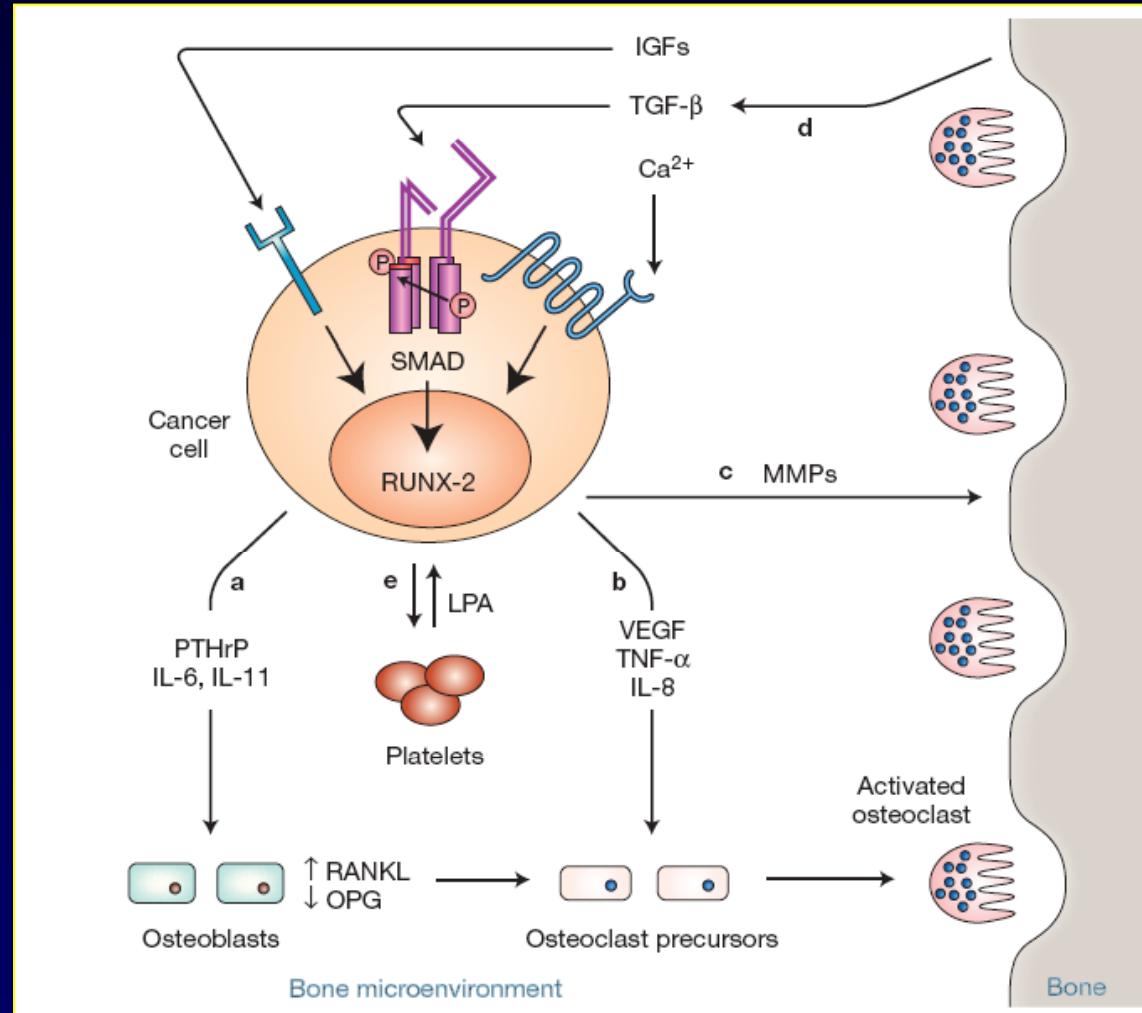


Bone-Targeted Therapy: A Unique and Emerging Addition to Our Armamentarium

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Sheffield, United Kingdom

Basic Molecular Mechanisms in Osteolytic Metastases



Potential Mechanisms for Improved Outcomes with BP Therapy

BPs

↓SREs or fractures

Anticancer effects

↑ Therapy options
(preservation
of function)

↓ SRE-related
mortality

Effects on vicious
cycle (bone) and
anticancer response

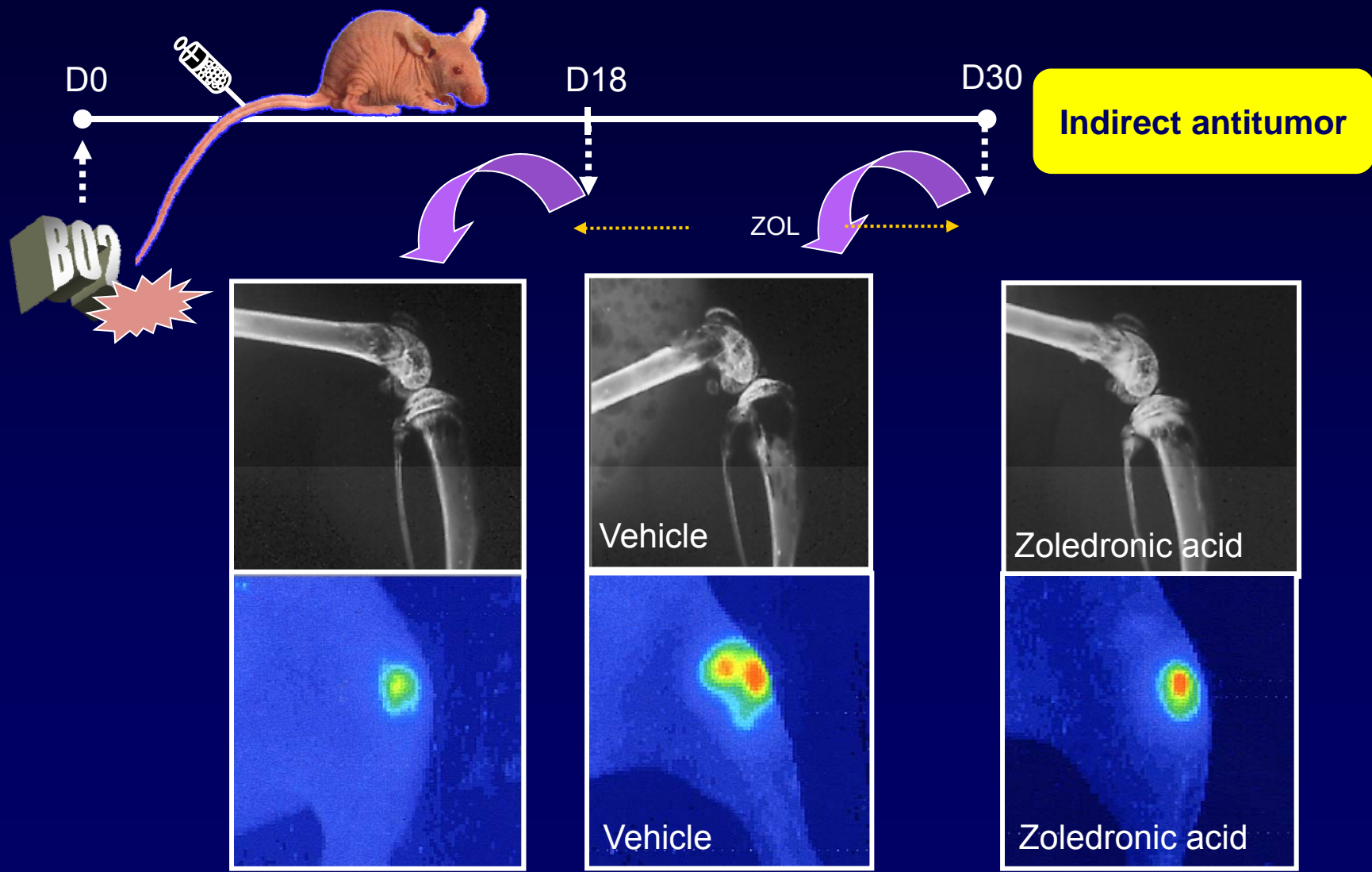
Effects on cancer
cells
(alone or with chx)

Improved disease outcomes

- Delayed disease progression
- Prolonged survival

BPs, bisphosphonates; SRE, Skeletal-related event.

Zoledronic Acid Inhibits the Progression of Osteolytic Lesions in Animals

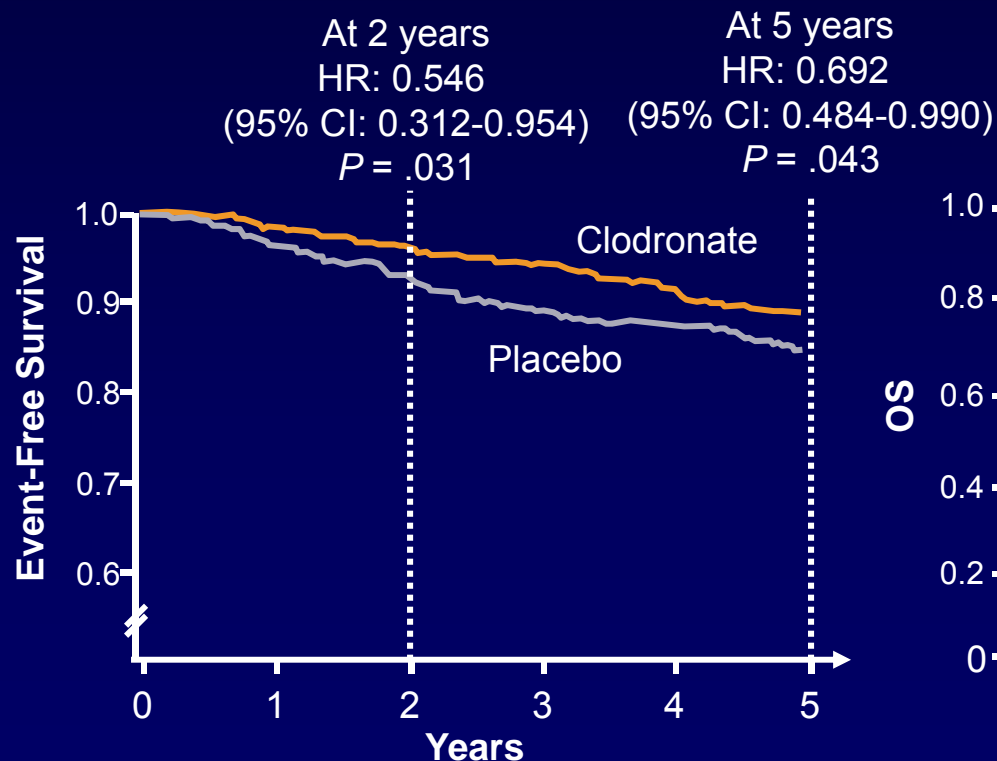


Clodronate Improves Survival in Patients With Breast Cancer

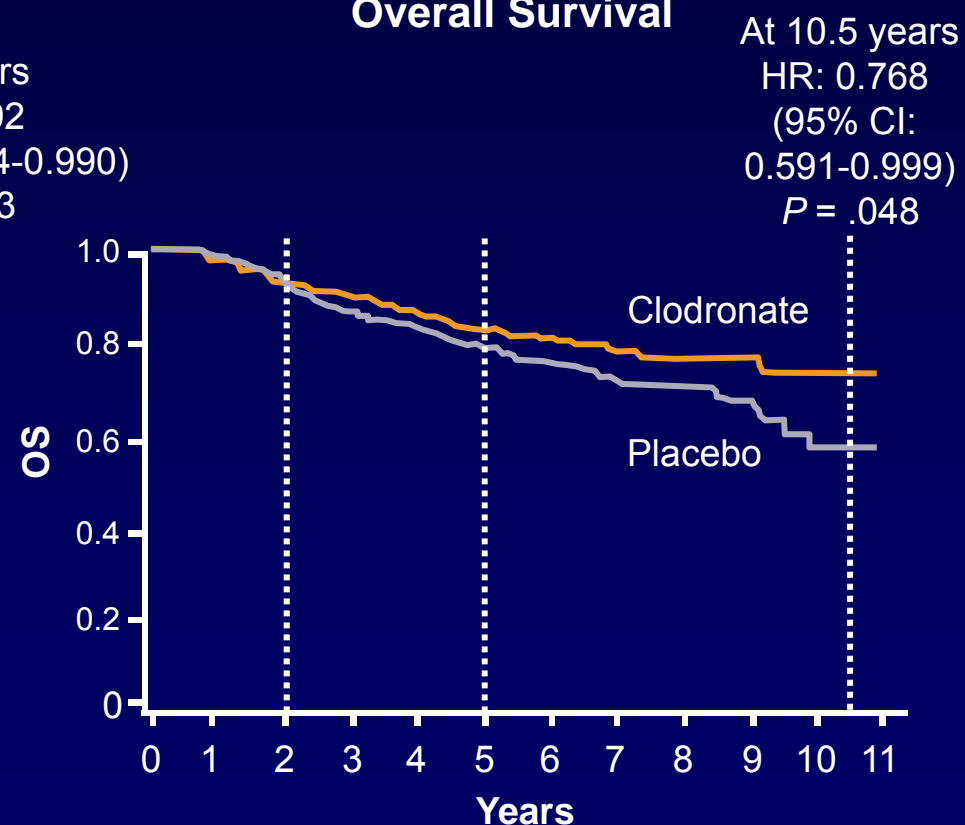
N = 1069 patients

Primary breast cancer

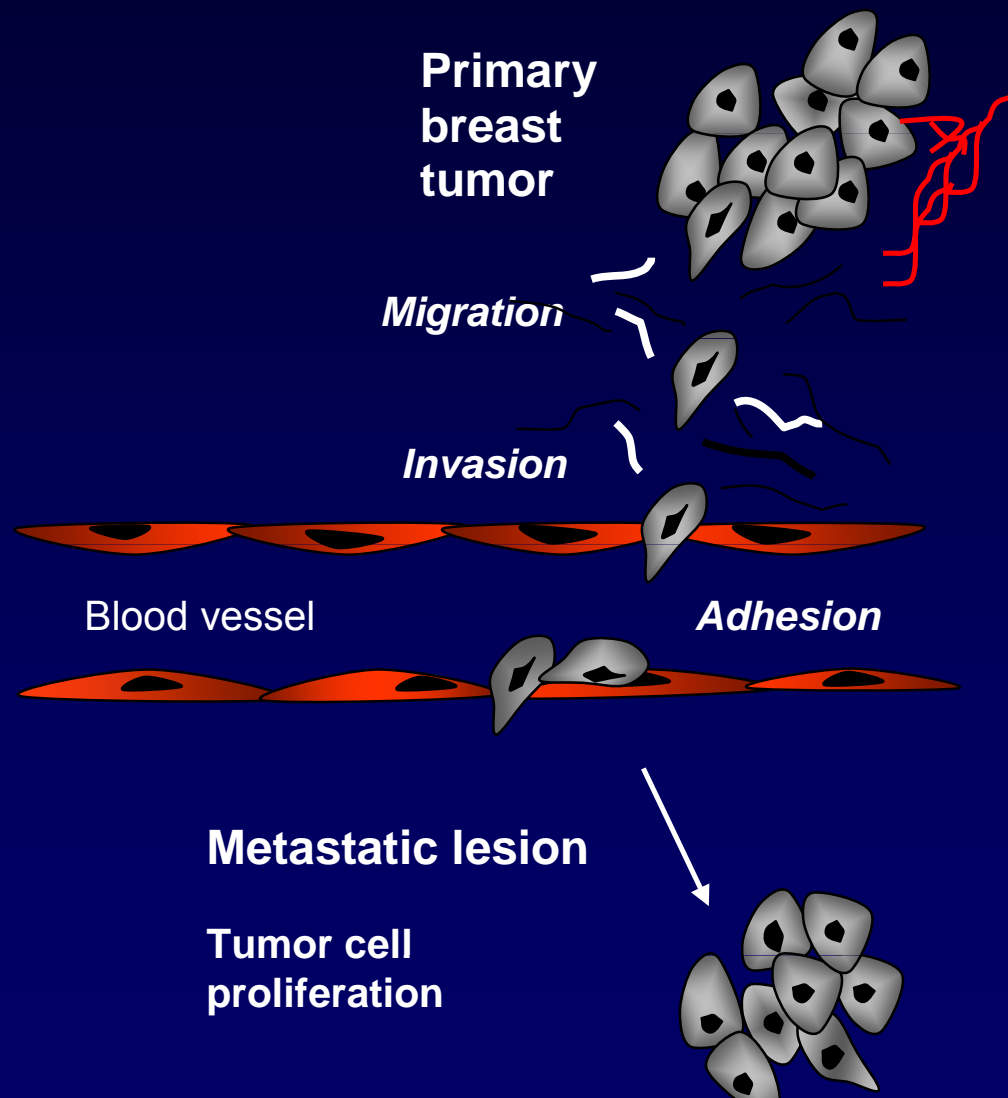
Bone Metastasis-Free Survival



Overall Survival



Schematic Illustration of the Antitumor Activity of Zoledronic Acid



Inhibition of angiogenesis

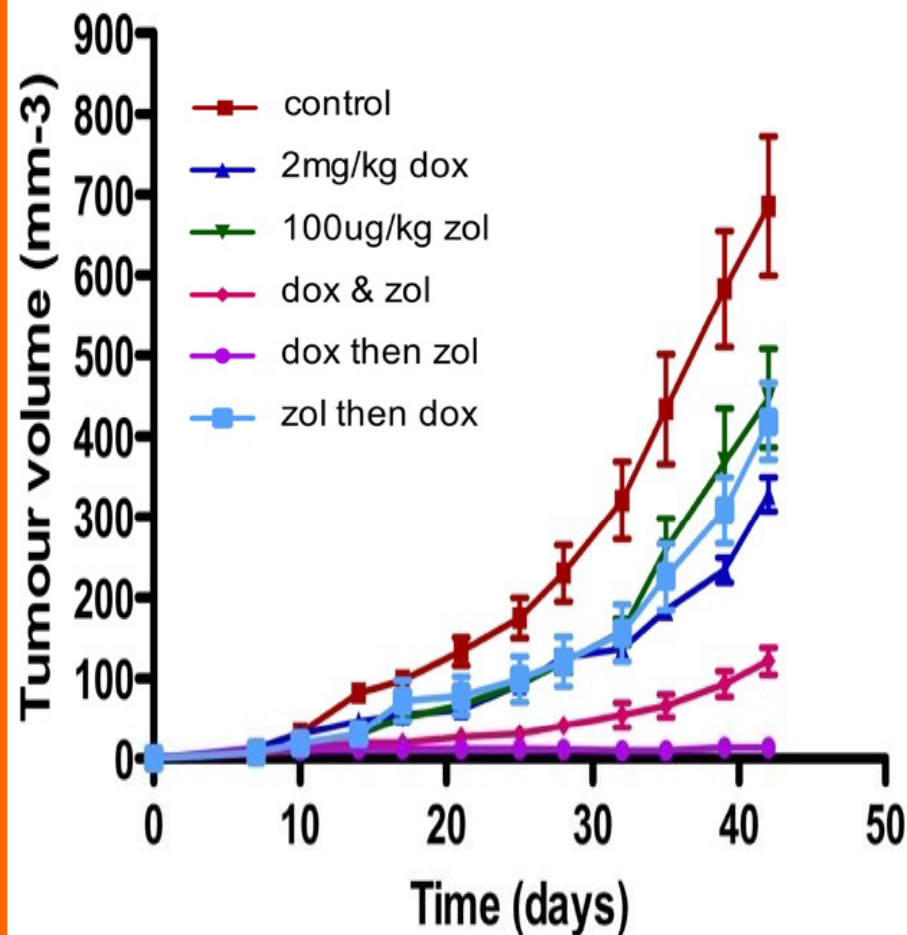
Inhibition of invasion and adhesion

Induction of tumor cell apoptosis

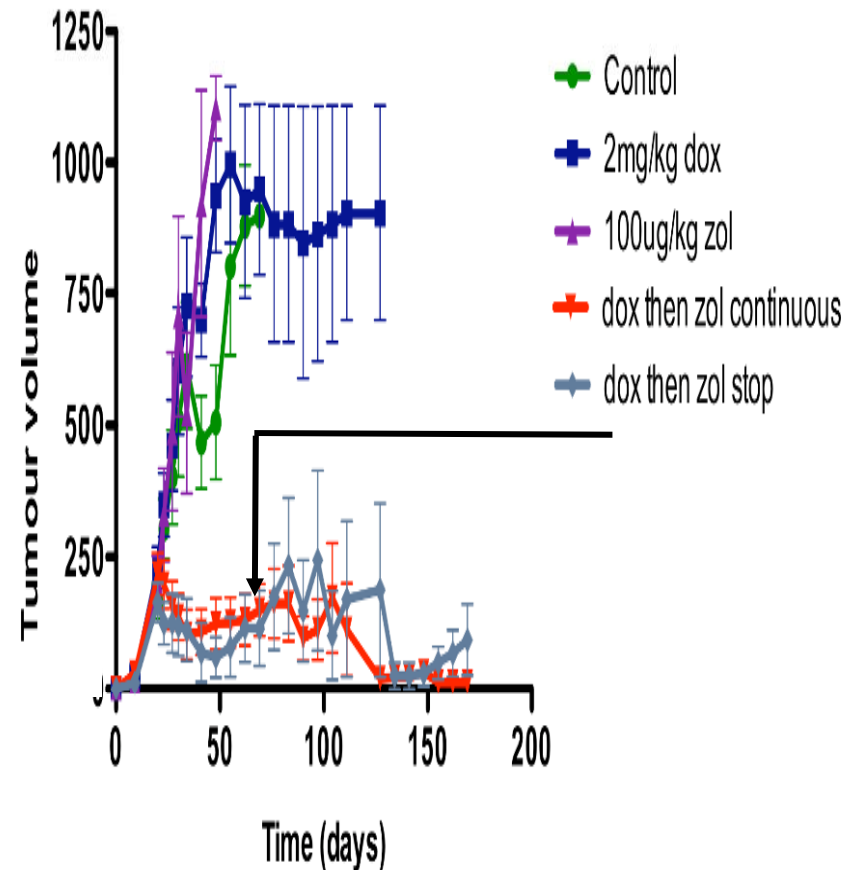
Inhibition of tumor cell proliferation

Synergistic antitumor activity with cytotoxic drugs

In Vivo Evidence for Synergistic Antitumor Activity of Chemotherapy + Zoledronic Acid



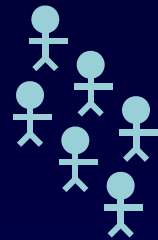
Ottewell PD, et al. *J Natl Cancer Inst.* 2008
100(16):1167-1178.



Ottewell PD, et al. *Int J Cancer.* 2010;126(2):522-532.

Zoledronic Acid May Reduce Bone Marrow Micrometastases

Lin et al¹
EBCC 2008



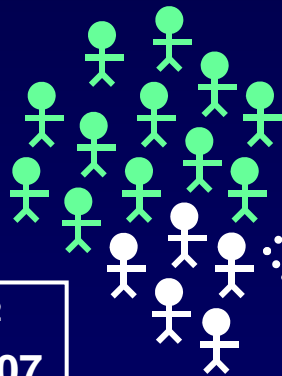
N = 45 with BM micromets
after adjuvant chemotherapy

Zoledronic acid
4 mg/month × 2 year

77%
Reduced BM
micromets at
1 year

Rack et al²
SABCS 2007

N = 172 with BM
micromets after
adjuvant chemotherapy



n = 31

Zoledronic acid 8 mg,
then 4 mg/month × 6 months

13%
Persistent BM
micromets at
39 months

n = 141

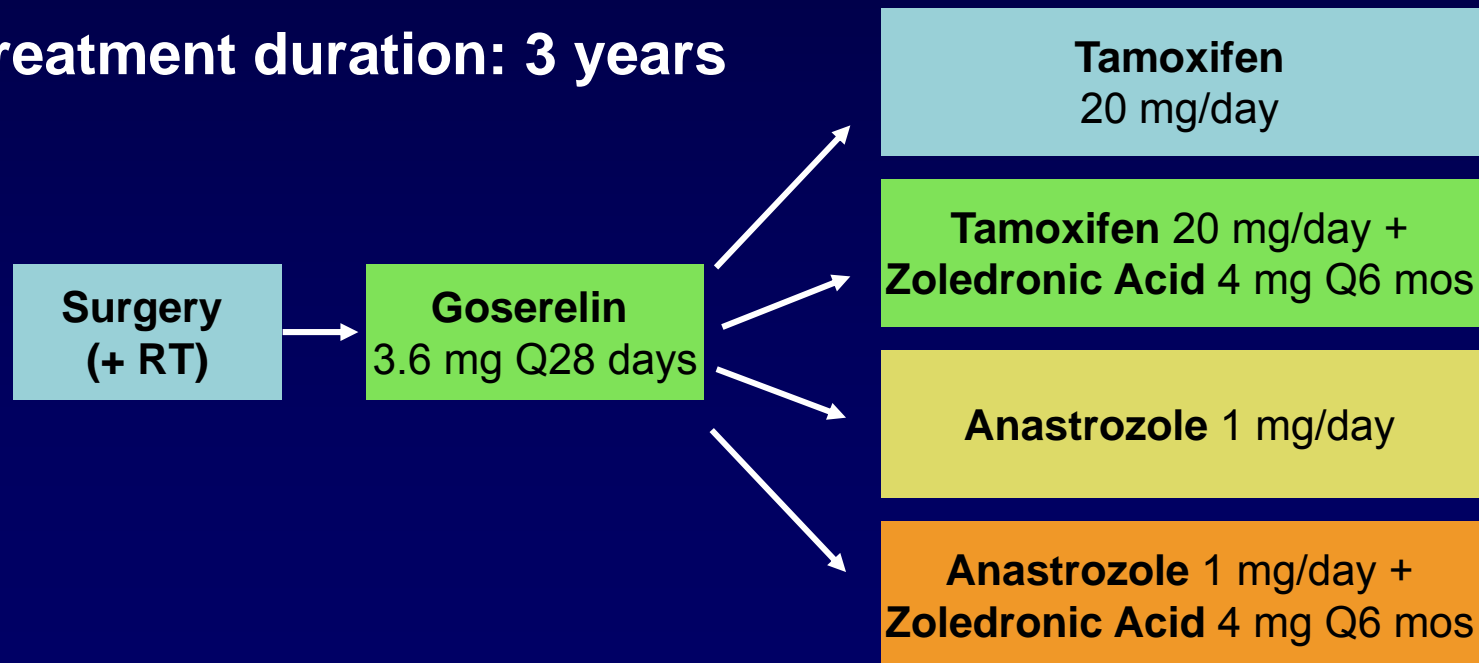
No zoledronic acid

27%
Persistent BM
micromets at
39 months

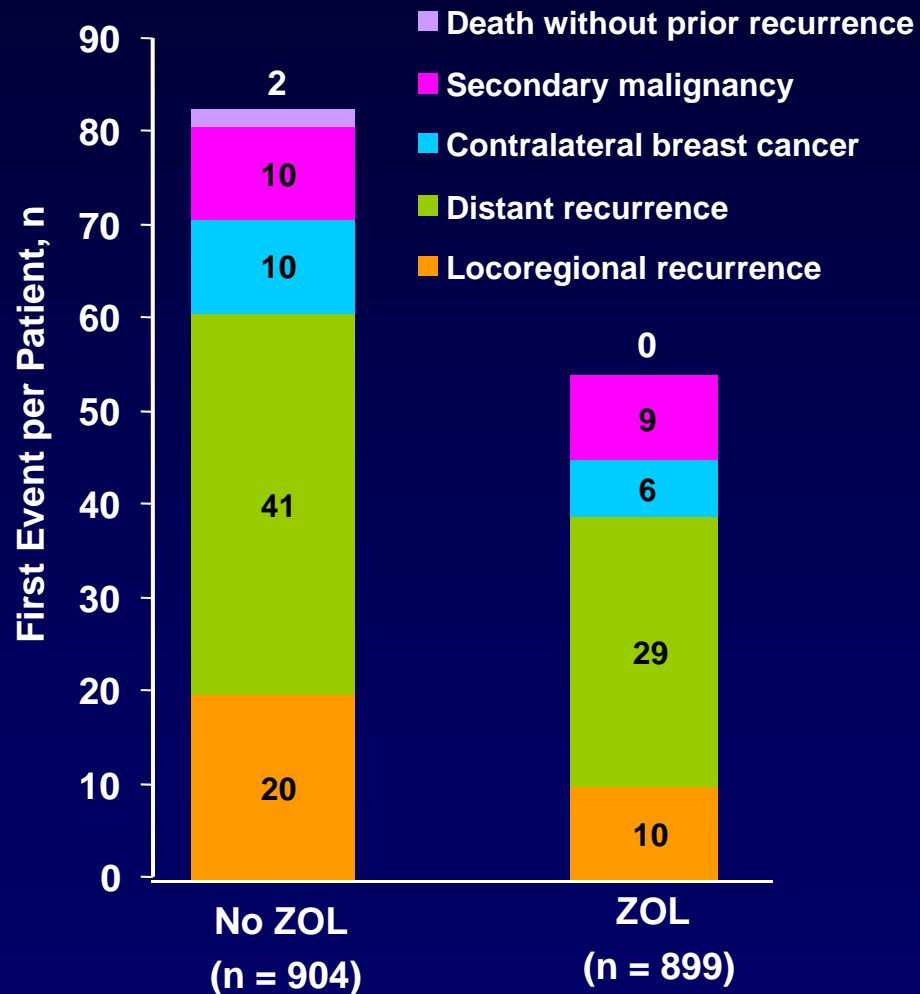
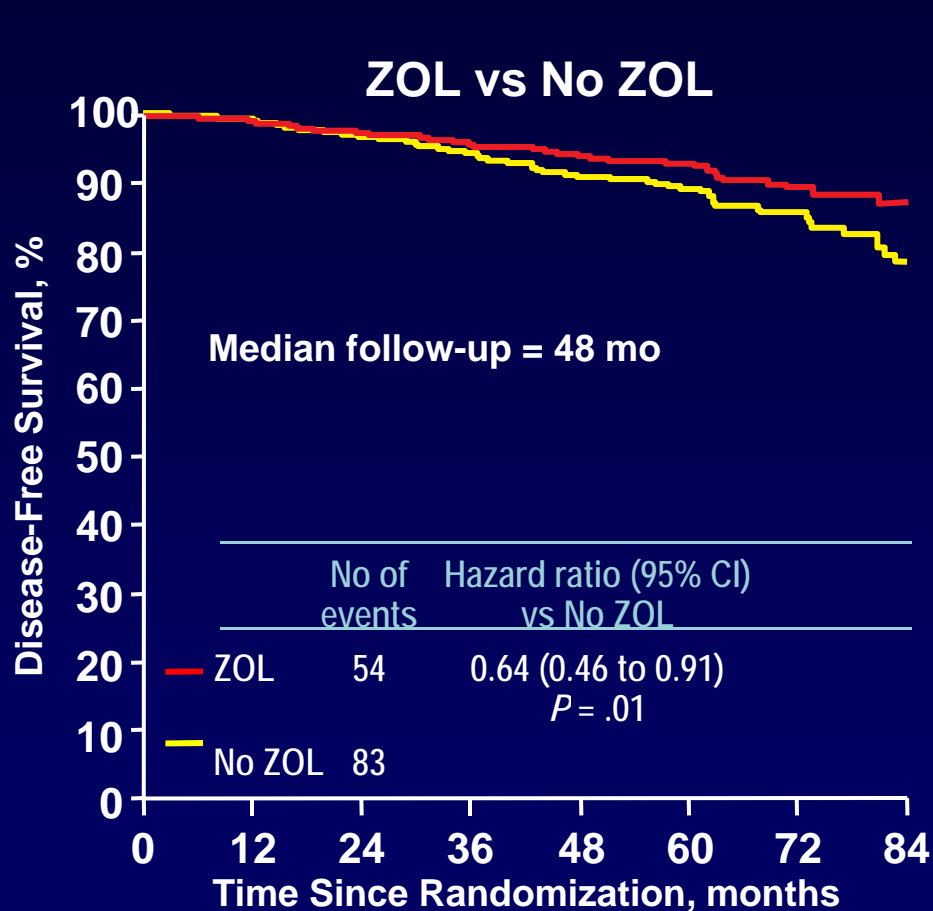
1. Lin A, et al. Presented at: EBCC-6; 15-19 April, 2008; Berlin, Germany. Abstract 242.
2. Rack B, et al. *Breast Cancer Res Treat.* 2007;106(suppl 1): Abstract 511.

ABCESG-12 Trial Design

- **Accrual 1999-2006**
- **1803 premenopausal patients with breast cancer**
- **Endocrine-responsive (ER and/or PgR positive)**
- **Stage I and II, <10 positive nodes**
- **Treatment duration: 3 years**



ZOL Significantly Improved DFS vs Endocrine Therapy Alone: ABCSG-12



TAM, tamoxifen; ANA, anastrozole; ZOL, zoledronic acid; CI, confidence interval.

Z-FAST, ZO-FAST, EZO-FAST: Zoledronic Acid + Letrozole Adjuvant Synergy Trials

Key endpoints

Primary: Bone mineral density

Secondary: Bone markers; fractures; and time to recurrence/relapse

Patients with stage I-IIIa breast cancer, who are:

- Postmenopausal or amenorrheic due to cancer treatment
- ER+ and/or PgR+
- T-score \geq -2 SD

N = 2195

Treatment duration 5 years



*If 1 of the following occurs:
BMD T score $<$ -2 SD, clinical fracture, or
asymptomatic fracture at 36 months

DFS Results in Z-FAST, ZO-FAST & E-ZO-FAST Trials of 6 Monthly Zoledronic Acid

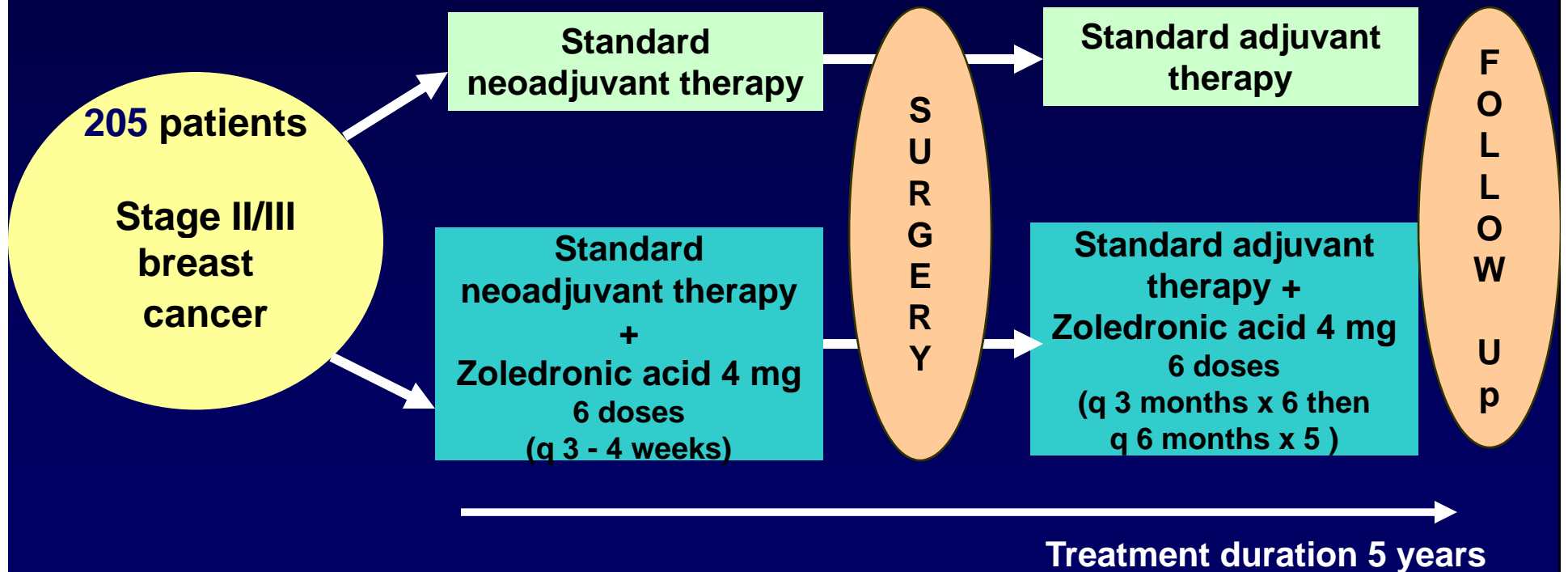
Median follow-up	ZO-FAST 48 months		Z-FAST ^a 61 months		E-ZO-FAST 36 months	
	Upfront (n = 532)	Delayed ^b (n = 533)	Upfront (n = 300)	Delayed ^b (n = 300)	Upfront (n = 263)	Delayed ^b (n = 264)
Disease recurrence	29	49	16	21	18	11
Disease recurrence or death	45	75	23	25	27	13
DFS HR for upfront vs delayed ZOL	0.59 (P = .0175)		0.80 (P = .6283)		1.74 (P = .1397)	

^a End of study.

^b Approximately 18% to 26% of patients initiated delayed zoledronic acid according to protocol.

AZURE: (Neo) Adjuvant Zoledronic Acid in Breast Cancer

Subset of 3360 patients included in AZURE who received neoadjuvant chemotherapy



Zoledronic Acid (ZA) Plus Chemotherapy in the Neoadjuvant Treatment of Breast Cancer

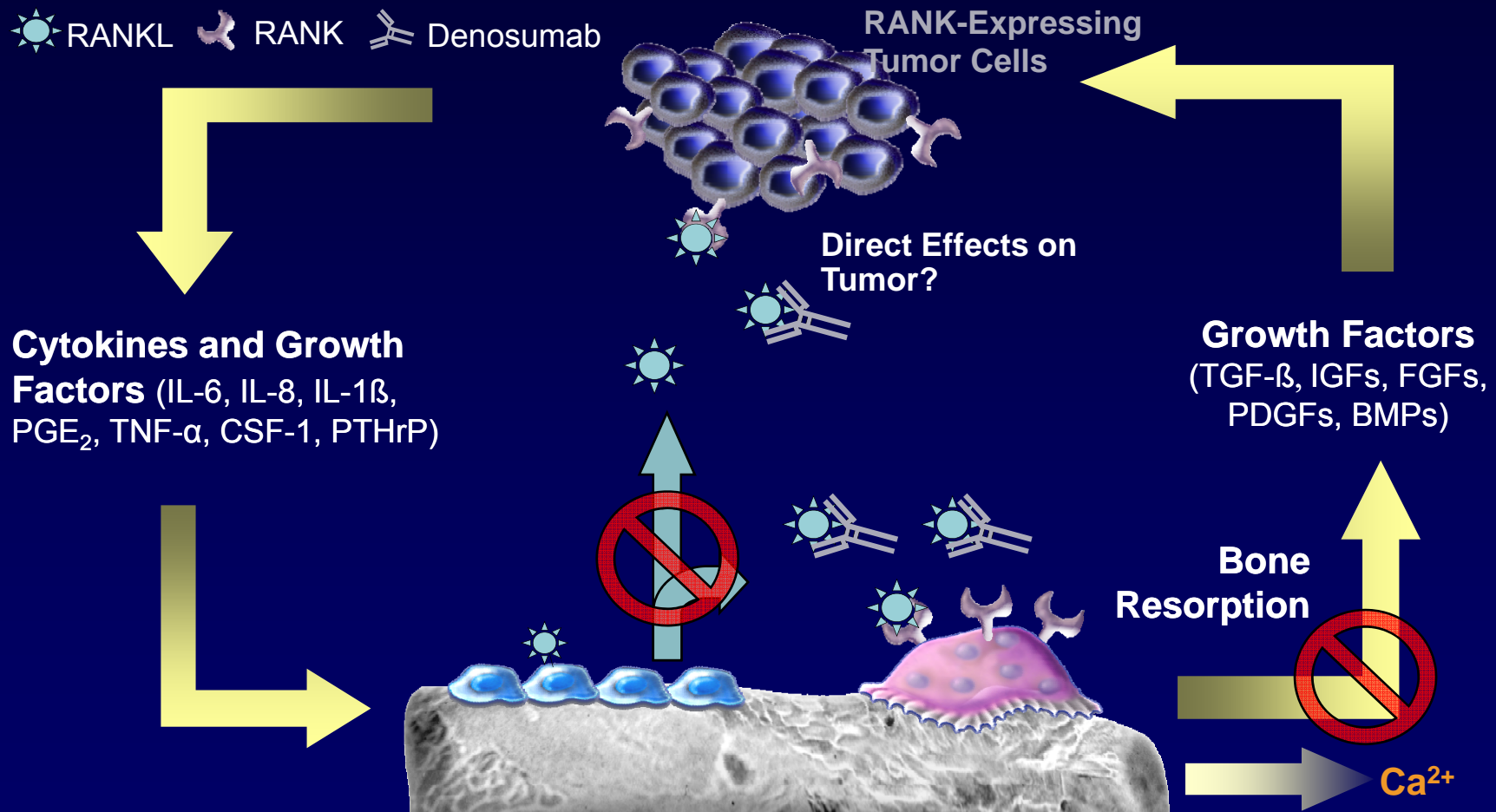
- 205 patients (6.1%) received neoadjuvant therapy

	N	CT alone	CT + ZA	P-Val
Mean residual tumor size	182	27.4 mm	15.5 mm	.0059
Pathologic complete response	195	6.9%	11.7%	.15

CT vs CT+ZA: 79% vs. 70% of patients requiring mastectomy

Possible antitumor effect of ZA in the neoadjuvant setting

Denosumab: Potential Mechanism of Action Supports Adjuvant Trials



Adapted from Roodman GD. *N Engl J Med.* 2004;350(16):1655-1664.

Denosumab vs Zoledronic Acid Phase III Study

Key Inclusion

Adults with advanced breast cancer and confirmed bone metastases

Key Exclusion

Current or prior intravenous bisphosphonate administration

N = 1026 Denosumab 120 mg SC and Placebo IV every 4 weeks

Supplemental Calcium and Vitamin D

N = 1020 Zoledronic acid 4 mg IV and SC placebo every 4 weeks

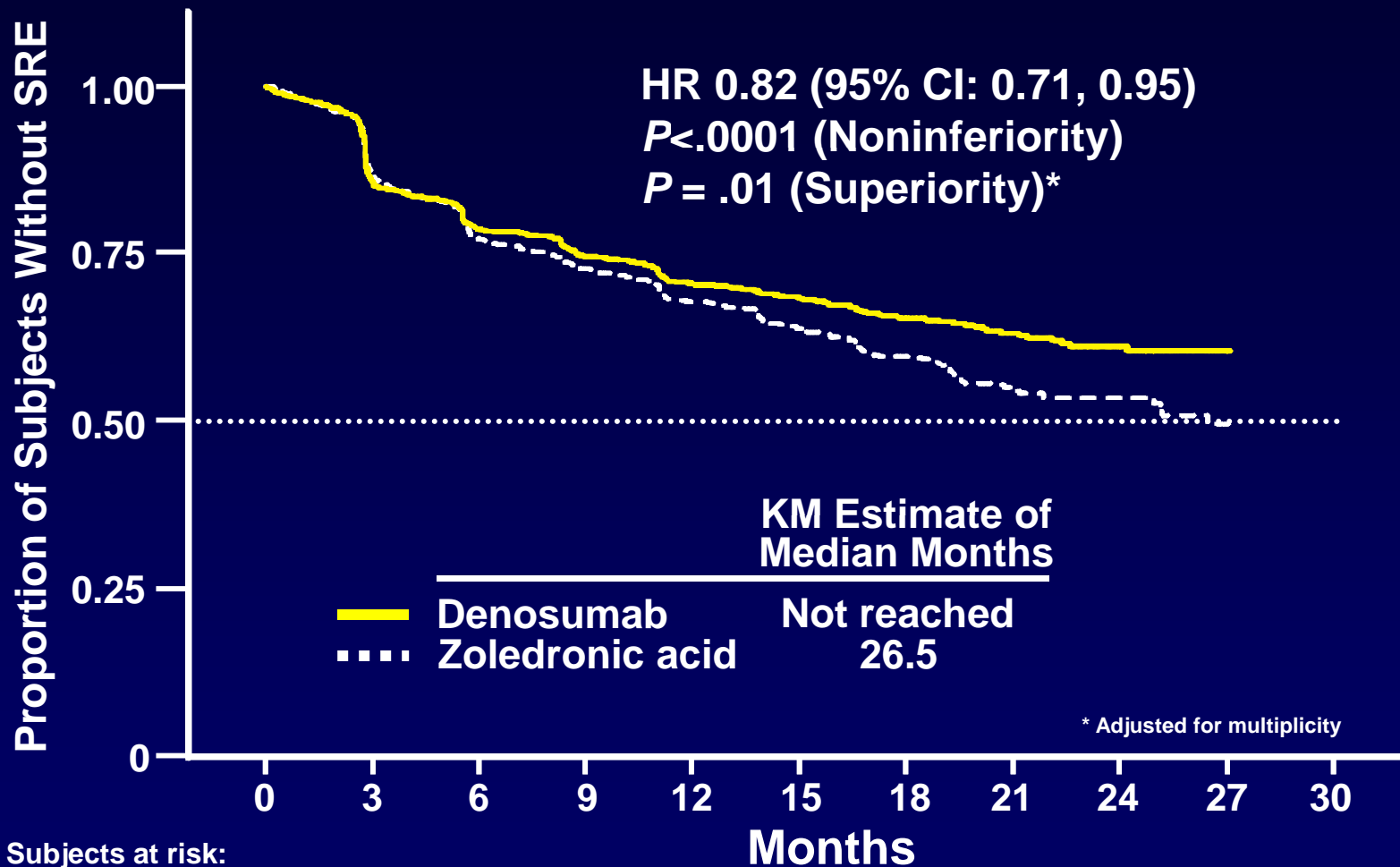
1° Endpoint

- Time to first on-study SRE (noninferiority)

2° Endpoints

- Time to first on-study SRE (superiority)
- Time to first and subsequent on-study SRE (superiority)

Denosumab vs Zoledronic Acid Phase III Study—Time to First On-Study SRE



Subjects at risk:

	0	3	6	9	12	15	18	21	24	27	30
Zoledronic Acid	1020	829	676	584	498	427	296	191	94	29	
Denosumab	1026	839	697	602	514	437	306	189	99	26	

Stopeck A, et al. *Eur J Can Suppl.* 2009;7:2. Abstract 2LBA and oral presentation.

Stopeck A, et al. *Cancer Res.* 2009;69(24 Suppl): Abstract 22.

Ongoing Trials Evaluating the Anticancer Activity of Antiresorptives in Breast Cancer

Study	Bisphosphonate	Region	Accrual Closed / Open
NSABP B34	CLO	Canada/US	3400
AZURE	ZOL	UK/Australia	3360
SUCCESS	ZOL	Germany	3754
SWOG 0307	CLO vs IBA vs ZOL	US	5400 ^a
AZAC	ZOL	France	600
NATAN	Postoperative ZOL	Germany, Austria	659
ABCSG-18	Denosumab	Austria	2800
GAIN	IBA	Germany	3024
ICE	IBA	Germany	1409

Accrual complete; currently enrolling.

BC, breast cancer; CLO, clodronate; IBA, ibandronate; ZOL, zoledronic acid.

^a Ibandronate arm closed to accrual as of September 2009.

Conclusions

- **Bone metastases result from complex interactions between cancer / bone / stem cells in the bone marrow microenvironment**
- **Bone targeted therapy may be indicated in routine early cancer management**
 - **Prevent treatment induced bone loss**
 - Clinically indicated in patients at high risk of fracture
 - **May prevent disease recurrence**
 - Encouraging data in ER+ breast cancer
 - Definitive study results imminent