OPTIMAL BONE HEALTH MANAGEMENT STRATEGIES IN PATIENTS WITH PROSTATE CANCER

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September 2020

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This content is supported by an Independent Educational Grant from Bayer.

Dr. Daniel Keizman has received financial support/sponsorship for research support, consultation or speaker fees from the following companies:

- Astellas, AstraZeneca, Bayer, BMS, Janssen, MSD, Neopharm, Novartis, Pfizer, Roche, Sanofi, Teva

WHY IS BONE HEALTH IMPORTANT IN PROSTATE CANCER?

BACKGROUND

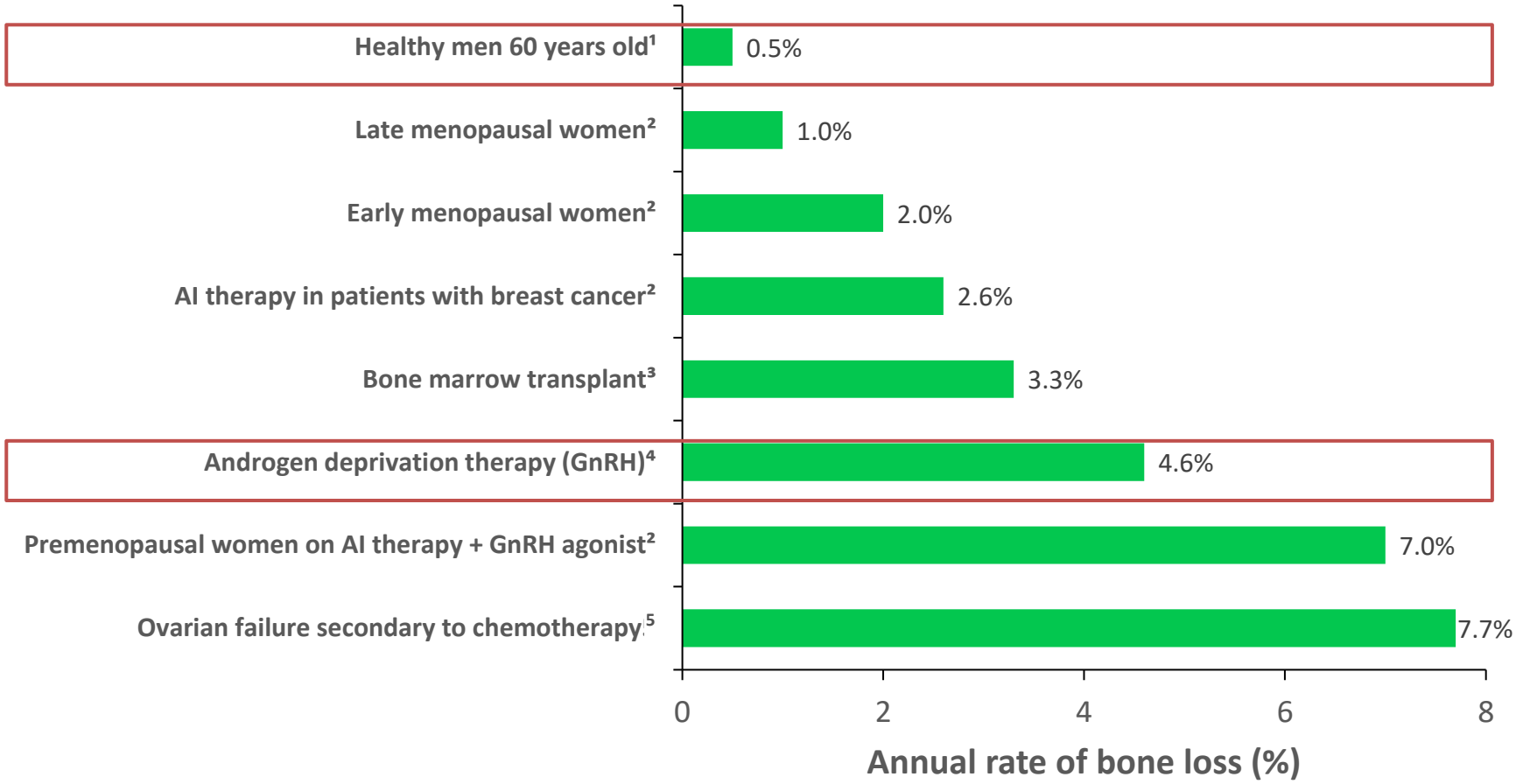
Bone targeted agents are given to patients with prostate cancer for the following reasons:

- **Preventing bone mass loss** associated with **androgen deprivation therapy** (ADT)[1,2]
- To **prevent skeletal related events** (SREs) in patients with bone metastases[3]
  - SREs include pathologic fractures, severe pain, and risk of spinal cord compromise
  - SREs can be severe, cause invalidity and have a negative effect on Quality of Life (QoL) and mobility
- As **active therapy to treat bone metastases** and prolong survival[1]

ADT, androgen deprivation therapy; SRE, skeletal related events

1. Suzman D, et al. Cancer Metastasis Rev 2014;33:619-28; 2. El Badri S, et al. Curr Osteoporos Rep 2019;17:527-37;
3. Hussain A, et al. Critical Reviews in Oncology/Hematology 2019; 139: 108-116

EXTENT OF BONE LOSS ACROSS VARIOUS POPULATIONS

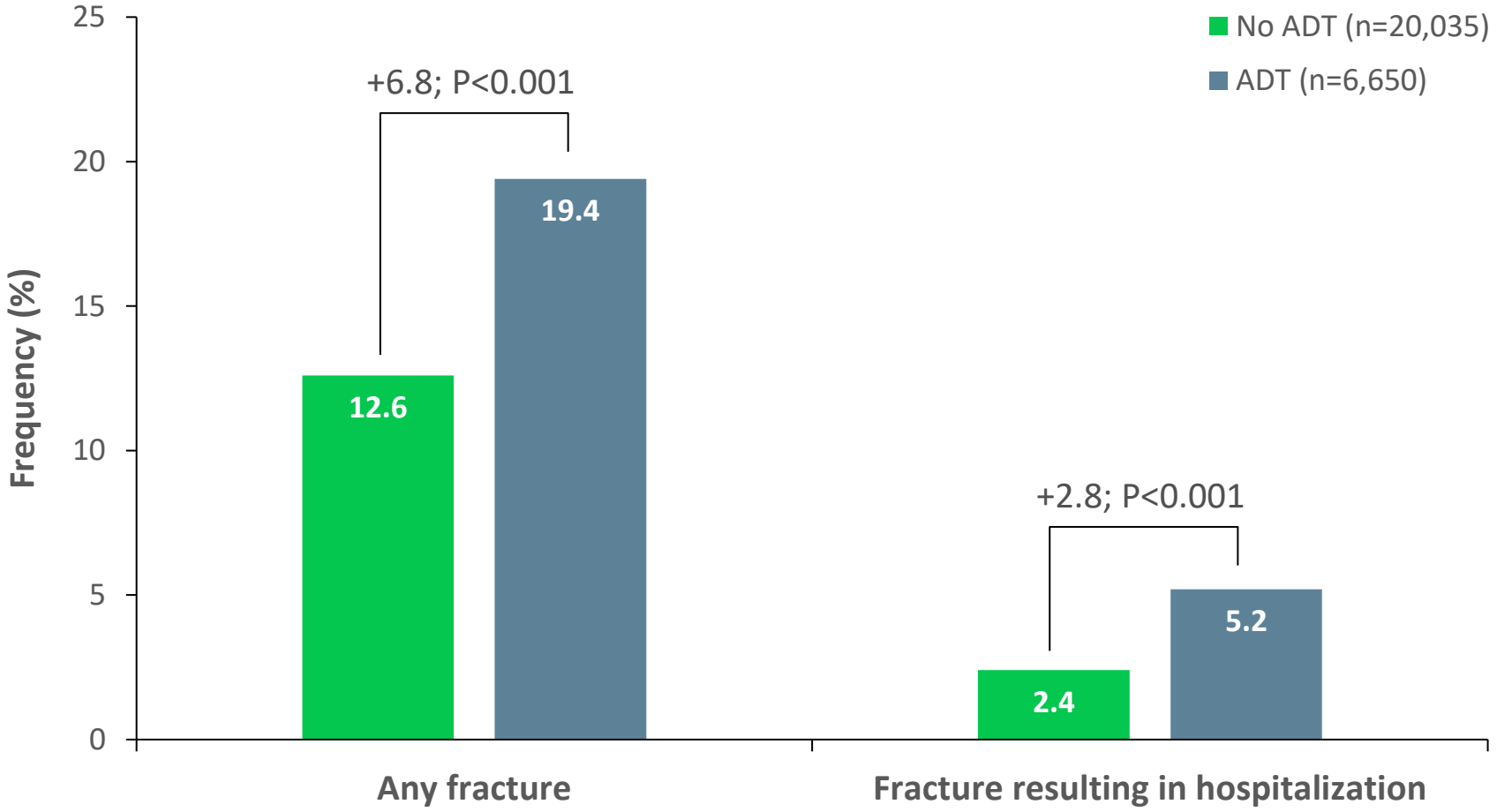


Data presented on one graphic for illustrative purposes only

AI, aromatase inhibitor; GnRH, Gonadotropin-releasing hormone

1. D'Amelio P, et al. Int J Endocrinol 2015;2015:907689; 2. Perez E, et al. Oncology 2006;20(9):1029-1048; 3. Lee WY, et al. J Clin Endocrinol Metab 2002;87:329-35; 4. Maillefert JF, et al. J Urol 1999;161:1219-22; 5. Shapiro CL, et al. J Clin Oncol 2001;19:3306-11

PROPORTION OF PC PATIENTS WITH FRACTURES 1-5 YEARS AFTER CANCER DIAGNOSIS



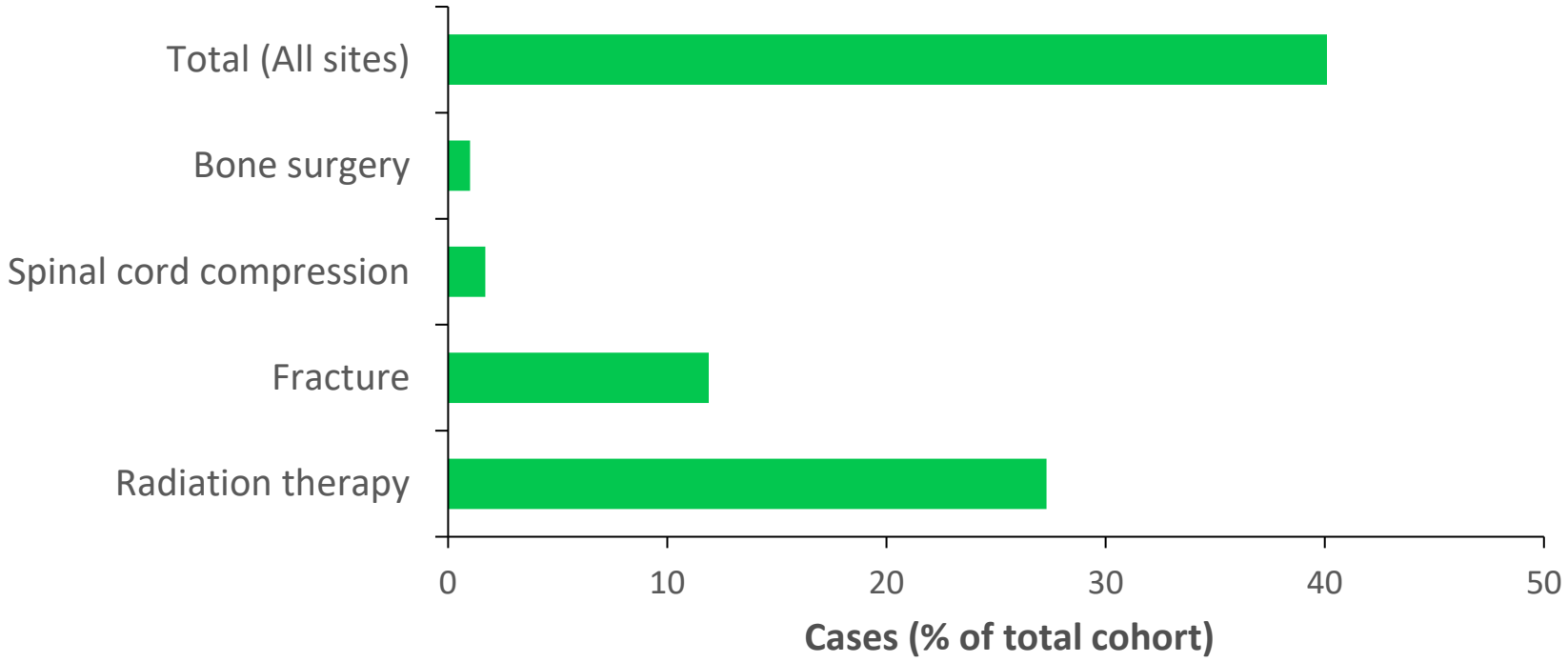
ADT, androgen deprivation therapy; PC, prostate cancer

Shahinian VB, et al. N Engl J Med 2005;352:154-64

BONE METASTASES AND SREs IN CRPC

- Approx. 90% of patients with mCRPC develop bone metastases[1,2]
- Approx. 50% of PC patients with bone metastases will have SREs[3]

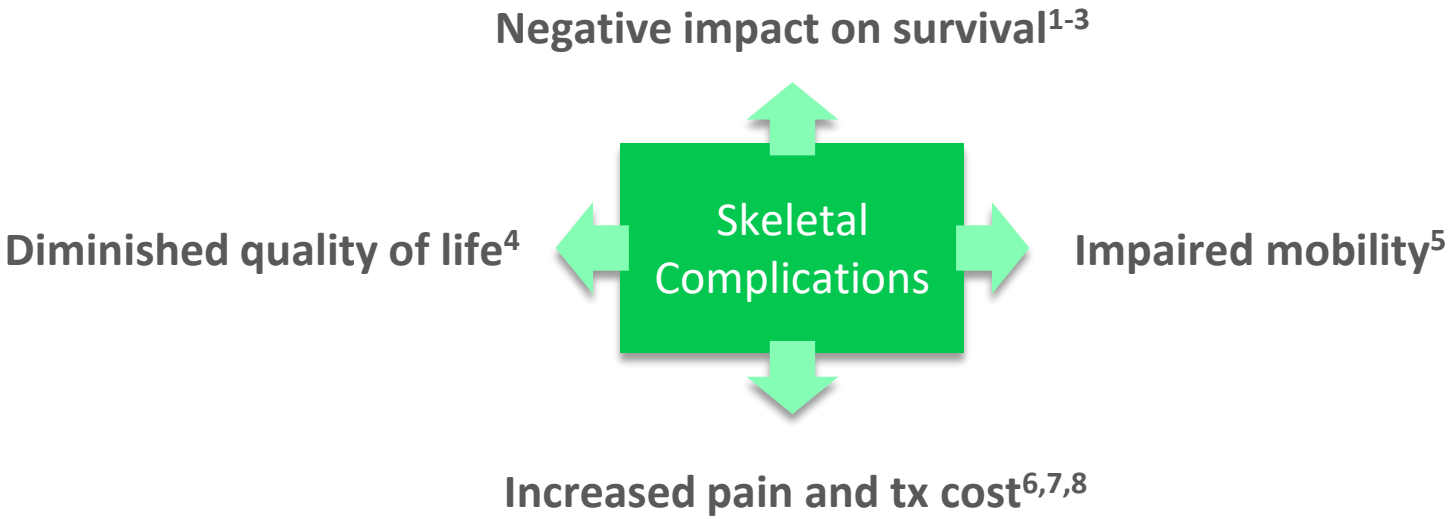
NUMBER OF FIRST CASES OF SRE[4]



CRPC, castration resistant prostate cancer; mCRPC, metastatic castration resistant prostate cancer; PC, prostate cancer; SREs, skeletal related events

1. Bubendorf L, et al. Hum Pathol 2000;31:578-83; 2. Tannock IF, et al. NEJM 2004;352:1502-12; 3. Yong C, et al. Curr Opin Oncol 2014;26:274-83; 4. Kawai A, et al. Prostate Cancer 2019; https://doi.org/10.1155/2019/5971615

IMPACT OF SKELETAL RELATED EVENTS IN CRPC



CRPC, castration resistant prostate cancer; tx, treatment

1. DePuy V, et al. Support Care Cancer 2007;15:869-76; 2. Norgaard M, et al. J Urol 2010;184:162-7; 3. Oefelein MG, et al. J Urol 2002;168:1005-7; 4. Weinfurt KP, et al. Ann Onc 2005;16:579-84; 5. Gralow JR, et al. J Natl Compr Canc Netw 2009;7(supp. 3):S1-32; 6. Goh P, et al. Curr Onc 2007;14:9-12; 7. Inoue T, et al. Urology 2009;73:1104-9; 8. Yong C, et al. Curr. Opin. Oncol. 2014, 26: 274-283

BONE HEALTH AGENTS

BONE HEALTH AGENTS

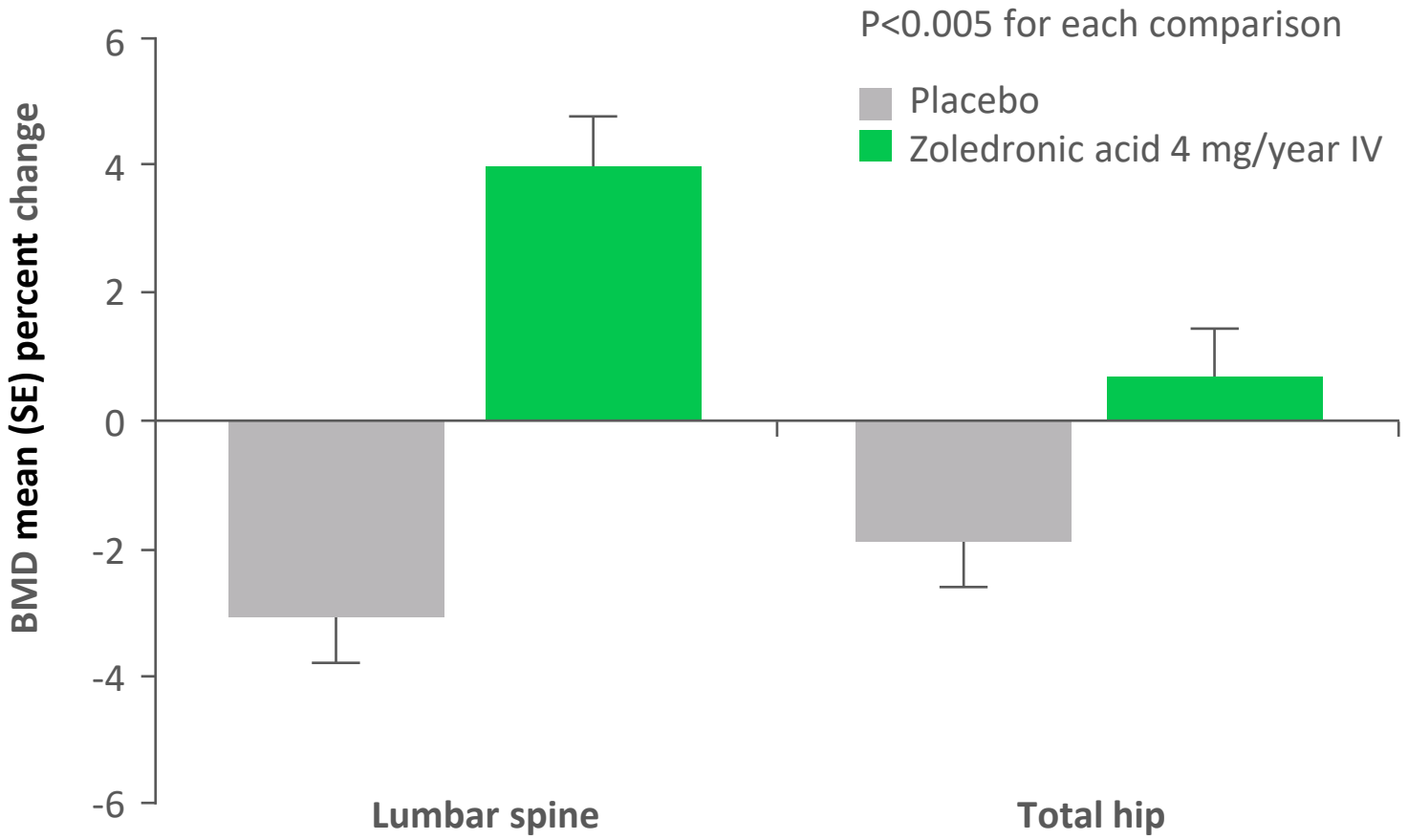
- Commonly used bone health agents for the treatment of patients with prostate cancer include:
  - **Zoledronic acid (ZA):** a bisphosphonate that inhibits tumour formation at the bone matrix, osteoclast development from precursor cells and inhibits angiogenesis. Bisphosphonates can also initiate apoptosis of both osteoclasts and tumour cells
  - **Denosumab:** human monoclonal RANKL antibody, inhibits osteoclast maturation and bone turnover by mimicking the native osteoprotegerin-RANK interaction

RANK, receptor activator of nuclear factor-kB; RANKL, RANK ligand

Suzman D, et al. Cancer Metastasis Rev 2014;33:619-28

ANNUAL ZOLEDRONIC ACID INCREASES BMD DURING GnRH AGONIST THERAPY

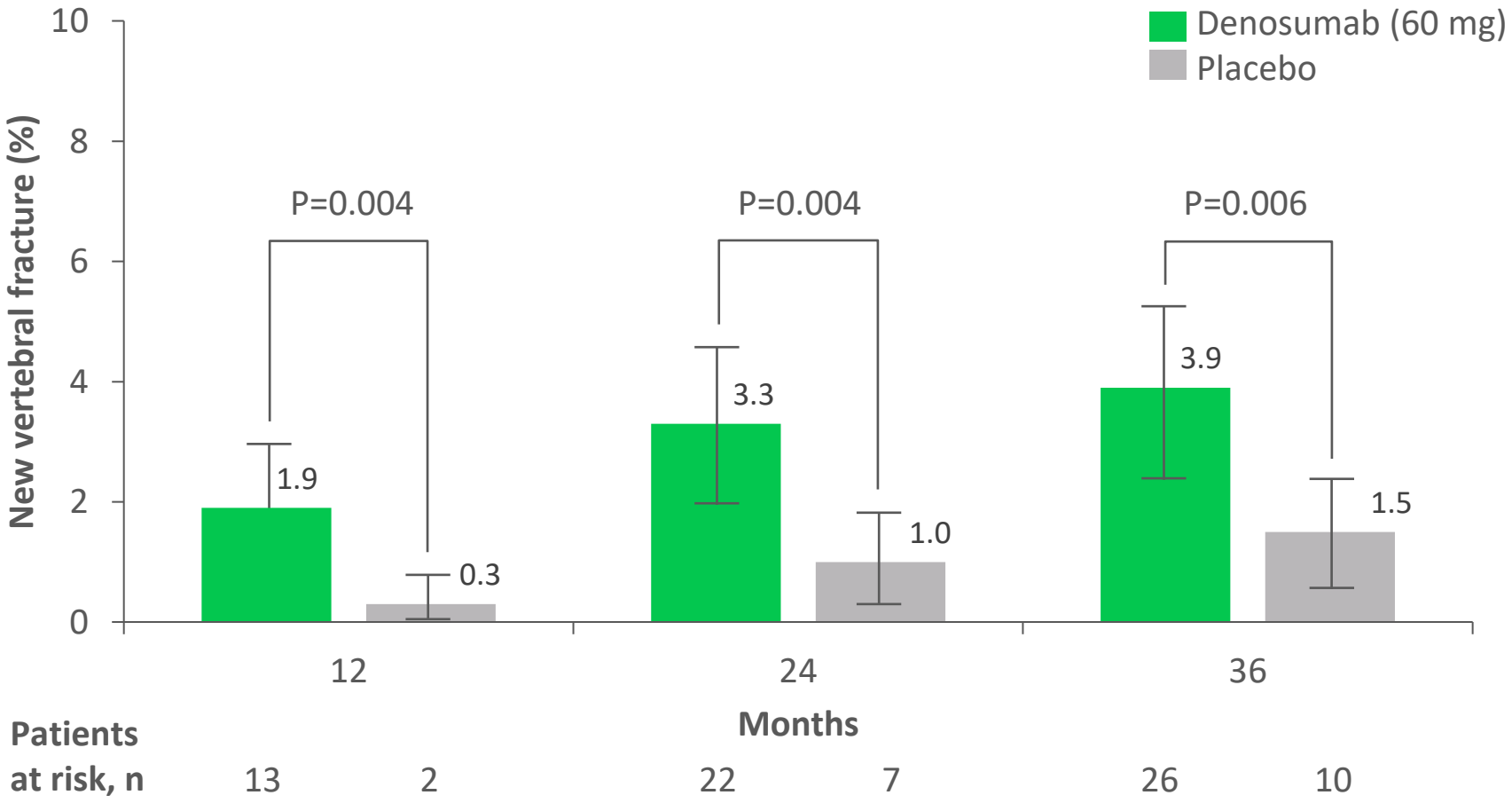
FINAL 12-MONTH DATA



BMD, bone mineral density; GnRH, Gonadotropin-releasing hormone; IV, intravenous

Michaelson MD, et al. J Clin Oncol 2007;25:1038-42

DENOSUMAB FOR FRACTURE PREVENTION DURING ADT

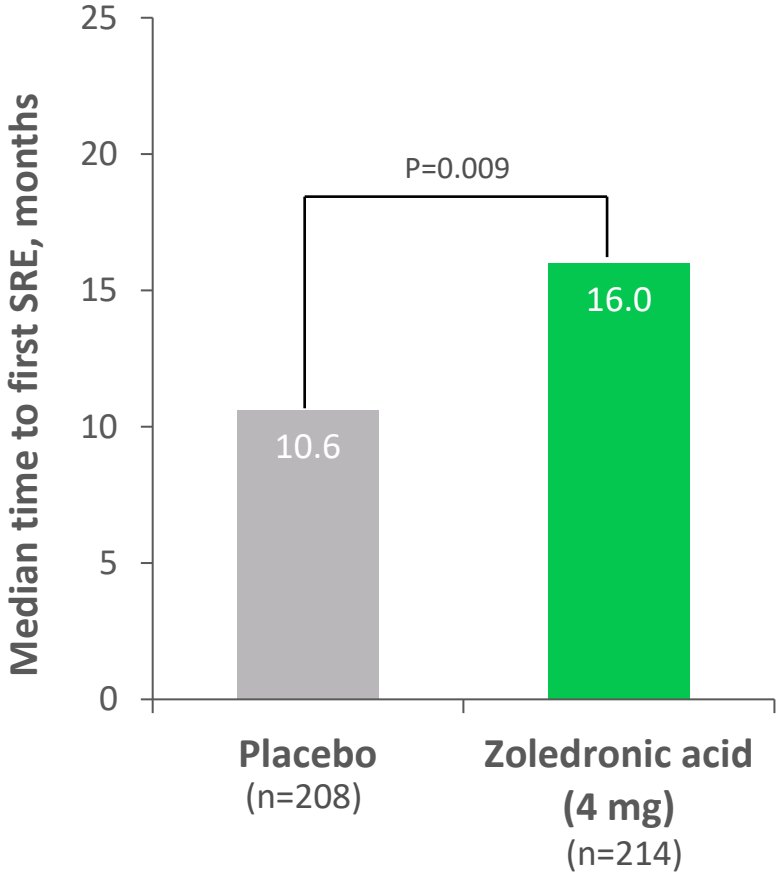


ADT, androgen deprivation therapy

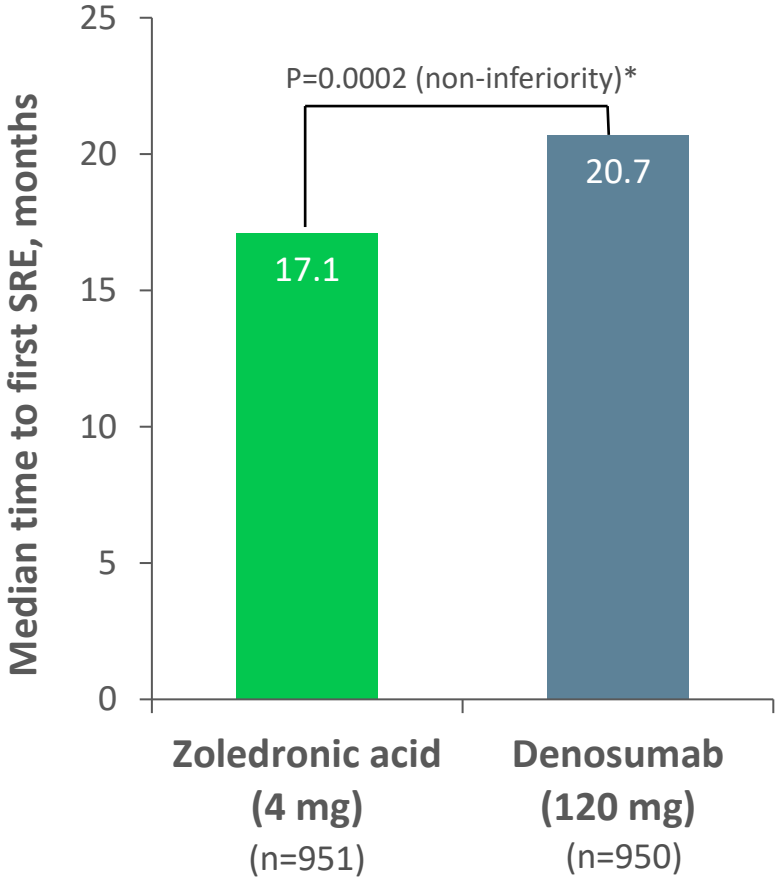
Smith MR, et al. N Engl J Med 2009;361:745-55

BENEFIT OF SRE PREVENTION IN mCRPC

TIME TO FIRST SRE[1]



TIME TO FIRST SRE[2]

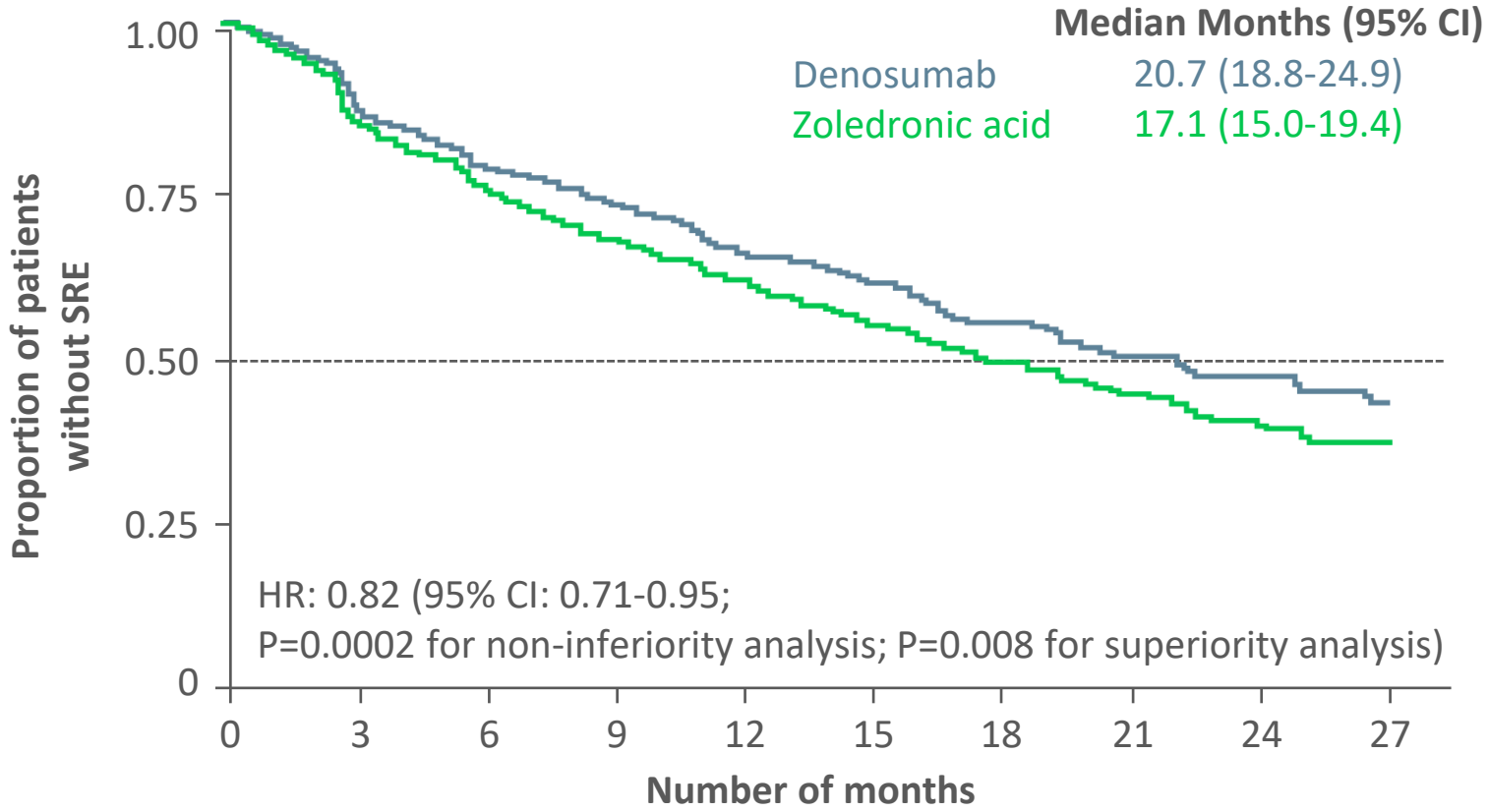


*P=0.008 (superiority) assessed as secondary endpoint

mCRPC, metastatic castration resistant prostate cancer; SRE, skeletal related event

1. Saad F, et al. J Natl Cancer Inst 2004;96(11):879-882; 2. Fizazi K, et al. Lancet 2011;377(9768):813-22

DENOSUMAB VS ZA: TIME TO FIRST ON-STUDY SRE



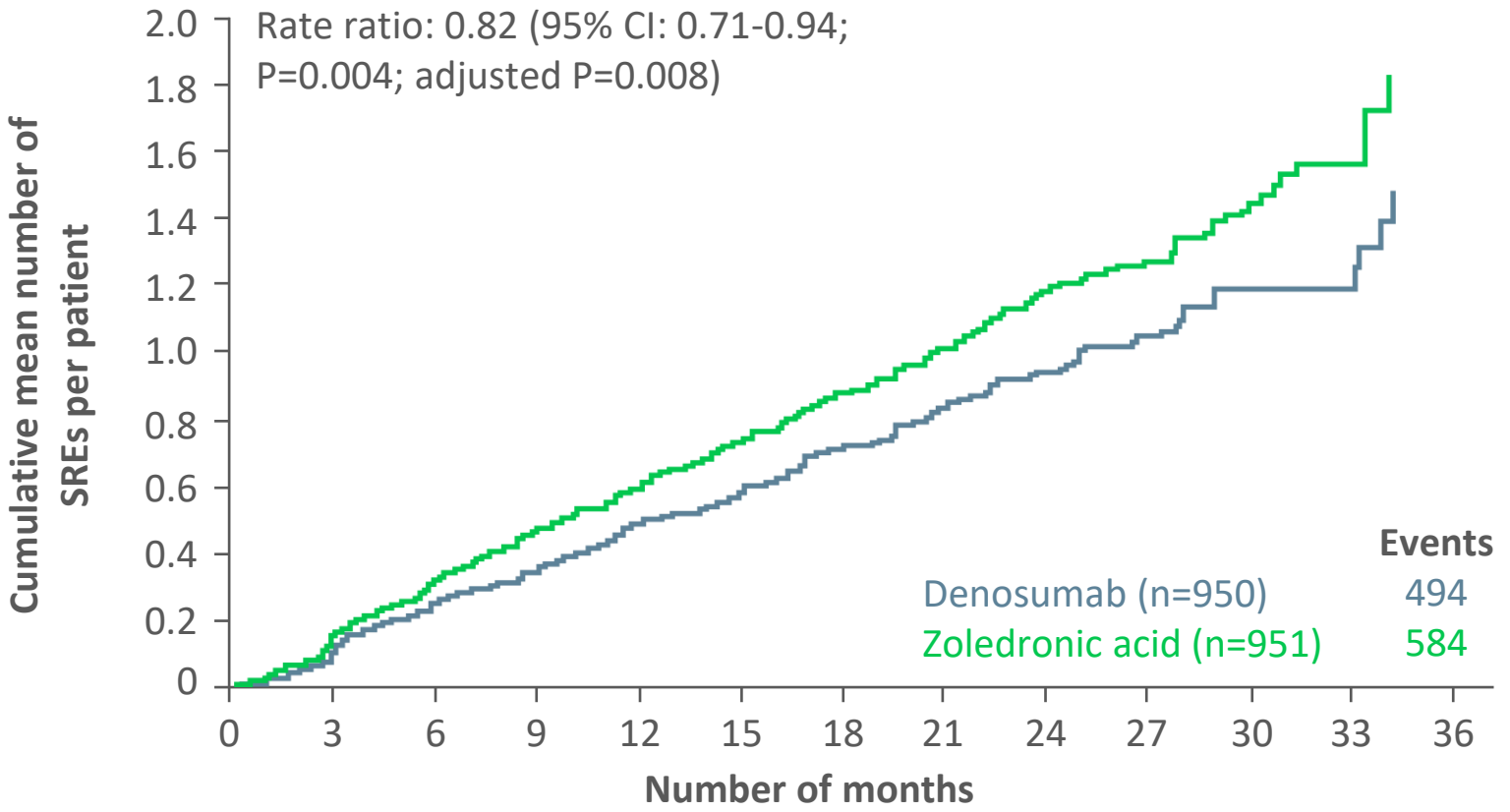
Patients at risk, n

Denosumab	950	758	582	472	361	259	168	115	70	39
Zoledronic acid	951	733	544	407	299	207	140	93	64	47

CI, confidence interval; HR, hazard ratio; SRE, skeletal related event; ZA, zoledronic acid

Fizazi K, et al. Lancet 2011;377:813-22

TIME TO FIRST AND SUBSEQUENT ON-STUDY SRE (MULTIPLE EVENT ANALYSIS)*



*Events occurring at least 21 days apart

CI, confidence interval; SRE, skeletal related event

Fizazi K, et al. Lancet 2011;377:813-22

TOXICITIES ASSOCIATED WITH ZOLEDRONIC ACID AND DENOSUMAB

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Zoledronic acid vs denosumab

Phase 3 trial, comparing zoledronic acid with denosumab in patients with mCRPC

The most common adverse events *(occurring at a similar rate in both treatment arms)*:

- Anaemia, back pain, decreased appetite, nausea, fatigue, constipation and bone pain

AEs of interest	Zoledronic Acid N=945	Denosumab N=943	P value
Infectious AE	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

AE, adverse event; mCRPC, metastatic castration resistant prostate cancer

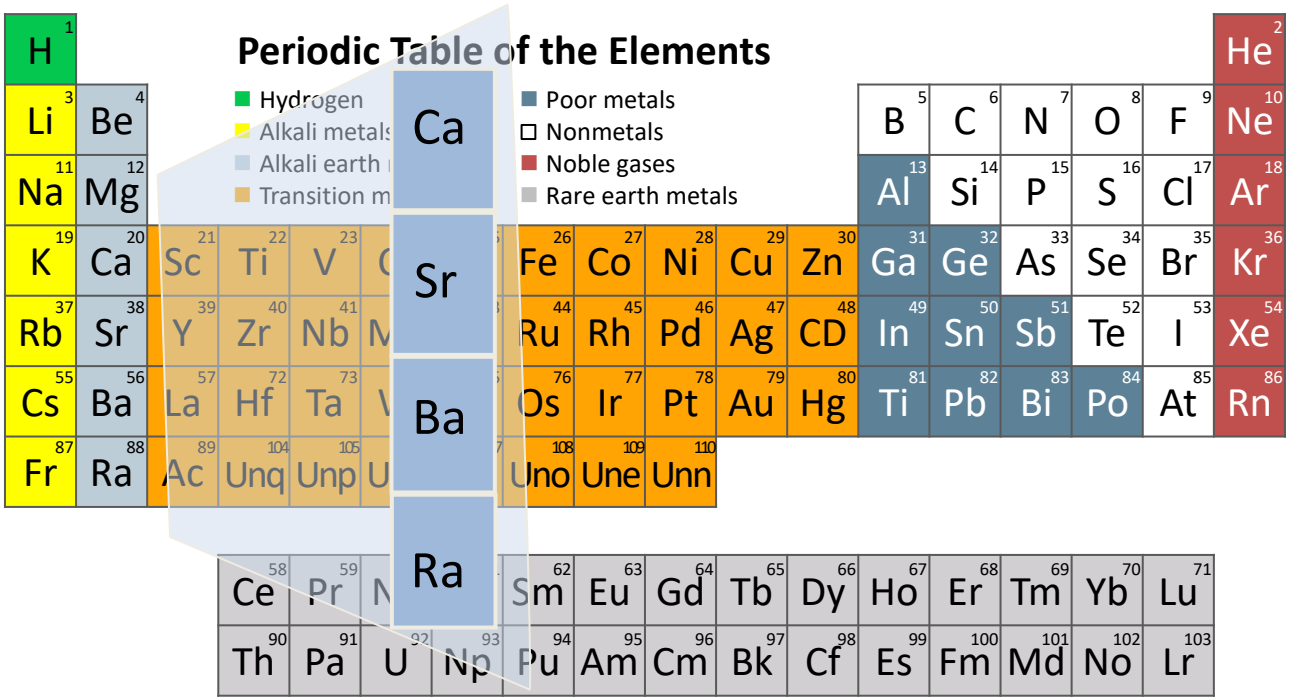
1. Fizazi K, et al. Lancet 2011; 377: 813-22; 2. Gartrell B, et al. Eur Urol 2014; 65:278-86

BONE TARGETED AGENTS

Radiopharmaceuticals

RADIUM-223

- Radium-223 is an alpha particle emitting radiopharmaceutical that works at the site of bone metastases
- It belongs to the same group in the Periodic Table of the Elements as alkaline earth elements [calcium (Ca), strontium (Sr), barium (Ba), and radium (Ra)] and has similar bone seeking properties

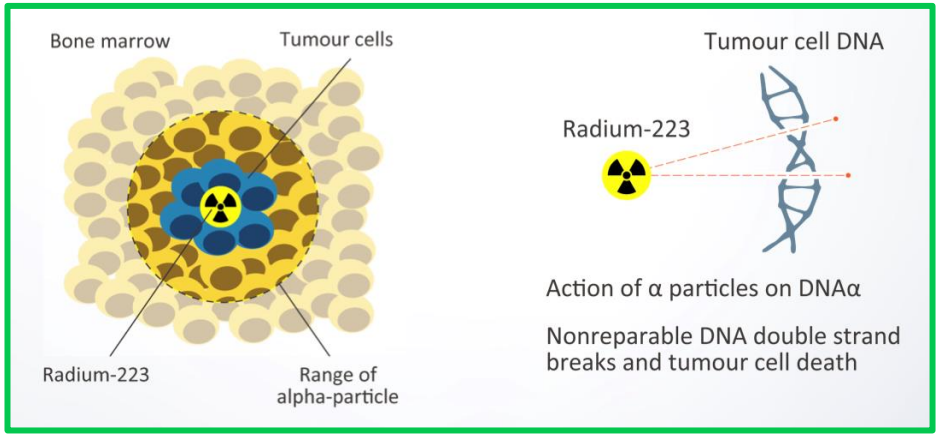


BONE-TARGETING RADIOPHARMACEUTICALS: α-EMITTERS VS β-EMITTERS

	α – Emitters	β – Emitters
Example emitters	Radium-223	Strontium-89, Samarium-153
Size Relative mass	2 neutrons+2 protons 7300	1 electron 1
Linear energy transfer (KeV/µm)	60-230	0.1-1.0
Range in tissue (µm)	40-100 Less radiation damage to adjacent normal tissue Higher localised dose to bone and endosteal layer	50-12,000 Delivers more radiation to adjacent normal tissue Penetrate bone marrow region
DNA damage	Irreparable Double strand DNA breaks	Repairable Single strand DNA breaks

1. Brechbiel M, et al. Dalton Trans 2007;43:4918-28; 2. Kassis A, et al. Semin Nucl Med 2008;38:258-66; 3. Nilsson S, et al. ASTRO 2010 poster presentation 2385; 4. Choi JY, et al. Nucl. Med. Mol Imaging 2018;52:200-7; 5. Sadremomtaz A, et al. J Med Imaging Radiat Sci 2019;50:272-9; 6. Cheetham PJ, et al. Oncology 2012;26:330-341 (PMID: 22655525); 7. Silberstein EB. Oncology 2012;26:345,348 (PMID: 22655527); 8. Jadvar H, et al. Clin Nucl Med. 2013;38(12):966-971.

RADIUM-223 IN BONE METASTASES



- Alpha particle-emitting isotope **radium-223** (as radium Ra 223 dichloride), **mimics calcium and forms complexes with the bone mineral** hydroxyapatite at areas of increased bone turnover, such as bone metastases
- The high linear energy transfer of alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in an anti-tumour effect on bone metastases
- The **alpha particle range from radium-223** dichloride is **less than 100 micrometers** (less than 10 cell diameters) which **limits damage to the surrounding normal tissue**
- Radium-223 is excreted in the faeces

keV, kiloelectron volt; Ra-233, radium-233.

Radium-223 Prescribing Information Dec 2019. Accessed 10 Jul 2020
Figure adapted from: Deshayes E, et al. Drug Des Devel Ther 2017;11:2643-51

RADIUM-223 ADMINISTRATION AND DOSE

- Ra-223 must be administered by a radiation oncologist or nuclear medicine physician in a designated clinical setting, including a licensed practice or a hospital outpatient setting

- The patient-ready dose is 1.49 microcurie (55 kBq) per kg body weight

The volume to be administered to a given patient is calculated as follows:

$$\text{Volume to be administered (mL)} = \frac{\text{Body weight in kg} \times 55\ \text{kBq/kg body weight}}{\text{Decay factor} \times 1100\ \text{kBq/mL}} \quad \textbf{OR} \quad \frac{\text{Body weight in kg} \times 1.49\ \text{mCi/kg body weight}}{\text{Decay factor} \times 30\ \text{mCi/mL}}$$

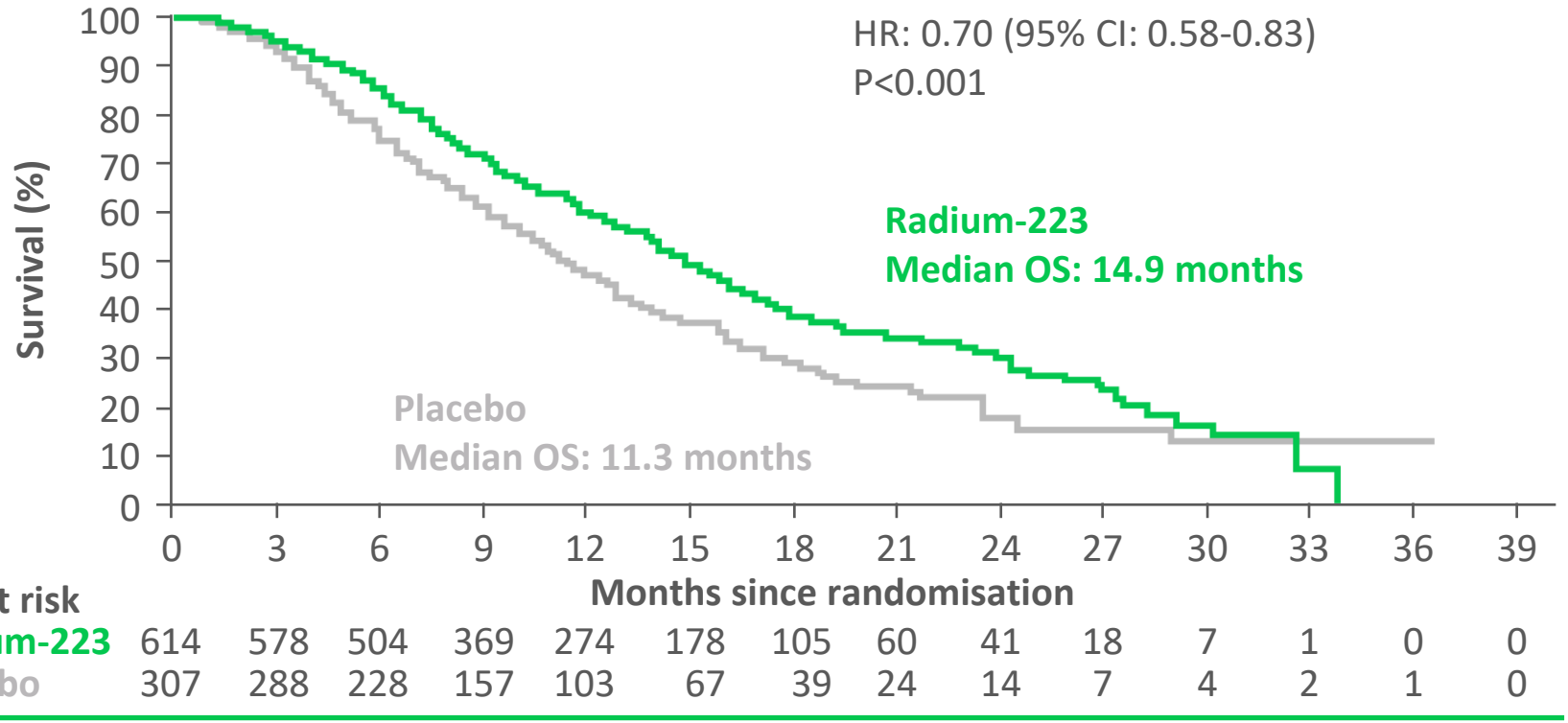
- Ra-223 is a ready-to-use solution and should not be diluted or mixed with any other solutions
- Patient goes home after treatment

kBq, kilobecquerel; Ra-233, radium-233

Radium-223 Prescribing Information Dec 2019. Accessed 10 Jul 2020

RADIUM-223: ALSYMPCA TRIAL

- Radium-223 significantly improved overall survival compared to placebo in mCRPC patients with symptomatic bone metastases
- Radium-223 was associated with low myelosuppression rates and fewer adverse events compared to placebo



CI, confidence interval; HR, hazard ratio; OS, overall survival

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

BONE SUPPORT DURING RADIUM-223 TREATMENT

PEACE III STUDY

- Bone support with bisphosphonates or denosumab has been shown to prevent excess fractures whilst patients receive radium-223 in combination with enzalutamide

Time point	Treatment and use of bone protecting agents			
	With exposure to BHA		Without exposure to BHA	
	Enza+Rad (N=39)	Enza (N=49)	Enza+Rad (N=37)	Enza (N=35)
	Cum Incidence (95% CI)*	Cum Incidence (95% CI)	Cum Incidence (95% CI)	Cum Incidence (95% CI)
3 months	0 (-)	0 (-)	0 (-)	5.7 (1.0-16.7)
6 months	0 (-)	0 (-)	5.6 (1.0-16.3)	8.8 (2.2-21.0)
9 months	0 (-)	0 (-)	22.6 (10.6-37.3)	8.8 (2.2-21.0)
12 months	**0 (-)**	**0 (-)**	**37.4 (21.8-53.1)**	**12.4 (3.9-26.2)**
15 months	0 (-)	0 (-)	43.6 (26.8-59.3)	16.6 (5.9-32.0)
18 months	0 (-)	0 (-)	43.6 (26.8-59.3)	16.6 (5.9-32.0)

* the one fracture in this group occurred at month 27

BHA, bone health agents; CI, confidence interval; Cum, cumulative; Enza, enzalutamide; Rad, radium-223.

Tombal B, et al. JCO 2019;37(no. 15_suppl):5007

SUMMARY

- **Prostate cancer patients are now living longer, and many patients receive several lines of therapy**, which can have a **cumulative impact on bone health** over a period of years[1]
  - Early recognition and optimization of bone health is therefore important in this patient group
- Bone health agents such as **zoledronic acid and denosumab are effective for reducing the time to first SRE**, overall bone health and to prevent osteoporosis[2-5]
  - Denosumab more effective than zoledronic acid in delaying SREs[5]
- **Radium-223** is a therapeutic bone targeted drug that has **demonstrated an OS benefit** for mCRPC patients with symptomatic bone metastases and no visceral metastases, together with QoL benefits and a favourable safety profile[6,7]
  - Bone support with bisphosphonates or denosumab has been shown to prevent excess fractures whilst patients receive radium-223, in combination with enzalutamide[8]

mCRPC; metastatic castration resistant prostate cancer; OS, overall survival; QoL, quality of life; SRE, skeletal related event

1. El Badri S, et al. Curr Osteoporos Rep 2019;17:527-37; 2. Smith M, et al. N Engl J Med 2009;361:745-55; 3. Michaelson M, et al. J Clin Onc 2007;25:1038-42; 4. Saad F, et al. J Natl Cancer Inst 2004;96(11):879-882; 5. Fizazi K, et al. Lancet 2011;377(9768):813-22; 6. Parker C, et al. N Engl J Med 2013;369:213-223; 7. Nilsson S, et al. Ann Oncol 2016; 27: 868-874; 8. Tombal B, et al. JCO 2019;37(no. 15_suppl):5007

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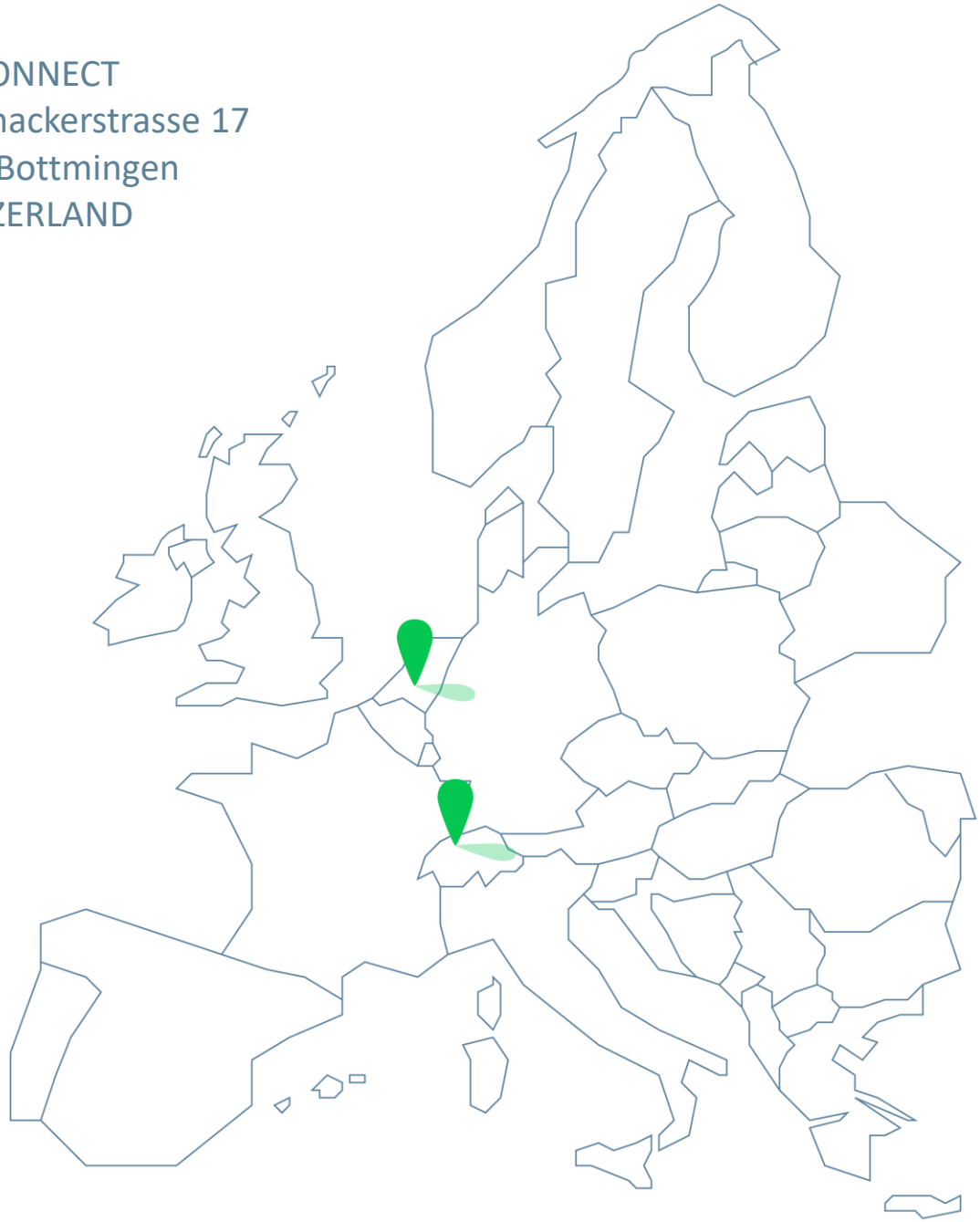

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