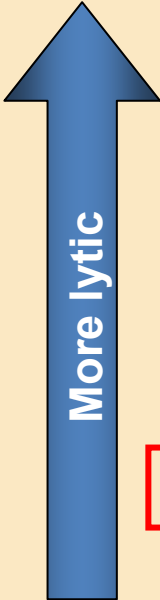


# Bisphosphonates in Breast Cancer: Preventing More than Bone Fractures?

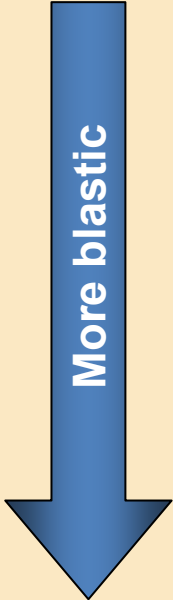
**Prof. Dr. med. Peyman Hadji**  
*Philipps-University of Marburg*  
*Marburg, Germany*

# Bone Disease Is Prevalent in Patients with Metastatic Breast Cancer

	5-year world prevalence, thousands <sup>1</sup>	Incidence of bone metastases in cancers <sup>2</sup>	Median survival, months <sup>2-4</sup>
<b>Myeloma</b>	<b>144</b>	<b>70 - 95</b>	<b>6 - 54</b>
<b>Renal</b>	<b>480</b>	<b>20 - 25</b>	<b>12</b>
<b>Melanoma</b>	<b>533</b>	<b>14 - 45</b>	<b>6</b>
<b>Bladder</b>	<b>1,000</b>	<b>40</b>	<b>6 - 9</b>
<b>Thyroid</b>	<b>475</b>	<b>60</b>	<b>48</b>
<b>Lung</b>	<b>1,394</b>	<b>30 - 40</b>	<b>6 - 7</b>
<b>Breast</b>	<b>3,860</b>	<b>65 - 75</b>	<b>19 - 25</b>
<b>Prostate</b>	<b>1,555</b>	<b>65 - 75</b>	<b>12 - 53</b>



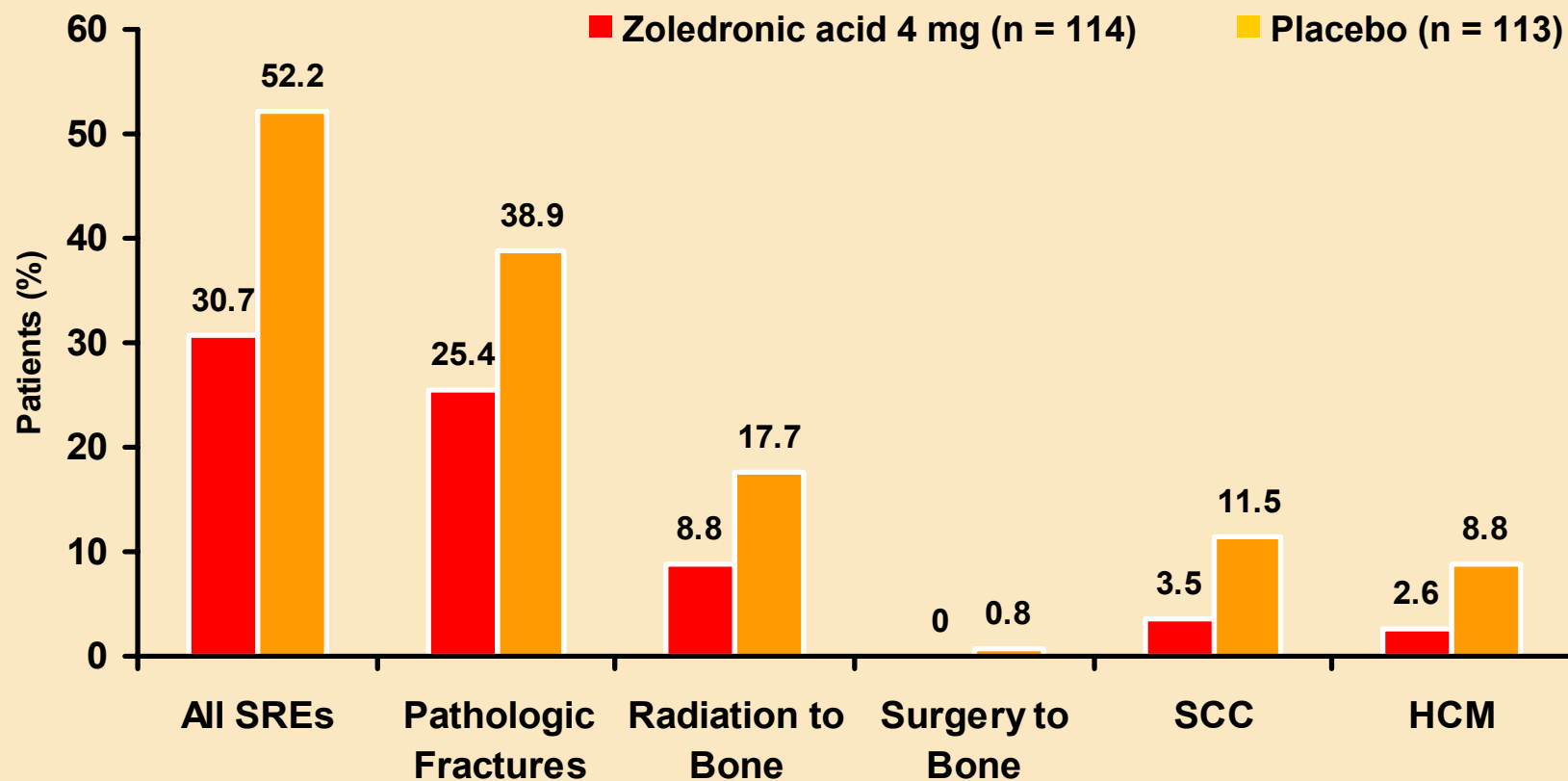
More lytic



More blastic

1. Parkin DM, et al. *Int J Cancer*. 2001;94(2):153-156; 2. Coleman RE. *Cancer Treat Rev*. 2001;27(3):165-176; 3. Coleman RE. *Cancer*. 1997;80(8):1588-1594; 4. Zekri J, et al. *Int J Oncol*. 2001;19(2):379-382.

# Zoledronic Acid Reduced All Types of SREs at 1 Year in Patients with Bone Metastases From BC



SRE, skeletal-related event; BC, breast cancer; SCC, spinal cord compression; HCM, hypercalcemia of malignancy.

# Bone-Targeted Therapies Indicated in Breast Cancer

	Indication				
	Prevention of SREs				
	HCM	Multiple myeloma	Breast cancer	Prostate cancer <sup>a</sup>	Other solid tumors
Clodronate (oral)	✓	✓	✓		
Pamidronate (IV)	✓	✓	✓		
Zoledronic acid (IV)	✓	✓	✓	✓	✓
Ibandronate (oral and IV)	✓		✓		

 = European Registration
  = Worldwide Registration

BC, breast cancer; SRE, skeletal-related event; HCM, hypercalcemia of malignancy; IV, intravenous.

<sup>a</sup> In the United States, prostate cancer must have progressed despite hormone therapy.

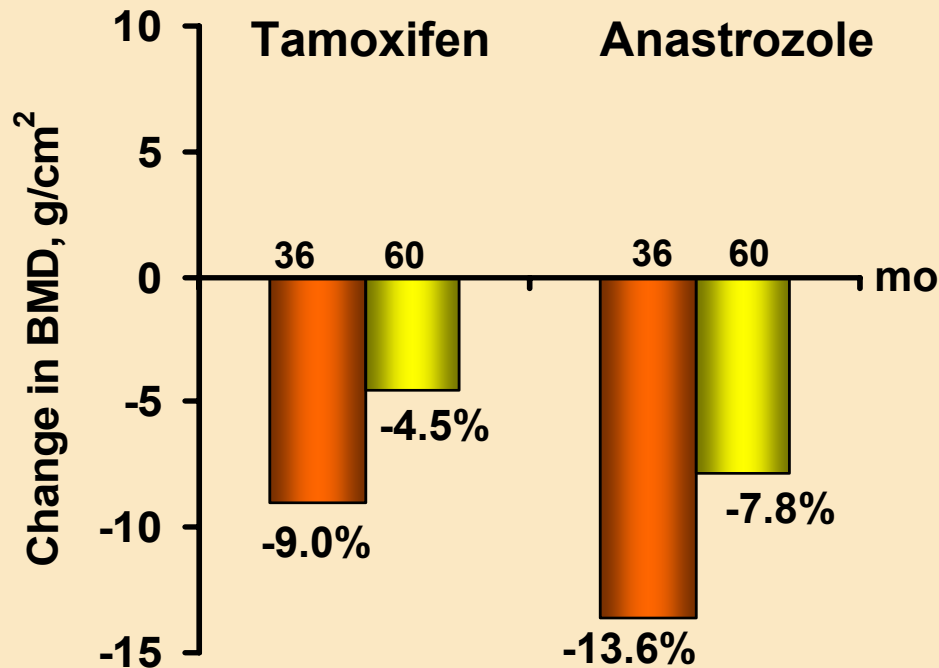
Prescribing information for pamidronate and zoledronic acid is available at: [www.pamidronate.com](http://www.pamidronate.com) and [www.zometa.com](http://www.zometa.com). Further information for clodronate and ibandronate is available at [www.bayer.nl/ebbsc/cms/nl/healthcare/bayer\\_schering\\_pharma](http://www.bayer.nl/ebbsc/cms/nl/healthcare/bayer_schering_pharma) and [www.roche.com](http://www.roche.com).

# Summary: Prevention of SREs in Women With Metastatic Breast Cancer

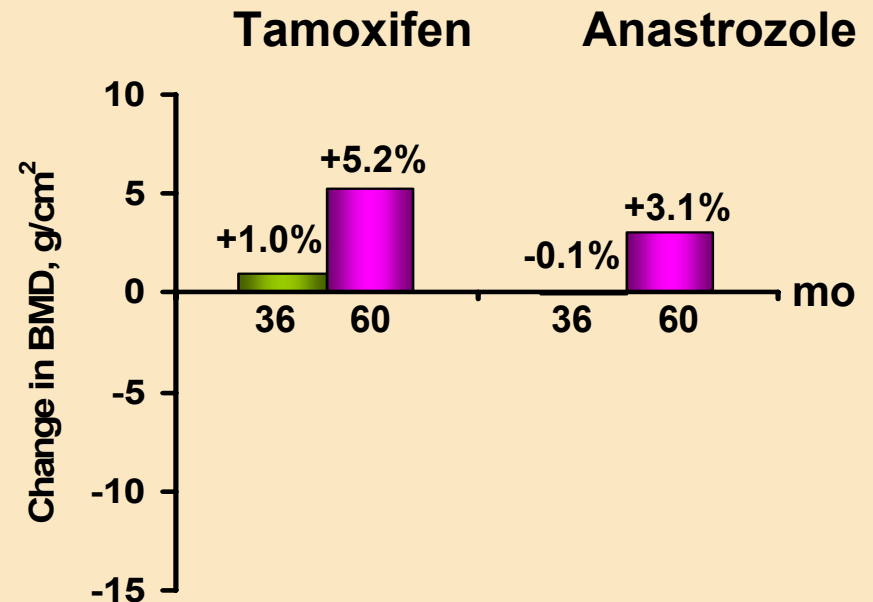
- The goal of bone targeted therapy is to prevent/delay skeletal related events (SREs):
  - Pathological fracture, spinal cord compression, need for radiotherapy or surgery to bone
  - Palliation and control of bone pain
- Bisphosphonates have long-term efficacy and known safety profile profiles
  - Zoledronic acid has been used in more than 3 million patients worldwide since its approval

# ABCESG-12 Bone Substudy: Continued Improvement in BMD 2 Years After Cessation of ZOL Treatment (N=404)

## No zoledronic acid



## Zoledronic acid



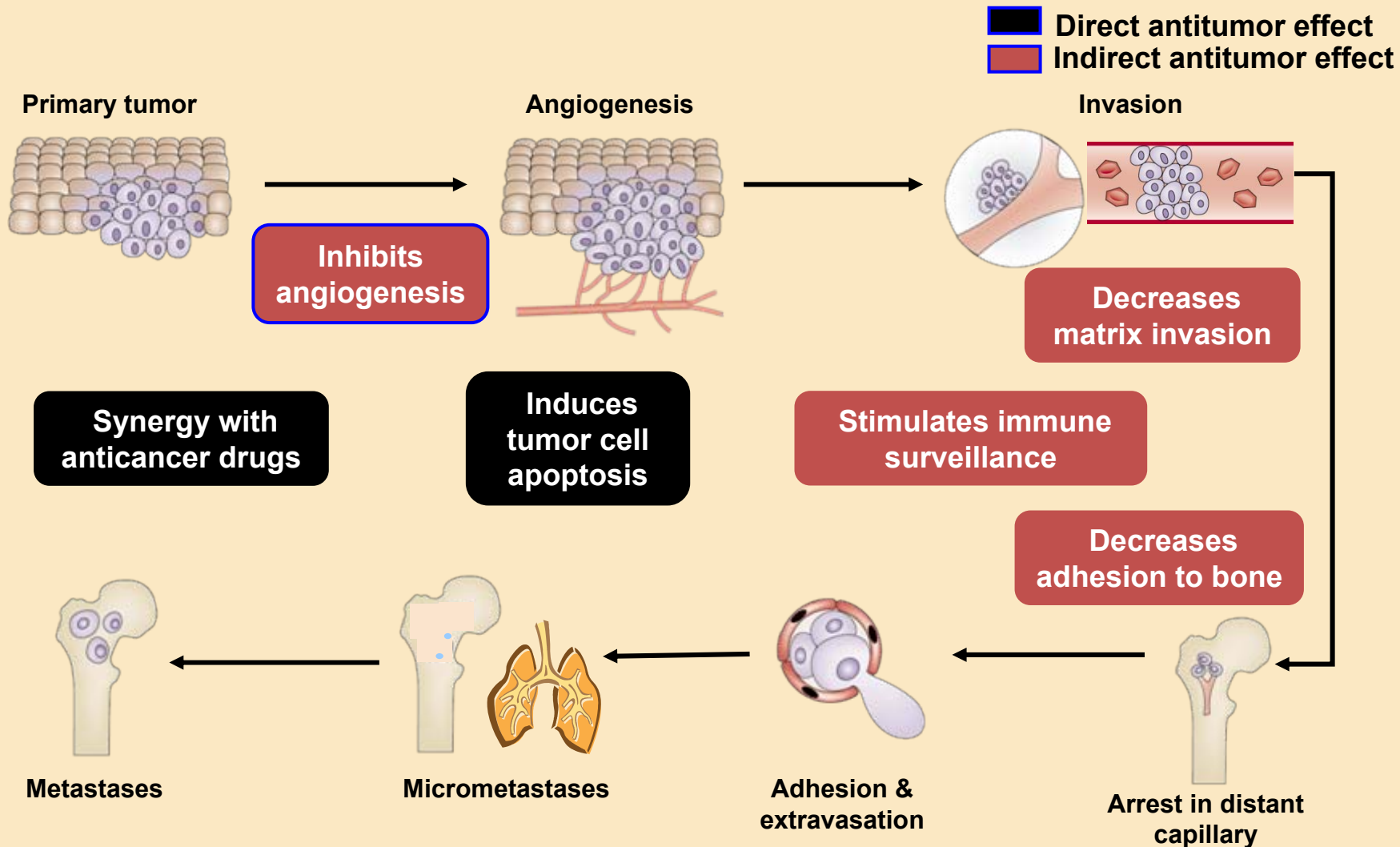
BMD, bone mineral density, ZOL, zoledronic acid.

Adapted from Grant MF, et al. *Lancet Oncol.* 2008;9(9):840-849.

# Summary: Bone Therapies in Reducing Treatment-Associated Bone Loss

- Maintaining bone health during cancer treatments (AIs, chemo) is important to prevent fracture
- Effective bone-targeted treatment, such as IV bisphosphonates, may be required to prevent substantial bone loss and reduce fracture risk
- Timing of bisphosphonate therapy may play a key role in reducing AIBL

# Rationale for Using Zoledronic Acid to Reduce Disease Recurrence in the Adjuvant Setting

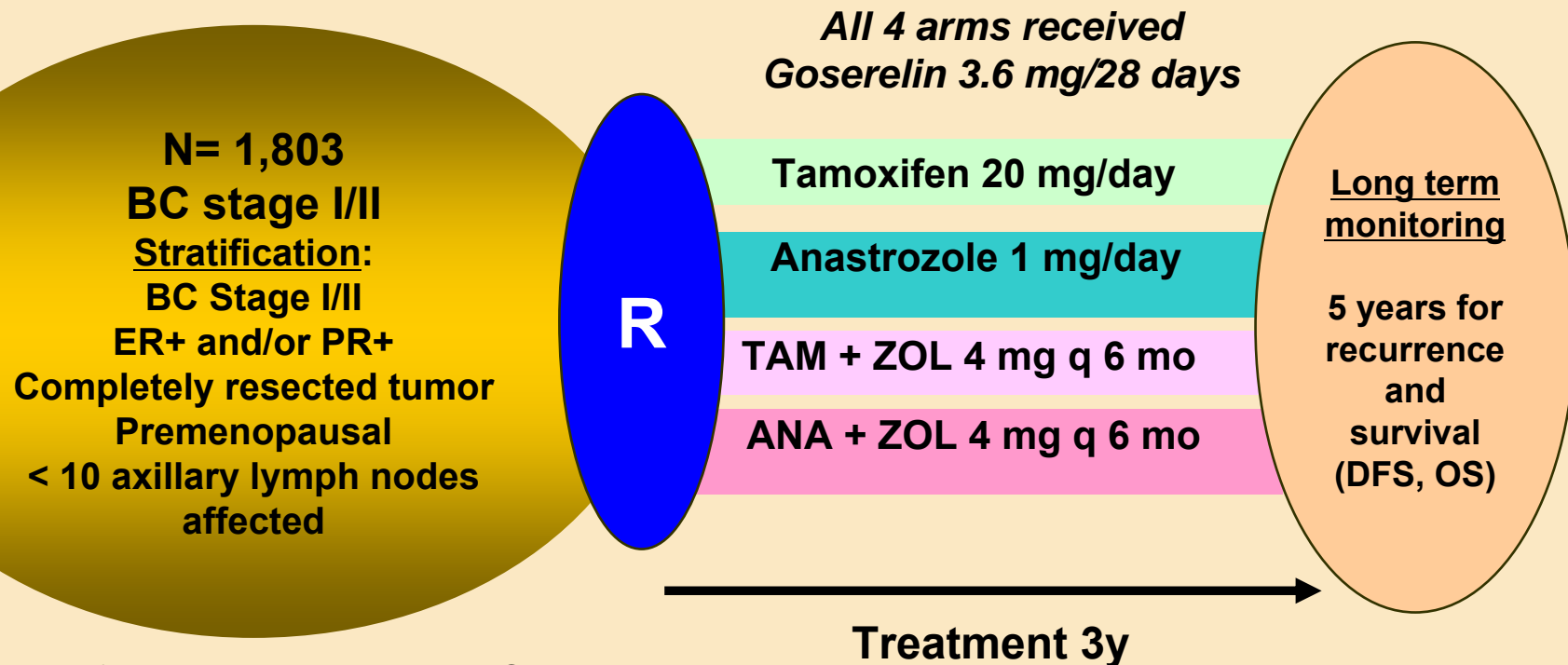


Adapted from Mundy GR, et al. *Nature Reviews Cancer*. 2002;2:584-593.

# ABCESG-12 Trial Design: Premenopausal Women With Breast Cancer

## Key Endpoints:

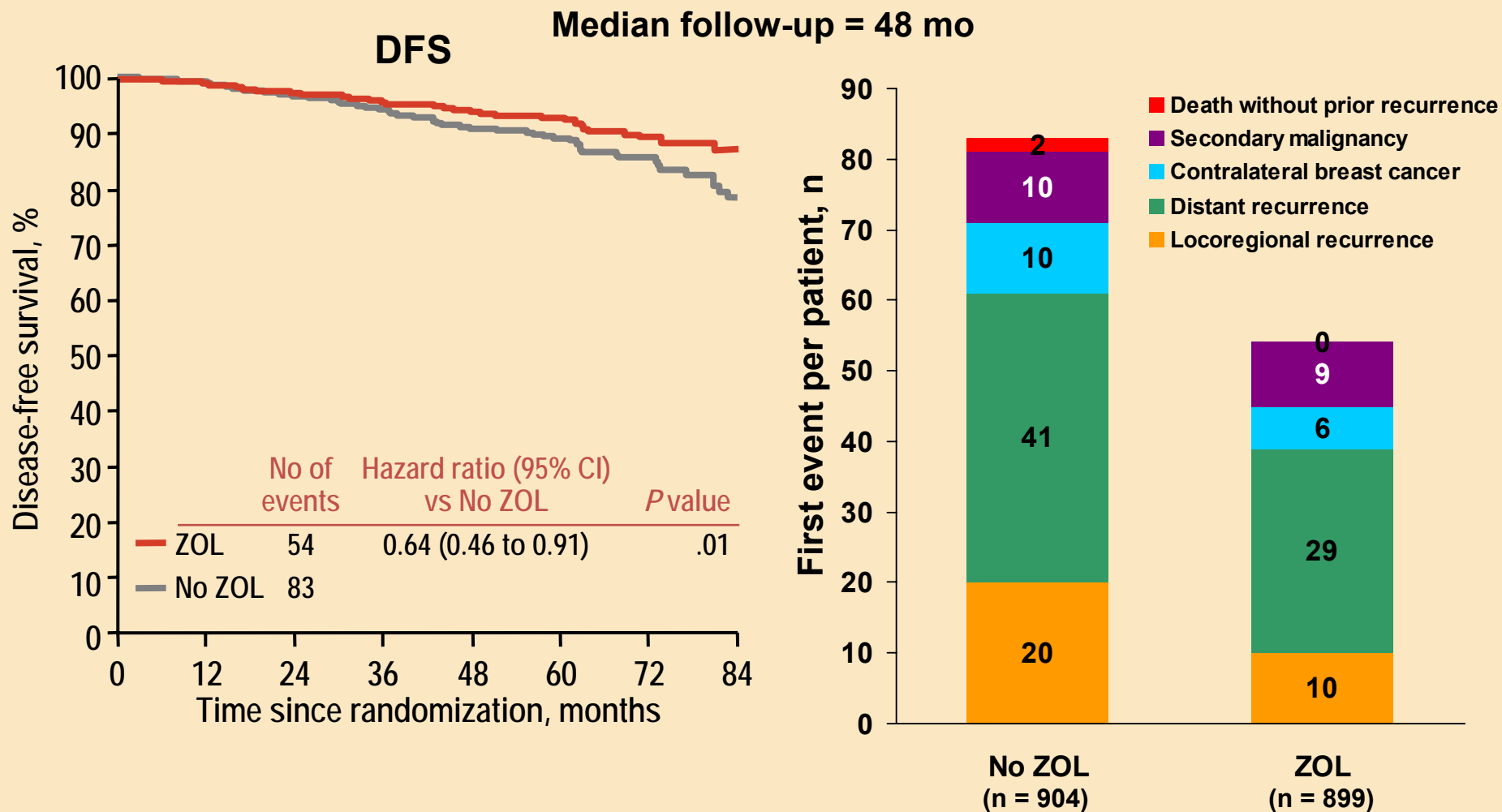
- **Primary:** Disease-free survival (DFS)
- **Secondary:** Relapse-free survival (RFS) , OS, safety, bone metastases-free survival (BMFS)



TAM = Tamoxifen; ANA = Anastrozole; ZOL = Zoledronic acid.

# ABCSG-12

## ZOL Significantly Improves DFS by 36%

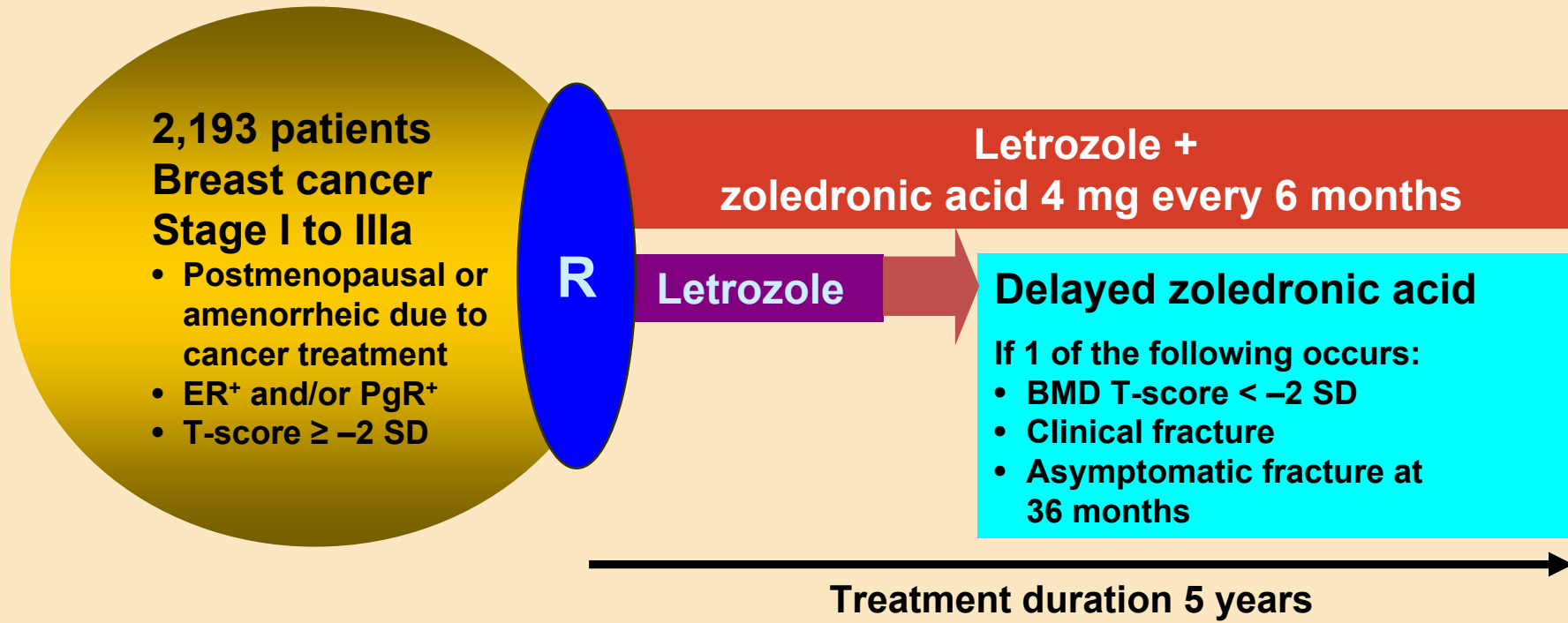


ZOL, zoledronic acid; CI, confidence interval.

Adapted from Gnant M, et al. *N Engl J Med*. 2009;360(7):679-691.

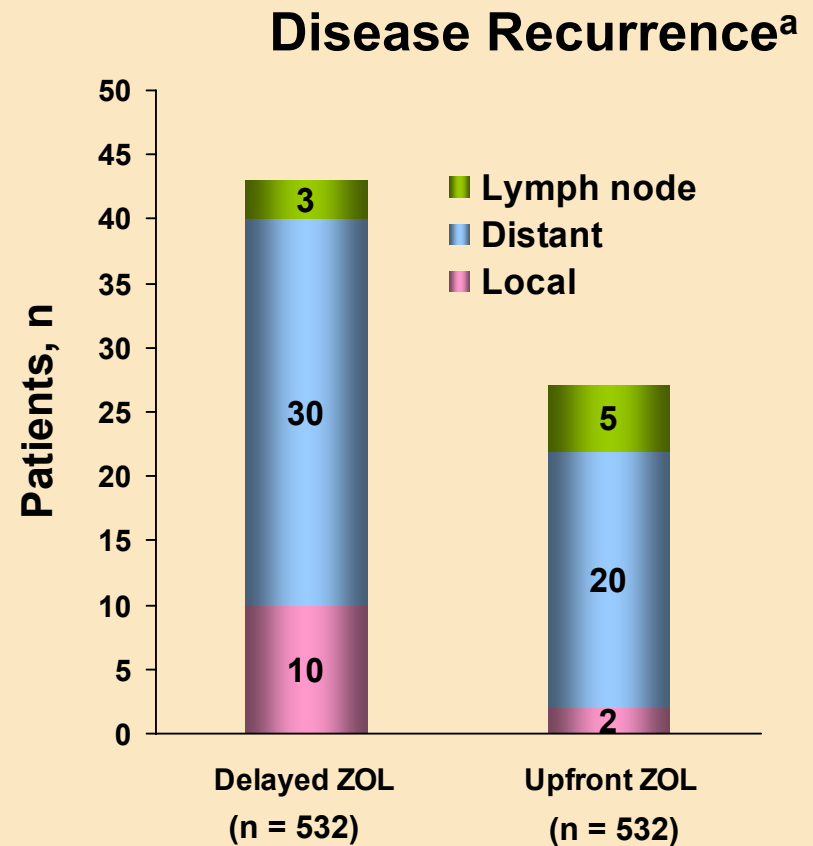
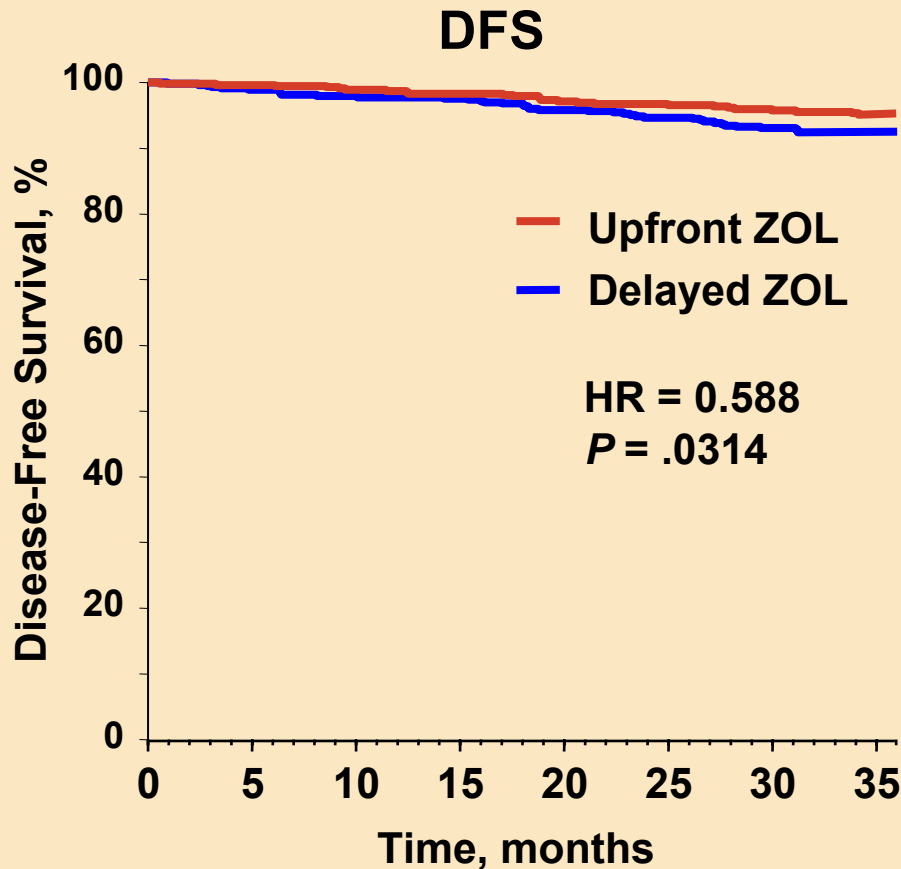
# Z-FAST / ZO-FAST / E-ZO-FAST— ZOMETA-Femara Adjuvant Synergy Trials

- Primary endpoint: 12 month lumbar spine BMD
- Secondary endpoints: Fracture, disease recurrence, disease free-survival, bone markers



BMD, bone mineral density; ER, estrogen receptor; PgR, progesterone receptor; R, randomization; SD, standard deviation.

# ZO-FAST 36 mo: Upfront ZOL significantly ↓ the risk of DFS events by 41%



ZOL, zoledronic acid; HR, hazard ratio (Cox regression); DFS, disease-free survival.

<sup>a</sup> Multiple sites of metastases may be reported for the same patient.

Sites of distant metastases include: bone, brain, liver, lung, skin, lymph node, and other.

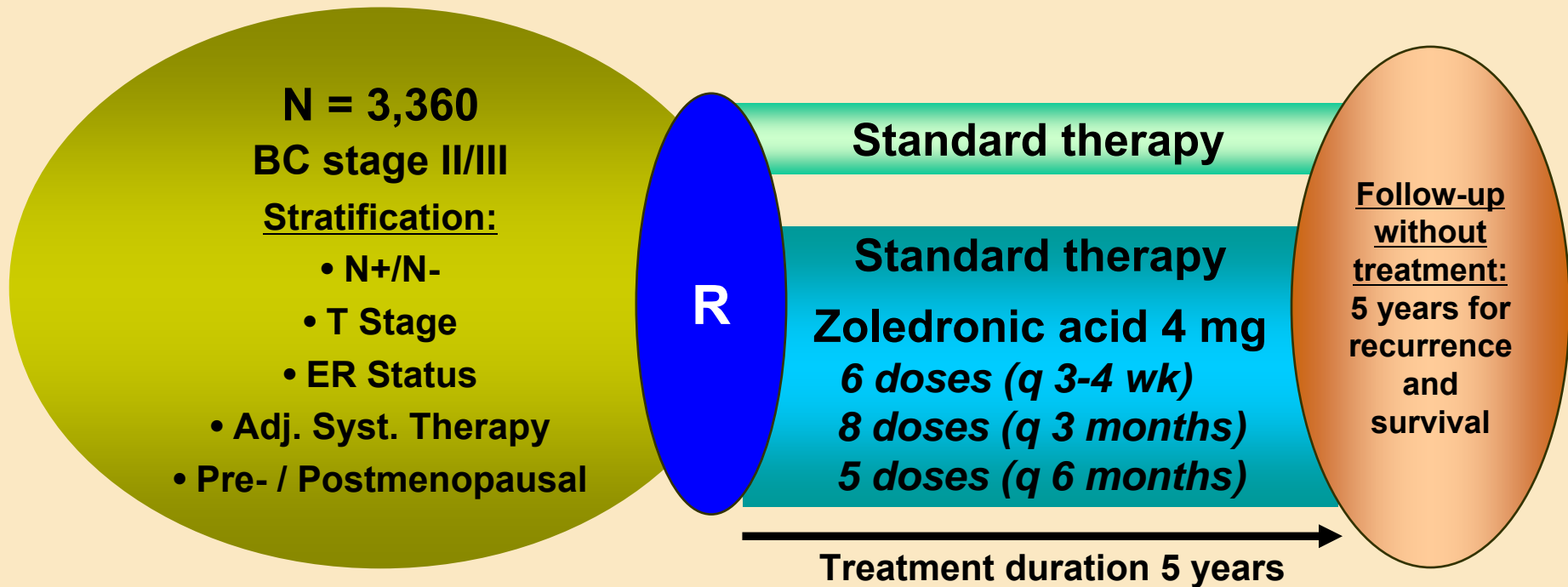
Adapted from Eidtmann H, et al. Presented at: 31st Annual San Antonio Breast Cancer Symposium; December 10-14, 2008; San Antonio, TX. Abstract 44.

# AZURE: Zoledronic Acid for the Prevention of Bone Metastases in Breast Cancer

Key endpoints:

Primary: Disease-free survival

Others: Time to bone mets / distant mets, SREs, overall survival



mets, metastases; SREs, skeletal-related events; ER, estrogen receptor.

# Summary: Antitumor Activity and Prevention of Bone Metastases

- Clodronate and pamidronate have not shown consistent antitumor benefits or improvements in disease outcomes
- Clinical benefits of zoledronic acid in breast cancer extend beyond management of bone metastases
  - Direct and indirect antitumor activities
  - Significantly improves disease-free survival beyond that achieved with endocrine therapy alone
  - Favorable safety profile in the adjuvant setting
    - No case of ONJ or renal toxicity

# Overall Summary: Bisphosphonates in Breast Cancer

**Bisphosphonate therapy is an important component in the breast cancer continuum – from the adjuvant to the metastatic setting**

- Reduces the number and severity of SREs
- Prevents bone loss during endocrine or chemotherapy
- Zoledronic acid reduces risk of recurrences and improves outcomes when combined with endocrine therapy
- Long-term efficacy and safety profiles known