ESMO Clinical Practice Guidelines: Prostate Cancer

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Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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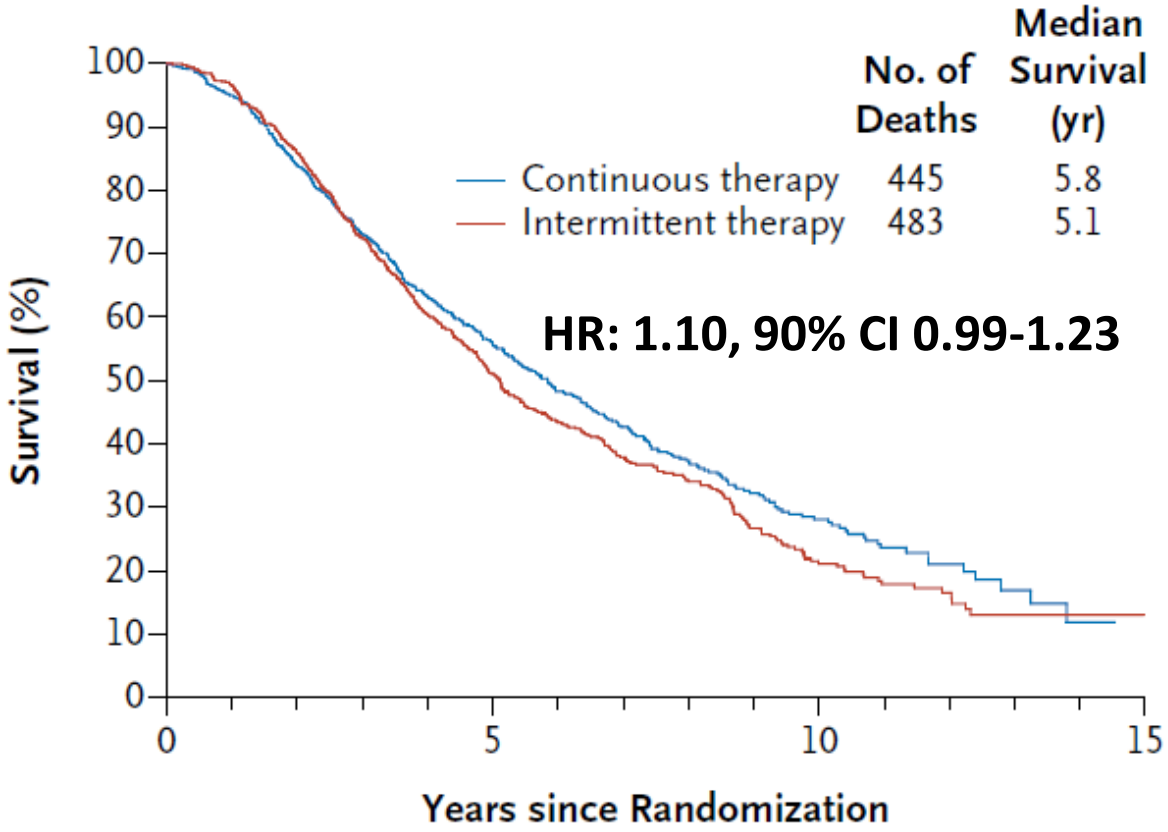
management of advanced/metastatic disease

recommendations

- Continuous ADT is recommended as first-line treatment of metastatic, hormone-naïve disease [I, A].
- Men starting ADT should be informed that regular exercise reduces fatigue and improves quality of life [31] [I, A].
- ADT plus docetaxel is recommended as first-line treatment of metastatic, hormone-naïve disease in men fit enough for chemotherapy [1, A].

Intermittent vs. Continuous ADT



No. at Risk

Continuous therapy	765	325	64
Intermittent therapy	770	291	52

M Hussain et al, New Eng J Med, 368: 1314, 2013

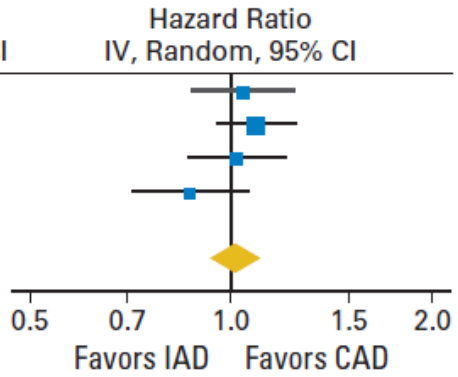
Intermittent vs. Continuous ADT

Overall Survival

A

Study or Subgroup	Sample Size	Weight, %	Hazard Ratio IV, Random, 95% CI
daSilva (2011)	626	22.4	1.04 (0.87 to 1.24)
Hussain (2012)	1,535	35.5	1.09 (0.95 to 1.25)
Crook (2012)	1,386	24.3	1.02 (0.86 to 1.21)
Salonen (2012)	554	17.9	0.87 (0.71 to 1.06)
Total (95% CI)		100.0	1.02 (0.93 to 1.11)

Heterogeneity: $\chi^2 = 3.35$, df = 3 ($P = .34$); $I^2 = 10\%$
Test for overall effect: Z = 0.42 ($P = .67$)

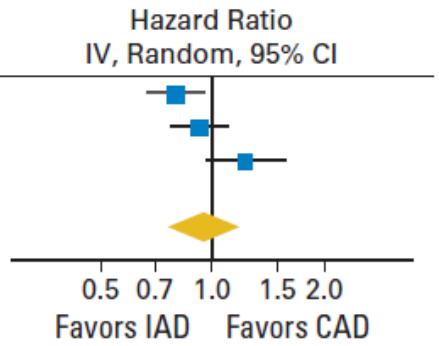


Time to Progression

B

Study or Subgroup	Sample Size	Weight	Hazard Ratio IV, Random, 95% CI
Crook (2012)	1,386	35.5	0.80 (0.67 to 0.96)
Salonen (2012)	554	35.1	0.93 (0.77 to 1.11)
daSilva (2011)	656	29.4	1.23 (0.96 to 1.58)
Total (95% CI)		100.0%	0.96 (0.76 to 1.20)

Heterogeneity: $\chi^2 = 7.65$, df = 2 ($P = .02$); $I^2 = 74\%$
Test for overall effect: Z = 0.39 ($P = .69$)

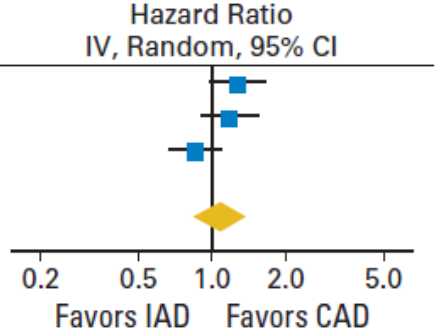


Prostate Cancer Specific Survival

C

Study or Subgroup	Sample Size	Weight	Hazard Ratio IV, Random, 95% CI
daSilva (2011)	626	33.4	1.27 (0.98 to 1.65)
Crook (2012)	1,386	32.3	1.18 (0.90 to 1.55)
Salonen (2012)	554	34.2	0.85 (0.66 to 1.10)
Total (95% CI)		100.0	1.08 (0.85 to 1.38)

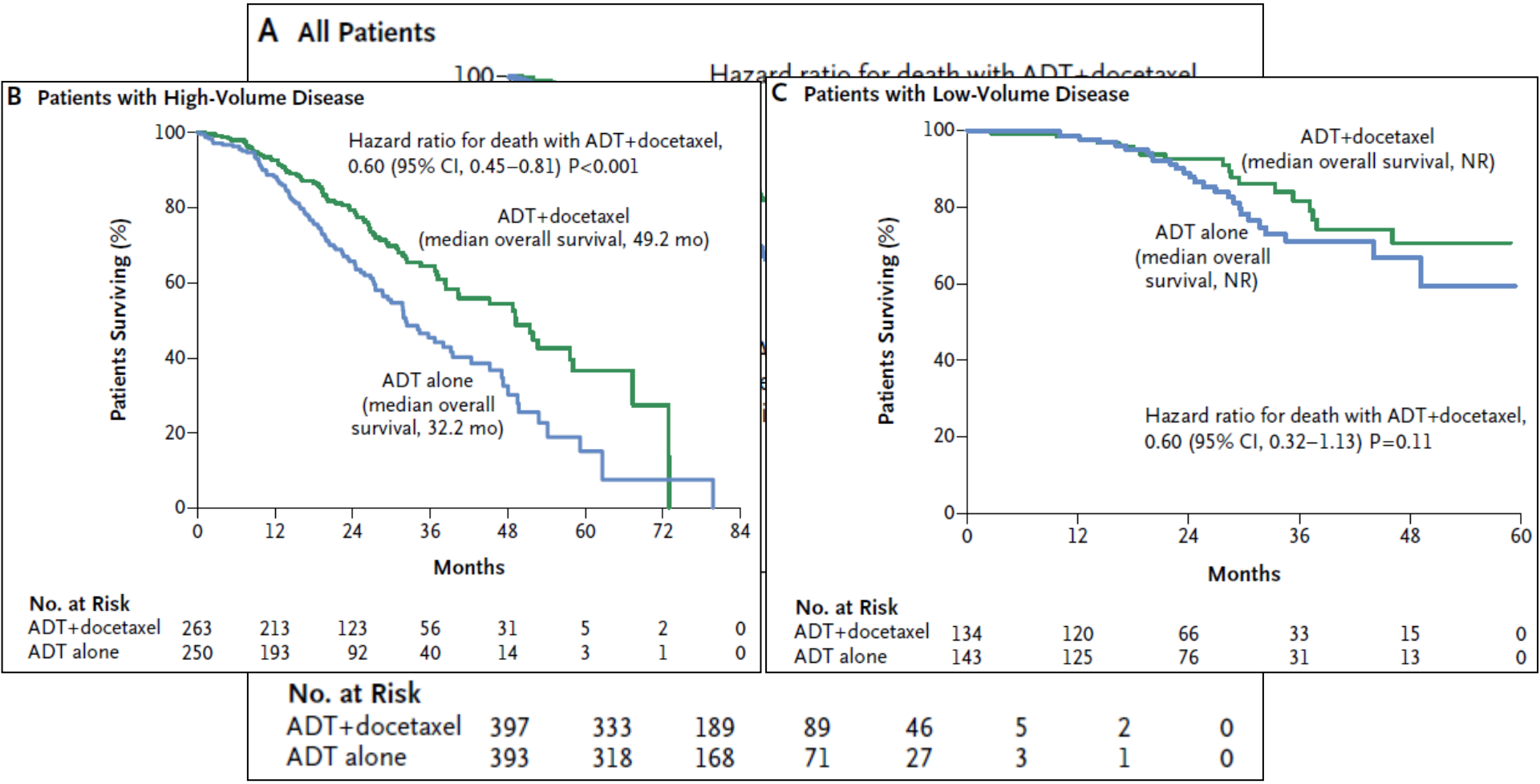
Heterogeneity: $\chi^2 = 5.24$, df = 2 ($P = .07$); $I^2 = 62\%$
Test for overall effect: Z = 0.64 ($P = .52$)



S Niraula, LW Le, IF Tannock, J Clin Oncol, 31: 2029, 2013

ADT +/- Docetaxel

CHAARTED: Overall Survival



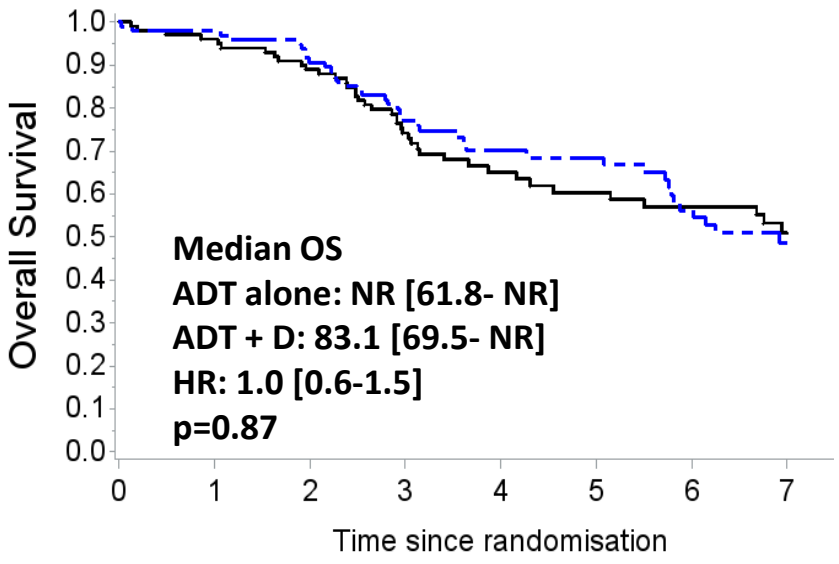
C Sweeney et al, New Eng J Med, 373: 737, 2015

ADT +/- Docetaxel

GETUG-15: Updated Analysis

LOW VOLUME METASTASES

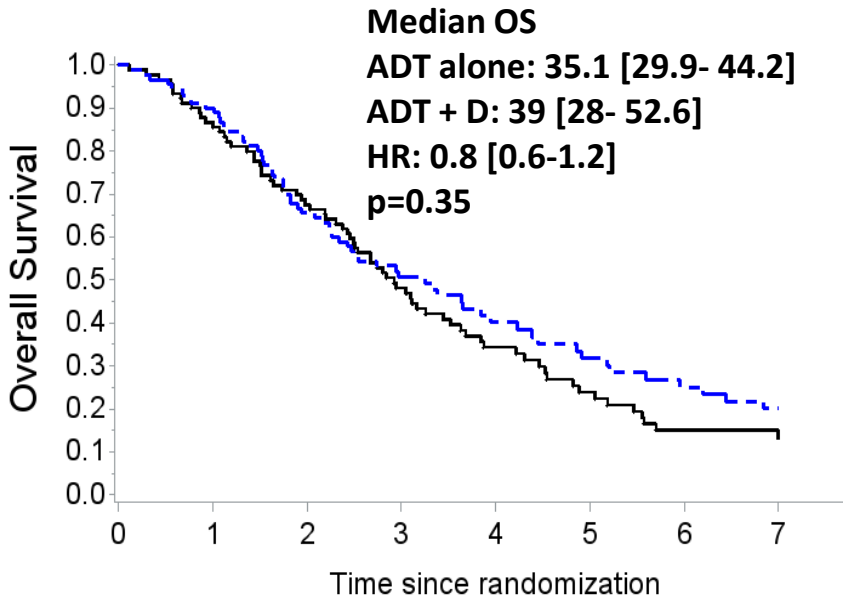
Median follow-up 81.3 months [69.2-83.7]



ADT	102	95	88	65	43	37	33	21
ADT +D	100	94	86	62	45	39	32	18

HIGH VOLUME METASTASES

Median follow-up: 84.0 months [82.9-84.0]

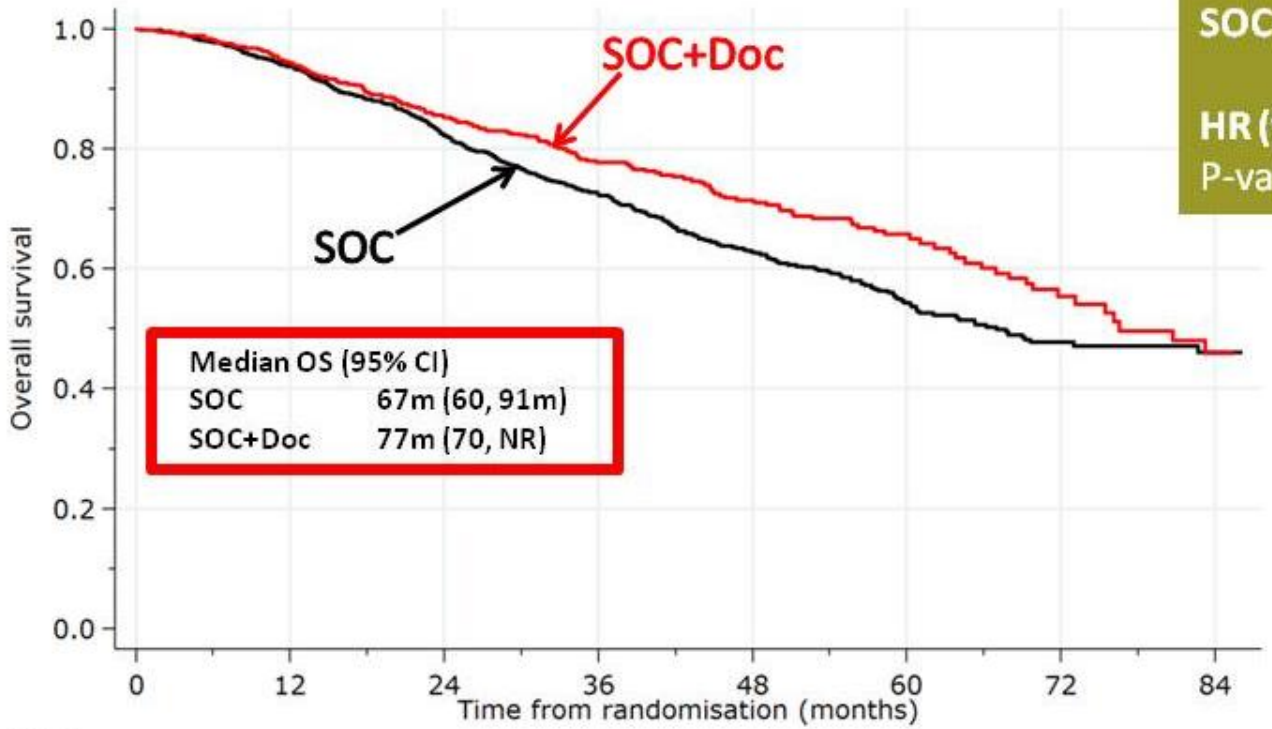


ADT	91	76	60	40	23	16	10	8
ADT +D	92	81	59	38	25	19	15	9

G Gravis, et al. J Clin Oncol 33, 2015 (suppl 7; abstr 140)

ADT +/- Docetaxel

STAMPEDE: All Patients (M0 and M1)



SOC	405 deaths
SOC+Doc	165 deaths
HR (95%CI)	0.76 (0.63, 0.91)
P-value	0.003

Non-PH p-value 0.51

Group At risk (events)															
SOC	1184	(73)	1092	(130)	860	(89)	521	(59)	310	(33)	156	(17)	81	(2)	36
SOC+Doc	592	(33)	545	(51)	437	(32)	283	(19)	180	(12)	91	(12)	48	(6)	18

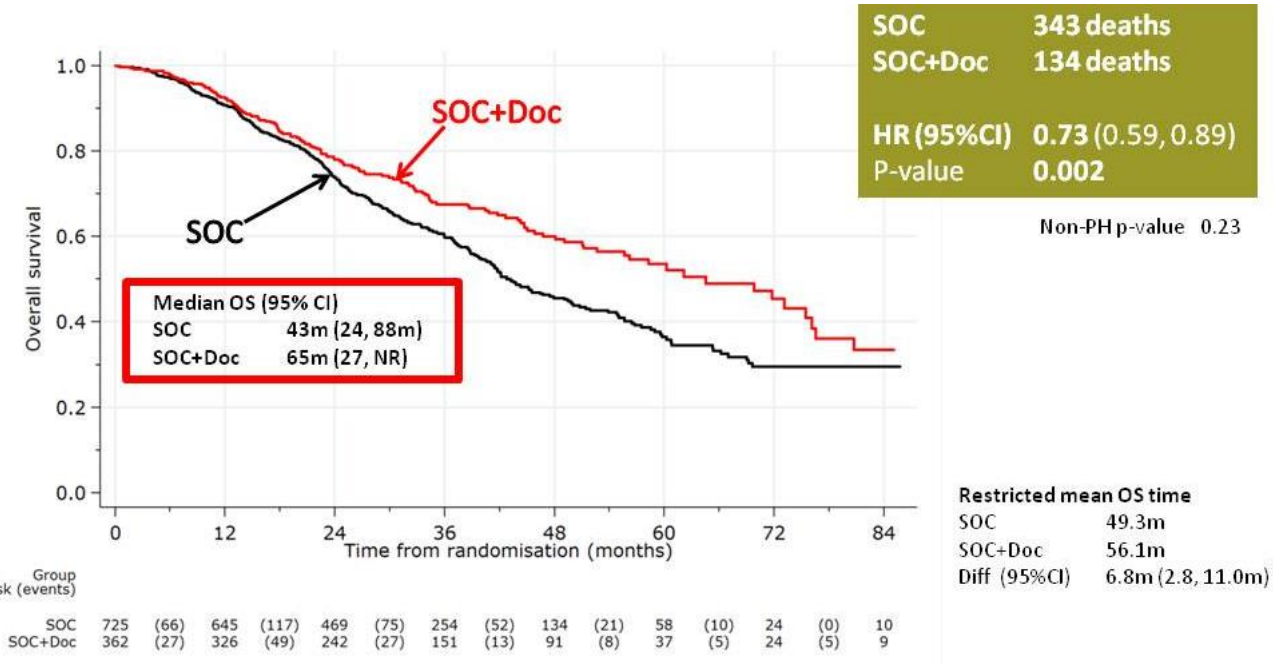
Restricted mean OS time

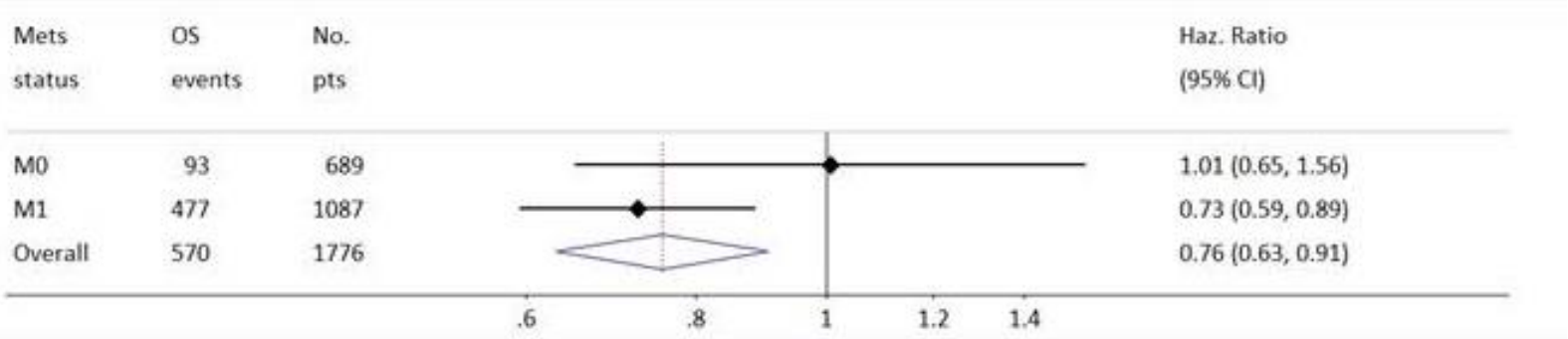
SOC	58.8m
SOC+Doc	63.4m
Diff (95%CI)	4.6m (1.8, 7.3m)

ND James et al, J Clin Oncol 33, 2015 (suppl; abstr 5001)

ADT +/- Docetaxel

STAMPEDE: M1 Patients





ND James et al, J Clin Oncol 33, 2015 (suppl; abstr 5001)

GETUG-15 vs. CHAARTED vs. STAMPEDE

	GETUG-15		CHAARTED		STAMPEDE	
	ADT + D x 9	ADT	ADT + D x 6	ADT	ADT + D x 6	ADT
Accrual years	2004-2008		2006-2012		2005-2013	
Sample size	192	193	397	393	592	1184
Characteristics						
Median Age	63 y	64 y	64 y	63 y	65 y	
High Volume	92 (48%)	91 (47%)	263 (66%)	251 (64%)	NR	
TX related death	5%	0%	<1%	0%	NR	NR
Febrile Neutropenia	8%	0%	6%	0%	12%	0%
Median OS						
All M1 Patients	58.9 m	54.2 m	57.6 m	44.0 m	65 m	43 m
"High Volume"	39 m	35.1 m	49.2 m	32.2 m	NR	NR

[a] Radiographic Progression; [b] Symptomatic or radiographic progression
[c] Calculated from total N; [d] Calculated from patients that progressed;

My Practice

- Continuous ADT is standard
  - Consider intermittent in good responders who have poor quality of life on ADT, but this requires close follow-up
- Addition of docetaxel x 6 cycles to initial ADT improves overall survival in patients with metastatic disease
  - Recommend to patients with high volume metastases (≥ 4 bone mets with ≥ 1 outside spine/pelvis or visceral mets)
  - Consider for patients with non-high volume disease but risk vs. benefit ratio needs to be considered
  - Do not consider in patients without metastatic disease

clinical practice guidelines

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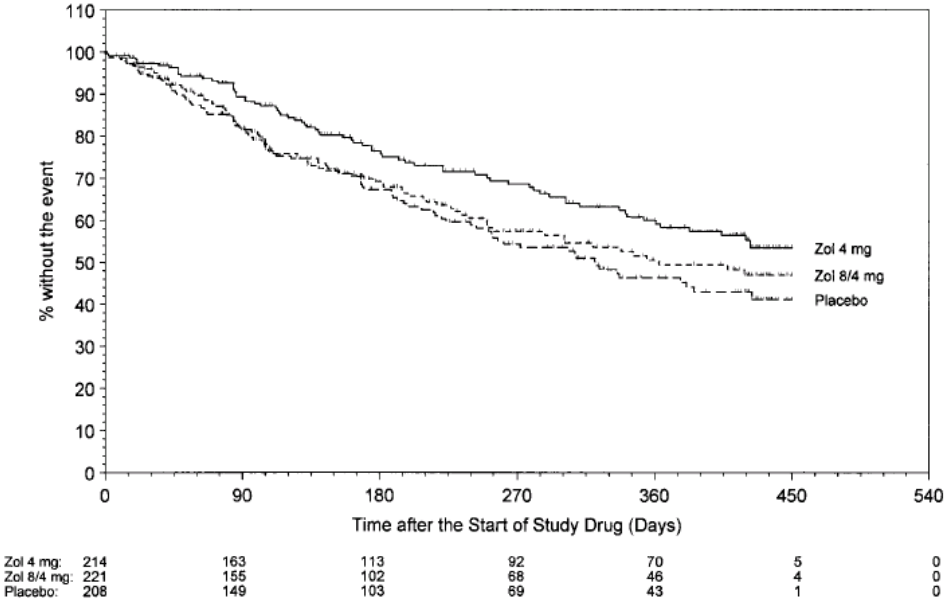
palliative care

recommendation

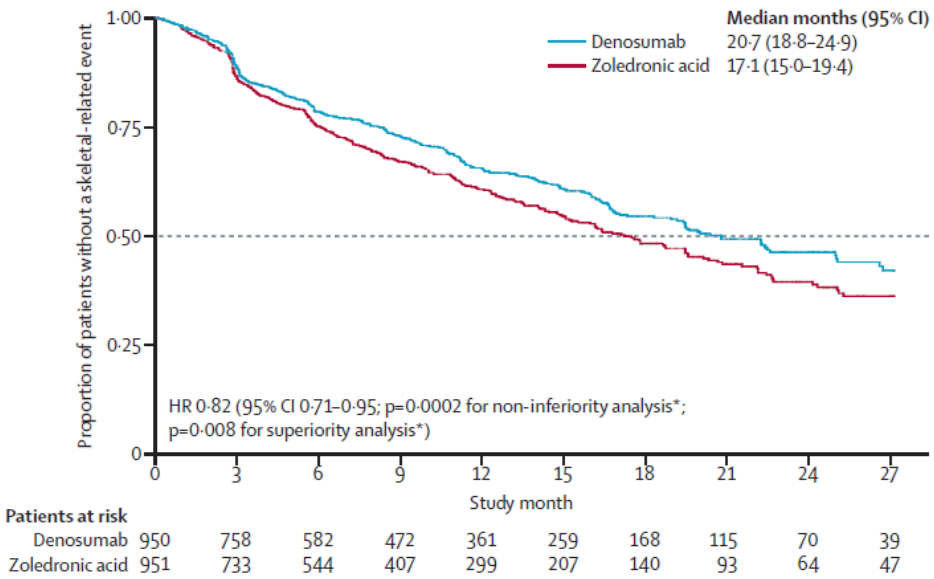
- In patients with bone metastases from CRPC, at high risk for clinically significant SREs, denosumab or zoledronate can be recommended [I, B].

Zoledronic Acid and Denosumab for CRPC

Zoledronic Acid



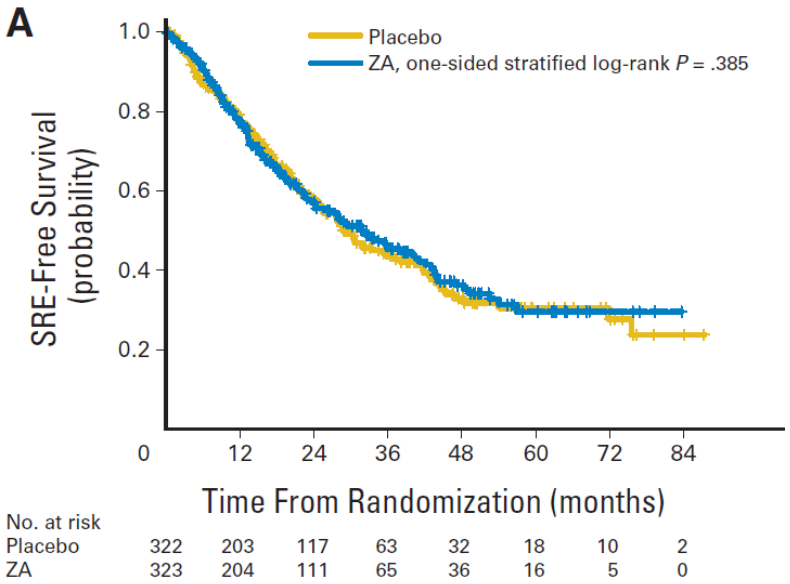
Denosumab



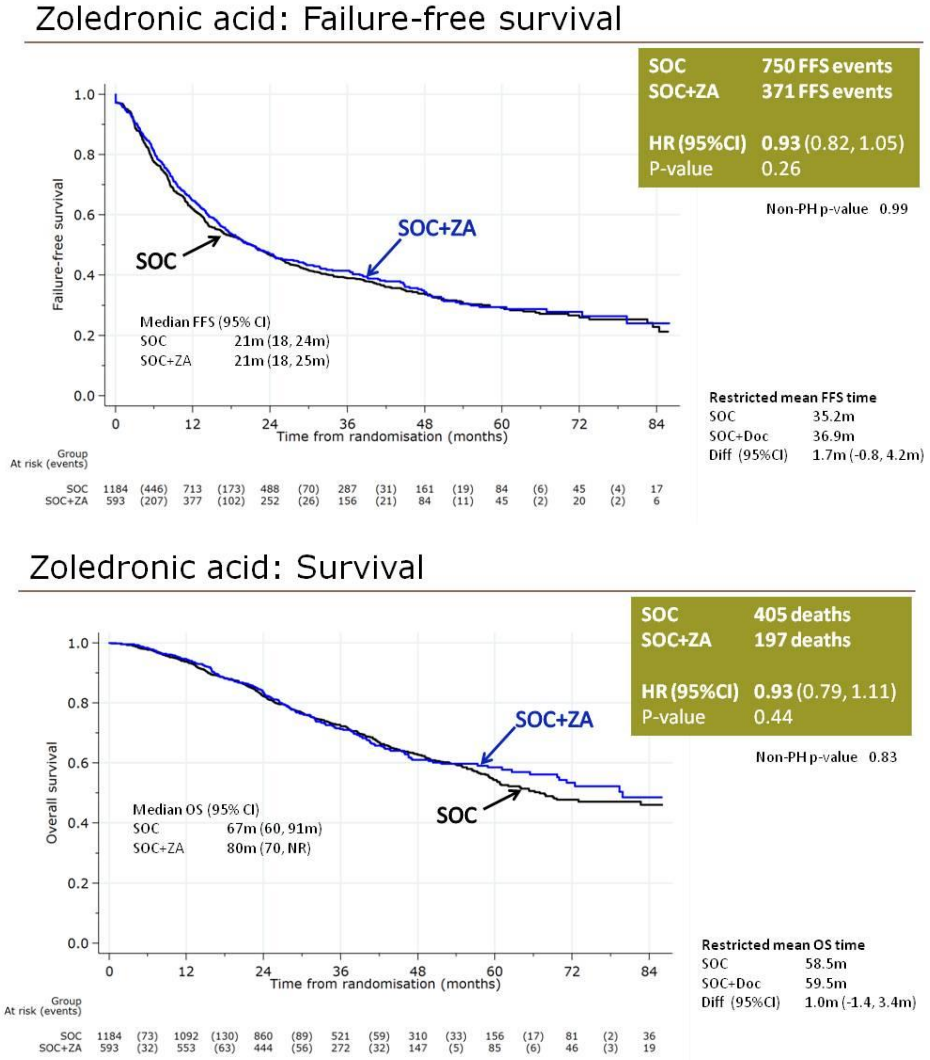
F Saad et al, J Natl Cancer Inst, 94:1458, 2002; K Fizazi et al, Lancet, 377:813, 2011

Zoledronic Acid for Castration Sensitive

CALGB 90202



STAMPEDE



MR Smith J Clin Oncol, 32:1143, 2014
ND James et al, J Clin Oncol 33, 2015 (suppl; abstr 5001)

clinical practice guidelines

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treatment of castrate-resistant prostate cancer

recommendations

- Abiraterone or enzalutamide are recommended for asymptomatic/mildly symptomatic men with chemotherapy-naïve metastatic CRPC [I, A].
- Radium-223 is recommended for men with bone-predominant, symptomatic metastatic CRPC without visceral metastases [I, A].
- Docetaxel is recommended for men with metastatic CRPC [I, A].
- Sipuleucel-T is an option in asymptomatic/mildly symptomatic patients with chemotherapy-naïve metastatic CRPC [II, B].

Phase III CRPC Trials Showing OS Benefit

Drug	Prior Therapy	Symptom Improvement/ Delay	Control	OS	
				Median Δ (Months)	HR
Docetaxel	Chemo-naïve	+	MTX	2.4	0.76
Sipuleucel-T	+/- chemo	-	Placebo	4.1	0.78
Cabazitaxel	Post-docetaxel	+/-	MTX	2.4	0.70
Abiraterone	Post-docetaxel	+	Prednisone	4.6	0.74
Enzalutamide	Post-docetaxel	+	Placebo	4.8	0.63
Radium-223	+/- chemo	-	Placebo	3.6	0.70
Abiraterone	Chemo-naïve	+	Prednisone	4.4	0.81
Enzalutamide	Chemo-naïve	+	Placebo	2	0.70

SELECTION?

SEQUENCING?

ABI or ENZA for CRPC?

COU-302 and PREVAIL Outcomes

Endpoints	AA + P	PL + P
Median rPFS (months)	**16.5**	3.9
	HR: 0.43, P<0.001	
Median OS (months)	**34.7**	30.3
	HR: 0.81, P=0.003	
PSA Decline >50%	**62**	24
	P<0.001	
Median Time to FACT-P decline (months)	**12.7**	8.3
	HR: 0.78, P =0.003	
Median time to chemo initiation (months)	**26.5**	16.8
	HR: 0.61, P<0.001	
Median time to PSA progression (months)	**11.1**	5.6
	HR: 0.50, P<0.001	
ORR (%)	**36**	16
	P<0.001	

Endpoints	ENZA	PLACEBO
Median rPFS (months)	**NR (~15-18)**	3.9
	HR: 19, P<0.001	
Median OS (months)	**32**	30
	HR: 0.71 , P<0.001	
PSA Decline >50%	**78**	3
	P<0.001	
Median Time to FACT-P decline (months)	**11.3**	5.6
	HR: 0.625, P<0.0001	
Median time to chemo initiation (months)	**28.0**	10.8
	HR: 0.35, P<0.0001	
Median time to PSA progression (months)	**11.2**	2.8
	HR: 0.169, P<0.0001	
ORR (%)	**59**	5
	P<0.0001	

Selected AEs in COU-302 and PREVAIL

COU-301 Adverse event (AE)	AA + P		PL + P	
	All grades	Grade 3-4	All grades	Grade 3-4
Fluid retention or edema	28%	<1%	24%	2%
Hypokalemia	17%	2%	13%	2%
Hypertension	22%	4%	13%	3%
Cardiac disorders*	19%	6%	16%	3%
LFT abnormalities	12%	5%	5%	<1%

AFFIRM Adverse event (AE)	Enzalutamide		Placebo	
	All grades	Grade ≥3	All grades	Grade ≥3
Fatigue	36%	2%	26%	2%
Hypertension	13%	7%	4%	2%
Cardiac Disorders	10%	3%	8%	2%
Myocardial Infarction	0.3%	0.3%	0.5%	0.5%
LFT Abnormalities*	1%	<1%	1%	<1%
Seizure	<1%	<1%	<1%	0.0%

Abiraterone and Enzalutamide Sequencing

	N	Prior Docetaxel	PSA ≥30% (%)	PSA ≥50% (%)	Median TTP, mo	Median PFS, mo
ABIRATERONE (AFTER ENZALUTMIDE)						
Noonan	**27**	**Y**	**11**	**4**	**-**	**3.5**
Loriot	**38**	**Y**	**18**	**8**	**-**	**2.7**
ENZALUTMIDE (AFTER ABIRATERONE)						
Schrader	**35**	**Y**	**37**	**29**	**4.0**	**-**
Bianchini	**39**	**Y**	**41**	**13**	**2.2**	**2.8**
Badrising	**61**	**Y**	**46**	**21**	**4.0**	**2.8**
Cheng	**122**	**Y**	**39**	**26**	**-**	**-**
Azad	**68**	**Y**	**-**	**22**	**4.6**	**-**
Cheng	**28**	**N**	**40**	**36**	**-**	**-**
Azad	**47**	**N**	**-**	**26**	**6.6**	**-**

Noonan KL et al. *Ann Oncol*. 2013;24:1802-1807; Loriot Y et al. *Ann Oncol*. 2013;24:1807-1812; Schrader AJ et al. *Eur Urol*. 2014;65:30-36; Bianchini D et al. *Eur J Cancer*. 2014;50:78-84; Badrising S et al. *Cancer*. 2014;12:968-975; Cheng et al. *J Clin Oncol*. 2014;32(suppl 4):Abstract 18; Azad et al. Eur Urol. 2015; 67:23-29

Docetaxel After Abiraterone

	N	% Patients with PSA decline >50%	Partial Response, %	Median Time to PSA Progression (months)	Median OS (months)	Chemo Cycles
Mezynski All Patients	35	25	11	4.6	12.5	6 (2-12)
Mezynski ABI "Refractory"	8	0	0	-	-	3 (2-10)
Aggarwal All Patients	14	43	33	4.3	-	
Azad ABI Responders	14	28	NR	3.4	8.9	4 (1-13)
Azad ABI Non-Responders	26	36	NR	3.1	11.1	6 (1-10)
DeBono COU-302	265	47	NR	7.6	NR	3 months

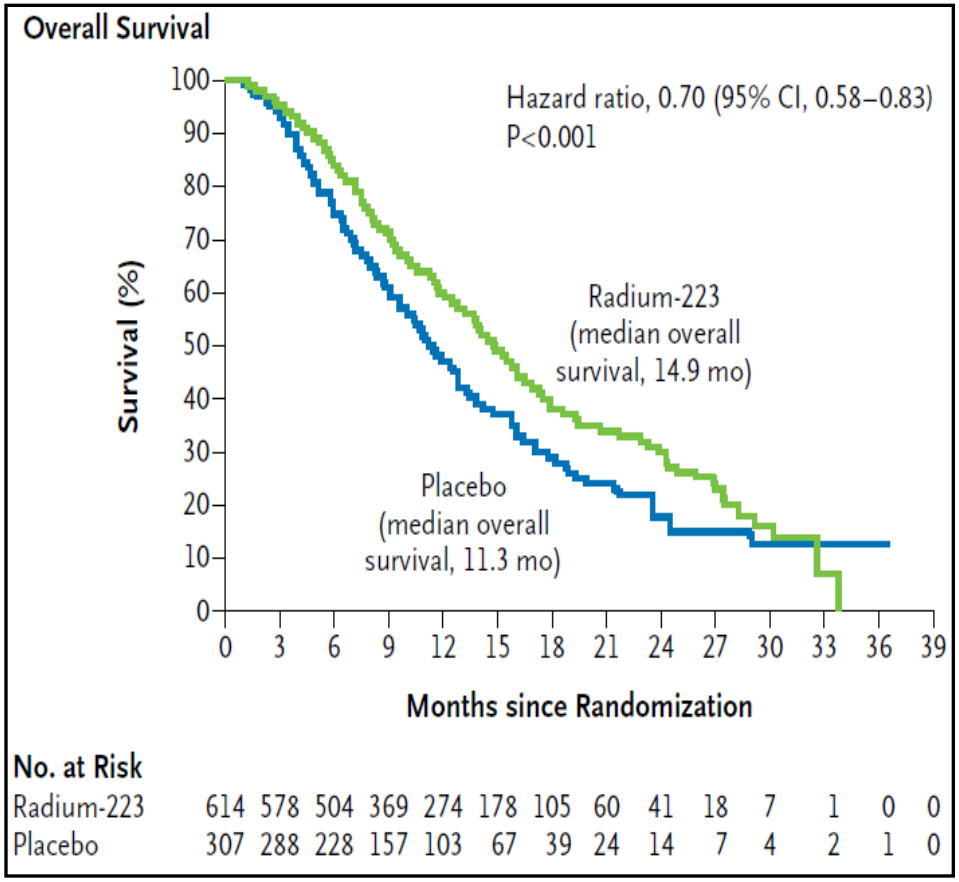
1. Mezynski J et al. *Ann Oncol*. 2012;23:2943-2947. 2. Aggarwal RR. *J Clin Oncol.* 2012;30(suppl 5):Abstract 196.
3. Azad A et al. *J Clin Oncol*. 2014;32(suppl 4):Abstract 97. 4. De Bono JS et al. *J Clin Oncol.* 2015;33 (suppl 7):Abstract 184)

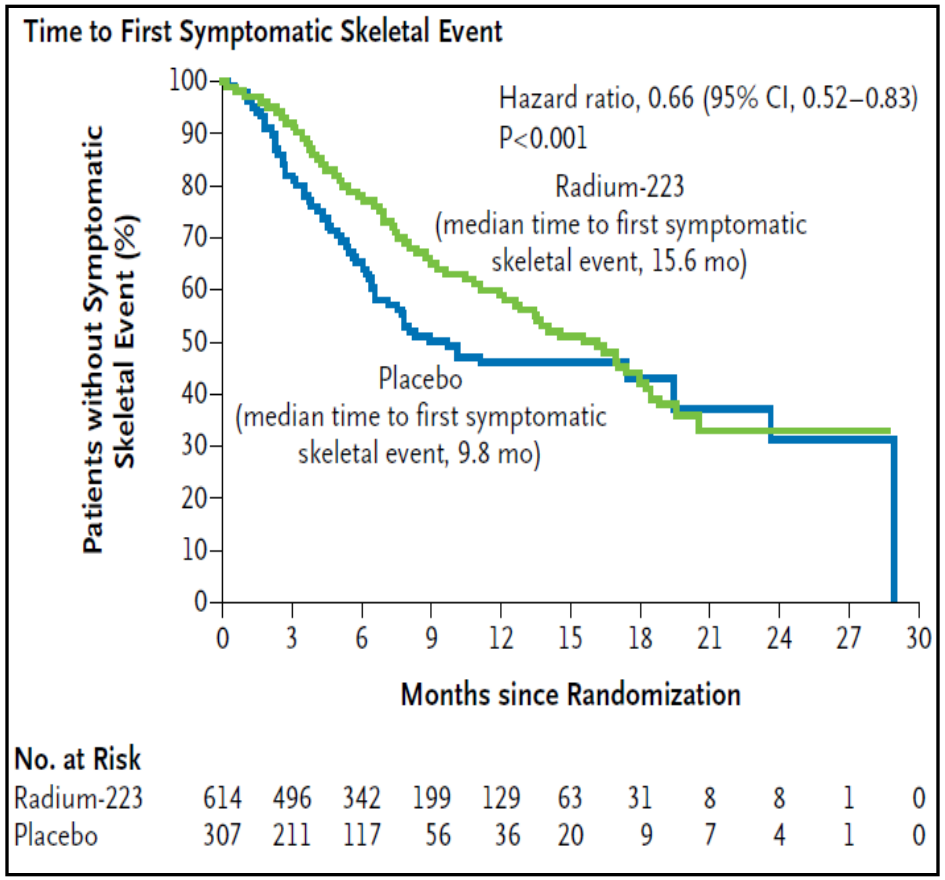
Cabazitaxel After Abiraterone/Enzalutamide

	N	Prior Docetaxel	Prior AA or ENZA	% Patients With PSA Decline ≥50%	Objective Response Rate, %	Median PFS, mo	Median OS, mo
Pezaro[1]	**37**	**Y**	**Y**	**39**	**14**	**4.6**	**15.8**
Sella[2]	**23**	**Y**	**Y**	**30**	**-**	**-**	**8.2**
Saad[3]	**26**	**Y**	**Y**	**43**	**-**	**5.9**	**-**

1. Pezaro CJ et al. *Eur Urol.* 2014;65:270-273. 2. Sella A et al. *J Clin Oncol*. 2013;31(suppl 6):Abstract 186. 3. Saad F et al. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 5062)

Radium-223: ALSYMPCA Trial





C. Parker et al, NEJM, 369:213, 2013

Radium-223: ALSYMPCA Trial

Table 2. Main Secondary Efficacy End Points in the Intention-to-Treat Population.

End Point	Radium-223 (N=614)	Placebo (N=307)	Hazard Ratio (95% CI)	P Value
Median time to first symptomatic skeletal event — mo	15.6	9.8	0.66 (0.52–0.83)	<0.001
Median time to increase in total alkaline phosphatase level — mo	7.4	3.8	0.17 (0.13–0.22)	<0.001
Median time to increase in PSA level — mo	3.6	3.4	0.64 (0.54–0.77)	<0.001
Patients with ≥30% reduction in total alkaline phosphatase response — no. /total no. (%)	233/497 (47)	7/211 (3)		<0.001
Patients with normalization of total alkaline phosphatase level — no./total no. (%)*	109/321 (34)	2/140 (1)		<0.001

C. Parker et al, NEJM, 369:213, 2013

Radium-223: ALSYMPCA Trial

Table 3. Adverse Events That Occurred in at Least 5% of Patients in Either Study Group in the Safety Population.

Adverse Event	Radium-223 (N = 600)				Placebo (N = 301)			
	All Grades	Grade 3	Grade 4	Grade 5*	All Grades	Grade 3	Grade 4	Grade 5*
	number of patients (percent)							
Hematologic								
Anemia	187 (31)	65 (11)	11 (2)	0	92 (31)	37 (12)	2 (1)	1 (<1)
Thrombocytopenia	69 (12)	20 (3)	18 (3)	1 (<1)	17 (6)	5 (2)	1 (<1)	0
Neutropenia	30 (5)	9 (2)	4 (1)	0	3 (1)	2 (1)	0	0
Nonhematologic								
Constipation	108 (18)	6 (1)	0	0	64 (21)	4 (1)	0	0
Diarrhea	151 (25)	9 (2)	0	0	45 (15)	5 (2)	0	0

C. Parker et al, NEJM, 369:213, 2013

My Practice

- CRPC: First-Line
  - Abiraterone acetate + prednisone or enzalutamide - choice depending on patient factors
  - Consider “legacy” second-line hormone therapies (NSAA, corticosteroids) in asymptomatic, slowly progressive, good prognosis patients
- CRPC: Second-Line
  - Docetaxel if chemotherapy eligible
  - Radium-223 if bone metastases, no significant soft tissue disease, and chemotherapy ineligible
- CRPC: Third-line
  - Radium-223 if bone metastases and no significant soft tissue disease
  - Cabazitaxel if chemotherapy eligible
- Liberal use of palliative radiotherapy
- Always consider clinical trials