National Comprehensive Cancer Network®

Monthly Oncology Tumor Boards:
A Multidisciplinary Approach to Individualized Patient Care

Prostate Cancer: Castrate Resistant

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Moderated by Mark Geisler
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Faculty Biography

Andrew J. Armstrong, MD, ScM, is Associate Professor of Medicine and Co-Director of the Clinical Research Program at Duke Cancer Institute. He is a medical oncologist and an internationally recognized expert in experimental therapeutics and biomarker development in genitourinary cancers, particularly prostate cancer.

Dr. Armstrong trained at Duke University as a biomedical engineer and received his medical degree at the University of Virginia School of Medicine. He completed a residency in internal medicine at the Hospital of the University of Pennsylvania and a fellowship at Johns Hopkins Hospital, followed by public health clinical investigation training at the Bloomberg School of Public Health. Dr. Armstrong joined Duke's faculty in 2006, where he has subsequently remained.

As a clinical and translational investigator, Dr. Armstrong's research examines experimental therapeutics for patients with advanced genitourinary malignancies, particularly with a focus on prostate cancer and the investigation of biomarkers of response and benefit. His reasearch for circulating tumor cell biology and epithelial plasticity is funded by the US Department of Defense, the Prostate Cancer Foundation and Movember, the NIH, and the American Cancer Society. He has developed a number of experimental agents in prostate and renal cell cancer, including completed or ongoing trials of mTOR inhibitors and PI3 kinase inhibitors, immunomodulatory agents, hormonal therapies, and anti-angiogenic agents. He also is heavily involved in the leadership of several phase 3 studies in advanced prostate cancer (dasatinib, tasquinimod, enzalutamide) in CRPC and is principal investigator on 8 investigator-initiated clinical trials and approximately 12 industry or cooperative group sponsored clinical trials.

Dr. Armstrong is a member of the NCCN Prostate Cancer Panel. He also contributes to the NCCN Oncology Research Program (ORP) by serving on the Enzalutamide Scientific Review Committee and the Temsirolimus Scientific Advisory Board and Scientific Review Committee.

Faculty Biography

Bridget Koontz, MD, is Associate Professor in the Department of Radiation Oncology at Duke University Medical Center and Medical Director of Radiation Oncology Services at Durham Regional Hospital.

Dr. Koontz earned her medical degree from Harvard Medical School. She completed an internship in internal medicine at UNC-Chapel Hill Hospitals and a residency in radiation oncology at Duke University Medical Center, during which she served as Chief Resident in her final year. She went on to complete a fellowship in low-dose rate (LDR) brachytherapy through the American Brachytherapy Society and the Seattle Prostate Institute.

Dr. Koontz's research and clinical interest is in genitourinary cancers, with a specific focus on minimizing the side effects of radiotherapy in the treatment of prostate cancer. Collaborating with a multidisciplinary team, her laboratory studies the mechanisms of radiation-induced erectile dysfunction and tests interventions to treat and prevent this devastating side effect. As part of her work, Dr. Koontz works to improve patient-provider interactions when discussing how cancer therapies affect sexuality and intimacy during and after treatment.

Dr. Koontz is a member of several professional organizations, including the American Society for Radiation Oncology, the American Society of Clinical Oncology, the American Urological Association, the International Society of Sexual Medicine, and the Sexual Medicine Society of North America. She also serves on a number of committees, including the Sexual Medicine Society of North America Basic Science Committee, the ASTRO Education Committee, the NRG Cancer Prevention and Control Committee, and the NRG Cooperative Group GU Steering Committee. Additionally, she serves as Co-Chair for the Integrating the Healthcare Enterprise – Radiation Oncology (IHE-RO) Planning Committee and Vice-Chair for the ASTRO Clinical Translational Basic Science Advisory Committee.

In addition to her professional memberships, Dr. Koontz serves as Associate Senior Editor of the *International Journal of Radiation Oncology, Biology, Physics.* She also has served as a reviewer for a number of prominent academic journals, including *European Urology*, *Journal of Sexual Medicine*, *Practical Radiation Oncology*, *Cancer and Prostatic Disease*, the Journal of Urology, and *Annals of Urology*.

Learning Objectives

- Outline novel therapies for castrate-resistant prostate cancer (CRPC) that received approval in recent years
- Assess available treatment options appropriate to different settings based on symptoms, overall health, and risk-benefit ratios

Illustrative Case #1

- 70yo white male with prostate cancer:
  - October 2004 – cT2b G4+3 7/10, 50% to 75% cores, PSA 15 ng/mL
  - Metastatic workup: negative
- February 2005 – Combined brachytherapy (Pd103) and external beam radiation therapy (EBXRT [IMRT])
- 2005 through 2006 – GnRH agonist monotherapy
  - PSA decreases to <0.01 but rises 6 years later in the setting of normal testosterone levels to 2.6
  - Restaging scans are normal, no evidence of local recurrence or adenopathy, visceral or bony metastases
- August 2012 – Bicalutamide and leuprolide
  - PSA dropped <0.1 ng/mL
- Late 2012-early 2013 – PSA rise; rapid PSA doubling time (PSADT) = 3 months

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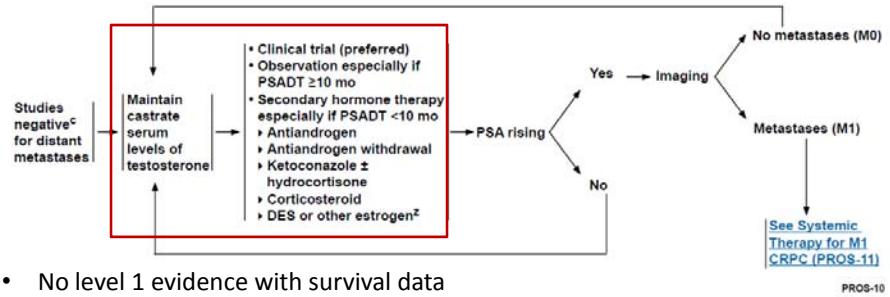
NCCN Guidelines Version 2.2016
Prostate Cancer

NCCN Schema: M0 CRPC



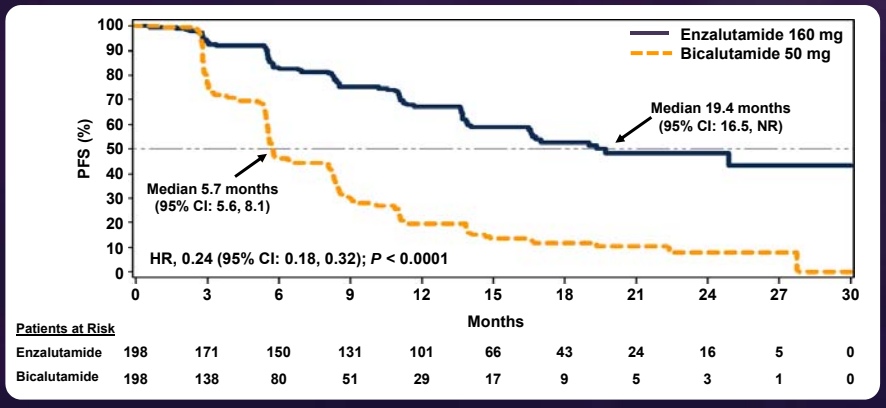
- No level 1 evidence with survival data
- Improved response and PFS (PSA, radiographic) with enzalutamide over bicalutamide
- Unclear if early M0 vs standard M1 CRPC use of enzalutamide is more advantageous
- Ongoing phase 3 trials in M0 CRPC setting will address this, and trial enrollment is encouraged

Secondary hormonal manipulations
(excluding abiraterone, enzalutamide)

- Median duration of PSA response
  - 3-6 months, but some respond for >1 year
- Objective responses uncommon

- STRIVE trial is first randomized trial to include M0 CRPC patients

STRIVE: Enzalutamide vs. Bicalutamide



Similar results observed with TERRAIN in M1 CSPC (n=375):
median PFS 5.8→15.7 months with enzalutamide vs. bicalutamide
(HR = 0.44; 95% CI, 0.34-0.57; P <.0001), time to FACT-P deterioration 8.5→13.8 months

CI = confidence interval; HR = hazard ratio; NR = not reached.

Penson D, Armstrong AJ et al, JCO 2016

ClinicalTrials.gov identifier: NCT01664923.

AUA Annual Meeting May 15 – 19, 2015 New Orleans, LA, USA

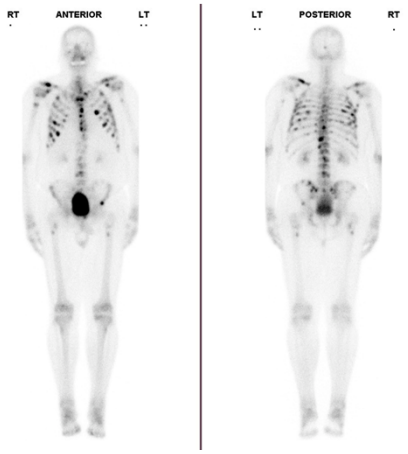
Activity in M0 CRPC

End Point	Enzalutamide No./Total (%)	Enzalutamide 95% CI	Bicalutamide No./Total (%)	Bicalutamide 95% CI	HR	95% CI	P
Overall	(n = 198)		(n = 198)				
Median PFS, months	19.4	16.5 to NR	5.7	5.6 to 8.1	0.24	0.18 to 0.32	< .001*
Median time to PSA progression, months	NR	19.4 to NR	8.3	5.7 to 8.5	0.19	0.14 to 0.26	< .001†
PSA response							
Patients with ≥ 1 postbaseline PSA assessment	192		195				
Confirmed PSA decline ≥ 50% from baseline	156/192 (81)		61/195 (31)				< .001†
Confirmed PSA decline ≥ 90% from baseline	124/192 (65)		17/195 (9)				< .001
rPFS	198		198				
Median, months	NR	NR to NR	11.2	8.4 to 16.6	0.30	0.21 to 0.44	< .001
Nonmetastatic	(n = 70)		(n = 69)				
Median PFS, months‡	NR	19.4 to NR	8.6)	8.1 to 11.1	0.24	0.14 to 0.42	< .001
Median time to PSA progression, months	NR	NR to NR	11.1	8.4 to 13.9	0.18	0.10 to 0.34	< .001
PSA response							
Patients with ≥ 1 postbaseline PSA assessment	66		69				
Confirmed PSA decline ≥ 50% from baseline	60/66 (91)		29/69 (42)				< .001
Confirmed PSA decline ≥ 90% from baseline	50/66 (76)		8/69 (12)				< .001
Median rPFS, months	NR	NR to NR	NR	14.1 to NR	0.24)	0.10 to 0.56	< .001

Penson D, Armstrong AJ et al, JCO 2016

Illustrative Case #1 (cont)

- Taken off antiandrogen but no withdrawal response
  - testosterone 25 ng/dL
- May 2013 – 11.2 ng/mL
- Imaging:
  - Bone scan: widespread osseous metastases
  - CT AP: no visceral involvement (subcentimeter pulmonary nodules and mesenteric nodes)
- Asymptomatic



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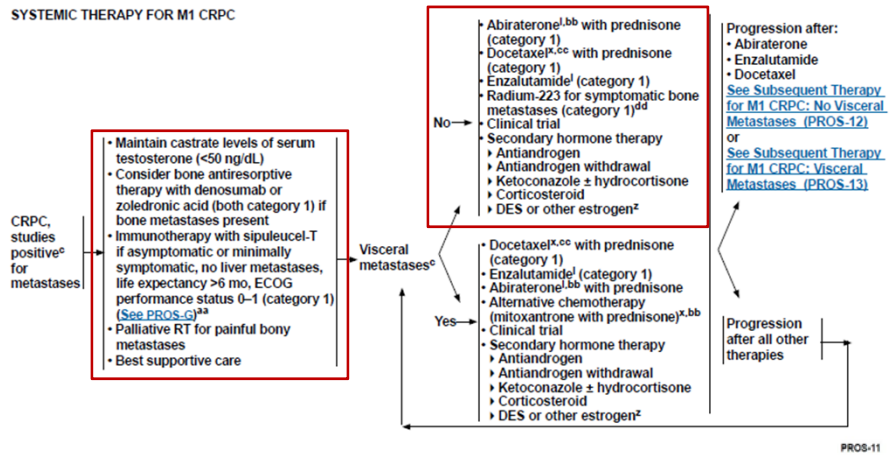
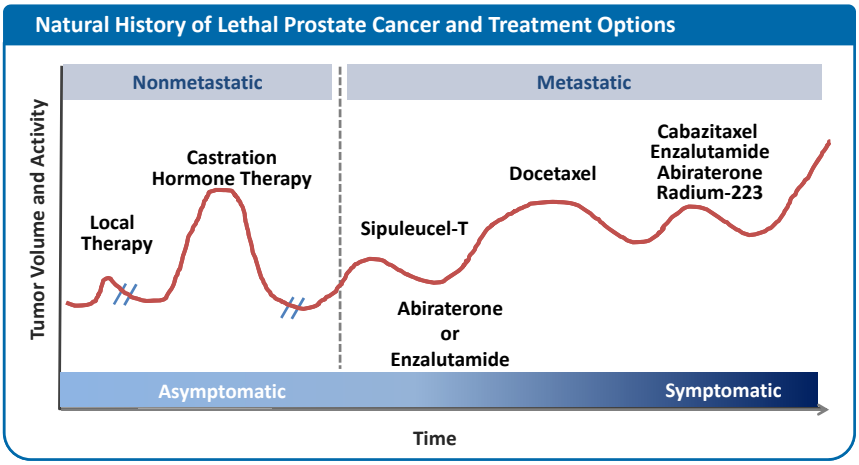
NCCN Guidelines Version 2.2016
Prostate Cancer

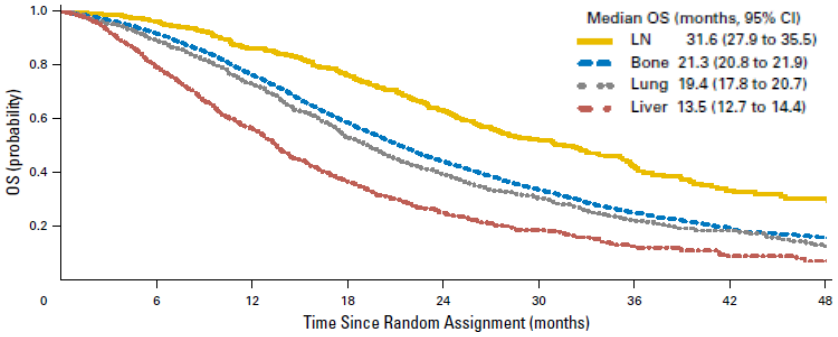
NCCN Schema: M1 CRPC



Multiple Treatment Options Are Now Available for Men With Metastatic Prostate Cancer



Pattern of Spread is Important for Prognosis



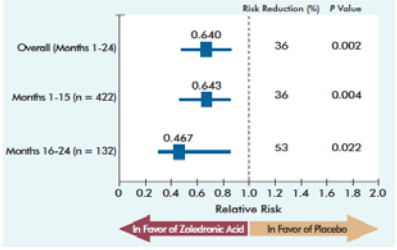
Note: the expected survival of men with mCRPC and lung metastases is similar to that of men with mCRPC and bone metastases, while men with liver metastases have the poorest survival

Halabi et al JCO 2016

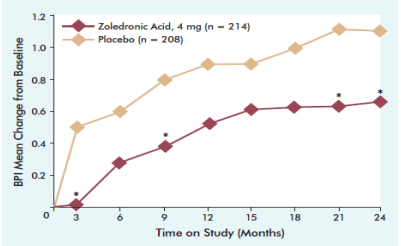
Zoledronic Acid

Parameter	Core plus Extension Phase		
	Zoledronic Acid, 4 mg (n = 214)	Placebo (n = 208)	*P* Value
Patients with ≥ 1 Skeletal-Related Event (%)	81 (38)	101 (49)	0.028
Median Time to First Skeletal-Related Event (Days)	488	321	0.009
Mean Incidence of Skeletal-Related Events per Year	0.77	1.47	0.005
Multiple-Event Analysis (Risk Ratio)	0.64	–	0.002
BPI Score (Mean Increase from Baseline)*	0.58	1.05	0.024
Analgesic Score (Mean Increase from Baseline)*	1.04	1.17	0.491

Zoledronic Acid Reduced Relative Risk of Skeletal Complications[16,19,26]



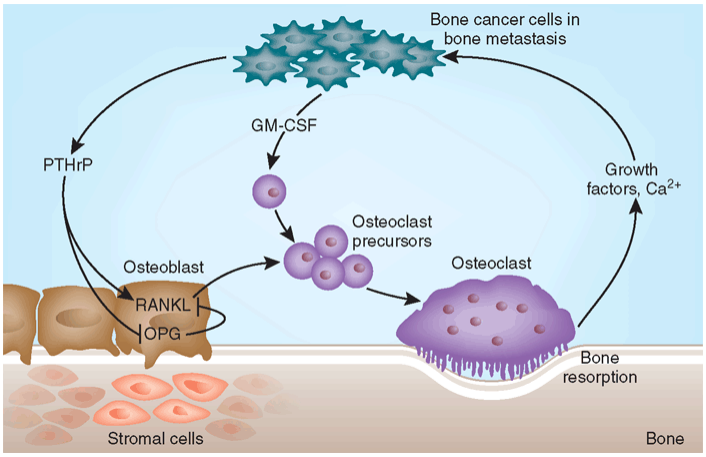
Zoledronic Acid Reduced Brief Pain Inventory Pain Scores[22]



Saad et al Clin GU Cancers 2005, JNCI 2004

Denosumab: RANKL mAb

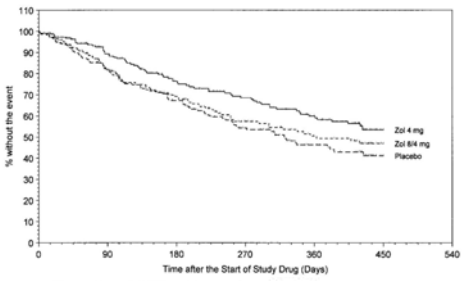
Positive phase III data in solid tumors to prevent SREs



Roodman et al Nature Medicine 2007

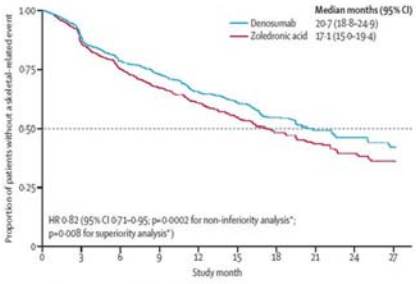
Phase 3 RCTs of Osteoclast-Targeted Therapy: *Time to First Skeletal Related Event*

Zoledronic acid versus Placebo



Saad et al (2002) J Natl Cancer Inst

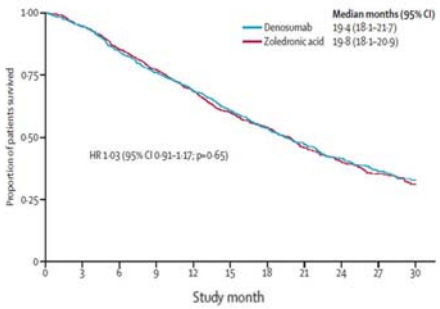
Denosumab versus Zoledronic acid



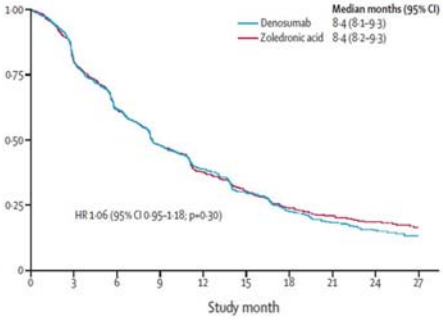
Fizazi et al (2011) Lancet

Phase 3 RCT of Denosumab versus Zoledronic Acid

Overall Survival



Time to Disease Progression



Fizazi et al Lancet 2011

Risk / Benefit Profile for Denosumab vs. Zoledronic Acid

	Zoledronic acid (n=951)	Denosumab (n=950)
Total confirmed events	386 (41%)	341 (36%)
Radiation to bone	203 (21%)	177 (19%)
Pathological fracture	143 (15%)	137 (14%)
Spinal cord compression	36 (4%)	26 (3%)
Surgery to bone	4 (<1%)	1 (<1%)

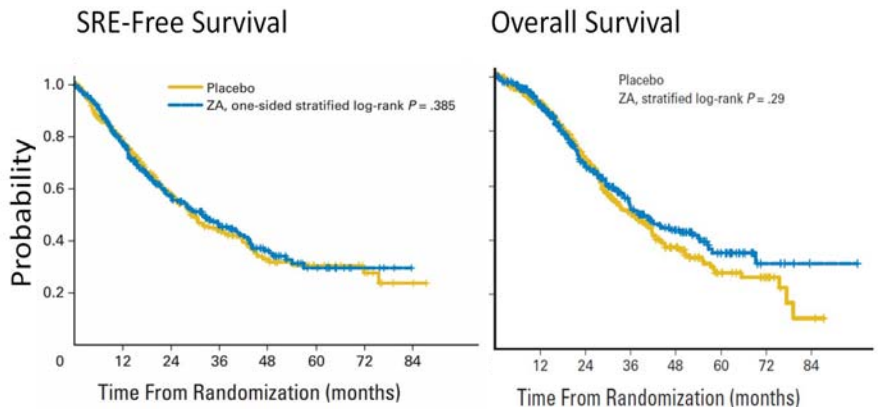
Acute phase reactions: 18 vs. 8% favoring denosumab

Renal impairment: 15 vs. 16%

	Zoledronic acid (n=945)	Denosumab (n=943)	p value*
Overall safety summary			
Any adverse event	918 (97%)	916 (97%)	1·00
Adverse events occurring with ≥20% frequency in either treatment group			
Anaemia	341 (36%)	337 (36%)	0·89
Back pain	287 (30%)	304 (32%)	0·40
Decreased appetite	274 (29%)	267 (28%)	0·76
Nausea	245 (26%)	272 (29%)	0·16
Fatigue	222 (23%)	257 (27%)	0·06
Constipation	251 (27%)	236 (25%)	0·46
Bone pain	245 (26%)	235 (25%)	0·63
Asthenia	239 (25%)	239 (25%)	1·00
Arthralgia	202 (21%)	194 (21%)	0·69
Pain in extremity	196 (21%)	197 (21%)	0·95
Peripheral oedema	174 (18%)	192 (20%)	0·30
Adverse events leading to treatment discontinuation	138 (15%)	164 (17%)	0·10
CTCAE grade 3 or 4 adverse events	628 (66%)	678 (72%)	0·01
Serious adverse events	568 (60%)	594 (63%)	0·20
Fatal adverse events	276 (29%)	283 (30%)	0·72
Adverse events of interest			
Infectious adverse events†	375 (40%)	402 (43%)	0·21
Cumulative osteonecrosis of the jaw (total)	12 (1%)	22 (2%)	0·09
Year 1	5 (1%)	10 (1%)	..
Year 2	8 (1%)	22 (2%)	..
Hypocalcaemia	55 (6%)	121 (13%)	<0·0001
New primary malignant disease	10 (1%)	18 (2%)	0·13

Fizazi et al Lancet 2011

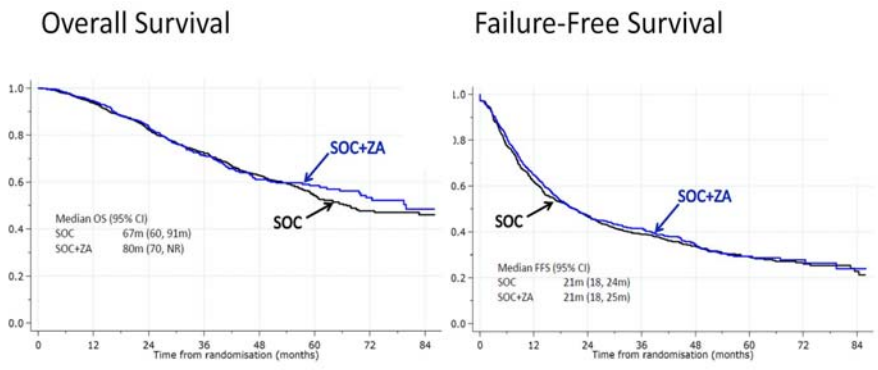
CALGB/ALLIANCE 90202: RCT of Early Versus Standard Zoledronic Acid



SRE, skeletal-related event

Smith et al JCO 2014

STAMPEDE: Zoledronic Acid



SOC, standard of care

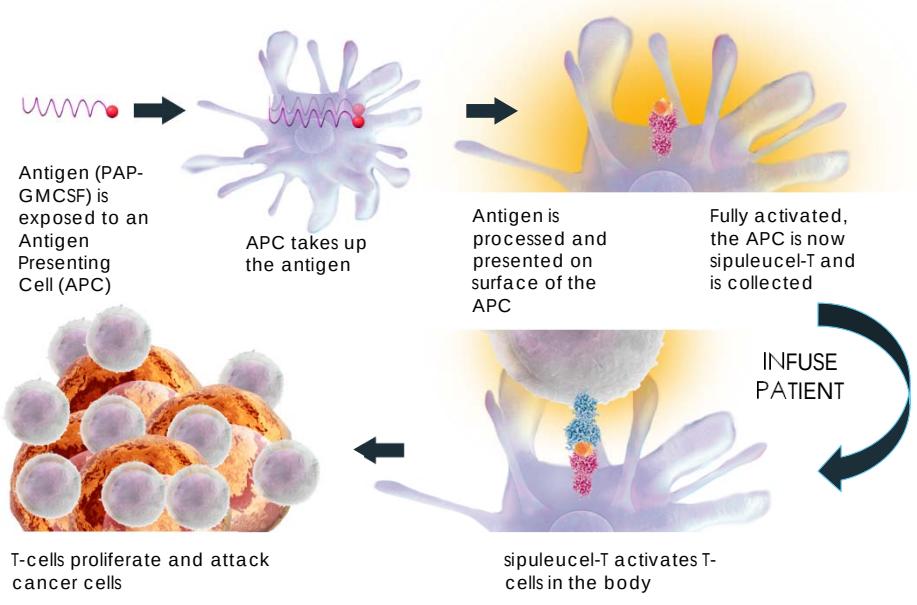
James et al Proc ASCO 2015

NCCN Guidance for Bone Anti-Resorptive Therapies

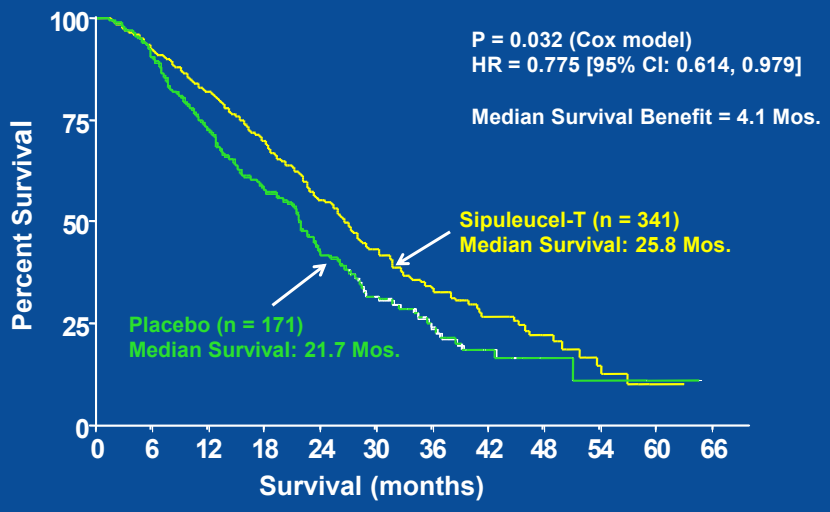
- Both zoledronic acid and denosumab are effective at delaying the time to skeletal related events (spinal cord compression, radiation, surgery to bone, pathologic fractures) in men with mCRPC
- **No known clinical activity in hormone-sensitive disease and not recommended in this setting regardless of bone metastases**
- These agents do not improve survival or delay progression-free survival
- Risk of osteonecrosis of the jaw (ONJ) increases over time and with more frequent dosing

NCCN Guidelines for Prostate Cancer, V2.2016.

Sipuleucel-T: Mechanism of Action



IMPACT Overall Survival



Kantoff et al NEJM 2010

IMPACT: Sipuleucel-T Trend Toward Greater Survival Benefit With Lower Baseline PSA

	Baseline PSA, ng/mL			
	≤22.1 (n=128)	>22.1-50.1 (n=128)	>50.1-134.1 (n=128)	>134.1 (n=128)
Median OS, months				
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 (95% CI)	0.51 (0.31-0.85)	0.74 (0.47-1.17)	0.81 (0.52-1.24)	0.84 (0.55-1.29)

- Earlier use of sipuleucel-T prior to abiraterone/enzalutamide is preferred, given lack of short term benefits on PSA, disease control and possible improved survival impact earlier in the disease course

Schellhammer et al Urology 2013

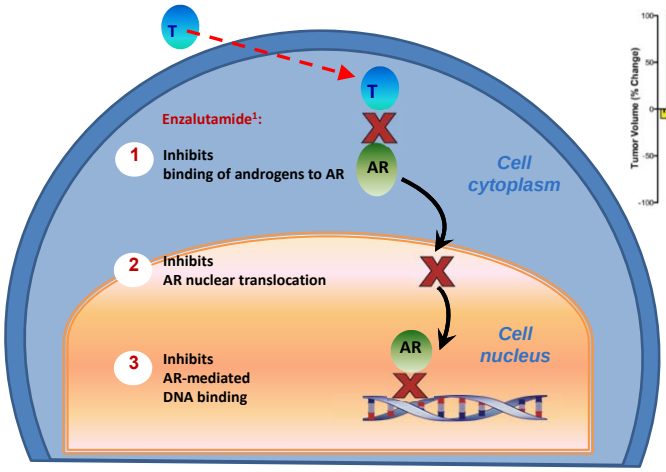
Sipuleucel-T

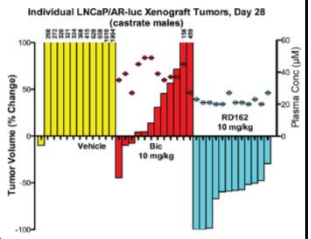
- FDA Approved April 2010
- Toxicities are mild, infusion related: fever, chills
- Slightly higher risk of spinal cord compression in men treated with sipuleucel-T, thus consideration of spinal imaging (MRI) in men with higher volume spinal disease
- Ideally used early with lower volume disease or before numerous other therapies
- No impact on PSA or radiographic response, PFS
- NCCN category 1 recommendation if asymptomatic to minimally symptomatic (no opiates for cancer pain), no liver metastases, life expectancy >6 mo, ECOG 0-1

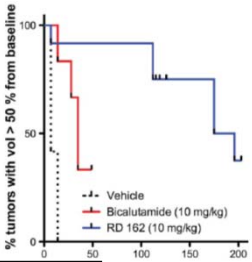
Illustrative Case #1 (cont)

- Immunotherapy:
  - June 2013 – Sipuleucel-T x 3 infusions
    - Leuprolide continued
    - Denosumab q4weeks
- Surveillance post-sipuleucel-T:
  - **July 2014** – Bone scan: progression of osseous metastatic disease
  - CT a/p: Unchanged subcentimeter pulmonary nodules and mesenteric nodes
  - **PSA 114 ng/mL, testosterone 15 ng/dL**
  - LDH 261, Alk phos 264, Hgb 13.1, LFTs NL
  - Remains minimally symptomatic
- Discussion point:
  - Options and timing for next systemic therapy in mCRPC—abiraterone/enzalutamide vs docetaxel vs radium-223 vs clinical trials

Enzalutamide: Second Generation Androgen Receptor Inhibitor



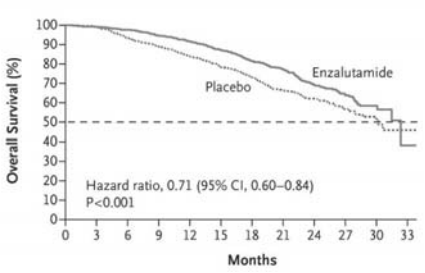




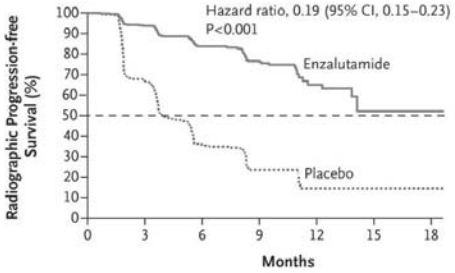
AR = androgen receptor; T = testosterone.
Tran et al. *Science*. 2009;324:787-790; Scher et al. *N Engl J Med*. 2012;367:1187-1197.

PREVAIL: Chemo-Naïve CRPC

Overall survival



rPFS

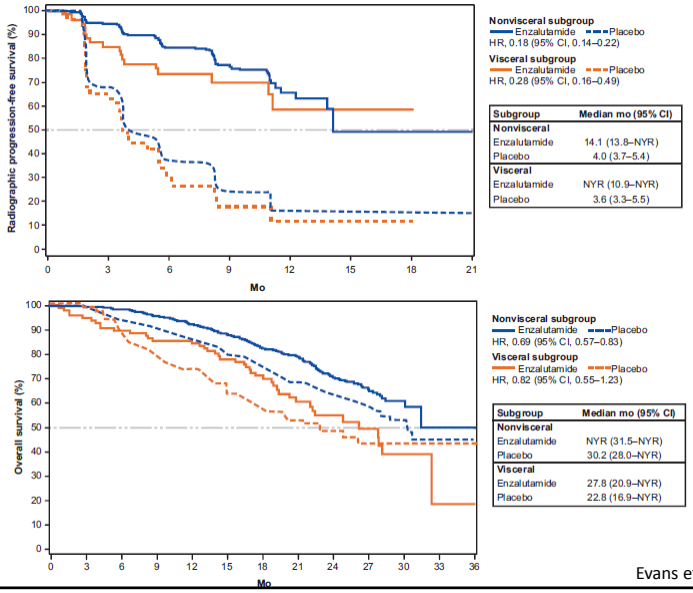


N=1717, randomized 1:1 Enzalutamide vs placebo

All subgroups benefited
rPFS 3.9→NYR (15-19 mo)
PSA PFS 2.8→11.2 months
OS updated 2015 35.3 vs. 31.3 months (HR 0.77 p=0.002)
PSA 50/90% or greater decline in 78/47%
RECIST responses in 59%
Time to chemo: 28 vs. 10.8 months
QOL responses in 40 vs. 23%, TTQOL decline 11.3 vs. 5.6 mo

Beer, Armstrong et al NEJM 2014

Activity of Enzalutamide in Men with mCRPC Based on Pattern of Spread



Subgroup	Median mo (95% CI)
Nonvisceral	
Enzalutamide	14.1 (13.8–NYR)
Placebo	4.0 (3.7–5.4)
Visceral	
Enzalutamide	NYR (10.9–NYR)
Placebo	3.6 (3.3–5.5)

Subgroup	Median mo (95% CI)
Nonvisceral	
Enzalutamide	NYR (31.5–NYR)
Placebo	30.2 (28.0–NYR)
Visceral	
Enzalutamide	27.8 (20.9–NYR)
Placebo	22.8 (16.9–NYR)

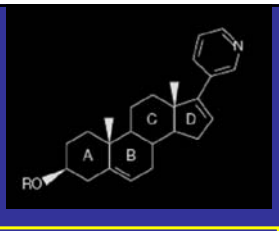
Evans et al Eur Urol 2016

Chemo-Naïve Enzalutamide Risks

Adverse Events	Enzalutamide (N=871)		Placebo (N=844)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Most common adverse events*				
Fatigue	310 (36)	16 (2)	218 (26)	16 (2)
Back pain	235 (27)	22 (3)	187 (22)	25 (3)
Constipation	193 (22)	4 (<1)	145 (17)	3 (<1)
Arthralgia	177 (20)	12 (1)	135 (16)	9 (1)
Decreased appetite	158 (18)	2 (<1)	136 (16)	6 (1)
Hot flush	157 (18)	1 (<1)	65 (8)	0
Diarrhea	142 (16)	2 (<1)	119 (14)	3 (<1)
Hypertension	117 (13)	59 (7)	35 (4)	19 (2)
Asthenia	113 (13)	11 (1)	67 (8)	8 (1)
Fall	101 (12)	12 (1)	45 (5)	6 (1)
Weight loss	100 (11)	5 (1)	71 (8)	2 (<1)
Edema peripheral	92 (11)	2 (<1)	69 (8)	3 (<1)
Headache	91 (10)	2 (<1)	59 (7)	3 (<1)
Specific adverse events				
Any cardiac adverse event	88 (10)	24 (3)	66 (8)	18 (2)
Atrial fibrillation	16 (2)	3 (<1)	12 (1)	5 (1)
Acute coronary syndromes	7 (1)	7 (1)	4 (<1)	2 (<1)
Acute renal failure	32 (4)	12 (1)	38 (5)	12 (1)
Ischemic or hemorrhagic cerebrovascular event	12 (1)	6 (1)	9 (1)	3 (<1)
Elevation in alanine aminotransferase level	8 (1)	2 (<1)	5 (1)	1 (<1)
Seizure	1 (<1)†	1 (<1)†	1 (<1)	0

Beer, Armstrong et al NEJM 2014

Abiraterone Acetate + Prednisone

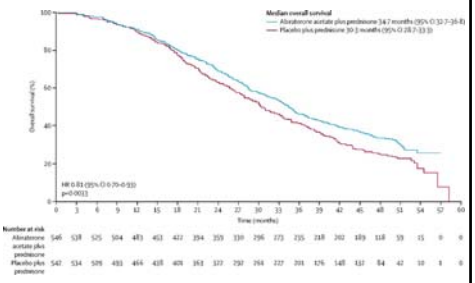


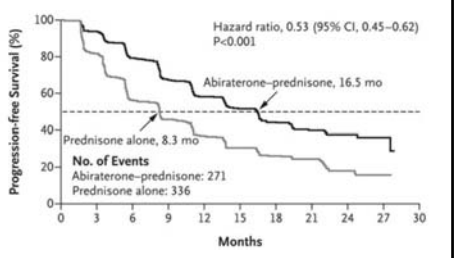
Attard et al JCO 2008

Abiraterone Acetate

OS 30.2→34.7 months
HR 0.81 p=0.0033

- Superiority over prednisone demonstrated post-docetaxel and in chemo-naïve men with mCRPC
- Dose is 1000 mg daily without food plus prednisone 5 mg bid
- Improved OS accompanied by improvements in QOL, pain, PFS, response rates, and fewer adverse events than placebo
- Prevention of pain, performance status deterioration, need for chemotherapy improved pre-docetaxel
- Abiraterone acetate with prednisone is now FDA approved for men with metastatic CRPC prior to docetaxel





Ryan et al Lancet Oncol 2015
Ryan et al NEJM 2012

Abiraterone acetate side effects

	Abiraterone acetate group (n=542)				Placebo group (n=540)*			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Fluid retention/oedema	161 (30%)	6 (1%)	0 (0%)	0 (0%)	123 (23%)	8 (1%)	1 (<1%)	0 (0%)
Hypokalaemia	87 (16%)	12 (2%)	2 (<1%)	0 (0%)	59 (11%)	10 (2%)	0 (0%)	0 (0%)
Hypertension	104 (19%)	25 (5%)	0 (0%)	0 (0%)	57 (11%)	17 (3%)	0 (0%)	0 (0%)
Cardiac disorders	81 (15%)	35 (6%)	6 (1%)	4 (<1%)	73 (14%)	17 (3%)	3 (<1%)	3 (<1%)
Atrial fibrillation	20 (4%)	8 (1%)	2 (<1%)	1 (<1%)	22 (4%)	5 (<1%)	0 (0%)	0 (0%)
ALT increased	40 (7%)	28 (5%)	4 (<1%)	0 (0%)	23 (4%)	3 (<1%)	1 (<1%)	0 (0%)
AST increased	47 (9%)	18 (3%)	0 (0%)	0 (0%)	21 (4%)	5 (<1%)	0 (0%)	0 (0%)

Data are n (%). ALT=alanine aminotransferase. AST=aspartate aminotransferase. *Before crossover.

Ryan et al Lancet Oncol 2015

Abiraterone vs. Enzalutamide in Chemotherapy Naïve Men with mCRPC

	Abiraterone Acetate	Enzalutamide
Requires prednisone	Y	N
May cause mineralocorticoid excess	Y	N
Evaluated in visceral disease	Y (post-chemo only)	Y (pre/post chemo)
Major side effects	Hypertension, hypokalemia, LFTs, edema, some cardiac, fatigue, hot flush	Hypertension, rare seizures (<0.2%), some cardiac, fatigue, falls (19%), hot flush
Grade 3-4 AE Risk (%)	48%	43%
PSA response rate (>50%)	62%	78%
Radiographic response rate	36%	59%
rPFS	16.5 months	15-18 months
OS	34.7 months	35.3 months
Time to chemotherapy	25 months	28 months

Zhang Armstrong et al *Exp Opin Pharmacother* 2015

Timing and Selection of Secondary Androgen Receptor (AR)-Directed Therapies

- Choice of abiraterone vs. enzalutamide cannot be dictated based on differences in efficacy
  - Similar OS, PFS from cross-trial comparisons
  - Enzalutamide has been evaluated in men with visceral metastases in the chemo-naïve setting
  - Both considered category 1 recommendations in NCCN guidelines
- Therefore choice is based on differential toxicity
  - Abiraterone acetate for seizure-prone men and those more frail elderly (>75y) men at high risk for falls
  - Enzalutamide for men with significant CV risk factors, contraindications to prednisone, brittle diabetes and metabolic syndrome, contraindications to prednisone

Practical Aspects of Enzalutamide Use

- NCCN category 1 recommendation in 2016 in the mCRPC setting regardless of prior docetaxel, pattern of spread, symptoms
- Prescription is for 4 40-mg capsules taken once daily, with or without food
- I recommend home BP monitoring given the 7% risk of severe HTN with enzalutamide (160/100) of unclear cause
- Exercise encouraged to reduce fall risk
- No driving restrictions given rare seizure risk but important to avoid enzalutamide in patients with a prior history of seizures or epilepsy or those men at very high risk of seizures (brain tumors, prior major strokes, CNS metastases, taking concurrent medications that lower the seizure threshold)

Practical Aspects of Abiraterone Acetate with Prednisone Use

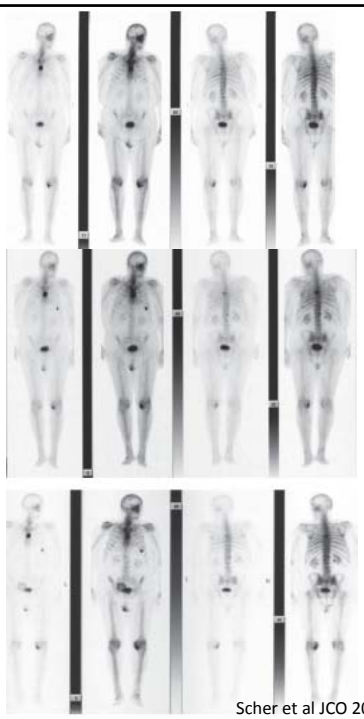
- NCCN category 1 recommendation in 2016 in the mCRPC setting regardless of prior docetaxel, symptoms
- Prescription is for 4 500-mg tablets taken once daily, 1 hour prior to food intake or 2 hours after food (water OK)
  - Taking with food increases bioavailability substantially, may increase toxicity
- I recommend home BP monitoring given the 5-10% risk of severe HTN with abiraterone (160/100) due to mineralocorticoid excess
  - Eplerenone may reverse this (mineralocorticoid antagonist)
- Exercise encouraged to reduce fall risk, fatigue
- Liver function and electrolyte, renal monitoring every 6 weeks initially, then every 12 weeks
  - Treatment of fluid retention, hypokalemia is common
- Pre-treatment cardiac evaluation reasonable in patients with significant underlying congestive heart failure (CHF), coronary artery disease (CAD), or arrhythmias

Practical Aspects of Abiraterone/ Enzalutamide Use: Follow-up

- I check PSA at 6 weeks and then every 12 weeks and perform CT, bone scans every 12 weeks
- Radiographic progression typically follows PSA progression, but occasionally radiographic progression can be observed first
- Bone scan progression can be misclassified due to healing response, so confirmation of additional new lesions over time is needed before declaring progression based on bone scan alone
- CT remains important to document soft tissue/visceral metastases which can develop over time
- I do not stop abiraterone/enzalutamide for PSA-only progression because there is clear clinical benefit of these agents for multiple other disease manifestations (pain, QOL, radiologic)

Bone Scans in CRPC

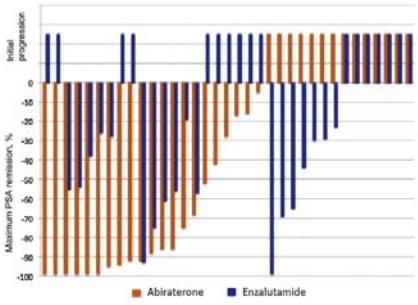
1. Difficult to interpret
2. Images osteoblast activity
3. Healing may appear more intense!
4. New lesions are best measures of progression vs. flare (within clinical context)
5. Confirmation scans showing continued additional new lesions required—flare is common (40% with abiraterone/enzalutamide!)
6. Prostate Cancer Working Group 2 Guidelines are new criteria for determining progression
7. Often will be performed on site and centrally along with clinical read
8. Thus, misclassification of progression is common!



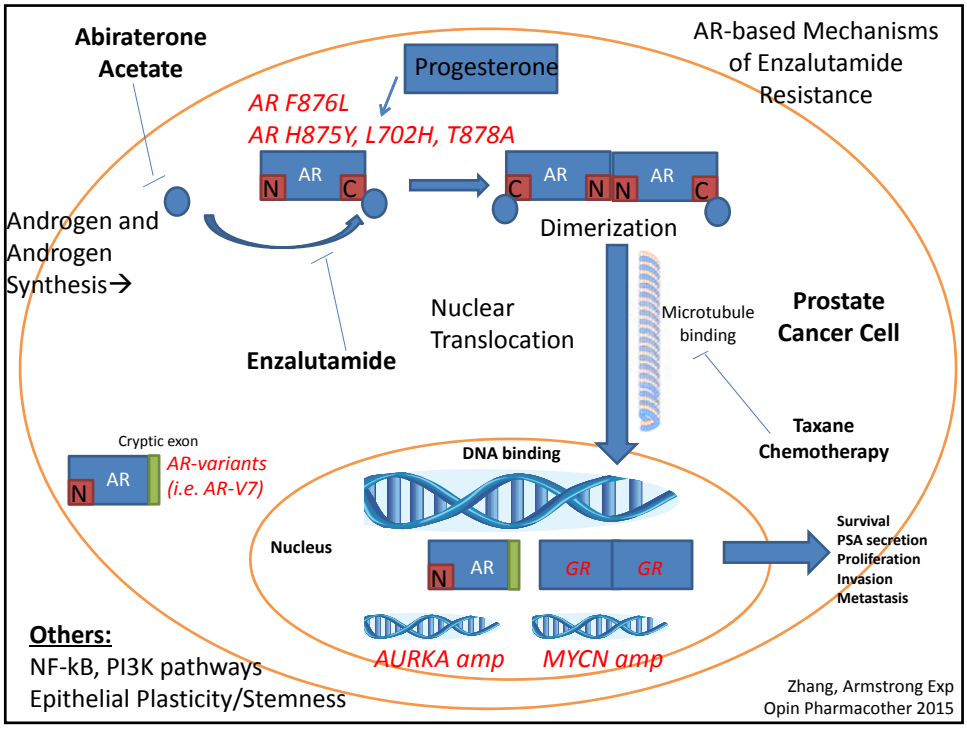
Scher et al JCO 2008, 2016

Cross-Resistance in the Clinic

- **Enzalutamide after abiraterone** can result in PSA responses (>50% decline) but this was observed in <1/3 of men in the post-docetaxel CRPC setting with a short TTP of 4 months and rare radiographic responses
- Similar for abiraterone after enzalutamide and in pre-docetaxel setting
- Response to enzalutamide was **not** possible to predict based on prior response to abiraterone

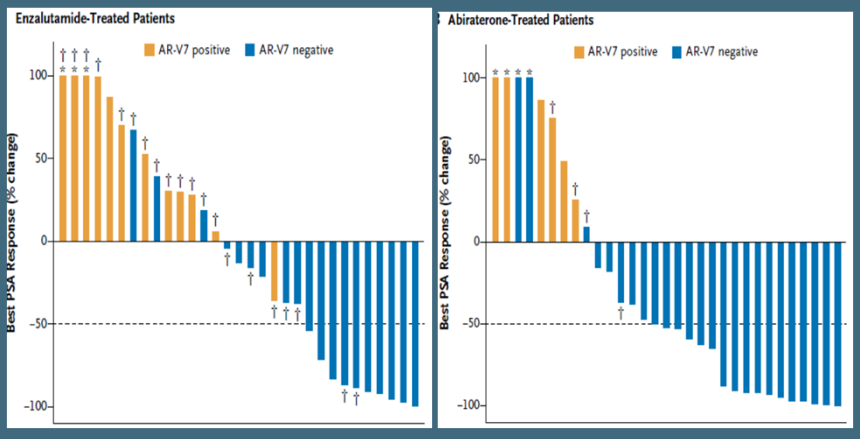


Schrader Eur Urol 2013
Zhan, Armstrong CGUC 2015



AR-v7 and Cross-Resistance

Measured through a circulating tumor cell (CTC) assay and an AR-v7 rt-PCR based probe

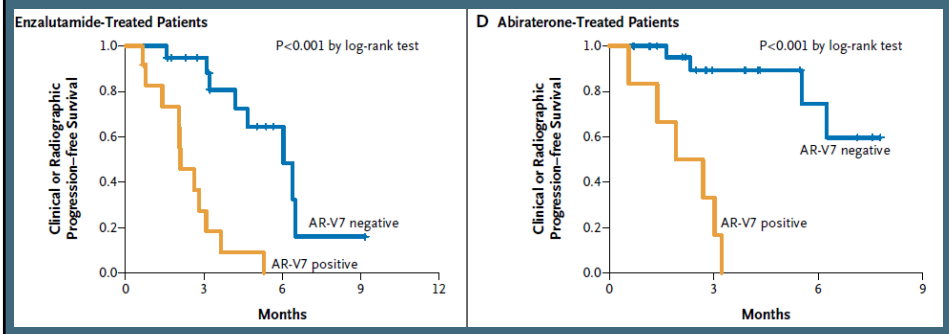


Limitation: not yet externally validated in a multicenter trial

Antonarakis et al NEJM September 2014

AR-v7 and Cross-Resistance

Note: CTC AR-V7 test has not yet been externally validated and thus remains a research biomarker at this time (ongoing studies)



HR, 6-16!

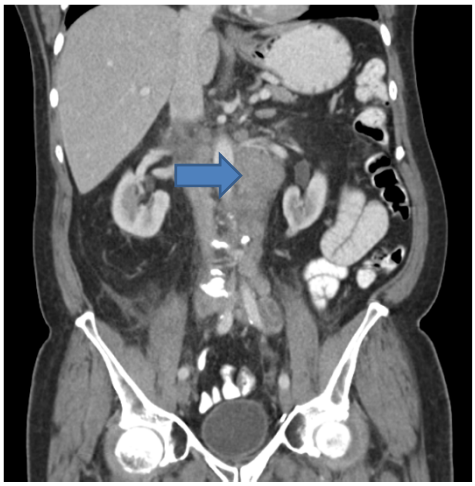
Associated with prediction of poor OS or clinical benefit

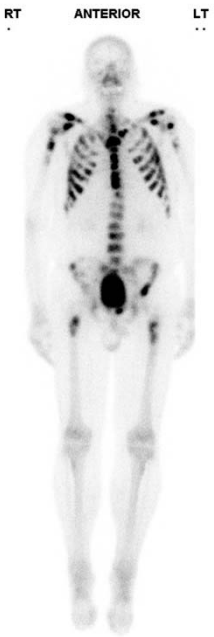
Antonarakis et al NEJM September 2014

Illustrative Case #2

- 69yo male with prostate cancer:
  - cT2b G9 PSA 2.4 ng/mL
  - Metastatic workup: negative
- RP: pT3a GS4+3, tertiary 5, R1
- Adjuvant XRT
- One year later, PSA rise from 0.1→9→44
- Restaging scans:
  - CT/BS shows multiple bone mets and bulky RP nodes up to 7.7cm
- ADT + docetaxel initiated

Images





Illustrative Case #2 (cont)

- Restaging after docetaxel induction chemotherapy/ADT reveals resolution of adenopathy, persistent bone metastases, PSA is 2.0
- Within 12 months, PSA rises to 14 and diffuse bone pain develops. Staging confirms additional new bone lesions in axial spine, no visceral/nodal metastases
- Patient is treated with enzalutamide and responds but progresses within 6 months

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Prostate Cancer

How to treat Men with mCRPC who progress following docetaxel?

SUBSEQUENT SYSTEMIC THERAPY FOR M1 CRPC[ee]

Prior therapy enzalutamide/ abiraterone

- Docetaxel with prednisone (category 1)[x]
- Abiraterone[l] with prednisone
- Enzalutamide
- Radium-223 for symptomatic bone metastases (category 1)
- Sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0–1
- Clinical trial
- Other secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole ± hydrocortisone
  - Corticosteroid
  - DES or other estrogen[z]
- Best supportive care

No visceral metastases

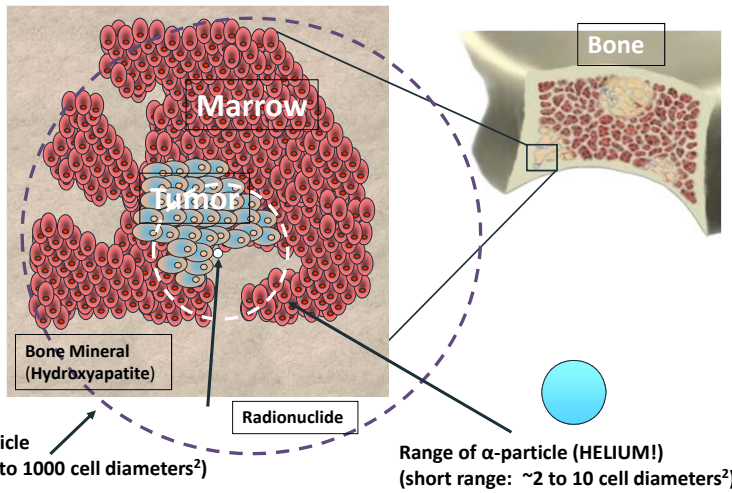
Prior therapy docetaxel

- Enzalutamide (category 1)
- Abiraterone[l] with prednisone (category 1)
- Radium-223 for symptomatic bone metastases (category 1)
- Cabazitaxel with prednisone (category 1)[x]
- Sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0–1
- Clinical trial
- Docetaxel rechallenge[x]
- Alternative chemotherapy (mitoxantrone with prednisone)[x]
- Other secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole ± hydrocortisone
  - Corticosteroid
  - DES or other estrogen[z]
- Best supportive care

PROS-12

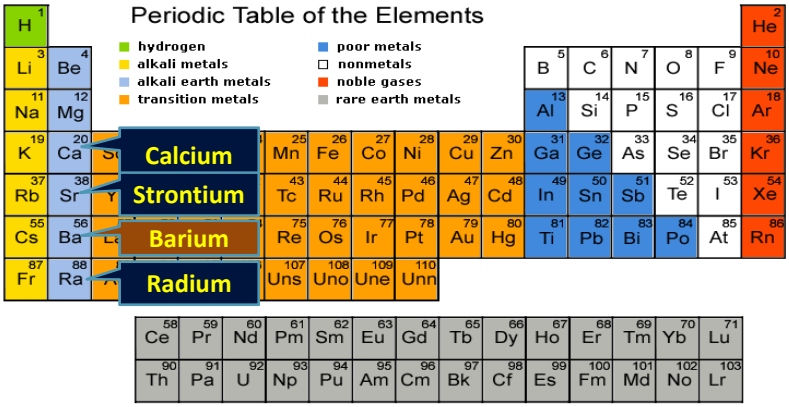
Range of α-emitting Radiopharmaceutical Compared with β-emitter

Short range of α-particles reduces bone marrow exposure



Henriksen G et al. *Cancer Res*. 2002.

Radium Targets Osteoblastic Bone Metastases by Acting as a Calcium



Radium (Ra 223 dichloride) prescribing information, 2013.

ALSYMPCA: Phase III Study Design

PATIENTS

N = 921
- Confirmed symptomatic CRPC
- ≥2 bone metastases
- No known visceral metastases
- Post-docetaxel or unfit for docetaxel**

STRATIFICATION
- Total ALP: <220 U/L vs. ≥220 U/L
- Bisphosphonate use: Yes vs. No
- Prior docetaxel: Yes vs. No

TREATMENT PHASE

2:1

Radium-223 dichloride (55* kBq/kg) + best standard of care†

6 injections at 4-week intervals

Placebo (saline) + best standard of care†

PRIMARY ENDPOINT: OVERALL SURVIVAL

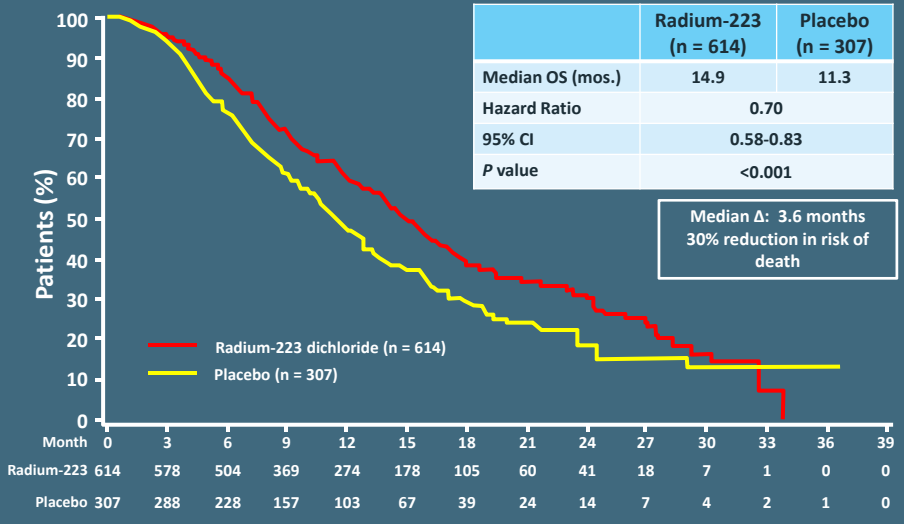
136 centers in 19 countries
Planned follow-up is 3 years

**Unfit for docetaxel includes patients who were ineligible for docetaxel, refused docetaxel, or lived where docetaxel was unavailable.
†Best standard of care defined as a routine standard of care at each center, eg, local external-beam radiotherapy, corticosteroids, antiandrogens, estrogens (e.g., diethylstilbestrol or estramustine), or ketoconazole.**

*National Institute of Standards and Technology (NIST) update 2016

Parker et al NEJM 2013

ALSYMPCA Updated Analysis: OS



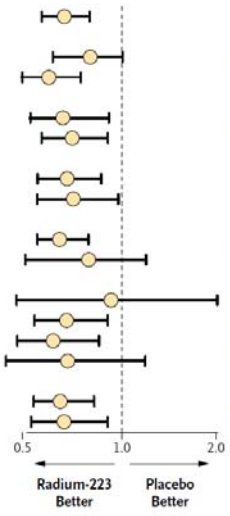
	Radium-223 (n = 614)	Placebo (n = 307)
Median OS (mos.)	14.9	11.3
Hazard Ratio	0.70	
95% CI	0.58-0.83	
P value	<0.001	

Median Δ: 3.6 months
30% reduction in risk of death

Parker et al NEJM 2013

Predictors of Radium-223 Benefit?

Subgroup	Radium-223	Placebo	Radium-223	Placebo	Hazard Ratio (95% CI)
	no. of patients		*median overall survival (mo)*		
All patients	614	307	14.9	11.3	0.70 (0.58–0.83)
Total ALP level at baseline					
<220 U/liter	348	169	17.0	15.8	0.82 (0.64–1.07)
≥220 U/liter	266	138	11.4	8.1	0.62 (0.49–0.79)
Current bisphosphonate use					
Yes	250	124	15.3	11.5	0.70 (0.52–0.93)
No	364	183	14.5	11.0	0.74 (0.59–0.92)
Previous docetaxel use					
Yes	352	174	14.4	11.3	0.71 (0.56–0.89)
No	262	133	16.1	11.5	0.74 (0.56–0.99)
Baseline ECOG performance-status score					
0 or 1	536	265	15.4	11.9	0.68 (0.56–0.82)
≥2	77	41	10.0	8.4	0.82 (0.50–1.35)
Extent of disease					
<6 metastases	100	38	27.0	NE	0.95 (0.46–1.95)
6–20 metastases	262	147	13.7	11.6	0.71 (0.54–0.92)
>20 metastases	195	91	12.5	9.1	0.64 (0.47–0.88)
Superscan	54	30	11.3	7.1	0.71 (0.40–1.27)
Opioid use					
Yes	345	168	13.9	10.4	0.68 (0.54–0.86)
No	269	139	16.4	12.8	0.70 (0.52–0.93)



Parker et al NEJM 2013

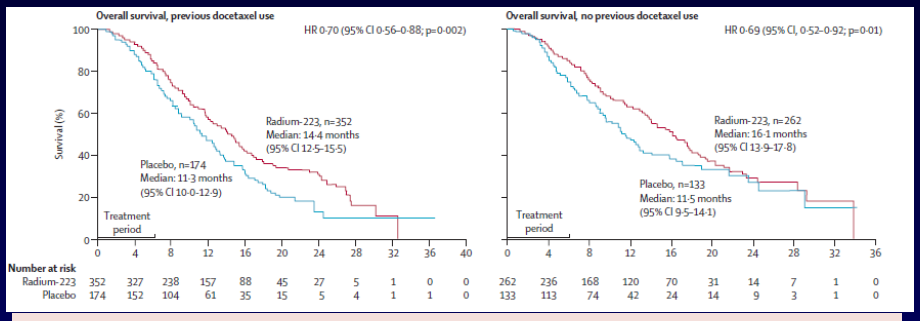
Radium-223 Updated Analysis Adverse Events (AEs) of Interest

	All Grades		Grades 3 or 4	
Patients with AEs n, (%)	**Radium-223 n = 600**	**Placebo n = 301**	**Radium-223 n = 600**	**Placebo n= 301**
Hematologic				
Anemia	187 (31)	92 (31)	77 (13)	39 (13)
Neutropenia	30 (5)	3 (1)	13 (2)	2 (1)
Thrombocytopenia	**69 (12)**	17 (6)	**38 (6)**	6 (2)
Non-Hematologic				
Bone pain	300 (50)	187 (62)	125 (21)	77 (26)
Diarrhea	151 (25)	45 (15)	9 (2)	5 (2)
Nausea	213 (36)	104 (35)	10 (2)	5 (2)
Vomiting	111 (19)	41 (14)	10 (2)	7 (2)
Constipation	108 (18)	64 (21)	6 (1)	4 (1)

The safety of taxane chemotherapy following radium-223 has not been well characterized

Parker et al NEJM 2013

Radium-223 and Prior Docetaxel Use



	Previous docetaxel use								No previous docetaxel use							
	Radium-223 (n=347)				Placebo (n=171)				Radium-223 (n=253)				Placebo (n=130)			
	All grades	Grade 3	Grade 4	Grade 5	All grades	Grade 3	Grade 4	Grade 5	All grades	Grade 3	Grade 4	Grade 5	All grades	Grade 3	Grade 4	Grade 5
Patients with at least one adverse event	330 (95%)	126 (36%)	38 (11%)	49 (14%)	168 (98%)	79 (46%)	12 (7%)	37 (22%)	228 (90%)	82 (32%)	15 (6%)	48 (19%)	122 (94%)	43 (33%)	5 (4%)	29 (22%)
Haematological adverse events that occurred in at least 5% of patients in either treatment group																
Anaemia	120 (35%)	42 (12%)	8 (2%)	0	61 (36%)	23 (14%)	1 (1%)	1 (1%)	67 (27%)	24 (10%)	3 (1%)	0	31 (24%)	14 (11%)	1 (1%)	0
Leukopenia	21 (6%)	5 (1%)	0	0	1 (1%)	1 (1%)	0	0	4 (2%)	2 (1%)	1 (<1%)	0	0	0	0	0
Neutropenia	24 (7%)	8 (2%)	3 (1%)	0	2 (1%)	1 (1%)	0	0	6 (2%)	1 (<1%)	1 (<1%)	0	1 (1%)	1 (1%)	0	0
Thrombocytopenia	53 (15%)	15 (4%)	16 (5%)	0	13 (8%)	4 (2%)	1 (1%)	0	16 (6%)	5 (2%)	2 (1%)	1 (<1%)	4 (3%)	1 (1%)	0	0

Hoskin et al Lancet Oncol 2015

Subgroup Analysis of Hazard Ratios for Death in the Two Study Groups

Subgroup	Radium-223	Placebo	Radium-223	Placebo	Hazard Ratio (95% CI)
	no. of patients		*median overall survival (mo)*		
All patients	614	307	14.9	11.3	0.70 (0.58–0.83)
Total ALP level at baseline					
<220 U/liter	348	169	17.0	15.8	0.82 (0.64–1.07)
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Superscan	54	30	11.3	7.1	0.71 (0.40–1.27)
Opioid use					
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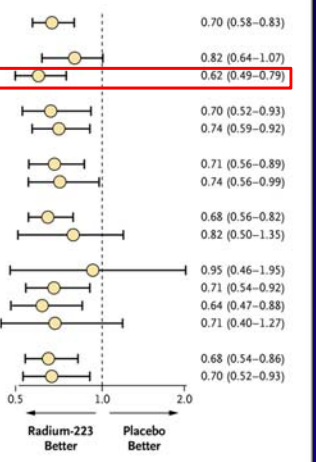

Parker et al NEJM 2013

Radium-223: Summary

Administration:

- Once every 4 weeks for 6 months
- 60 second IV infusion
- Given by radiation oncologist or nuclear medicine radiologist
- Enteric excretion
- No pre-medication, no post-medication
- CBC check before each treatment

Clinical Benefit:

- Primary endpoint of improvement in symptomatic SRE
- 3.6 month benefit in OS
- Perhaps greater in men with high alkaline phosphatase
- Should be considered in symptomatic men with bone-predominant mCRPC
- Consider spinal imaging for epidural disease in men with high burden of disease and rapid progression; palliative EBXRT should be used if high risk for spinal cord compression
- No head to head data vs. docetaxel yet, and optimal timing/sequencing/combination with hormonal therapies and chemotherapy is currently being established

NCCN Guidelines

- Radium-223 recommended for men with symptomatic bone-predominant mCRPC
- Can be used before or after docetaxel given similar survival benefit
- Patients should be followed carefully for bone marrow toxicity prior to dosing and over time
- Concurrent use of hormonal therapies, external beam palliative radiation, steroids are reasonable given the lack of drug interactions and safety, palliative goals

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer (Version 2.2016). © 2016 National Comprehensive Cancer Network, Inc.

NCCN Summary Recommendations: M1 CRPC

	NO VISCERAL METASTASES	WITH VISCERAL METASTASES
Abiraterone with prednisone		
Corticosteroid		
Docetaxel with prednisone		
Enzalutamide		
Ketoconazole		
Ketoconazole + hydrocortisone		
Mitoxantrone with prednisone		—
Radium-223		—
Sipuleucel-T		—

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) with NCCN Evidence Blocks™ for Prostate Cancer (Version 2.2016).
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