Year in Review

Proceedings from a Multitumor CME Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Endocrine and Bone-Targeted Therapy for Prostate Cancer — Charles G Drake, MD, PhD

Select Publications

Antonarakis ES et al. **Androgen receptor splice variant 7 and efficacy of taxane chemotherapy in patients with metastatic castration-resistant prostate cancer.** *JAMA Oncol* 2015;1(5):582-91.

Antonarakis ES et al. **AR splice variant 7 (AR-V7) and response to taxanes in men with metastatic castration-resistant prostate cancer (mCRPC).** Genitourinary Cancers Symposium 2015;**Abstract 138**.

Antonarakis ES et al. **AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer.** *N Engl J Med* 2014;371(11):1028-38.

Duchesne GM et al. **TROG 03.06 and VCOG PR 01-03: The "Timing of androgen deprivation therapy in prostate cancer patients with a rising PSA (TOAD)" collaborative randomised phase III trial.** *Proc ASCO* 2015;**Abstract 5007**.

Penson D et al. **A multicenter Phase 2 study of enzalutamide (ENZA) versus bicalutamide (BIC) in men with nonmetastatic (M0) or metastatic (M1) castration-resistant prostate cancer (CRPC): The STRIVE trial.** *Proc AUA* 2015;**Abstract LBA10**.

Saad F et al. **Radium-223 in an international early access program (EAP): Effects of concomitant medication on overall survival in metastatic castration-resistant prostate cancer (mCRCP) patients.** *Proc ASCO* 2015;**Abstract 5034**.

Shore N et al. **Radium-223 dichloride in expanded-access setting in the United States: Overall and concurrent experience with abiraterone or enzalutamide.** *Proc AUA* 2015;**Abstract MP87-12**.

Vogelzang NJ et al. **Radium-223 dichloride (Ra-223) in US expanded access program (EAP).** Genitourinary Cancers Symposium 2015;**Abstract 247**.

Endocrine and Bone-Targeted Therapy for Prostate Cancer

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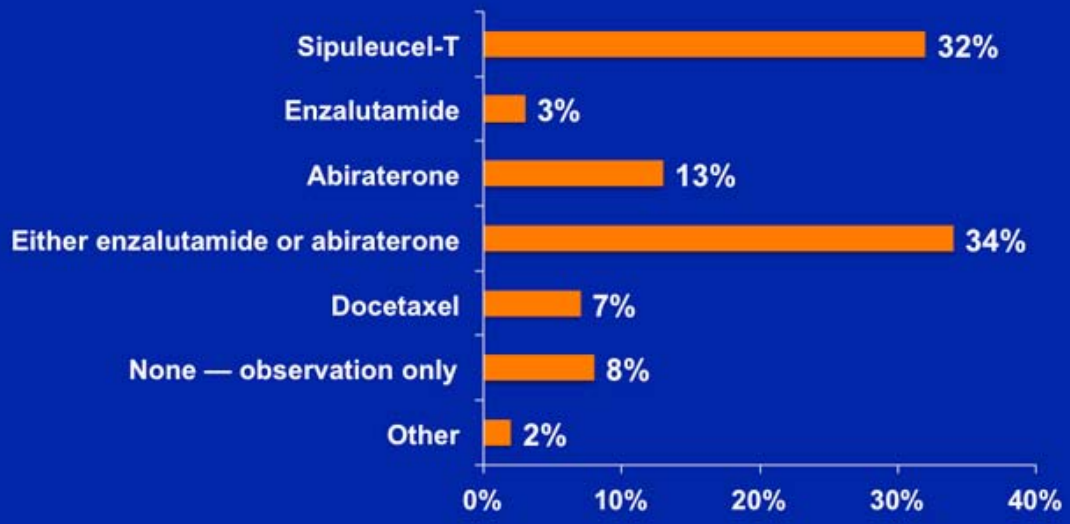
Disclosures

Consulting Agreements	Amplimmune Inc, Bristol-Myers Squibb Company, Compugen, Dendreon Corporation, Eisai Inc, Genentech BioOncology, ImmuneXcite Inc, ImmuNext Inc, Novartis Pharmaceuticals Corporation, Potenza Therapeutics, Roche Laboratories Inc, Sanofi
Patents	Amplimmune Inc, Bristol-Myers Squibb Company, Potenza Therapeutics
Stock Ownership	Compugen, ImmuneXcite Inc, ImmuNext Inc

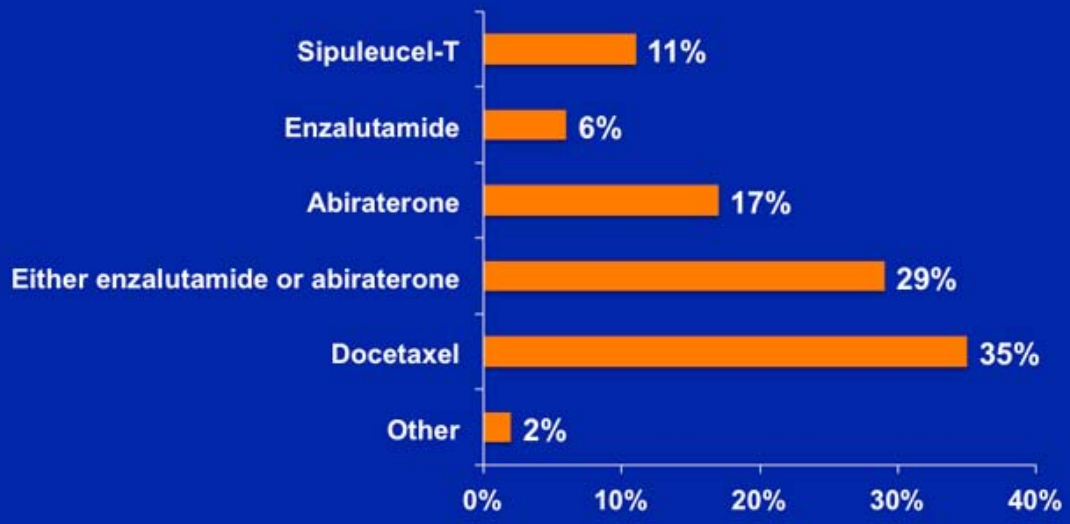
AUDIENCE POLL

A 60-year-old man presents with asymptomatic bone and nodal metastases that develop while he is receiving androgren deprivation therapy (ADT) for PSA-only disease. What therapy (in addition to bone-targeted treatment, if any) would you most likely recommend?



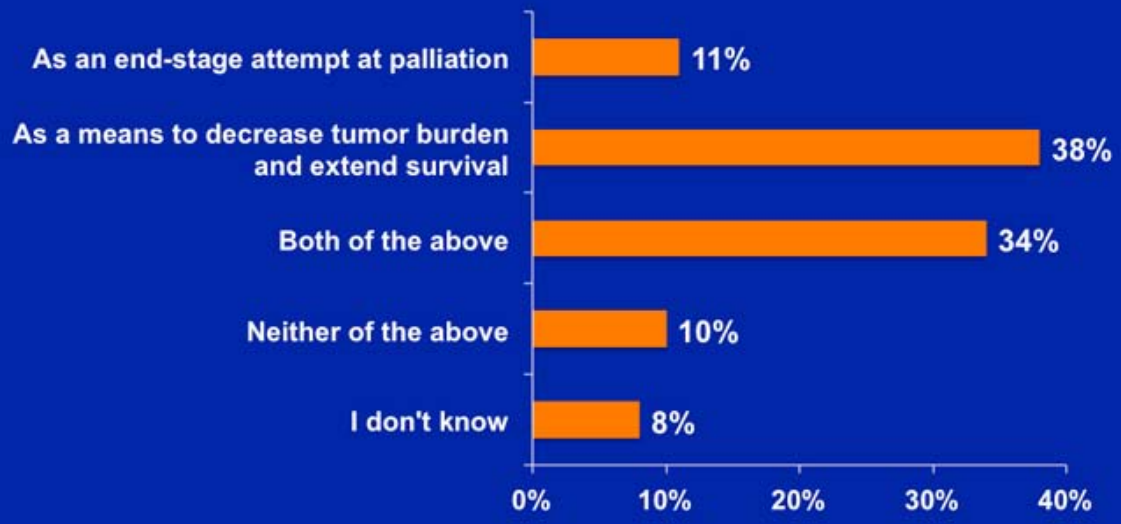
AUDIENCE POLL

A 60-year-old man presents with symptomatic bone and soft tissue metastases after receiving ADT for PSA-only disease. What therapy (in addition to bone-targeted treatment, if any) would you most likely recommend?



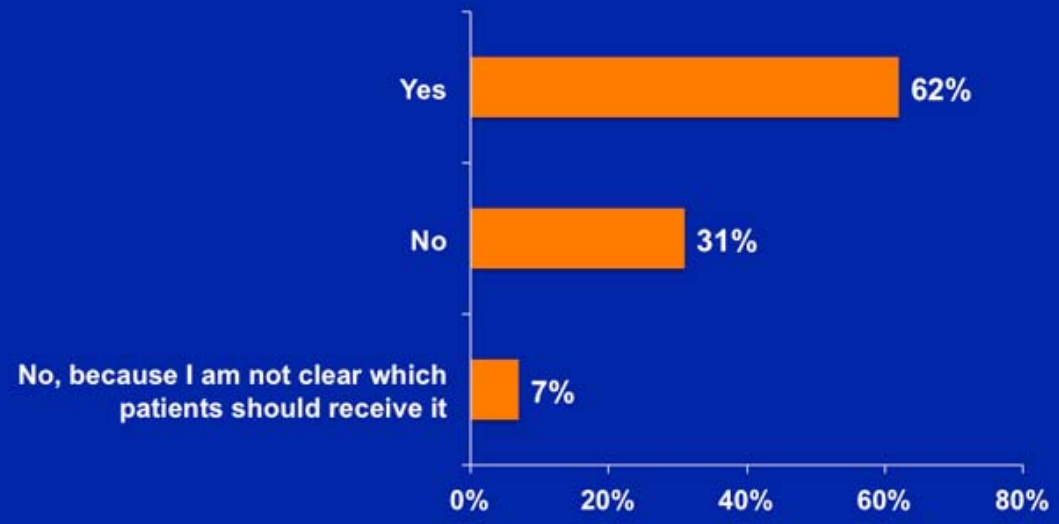
AUDIENCE POLL

How do you conceptualize the role of radium-223 in the treatment of metastatic prostate cancer?



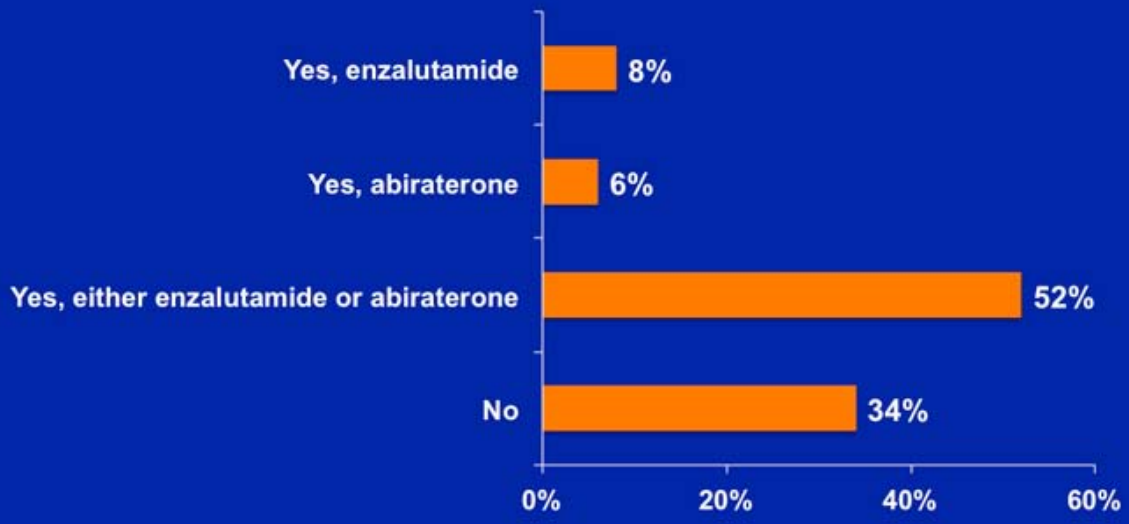
AUDIENCE POLL

Have you referred patients with prostate cancer for treatment with radium-223?



AUDIENCE POLL

Cost and reimbursement issues aside, are there patients with PSA-only disease to whom you would administer enzalutamide or abiraterone?



Research

Original Investigation

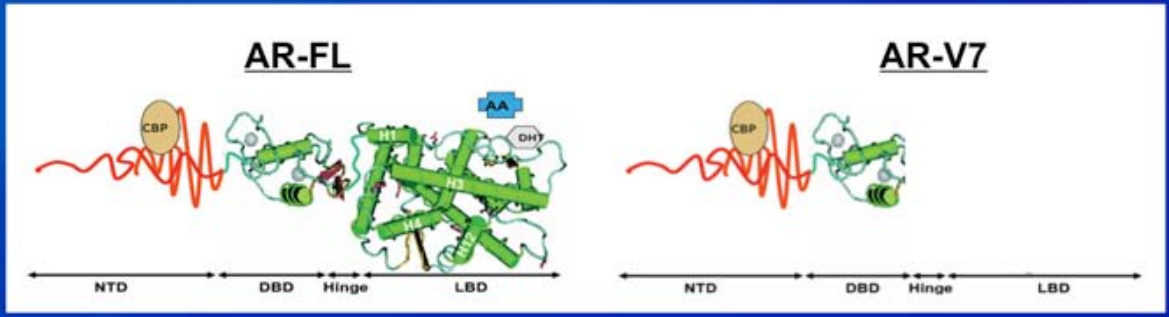
Androgen Receptor Splice Variant 7 and Efficacy of Taxane Chemotherapy in Patients With Metastatic Castration-Resistant Prostate Cancer

Emmanuel S. Antonarakis, MD; Changxue Lu, PhD; Brandon Luber, ScM; Hao Wang, PhD; Yan Chen, PhD; Mary Nakazawa, MHS; Rosa Nadal, MD; Channing J. Paller, MD; Samuel R. Denmeade, MD; Michael A. Carducci, MD; Mario A. Eisenberger, MD; Jun Luo, PhD

Antonarakis ES et al. *JAMA Oncol* 2015;1(5):582-91.

Androgen Receptor Variant-7 (AR-V7)

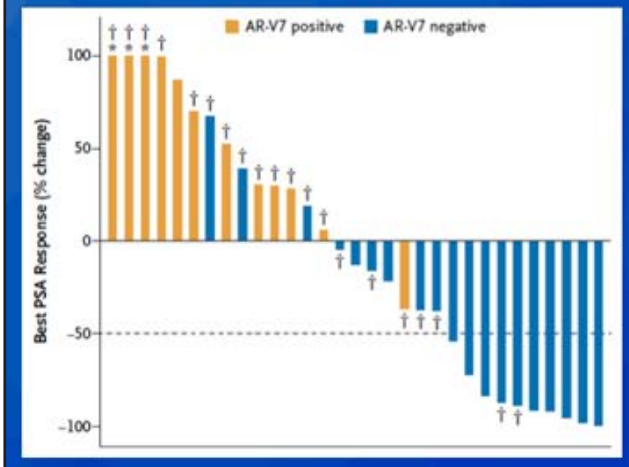
- AR-V7 is a truncated form of the AR that lacks the ligand binding domain
- AR-V7 is a target of abiraterone and enzalutamide but remains constitutively active as a transcription factor



Antonarakis ES et al. Genitourinary Cancers Symposium 2015;Abstract 138.

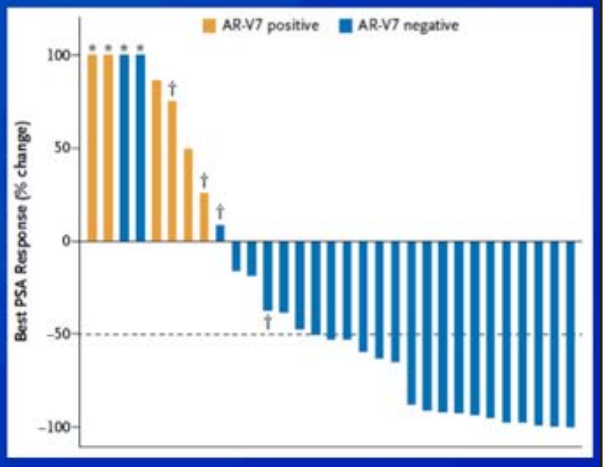
Best PSA Response to Enzalutamide or Abiraterone by AR-V7 Status

Enzalutamide Treated



AR-V7 (-) = 53%
AR-V7 (+) = 0

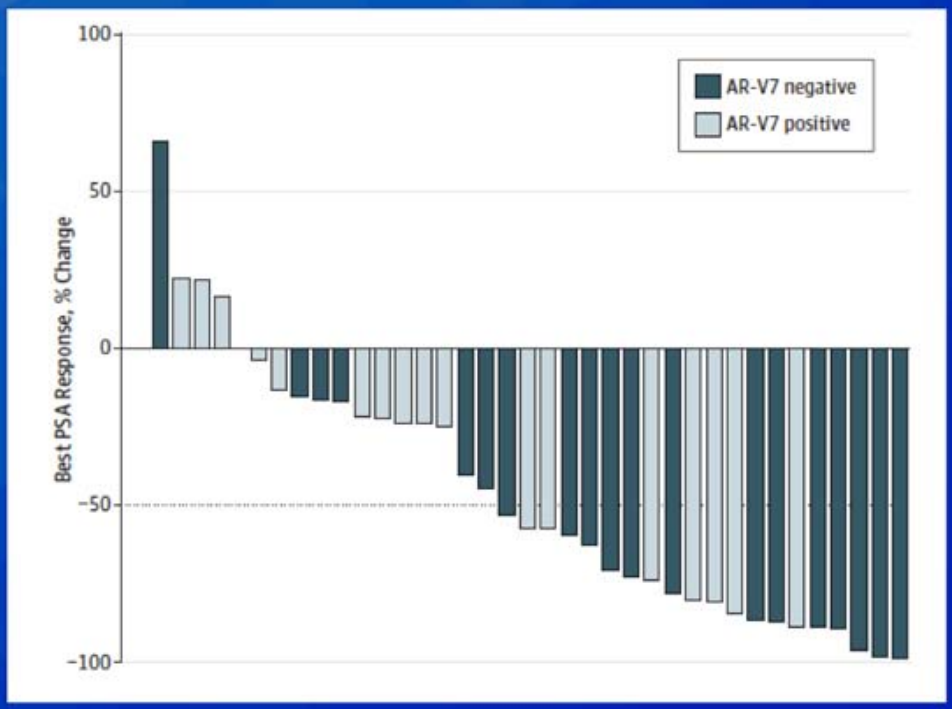
Abiraterone Treated



AR-V7 (-) = 68%
AR-V7 (+) = 0

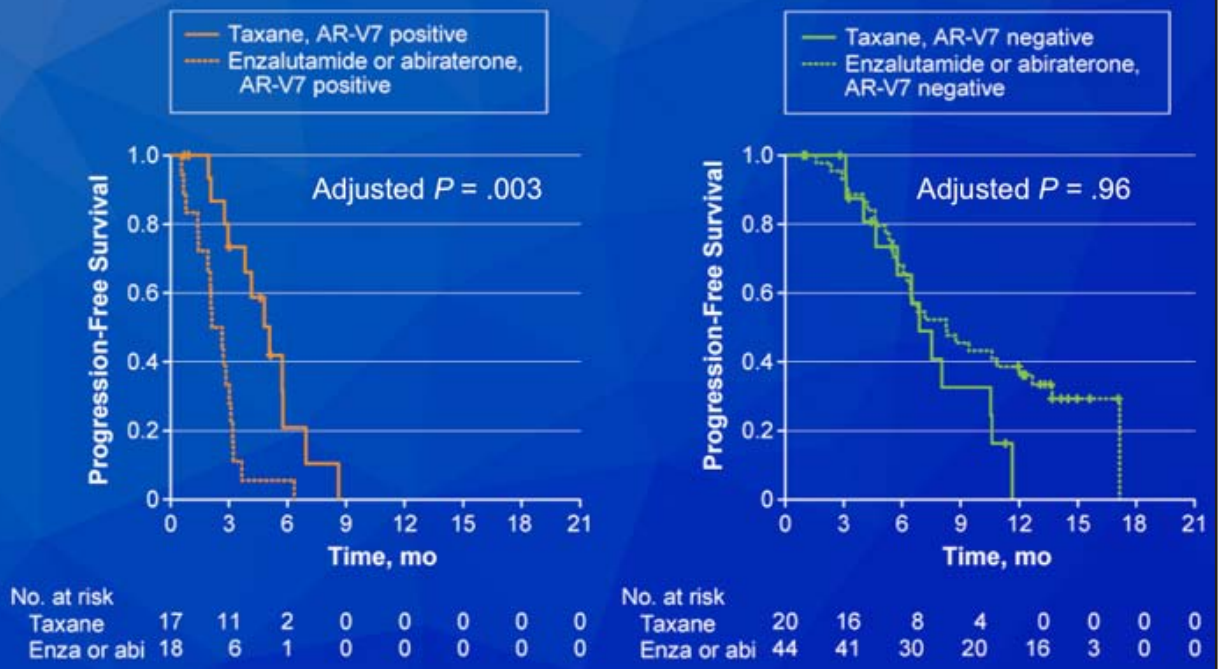
Antonarakis ES et al. *N Engl J Med* 2014;371(11):1028-38.

Best PSA Response in Taxane-Treated Patients According to AR-V7 Mutation Status in CTCs (n = 37)



Antonarakis ES et al. *JAMA Oncol* 2015;1(5):582-91.

PFS by AR-V7 Mutation Status and Treatment Type



Antonarakis ES et al. *JAMA Oncol* 2015;1(5):582-91.

Conclusions

Critical finding(s):

1) If CTC test is **NEG** for AR-V7: Taxane ≈ second-line hormonal therapy
2) If CTC test is **POS** for AR-V7: Taxane-based therapy yields a superior PSA response rate

Clinical implication(s): These prospective data suggest that men with mCRPC and the AR-V7 mutation should possibly be treated with chemotherapy rather than additional lines of hormonal therapy.

Conclusions

Research relevance:

Small sample, prospective but NOT randomized

Requires confirmation in a prospective RCT

PRIMCAB: Phase II trial randomly assigns men with resistance to abiraterone or enzalutamide to abiraterone or enzalutamide or cabazitaxel. Will measure AR-V7, but it's not a stratification factor.

A Multicenter Phase 2 Study of Enzalutamide (ENZA) versus Bicalutamide (BIC) in Men with Nonmetastatic (M0) or Metastatic (M1) Castration-Resistant Prostate Cancer (CRPC): The STRIVE Trial

Penson D et al.

Proc AUA 2015;Abstract LBA10.

STRIVE Trial Efficacy Results

Endpoints	M0		M1	
	ENZA (N = 70)	BIC (N = 69)	ENZA (N = 128)	BIC (N = 129)
Median PFS (months)	NR	8.6	16.5	5.5
HR (95% CI)	0.24 (0.14-0.42)		0.24 (0.17-0.34)	
Median radiographic PFS (months)	NR	NR	NR	8.3
HR (95% CI)	0.24 (0.10-0.56)		0.32 (0.21-0.50)	
Median Time to PSA Progression (months)	NR	11.1	24.9	5.7
HR (95% CI)	0.18 (0.10-0.34)		0.19 (0.13-0.28)	
PSA Response (?50%)	90.9%	42.0%	76.2%	25.4%

M0 = nonmetastatic; M1 = metastatic; ENZA = enzalutamide; BIC = bicalutamide; NR = not reached; HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen

Penson D et al. *Proc AUA* 2015;Abstract LBA10.

Conclusions

Critical finding(s):

1) All outcome parameters superior with ENZA, including PFS
2) In M0 patients, median PFS was NR vs 8.6 months
3) Serious AE rates similar: 29.4% in ENZA and 28.3% for BIC
4) Lower-grade AEs more frequent in ENZA: Fatigue (37.6% vs 28.3%), back pain, flushing, falls, HTN and dizziness

Conclusions

Clinical implication(s):

Enzalutamide is likley superior to bicalutamide in men with progressive CRPC

Research relevance:

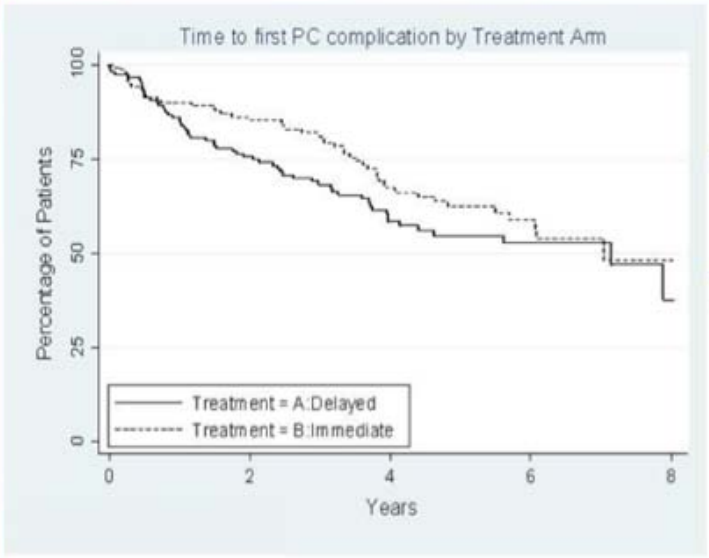
When viewed in context of TERRAIN, seems unlikely that further studies (OS?) are needed

TROG 03.06 and VCOG PR 01-03: The "Timing of Androgen Deprivation Therapy in Prostate Cancer Patients with a Rising PSA (TOAD)" Collaborative Randomised Phase III Trial

Duchesne GM et al.

Proc ASCO 2015;Abstract 5007.

Time to first prostate cancer complication

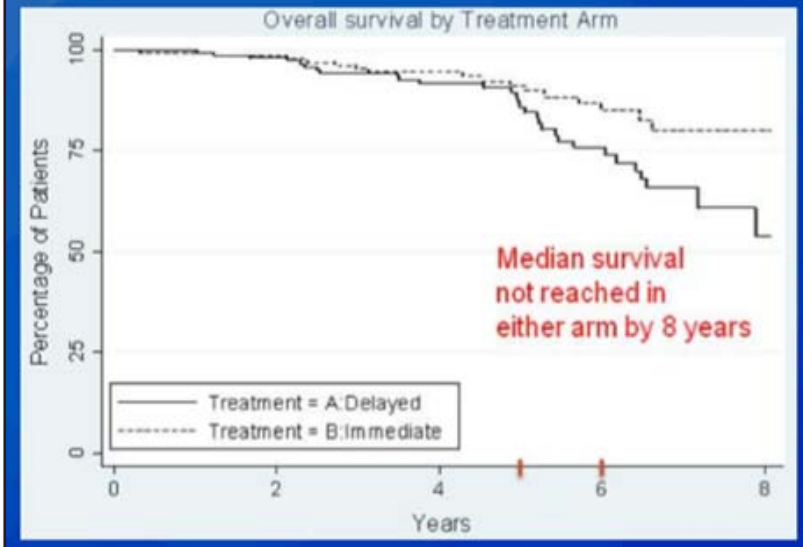


Adjusted HR B vs A:
0.78 (0.54, 1.11) p=0.16

Those experiencing any complication:
Arm A: 61/150 (41%)
Arm B: 48/140 (34%)

Duchesne GM et al. *Proc ASCO* 2015;Abstract 5007.

Primary endpoint: Overall Survival (OS)



Logrank test:
Arm B (immediate) had significantly higher OS than Arm A, $p = 0.047$

Cox regression unadjusted:
Arm B vs Arm A
Hazard ratio 0.55 (0.30, 1.00)
$p = 0.05$

Cox regression adjusted:
Arm B vs Arm A
Hazard ratio 0.54 (0.27, 1.06)
$p = 0.074$

Duchesne GM et al. *Proc ASCO* 2015;Abstract 5007.

Conclusions

Critical finding(s):

1) No M1 patients were accrued into Study 2, so approximately 150 patients each were accrued into the immediate versus delayed ADT arms
2) Immediate treatment arm had a numerically higher OS: Cox regression adjusted HR 0.54 (0.27-1.06, $p = 0.074$)
3) Trial recruited slowly and was underpowered because 5-year survival was better than expected: 85% vs 76% in the immediate versus delayed arms
4) Symptoms reported by 80% vs 50% in immediate vs delayed treatment arms

Conclusions

Clinical implication(s):

Provides a moderate level of support to immediate versus delayed ADT

Immediate treatment needs to be weighed against the development of symptoms

Research relevance:

Further survival follow-up is needed

Radium-223 dichloride (Ra-223) in US Expanded Access Program (EAP)[1]

Radium-223 Dichloride in Expanded-Access Setting in the United States: Overall and Concurrent Experience with Abiraterone or Enzalutamide[2]

[1] Vogelzang NJ et al.
Genitourinary Cancers Symposium 2015;Abstract 247.
[2] Shore N et al.
Proc AUA 2015;Abstract MP87-12.

Ra-223 Expanded Access Program (EAP) in the United States: Safety

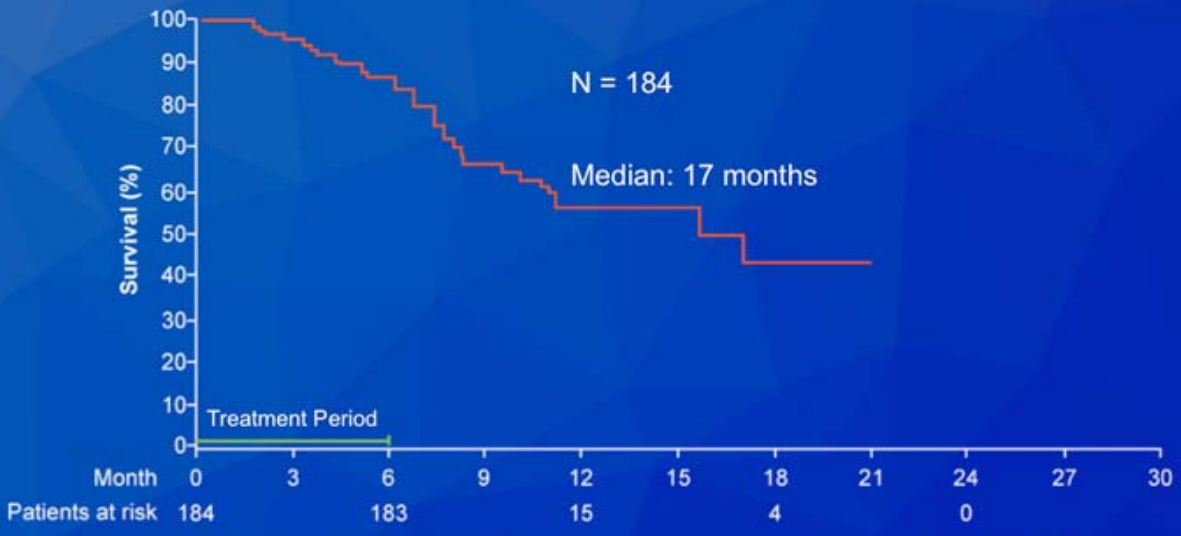
Treatment-emergent adverse event (TEAE)[1]	EAP (n = 184)	ALSYMPCA (n = 600)
≥1 TEAE (any grade)	133 (72%)	553 (92%)
Grade 3	58 (32%)	207 (35%)
Grade 4	9 (5%)	53 (9%)
Grade 5*	8 (4%)	97 (16%)
TEAEs leading to dose modification, delays	18 (10%)	65 (11%)
TEAEs leading to discontinuation	30 (16%)	99 (17%)

* In the EAP, none of the 8 deaths were related to Ra-223.

- The rate of Grade 3-5 TEAEs was similar across patient groups who had received concurrent (abi 37%, enza 36%) and prior (abi 43%, enza 42%) hormonal therapy vs overall (41%).[2]

[1] Vogelzang NJ et al. Genitourinary Cancers Symposium 2015;Abstract 247; [2] Shore N et al. *Proc AUA* 2015;Abstract MP87-12.

Ra-223 Expanded Access Program: Overall Survival



- Median OS in the EAP was 17 mo[1, 2] compared to 14.9 mo in ALSYMPCA.
- Due to shorter follow-up time in EAP, there was a greater percentage of patients censored in the EAP versus ALSYMPCA.

[1] Vogelzang NJ et al. *Proc ASCO* 2015;Abstract 247; [2] Shore N et al. *Proc AUA* 2015;Abstract MP87-12.

Conclusions

Critical finding(s):

1) About half (44%) of patients received all 6 planned injects of RAD223 (q4wk)
2) Median OS similar to the pivotal ALSYMPCA study at 17 months
3) Median time to PSA progression = 4 months, 6% of patients had a PSA response
4) AEs similar to ALYSMPCA: Most common Grade 3/4 AE = anemia at 11%. Other AEs (≥10%) = fatigue, diarrhea and nausea

Conclusions

Clinical implication(s):

EAP shows activity and tolerability of RAD223 similar to that observed in the pivotal Phase III study, with similar efficacy and no new safety signals.

Research relevance:

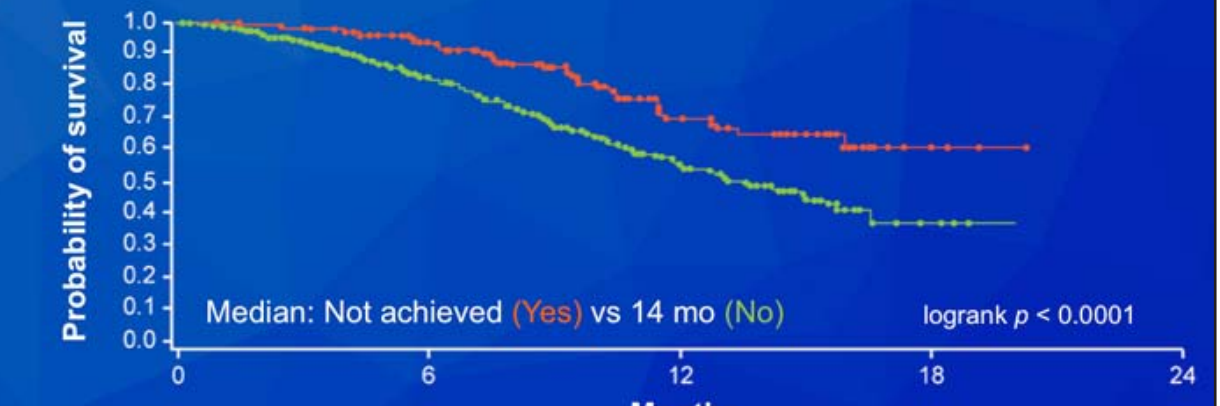
ALSYMPCA results likely apply broadly to mCRPC patients, which is not always the case for the translation of Phase III data into a broader clinical setting.

Radium-223 in an International Early Access Program (EAP): Effects of Concomitant Medication on Overall Survival in Metastatic Castration-Resistant Prostate Cancer (mCRPC) Patients

Saad F et al.

Proc ASCO 2015;Abstract 5034.

International Ra-223 Early Access Program: Overall Survival by Concomitant Abiraterone Use at Baseline

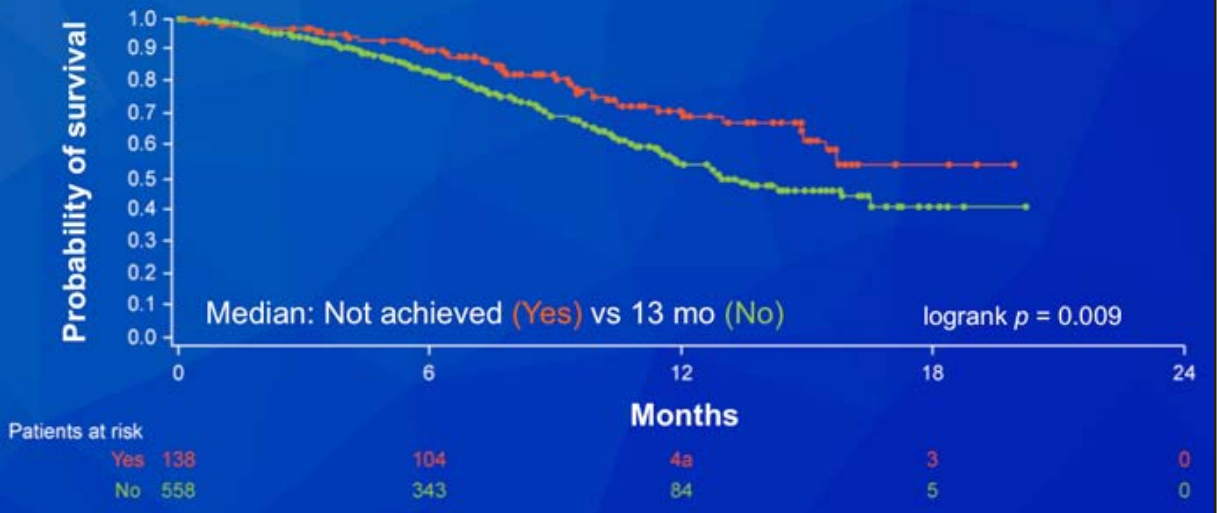


Patients at risk

Yes	156	119	45	4	0
No	540	328	80	4	0

Saad F et al. *Proc ASCO* 2015;Abstract 5034.

International Ra-223 Early Access Program: Overall Survival by Concomitant Denosumab Use at Baseline

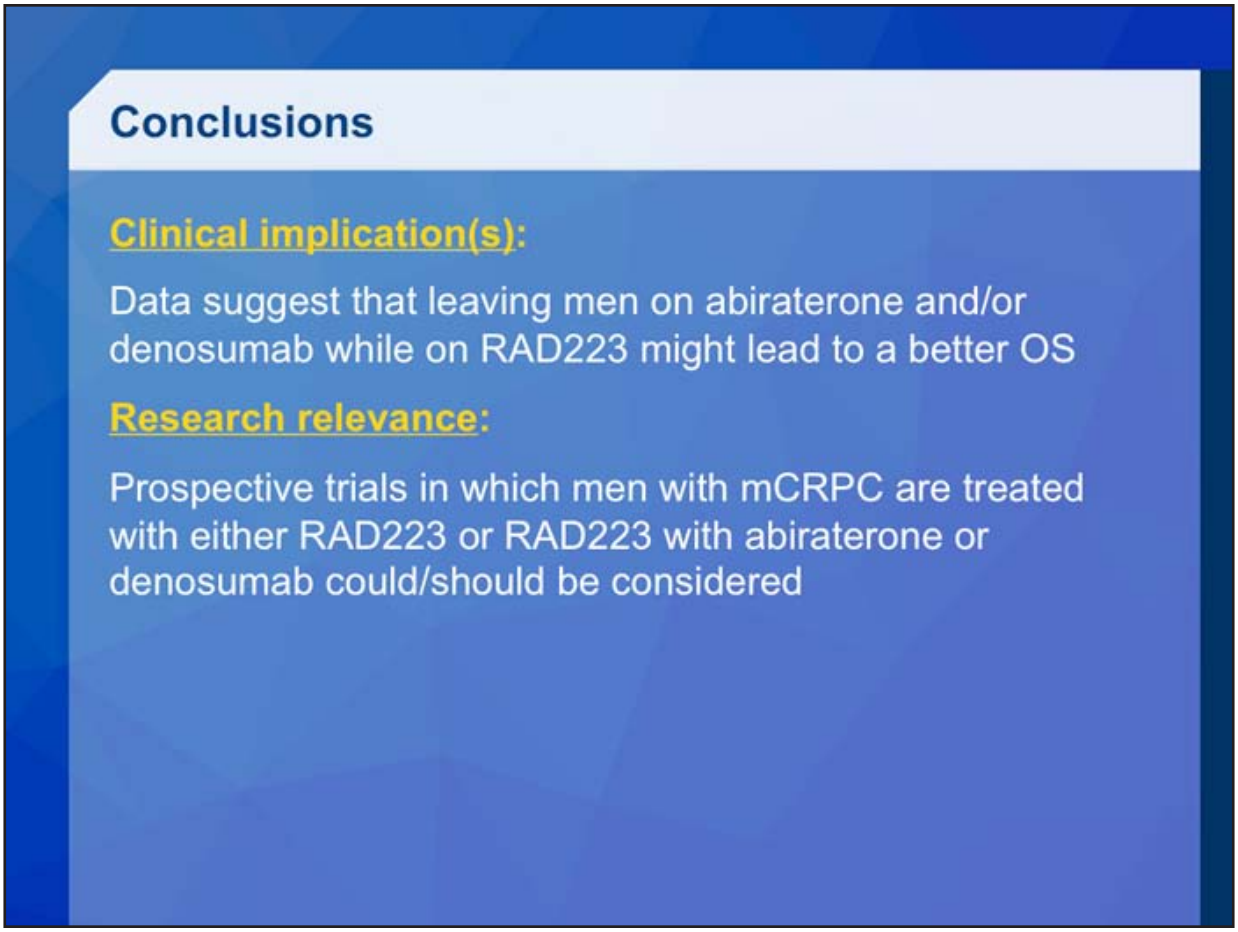


Saad F et al. *Proc ASCO* 2015;Abstract 5034.

Conclusions

Critical finding(s):

1) Median OS similar to both ALSYMPCA and US EAP: Approximately 16.0 months
2) Better ECOG PS, a lower alk phos and no baseline pain all associated with a longer OS
3) Concomitant denosumab and concomitant abiraterone acetate also associated with a longer OS


Conclusions
Clinical implication(s):
Data suggest that leaving men on abiraterone and/or denosumab while on RAD223 might lead to a better OS
Research relevance:
Prospective trials in which men with mCRPC are treated with either RAD223 or RAD223 with abiraterone or denosumab could/should be considered