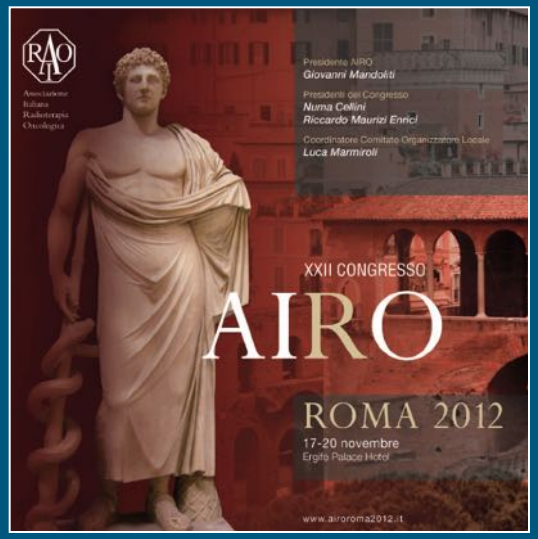


Il rank-ligando nelle complicanze scheletriche da metastasi ossee

Umberto Ricardi
Università di Torino

Agenda

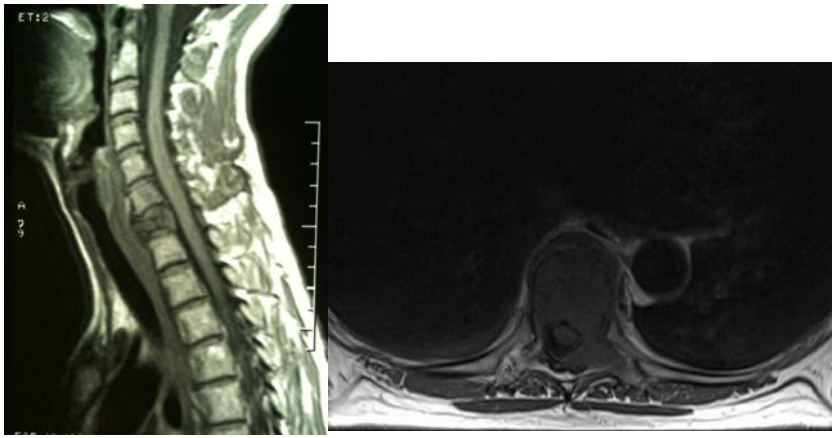
- Burden of bone metastases from solid tumors
- Unmet medical need
- The role of rank-ligand inhibition
- Clinical results of denosumab in SRE prevention
- Conclusions

Agenda

- **Burden of bone metastases from solid tumors**
- Unmet medical need
- The role of rank-ligand inhibition
- Clinical results of denosumab in SRE prevention
- Conclusions

Advanced solid tumours commonly metastasise to bone

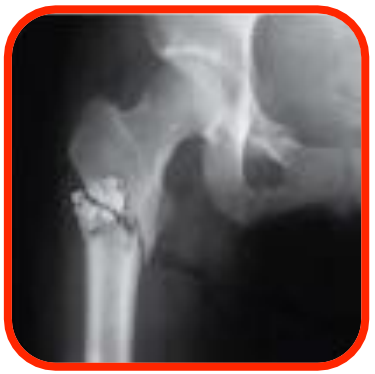
Cancer	Incidence of bone metastases
Breast cancer	65–75%
Prostate cancer	65–75%
Lung cancer	30–40%



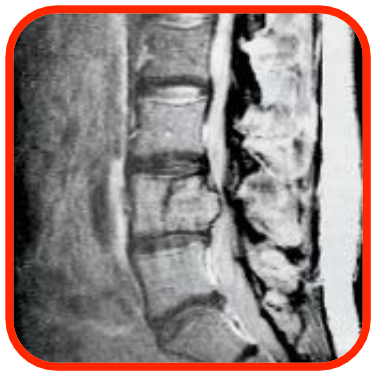
Bone metastases may result in clinically significant and serious consequences of skeletal-related events (SREs)

- SREs are defined as:

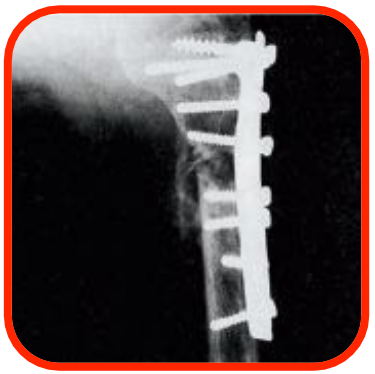
Radiation to bone



Pathological fracture



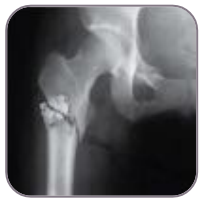
Spinal cord compression

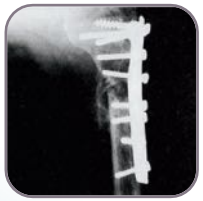


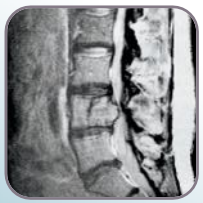
Surgery to bone

Saad F, et al. J Natl Cancer Inst 2004;96:879-82; .

SREs have associated down-stream implications







SRE	Potential complications
Pathological fracture	Extended healing time Reduced survival Loss of mobility Need for care/ nursing home residence (especially hip fracture)
Radiation to bone	Potential for ‘pain flare’ after therapy Myelosuppression Patients’ disconfort (repeat visits for RO treatment)
Surgery to bone	Hospital stay In-hospital mortality rate ~8% High rate of surgical complications High failure rate; inability to restore function
Spinal cord compression	Excruciating pain Need for steroidal medications Repeat visits for radiotherapy Irreversible paraparesis or paraplegia Loss of continence

Radiotherapy for Bone Metastases

Pain relief

'Prophylactic' - prevent fracture

Post surgical fixation

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 4, pp. 965–976, 2011

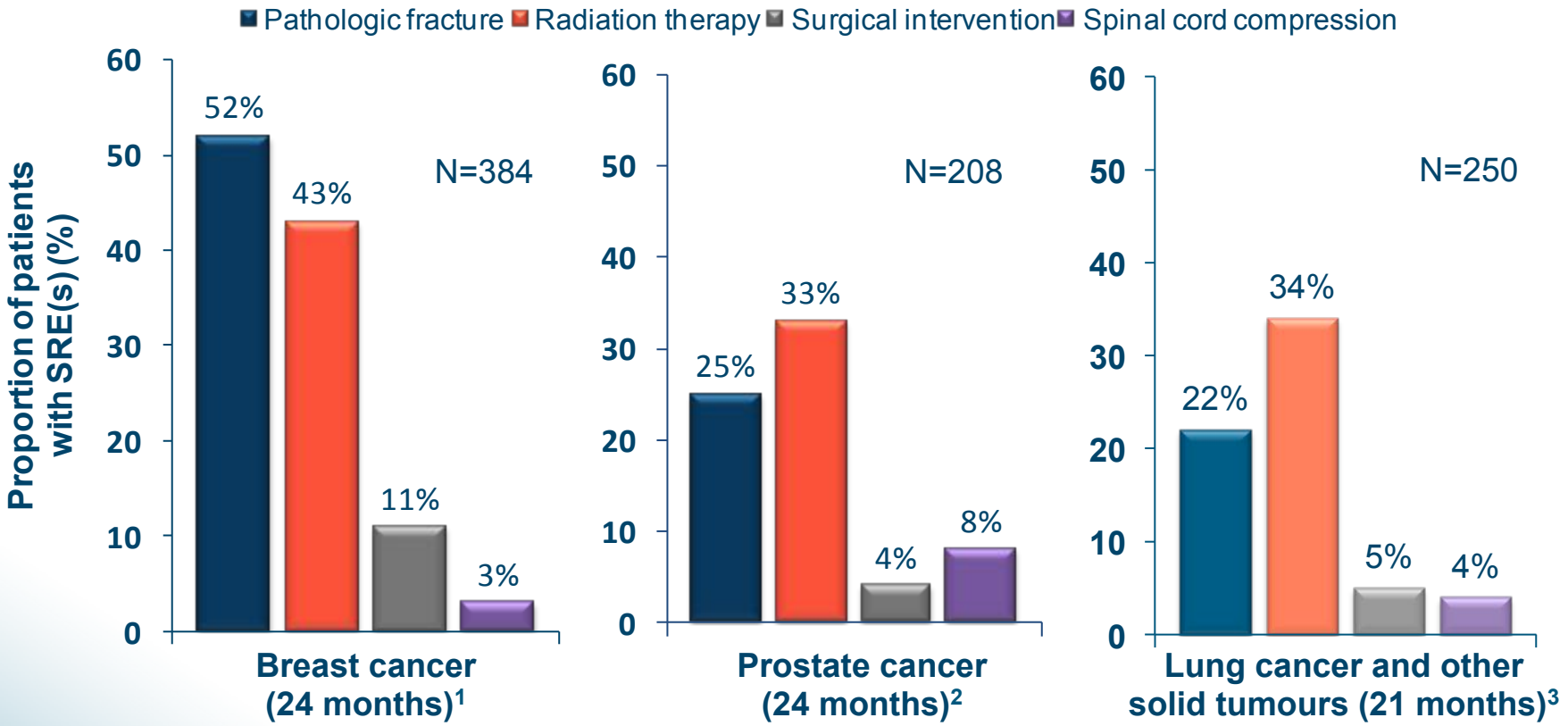
0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.11.026

ASTRO GUIDELINE

PALLIATIVE RADIOTHERAPY FOR BONE METASTASES: AN ASTRO EVIDENCE-BASED GUIDELINE

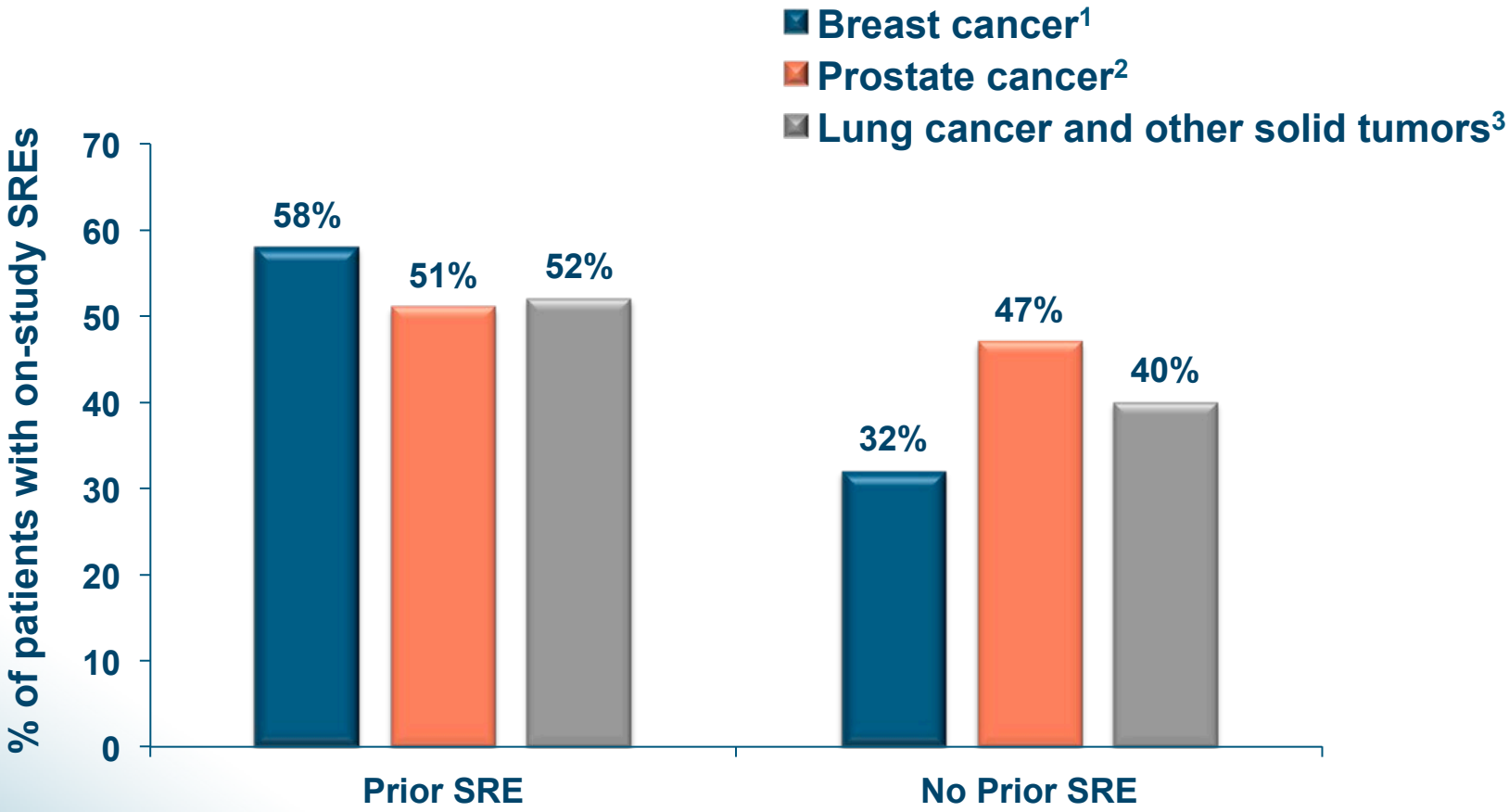
Distribution of SREs in patients with metastatic breast, prostate, and lung cancer



Data are from the placebo arms of 3 major trials of placebo vs. IV bisphosphonate in different tumour types

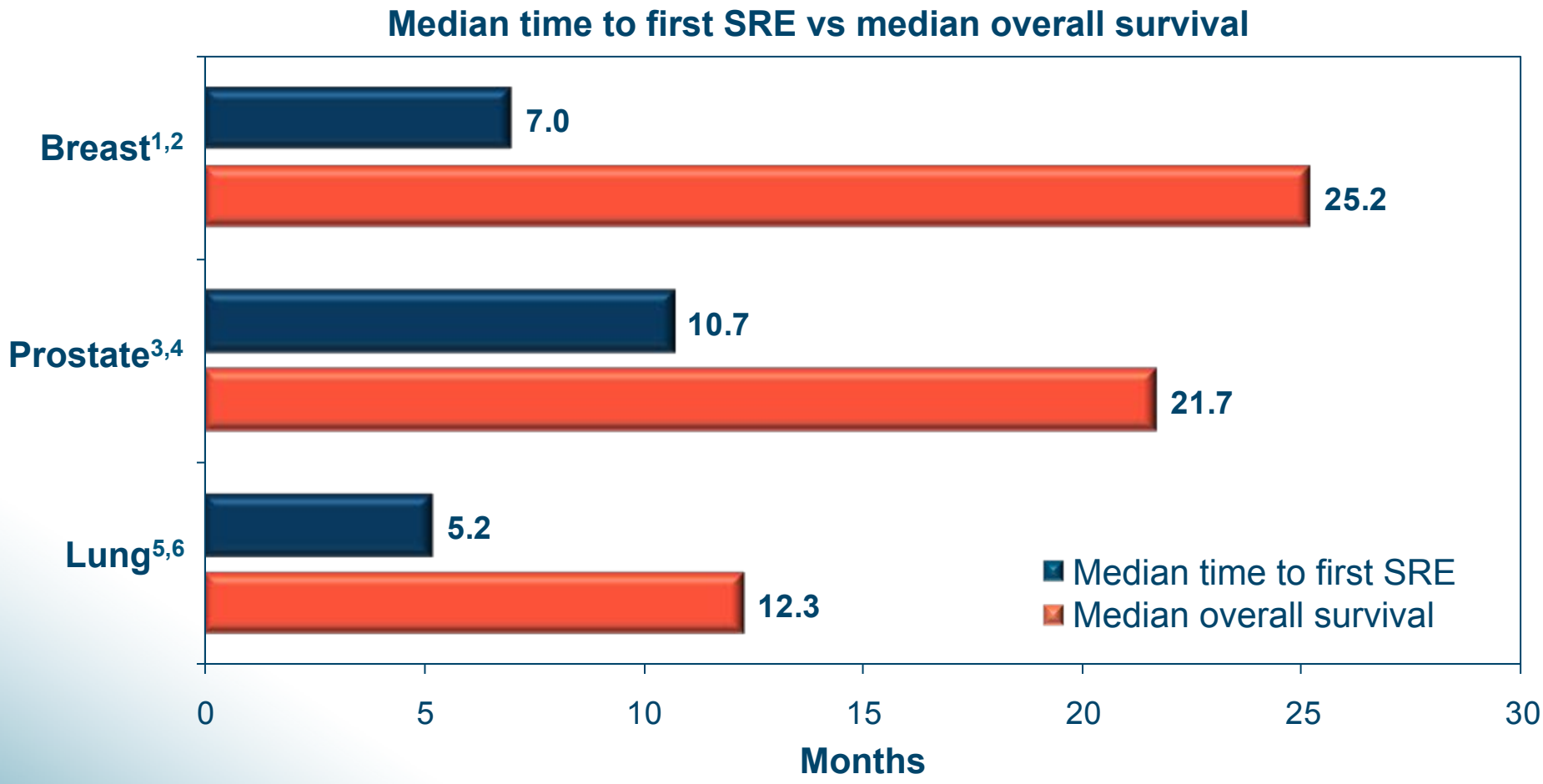
Lipton A, Theriault RL, Hortobagyi GN, et al. Cancer 2000;88:1082–90;
Saad F, Gleason DM, Murray R, et al. J Natl Cancer Inst 2002;94:1458–68;
Rosen LS, et al. Cancer 2004;100:2613-21.

Prior SRE increases the risk for subsequent SREs



1. Kaminski M, et al. Poster presented at: ASCO Annual Meeting. June 5-8, 2004; New Orleans, LA. Abstract 857;
2. Saad F, et al. Clin Genitourin Cancer 2007;5:390-6;
3. Hirsh V, et al. Clin Lung Cancer 2004;6:170-4.

Patients have increased chances of developing SREs as survival times improve



1. Lipton A, et al. Cancer 2000;88:1082-90; 2. Miller K, et al. N Engl J Med 2007;357:2666-76;
3. Saad F, et al. J Natl Cancer Inst 2002;94:1458-68; 4. Kantoff PW, et al. N Engl J Med 2010;363;411-22;
5. Rosen LS, et al. Cancer 2004;100:2613-21; 6. Sandler A, et al. N Engl J Med 2006;355:2542-50.

In clinical practice, decision to treat bone metastasis occurs mostly in case of symptomatic disease

The **decision to treat bone metastasis** is mainly made due to the presence of

- **symptomatic disease** (82%)
- metastatic site (58%)
- potential risk of SREs (55%)

However, **82% of oncologists sometimes decide not to treat bone metastasis**:

- short life expectancy of the patient (62%)
- low performance status (55%)
- asymptomatic metastasis (52%)

The Italian cross-sectional survey of the management of bone metastasis: ZeTa study, Journal of Bone Oncology 2012

In the treatment of SREs, initiation of therapy should start at evidence of bone metastasis

AIOM Associazione Italiana di Oncologia Medica

Visto il beneficio dei bisfosfonati sulla prevenzione anche del primo SRE e sul dolore, viene consigliato di iniziare tale trattamento al momento dell'evidenza radiologica di metastasi ossee anche in assenza di sintomi.

ESMO Metastatic breast

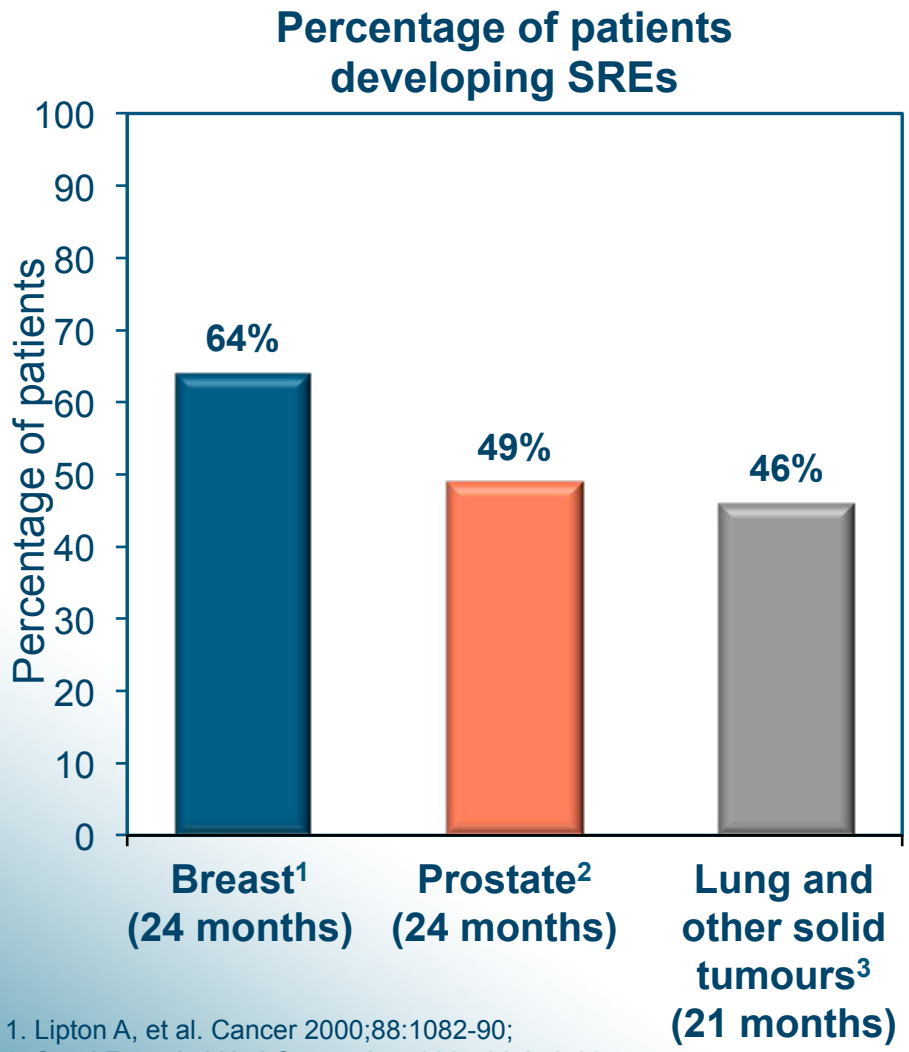
Bone-directed therapy should be started following a diagnosis of bone metastases

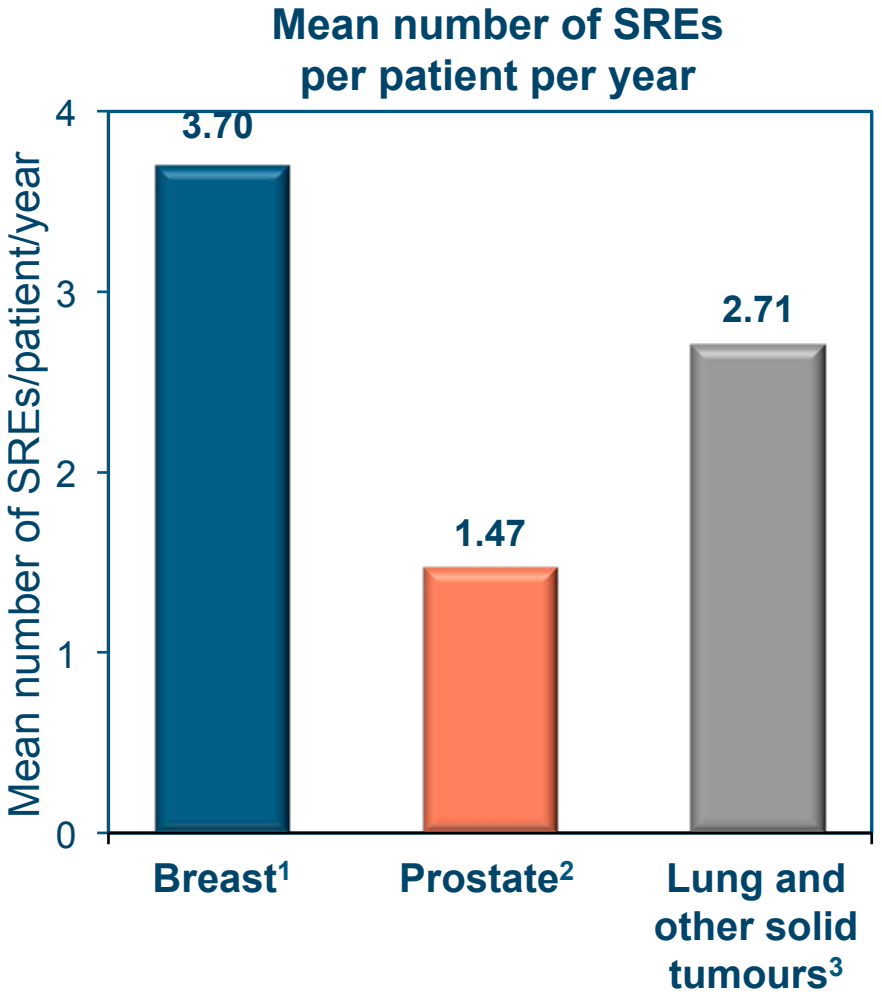
1. Linee Guida AIOM 2010 – Trattamento delle metastasi ossee
3. ESMO Breast Cancer Guidelines 2012, http://www.esmo.org/education-research/esmo-clinical-practice-guidelines/topics/breast-cancer.html

Agenda

- Burden of bone metastases from solid tumors
- **Unmet medical need**
- The role of rank-ligand inhibition
- Clinical results of denosumab in SRE prevention
- Conclusions

SREs are both common and frequent in patients with advanced cancer untreated for bone metastases

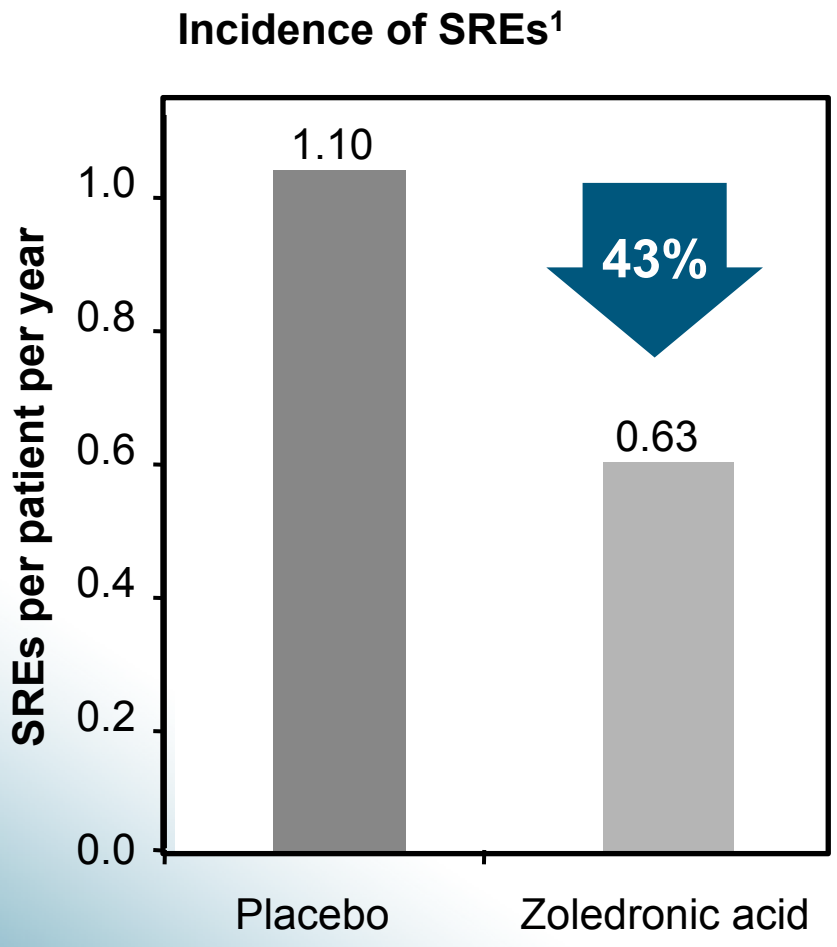


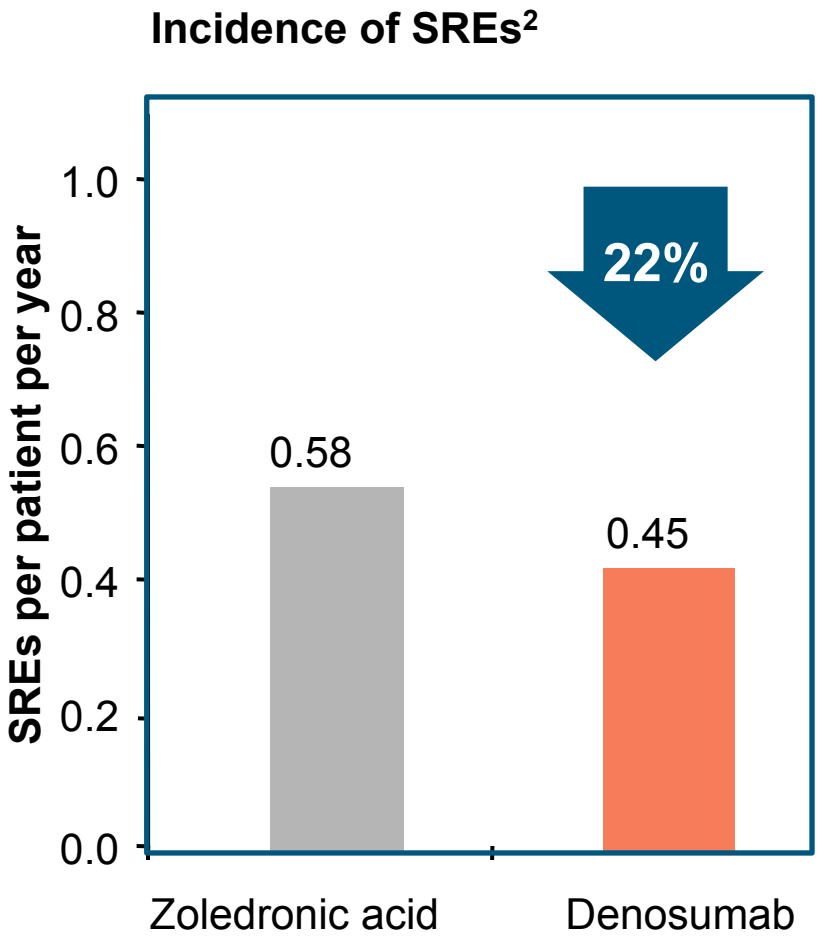


1. Lipton A, et al. Cancer 2000;88:1082-90;
2. Saad F, et al. J Natl Cancer Inst 2004;96:879-82;
3. Rosen LS, et al. Cancer 2004;100:2613-21.

Data are from the placebo arms of 3 major trials of placebo vs. IV bisphosphonate in different tumour types

Denosumab provides meaningful additional benefit over current standard of care (breast cancer)



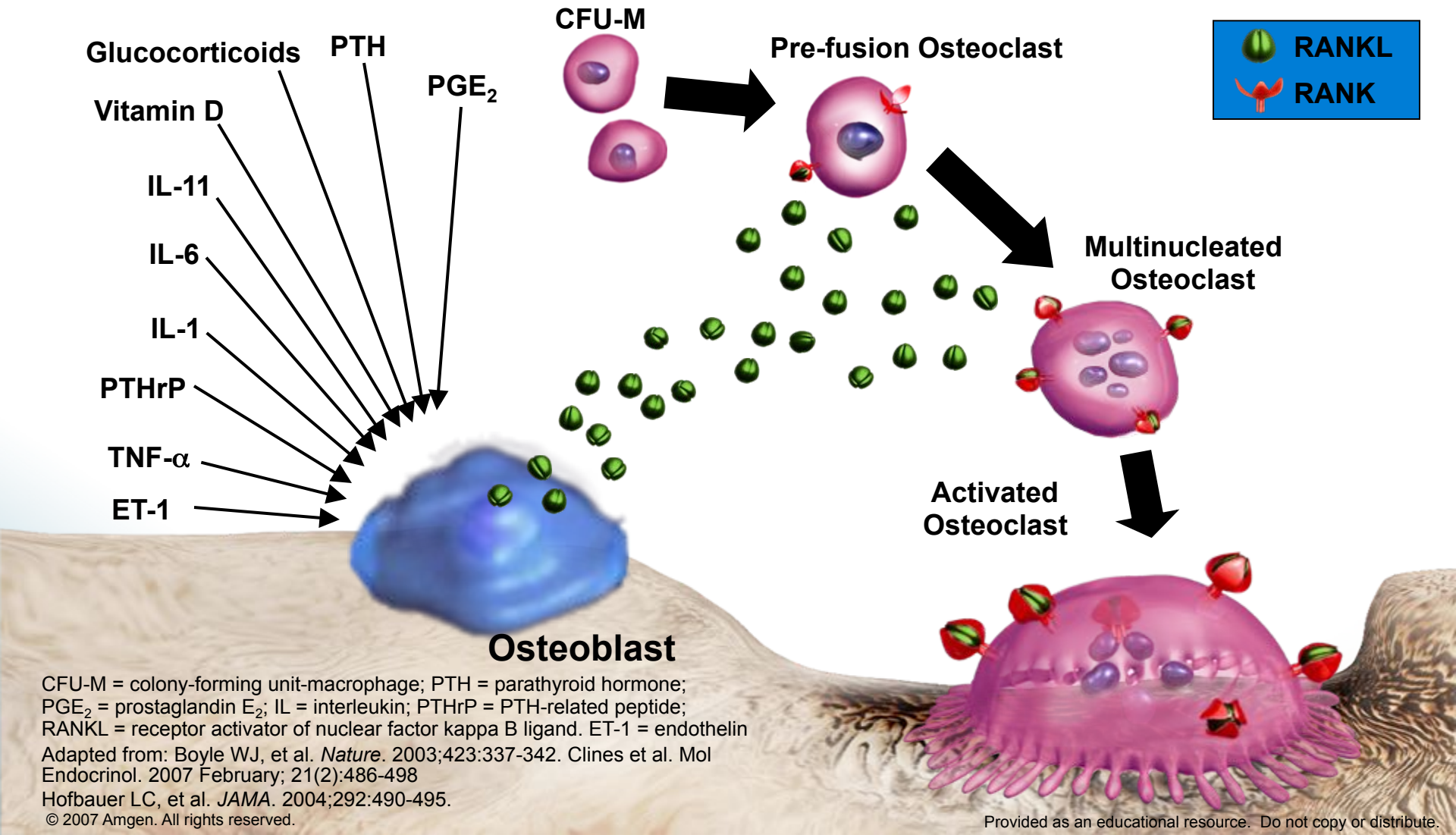


1. Kohno N et al. J Clin Oncol 2005;23:3314–21.
2. Stopeck AT et al. J Clin Oncol 2010;28:5132–9.

Agenda

- Burden of bone metastases from solid tumors
- Unmet medical need
- **The role of rank-ligand inhibition**
- Clinical results of denosumab in SRE prevention
- Conclusions

Many Factors Stimulate Osteoblast Expression of RANK Ligand

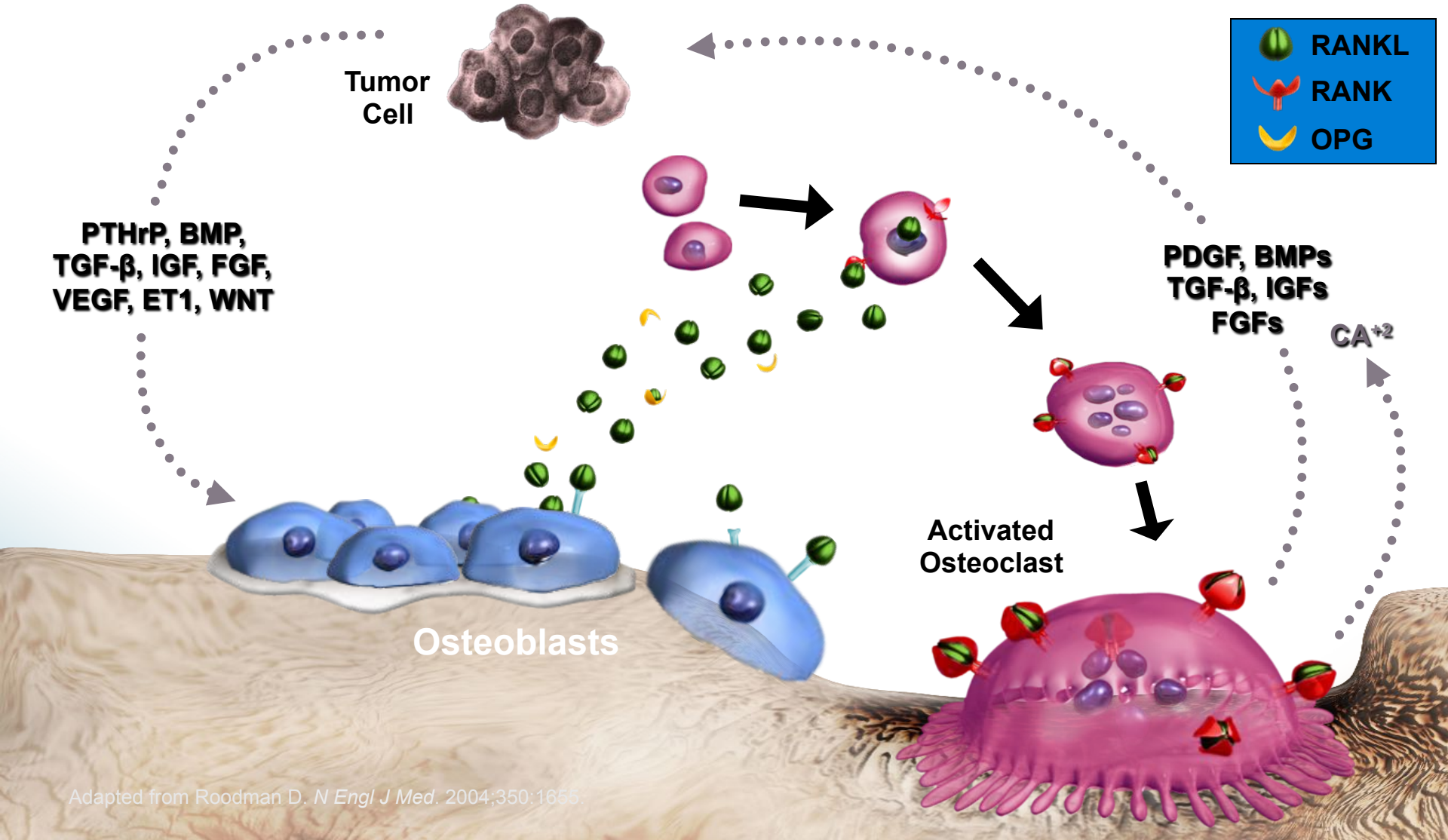


CFU-M = colony-forming unit-macrophage; PTH = parathyroid hormone; PGE_2 = prostaglandin E_2; IL = interleukin; PTHrP = PTH-related peptide; RANKL = receptor activator of nuclear factor kappa B ligand. ET-1 = endothelin

Adapted from: Boyle WJ, et al. *Nature*. 2003;423:337-342. Clines et al. Mol Endocrinol. 2007 February; 21(2):486-498

Hofbauer LC, et al. *JAMA*. 2004;292:490-495.

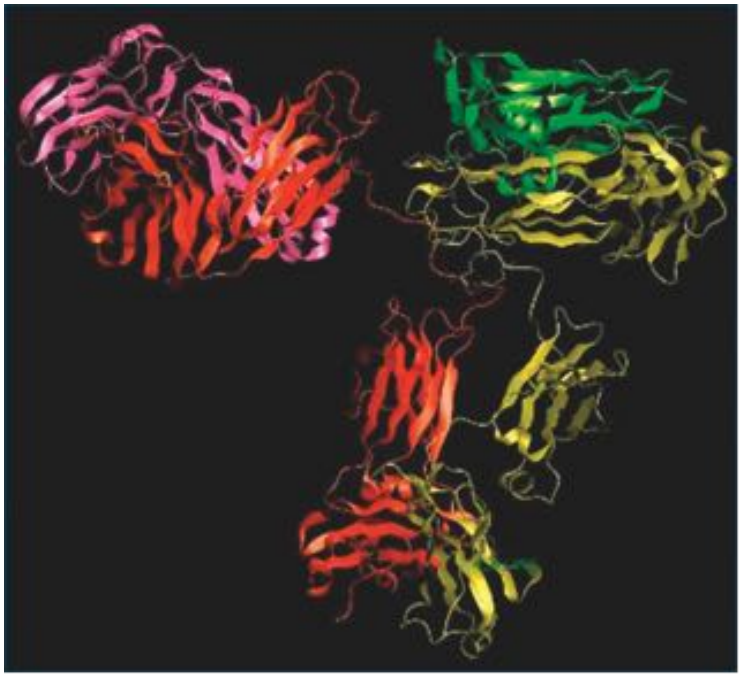
The "Vicious Cycle" Hypothesis of Bone Destruction in Metastatic Cancer



Adapted from Roodman D. *N Engl J Med*. 2004;350:1655.

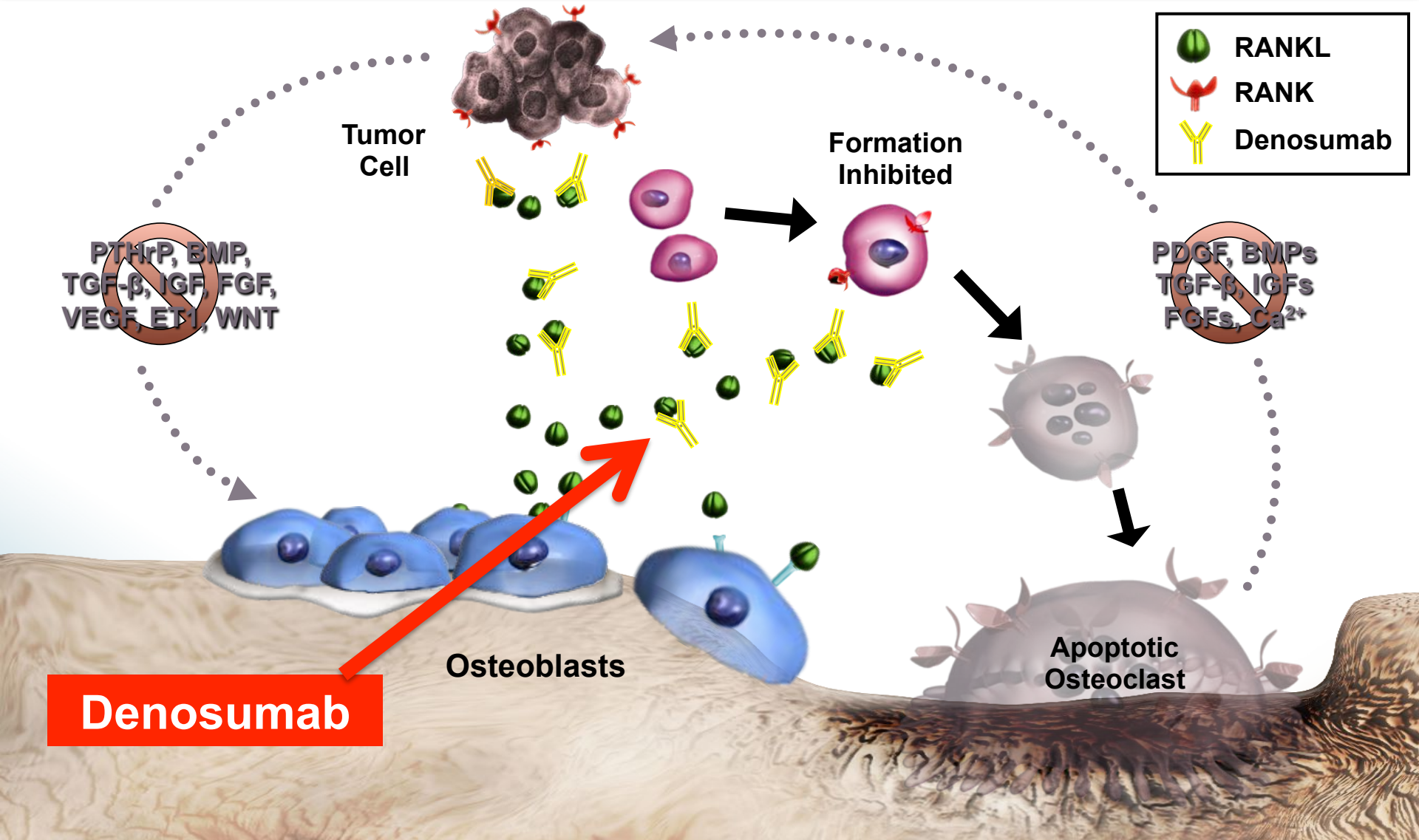
Denosumab, RANK/RANK ligand (RANKL) inhibitor

- Anticorpo monoclonale IgG2: gli anticorpi IgG hanno una bassa massa molecolare e una lunga emivita.
- Elevata affinità per il ligando di RANK: l'anticorpo monoclonale si lega prontamente all'antigene.



Modello strutturale di denosumab rappresentato utilizzando un diagramma a nastro

RANKL Inhibition May Interrupt The "Vicious Cycle" of Cancer-Induced Bone Destruction



Agenda

- Burden of bone metastases from solid tumors
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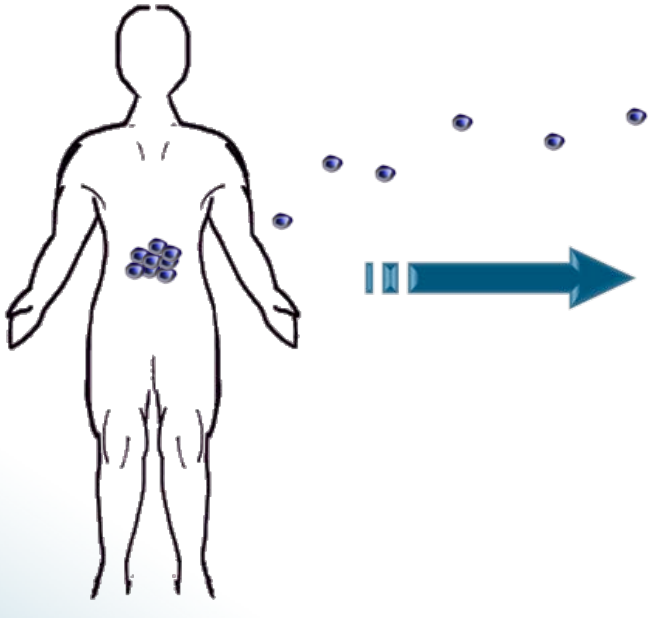
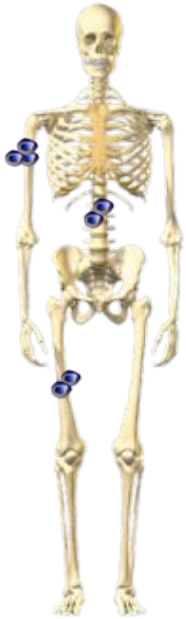
- The role of rank-ligand inhibition
- **Clinical results of denosumab in SRE prevention**
- Conclusions

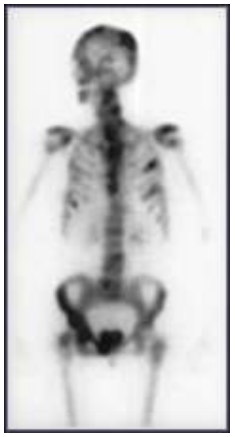
Oncology Denosumab Phase 3 Registration Programme

Early Cancer

Advanced Cancer







SRE prevention: ~6000 patients

Cancer Treatment–Induced Bone Loss	Delay of Bone Metastasis	Prevention of SREs
20040138 (HALT PC) 20040135 (HALT BC) 20060209 (ABCSG18)	20050147 (Prostate) 20060359 (Adjuvant Breast)	20050103 (Prostate) 20050136 (Breast) 20050244 (Solid Tu/MM)
60 mg Q6M	**120 mg Q4W**	**120 mg Q4W**

European Journal of Cancer (2012) 48, 3082–3092

Available at www.sciencedirect.com

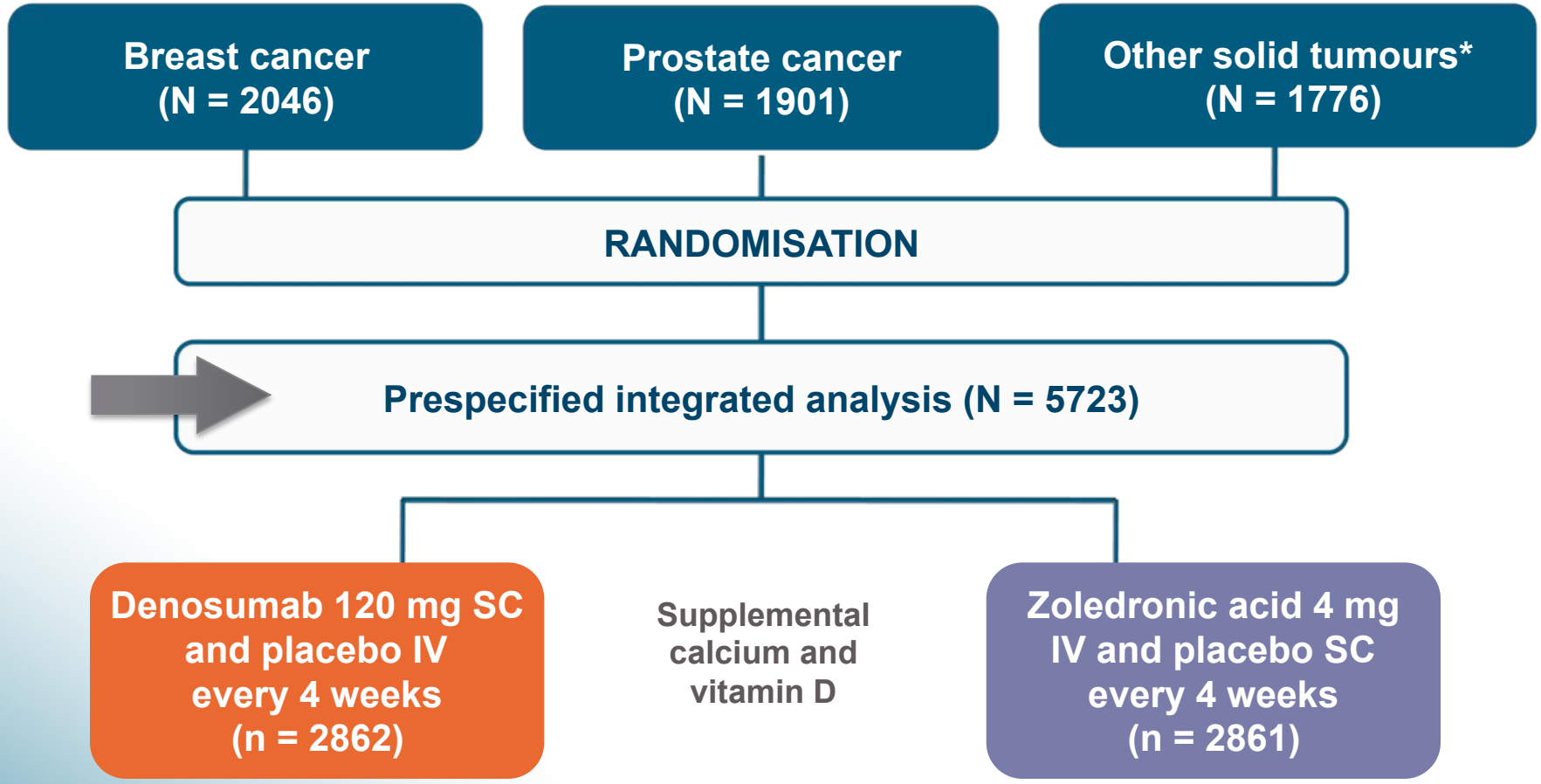
SciVerse ScienceDirect

journal homepage: www.ejcancer.info

Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: A combined analysis of 3 pivotal, randomised, phase 3 trials ☆

Allan Lipton [a,*], Karim Fizazi [b], Alison T. Stopeck [c], David H. Henry [d], Janet E. Brown [e], Denise A. Yardley [f], Gary E. Richardson [g], Salvatore Siena [h], Pablo Maroto [i], Michael Clemens [j], Boris Bilynskyy [k], Veena Charu [l], Philippe Beuzeboc [m], Michael Rader [n], Maria Viniegra [o], Fred Saad [p], Chunlei Ke [q], Ada Braun [q], Susie Jun [q]

Pivotal head-to-head studies of denosumab vs zoledronic acid for SRE prevention



*Excluding breast or prostate.

Lipton A, et al. European J Cancer 2012

Integrated analysis endpoints

Primary

Time to first on-study SRE (**non-inferiority**)

Secondary

- Time to first on-study SRE (**superiority**)[1]
- Time to first and subsequent on-study SRE (**superiority**, multiple event analysis)[1]

Exploratory

- Overall survival, disease progression, individual SREs and skeletal morbidity rate[1]
  - Pain prevention, pain palliation and analgesic use[2]
  - ONJ-related attributes[1]

1. Lipton A, et alEuropean J Cancer 2012

2. Cleeland CS, et al. Ann Oncol 2010;21(Suppl 8):viii379 (Abstract 1248P).

Patients with a broad range of solid tumour types enrolled

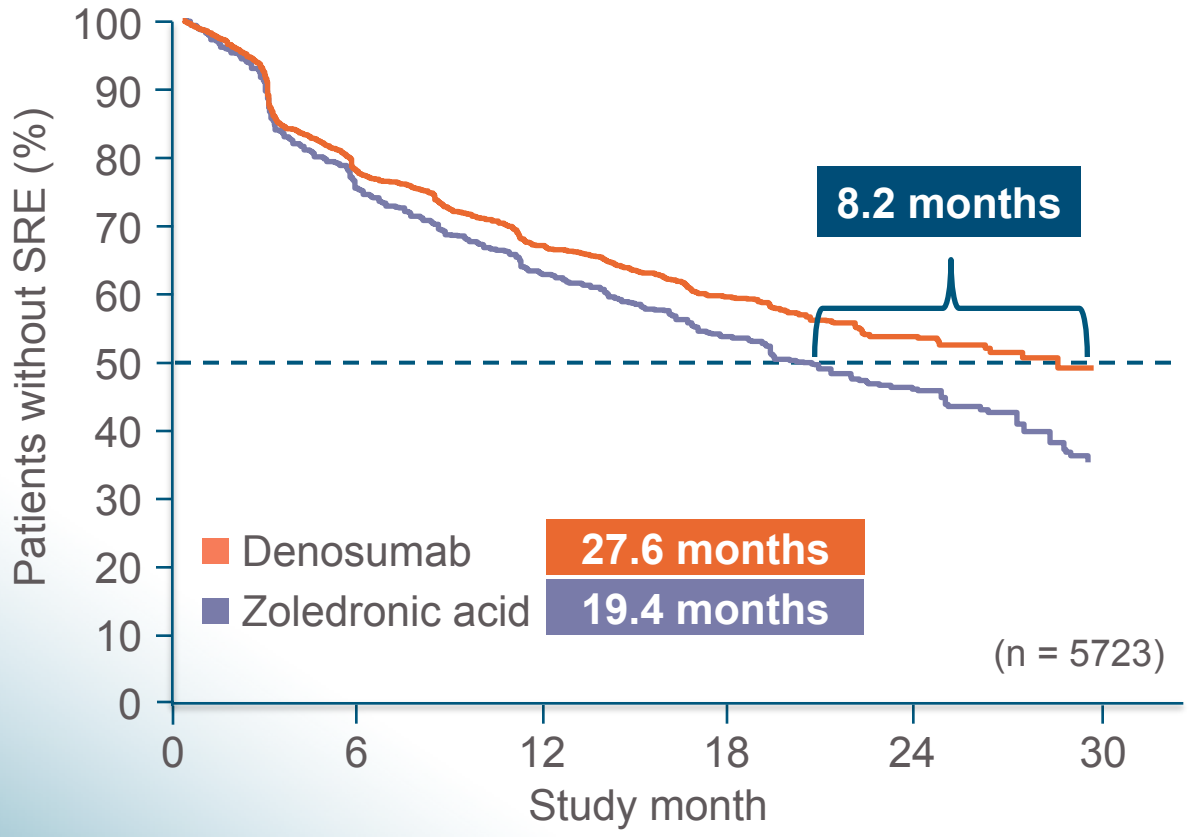
Integrated Analysis

Baseline characteristic, n (%) or median	Denosumab (n = 2862)	Zoledronic acid (n = 2861)
Women	1316 (46.0)	1349 (47.2)
Age, years	63.0	63.0
ECOG status of 0 or 1	2585 (90.3)	2546 (89.0)
Tumour type*		
Breast	1026 (35.8)	1020 (35.7)
Prostate	950 (33.2)	951 (33.2)
Non-small cell lung	350 (12.2)	352 (12.3)
Multiple myeloma	87 (3.0)	93 (3.3)
Renal	70 (2.4)	85 (3.0)
Small cell lung	61 (2.1)	48 (1.7)
Other	318 (11.1)	312 (10.9)
Time from first bone metastasis to randomisation, months	2.17	2.30
Previous SRE†	**1112 (39)**	**1157 (40)**

Lipton A et al. European J Cancer 2012

*ECOG, Eastern Cooperative Oncology Group; †Based on randomisation.

Significantly longer time without an SRE with denosumab vs zoledronic acid



Time to first SRE

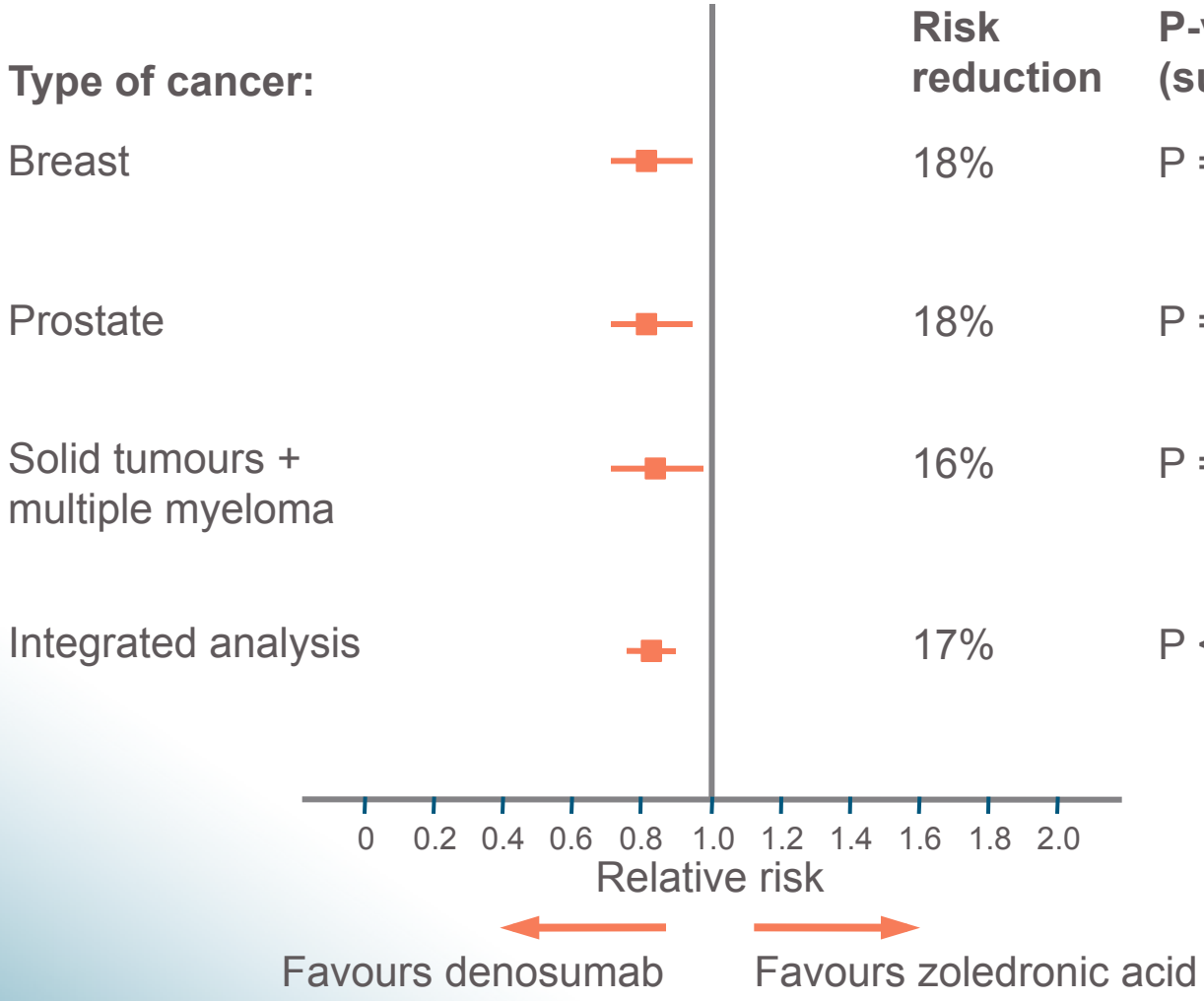
17% Risk Reduction

HR = 0.83
(95% CI, 0.76–0.90)
P < 0.001 (superiority)

Lipton A. et al., Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: A combined analysis of 3 pivotal, randomised, phase 3 trials, Eur J Cancer (2012)

HR, hazard ratio.

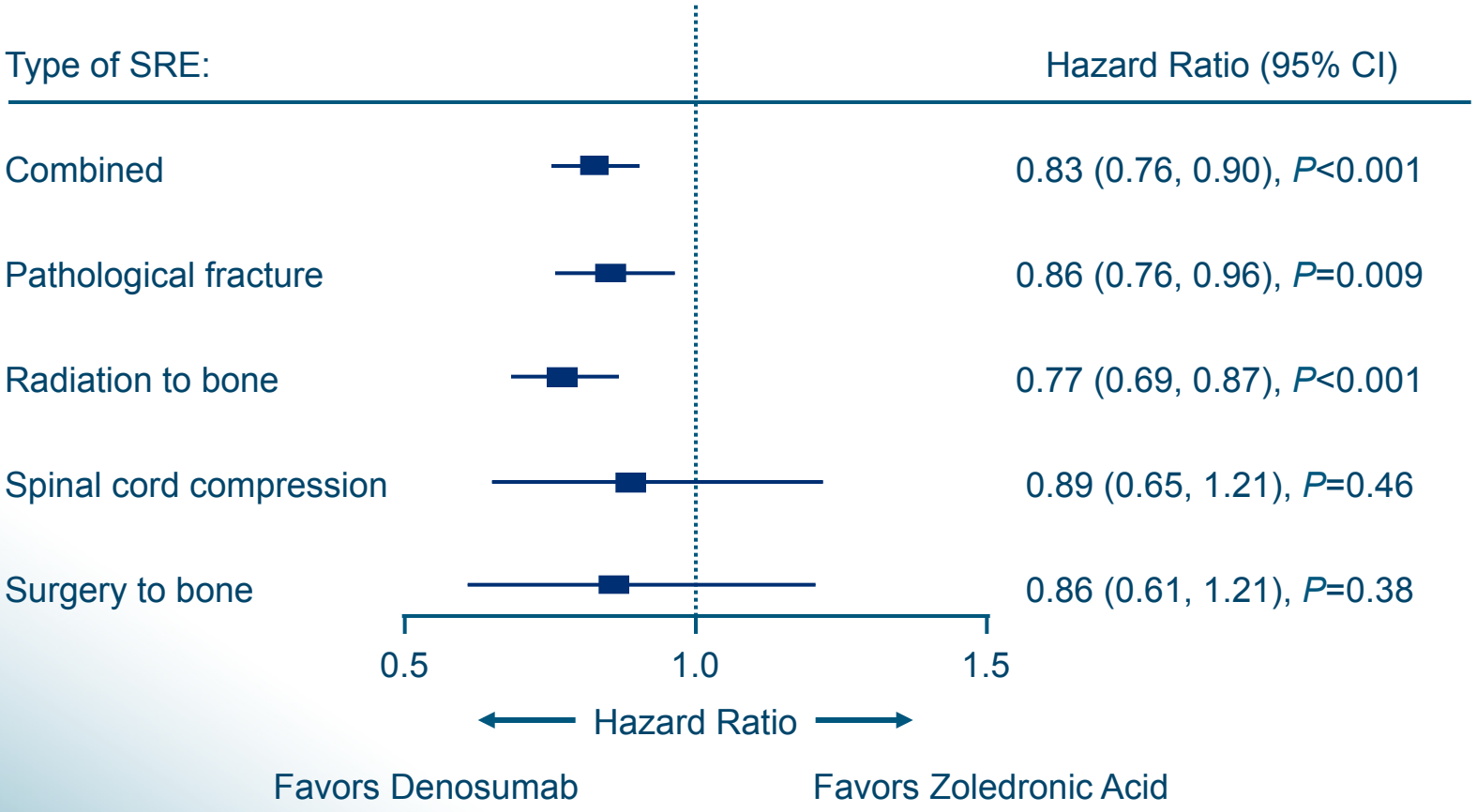
Denosumab consistently reduces risk of SRE across all tumour types



Denosumab (120 mg Q4W) is not approved for use in patients with advanced cancer to delay SREs. Denosumab is investigational in that setting.

Lipton, et al. ESMO 2010 (P1249).

Time to First On-Study SRE by SRE Type

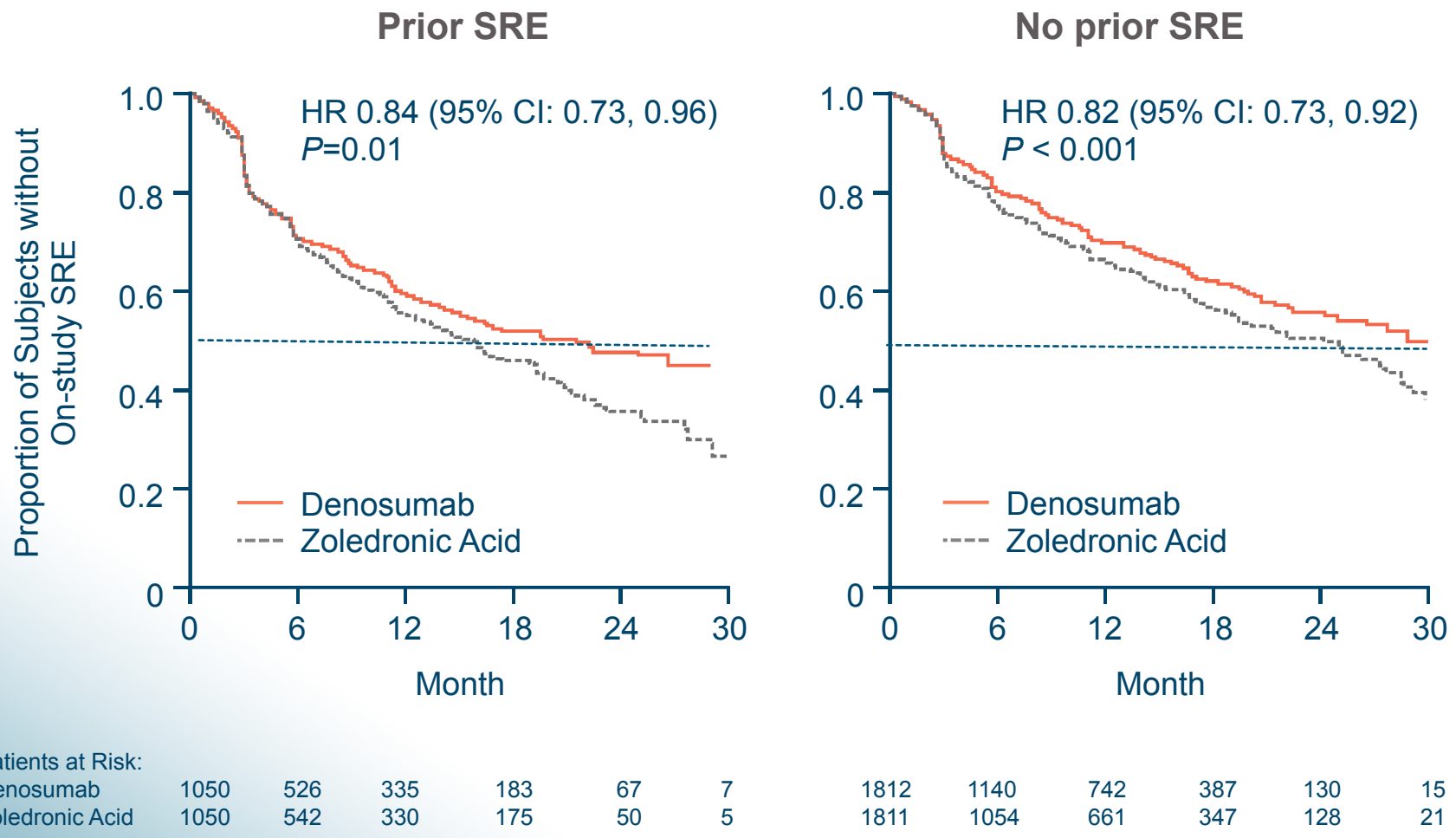


Lipton A, Fizazi K, Stopeck A, et al. *Eur J Cancer* 2012; http://dx.doi.org/10.1016/j.ejca.2012.08.002.

Time to First SRE by Previous SRE History

Integrated Analysis

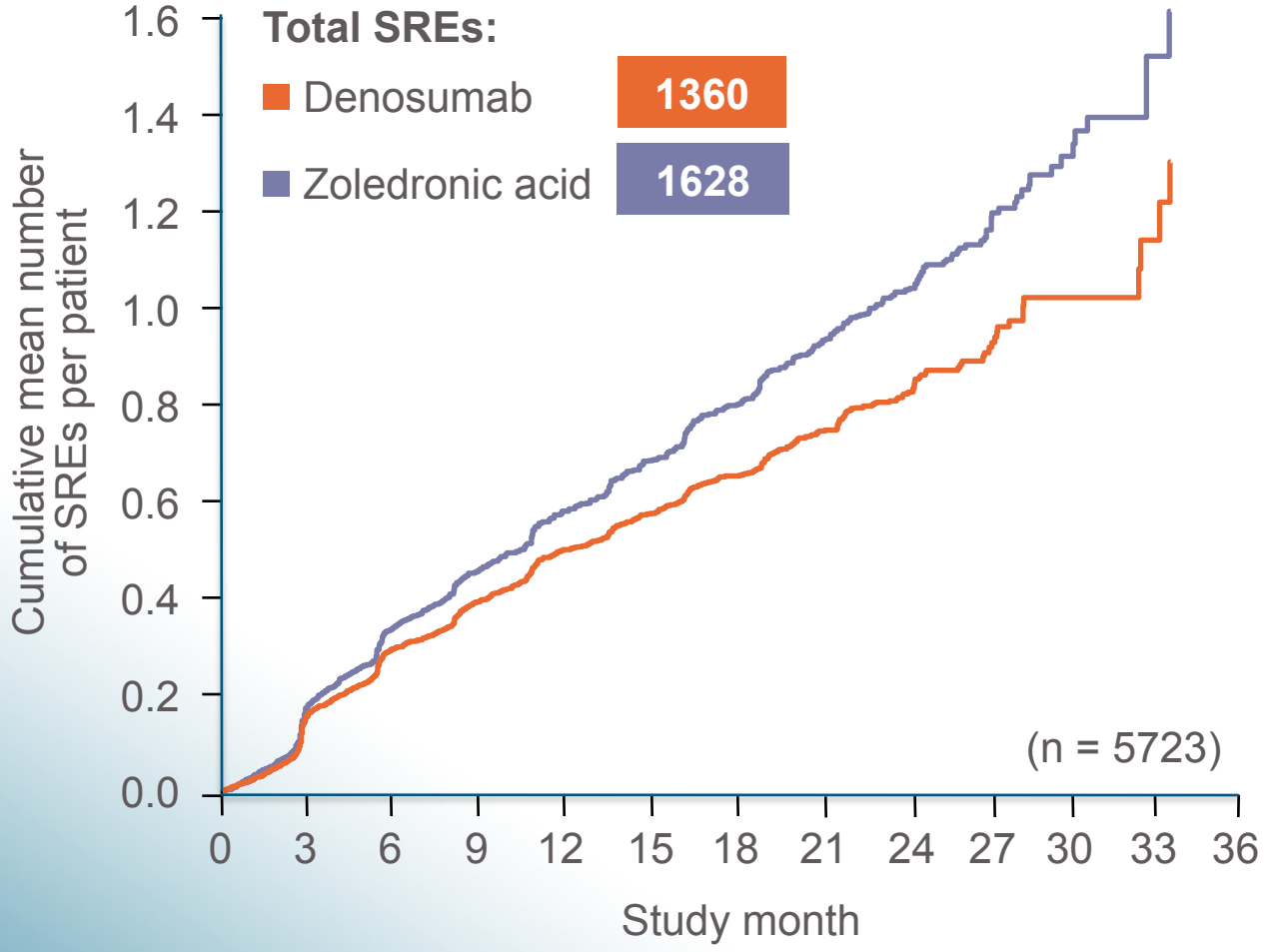
Longer time without an SRE with denosumab vs zoledronic acid regardless of SRE history



Patients at Risk:												
Denosumab	1050	526	335	183	67	7	1812	1140	742	387	130	15
Zoledronic Acid	1050	542	330	175	50	5	1811	1054	661	347	128	21

Lipton A, Fizazi K, Stopeck A, et al. *Eur J Cancer* 2012; http://dx.doi.org/10.1016/j.ejca.2012.08.002.

Significantly fewer SREs with denosumab vs zoledronic acid



Time to first and subsequent SREs

18% Risk Reduction of multiple SRE

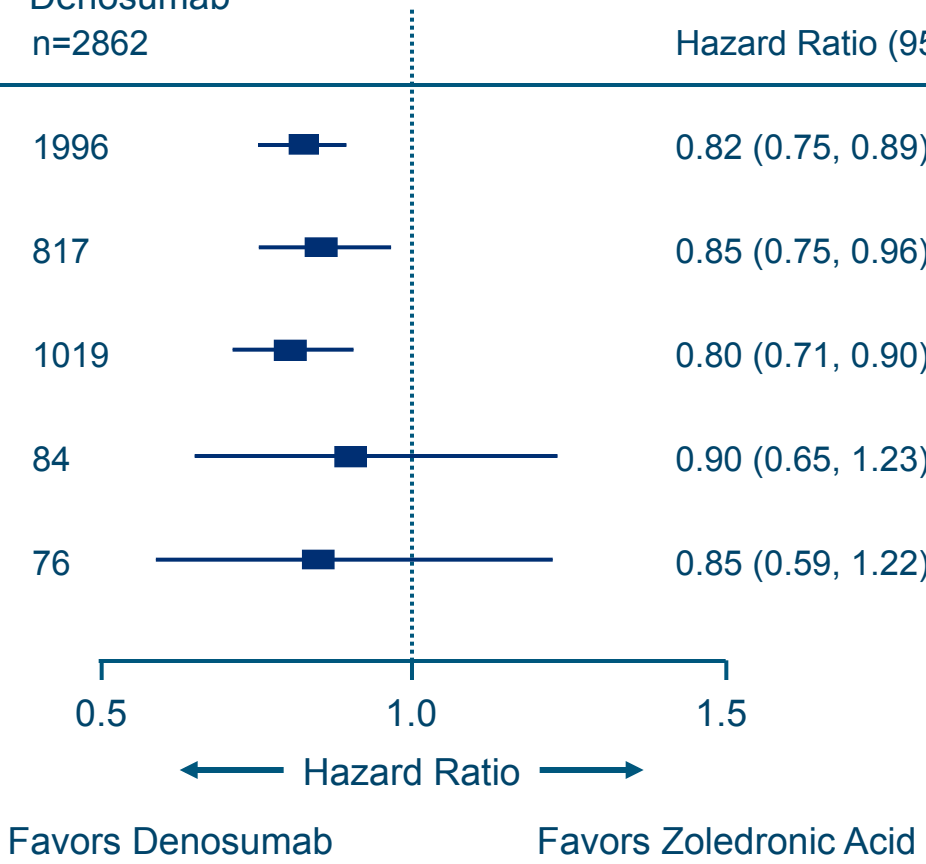
RR = 0.82
(95% CI, 0.75–0.89)
P < 0.001 (superiority)

Lipton A. et al., Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: A combined analysis of 3 pivotal, randomised, phase 3 trials, Eur J Cancer (2012)

Events occurring at least 21 days apart (multiple event analysis)
RR, rate ratio.

Time to First and Subsequent On-Study SRE by SRE Type

Type of SRE:	Zolcedronic Acid n=2861	Denosumab n=2862	Hazard Ratio (95% CI)
Combined	2422	1996	0.82 (0.75, 0.89), *P*<0.001
Pathological fracture	969	817	0.85 (0.75, 0.96), *P*=0.008
Radiation to bone	1269	1019	0.80 (0.71, 0.90), *P*<0.001
Spinal cord compression	95	84	0.90 (0.65, 1.23), *P*=0.50
Surgery to bone	89	76	0.85 (0.59, 1.22), *P*=0.37



Test for heterogeneity, *P*=0.5377

Lipton A, Fizazi K, Stopeck A, et al. *Eur J Cancer* 2012; http://dx.doi.org/10.1016/j.ejca.2012.08.002.

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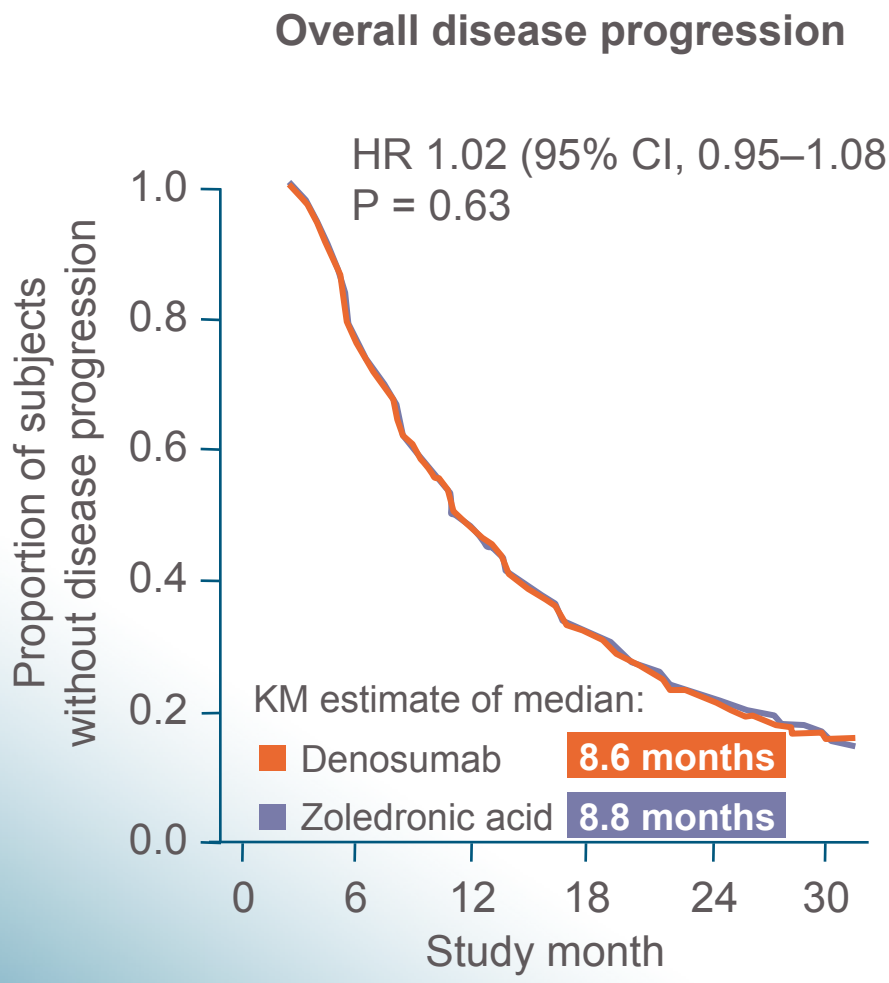
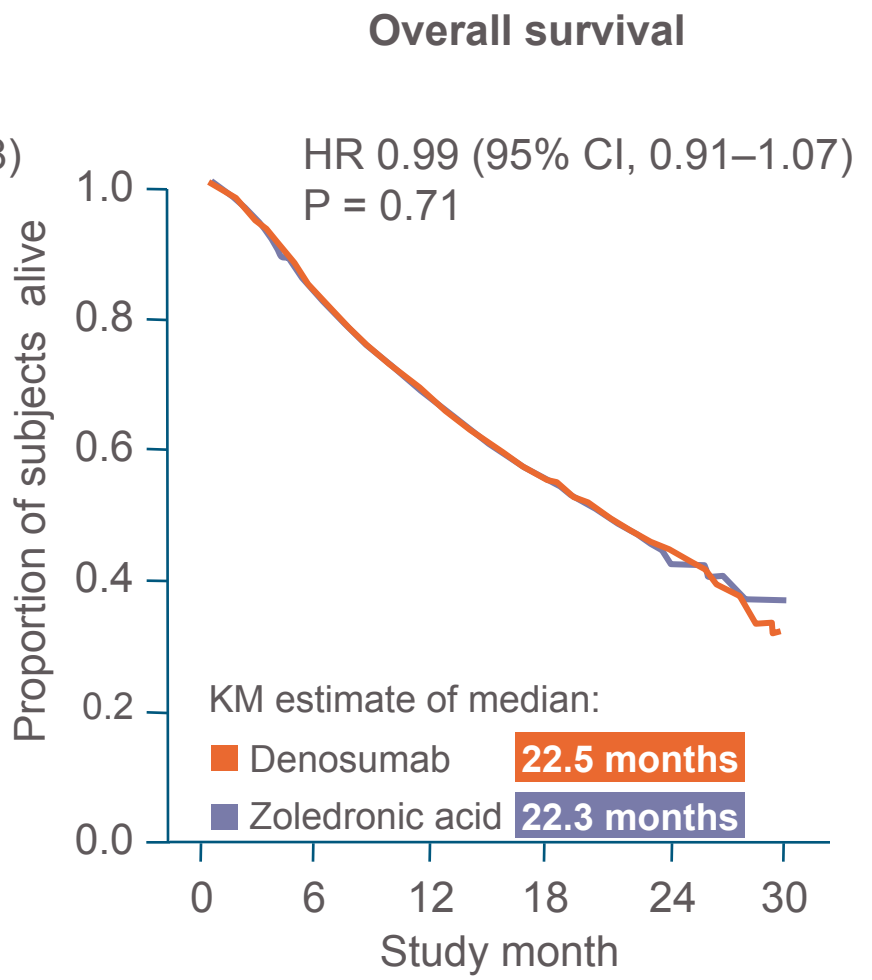
  - ONJ-related attributes[1]

1. Lipton A, et alEuropean J Cancer 2012

2. Cleeland CS, et al. Ann Oncol 2010;21(Suppl 8):viii379 (Abstract 1248P).

Similar disease progression and overall survival between treatment groups



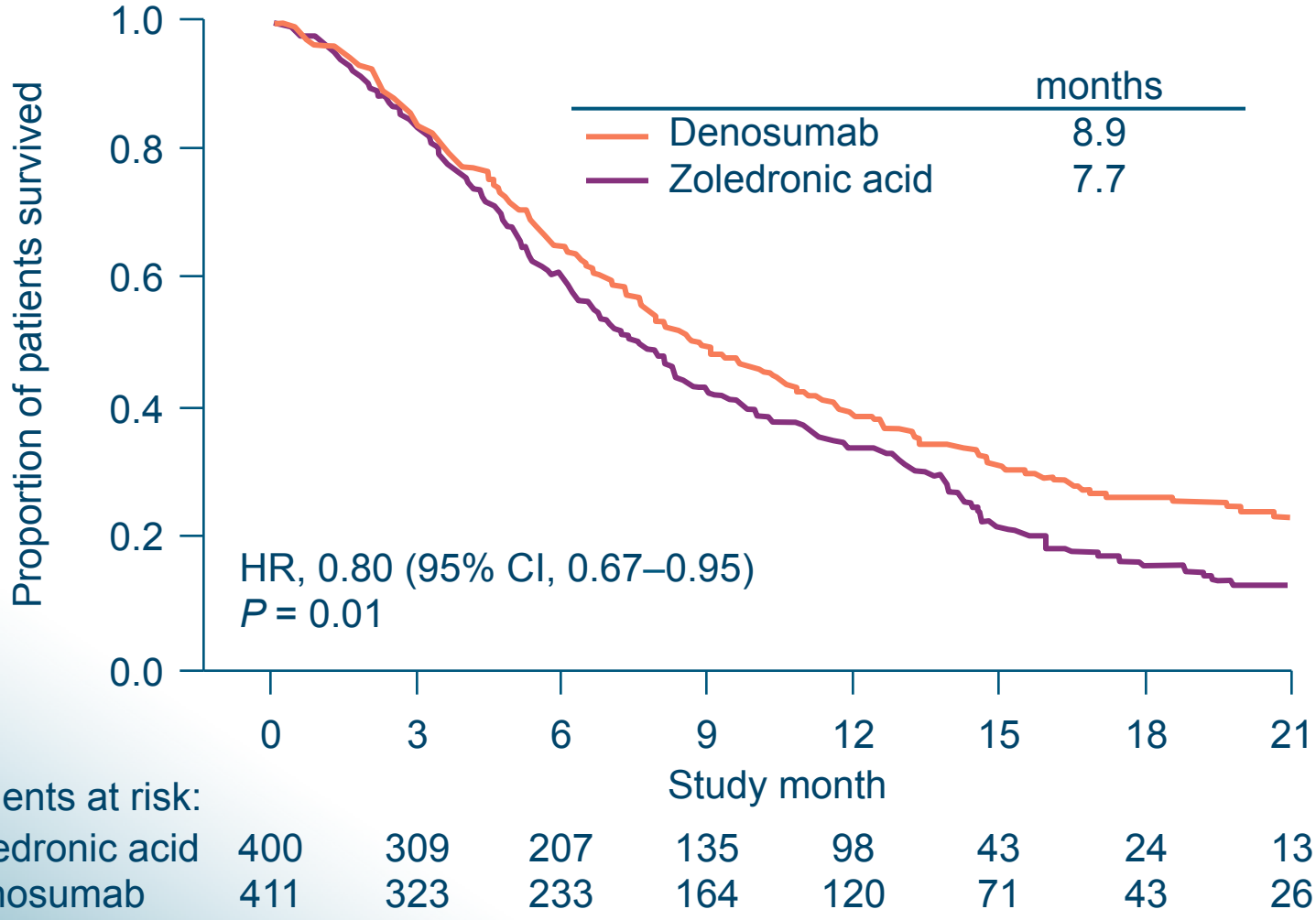


Lipton A. et al., Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: A combined analysis of 3 pivotal, randomised, phase 3 trials, Eur J Cancer (2012)

Overall survival: patients with lung cancer

OST Lung

Results from a post hoc analysis on survival among patients with lung cancer, including non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) from pivotal phase 3 trial (patients with solid tumours (other than breast or prostate) and bone metastasis or multiple myeloma), excluding multiple myeloma



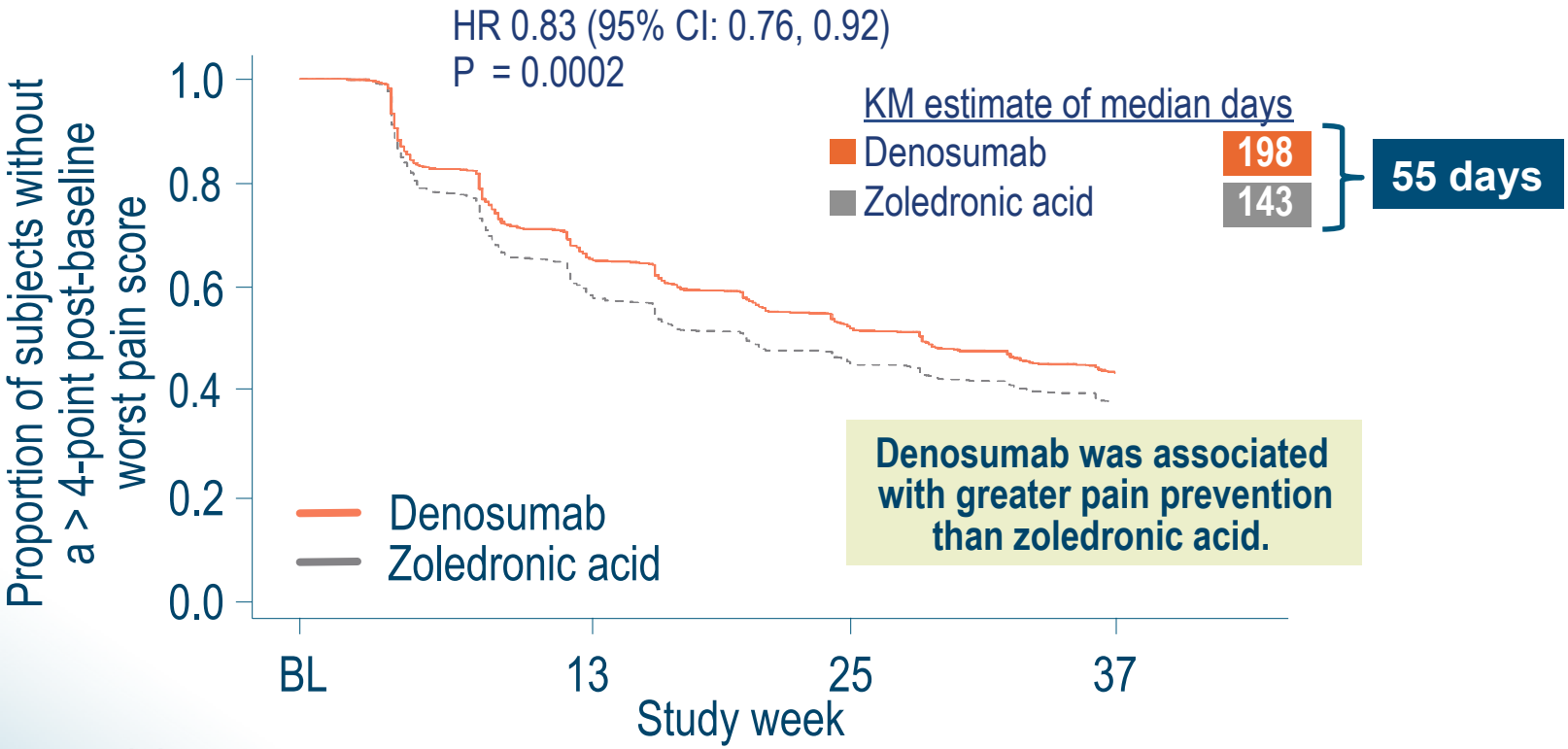
Scagliotti G, et al : JTO, 2012

Results – Pain prevention

Time to moderate or severe pain (> 4 points) in patients with no or mild pain (0-4) at baseline

Integrated Analysis

Pain



Patients at risk:				
Zoledronic acid	1341	733	521	398
Denosumab	1424	880	637	492

Cleeland CS, et al. *Ann Oncol* 2010;21:8s (abstract 1248P)

Drug Exposure and Adjustments for Renal Function

Overall Exposure	SC Denosumab	IV Zoledronic Acid
Median number of active doses, n (Q1, Q3)	13 (6, 20)	11 (5, 19)
Cumulative exposure (patient-years)	2969	2852
Adjustments for Renal Function		
Patients with **dose adjustments for creatinine clearance at baseline**, n (%)	NA	502 (18)
Patients with doses **withheld for serum creatinine increases on study**, n (%)	NA	277 (10)
Patients with prostate cancer	NA	143 (52)
Patients with solid tumors	NA	78 (28)
Patients with multiple myeloma	NA	56 (20)
Total number of doses withheld due to serum creatinine increases on study	NA	1181

NA=Not applicable per protocol

Adapted from Lipton A, Fizazi K, Stopeck A, et al. *Eur J Cancer* 2012; http://dx.doi.org/10.1016/j.ejca.2012.08.002.

Adverse events: safety analysis set

Patient incidence, n (%)	Denosumab (n = 2841)	Zoledronic acid (n = 2836)
Infectious adverse events (AEs)	1233 (43.4)	1218 (42.9)
Infectious serious AEs	329 (11.6)	309 (10.9)
Acute phase reactions (first 3 days)	**246 (8.7)**	**572 (20.2)**
Cumulative rate of ONJ	**52 (1.8)**	**37 (1.3)**
Hypocalcaemia	273 (9.6)	141 (5.0)
New primary malignancy	28 (1.0)	18 (0.6)
AEs leading to study discontinuation	**270 (9.5)**	**280 (9.9)**

Very few injection site reactions were reported [10 (0.4%) vs 5 (0.2%)]

Lipton A. et al., Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: A combined analysis of 3 pivotal, randomised, phase 3 trials, Eur J Cancer (2012)

Conclusion

- This combined analysis in over 5700 patients with advanced cancer showed that RANKL inhibition with denosumab provided superior efficacy for prevention of SRE in patients with bone metastases relative to zoledronic acid, without the additional burden of renal toxicity or acute-phase reactions

- Denosumab extended the time to a first SRE by over 8 months relative to zoledronic acid and maintained superiority in preventing multiple SRE

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ASSESSMENT REPORT FOR XGEVA

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/002173

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of XGEVA in the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours was favourable and therefore recommended the granting of the marketing authorisation.

Furthermore, the CHMP reviewed the data submitted by the Applicant taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and considered by consensus the indication to be new for denosumab and that it would bring a significant clinical benefit in comparison with existing therapies for this indication.

Denosumab 120 mg Q4W
EMA marketing authorization

Therapeutic indications

Prevention of SRE (skeletal related events: pathological fracture, surgery to bone, radiation to bone, spinal cord compression) **in adults with bone metastases from solid tumours**.

Posology

The recommended dose of XGEVA is **120 mg** administered as a **single subcutaneous injection once every 4 weeks** into the thigh, abdomen or upper arm.

Supplementation of at least 500 mg calcium and 400 IU vitamin D is required in all patients, unless hypercalcaemia is present

Denosumab 120 mg non è ancora stato autorizzato in Italia per l'immissione in commercio (AIC)

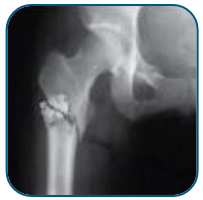
XGEVA - SPC-13th July 2011

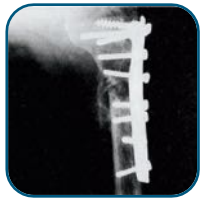
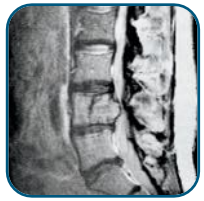
Agenda

- Burden of bone metastases from solid tumors
- Unmet medical need
- The role of rank-ligand inhibition
- Clinical results of denosumab in SRE prevention
- **Conclusions**

Conclusions(I)
SREs

- Advanced solid tumours, including breast, prostate, and non-small cell lung cancer, commonly metastasize to bone
- Bone metastases can have serious and clinically-significant consequences known as SREs



- SREs are both common and frequent in patients with advanced cancer untreated for bone metastases
- There is an unmet need for more effective bone-targeted treatments for bone metastases to prevent or delay SREs

Conclusions (II)
Denosumab

Efficacy

- Denosumab significantly prevented or delayed the time to first on-study SRE by **8.2 months**
- Denosumab significantly **reduced the incidence of multiple SREs**
- Effect of denosumab was **consistent across all 4 types of SREs**
- Denosumab **delayed pain by nearly 2 months** vs zoledronic acid

Safety

- Incidence of **ONJ** was infrequent and **similar** between treatment groups
- **Fewer acute-phase reactions; no contraindications for renal impaired patients**
- Increased incidence of hypocalcaemia in denosumab group

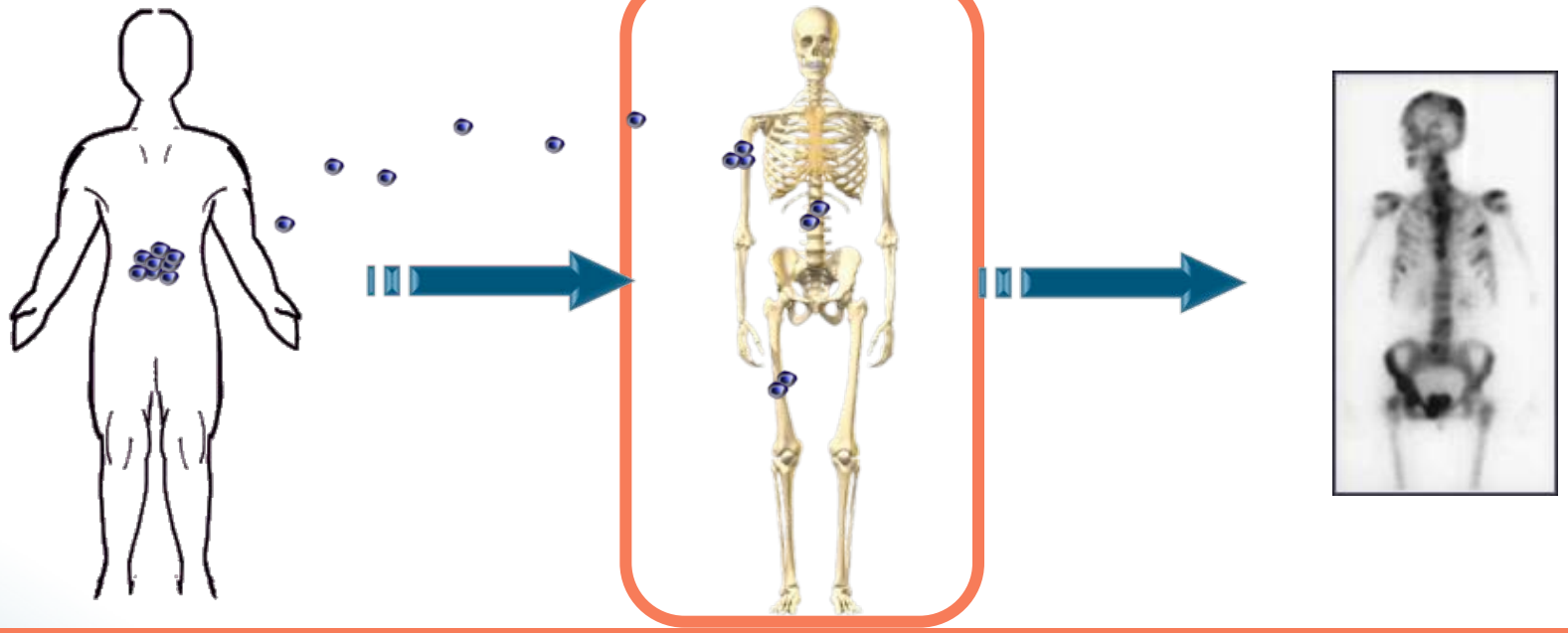
Management

- **Administered as a monthly SC injection**
- **No need for renal monitoring or dose adjustment**
- **Fewer acute phase reactions**

Denosumab in oncologia

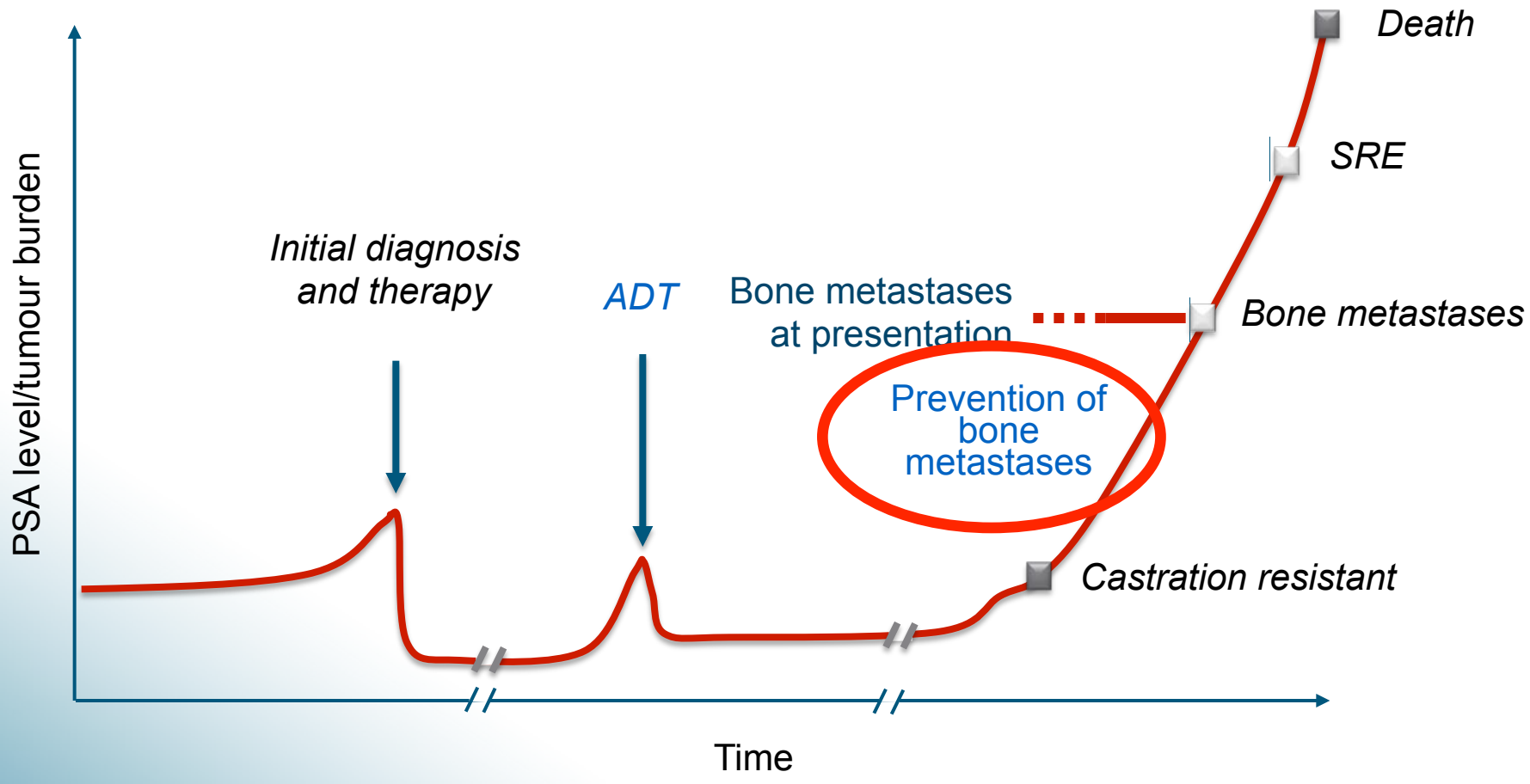
Early Cancer

Advanced Cancer



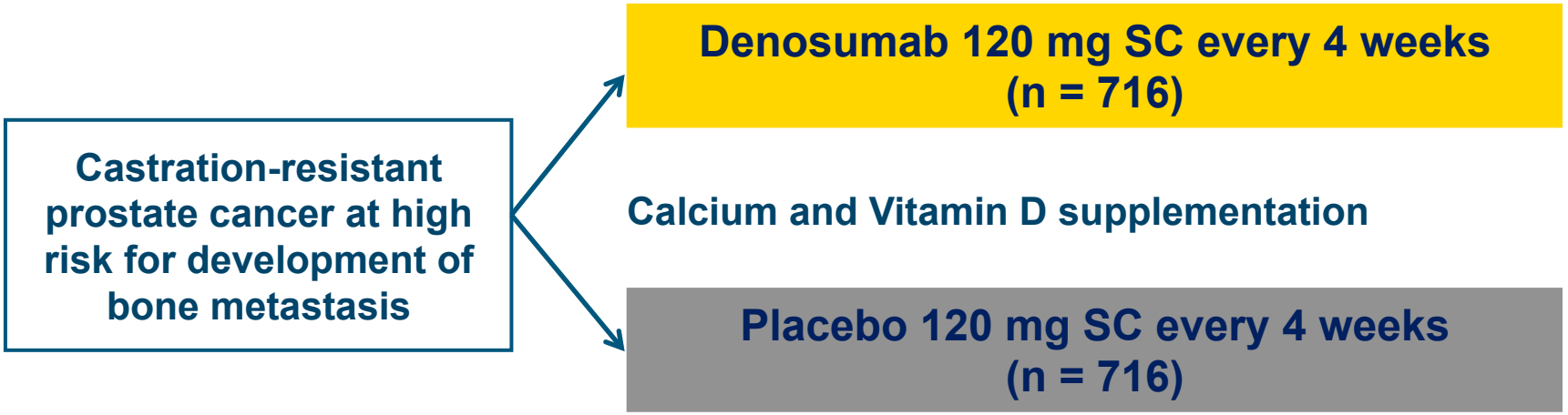
Cancer Treatment–Induced Bone Loss (CTIBL)	Delay of Bone Metastasis 5932 pts (BMFS)	Prevention of SREs ≅6000 pts (SRE)
20040138 (HALT PC) 20040135 (HALT BC) 20060209 (ABCSG18)	20050147 (Prostate) 1432 pts 20060359 (Adjuvant BC) 4500 pts	20050103 (Met Prostate) 20050136 (Met Breast) 20050244 (Solid Tu/MM)
60 mg Q6M	**120 mg Q4W**	**120 mg Q4W**

BMFS within the natural history of prostate cancer



ADT, androgen-deprivation therapy; PSA, prostate-specific antigen; SRE, skeletal-related event.
Adapted from Abrahamsson. Eur Urol Suppl 2009;8:821–38.

Study design: international, randomised, double-blind, placebo-controlled trial



Primary endpoint:

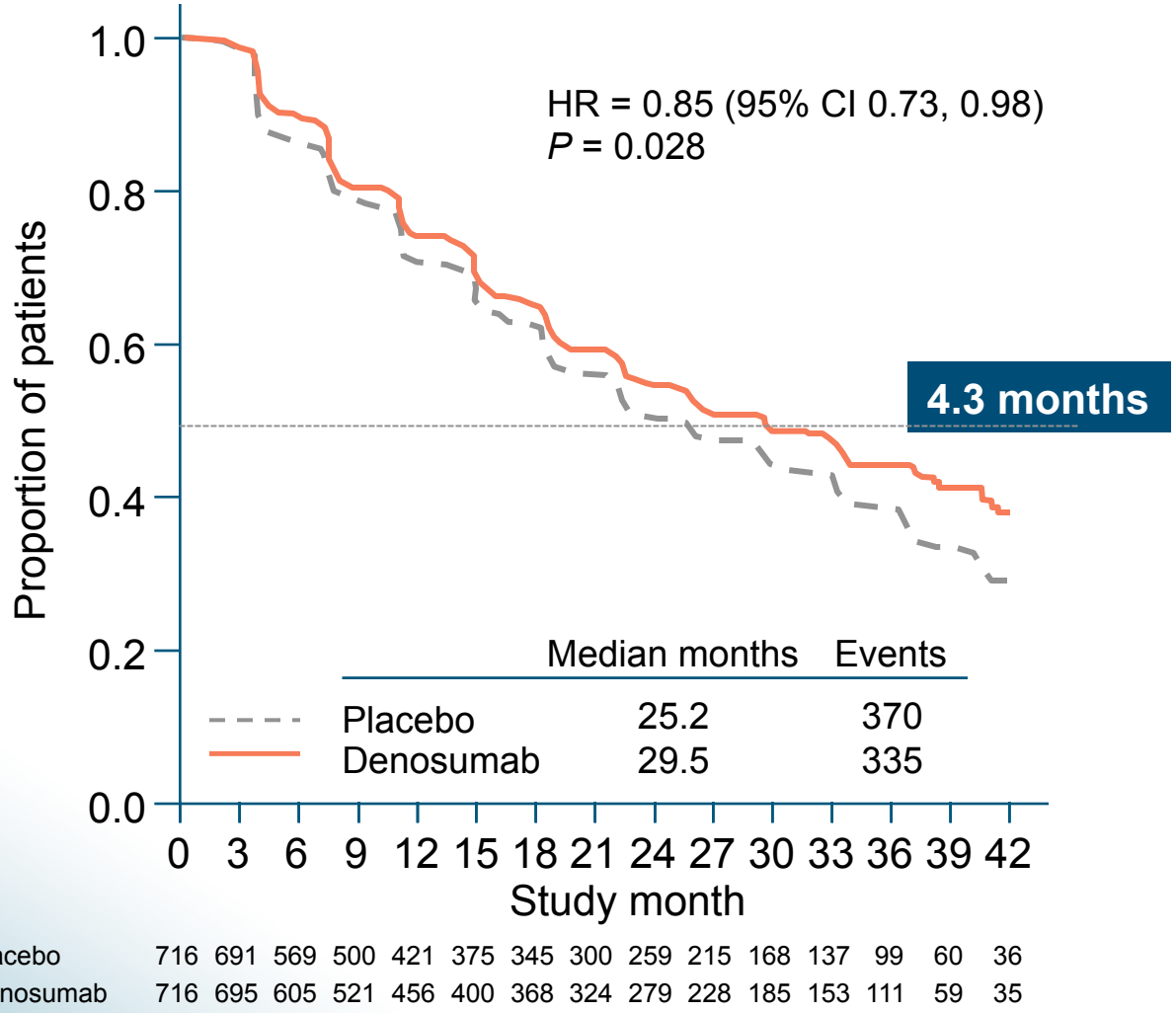
- **Bone metastasis-free survival**
  Time to first bone metastasis (symptomatic or asymptomatic) or death on study

Secondary endpoints:

- **Time to first bone metastasis**
  Either symptomatic or asymptomatic
- **Overall survival**
  Including deaths on-study and during follow-up

Smith, et al. Lancet. 2012;379:39–46.

Bone metastasis-free survival



Smith, et al. Lancet. 2012;379:39–46.

BMFS
Conclusions

Efficacy

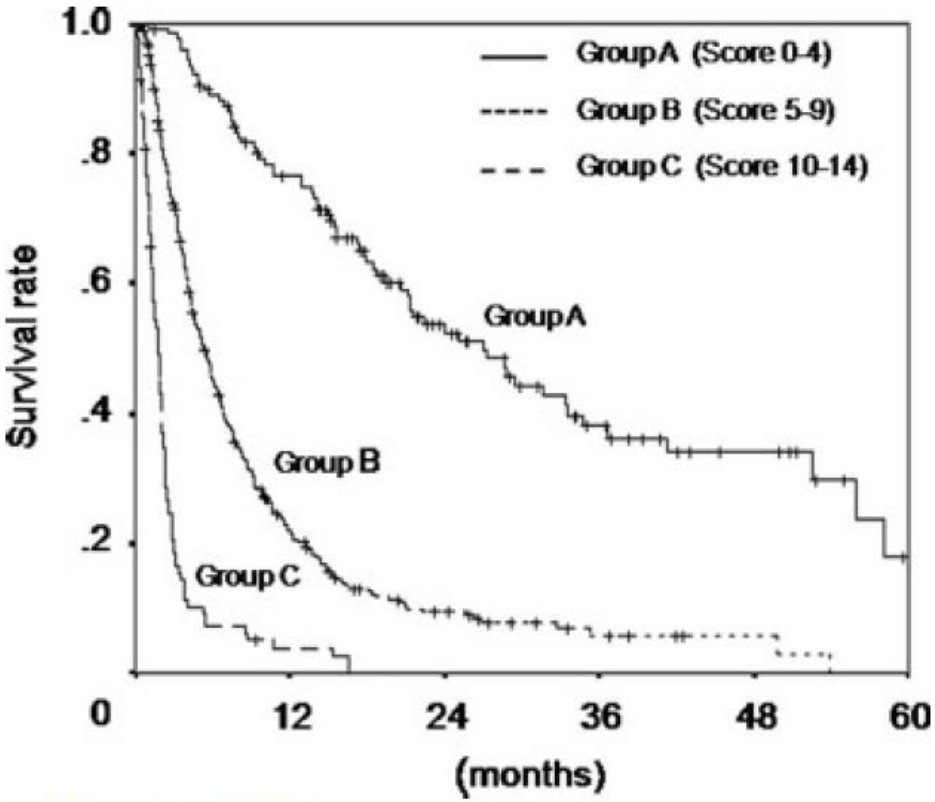
Denosumab **significantly increased bone metastasis-free survival and time to first bone metastasis**

Prognostic Factors and a Scoring System for Survival After Radiotherapy for Metastases to the Spinal Column

Masashi Mizumoto, MD[1]

Prognostic Factor	Sc
Type of primary tumor	
Favorable*	0
Unfavorable	3
ECOG PS ≥3	3
Visceral metastases	2
Previous chemotherapy	2
Hypercalcemia	2
Multiple bone metastases	1
Elderly (≥71 y)	1

ECOG PS indicates Eastern Cooperative Oncology Group performance status.
*Breast, prostate, lymphoma, and thyroid cancer (except anaplastic cancer).



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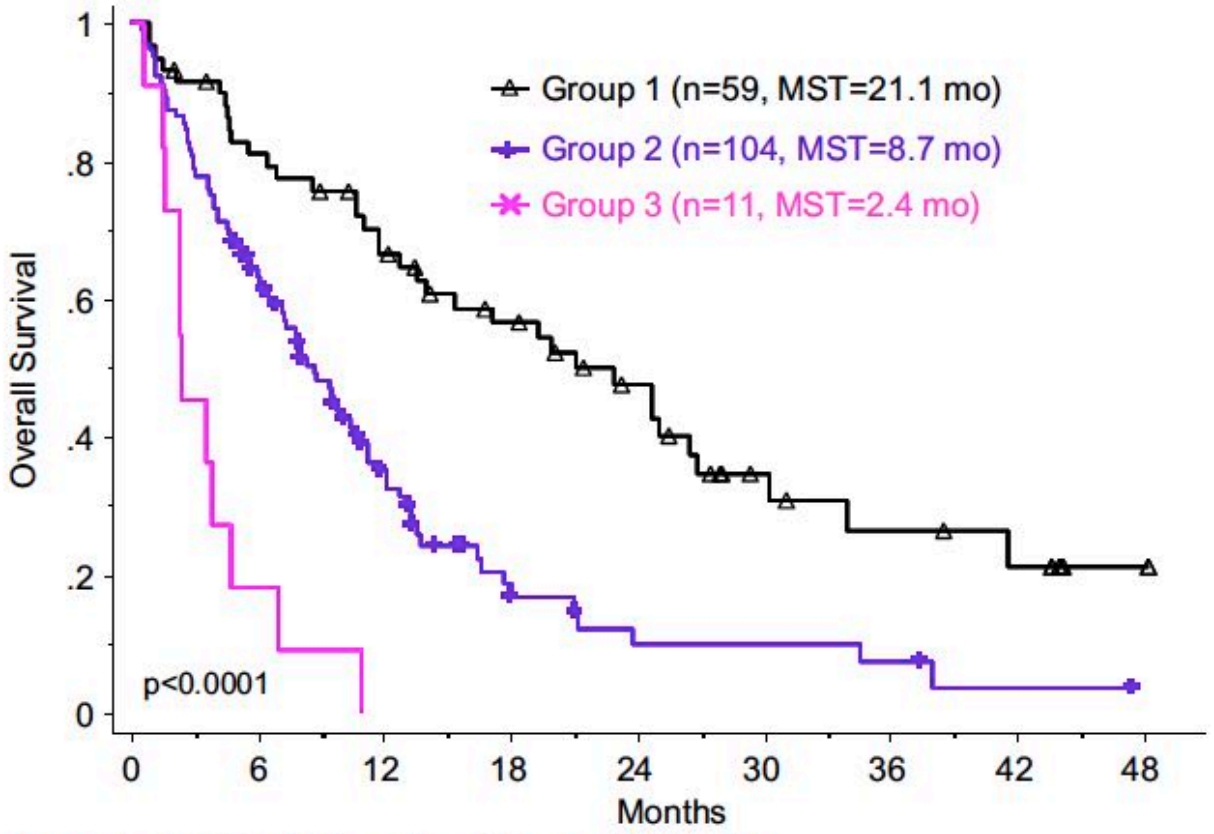
RECURSIVE PARTITIONING ANALYSIS INDEX IS PREDICTIVE FOR OVERALL SURVIVAL IN PATIENTS UNDERGOING SPINE STEREOTACTIC BODY RADIATION THERAPY FOR SPINAL METASTASES

Samuel T. Chao, M.D.,*‡§ Shlomo A. Koyfman, M.D.,*§ Neil Woody, B.S.,*§ Lilyana Angelov, M.D.,†‡ Sherry L. Soeder, C.N.P.,*‡§ Chandana A. Reddy, M.S.,*§ Lisa A. Rybicki, M.S.,§ Toufik Djemil, Ph.D.,*§ and John H. Suh, M.D.*‡§



Group 1= Time from Primary Dx >30 mo and KPS >70
Group 2= Time from Primary Dx >30 mo and KPS ≤70 or Time from Primary Dx ≤30 mo and Age <70
Group 3= Time from Primary Dx ≤30 mo and Age ≥70

STEREOTACTIC BODY RADIOTHERAPY FOR LESIONS OF THE SPINE AND PARASPINAL REGIONS