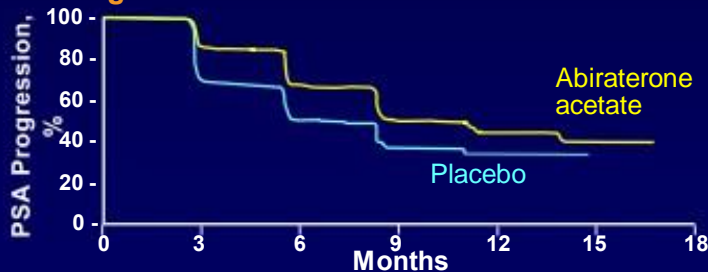
Abiraterone/Prednisone & Enzalutamide: Overall Survival Post-Docetaxel

Overall Survival



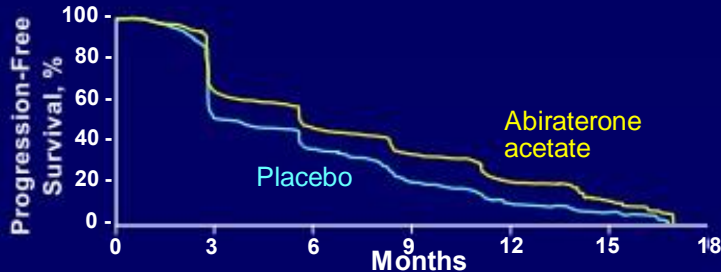
No at risk	0	3	6	9	12	15	18	21
Abiraterone acetate	797	736	657	520	282	68	2	0
Placebo	398	355	306	210	105	30	3	0

Time to PSA Progression



No at risk	0	3	6	9	12	15	18
Abiraterone acetate	797	490	292	139	59	7	0
Placebo	398	145	58	28	12	0	0

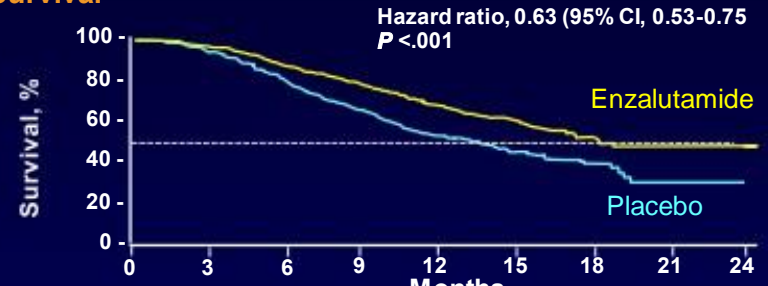
Progression-Free Survival



No at risk	0	3	6	9	12	15	18
Abiraterone acetate	797	490	352	202	76	14	0
Placebo	398	193	129	64	22	4	0

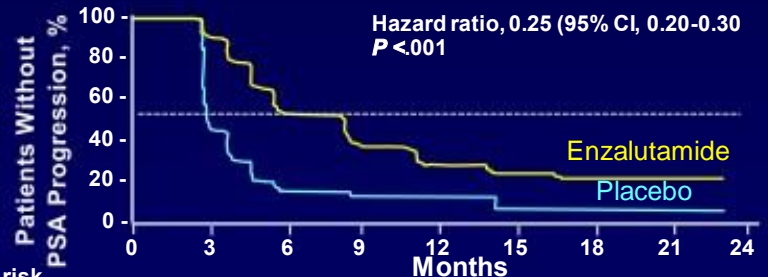
de Bono JS, et al. *N Engl J Med.* 2011;364(21):1995-2005.

Overall Survival



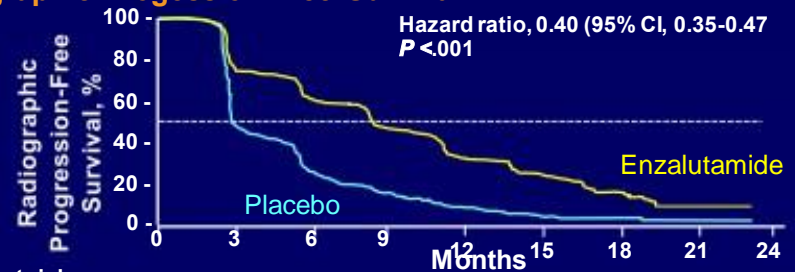
No at risk	0	3	6	9	12	15	18	21	24
Enzalutamide	800	775	701	628	400	211	72	7	0
Placebo	399	376	317	263	167	81	33	3	0

Time to PSA Progression



No at risk	0	3	6	9	12	15	18	21	24
Enzalutamide	800	603	287	145	68	27	7	1	0
Placebo	399	107	12	5	2	1	0	1	0

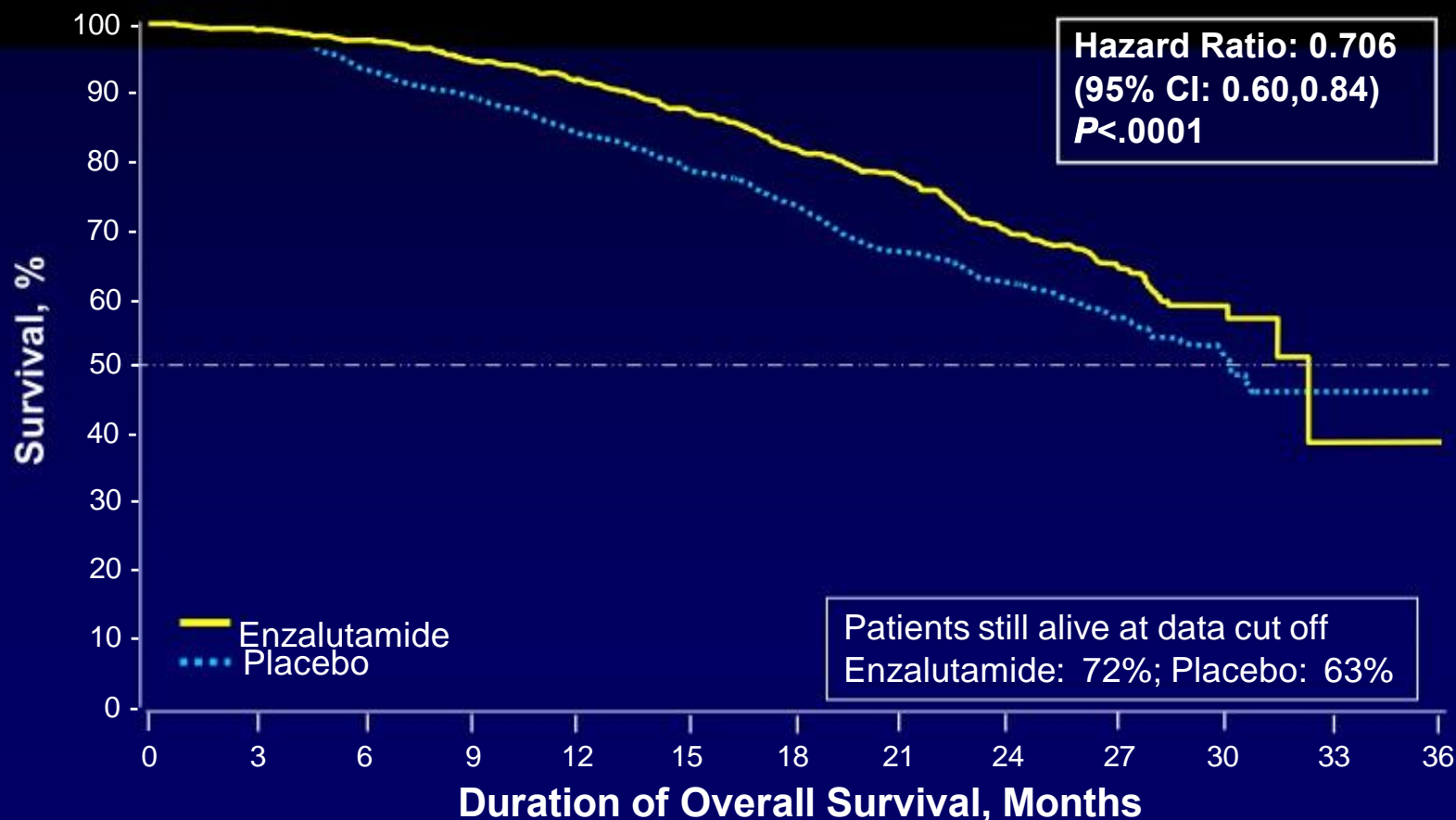
Radiographic Progression-Free Survival



No at risk	0	3	6	9	12	15	18	21	24
Enzalutamide	800	583	447	287	140	58	13	1	0
Placebo	399	176	86	46	20	7	3	0	0

Scher HI, et al. *N Engl J Med.* 2012;367(13):1187-1197.

A Phase III Trial of Enzalutamide After Progression on Androgen Deprivation Therapy in Men With Metastatic Prostate Cancer



Patients at Risk

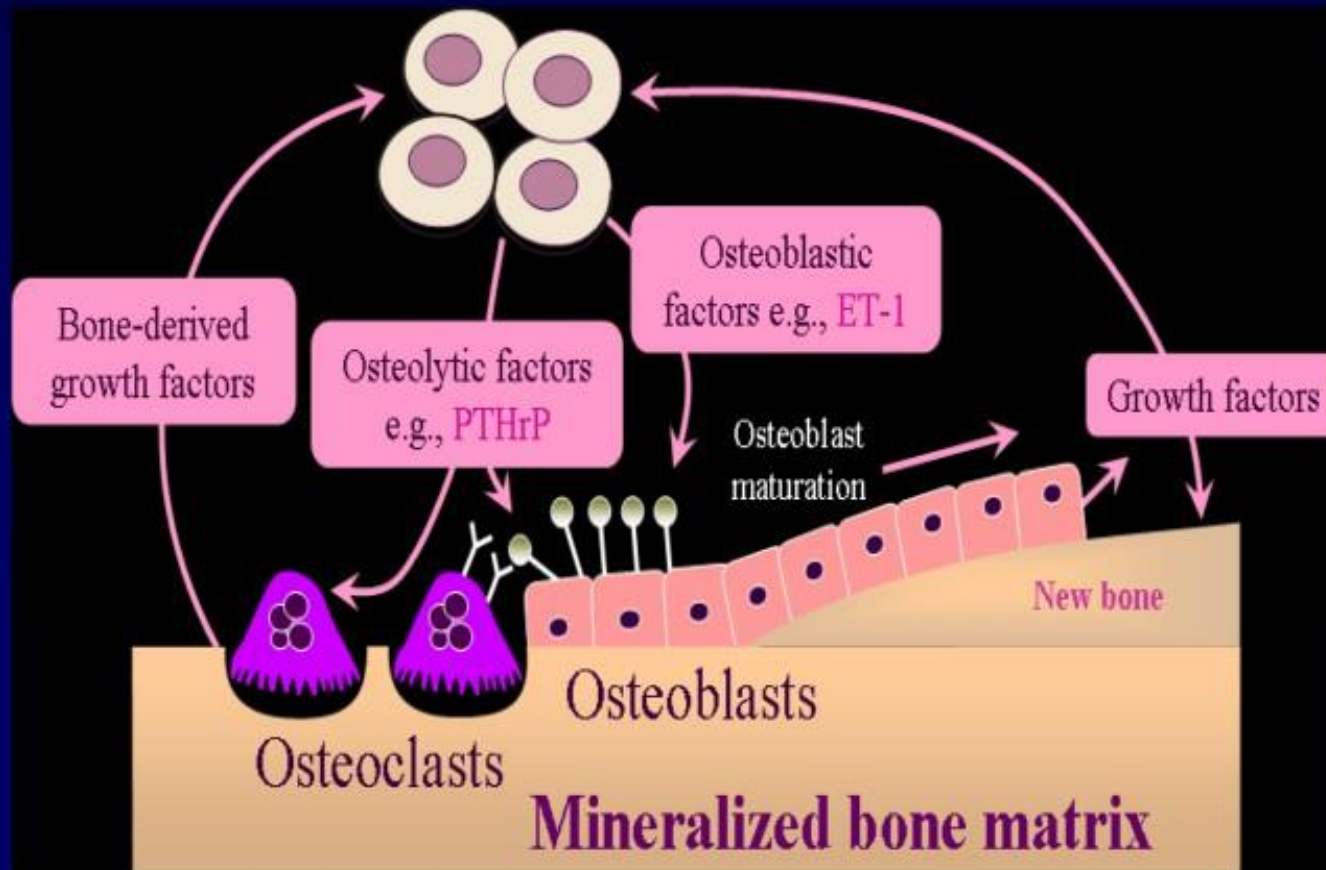
Enzalutamide	872	863	850	824	797	745	566	395	244	128	33	2	0
Placebo	845	835	781	744	701	644	484	328	213	102	27	2	0

Estimated median OS, months (95% CI): Enzalutamide: 32.4 (30.1, NYR); Placebo: 30.2 (28.0, NYR)

Bone Metastases: The Hallmark of Metastatic Prostate Cancer

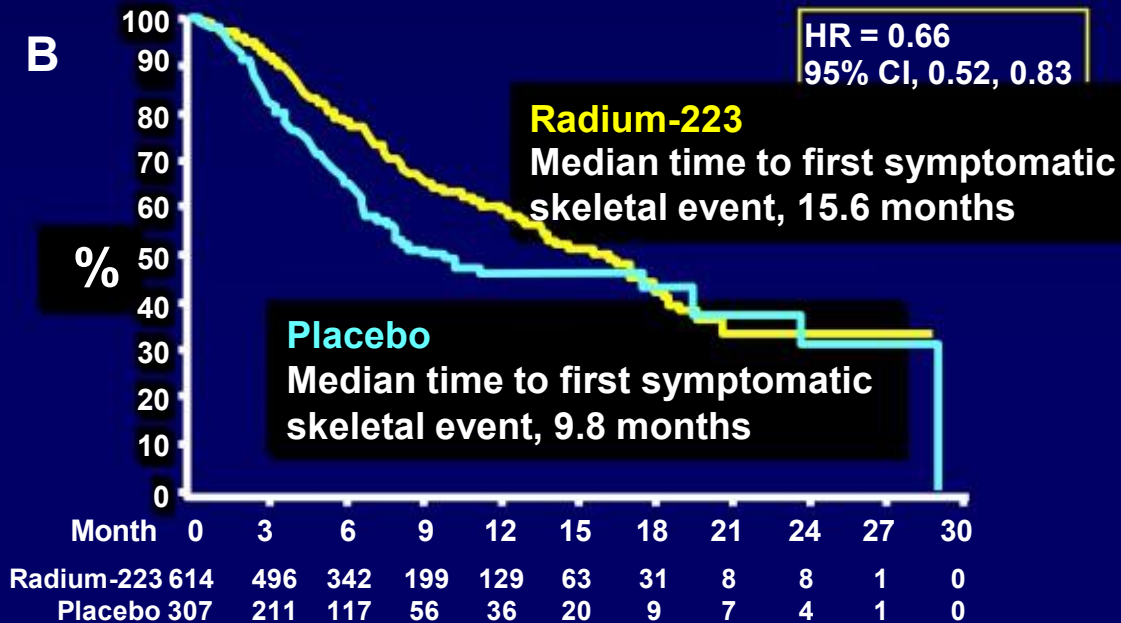
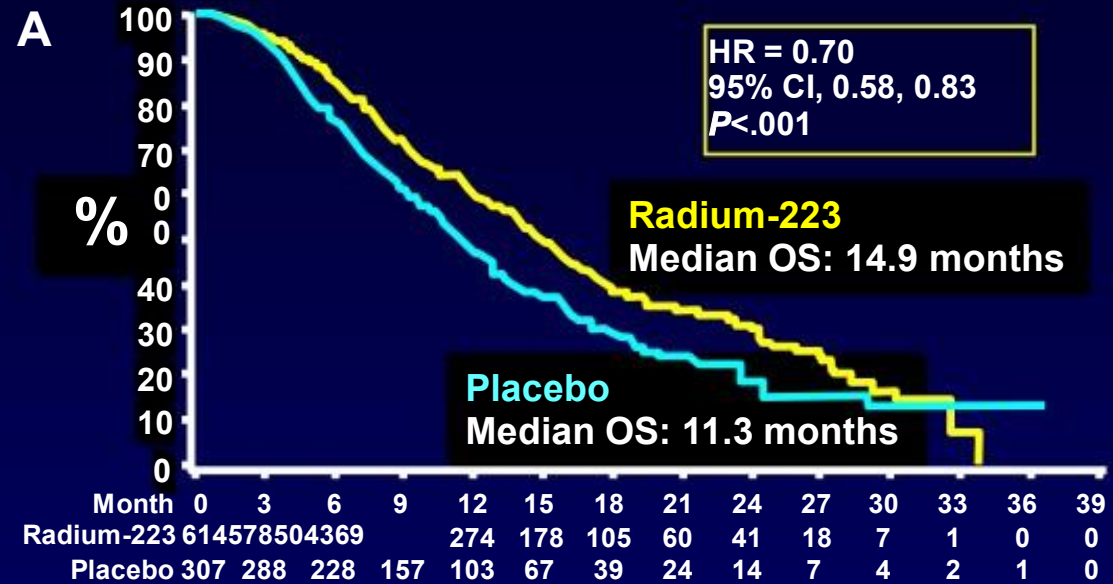
Tumor-Bone Cell Interactions

Prostate Cancer cells



Radium-223: Overall Survival and Time to First Symptomatic Skeletal Events in mCRPC

Radium-223 (a targeted alpha emitter): Bone-seeking calcium mimetic, which selectively binds to areas of increased bone turnover in bone metastases (newly formed bone stroma, especially within the microenvironment of osteoblastic or sclerotic metastases)



So Are We There Yet ?

Good news: “Embarrassment of riches”

Glaring deficiency:

- **Impact on survival in mCRPC is modest (2-5 months)**
 - All non-chemo agents tested against placebo
- **We still use a “one size fits all” treatment approach**
(No predictive biomarkers & no personalized therapeutics)

Opportunities:

- How to maximize therapeutic efficacy
- How to best sequence/combine current approved agents
 - **Who will fund such trials ?**
- Where/How best to develop new agents/combinations
- Need more focus on hormone-sensitive metastatic PCa
- How to control escalating costs

“Price is what you pay. Value is what you get” (W. Buffett)

Drug	Dose/Route	AWS Cost per cycle - Drug Only	# of Cycles	Survival
Docetaxel	150 mg IV (75 mg/m ² x 2 m ²)	\$2921.20	Median: 6	Yes
Cabazitaxel	50 mg IV (25 mg/m ² x 2 m ²)	\$8408.08	Median :6	Yes
Abiraterone	1000 mg PO (30-day)	\$8203.91	Median 8 ms	Yes
Enzalutamide	160 mg PO (30-day)	\$9467.46	Median 8 ms	Yes
Sipuleucel-T	IV	\$37,200	3 cycles	Yes
Radium-223	IV	\$28,173	6 cycles	Yes
Denosumab	120 mg SC	\$2017.68	Monthly	No
Zoledronic Acid	4 mg IV	\$360 (generic) - \$1196.56	Monthly	No

Too Many Negative Phase III Trials

- Allogeneic prostate cancer cell-line vaccine X 2
- Satraplatin
- Docetaxel + DN101
- **TAK700 X 2**
- **Ipilimumab**
- **Custirsen**
- **Bone**
 - Docetaxel +/- dasatinib
 - Atrasentan X 2
 - Docetaxel +/- atrasentan
 - Zibotentan
- **VEGF/Angiogenesis**
 - Docetaxel +/- bevacizumab
 - Docetaxel +/- aflibercept
 - Docetaxel +/- lenalidomide
 - Sunitinib



Importance of the
Biological Context

Targeting ETS Fusions

NCI9012: Randomized ETS Gene Fusions Stratified Trial of Abiraterone +/-ABT888 for Patients With mCRPC

Registration

Metastatic tissue biopsy adequate for ETS fusion status evaluation

Metastatic tissue biopsy inadequate for ETS fusion status evaluation

Stratification

Off Protocol

ETS fusion-positive
(~50% of cases)

ETS fusion-negative
(~50% of cases)

Abiraterone

Abiraterone +
PARP1 inhibitor

Abiraterone

Abiraterone +
PARP1 inhibitor

Multicenter (12 Centers)

Funding: CTEP Sponsored, DoD PC080189, N01
Early Therapeutic Development, PCF, SU2C

Ongoing Phase III Trials in Advanced Prostate Cancer

- **Hormone Sensitive**
 - **SWOG1216: ADT +/- Orteronel**
- **Nonmetastatic CRPC**
 - **Enzalutamide , ARN-509**
- **Metastatic CRPC**

Chemotherapy-Naive	First-Line Chemotherapy	Post-Docetaxel
<ul style="list-style-type: none">• Tasquinimod• Ipilimumab• Abiraterone +/- Radium	<ul style="list-style-type: none">• Docetaxel/Prednisone +/- Zibotentan• Docetaxel vs Cabazitaxel	<ul style="list-style-type: none">• Cabozantinib vs Mitoxantrone• Cabazitaxel +/- Custirsen

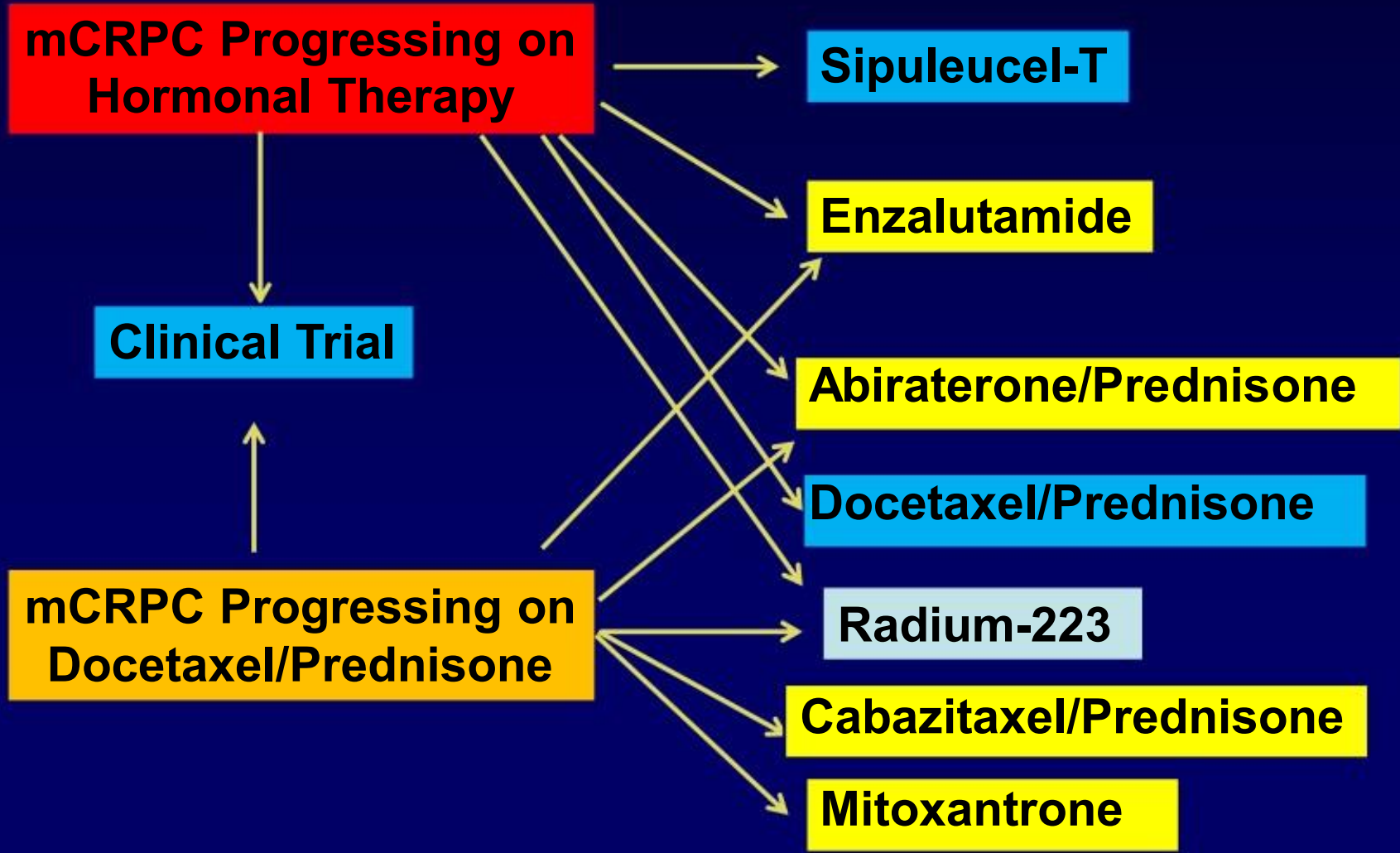
Metastatic Hormone-Sensitive Prostate Cancer: Standards in 2014

- 1. Continuous androgen deprivation therapy (ADT) is the standard based on optimal survival outcomes**
 - Patients interested in intermittent ADT should be counseled regarding potential negative impact on survival and modest impact on QoL
- 2. Patients with new high-volume M1 prostate cancer should be offered combination ADT + docetaxel**
- 3. Patients should be offered access to clinical trials**

Metastatic Castration Resistant Prostate Cancer: Standards in 2014

- **Symptoms**
- **Performance status & comorbidities**
- **Sites/extent of metastatic disease**
- **Prior therapy and quality of response & tolerance**
- **Cost/logistics**
- **Patient preferences**

mCRPC: Standards in 2014



Clinical Scenario 3

How I Would Treat This Patient

- **75-year-old man with known bone metastases from prostate cancer**
- **Coronary artery bypass graft 8 years ago**
 - **No cardiac symptoms**
- **3-year remission on ADT**
- **PSA slowly rising for past 6 months**
- **Pain-free until 4 weeks ago**
 - **Left hip pain relieved by NSAIDs**
- **PSA doubling time 8 months**
- **Bone scan shows multiple pelvic and spinal metastases**
- **CT - no visceral disease**
- **Renal, hepatic, and bone marrow function normal**

Clinical Scenario 3

How I Would Treat This Patient

- **Received 7 cycles of docetaxel**
 - **Discontinued following two neutropenic septic episodes**
- **9 months later disease progressing**
 - **Received palliative radiotherapy to spine**
 - **Commenced abiraterone**
 - **Changed from zoledronic acid to denosumab**
- **8 months later has further symptomatic progression**
 - **Widespread bone involvement**
 - **No visceral metastases**

Questions About Clinical Trials

