XXI Congresso Nazionale AIRO

Approccio multidisciplinare nel trattamento delle metastasi vertebrali:

«Terapie sistemiche: il parere dell'oncologo medico»

Genova, 20 novembre 2011

Prof. Francesco Boccardo

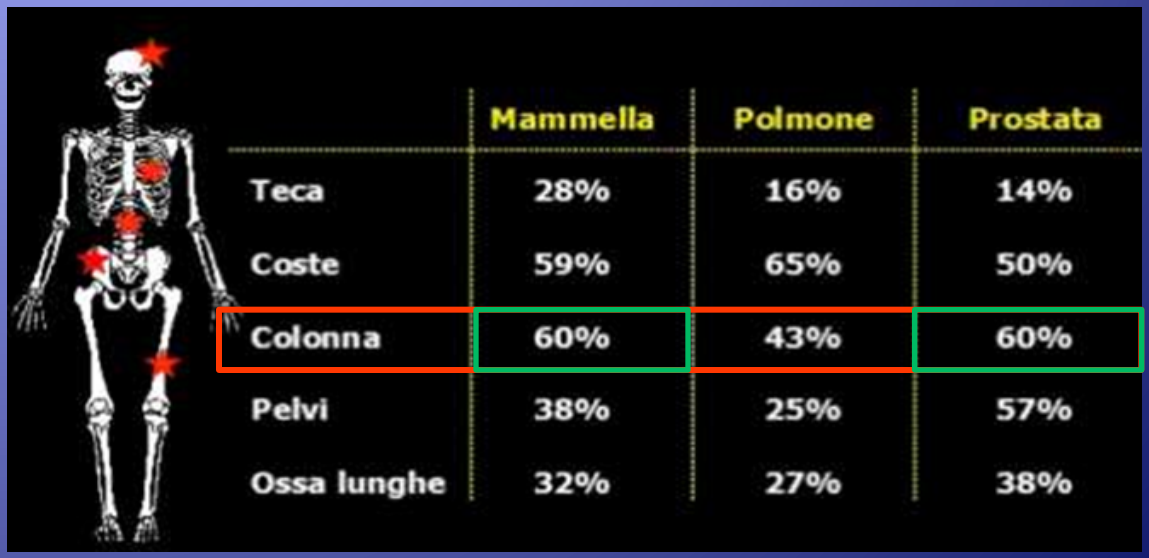
IRCCS Azienda Ospedaliera Universitaria San Martino - IST
Istituto Nazionale per la Ricerca sul Cancro

Università degli Studi di Genova

Clinical Relevance and Prognosis of Bone Metastases

NCI, 1997; International Myeloma Foundation, 2001.

	Disease prevalence, U.S. (in thousands)	Bone mets. incidence (%)	Median survival (mos)
Myeloma	75 - 100	70 - 95	24
Renal	198	20 - 25	12
Melanoma	467	14 - 45	6
Bladder	582	40	6 - 9
Thyroid	207	60	48
Lung	386	30 - 40	7
Breast	1,993	65 - 75	24
Prostate	984	65 - 75	36



	Mammella	Polmone	Prostata
Teca	28%	16%	14%
Coste	59%	65%	50%
Colonna	60%	43%	60%
Pelvi	38%	25%	57%
Ossa lunghe	32%	27%	38%

Table 14–1. Relative Frequencies of Spinal Metastases According to Location of Spinal Involvement

Author	Total	Extradural		Intradural Extramedullary		Intramedullary	
		No.	%	No.	%	No.	%
Rogers and Heard (1958)	17	16	94	1	6	—	—
Barron et al. (1959)	125	123	98	—	—	2	1.6
Edelson et al. (1972)	175	169	97	—	—	6	3.4
Perrin et al. (1982)	200	189	94	10	5	1	0.5

Table 14–2. Relative Frequencies of Spinal Metastases According to Level of Spinal Involvement

Author	Total	Cervical		Thoracic		Lumbosacral	
		No.	%	No.	%	No.	%
Sorensen et al. (1994)*	57	3	5	33	58	21	37
Helweg-Larsen (1996)	153	7	4.6	102	66.7	44	28.7
Tatsui et al. (1996)	695	106	15.3	203	29.2	386	55.5
Maranzano et al. (1997)	49	2	4	25	51	22	45
Schiff et al. (1998)	337	33	10	206	61	98	29
Brown et al. (1999)	40	5	12.5	13	32.5	22	55
Khaw et al. (1999)*	160	11	7	123	77	26	16
Kovner et al. (1999)	85	7	8	45	53	33	39
Rompe et al. (1999)*	106	9	8	76	72	21	20
Totals	1682	183	11	826	49	673	40

*In these studies, totals in the lumbosacral column refer to lumbar involvement only.

Spinal Axis Metastasis, Perrin RC, 2002

"Metastatic lesions occur at multiple non-contiguous levels in 38% to 58% of cases…."

Current Surgical Management of Metastatic Spinal Disease, Gerszten PC, 2000

THE FUNCTION OF THE VERTEBRAL VEINS AND THEIR RÔLE IN THE SPREAD OF METASTASES*

OSCAR V. BATSON, M.A., M.D.

PHILADELPHIA, PA.

FROM THE GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

METASTATIC ABSCESSES and metastatic tumors can appear in locations that do not seem to be in line of direct spread from their primary focus. There is ev stases. Empirically, th noma of the prostate wh sions in the pelvis. Ad typical and peculiar dis o me, is not at all that c arren, *et al.*[1] It is not the omic system into which s plexiform ramification ine, and the adjacent wi t the architecture of t ntage of the pelvic anast connections and the col hose of the prostatic ple veins of this region are toward the sacral veno preliminary report was s, in Philadelphia, Jan Sacrum in Relation to rk has been continued a f the vessels of the head background for this stu m organs in other regio lered. This has led to a s in normal physiology.

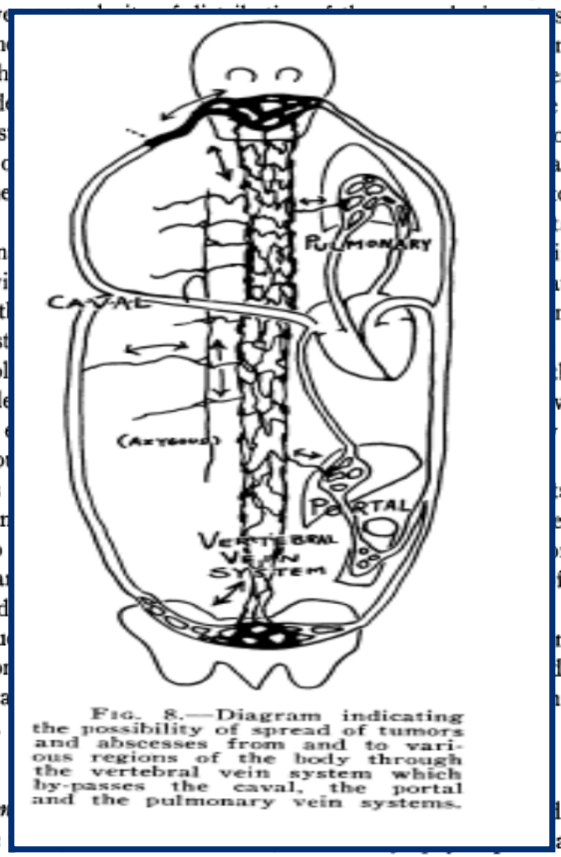


FIG. 8.—Diagram indicating the possibility of spread of tumors and abscesses from and to various regions of the body through the vertebral vein system which by-passes the caval, the portal and the pulmonary vein systems.

Experim the dorsal vein of the and injected a thick radiopaque material toward the pelvis. Specifically, we used Weber's,

* Part of the material of this paper was given in an address before the Philadelphia Laryngologic Society, March 5, 1940, under the title, "The Circulation of the Head, Especially Venous, with Reference to Osteomyelitis, Brain Abscess and Malignant Metastasis." Part was also presented before the Philadelphia Neurologic Society, March 22, 1940, under the title, "The Cerebrospinal Veins."

Submitted for publication June 5, 1940.

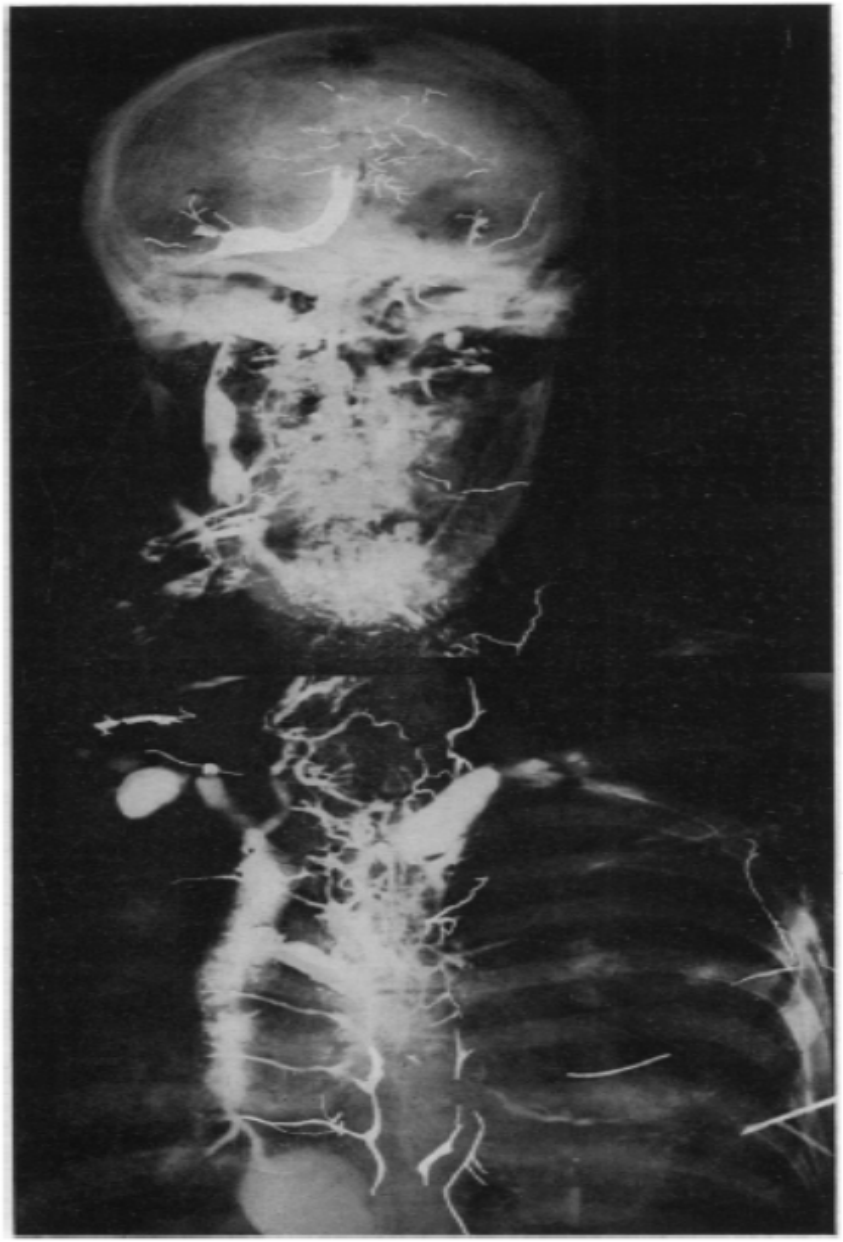
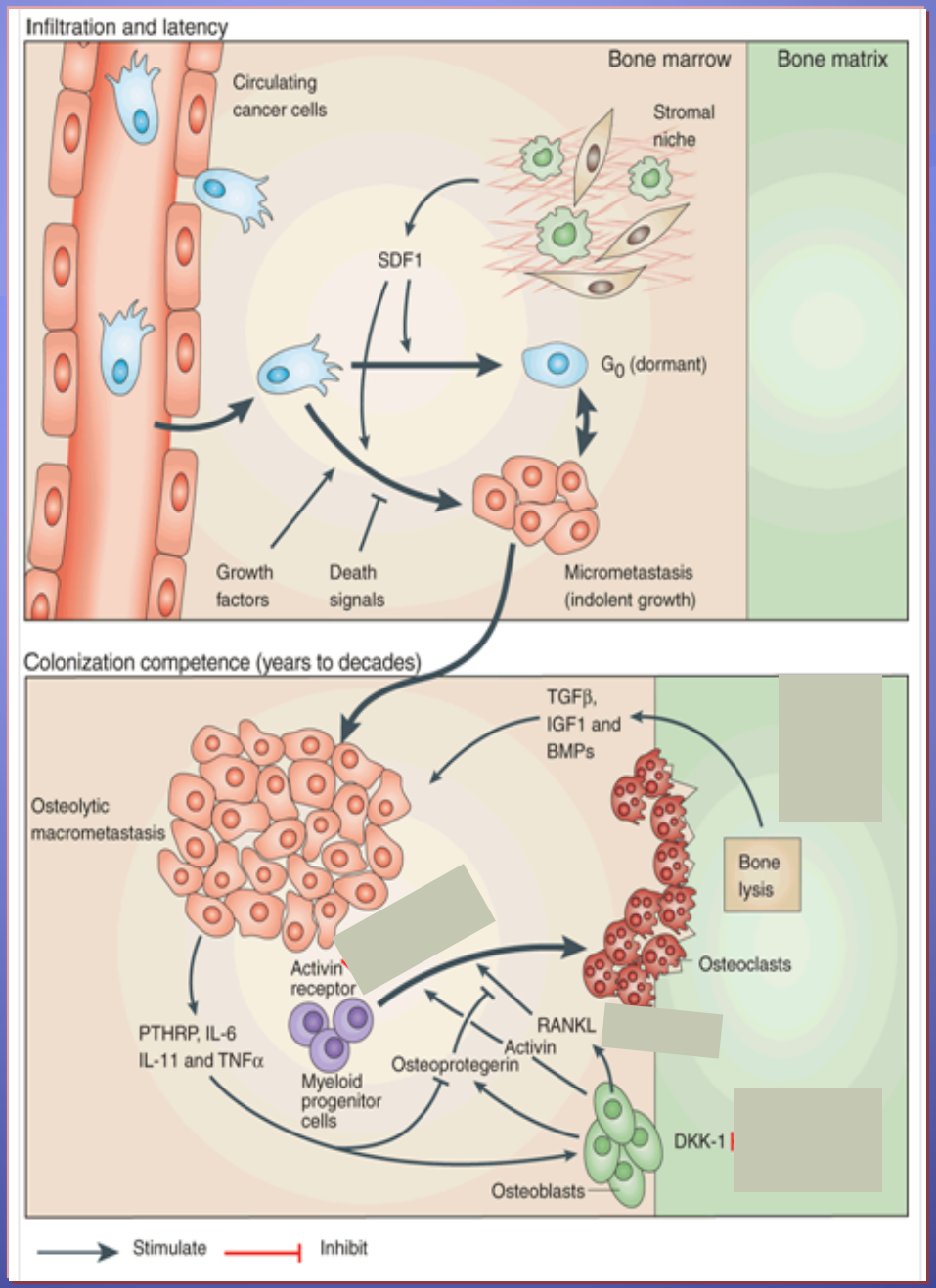
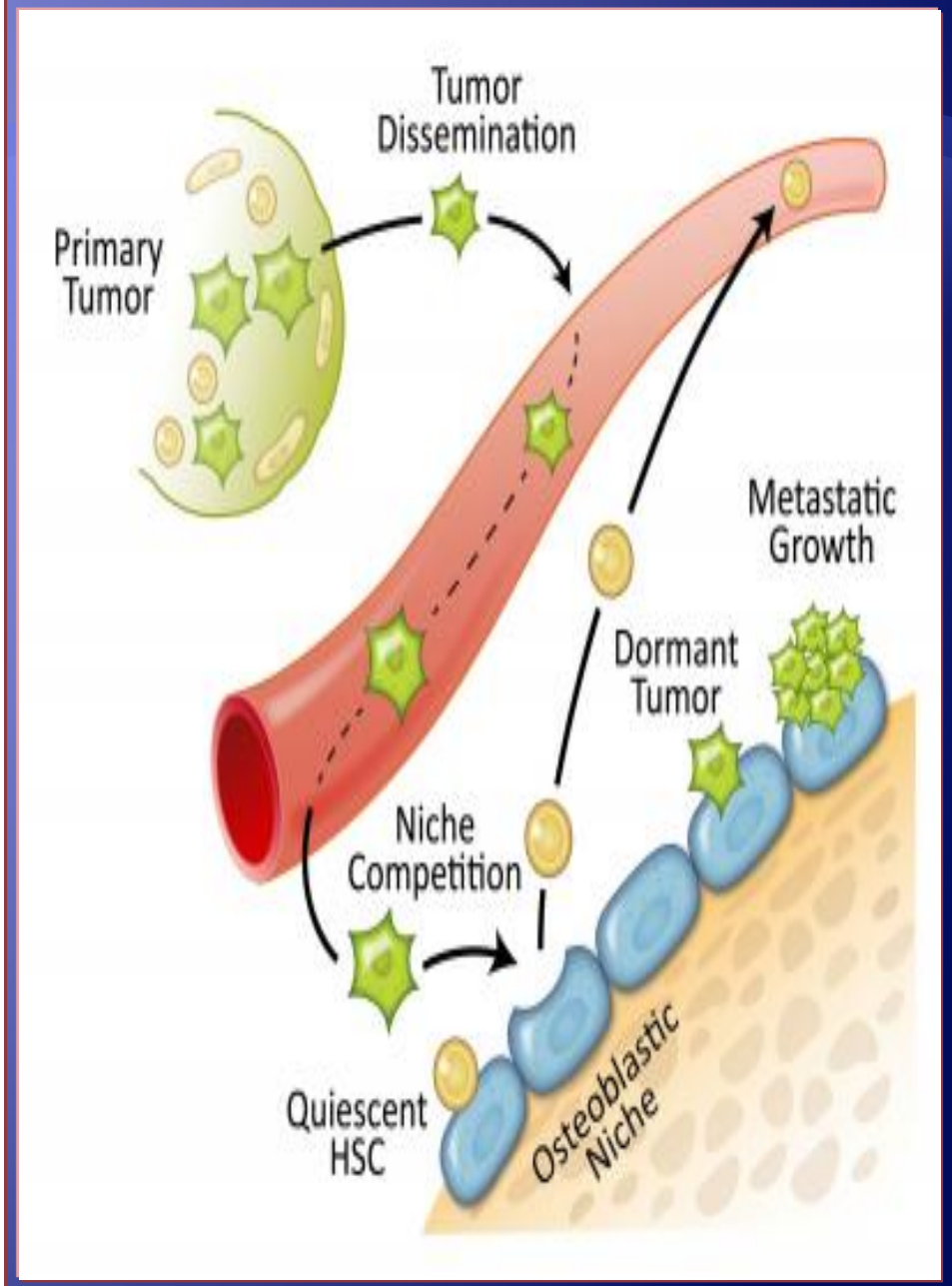


FIG. 5.—Composite anteroposterior roentgenogram of female cadaver after injection of radiopaque material into a venule of the left breast. Note the extensive filling of the vertebral veins, the superior longitudinal sinus, transverse sinus as well as in other dural and cerebral veins.

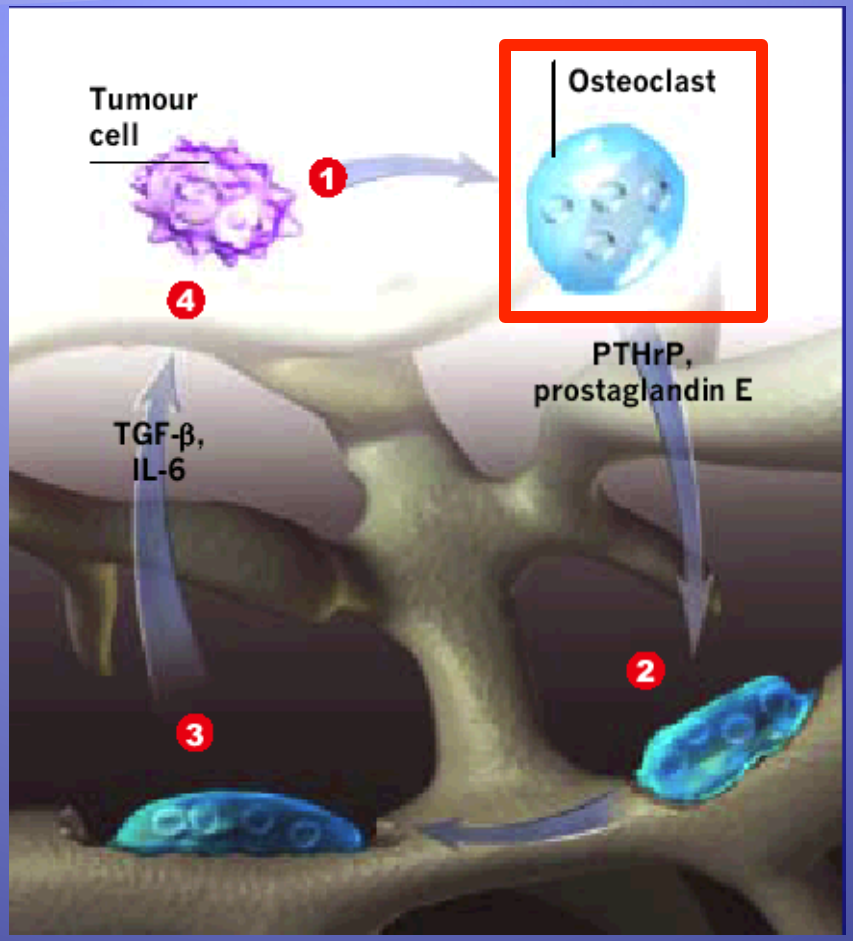
Cellular pathways associated with bone metastases



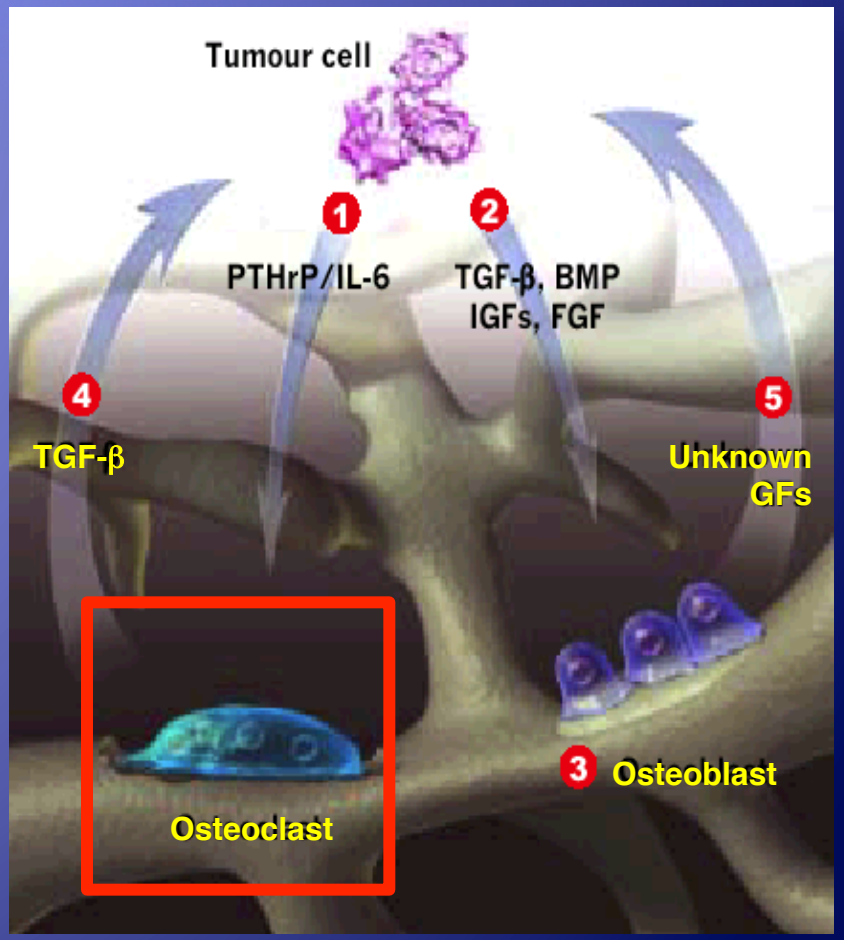


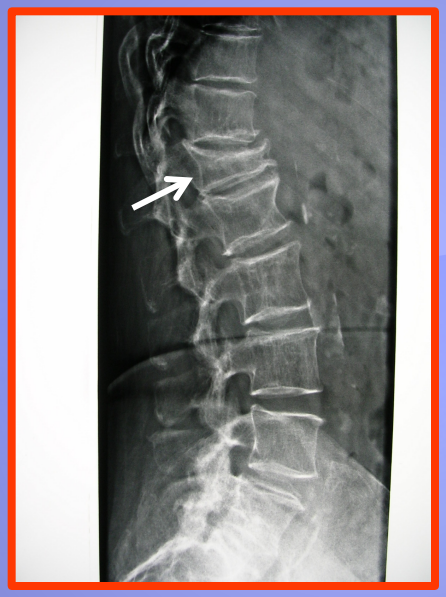
Cancer and Bone Cell Interactions

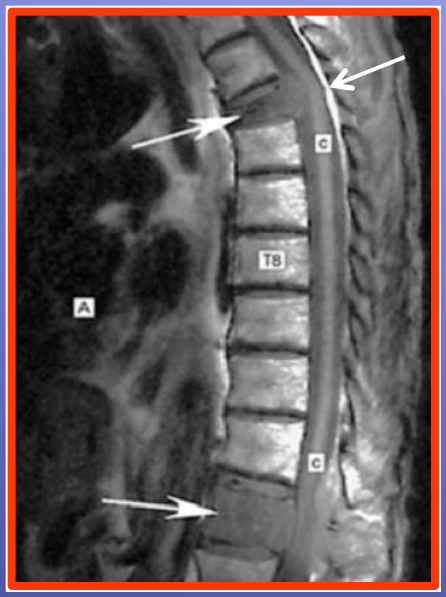
Osteolytic bone disease



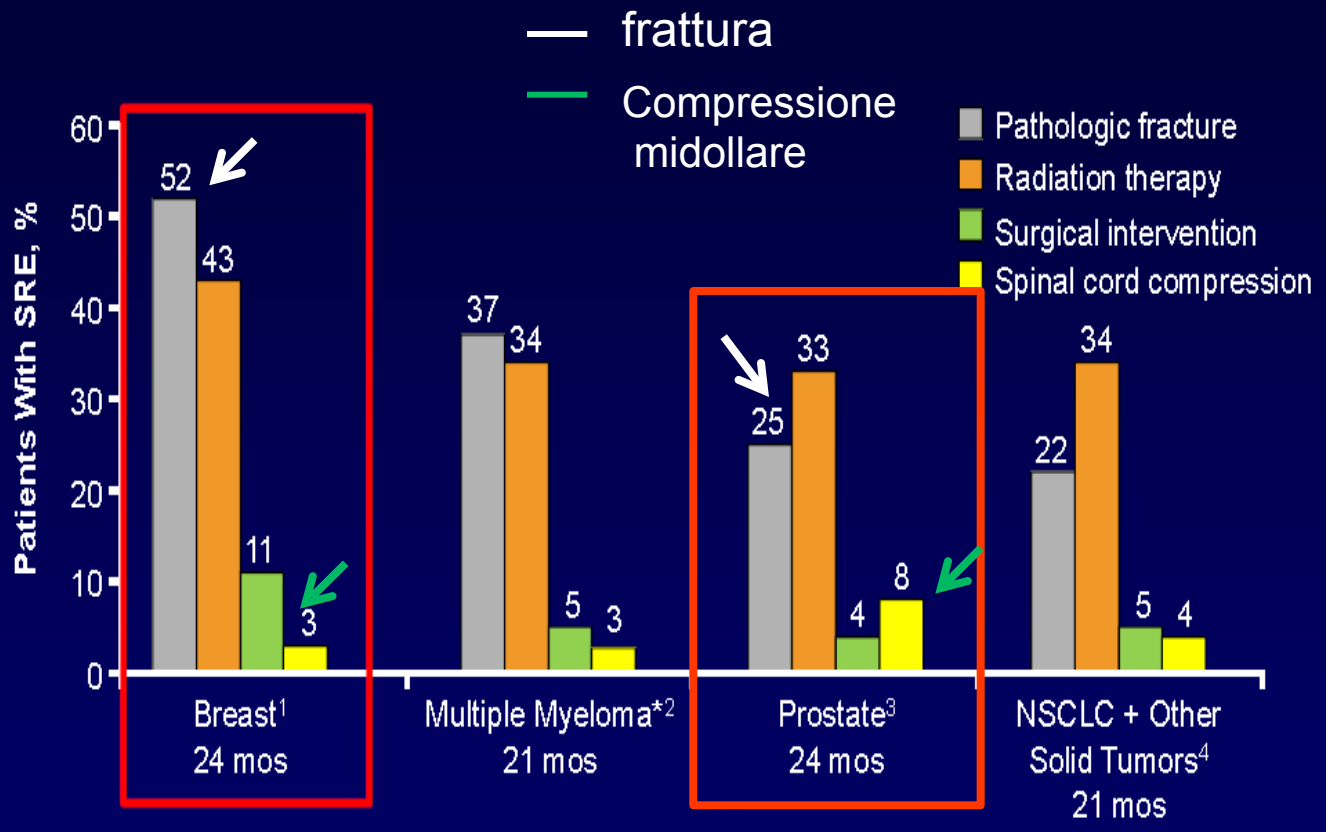
Osteoblastic bone disease







Skeletal Complications in Large, Randomized Trials: Placebo Arms



*21-month data except for surgical intervention and spinal cord compression, for which only 9-month data are available.

1. Lipton A, et al. *Cancer*. 2000;88(5):1082-1090. 2. Berenson JR, et al. *J Clin Oncol*. 1998;16(2):593-602. 3. Saad F, et al. Presented at the 2003 Annual Meeting of the American Urological Association; April 26 – May 1, 2003: Chicago, Illinois. Abstract 1472. 4. Rosen LS, et al. *Cancer*. 2004;100:2613-2621.

Consequences of vertebral metastasis

- PAIN
- FUNCTIONAL IMPAIRMENT (DISABILITY)
- QUALITY OF LIFE
- PATIENT SURVIVAL
- HEALTH COSTS

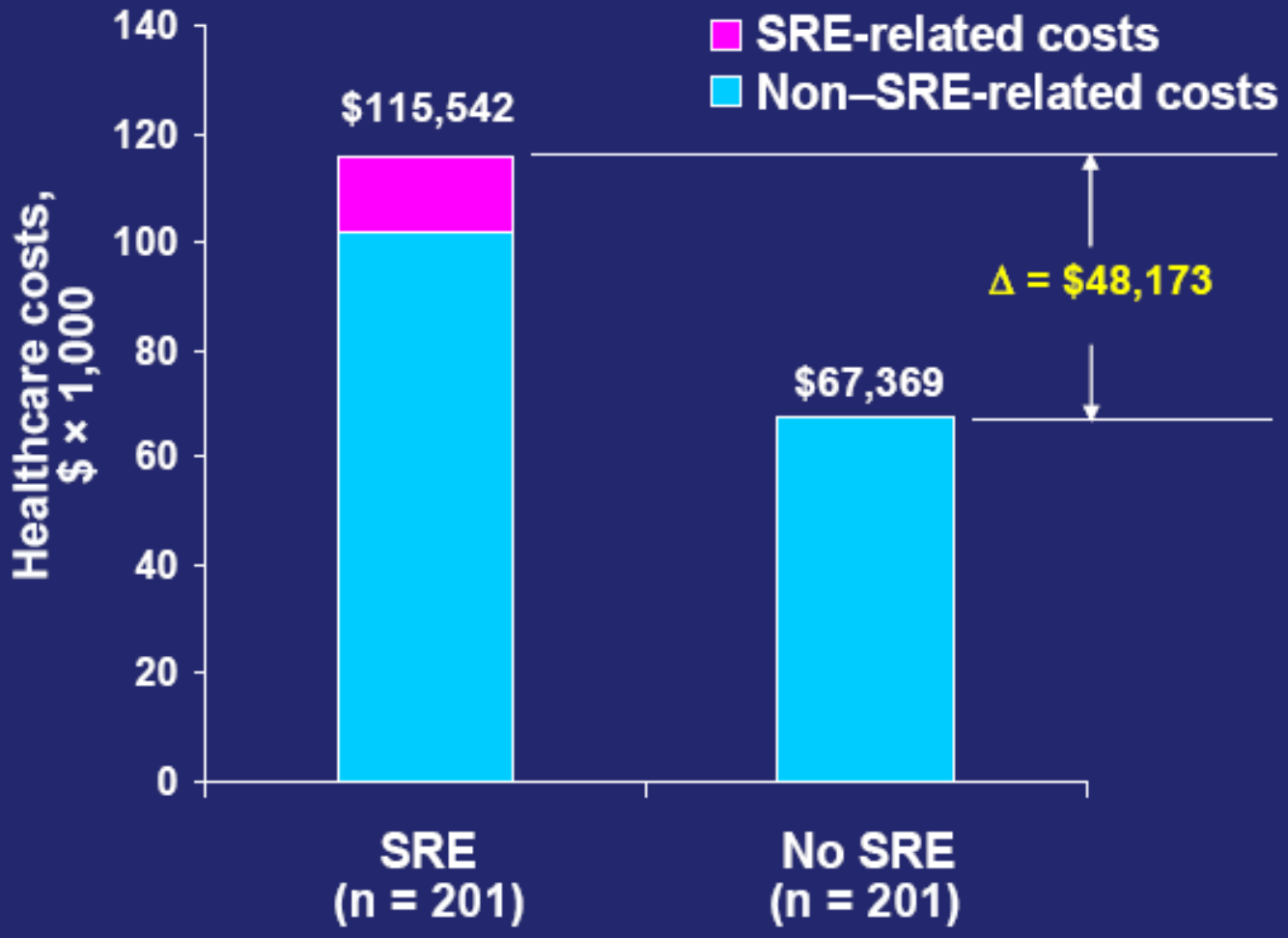
Impact on Survival: Fractures Negatively Affect Survival

- Pathologic fractures correlate with a significantly increased relative risk of death[1,2]

– Breast cancer	1.52 (1.28, 1.81)	*P* < .0001
– Multiple myeloma	1.44 (1.06, 1.95)	*P* = .02
– Prostate cancer	1.29 (1.01, 1.65)	*P* = .04
– Lung cancer / Other	1.08 (0.87, 1.34)	*P* = .49

1. Hei Y-J, et al. Presented at: 28th Annual SABCS, 2005, Abstract 6036.
2. Saad F, et al. Presented at: ECCO 2005. Abstract 1265.

Preventing SREs Reduces Cost of Managing Breast Cancer Patients With Bone Metastases



SRE = Skeletal-related event.

Data from Delea T, et al. *J Support Oncol*. 2006;4:341-347.

Treatment of Bone Metastases

Systemic treatments

Tumor targeted treatments

- endocrine manipulations
- chemotherapy
- targeted treatments (biologicals)

Bone cells targeted treatments

- osteoclast inhibitors (BFs, Denosumab)

Local treatments

- Surgery, EB Radiotherapy..

Pain palliation and supportive measures

[CANCER RESEARCH 55, 3068–3072, July 15, 1995]

Distant Metastases from Prostatic Carcinoma Express Androgen Receptor Protein[1]

Alfred Hobisch, Zoran Culig,[2] Christian Radmayr, Georg Bartsch, Helmut Klocker, and Anton Hittmair

Departments of Urology [A. Ho., Z. C., C. R., G. B., H. K.] and Pathology [A. Hi.], University of Innsbruck, A-6020 Innsbruck, Austria

Table 1 *AR and PSA expression in prostatic carcinoma metastases*

Patient no.	Tumor grade	Localization of metastasis	Expression of AR[a]	Expression of PSA[a]	Therapy[b]
1	III	Bone (C)	+++	+	O+DES
2	II	Bone (ilium)	+	+	O+F
3	III	Bone (femur)	+++	-	O+DES
4	III	Epidural space	+++	+	O+DES
5	II	Bone (VC)	++	++	O+F
5	II	Bone (humerus)	+++	++	O+F
6	II	Bone (VC)	++	+	I
7	III	Bone (VC)	+++	+	DCP+CPA
8	II	Bone (ilium)	++	+++	O
9	II	Bone (VC)	++	+++	O+F
10	III	Bone (VC)	++	+	O+F
10	III	Bone (humerus)	+++	+	O+F
11	III	Bone (VC)	+++	+++	O+F
11	III	Bone (humerus)	+++	++	O+F
12	III	Bone (VC)	++	+++	O
13	II	Bone (VC)	++	+++	O
14	III	Periosteum (C)	+	+	O
15	III	Bone (VC)	++	++	O+F
15	III	Epidural space	+	+	O+F
16	II	Bone (VC)	++	+++	DCP+CPA
17	III	Epidural space	+	+	F
18	III	Bone (VC)	++	++	O+F

[a] -, negative staining; +, <10% cells positive; ++, 10–50% cells positive; +++, >50% cells positive.

[b] O, orchiectomy; DES, diethylstilbestrol; F, hydroxyflutamide; I, irradiation; DCP, LHRH analogue decapeptyl; CPA, cyproterone acetate; C, cranium; VC, vertebral column.

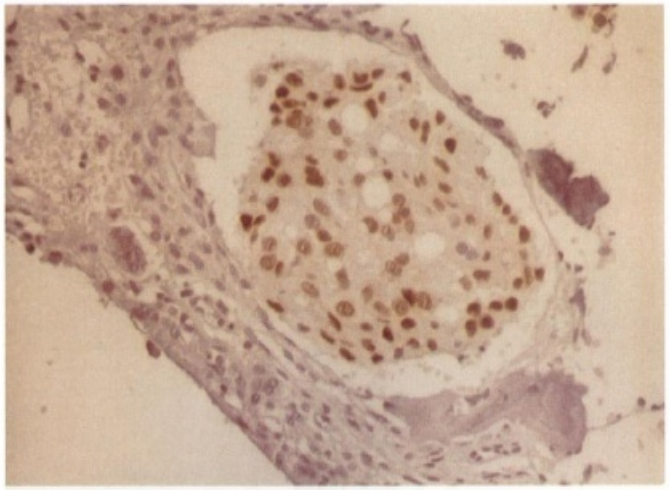


Fig. 1. AR-positive cells in a bone metastasis from prostate cancer (× 200). Paraffin-embedded sections fixed in formalin were stained with the polyclonal antibody PG-21 as described in "Materials and Methods."

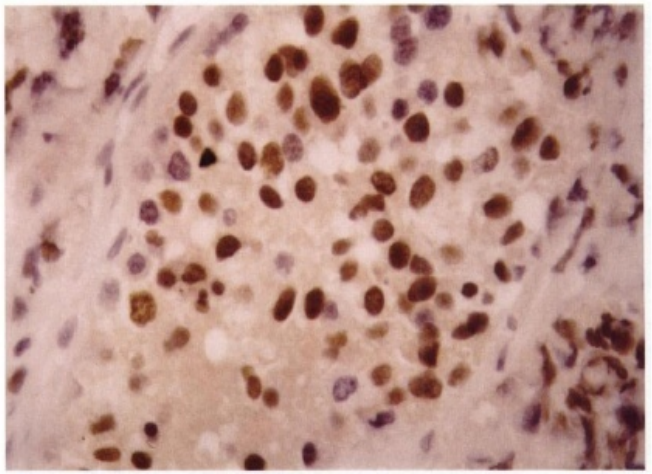
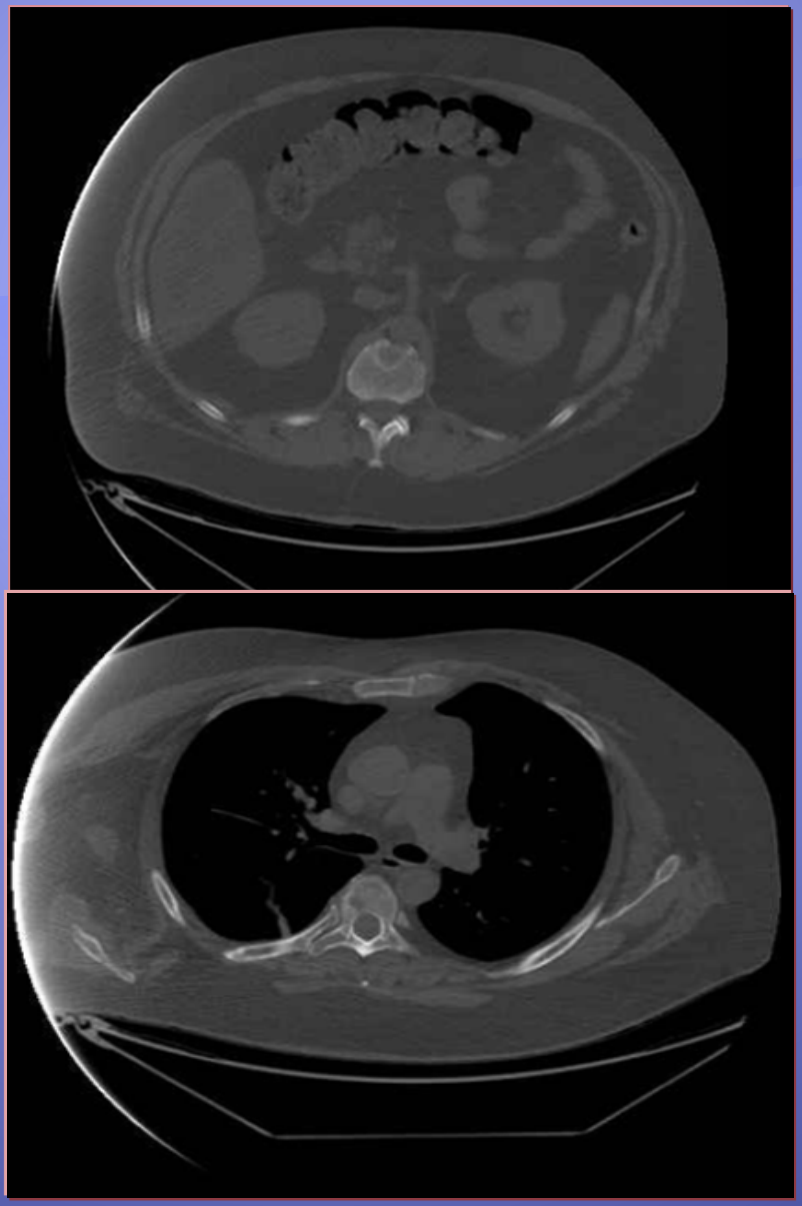
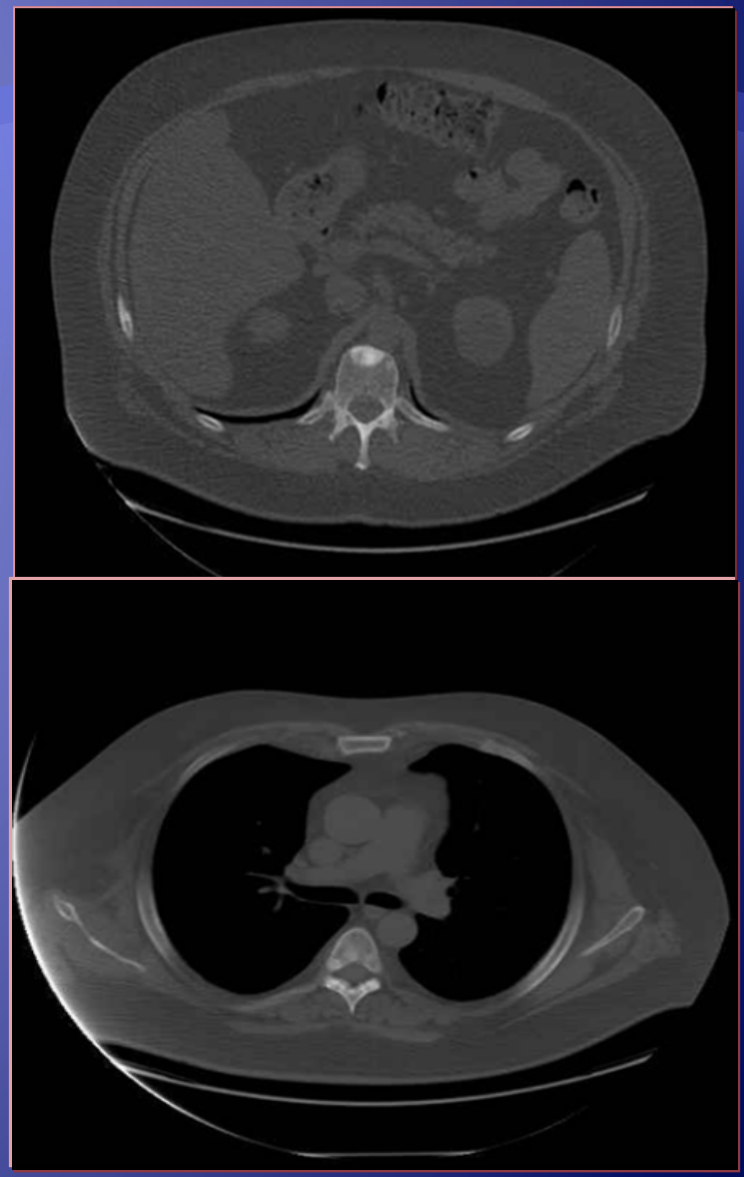


Fig. 2. Nuclear expression of AR in metastatic prostatic cancer localized in the epidural space (× 400).

September 2011

November 2011





PSA: 267 ng/ml PAL: 1515 U/L Uncontr pain

PSA: 37 ng/ml PAL: 911 U/L control pain

MAB - Zoledronic Acid - Cal + Vit D suppl

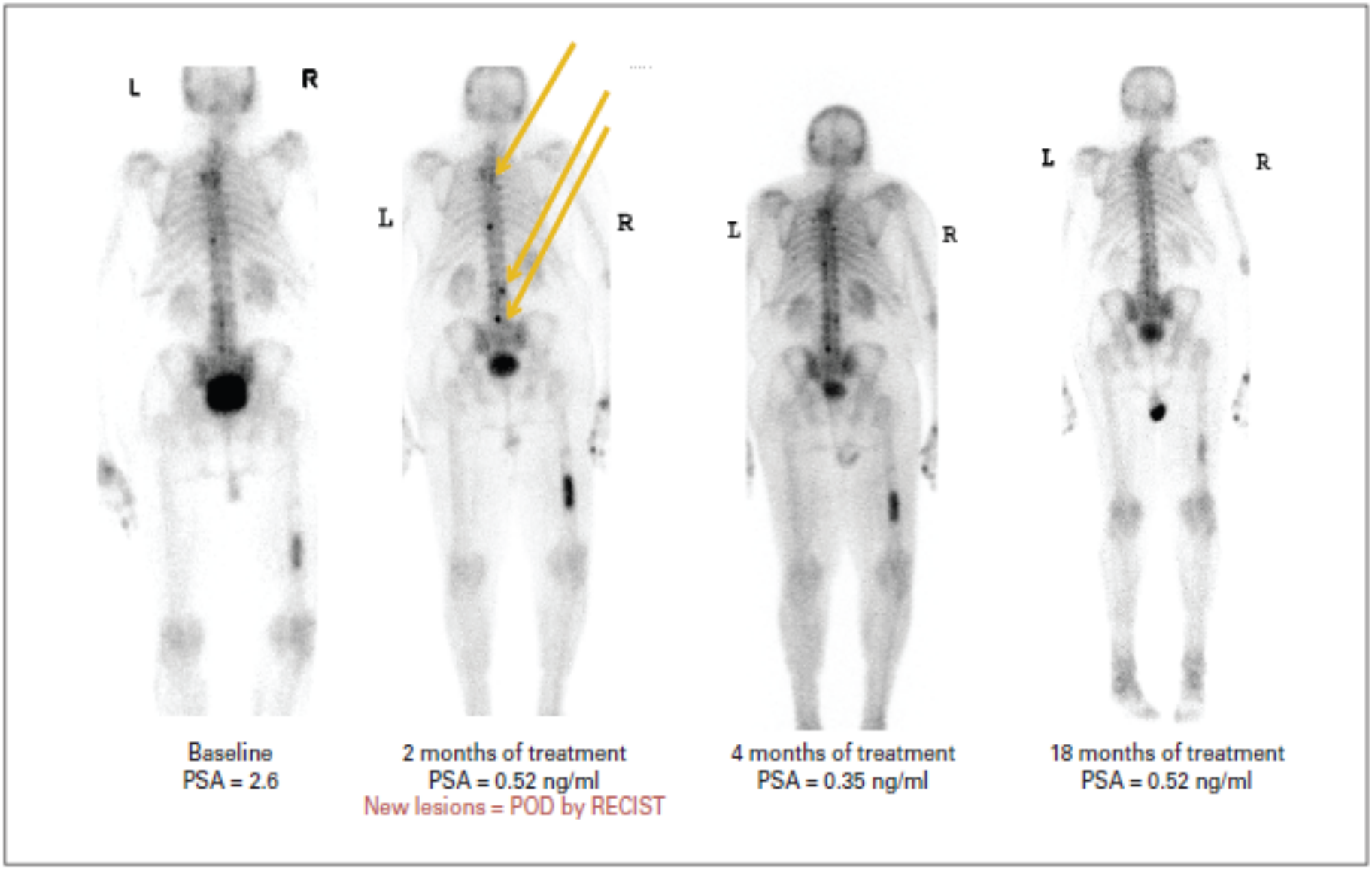
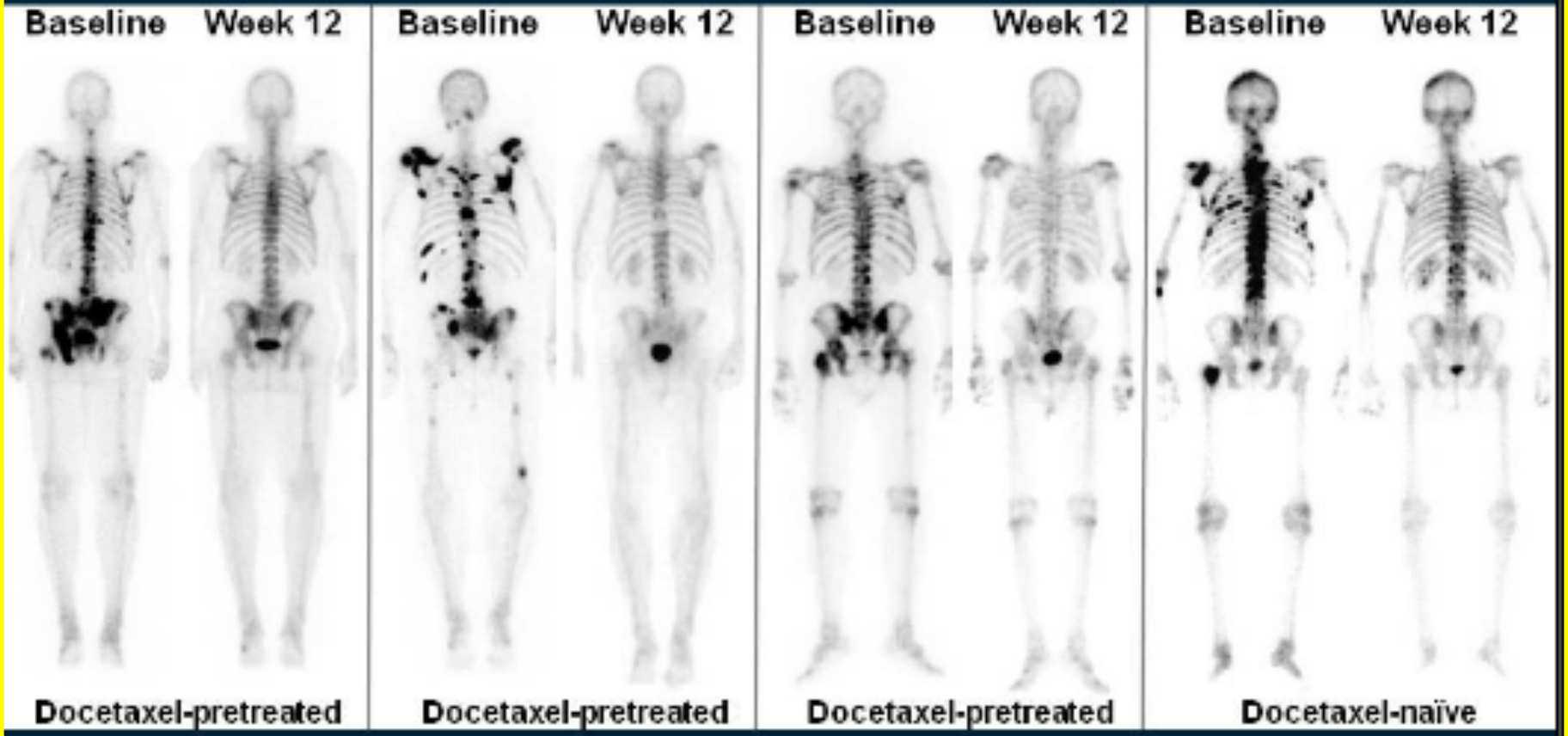


Fig 3. Flare on bone scan. Two new lesions at 8 weeks were not followed by subsequent additional lesions, so patient remained on study; bone scan markedly improved over 18 months. POD, progression of disease; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.

(Cabozantinib I)

Bone Scan Effects: Representative Images



Each Patient had PR + Pain Improvement

(Cabozantinib II)

Conclusions

- In mCRPC patients with progressive disease, Cabozantinib has substantial antitumor activity:
  - 68% overall objective disease control at Week 12
  - 74% measurable disease regression
  - 76% complete or partial resolution of bone scans
  - 67% pain improvement in patients with pain at baseline
  - 29 weeks overall median PFS
    - Significant PFS improvement post-randomization
- Moderate but manageable AE profile; with similarities to other TKIs
- Cabozantinib is being evaluated in docetaxel-pretreated mCRPC patients (NCT00940225)

Epidural compression of the cauda equina caused by vertebral osteoblastic metastasis of prostatic carcinoma: resolution by hormonal therapy

Department of Neurology, Higashimatsudo Municipal Hospital, Chiba, Japan
K Susuki
S Matsumoto

Department of Urology, Matsudo Municipal Hospital, Chiba, Japan
N Kitagawa

Department of Orthopaedic Surgery, Matsudo Municipal Hospital, Chiba, Japan
H Shinohara

Department of Neurology, Yokohama City University, Yokohama, Japan
O Hasegawa
Y Kuroiwa

Correspondence to:
Dr Keiichiro Susuki, Department of Neurology, Dokkyo University School of Medicine, 880 Kitakobayashi, Mibu, Shimotsuga, Tochigi 321–0293, Japan
email KSusuki@aol.com
Received 26 April 1999 and in revised form 16 August 1999 Accepted 25 August 1999

Keiichiro Susuki, Shunsuke Matsumoto, Norikazu Kitagawa, Hiroyasu Shinohara, Osamu Hasegawa, Yoshiyuki Kuroiwa

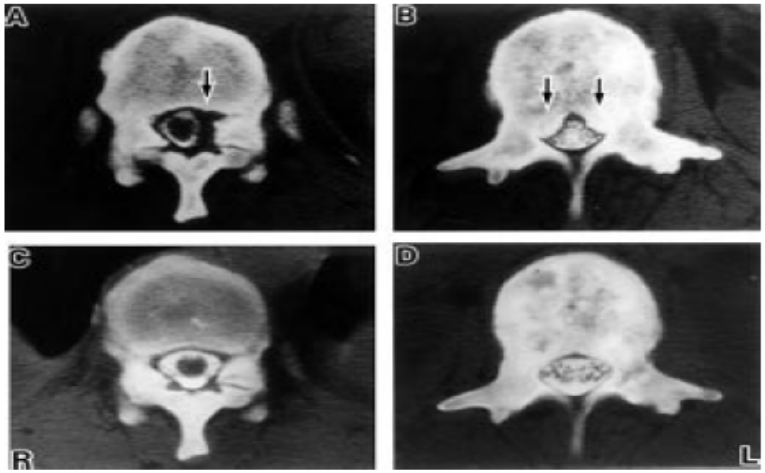
Abstract

A 59 year old man with prostatic carcinoma developed epidural compression of the cauda equina caused by bony expansion from a vertebral osteoblastic metastasis. For medical reasons he could not undergo radiation or surgery. Hormonal therapy alone relieved his low back pain and restored ambulation and urinary function. Postmyelography CT showed that the bony expansion from the vertebra had completely disappeared after treatment. This is the first report of remarkable improvement due to hormonal therapy alone.

(*J Neurol Neurosurg Psychiatry* 2000;**68**:514–515)

Keywords: prostatic carcinoma; osteoblastic metastasis; epidural compression; hormonal therapy

Compression of the spinal cord and cauda equina is an important neurological complication of prostatic carcinoma.[1] Direct tumour extension from a vertebral metastasis is the most common mechanism. Epidural compression caused by bony expansion from a vertebral osteoblastic metastasis, a rare occurrence,[2–5] is thought to be an absolute indication for surgical decompression.[2] We describe a case of epidural compression of the cauda equina due to such an uncommon condition, which was treated successfully with hormonal therapy alone.



Postmyelography spinal CT. Before treatment: (A) the spinal cord is compressed laterally by the epidural mass (arrow) on the left side of the body of Th11; (B) the vertebral canal is narrowed by bony expansion (arrows) from both sides of the body at L2. After treatment: (C) the epidural mass in the body of Th11 has disappeared; (D) bony expansion from the body of L2 has also disappeared.

Case report

A previously healthy 59 year old man developed low back pain in September 1997, and the pain gradually worsened. He began to notice paraesthesia in both legs in February 1998. One month later, he developed weakness and severe paraesthesia in both legs and could not walk.

In August 1998, he was admitted to our hospital, at which time anaemia was apparent. There was no neurological abnormality in the cranial nerves or upper limbs. Atrophy of the right lower limb was apparent. Muscle tone was decreased to grade 3–4 (Medical Research Council) power in the right lower limb and grade 4–5 in the left. Deep tendon reflexes were pathologically depressed in both lower limbs, and the Lasègue sign was positive on both sides. Hypaesthesia was present below L1 area on his right side and the S1 area on the left side, but the saddle area was normal. Although bowel dysfunction was not apparent, he developed urinary retention several days after admission.

Haematological investigations disclosed anaemia (Hb 7.3 g/dl) and thrombocytopenia (84 000/μl). Serological investigations showed an increased alkaline phosphatase of 5301 U/l, and lactic dehydrogenase of 751 U/l. Cerebrospinal fluid had increased protein, 63 mg/dl, but normal cellularity. Plain radiography showed multiple osteoblastic lesions involving the thoracic and lumbar vertebral bodies, and pelvis. A nuclear bone scan showed multiple hot spots in the skull, vertebrae, ribs, humeri, and femora, consistent with multiple bone metastases. Myelography showed narrowing of the vertebral canal in the body of Th11, L2. Postmyelography spinal CT showed an epidural mass in the body of Th11 and bony expansion from the body of L2 into the vertebral canal (figure).

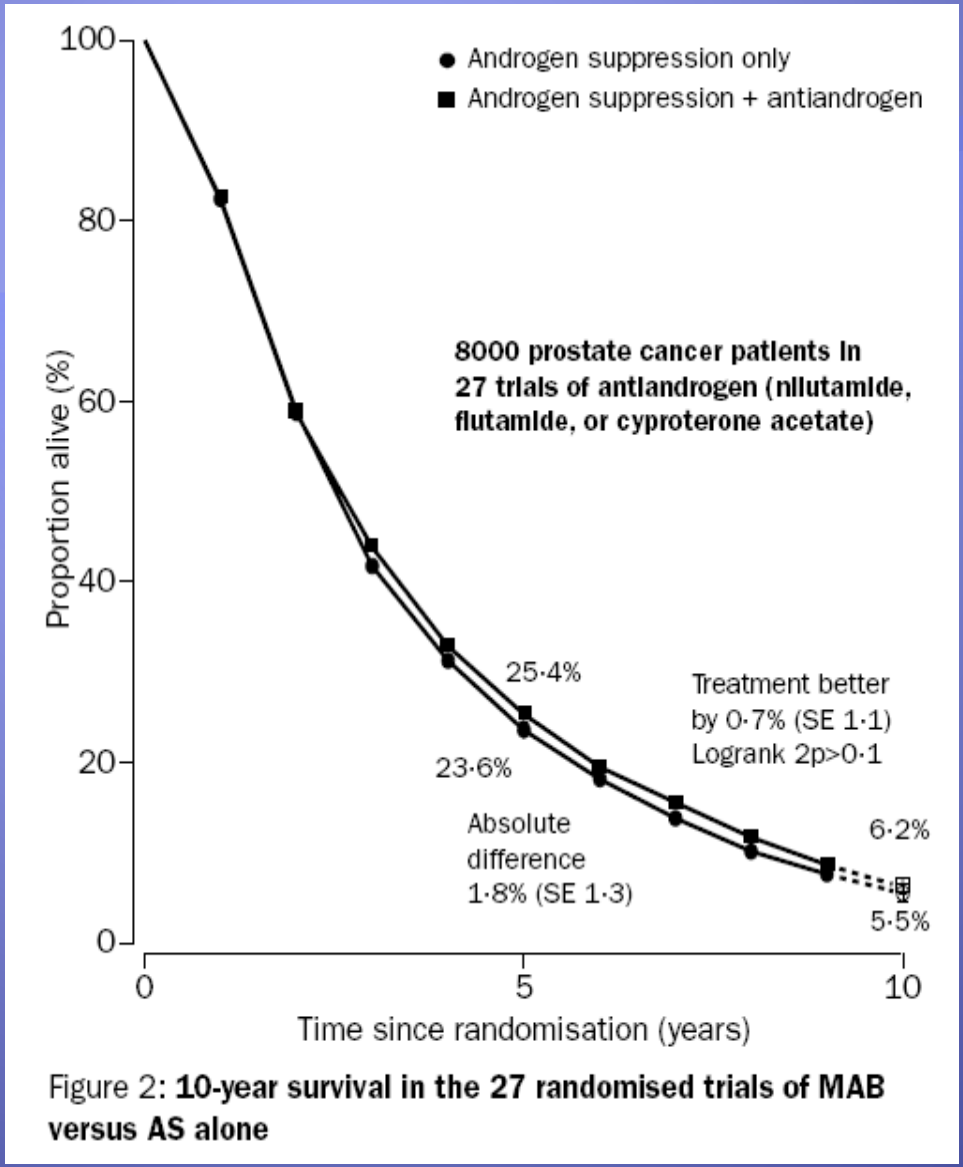
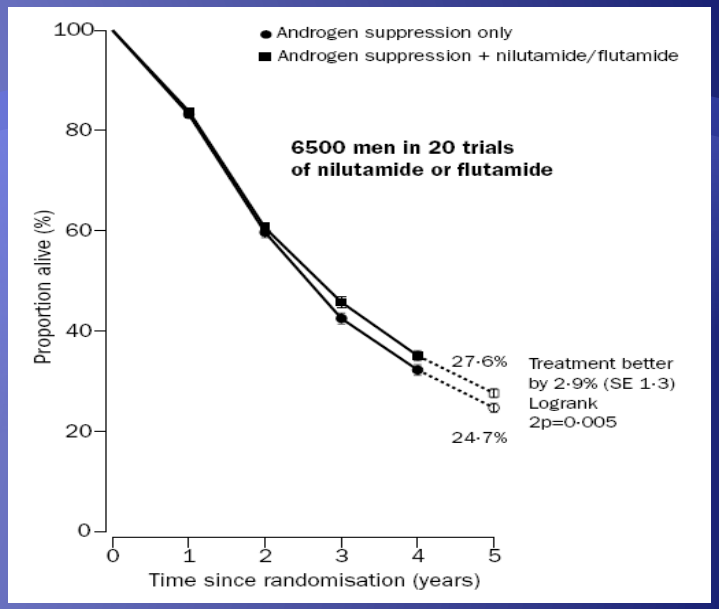
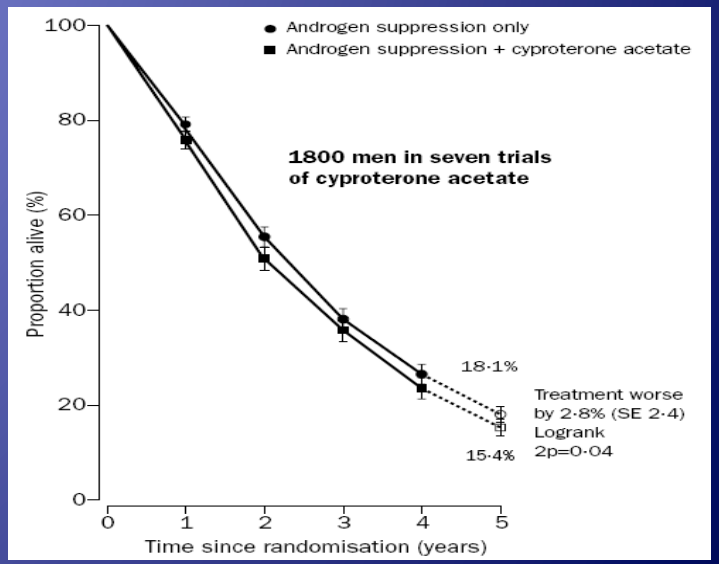


Figure 2: **10-year survival in the 27 randomised trials of MAB versus AS alone**





The Lancet, 2000,355;1491-98

Androgens and Prostate Cancer Bone Metastases: Effects on Both the Seed and the Soil

Endocrinol Metab Clin N Am 40 (2011) 643–653

Wei Yang, BA, Alice C. Levine, MD*

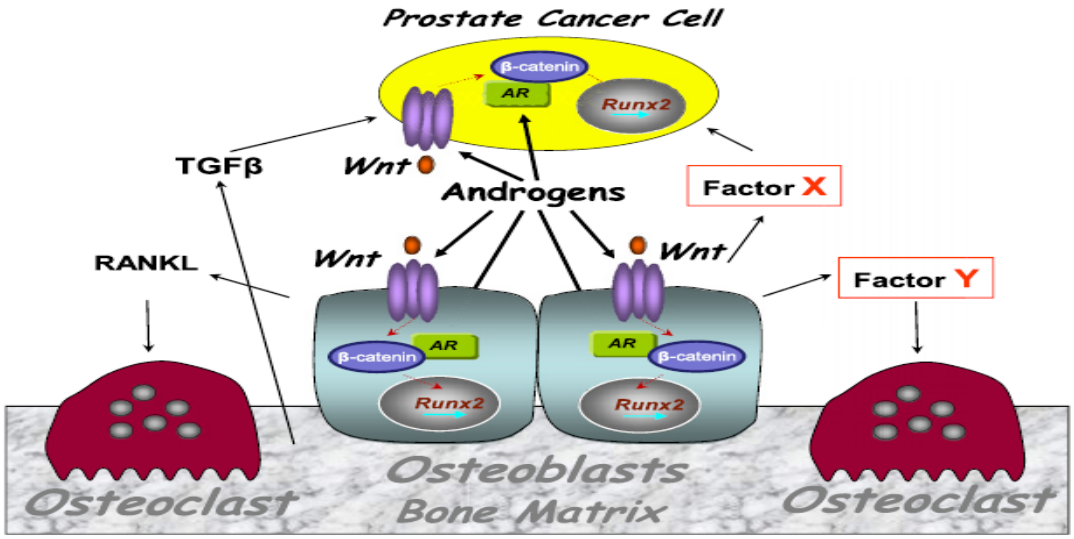
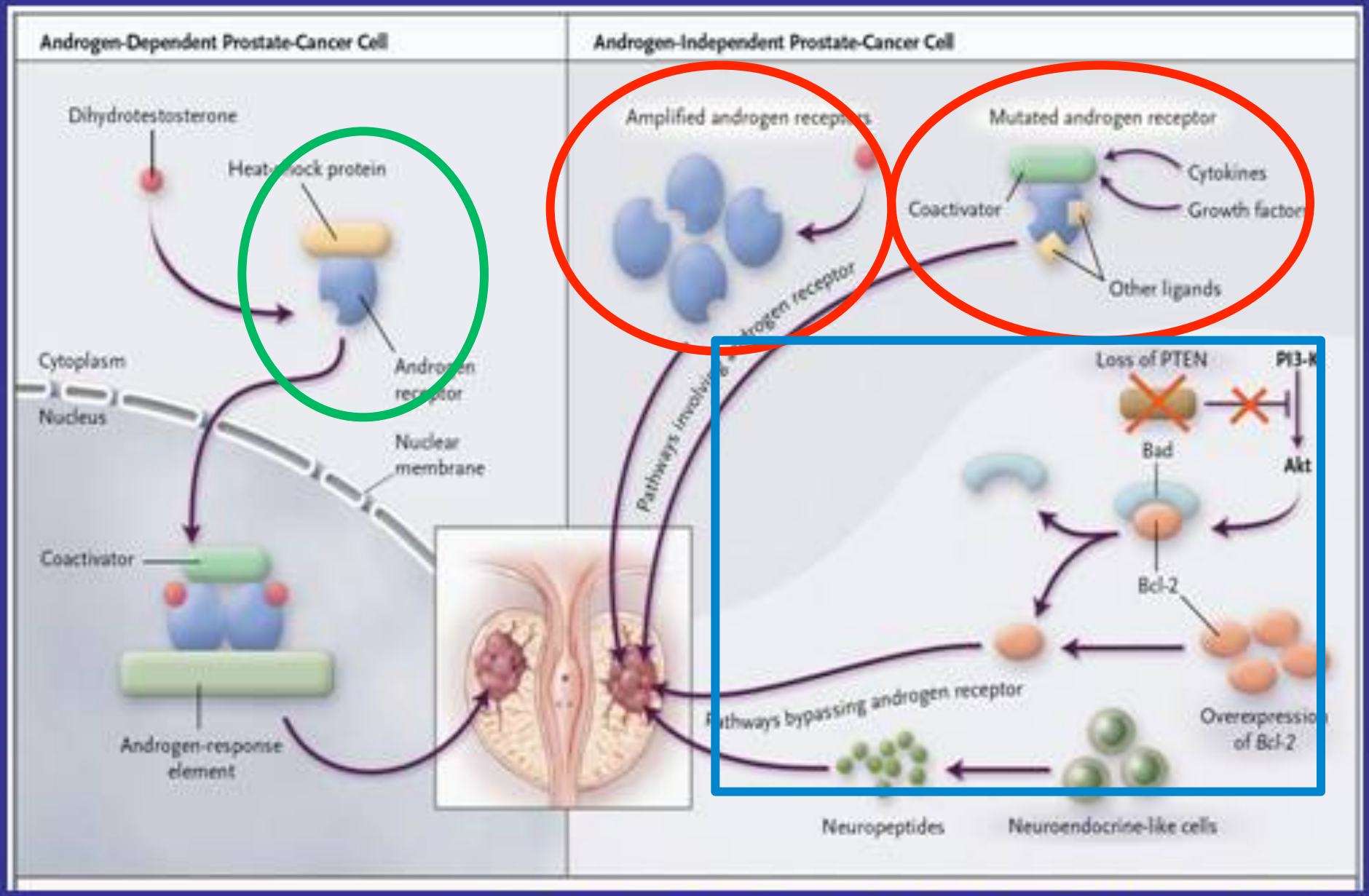


Fig. 2. Androgens/AR interactions with TGF-β and Wnt signaling systems in PCa and bone cells. Androgens modulate Runx2 activity in PCa cells and may thereby promote EMT and PCa metastatic potential. In PCa cells, AR also interacts with β-catenin, an important component of the canonical Wnt signaling system. Androgens stimulate Wnt signaling in osteoblasts leading to increases in Runx2 expression, osteoblast differentiation, and enhanced secretion of both known (RANKL) and, possibly, unknown growth factors that promote osteoclast differentiation. These mature osteoclasts initiate bone resorption with the release of growth factors from the bone matrix, most notably TGF-β, which, in collaboration with androgens/AR, can stimulate further PCa growth and EMT. Thus, the androgenic signaling pathway profoundly influences the vicious cycle of bone metastases at multiple steps in the process.



Debes S, Tindall D. New England Journal of Medicine 2006

Additional Outcomes

	AA (n = 797)	Placebo (n = 398)	*P* Value
Overall survival			
Median, months	14.8	10.9	< 0.0001
PSA response rate			
Total	38.0%	10.1%	< 0.0001
Confirmed	29.1%	5.5%	< 0.0001
Radiographic PFS			
Median, months	5.6	3.6	< 0.0001
Time to first SRE (pathologic fracture/spinal cord compression/ palliative radiation/bone surgery)			
25th percentile, days	301.0	150.0	< 0.0001

Advanced breast cancer with bone-only metastases

A chemotherapeutically responsive pattern of metastases*

Richard V Smalley,M.D. Deborah Mayer Scogna,CRNP,Leon S. Manuel ,MD

AJC 1982;5(2):161-6

Issues concerning the role of chemotherapy and hormonaltherapy in the treatment of bone metastases from breast cancer

Harvey,Cancer,1997

TABLE 2
Response of Osteolytic Lesions to Chemotherapy: Breast Cancer Protocol 019 (N = 195)[a]

Patients with only bone metastases n = 117 (60%)			
Radiologic response (UICC criteria)		**Skeletal complications (24-month follow-up)**	
CR	0%	Patients with ≥1 skeletal events	65%
PR	18%	Skeletal morbidity rate	2.5/year
No change	32%	Median time to first event	7.0 months

TABLE 3
Response of Osteolytic Lesions to Hormonal Therapy: Breast Cancer Protocol 018 (N = 189)[a]

Patients with only bone metastases n = 137 (72%)			
Radiologic response (UICC criteria)		**Skeletal complications (24-month follow-up)**	
CR	0%	Patients with ≥1 skeletal events	83%
PR	21%	Skeletal morbidity rate	3.8/year
No change	32%	Median time to first event	6.9 months
Progression	37%		

UICC: International Union Against Cancer; CR: complete response; PR: partial response.
[a] Patients from control arm of study comparing various hormonal agents ±/− pamidronate.

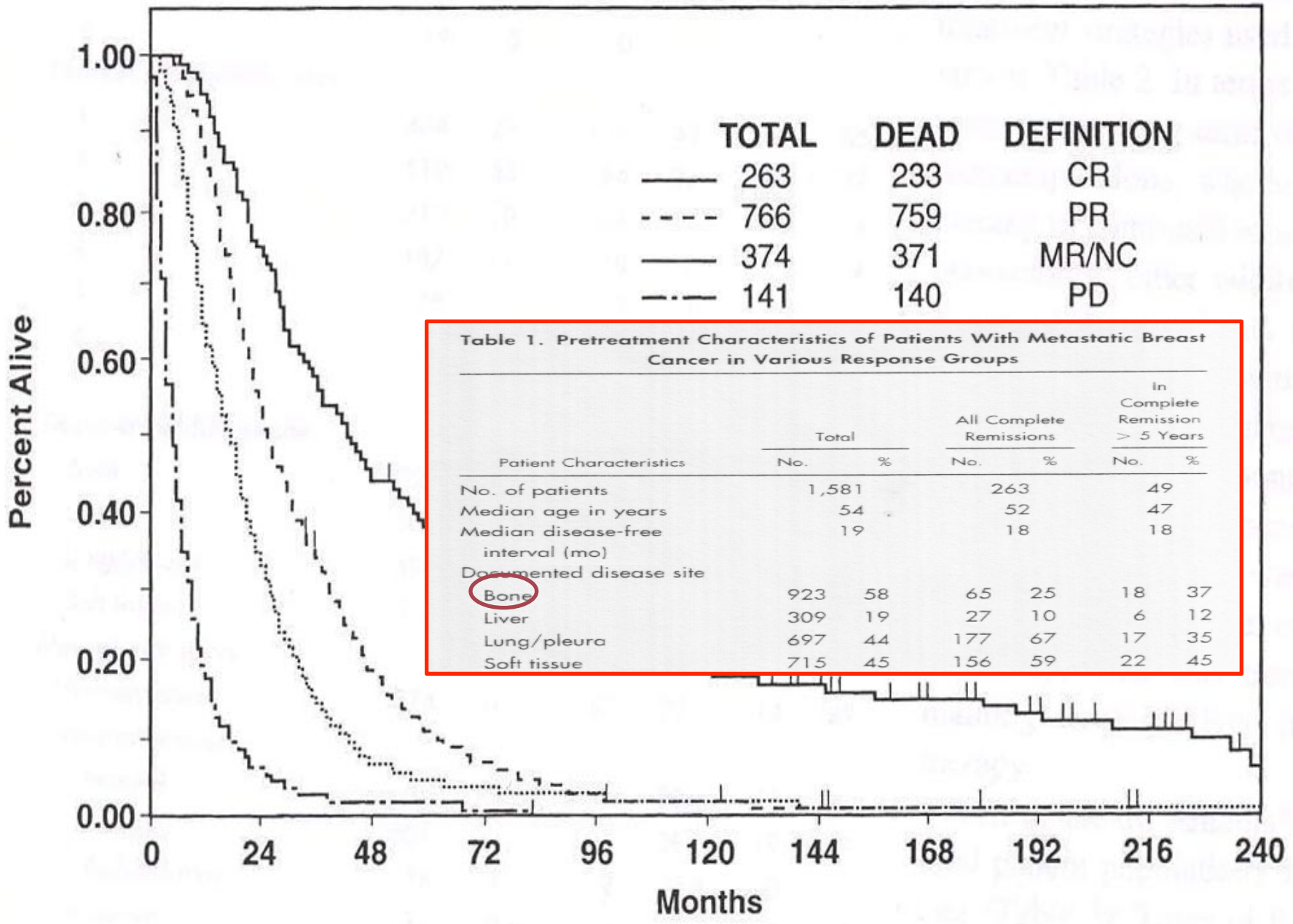


Table 1. Pretreatment Characteristics of Patients With Metastatic Breast Cancer in Various Response Groups

Patient Characteristics	Total No.	Total %	All Complete Remissions No.	All Complete Remissions %	In Complete Remission > 5 Years No.	In Complete Remission > 5 Years %
No. of patients	1,581		263		49	
Median age in years	54		52		47	
Median disease-free interval (mo)	19		18		18	
Documented disease site						
Bone	923	58	65	25	18	37
Liver	309	19	27	10	6	12
Lung/pleura	697	44	177	67	17	35
Soft tissue	715	45	156	59	22	45

Greenberg PAC et al, 1996

Palliative Effect of Chemotherapy: Objective Tumor Response Is Associated With Symptom Improvement in Patients With Metastatic Breast Cancer

By Paul Geels, Elizabeth Eisenhauer, Andrea Bezjak, Benny Zee, and Andrew Day

Purpose: Because one of the goals of chemotherapy for metastatic breast cancer is to provide symptom palliation, we were interested in identifying the relationship between tumor shrinkage and improvement in disease-related symptoms.

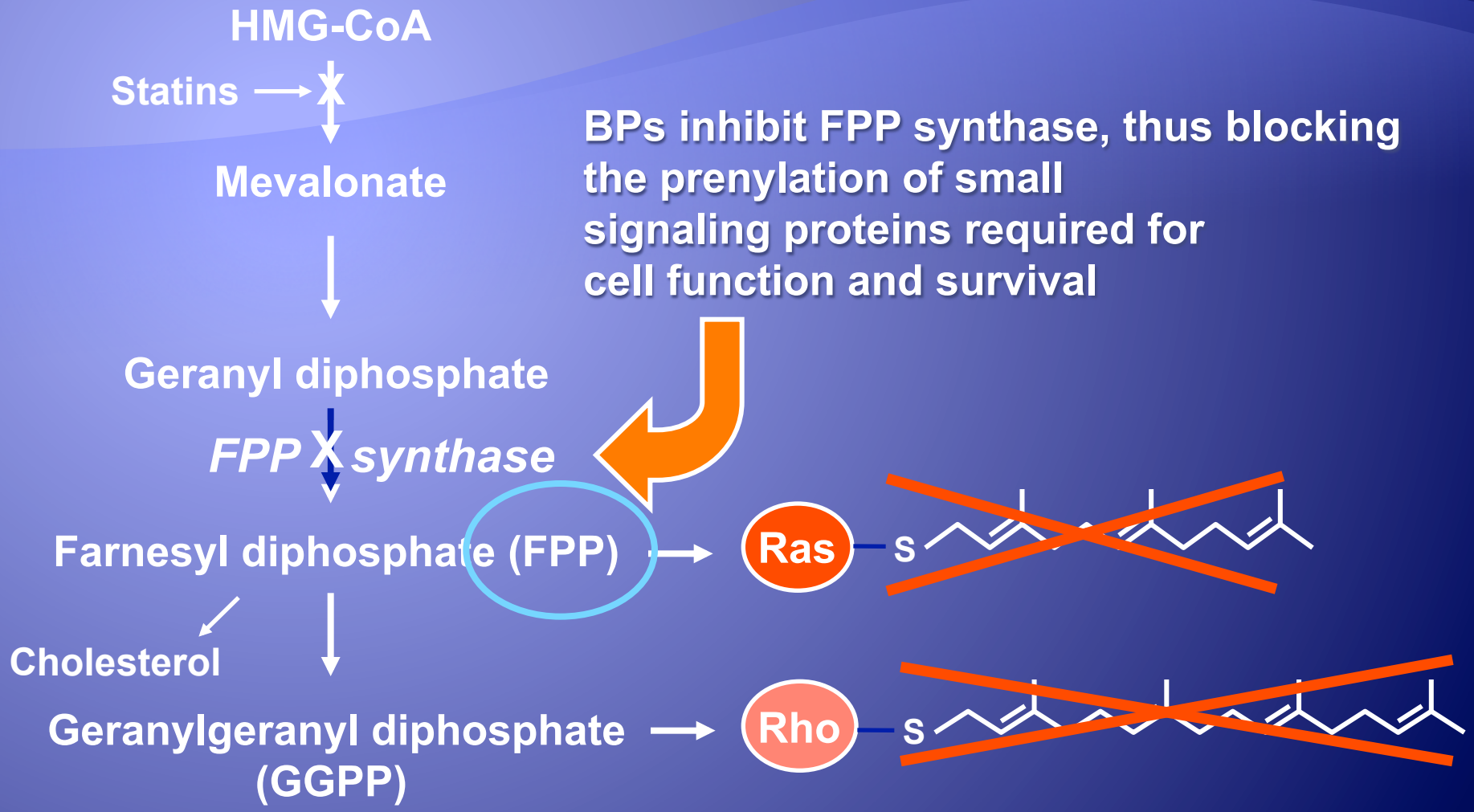
Patients and Methods: Three hundred patients enrolled onto a randomized trial of metastatic breast cancer formed the basis of our study. The nine most common baseline symptoms were identified and followed. Changes from baseline (improvement, stable, worsening) were defined using patient responses to a quality-of-life (QoL) questionnaire (the European Organization for Research and Treatment of Cancer EORTC QLQ-C30) as well as using graded toxicity data collected on case report forms (CRFs). The association between symptom improvement and tumor response was assessed using a linear trend test via a logistic regression model.

Results: The most commonly reported baseline symptoms were cancer pain in 38% (CRF data) and 81% of patients (QoL data) and tiredness in 26% (CRF data) and 89% (QoL data) of patients. Three symptoms—cancer pain, shortness of breath, and abnormal mood—showed a significant relationship between improvement and objective response, using both CRF and QoL assessments. Constipation, anorexia, and nausea showed a similar trend when QoL data were used but not when CRF information was used. The converse was seen for lethargy. There was no correlation between symptom change and response for cough and insomnia.

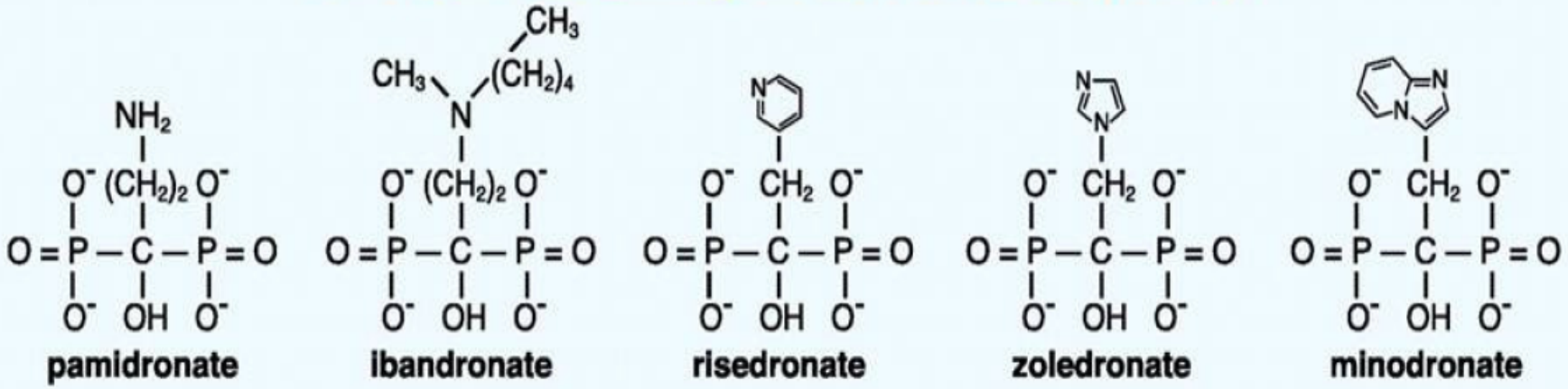
Conclusion: For some symptoms, we found a significant association between symptom improvement and objective tumor regression. In these cases, symptom improvement was greatest in those patients who had complete or partial responses, followed by those with stable disease and then those with progressive disease. Further work in this area will be useful in determining the surrogate value of objective tumor response in identifying the efficacy of palliative chemotherapy.

J Clin Oncol 18:2395-2405.

Bisphosphonates: Molecular mechanism of action



Nitrogen-containing bisphoshonates (NBPs)

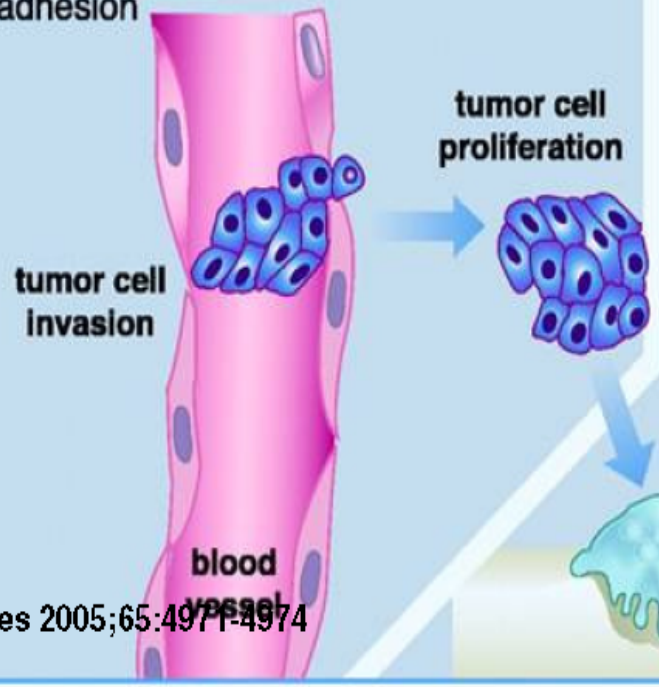


Direct antitumor effects of NPBs

- ↓ tumor cell invasion and adhesion
- ↓ tumor cell proliferation
- ↑ tumor cell apoptosis

Indirect antitumor effects of NPBs

- ↓ osteoclast activity
- ↓ tumor angiogenesis
- ↑ γδ T cell antitumor activity



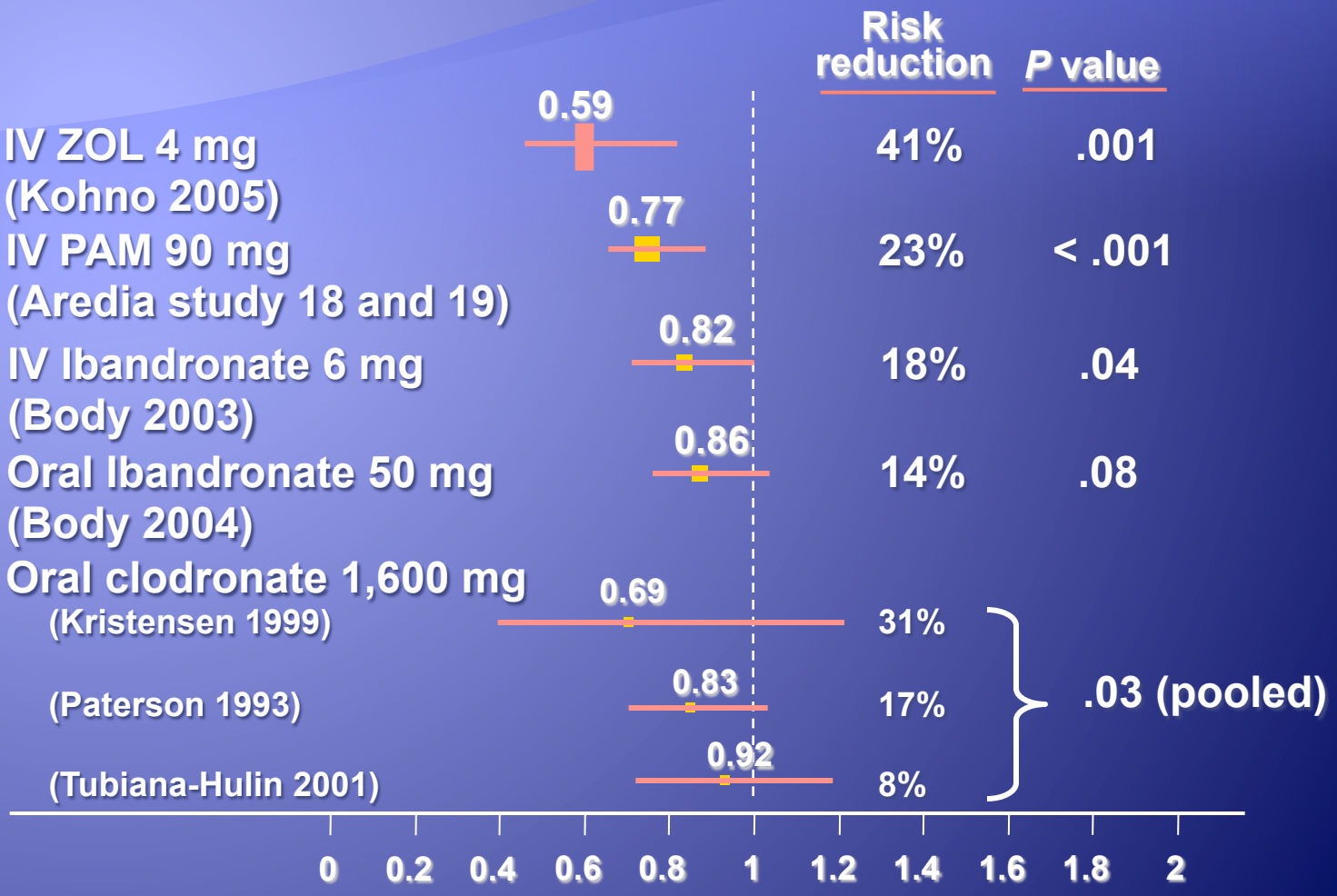
Clezardin, P. et al. Cancer Res 2005;65:4971-4974

The Goal of Bisphosphonate Therapy

- **Bisphosphonates proven benefits**
  - Prevent skeletal-related events (SREs)
    - Prevent first and subsequent SREs
    - Delay the onset of the first SRE
  - Palliate and control bone pain
    - Reduce the need for analgesics and palliative radiotherapy

⇒ Bisphosphonates improve patient's quality of life

Independent Meta-analysis of Phase III Trials of Bisphosphonates for Prevention of SREs in mBC

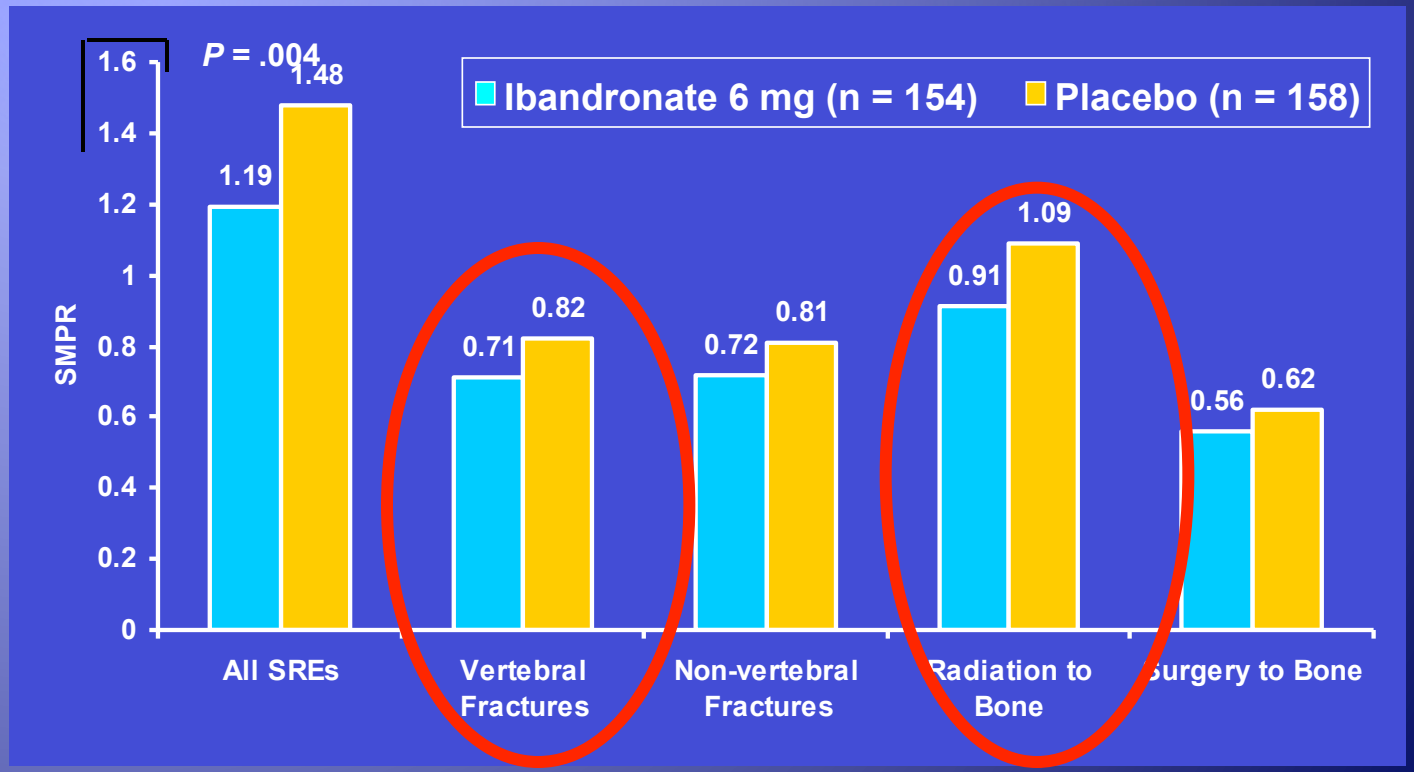


Cochrane database comparing placebo-controlled trials in breast cancer setting.

IV, intravenous; mBC, metastatic breast cancer; PAM, pamidronate; SRE, skeletal-related event; ZOL, zoledronic acid.
Adapted from Pavlakis N, et al. *Cochrane Database Syst Rev*. 2005:CDC003474.

Ibandronate Reduced the Skeletal Morbidity Period Rate (SMPR) in Patients With Bone Metastases From BC

- **Skeletal Morbidity Period Rate defined as "frequency of 12-week period with SREs" during the study (2 years)**

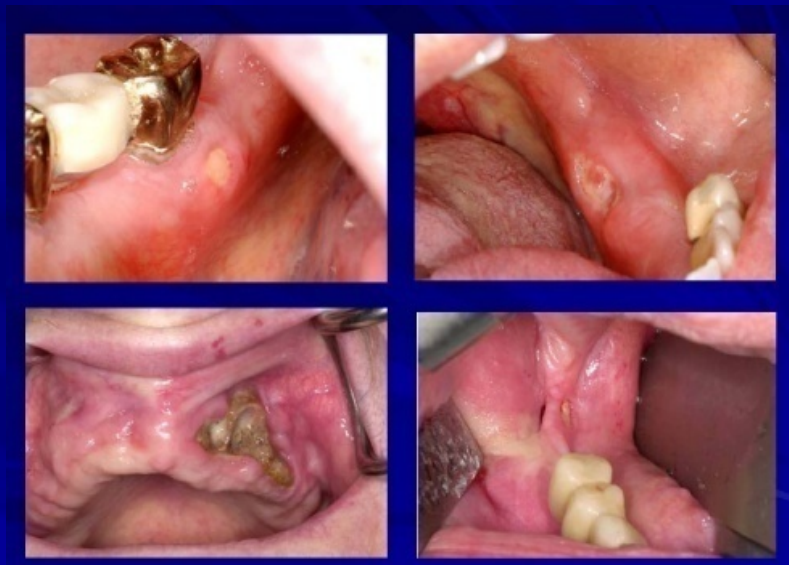


BC, breast cancer; SRE, skeletal-related event.

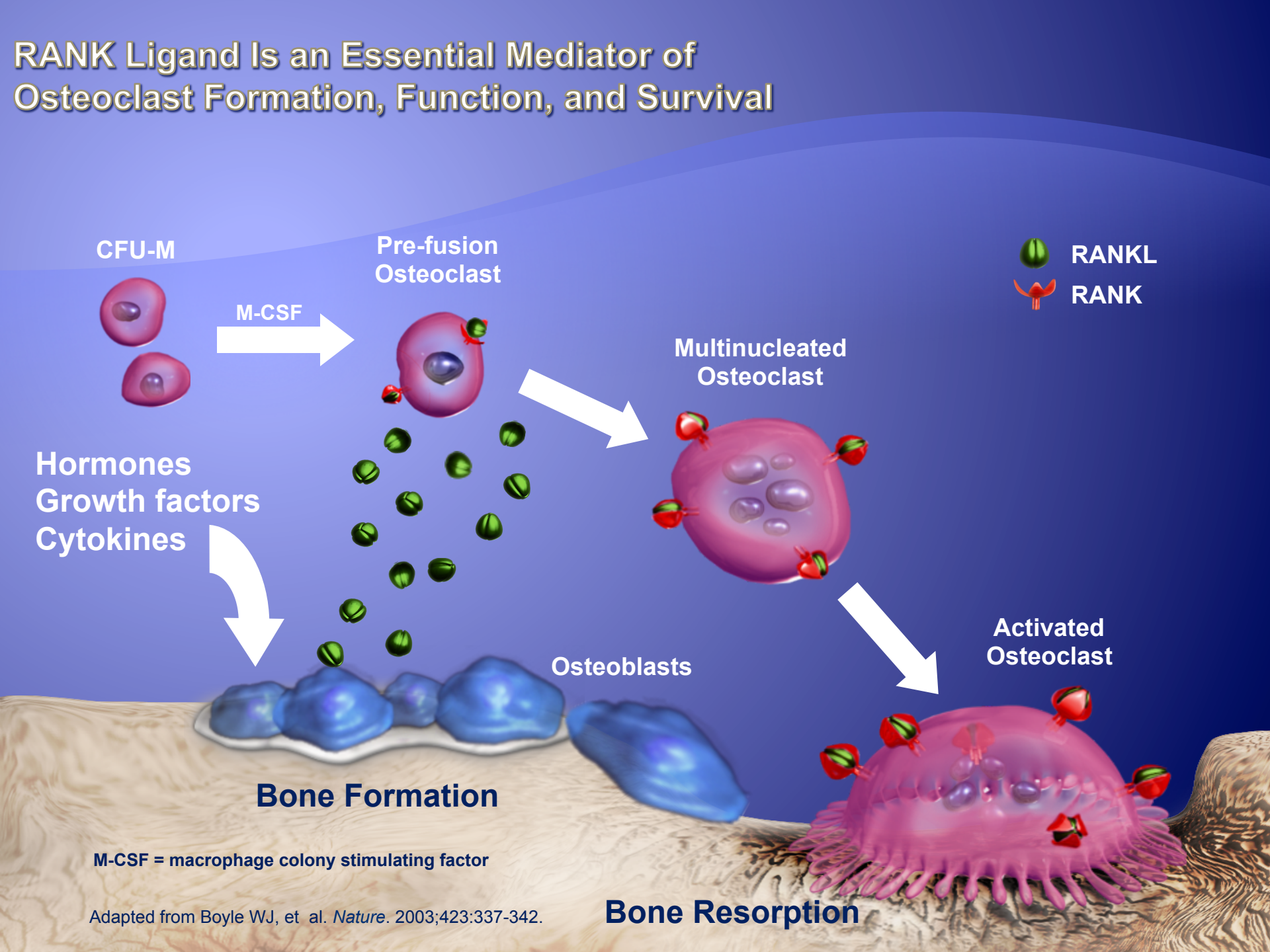
Data from Body J-J, et al. *Ann Oncol.* 2003;14(9):1399-1405.

Side effects of Bisphosphonates Zoledronic Acid

- Fever, weakness
- Nausea
- Vertigo
- Asthenia
- Myalgia/arthralgia
- Renal tubular necrosis
- Osteonecrosis of the jaw



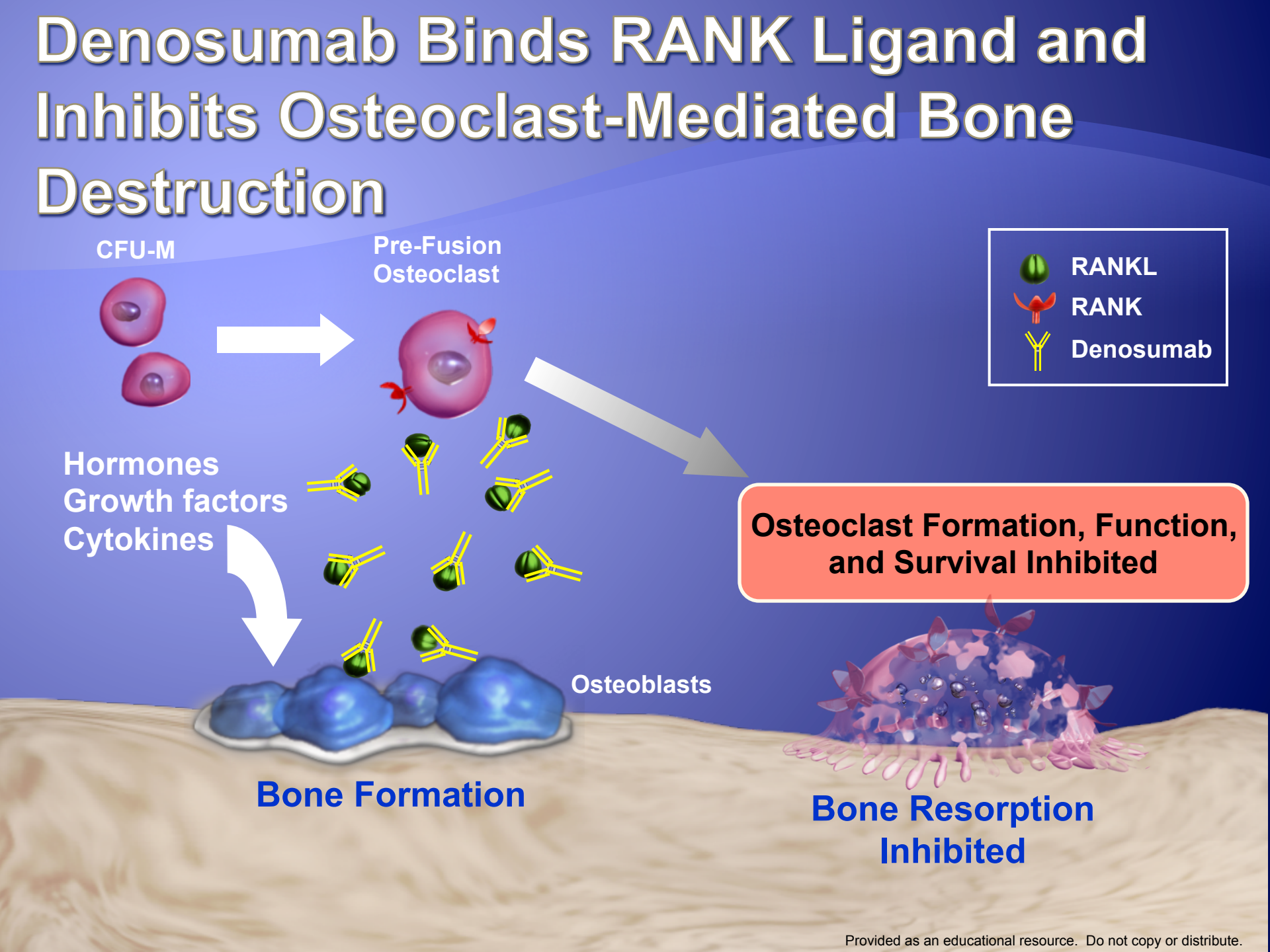
RANK Ligand Is an Essential Mediator of Osteoclast Formation, Function, and Survival



M-CSF = macrophage colony stimulating factor

Adapted from Boyle WJ, et al. *Nature*. 2003;423:337-342.

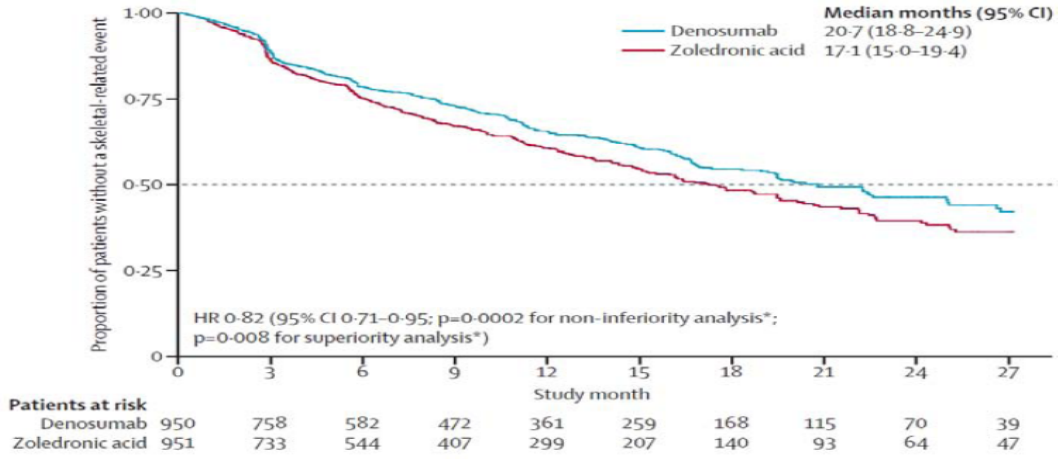
Denosumab Binds RANK Ligand and Inhibits Osteoclast-Mediated Bone Destruction



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

Denosumab vs zoledronic acid: Time to first skeletal-related event

Kaplan–Meier estimates of time to first on-study skeletal-related event



Patients at risk

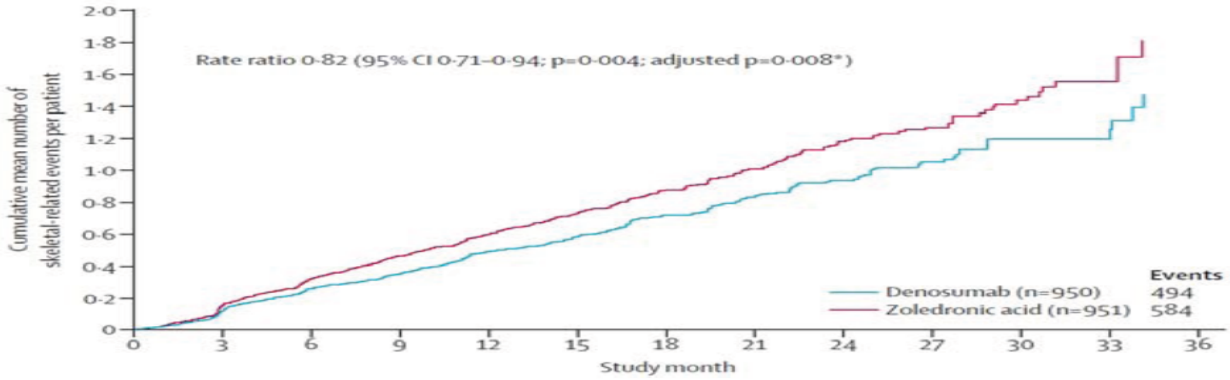
Denosumab	950	758	582	472	361	259	168	115	70	39
Zoledronic acid	951	733	544	407	299	207	140	93	64	47

Patients were assessed from baseline to the primary analysis cut-off date.
*p values were adjusted for multiplicity

European Society for Medical Oncology

SRE (multiple event analysis)

Time to first and subsequent on-study skeletal-related events



Events occurred at least 21 days apart. *Adjusted for multiplicity
No difference in median OS or time to disease progression

*Reprinted from the Lancet, volume 377, Fizazi K et al. 'Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study', pages 813-22. Copyright 2011, with permission from Elsevier

Denosumab vs zoledronic acid: Adverse events

Adverse event, n (%)	Zoledronic acid (n=945)	Denosumab (n=943)
Total adverse events	918 (97)	916 (97)
Most common adverse events in either arm		
▪ Anemia	341 (36)	337 (36)
▪ Back pain	287 (30)	304 (32)
▪ Decreased appetite	274 (29)	267 (28)
▪ Nausea	245 (26)	272 (29)
▪ Fatigue	222 (24)	257 (27)
CTC Grade 3, 4, or 5 adverse events	672 (71)	718 (76)
Serious adverse events	568 (60)	594 (63)
Adverse events leading to treatment discontinuation	138 (15)	164 (17)
Osteonecrosis of the jaw, cumulative	12 (1)	22 (2)

*Reprinted from the Lancet, volume 377, Fizazi K et al. 'Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study', pages 813-22. Copyright 2011, with permission from Elsevier