METASTASI SCHELETRICHE da TUMORI SOLIDI

Alessandria 14 Maggio 2008

Il Carcinoma della Mammella

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Oncologia Medica I

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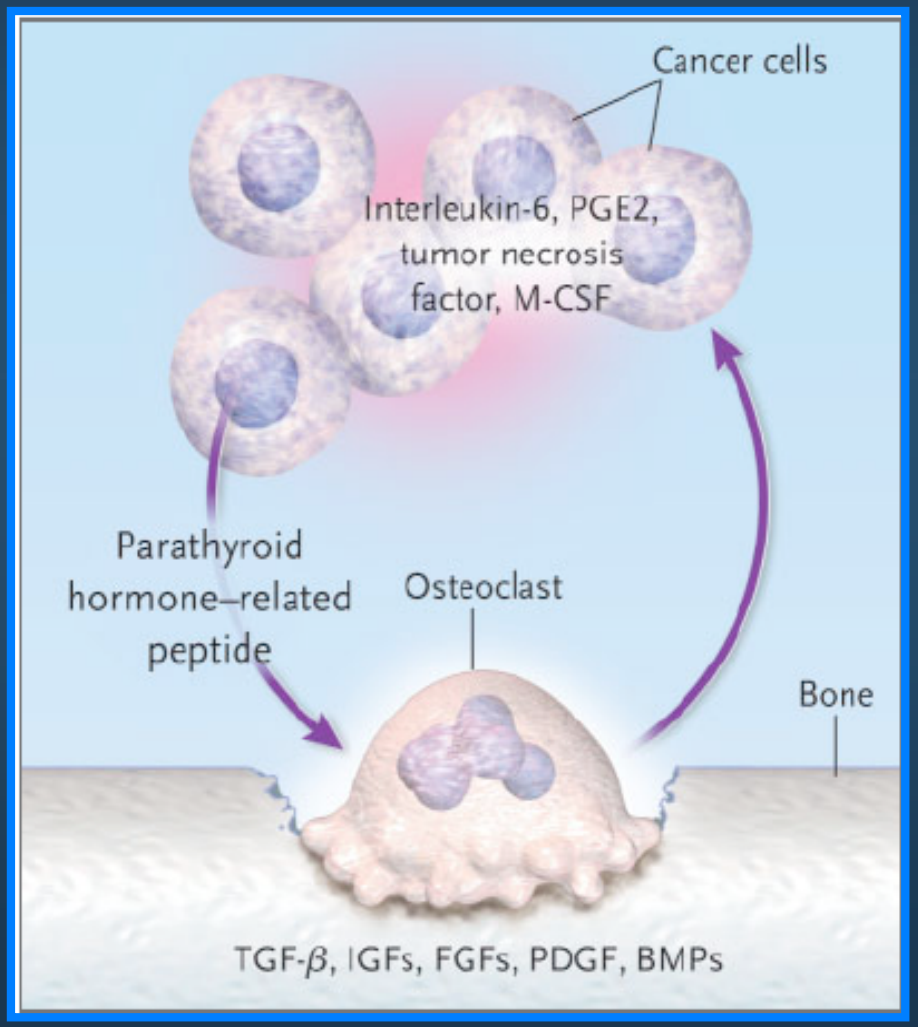
LE METASTASI OSTEOLITICHE
DA CARCINOMA MAMMARIO



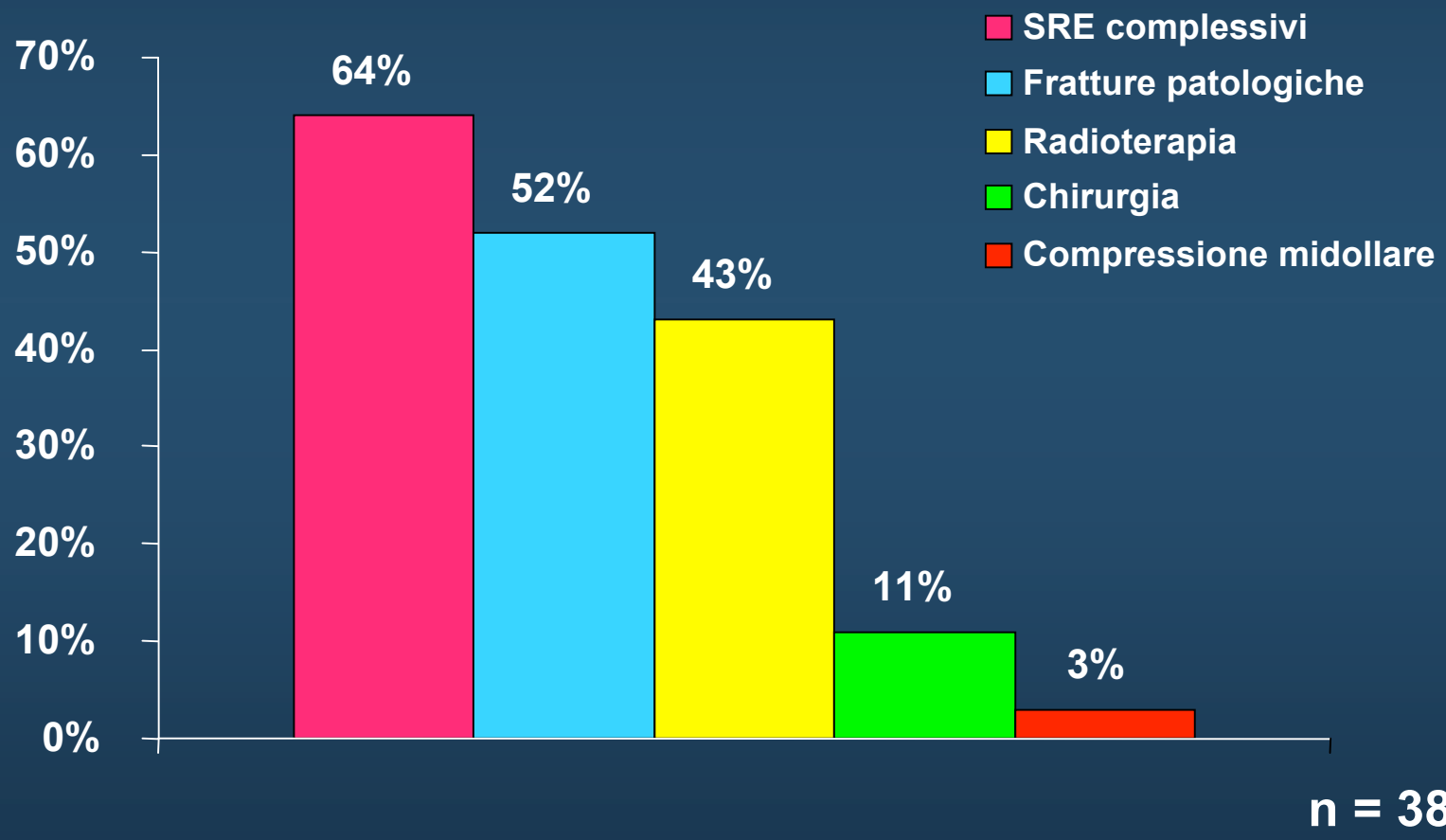
La distruzione ossea è mediata dagli osteoclasti

Le cellule tumorali producono fattori che inducono il reclutamento e l'attivazione osteoclastica

Gli osteoclasti riassorbono il tessuto osseo e ciò fa rilasciare fattori di crescita che stimolano lo sviluppo tumorale e quindi con un circolo vizioso la lisi ossea

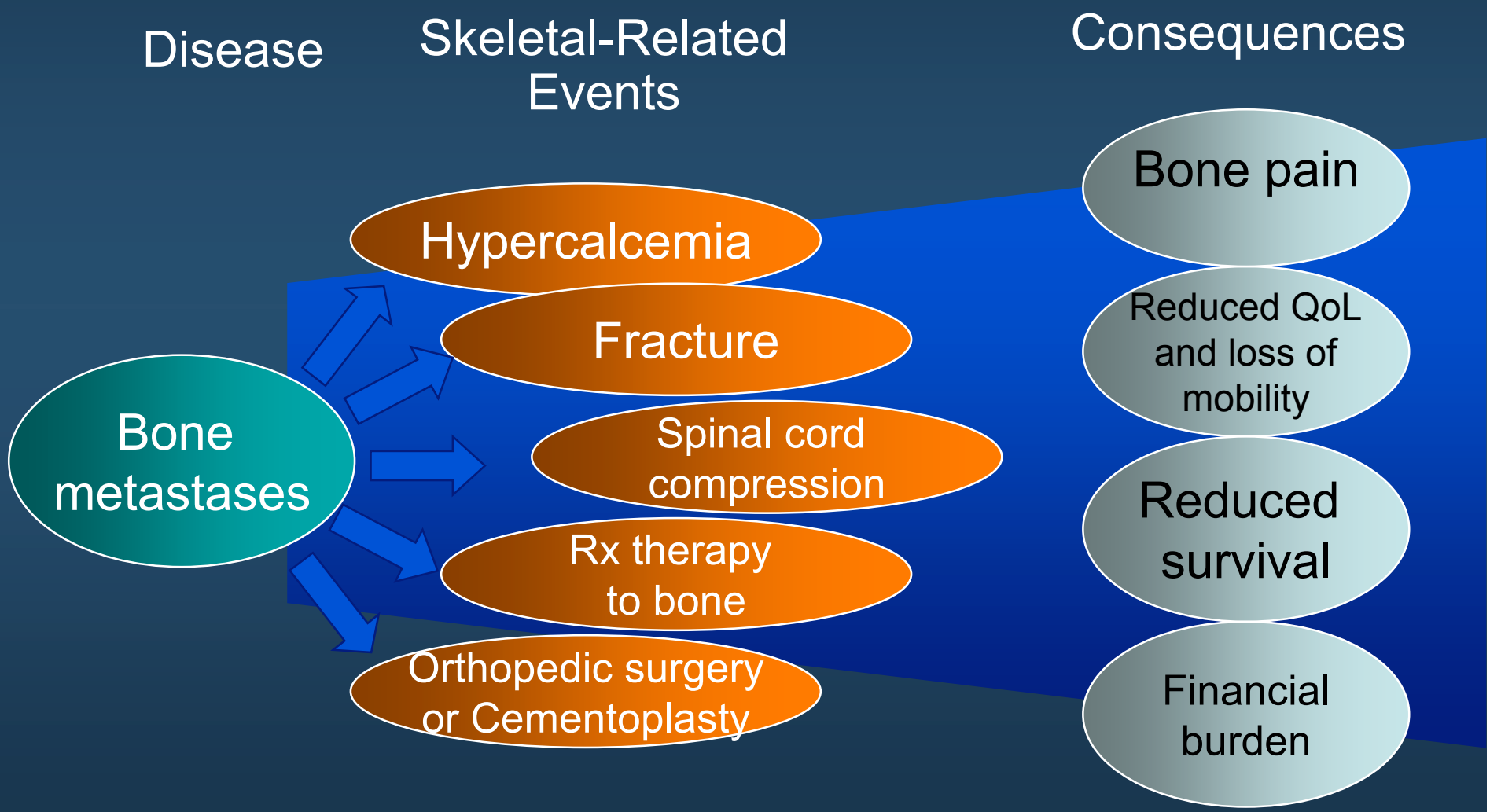
Roodman G.D. et al, NEJM 2004

Carcinoma della mammella e SRE



Dati a 24 mesi dai Gruppi Placebo TCR
Lipton A, et al. *Cancer*. 2000;88:1082-1090

Consequences of Bone Metastases



Carcinoma della mammella: evidenze da TCR

BP	Study	*N*	Dose	Design and control	1 end point	Relative risk of skeletal events RR (95% confidence interval)
i.v. IBA	Body *et al.* [30]	462	2 or 6 mg	• Double blind • Placebo • Monthly, up to 2 years	SMPR	0.82 (0.67, 1.00)
p.o. IBA	Body *et al.* [31]	564	50 mg	• Double blind • Placebo • Daily, up to 96 weeks	SMPR	0.86 (0.73, 1.02)
p.o. CLO	Kristensen *et al.* [32]	100	1600 mg	• Randomized • Open label • Controlled • Daily, for 2 years	Number of skeletal events	0.69 (0.40, 1.20)
p.o. CLO	Paterson *et al.* [33]	185	1600 mg	• Double blind • Placebo • Daily for 3 years	Combined rate of morbid skeletal events	0.83 (0.68, 1.02)
p.o. CLO	Tubiana-Hulin *et al.* [34]	144	1600 mg	• Randomized • Double blind • Controlled • Daily, up to 1 year	New bone event	0.92 (0.92, 1.19)
i.v. PAM	Hortobagyi *et al.* [29] Theriault *et al.* [35]	754	90 mg	• Randomized • Double blind • Placebo • Every 3–4 weeks, up to 24 cycles	Skeletal morbidity rate (events/ per year)	0.77 (0.69, 0.87)[a]
i.v. ZOL	Kohno *et al.* [26]	228	4 mg	• Randomized • Double blind • Placebo • Every 4 weeks, for 1 year	SRE rate ratio	0.59 (0.42, 0.82)
i.v. ZOL	Rosen *et al.* [36]	412[b]	4 mg	• Randomized • Double blind • PAM • Every 4 weeks, for 2 year	Proportion of patients who experienced ≥1 SRE	0.80 (0.66, 0.97) [36]

Aapro M. Et al., Annl of Onc 2008

Long-Term Efficacy and Safety of Zoledronic Acid Compared with Pamidronate Disodium in the Treatment of Skeletal Complications in Patients with Advanced Multiple Myeloma or Breast Carcinoma

A Randomized, Double-Blind, Multicenter, Comparative Trial

Table 5. Summary of clinical end points comparing 4-mg zoledronic acid with 90-mg pamidronate for the prevention of SREs in patients with breast cancer and bone metastases

End point	Zoledronic acid 4 mg (n = 377)	Pamidronate 90 mg (n = 389)	p value
Patients with ≥1 SRE (%)	46	49	0.340
Median time to first SRE (days)	376	366	0.186
Mean SMR	0.9	1.57	0.102
Multiple event analysis[a]	20% ↓ risk of SREs	–	0.025
Multiple event analysis[b]	20% ↓ incidence of SREs	–	0.046

Acido Zoledronico superiore ad un altro BF (pamidronato) alla Multiple Event Analisys

ANDERSEN-GILL

MULTIPLE EVENT ANALISYS

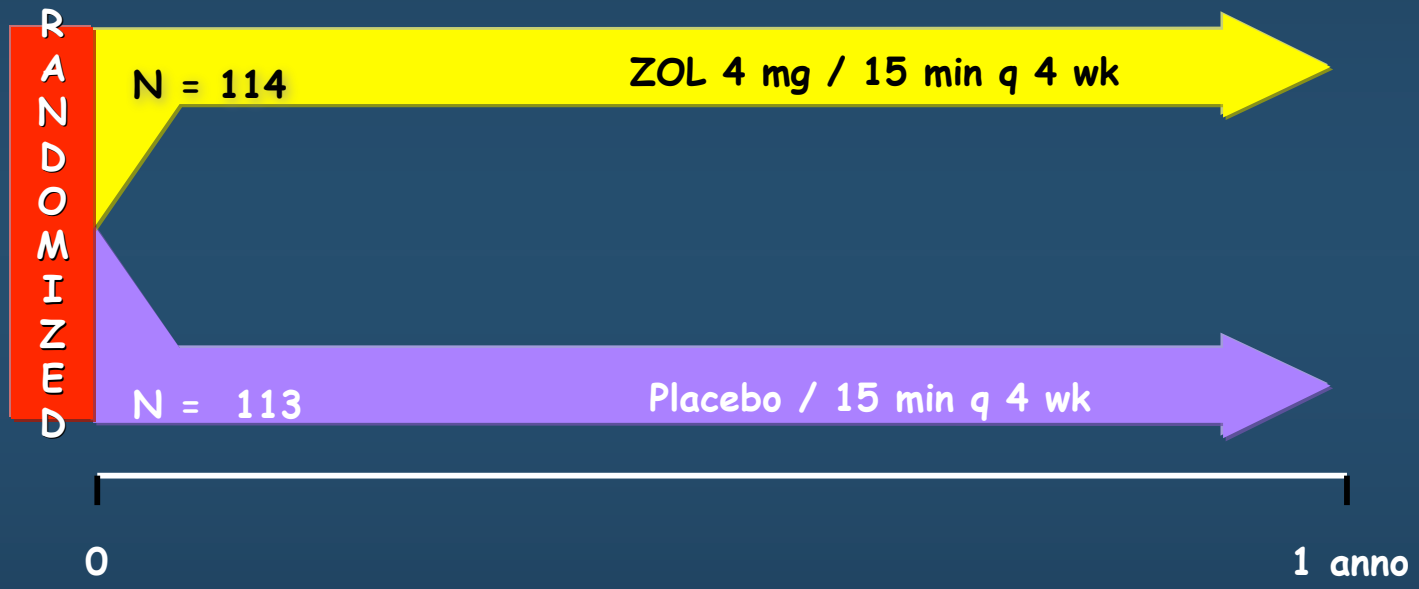
Analisi del numero totale di SRE sviluppati e ne considera anche il timing di comparsa

Dimostra l'effetto della terapia durante tutta la durata dello studio

Rosen, Cancer 2003

Zoledronic Acid Significantly Reduces Skeletal Complications Compared With Placebo in Japanese Women With Bone Metastases From Breast Cancer: A Randomized, Placebo-Controlled Trial

Norio Kohno, Kenjiro Aogi, Hironobu Minami, Seigo Nakamura, Taro Asaga, Yuichi Iino, Toru Watanabe, Carsten Goessl, Yasuo Ohashi, and Shigemitsu Takashima



Per ottenere la registrazione in Giappone

Primary endpoint: Riduzione incidenza degli SRE

Kohno N et al. *J Clin Oncol*. 2005

Risultati ad 1 anno

Table 3. Secondary Efficacy End Points

Clinical End Point	Zoledronic Acid, 4 mg (n = 114)	Placebo (n = 113)	*P*
Percentage of patients with at least one SRE			
Excluding HCM	29.8	49.6	.003*
Including HCM	30.7	52.2	.001*
Median time to first SRE, days			
Excluding HCM	NR	364	.007†
Including HCM	NR	360	.004†
Risk ratio for developing SREs‡			
Excluding HCM	0.59		.019§
95% CI	0.375 to 0.914		
Including HCM	0.56		.009§
95% CI	0.363 to 0.867		

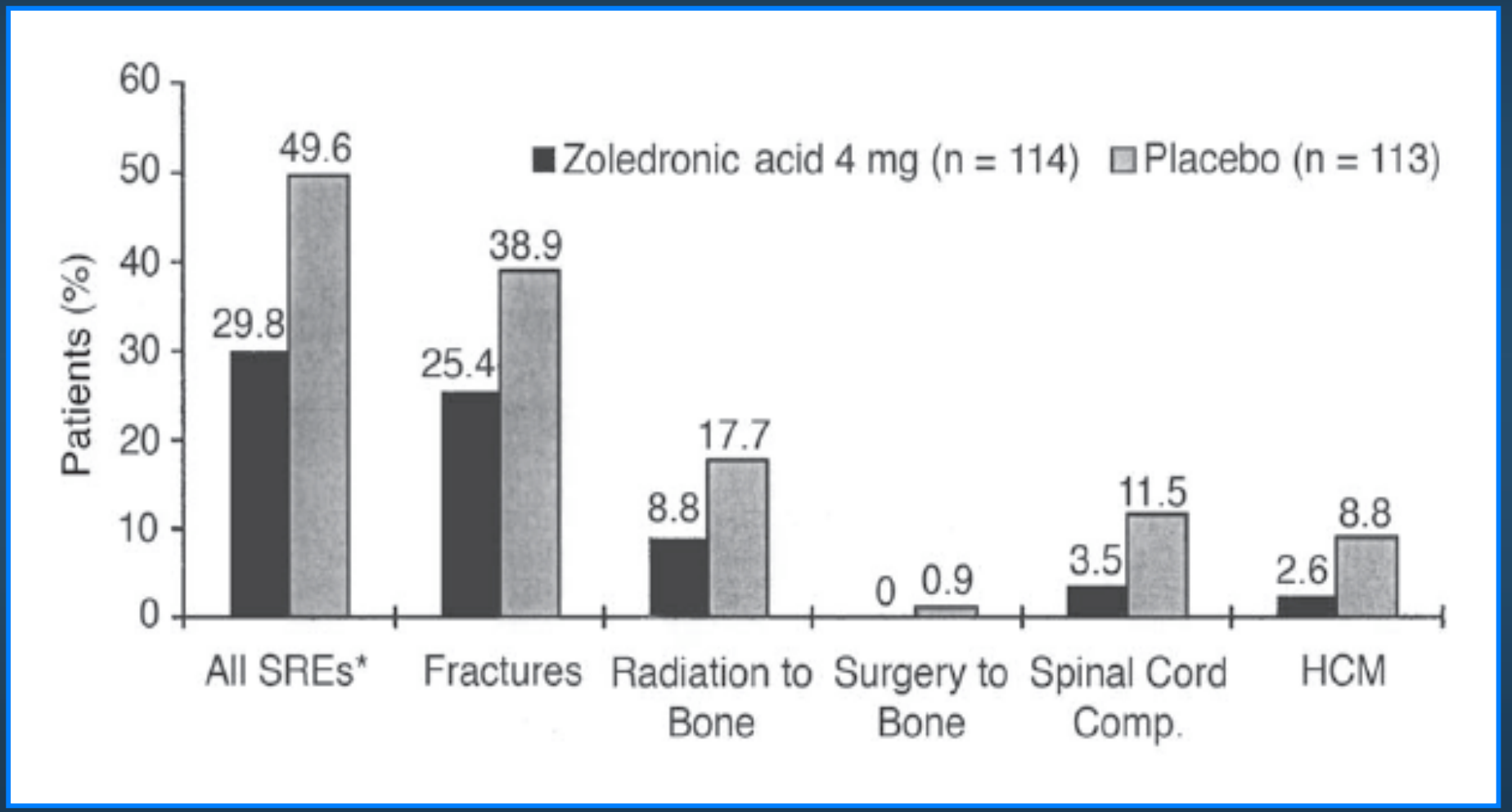
HR

Riduzione R 41%

Abbreviations: SRE, skeletal-related event; HCM, hypercalcemia of malignancy; NR, not reached.
*Cochran-Mantel-Haenszel test stratified by prior fracture.
†Cox regression (Wald test of the regression coefficient) stratified by prior fracture.
‡Andersen-Gill multiple-event analysis.[17]
§Wald test of the regression coefficient using robust variance; stratified by prior fracture.

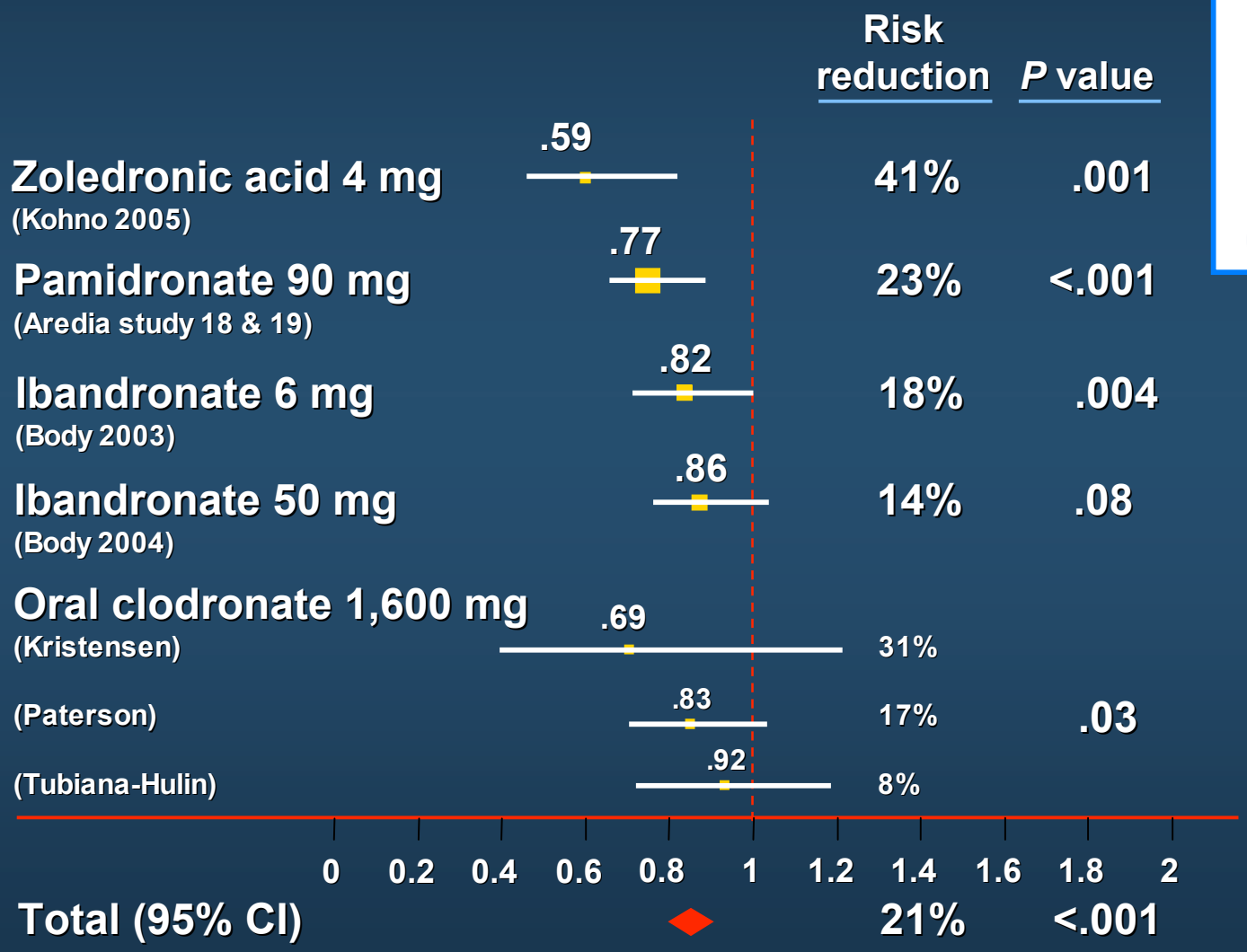
Kohno N et al. *J Clin Oncol*. 2005

Risultati ad 1 anno



Kohno N et al. *J Clin Oncol*. 2005

Cochrane Review



THE COCHRANE COLLABORATION®

Pavlakis N, et al. Cochrane Database Syst Rev. 2005

Bifosfonati nel carcinoma mammario (Cochrane Review)

L'utilizzo di bifosfonati (ev o per os):

- ↓ il rischio di eventi scheletrici
- ↓ l'incidenza di eventi scheletrici
- ↑ il tempo alla comparsa di eventi scheletrici
- ↓ il dolore nelle donne con metastasi ossee

Pavlakis N et al., The Cochrane Library, Issue 2, 2005

Bifosfonati: le indicazioni

	Indicazioni				
	HCM	Mammella	Mieloma Multiplo	Prostata	Altri tumori solidi
CLOD	✓	✓	✓		
PAM	✓	✓	✓		
ZOL	✓	✓	✓	✓	✓
IBAN	✓	✓			

✓ = Registrazione EU

✓ = Registrazione mondiale

Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases

Body J.J. Et al. Annals of Oncology 2003

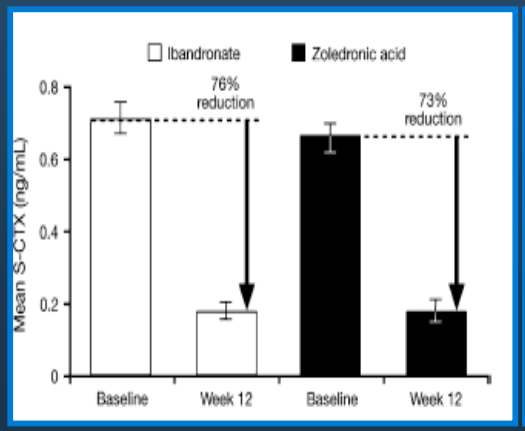
3 studi randomizzati in doppio-cieco, CON CONTROLLO PLACEBO

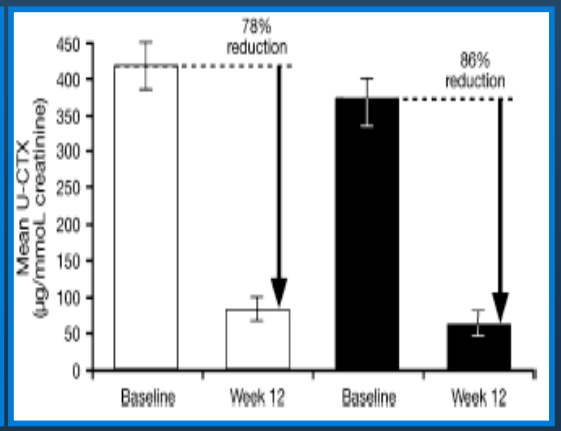
MF 4265 : IBADRONATO E.V. 2 e 6 mg ogni 3-4 settimane

MF 4434 : IBADRONATO OS

MF 4414 : IBADRONATO OS

Oral ibandronate is as active as intravenous zoledronic acid for reducing bone turnover markers in women with breast cancer and bone metastases

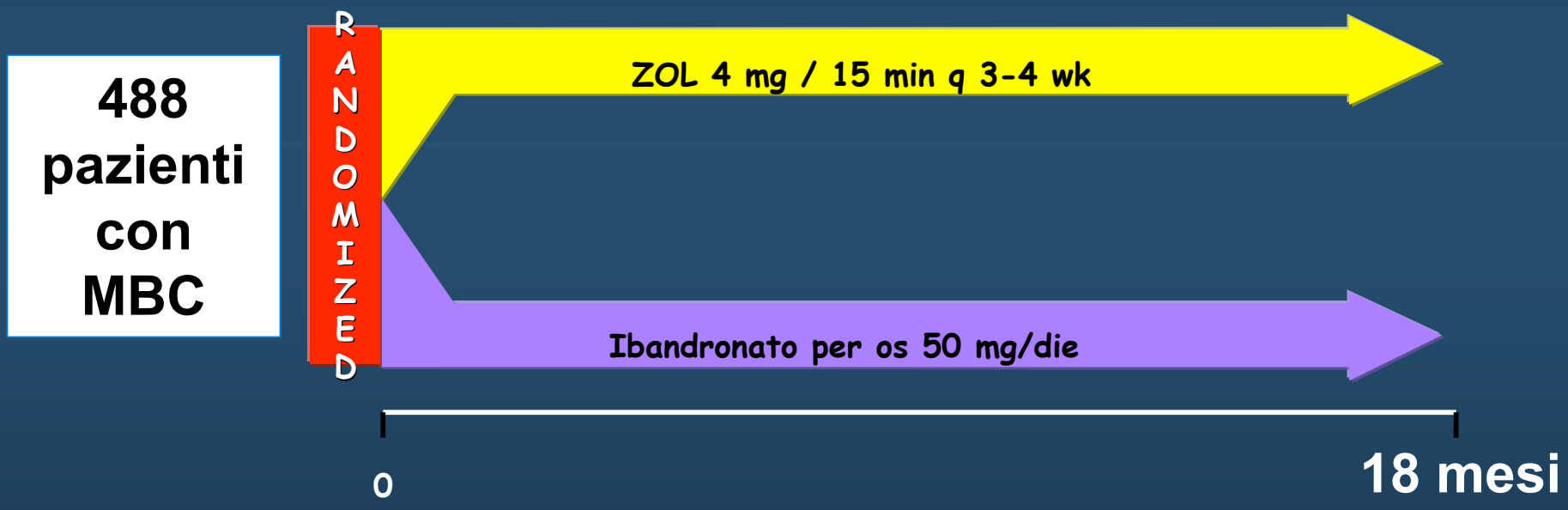




Body J.J. Et al. Annals of Oncology 2007

Ibandronato orale vs acido zoledronico nel carcinoma mammario con mts ossee

SWOG Trial S0308 -- USA



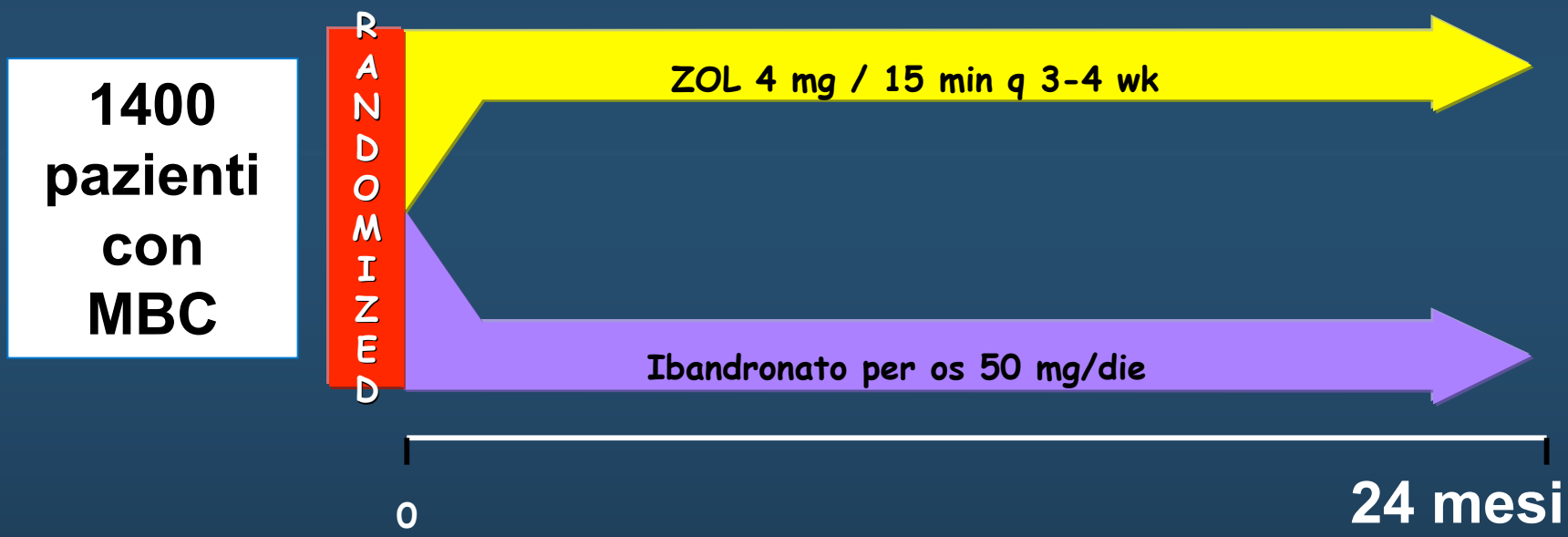
Inizio reclutamento inizio 2006, completamento 2010

Endpoint primario: proporzione di pazienti con almeno 1 SRE

Rivkin S., Bone 2006

Ibandronato orale vs acido zoledronico nel carcinoma mammario con mts ossee

ZICE Trial -- UK

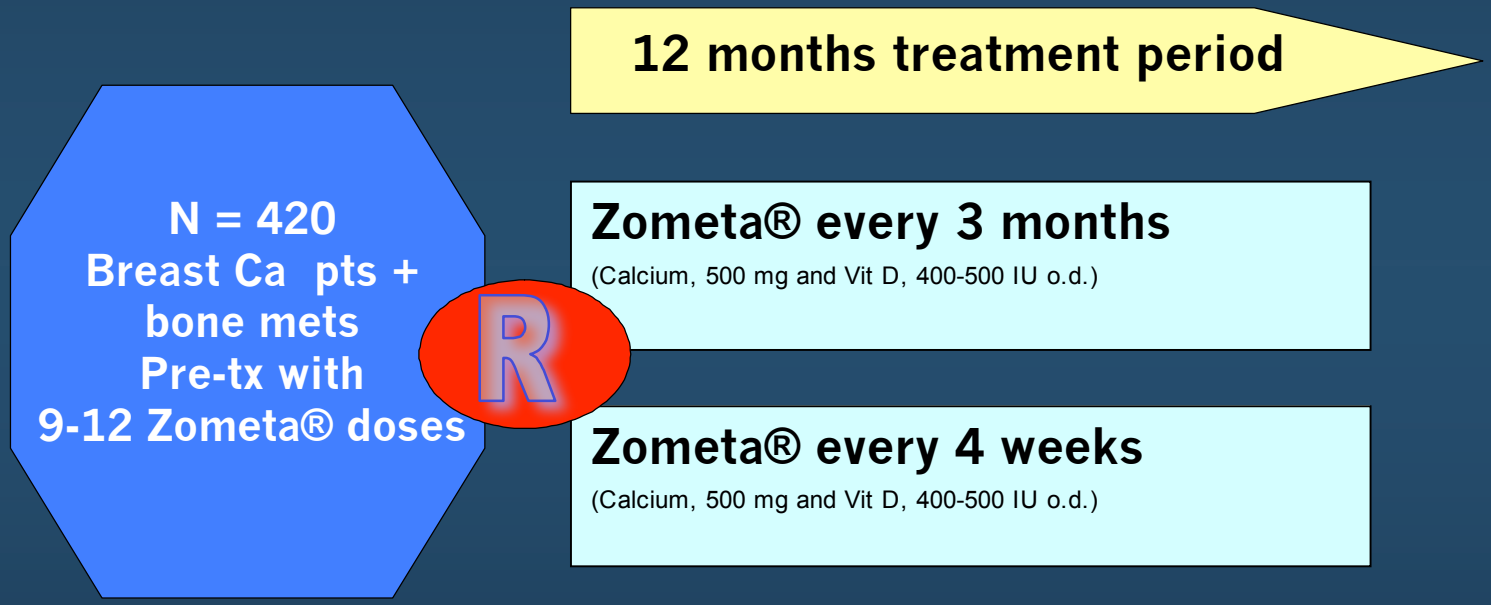


Inizio reclutamento FINE 2005

Endpoint primario: Frequenza e Timing SRE (Multiple Event Analysis)

Barrett-Lee PJ. Et al., Abstract 62 Bone 2006

Mts ossee da carcinoma mammario e TCR in corso: **ZOOM**



Arruolamento in corso

Mts ossee da carcinoma mammario e TCR in corso: **BISMARK**

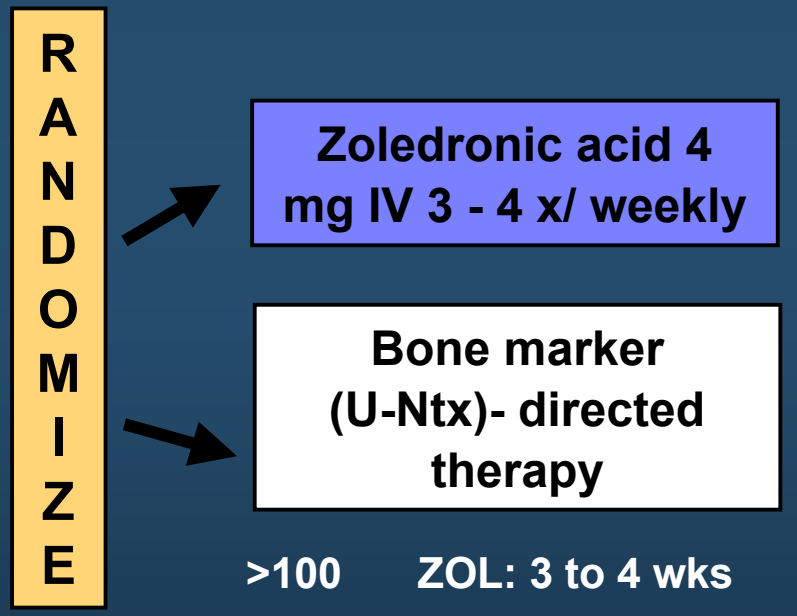
Marcatori di riassorbimento osseo per guidare la terapia con Zometa

Studio di non inferiorità tra braccio standard e somministrazione guidata dai markers
Primary endpoint: skeletal events

ARRUOLAMENTO IN CORSO
(previsti = 1.400 pazienti)

Risultati attesi per il 2011

PI: Robert Coleman



Bifosfonati nel Trattamento Adiuvante del Carcinoma Mammario: prevenzione delle metastasi ossee

Argomento controverso …. Valore non chiaro dei BF ….

	Duration of follow-up	Bone metastases	Disease-Free survival	Overall survival
Oral clodronate				
Jaschke et al.[30]	103 Months	= (P = 0.770)	NA	↑ (P = 0.049)*
Powels et al.[31]	10 Years	↓ (P = 0.043)[b]	NA	↑ (P = 0.048)
Saarto et al.[32]	10 Years	= (P = 0.35)	↓ (P = 0.01)	= (P = 0.13)
IV Pamidronate				
Kokufu et al.[33]	Median = 5 Years	↓ (P = 0.005)	= (P = 0.26)	= (P = 0.3)

* P value versus control group (standard systemic treatment)
[a]From Clemons and Rea[34]
[b]5-Year follow-up

In corso …

Study	No. of patients	Primary cancer	Treatment regimen
NSABP B-34	3,300	Stage I/II breast cancer	Clodronate (1,600 mg/day) vs. placebo for 3 yrs
AZURE (Coleman et al. [42])	3,300	Stage II/III breast cancer	Adjuvant therapy, with or without zoledronic acid (4 mg) for 5 yrs
ICE	1,400	Early breast cancer	i.v./oral ibandronate with or without capecitabine (six cycles) for 2 yrs
GAIN	3,000	Node-positive breast cancer	Epirubicin, paclitaxel, and cyclophosphamide with or without ibandronate or epirubicin, paclitaxel, cyclophosphamide, and capecitabine with or without ibandronate

Abbreviations: AZURE, Adjuvant zoledronic acid to reduce recurrence; GAIN, German Adjuvant Intergroup Node-Positive study; ICE, Ibandronate with or without Capecitabine in elderly patients with Early breast cancer; NSABP, National Surgical Adjuvant Breast and Bowel Project.

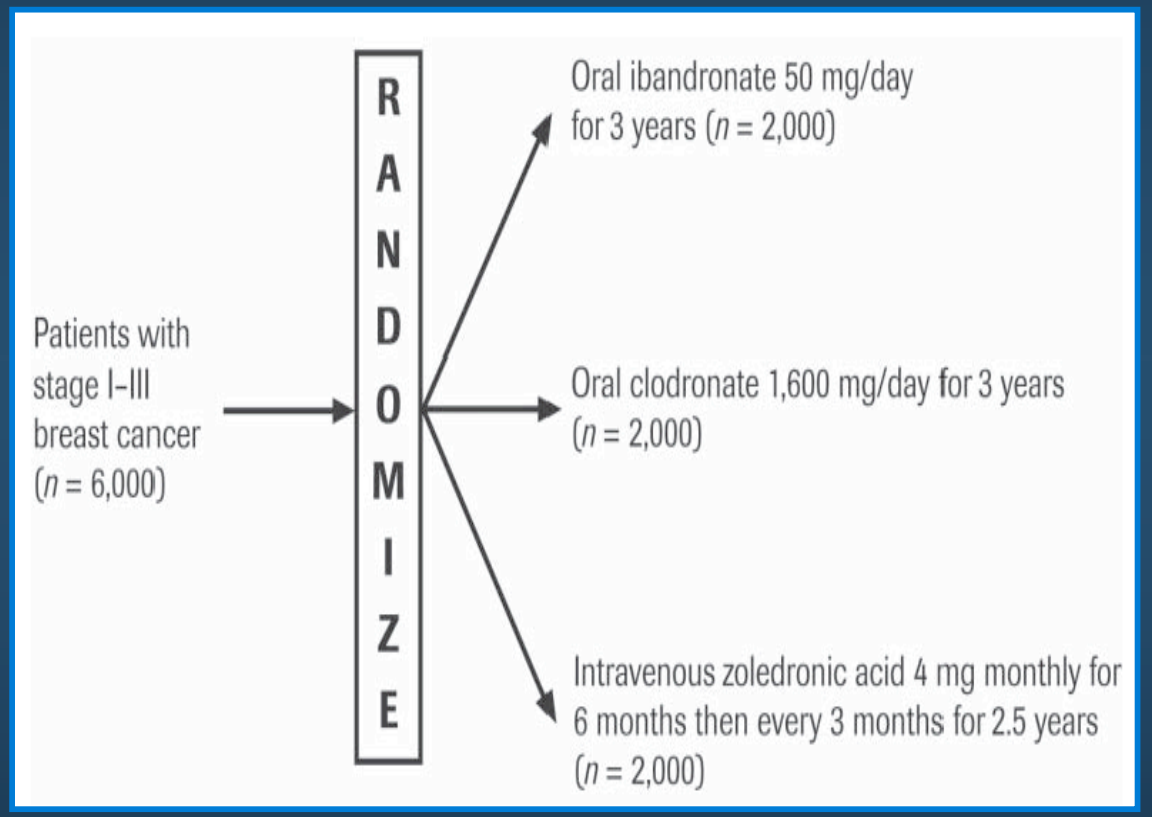
Bifosfonati nel Trattamento Adiuvante del Carcinoma Mammario: prevenzione delle metastasi ossee

SWOG S0307

Avviato a Fine 2005

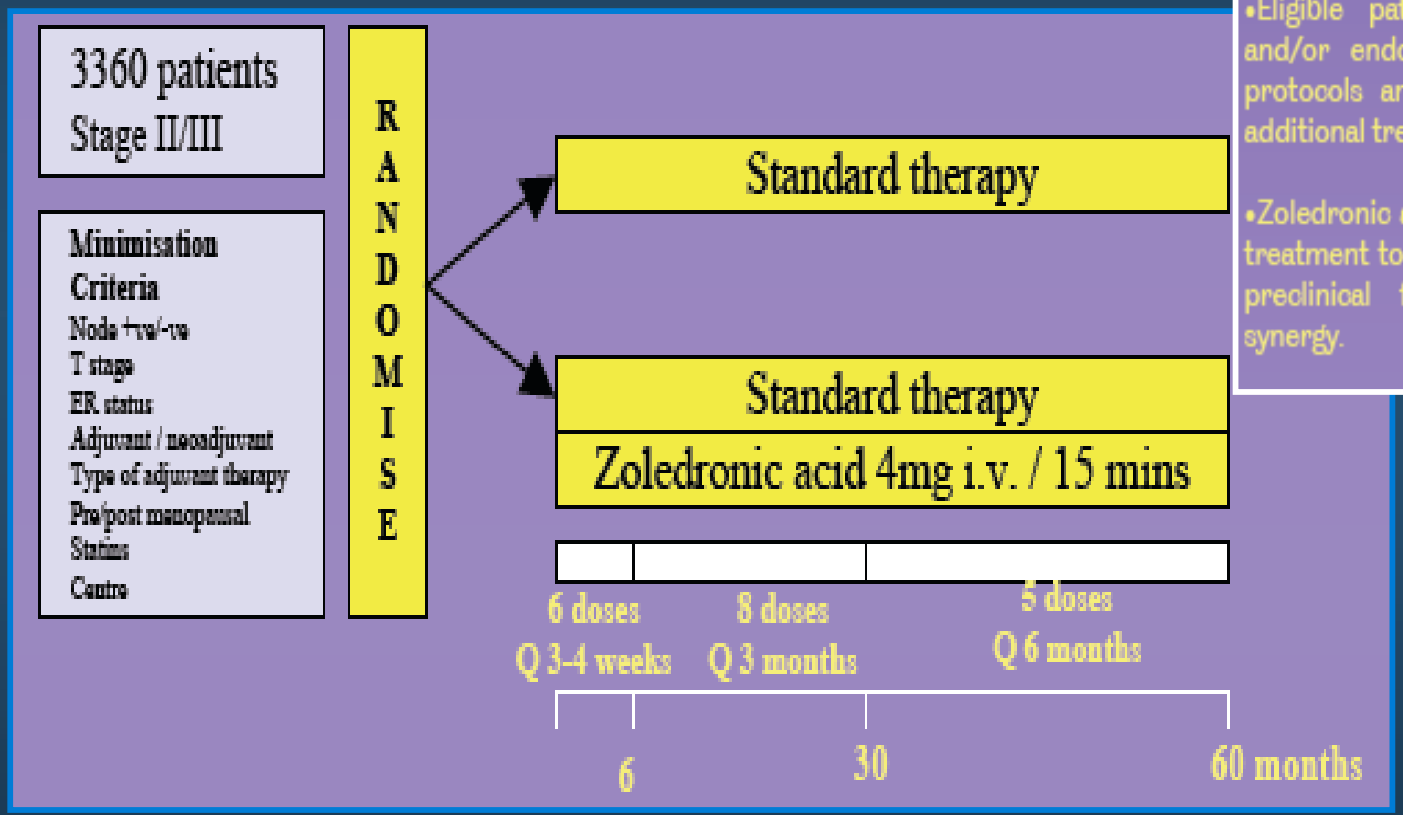
Randomizzazione ad uno dei 3 bifosfonati in aggiunta alla terapia adiuvante standard

EP PRIMARIO: DFS



Zoledronic acid is well tolerated and can be safely administered with adjuvant chemotherapy – First safety data from the AZURE trial (BIG01/04).

R. Coleman*, H.Thorpe, D. Cameron, R. Bell, D. Dodwell, M. Keane, M. Gil, J. Cousins and R. Burkinshaw on behalf of the AZURE investigators, *Academic Unit of Clinical Oncology, Weston Park Hospital, Sheffield, UK.



- Eligible patients received (neo)adjuvant CT and/or endocrine therapy according to local protocols and were randomized to either no additional treatment or Zol as shown in *Figure 1.*
- Zoledronic acid was administered after each CT treatment to exploit any clinical advantage of the preclinical findings of sequence dependent synergy.

Valutazione dell'effetto di A.Z. sulla DFS

Sabcs 2006

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R. Coleman*, H.Thorpe, D. Cameron, R. Bell, D. Dodwell, M. Keane, M. Gil, J. Cousins and R. Burkinshaw on behalf of the AZURE investigators, *Academic Unit of Clinical Oncology, Weston Park Hospital, Sheffield, UK.

SAE	CT	CT+Zol
Neutropaenic sepsis	157 (9.8%)	155 (9.7%)
Infection	74 (4.6%)	75 (4.7%)
Haematological	58 (3.3%)	46 (2.8%)
Vomiting	18 (1.1%)	38 (2.4%)
Pyrexia	18 (1.1%)	37 (2.3%)

AE (All grades)	CT	CT+Zol
Alopecia	2955 (38%)	3058 (39%)
Fatigue	2084 (27%)	2065 (26%)
Nausea	2027 (26%)	2026 (26%)
Constipation	1048 (14%)	1155 (15%)
Vomiting	760 (10%)	790 (10%)
Mucositis	748 (10%)	767 (10%)
Myalgia/arthralgia	528 (7%)	686 (9%)
Infection	411 (5%)	369 (5%)
Diarrhoea	383 (5%)	401 (5%)
Indigestion	345 (4%)	362 (5%)

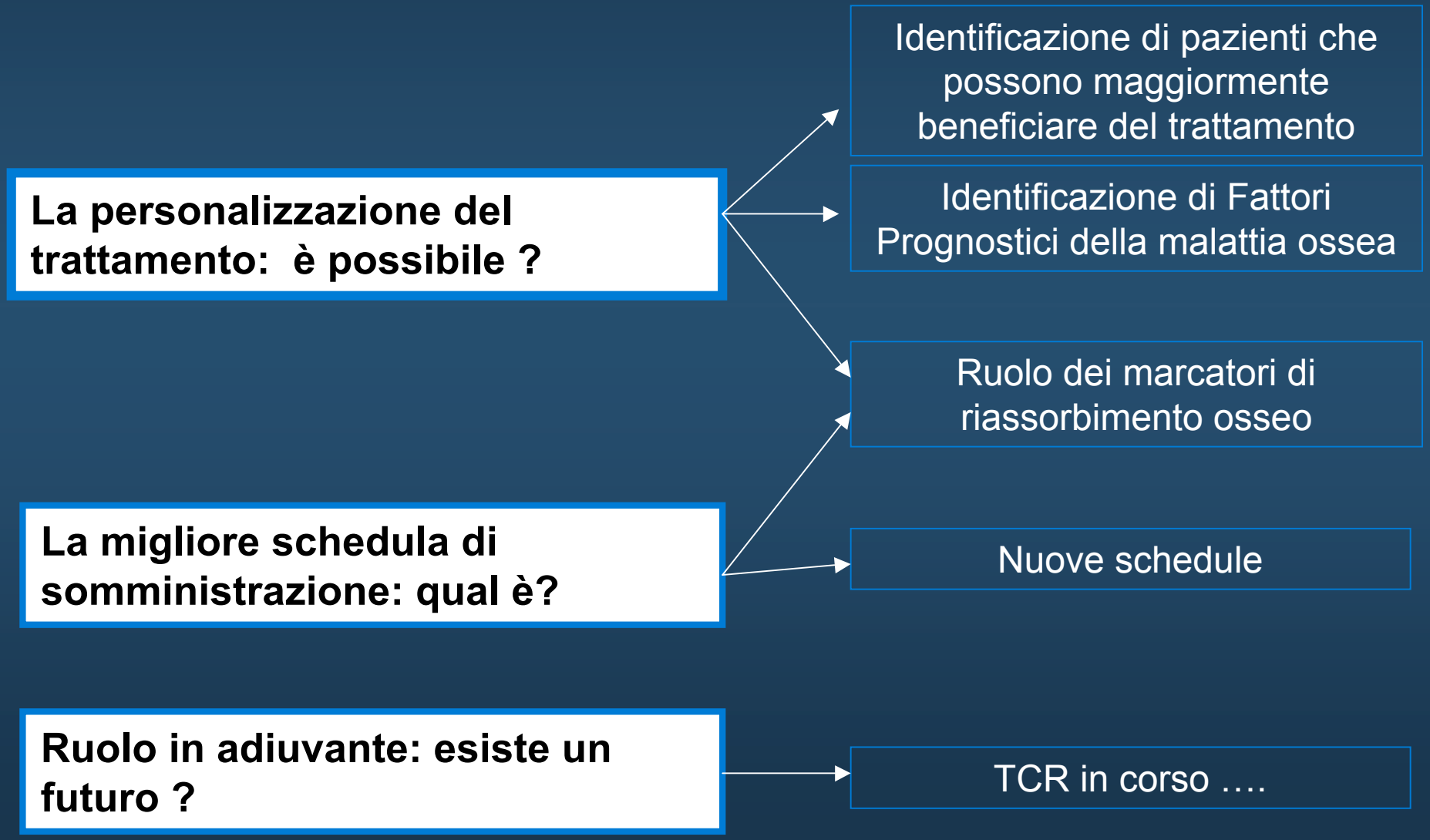
- Seven cases of osteonecrosis of the jaw (ONJ) have been reported following a median of 8 treatments with Zol (range 1-12).
- Advice on dental health and detection and management of ONJ is provided to all investigators and patients.

Conclusions:

- This is the largest safety analysis of Zoledronic acid in patients without the confounding influence of metastatic disease and indicates that Zoledronic acid is well tolerated and can be safely combined with adjuvant CT without any increase in myelotoxicity or effect on dose intensity.
- First efficacy data are anticipated in 2008.

Sabcs 2006

I bifosfonati riducono la morbidità scheletrica ma … come usarli al meglio ?



Grazie per l'attenzione

“ Tramonto a Camogli ”