Bisphosphonates in Breast Cancer: From Prevention of Bone Loss to Prevention of Recurrence

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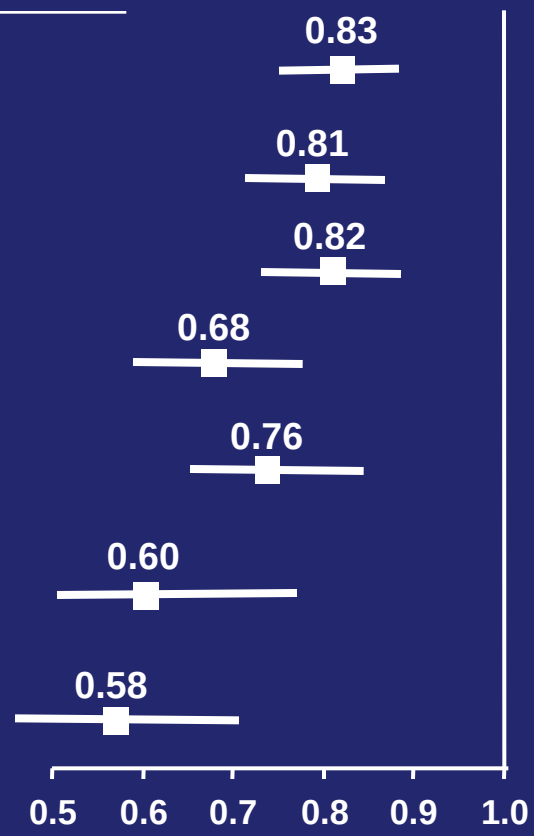
Aromatase Inhibitors Are Consistently Superior to Tamoxifen (Disease-Free Survival)

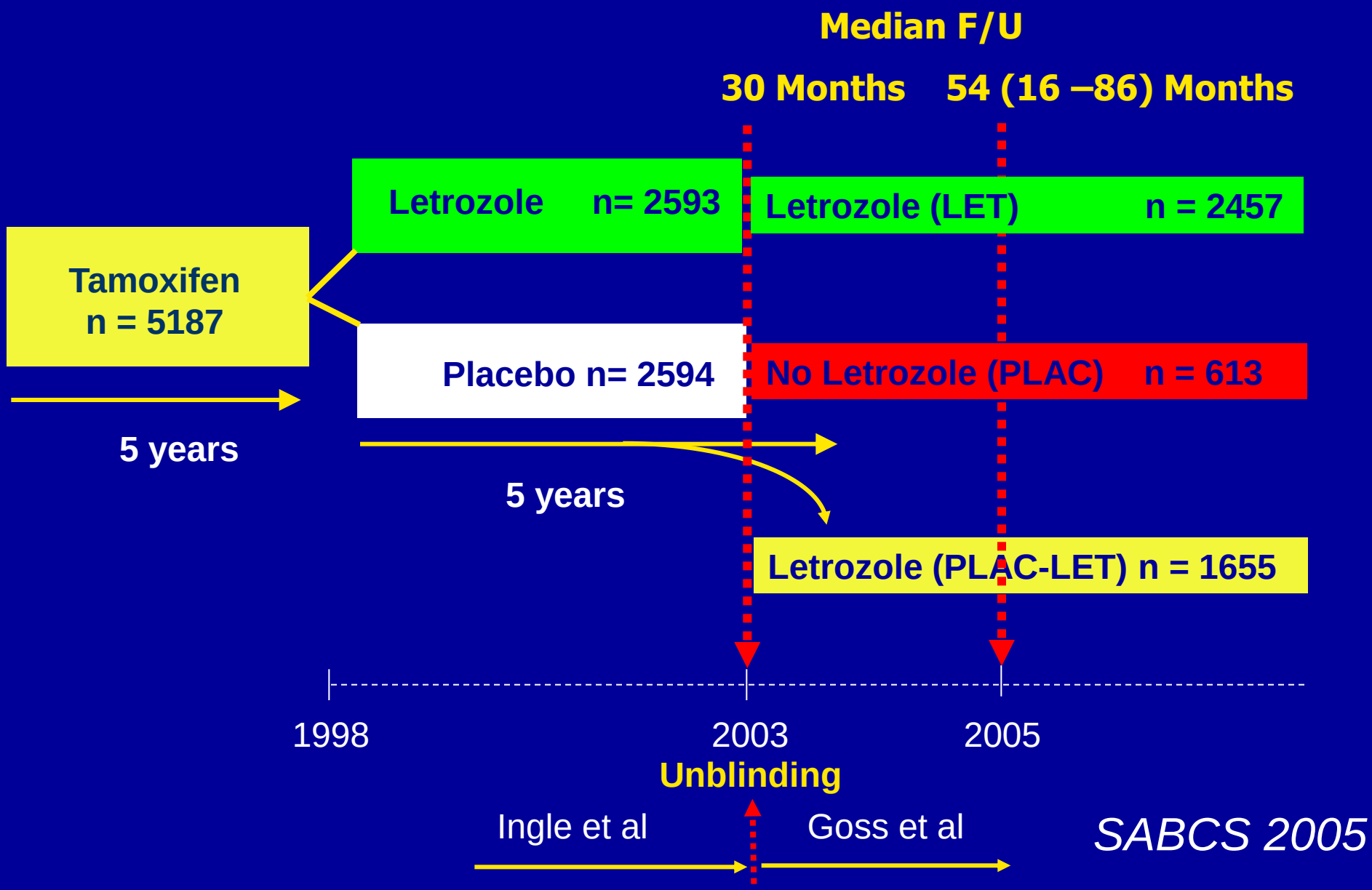
Trial (months)	Aromatase inhibitor	Absolute benefit, %
ATAC (68)[1]	Anastrozole up front (5 yr)	2.5
BIG 1-98 (26)[2]	Letrozole up front (5 yr)	2.6
BIG 1-98 (51)[3]*	Letrozole up front (5 yr)	2.9
IES (30)[4]	Exemestane (3 yr)	4.7
IES (56)[5]	Exemestane (5 yr)	3.4
ARNO/ ABCSG (28)[6]	Anastrozole (2 yr)	3.1
MA-17 (30)[7]	Letrozole (5 yr) vs placebo	4.9



***Analysis restricted to monotherapy arm A vs arm B.**

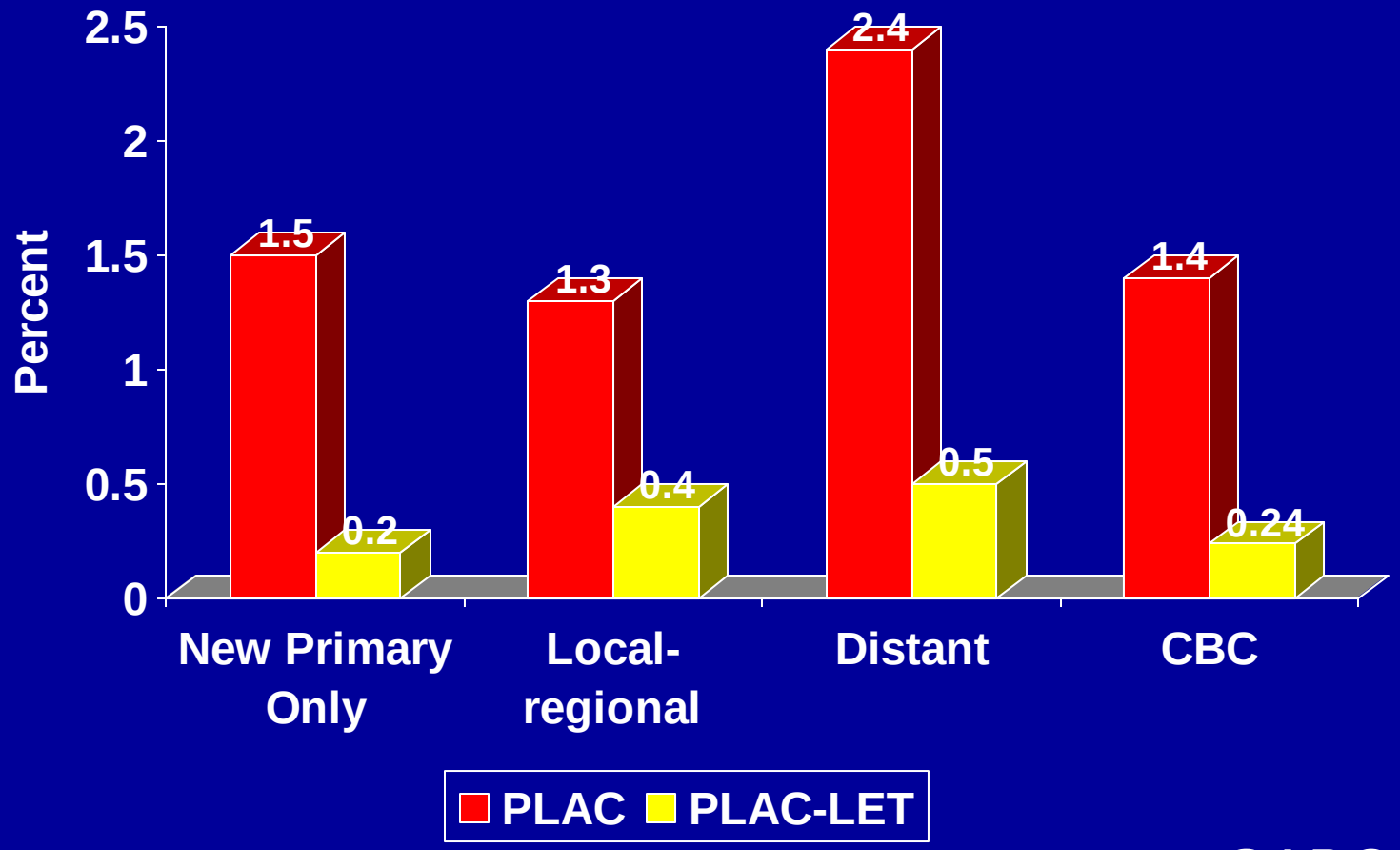
1. Howell A, et al. *Lancet*. 2005;365:60-62; 2. Thurlimann B, et al. *New Engl J Med*. 2005;353:2747-2757; 3. Coates A, et al. *J Clin Oncol.* 2007;486:492-494; 4. Coombes RC, et al. *New Engl J Med.* 2004;350:1081-1092; 5. Coombes RC, et al. *Lancet*. 2007;369:559-570;
6. Jakesz R, et al. *Lancet*. 2005;366:455-462; 7. Goss P, et al. *J Natl Cancer Inst*. 2005;97:1262-1271.

MA.17 Post-Unblinding Cohorts



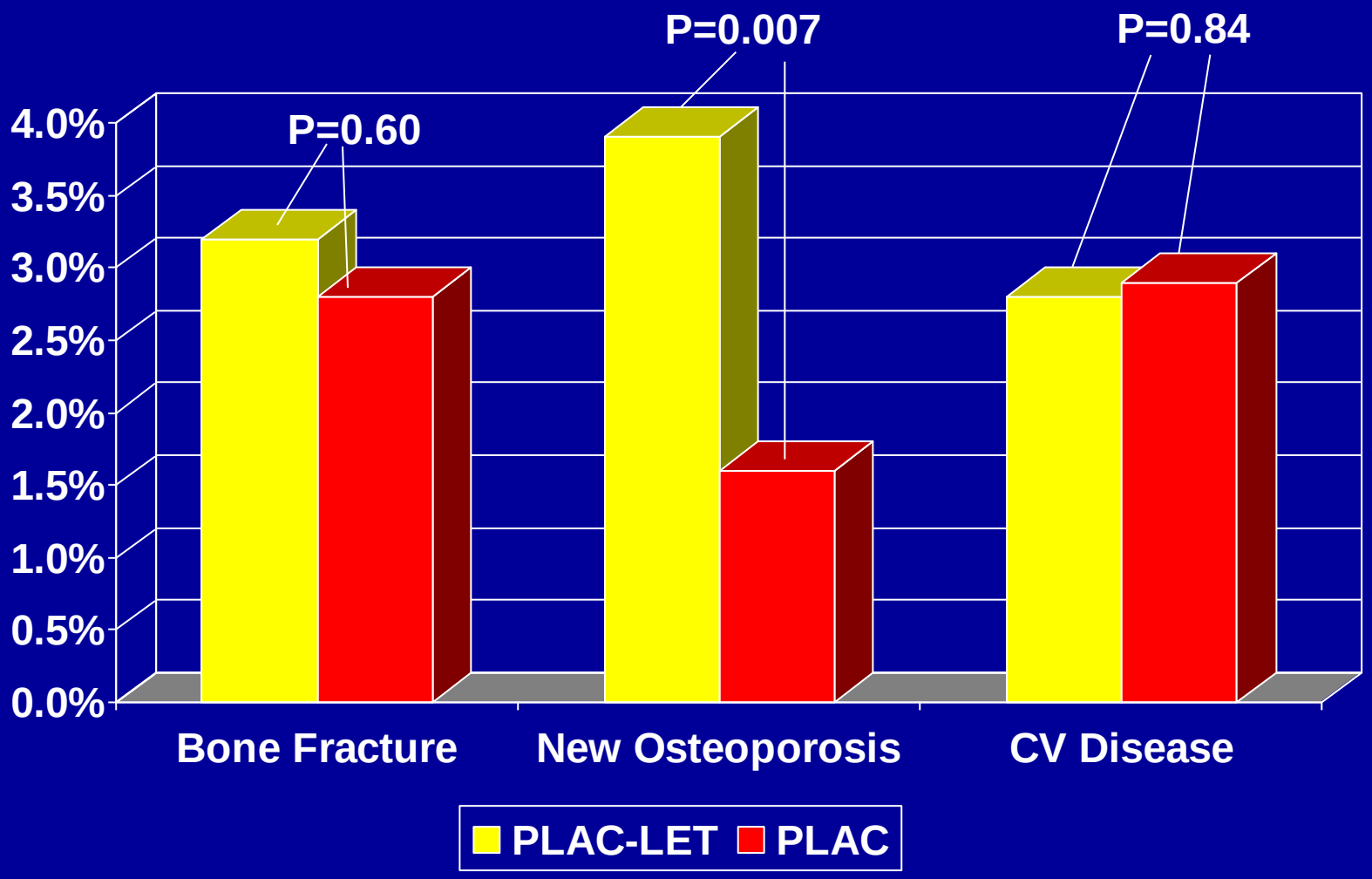
SABCS 2005

Percentage of Patients with Recurrence



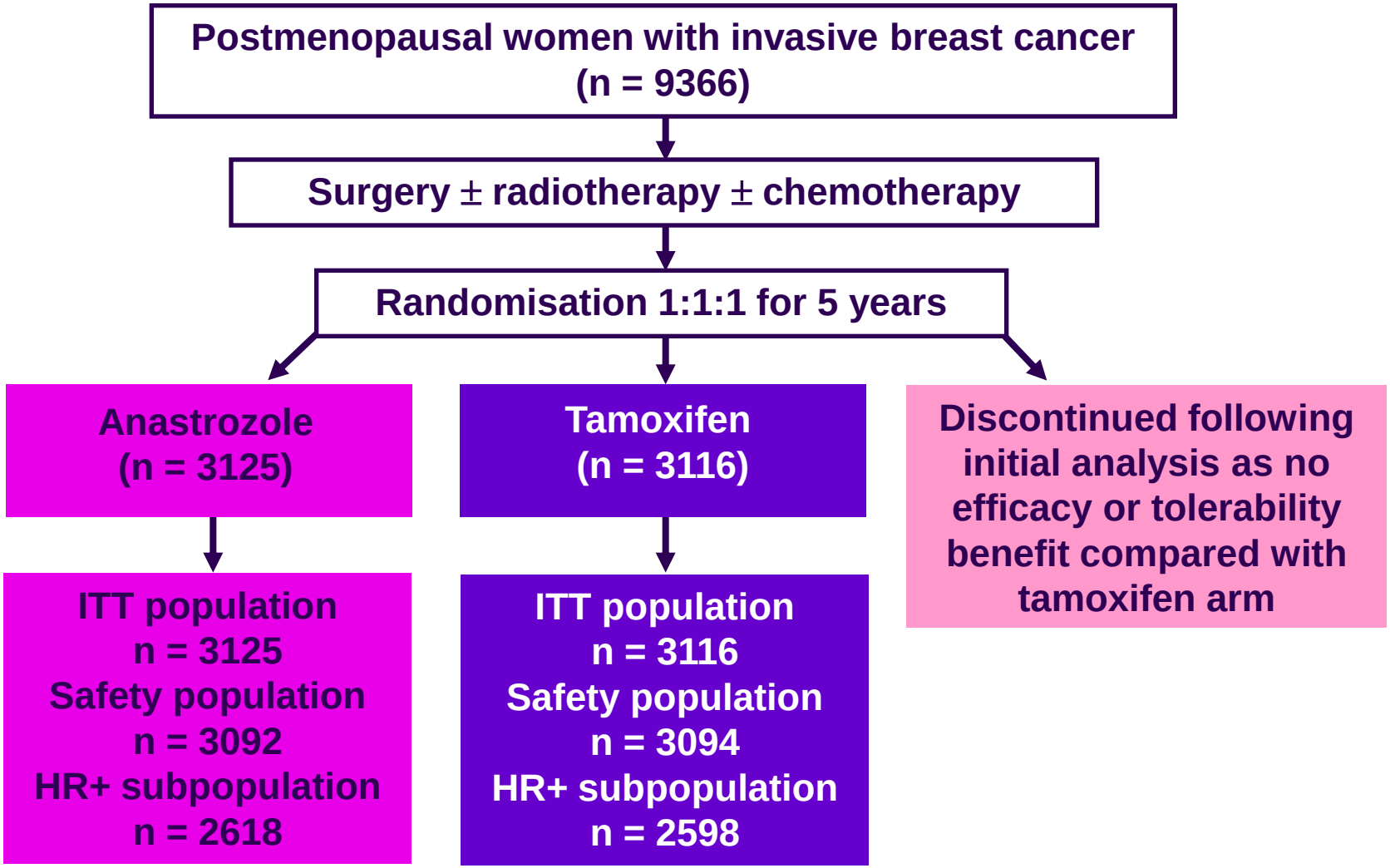
SABCS 2005

Adverse Events After Unblinding



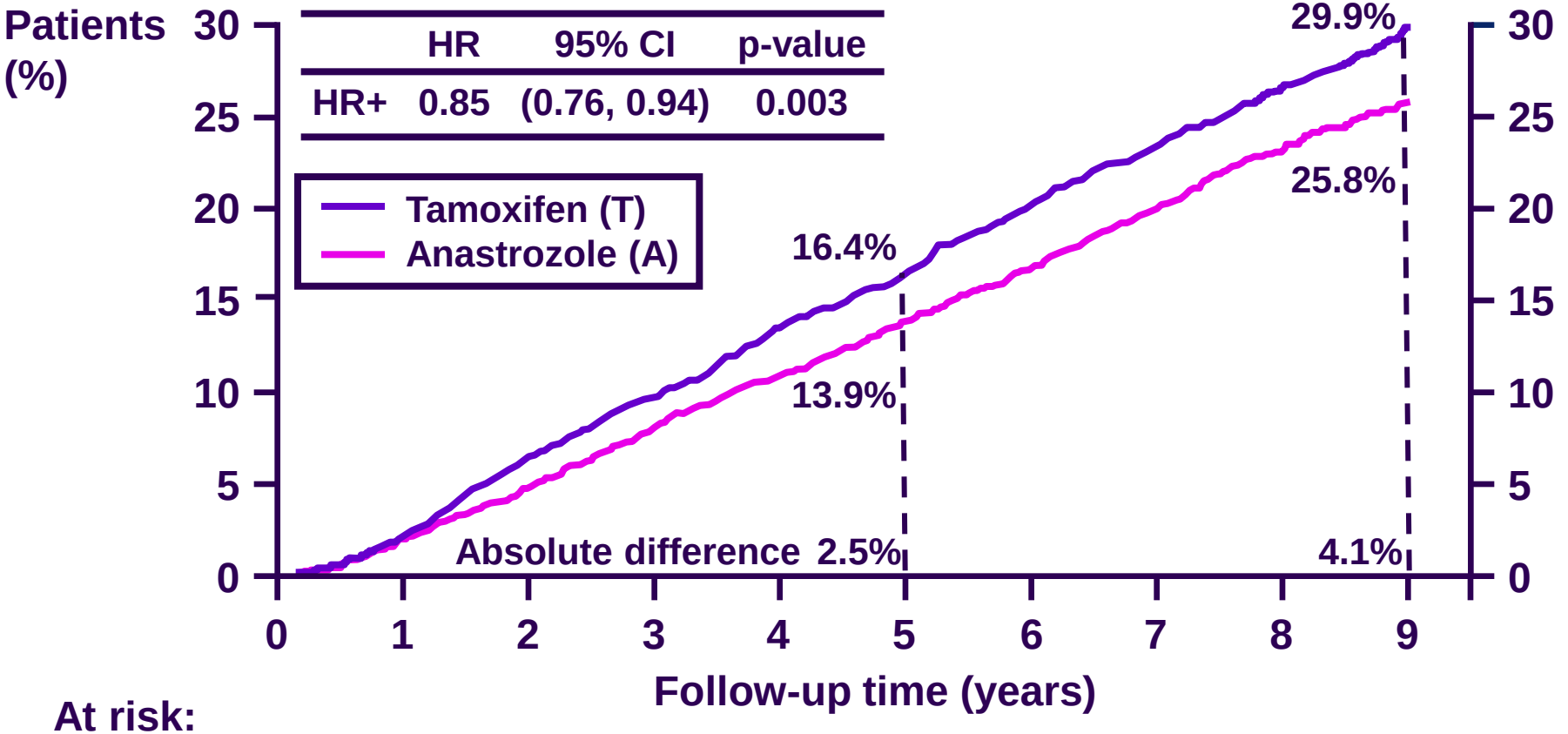
SABCS 2005

ATAC trial design



ITT, intent-to-treat; HR+, hormone receptor-positive

Disease-free survival
HR+ patients



At risk:

A	2618	2541	2453	2361	2278	2159	1995	1801	1492	608
T	2598	2516	2400	2306	2196	2075	1896	1711	1396	547

HR, hazard ratio; CI, confidence interval

All AIs Significantly Reduce Estrogen Levels

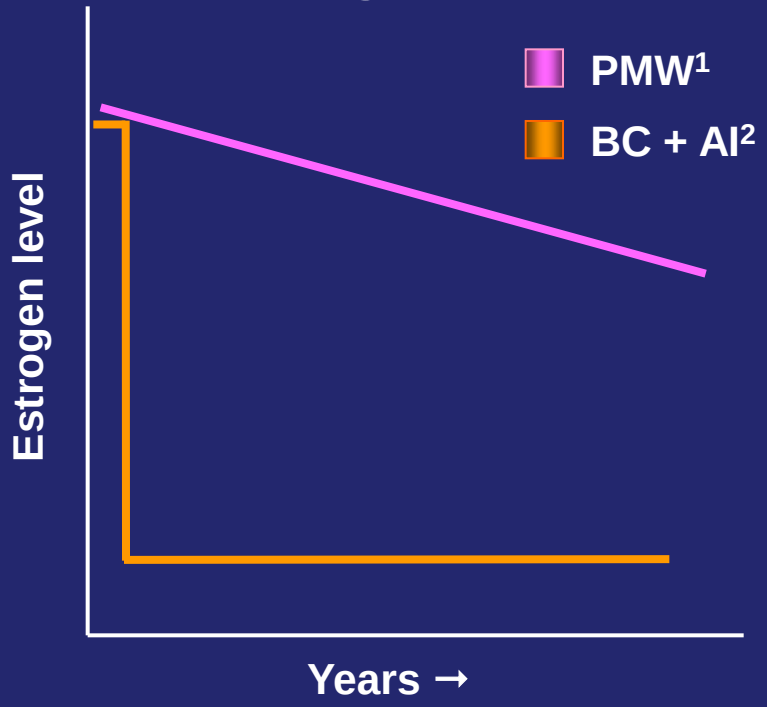
AI drug	Aromatase inhibition, %	Plasma estradiol
Letrozole[1]	> 99.1	12/12 *undetectable* Mean 2.1 pmol/L
Anastrozole[1]	97.3	9/12 *undetectable* Mean 2.6 pmol/L
Exemestane[2]	97.9	7/9 *undetectable* Mean 2.8 pmol/L

AI = Aromatase inhibitor.

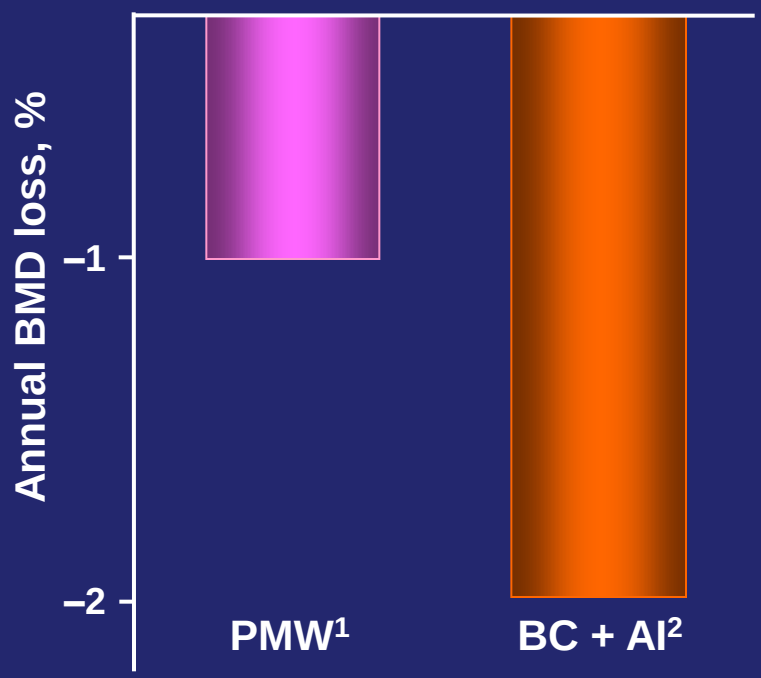
1. Geisler J, et al. *J Clin Oncol.* 2002;20:751-757; 2. Geisler J, et al. *Clin Cancer Res.* 1998;4:2089-2093.

Aromatase Inhibition Is Associated With Higher Rate of Estrogen Depletion Compared With PMW

Change in estrogen levels



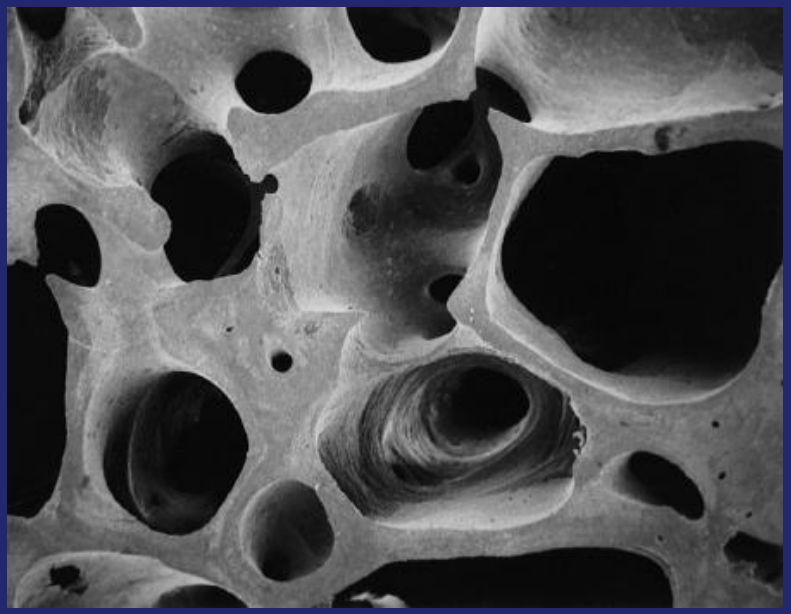
Corresponding bone loss at hip



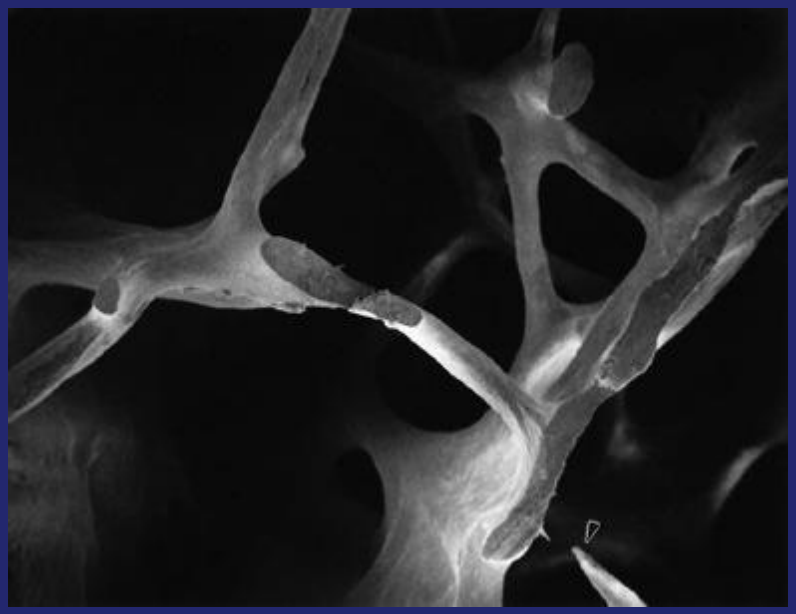
PMW = Postmenopausal women; BC = Breast cancer; AI = Aromatase inhibitor.

1. Stone K, et al. *J Bone Miner Res*. 1998;13:1167-1174; 2. Eastell R, et al. *J Bone Miner Res*. 2006;21:1215-1223.

Bone Architecture is Compromised by Estrogen Deficiency and Increased Bone Turnover



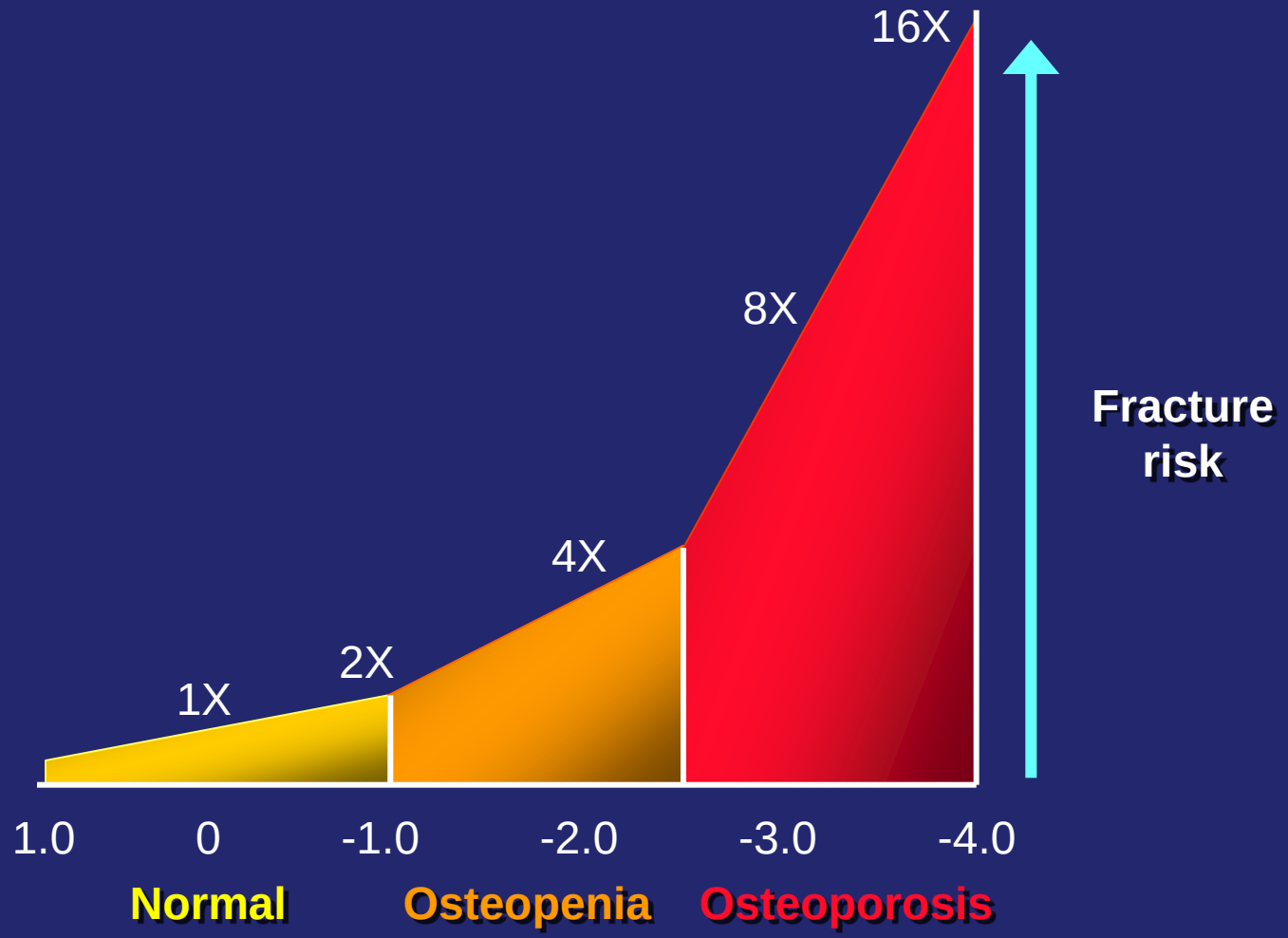
Normal



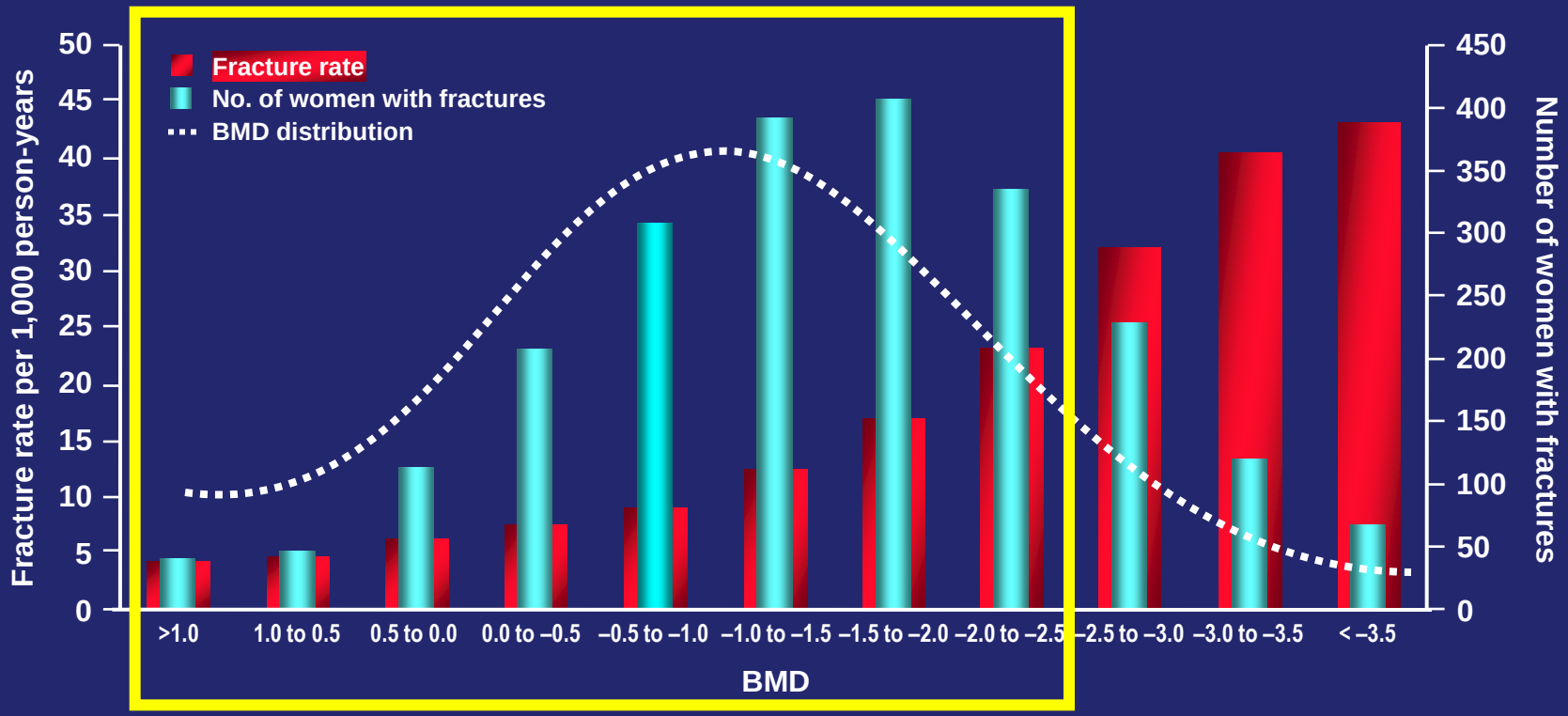
Osteoporosis

Dempster DW. *J Bone Miner Res.* 2000;15:20-23.

Decrease in Bone Mineral Density (BMD) is Associate with Fracture Risk



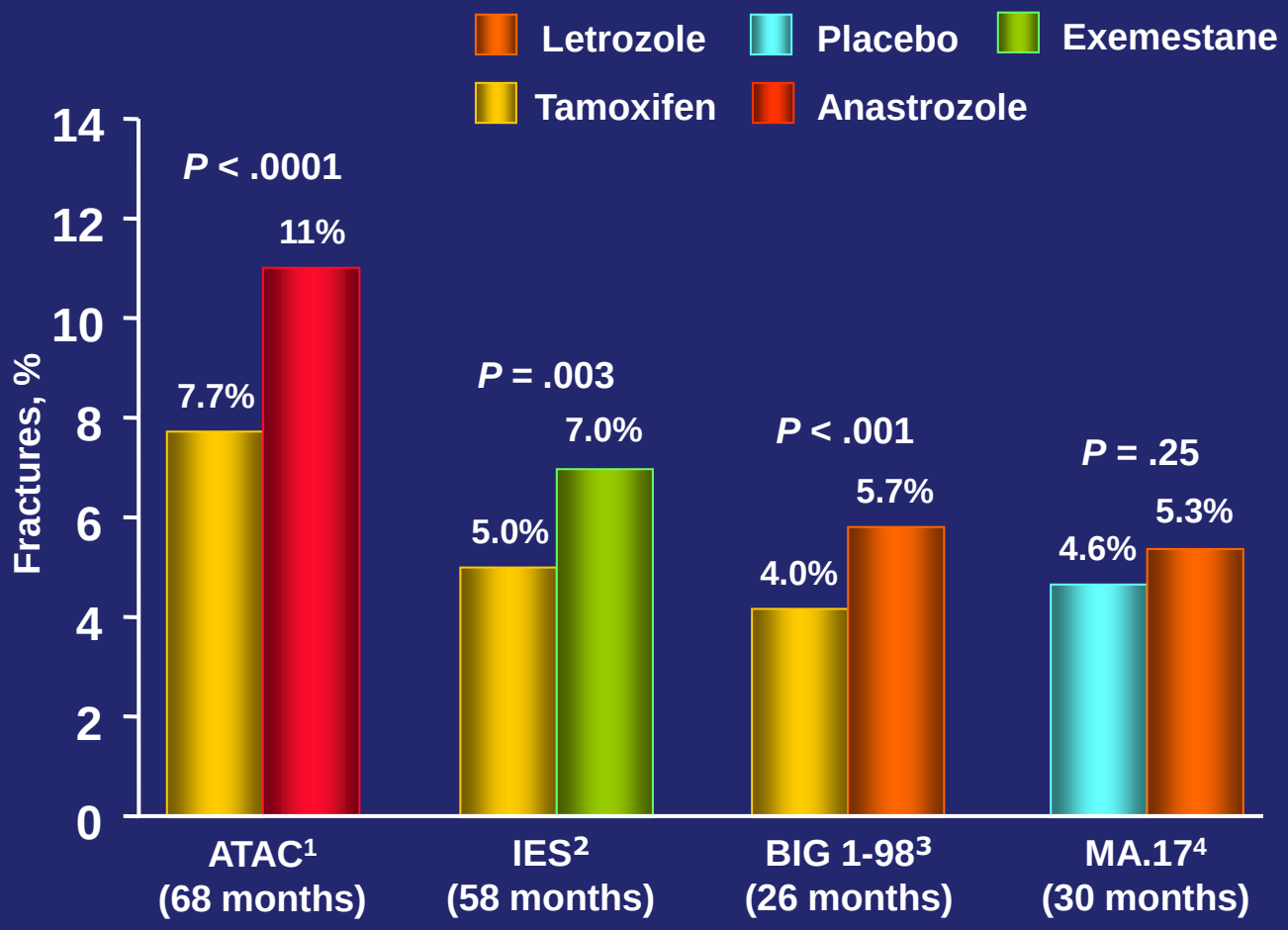
80% of Fractures Occur in Women Who Are Not Osteoporotic



- Fracture rate increases ~2-fold in osteopenic women
- Majority of fractures occur in osteopenic women (T-Score between -1.0 to -2.5)

Reprinted from Siris ES, et al. *Arch Intern Med*. 2004;164:1108-1112.

All AIs Increase Fracture Risk



AI = Aromatase inhibitor.

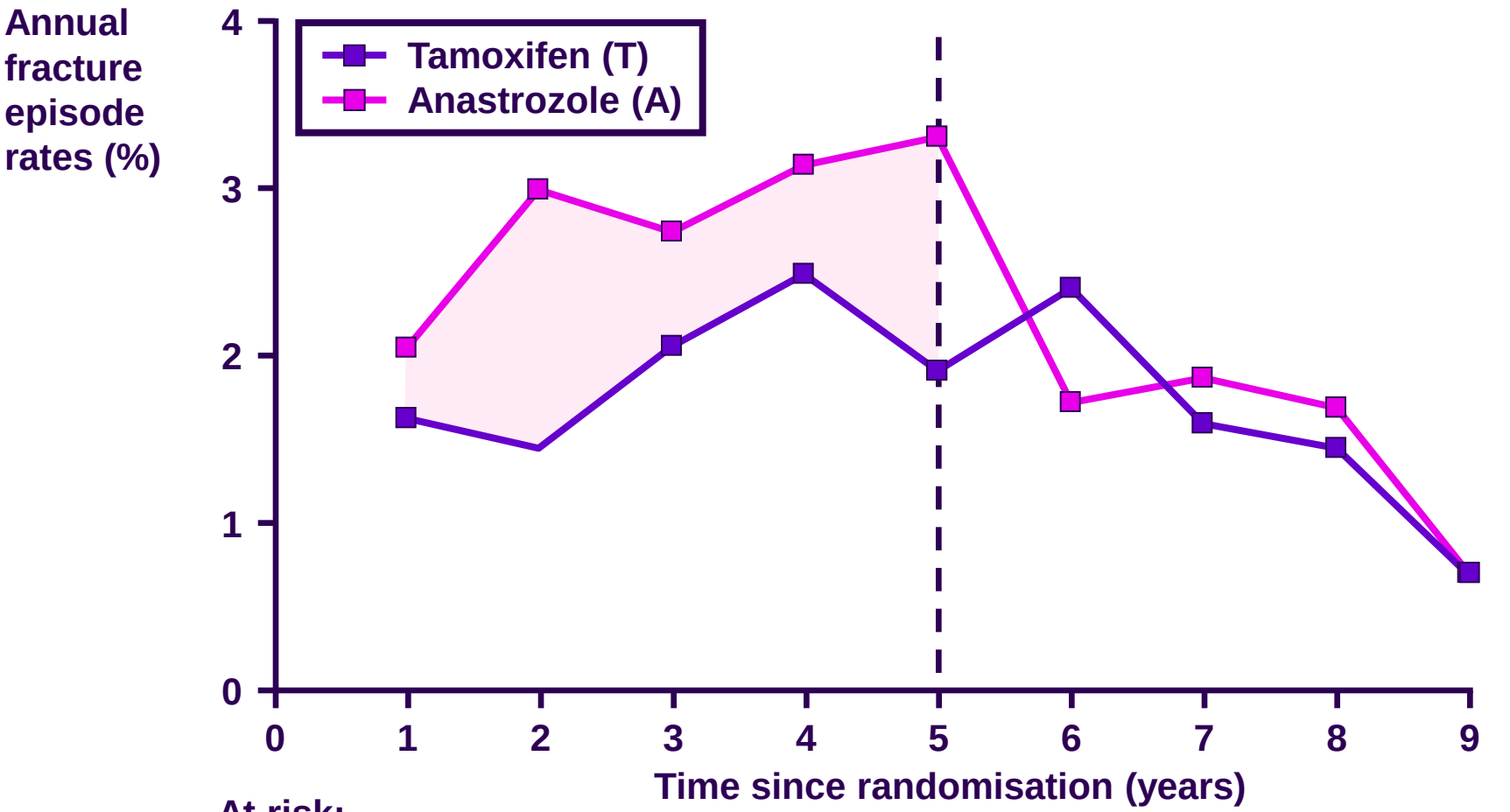
1. Howell A, et al. *Lancet*. 2005;365:60-62; 2. Coleman RE, et al. *Lancet Oncol*. 2007;8:119-127; 3. Thurlimann B, et al. *N Engl J Med*. 2005;353:2747-2757; 4. Goss PE, et al. *J Natl Cancer Inst*. 2005;97:1262-1271.

Fractures
(occurring at any time before recurrence)

Fractures before recurrence	A N=3092 (%)	T N=3094 (%)	A vs T Odds ratio	95% CI	p-value
Patients with one or more fracture episodes	421 (13.6)	311 (10.1)	1.41	1.21-1.65	<0.0001
Hip	49 (1.6)	42 (1.4)	1.17	0.75-1.82	0.46
Spine	60 (1.9)	37 (1.2)	1.64	1.08-2.48	0.02
Wrist / colles	94 (3.0)	83 (2.7)	1.14	0.84-1.54	0.4
All other sites	270 (8.7)	191 (6.2)	1.46	1.20-1.77	0.0001

A, anastrozole; T, tamoxifen

Fracture episode rates throughout the study

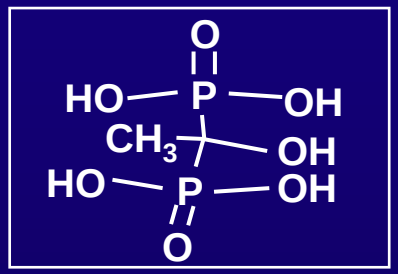


At risk:

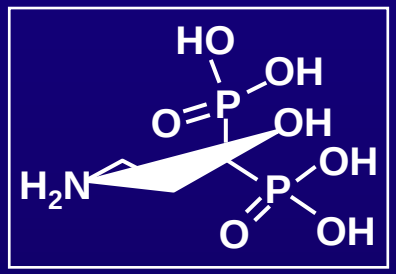
A	2984	2859	2745	2640	2496	2306	2077	1713	702
T	2976	2824	2699	2572	2419	2208	2000	1645	659

Bone Loss in Breast Cancer and Its Management

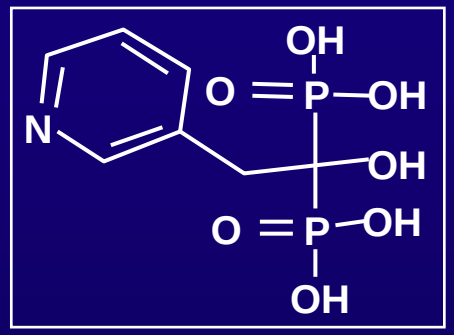
Different Classes of Bisphosphonates



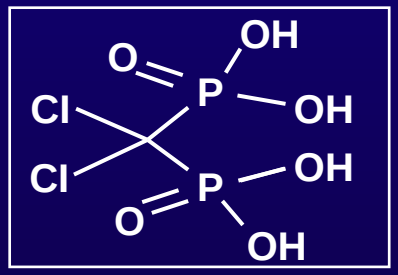
Etidronate



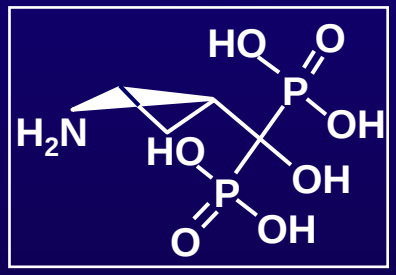
Pamidronate



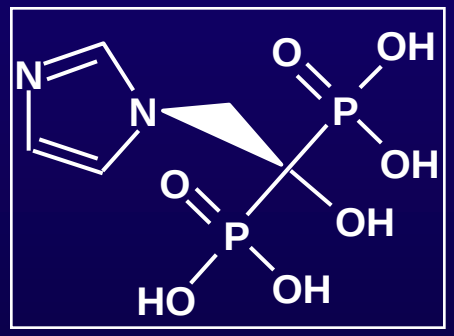
Risedronate



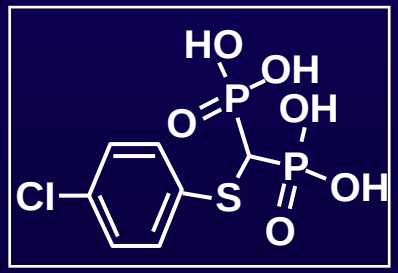
Clodronate



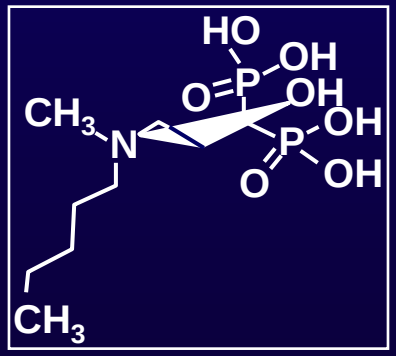
Alendronate



Zoledronic acid



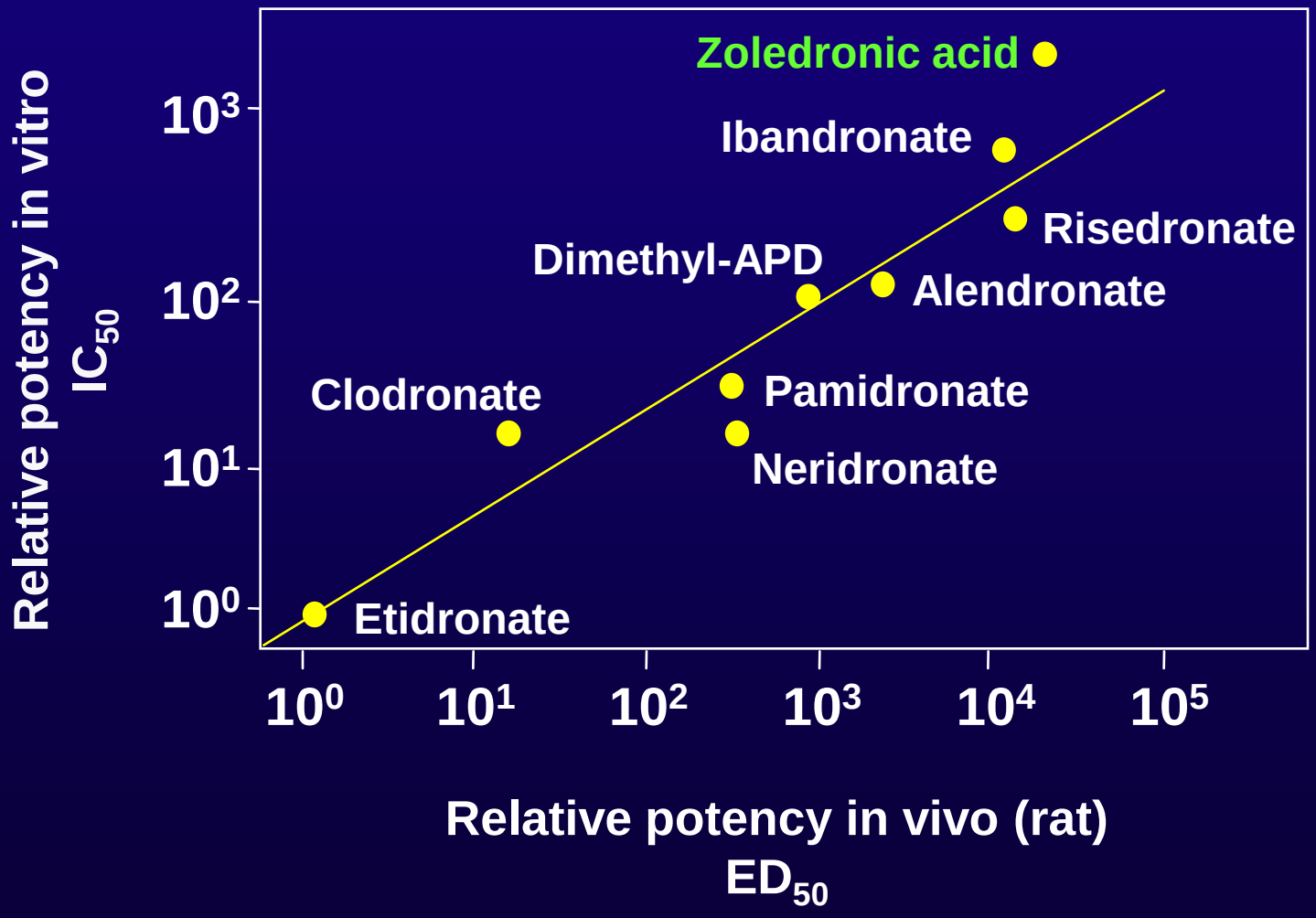
Tiludronate



Ibandronate

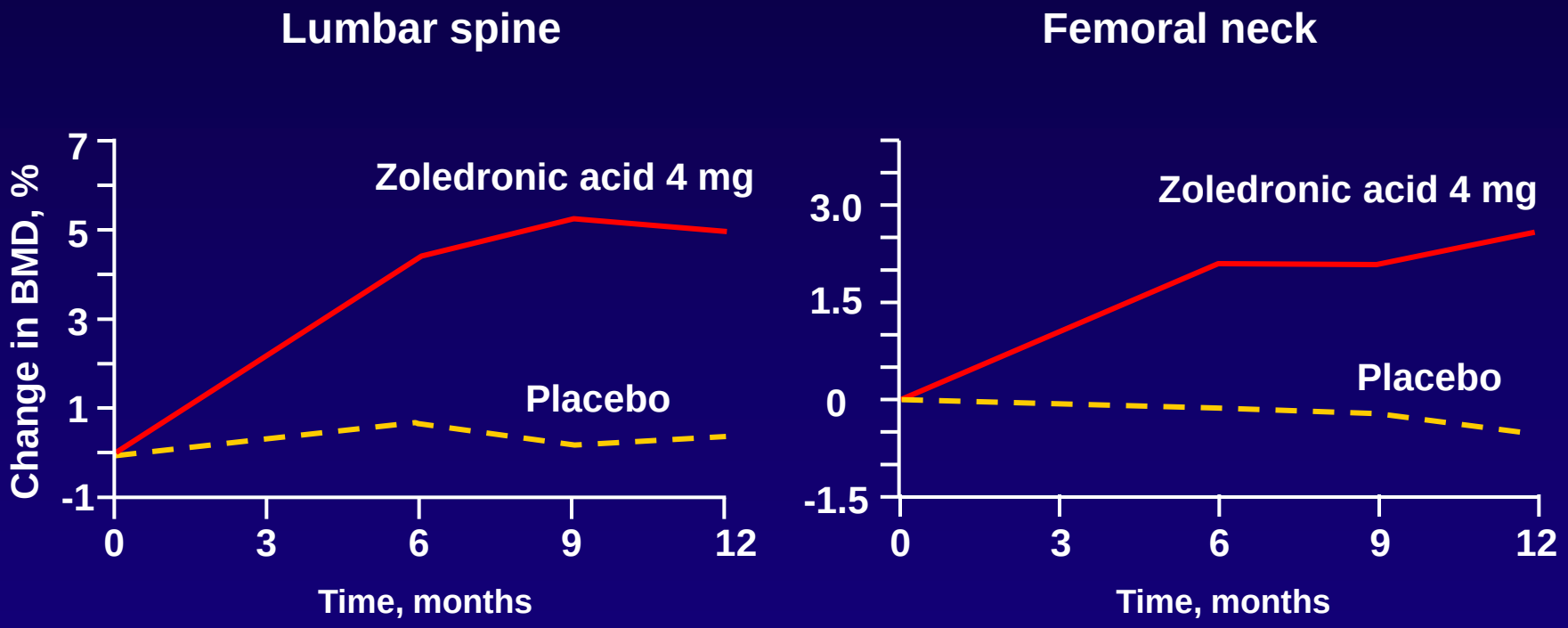
Thurlimann. *Bisphosphonates in Clinical Oncology: The Development of Pamidronate*. 1999.
Fleisch. *Endocr Rev*. 1998;19:80.

Relative Potency of Bisphosphonates



Zoledronic Acid and Bone Health Management- AIBL

Zoledronic Acid Increases BMD in Postmenopausal Women With Low BMD



Reid IR, et al. *N Engl J Med*. 2002;346:653-661.

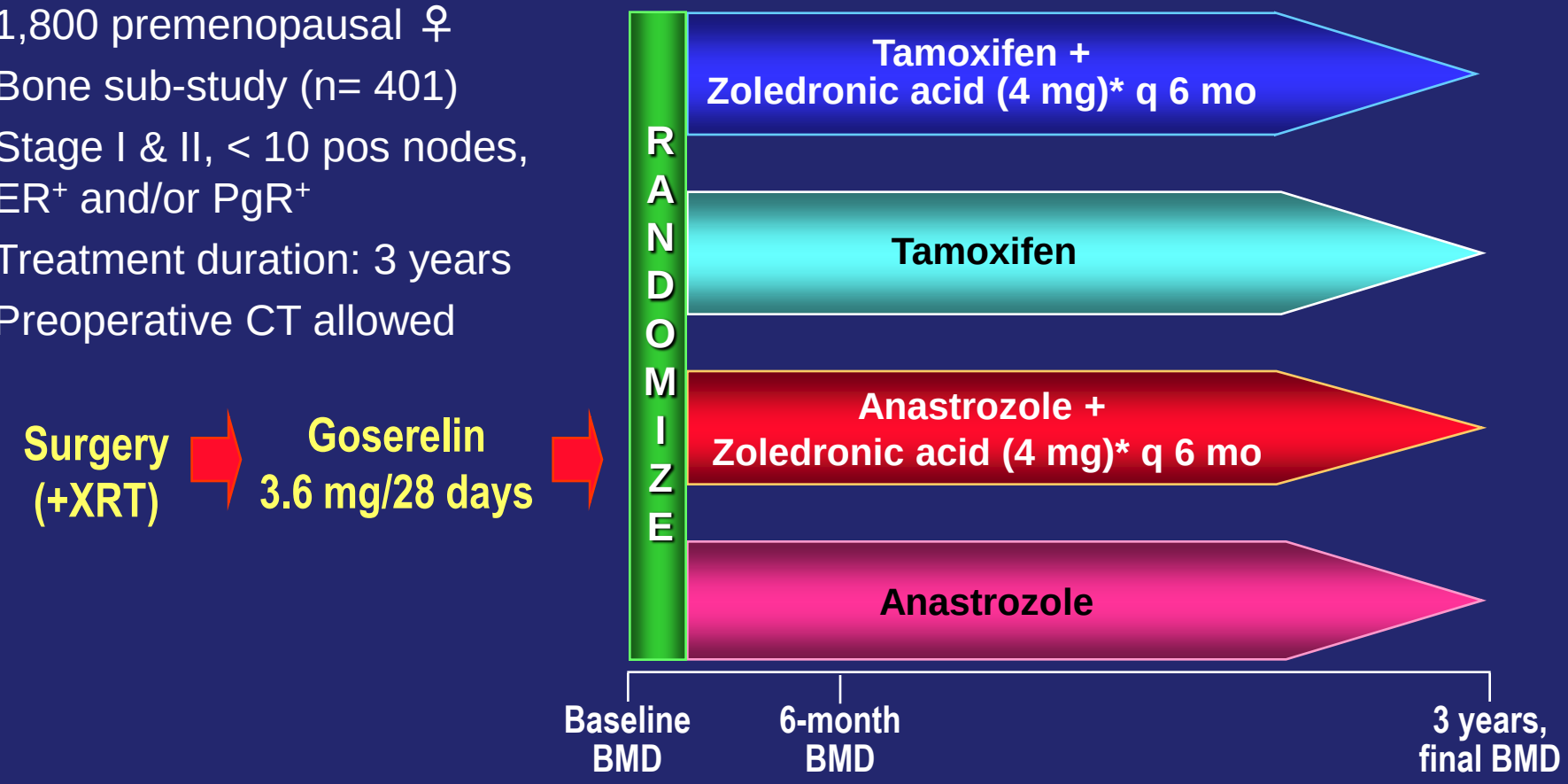
Ongoing Trials of Zoledronic Acid For Prevention of Aromatase Inhibitor-Induced Bone Loss (AIBL)

- **Premenopausal**
  - ABCSG-12 (n= 401)
- **Postmenopausal**
  - Z-FAST (n= 602)
  - ZO-FAST (n=1,066)
  - E-ZO-FAST (n= 526)

Total of patients treated with Zoledronic acid n= 2,595

ABCSG-12: BMD in Premenopausal Women Receiving Adjuvant Hormonal Therapy

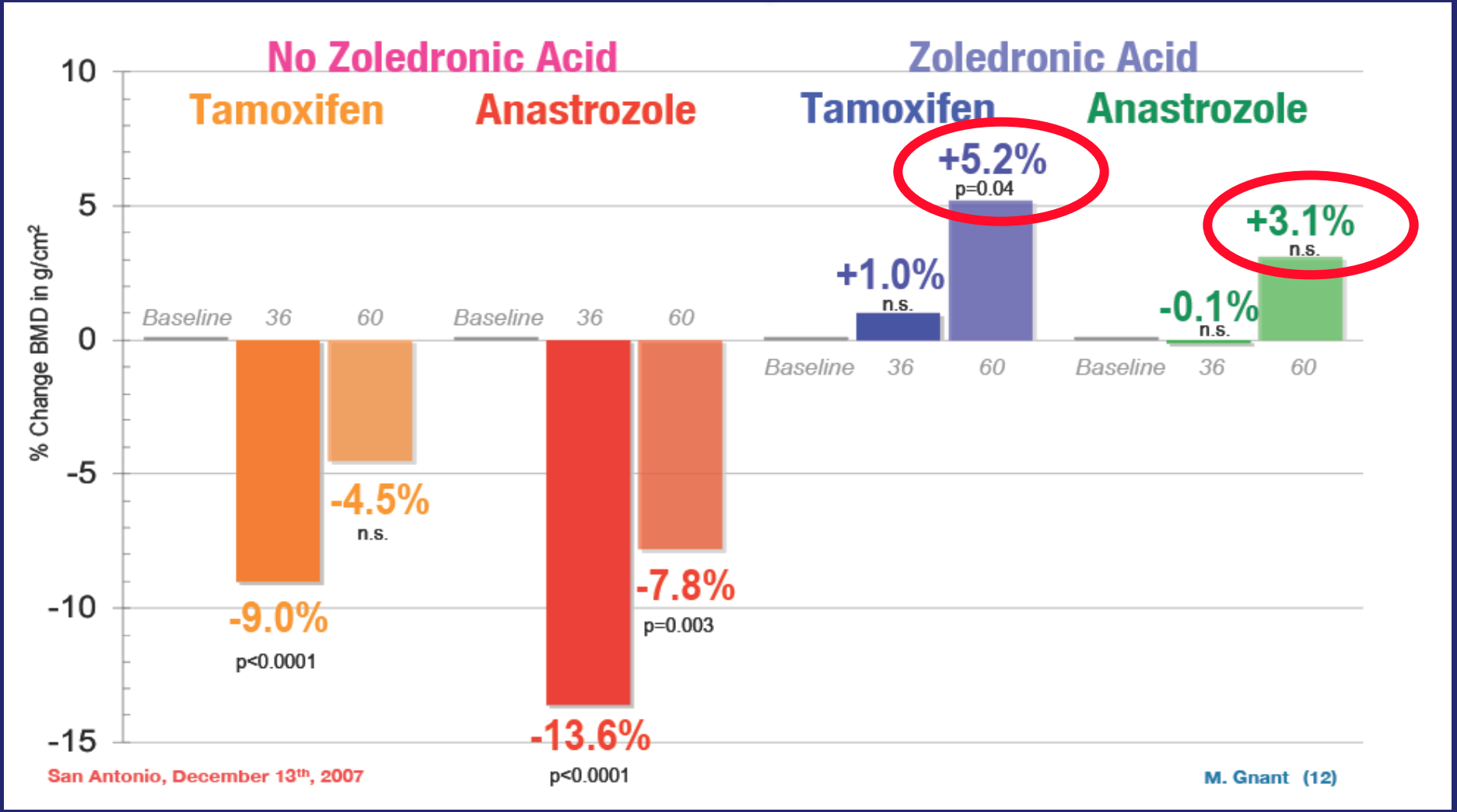
- Accrual 1999 to 2006
- 1,800 premenopausal ♀
- Bone sub-study (n= 401)
- Stage I & II, < 10 pos nodes, ER^+ and/or PgR^+
- Treatment duration: 3 years
- Preoperative CT allowed



ABCSG-12 = Austrian Breast and Colorectal Cancer Study Group Trial 12; BMD = Bone mineral density; CT = Chemotherapy; XRT=Preoperative radiotherapy.
*8 mg reduced to 4 mg.

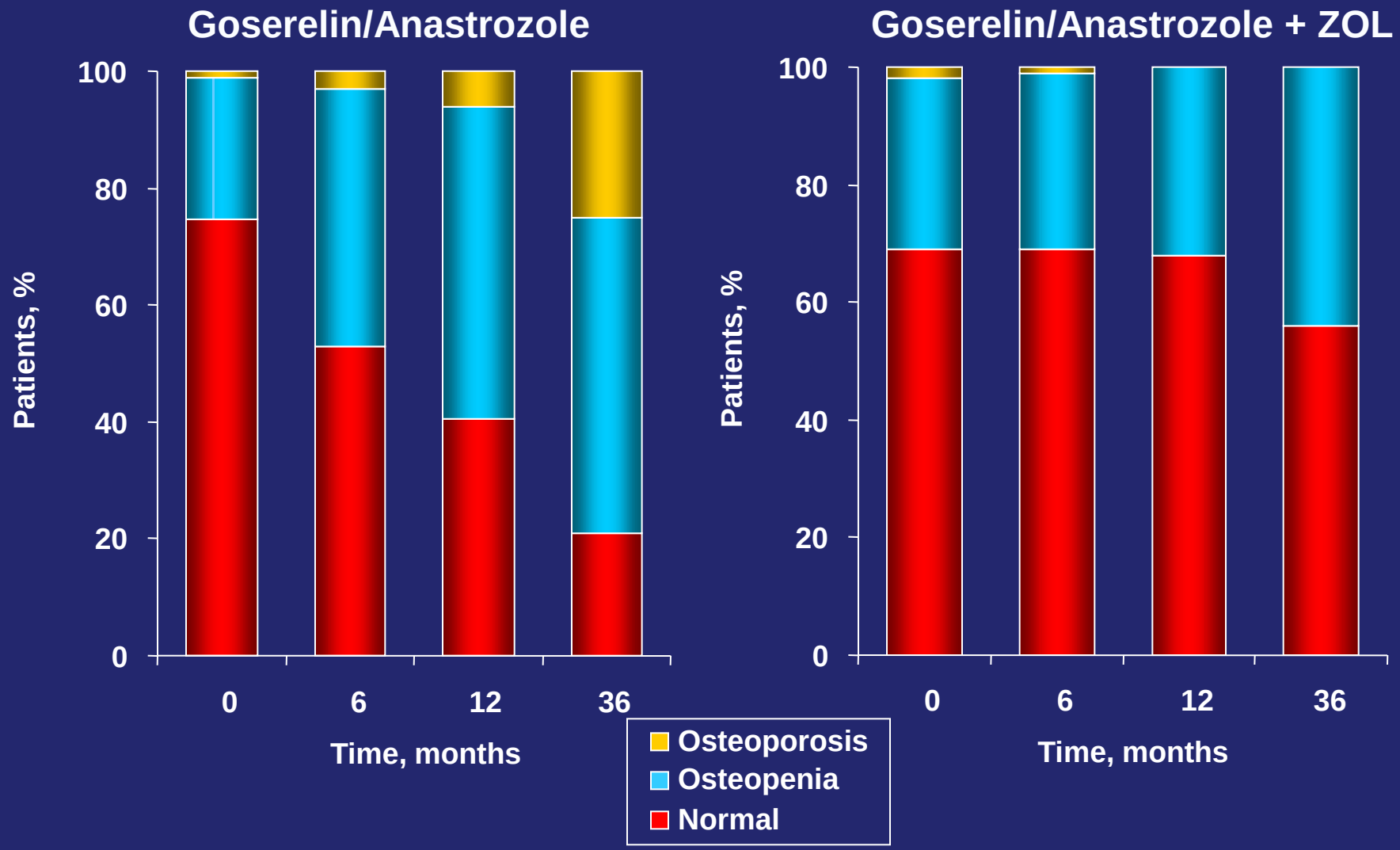
Gnant MF, et al. *J Clin Oncol*. 2007;25:820-828.

ABCSG-12 (Follow-up 5 years): % BMD change at the LS



Gnant MF. Presented at SABCS 2007, Abstract #26

Zoledronic Acid Preserves BMD Over 3 Years of Adjuvant Therapy



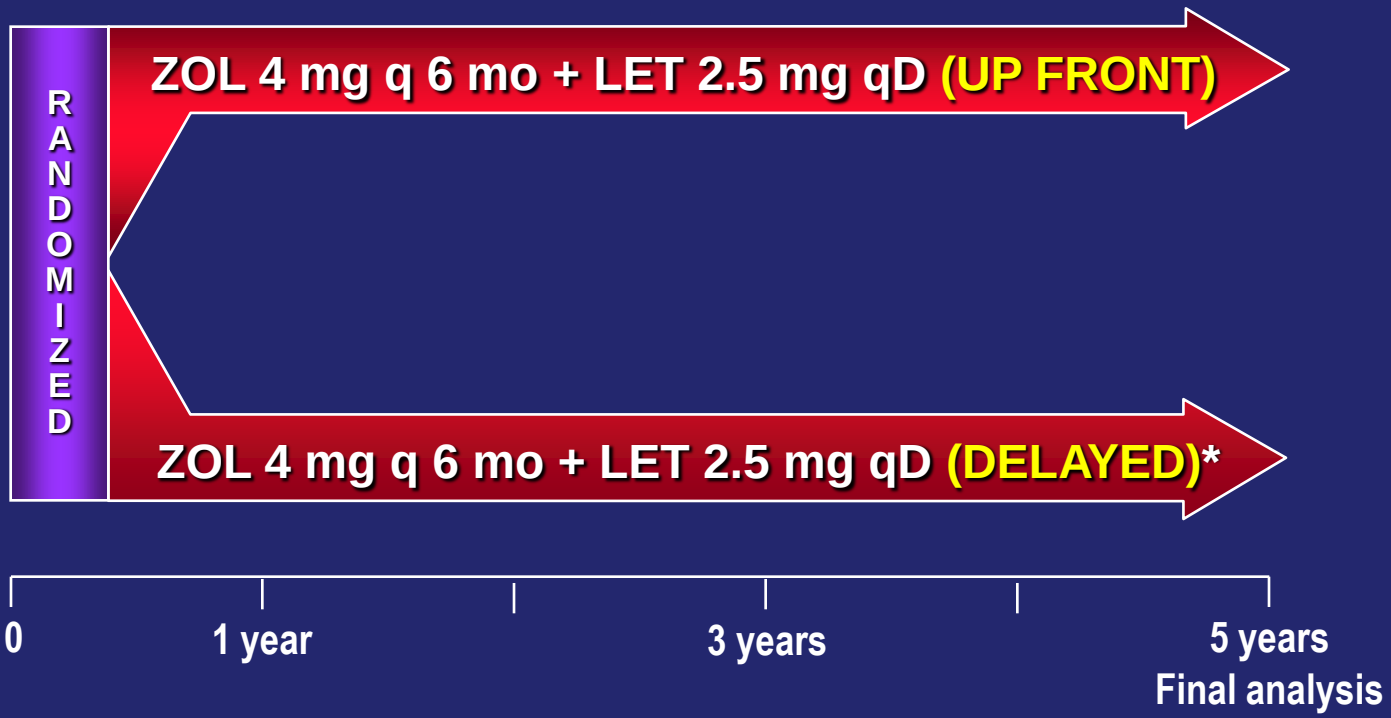
BMD = Bone mineral density; ZOL = Zoledronic acid.

Adapted with permission from Gnant MF, et al. *J Clin Oncol*. 2007;25:820-828.

Z-FAST,[1] ZO-FAST[2], and E-ZO-FAST[3] Study Design

Eligibility
- ER+/PgR+ BCa
- PMW with T-score ≥ –2

Stratification
- Adjuvant CT (yes or no)
- T score (> –1 or between –1 and –2)



Accrual completed: Z-FAST: N = 602
ZO-FAST: N = 1066
E-ZO-FAST: N = 526

PMW = Postmenopausal women; CT = Chemotherapy. *Initiation of zoledronic acid determined by postbaseline BMD T-score < –2.0, any clinical fracture, or any asymptomatic fracture at 36 months.

1. Adapted with permission from Brufsky A, et al. Presented at SABCS, 2007. Abstract 27;
2. Bundred N, et al. Presented at EBBC, 2006. Abstract 12;
3. Schenk N, et al. Presented at ECCO, 2007. Abstract 2008.

Zoledronic Acid Initiation in Delayed Group

Delayed Group Patients Who Initiated Zoledronic Acid	No. of Patients (%)
12-mo visit	
All patients	44 (14.7)
Per protocol[a]	28 (9.3)
24-mo visit	
All patients	54 (18.0)
Per protocol[a]	37 (12.3)
36-mo visit	
All patients	62 (20.7)
Per protocol[a]	45 (15.0)

First Zoledronic Acid Infusion in Delayed Group	Time to Initiation, mo
Mean (SD)	13.5 (10.2)
Median	11.5
Range	0.03–37.1

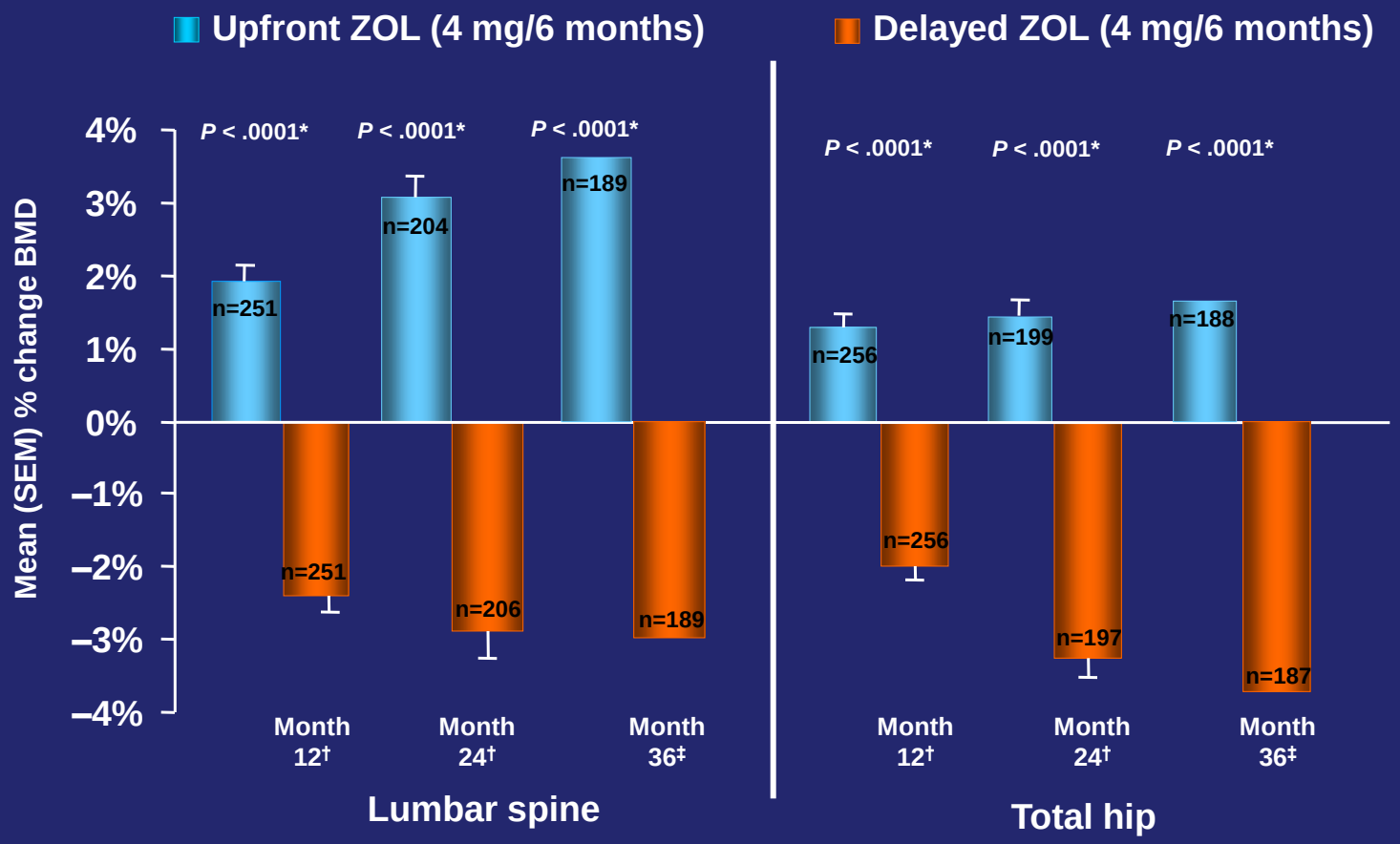
[a]Initiation of zoledronic acid determined by postbaseline T score < -2.0, any clinical fracture, or any asymptomatic fracture at 36 mo.

Intragroup comparisons from baseline to month 12 or 24 for all treatment groups were significant (*P* < .0001 for all).

Adapted from Brufsky A, et al. Presented at: 29th Annual SABCS; December 14-17, 2006; San Antonio, TX. Abstract 5060.

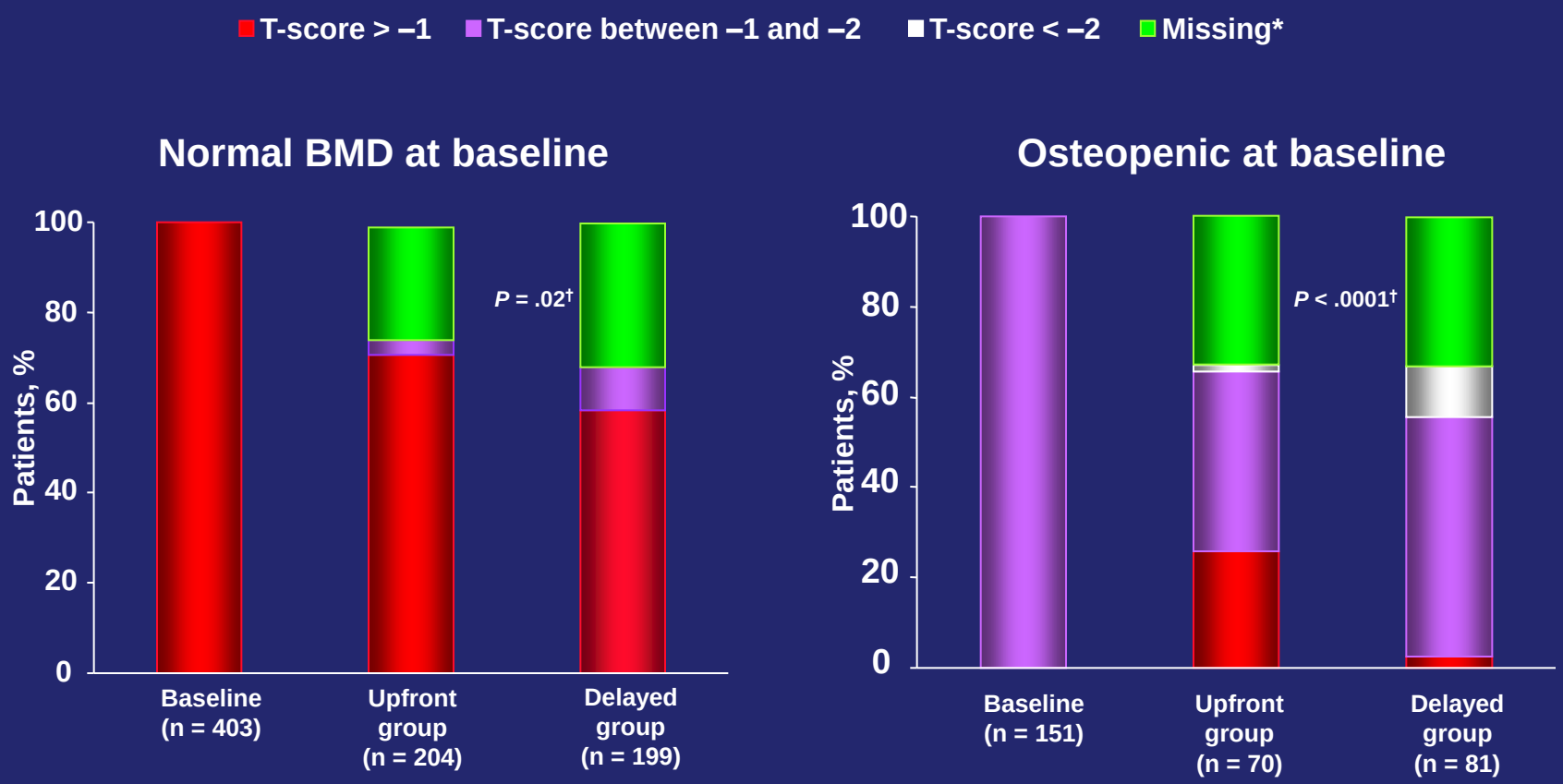
‡Brufsky A, et al. Presented at SABCS, 2007. Abstract #27

Z-FAST: Upfront Zoledronic Acid Increases BMD in Lumbar Spine and Hip



SEM = Standard error of the mean; BMD = Bone mineral density; ZOL = Zoledronic acid.
***P* values correspond to intergroup comparisons.**
†Intragroup comparisons from baseline to month 12 or 24 for all treatment groups were significant (*P* < .0001 for all).
Adapted from Brufsky A, et al. Presented at: 29th Annual SABCS; December 14-17, 2006; San Antonio, TX. Abstract 5060.
‡Brufsky A, et al. Presented at SABCS, 2007. Abstract #27

Z-FAST: Upfront Zoledronic Acid Shifts Lumbar Spine T-Score Distribution at 36 Months



BMD = Bone mineral density. *Missing includes patients discontinued from the study.
†*P* values correspond to intergroup comparisons at month 24.

Novartis data on file.

Fracture Rates: Z-FAST (36 months)

Type of Fracture	No. of Patient (%) Upfront Group (n=300)	Delayed Group (n=300)
Clinical		
Significant trauma	11 (3.7)	12 (4.0)
Minimal or no trauma	2 (0.7)	3 (1.0)
Asymptomatic	2 (0.7)	1 (0.3)
Other	1 (0.3)	2 (0.7)
Radiological spine	1 (0.3)	1 (0.3)
Total	**17 (5.7)**	**19 (6.3)**

Brufsky A, et al. Presented at SABCS, 2007. Abstract #27

Additional Adverse Events: Z-FAST

- Renal disorders
  - Grade 1-2 renal failure
    - Upfront group, 2 patients
    - Delayed group, 0 patients
  - Both suspected to be related to zoledronic acid

- Atrial fibrillation
  - Grade 1-2
    - Upfront group: 3 patients
    - Delayed group: 0 patients
  - Grade 3-4
    - Upfront group: 4 patients
    - Delayed group: 4 patients
  - None suspected to be related to study drugs

- Osteonecrosis of the jaw
  - No confirmed cases

Oral Bisphosphonates Improve AIBL

- SABRE (Van Posnak, SABCS #502, 2007): risedronate (35 mg PO weekly) substantially improved BMD in the LS and TH at 12 months versus placebo in women receiving anastrozole as adjuvant therapy (n=144)
- IBIS-II Sub-study (Singh, SABCS #28, 2007): risedronate (35 mg PO weekly) substantially improved BMD in the LS and TH at 12 months versus placebo in women receiving anastrozole as prevention (n=59)
- ARIBON (Lester, ASCO #553, 2007): ibandronate (150 mg PO qmonth) substantially improved BMD in the LS and TH at 12 months versus placebo in women receiving anastrozole as adjuvant therapy (n=131)

The Impact of Risk Factors on the Incidence of Fracture

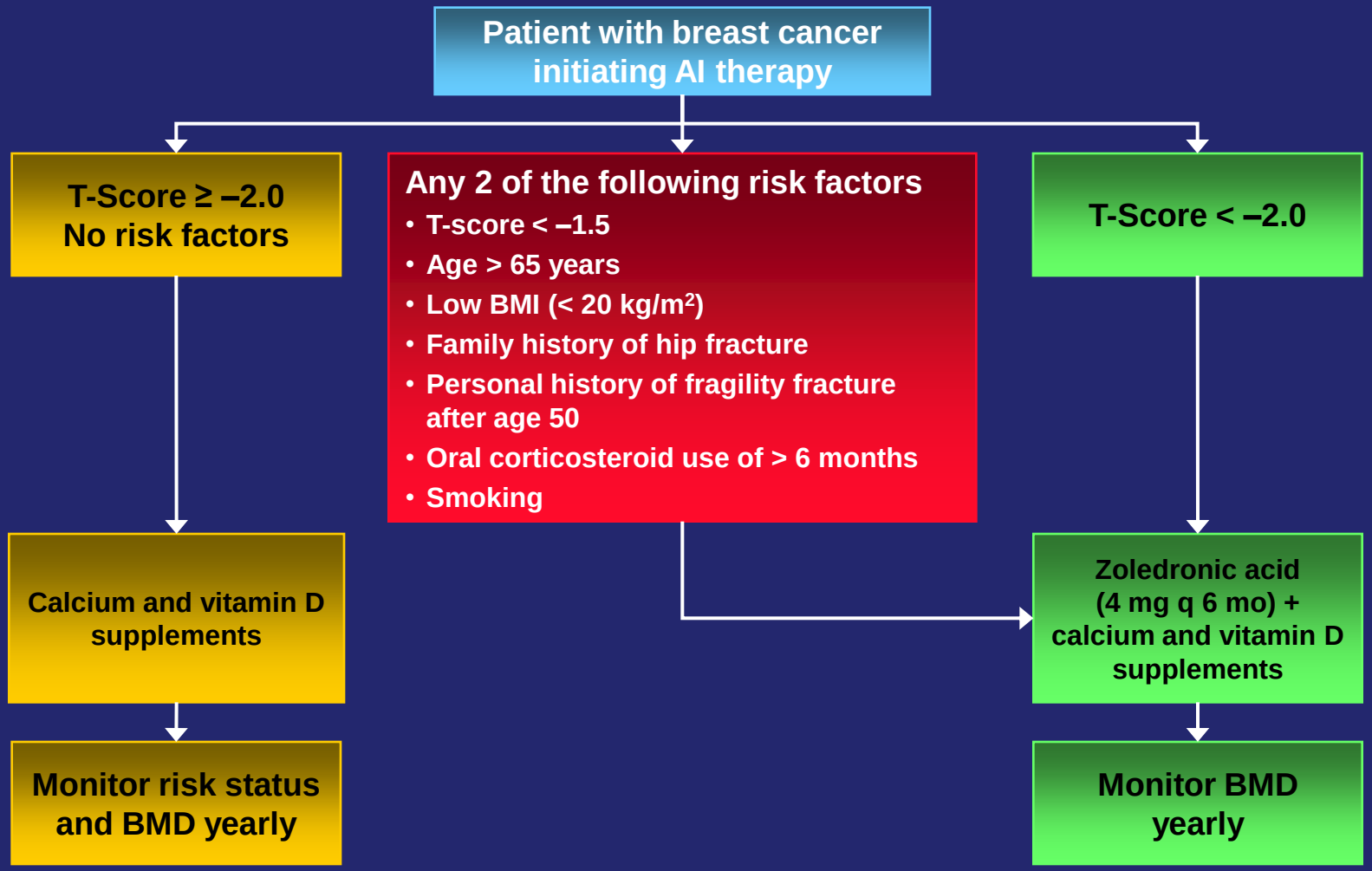
Who Should Be Treated With Bisphosphonates to Reduce Risk? (current guidance)

- WHO osteoporosis guidelines[1]
  - T-Score ≤ –2.5
  - Osteopenic patients with additional strong risk factors
- NOF guidelines[2]
  - T-score < –2.0 with no risk factors
  - T-score < –1.5 with 1 or more risk factors
  - Prior vertebral or hip fracture
- ASCO guidelines[3]
  - Treat all patients with T-score ≤ –2.5
  - Breast cancer patients with T-score –1.0 to –2.0 should receive individualized therapy

WHO = World Health Organization; NOF = National Osteoporosis Foundation; ASCO = American Society of Clinial Oncology.

1. *WHO Tech Rep Ser 921.* Geneva, 2003; 2. National Osteoporosis Foundation guidelines. www.nof.org/physguide/pharmacologic.htm; 3. Hillner BE, et al. *J Clin Oncol.* 2003;21:4042-4057.

Treatment Guidelines: Women With Breast Cancer Initiating AI Therapy



AI = Aromatase inhibitor; BMD = Bone mineral density; ZOL = Zoledronic acid; BMI = Body mass index.

Hadji P, et al. *Presented at SABCS 2007, Abstract #504.*

Implications for clinical practice

- Issues of bone loss and fracture are real
- DEXA on every pt receiving AIs? (yes)
- DEXA every other year? (yes)
- If osteopenic (T<-2.0), change to tam or add oral bisphosphonate (aledronate, risidronate)? (maybe)
- Consider zometa q6months? (soon)

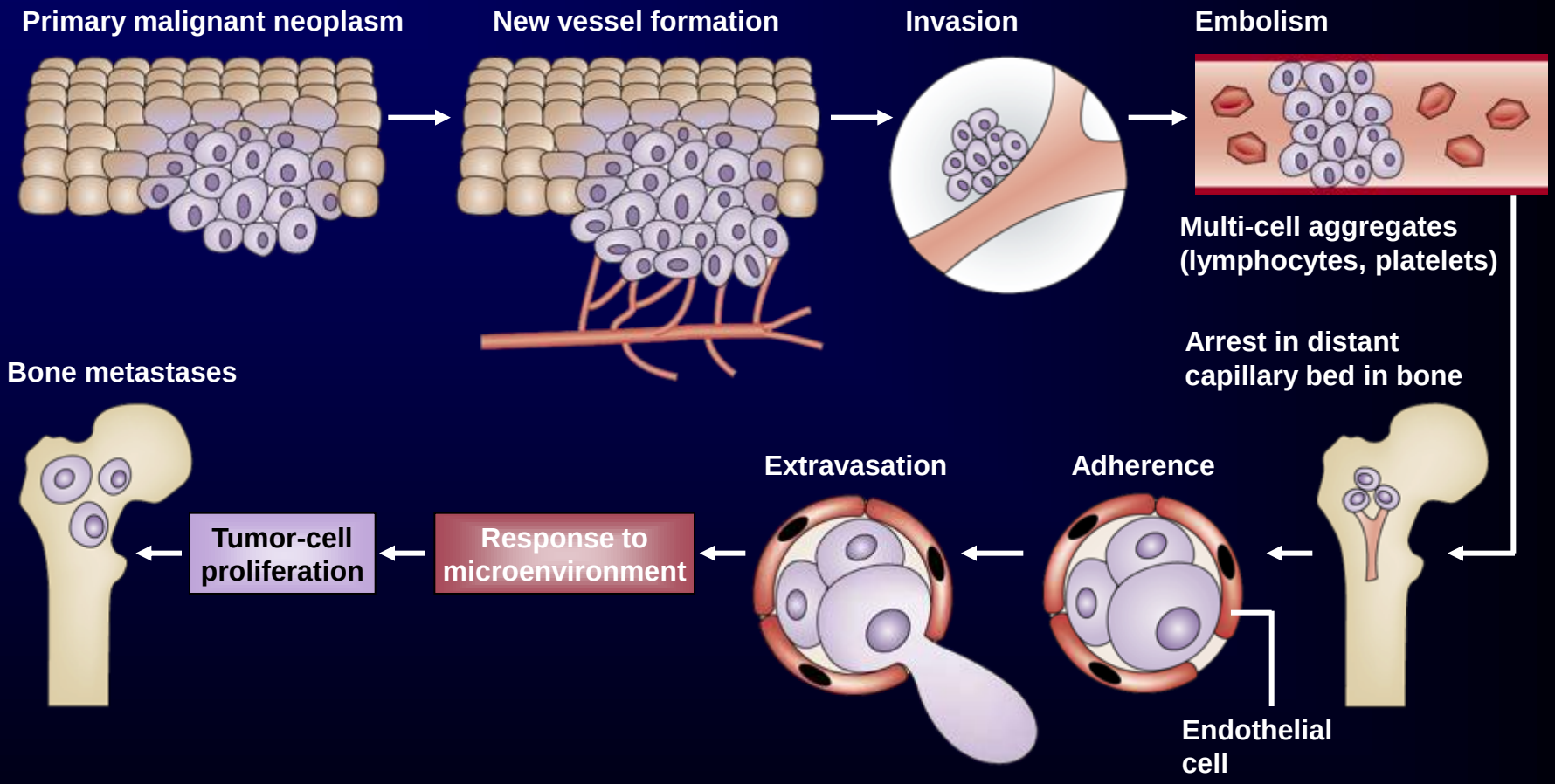
SEED AND SOIL Hypothesis

Stephen Paget
1855-1926

"While many researchers have been studying 'the seed,' the properties of 'the soil' may reveal valuable insights into the 'metastatic peculiarities' in cancer cases."

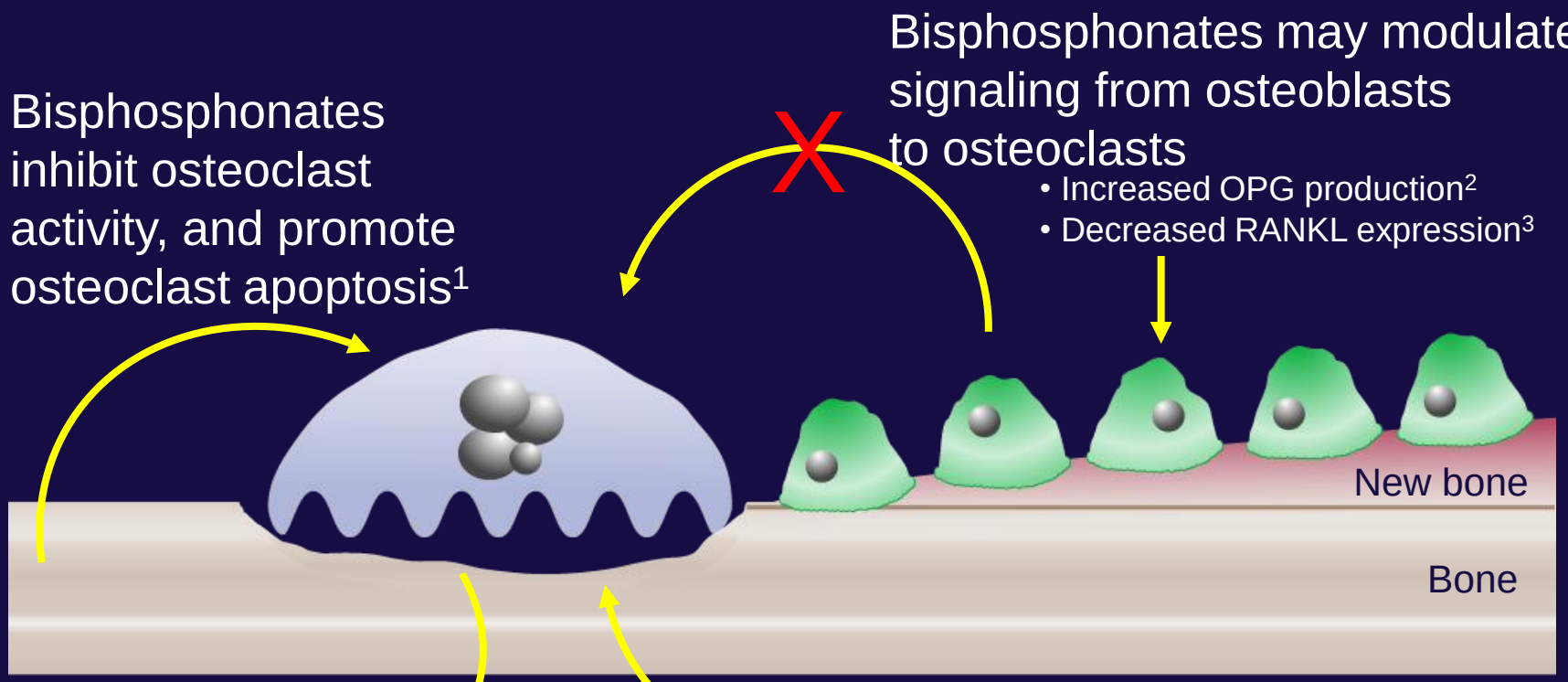
The Distribution of Secondary Growths in Cancer of the Breast
The Lancet, 1889

Steps Involved in Tumor Cell Metastasis From Primary Site to Bone



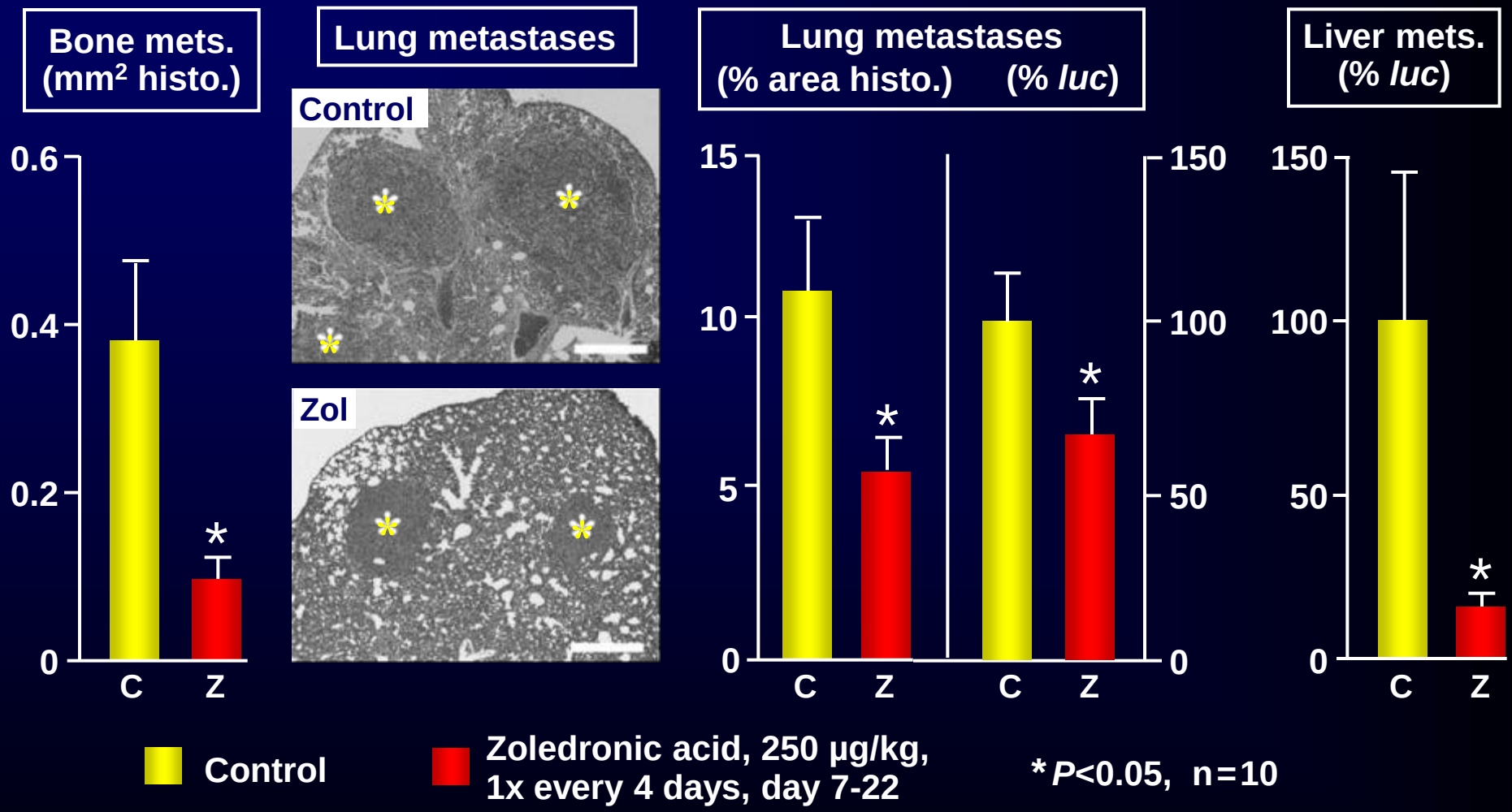
Mundy GR, et al. *Nature Reviews Cancer*. 2002;2:584-593.

Bisphosphonate Inhibition of Osteoclast Activity: Mechanism of Action



1. Reszka AA et al. *Curr Rheumatol Rep*. 2003;5:65-74; 2. Vierech V et al. *Biochem Biophys Res Commun*. 2002;291:680-686. 3. Pan B et al. *J Bone Miner Res*. 2004;19:147-154.

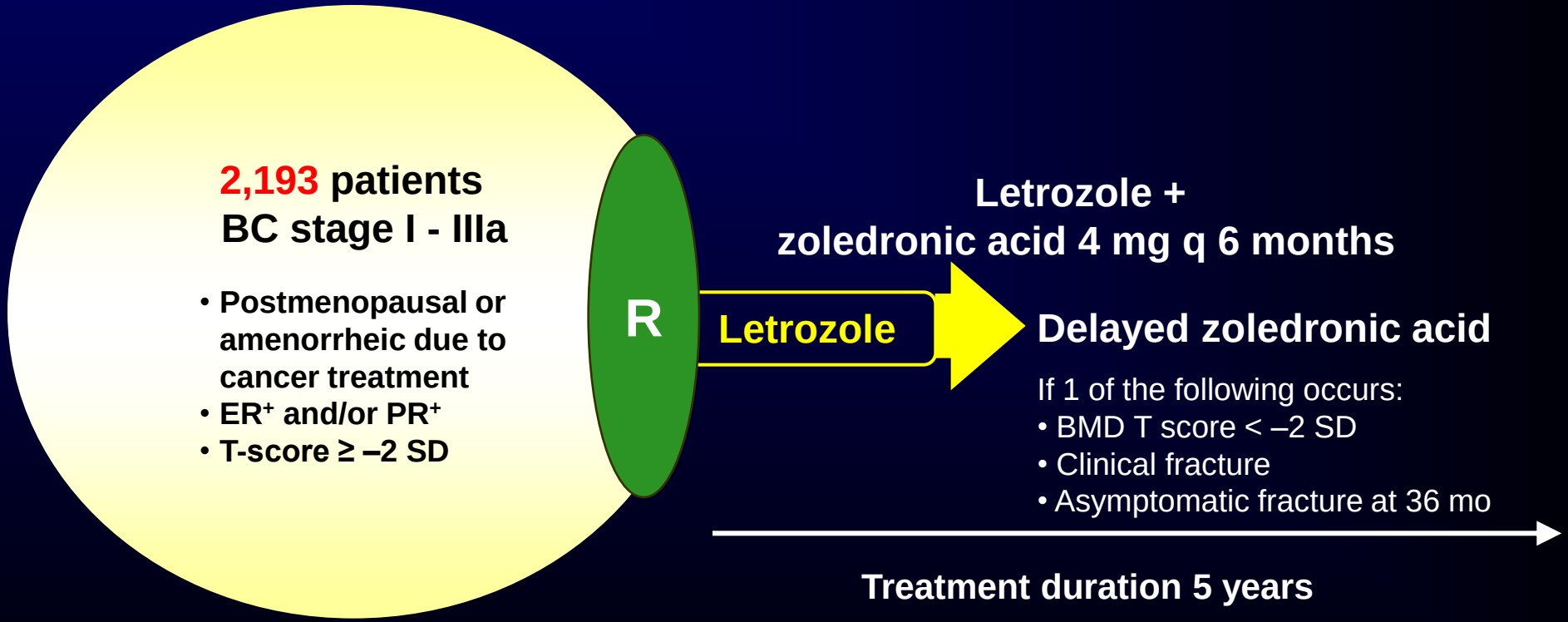
Zoledronic Acid Reduces Bone, Liver and Lung Metastases in the Murine 4T1/luc Orthotopic Breast Cancer Model



Hiraga et al. *Clin Cancer Res*. 2004;10:4559.

Z- FAST: Zometa-Femara Adjuvant Synergy Trials

- Key end points
  - BMD; bone markers; fractures; and time to recurrence/relapse



BMD = Bone mineral density; BC = Breast cancer; ER = Estrogen receptor; PR = Progesterone receptor; SD = Standard deviation; CT = Chemotherapy.

Z-FAST: Upfront Zoledronic Acid (4 mg q 6 months) - Disease Recurrence

	Patients, n (%)		
Month	Upfront group	Delayed group	*P* value
12[1]	1 (0.3)	6 (2.0) Δ 1.7	0.056
24[2]	7 (2.3)	12 (4.0) Δ 1.7	0.21
36[3]	9 (3.0)	14 (5.3) Δ 2.3	0.24

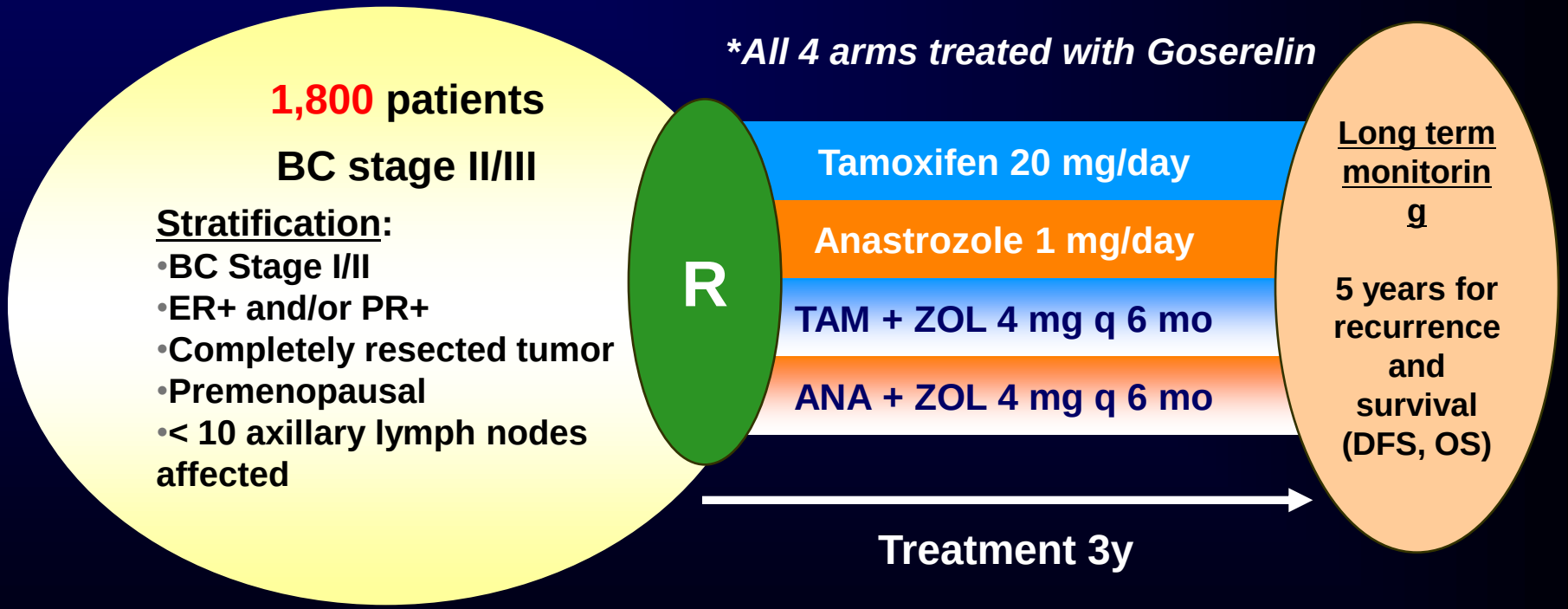
1. Brufsky et al. *J Clin Oncol.* 2007;25:829.
2. Brufsky et al. *Breast Cancer Res Treat.* 2006;100(suppl 1):S233. Abstract 5060.
3. Brufsky et al. *Breast Cancer Res Treat.* 2007;106(suppl 1):S8. Abstract 27.

Breast Cancer: ABCSG-12

Key End points:

Primary: Disease-free survival (DFS) at 5 y (TAM vs ANA, ZOL vs no-ZOL)

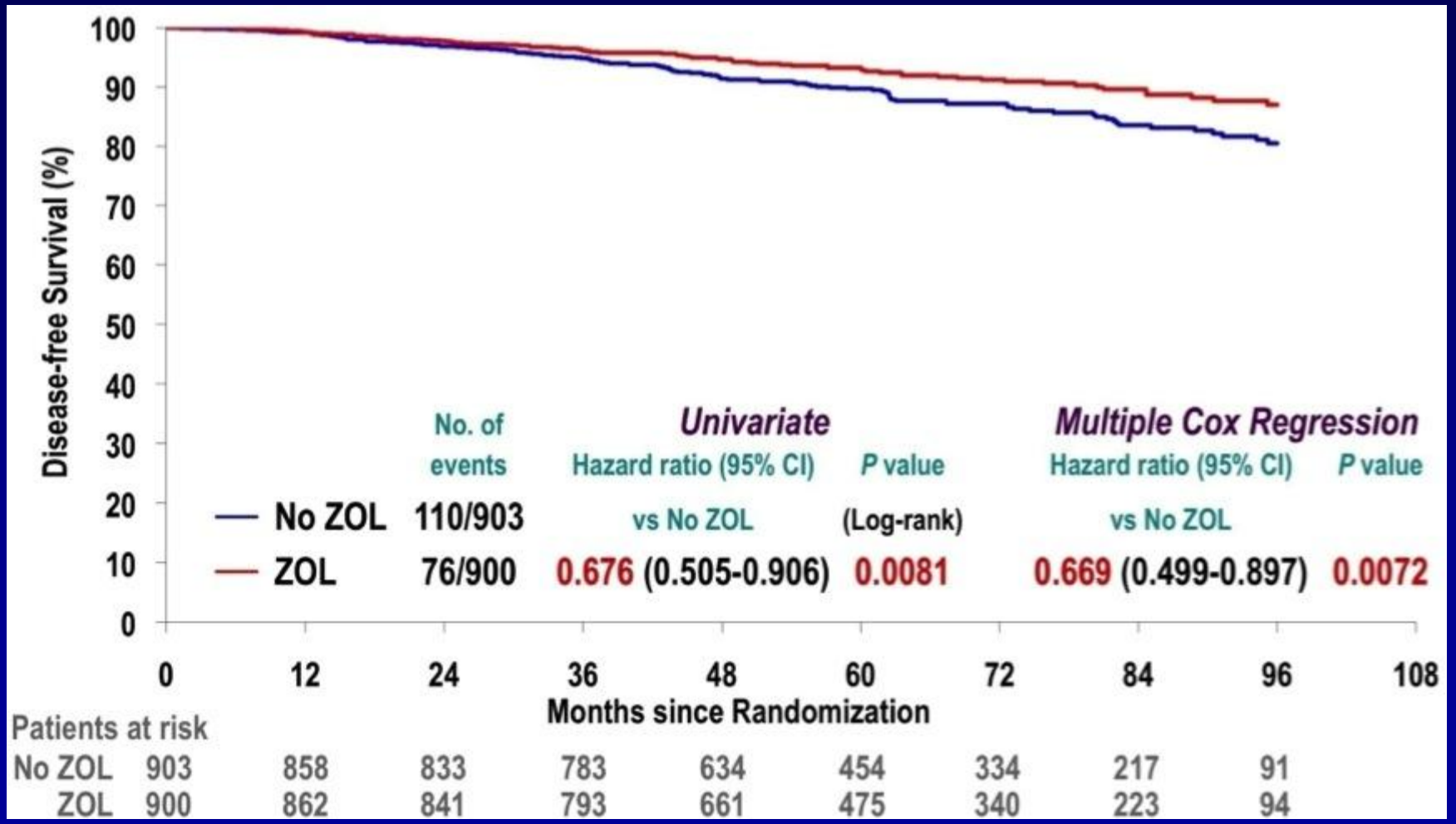
Secondary: Relapse-free survival (RFS) at 5y, OS at 3y (TAM vs ANA, ZOL vs no-ZOL)



TAM = tamoxifen, ANA = anastrozole.

Primary Endpoint: DFS

Zoledronic Acid Significantly Improves DFS Compared With Endocrine Therapy Alone



Reproduced with permission from Gnant. *ASCO.* 2009 (abstr 533).

Multivariate Adjusted HRs for Breast Cancer Incidence by Bisphosphonate Use

	Bisphosphonate Use				
	No	Yes	Multivariate		
	Rate/1000 person yr	Rate/1000 person yr	HR	95% CI	*P* Value
Invasive breast cancer	4.38	3.29	0.68	(0.52-0.89)	<0.01
ER positive	3.28	2.56	0.70	(0.52-0.95)	0.02
ER negative	0.61	0.41	0.66	(0.31-1.39)	0.27

Adjusted for age, ethnicity, smoking, alcohol use, physical activity, BMI, mammogram in the last 2 years, prior hormone use, total calcium, total vitamin D, 5-yr hip fracture risk, and Gail 5-yr breast cancer risk, and stratified on WHI trial randomization arm

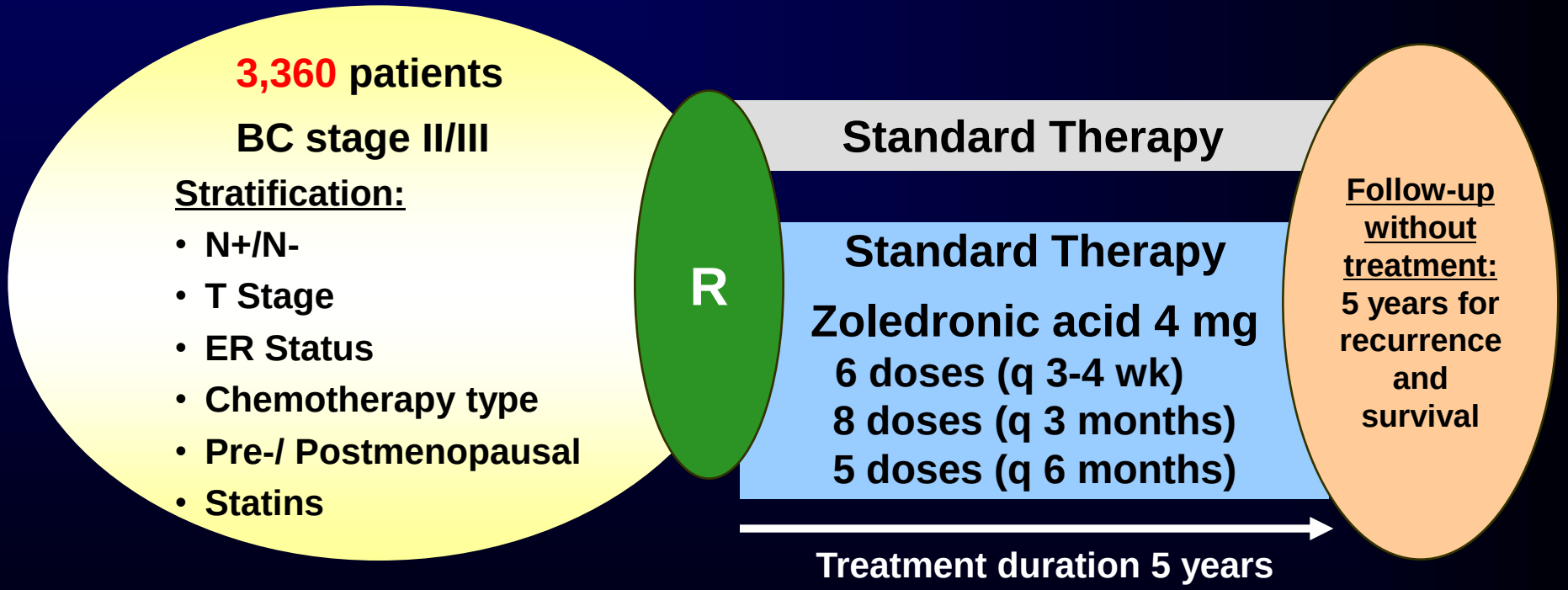
Chlebowski. *SABCS.* 2009 (abstr 21).

AZURE: Does Adjuvant Zoledronic Acid RedUce REcurrence in Breast Cancer?

Primary end point: Disease free survival

Secondary endpoints: Bone metastases free survival, SREs, overall survival, adverse events, predictive biomarkers

First interim analysis expected 2008



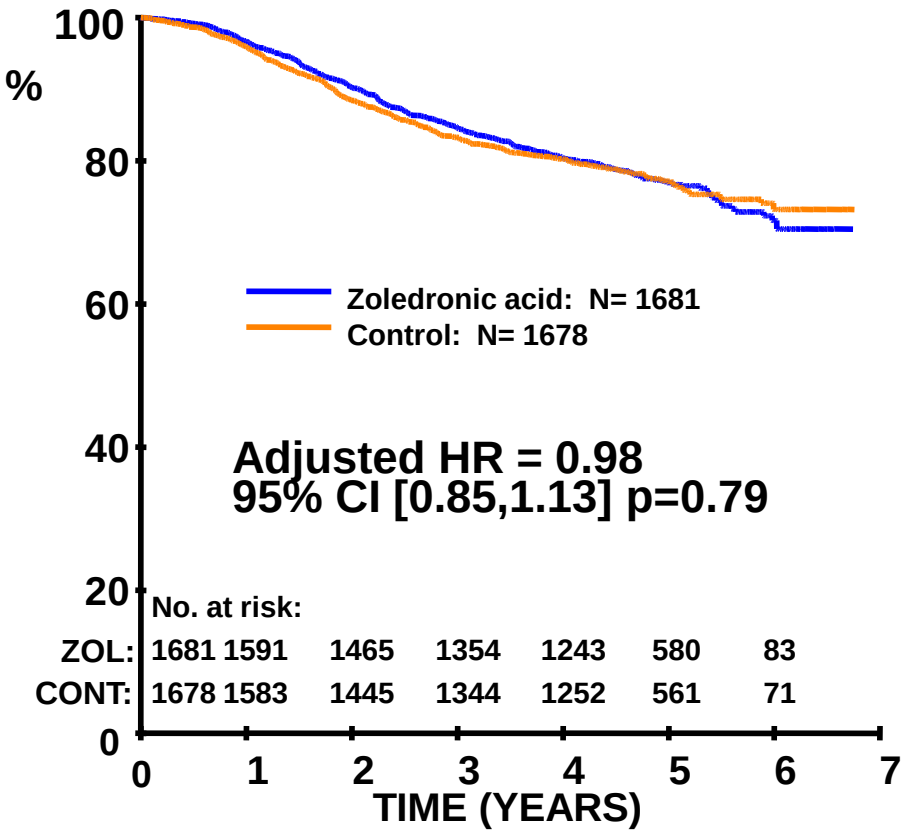
SREs = Skeletal-related events; BC = Breast cancer; ER = Estrogen receptor.

PI: Rob Coleman
Accrual completed February 2006

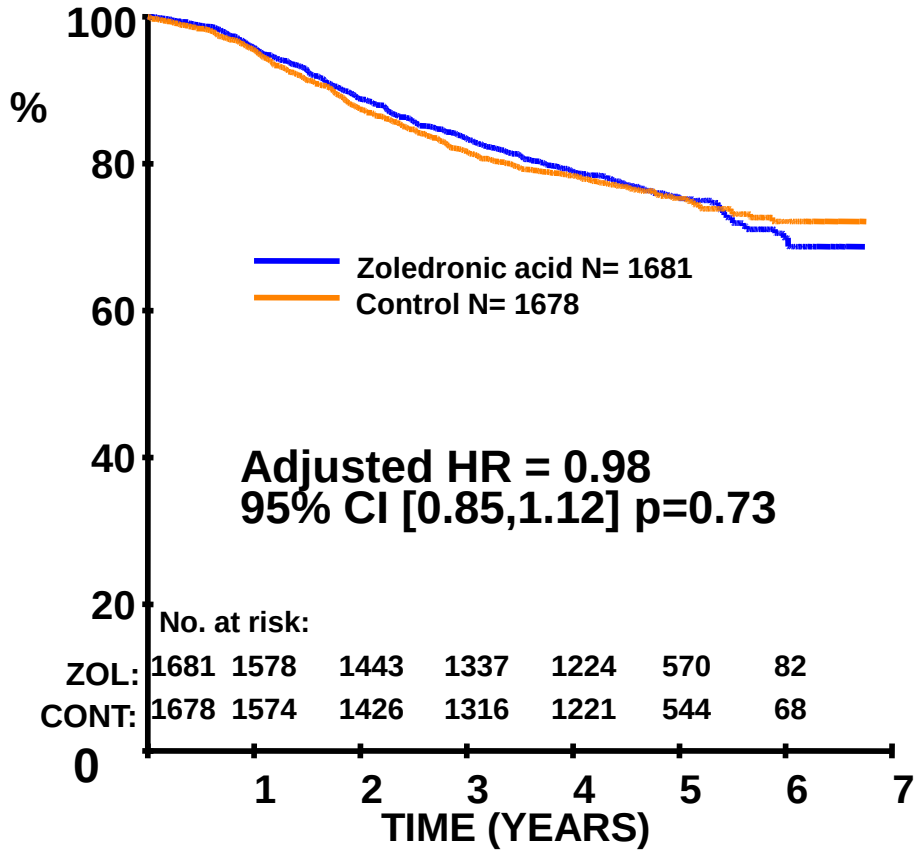
AZURE: Disease (DFS) and Invasive Disease Free Survival (IDFS)

The University Of Sheffield.

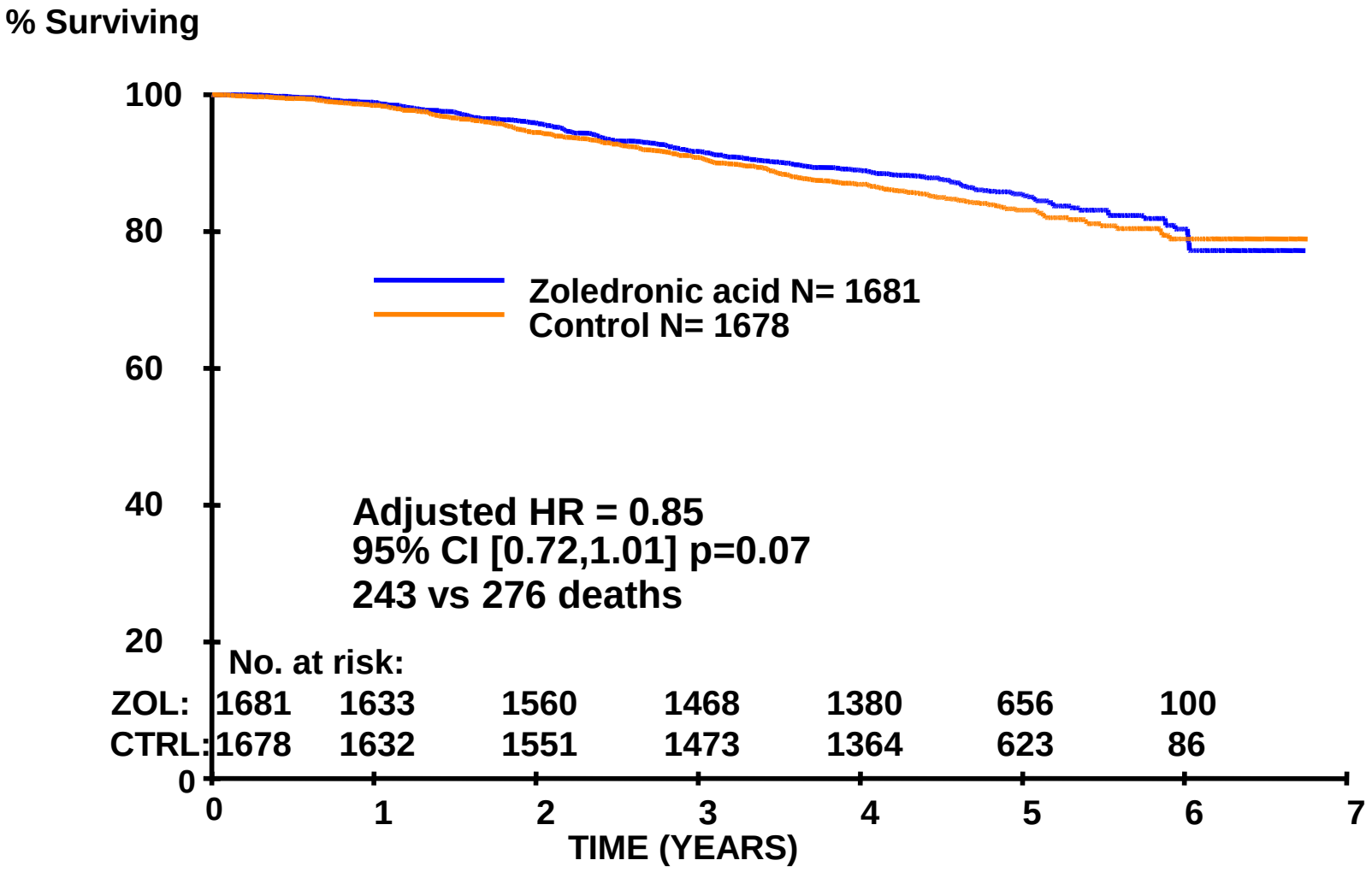
DFS



IDFS



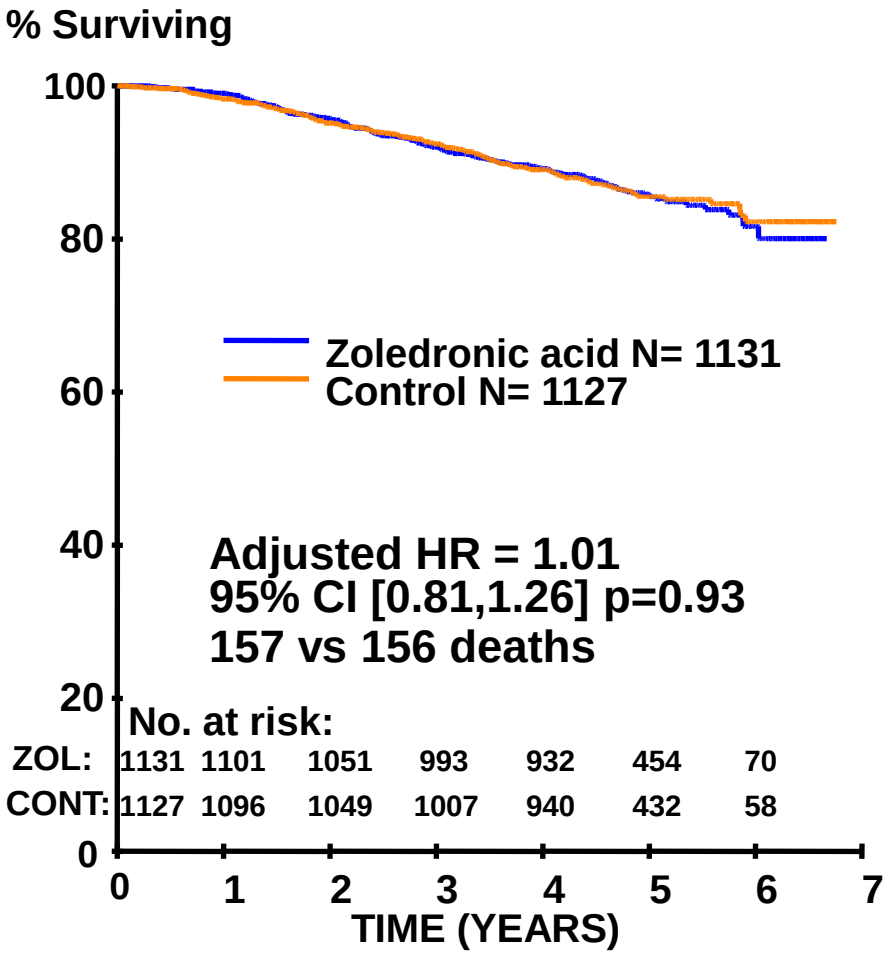
AZURE: Overall Survival



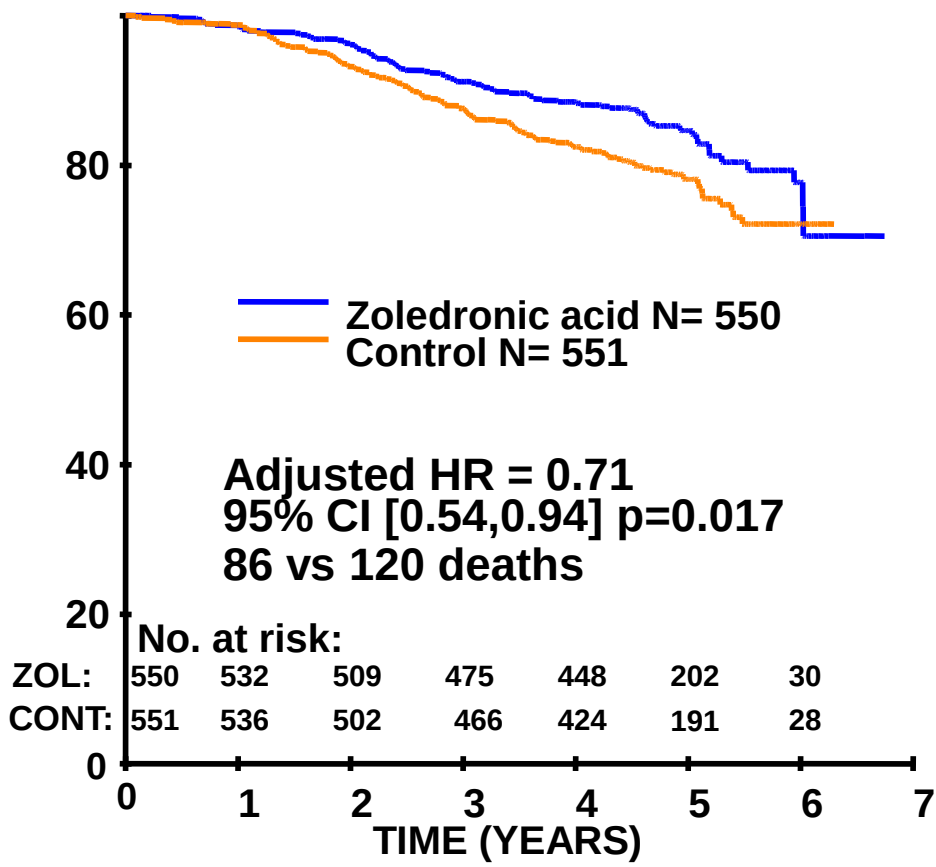
AZURE: Overall Survival by Menopausal Status

The University Of Sheffield.

Pre, peri and unknown menopausal status



>5 years post-menopausal or age > 60



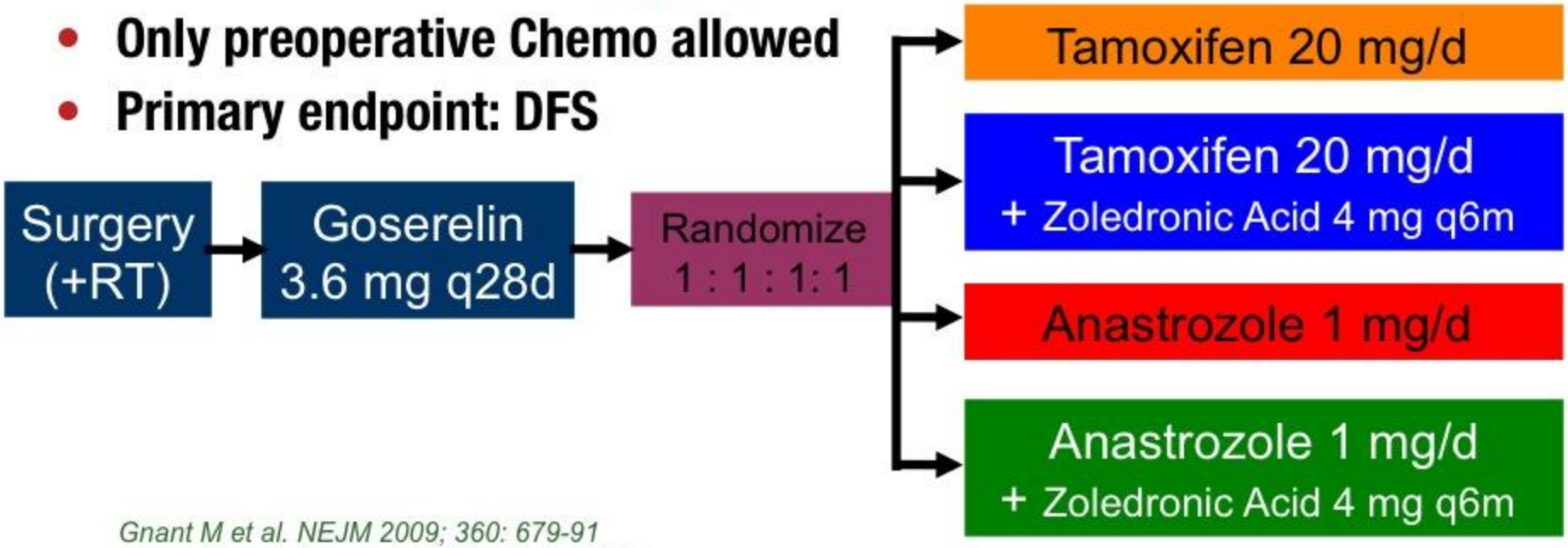
Effects independent of ER

Questions Outstanding

- What about long term survival in zoledronic acid treated patients (ABSCG-12)?
- What about long term DFS with zoledronic acod and letrozole (ZO-FAST)?
- What about other bisphosphonates (B-34)?

ABCSG-12 Trial Design

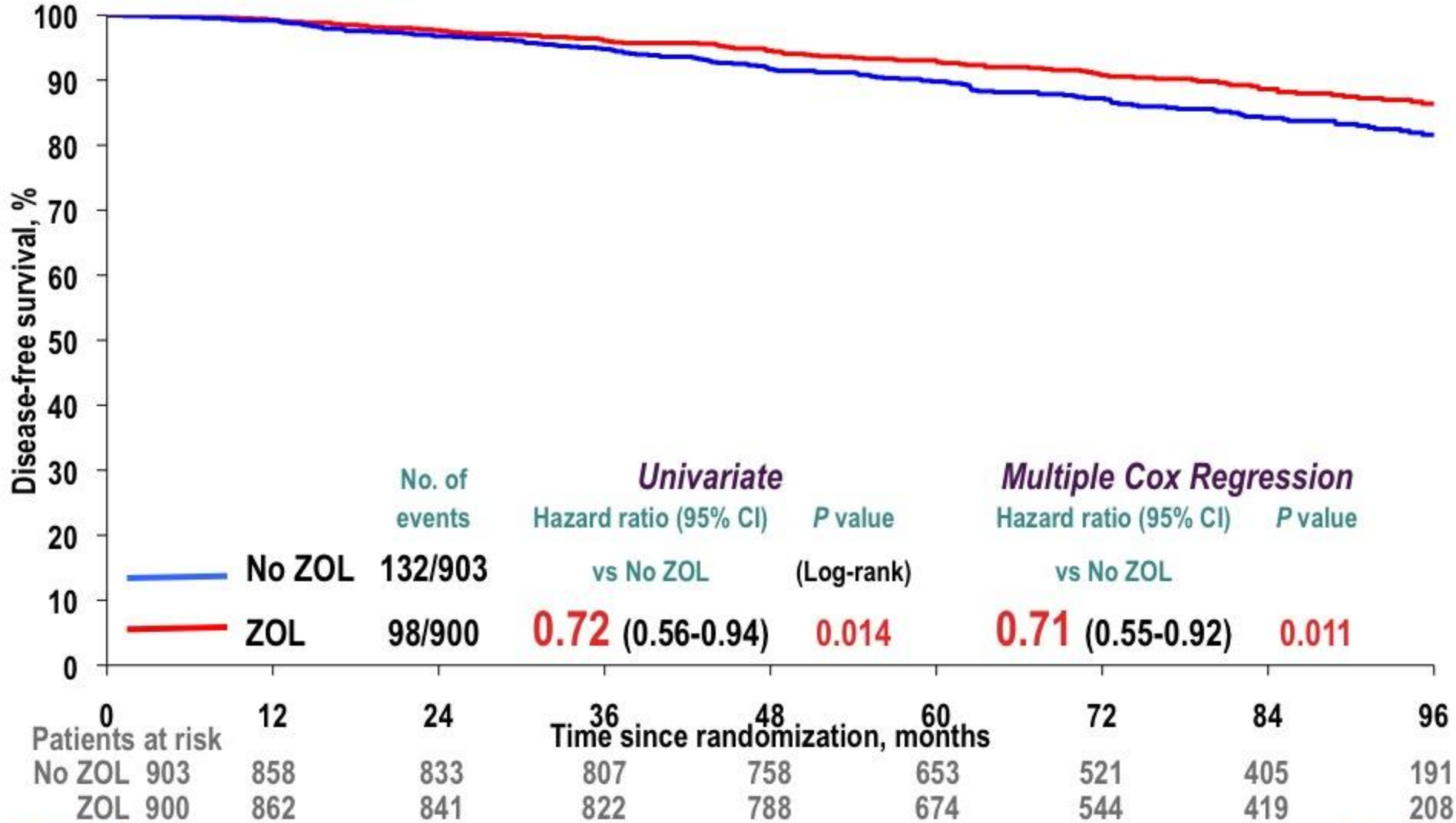
- Recruitment 1999-2006
- 1,803 premenopausal patients
- Stage I&II, ER+ and/or PgR+
- Duration of treatment: 3 years
- Only preoperative Chemo allowed
- Primary endpoint: DFS



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

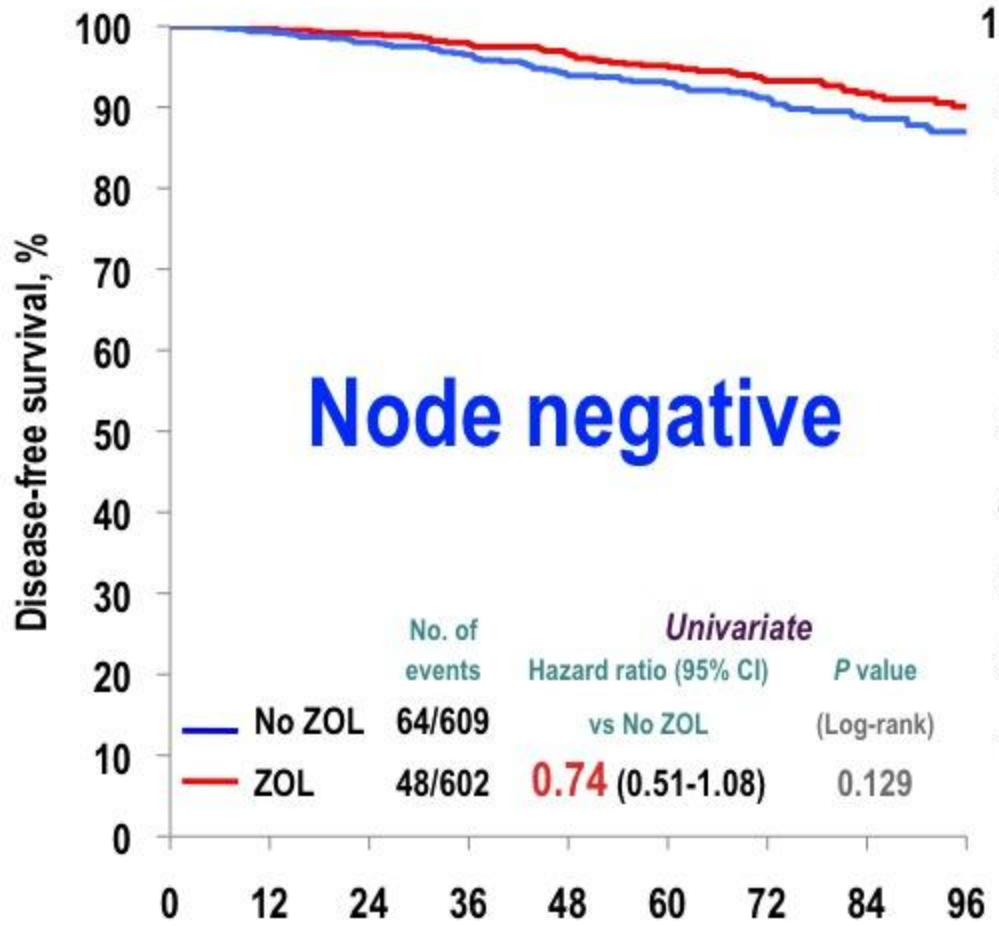
Primary Endpoint: Disease-Free Survival

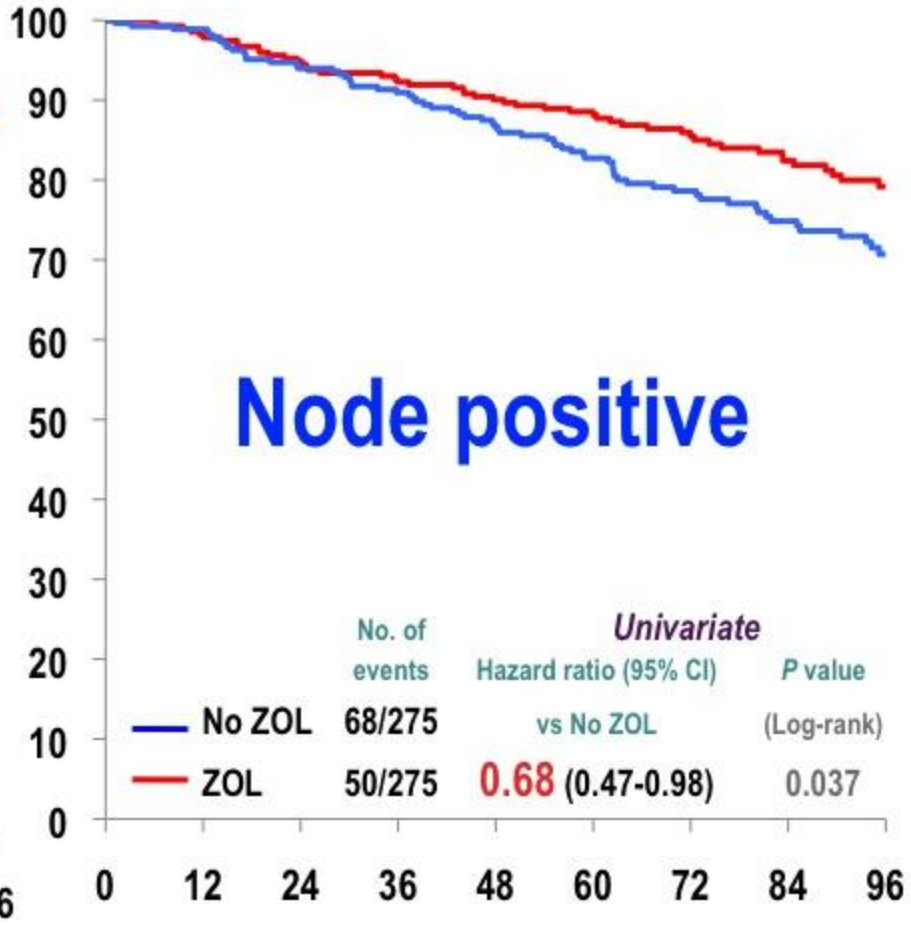
Zoledronic Acid Significantly Improves DFS Compared With Endocrine Therapy Alone



ZOL *vs.* No ZOL in N- and N+ Cohorts

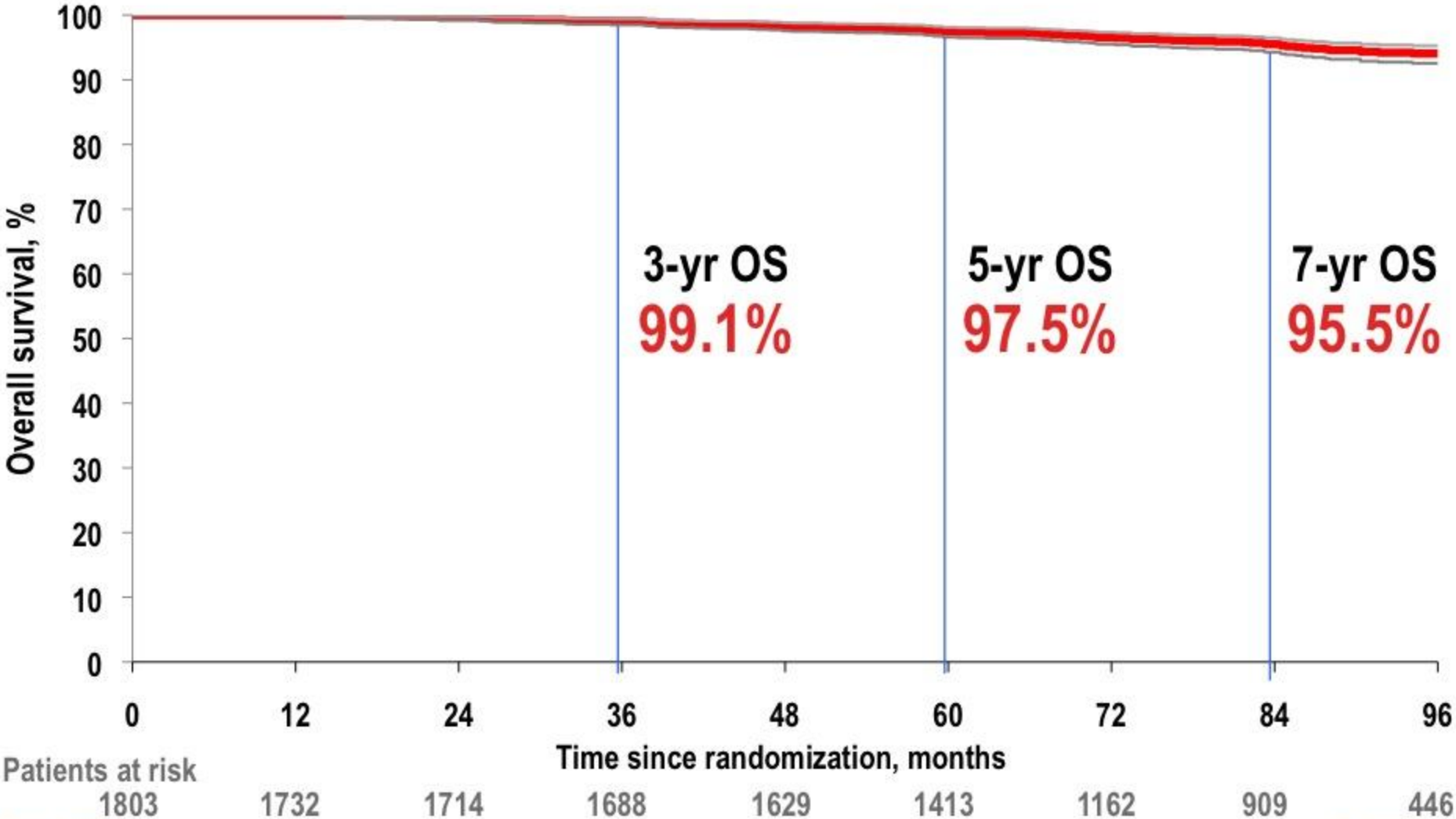
Disease-Free Survival





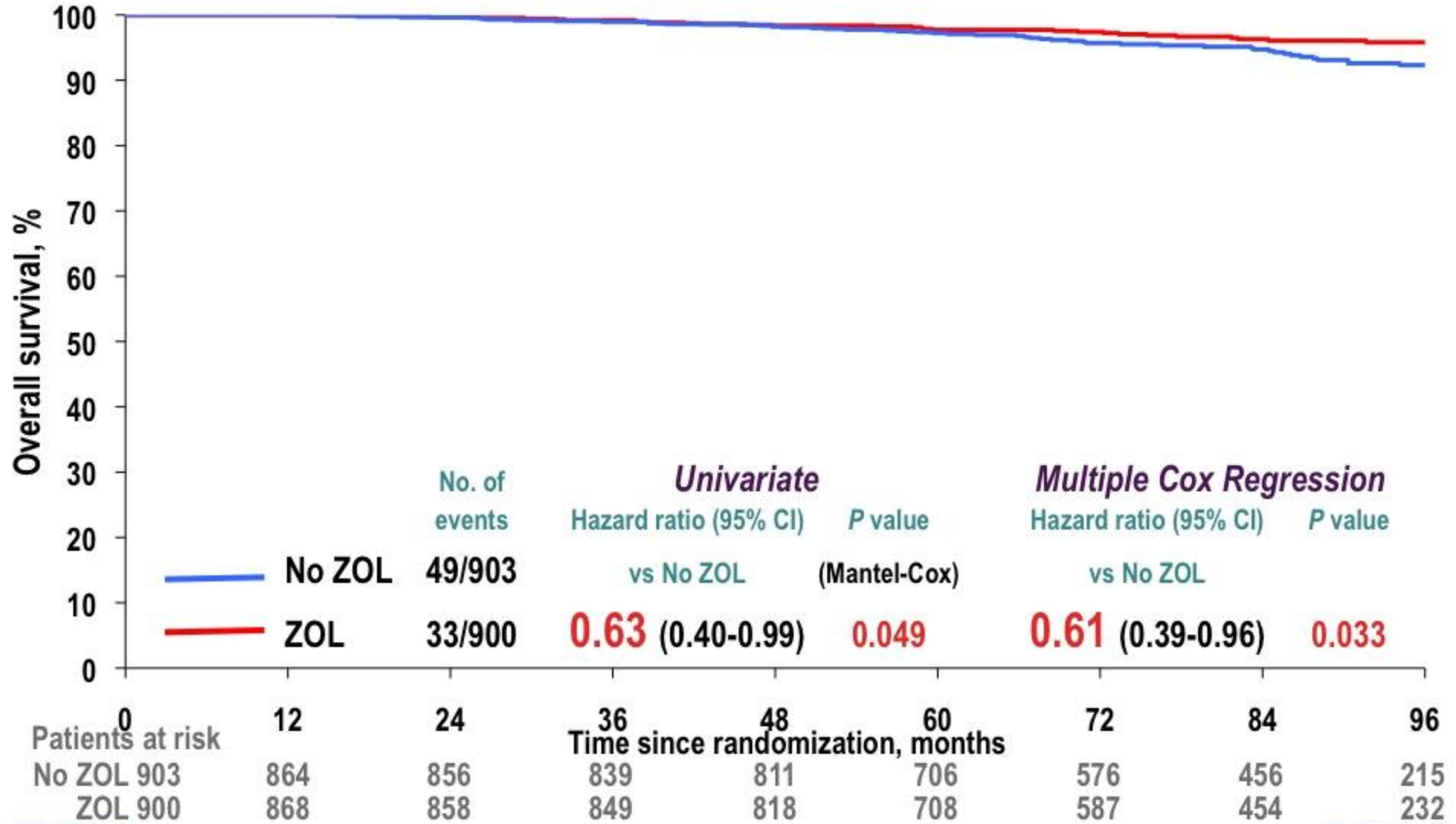
Overall Survival: All Patients

Adjuvant endocrine therapy based on ovarian function suppression yields excellent results in premenopausal patients with HR-positive breast cancer



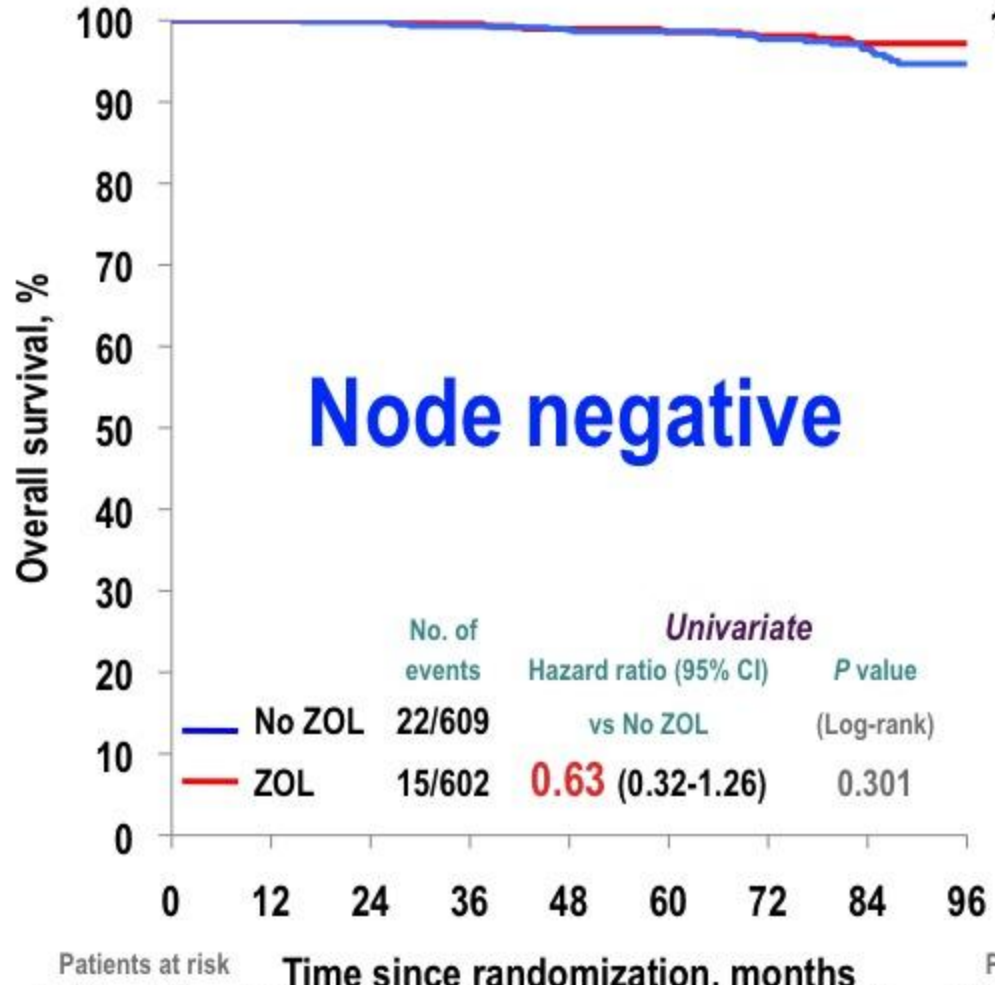
Overall Survival: Zol *vs* No ZOL

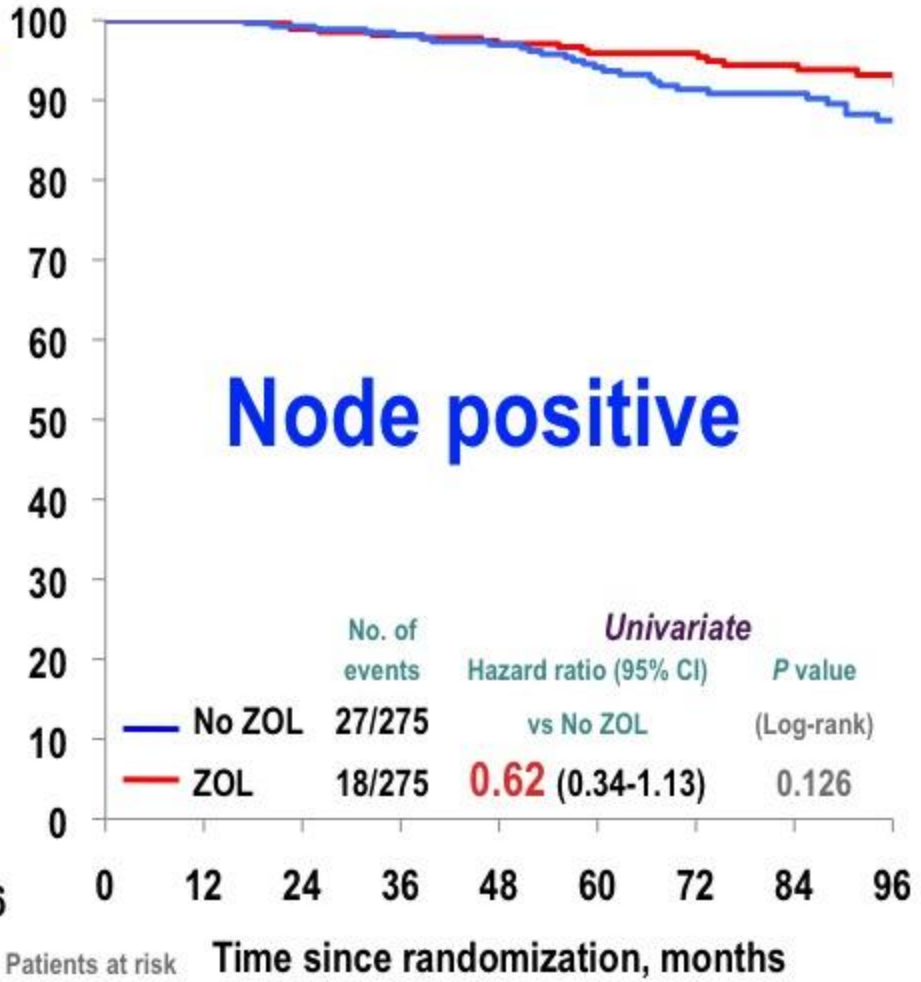
Zoledronic Acid Improves OS Compared With Endocrine Therapy Alone



ZOL *vs.* No ZOL in N- and N+ cohorts

Overall Survival





Conclusion and Perspectives

- The anticancer effects of adjuvant zoledronic acid are now well established in endocrine-responsive patients
  - Safe and well tolerated in several phase-III trials (N > 7,000)
  - ABCSG-12, ZO-FAST, and the postmenopausal AZURE sub-group demonstrate significant outcome (including OS) benefits
- Bone-targeted treatments modify the bone (marrow) microenvironment and (may) affect cancer stem cells
- Adjuvant zoledronic acid is a successful treatment approach in early breast cancer, and should be considered in patients who fit these trials' inclusion criteria

San Antonio Breast Cancer Symposium – December 6-10, 2011. Abstract S1-3.

Long-term Survival Outcomes Among Postmenopausal Women With Hormone Receptor-Positive Early Breast Cancer Receiving Adjuvant Letrozole and Zoledronic Acid: 5-year Follow-up of ZO-FAST

R.H. de Boer,1 N. Bundred,2 H. Eidtmann,3 P. Neven,4 G. von Minckwitz,5 N. Martin,6 A. Modi,6 R. Coleman7

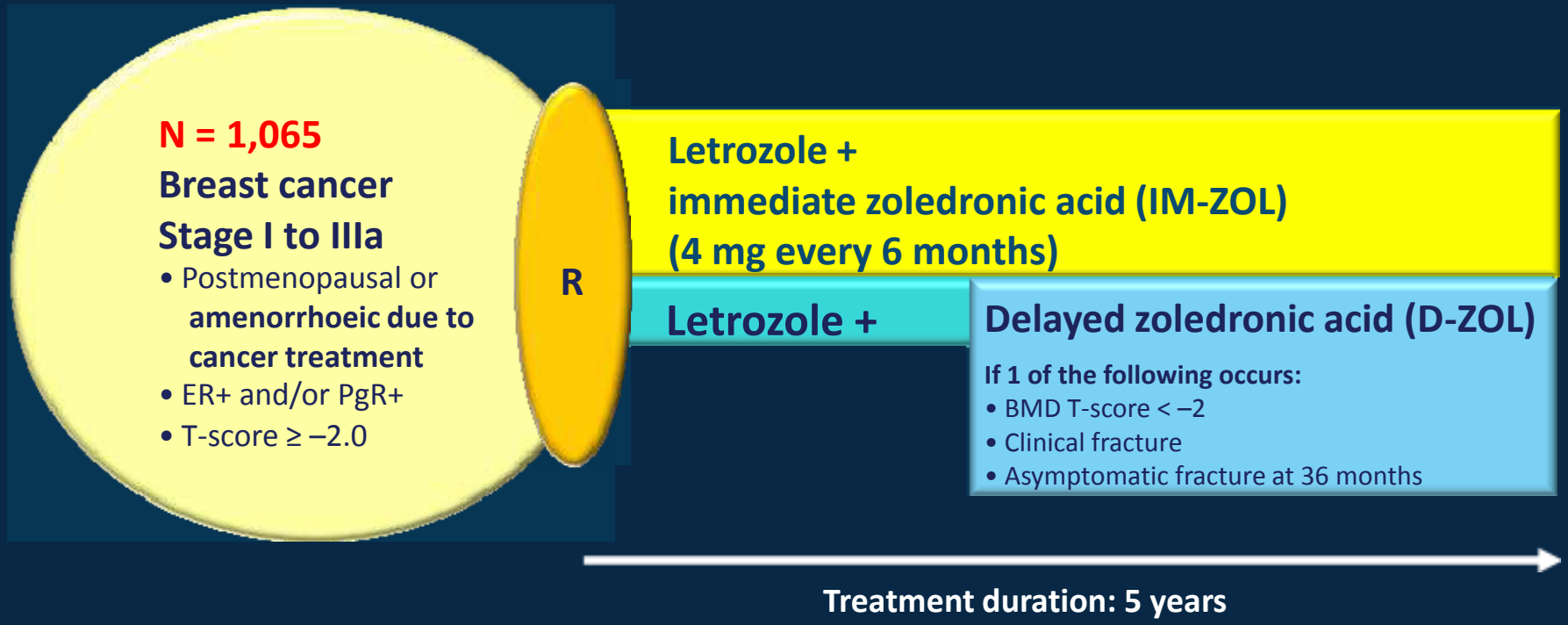
1Royal Melbourne Hospital, Victoria, Australia; 2South Manchester University Hospital, Academic Surgery, Education and Research Center, Manchester, UK; 3Universitäts Frauenklinik Kiel, Germany; 4Breast Clinic, UZ Gasthuisberg, Leuven, Belgium; 5German Breast Group, Frankfurt, Germany; 6Novartis Pharma AG, Basel, Switzerland; 7Academic Unit of Clinical Oncology, Weston Park Hospital, Sheffield, UK

ZO-FAST: Trial Design

Key endpoints

Primary: Bone mineral density (BMD) at 12 months

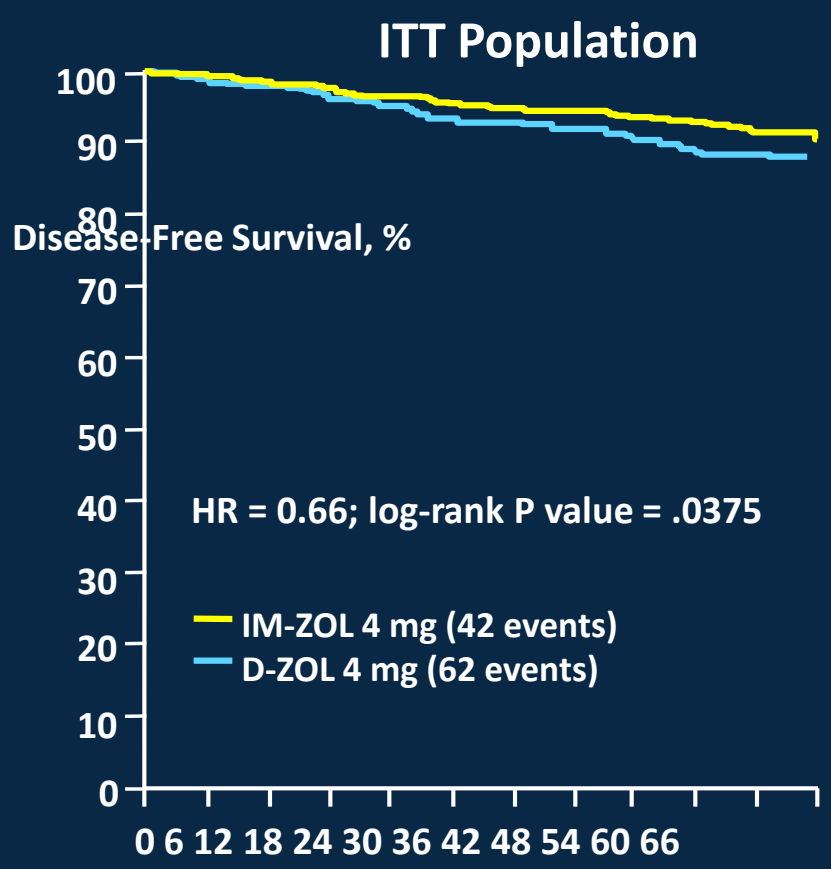
Secondary: BMD at 36 and 60 months, disease recurrence, fractures, safety

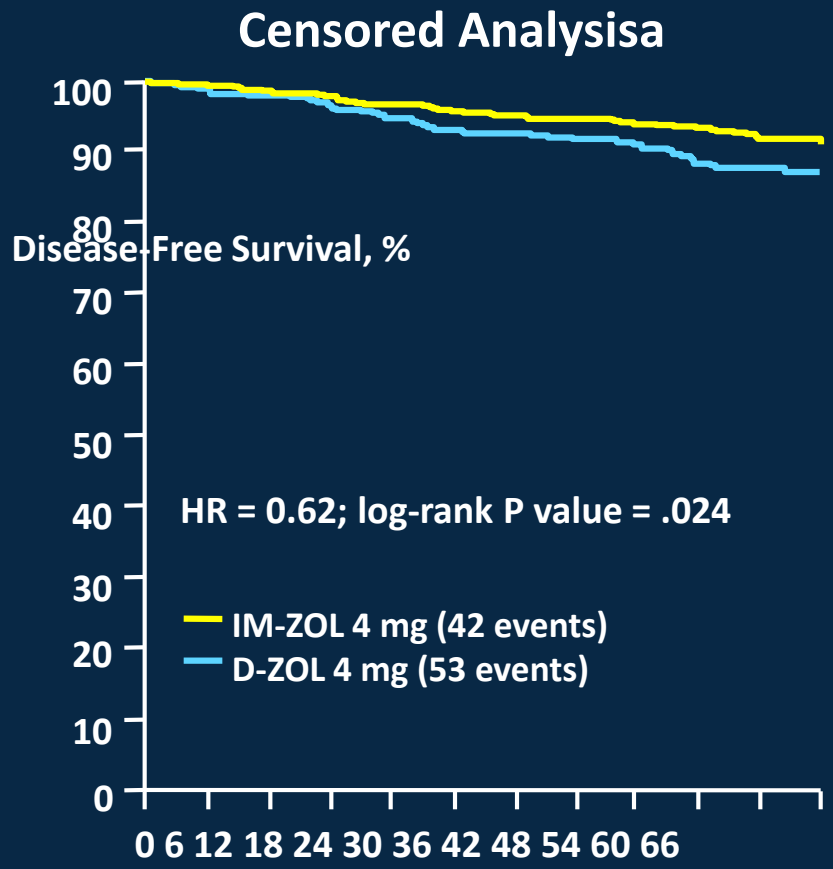


Abbreviations: BMD, bone mineral density; ER, oestrogen receptor; PgR, progesterone receptor; R, randomisation.

http://www.clinicaltrials.gov. Identifier: NCT00050011.

ZO-FAST: Disease-Free Survival

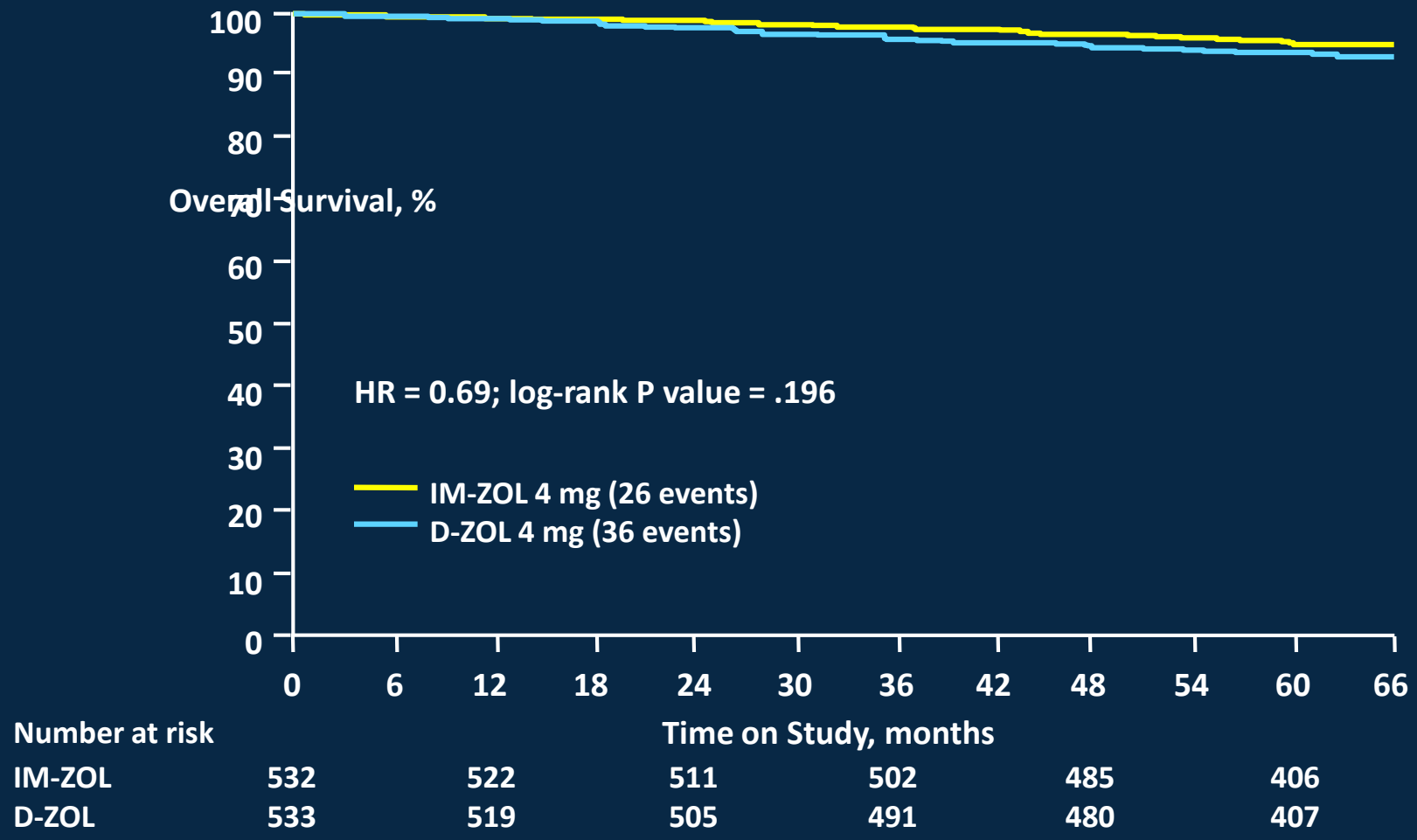




a Censored patients at initiation of delayed ZOL (n=144).

Abbreviations: DFS, disease-free survival; D-ZOL, delayed zoledronic acid; HR, hazard ratio; IM-ZOL, immediate zoledronic acid.

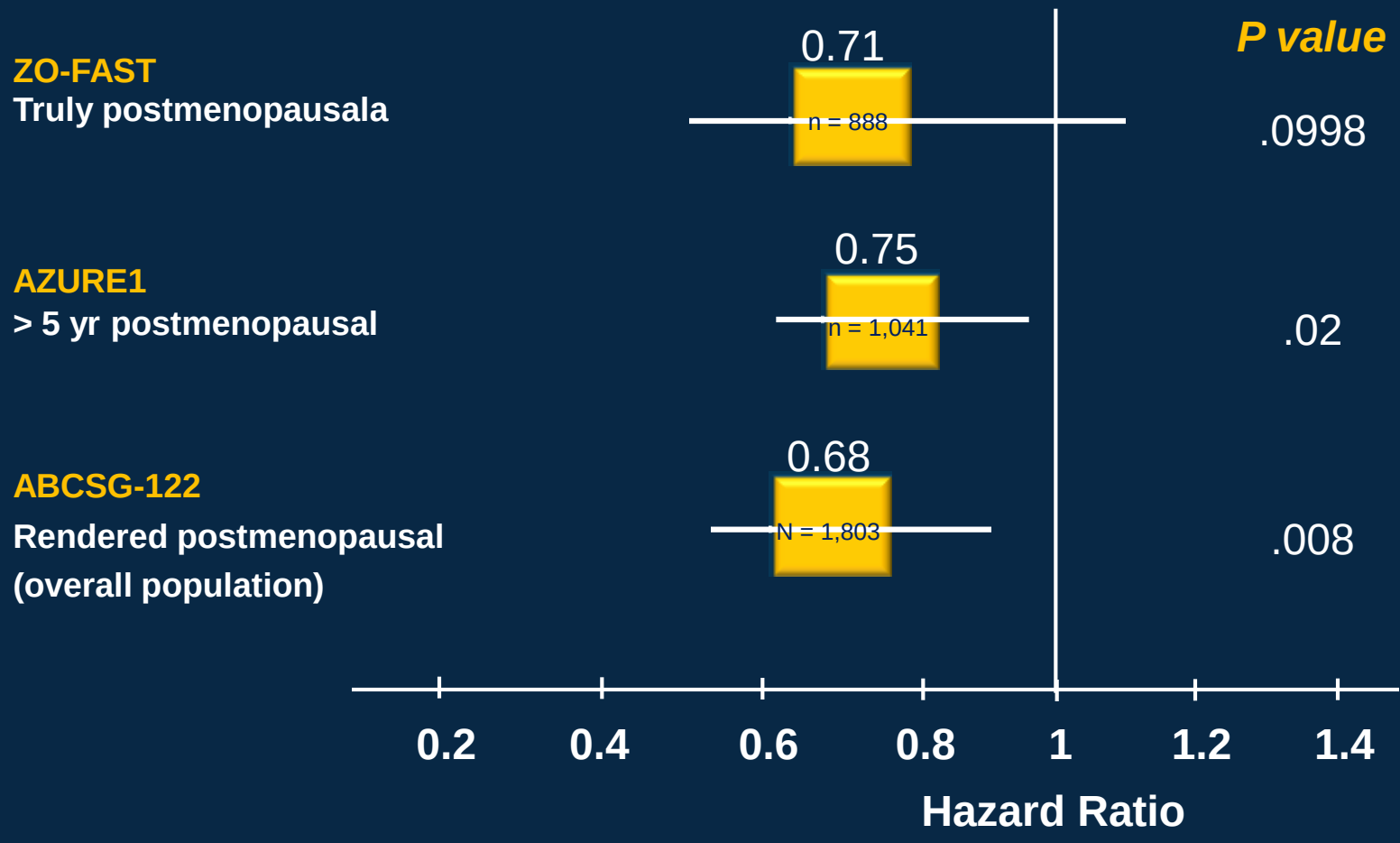
ZO-FAST: Overall Survival (ITT Population)



Number at risk						
IM-ZOL	532	522	511	502	485	406
D-ZOL	533	519	505	491	480	407

Abbreviations: D-ZOL, delayed zoledronic acid; HR, hazard ratio; IM-ZOL, immediate zoledronic acid.

ZO-FAST, AZURE, and ABCSG-12: DFS Comparison



[a] Defined as naturally occurring menopause prior to diagnosis.

1. Data from Coleman RE, et al. N Engl J Med. 2011;365(15):1396-1405; 2. Data from Gnant M, et al. Lancet Oncol. 2011;12(7):631-641.

Conclusions

- The 60-month follow-up of ZO-FAST trial confirms and extends the BMD improvement seen with immediate zoledronic acid as reported at earlier time points

- There is a 34% improvement in DFS at 5 years between the immediate and delayed zoledronic acid groups, with a 3.6% absolute difference (91.9% vs 88.3%, respectively)

- As per the improved DFS results seen in the ABCSG-12 and AZURE trials (> 5 years postmenopausal subset), the data support the hypothesis that the anticancer potential of zoledronic acid might be best realized in a low-estrogen environment

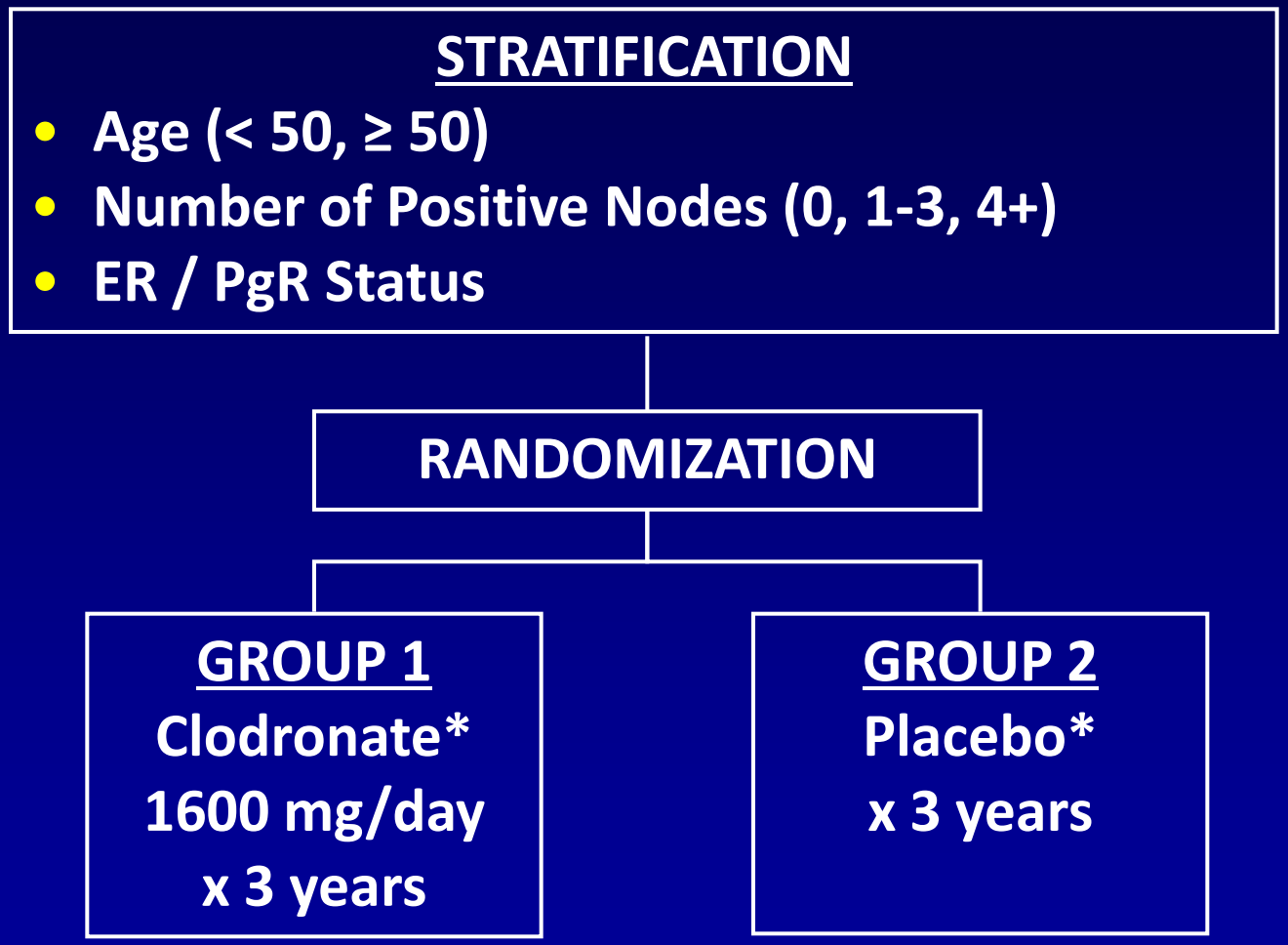
Abbreviations: BMD, bone mineral density; DFS, disease-free survival;

NSABP Protocol B-34: A Clinical Trial Comparing Adjuvant Clodronate vs. Placebo In Early Stage Breast Cancer Patients Receiving Systemic Chemotherapy and/or Tamoxifen or No Therapy – Final Analysis

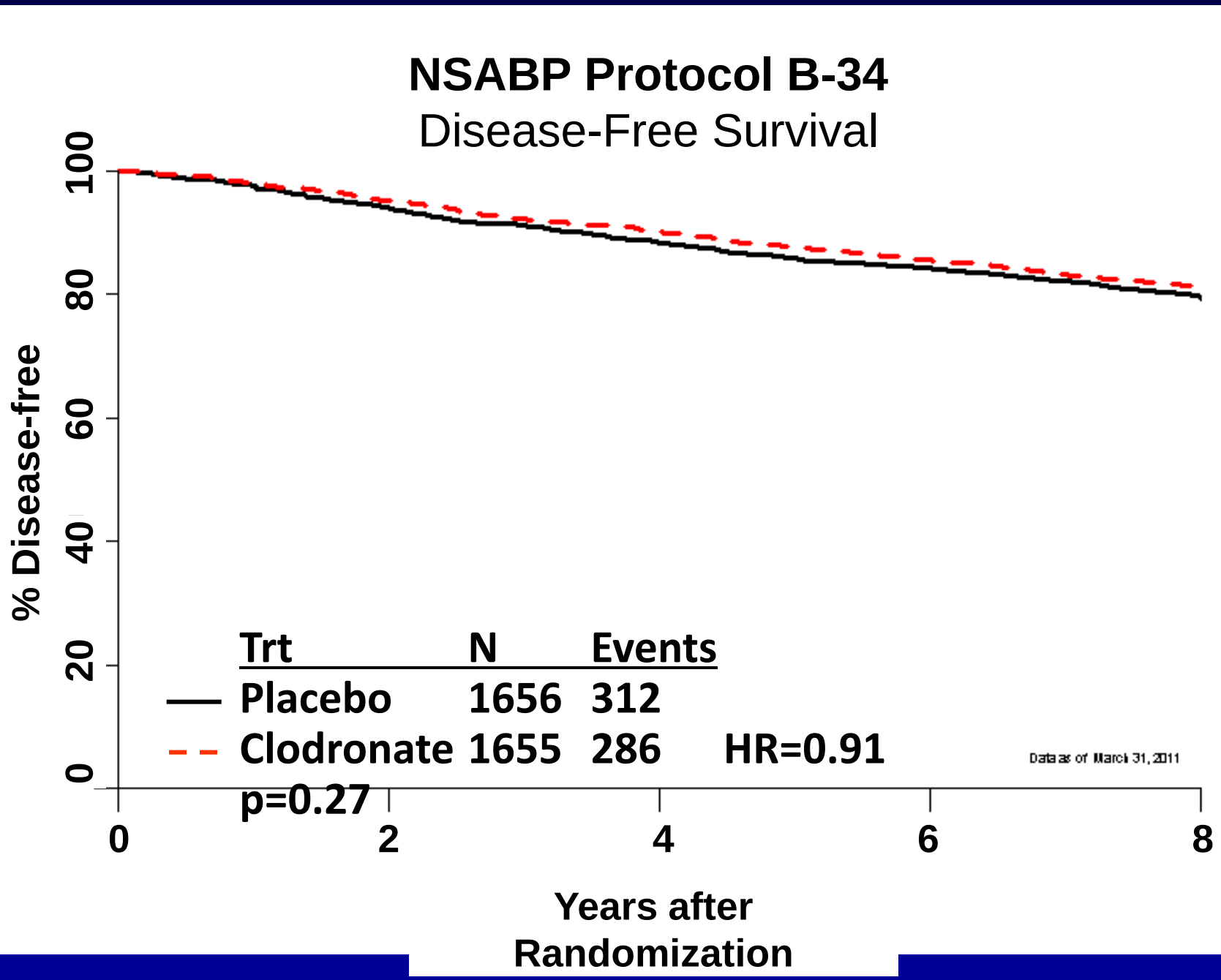
AHG Paterson[1,2], SJ Anderson[1,3], BC Lembersky[1,4], L Fehrenbacher[1,5], CI Falkson[1,6], KM King[1,7], LM Weir[1,8], AM Brufsky[1,9], S Dakhil[1,10], T Lad[1,11], L Baez-Diaz[1,12], JR Gralow[13], A Robidoux[1,14], EA Perez[15], P Zheng[1,3], CE Geyer[1,16], SM Swain[1,17], JP Costantino[1,3], EP Mamounas[1,18], Norman Wolmark[1,19]

[1]National Surgical Adjuvant Breast and Bowel Project (NSABP); [2]Tom Baker Cancer Centre; [3]Biostatistics, University of Pittsburgh Graduate School of Public Health; [4]University of Pittsburgh Cancer Institute School of Medicine; [5]Kaiser Permanente, Northern California; [6]University of Alabama at Birmingham/ECOG; [7]Cross Cancer Institute; [8]British Columbia Cancer Agency; [9]University of Pittsburgh/Magee Women's Hospital; [10]Cancer Center of Kansas; [11]Stroger Hospital Cook County MBCCOP; [12]San Juan MBCCOP; [13]University of Washington/SWOG; [14]Centre Hospitalier de l'Université de Montréal; [15]Mayo Clinic Jacksonville/NCCTG; [16]University of Texas Southwestern Medical Center; [17]Washington Cancer Institute, Washington Hospital Center; [18]Aultman Health Foundation; [19]Allegheny General Hospital

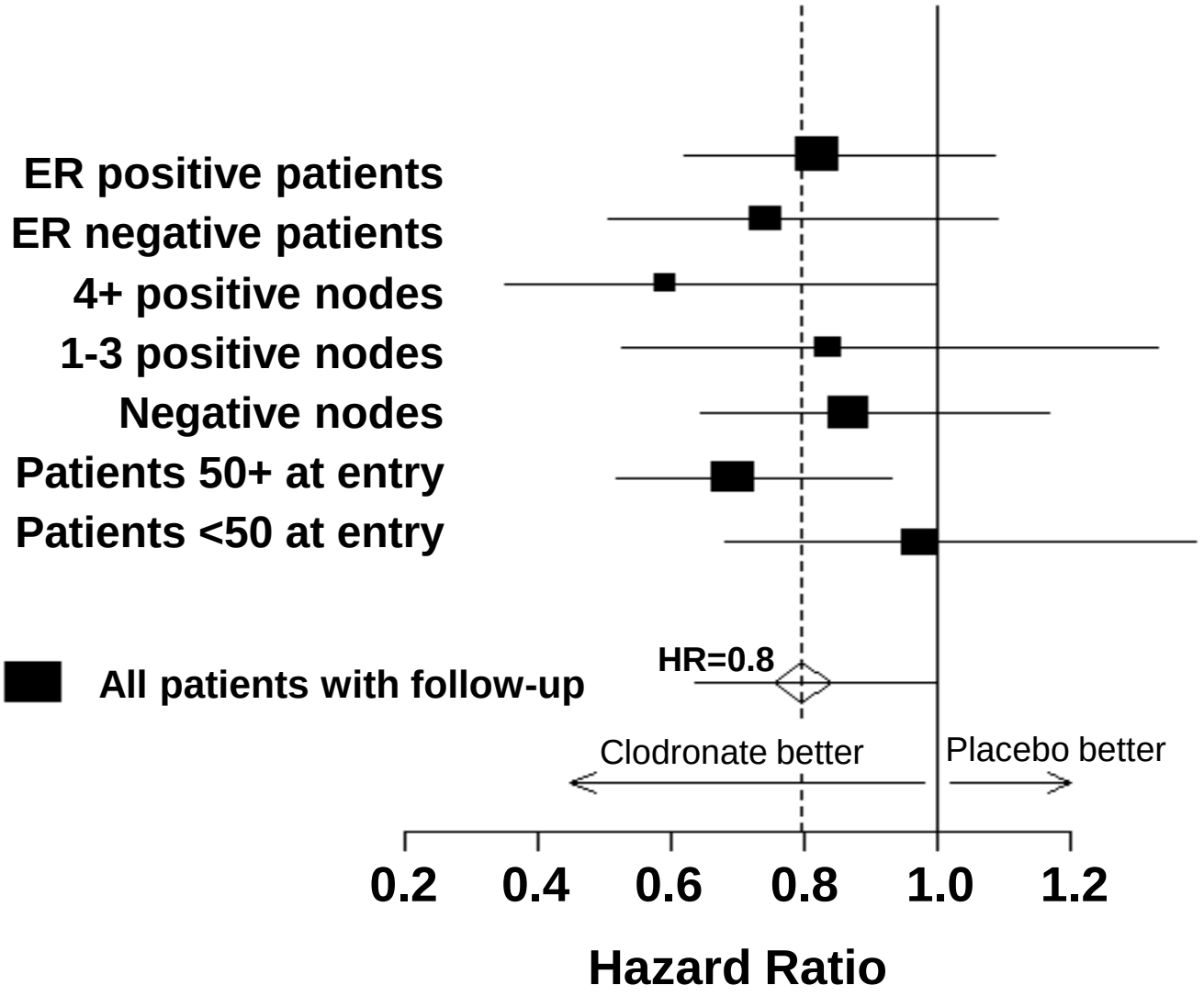
B-34 Study Design



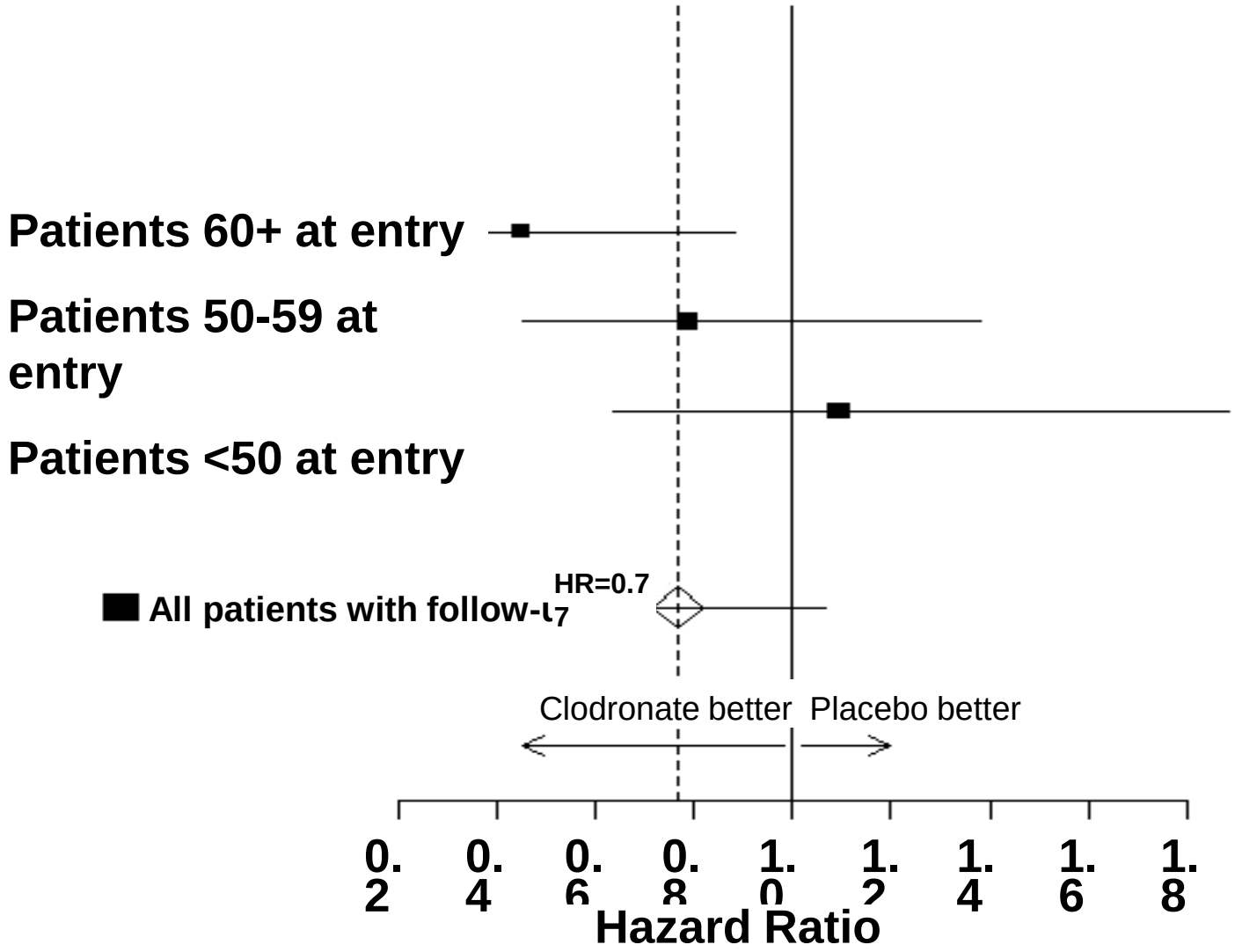
*At the discretion of the investigator, patients may receive adjuvant systemic chemotherapy and/or tamoxifen, or no adjuv


NSABP Protocol B-34
Disease-Free Survival
% Disease-free
100
80
60
40
20
0
Trt N Events
Placebo 1656 312
Clodronate 1655 286 HR=0.91
p=0.27
Data as of March 31, 2011
0
2
4
6
8
Years after Randomization

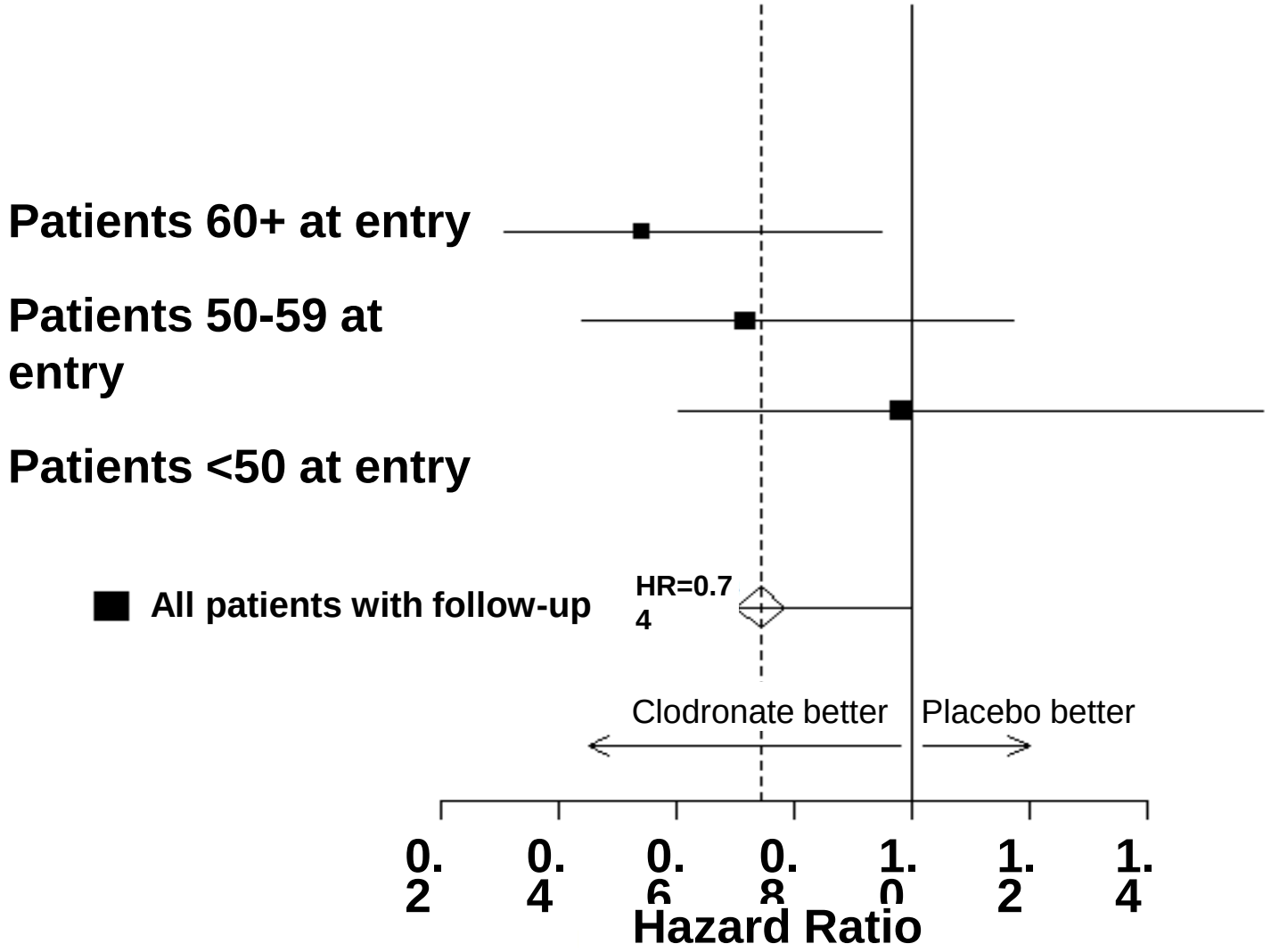
NSABP B-34 Hazard Ratios of RFI between Groups According to Stratification Variables



B-34 Post-hoc Analysis
Hazard Ratios of Skeletal Metastases between Groups by Age Categories (<50, 50-59, 60+)

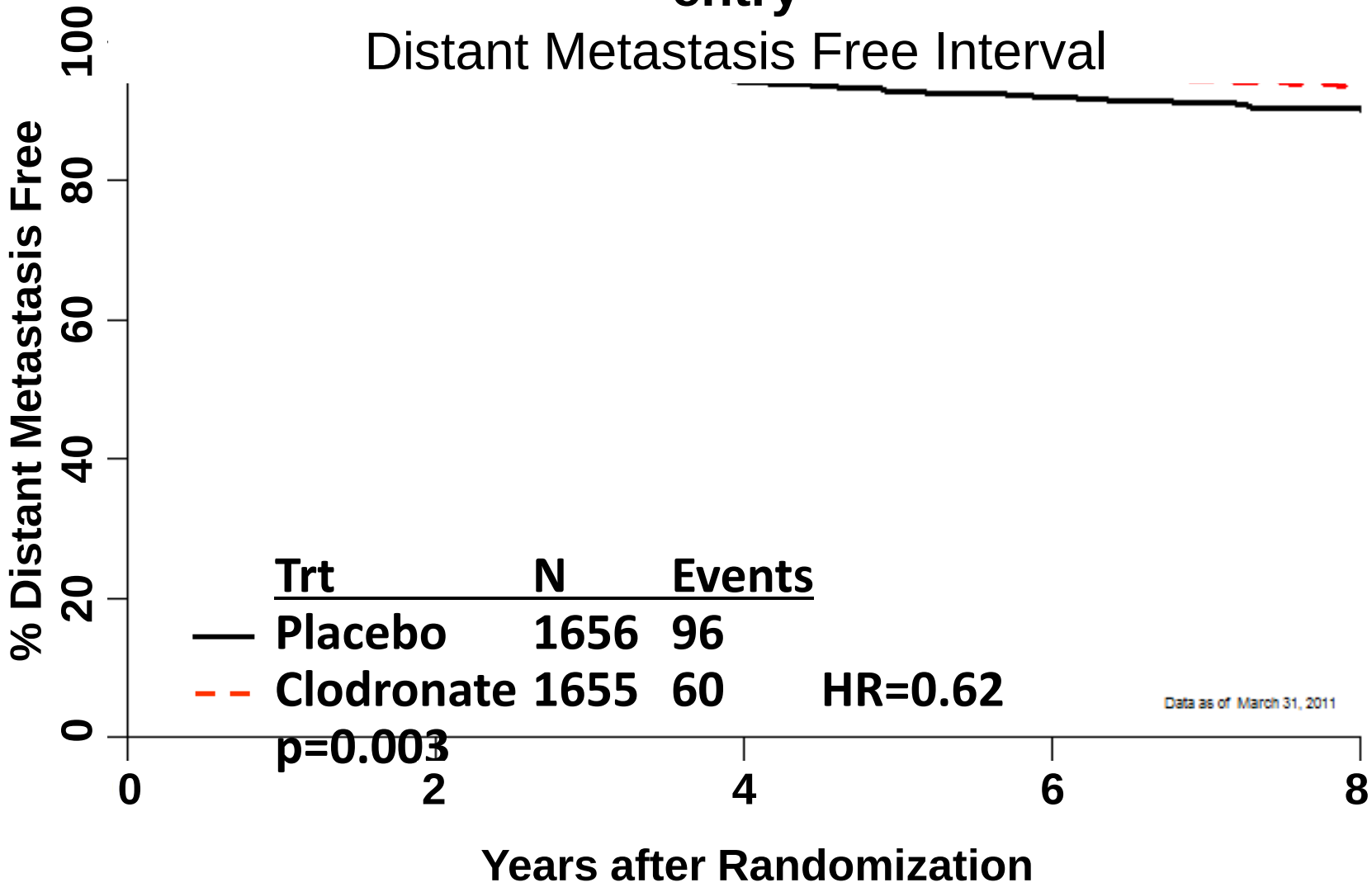


B-34 Post-hoc Analysis
Hazard Ratios of Non-Skeletal Metastases between Groups by Age Categories (<50, 50-59, 60+)

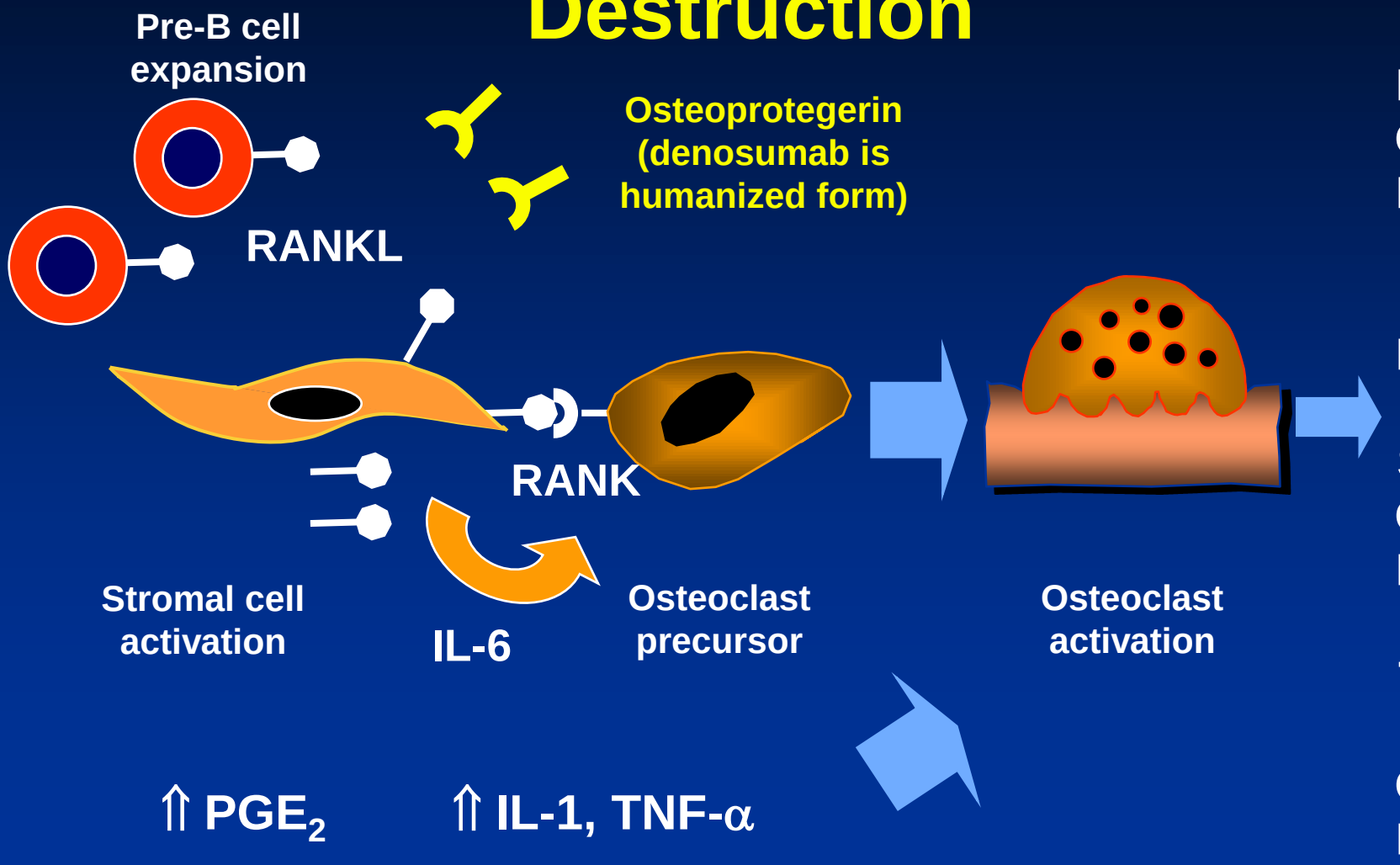


NSABP Protocol B-34: Women 50+ years old at entry

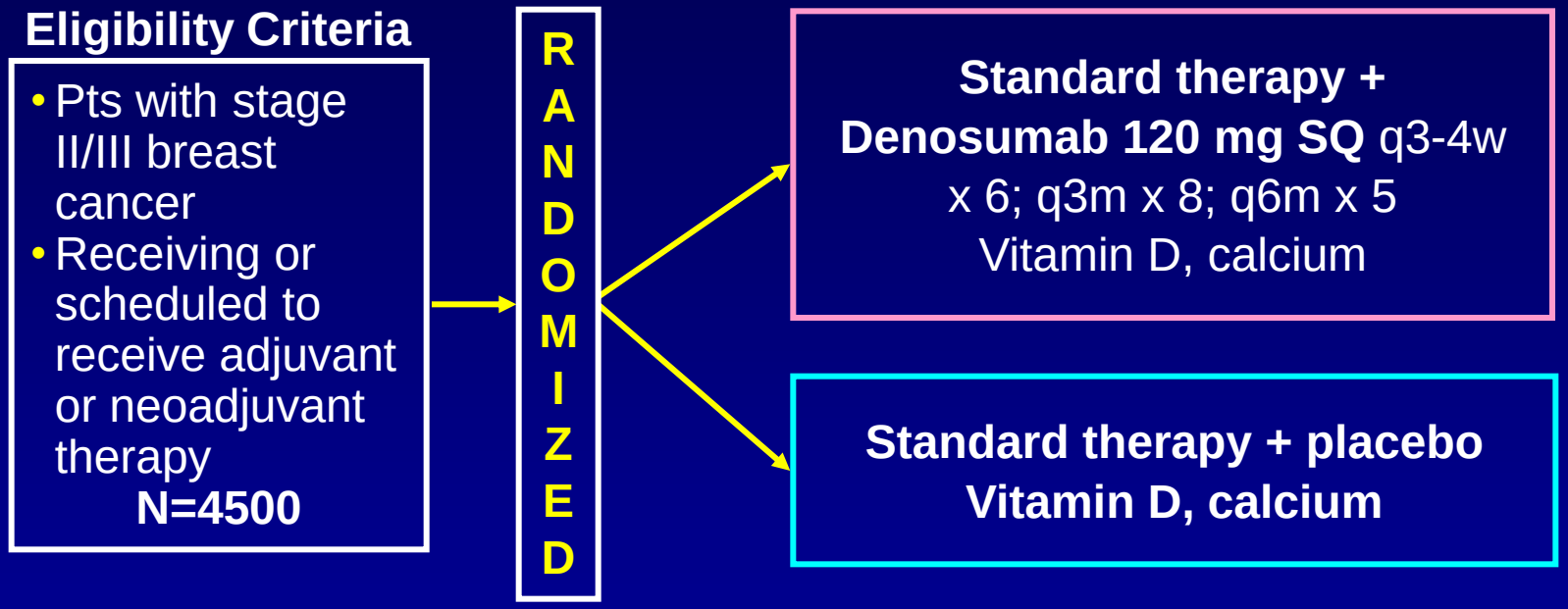
Distant Metastasis Free Interval



Bone Microenvironment Tumor Cell Interactions and Bone Destruction



D-CARE: Potential Direct Antitumor Effect of Bone-Targeting Therapy for Patients With Breast Cancer



- Primary endpoint: Disease free survival
- Secondary endopints:

Winter. *SABCS*. 2008 (abstr 5101).

Implications for Clinical Practice

- Adjuvant zoledronic acid appears to provide a DFS benefit when used as adjuvant therapy in women with suppressed estrogen
- Adjuvant bisphosphonates used for prevention of bone metastases?
  - In premenopausal women not on GNRH? (No)
  - In postmenopausal women or women on GNRH? (Quite possibly yes)
- An issue for thought: why does bone suppression affect breast cancer DFS in an low estrogen state? It's time we really think about the "soil" in cancer pathogenesis