

Radium-223 in the treatment sequencing of mCRPC

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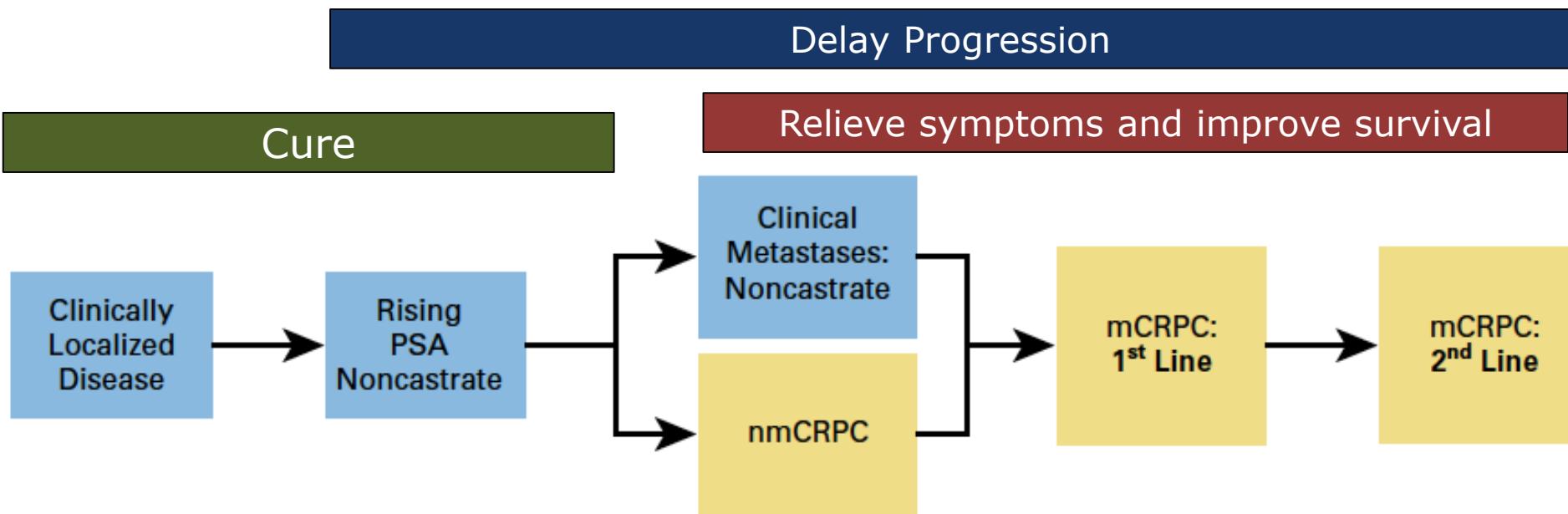
Disclosures

- **Honoraria:** Bayer, Roche, MSD, Novartis, Janssen, Astellas.
- **Research Funding:** Janssen, Astellas, Pfizer.
- **Consultant:** Janssen, Roche, MSD, BMS, Astellas, Bayer.

Agenda

- **Clinical States**
- **Current treatment paradigm**
- **Real life data of Ra223**
- **New data regarding:**
 - Dose / schedule modifications
 - Potential Biomarkers
 - Sequencing

Main treatment goals and endpoints



Overall Survival (OS)

Quality of Life (QoL)

Biochemical relapse

Metastasis-free survival (MFS)

Progression-free survival (PFS)

PSA < 0.2 ng/mL

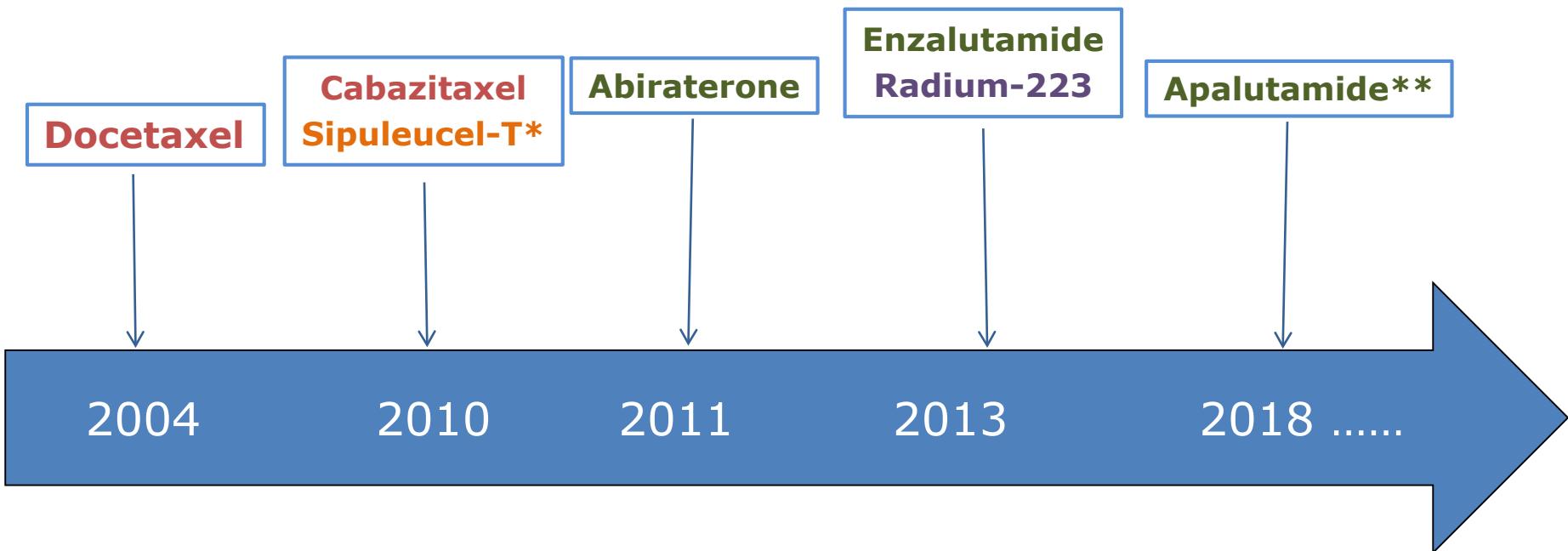
PSA nadir (< 0.2 ng/mL)

Biochemical Progression-free survival

Radiographic Progression-free survival (rPFS)

Skeletal related events (SRE)

CRPC Therapy Timeline – Survival prolonging therapies



* not available in Brazil

** indicated for M0 CRPC

Life-prolonging agents for mCRPC available in Brazil

Study	Year	Indication	N	PSA decline >50%	mPFS (months)	Overall Survival		
						Median	HR	P value
Docetaxel vs. mitoxantrone ^a	2004	1 st line chemo	1,006	45% vs 32%	NS	18.9 vs 16.5	0.76	0.009
Cabazitaxel vs. mitoxantrone ^a	2010	Post docetaxel	755	39% vs 18%	2.8 vs 1.4	15.1 vs 12.7	0.70	<0.001
Abiraterona vs. placebo ^a	2012	Pre docetaxel	1,088	62% vs 24%	16.5 vs 8.2	35.3 vs 30.1	0.79	0.0151
Enzalutamide vs. placebo	2014	Pre docetaxel	1,717	78% vs 3%	NR vs 3.9	35.3 vs. 31.3	0.77	0.0002
Radium-223 vs. Placebo	2013	Pre and Post Docetaxel	921	16% vs 6%	15.6 vs 9.8 ^b	14.9 vs 11.3	0.70	<0.001

a. Prednisone in both arms

b. PSA decline > 30%

c. Time to 1st symptomatic skeletal event

N Engl J Med 2004; 351: 1502-1512

Eur Urol 2014; 5:815-825

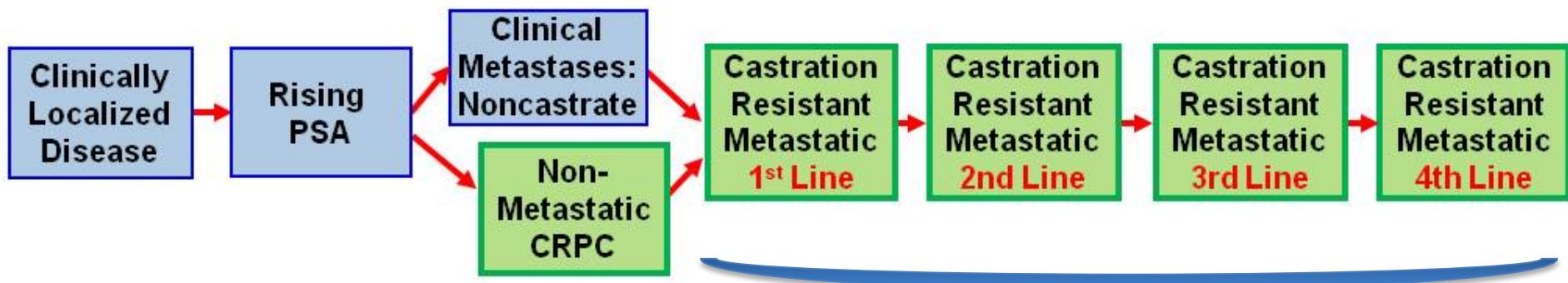
N Engl J Med 2013; 369: 213-223

Lancet 2010; 376: 1147-1154

N Engl J Med 2014; 371: 424-433

PCWG 3

Eligibility: A Revised Clinical States Model to Account for the Effect of Prior Therapy(ies) on Disease Biology



How to sequence the available life-prolonging agents?

- Histology
- Prior therapies

Symptoms / LKPC

Predictive biomarkers for treatment selection are urgently needed

- AR-V7, DDR, MSI, others?

Abiraterone

Enzalutamide

Docetaxel

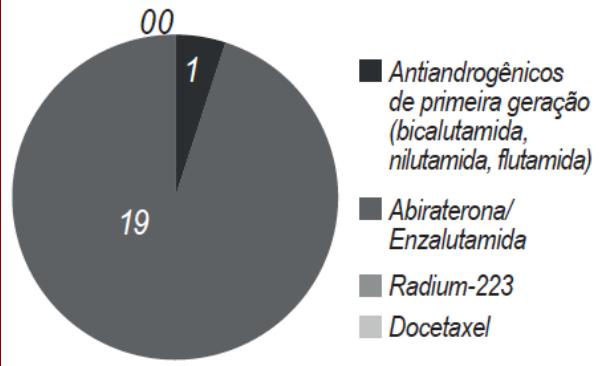
Cabazitaxel

Radium-223

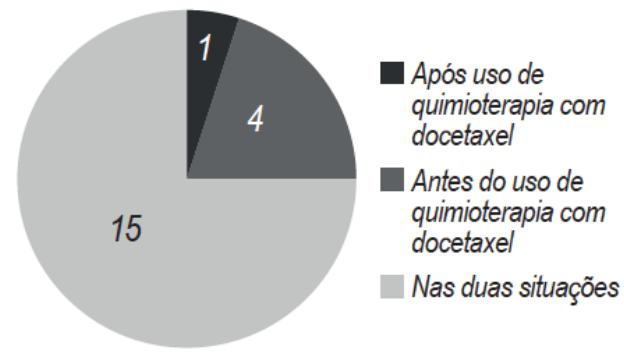
First brazilian consensus of advanced prostate cancer: recommendations for clinical practice

Andre Dekee Sasse ¹, Evanius Garcia Wiermann ², Daniel Herchenhorn ³, Diogo Assed Bastos ^{4,5}, Fabio A. Schutz ⁶, Fernando Cotait Maluf ^{6,7}, George Coura Filho ⁸, Igor Alexandre Protzner Morbeck ⁹, Juliano J. Cerci ¹⁰, Oren Smaletz ⁷, Volney Soares Lima ¹¹, Ari Adamy Jr. ¹², Franz Santos de Campos ³, Gustavo Franco Carvalhal ¹³, Leandro Casemiro Cezar ¹⁴, Marcos Francisco Dall’Oglio ¹⁵, Marcus Vinicius Sadi ¹⁶, Rodolfo Borges dos Reis ¹⁷, Lucas Nogueira ¹⁸

19. Qual seria a recomendação preferencial de tratamento em primeira linha no CPRCm para pacientes assintomáticos se todas as opções estivessem disponíveis?



33. Em que momento o radium-223 deverá ser utilizado para pacientes com CPRCm e metástases ósseas sintomáticas sem metástases viscerais?



Clinical Trial vs Real World Data

	ALSYMPCA	ERA 223	REASSURE	iEAP	FLATIRON
Dates	2008 – 2011	2014 – 2016	2014 – 2017	2012 – 2013	2013 – 2017
N	614	401	1435	708	625
Median age	71	71	73	72	73
Prior docetaxel	57%	0	37%	60%	26%
Asymptomatic	2%	49%	NR	19%	NR
Concurrent steroids	<50%	100%	NR	NR	NR
Use of Bone health agent, %	41%	39%	39%(concomitant)	34% (concomitant)	67% (prior)
PSA, median	146	30	59	143	38
ALP	211	129	22% ≥ 220	149	108
LDH	315	224	21% ≥ 250	NR	196
Median OS (mos)	14.9	30.7	15.5	15.9	15.2
Fracture rate% Pathological/S AE	4/NR	18/26	NR/3	6/NR	10/NR

Radium 223 – important questions

- Combination with abiraterone or enzalutamide
 - ERA-223 trial
 - R-223 + Enzalutamide trials – phase II randomized looks safe and promising (Maughan B.L, et al. ASCO 2018)
- Increase dose or number of cycles
- Re-treatment – is it safe?
- Treatment sequencing – real life data

Radium-223 and ERA Trial

EMA guidance on radium-223 dichloride in prostate cancer

The European Medicines Agency (EMA) has issued a formal warning against using the drug Xofigo (radium-223 dichloride) in combination with Zytiga (abiraterone acetate) plus prednisone or prednisolone in patients with metastatic prostate cancer because of an increased risk of death and fractures in a review of an ongoing phase 3 trial by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC).

Radium-223 dichloride, which has been approved for use in patients with prostate cancer-derived symptomatic bone metastases since November, 2013, was given in combination with abiraterone acetate plus prednisone or prednisolone alone to patients, some of whom had not previously received chemotherapy and had no symptoms or had only mild symptoms. In the announcement made on March 9, 2018, preliminary data showed that 35% of patients

using radium-223 dichloride in combination with abiraterone acetate and prednisone or prednisolone alone have died to date, compared with 28% of patients who were given placebo with abiraterone acetate plus prednisone or prednisolone alone.

The prevalence of fractures was also higher in the radium-223 dichloride combination groups (26%) than the placebo combination groups (8%). The study sponsor Bayer has unblinded the trial, the radium-223 dichloride-based combinations are no longer being administered, and all patients are undergoing close monitoring.

The EMA advises not to use this treatment combination, and to stop and find an alternative treatment for those patients already on any of these combinations.

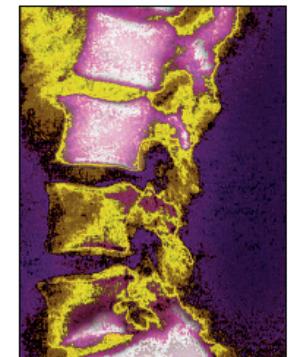
"In view of the seriousness of the events reported, the PRAC has taken action by introducing a

contraindication as a temporary measure to protect patients' safety while an in-depth review of the benefits and risks of Xofigo is ongoing", commented Camelia Enachioiu (EMA, London, UK).

"[These results] are quite surprising and should be reported in full and compared with the favourable results from previous studies of this combination", added Ugo de Giorgio (Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola, Italy).

"The EMA statement should have a limited impact on daily clinical practice", mediated Orazio Caffo (Santa Chiara Hospital, Trento, Italy). "The trial results should be applied to the combined use only and to date do not imply concerns about the sequential use of these agents."

Elizabeth Gourd



Franzini Iamad/RCDI/Science Photo Library

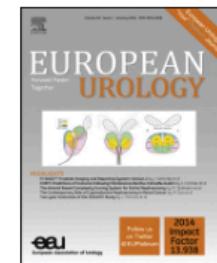
Lancet Oncol 2018

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[http://dx.doi.org/10.1016/S1470-2045\(18\)30216-X](http://dx.doi.org/10.1016/S1470-2045(18)30216-X)

For the formal warning by the European Medicines Agency see http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Xofigo/human_referral_prac_000071.jsp&mid=WC0b01ac05805c516f



Research Letter

The Case Against the European Medicines Agency's Change to the Label for Radium-223 for the Treatment of Metastatic Castration-resistant Prostate Cancer

Joe M. O'Sullivan^{a,}, Daniel Heinrich^b, Nicholas D. James^c, Sten Nilsson^d, Piet Ost^e, Christopher C. Parker^f, Bertrand Tombal^g*

We write regarding a recent label change recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) and implemented by the European Medicines Agency (EMA) for the bone-targeted agent radium-223 (Xofigo) [1].

The EMA has concluded its review of the cancer medicine and has recommended restricting its use to patients who have had two previous treatments for metastatic castration-resistant prostate cancer (mCRPC) or who cannot receive other treatments. Depending on how these recommendations are interpreted, they might effectively restrict the use of this agent to the terminal phase of the illness. We believe that these restrictions are not justified on the basis of the available evidence and could result in fewer patients benefiting from this drug.

Radium 223 – important questions

- Combination with abiraterone or enzalutamide
 - ERA-223 trial
 - R-223 + Enzalutamide trials – phase II randomized looks safe and promising (Maughan B.L, et al. ASCO 2018)
- Increase dose or number of cycles
- Re-treatment – is it safe?
- Treatment sequencing – real life data

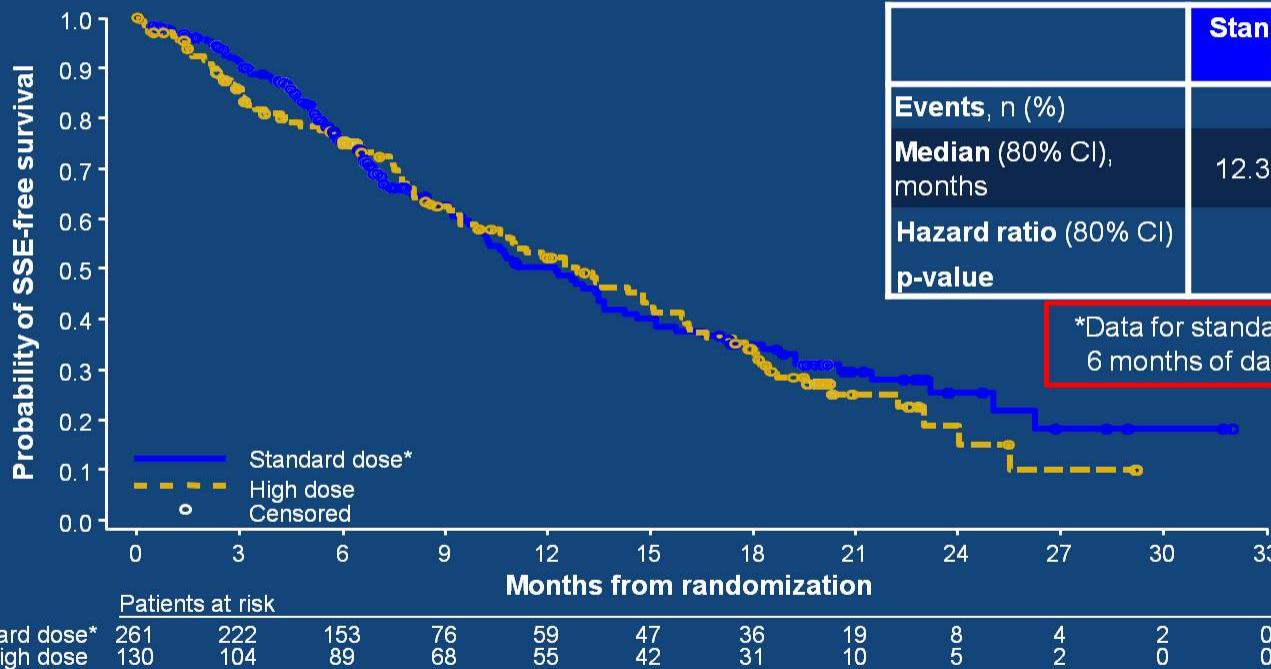
Study design (n=391)



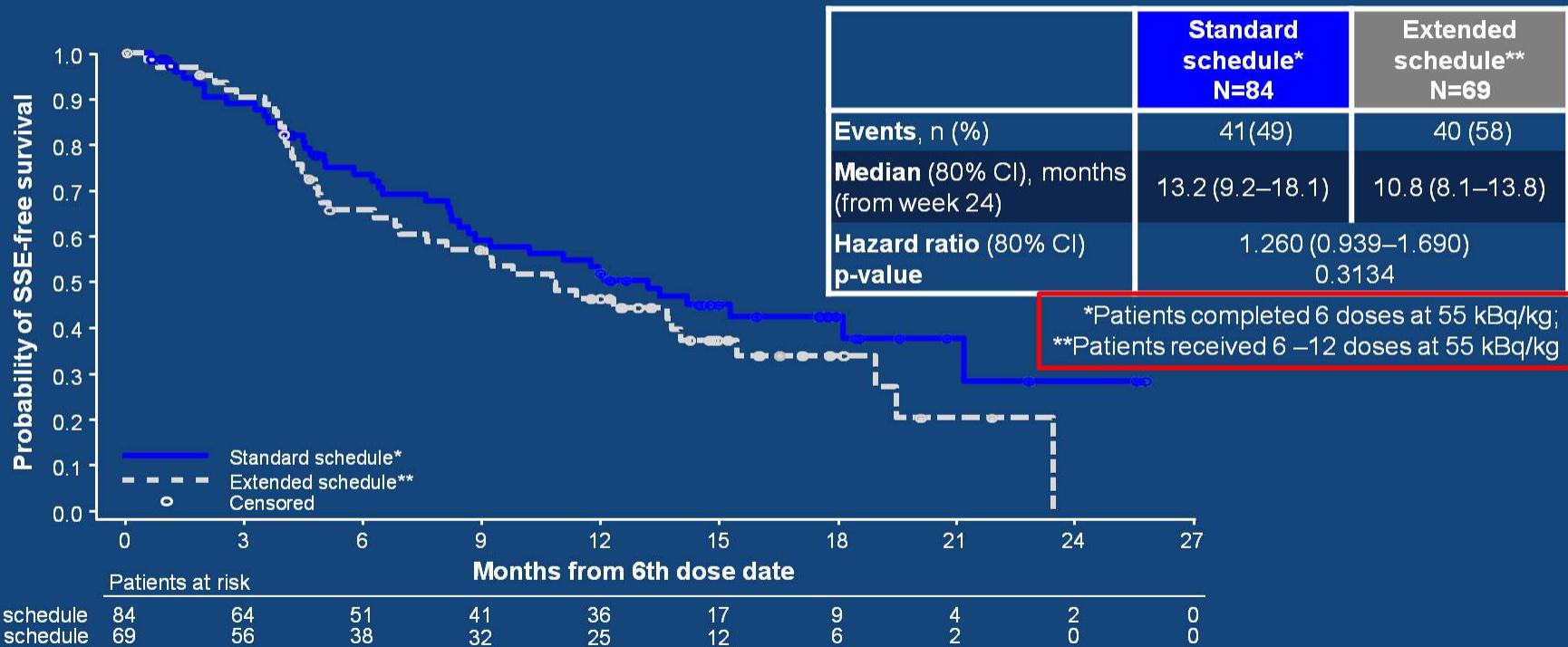
- Stratification:
 - Prior chemotherapy: ≤1 prior regimen vs >1 prior regimen
 - Total ALP: <220 U/L vs ≥220 U/L
 - Worst pain score by BPI: ≤4 vs >4
- Concomitant therapy allowed: hormonal, bisphosphonates, RANK ligand inhibitors

ALP, alkaline phosphatase; BPI, brief pain inventory; SSE-free survival, symptomatic skeletal event-free survival

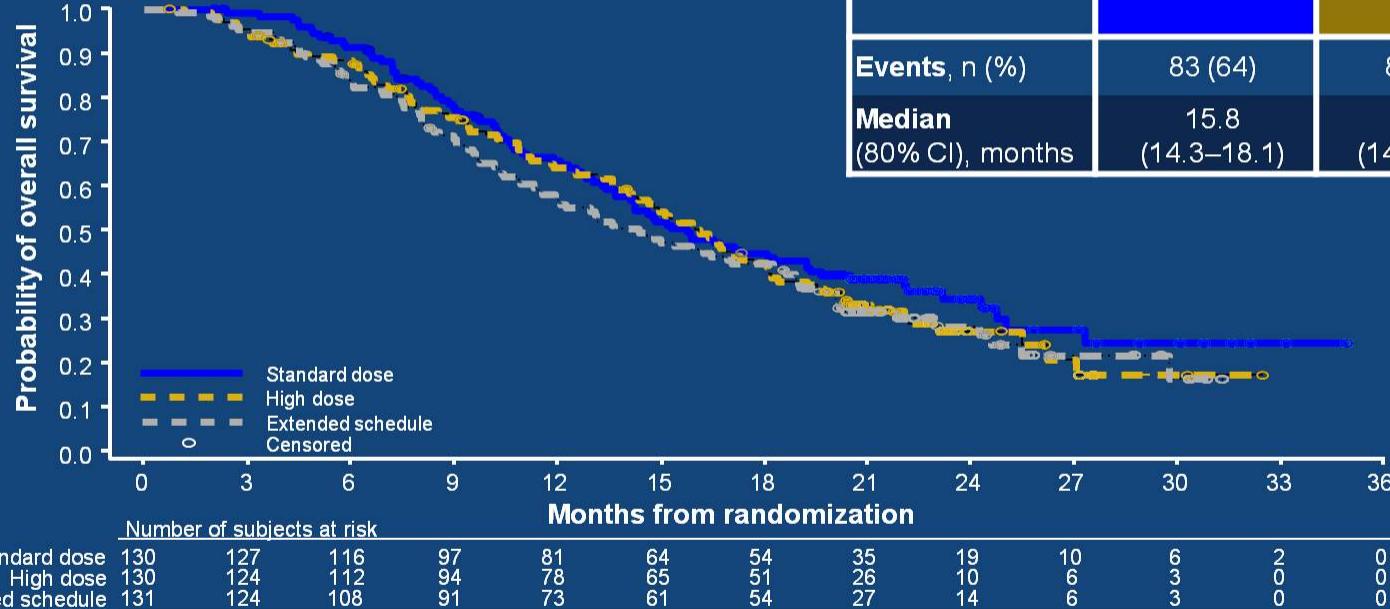
SSE-FS: High vs standard dose



SSE-FS: Extended vs standard schedule



Overall survival



	Standard dose N=130	High dose N=130	Extended schedule N=131
Events, n (%)	83 (64)	89 (68)	93 (71)
Median (80% CI), months	15.8 (14.3–18.1)	16.0 (14.7–17.2)	14.4 (12.1–16.5)

Common treatment-emergent adverse events occurring in ≥20% of patients

All grades	Standard dose N=125	High dose N=124	Extended schedule N=121
Fatigue	39 (31)	37 (30)	35 (29)
Anemia	31 (25)	34 (27)	31 (26)
Nausea	31 (25)	29 (23)	28 (23)
Decreased appetite	31 (25)	24 (19)	26 (21)
Diarrhea	26 (21)	28 (23)	26 (21)
Bone pain	26 (21)	19 (15)	28 (23)
Back pain	20 (16)	19 (15)	25 (21)

Data are n (%)

Approved Use of Radium 223

- Monitor blood counts at baseline and prior to every dose
- Prior to first administering :
 - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$
 - Platelet count $\geq 100 \times 10^9/L$
 - Hemoglobin $\geq 10 \text{ g/dL}$
- Prior to subsequent administrations:
 - ANC $\geq 1 \times 10^9/L$
 - Platelet count $\geq 50 \times 10^9/L$
- Discontinue if hematologic values do not recover within 6 to 8 weeks after the last administration

Radium-223 Re-treatment in an International, Open-Label, Phase 1/2 Study in Patients With Castration-Resistant Prostate Cancer and Bone Metastases: 2-Year Follow-up

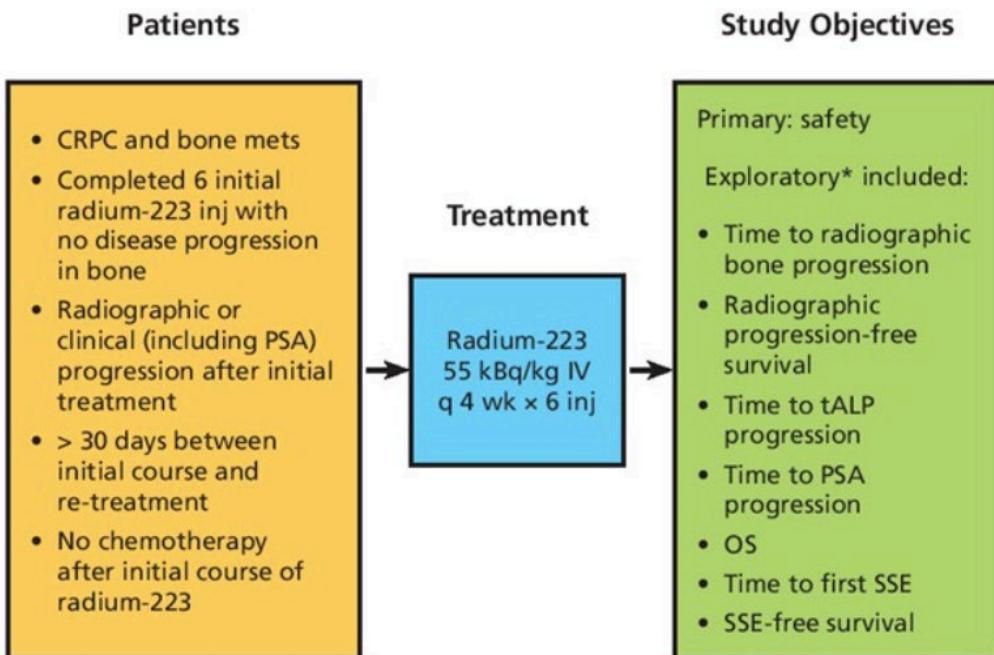


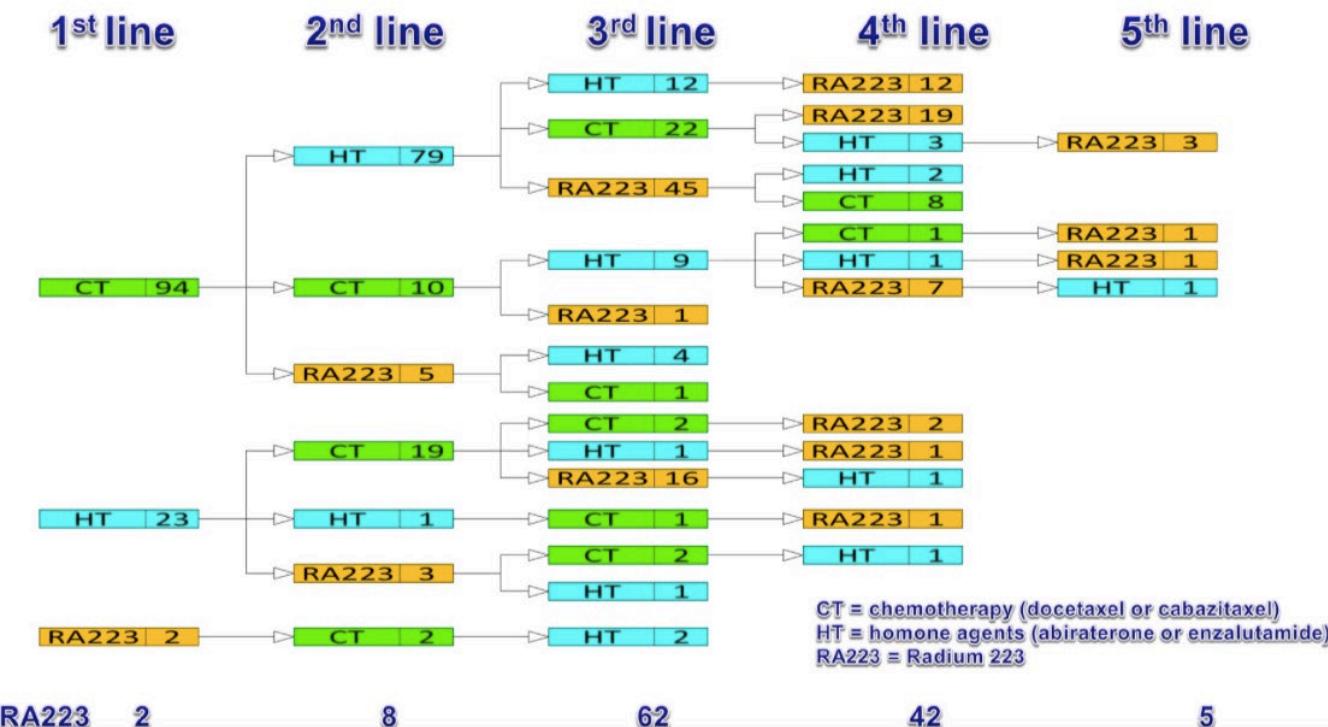
Table 1. Demographics and Baseline Characteristics

	Re-treatment N = 44
Age, median (range), y	71 (52-91)
ECOG PS, n (%)	
0	14 (32)
1	27 (61)
2	3 (7)
Extent of disease, bone metastases, n (%)	
< 6	18 (41)
6-20	15 (34)
> 20, not superscan	6 (14)
Superscan	5 (11)
Prior systemic anticancer therapies, n (%)	
Docetaxel	20 (45)
Abiraterone	27 (61)
Enzalutamide	13 (30)
Prior bone-supportive therapies, n (%)	
Bisphosphonates	5 (11)
Denosumab	21 (48)
Laboratory values, median (range)	
Hemoglobin, g/dL	12 (9-16)
Albumin, g/L	39 (32-44)
PSA, µg/L	68 (< 1-2349)
LDH, U/L	203 (115-532)
tALP, U/L	85 (29-705)

mCRPC treatment sequencing - Italian Data

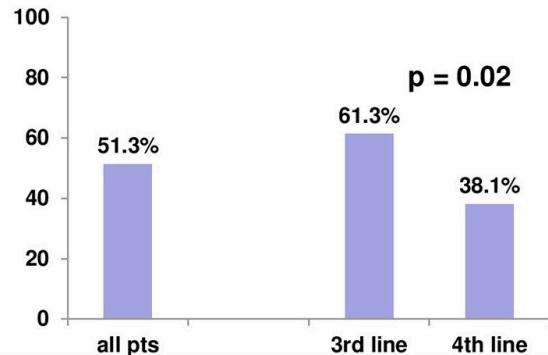
Sequencing Radium 223 (RA223) for metastatic castration-resistant prostate cancer (mCRPC) patients (pts) in the daily practice: preliminary results from a retrospective study in Italian Centers.

N= 119 patients



mCRPC treatment sequencing - Italian Data

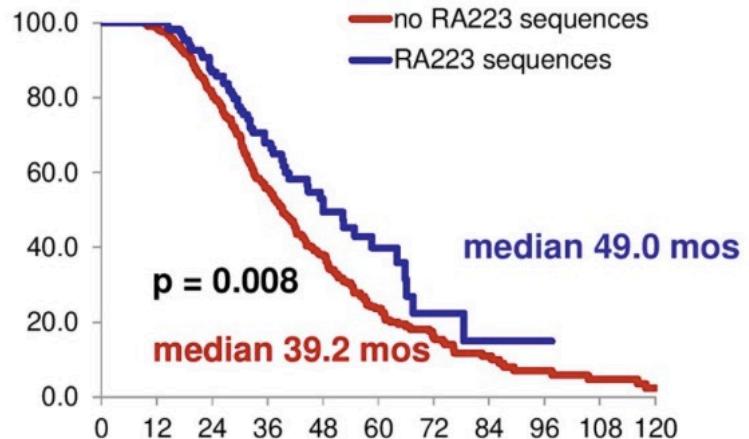
RA223 full delivery (6 courses) rates



Biochemical and objective response rates

PSA reduction > 50%	7.2%
Objective partial response	11.3%
Objective stable disease	24.5%

Overall survival from 1st treatment line for mCRPC *



*contemporary series of 405 pts w/o visceral mets
treated with 2 ADs after DOC

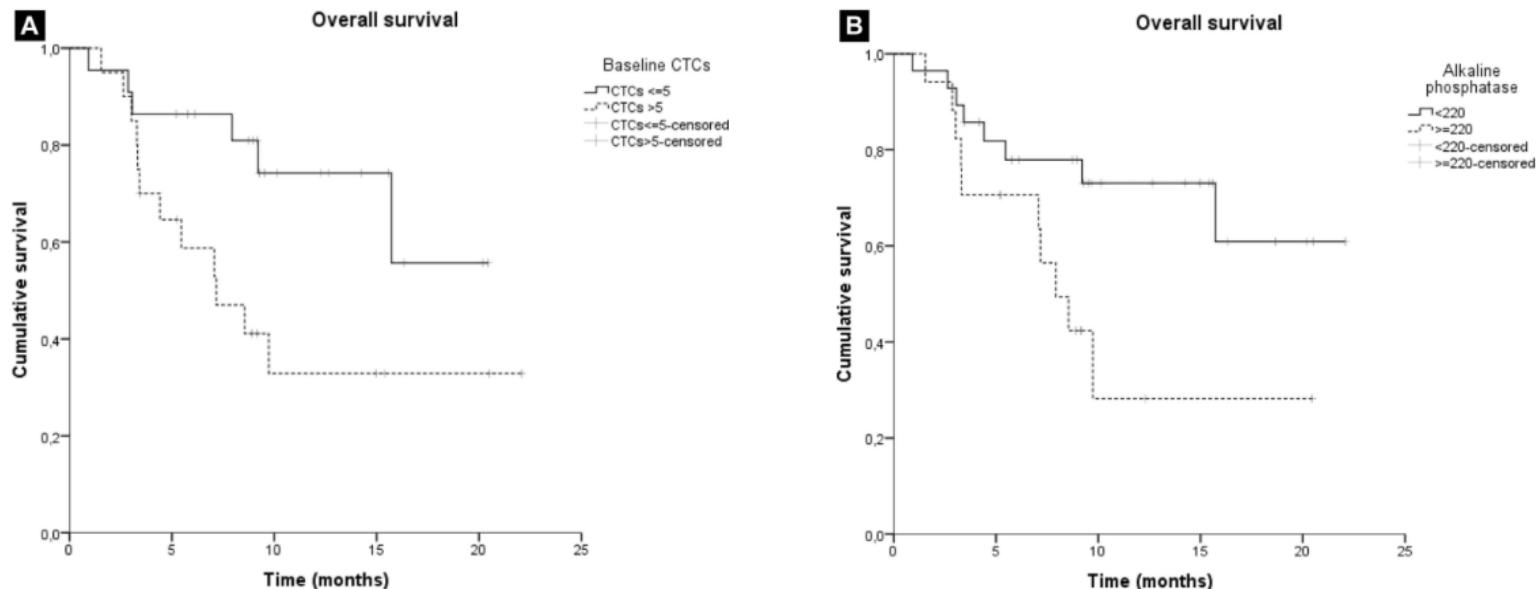
Potential biomarkers for mCRPC therapy-selection

Potential Predictive Biomarker	Therapy Selection
AR-V7 ^{20,35,40,61}	Not detected: ARS inhibitors Detected: taxane chemotherapy
Activating AR-LBD mutations and/or <i>AR</i> gene amplification ^{62,63} x	Not detected: ARS inhibitors Detected: taxane chemotherapy
CTC heterogeneity ⁶⁴ (Shannon index)	Low (Shannon <1.5): ARS inhibitors High (Shannon ≥1.5): taxane chemotherapy
DDR gene alterations	PARP inhibitors ⁶⁵ or platinum agents ⁶⁶
Microsatellite instability (MSI-high)	Immunotherapy with anti-PD-1 (pembrolizumab) ⁶⁷

Circulating Tumor Cells as a Biomarker of Survival and Response to Radium-223 Therapy: Experience in a Cohort of Patients With Metastatic Castration-Resistant Prostate Cancer

Joan Carles,¹ Daniel Castellano,² María-José Méndez-Vidal,³ Begoña Mellado,⁴ María-Isabel Saez,⁵ Aránzazu González del Alba,⁶ José-Luis Perez-Gracia,⁷ José Jimenez,⁸ Cristina Suárez,¹ Juan M. Sepúlveda,² Ray Manneh,^{2,9} Ignacio Porras,³ Cristina López,¹⁰ Rafael Morales-Barrera,¹ José-Ángel Arranz¹⁰

- N= 45 patients treated with Ra223
- Completed 6 cycles: **CTC≤5: 73% ; CTC >5: 30%, P=0.05**



Platinum Priority – Prostate Cancer

Editorial by XXX on pp. x-y of this issue

Efficacy of Radium-223 in Bone-metastatic Castration-resistant Prostate Cancer with and Without Homologous Repair Gene Defects

*Pedro Isaacsson Velho^a, Fahad Qazi^b, Sayeedul Hassan^c, Michael A. Carducci^{a,d},
Samuel R. Denmeade^{a,d}, Mark C. Markowski^a, Daniel L. Thorek^{a,e}, Theodore L. DeWeese^{a,d,f},
Daniel Y. Song^{a,d,f}, Phuoc T. Tran^{a,d,f}, Mario A. Eisenberger^{a,d}, Emmanuel S. Antonarakis^{a,d,*}*

N= 28 pts: 10 HRD+ (35.7%): BRCA2, ATM, ATR, CHECK2

HRD+ vs HRD- (all treated with Ra223):

- PSA decline >50%: 0% vs 0%
- ALP decline > 30%: 80% vs 39%, P=0.04
- Time to ALP progression: 10.4 vs 5.8 months, P=0.005
- Overall Survival: 36.9 vs 19 months, P=0.11

CONCLUSIONS

- Radium-223 is a life-prolonging therapy for CRPC with bone predominant disease.
- Studies have demonstrated a good tolerability and safety profile.
- Radium-223 is also associated with longer time to symptomatic skeletal event, pain control and improved quality of life.
- The best timing for use is not currently known – but more important than which drug to use first is to sequence the available options.
- Combination to new-generation AR-targeted therapy should not be used at this point.

**Thank you!
Obrigado!**

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