

**In the Near Future, Evidence From  
Randomized Clinical Trials Will  
Support Inclusion of Zoledronic Acid  
as a Component of Adjuvant Systemic  
Therapy for Early Breast Cancer**

**CONTRA**

**Paolo Pronzato,MD**

**Ist Nazionale per la Ricerca sul Cancro  
Genova**

# The real news at ASCO 2008!



- “...Se uno studio clinico europeo, e per di più indipendente, va nella sessione plenaria del maggiore congresso dell'oncologia mondiale, l'attenzione è d'obbligo. Se poi a presentarlo è un giovanottone austriaco
- scatta anche la curiosità...”

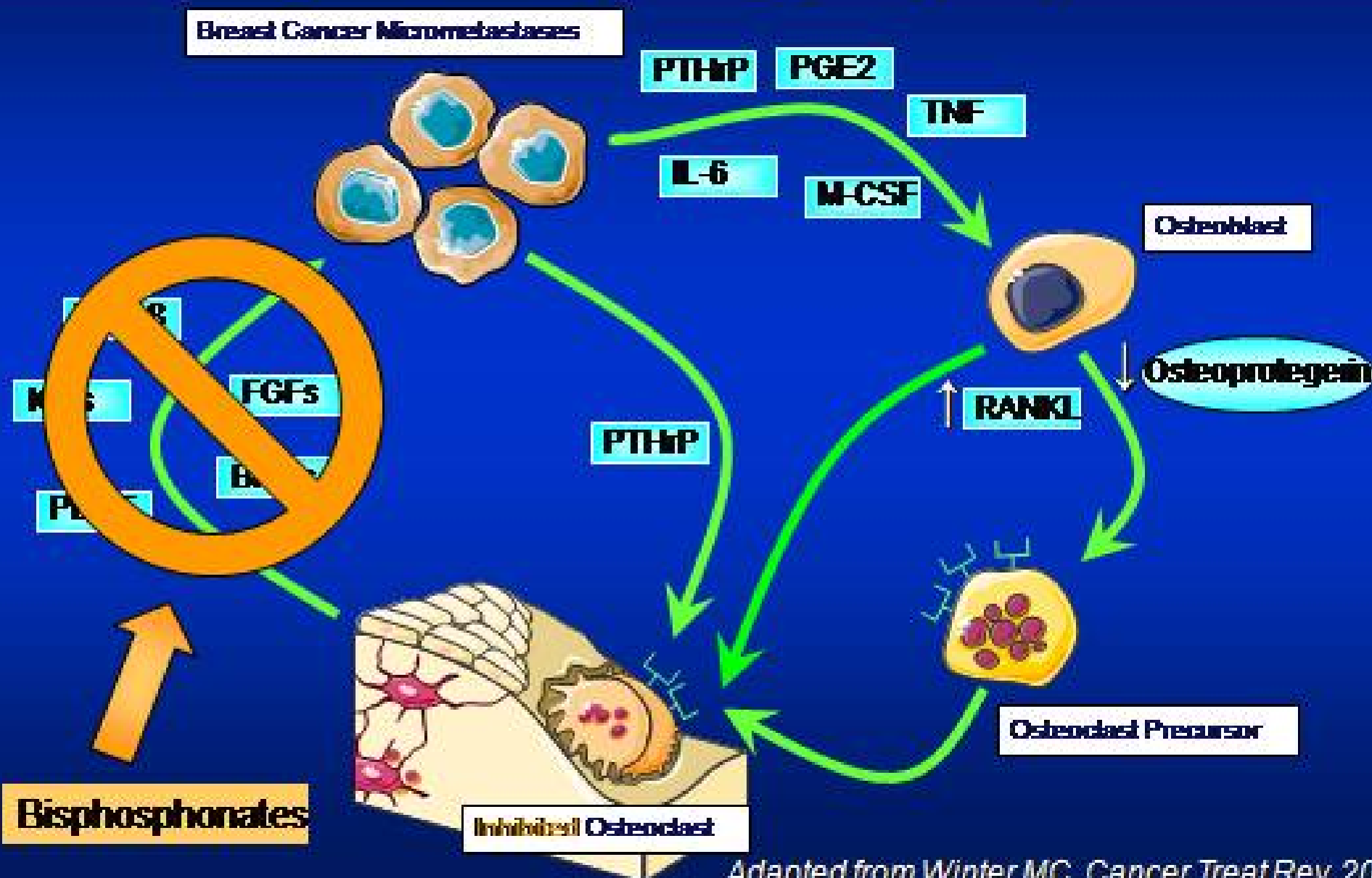


Venerdì 22 agosto 2008: Intervista a Michael Gnant



# BONE MICROENVIRONMENT

## A Vicious Cycle Interrupted by Bisphosphonates



# CALGB: 12-Month Reports

- **Methods:**

- 430 BC pts undergoing adjuvant chemo +/- ZOL 4 mg q 3 mo
- BMD assessed at baseline and 12 mo

- **Results:**

- Most AEs with ZOL were grade 1 or 2; 1 possible ONJ case (0.5%)
- Grade 3: fever (3%), pain (3%), and fatigue (2%)
- Mean change in LS BMD: ZOL (+2.6%) vs Control (-6.4%)  $P < .0001$  ( $\Delta$  9.0%)

- **Conclusions:**

- ZOL combined with adjuvant chemo is feasible and  $\uparrow$  BMD in pts with BC
- Confirms the results from E/Z/ZO-FAST in the premenopausal setting

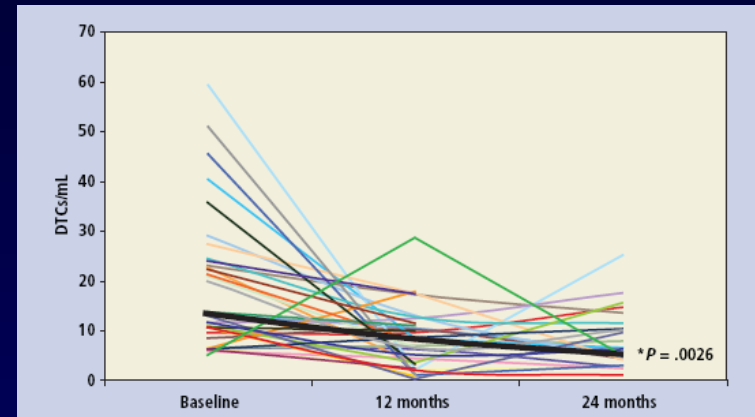
# ZOL and Disseminated Tumor Cells

- **Methods**

- 45 BC pts stage I-III were evaluated for disseminated tumor cells (DTC) by bone marrow (BM) aspirations following neoadjuvant or adjuvant CTX
- Pts received ZOL 4mg IV monthly for 2 yrs

- **Results:**

- Interim analysis of baseline, 1 yr and 2 yr
- Mean baseline DTC was 25.6 DTC/mL
- At 1 yr: 66% pts had a ↓ in DTC ( $P = .0018$ )
- At 2 yr: 71% pts had a ↓ in DTC ( $P = .01$ )



- **Conclusions**

- Data support antitumor effects and mechanism effects of ZOL observed in the clinical setting
- Supports the preclinical evidence showing synergistic activity of ZOL with CT

# Phase II Study of Neoadjuvant CT and ZOL on DTC in BC Pts

## • Methods:

- 120 BC pts receiving neo-adj & adj chemo +/- ZOL (4 mg IV q 3 wks for 12 mo) bone marrow aspirations collected at baseline, surgery (3 mo) and 1 yr

## • Results:

- DTC at baseline: 47% ZOL vs 43% non-ZOL ( $P = .651$ )
- DTC at 3 mo: DTC 30% ZOL vs 47% non-ZOL ( $P = .071$ )
- DTC at 1 yr: 34% of both groups
- In pts with no DTCs at baseline:
  - 79% ZOL vs 51% of non-ZOL pts at 3 mo ( $P = .028$ )
  - 38% ZOL vs 25% of non-ZOL pts at 1 yr

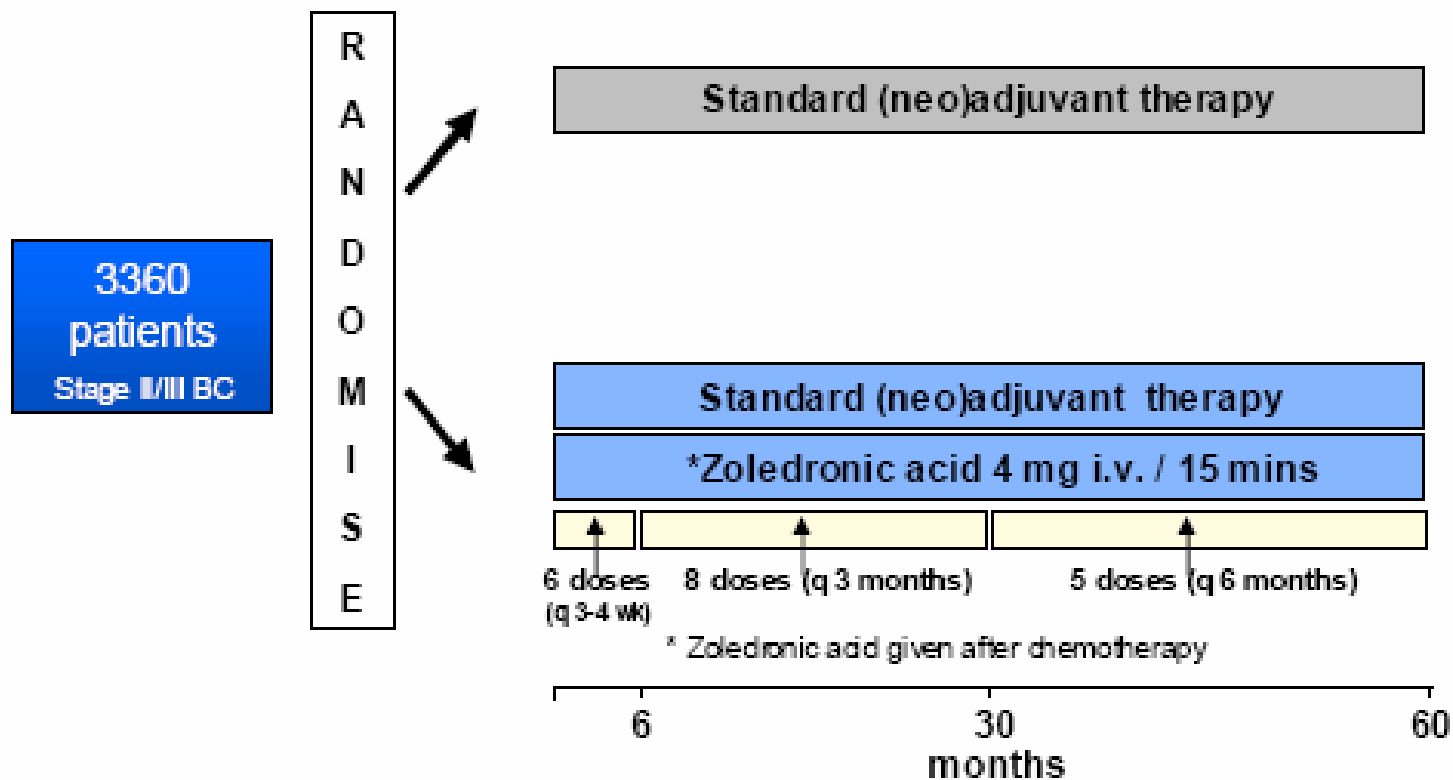


## • Conclusions:

- ZOL post-chemo helps maintain DTC-negative status

### Figure 3: AZURE<sup>®</sup> Study design

Does Adjuvant Zoledronic acid redUce REcurrence in patients with high-risk, localised breast cancer?



205 patients (6.1%) received neoadjuvant chemotherapy

Figure 4: Multivariate analysis investigating residual invasive tumor size by treatment (n=171)

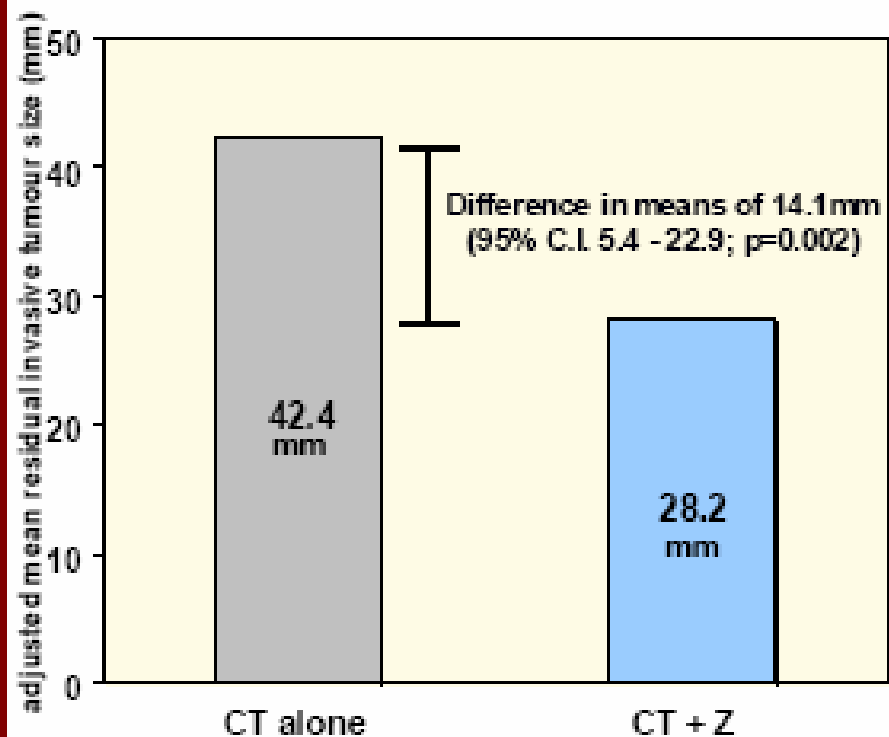
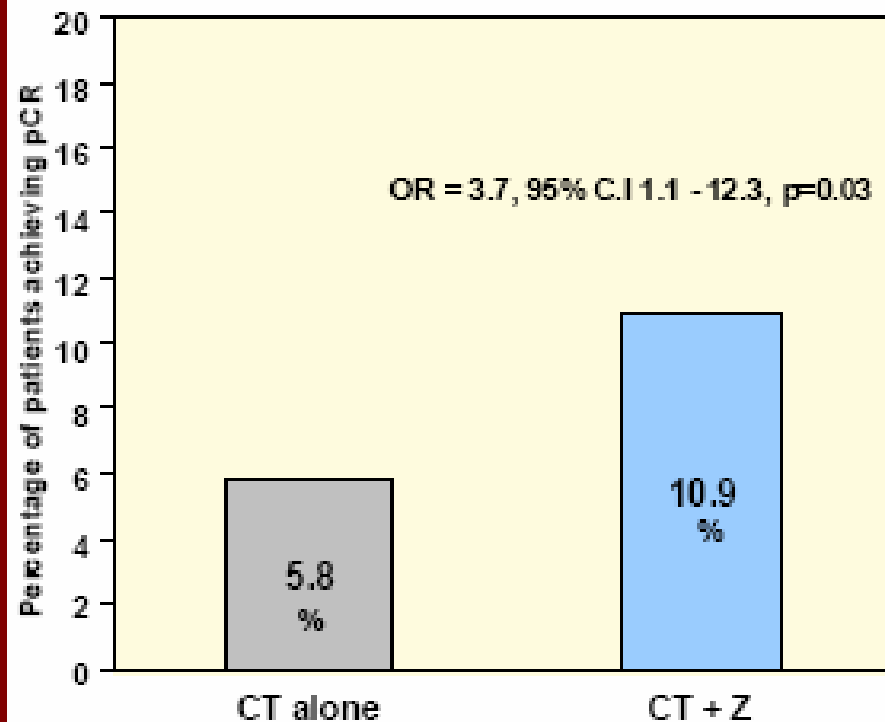


Figure 5: Achievement of pathological Complete Response by treatment group (n=180)



Abstract LBA4: M. Gnant, B. Mlineritsch, W. Schippinger, G. Luschin-Ebengreuth, S. Poestlberger, C. Menzel, R. Jakesz, E. Kubista, C. Marth, R. Greil, on behalf of the ABCSG

# Adjuvant Ovarian Suppression Combined With Tamoxifen or Anastrozole, Alone or in Combination With Zoledronic Acid, in Premenopausal Women With Hormone- Responsive, Stage I and II Breast Cancer: First Efficacy Results From ABCSG-12

Michael Gnant

Professor of Surgery, Medical University of Vienna  
Austrian Breast & Colorectal Cancer Study Group

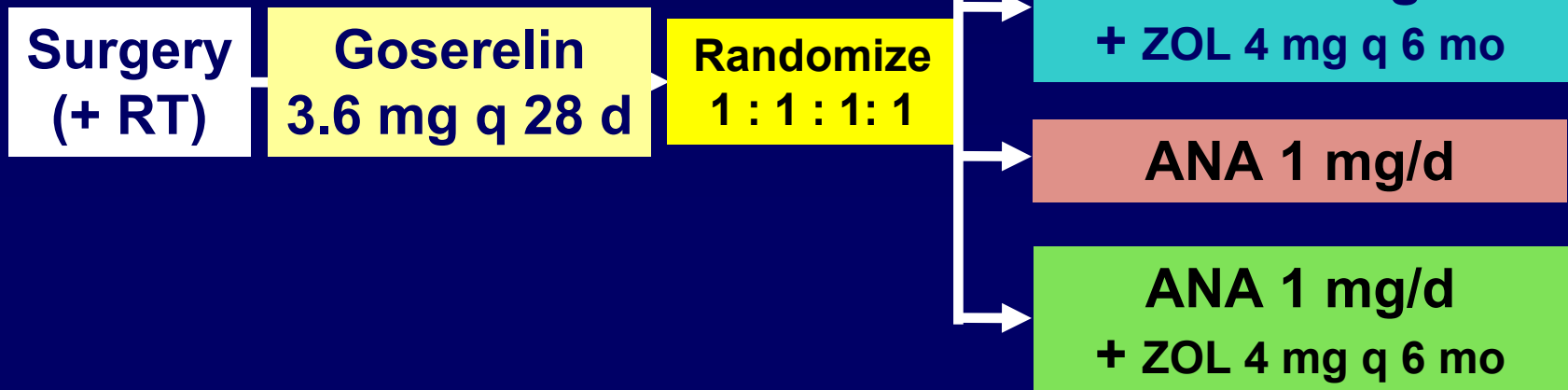


ASCO 2008 Annual Meeting  
Chicago, Illinois; June 1, 2008

# ABCSG-12 Trial Design

- Accrual 1999-2006
- 1,803 premenopausal breast cancer pts
- Endocrine-responsive (ER<sup>+</sup> and/or PgR<sup>+</sup>)
- Stage I and II, < 10 positive nodes
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years

**2 Key Comparisons:**  
TAM vs ANA  
ZOL vs no ZOL

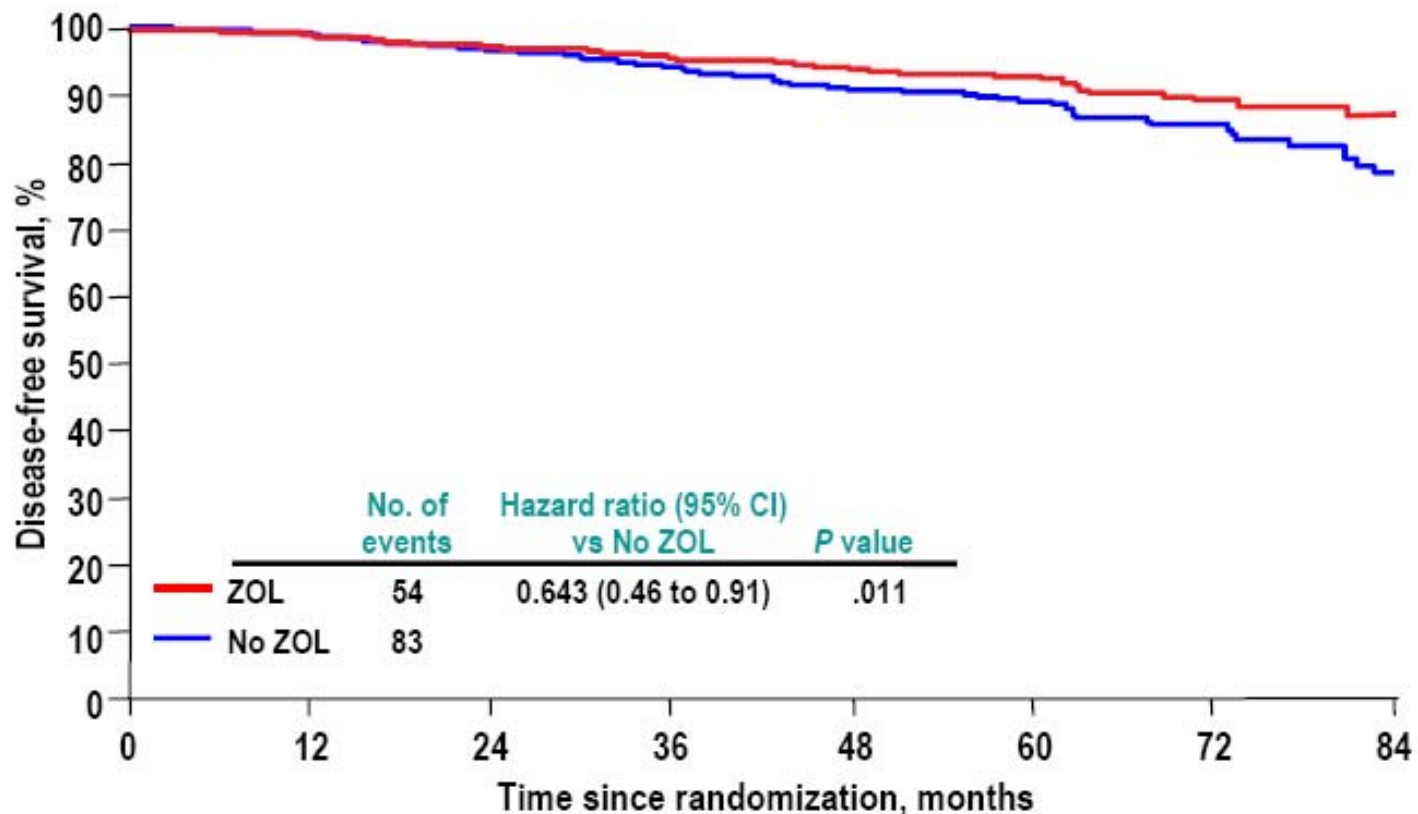


# Patients

n (%)	TAM (n = 452)	TAM + ZOL (n = 449)	ANA (n = 450)	ANA + ZOL (n = 449)
Median age, years	45.5	45.3	45.0	44.5
T1	338 (75.1)	335 (74.6)	348 (77.0)	339 (75.5)
≥ T2	99 (22.0)	98 (21.8)	93 (20.6)	97 (21.6)
Node negative	301 (66.9)	295 (65.7)	303 (67.0)	302 (67.3)
Node positive	136 (30.2)	138 (30.7)	139 (30.8)	135 (30.1)
ER + / ++	216 (48)	212 (47.3)	218 (48.3)	213 (47.4)
ER +++	205 (45.6)	202 (45.0)	208 (46.0)	207 (46.1)
PgR + / ++	211 (46.9)	200 (44.6)	206 (45.6)	182 (40.6)
PgR +++	186 (41.3)	201 (44.8)	201 (44.5)	219 (48.8)
Grading III	93 (20.7)	89 (19.8)	97 (21.5)	98 (21.8)
Breast conservation	359 (79.6)	357 (79.5)	364 (80.4)	358 (79.6)
Neoadjuvant chemo	24 (5.3)	23 (5.1)	24 (5.3)	26 (5.8)
Per-protocol treatment	413 (91.6)	406 (90.4)	419 (92.5)	415 (92.2)

# Primary Endpoint: Disease-Free Survival

Zoledronic Acid Significantly Improves DFS Compared With Endocrine Therapy Alone



Number at risk

No ZOL	904	838	735	565	441	265	161	60
ZOL	899	851	744	573	434	270	131	59

# Selected Adverse/Serious Adverse Events

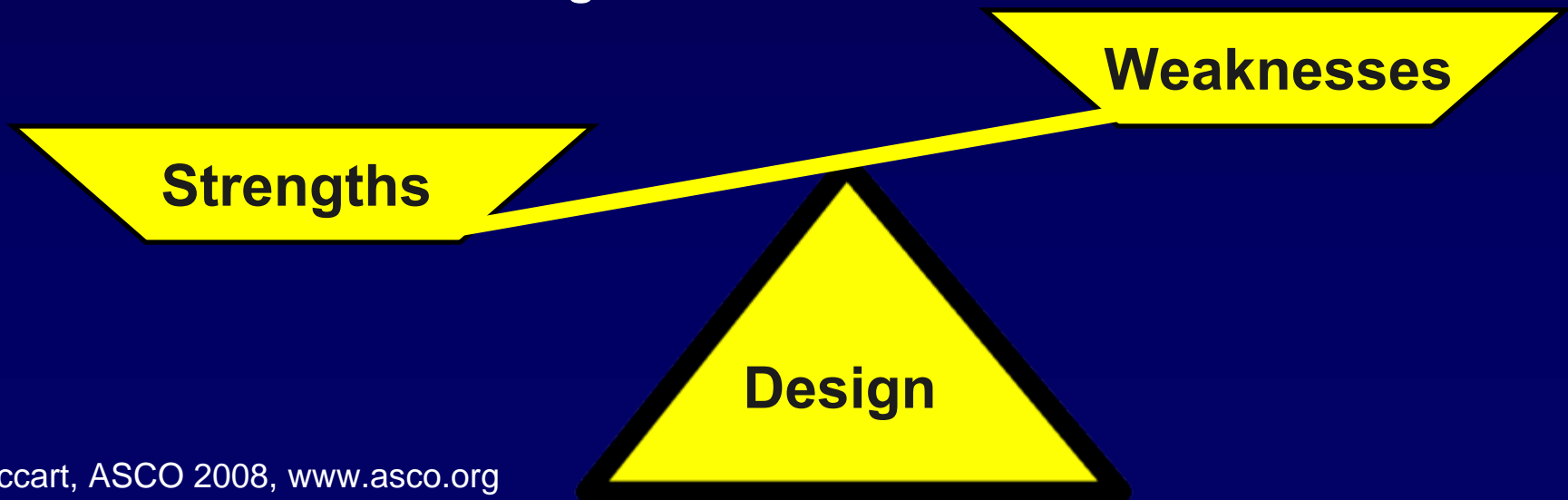
	TAM (n = 435)	TAM + ZOL (n = 434)	ANA (n = 436)	ANA + ZOL (n = 439)	P value 4-group comparison, Fisher's exact test
<b>AE, n (%)</b>					
Arthralgia	52 (11.5)	65 (14.5)	112 (24.7)	150 (33.3)	<.0001
Bone pain	94 (20.8)	132 (29.4)	128 (28.3)	185 (41.1)	<.0001
Fever	9 (2.0)	34 (7.6)	11 (2.4)	46 (10.2)	<.0001
Periodontal disease <sup>a</sup>	5 (1.1)	3 (0.7)	0 (0.0)	6 (1.3)	.054
<b>SAE, n (%)</b>					
Arthralgia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	.374
Bone pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	.499
Fever	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.4)	.882
Fracture	6 (1.3)	4 (0.9)	4 (0.9)	7 (1.6)	.747
Thrombosis	3 (0.7)	5 (1.1)	0 (0.0)	0 (0.0)	.012
Uterine polyp	40 (8.9)	51 (11.4)	7 (1.6)	5 (1.1)	<.0001
Periodontal disease <sup>a</sup>	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	.374

TAM = tamoxifen; ANA = anastrozole; ZOL = zoledronic acid; AE = adverse event; SAE = serious adverse event.

<sup>a</sup> No confirmed cases of osteonecrosis of the jaw.

# ABCSG-12: Strengths and Weaknesses

- 2x2 Factorial design with virtually no chemo background
- Previous trial ABCSG-5 showed Goserelin + Tam > chemotherapy
- Quantification of ER/PgR
- Not double-blind!
- “Control-arm” Goserelin + Tam 3 years not broadly accepted
- No stratification for HER2



# ABCSG-12: Strengths and Weaknesses

- Current report is event- and IDMC-driven
- Intent-to-treat analyses: 2-sided significance levels of 2.5% for primary endpoint
- Underpowered trial for the endocrine question (HR 0.55!)



**ABCSG-12  
is all  
about two  
GREAT  
STORIES**

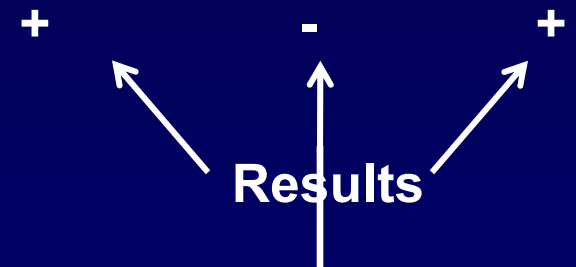
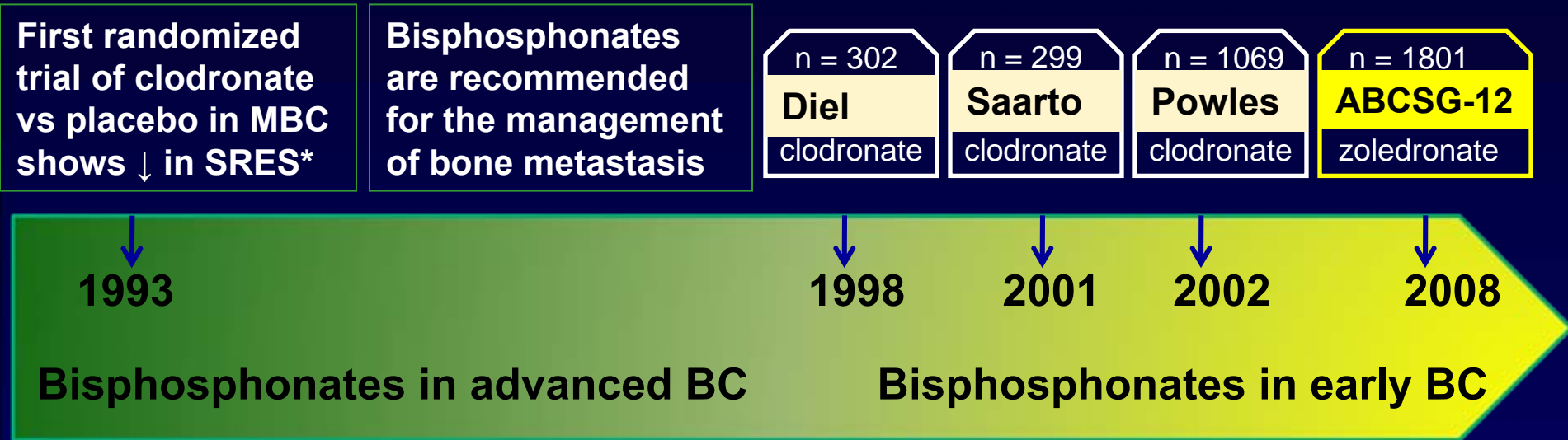
**The  
bisphosphonate  
story**

**The “seed and  
soil” hypothesis  
*S. Paget*  
*The Lancet, 1889***



**THE SOIL MATTERS**

# History of the Clinical Use of Bisphosphonates in Breast Cancer



- In ER+/ER- pre/postmen women
- Against a background of chemo and endocrine treatment
- Inconclusive meta-analysis

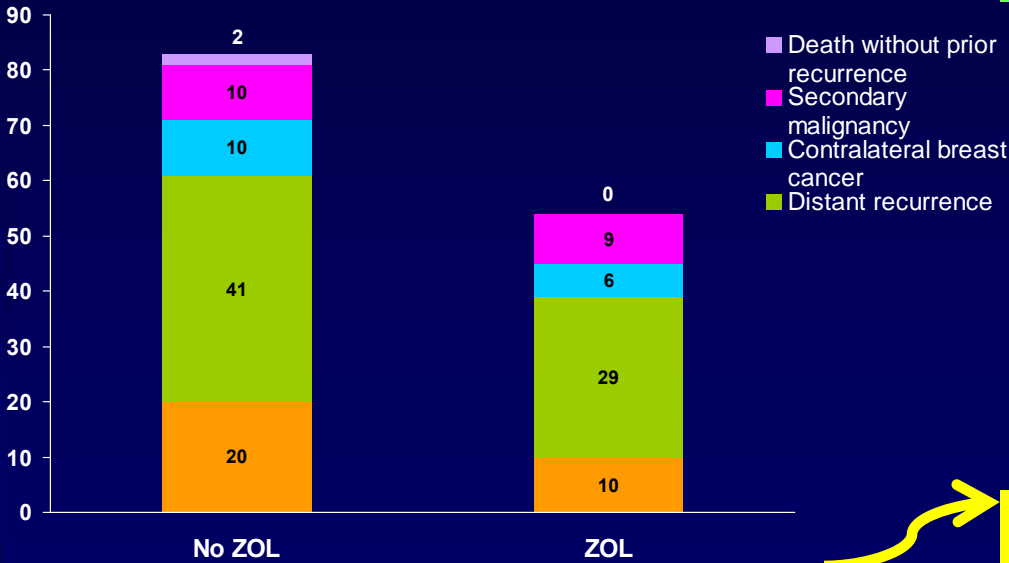
\*skeletal related events

# ABCESG-12: BISPHOSPHONATE QUESTION

## Alendronate – on a Background of Goserelin + Tam or Ana – Markedly Reduces the Risk of a DFS Event

Zoledronate vs nil  
 HR 0.643  
 (95% CI 0.46 – 0.91)  
 (P = .001)

The magnitude of benefit is substantial (with no safety issues)



...and all relapses appear to be reduced!  
 ...but <10% of the women enrolled (n = 137/1803) experienced an event!

The observed benefit could be driven by the anastrozole cohort...



# ABCSG-12 Leaves Many Open Questions about Adjuvant Use of Zoledronic Acid

- What is the mechanism of the beneficial effect (seed, soil, both)?
- Is the magnitude of benefit larger for an AI than for Tam?
- Are efforts at “tailoring” ZA worthwhile in an era in which women are screened and treated for osteoporosis?
- Could a more intensive schedule of ZA be even more effective? ... But will it be safe?
- How long should ZA be continued?
- What are the implications for other tumor types?

**AZURE**

(Big 1-04)

N = 3349

Zoledronate x 5y  
vs nil S  
tage II

Clodronate x 3y vs  
placebo  
Stage I/II

Other important  
first generation  
bisphosphonate  
trials in early BC  
(any HR, any  
menop status)

Ibandronate PO x  
2y vs nil  
Stage II

Zoledronate x 5y  
vs nil  
Stage II

**NSABP-B34**

N = 3323

**GAIN**

N = 3300

M Piccart, ASCO 2008, [www.asco.org](http://www.asco.org)

**NaTan**

N = 543

# Conclusions

- **An important trial, announcing a paradigm shift: targeting both seed and soil**
- **Results of ongoing trials are needed**
  - **Adjuvant Chemotherapy**
  - **Optimal adjuvant hormonotherapy**