Bone Targeted Agents

Danish Mazhar
Consultant Medical Oncologist
Addenbrooke's Hospital
Cambridge

BAUN
BRITISH ASSOCIATION of UROLOGICAL NURSES

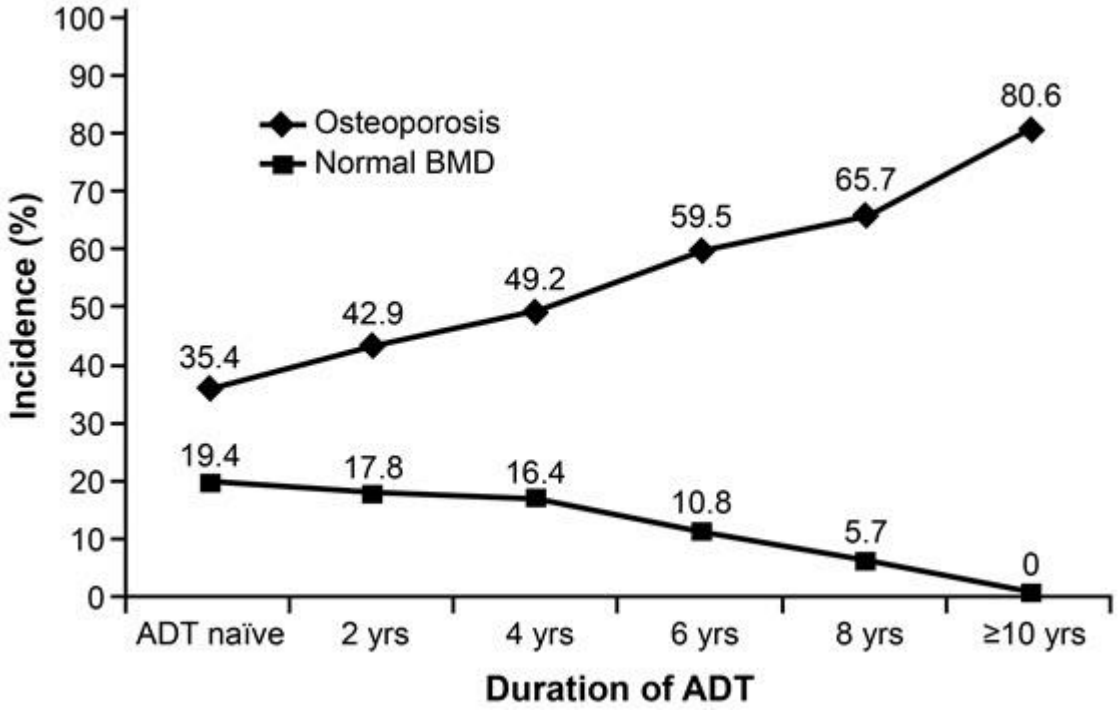
Main areas to cover

- Bone Health
- Bisphosphonates
- Denosumab
- Alpharadin

Other treatments for bone metastases

- Palliative external beam radiotherapy
- Systemic therapies (hormonal, chemotherapy, immunotherapy)

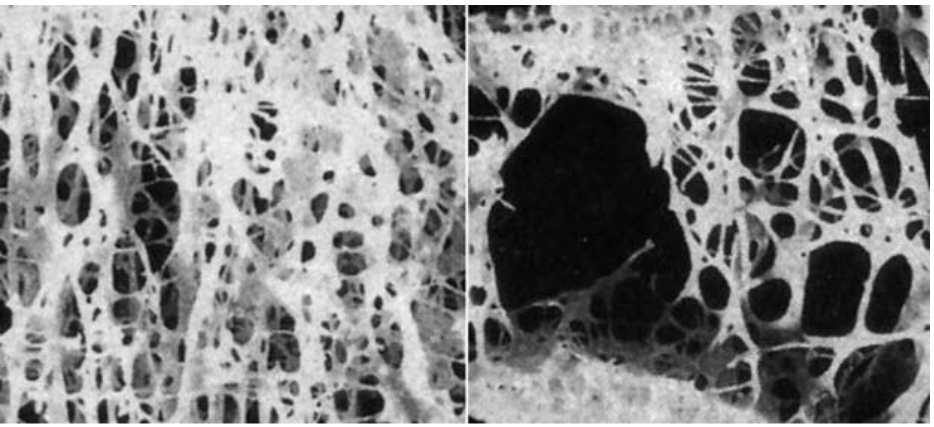
Men having long-term androgen deprivation therapy for prostate cancer have an increased fracture risk.

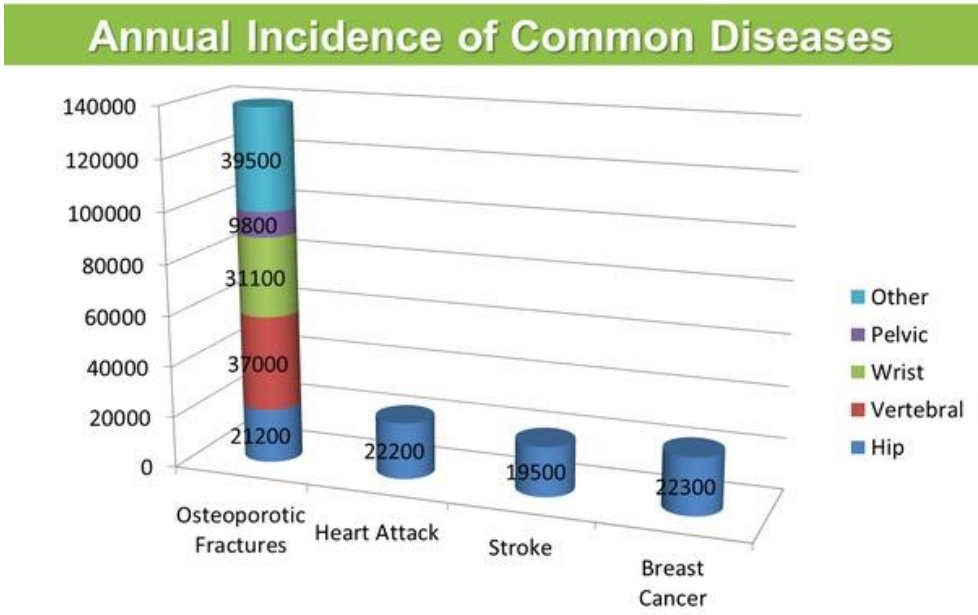


http://www.nice.org.uk/guidance/CG146

Osteoporosis

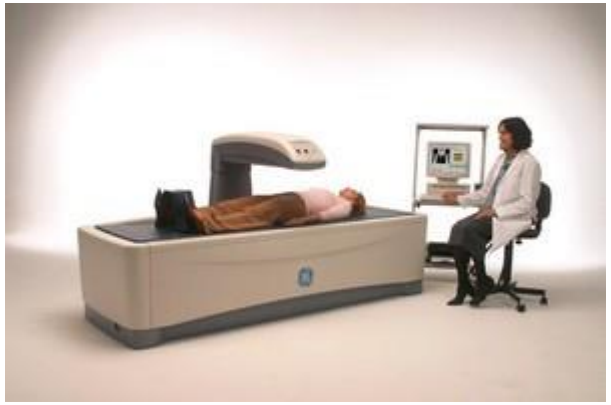
- Low mineral density
- Structural deterioration
- Increased fragility and risk of fracture

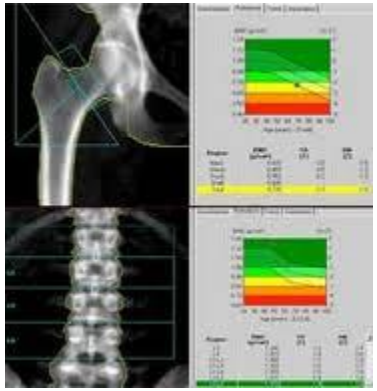


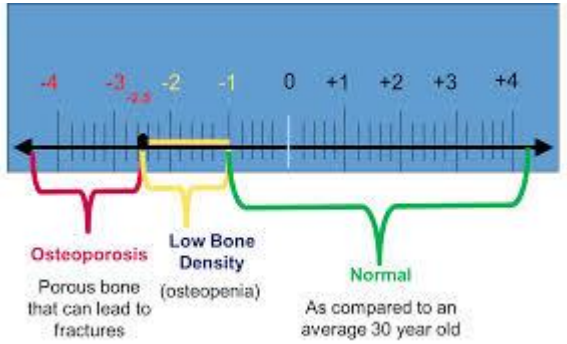


All patients on long term ADT

- Exercise
- Diet
- Vit D
- Calcium
- Bisphosphonates

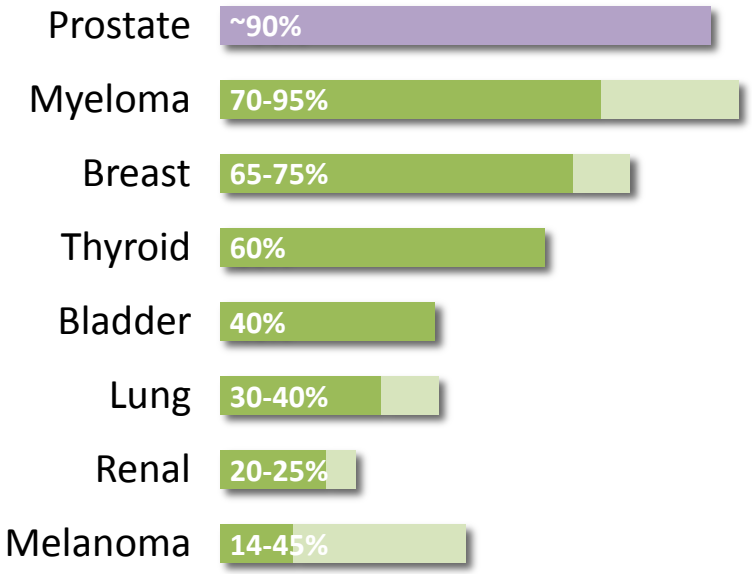






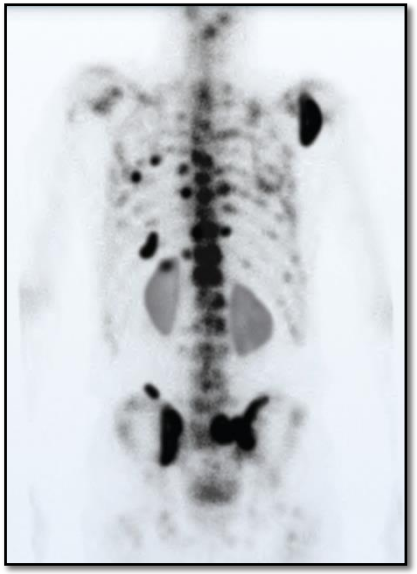
Bone Metastases: Very Common in Prostate Cancer

ESTIMATED INCIDENCE[1,3,a]



It is estimated that >350,000 people die with bone metastases annually in the US[2]

BONE METASTASIS

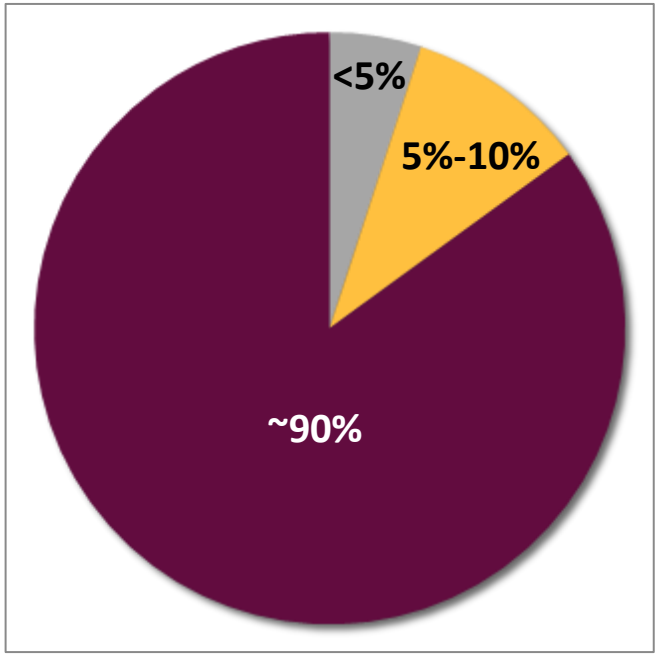


Bone metastasis occurs in most prostate cancer patients during the natural course of their disease[3] and typically targets the lumbar spine and pelvis[4]

a. Incidence of bone metastases at autopsy.

1. Coleman R, et al. *Cancer Treat Rev*. 2001;27:165-176. **2.** Mundy G. *Nat Rev Cancer*. 2002;2:584-593. **3.** Goh P, et al. *Curr Oncol*. 2007;14:9-12. **4.** Bubendorf L, et al. *Hum Pathol*. 2000;31:578-583.

Bone is the Most Common Site of Metastases in Prostate Cancer Patients



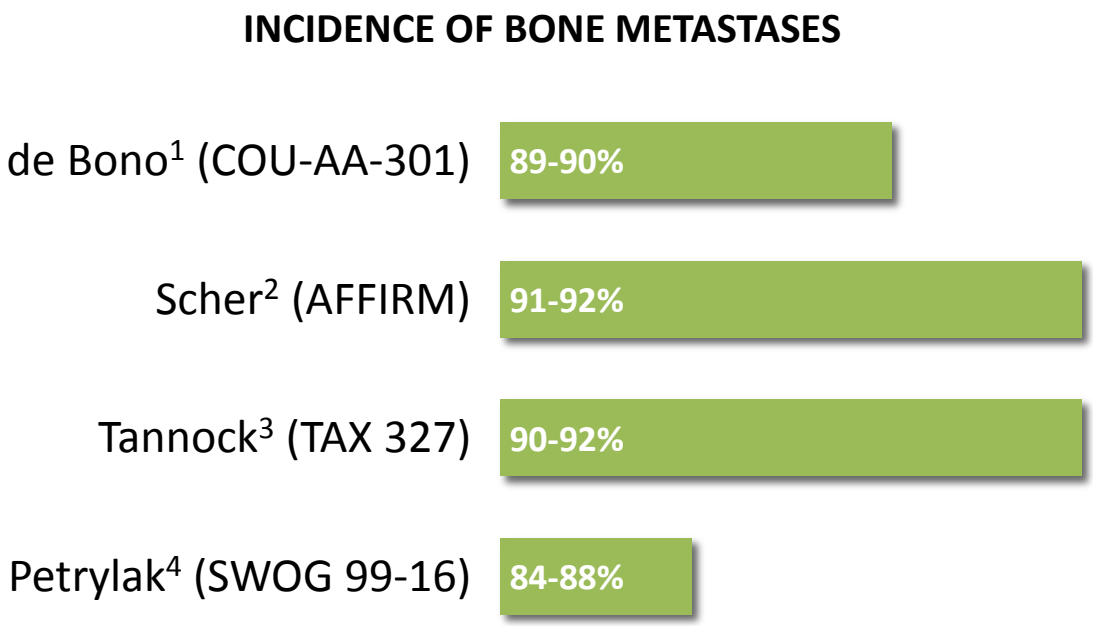
SITE OF METASTASES[1,2]

Debilitating bone pain is experienced by up to 80% of patients with bone metastases[3]

Visceral metastases are less common and may occur in the lungs or liver[4]

1. de Bono J, et al. *N Engl J Med*. 2011;364:1995-2005. **2.** Scher H, et al. *N Engl J Med*. 2012;367:1187-1197 supplemental appendix . **3.** Goh P, et al. *Curr Oncol*. 2007;14:9-12.
4. Bubendorf L, et al. *Hum Pathol*. 2000;31:578-583.

Approximately 90% of Men with Metastatic CRPC in Clinical Trials Have Evidence of Bone Metastases[1-4]



1. de Bono J, et al. *N Engl J Med*. 2011;364:1995-2005. **2.** Scher H, et al. *N Engl J Med*. 2012;367:1187-1197, supplemental appendix.
3. Tannock I, et al. *N Engl J Med*. 2004;351:1502-1512. **4.** Petrylak D, et al. *N Engl J Med*. 2004;351:1513-1520.

Bisphosphonates

Non-Nitrogenous

- Etidronate
- Clodronate

Nitrogenous

- Pamidronate
- Alendronate
- Ibandronate
- Risidronate
- Zolendronate

Properties of bisphosphonates

Absorption

- Low oral bioavailability
- Dose = side effects
- Food

Elimination

- renal
- bound to bone

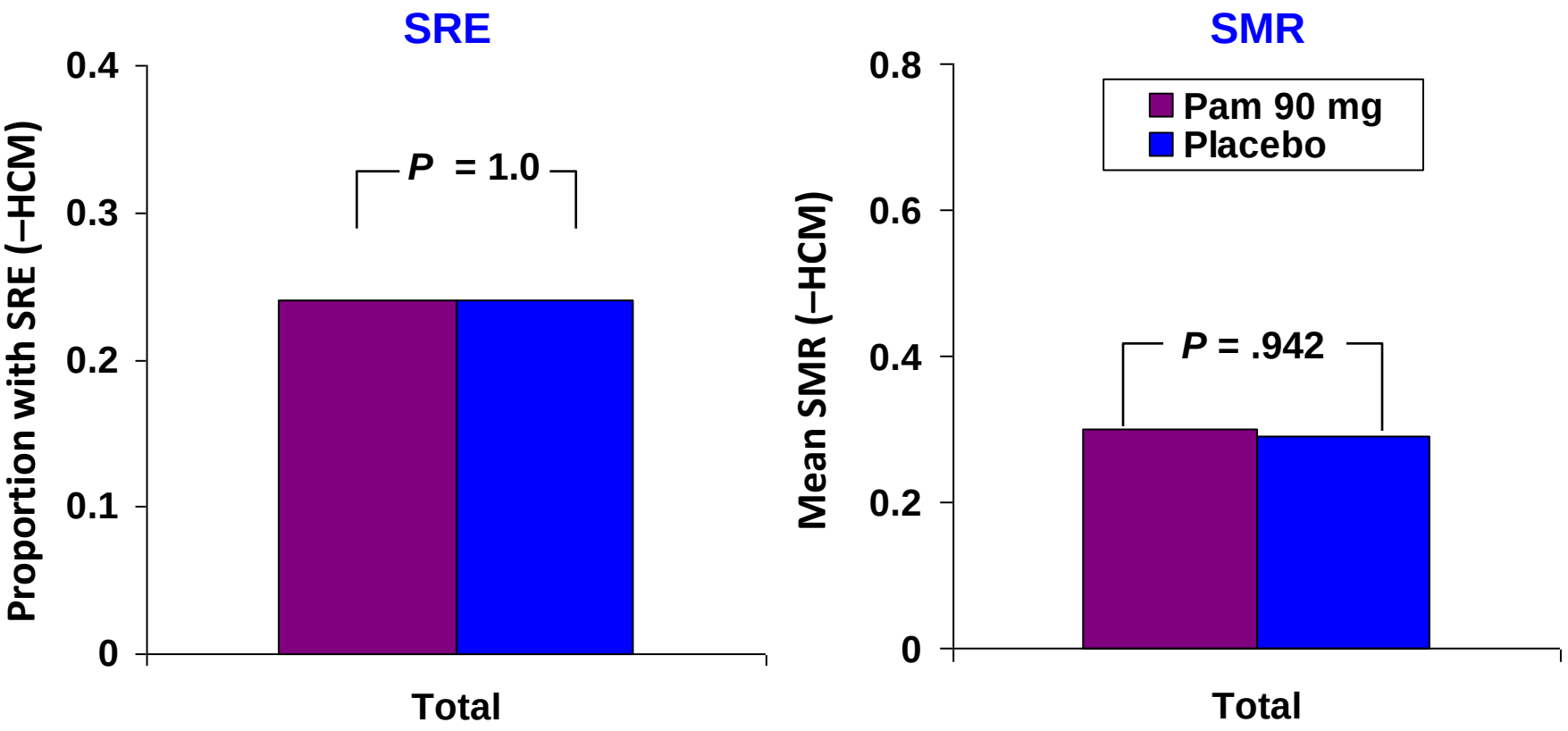
Side Effects

- flu-like symptoms
- bone pain
- GI complaints
- dyspnea
- lower limb oedema

Pamidronate in Prostate Cancer
No Effect on Proportion of Patients With SRE and Mean SMR

(–HCM) at 6 months—Protocols 032 and INT05

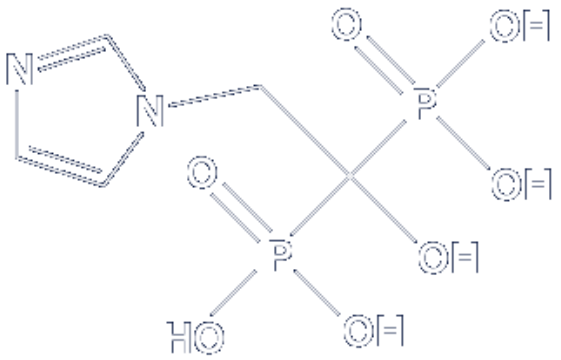
Total N = 378

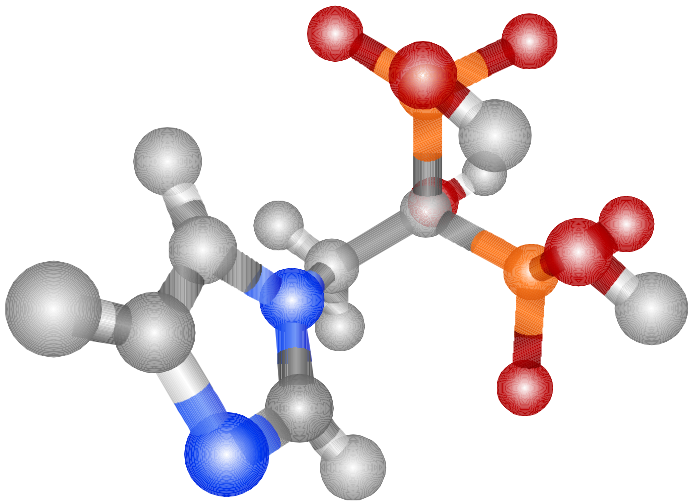


Lipton A, et al. *Cancer Invest*. 2001;20:45-47.

Zoledronic Acid

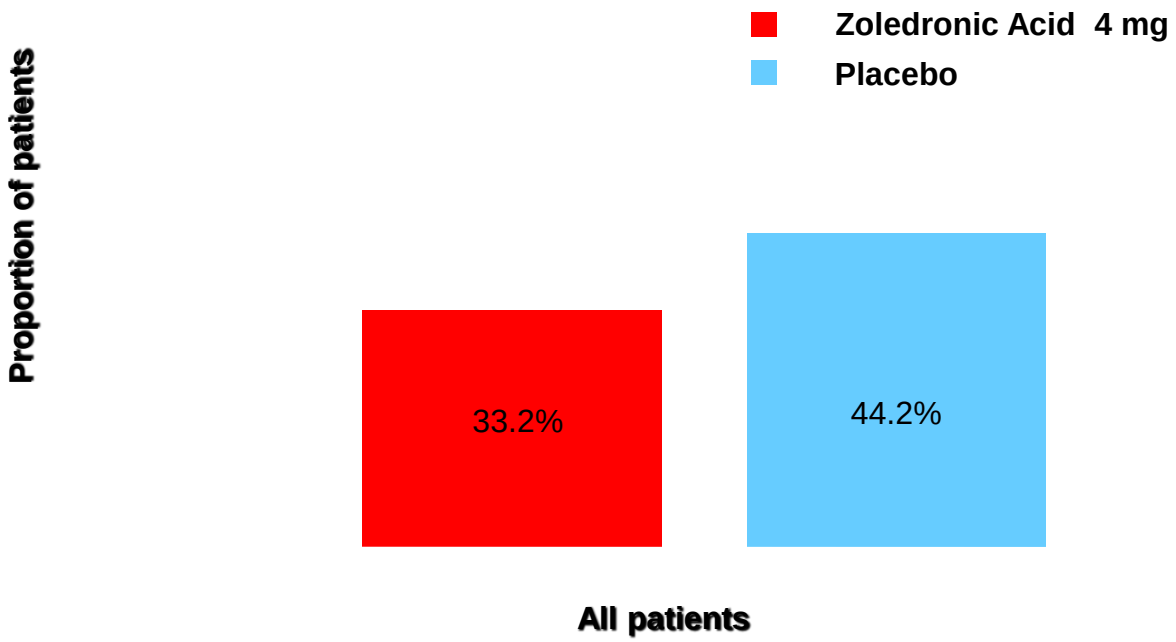
- Highly potent 3rd generation bisphosphonate
- Heterocyclic nitrogen-containing molecule with:
  - A core bisphosphonate moiety
  - An imidazole-ring side chain containing 2 critically positioned nitrogen atoms





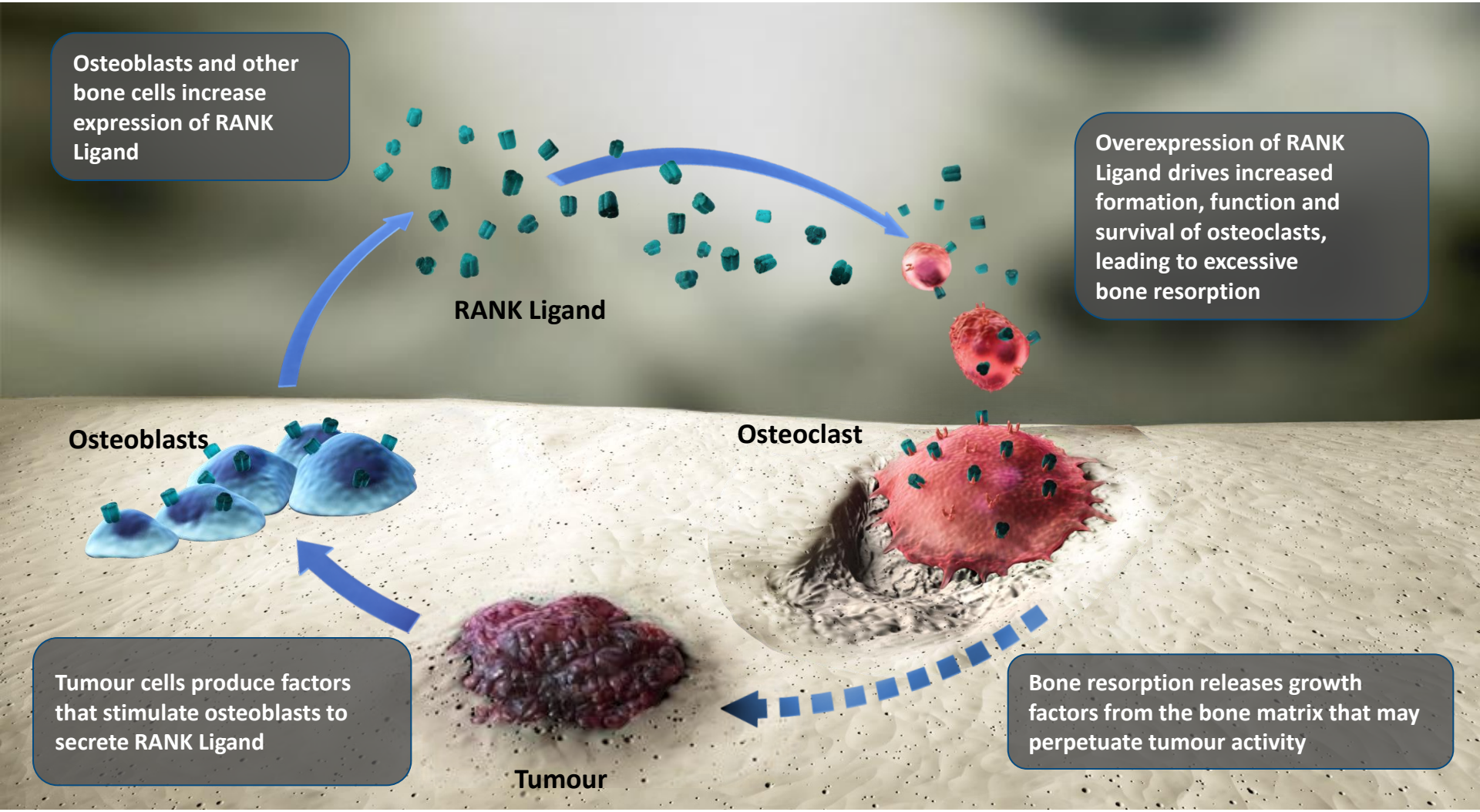
Green JR, et al. *J Bone Miner Res*. 1994;9:745-751.
Green JR, et al. *Pharmacol Toxicol.* 1997;80:225-230.

Patients with skeletal-related events (SRE)



Saad F, et al. Journal of the National Cancer Institute. 2002; 94 : 1458 - 1468.

A vicious cycle of bone destruction may develop in the presence of tumour cells

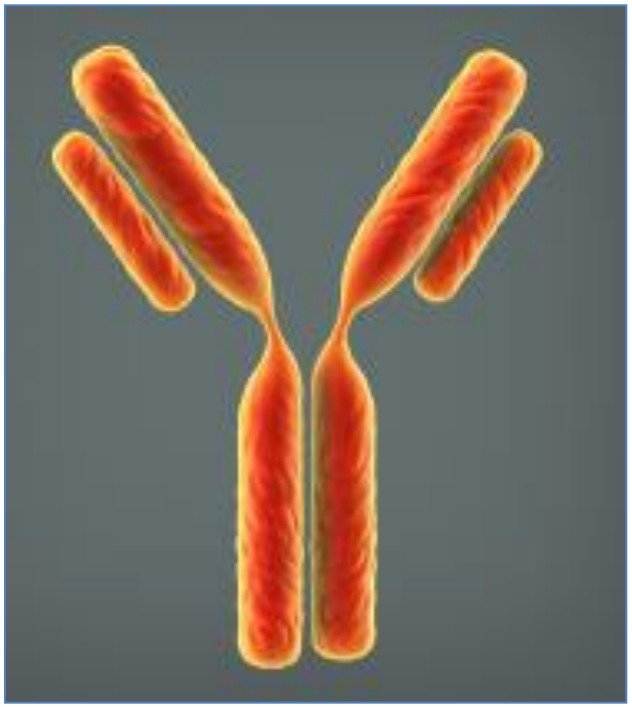


Adapted from Roodman GD. N Engl J Med 2004;350:1655–64;
Mundy GR. Nat Rev Cancer 2002;2:584–93.

Denosumab has been developed as two products with different dosing regimens and therapeutic indications

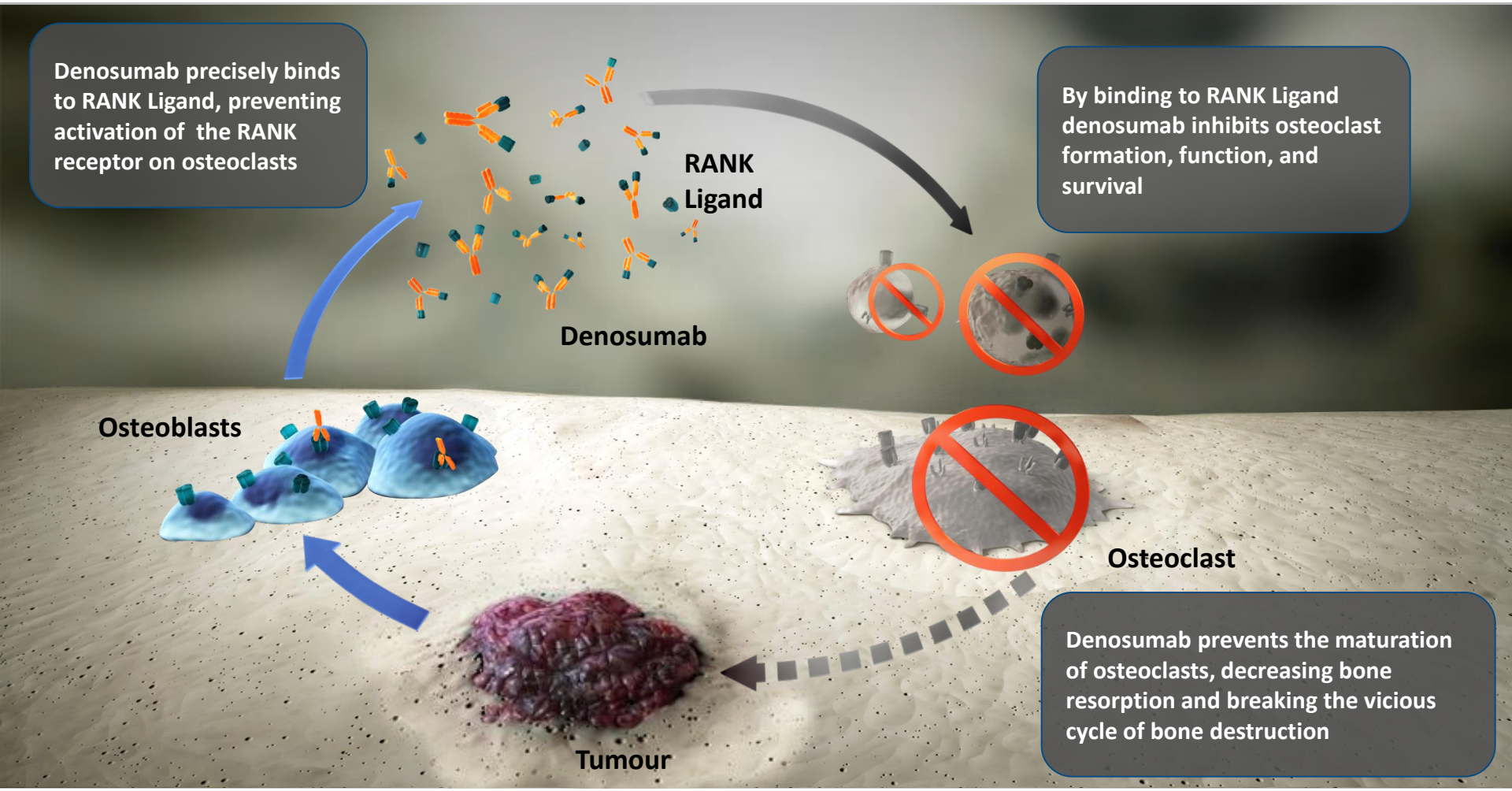
- Denosumab is a fully human monoclonal antibody that binds human RANK Ligand with high affinity and specificity[1]

	Prolia® (denosumab)[2]	XGEVA® (denosumab)[3]
Dose	**60 mg SC**	**120 mg SC**
Regimen	**Every 6 months**	**Every 4 weeks**
Indication(s)	Treatment of **bone loss associated with hormone ablation** in men with prostate cancer at increased risk of fractures Treatment of **osteoporosis** in postmenopausal women at increased risk of fractures	Approved in UK for prevention of SREs in patients with **bone metastases from solid tumours**



1.McClung MR et al. New Engl J Med 2006;354:821–31;
2. Prolia® (denosumab) summary of product characteristics (SmPC), Amgen.
3. XGEVA® (denosumab) summary of product characteristics (SmPC), Amgen

Denosumab targets RANK Ligand to break the vicious cycle



Adapted from Roodman GD. N Engl J Med 2004;350:1655–64;
Mundy GR. Nat Rev Cancer 2002;2:584–93.

Denosumab Versus Zoledronic Acid for Treatment of Bone Metastases in Men With Castration-Resistant Prostate Cancer: A Randomised, Double-Blind Study

Fizazi K, et al. Lancet. 2011;377:813–822

Job Bag Number - DMO-UKIRE-AMG-224-2011 - 103
Date of Preparation – August 2011

Study Design: International, Randomized, Double-Blind, Active-Controlled

Key Inclusion Criteria

- Castration-resistant prostate cancer and ≥1 bone metastases

Key Exclusion Criteria

- Current or prior IV bisphosphonate treatment

N = 950 denosumab 120 mg SC
and placebo IV Q4W

Supplemental calcium and vitamin D strongly recommended

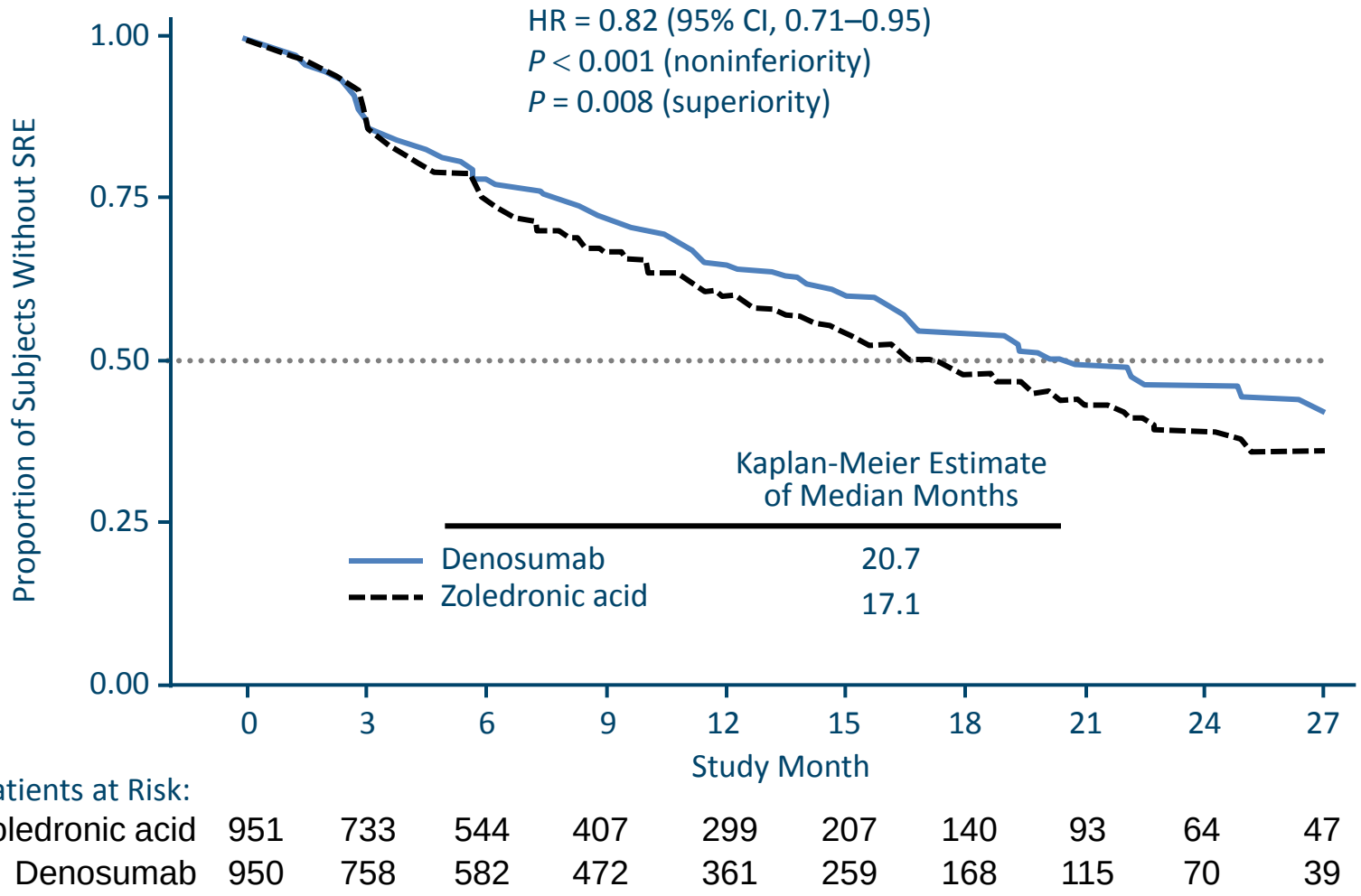
N = 951 zoledronic acid 4 mg IV*
and placebo SC Q4W

Primary Endpoint	• Time to first on-study skeletal-related event (SRE) (noninferiority)
Secondary Endpoints	• Time to first on-study SRE (superiority) • Time to first and subsequent on-study SRE(s) (superiority)

*Per protocol and IV zoledronic acid label, product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine. No SC dose adjustments made due to increased serum creatinine.

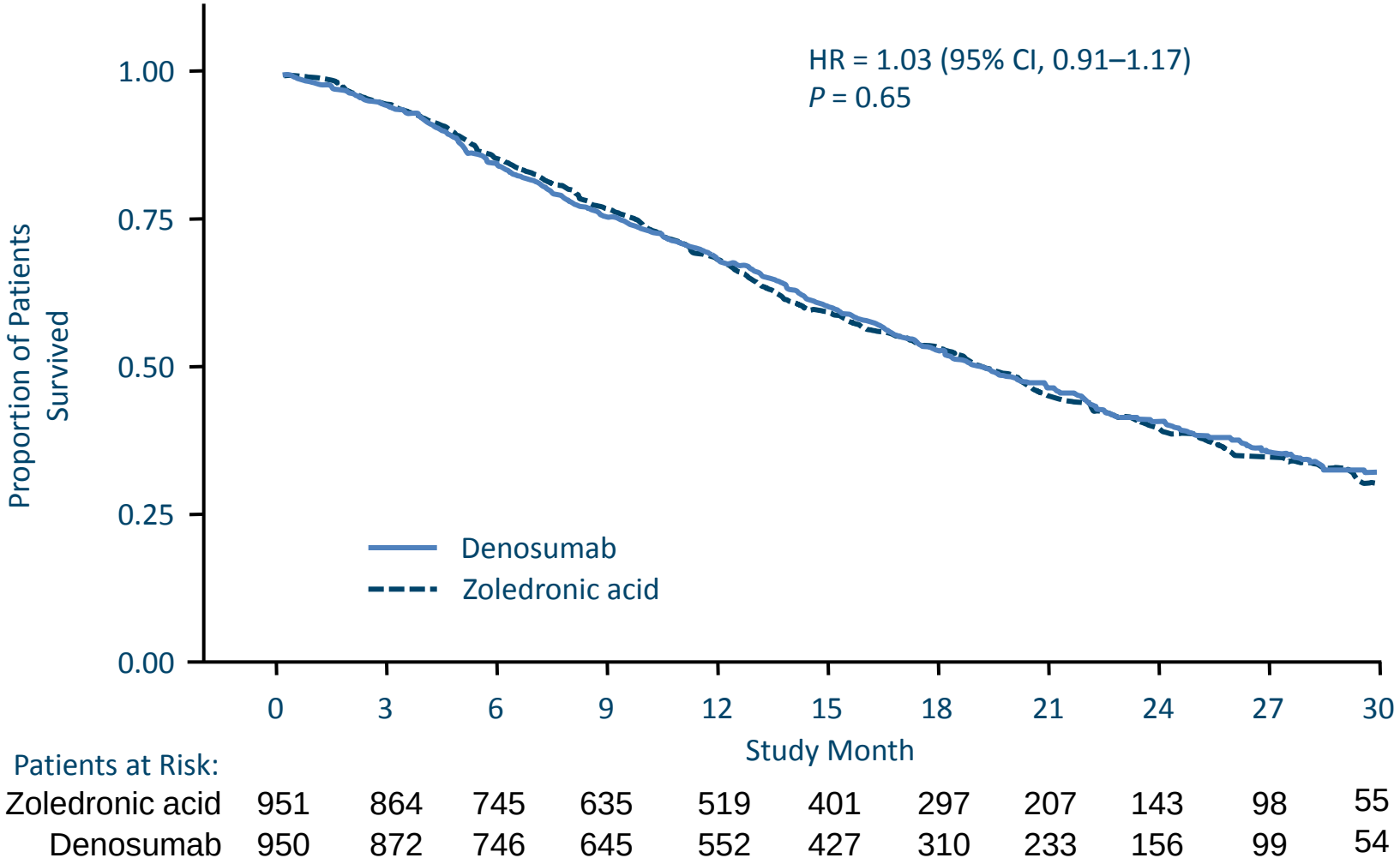
Fizazi K, et al. Lancet. 2011;377:813–822.

Endpoint: Time to First On-Study SRE



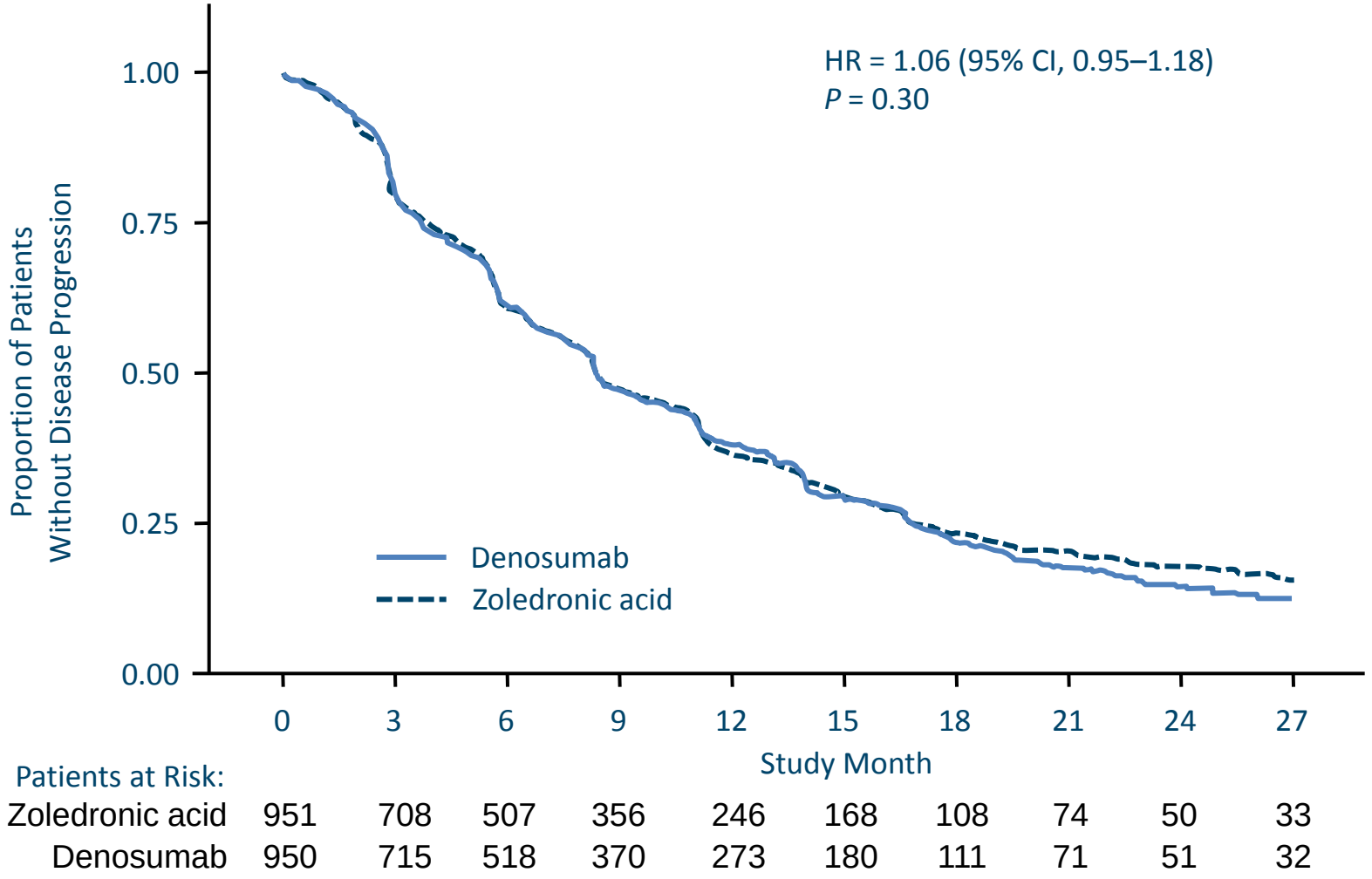
Fizazi K, et al. Lancet. 2011;377:813–822.

Exploratory Endpoint



Fizazi K, et al. Lancet. 2011;377:813–822.

Exploratory Endpoint: Overall Disease Progression



Fizazi K, et al. Lancet. 2011;377:813–822.

Summary of Adverse Events

Patient Incidence	Denosumab (N = 943) n (%)	Zoledronic Acid (N = 945) n (%)
Any adverse event (AE)	916 (97)	918 (97)
Most Common AEs in Either Arm		
Anaemia	337 (36)	341 (36)
Back pain	304 (32)	287 (30)
Decreased appetite	267 (28)	274 (29)
Nausea	272 (29)	245 (26)
Fatigue	257 (27)	222 (23)
CTCAE grade 3 or 4 AEs	678 (72)	628 (66)
Serious AEs	594 (63)	568 (60)
AEs leading to treatment discontinuation	164 (17)	138 (15)

Hypocalcaemia occurred more frequently in the denosumab arm vs the zoledronic acid arm (121 [13%] vs 55 [6%]).
CTCAE = Common Terminology Criteria for Adverse Events.
Fizazi K, et al. Lancet. 2011;377:813–822.

Summary of Adverse Events *(continued)*

Patient Incidence	Denosumab (N = 943) n (%)	Zoledronic Acid (N = 945) n (%)
Infectious AEs*	402 (43)	375 (40)
Acute phase reactions (first 3 days)	79 (8)	168 (18)
Renal AEs†	139 (15)	153 (16)
Cumulative rate of osteonecrosis of the jaw (ONJ)‡	22 (2)	12 (1)
Year 1	10 (1)	5 (1)
Year 2	22 (2)	8 (1)
Hypocalcaemia	121 (13)	55 (6)
New primary malignancy	18 (2)	10 (1)

*Based on Medical Dictionary for Regulatory Activities (MedDRA; version 12.1) system organ class categorization of infections and infestations.
†Includes renal failure, increased blood creatinine, acute renal failure, renal impairment, increased blood urea, chronic renal failure, oliguria, hypercreatininaemia, anuria, azotemia, decreased creatinine renal clearance, decreased urine output, abnormal blood creatinine, proteinuria, decreased glomerular filtration rate, and nephritis.
‡P = 0.09.

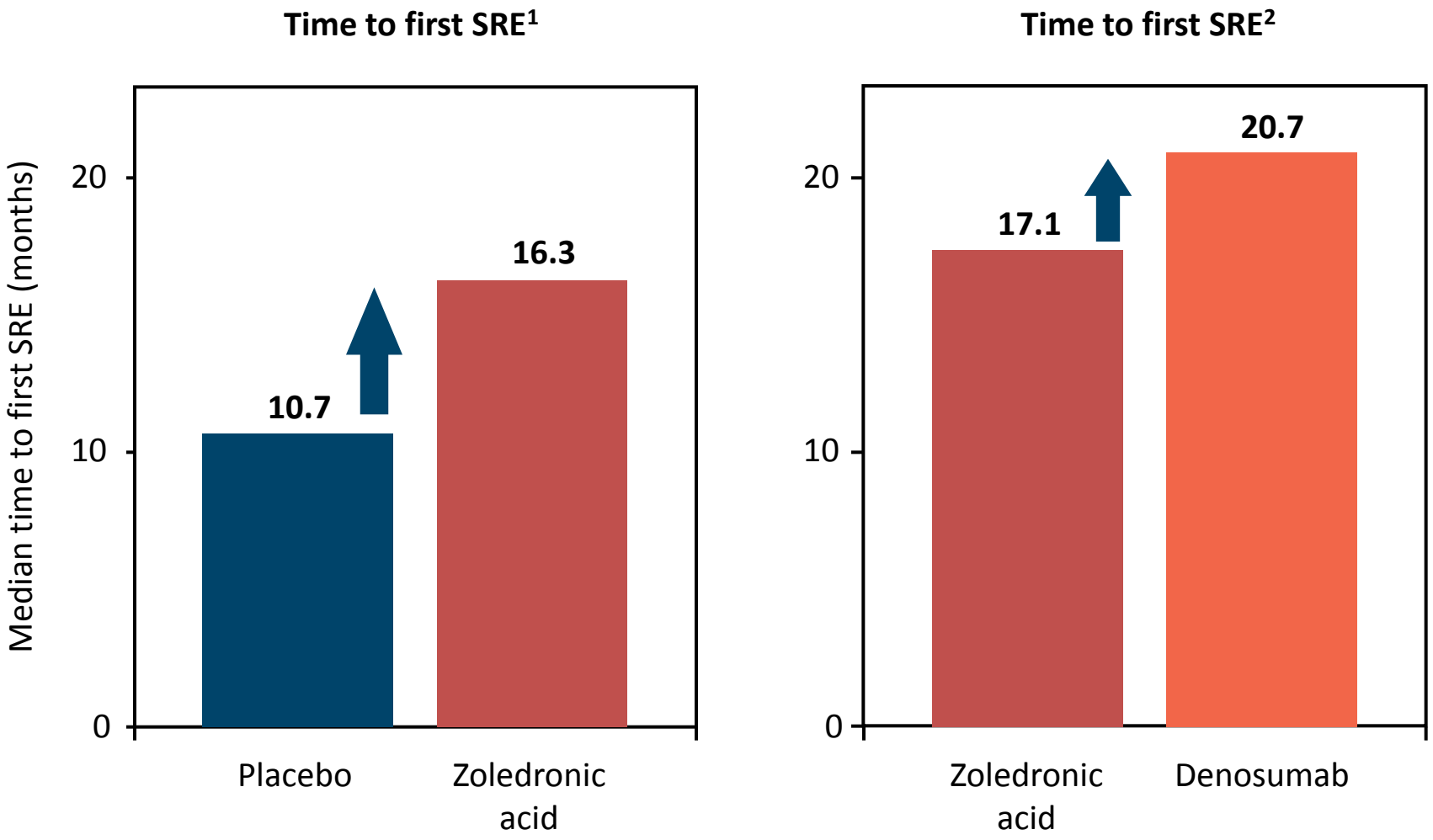
Fizazi K, et al. Lancet. 2011;377:813–822.

Patient Incidence	Denosumab n (%)	Zoledronic Acid n (%)
Patients with positively adjudicated ONJ	22 (2)	12 (1)
Risk Factors		
Tooth extraction, dental appliance, or poor oral hygiene	17 (77)	10 (83)
Chemotherapy	14 (64)	9 (75)
Treatment*		
Limited surgery (eg, debridement)	10 (45)	3 (25)
Bone resection	2 (9)	1 (8)

*As of April 2010.

Fizazi K, et al. Lancet. 2011;377:813–822.

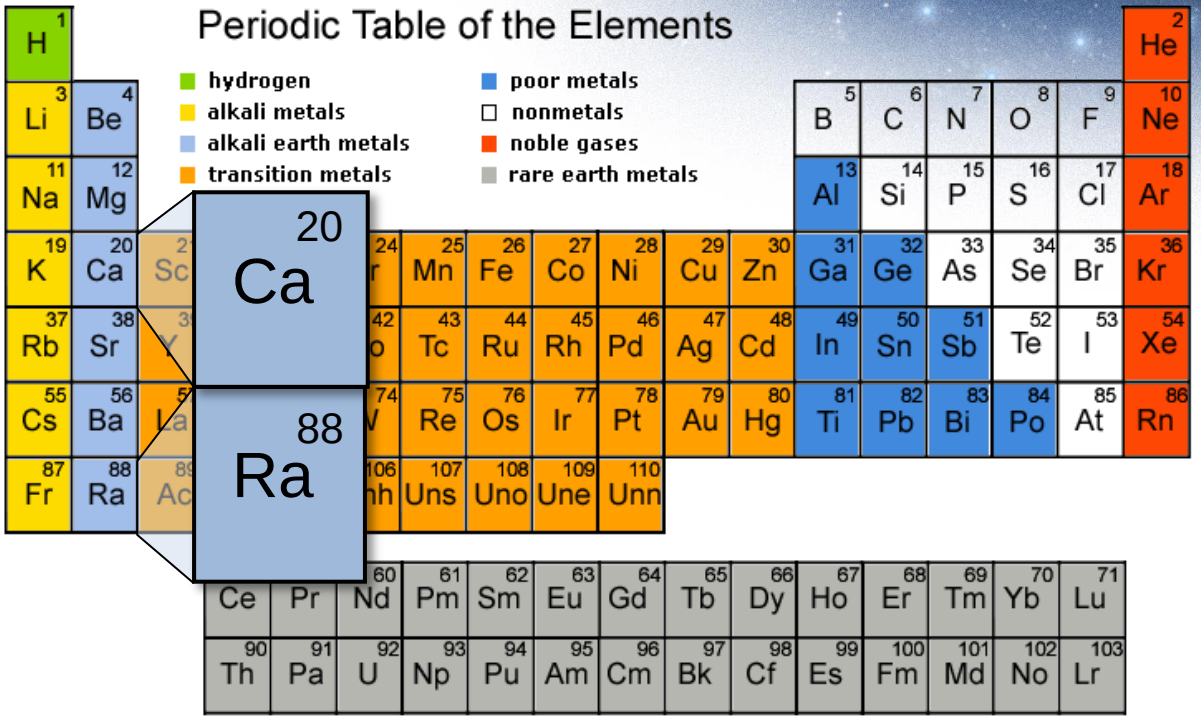
Denosumab provides meaningful additional benefit over current standard of care



1. Saad F et al. J Natl Cancer Inst 2004;96:879–82;
2. Fizazi K et al. Lancet 2011;377:813–22.

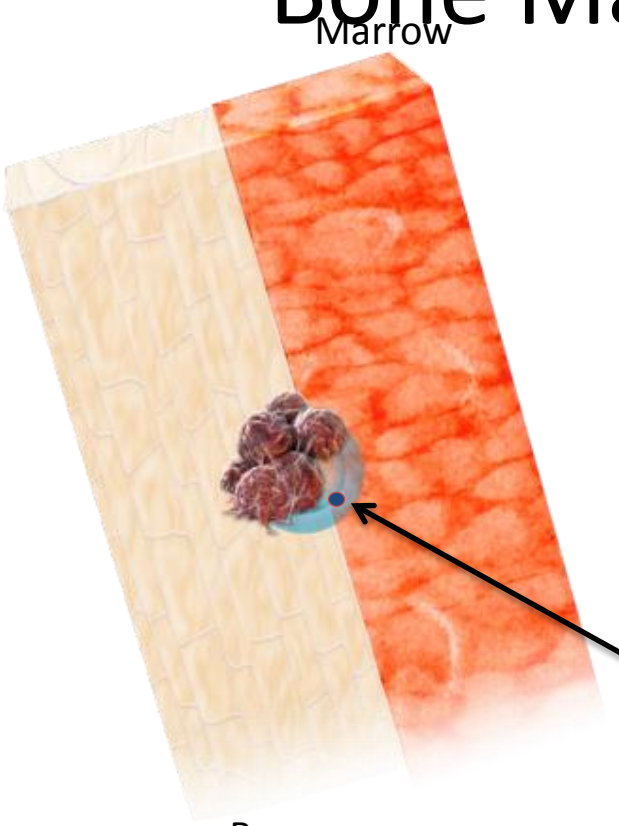
Radium-223 Dichloride is an Investigational Alpha-particle Emitting Radiopharmaceutical in Development for Cancer Patients with Prostate Bone Metastases

- Radium belongs to the same group of elements as Calcium
- Radium is a calcium-mimetic element
- Radium (Ra-223) is quickly taken up in newly forming bone

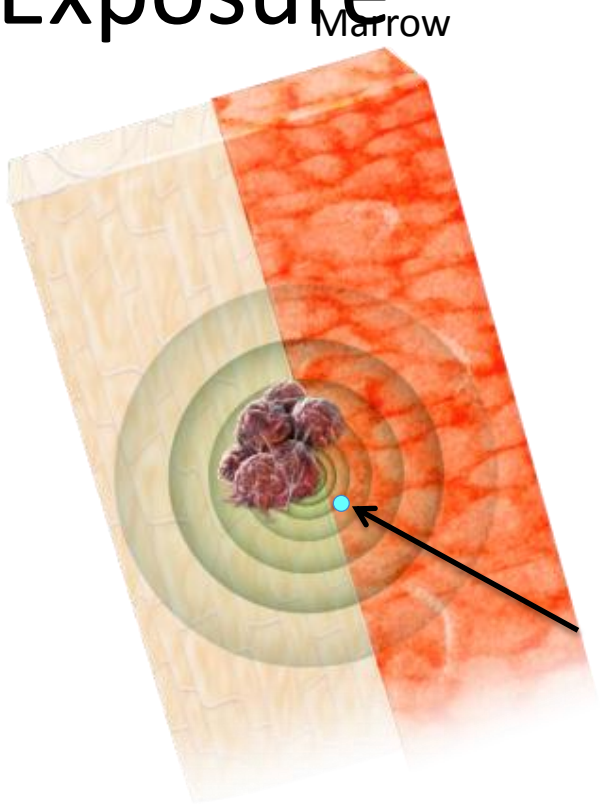


SOURCE: Parker C, et al. *N Engl J Med.* 2013;369(3):213-23.

Short Range of α-Emitters Reduces Bone Marrow Exposure[1]



Range of α-particle:
(short range – 2 to 10 cell diameters[2])



Range of β-particle:
(long range – 10 to 1000 cell diameters[2])

SOURCE: 1. Henriksen G, et al. *Cancer Res.* 2002;62:3120–3125. **2.** Brechbiel MW. *Dalton Trans.* 2007;43:4918-4928.

Radium-223 Dichloride Solution for Injection

- Standardized, stable, vial-based product
- Ready to use, direct injection via syringe
- 10 mL vial; 6 mL solution,
- 6 MBq (162 µCi)
  radium-223 dichloride
  (at reference date)
- Radioactivity concentration
  = 1000 kBq/mL (at reference day)
- Detectable with standard dose calibrators/probes
- Shelf-life: 28 days
  - Half live 11.4 days
- No long-lived radioactive decay products

Easy-to-implement radiation safety practices

Standard safety practices, according to local guidance and regulation, are adequate for handling

Requires only basic shielding for healthcare personnel

Xofigo can be disposed of as per local disposal guidelines in a suitable, clinical, radioactive waste stream after an appropriate amount of time (decay-in-storage)

SOURCE 1. Xofigo SmPC November 2013

Xofigo is indicated for the treatment of adults with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastases.

- Radium-223 Phase III ALSYMPCA trial

ALSYMPCA: Study Design

PATIENTS (N=921)

- Confirmed symptomatic CRPC
- ≥2 bone metastases
- No known visceral metastases
- Post-docetaxel, unfit for docetaxel, or refused docetaxela

STRATIFICATION

- Total ALP:
  <220 U/L vs ≥220 U/L
- Bisphosphonate use: Yes vs No
- Prior docetaxel:
  Yes vs No

Radium-223 (50 kBq/kg IV) 6 injections at 4-week intervals + best standard of care

Placebo (saline) 6 injections at 4-week intervals + best standard of care

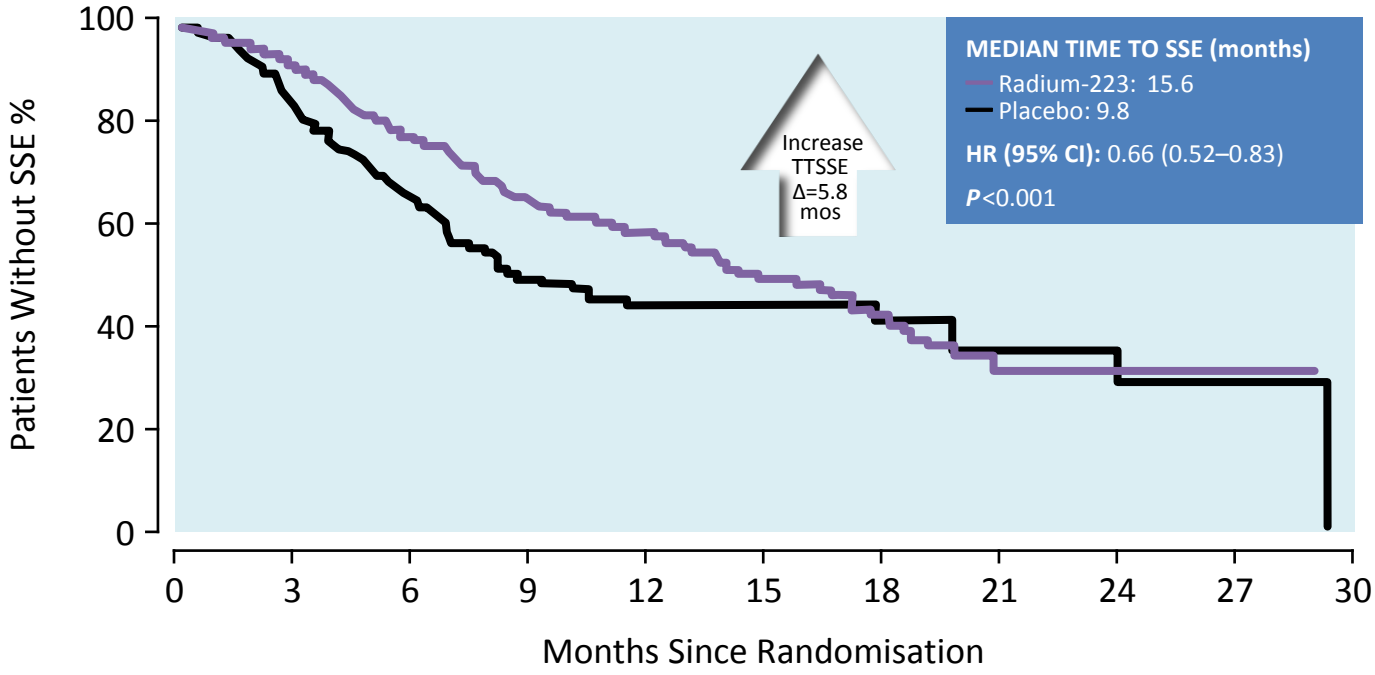
- 136 centers in 19 countries
- Planned follow-up is 3 years

- ALSYMPCA was halted early after the positive efficacy results reported from a planned interim analysis when 314 deaths occurred. An updated analysis of efficacy and safety was performed from all 921 enrolled patients when 528 deaths had occurred.

ALP, alkaline phosphatase; ALSYMPCA, ALpharadin in SYMptomatic Prostate CAncer; CRPC, castration-resistant prostate cancer. Unfit for docetaxel includes patients who were ineligible for docetaxel, refused docetaxel, or lived where docetaxel was unavailable. Best standard of care defined as a routine standard of care at each center, e.g., local external beam radiation therapy, corticosteroids, anti-androgens, oestrogens (e.g., stilbestrol), estramustine, or ketoconazole.

SOURCE: Parker C, et al. *N Engl J Med*. 2013;369(3):213-23.

ALSYMPCA Updated Analysis: Radium-223 Significantly Improved Time to SSE



Radium-223	614	496	342	199	129	63	31	8	8	1	0
Placebo	307	211	117	56	36	20	9	7	4	1	0

SOURCE: Parker C, et al. *N Engl J Med.* 2013;369(3):213-23.

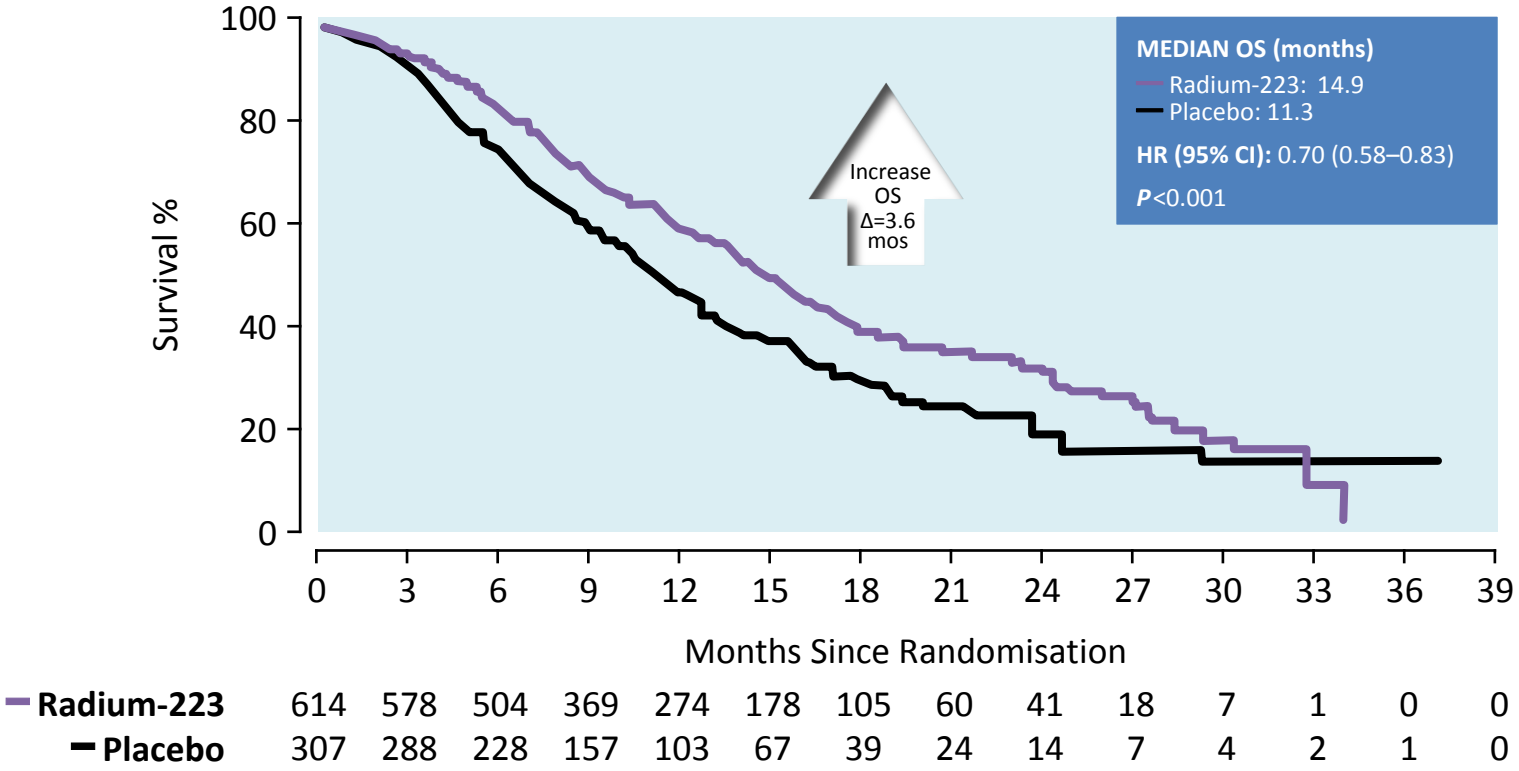
ALSYMPCA Updated Analysis Adverse Events of Interest

	All grades		Grade 3 or 4	
Patients with AEs n (%)	**Radium-223 n= 600**	**Placebo n=301**	**Radium-223 n=600**	**Placebo n=301**
Haematologic				
Anaemia	187(31)	92(31)	76(13)	39(13)
Neutropenia	30(5)	3(1)	13(3)	2(1)
Thrombocytopenia	69(12)	17(6)	38(6)	6(2)
Non-haematologic				
Bone pain	300(5)	187(62)	125(21)	78(26)
Diarrhoea	151(25)	45(15)	9(2)	5(2)
Nausea	213(36)	104(35)	10(2)	5(2)
Vomiting	111(18)	41(14)	10(2)	7(2)
Constipation	108(18)	64(21)	6(1)	4(1)

SOURCE: Parker C, et al. *N Engl J Med.* 2013;369(3):213-23.

ALSYMPCA Updated Analysis: Radium-223 Significantly Improved Overall Survival

The updated analysis confirmed the 30% reduction in risk of death (HR=0.70) for patients in the radium-223 group compared with placebo.



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

SOURCE: Parker C, et al. *N Engl J Med.* 2013;369(3):213-23.

Thank you for your attention!

Questions?