



## VII Sessione: I NUOVI FARMACI OSTEO-ONCOLOGICI NELLE NEOPLASIE BIG KILLERS

# Bone targeted therapy nella malattia metastatica del carcinoma mammario

**Giovanna Garufi**

*Università Cattolica del Sacro Cuore, Roma, Italy*

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# Topics



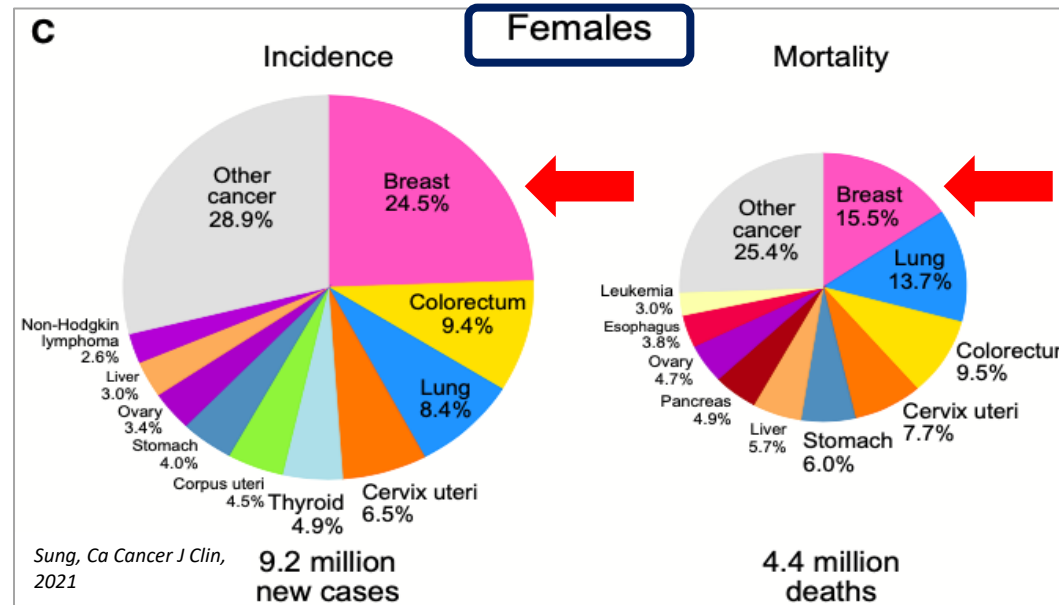
- **Incidence and Impact on QoL of Breast Cancer Bone Metastases**
- **Bone Targeted Agents in Bone Metastatic Breast Cancer**
- **Future perspective: Prevention of Bone Metastases in Early BC**

# Topics



- **Incidence and Impact on QoL of Breast Cancer Bone Metastases**
- **Bone Targeted Agents in Bone Metastatic Breast Cancer**
- **Future perspective: Prevention of Bone Metastases in Early BC**

# Incidence of BC and BC Bone Metastases



**Table 1.** Incidence of bone metastases at postmortem examination in different cancers

*Coleman, Clin Cancer Res, 2006*

Primary tumor	Incidence of bone metastases (%)
Breast	73
Prostate	68
Thyroid	42
Kidney	35
Lung	36
Gastrointestinal tract	5

*Colleoni, JCO, 2000*

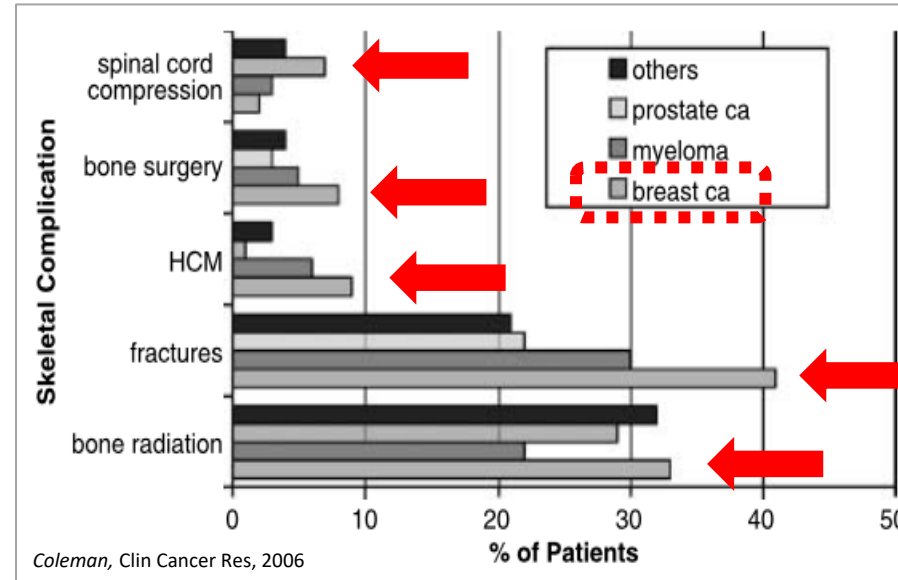
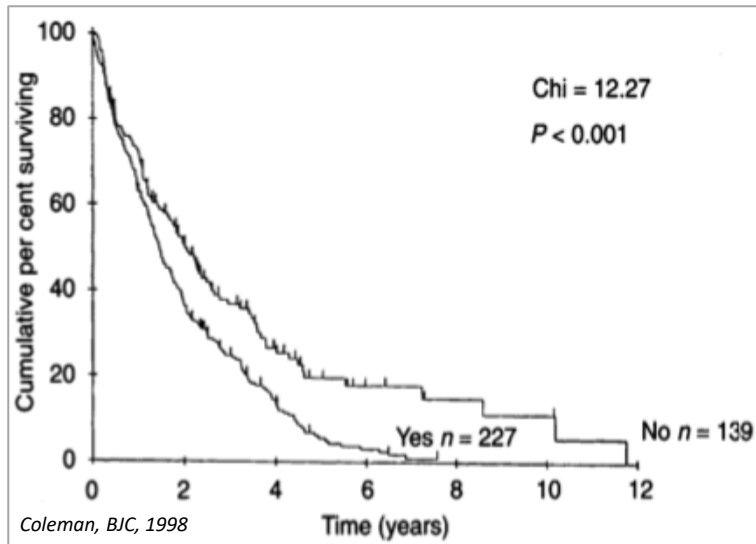
**Recurrence in bone at any time**

	No. of Events	% of Patients*	Incidence (%)				P
			2-Year	5-Year	10-Year	15-Year	
Total	391	32.1	21.1	32.0	36.7	38.6	
Nodal status							
Node-negative	39	27.9	16.4	25.8	31.2	—	.08
1-3 positive nodes	153	29.7	18.8	30.4	35.8	38.8	
≥ 4 positive nodes	199	35.2	24.2	35.1	38.9	—	
Pathologic tumor size							
≤ 2 cm	119	28.6	20.5	29.0	34.6	—	.17
> 2 cm	259	34.1	21.8	33.3	37.4	40.0	

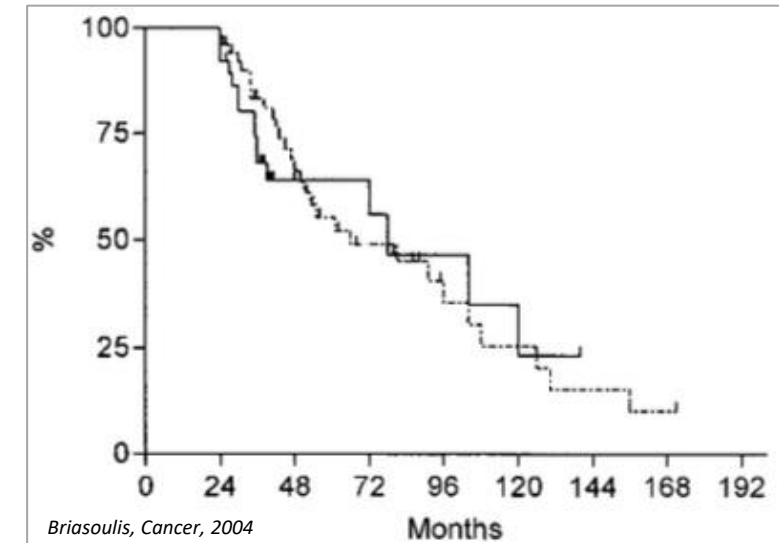
# Impact of BC Bone Metastases on Survival and QoL

## Skeletal-related events (SREs)

### Survival after first recurrence in the bone



### Survival after first recurrence in the bone



- Frequency of Breast Cancer Bone Metastases
- Negative impact of Bone Metastases on QoL
  - Relatively longer survival of Breast Cancer Patients



Research focus on pathophysiology, treatment and prevention of Bone Metastases from BC

# Topics

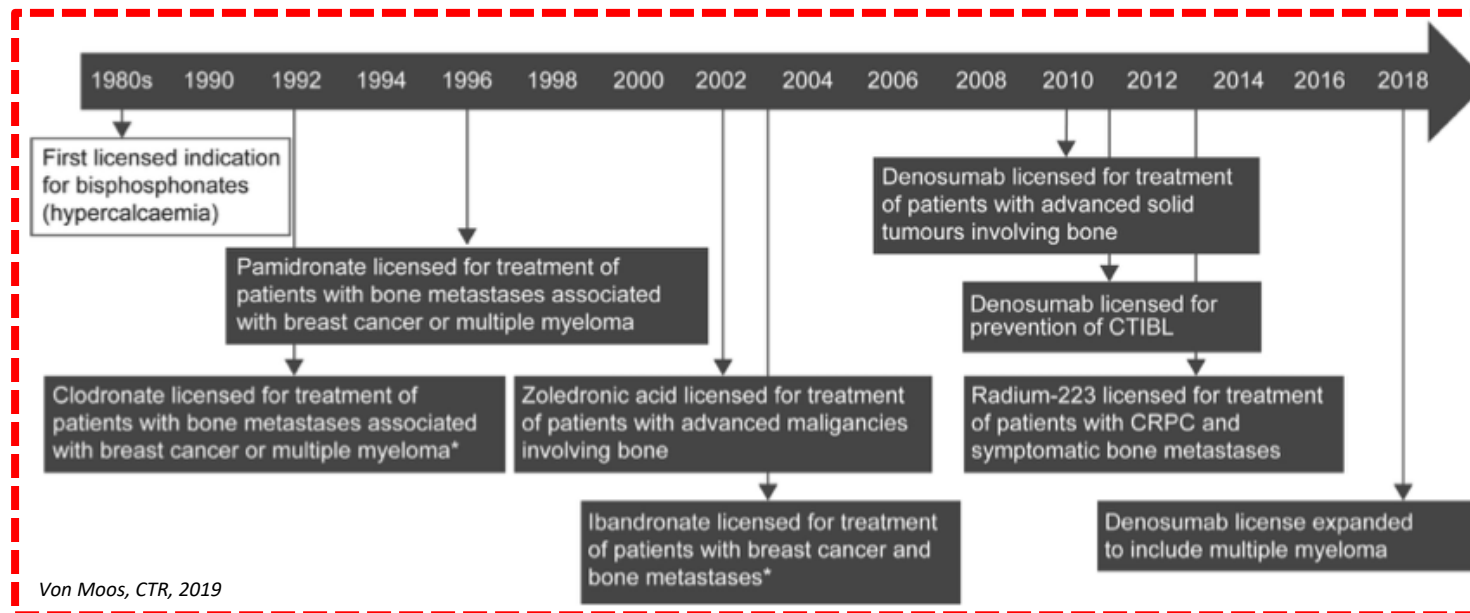


- **Incidence and Impact on QoL of Breast Cancer Bone Metastases**
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# Management of BC bone metastases: BTA

## Conventional treatments for BC bone metastases

Therapeutic Options	Main Indications
Systemic endocrine therapy Systemic chemotherapy Systemic targeted therapy	Disease control
Adjuvant bone-targeted therapy (bisphosphonates, denosumab)	SREs, bone loss and metastasis prevention
Radiotherapy	Bone pain relief Bone recalcification Metastatic spinal cord compression control (administered with concomitant steroids)
Surgical intervention	Bone pain relief Independence/mobility improvement SREs prevention
Analgesics	<i>Shao, Cells, 2022</i> Chronic pain relief



## Goal:

- SRE prevention
- Pain reduction

↓  
QoL improvement

# BTA: Bisphosphonates and Denosumab

## The 3 generations of Bisphosphonates

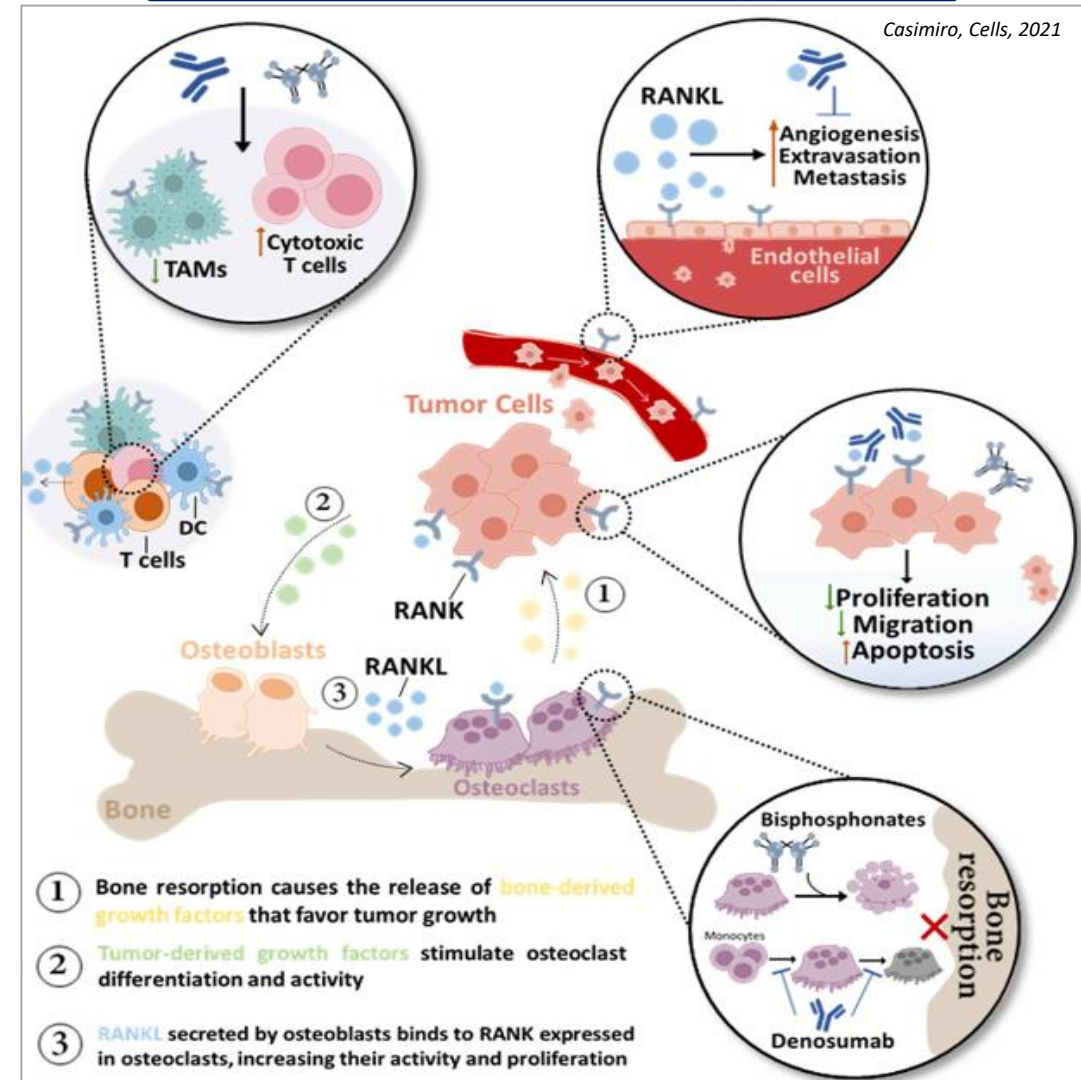
1st Generation	2nd Generation	3rd Generation
clodronate	alendronate	zoledronat
etidronate	ibandronate	minodronate
<i>Gampenrieder, Breast Care, 2014</i>	pamidronate	risedronate

## Differences among 3 generations of bisphosphonates

Bisphosphonates	Generation	Name	R1	R2
Non-Nitrogenous	First	Etidronate	-OH	-CH3
		Clodronate	-Cl	-Cl
	Second	Tiludronate	-H	<chem>*Sc1ccc(Cl)cc1</chem>
		Pamidronate	-OH	<chem>CCCCN</chem>
Nitrogenous		Alendronate	-OH	<chem>CCCCCN</chem>
		Neridronate	-OH	<chem>CCCCCCCCN</chem>
		Olpadronate	-OH	<chem>CCCN(C)C</chem>
	Third	Ibandronate	-OH	<chem>CCN(C)CCCC</chem>
		Risedronate	-OH	<chem>CCc1cccnc1</chem>
		Zoledronic acid	-OH	<chem>CCn1cncn1</chem>

Shao, Cells, 2022

**Denosumab:**  
the first, and to date only, RANKL-targeted monoclonal antibody





# BTA: Bisphosphonates

## Studies of BTA for solid tumors with bone metastases/MM

Treatment	SRE (%)	Median time to first SRE (days)	Other end points
<i>Coleman, Nature Reviews, 2020</i>			
<b>Breast cancer</b>			
Clodronate <sup>a</sup> vs placebo	NE	NE	SMR: 219 vs 305
Pamidronate vs placebo	43 vs 56	399 vs 213	Improved QOL and pain
Pamidronate vs placebo	56 vs 67	317 vs 210	Improved QOL and pain
Zoledronate vs placebo	30 vs 50	NR vs 364	Improved pain
Zoledronate vs pamidronate	43 vs 45	310 vs 174	SRE: 20% risk reduction
Oral ibandronate <sup>a</sup> vs placebo	NE	632 vs 454	SMPR: 0.99 vs 1.15
Intravenous ibandronate <sup>a</sup> vs placebo	51 vs 62	354 vs 232	SMPR: 1.19 vs 1.48
Denosumab vs zoledronate	NE	NR vs 804	SRE: 23% risk reduction

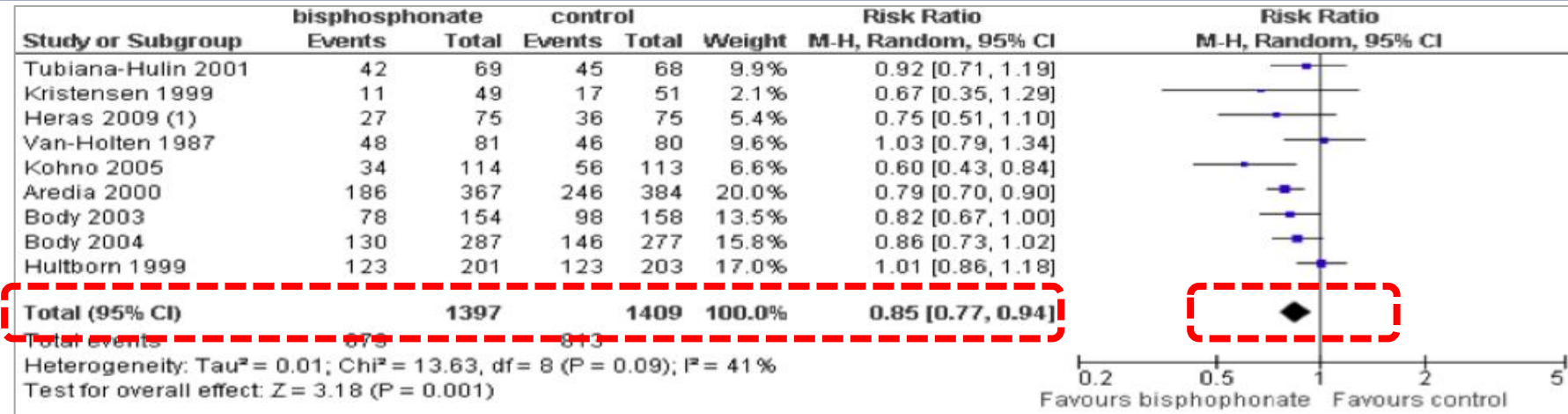
## Zoledronic Acid vs Placebo in Japanese Women With Bone Metastases From BC: A Randomized, Placebo-Controlled Trial

Primary endpoint	SRE Rate, Events/Year		SRE Rate Ratio*		P‡
	Zoledronic acid, 4 mg (n = 114)	Placebo (n = 113)	Unadjusted Ratio	Adjusted Ratio†	
All patients	0.63	1.10	0.57		.016
No. of events/patient years	65/103.5	109/99.5			
Patients with prior fracture	1.55	1.91	0.81	0.61	.027†
No. of events/patient years	39/25.2	53/27.8			
Patients without prior fracture	0.33	0.78	0.43		
No. of events/patient years	26/78.2	56/71.7			

*Kohn, JCO, 2005*

# BTA: Bisphosphonates

## Forest plot of comparison: Overall risk of SRE in BC bone metastases: bisphosphonate versus control



## Median time to SRE in BC bone metastases: bisphosphonate versus control

Study	Treatment (T)	Control (C)	N	TSE-(T)	TSE-(C)	T/C	P value
<b>Breast cancer with bone metastases (BCBM): bisphosphonate versus control</b>							
Kohno 2005	Zolen-dronate 4 mg	Placebo	228	NR	52	NR	0.007
Aredia 2000	Pamidronate 90 mg i.v.	Placebo	751	12.7	7	1.81	< 0.001
Hultborn 1999	Pamidronate 60 mg i.v.	Placebo	404	11.8	8.4	1.4	0.006

## Bone pain in BC bone metastases: bisphosphonate versus control

Study	Treatment	Control	N	Pain tool used	Reviewer rating	Reported value
<b>Breast cancer with bone metastases: bisphosphonate versus control</b>						
Kohno 2005	Zolendronate 4 mg	Placebo	228	Brief Pain Inventory	Significantly better	Not reported
Aredia 2000	Pamidronate 90 mg i.v.	Placebo	751	Yes. Reference to validation	Significantly better in favour of pamidronate	0.001
Martoni 1991	Clodronate i.v.	Placebo	33	Scott-Huskisson visual analog method	No difference	NS
Tubiana-Hulin 2001	Clodronate 1600 mg/daily	Placebo	137	Visual pain scale. No ref-	Significantly better	0.01
Body 2004	Ibandronate 50 mg p.o.	Placebo	564	Yes - patient-rated scale	Significantly better	0.001

# BTA: Bisphosphonates

## QoL in BC bone metastases: bisphosphonate versus control

Study	Treatment	Control	N	Pain tool used	Reviewer rating	Reported value	P
<b>Breast cancer with bone metastases: bisphosphonate versus control</b>							
Kohno 2005	Zolendronate 4 mg	Placebo	228	Brief Pain Inventory	Significantly better	Not reported	
Aredia 2000	Pamidronate 90 mg i.v.	Placebo	751	Yes. Reference to validation	Significantly better in favour of pamidronate	0.001	
Hultborn 1999	Pamidronate 60 mg i.v.	Placebo	404	Yes- Questionnaire + visual analog scale	Trend better	NS	
Martoni 1991	Clodronate i. v.	Placebo	33	Scott-Huskisson visual analog method	No difference	NS	
Van Holten 1987	Pamidronate 300 mg/daily	Open	144	Within a validated QoL in-	Significantly better	0.007	
Tripathy 2004	Ibandronate 20 mg or 50 mg p.o.	Placebo	287 (20 mg ibandronate and placebo arms)	Yes - 4 point scale	Trend better for 20 mg arm versus placebo; No difference with 50 mg ibandronate	0.07 (20 mg ibandronate versus placebo)	
Body 2003	Ibandronate 6 mg i.v.	Placebo	462	Yes - 4 point scale. No reference to validation in abstract	Significantly better	< 0.001	
Body 2004	Ibandronate 50 mg p.o.	Placebo	564	Yes - patient-rated scale	Significantly better	0.001	

## Median Survival in BC bone metastases: bisphosphonate versus control

Study	Treatment (T)	Control (C)	N	MS - T	MS- C	T/C	P value
<b>Breast cancer with bone metastases: bisphosphonate versus control</b>							
Kohno 2005	Zolendronate 4 mg	Placebo	288	-	-	-	-
Aredia 2000	Pamidronate 90 mg i.v.	Placebo	751	19.8	17.8	1.11	0.98
Hultborn 1999	Pamidronate 60 mg i.v.	Placebo	404	18.3	18.3	1.00	NS
Body 2004	Ibandronate 50 mg p.o.	Placebo	564	-	-	-	NS
Martoni 1991	Clodronate i.v./i.m.	Placebo/open	33	-	-	-	-
Tubiana-Hulin 2001	Clodronate 1600 mg p.o./daily	Placebo	137	-	-	-	-
Kristensen 1999	Clodronate 800 mg b.i.d	Open	100	18.3	18	1.02	0.97
Paterson 1993	Clodronate 1600 mg p.o./daily	Placebo	185	-	-	-	0.198

# BTA: Denosumab

Phase III RCTs comparing zoledronic acid (4 mg every 4 weeks iv) with denosumab (120 mg every 4 weeks sc) in bone metastatic solid tumors

Author, year [ref.]	Patients, n	Population	Results (primary endpoint)
Stopeck et al., 2010 [25]	2,046	breast cancer	delayed time to first on-study SRE (HR 0.82, $p < 0.001$ non-inferiority, $p = 0.01$ superiority)
Fizazi et al., 2011 [26]	1,901	prostate cancer	delayed time to first on-study SRE (HR 0.82, $p = 0.0002$ non-inferiority, $p = 0.008$ superiority)
Henry et al., 2011 [24]	1,776	solid tumors (except breast or prostate) and multiple myeloma	delayed time to first on-study SRE (HR 0.84, $p = 0.0007$ non-inferiority, $p = \text{n.s.}$ superiority)
Henry et al., 2014 [27]	1,597	solid tumors (except breast or prostate) with multiple myeloma excluded	delayed time to first on-study SRE (HR 0.81, $p = 0.017$ superiority)

Gampenrieder, Breast Care, 2014

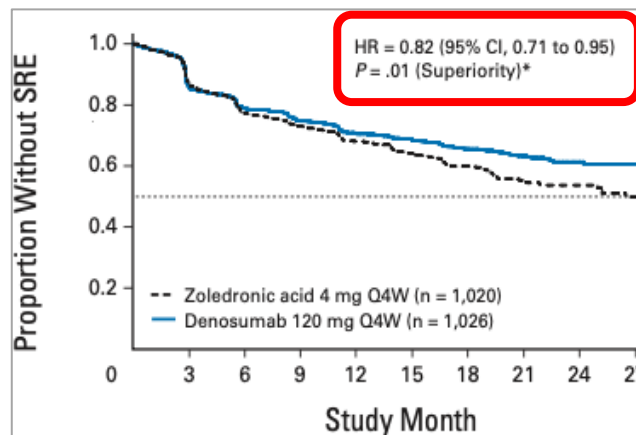
Integrated analysis of 3 head-to-head studies (n=5723)

Parameter	Hazard ratio (95% CI)*	P-value
Time to first SRE (primary endpoint)	0.83 (0.76–0.90)	$< 0.001$
Time to multiple SREs	0.83 (0.76–0.90)	$< 0.001$
Pain worsening	0.92 (0.86–0.99)	0.026
Overall survival	0.98 (0.91–1.06)	0.617
Disease progression	1.02 (0.96–1.09)	0.697

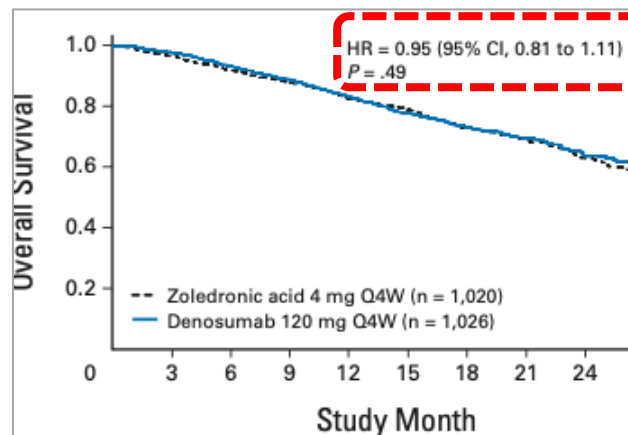
Von Moos, CTR, 2019

Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in BC Patients

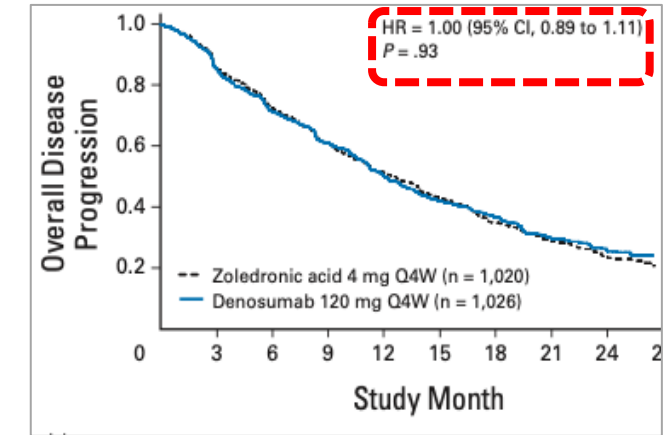
Time to first SRE



Overall survival



Time to disease progression



# BTA: Denosumab

## BC trial: Adverse Events

	Zoledronic Acid Q4W (4 mg) (n = 1,013)		Denosumab Q4W (120 mg) (n = 1,020)	
	No.	%	No.	%
<b>Overall safety summary</b>				
Any adverse event	985	97.2	977	95.8
CTCAE grade $\geq 3$ adverse events	635	62.7	609	59.7
CTCAE grade $\geq 3$ adverse events occurring with $\geq 5\%$ frequency in either group				
Neutropenia	93	9.2	87	8.5
Dyspnea	61	6.0	82	8.0
Anemia	68	6.7	69	6.8
Fatigue	63	6.2	62	6.1
Adverse events leading to treatment discontinuation	125	12.3	98	9.6
Serious adverse events	471	46.5	453	44.4
<b>Adverse events of interest</b>				
Infectious adverse events	494	48.8	473	46.4
Infectious serious adverse events*	83	8.2	71	7.0
New primary malignancy	5	0.5	5	0.5
Adjudicated positive ONJ†	14	1.4	20	2.0
Resolved	6 of 14	42.9	10 of 20	50.0
Ongoing	1 of 14	7.1	2 of 20	10.0
Continued until death	5 of 14	35.7	5 of 20	25.0
Unknown‡	2 of 14	14.3	3 of 20	15.0
Local infection	9 of 14	64.3	10 of 20	50.0
Surgical treatment	7 of 14	50.0	7 of 20	35.0
Limited surgery	7 of 14	50.0	7 of 20	35.0
Bone resection	0	0	0	0
Acute phase reactions (first 3 days)§	277	27.3	106	10.4
Adverse events potentially associated with renal toxicity¶	86	8.5	50	4.9
Adverse events potentially associated with renal toxicity occurring with $\geq 1\%$ frequency¶				
Increased blood creatinine	41	4.0	31	3.0
Renal failure	25	2.5	2	0.2
CTCAE grade $\geq 3$ adverse events potentially associated with renal toxicity	22	2.2	4	0.4
Serious adverse events potentially associated with renal toxicity	15	1.5	2	0.2

## Summery of AEs

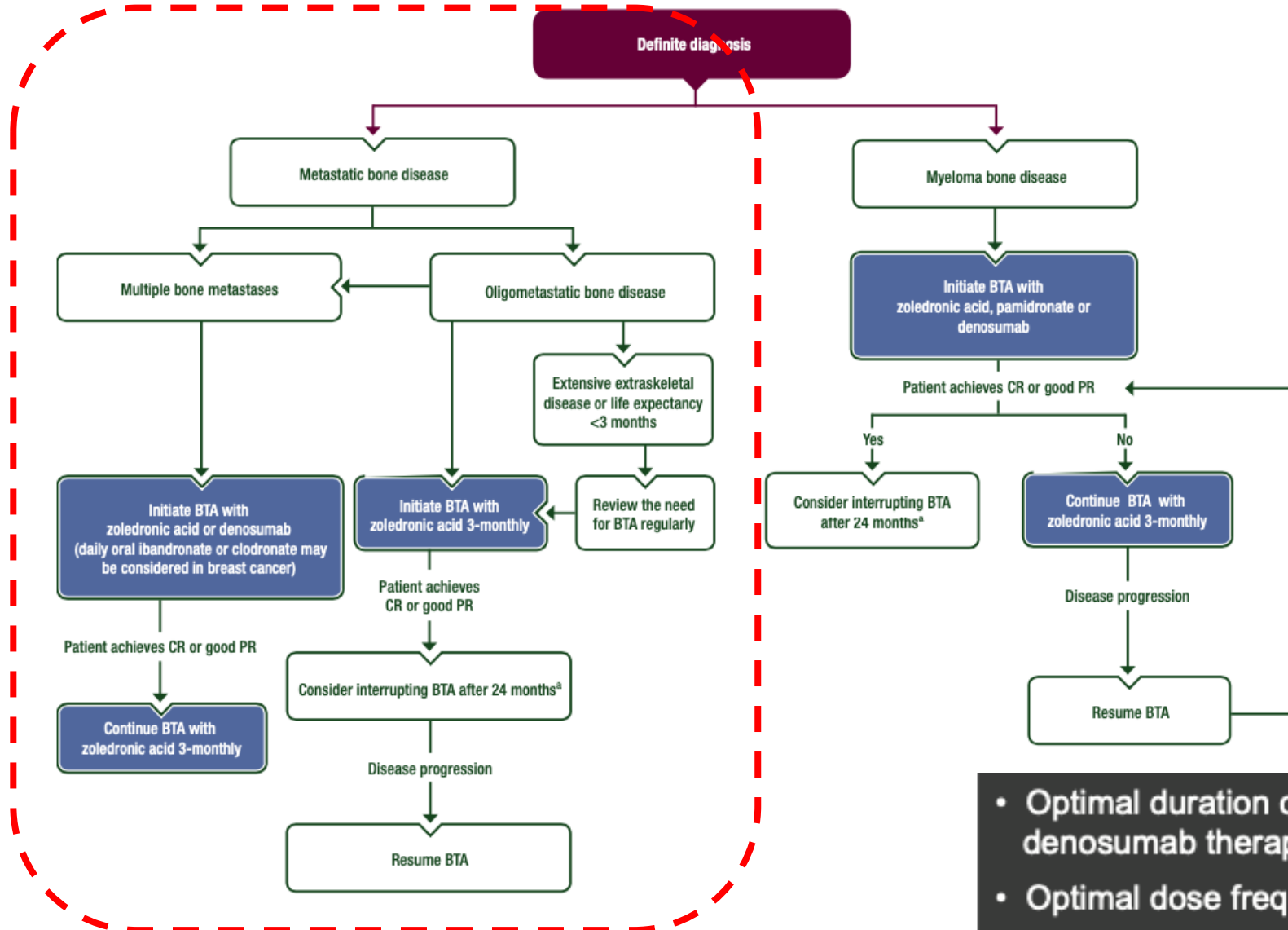
	Denosumab Events/Total	ZA Events/Total	RR (95% CI)†
Any AEs			
Stopeck et al <sup>25</sup>	977/1020	985/1013	0.98 (0.97-1.00)
Henry et al <sup>24</sup>	841/878	842/878	0.99 (0.98-1.02)
Fizazi et al <sup>23</sup>	916/943	918/945	1.00 (0.98-1.02)
Total	2734/2841	2745/2836	0.99 (0.98-1.00)
Serious AEs			
Stopeck et al <sup>25</sup>	453/1020	471/1013	0.95 (0.87-1.05)
Henry et al <sup>24</sup>	552/878	581/878	0.95 (0.89-1.02)
Fizazi et al <sup>23</sup>	594/943	568/918	1.04 (0.98-1.13)
Total	1599/2841	1620/2809	0.99 (0.94-1.03)
AEs associated with renal impairment			
Stopeck et al <sup>25</sup>	50/1020	86/1013	0.58 (0.41-0.81)
Henry et al <sup>24</sup>	73/878	96/878	0.76 (0.57-1.02)
Fizazi et al <sup>23</sup>	139/943	153/918	0.91 (0.74-1.12)
Total	262/2841	335/2809	0.76 (0.59-0.98)*
ONJ			
Stopeck et al <sup>25</sup>	20/1020	14/1013	1.42 (0.72-2.79)
Henry et al <sup>24</sup>	10/878	11/878	0.91 (0.39-2.13)
Fizazi et al <sup>23</sup>	22/943	12/918	1.78 (0.89-3.58)
Total	52/2841	37/2809	1.39 (0.91-2.11)

Sun, Am J Clin Oncol, 2013



# BTA: Guidelines

## Algorithm for use of BTA for bone metastases bone disease



Open Issues

- Optimal duration of bisphosphonate and denosumab therapy based on risk/benefit ratio
- Optimal dose frequency

# BTA: Guidelines

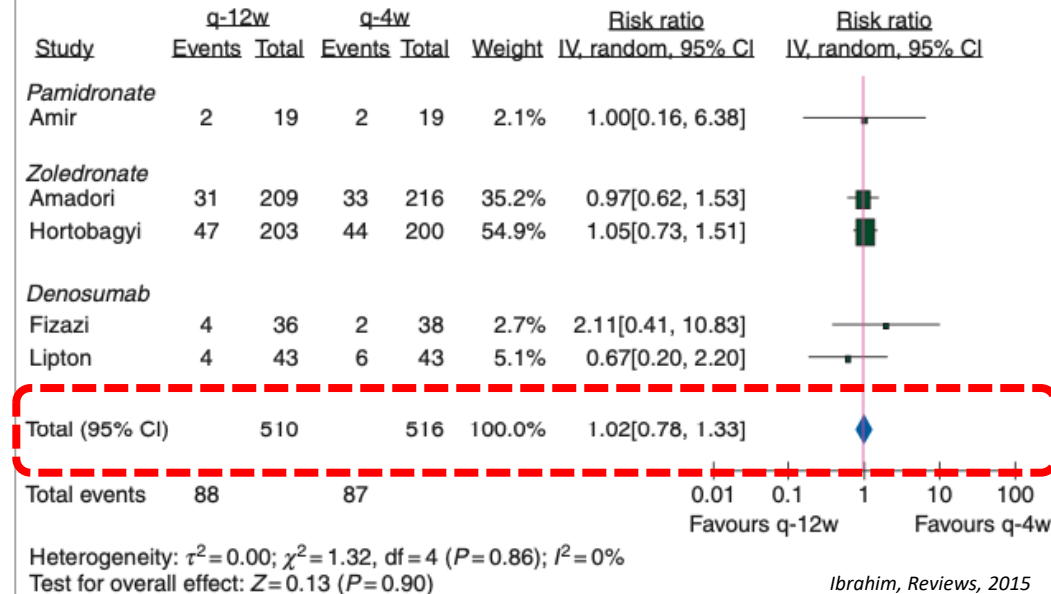
Optimal dose frequency: de-escalation vs standard dosing

## Dosing Interval Non-Inferiority Trials: Zoledronic Acid

Study and Dosing Interval	No. of Patients Completing Study (%)	Prior IV BMA	% With SRE at Baseline	Median Time to First SRE (months)	Skeletal Morbidity Rate	SRE Rate
CALGB 70604 every 4 weeks	212 of 427 (50)	No	26.2	15.7	0.4*	29.5
			Breast cancer cohort	Entire study population	Entire study population	Entire study population
CALGB 70604 every 12 weeks	178 of 428 (42)	No	25.7	16.8	0.4	28.6
			Breast cancer cohort	Entire study population	Entire study population	Entire study population
ZOOM every 4 weeks	142 of 216 (66)	Yes	57	NR†	0.22‡	15
ZOOM every 12 weeks	149 of 209 (71)	Yes	57	NR†	0.26	15
OPTIMIZE-2 every 4 weeks	106 of 200 (53)	Yes	NR	NR§	0.46	22
OPTIMIZE-2 every 12 weeks	127 of 203 (63)	Yes	NR	NR§	0.50	23.2

Van Poznak, JCO, 2017

## Meta-analysis for SRE in Bone Metastases BC patients



# BTA: Guidelines

## Optimal duration of treatment and validity of intermittent treatments

- A multidisciplinary approach is essential to manage patients with bone metastases and prevent skeletal-related events (SREs) [V, A].
- An orthopaedic evaluation is advised in case of significant lesions in long bones or vertebrae as well as in patients with metastatic spinal cord compression (MSCC) to discuss the possible role of surgery [IV, A].
- RT is recommended for lesions at moderate risk of fracture and those associated with moderate to severe pain [I, A].
- A single 8-Gy RT fraction is as effective as fractionated schemes in uncomplicated bone metastases [I, A].
- RT should be delivered after surgery for stabilisation or separation surgery for MSCC [III, B].
- Bone-modifying agents (BMAs), e.g. bisphosphonates or denosumab, are recommended for patients with bone metastases, regardless of symptoms [I, A].
- Zoledronate can be administered every 12 weeks in patients with stable disease after 3-6 monthly treatments [I, B].
- Denosumab should be administered every 4 weeks and is more effective than zoledronate in delaying first and subsequent SREs [I, B].
- Before BMA initiation, patients should have a complete dental evaluation and ideally complete any required dental treatment. Calcium and vitamin D supplements should be prescribed [III, A].
- The optimal duration of BMA therapy has not been defined but it is reasonable to interrupt therapy after 2 years for patients in remission [II, B].<sup>86</sup>
- The ideal sequence of therapies has not been defined but it seems reasonable to document tumour response with a systemic treatment before suggesting LRT [V, C].

Gennari, *Annals of Oncology*, 2021

There is a lack of consensus regarding the optimal duration of treatment. It is now recommended to start bisphosphonates or denosumab as soon as bone metastases are definitively diagnosed in order to delay the first SRE and reduce subsequent complications from metastatic bone disease. ASCO guidelines recommend that, once initiated, i.v. bisphosphonates should be continued until there is a substantial decline in the patient's general performance status [74]; however, criteria are lacking to determine whether and for how long an individual patient benefits from bone-targeted therapy. Stopping zoledronic acid therapy after several years, at least temporarily, or reducing the frequency of the infusions (e.g. an infusion every 3 months) are often considered in patients whose bone disease is not 'aggressive' and is well controlled by the antineoplastic treatment. However, ongoing treatment is recommended for patients with progression of underlying bone metastases, a recent SRE and/or elevated bone resorption markers.

Coleman, *Annals of Oncology*, 2014



# Topics



- **Incidence and Impact on QoL of Breast Cancer Bone Metastases**
- **Bone Targeted Agents in Bone Metastatic Breast Cancer**
- **Future perspective: Prevention of Bone Metastases in Early BC**

# Prevention of Bone Metastases in Early BC

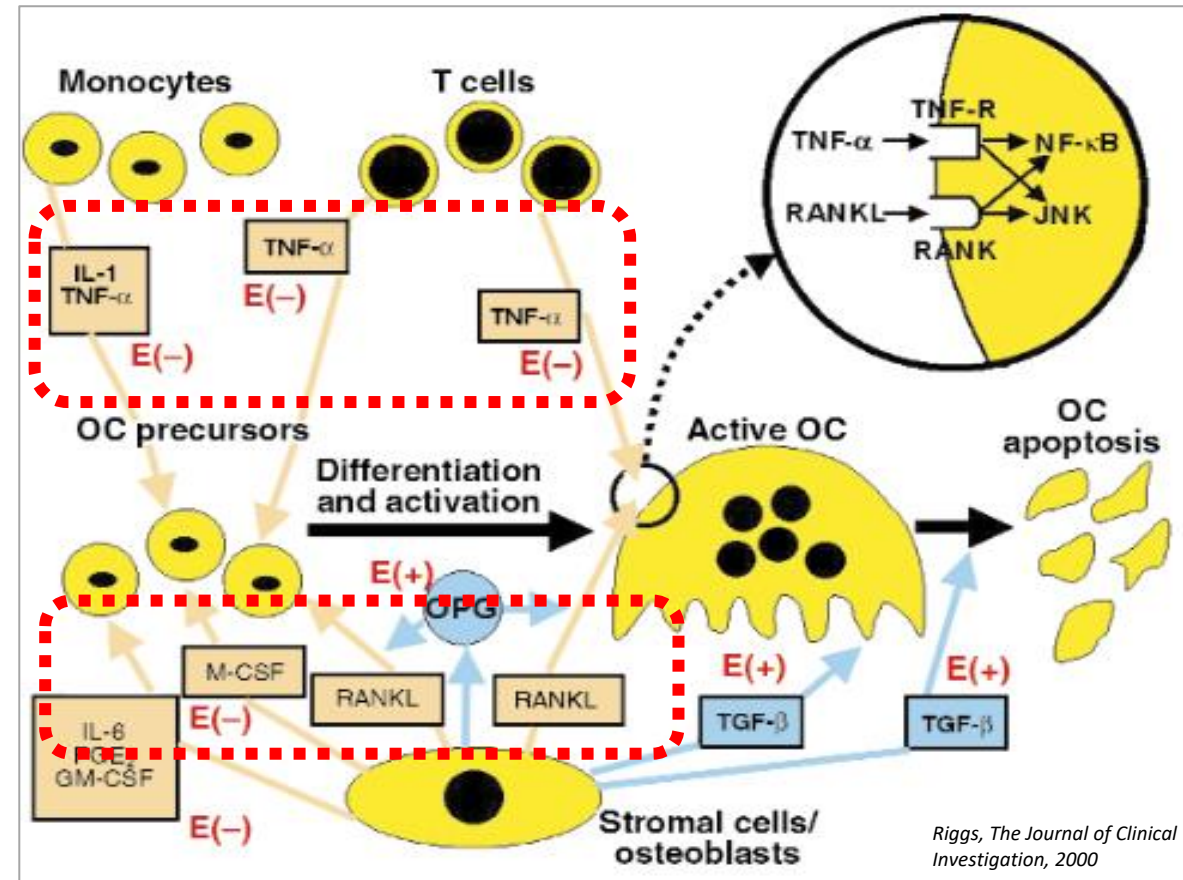
## Adjuvant BTA therapy

The antiresorptive agents (bisphosphonates and denosumab) have an established role as preventative and therapeutic agents for the management of osteoporosis,

### Recommendations

- Adjuvant bisphosphonates (i.v. zoledronate or daily oral clodronate or ibandronate) are recommended for postmenopausal women or premenopausal women treated with gonadotropin-releasing hormone (GnRH) analogues with early breast cancer deemed at significant risk for recurrence [I, A].
- Treatment should be initiated alongside (neo)adjuvant ChT (where indicated) and continued for 2–5 years [I, A].
- Bisphosphonates are neither recommended as disease-modifying agents for premenopausal women (not on GnRH analogues) with early breast cancer nor for men or women with other solid tumours [I, E].
- Denosumab is not recommended for the prevention of metastasis [I, D].

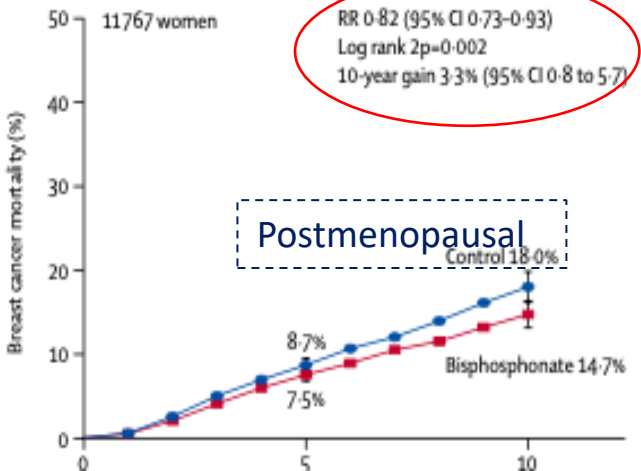
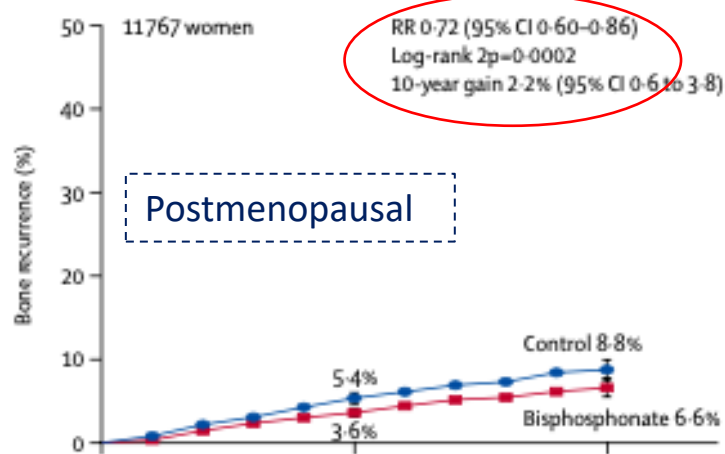
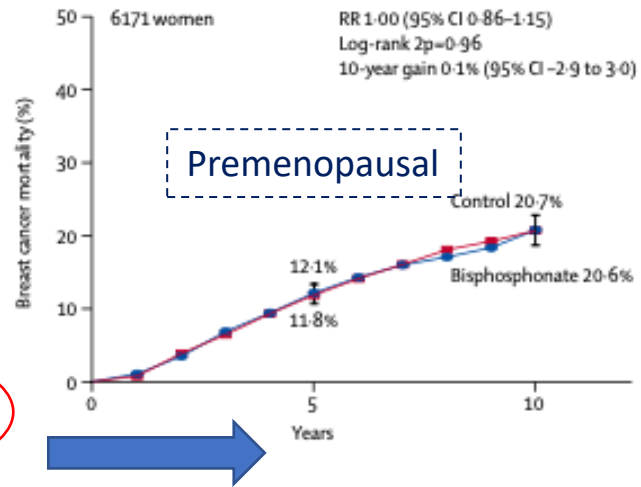
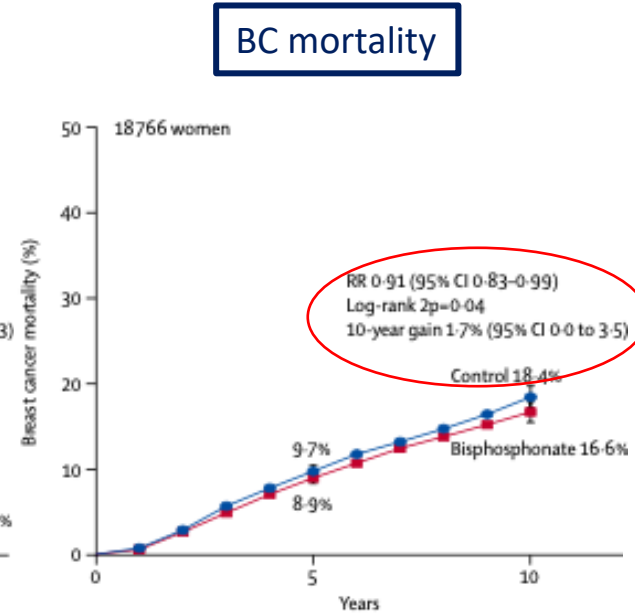
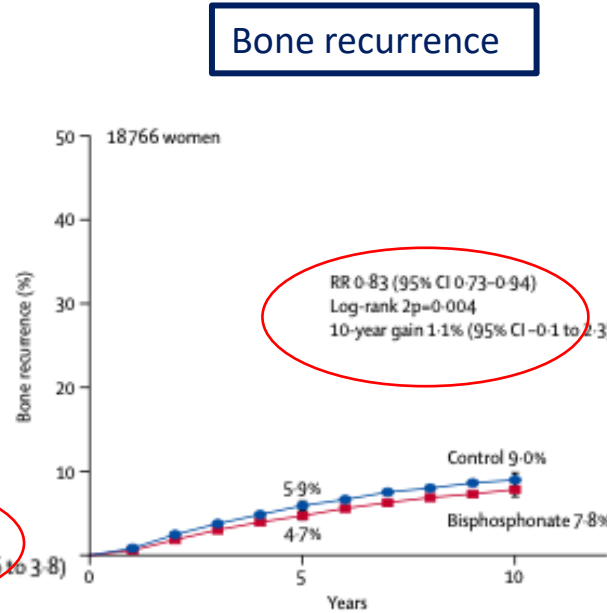
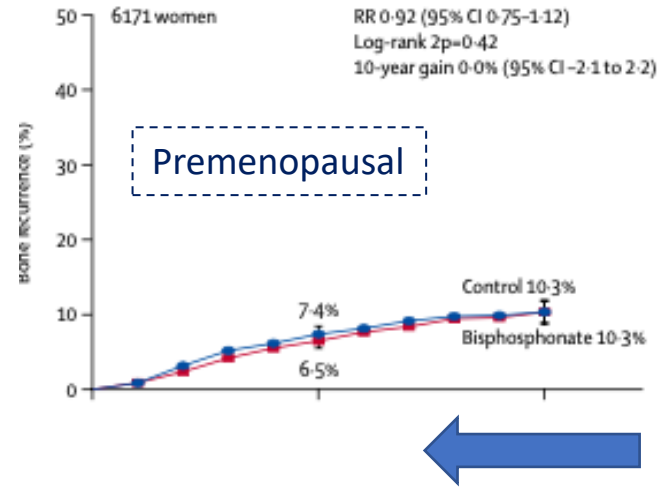
*Coleman, Annals of Oncology, 2014*



# Adjuvant Bisphosphonates and Bone Recurrence in Early BC

**Adjuvant bisphosphonate treatment in early breast cancer:  
meta-analyses of individual patient data from randomised  
trials**

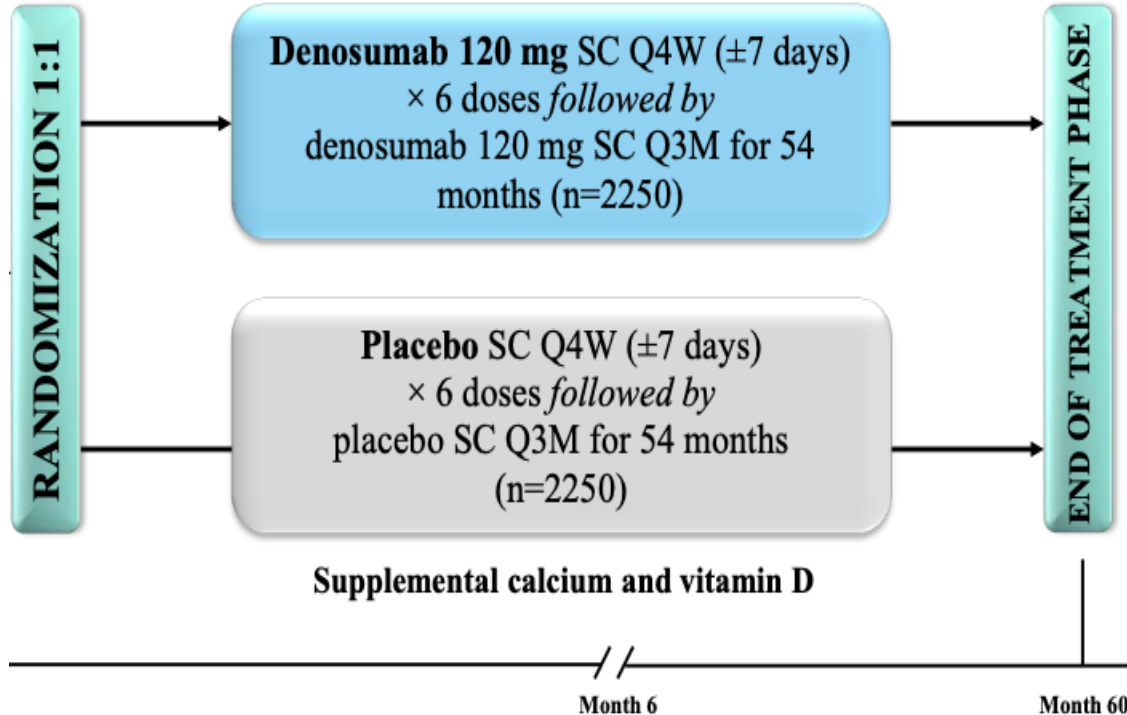
26 trials, 18766 participants



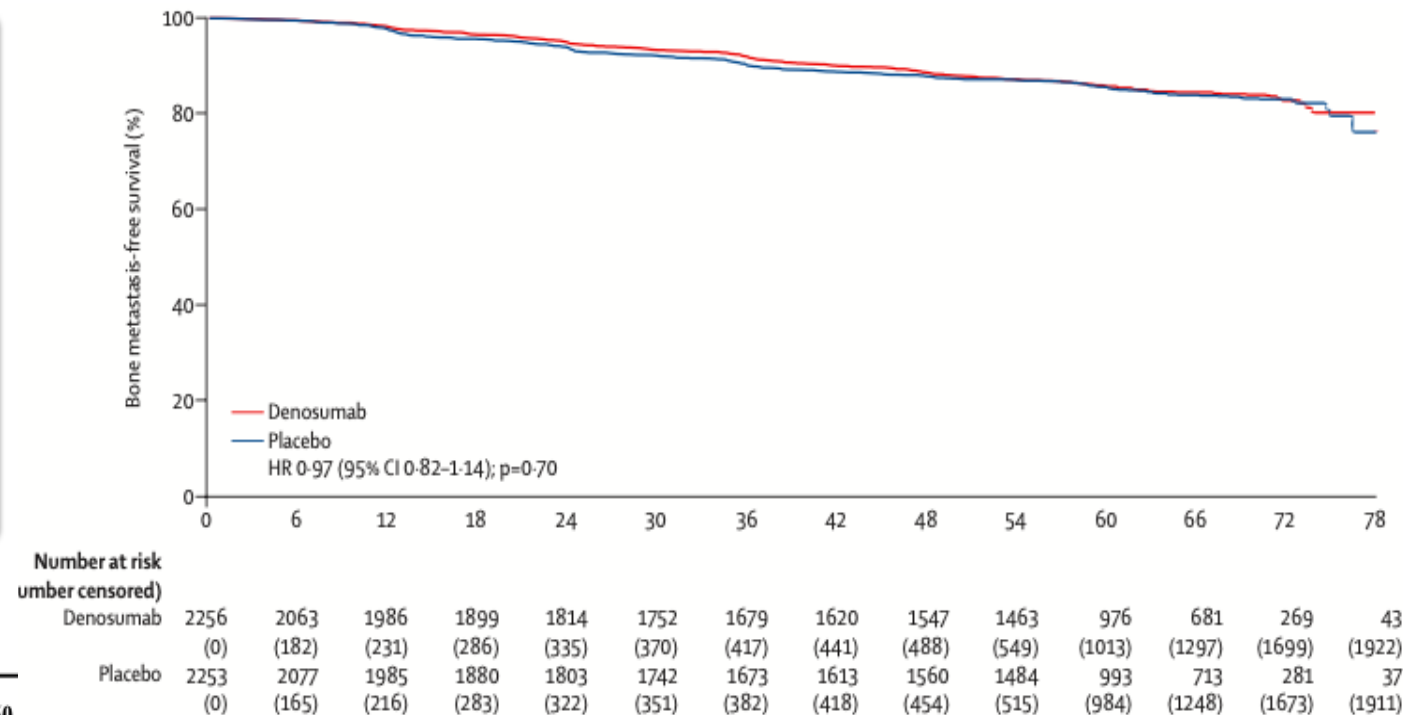
# Adjuvant Denosumab and Bone Recurrence in Early BC

**Adjuvant denosumab in early breast cancer (D-CARE):  
an international, multicentre, randomised, controlled,  
phase 3 trial**

## Study design



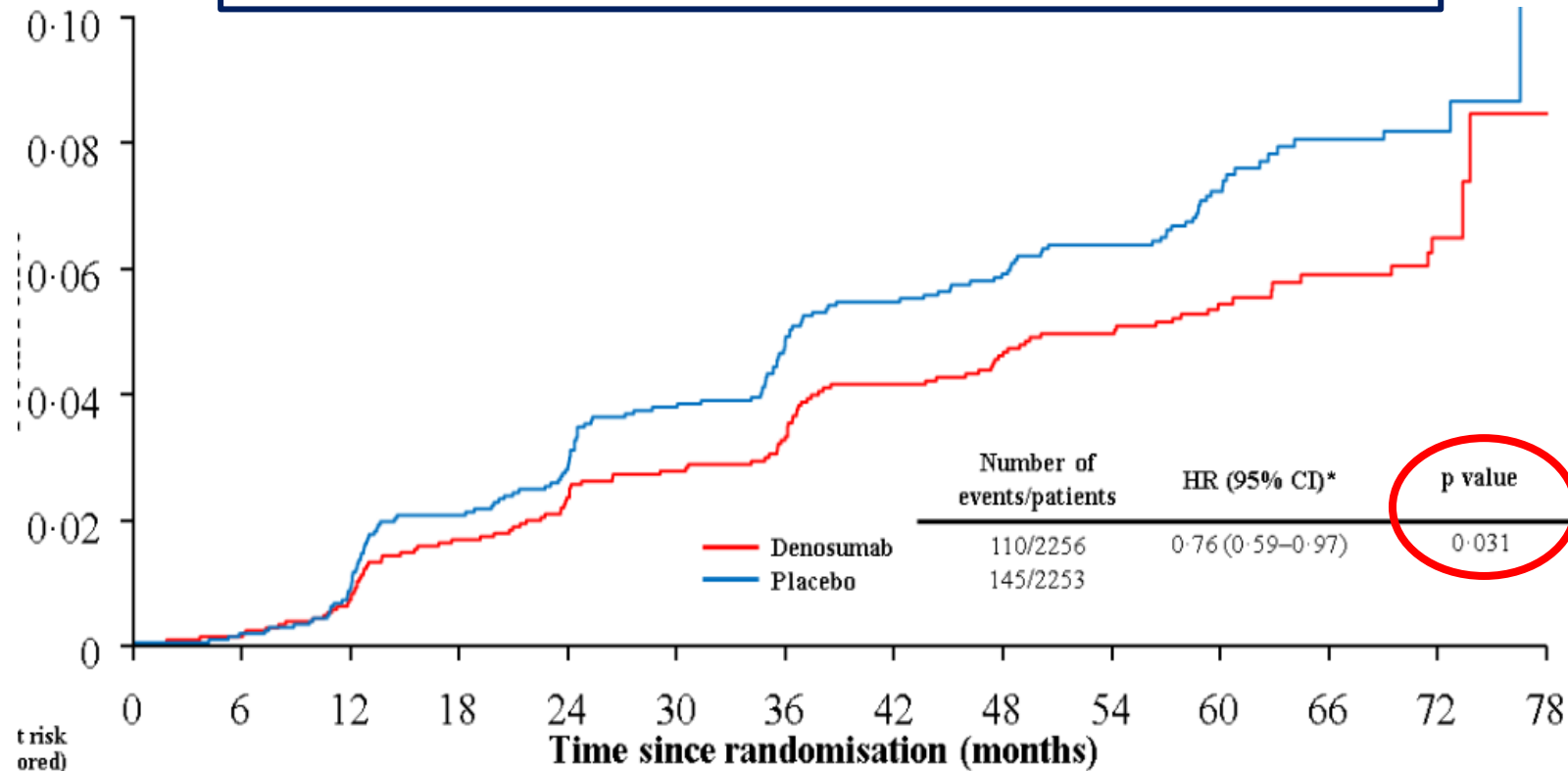
## Bone metastasis-free survival



# Adjuvant Denosumab and Bone Recurrence in Early BC

**Adjuvant denosumab in early breast cancer (D-CARE):  
an international, multicentre, randomised, controlled,  
phase 3 trial**

**Cumulative incidence of bone metastasis as site of first recurrence**



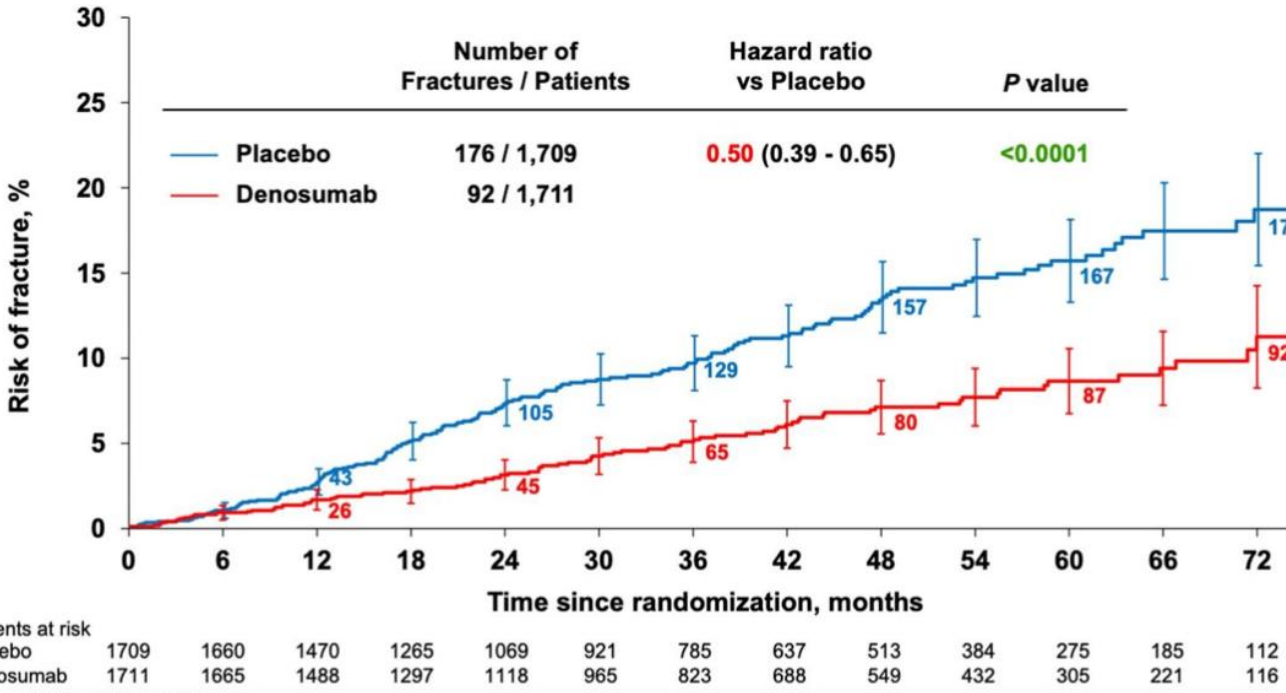
	Denosumab group (n=2256)	Placebo group (n=2253)
Total BMFS events	292 (13%)	305 (14%)
Total BMFS bone events	155 (7%)	189 (8%)
Bone metastasis as first recurrence	110 (5%)	145 (6%)
Loco-regional recurrence before bone metastasis	7 (<1%)	9 (<1%)
Non-bone distant recurrence before bone metastasis	31 (1%)	30 (1%)
Loco-regional and non-bone distant recurrence before bone metastasis	7 (<1%)	5 (<1%)
Total BMFS deaths	137 (6%)	116 (5%)
Death without recurrence	44 (2%)	44 (2%)
Death after local-regional recurrence	5 (<1%)	3 (<1%)
Death after non-bone distant recurrence	71 (3%)	59 (3%)
Death after local-regional and non-bone distant recurrence	17 (1%)	10 (<1%)

# Adjuvant Denosumab and Bone Recurrence in Early BC

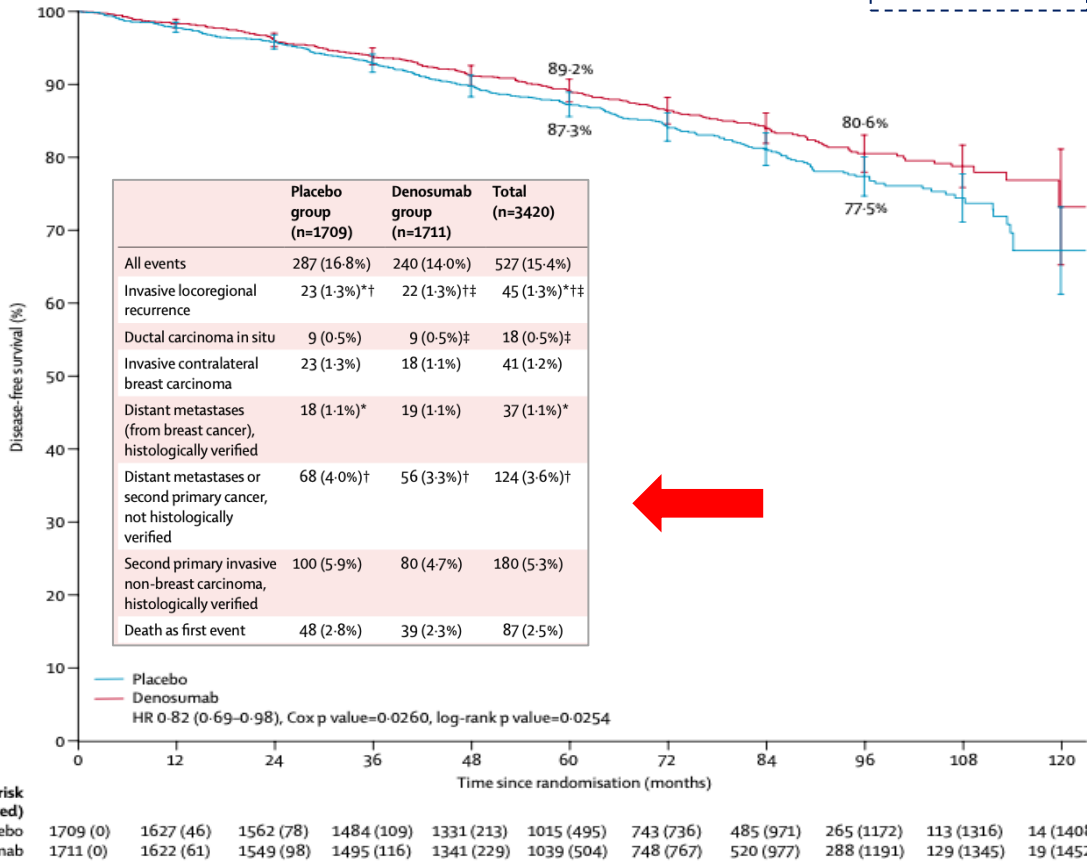
Adapted from Gnant, Lancet, 2015, Gnant, Lancet Oncol, 2019 and Gnant, ASCO, 2022

Adjuvant denosumab in breast cancer (ABCSG-18):  
a multicentre, randomised, double-blind, placebo-controlled trial

Time to first clinical fracture



Disease-free survival

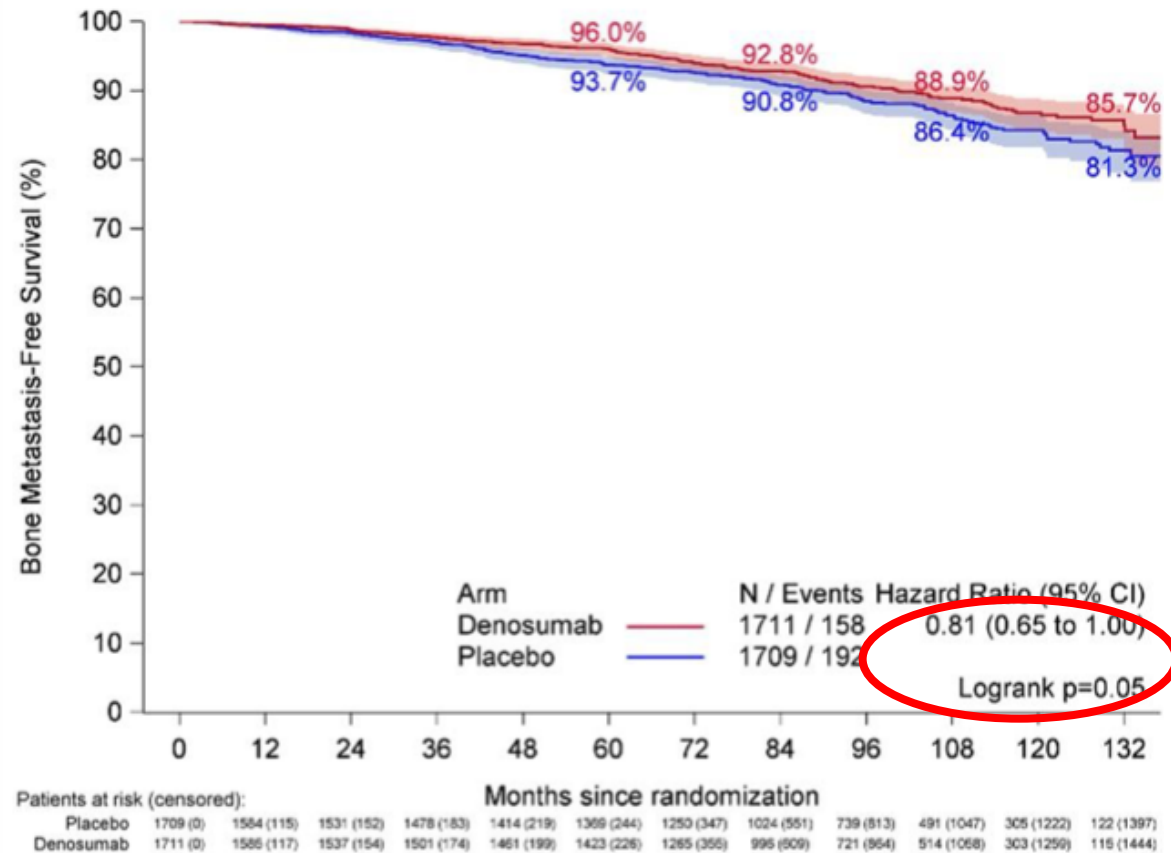




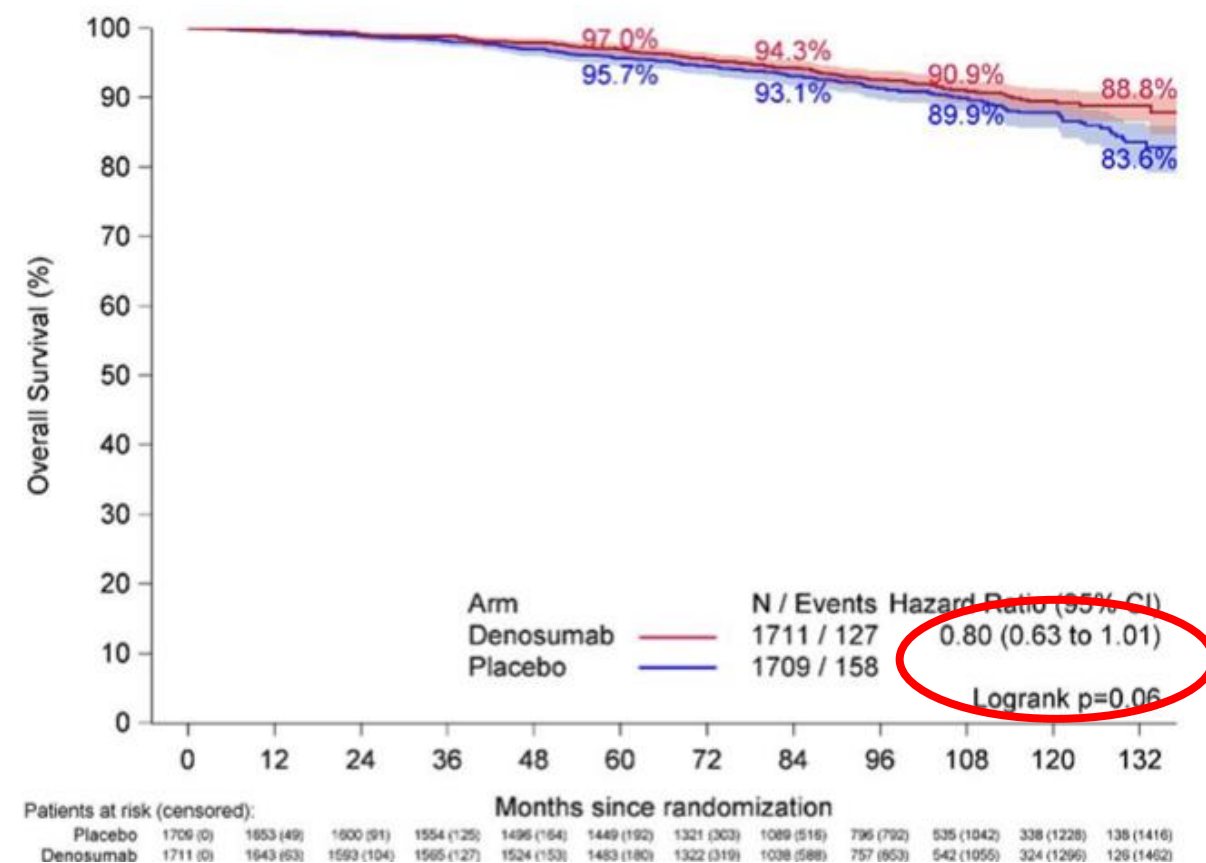
# Adjuvant Denosumab and Bone Recurrence in Early BC

Adjuvant denosumab in breast cancer (ABCSG-18):  
a multicentre, randomised, double-blind, placebo-  
controlled trial Median Follow-Up: 8 years

BMFS



Overall survival



# Conclusions

- **Zoledronate or denosumab are recommended in all BC patients with bone metastases for the prevention of SRE, regardless of symptoms**
- **Lack of differences in PFS and OS: the best choice between these two agent remain open:**

## **In favor of Denosumab:**

- Greater efficacy in clinically relevant endpoints (time to first and subsequent SRE in a phase III trial)
- Ease of subcutaneous injection
- Lower rate of renal toxicity

## **In favor of Zoledronate:**

- Lower rate of hypocalcemia
- Slightly lower rates of ONJ
- Significantly lower costs

- **Future perspective: prevention of over metastases**
  - ***Zoledronate and Denosumab: potential strategies to modify the complex interactions within the bone microenvironment***, particularly when estrogen deprivation therapy results in excessive bone turnover
  - ***It is crucial to identify patients who would benefit most from preventive BTA therapy***  
Randomized phase III *ENDEAVOR* study (NCT03324932): Denosumab's effect on BMD in early BC treated with adjuvant AI, with DFS and OS as secondary endpoints.



***Thank you for your attention***

E-mail: [giovanna.garufi@unicatt.it](mailto:giovanna.garufi@unicatt.it)