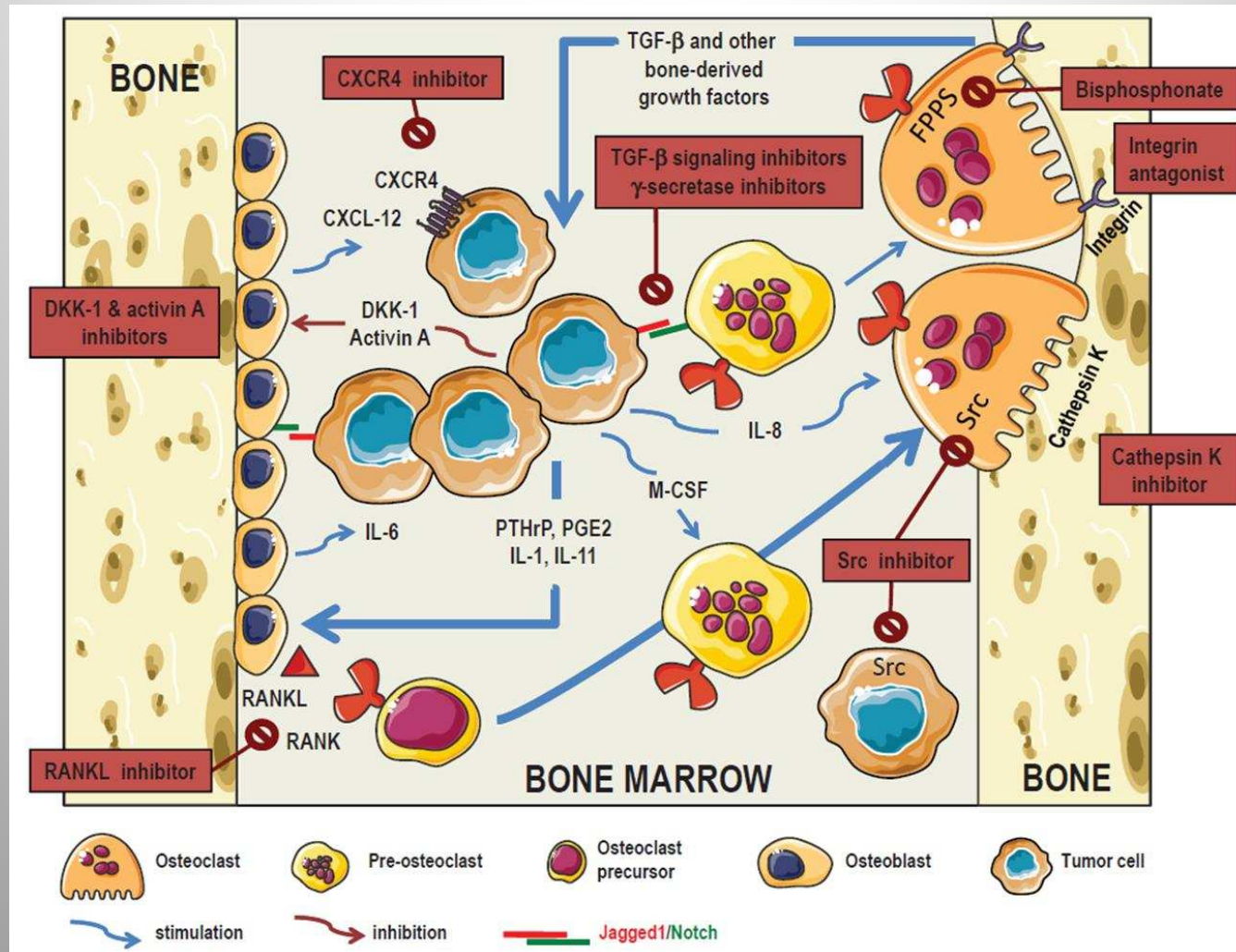


# BONE TARGETED THERAPIES IN BREAST CANCER

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LILLE



# Bone Targeted Therapies

- Bisphosphonates:
  - bone metastatic disease and hypercalcemia
  - cancer treatment induced bone loss
  - anti cancer treatment
- Denosumab : anti rank ligand
- Other bone targeted therapies

# Bisphosphonates (BP)

- Inhibitory effect of osteoclast function
- Nitrogen free BP ( clodronate, etidronate) substitute into the production of adenosine triphosphate
- Nitrogen containing BP ( pamidronate, zoledronate, Ibandronate) block the prenylation of small signaling proteins

# BP and bone metastatic disease

- All BP decrease the rate of bone events (Cochrane 2004) and bone pain (Cochrane 2002) and hypercalcemia.
- Even if nitrogen BP are more potent experimentally, there is no direct clinical comparison between oral and IV BP.
- Optimal duration of treatment unknown (for Zoledronate, long term data up to 25 months)(Rosen 2003)

# BP and treatment induced bone loss

- **In premenopausal patients,**

BP prevent bone loss induced by chemotherapy and hormonotherapy (Saarto 1997, Delmas 1997)

In the ABCSG -12 study, Zoledronate decreased the loss in bone density in pts receiving Tamoxifen or anastrozole together with LHRH analogs (Gnant 2011)

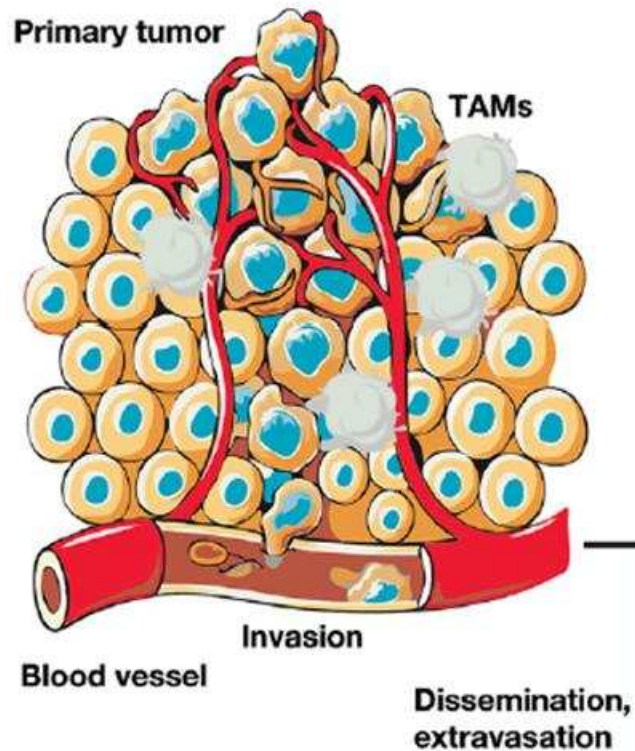
Risedronate did not prevent bone loss in pts receiving chemotherapy (Hines 2009)

# BP and treatment induced bone loss

- **In postmenopausal patients** treated with Aromatase Inhibitors (AI)
  - Zoledronate prevents bone loss: Z FAST(Brufsky 2007) and ZO FAST (Bundred 2008)
  - Similar results with Risedronate( Greenspan 2008)

**BP AS ANTI TUMOR AGENTS**





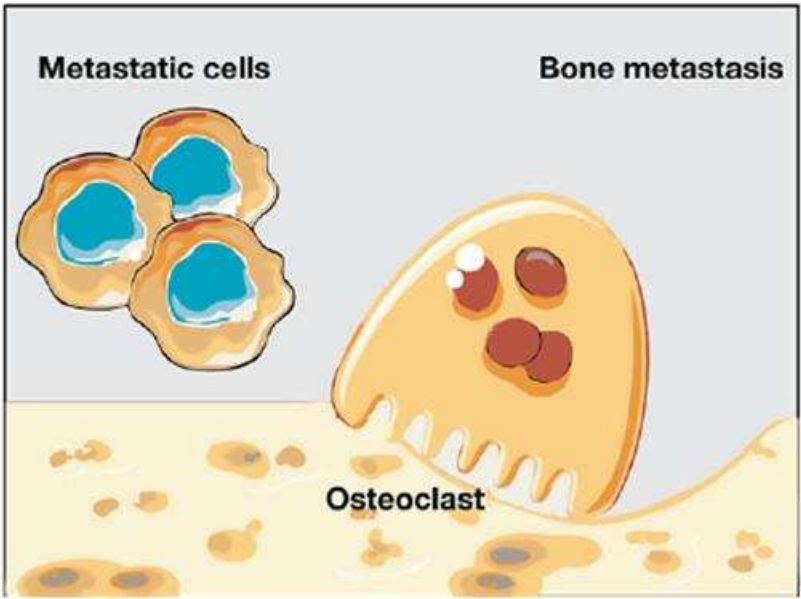
**Potential antitumor activity of bisphosphonates:**

- ↓ Tumor cell migration, invasion, and adhesion
- ↓ Tumor cell proliferation
- ↓ Tumor angiogenesis
- ↓ Tumor-associated macrophages (TAMs)
- ↑ Tumor cell apoptosis
- ↑ Cytotoxicity of  $\gamma\delta$  T cells

**Synergistic antitumor activity with cytotoxic drugs**

**Bisphosphonate activity in bone:**

- ↓ Osteoclast formation and activity, inhibiting osteoclast-mediated bone resorption
- ↓ Skeletal tumor burden
- ↓ Progression of bone metastases

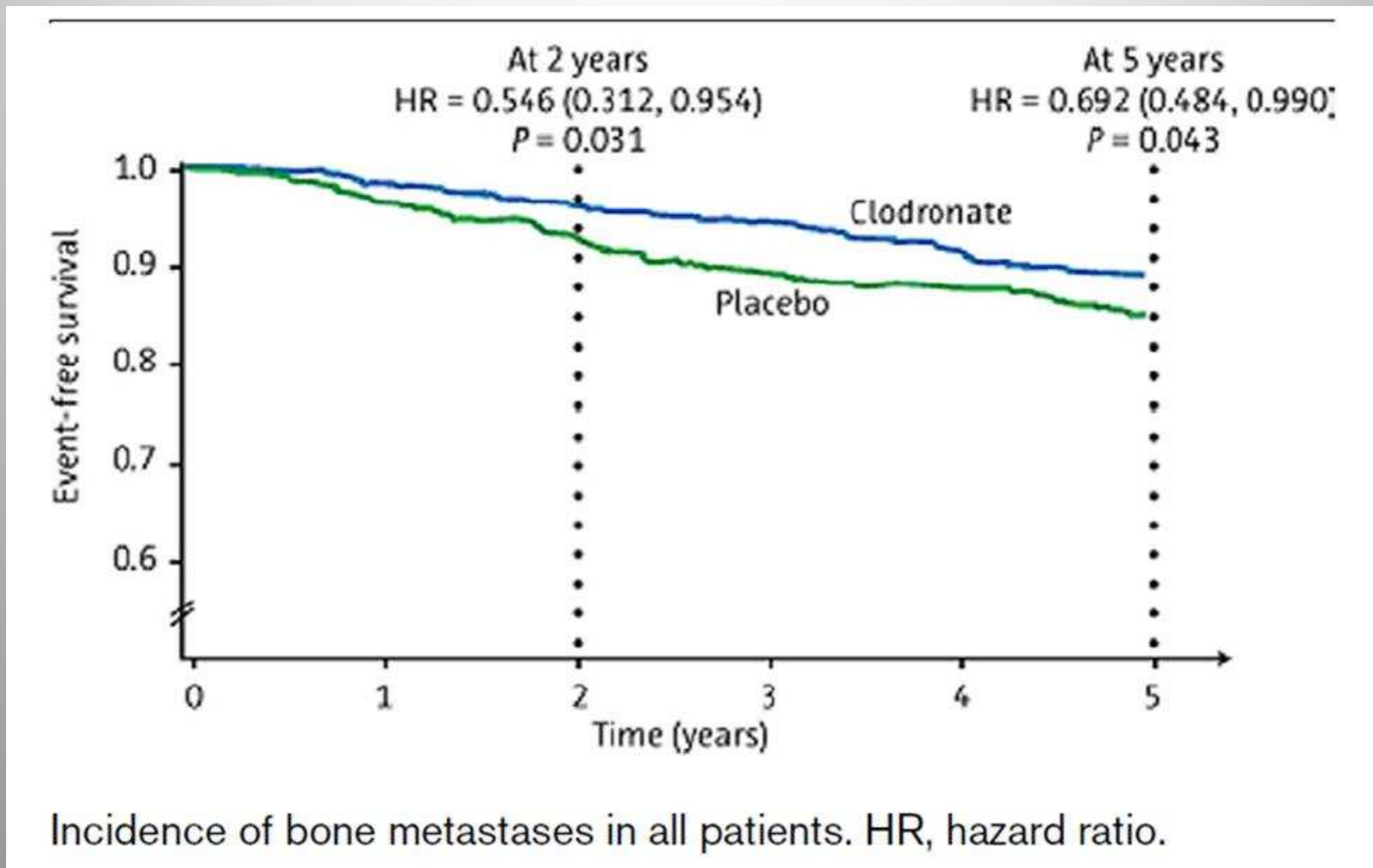


# BP as an anti tumor agent

## Adjuvant studies

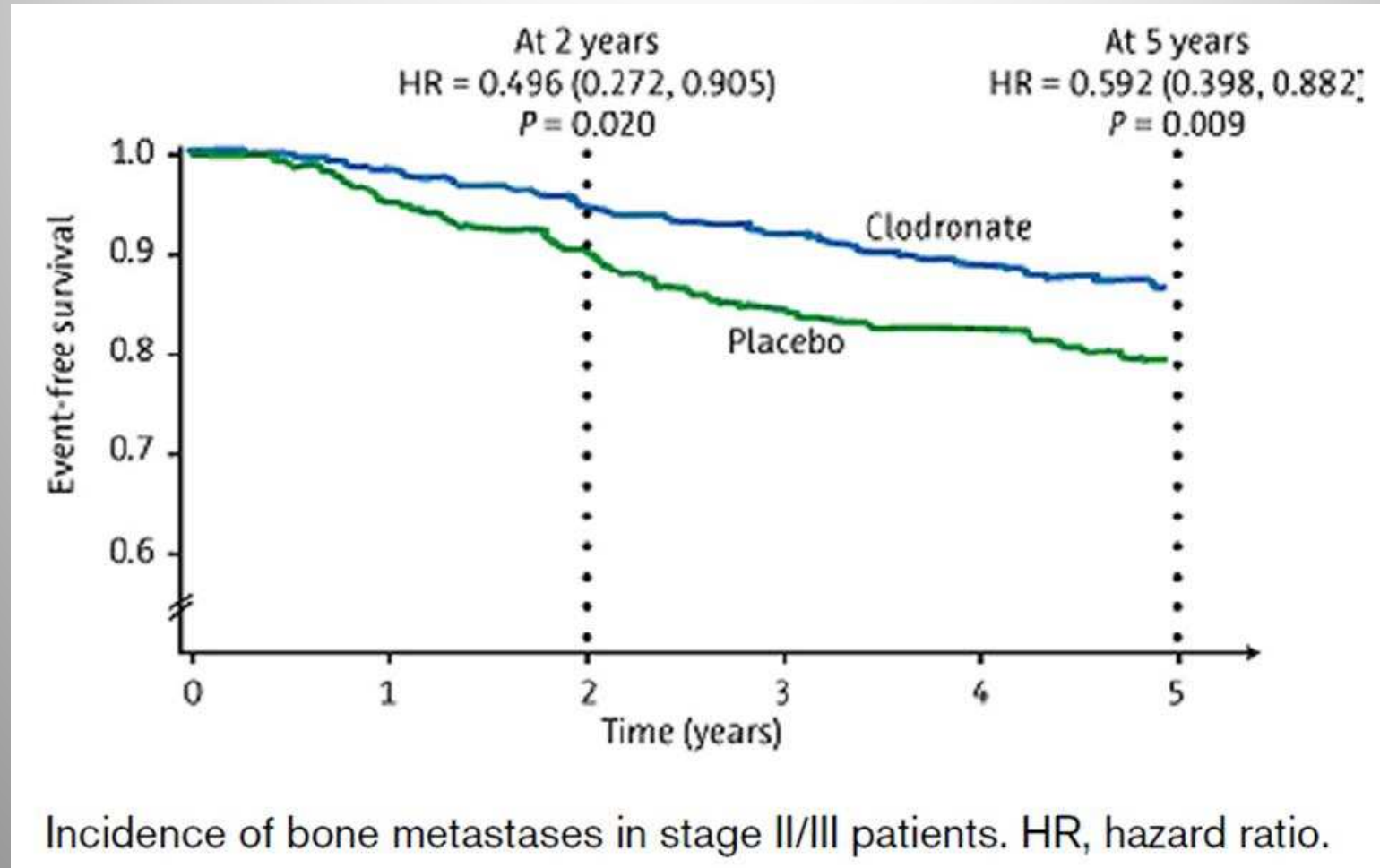
- Clodronate ( Powles 2006, Diel 2008, Sartoo 2001, Paterson 2011)
- Ibandronate (Möbus 2011)
- Zoledronate ( Bundred 2008, Gnant 2011, Coleman 2010)

# **ANTI TUMOR EFFECT OF CLODRONATE**



Reduction in bone relapse and improved survival with **oral clodronate** for adjuvant treatment of operable breast cancer [

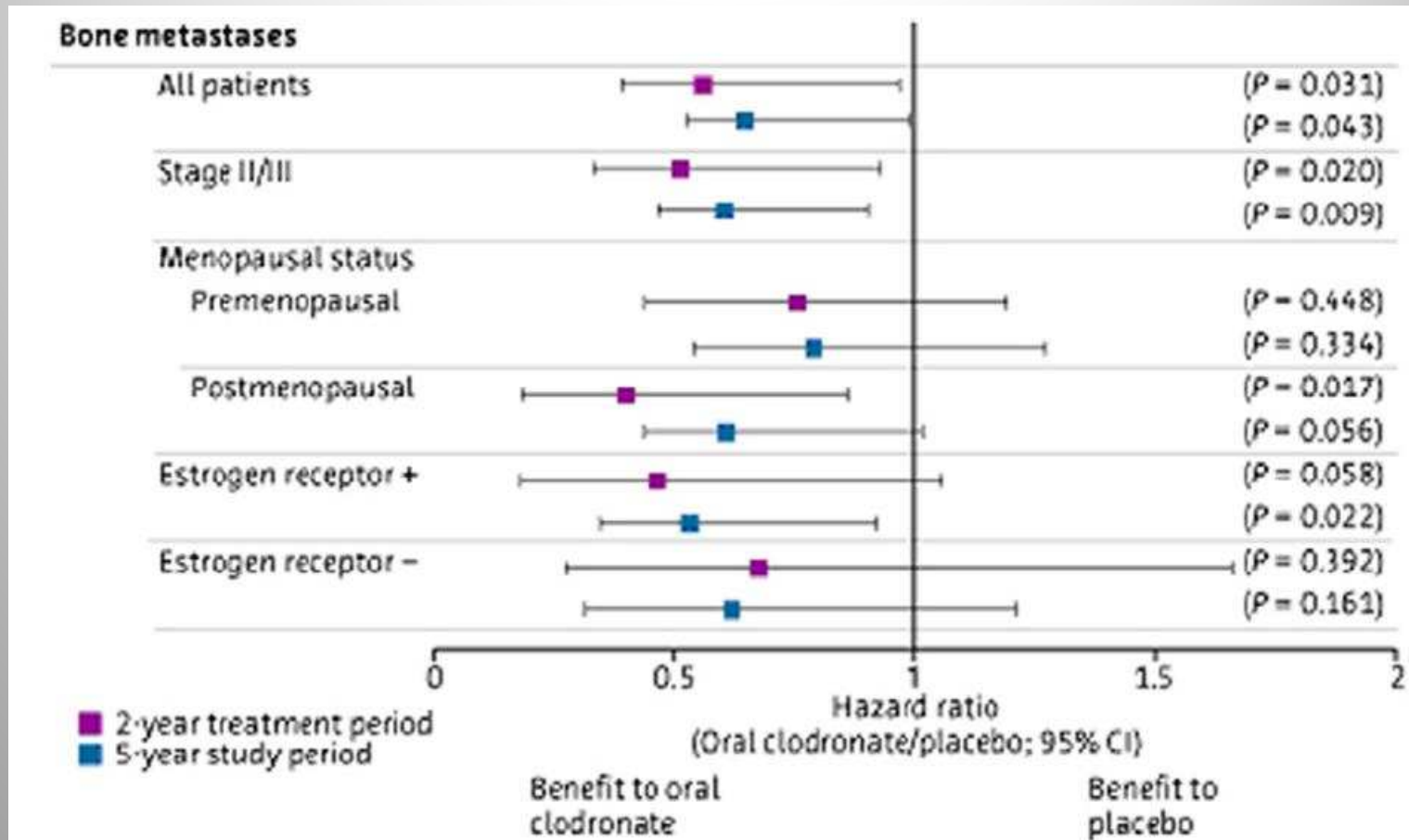
**Powles T**, Breast Cancer Res. 2006;8(2):R13.



Incidence of bone metastases in stage II/III patients. HR, hazard ratio.

Reduction in bone relapse and improved survival with **oral clodronate** for adjuvant treatment of operable breast cancer

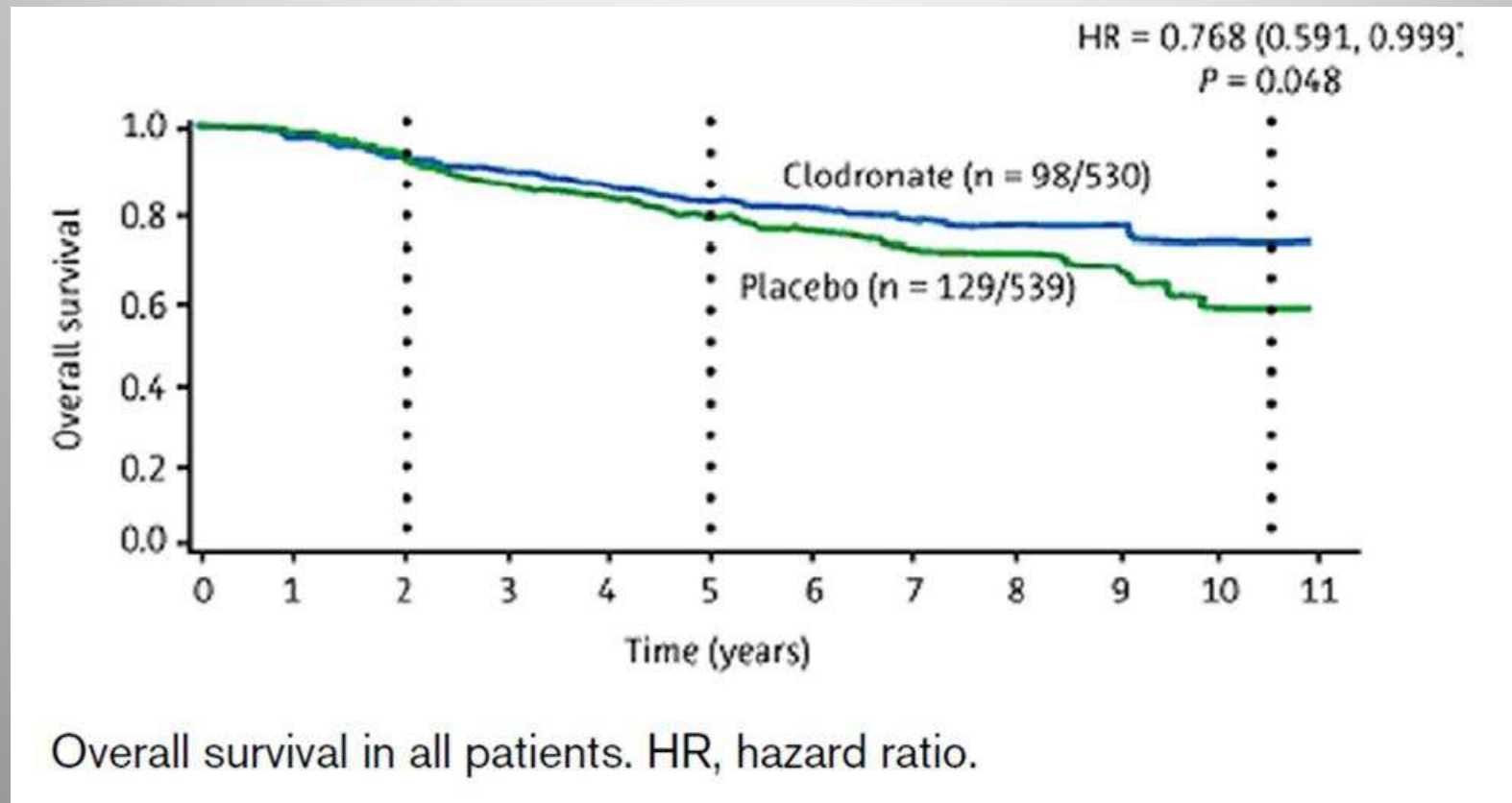
**Powles T**, Breast Cancer Res. 2006;8(2):R13.



Hazard ratios and 95% confidence intervals (CI) for the incidence of bone metastases in patient subgroups.

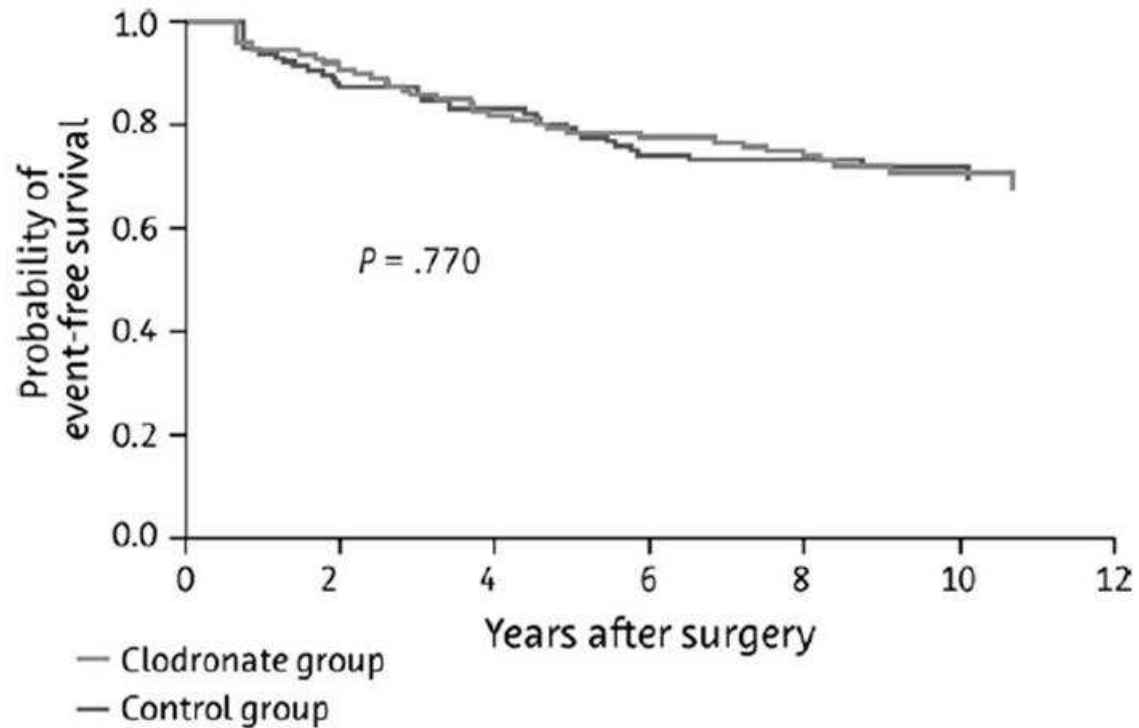
Reduction in bone relapse and improved survival with **oral clodronate** for adjuvant treatment of operable breast cancer

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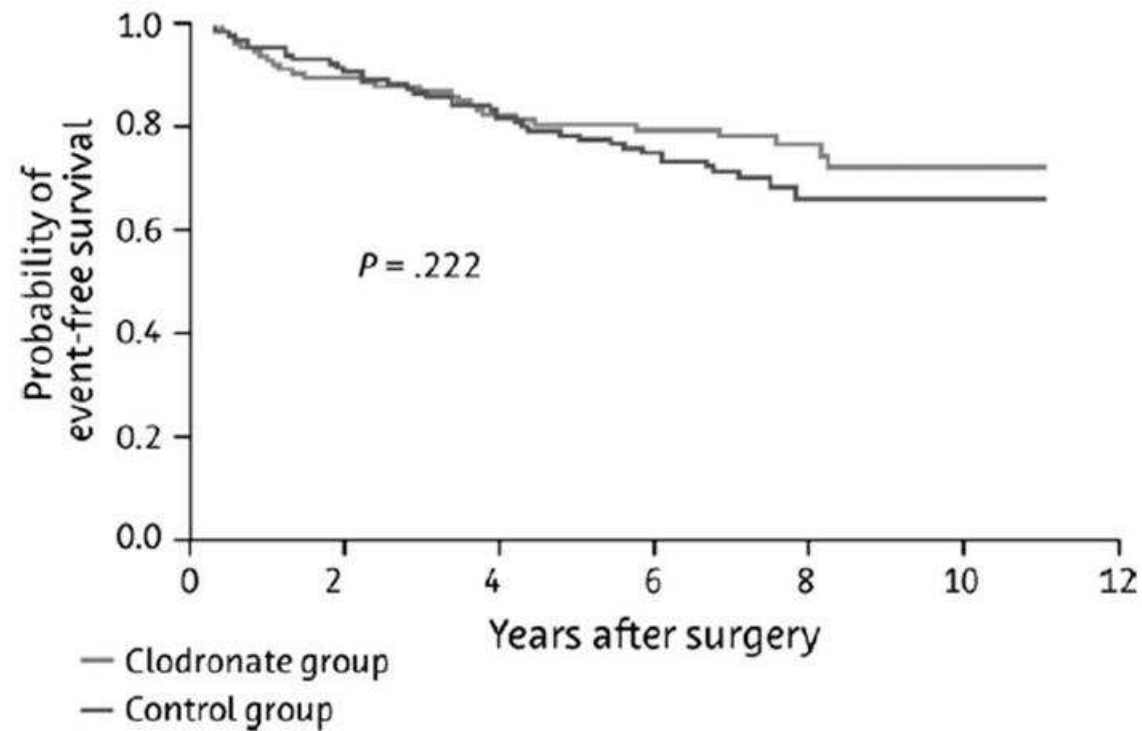


**Figure 1.** Kaplan-Meier curve of bone metastasis-free survival among patients treated with oral clodronate compared with standard follow-up therapy ( $N = 209$ ).

Adjuvant **oral clodronate** improves the overall survival of primary breast cancer patients with **micrometastases to the bone marrow**:

**Diel IJ**, Ann Oncol. 2008 Dec;19(12):2007-11.

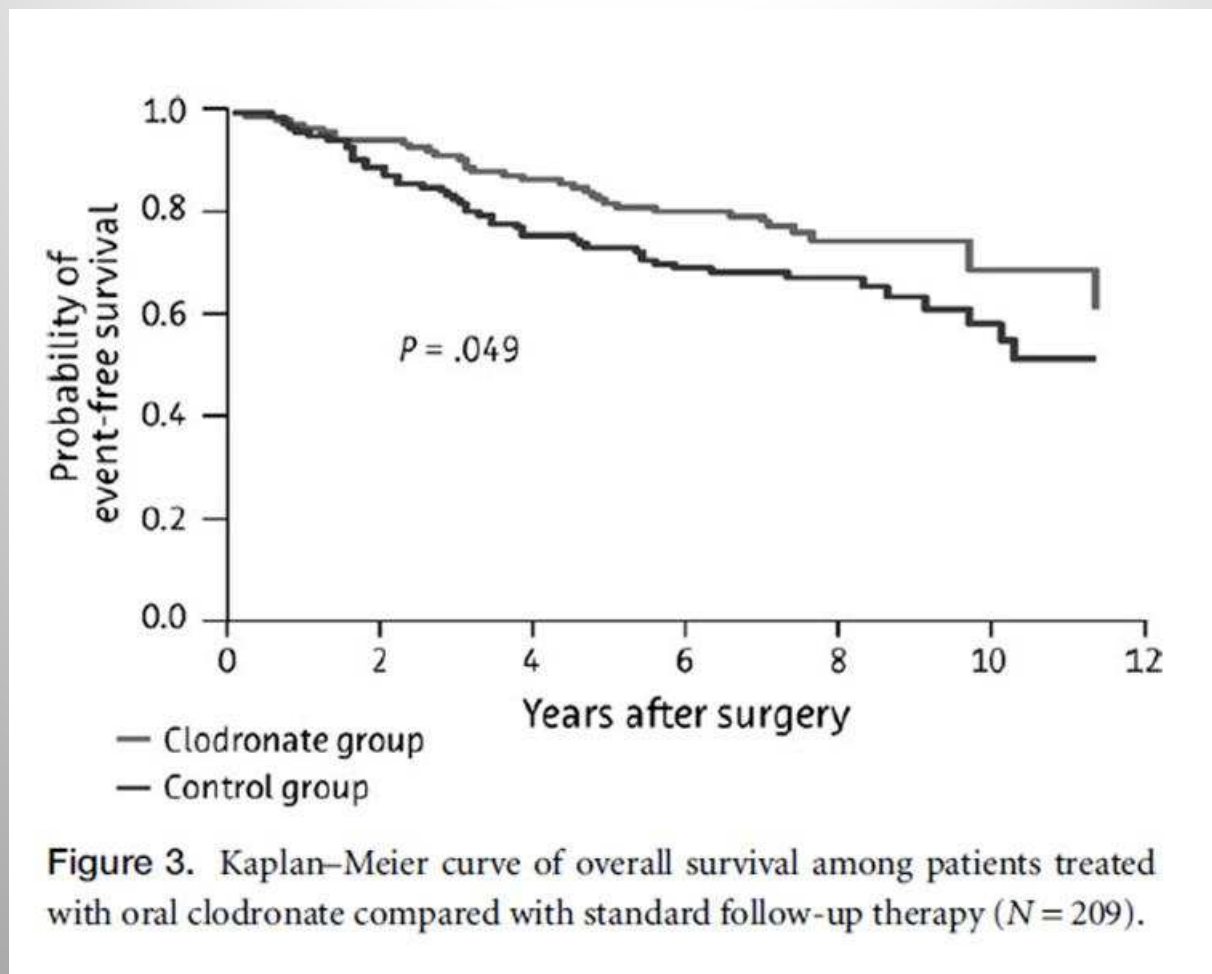




**Figure 2.** Kaplan–Meier curve of visceral metastasis-free survival among patients treated with oral clodronate compared with standard follow-up therapy ( $N = 209$ ).

Adjuvant **oral clodronate** improves the overall survival of primary breast cancer patients with **micrometastases to the bone marrow**:

**Diel IJ**, Ann Oncol. 2008 Dec;19(12):2007-11.



Adjuvant **oral clodronate** improves the overall survival of primary breast cancer patients with **micrometastases to the bone marrow**

**Diel IJ**, Ann Oncol. 2008 Dec;19(12):2007-11.

# NSABP B-34 design

(Paterson 2011)

## Stratification

- Age ( <50, ≥ 50 )
- Number of positive nodes (0, 1-3, 4+)
- ER/PgR status (negative [ER- and PgR-], positive [ER+ and/or PgR+])

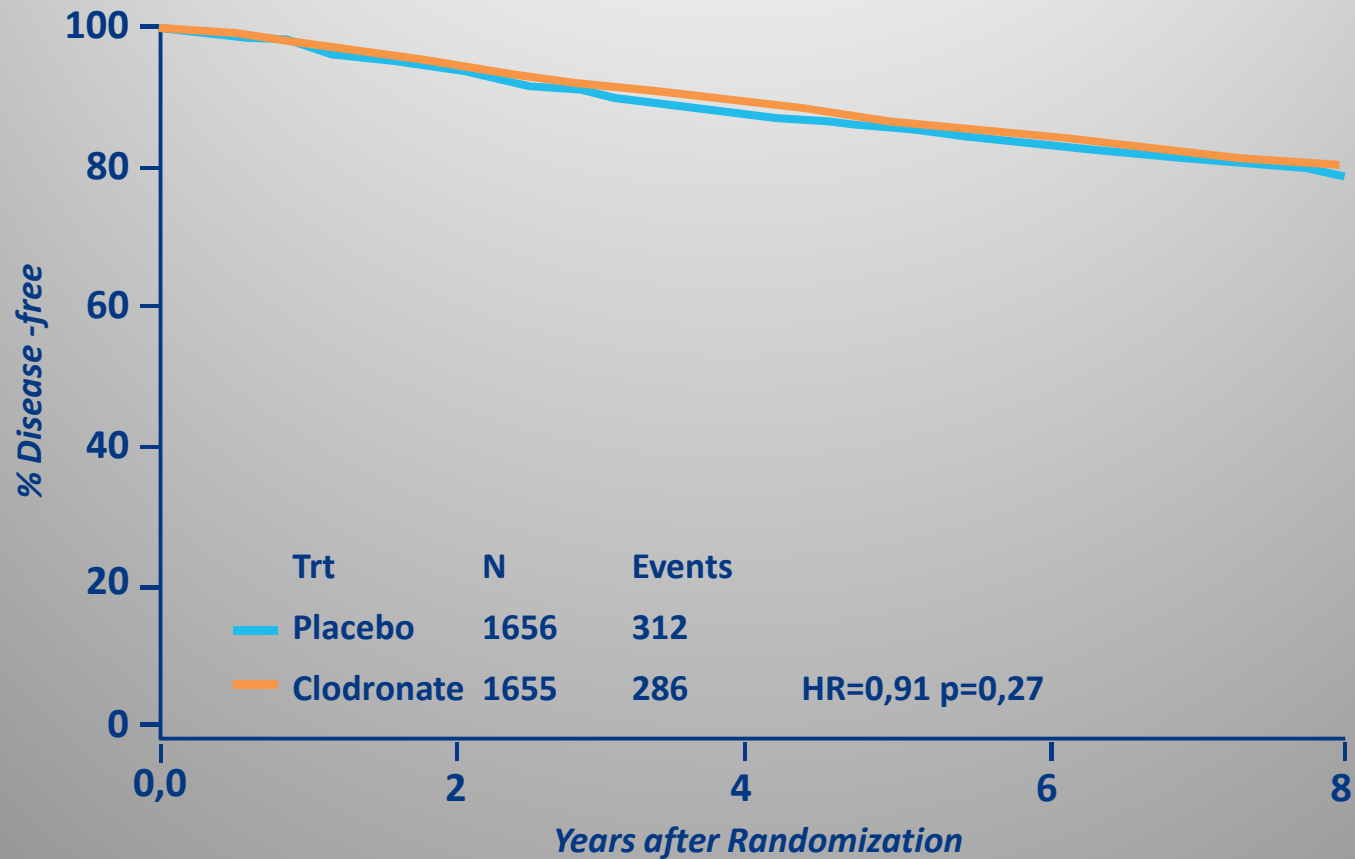
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**GROUP 1**  
Clodronate<sup>1</sup>  
1600mg/day x 3 years

**GROUP 2**  
Placebo<sup>1</sup>  
x 3 years

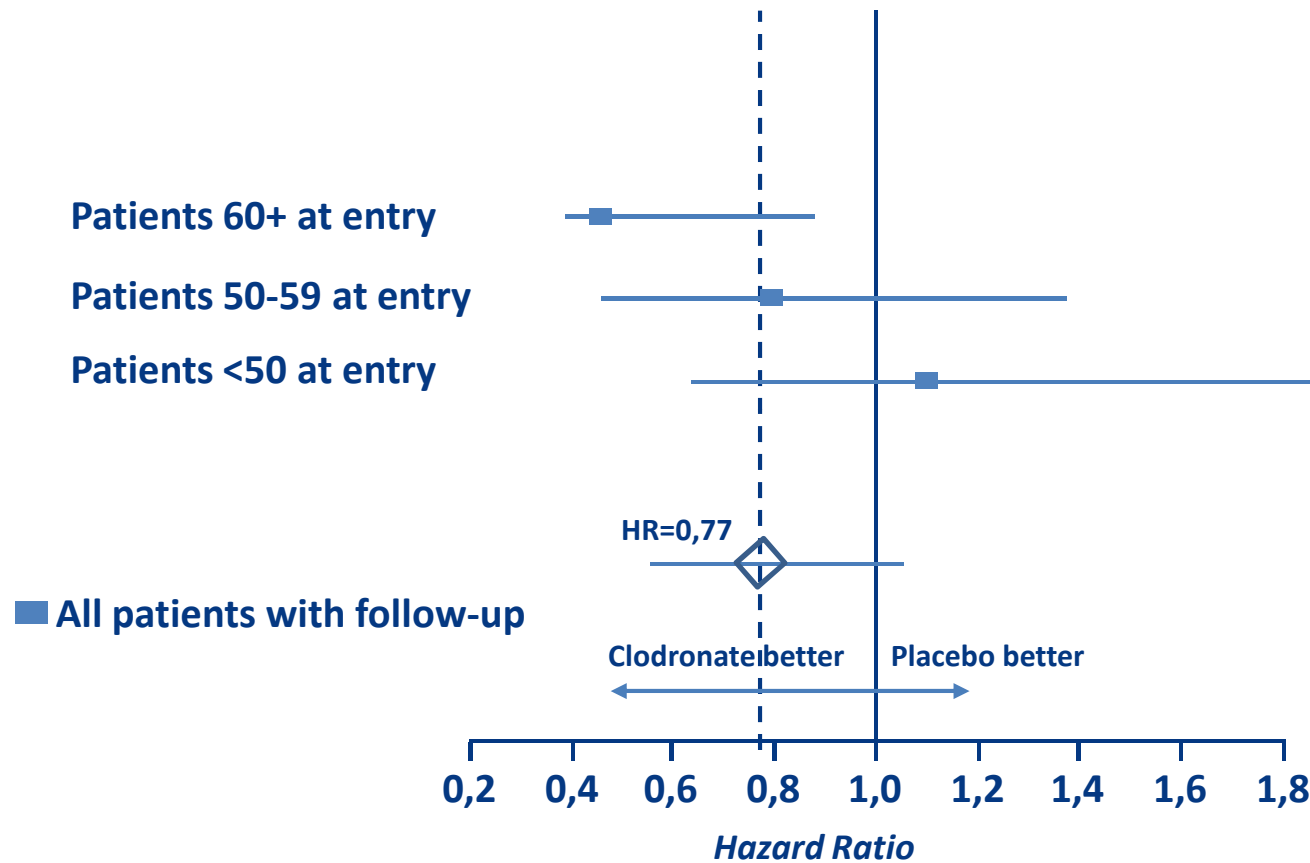
# NSABP B-34 Study

- Disease-Free Survival



# NSABP B-34 study

## Bone relapse according to age



# **ANTI TUMOR EFFECT OF IBANDRONATE**

# GAIN study

(Möbus 2011)

## Arm A1:

Epirubicin  
150 mg/m<sup>2</sup>  
q 2w



Paclitaxel  
225 mg/m<sup>2</sup>  
q 2w

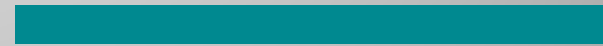


Cyclophosphamide  
2000 mg/m<sup>2</sup>  
q 2w



## Arm B1:

Ibandronate  
50 mg daily p.o  
2 yrs



## Arm AZ:

Epirubicin  
112.5 mg/m<sup>2</sup>  
Cyclophosphamide  
600 mg/m<sup>2</sup> q 2w



Paclitaxel  
67.5 mg/m<sup>2</sup> weekly  
Capecitabine  
2000 mg/m<sup>2</sup> d1-d14 q3w

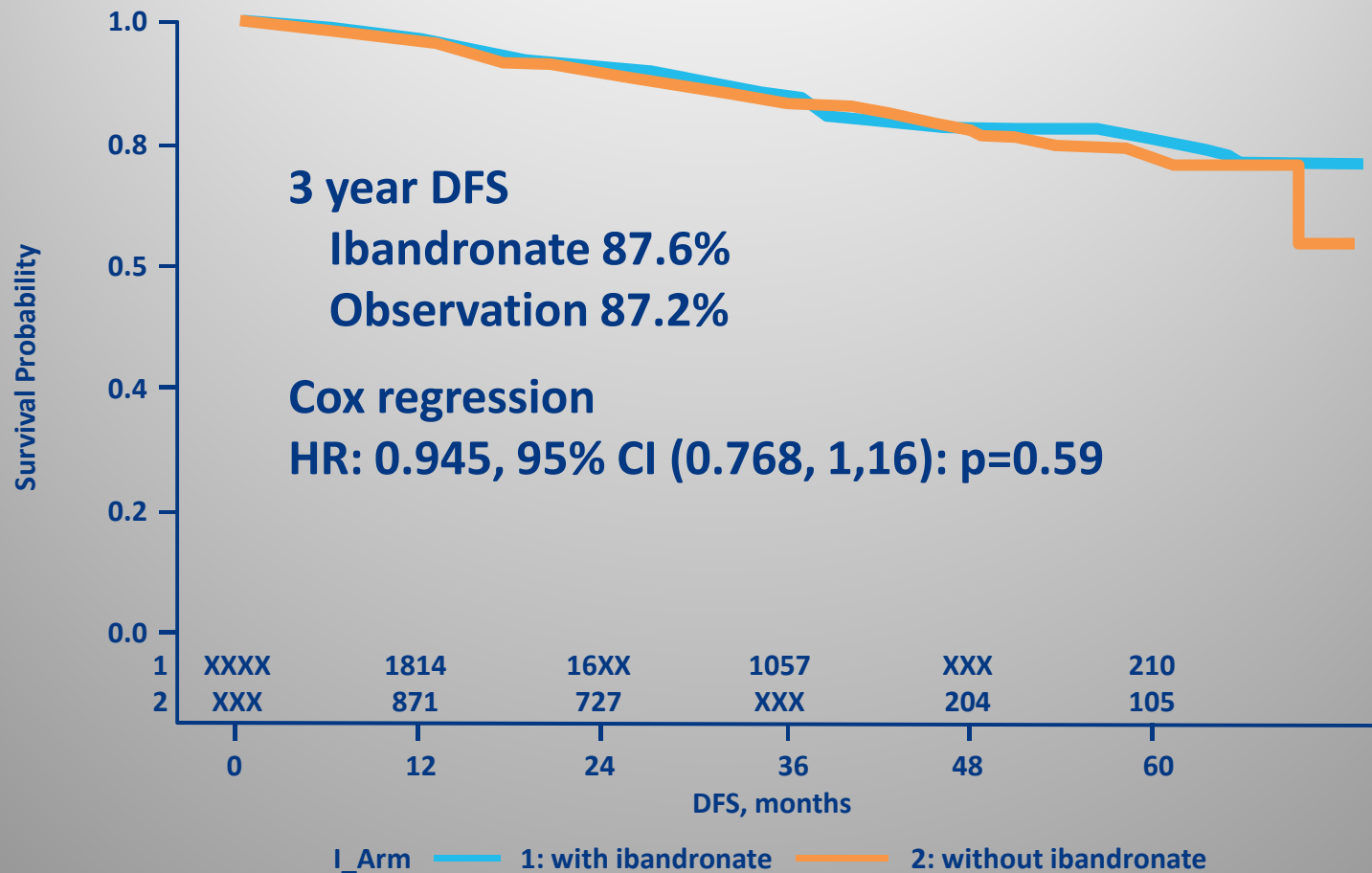


## Arm B2:

Observation

# GAIN Study

## Disease free survival



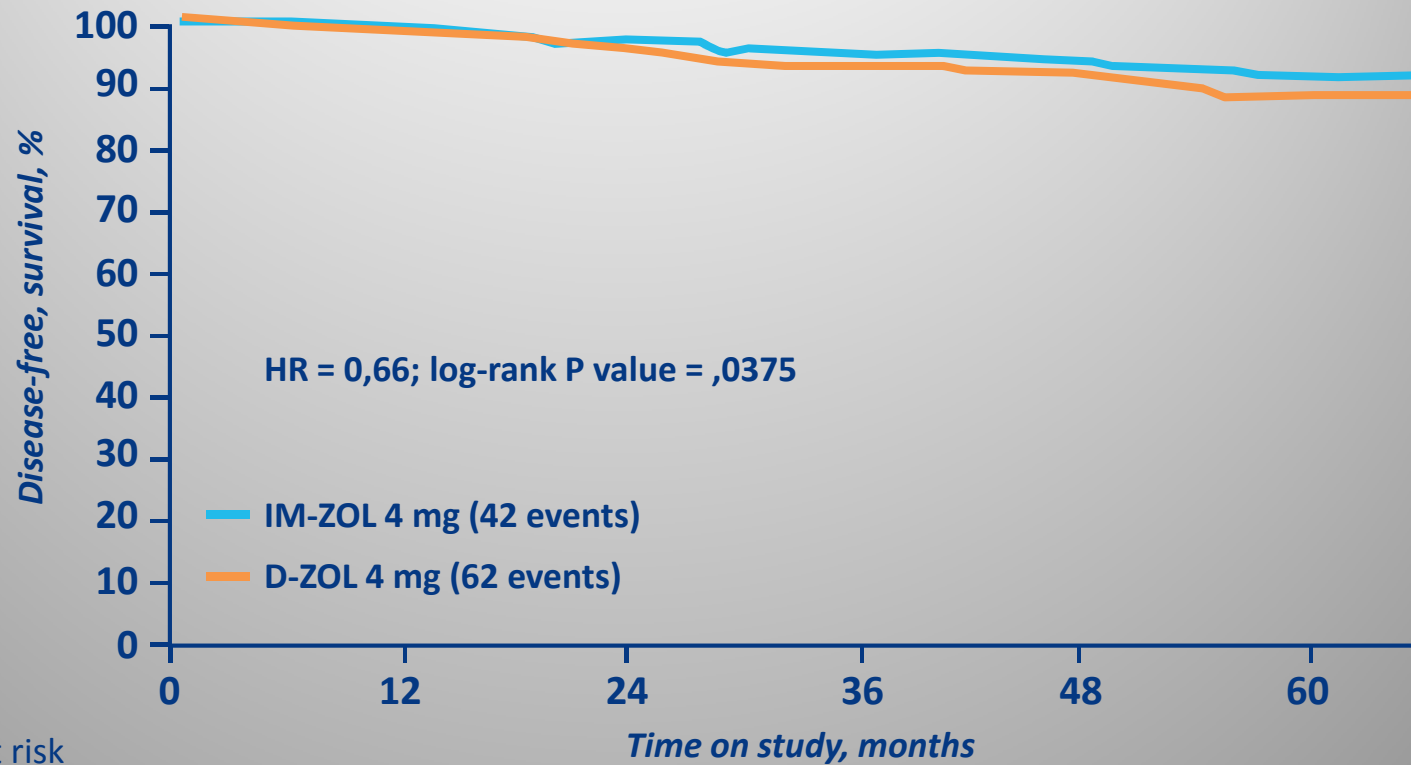


# **ANTI TUMOR EFFECT OF ZOLEDRONATE**

# ZO-FAST study

## Disease free survival

ITT population

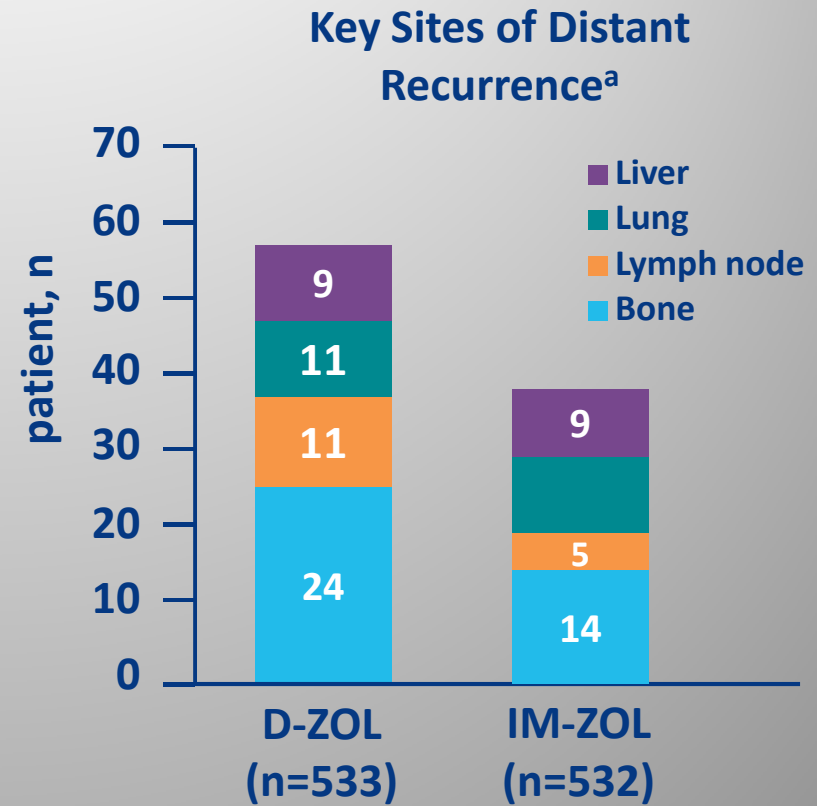
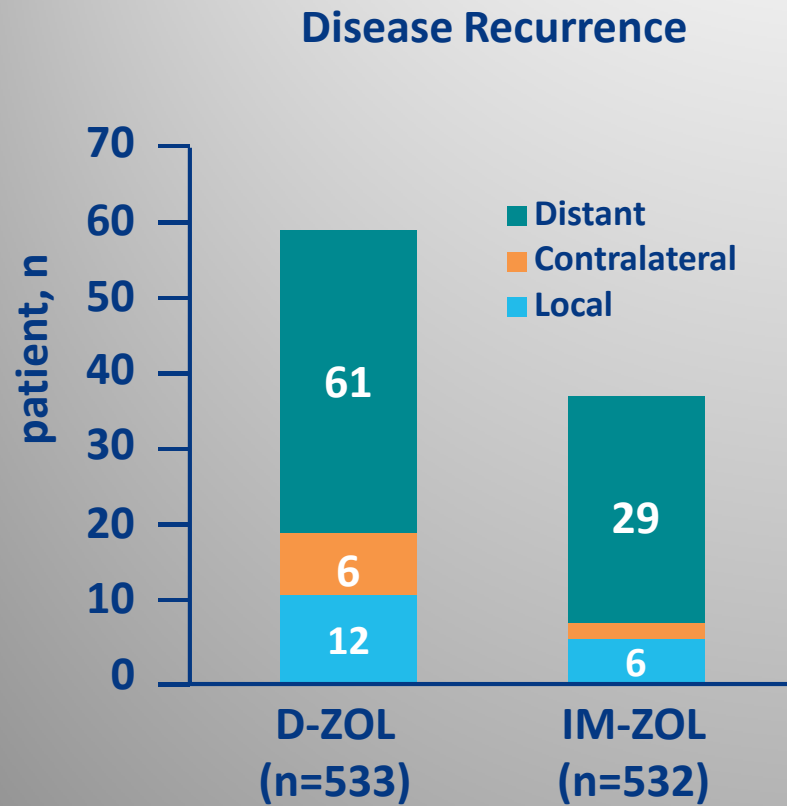


Numbers at risk

	0	12	24	36	48	60
IM - ZOL	532	518	500	488	475	376
D - ZOL	533	511	491	475	463	368

# ZO-FAST study

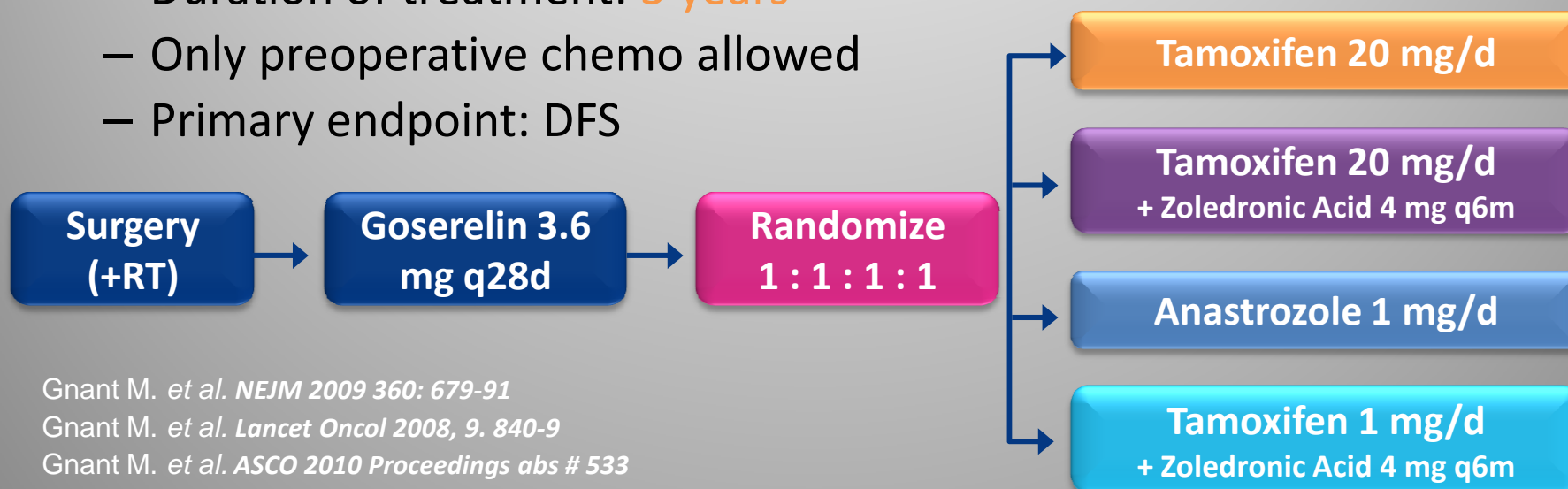
## Site of recurrence



# ABCESG-12 study

(Gnant 2011)

- ABCESG-12 Trial Design
  - Recruitment 1999-2006
  - 1,803 premenopausal patients
  - Stage I & II, ER+ and/or PgR +
  - Duration of treatment: 3 years
  - Only preoperative chemo allowed
  - Primary endpoint: DFS



Gnant M. *et al. NEJM* 2009 360: 679-91

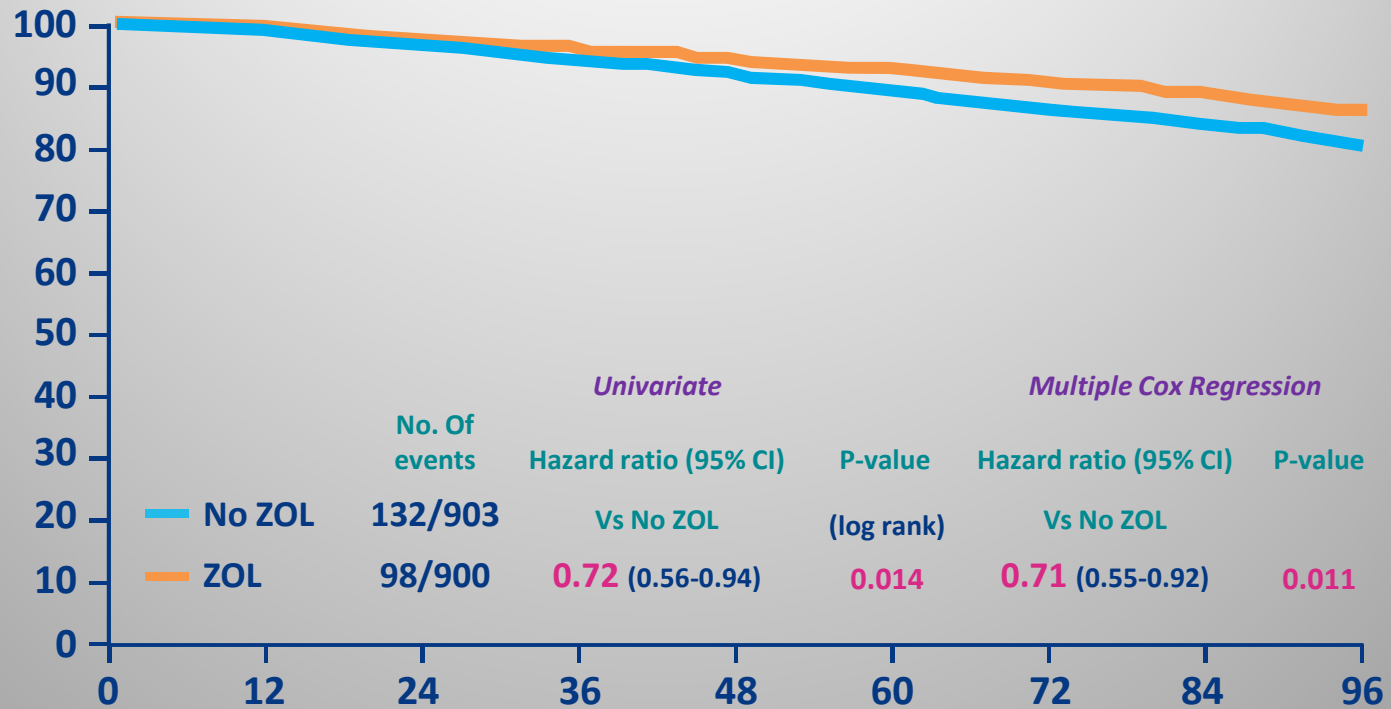
Gnant M. *et al. Lancet Oncol* 2008, 9. 840-9

Gnant M. *et al. ASCO 2010 Proceedings abs # 533*

Gnant M. *et al. Lancet Oncol* 2011, 12. 631. 41

Gnant M. *et al. ASCO 2011 Proceedings; abs # 520*

# ABCESG-12 Study Relapse free survival

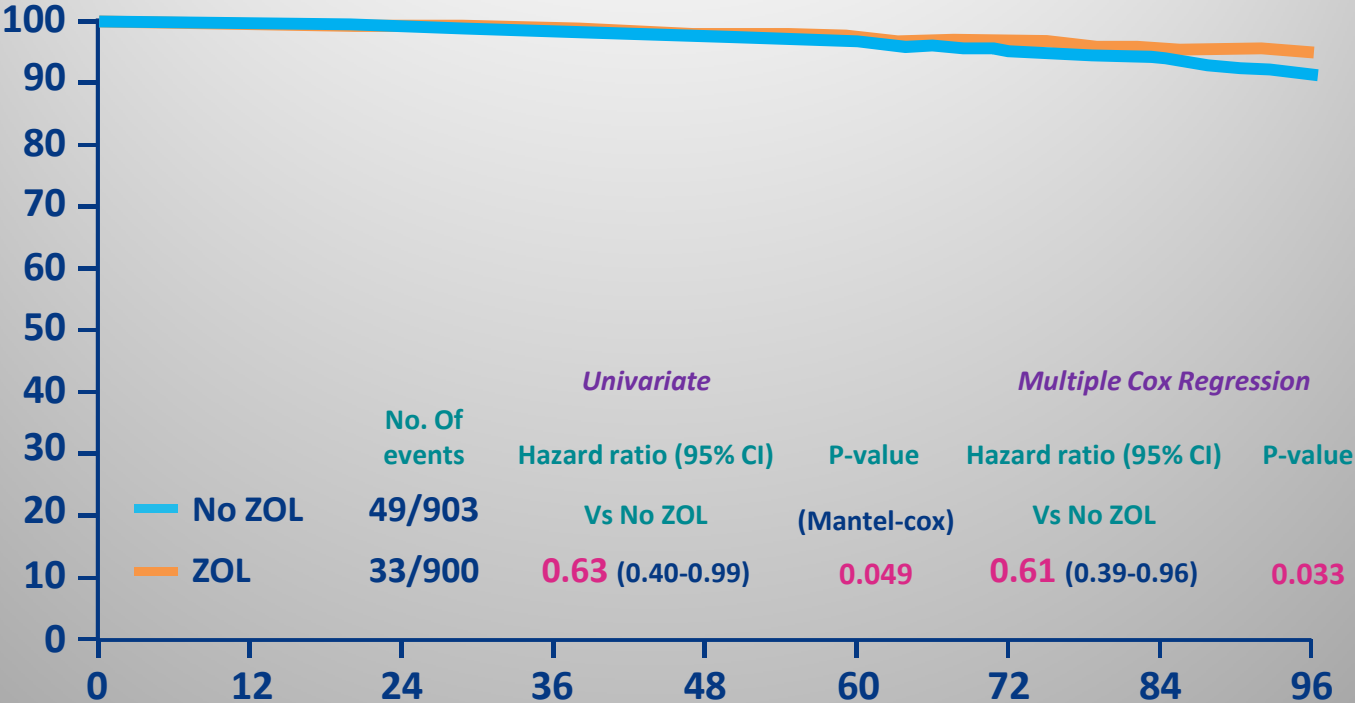


Patients at risk

Time since randomized, months

No ZOL	903	858	833	807	758	653	521	405	191
ZOL	900	862	841	822	788	674	544	419	208

# ABCESG-12 Study Overall Survival



Patients at risk

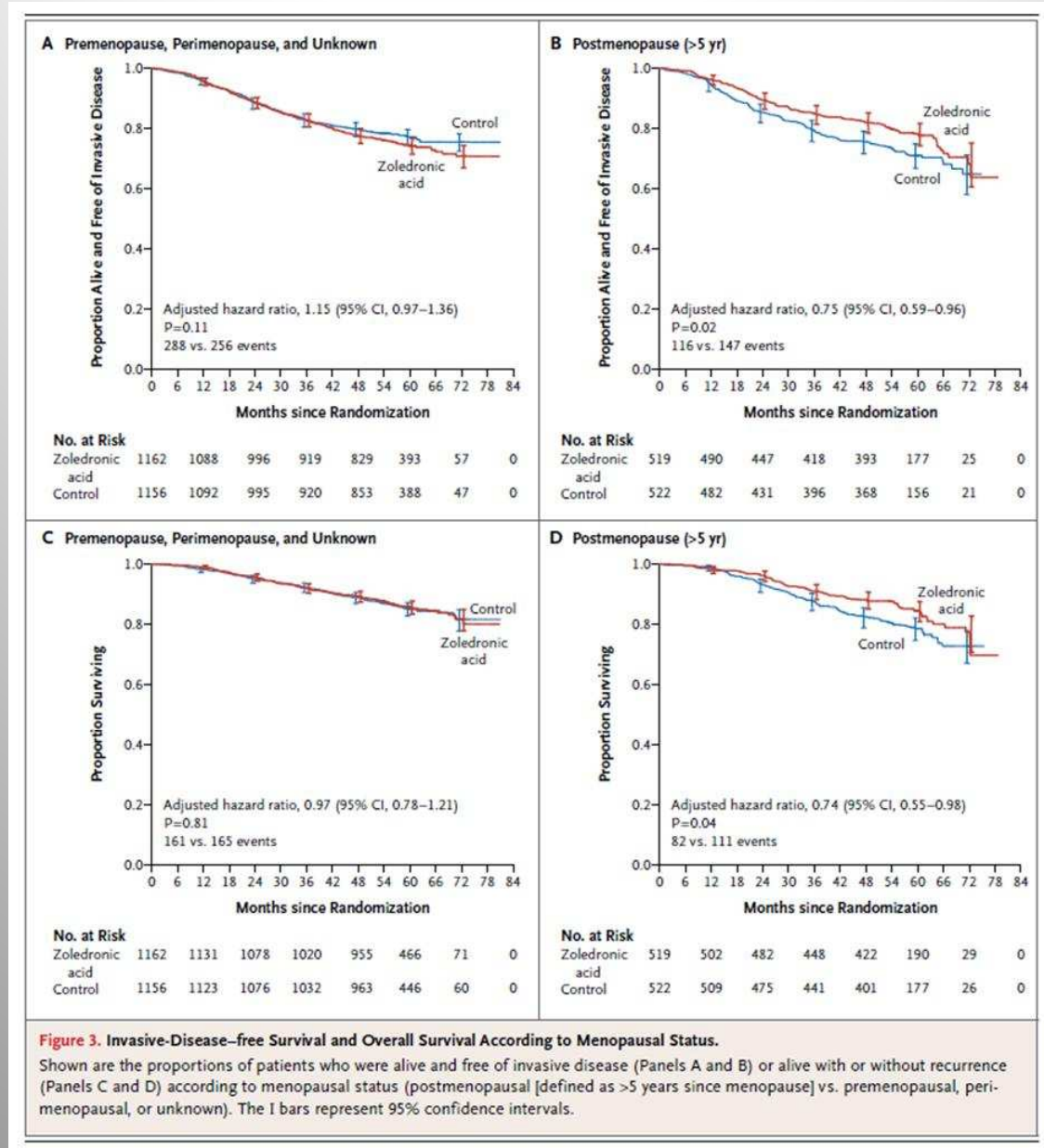
Time since randomized, months

No ZOL	903	864	856	839	811	706	576	456	215
ZOL	900	868	858	849	818	708	587	454	232

# AZURE study

( Coleman 2010)

- Node positive
- 95% received chemotherapy
- 45% premenopausal pts
- Zoledronate vs no Zoledronate



Breast-cancer adjuvant therapy with **zoledronic acid**.

**Coleman RE.** N Engl J Med. 2011 Oct 13;365(15):1396-405

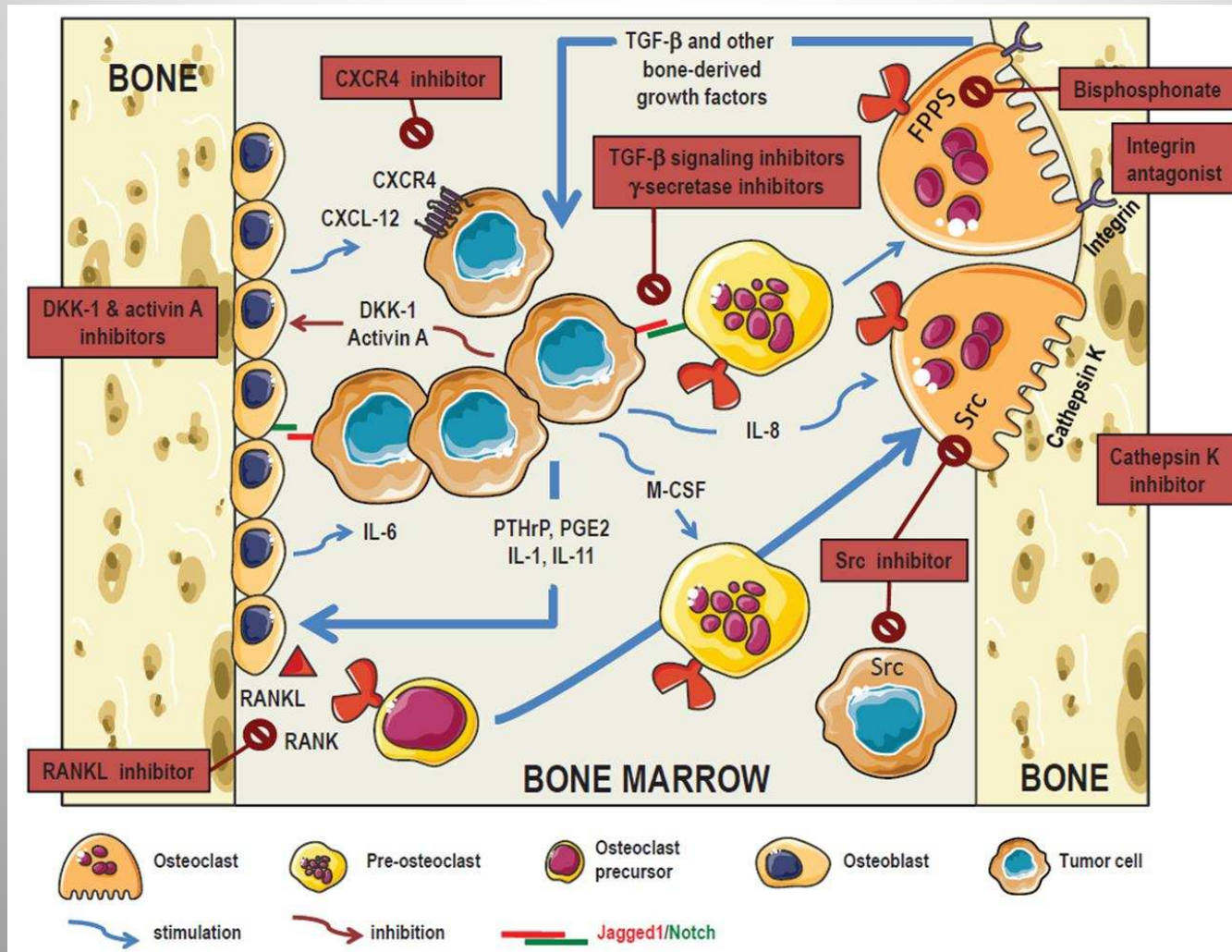


# Ongoing trials of BP in early breast cancer

- SWOG 0307 ( n= 6069): comparison clodronate vs ibandronate vs zoledronate
- ICE (n=1409) : Ibandronate alone for 2 years vs Ibandronate and capecitabine in elderly patients

# Denosumab

- Rank ligand inhibitor
- Denosumab was better than Zoledronate in delaying and preventing skeletal related events in metastatic pts with bone disease ( Stopeck 2008)
- Denosumab decreases bone loss in pts receiving AI and having a low bone mass excluding osteoporosis ( Ellis 2008)
- Ongoing trials in the adjuvant setting:
  - ABCSG 18: Aromatase inhibitor with or without Denosumab in 3400 pts
  - D CARE : Denosumab vs placebo for 5 years



# Other Bone Targeted Therapies (1)

(Cleazardin 2011)

- Integrin  $\alpha v \beta 3$  stimulates osteoclasts by activating src and syk tyr kinases
  - 2 inhibitors ( cilengitide et IMGN 388 in phase I)
- c src stimulates osteoclastic activity:
  - saracatinib ( AZD 0530) inhibits src and abl (phase II)
  - dasatinib with or without zoledronate in phase II
- Cathepsine K plays a major role in bone resorption:
  - balicatib ( AAE 581)
  - Odanacatib ( MK 0822)

# Other bone targeting therapies (2)

(Cleazardin 2011)

- DKK1 blocks the interaction with wnt1 and inhibits osteoblast differentiation . No trial in breast cancer ( but in myeloma with zoledronate)
- Activin A stimulates osteoclast differentiation and inhibits osteoblast differentiation : Inhibitor ACE 011 studied in myeloma ; no trial in breast cancer
- Endothelins stimulate osteoblasts : no study in breast cancer , one inconclusive of atrasentan in prostate cancer
- TGF beta and CXCL-12/CXCR4 inhibitors might be interesting.

# Conclusion

## Bisphosphonates

- Decrease bone events in patients with bone metastases
- Decrease bone loss induced by anti cancer treatment.
- May decrease the risk of relapse and the risk of death , at least some of them and in postmenopausal patients (?)

## Other bone targeted therapies :

- denosumab ( anti rank ligand) has similar effect in bone metastatic disease and in the prevention of bone loss
- Others are in early development