FACULTY OF MEDICINE AND HEALTH SCIENCES

DEPARTMENT OF RADIATION ONCOLOGY AND EXPERIMENTAL CANCER RESEARCH

RADIUM-223

The role in the mCRPC landscape

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CONFLICT OF INTERESTS

Type of affiliation / financial interest	Name of commercial company
Institutional receipt of grants/research supports:	Merck, Bayer, Ferring,
Receipt of honoraria or consultation fees:	Astellas, Bayer, Ferring, Janssen
Participation in a company sponsored speaker's bureau:	None
Stock shareholder:	None
Spouse/partner:	None
Other support (please specify):	None

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BONE HEALTH

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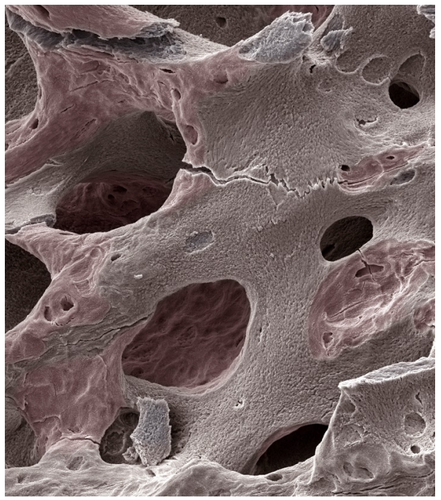
IMPORTANCE OF BONE HEALTH

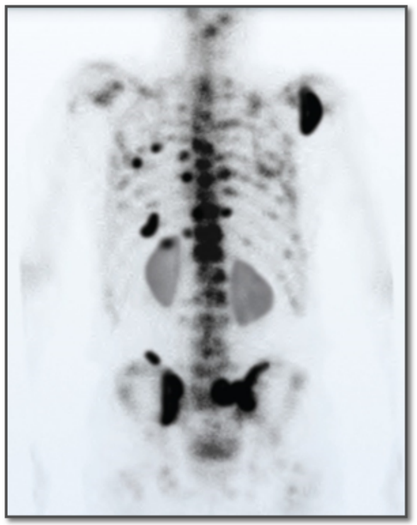
Therapy induces bone loss



50%

+

Bone metastases



90%

=

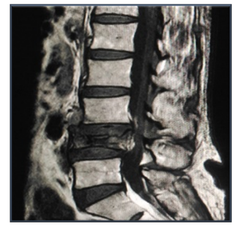
Skeletal-related events (SREs)[3]



Radiation to bone



Pathological fracture



Spinal cord compression



Surgery to bone

10%

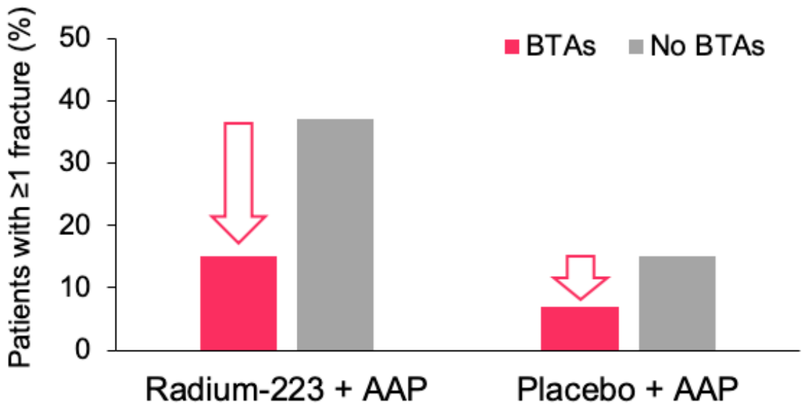
1. Auchus RJ et al. Oncologist 2014;19:1231–40; 2. Morote J et al. Urology 2007;69:500–4; 3. Liu C et al. Cancer Manag Res 2018;10:3809–23

IMPORTANCE OF BONE HEALTH

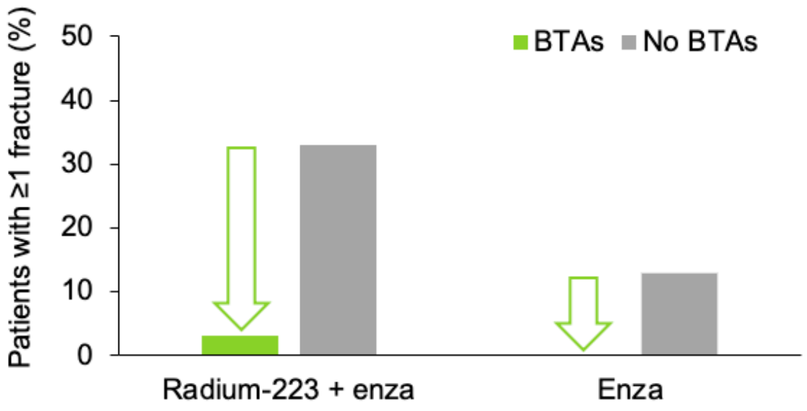
Osteoporosis + Bone metastases ≠ Skeletal-related events (SREs)[3]

BONE HEALTH agents decrease SRE's

ERA-223[1]



PEACE III[2]



WHY RADIO-ISOTOPES?

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BONE METASTASES

- Important cause of debilitating symptoms:
  - Pain, cord compression, SRE

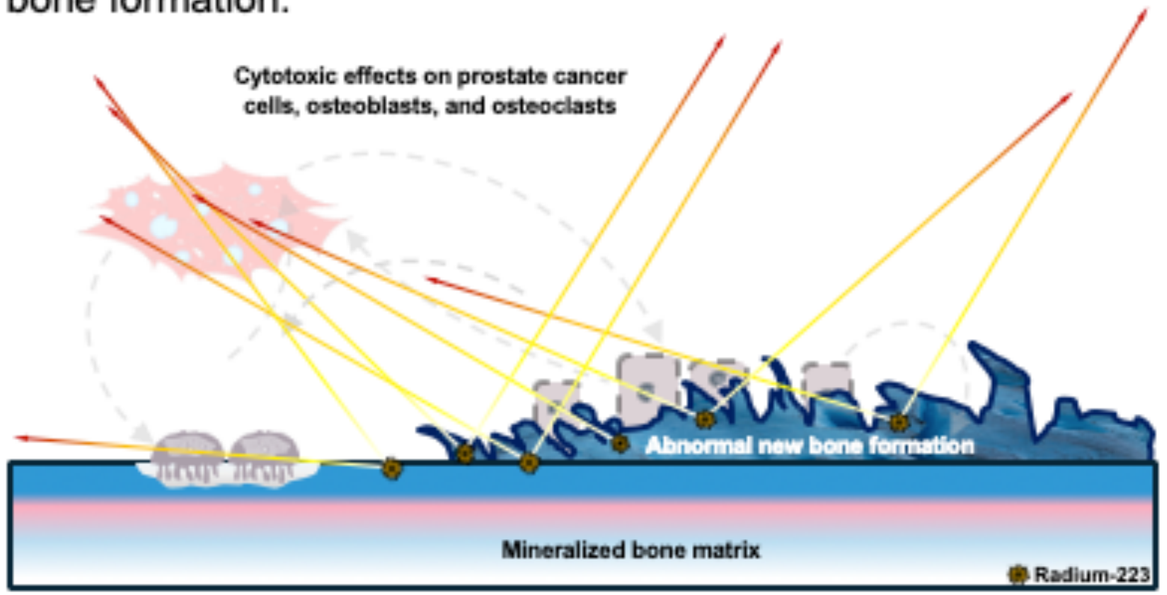
- Important cause of PCa mortality

- Bone metastases are often an initial site and provide a source for further seeding

RADIOISOTOPES

- Preferred homing to areas of bone turnover
- Local irradiation of cancer cells, osteoblast/clasts

Radium-223 is a targeted alpha therapy, that affects the cancer cells and the tumor microenvironment and thus disrupts the vicious cycle of tumor growth and abnormal bone formation.



Adapted from Suominen et al Mol Cancer Ther 2015;14(12 Suppl 2):Abstract nr A109.

ALP, Alkaline phosphatase;
RANKL, Receptor activator of nuclear factor kappa-B ligand

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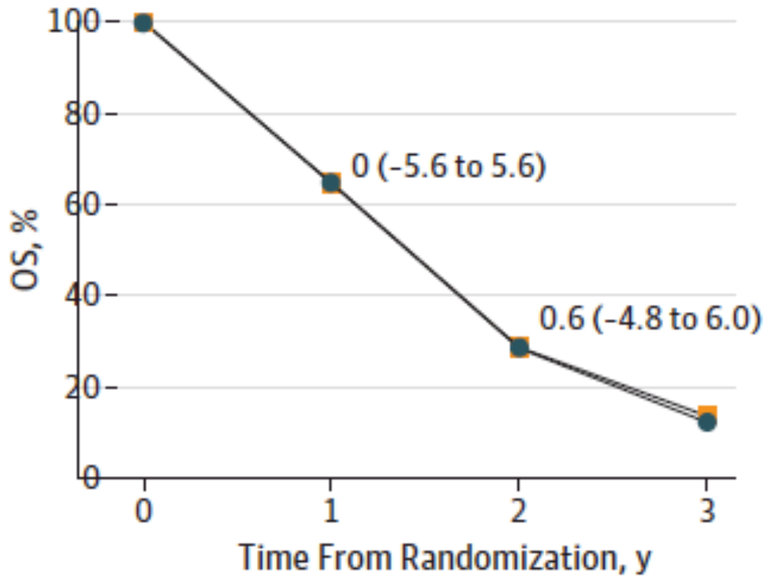
B-EMITTING RADIOISOTOPES

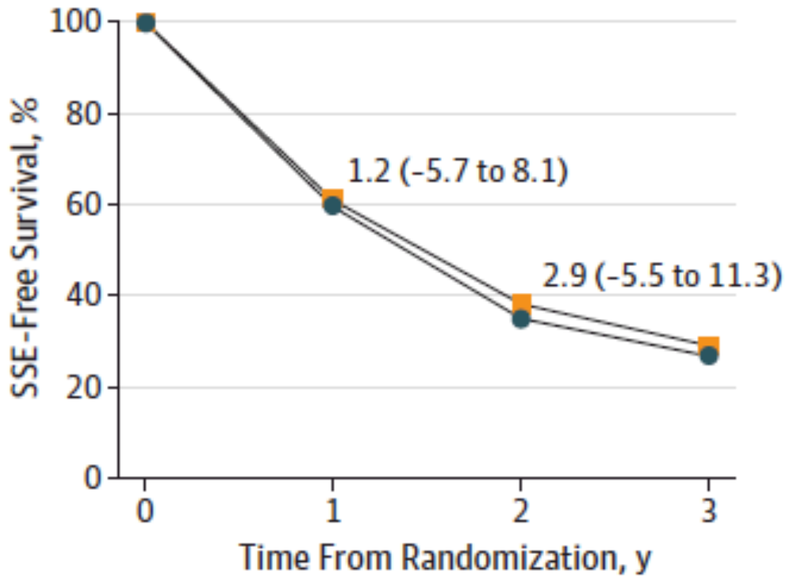
- Improve symptoms, not OS

C OS in β-emitting RI trials



Trials	No. of Deaths/Person-Years		
	0-1	1-2	>2
RI use	193/451	177/223	79/107
No RI use	201/457	181/216	86/106

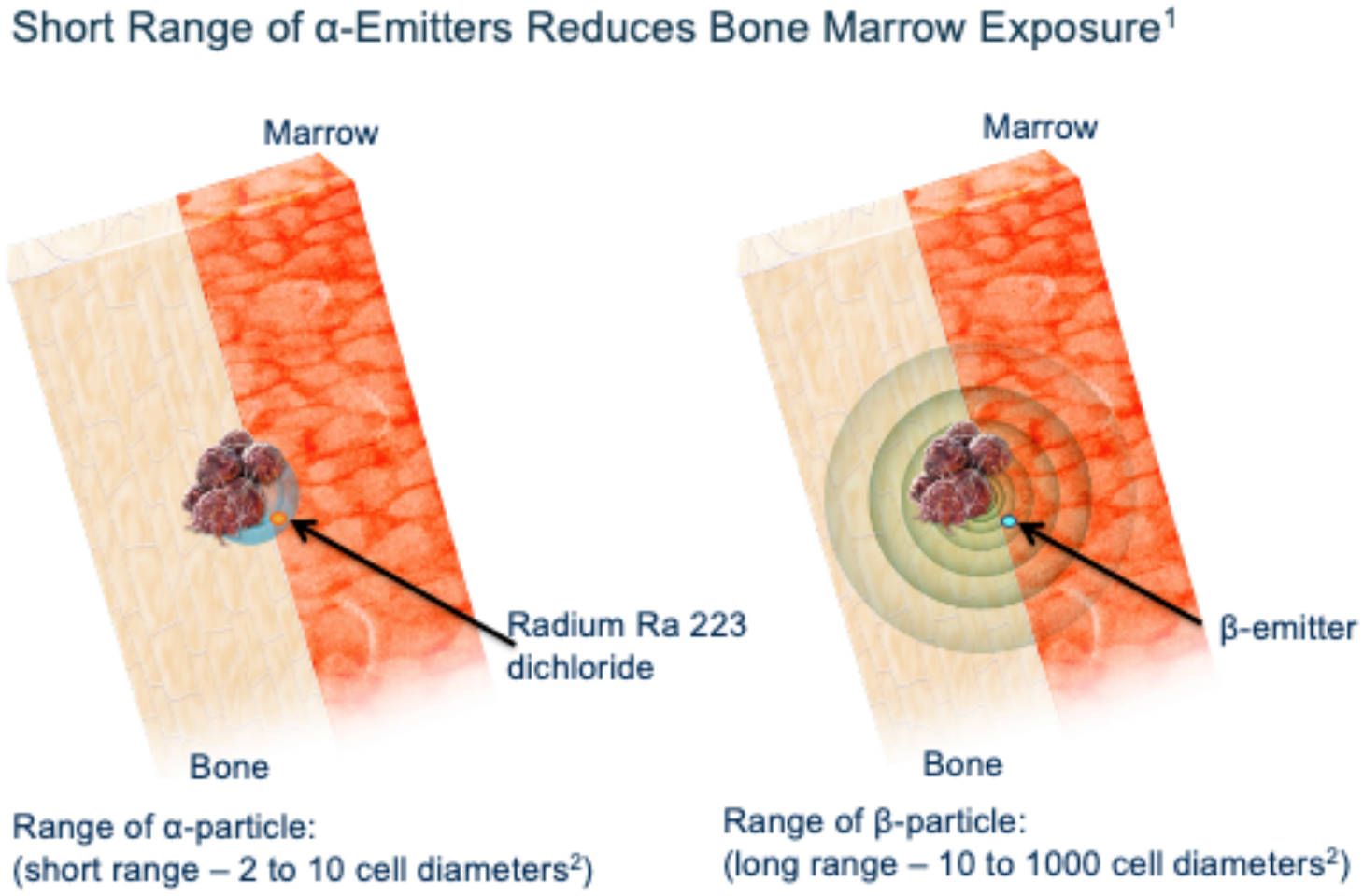
F SSE-free survival in β-emitting RI trials



Trials	No. of SSE Events/Person-Years		
	0-1	1-2	>2
RI use	148/293	48/105	11/43
No RI use	154/294	48/88	7/24

Terrisse et al. JAMA Oncol. doi:10.1001/jamaoncol.2019.4097

A-EMITTING RADIOISOTOPES



Double strand DNA breaks

Single strand DNA breaks

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RADIUM FIRST USE IN HUMANS…











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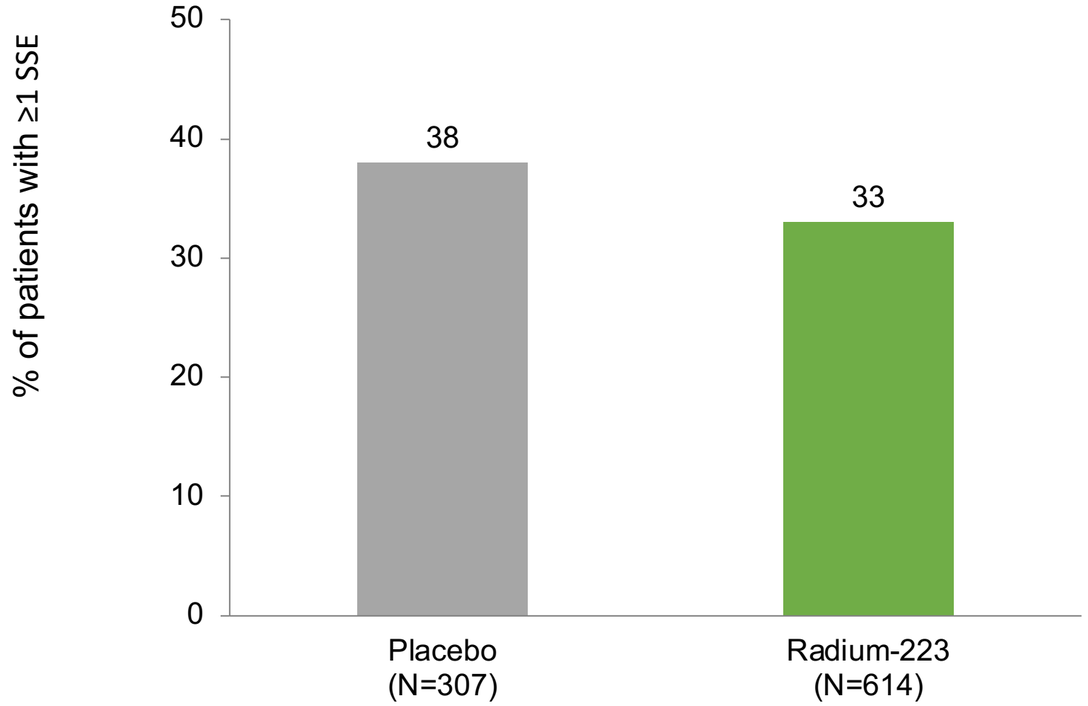
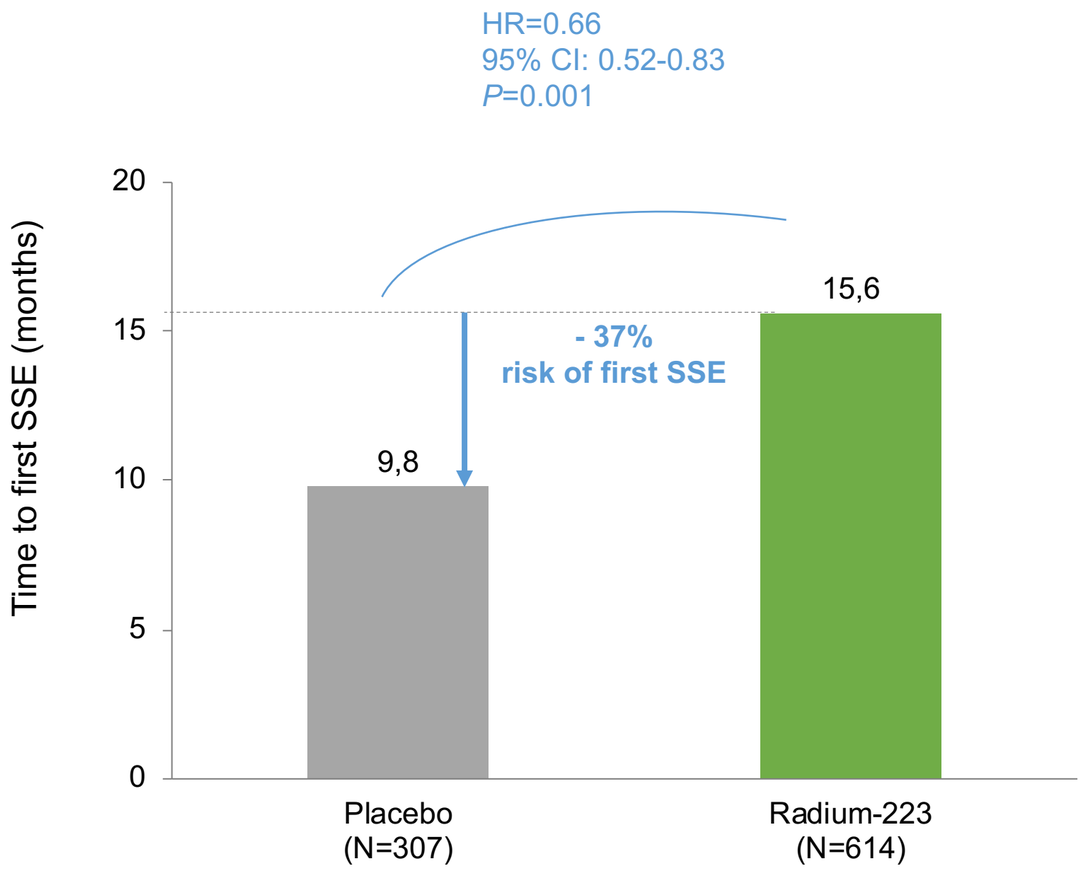
Thanks to K. Muylle for providing this background.

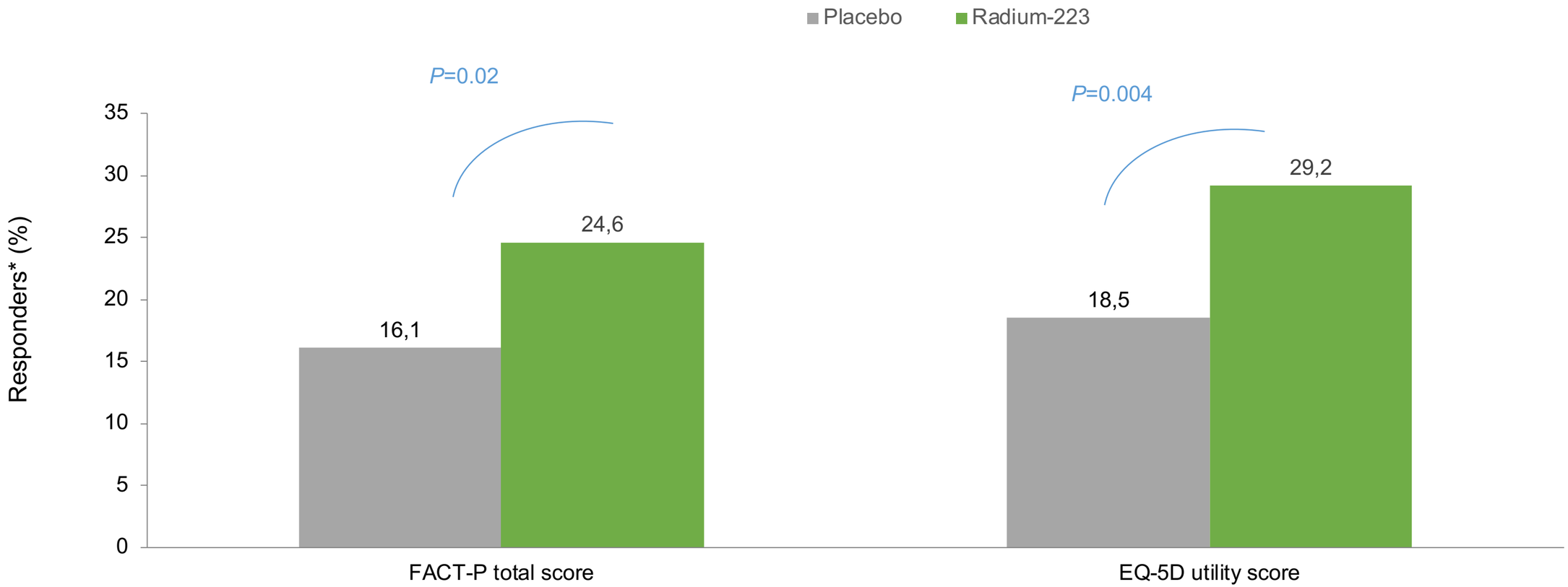
EFFECT OF RADIUM-223 ON SYMPTOMATIC SKELETAL EVENTS (SSE)





Sartor O et al. Lancet Oncol 2014;15:738-46

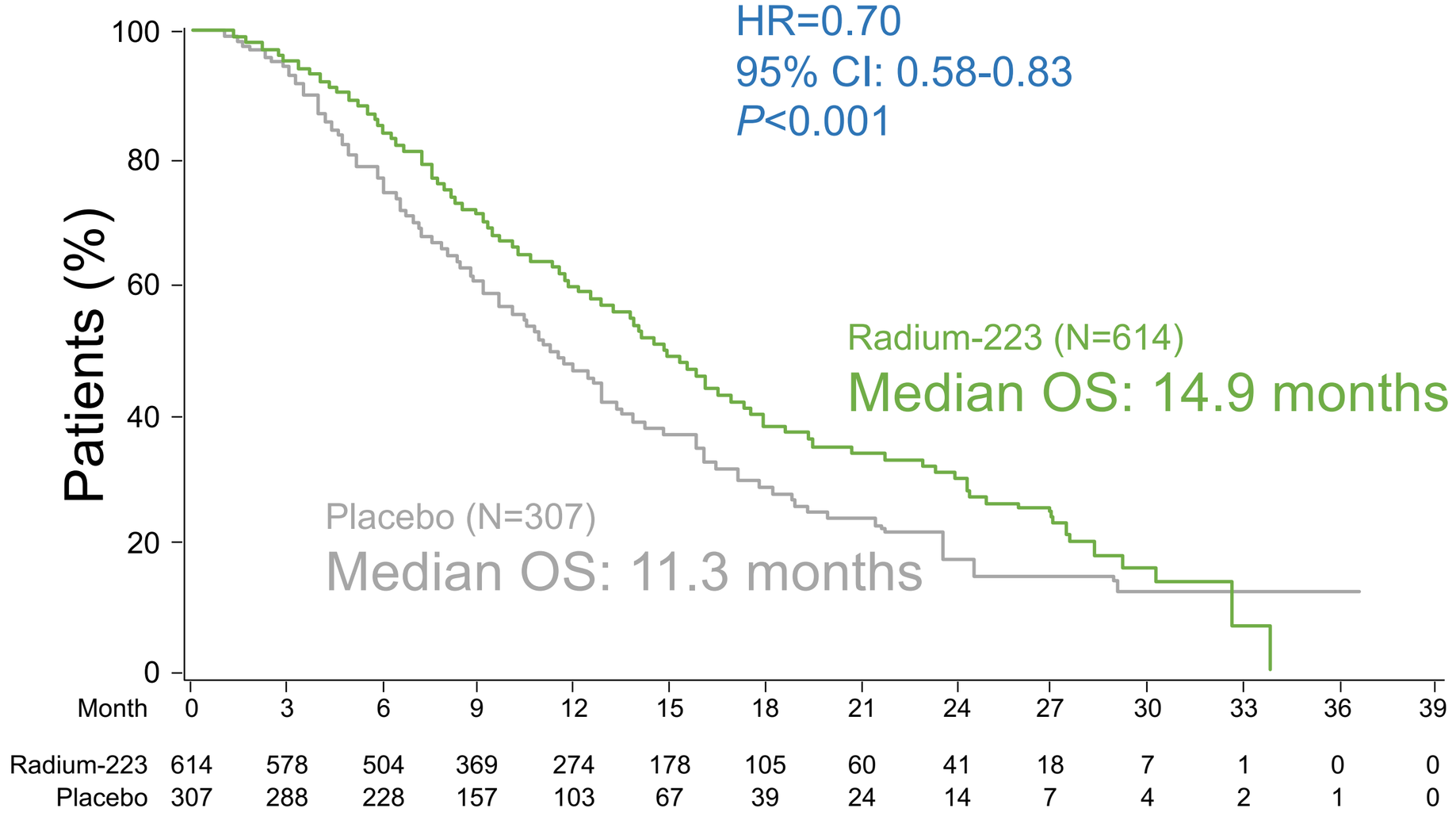
RADIUM-223 HAS SIGNIFICANT QOL BENEFITS



*Increase in (1) FACT-P total score of ≥10 or (2) EQ-5D utility score of ≥0.1 from baseline at 16 and/or 24 weeks

Nilsson S et al. Ann Oncol 2016;27:868-74

RADIUM-223 REDUCED RISK OF DEATH WITH 30%



Parker C et al. N Engl J Med 2013;369:213-23

3-YEAR SAFETY PROFILE

Patients with AEs (%)	All Grades		Grades 3 or 4	
	Placebo N=167	Radium-223 N=405	Placebo N=167	Radium-223 N=405
Haematologic				
Anaemia	3	3	1	1
Thrombocytopenia	0	1	0	0
Neutropenia	0	<1	0	<1
Non-Haematologic				
Pain	0	<1	0	0
Diarrhoea	0	<1	0	<1
Nausea	1	0	0	0
Vomiting	0	<1	0	0
Constipation	0	<1	0	0

Minimal nonhematologic AEs, a low incidence of myelosuppression with long-term preservation of hematopoietic function

Parker et al. Eur Urol 2017.

COMBINING RADIUM

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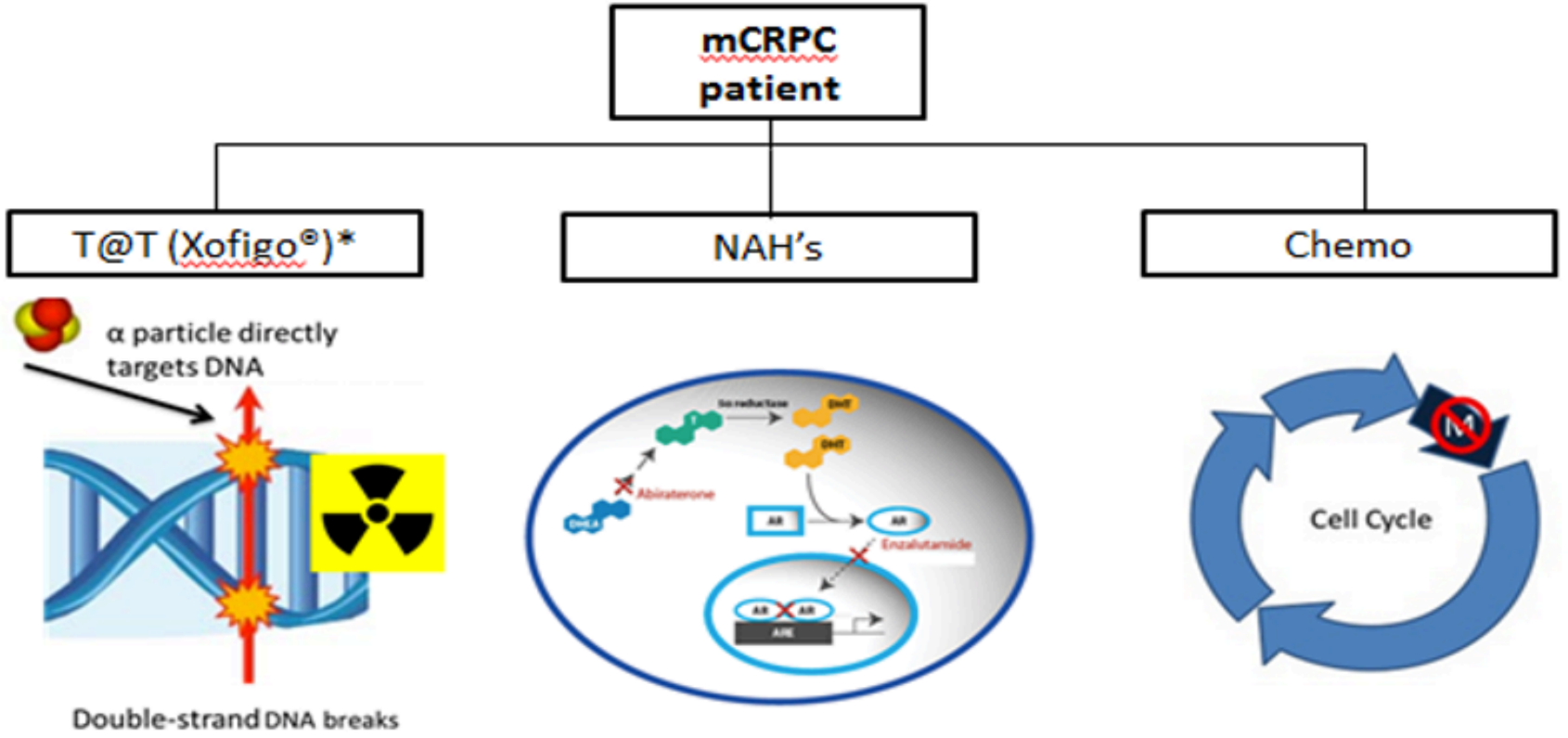
WHY NOT COMBINE DIFFERENT TREATMENT CLASSES IN MCRPC?



Targets DNA of tumor cell directly independent of disease heterogeneity**

Targets AR-signaling pathway

Interference microtubili

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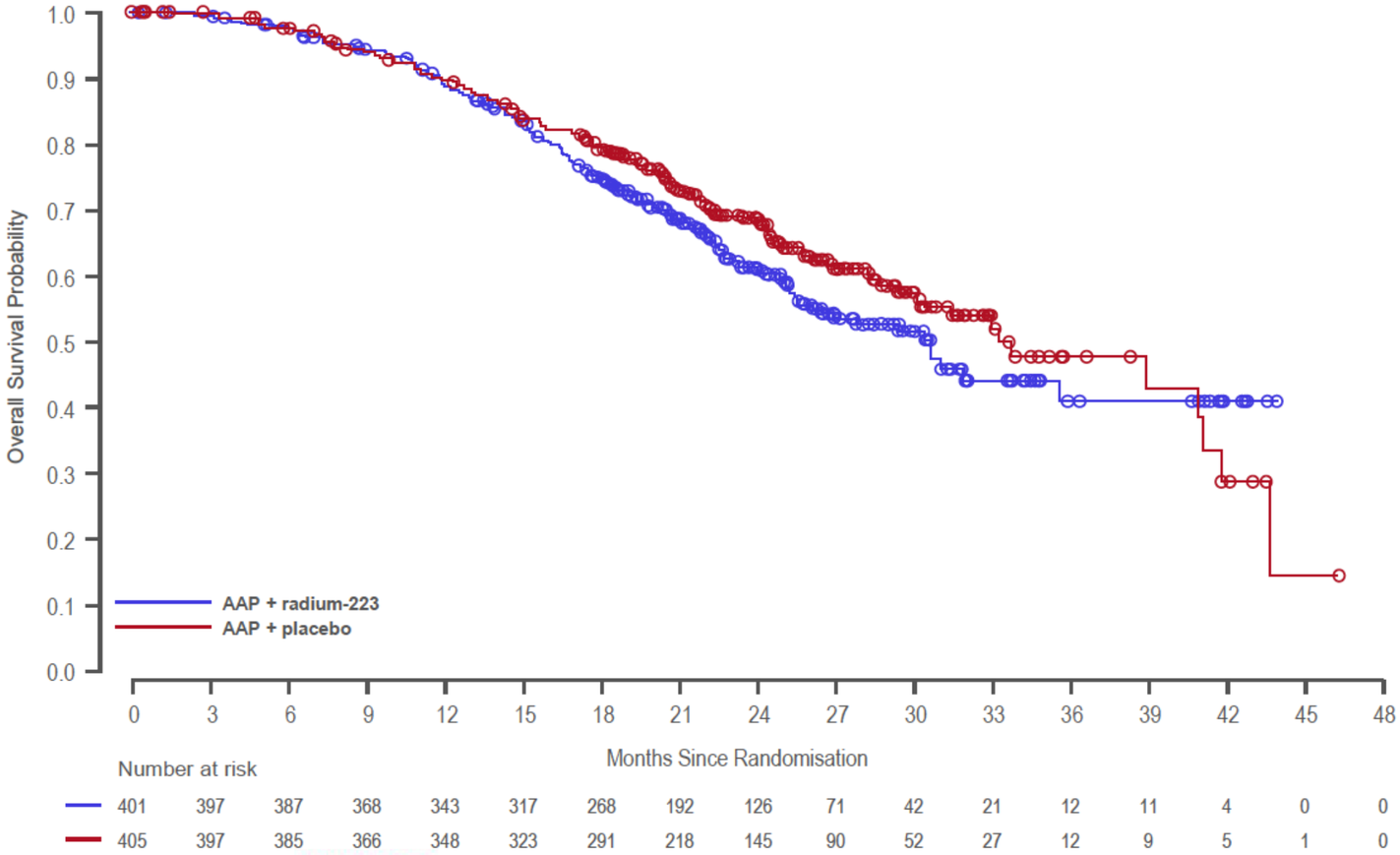
RADIUM + ABIRATERONE

Overall Survival (ITT)



OS	AAP + radium-223 N=401	AAP + placebo N=405
Deaths, n (%)	155 (39)	141 (35)
Median (95% CI), months	30.7 (25.8–NE)	33.3 (30.2–41.1)
HR (95% CI)	1.195 (0.950–1.505)	
P-value (2-sided)	0.1280	

Final OS analysis to be performed after 500 events

MUNICH 2018 ESMO congress

AAP, abiraterone acetate and prednisone/prednisolone; ITT, intention-to-treat; NE, not estimable; OS, overall survival.

WHAT WENT WRONG?

- Abiraterone promotes the osteoblastic activity in the bone

- ^{223}Ra is most active in the bone remodeling sites.

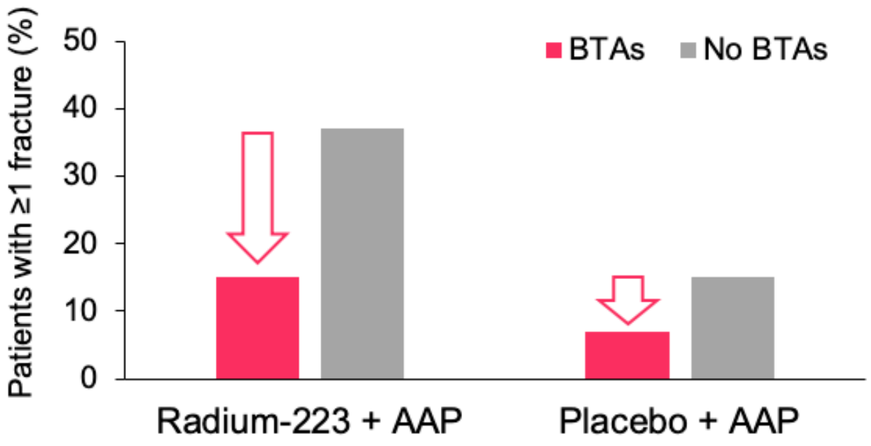


Increased dose to the healthy bone induced by abiraterone

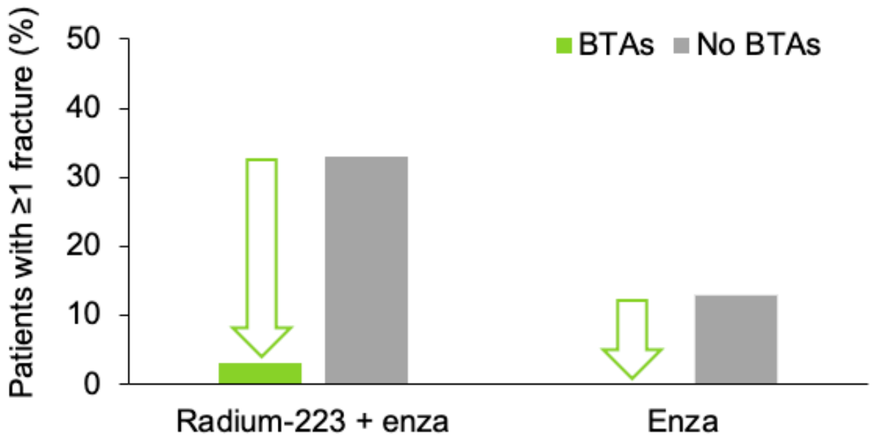
FUTURE OF COMBINATIONS?

- Maybe adding Xofigo following an induction period with an NAH makes more sense?
- Maybe effect is less pronounced with other NAH?
- Bone health agents reduce the unwanted effect

ERA-223[1]



PEACE III[2]



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WHERE DOES RADIUM-223 FIT IN?

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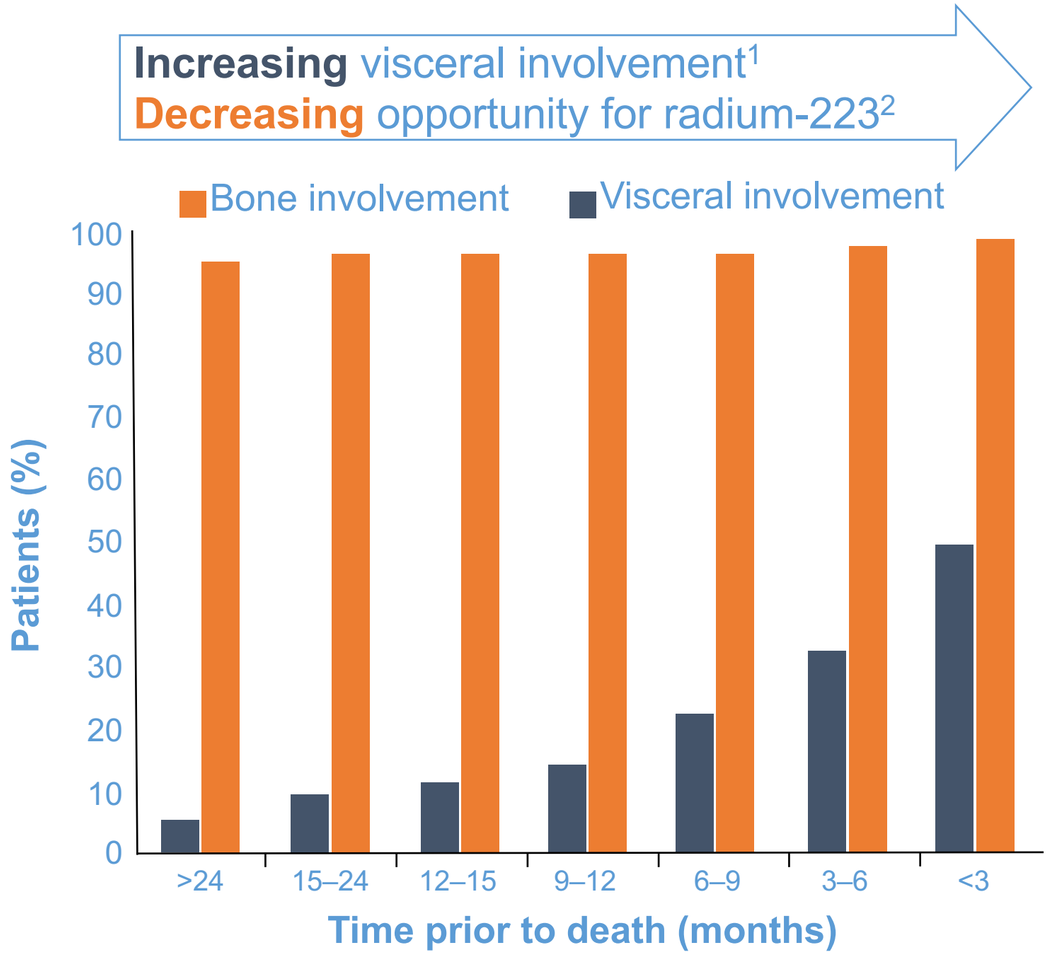
RADIUM-223 SHOULD BE CONSIDERED EARLY



Approximately 80% of patients will have bone metastases at some point during their disease course[3]

After progression on first-line NAH, ~60% of patients with mCRPC have bone-only progression[4–6]

1. Pezaro C et al. Eur Urol 2014;65:270–3; 2. Bayer AG. Radium-223 SmPC, 2018. Available at: https://www.ema.europa.eu/en/documents/product-information/xofigo-epar-product-information_en.pdf (accessed September 2019); 3. Tombal B, Lecouvet F. Adv Urol 2012;2012:8931934; 4. Smith MR et al. New Engl J Med 2018;387:1408–18; 5. Hussain M et al. New Engl J Med 2018;378:2465–74; 6. Bryce AH et al. Prostate Cancer Prostatic Dis 2017;20:221–7

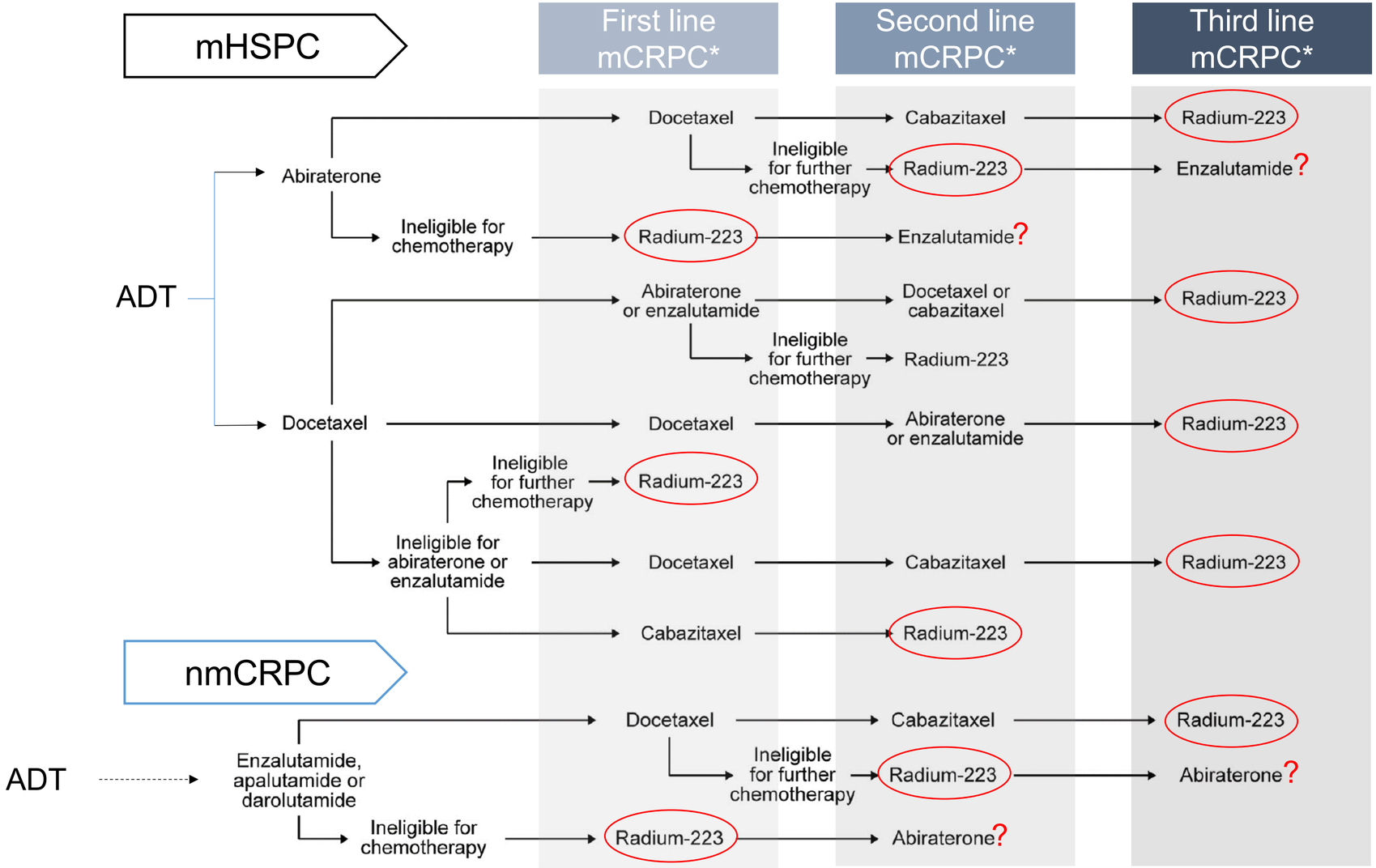
UPDATED RADIUM-223 EU LABEL

"Radium-223 monotherapy or in combination with luteinising hormone releasing hormone (LHRH) analogue is indicated for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), **symptomatic bone** metastases and **no** known **visceral metastases**, in progression after **at least two prior lines of systemic therapy for mCRPC** (other than LHRH analogues), or **ineligible** for any available systemic mCRPC treatment

Radium-223 is contraindicated in combination with abiraterone acetate and prednisone/prednisolone"

Bayer AG. Radium-223 SmPC, 2018. Available at: https://www.ema.europa.eu/en/documents/product-information/xofigo-epar-product-information_en.pdf (accessed April 2020)

TREATMENT SEQUENCING IN MCRPC IS BECOMING INCREASINGLY COMPLEX, AND IS INFLUENCED BY TREATMENTS RECEIVED IN PREVIOUS LINES



Near future:

- PARP inhibitors
- Lu-PSMA?

PRACTICLE EXAMPLE

- De novo mHSPC with multiple bone metastases treated with ADT + Abiraterone in 1st line treatment.
- At time of mCRPC and symptomatic bone metastases options are:
  - Docetaxel or radium (in case docetaxel ineligible)

BELGIAN CONSENSUS PAPER

Appropriateness of treatment options in patients with metastatic castration-resistant prostate cancer with a focus on radium-223: outcomes of a Belgian multidisciplinary consensus meeting

P. Ost, MD, PhD[1*], D. Schrijvers, MD, PhD[2*], L. Duck, MD[3], M. Gizzi, MD[4], K. Goffin, MD, PhD[5], S. Joniau, MD, PhD[6], S. Rottey, MD, PhD[7], T. Roumeguère, MD[8], E. Seront, MD, PhD[9], N. Withofs, MD, PhD[10], B. Tombal, MD, PhD[11*]

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BELG J MED ONCOL 2019;13(6): 240-250

SELECTING THE OPTIMAL PATIENT FOR RADIUM-223

- A **life expectancy of ≥6 months** was required for enrolment in ALSYMPCA[1]
  - 6 months is generally considered too short a length of time to derive maximal benefit from radium-223[2]
  - Patients should ideally have a life expectancy of ≥12 months before initiating radium-223[2]
- Patients with bone-predominant mCRPC who are earlier in their disease course are good candidates for radium-223[3]

- Exploratory analyses suggest patients with **less advanced, less pre-treated mCRPC** are more likely to complete radium-223 therapy,[4] and more likely to derive the greatest benefit
  - Prognostic factors including baseline LDH, PSA, ALP, haemoglobin, ECOG PS and pain may be useful in identifying patients who are earlier in their disease course[5,6]

ALP, alkaline phosphatase; EBRT, external bream radiation therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; PSA, prostate-specific antigen. 1. Parker C, et al. *N Engl J Med.* 2013;369(3):213–223; 2. Courtesy of Aurelius Omlin; 3. Heinrich D, et al. *Clin Genitourin Cancer.* 2017;16(1):e223–e231; 4. Sartor O, et al. *Oncologist*. 2017; Nov 28. Epub ahead of print; 5. Sartor O, et al. *Ann Oncol*. 2017;28(5):1090–1097; 6. Saad F, et al. *Lancet Oncol*. 2016;17(9):1306–1316.

CHARACTERISTICS OF PATIENTS RECEIVING 5-6 INJECTIONS

Patients who received 5-6 injections appear to have less advanced disease compared with those who received 1-4 injections (see patient characteristics table):

- Lower percentage with ECOG PS ≥2 (iEAP and ALSYMPCA)
- Lower PSA and ALP levels (iEAP and ALSYMPCA)
- Longer median time since prostate cancer diagnosis (iEAP and ALSYMPCA)
- Lower baseline pain (iEAP)
- Lower baseline LDH levels (ALSYMPCA)

A lower percentage of patients who received 5-6 injections discontinued for AEs (as the primary reason for treatment discontinuation) compared to those who received 1-4 injections

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Saad F, et al. *J Clin Oncol.* 34, 2016 (suppl; abstr 5082).

COST

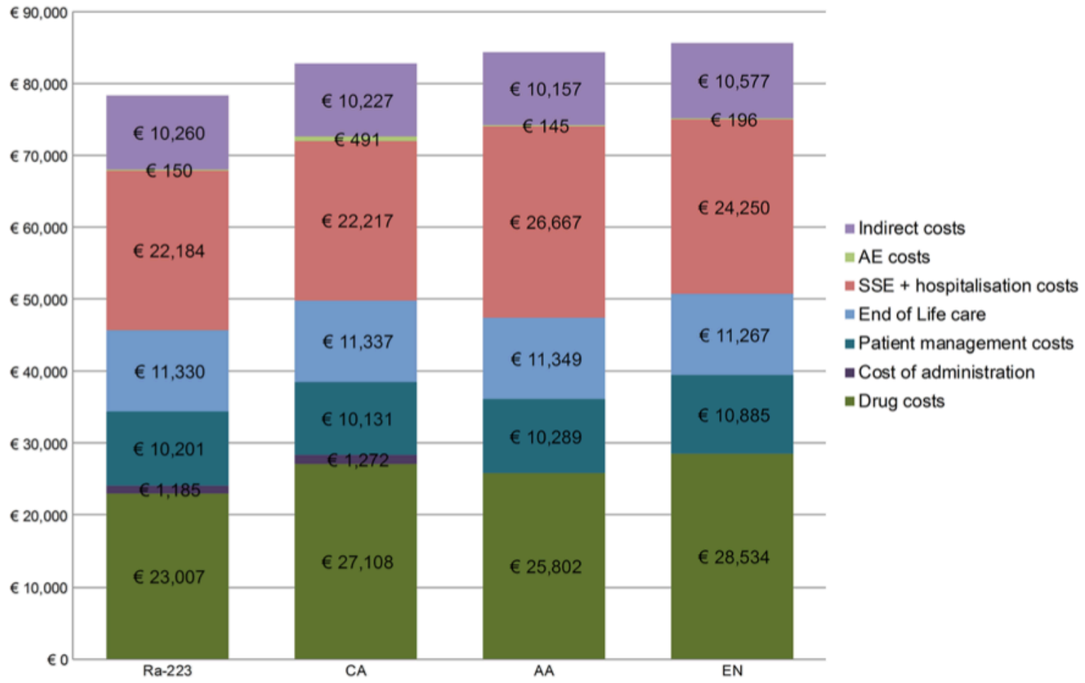
COST-EFFECTIVENESS RADIUM-223

Table 2 Results for costs and health benefits per comparison

Intervention and comparators	Discounted costs (€)	Incremental costs [Ra-223 vs. comparator] (€)	Discounted LYs	Incremental LYs [Ra-223 vs. comparator]	Discounted QALYs	Incremental QALYs [Ra-223 vs. comparator]	Incremental cost per QALY
Ra-223	78,318	–	1.39	–	0.8	–	
AA	84,410	−6092	1.36	0.03	0.78	0.02	Ra-223 dominates AA
CA	82,783	−4465	1.38	0.01	0.79	0.01	Ra-223 dominates CA
EN	85,708	−7390	1.5	−0.11	0.86	−0.06	Ra-223 slightly less effective and less costly

Costs are displayed in 2017 euros

AA abiraterone acetate, *CA* cabazitaxel, *EN* enzalutamide, *LY* life-year, *QALY* quality-adjusted life-year, *Ra-223* radium-223



Peters ML et al. Appl Health Econ Health Policy. 2018 Feb;16(1):133-143

CONCLUSIONS

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CONCLUSIONS ON RADIUM-223

- Take care of bone health!
- Radium-223 monotherapy improves overall survival and is safe
- Cost-effective
- Important place in the sequence, especially now that ARPIs are moving to an earlier phase.

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