Workshop:Trattamento delle metastasi ossee

Associazione con terapie sistemiche

Vincenzo Ravo
INT Fond.Pascale
Napoli

ISTITUTO NAZIONALE TUMORI
IRCCS – Fondazione Pascale

Therapeutic strategies for treating osteolytic bone metastases

Elise Verron[1], Heidy Schmid-Antomarchi[2], Hugues Pascal-Mousselard[3], Annie Schmid-Alliana[2], Jean-Claude Scimeca[2] and Jean-Michel Bouler[1]

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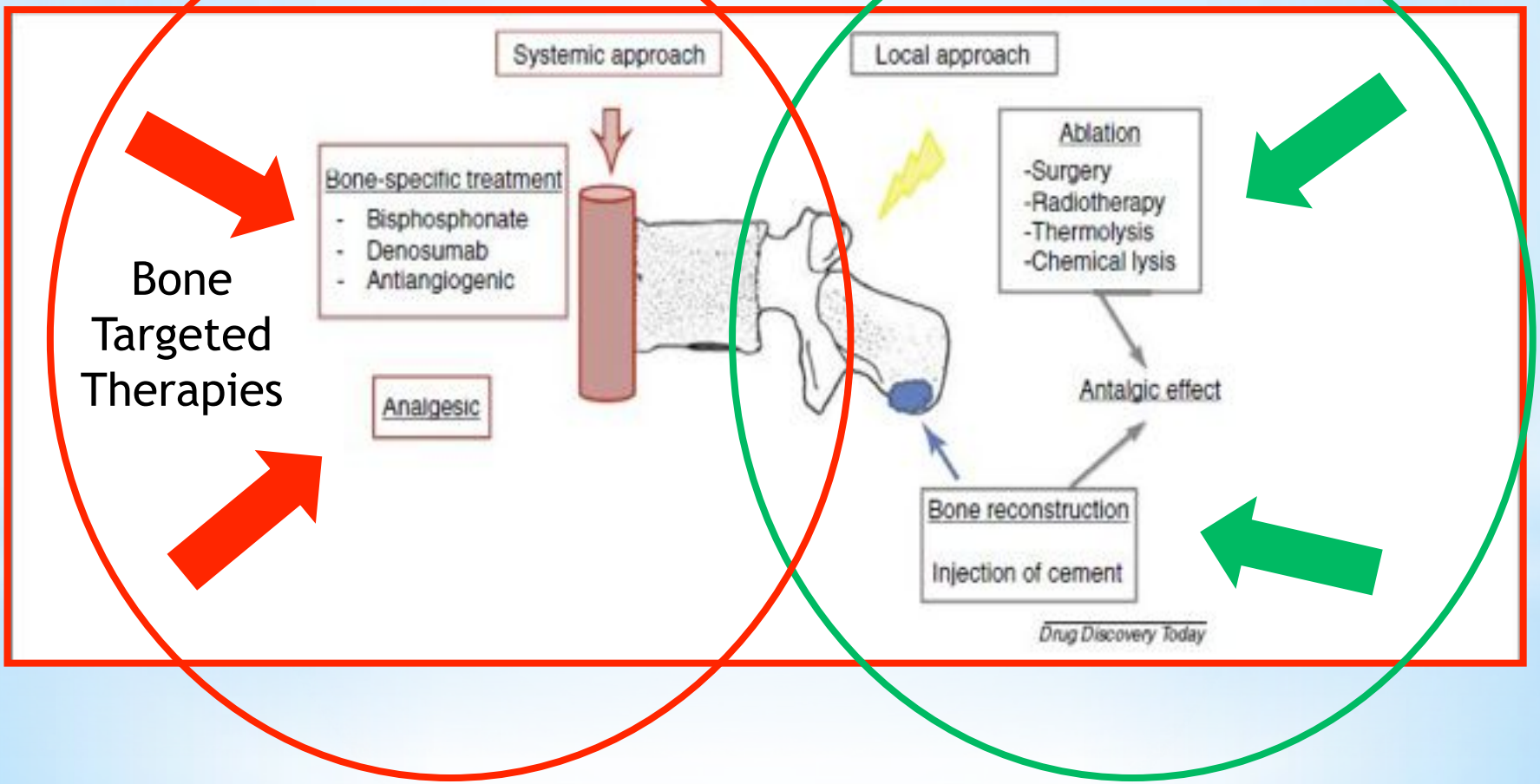

The INTER-ROMA Project - A survey among Italian radiation oncologists on their approach to the treatment of bone metastases.

Berardino De Bari[1], Silvia Chiesa[2], Andrea Riccardo Filippi[3], Maria Antonietta Gambacorta[2], Valentina D'Emilio[4], Paola Murino[5], and Lorenzo Livi[6] on the behalf of AIRO (Italian Association of Radiation On

122 questionnaires (40.6% of the total distributed)

Table 1 - Description of the clinical cases

Clinical case #1	– 64-year-old woman, PS: 0 (ECOG) – Breast cancer in 1999, pT2N0M0 ER+/PR-. She underwent lumpectomy + adjuvant radiotherapy (tangential fields 50 Gy + boost to tumor bed 10 Gy) + hormonal therapy with aromatase inhibitors for 5 years – Negative follow-up until today – Dorsal pain (D9-D10) + mild elevation of CA 15-3: bone scintigraphy and MRI of spine. Total-body CT scan: negative – Bone scintigraphy: multiple sites of pathological uptake particularly at the dorsal level (D3-D5-D9-D12). MRI: multiple spinal secondary mixed lesions (osteoblastic and osteolytic metastases). Symptomatic sites present secondary lesions. No radiological or clinical signs of spinal compression. No risk of immediate bone fracture – VAS: 7 without analgesics, 5 after regular non-opioid analgesics (first step of WHO pain scale)
Clinical case #2	– 68-year-old woman, PS: 1 (ECOG) – Right lung cancer in 2005, pT2N1M0. She underwent lobectomy + adjuvant chemotherapy. Radiotherapy has never been performed in the clinical history of the patient – Negative follow-up until today – Because of lumbar pain (L2-L3), she underwent bone scintigraphy and spine MRI. Total-body CT scan + brain CT scan: 3 hepatic lesions – Bone scintigraphy: multiple sites of pathological uptake. Spine MRI: multiple spinal secondary osteolytic lesions. Symptomatic sites present secondary lesions. No radiological or clinical signs of spinal compression. No risk of immediate bone fracture – VAS: 8 without analgesics, 3 after regular weaker opioid analgesics (second step of WHO pain scale)
Clinical case #3	– 73-year-old man, PS: 0 (ECOG) – Prostate cancer in 1998, cT2N1M0, Gleason score 4+4, initial PSA: 15 ng/mL, treated with radiotherapy (pelvic nodes: 46 Gy; prostate: 74 Gy) + concomitant and adjuvant (3 years) hormonal therapy with LH-RH inhibitor – Negative follow-up until today – Because of rising PSA, the patient underwent pelvic MRI + bone scintigraphy – Pelvic MRI: negative. Bone scintigraphy: solitary bone metastasis of right femoral diaphysis. CT scan of femurs: osteoblastic lesion of 3 cm diameter at diaphysis of right femur. No signs of fracture – VAS: 0 (asymptomatic patient)
Clinical case #4	– 78-year-old man, PS: 2 (ECOG) – Left lung cancer in 2007, pT3N0M0, treated with left pneumonectomy + adjuvant chemotherapy (6 cycles) – Negative follow-up until today – Sudden dorsal (D5-D6 e D10) and lumbar (L4) pain. No clinical signs of spinal compression. The patient does not report any other symptomatic site – MRI of the spine: multiple spinal secondary osteolytic lesions. Radiological signs of dorsal spinal compression (D10). Risk of pathological fracture at cervical level (C3). Total-body CT scan: multiple liver and lung metastases – VAS: 9 without analgesics, 3 after regular opioid analgesics (transdermal fentanyl 50 µg + NSAIDs if necessary, third step of WHO pain scale)

PS, performance status; VAS, visual analog scale; NSAIDs, non-steroidal anti-inflammatory drugs.

Tumori 2011;97(2):177-184

The INTER-ROMA Project - A survey among Italian radiation oncologists on their approach to the treatment of bone metastases.

Table 2 - Questions proposed to radiation oncologists for every clinical case

Question	Proposed answers
Do you treat this patient?	○ Yes ○ No, I prefer to optimize the medical therapy before treating the patient
Radiotherapy doses	○ 300 cGy × 10 ○ 400 cGy × 5 ○ 800 cGy × 1 ○ Other dose – specify: _____
Radiotherapy volumes*	○ Involved vertebra + 2 contiguous vertebrae above and below ○ Involved vertebra + 1 contiguous vertebra above and below ○ Only symptomatic vertebra ○ Other volumes – specify: _____
Field position	○ 1 posterior field ○ 2 AP-PA fields ○ 3 fields (1 post + 2 lateral fields) ○ 4 fields (1 ant + 1 post + 2 lateral fields) ○ Other – specify: _____
Prophylactic supportive therapy (multiple answers allowed)	○ Topical therapy for skin reactions ○ Treatment for nausea/vomiting ○ Proton pump inhibitors ○ Corticosteroids ○ Other prophylactic supportive therapy Specify: _____ ○ No prophylactic supportive therapy
Please indicate factors that influenced your choices (multiple answers allowed)	○ PS ○ Disease extent ○ Initial VAS ○ Response of VAS to analgesics ○ Site of metastasis ○ Patient age ○ Patient prognosis ○ Radiological aspect of the lesions ○ Expected RT toxicity ○ Personal habits ○ Patient comfort ○ Waiting list of your center ○ Financial aspects (reimbursement of radiotherapy treatment)

AP-PA, anteroposterior-posteroanterior; PS, performance status; VAS, visual analog scale.
*In case 3 the proposed volumes were: GTV + margins, the entire right femur, other volume (specify).

Tumori 2011;97(2):177-184

The INTER-ROMA Project - A survey among Italian radiation oncologists on their approach to the treatment of bone metastases.

*Tecnica : per le metastasi spinali la tecnica più diffusa era con un singolo campo posteriore (41.3% e 50.4% nei casi clinici 1 e 2).

*Il 65.5% prescriveva 30 Gy in 10 frazioni.

*Dal caso 1 al 4 nel 23%, 38%, 48.7% e 6.5% i Radioterapisti Oncologi dichiaravano di **non prescrivere terapie di supporto.**

*Solo 4/122 Radioterapisti Oncologi dichiaravano di seguire dei Trials Clinici sulla RT Palliativa nei loro reparti.

Tumori 2011;97(2):177-184

Contents lists available at SciVerse ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Review Article

Journal of Bone Oncology 1 (2012) 35–39

The Italian cross-sectional survey of the management of bone metastasis: ZeTa study

Daniele Santini[a,*], Francesco Bertoldo[b], Emanuela Dell'Aquila[a], Isabella Cecchini[c], Stefania Fregosi[c], Paolo Bortolussi[c], on behalf of the ZeTa study group[1]

[a] Oncologia Medica, University Campus Biomedico, Roma, Rome, Italy
[b] Department of Medicine, University of Verona, Verona, Italy
[c] GfK Eurisko, Milan, Italy

Table 1
Proportion of patients receiving a treatment for bone metastasis, according to the oncologists participating to the survey ($N=283$).

Metastasis therapy	Breast cancer	Lung cancer	Prostate cancer	Genito-urinary cancer
Any treatment (%)	85	82	90	78
Radiotherapy (%)	37	43	40	42
Radio-metabolic therapy (%)	2	1	7	2
Surgery (%)	3	2	2	2
Chemo/hormonal therapy (%)	63	57	63	64
Interventional radiology (%)	6	5	3	4
Bisphosphonates (%)	70	62	69	70

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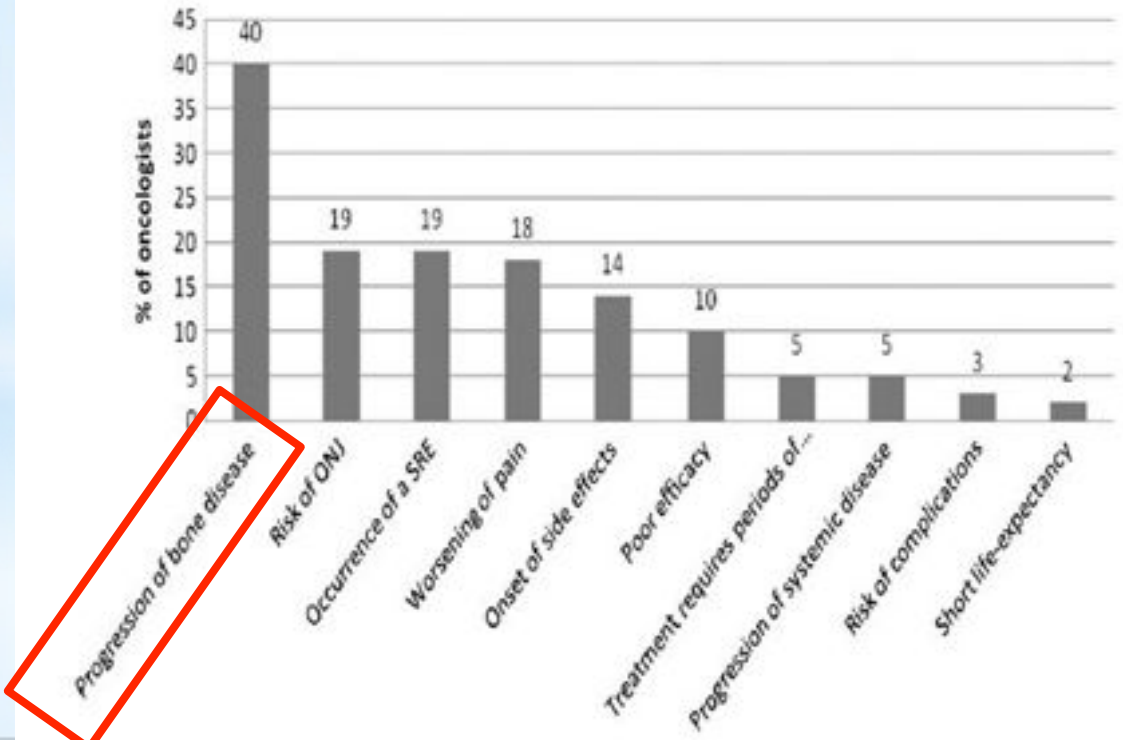
[a] Oncologia Medica, University Campus Biomedico, Roma, Rome, Italy
[b] Department of Medicine, University of Verona, Verona, Italy
[c] GfK Eurisko, Milan, Italy

Fig. 1. Reasons for prescribing a treatment of bone metastasis with bisphosphonates, according to the oncologists participating to the survey (N=283).



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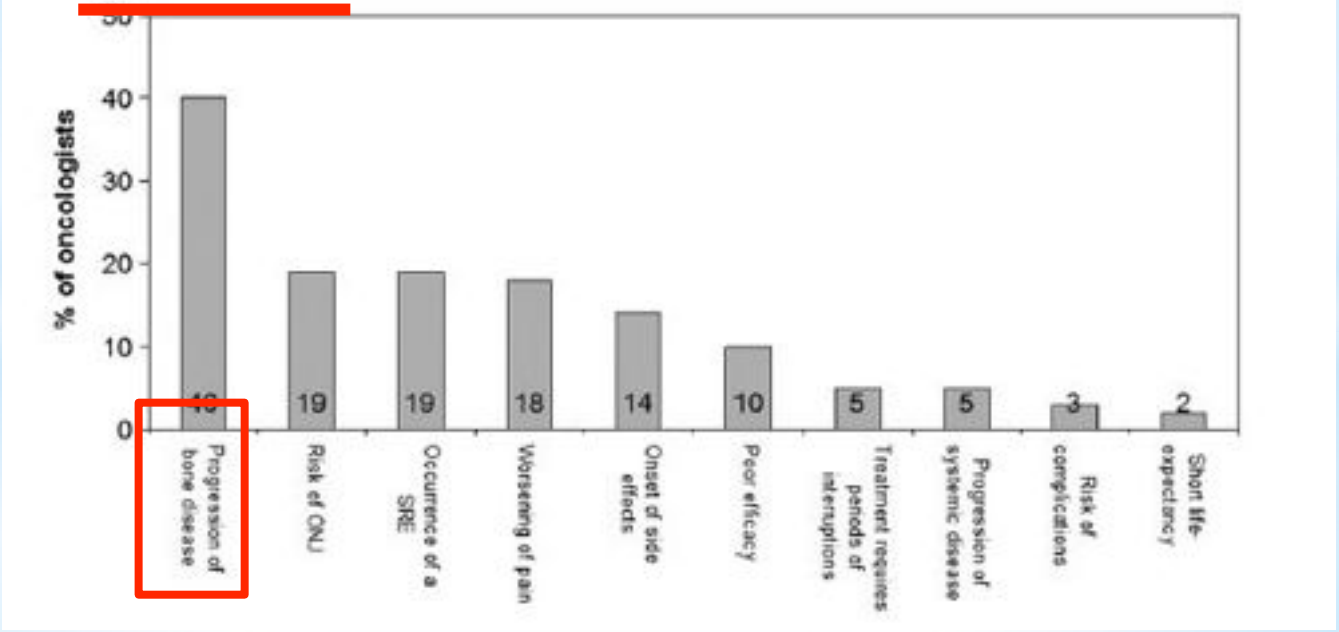
[a] Oncologia Medica, University Campus Biomedico, Roma, Rome, Italy
[b] Department of Medicine, University of Verona, Verona, Italy
[c] GfK Eurisko, Milan, Italy

Fig. 2. Reasons for the interruption of bisphosphonate treatment before 24 months according to the oncologists participating to the survey ($N=283$).



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[a] Oncologia Medica, University Campus Biomedico, Roma, Rome, Italy
[b] Department of Medicine, University of Verona, Verona, Italy
[c] GfK Eurisko, Milan, Italy

- Il **22%** degli oncologi dichiara di non conoscere le linee guida nazionali ed internazionali.
- L '**86%** dichiara che è molto importante conoscere le linee guida nella pratica quotidiana.

- Il **30%** non ritiene che gli SREs siano legati ad un maggior rischio di morte.
- Il **60%** dichiara di prescrivere i Bifosfonati (BP) indipendentemente dalla valutazione del rischio di SREs.

- Il **75%** delle prescrizioni di BP viene fatta a prescindere dalla valutazione del dolore.
- Il **78%** sospende i BP a 24 mesi, il **13%** sino alla progressione, il **9%** continua per sempre.

Annals of Oncology 23: 2215–2222, 2012
doi:10.1093/annonc/mds009
Published online 22 February 2012

Bone matters in lung cancer

Importanza della prevenzione degli SRE

T. Brodowicz[1*], K. O'Byrne[2] & C. Manegold[3]

[1]Clinical Division of Oncology, Department of Medicine I, Medical University of Vienna General Hospital, Vienna, Austria; [2]HOPE Department, St James's Hospital, Dublin, Ireland; [3]Interdisciplinary Thoracic Oncology and Department of Surgery, University Medical Centre Mannheim, Mannheim, Germany

Table 1 Comparison of median survival times of patients with stage III or stage IV NSCLC, with or without bone metastases and SREs *

NSCLC stage	Patients, *n*	Median survival time (days)
Stage III		
No bone metastases	81	314
≥1 bone metastases	14	298
Stage III + bone metastases[a]		
No SRE	4	255
≥1 SRE	10	240
Stage IV		
No bone metastases	79	268
≥1 bone metastases	56	237
Stage IV + bone metastases		
No SRE	31	366
≥1 SRE	25	187

* Tsuya A, Kurata T, Tamura K, Fukuoka M. Skeletal metastases in non-small cell lung cancer: a retrospective study. Lung Cancer 2007; 57: 229–232.

Bone Targeted Therapies

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Cancer Treatment Reviews 40 (2014) 730–738

Anti-Tumour Treatment

Recent advances in bone-targeted therapies of metastatic prostate cancer

Xiyun Deng [a,c,1], Guangchun He [a,1], Junwen Liu [b], Feijun Luo [b], Xiaoning Peng [a], Shigang Tang [a], Zhiyong Gao [a], Qinlu Lin [b], Jill M. Keller [d], Tao Yang [b,c,*], Evan T. Keller [d,*]

Table 1
Development of agents for bone-targeted therapies of metastatic prostate cancer.

Agents	Mechanism of action	Biochemical property	Molecular targets	Stage of development	Refs.
Zoledronic acid	Inhibiting resorption	Synthetic analog of pyrophosphate (N-containing)	Farnesyl pyrophosphate synthase	Approved	[23,24]
Clodronate	Inhibiting resorption	Synthetic analog of pyrophosphate (non-N-containing)	?	PR04/PR05	[25,26]
Denosumab	Inhibiting resorption	Humanized monoclonal antibody	RANKL	Phase III	[28–30]
RANK-Fc	Inhibiting resorption	Recombinant protein	RANKL	Preclinical	[31–33]
OPG-Fc	Inhibiting resorption	Recombinant protein	RANKL	Preclinical	[34,35]
Dasatinib (SPRYCEL®)	Inhibiting resorption	Tyrosine kinase inhibitor	Src, Abl	Phase III	[36–38]
Saracatinib (AZD-0530)	Inhibiting resorption	Tyrosine kinase inhibitor	Src, Abl	Phase II	-
KX2-391	Inhibiting resorption	Tyrosine kinase inhibitor	Src	Phase II	[39]#
Bosutinib (SKI-606)	Inhibiting resorption	Tyrosine kinase inhibitor	Src, Abl	Preclinical	[40]
Abegri (Etaracizumab, Vitaxin® or MEDI-522)	Inhibiting resorption	Humanized monoclonal antibody	Integrin alpha(nu)beta(3)	Phase II	&
MK-0429	Inhibiting resorption	Small molecule inhibitor	Integrin alpha(nu)beta(3)	Phase I	[20]
EMD 525797 (DI17E6)	Inhibiting resorption	Humanized monoclonal antibody	Integrin alpha(nu)	Phase I	[42]
GLPG0187	Inhibiting resorption	Non-peptide integrin antagonist	Integrin alpha(nu)	Preclinical	[43]
Atrasentan (ABT-627 or Xinlay)	Stimulating bone formation	Small molecule inhibitor	ETAR > ETBR	Phase III, further approval rejected	[46,47]
Zibotentan (ZD-4054)	Stimulating bone formation	Small molecule inhibitor	ETAR	Phase III	[49–52]
Samarium-153-EDTMP	Targeting bone matrix	Radiopharmaceutical (β-emitter)	?	Approved; Phase II for combination with Docetaxel	[56–58]
Radium-223 (Alpharadin, or Xofigo®)	Targeting bone matrix	Radiopharmaceutical (α-emitter)	Hydroxyapatite	Approved	$
Odanacatib (MK-0822)	Targeting bone matrix	Small molecule inhibitor	Cathepsin K	Phase III	^
PCK3145	Targeting bone matrix	Synthetic peptide	MMPs	Preclinical	[66]
Silibinin	Targeting bone matrix	Small molecule inhibitor	MMPs	Preclinical	[67]
AdTIMP-2	Targeting bone matrix	Recombinant adenovirus expressing TIMP-2	MMPs	Preclinical	[68]
MSC-hATF	Targeting bone matrix	MSCs engineered to express uPA antagonist hATF	uPA–uPAR	Preclinical	[70]
TGF-β1 shRNA	Targeting bone matrix	shRNA	TGF-β	Preclinical	[74]
TβRI-KI	Targeting bone matrix	Receptor kinase inhibitor	TGF-β receptor type I	Preclinical	[74]
BG_AII	Targeting bone matrix	Pan TGF-β binding protein	TGF-β	Preclinical	[74]
Ad.sTβR-Fc	Targeting bone matrix	Oncolytic virus expressing soluble TGF-β receptor type II fused with Fc	TGF-β	Preclinical	[75]
TAd.sTβR-Fc	Targeting bone matrix	A variant of Ad.sTβR-Fc	TGF-β	Preclinical	[75]
LY2109761	Targeting bone matrix	Small molecule inhibitor	TGF-β receptor type I	Preclinical	[76]

Difosfonati

Acido Zoledronico e gli altri difosfonati

1^generaz.

2^generaz.

3^generaz.

	Indication				
	HCM	Breast cancer	Multiple myeloma	Prostate cancer	Other solid tumors
Clodronate (oral)	✔	✔	✔		
Pamidronate (IV)	✔	✔	✔		
Zoledronic acid (IV)	✔	✔	✔	✔	✔
Ibandronate (oral)	✔	✔			

✔ = European registration ✔ = Global registration

Major P, Eur J Oncol Nurs, 2007

A Randomized, Placebo-Controlled Trial of Zoledronic Acid in Patients With Hormone-Refractory Metastatic Prostate Carcinoma

Fred Saad, Donald M. Gleason, Robin Murray, Simon Tchekmedyian, Peter Venner, Louis Lacombe, Joseph L. Chin, Jeferson J. Vinholes, J. Allen Goas, Bee Chen

For the Zoledronic Acid Prostate Cancer Study Group

Acido Zoledronico 4mg (214 pz)
vs
Acido Zoledronico 8mg (221pz)
vs
Placebo (208pz)
Ogni 3 settimane per 15 mesi

Table 3. Skeletal morbidity rate up to month 15 in patients with metastatic prostate cancer enrolled in a randomized, placebo-controlled, phase III trial of zoledronic acid*

	Skeletal morbidity rates* (95% CI) in treatment groups			P‡	
	Zoledronic acid				
Skeletal morbidity rate†	4 mg (N = 214)	8/4 mg (N = 221)	Placebo (N = 208)	4 mg versus placebo	8/4 mg versus placebo
All skeletal-related events	0.80 (0.57 to 1.03)	1.06 (0.77 to 1.35)	1.49 (1.03 to 1.94)	.006	.143
All pathological fractures	0.21 (0.11 to 0.31)	0.21 (0.13 to 0.28)	0.45 (0.27 to 0.63)	.009	.042
Vertebral fractures	0.04 (0.01 to 0.08)	0.10 (0.05 to 0.14)	0.16 (0.04 to 0.28)	.048	.818
Nonvertebral fractures	0.17 (0.08 to 0.27)	0.11 (0.06 to 0.16)	0.31 (0.17 to 0.46)	.071	.048
Radiation therapy to bone	0.44 (0.27 to 0.60)	0.64 (0.40 to 0.87)	0.88 (0.48 to 1.28)	.084	.208
Surgery to bone	0.03 (0.00 to 0.07)	0.05 (0.00 to 0.10)	0.06 (0.01 to 0.11)	.509	.766
Spinal cord compression	0.14 (0.00 to 0.28)	0.10 (0.04 to 0.17)	0.23 (0.04 to 0.42)	.247	.443
Change in antineoplastic treatment	0.10 (0.02 to 0.18)	0.22 (0.06 to 0.38)	0.12 (0.04 to 0.21)	.364	.531

Vantaggio in termini di riduzione degli SRE (-11%) e del dolore ma non in OS e DFS

Journal of the National Cancer Institute, Vol. 94, No. 19, October 2, 2002

NATURE CLINICAL PRACTICE ONCOLOGY MARCH 2009 VOL 6 NO 3

REVIEW

www.nature.com/clinicalpractice/onc

Effect of bisphosphonates on pain and quality of life in patients with bone metastases

Luis Costa* and Pierre P Major

Vantaggio su dolore e SRE

Zometa

Table 3 Summary of randomized clinical trials of 4 mg zoledronic acid.

Reference	Patient (*n*)	Tumor type	Regimen	Comparator	Efficacy results
Vogel *et al.* (2004)[81]	638	Several	4 mg every 3–4 weeks for 6 doses	Baseline	Decreased pain (–6.9 on VAS; $P<0.05$)
Kohno *et al.* (2005)[82]	228	Breast cancer	4 mg every 4 weeks for 1 year	Placebo	Decreased SRE ($P=0.027$) Decreased RR SRE ($P=0.019$)
Saad *et al.* (2002)[83]	643	Prostate cancer	4 mg every 3 weeks for 15 months	Placebo	Decreased SRE ($P=0.021$) Increased time to first SRE ($P=0.011$)
Saad *et al.* (2004)[24]	122[a]	Prostate cancer	4 mg every 3 weeks for 24 months	Placebo	Decreased SRE ($P=0.005$) Decreased RR SRE ($P=0.002$) Reduced BPI scores (0.58 vs 1.05; $P<0.024$)
Weinfurt *et al.* (2006)[84]	422	Prostate cancer	4 mg every 3 weeks for up to 15 months	Placebo	Decreased pain BPI ($P=0.04$)
Rosen *et al.* (2003)[85]	773	Lung cancer and other solid tumors	4 mg every 3 weeks for 9 months	Placebo	Decreased SRE ($P=$NS) Increased time to first SRE ($P=0.023$) Decreased RR SRE ($P=0.017$)
Rosen *et al.* (2004)[86]	773[b]	Lung cancer and other solid tumors	4 mg every 3 weeks for 21 months	Placebo	Decreased SRE ($P=$NS) Increased time to first SRE ($P=0.009$) Decreased annual incidence of SREs ($P=0.012$) Decreased RR SRE ($P=0.003$)
Rosen *et al.* (2001)[87]	1,648	Breast cancer Multiple myeloma	4 mg every 3–4 weeks for 12 months	Disodium pamidronate 90 mg intravenously every 3–4 weeks	Decreased pain BPI ($P=$NS) Decreased SMR (in those who also received EBRT; $P=0.018$)
Rosen *et al.* (2004)[88]	1,648[c]	Breast cancer Multiple myeloma	4 mg every 3–4 weeks for 24 months	Disodium pamidronate 90 mg intravenously every 3–4 weeks	Decreased RR for SREs ($P=0.030$)
Rosen *et al.* (2004)[88]	766	Breast cancer	4 mg every 3–4 weeks for 12 months	Disodium pamidronate 90 mg intravenously every 3–4 weeks	Decreased RR for SREs ($P=0.037$) Increased time to first SRE ($P=0.013$)
Wardley *et al.* (2005)[89]	101	Breast cancer	4 mg every 3 weeks for up to 27 weeks	Baseline	Decreased worst, average, and interfering pain (change in baseline from –0.5 to –0.8 overall BPI score; $P<0.04$ in last 7 days)
Wiktor-Jedrzejczak (2005)[90]	260	Several	4 mg every 3–4 weeks for up to 24 weeks	Baseline	Decreased pain (–20.9 on VAS; $P<0.001$) Increased QOL FACT-G score ($P<0.001$)

CANCER TREATMENT REVIEWS 2003; **29**: 321–327
doi:10.1016/S0305-7372(03)00013-6

TREATMENT OF COMPLICATIONS

CANCER TREATMENT REVIEWS

Bisphosphonates and radiation therapy for palliation of metastatic bone disease

P.J. Hoskin

Consultant Clinical Oncologist, Reader in Oncology, Mount Vernon Hospital, Rickmansworth Road, Northwood, Middlesex HA6 2RN, UK

TABLE 1 Published randomised trials of adjuvant bisphosphonates for bone metastases: rates of radiotherapy use

Author	Site	RT incidence		p value
		Control (%)	Bisphosphonate (%)	< RT
Paterson et al. (17)	Breast	48	40	>0.05
Hortobagyi et al. (18)	Breast	45	28	<0.001
Hultborn et al. (19)	Breast	*'Not different between the treatment groups'*		
Conte et al. (20)	Breast	58	46	*Not stated*
Thierault et al. (21)	Breast	27	16	0.02
Berenson et al. (22)	Myeloma			
	First line	13	15	0.6
	Second line	34	18	0.03
Lahtinen et al. (23)	Myeloma	*Not stated*		
McCloskey et al. (24)	Myeloma	<10	<10	*Not stated*
Saad et al. (25)	Prostate	29	24	0.02
Deamaley et al. (26)	Prostate	*Not stated in preliminary report; 'delayed symptomatic bone progression'*		

CANCER TREATMENT REVIEWS 2003 29: 323–327
doi:10.1016/S0305-7372(03)00013-6

TREATMENT OF COMPLICATIONS

CANCER TREATMENT REVIEWS

Bisphosphonates and radiation therapy for palliation of metastatic bone disease

P.J. Hoskin

Consultant Clinical Oncologist, Reader in Oncology, Mount Vernon Hospital, Rickmansworth Road, Northwood, Middlesex HA6 2RN, UK

INTERAZIONE TRA RADIOTERAPIA E BIFOSFONATI

L'interazione si esplica tramite meccanismi distinti

1. Effetto additivo
2. Effetto superadditivo

} **AZIONE SULL'OMEOSTASI CELLULARE**

3. Cooperazione spaziale — **AZIONE LOCALIZZATA vs NON SELETTIVA**

Vassiliou V et al J Surg Oncol 2008; 98:567-8.

Radiazioni + Bifosfonati

Riduzione della popolazione
di cellule tumorali con possibilità
per gli osteoblasti di riparare

Cellule tumorali

BIOLOGY CONTRIBUTION Int. J. Radiation Oncology Biol. Phys., Vol. 61, No. 2, pp. 535–542, 2005

SYNERGISTIC CYTOTOXIC EFFECTS OF ZOLEDRONIC ACID AND RADIATION IN HUMAN PROSTATE CANCER AND MYELOMA CELL LINES

ECE ALGUR, M.D., ROGER M. MACKIE, M.D., AND URS O. HAFELI, PH.D.

Radiation Oncology Department, The Cleveland Clinic Foundation, Cleveland, OH

Research article Breast Cancer Research Vol 8 No 4 Open Access

***In vitro* synergistic cytoreductive effects of zoledronic acid and radiation on breast cancer cells**

A Ugur Ural[1,2], Ferit Avcu[1,2], Muhammed Candir[3], Metin Guden[4] and M Ali Ozcan[5]

Osteoclasti

Precoce ed intensa diminuzione
dei mediatori degli osteoclasti
rilasciati dalle cellule tumorali

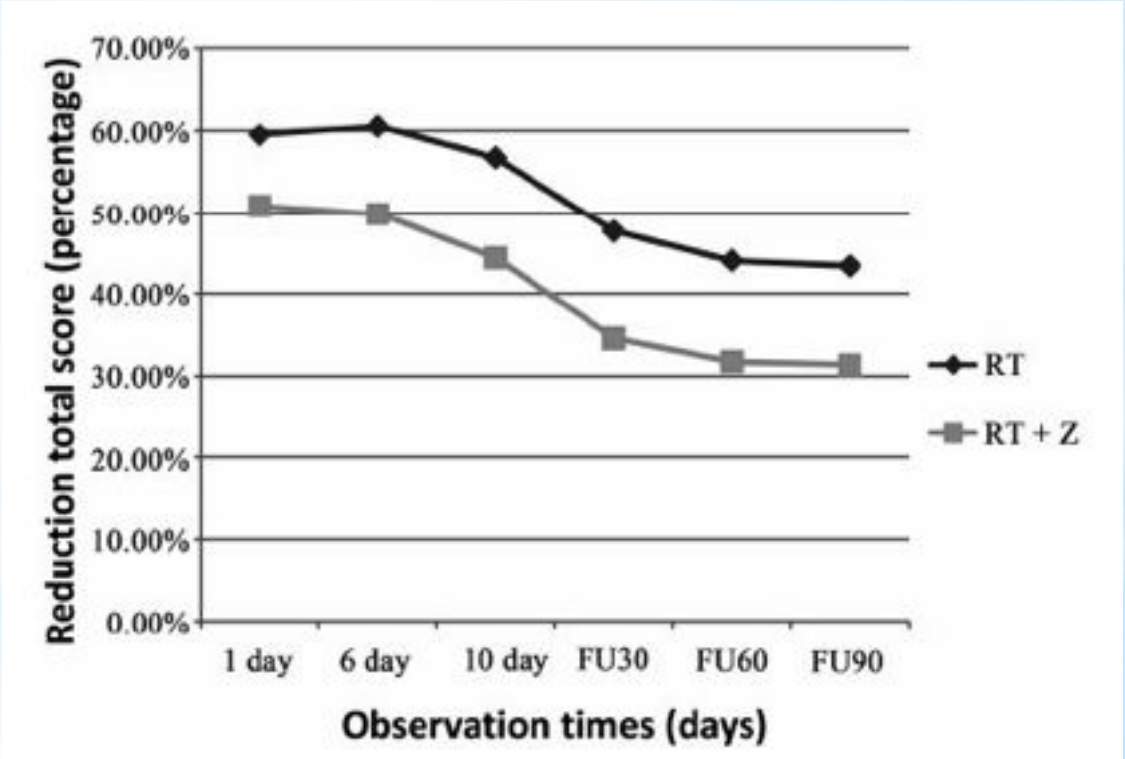
Apoptosi e soprattutto
Intensa e precoce
Inibizione degli osteoclasti

Management of Painful Bone Metastases: The Interaction between Radiation Therapy and Zoledronate

Rossella Di Franco[1], Mariagrazia Calvanese[1], Mariagrazia Cuomo[1], Roberto Manzo[2], Paola Murino[2], Salvatore Cappabianca[1], Vincenzo Ravo[2*]

Table 1. Baseline demographic and disease characteristics of patients with bone metastases.

Characteristics	Treatment group (RT)	(RT+Z)	
No. of patients	104	50	Total 154
Sex			
Female	56	20	76
Male	48	30	78
Age			
Median (range) age, years	63 (31-92)	66 (46-82)	
Histology			
Breast	30	20	50 (32%)
Prostate	6	14	20 (13%)
Lung	20	10	30 (19%)
Liver	8	0	8 (5%)
Colon	4	2	6 (4%)
Rectum	4	0	4 (2.5%)
Bladder	8	0	8 (5%)
Kidney	6	2	8 (5%)
Larynx	4	0	4 (2.5%)
Pleura	4	0	4 (2.5%)
Thyroid	2	2	4 (2.5%)
Parotid	2	0	2 (1%)
Mouth	2	0	2 (1%)
Unknow	4	0	4 (2.5%)
Metastasis site			
Cervical spine	2	2	4 (2%)
Thoracic spine	20	16	36 (18%)
Lumbar spine	32	16	48 (24%)
Pelvis	56	18	74 (37%)
Femur	8	10	18 (9%)
Tibia	4	0	4 (2%)
Scapula	0	2	2 (1%)
Humerus	2	0	2 (1%)
Sternum	4	0	4 (2%)
Foot	2	0	2 (1%)
Ribs	6	0	6 (3%)
No. of metastasis site			
single	64	24	88 (57%)
multiple	40	26	66 (43%)



Journal of Cancer Therapy, 2011, 2, **-**
Published Online December 2011 (http://www.SciRP.org/journal/jct)

VOLUME 27 · NUMBER 10 · APRIL 1 2009
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Denosumab (XGeva®)

Randomized Phase II Trial of Denosumab in Patients With Bone Metastases From Prostate Cancer, Breast Cancer, or Other Neoplasms After Intravenous Bisphosphonates

Karim Fizazi, Allan Lipton, Xavier Mariette, Jean-Jacques Body, Yasmin Rahim, Julie R. Gralow, Guozhi Gao, Ling Wu, Winnie Sohn, and Susie Jun

Premessa:
Livelli elevati di NTX (n-telopeptidi) urinari rappresentano un eccessivo riassorbimento osseo con incremento di SRE, progressione tumorale e morte

Study design (20040114)

SCREENING/ RANDOMISATION

- **Denosumab 180 mg SC Q4W**
- **Denosumab 180 mg SC Q12W**
- **Bisphosphonate IV Q4W**

Follow-up

111 pz con M+ ossee con uNTX>50nmol/L in cura con BP

25 weeks on treatment

With daily supplements of calcium and vitamin D

32 weeks off treatment

Anticorpo monoclonale inibitore di RANKL

VOLUME 27 · NUMBER 10 · APRIL 1 2009

JOURNAL OF CLINICAL ONCOLOGY

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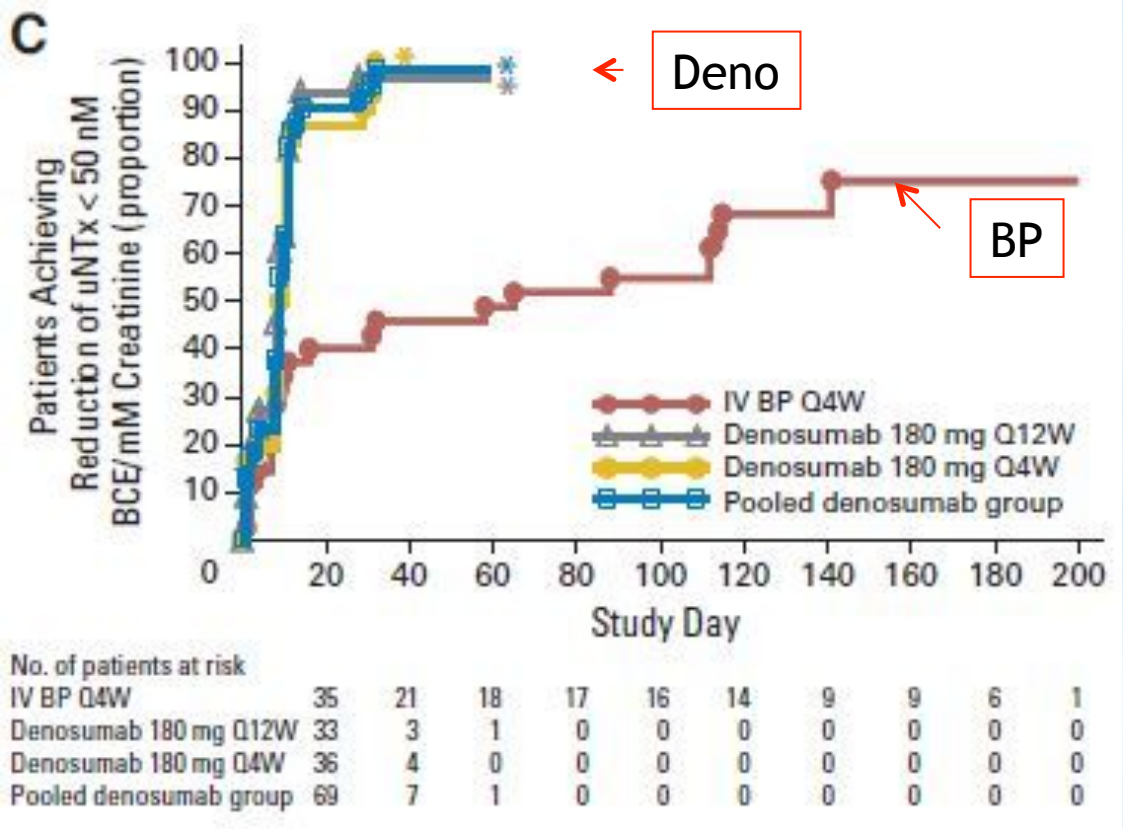
Il trattamento con denosumab permetteva di normalizzare un'elevata percentuale dei soggetti randomizzati a questa terapia (circa il 98%) contro il 70% circa di quelli che venivano mantenuti in trattamento con bisfosfonati (BP).

111 pz con M+ ossee con uNTX>50nmol/L in cura con BP



Riduzione NTX

Tempo medio riduzione uNTX <50 nmol/mol BCE Denosumab = 9gg, IV BP = 65 gg

VOLUME 27 · NUMBER 10 · APRIL 1 2009

JOURNAL OF CLINICAL ONCOLOGY

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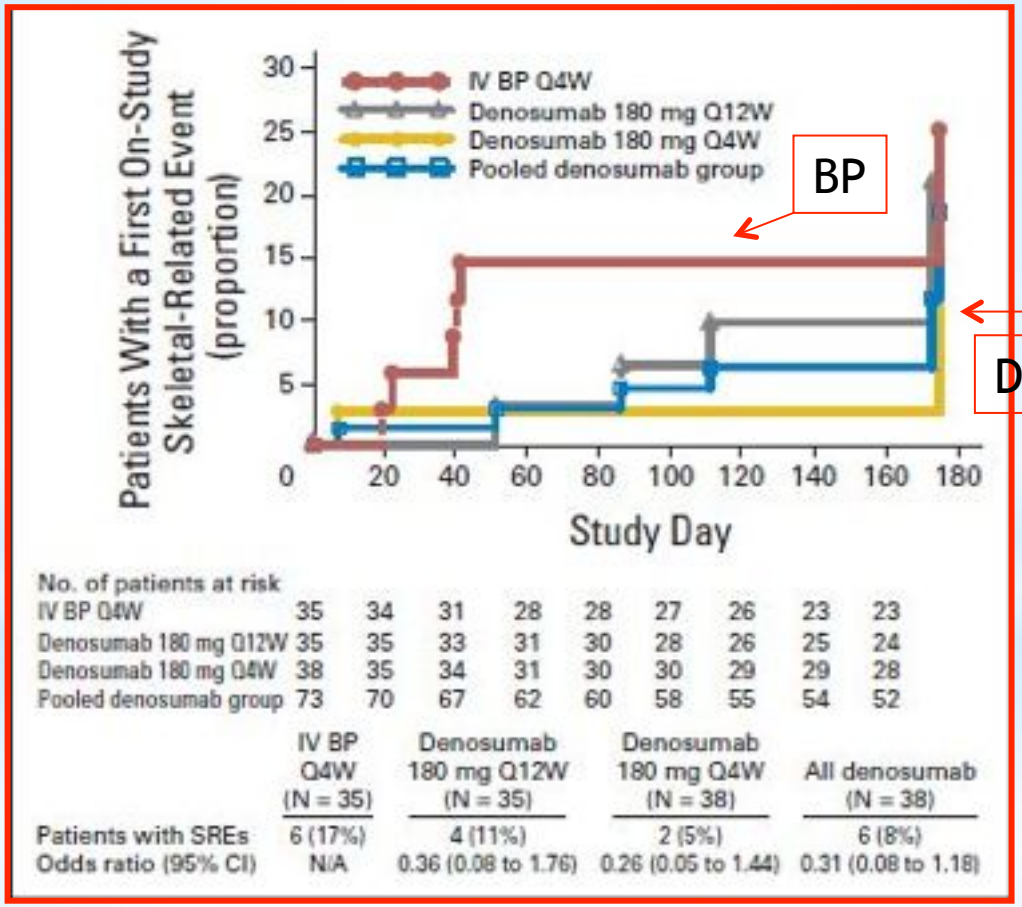

	IV BP Q4W (N = 35)	Denosumab 180 mg Q12W (N = 35)	Denosumab 180 mg Q4W (N = 38)	All denosumab (N = 38)
Patients with SREs	6 (17%)	4 (11%)	2 (5%)	6 (8%)
Odds ratio (95% CI)	N/A	0.36 (0.08 to 1.76)	0.26 (0.05 to 1.44)	0.31 (0.08 to 1.18)

Comparsa SRE

Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Denosumab *vs* Acido Zoledronico

Cancer Treatment Reviews 39 (2013) 97–104

General and Supportive Care

Denosumab in patients with cancer and skeletal metastases: A systematic review and meta-analysis

Prashanth Peddi [a], Maria A. Lopez-Olivo [a], Gregory F. Pratt [b], Maria E. Suarez-Almazor [a,*]

[a] Division of General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA
[b] Research Medical Library, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA

Studi di fase II e III

Table 1
Characteristics of the included studies.

Study	Follow-up (Months)	Population	Treated previously with IV bisphosphonates	Mean age (yrs)	Intervention	Control	Outcomes
Phase II trials							
Body (2006)[32]	2.8	Myeloma Breast cancer	No	60.5 55.5	DB SQ 0.1,0.3,1.0,3.0 mg/kg (one dose)	Pamidronate IV 90 mg (one dose)	BTM
Lipton (2007)[28,42]	3	Breast cancer	No	58.7	DB SQ 30,120,180 mg Q 4W 60, 180 mg Q 12W	Bisphosphonates IV Q 4W	Incidence of SRE BTM safety
Fizazi (2009)[33,42,60]	3	Prostate Breast Solid tumors (except lung) and uNTX >50nM BCE/mM	Yes	60.5	DB SQ 180 mg Q 4W or Q 12W	Bisphosphonates IV Q 4W	Incidence of SRE BTM safety
Phase III trials							
Stopeck (2010)[34,38,41]	34	Breast cancer	No	56.0	DB SQ 120 mg Q 4W	ZA IV 4 mg Q 4W	Incidence of SRE, Time to first on-study SRE Time to first and subsequent on-study SRE Overall survival Overall disease progression Pain, HRQL BTM Safety
Fizazi (2011)[35,40]	41	Castrate resistant prostate cancer	No	71.0	DB SQ 120 mg Q 4W	ZA IV 4 mg Q 4W	Incidence of SRE Time to first on-study SRE Time to first and subsequent on-study SRE Overall survival Overall disease progression Pain BTM Safety
Henry (2011)[36,39]	34	Solid tumors (except breast and prostate) Myeloma	No	60.5	DB SQ 120 mg 4W	ZA IV 4 mg Q 4W	Incidence of SRE Time to first on-study SRE Time to first and subsequent on-study SRE Overall survival Overall disease progression Pain BTM Safety

Contents lists available at SciVerse ScienceDirect

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General and Supportive Care

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Cancer Treatment Reviews 39 (2013) 97–104

>6000 pz

Table 5
Percent reduction in BTM at 13 weeks. Denosumab vs. bisphosphonates.

BTM	Denosumab (*N*)	Bisphosphonates (*N*)	Pooled mean difference	95% CI	I^2	*P*-value
Denosumab vs. Zoledronic Acid/Pamidronate/Ibandronate[a]						
uNTX[b28,32–36]	2980	2719	−14.9	−19.2,−10.7	78%	<0.0001
BSAP[34–36]	2771	2609	−6.5	−8.9,−4.2	13%	<0.0001
Denosumab vs. Zoledronic Acid						
uNTX	2650	2629	−12.5	−14.8,−10.3	53%	0.001
BSAP	2554	2552	−7.6	−9.9,−5.2	0%	<0.0001

Conclusions: Denosumab was more effective than zoledronic acid in reducing the incidence of SRE, and delayed the time to SRE. No differences were found between denosumab and zoledronic acid in reducing overall mortality, or in the frequency of overall adverse events.

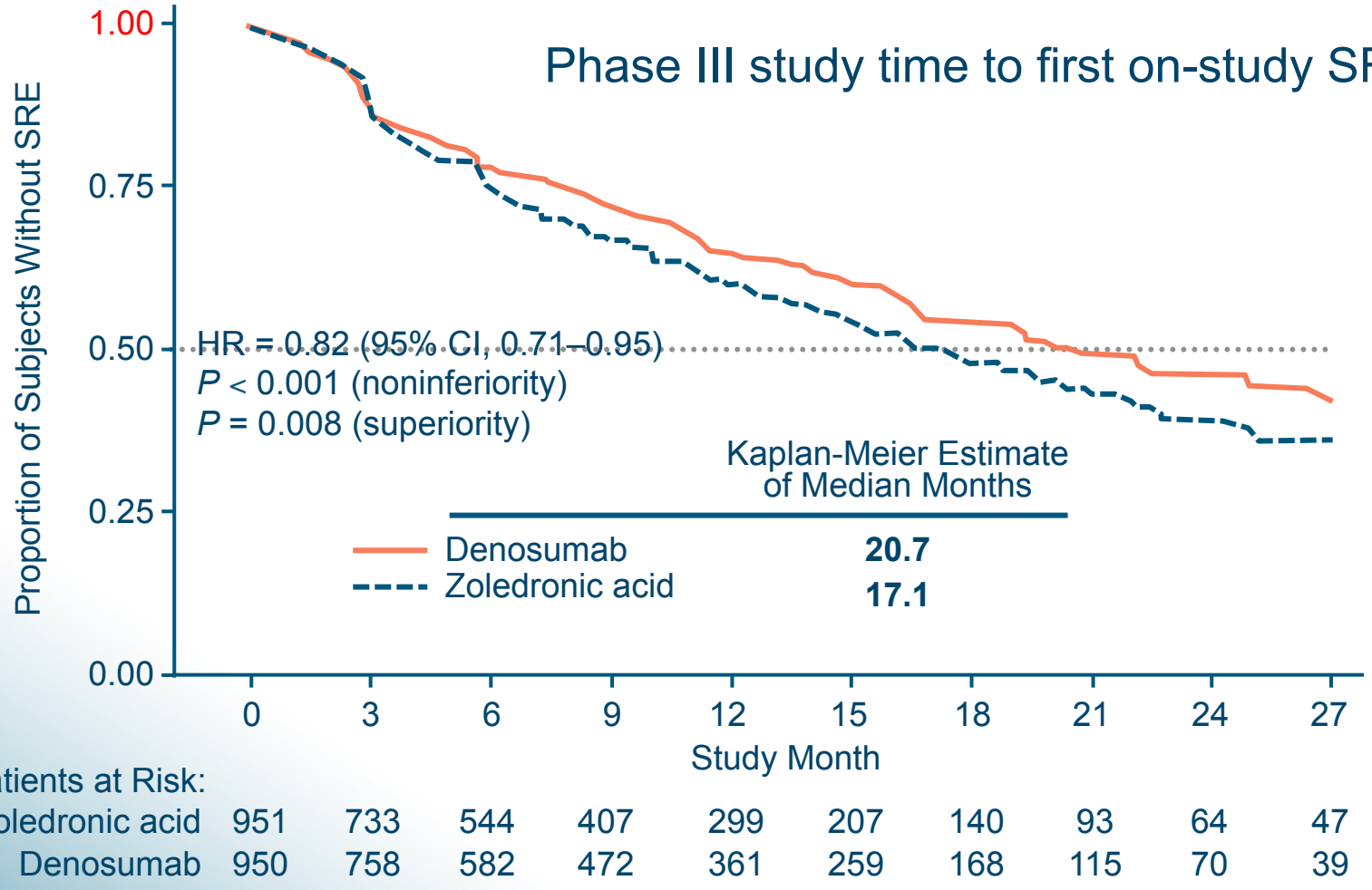
Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study

Lancet 377: 813–822, 2011

Karim Fizazi, Michael Carducci, Matthew Smith, Ronaldo Damião, Janet Brown, Lawrence Karsh, Piotr Milecki, Neal Shore, Michael Rader, Huei Wang, Qi Jiang, Sylvia Tadros, Roger Dansey, Carsten Goessl

1904pz

Primary Endpoint: Time to First On-Study SRE



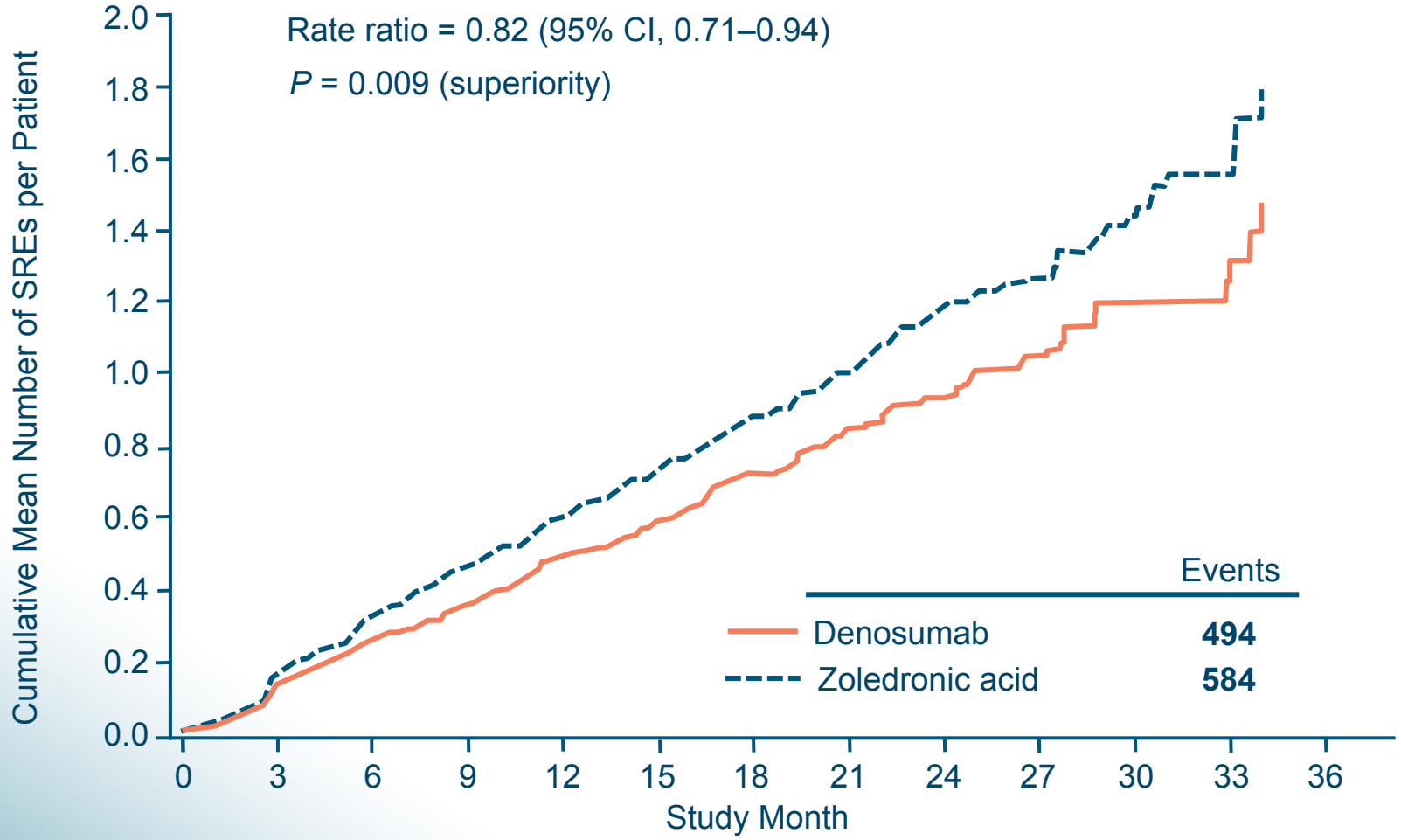
Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study

1904pz

Lancet 377: 813–822, 2011

Karim Fizazi, Michael Carducci, Matthew Smith, Ronaldo Damião, Janet Brown, Lawrence Karsh, Piotr Milecki, Neal Shore, Michael Rader, Huei Wang, Qi Jiang, Sylvia Tadros, Roger Dansey, Carsten Goessl

Secondary Endpoint: Time to First and Subsequent On-Study SRE(s)*



*Events occurring at least 21 days apart.

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

Support Care Cancer (2014) 22:679–687
DOI 10.1007/s00520-013-2022-1

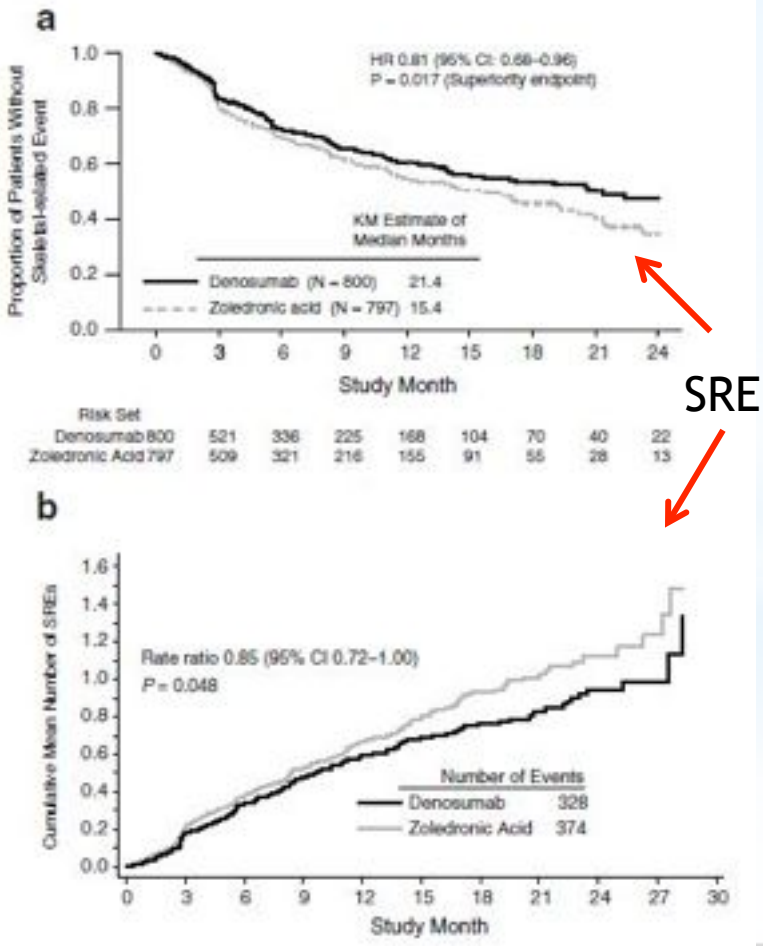
ORIGINAL ARTICLE

Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumors

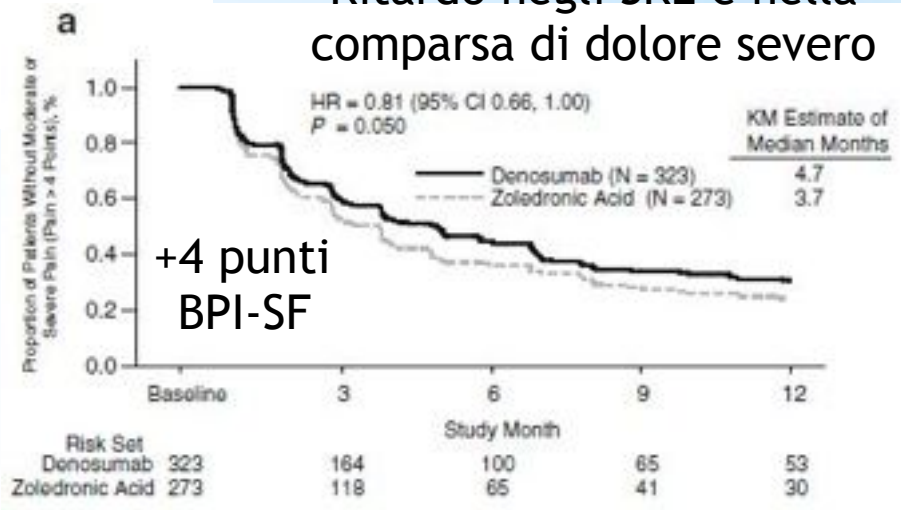
David Henry · Saroj Vadhan-Raj · Vera Hirsh · Roger von Moos · Vania Hungria · Luis Costa · Penella J Woll · Giorgio Scagliotti · Geoffrey Smith · Amy Feng · Susie Jun · Roger Dansey · Howard Yeh

Fase III
Randomizzato
1597pz

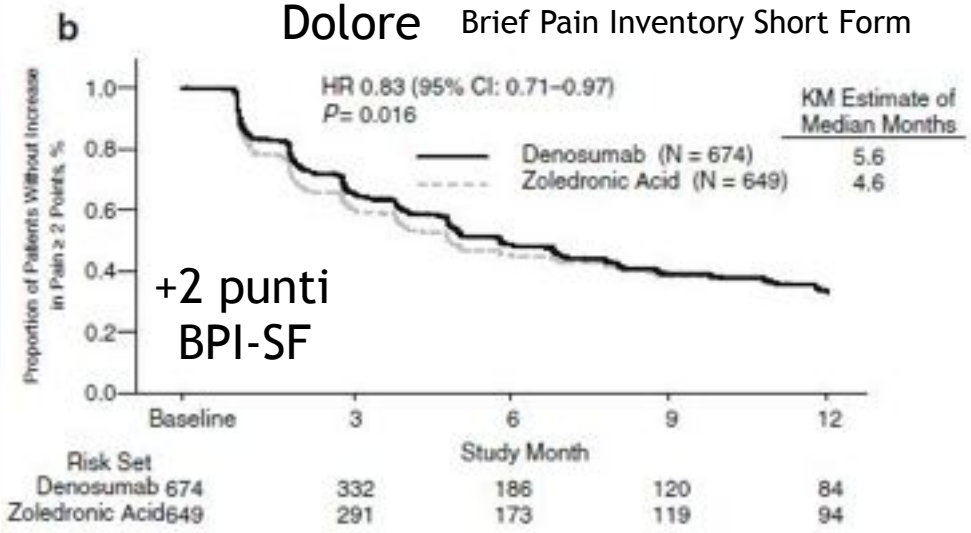
Ritardo negli SRE e nella comparsa di dolore severo



SRE



Dolore Brief Pain Inventory Short Form



NOTA INFORMATIVA IMPORTANTE
CONCORDATA CON LE AUTORITA' REGOLATORIE EUROPEE
E L'AGENZIA ITALIANA DEL FARMACO (AIFA)

Settembre 2014

Denosumab 120mg (XGEVA®)

Comunicazione agli operatori sanitari per minimizzare il rischio di osteonecrosi della mandibola/mascella e di ipocalcemia

Gentile Dottoressa, Egregio Dottore,

Amgen Europe B.V. desidera informarLa, in accordo con l'Agenzia Europea per i Medicinali (EMA) e con l'Agenzia Italiana del Farmaco (AIFA) delle nuove informazioni e raccomandazioni per minimizzare il rischio di osteonecrosi della mandibola/mascella (ONJ) e di ipocalcemia durante il trattamento con XGEVA.

In sintesi

Osteonecrosi della mandibola/mascella

- **l'ONJ è un effetto collaterale comune nei pazienti trattati con XGEVA.**
- **Prima del trattamento con XGE**
- **Non deve essere iniziato un tr**
  che richiede un intervento chir
- **Informare i pazienti che stanno ricevendo XGEVA di mantenere una buona igiene orale, di effettuare dei controlli odontoiatrici periodici, e di riportare immediatamente ogni sintomo riscontrato a livello orale come mobilità dentale,**

Ipocalcemia

- **L'ipocalcemia di grado ≥ 3 è un effetto collaterale comune di XGEVA. Il rischio aumenta con il grado di compromissione renale.**

Negli studi clinici, l'ipocalcemia grave (calcio sierico corretto < 7 mg/dL o < 1,75 mmol/L) si è verificata nel 3,1% dei pazienti in trattamento con XGEVA.

Nei pazienti con fattori di rischio per l'ONJ, prima di iniziare il trattamento con XGEVA, deve essere effettuata una valutazione individuale del rapporto beneficio/rischio.

Negli studi clinici con XGEVA l'incidenza di ONJ aumentava con la maggiore esposizione al trattamento.
L'incidenza di ONJ confermata, aggiustata per paziente anno è stata del 1,1% durante il primo anno di trattamento, del 3,7% durante il secondo anno e del 4,6% negli anni successivi. I pazienti con un'anamnesi di ONJ o osteomielite della mandibola/mascella, con flogosi dentale o mandibolare/mascellare attiva che richiede un intervento chirurgico, un esito di chirurgia dentale/orale non risolta, o pazienti per i quali erano state pianificate procedure odontoiatriche invasive, sono stati esclusi dagli studi clinici.

Per i pazienti che sviluppano l'ONJ durante il trattamento con XGEVA, i medici devono elaborare un piano di gestione in stretta collaborazione con un dentista o un chirurgo orale con esperienza nel trattamento dell'ONJ e l'interruzione temporanea del trattamento deve essere considerata fino a risoluzione della condizione e, dove possibile, a mitigazione dei fattori di rischio che hanno contribuito al suo insorgere.

I pazienti devono essere incoraggiati a mantenere una buona igiene orale, ad effettuare dei controlli odontoiatrici periodici, e a riferire immediatamente ogni sintomo riscontrato a livello orale come mobilità dentale, dolore o gonfiore durante il trattamento con XGEVA. Ai pazienti deve essere ricordato di fare riferimento al "Foglio Illustrativo: informazioni per il paziente" per informazioni sui sintomi dell'ONJ.

Ipocalcemia

Denosumab inibisce il riassorbimento osseo mediato dagli osteoclasti, diminuendo in tal modo il rilascio di calcio dall'osso al circolo ematico.

La maggior parte dei casi si sono verificati nelle prime settimane dall'inizio della terapia.
Il rischio di sviluppare ipocalcemia durante il trattamento con XGEVA è maggiore con l'aumento del grado di compromissione renale.
da tumore in stadio avanzato, il 19% dei pazienti con insufficienza renale grave (clearance della
ti sottoposti a dialisi hanno sviluppato ipocalcemia nonostante supplemento di calcio. L'incidenza
gnificativa è stata del 9%.

ire sintomi indicativi di ipocalcemia.
alcemia sintomatica grave hanno incluso prolungamento dell'intervallo QT, tetania, convulsioni e
e (incluso il coma). I sintomi di ipocalcemia negli studi clinici hanno incluso parestesie o rigidità muscolare.
muscolari.

itari devono, a norma di legge, trasmettere le segnalazioni di sospette reazioni avverse di Xgeva, tramite
ibile sul sito http://www.agenziafarmaco.gov.it/sites/default/files/tipo_filecb84.pdf) o compilando online la
agenziafarmaco.gov.it/sites/default/files/scheda_aifa_operatore_sanitario16.07.2012.doc), tempestivamente,
anza della struttura sanitaria di appartenenza o, qualora operanti in strutture sanitarie private, tramite la
abile di farmacovigilanza della ASL competente per territorio.

Support Care Cancer
DOI 10.1007/s00520-014-2142-2

ORIGINAL ARTICLE

The effects of denosumab on calcium profiles in advanced cancer patients with bone metastases

Breanne Lechner · Carlo DeAngelis · Noreen Jamal · Urban Emmenegger · Natalie Pulenzas · Angie Giotis · Parker Sheehan · May Tsao · Gillian Bedard · Edward Chow

midollo spinale o interventi chirurgici all'osso) negli adulti con metastasi ossee da tumori solidi.

Osteonecrosi della mandibola/mascella

ONJ è una condizione nella quale l'osso mandibolare/mascellare diventa necrotico, esposto e non guarisce entro otto settimane. L'eziologia dell'ONJ non è chiara, ma può essere associata inibizione del rimodellamento osseo.
Fattori di rischio noti per l'ONJ includono interventi odontoiatrici invasivi (ad es. estrazione dentale, impianti, interventi della cavità orale), scarsa igiene orale o altre malattie dentali pre-esistenti, infezioni, età avanzata, terapie concomitanti (ad es. chemioterapia, corticosteroidi, inibitori dell'angiogenesi, radioterapia della regione testa collo), fumo e un precedente trattamento con bisfosfonati. Durante il trattamento i pazienti devono evitare, se possibile, procedure odontoiatriche invasive.

Side effect	Number of patients
Hypocalcemia >Gr.2	9 (16.4 %)
Osteonecrosis of the jaw	0 (0 %)
Renal insufficiency	1 (1.8 %)
Flu-like symptoms	1 (1.8 %)
Mouth ulcers	1 (1.8 %)
Skin rash	1 (1.8 %)
"Locked jaw"	1 (1.8 %)

RESEARCH

Vol. 17, No. 8 October 2011 JMCP Journal of Managed Care Pharmacy

Economic Evaluation of Denosumab Compared with Zoledronic Acid in Hormone-Refractory Prostate Cancer Patients with Bone Metastases

Jipan Xie, MD, PhD; Madhav Namjoshi, PhD; Eric Q. Wu, PhD; Kejal Parikh, MSc; Melissa Diener, BS; Andrew P. Yu, PhD; Amy Guo, PhD; and Kenneth W. Culver, MD

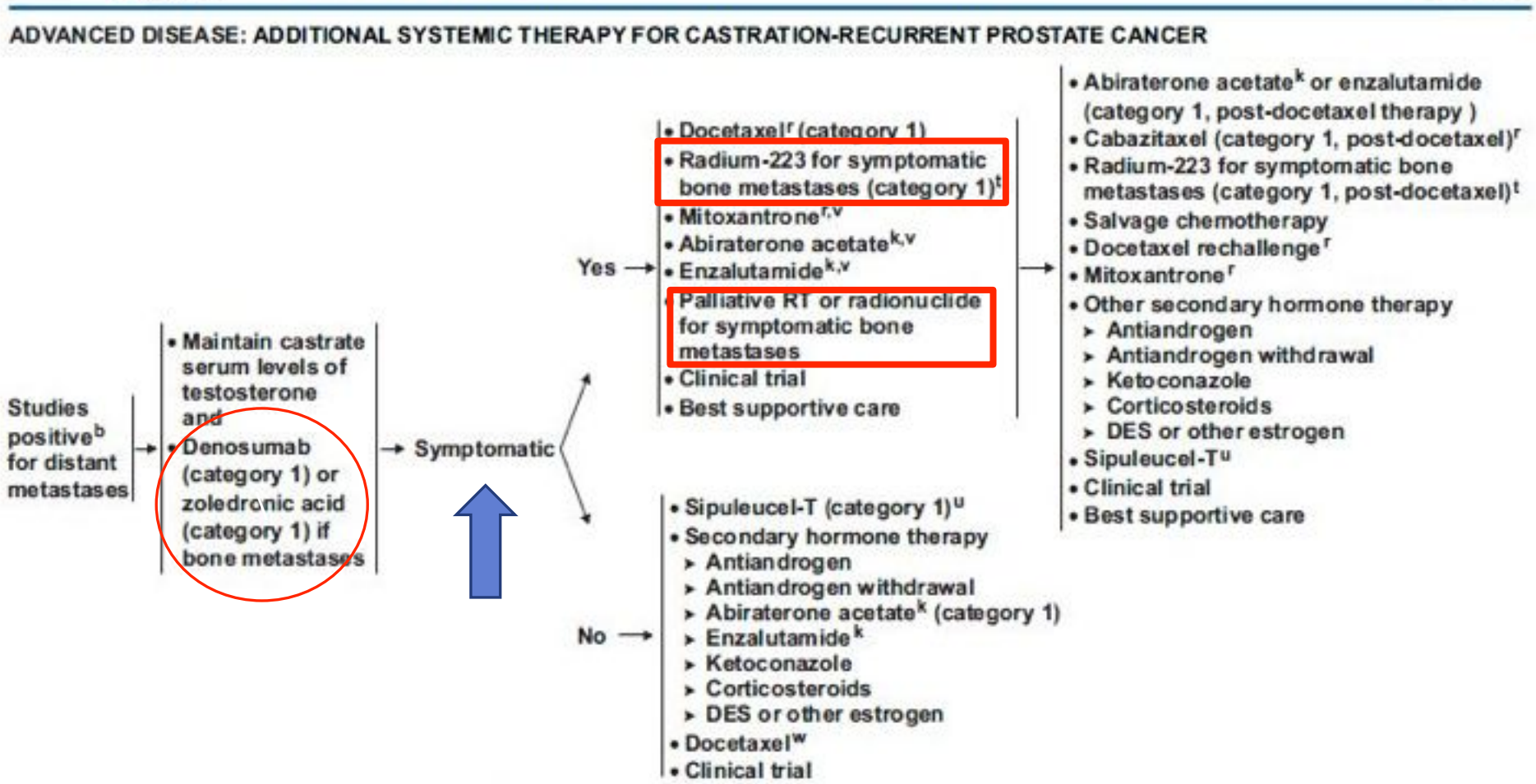
TABLE 4 Base-Case Cost-Effectiveness Analysis of Denosumab Versus Zoledronic Acid

	End of First Year of Treatment		End of Third Year of Treatment	
	Zoledronic Acid	Denosumab	Zoledronic Acid	Denosumab
Drug costs (total)	$10,960	$19,230	$19,972	$35,044
Drug acquisition costs	$10,099	$18,980	$18,404	$34,588
Health care professional costs	$777	$250	$1,415	$456
Drug monitoring costs	$84	—	$154	—
Nondrug costs (total)	$16,569	$16,111	$35,640	$34,424
Disease-related costs[a]	$13,585	$13,097	$26,819	$25,573
Progression costs	$10,643	$10,643	$19,681	$19,681
SRE costs	$2,942	$2,454	$7,137	$5,891
Terminal care costs	$2,649	$2,649	$8,487	$8,487
Adverse event costs	$334	$365	$334	$365
Total drug + nondrug costs[b]	$27,528	$35,341	$55,612	$69,468
SRE (#)	0.60	0.49	1.46	1.18
Incremental cost-effectiveness (total cost per SRE avoided)	—	**$71,027**	—	**$31,319**

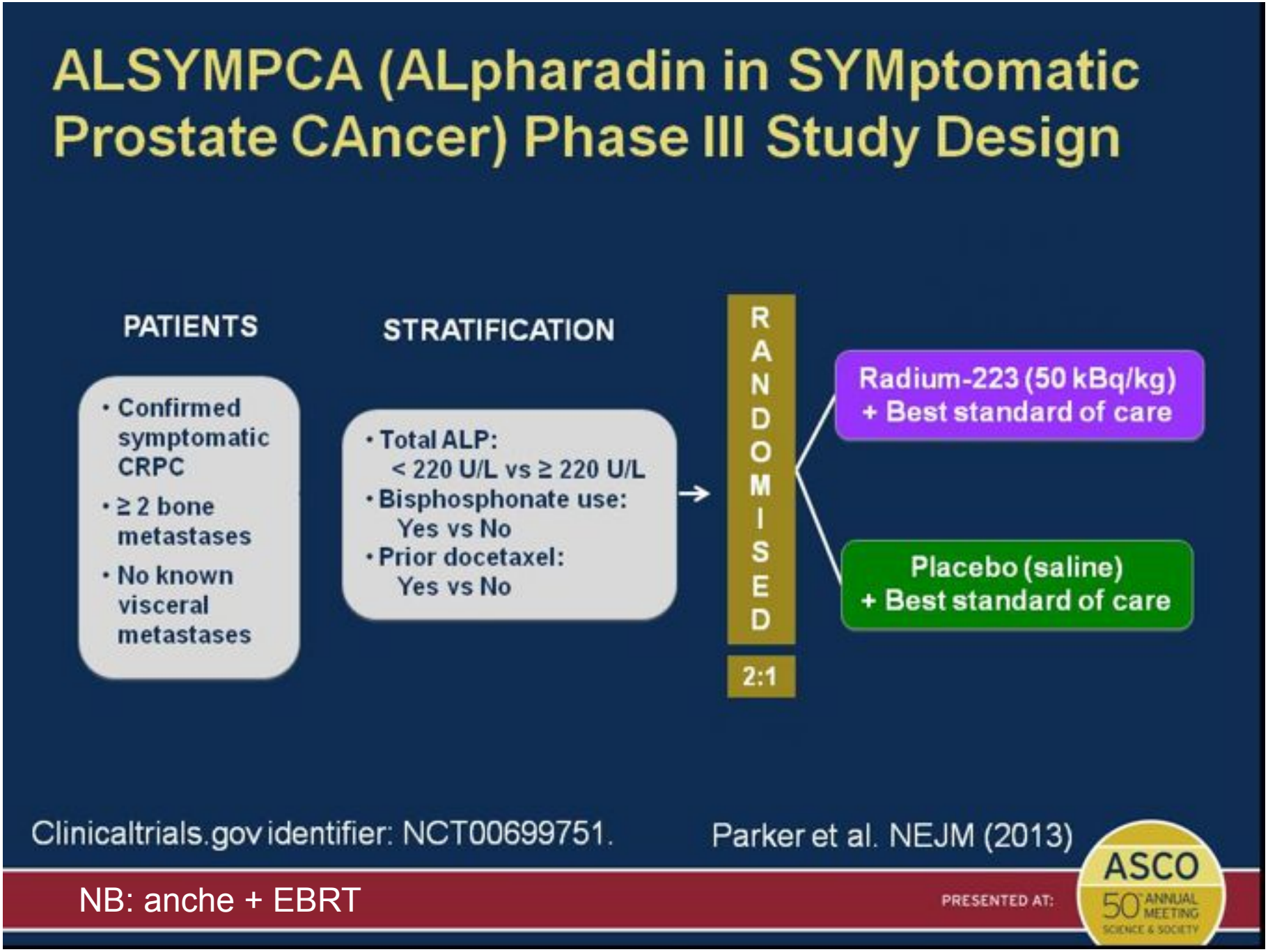
Il maggior costo del Denosumab è «compensato» dalla riduzione degli SRE

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
Prostate Cancer



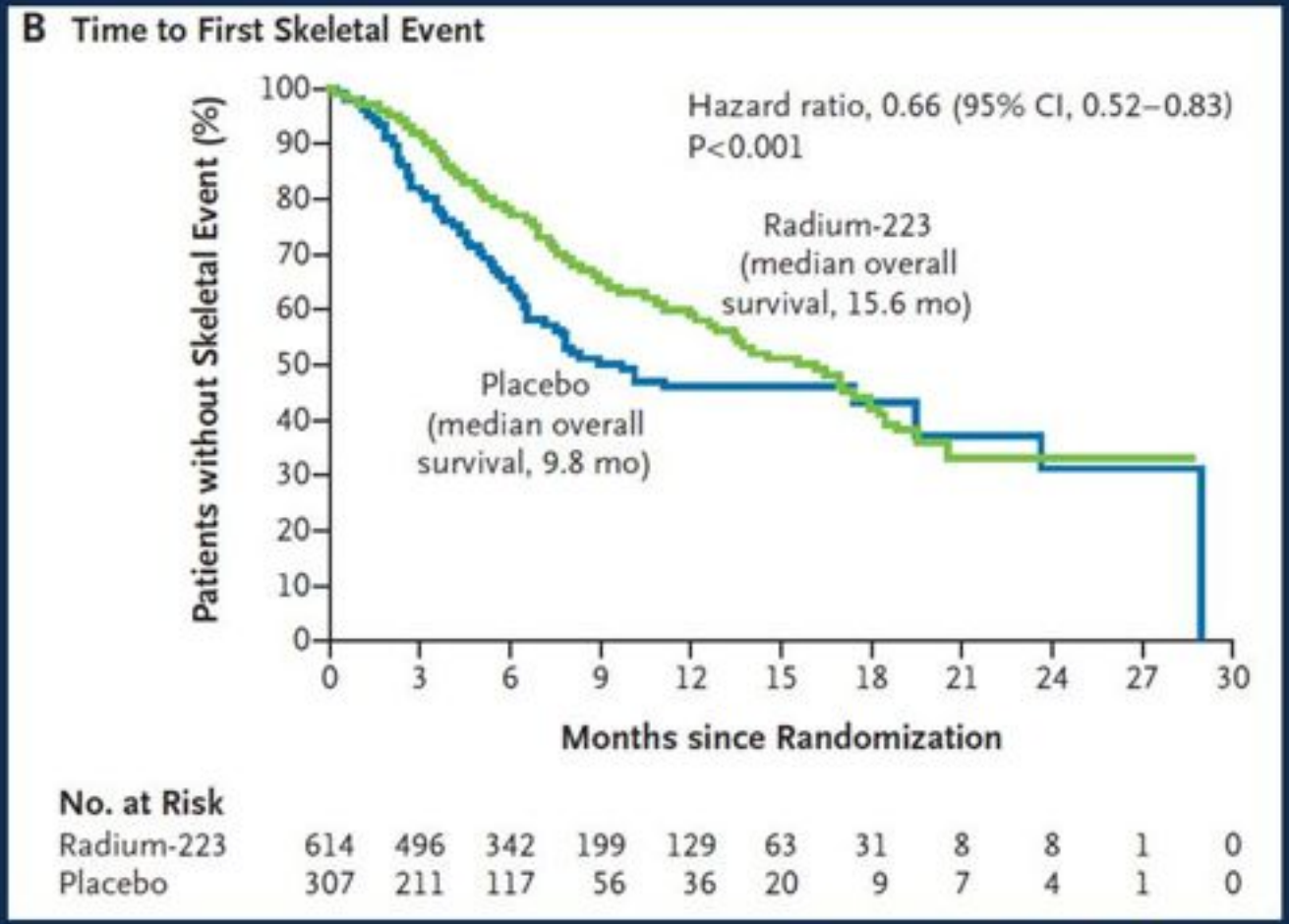
ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design



NB: anche + EBRT

Presented By Chris Parker at 2014 ASCO Annual Meeting

ALSYMPCA Time to First Skeletal-Related Event

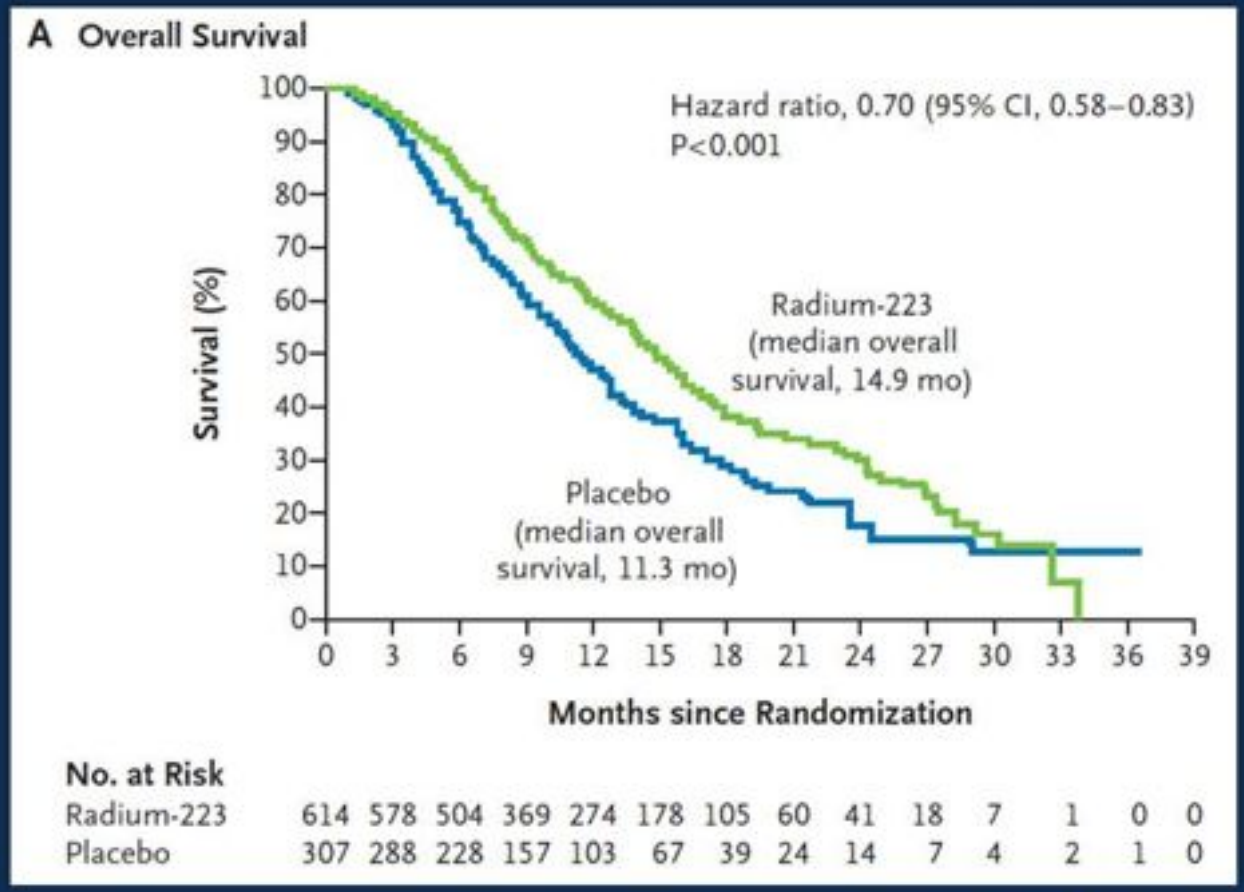


Parker et al. NEJM (2013)

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Presented By Chris Parker at 2014 ASCO Annual Meeting

ALSYMPCA Overall Survival



Parker et al. NEJM (2013)

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Presented By Chris Parker at 2014 ASCO Annual Meeting

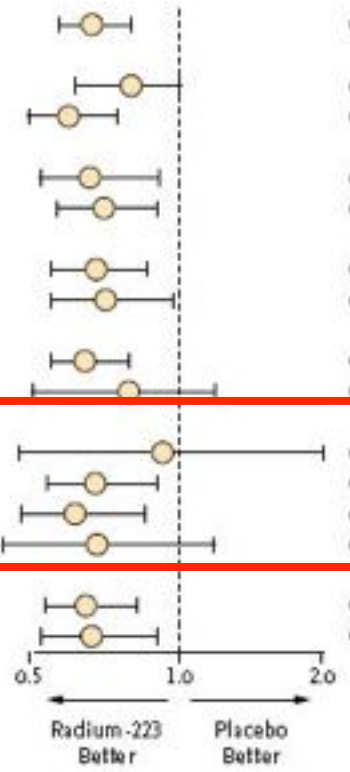
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*

Subgroup	Radium-223	Placebo	Radium-223	Placebo	Hazard Ratio (95% CI)
	no. of patients		*median overall survival (mo)*		
All patients	614	307	14.9	11.3	0.70 (0.58–0.83)
Total ALP level at baseline					
<220 U/liter	348	169	17.0	15.8	0.82 (0.64–1.07)
≥220 U/liter	266	138	11.4	8.1	0.62 (0.49–0.79)
Current bisphosphonate use					
Yes	250	124	15.3	11.5	0.70 (0.52–0.93)
No	364	183	14.5	11.0	0.74 (0.59–0.92)
Previous docetaxel use					
Yes	352	174	14.4	11.3	0.71 (0.56–0.89)
No	262	133	16.1	11.5	0.74 (0.56–0.99)
Baseline ECOG performance-status score					
0 or 1	536	265	15.4	11.9	0.68 (0.56–0.82)
≥2	77	41	10.0	8.4	0.82 (0.50–1.35)
Extent of disease					
<6 metastases	100	38	27.0	NE	0.95 (0.46–1.95)
6–20 metastases	262	147	13.7	11.6	0.71 (0.54–0.92)
>20 metastases	195	91	12.5	9.1	0.64 (0.47–0.88)
Superscan	54	30	11.3	7.1	0.71 (0.40–1.27)
Opioid use					
Yes	345	168	13.9	10.4	0.68 (0.54–0.86)
No	269	139	16.4	12.8	0.70 (0.52–0.93)



Paz.non metastatici!

clinical practice guidelines

Annals of Oncology 00: 1–14, 2014
doi:10.1093/annonc/mdu103

Bone health in cancer patients: ESMO Clinical Practice Guidelines†

R. Coleman[1], J. J. Body[2], M. Aapro[3], P. Hadji[4] & J. Herrstedt[5] on behalf of the ESMO Guidelines Working Group*

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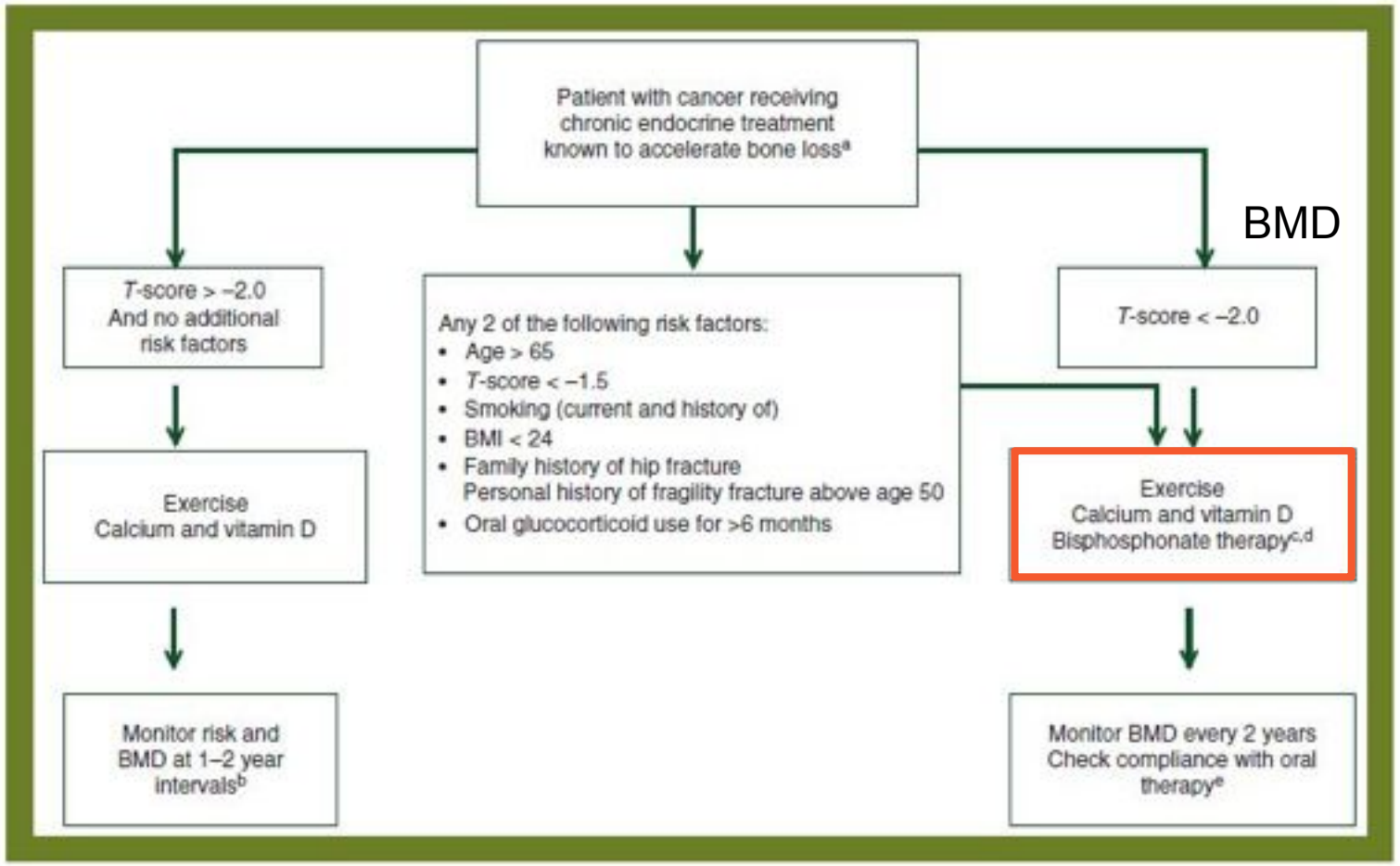
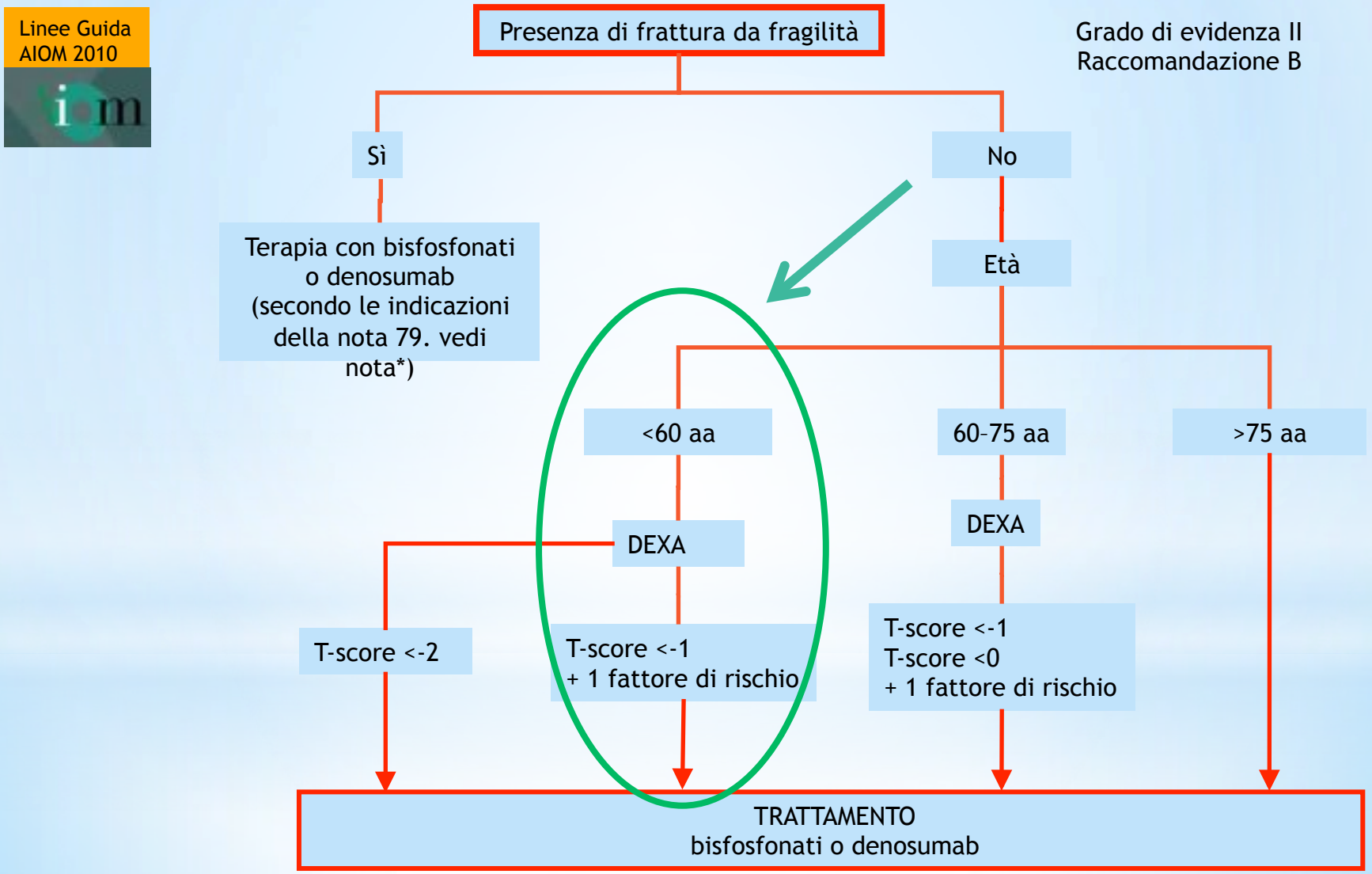


Algoritmo decisionale nella CTIBL in donne in post-menopausa con carcinoma della mammella

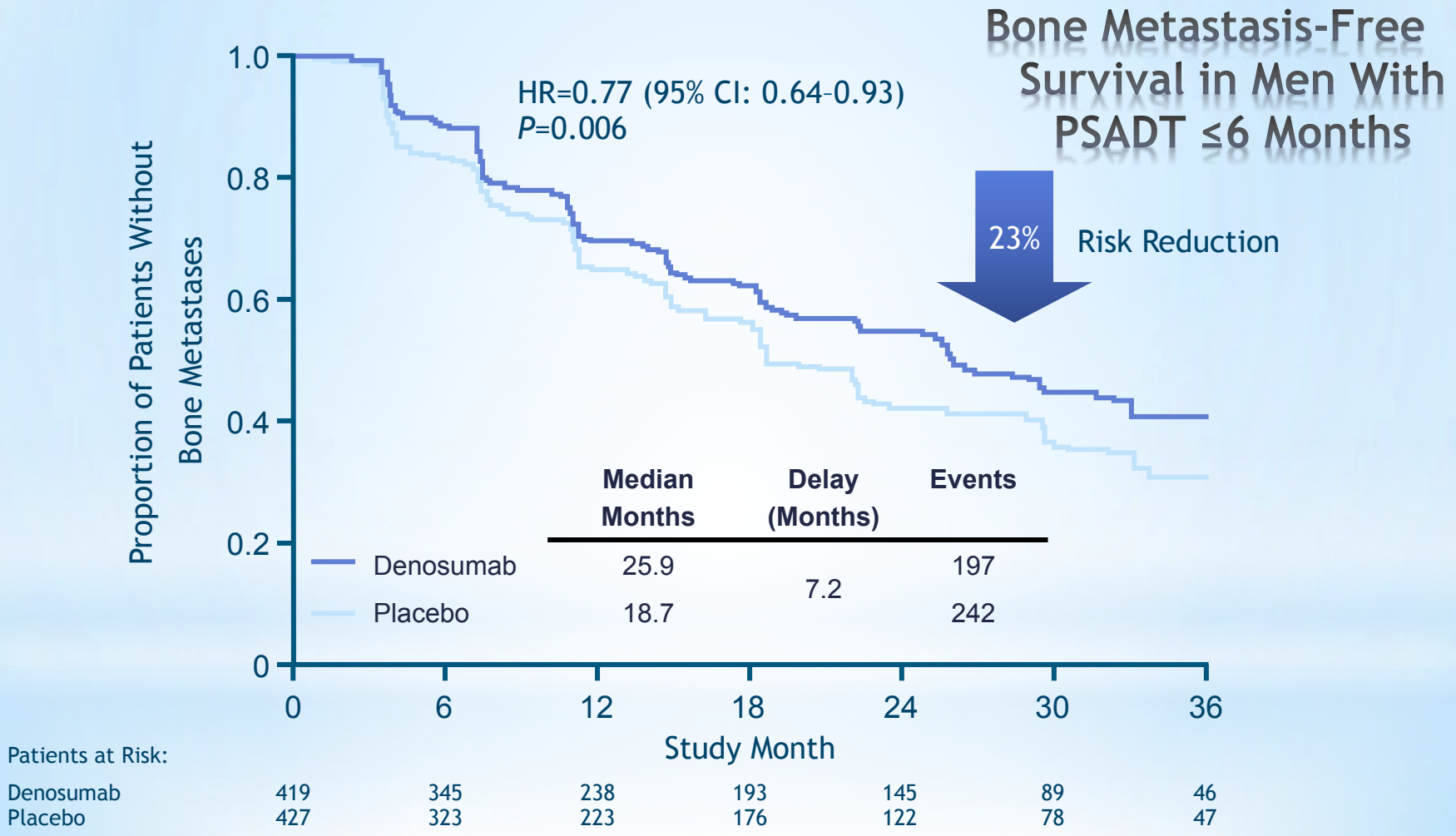
Linee Guida AIOM 2010



CTIBL: cancer treatment induced bone loss

Phase 3
20050147

Denosumab in Men With Nonmetastatic Castration-Resistant Prostate Cancer (CRPC) at High Risk for Bone Metastases



Smith MR, et al. *ECC 2013*: abstract P366 and poster presentation.

Denosumab is investigational in this setting. Denosumab (120 mg Q4W) is approved for 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 tumors.

Legge 15 marzo 2010, n. 38

"Disposizioni per garantire l'accesso alle cure palliative e alla terapia del dolore"

pubblicata nella *Gazzetta Ufficiale* n. 65 del 19 marzo 2010

ART. 5 (Reti nazionali per le cure palliative e per la terapia del dolore).

2. Con accordo stipulato entro tre mesi dalla data di entrata in vigore della presente legge in sede di Conferenza permanente per i rapporti tra lo Stato, le regioni e le province autonome di Trento e di Bolzano, su proposta del Ministro della salute, sono ***individuate le figure professionali con specifiche competenze ed esperienza nel campo delle cure palliative e della terapia del dolore, anche per l'eta' pediatrica, con particolare riferimento ai medici di medicina generale e ai medici specialisti in anestesia e rianimazione, geriatria, neurologia, oncologia, radioterapia, pediatria, ai medici con esperienza almeno triennale nel campo delle cure palliative e della terapia del dolore,*** agli infermieri, agli psicologi e agli assistenti sociali nonche' alle altre figure professionali ritenute essenziali. Con il medesimo accordo sono altresi' individuate le tipologie di strutture nelle quali le due reti si articolano a livello regionale, nonche' le modalita' per assicurare il coordinamento delle due reti a livello nazionale e regionale.

Breast Care

Review Article · Übersichtsarbeit

Breast Care 2012;7:113–120
DOI: 10.1159/000338579

Cancer Pain Management and Bone Metastases: An Update for the Clinician

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Table 3. Eleven basic rules for management of pain due to bone metastases

1. Rule out non-cancer related causes of pain! (E.g.: gastritis, urinary tract infection, pathologic fractures, myocardial infarction)
2. Consider radiotherapy in local bone (somatic nociceptive-) pain. Gold standard in combination with pharmacologic pain management
3. Consider radionuclids (e.g. samarium) in diffuse or multilocal bone pain.
4. Opioid therapy:
   - 4.1. If pain is moderate to severe: initiate opioid therapy according to WHO step III
   - 4.2. Start with potent pure μ agonist (e.g. morphine, hydromorphone, fentanyl, oxycodone)
   - 4.3. Provide both a baseline ('regular' or 'scheduled') opioid (e.g. SR morphine or SR hydromorphone) and on demand (rescue) opioid medication (e.g. immediate release morphine or rapid onset fentanyl)
     - Dosing of immediate release opioids: 1/6th or less than the daily dose of the baseline opioid
     - Beware of strict dose 'calculation' in case of high doses of baseline opioid and if baseline opioid is provided as transdermal opioid
     - Dosing of rapid onset fentanyl: start with lowest available dose, be prepared for rapid dose increase
   - 4.4. Adjust baseline opioids according to temporal pattern of pain; e.g.: If pain is higher during day, provide double morning dose of SR opioid
   - 4.5. Identify breakthrough pain (pain episodes, pain attacks)
   - Identify triggers (e.g. physical activity)
   - Educate patient to take on demand opioid in advance (e.g. 30 min before taking physical activity)
   - If pain episodes need fast onset of analgesia: rapid onset fentanyl (nasal / buccal)
   - 4.6. In case of dose escalation (>240 mg morphine/day) without suffient pain relief: consider opioid rotation
   - Calculate carefully, start with low doses but provide enough on-demand opioid medication
5. Identify concomitant neuropathic pain
   Initiate and titrate coanalgetic (e.g. pregabalin with anxiolytic effect)
6. Identify other factors that contribute to 'total pain'
   - Other symptoms (e.g. dyspnoea, anxiety, depression)
   - Psychosocial domain (feeling of left alone, no communication about disease, feeling urged to 'fight')
   - Spiritual burden (e.g. feeling of guilt)
   - Existential suffering (hopelessness, wish for hastening death, meaninglessness of life)
7. Advanced cancer: consider indication for glucocorticoids (e.g. dexamethasone 4 mg/d)
8. Provide non-opioid in a fixed, regular basis; e.g. dipyrone (metamizole, novaminsulfone) 2.5–5 g/d, ibuprofen 1,200–1,800 mg/d
9. Always check bisphosphonate therapy even if patient is 'pain free' or in early stage of the disease
10. Advanced disease: consider support of palliative care service
11. Invasive procedures (e.g. neuroaxial ananaesthesia): rarely necessary but important option

SR: Sustained-release.

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1. A rare case of rectus abdominis metastasis of lung adenocarcinoma.
Mundra V.
Am J Case Rep. 2012;13:177-9. doi: 10.12659/AJCR.883323. Epub 2012 Aug 8.
PMID: 23569522 [PubMed]
Related citations

2. Extranodal nasal-type NK/T-cell lymphoma of the palate and paranasal sinuses.
Nikolaos N, Grigorios P, Konstantinos K, Savvas T, Vassiliki Z, Alexandra S, Theodoros P.
Am J Case Rep. 2012;13:79-85. doi: 10.12659/AJCR.882802. Epub 2012 May 23.
PMID: 23569495 [PubMed]
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3. Gastrointestinal stromal tumor: a rare abdominal tumor.
Shaheen S, Guddati AK.
Case Rep Oncol. 2013 Jan;6(1):148-53. doi: 10.1159/000350061. Epub 2013 Mar 20.
PMID: 23569450 [PubMed]
Related citations

4. Feasibility and radiation induced toxicity regarding the first application of transperineal implementation of biocompatible balloon for high dose **radiotherapy** in patients with prostate carcinoma.
Vassilis K, Theodoros K, Kalliopi P, John G, George M, Dimitris C, Ivelina B, Panagiotis P, Charalambos A, John K, Nikolaos K.
Radiat Oncol. 2013 Apr 8;8(1):82. [Epub ahead of print]
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5. Intraoperative Electron Beam **Radiotherapy** (IOERT) in the management of locally advanced or recurrent cervical cancer.

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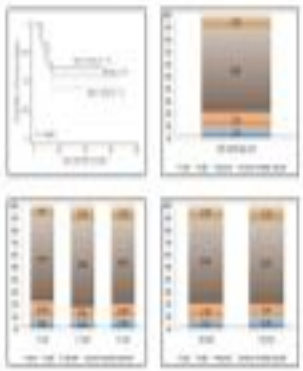

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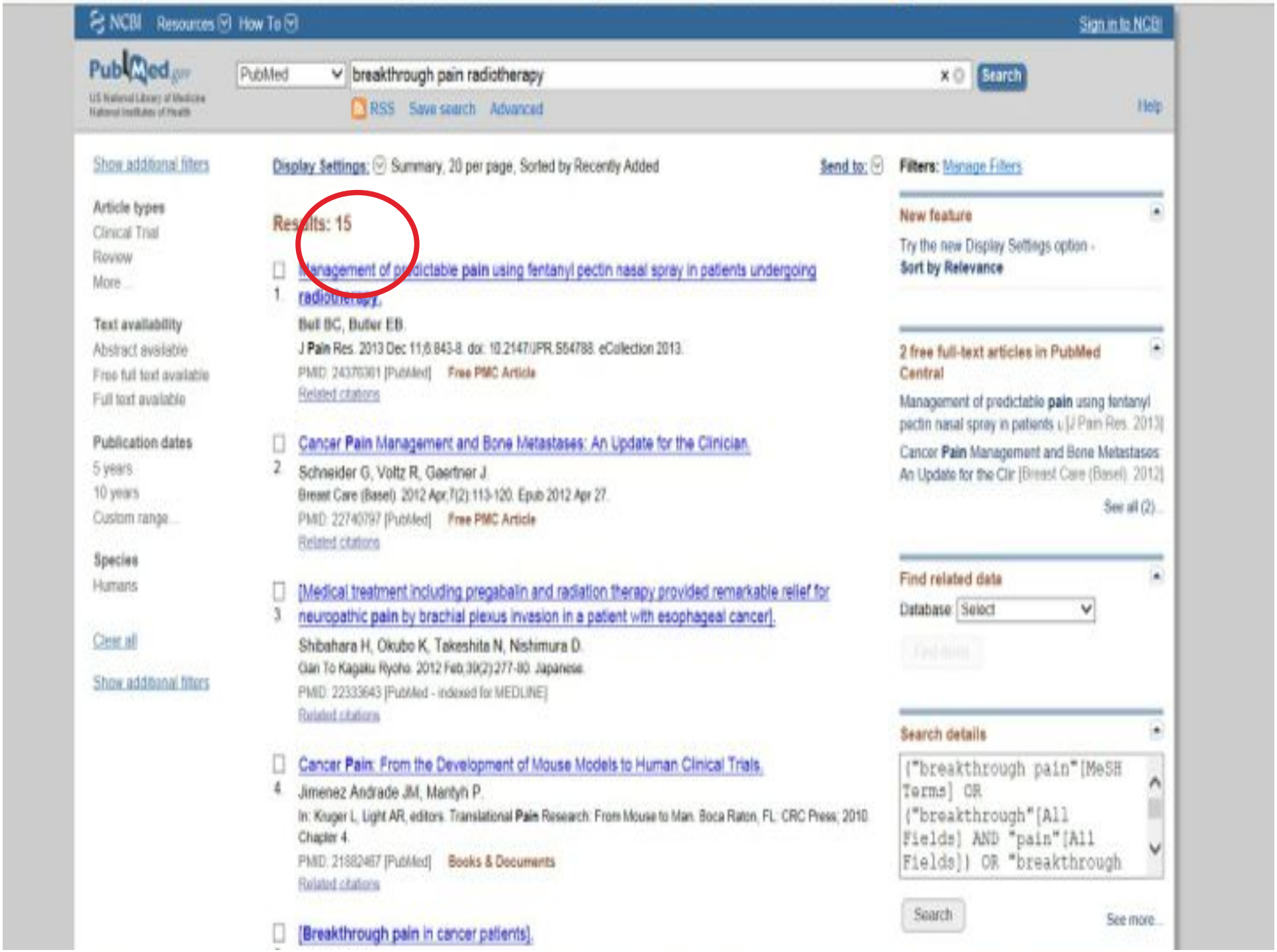
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1. Management of predictable pain using fentanyl pectin nasal spray in patients undergoing radiotherapy.
Bull BC, Butler EB.
J Pain Res. 2013 Dec 11;6:843-8. doi: 10.2147/JPR.S54788. eCollection 2013.
PMID: 24370381 [PubMed] Free PMC Article
Related citations
2. Cancer Pain Management and Bone Metastases: An Update for the Clinician.
Schneider G, Voltz R, Gaertner J.
Breast Care (Basel). 2012 Apr;7(2):113-120. Epub 2012 Apr 27.
PMID: 22740797 [PubMed] Free PMC Article
Related citations
3. [Medical treatment including pregabalin and radiation therapy provided remarkable relief for neuropathic pain by brachial plexus invasion in a patient with esophageal cancer].
Shibahara H, Okubo K, Takeshita N, Nishimura D.
Gan To Kagaku Ryoho. 2012 Feb;39(2):277-80. Japanese.
PMID: 22333643 [PubMed - indexed for MEDLINE]
Related citations
4. Cancer Pain: From the Development of Mouse Models to Human Clinical Trials.
Jimenez Andrade JM, Mantyh P.
In: Kruger L, Light AR, editors. Translational Pain Research: From Mouse to Man. Boca Raton, FL: CRC Press; 2010. Chapter 4.
PMID: 21882467 [PubMed] Books & Documents
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[Breakthrough pain in cancer patients].
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"Valutazione della tollerabilità dei Rapid Onset Opioids a base di Fentanyl nelle prevenzione del BTcP procedurale da radioterapia in pazienti oncologici in trattamento stabile con oppioidi forti per il controllo del dolore di base"

- **Rapid Onset Opioids utilizzato → Fentanyl**

•Endpoint primario→ Valutare la percentuale di pazienti che, al termine delle sedute radioterapiche, presentano una diminuzione dell'intensità di dolore (PID* ≤ 2) (responders).

•Endpoint secondari→

- % di sedute di radioterapia con PID>1 e PID ≤ 2
- Valutazione della tollerabilità espressa come General Impression (GI, su scala a 5 punti)
- Valutazione NRS** nel tempo
- Safety

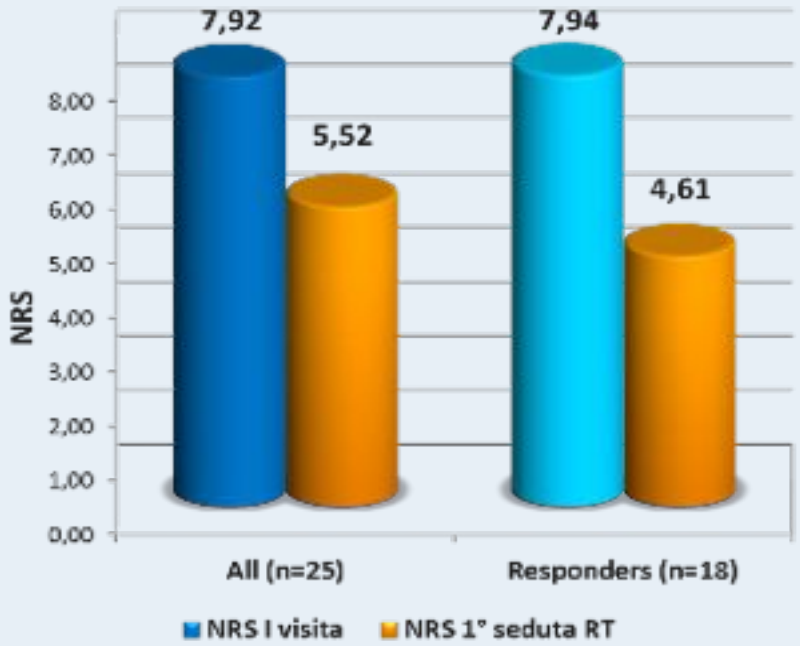
*Pain Intensity Difference (PID)

Numerical Rating Scale (NRS)** per l'Intensità del dolore (scala numerica a 11 punti in cui 0 corrisponde all'assenza di dolore, 10 al peggior dolore immaginabile

RILEVAZIONE DEL DOLORE (NRS) DEI PAZIENTI

18 pazienti su 25 sono responders(72%)

Responders = pazienti che, al termine della RT, presentano una diminuzione dell'intensità di dolore rispetto alla prima visita uguale o inferiore a 2 (PID ≤ 2).



	All	*Responders only*
PID	2.4	4

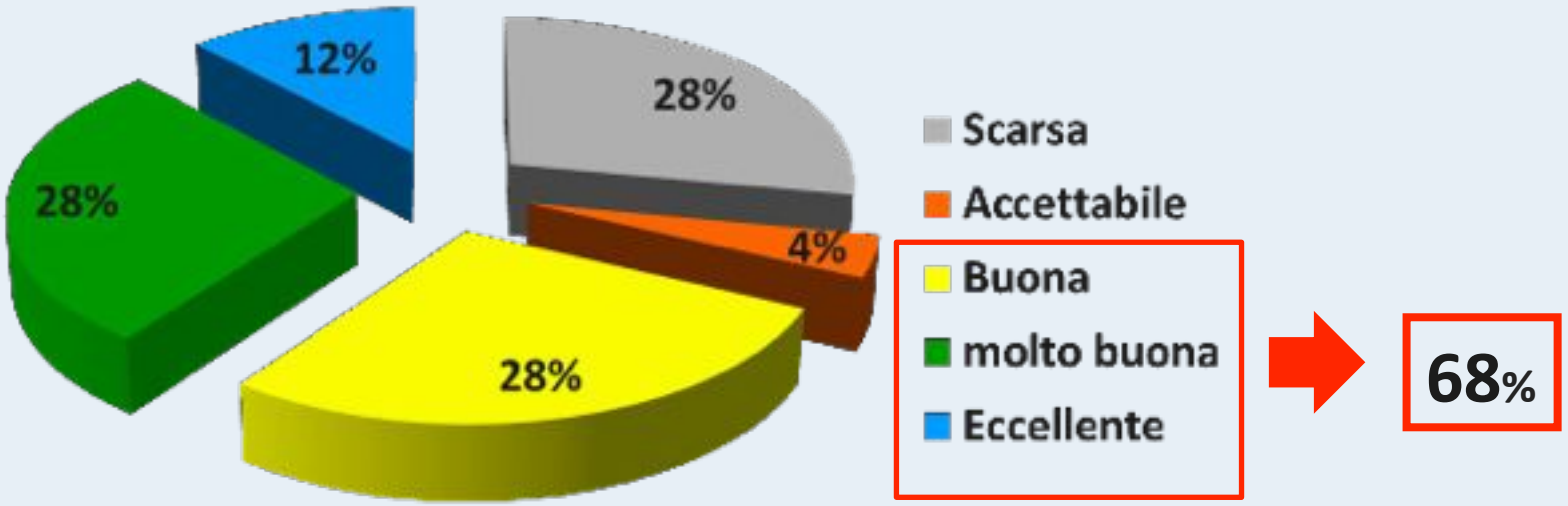
Numerical Rating Scale (NRS) per l'Intensità del dolore (scala numerica a 11 punti in cui 0 corrisponde all'assenza di dolore, 10 al peggior dolore immaginabile

Pain Intensity Difference (PID) (differenza dell'intensità del dolore tra un determinato tempo rispetto al tempo della somministrazione del farmaco ROO, misurato come NRS).

GENERAL IMPRESSION (GI)

GI= valutazione espressa dal paziente sul trattamento con Actiq per mezzo della scala verbale a 5 punti:

1=scarsa; 2= accettabile; 3=buona; 4 =molto buona; 5= eccellente



Il nuovo concetto di *bone health* nel paziente neoplastico

- Goserelin
- Chemioterapia
- Inibitori dell'aromatasi
- Menopausa
- Invecchiamento
- Ipovitaminosi D

ELEVATO TURNOVER OSSEO

OSTEOPOROSI

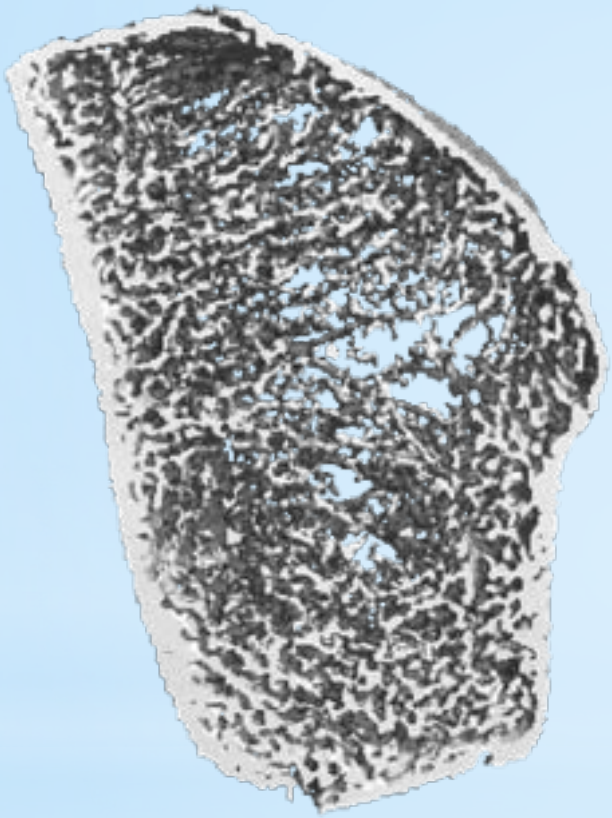
FRATTURE DA FRAGILITÀ

SRE

- Fratture
- Radioterapia
- Compressione spinale
- Chirurgia ortopedica
- Dolore

METASTASI OSSEA

Influence of anastrozole on trabecular microstructure after 3 months (Xtreme-CT)



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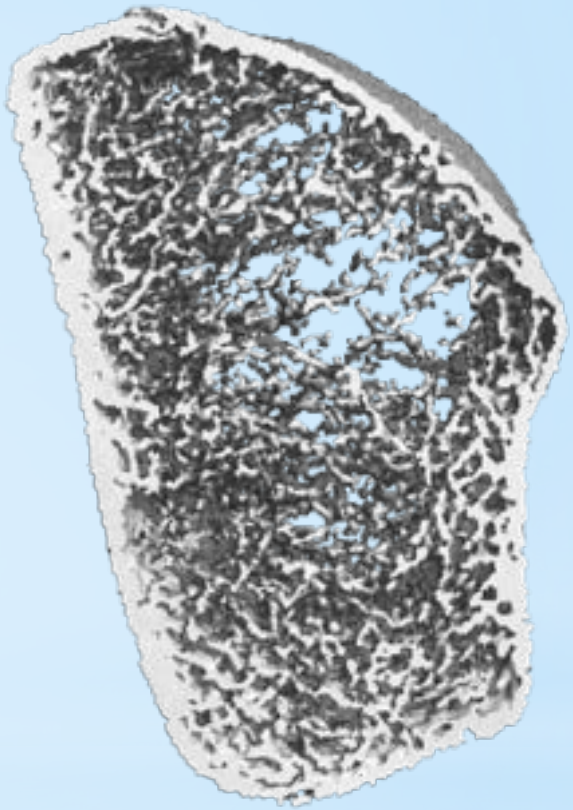

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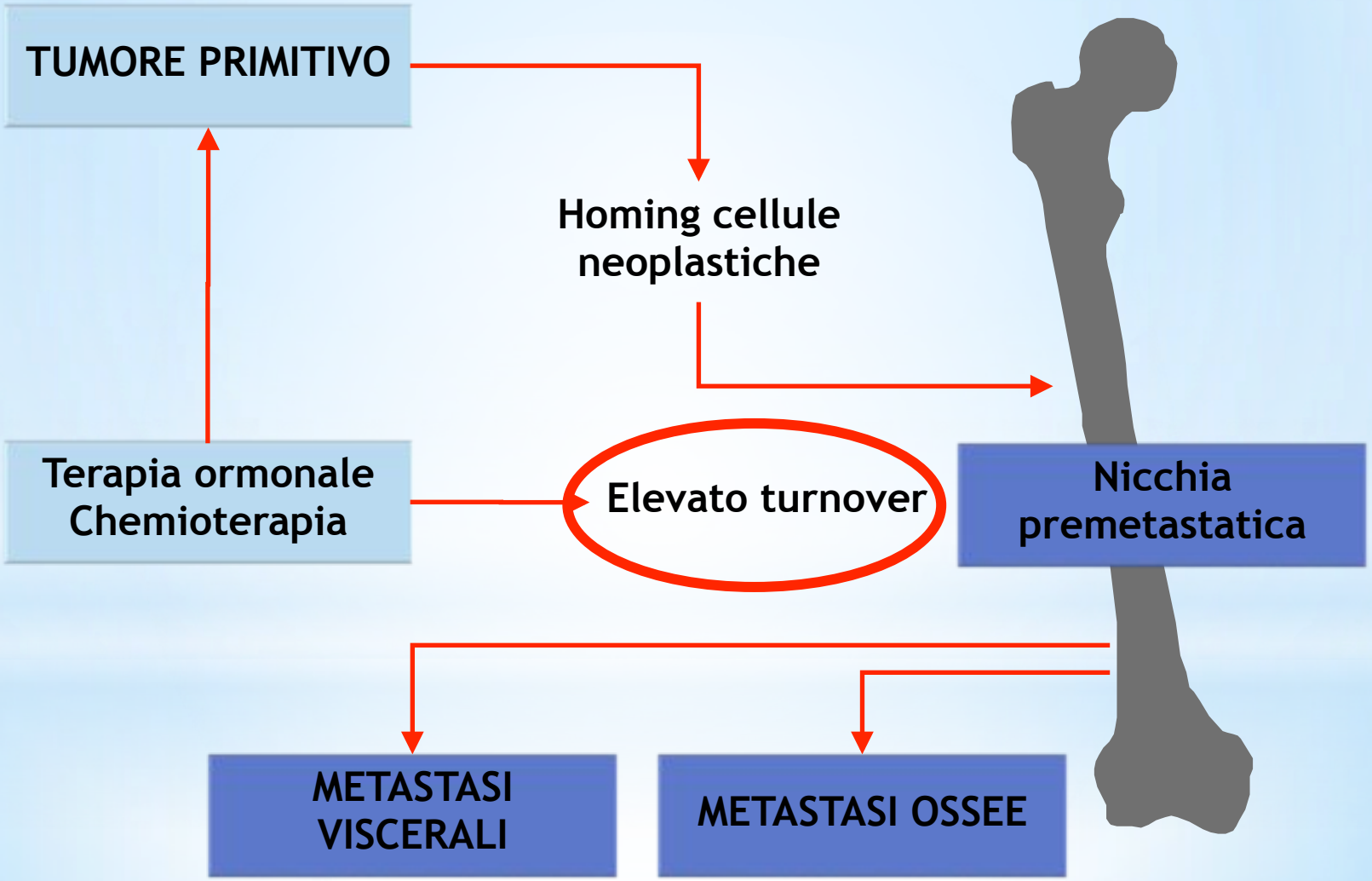
H. Radspieler, Center for Osteoporosis. Munich, Germany

Sequenza fisiopatologica per la formazione della nicchia pre-metastatica

Le terapie oncologiche aprono la strada alle metastasi?



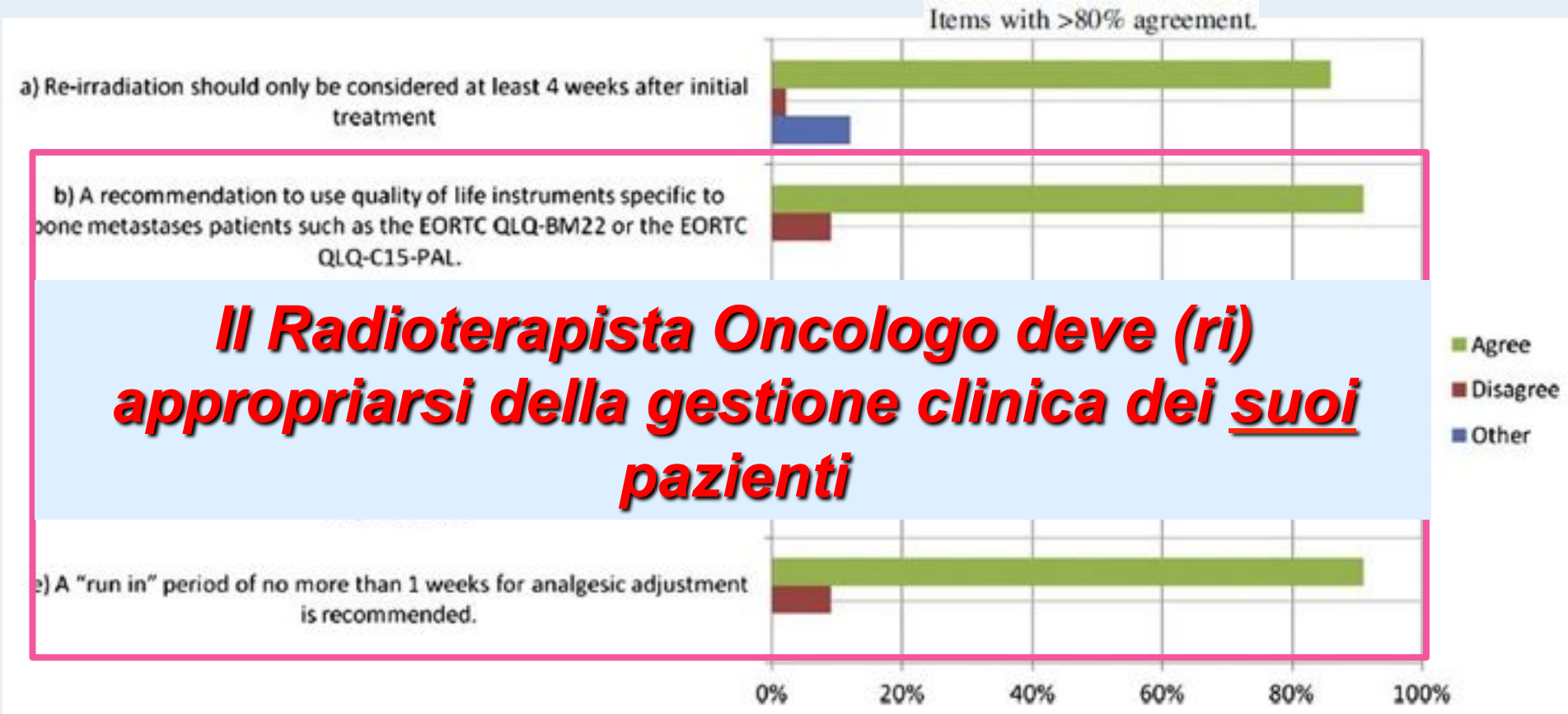
CLINICAL INVESTIGATION **Metastases**

UPDATE OF THE INTERNATIONAL CONSENSUS ON PALLIATIVE RADIOTHERAPY ENDPOINTS FOR FUTURE CLINICAL TRIALS IN BONE METASTASES

EDWARD CHOW, M.B.B.S.,* PETER HOSKIN, M.D.,† GUNITA MITERA, PH.D.(C),* LIANG ZENG, B.SC.(C),* STEPHEN LUTZ, M.D.,‡ DANIEL ROOS, M.D.,§ CAROL HAHN, M.D.,¶ YVETTE VAN DER LINDEN, M.D.,‖ WILLIAM HARTSELL, M.D.,# AND ESHWAR KUMAR, M.B.B.S. ** ON BEHALF OF THE INTERNATIONAL BONE METASTASES CONSENSUS WORKING PARTY

49 Esperti ASTRO, ESTRO, CARO, RANZCR

1. Eligibility criteria for future trials
2. Pain and analgesic assessments
3. Radiation techniques
4. Follow-up and timing of assessments
5. Parameters at follow-up
6. Endpoints
7. Reirradiation
8. Statistical analysis



Il Radioterapista Oncologo deve (ri) appropriarsi della gestione clinica dei <u>suoi</u> pazienti

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 5, pp. 1730–1737, 2012