5 Minute JournalClub

Key SABCS Presentations

Issue 2, 2011

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CME Information

LEARNING OBJECTIVES

- Describe the efficacy and safety of zoledronic acid when added to standard (neo)adjuvant therapy for patients with Stage II or III breast cancer.
- Recall the long-term effects on survival and the associated safety of adding zoledronic acid to anastrozole/goserelin or tamoxifen/goserelin for premenopausal patients with early-stage breast cancer.
- Compare the effects of immediate versus delayed therapy with zoledronic acid on bone mineral density, disease-free survival and safety for patients with Stage I to IIIA breast cancer who received letrozole for five years.

CREDIT DESIGNATION STATEMENT

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HOW TO USE THIS CME ACTIVITY

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CME Information (Continued)

FACULTY DISCLOSURES
The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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No real or apparent conflicts of interest to disclose.

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Paid Research: Merck and Company Inc, Onyx Pharmaceuticals Inc.

Adjuvant Treatment with Zoledronic Acid in Stage II/III Breast Cancer. The AZURE Trial (BIG 01/04)

Coleman RE et al.

Proc SABCS 2010;Abstract S4-5.

Endpoints

- Primary: Disease-free survival (DFS)
- Secondary:
  - Invasive DFS (IDFS)
  - Overall survival (OS)
  - Bone metastasis-free survival (BMFS)
  - Subgroup analyses based on minimization criteria (ie, study center, menopausal status, nodes, T-stage, chemotherapy type, ER status, and statin use)
  - Serious adverse events
  - Targeted adverse events (osteonecrosis of the jaw, fractures, atrial fibrillation)
  - Translational endpoints

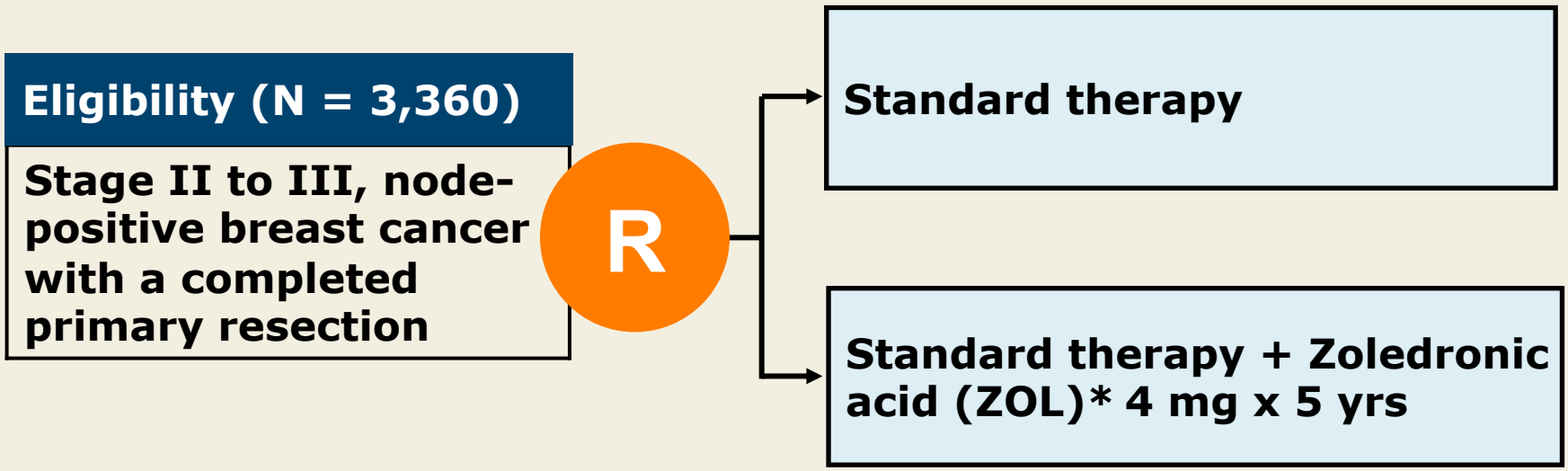
Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

Eligibility

- Stage II or III node-positive breast cancer with no evidence of metastases
  - T3/T4 or confirmed N+ neoadjuvant disease
  - Node-positive adjuvant disease
- Complete primary tumor resection
- Karnofsky PS ≥80
- No treatment with bisphosphonates in the last year
- No bone disease, including osteoporosis, at study entry
- No serum creatinine >1.5 x ULN
- No significant ongoing dental problems or planned dental surgery (since July 2005)
- No other malignancies

Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

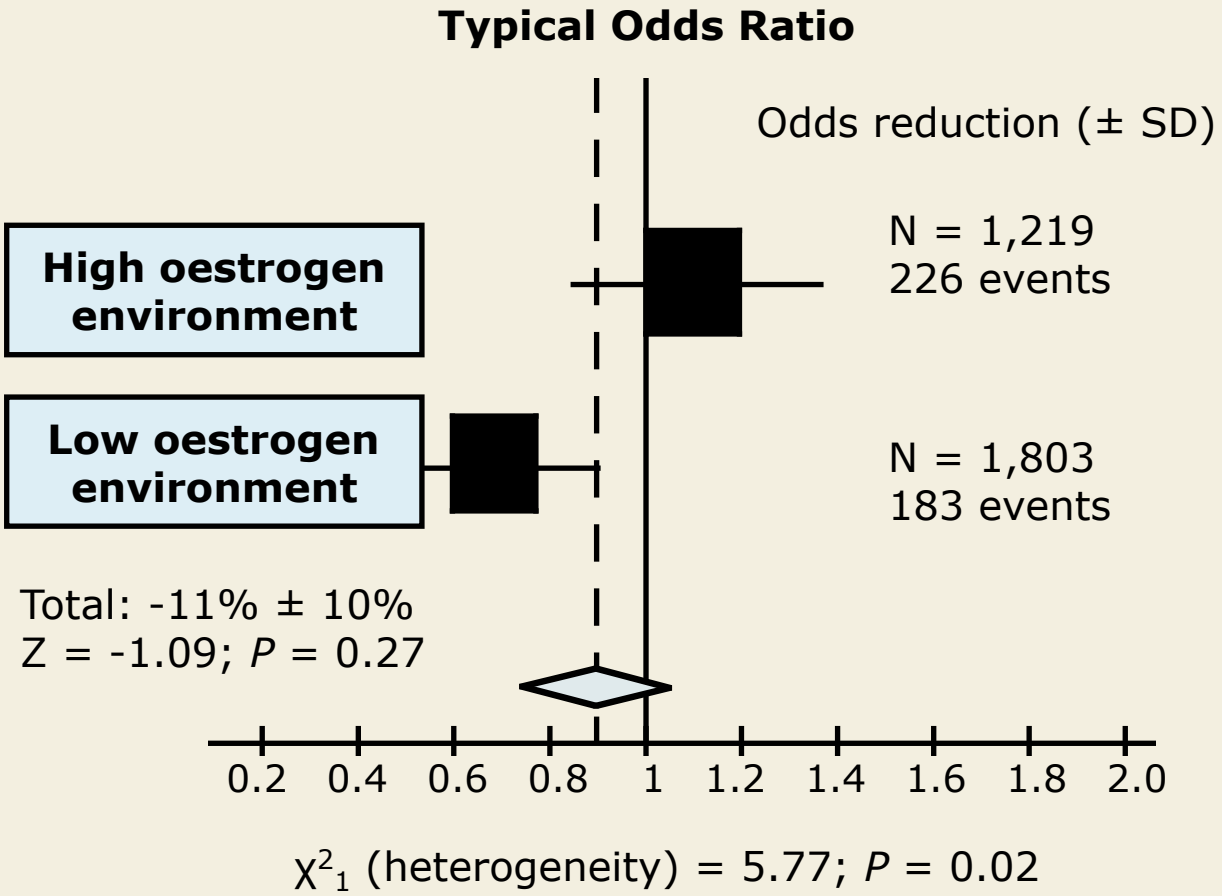
Study Schema



* Months 0-6, 6 doses q3-4 wks;
Months 7 to 30, 8 doses q3 mos;
Months 31 to 60, 5 doses, q6 mos

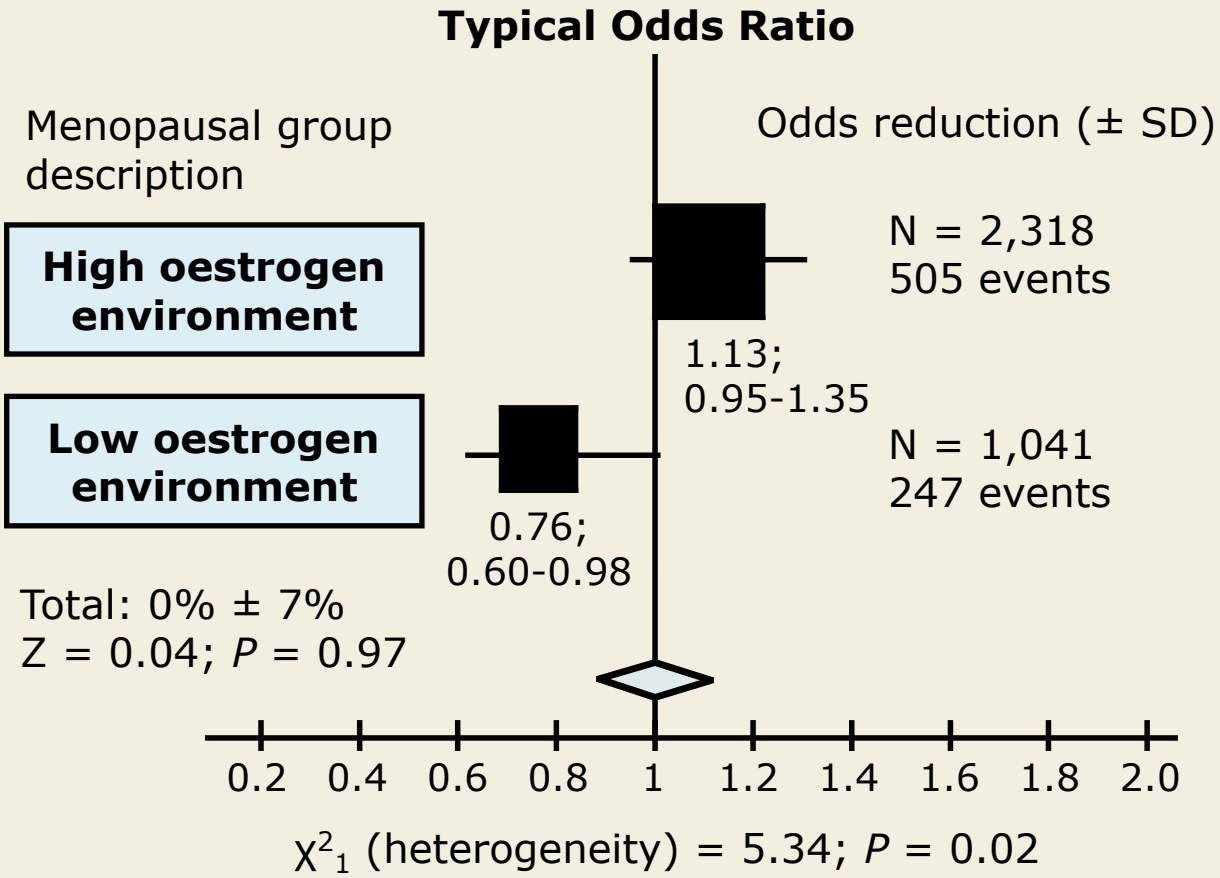
Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

DFS Comparison between AZURE and ABCSG-12



With permission from Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

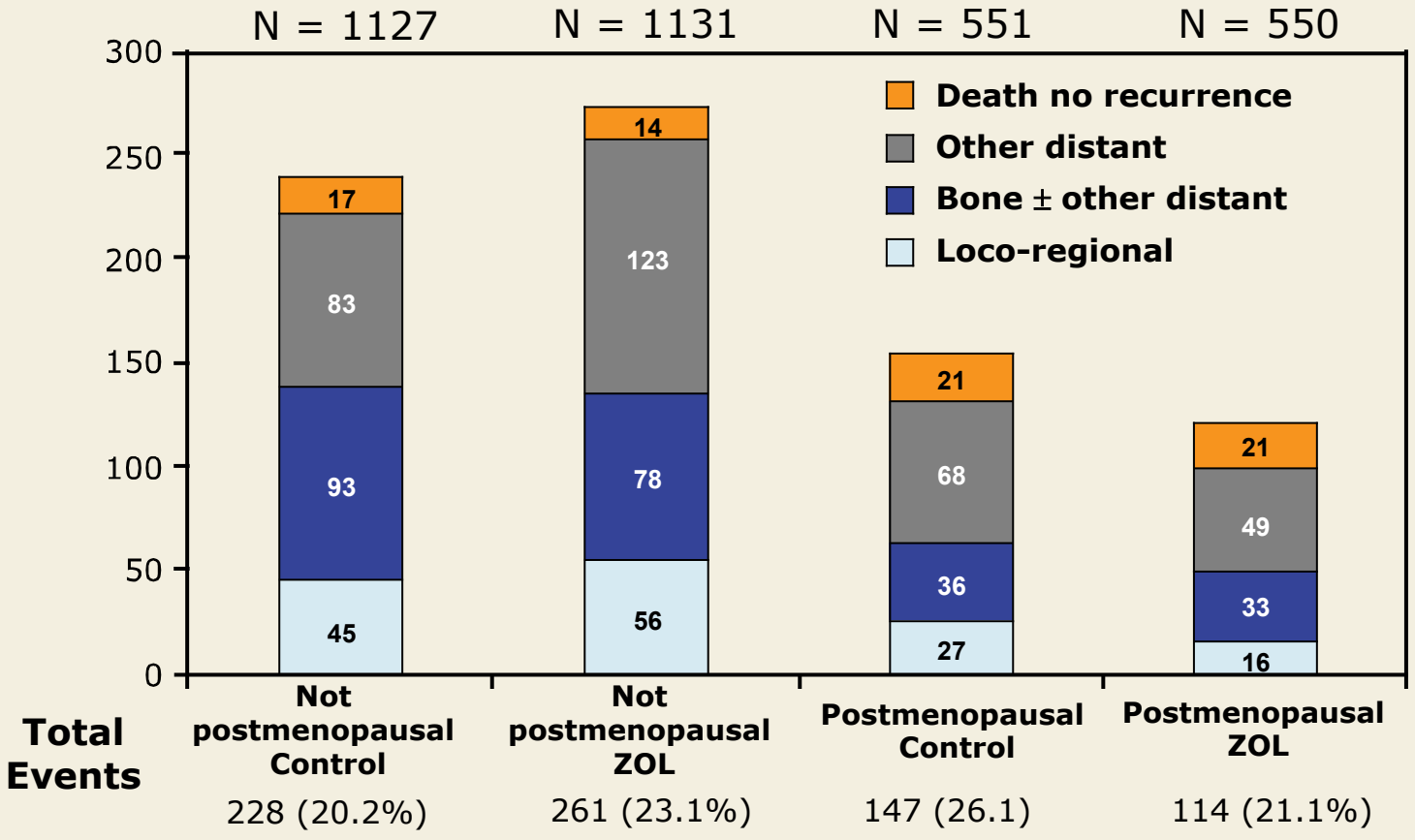
AZURE Treatment Effect* on DFS by Menopausal Status



* Adjusted for imbalances in ER, lymph node status and T stage

With permission from Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

Distribution of DFS Events by Menopausal Status

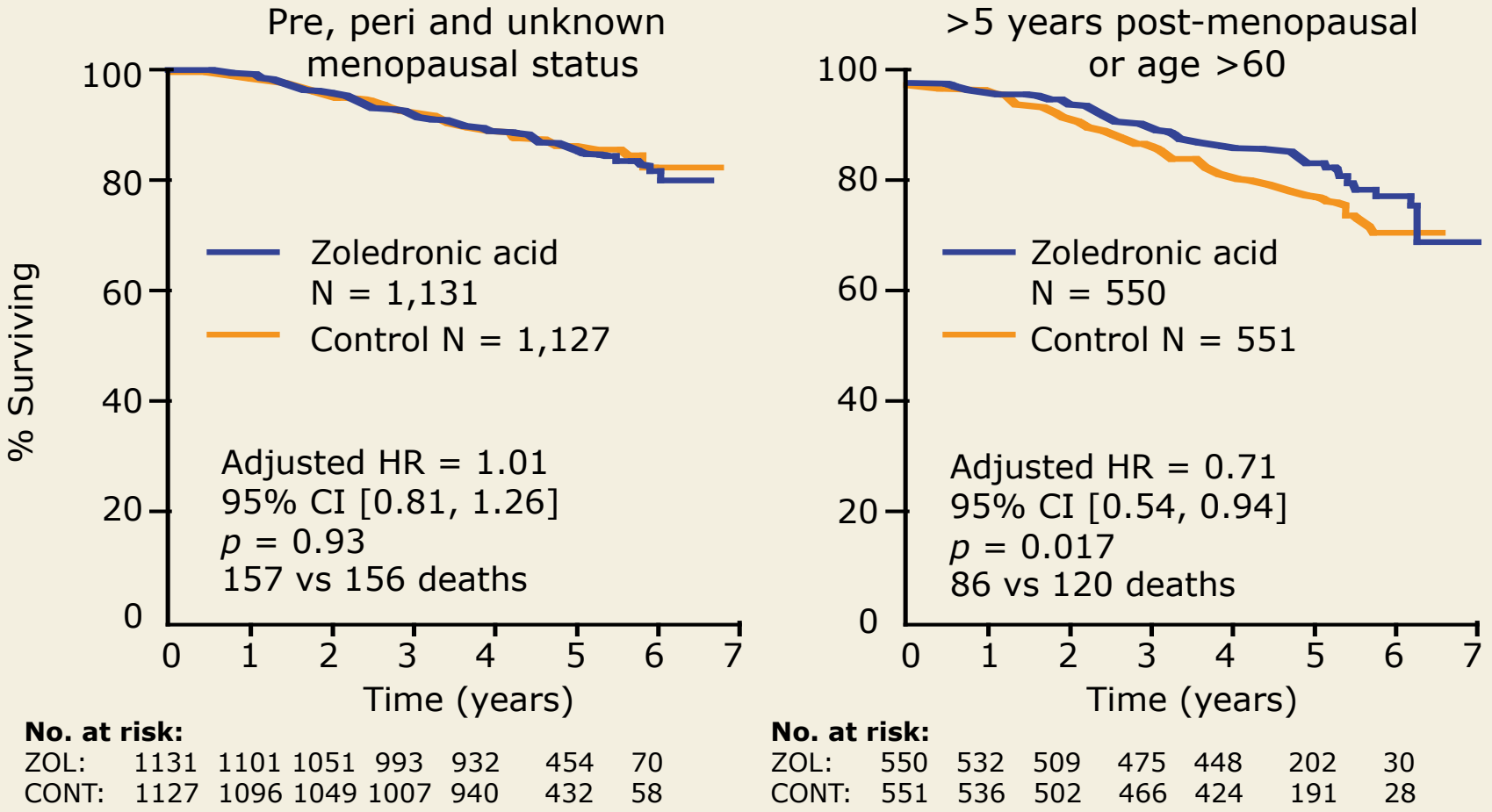


Effects independent of ER

Not menopausal = premenopausal, perimenopausal, unkown age < 60
Menopausal = >5 years since menopause or age > 60

With permission from Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

Overall Survival by Menopausal Status



Effects independent of ER

With permission from Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

Serious Adverse Events

	Standard Therapy (n = 1,678)	Standard Therapy + Zoledronic Acid (n = 1,681)
Neutropenic sepsis	9.5%	9.5%
Neutropenia	2.9%	2.5%
Pyrexia	1.4%	2.2%
Vomiting	1.4%	2.1%
Lower respiratory infection	2.0%	1.4%
Central line infection	1.3%	1.4%
Cellulitis	1.3%	1.3%

Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

Serious Adverse Events (cont'd)

	Standard Therapy (n = 1,678)	Standard Therapy + Zoledronic Acid (n = 1,681)
Pulmonary embolus	0.8%	1.5%
Confirmed osteonecrosis of the jaw	0	17*
Possible osteonecrosis of the jaw	0	9

* $P < 0.0001$

Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5.

Conclusions

- The adjuvant use of zoledronic acid did not improve DFS in this population of patients with stage II/III breast cancer (DFS, *P* = 0.79; IDFS, *P* = 0.73)
- A subgroup analysis of post-menopausal (>5 years) patients and those aged >60 years showed significant differences in OS between the control and zoledronic acid groups.
  - 120 vs 86 deaths (*P* = 0.017)
- The adjuvant use of bisphosphonates appears to be dependent on a low estrogen/inhibin concentration within the bone microenvironment.
- The AZURE data are strikingly different than those observed in the ABCSG XII trial.

Coleman RE et al. *Proc SABCS* 2010;Abstract S4-5;
Gnant M et al. *Proc ASCO* 2010;Abstract 522.

Investigator Commentary: AZURE Adjuvant Bisphosphonate Study

In the AZURE trial, no improvement in disease-free survival was evident for patients who received the adjuvant bisphosphonate versus those who did not, with a hazard ratio of 0.98. An interesting and exploratory subset analysis that can only be viewed as hypothesis generating was conducted to determine why these results are so discrepant from the results of ABCSG-12. This analysis suggests that a benefit may actually be present for women who are menopausal or in a low-estrogen setting. The findings for this subset would be consistent with the observed benefit of zoledronic acid (ZA) in the younger patients enrolled in ABCSG-12, who were premenopausal but received goserelin with either tamoxifen or an aromatase inhibitor. However, this explanation is hypothetical and is not clinically actionable, except perhaps to inform yet another clinical trial.

Commentary by Clifford Hudis, MD, December 11, 2010

AZURE was a larger study and included a broader range of patients with breast cancer than were enrolled in ABCSG-12, and there was absolutely no suggestion of an improvement in disease-free or overall survival. This was clearly a negative result and implies that clinicians should not be offering adjuvant ZA with the expectation of preventing cancer recurrence.

Interview with Harold J Burstein, MD, PhD, December 22, 2010

The Carry-Over Effect of Adjuvant Zoledronic Acid: Comparison of 48- and 62-Month Analyses of ABCSG-12 Suggests the Benefits of Combining Zoledronic Acid with Adjuvant Endocrine Therapy Persist Long after Completion of Therapy

Gnant M et al.

Proc SABCS 2010;Abstract P5-11-02.

Endpoints

- Primary: Disease-free survival (local recurrence, contralateral breast cancer [BC], distant metastasis, secondary carcinoma, death)

- Secondary:
  - Relapse-free survival (local recurrence, contralateral BC, distant metastasis, secondary carcinoma)
  - Overall survival (OS)
  - Safety
  - Bone mineral density (substudy)

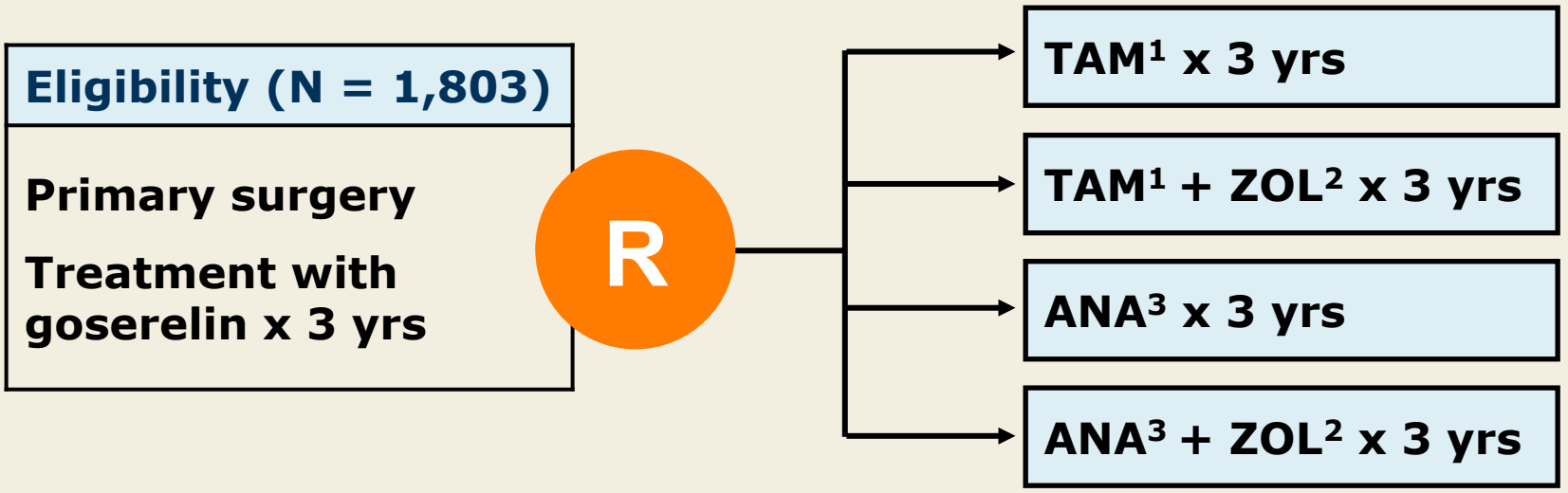
Gnant M et al. *Proc SABCS* 2010;Abstract P5-11-02.

Eligibility

- Premenopausal status
- Prior surgery for Stage I or II ER+ or PR+ breast cancer
- <10 positive lymph nodes
- Scheduled to receive standard therapy with goserelin for 3 yrs
- No T1a (except yT1a), T4d or yT4 breast cancer
- No history of other neoplasms
- No preoperative radiotherapy

Gnant M et al. *Proc SABCS* 2010;Abstract P5-11-02.

Study Schema



[1] Tamoxifen 20 mg/day
[2] Zoledronic acid (ZOL) 4 mg q 6 mos
[3] Anastrozole (ANA) 1 mg/day

Gnant M et al. *Proc SABCS* 2010;Abstract P5-11-02.

Efficacy Results: ZOL versus Endocrine Therapy Alone

Endpoint	ZOL	No ZOL	HR (*p*-value)
Disease-free survival			
48 mos (n = 899; 904)	94%	91%	0.64 (*p* = 0.01)
62 mos (n = 900; 903)	92%	88%	0.68 (*p* = 0.008)
Overall survival			
48 mos (n = 899; 904)	98%	97%	0.60 (*p* = 0.10)
62 mos (n = 900; 903)	97%	95%	0.67 (*p* = 0.143)

Gnant M et al. *Proc SABCS* 2010;Abstract P5-11-02.

Efficacy Results: ZOL versus Endocrine Therapy Alone in TAM and ANA Groups

Subgroup	ZOL	No ZOL	HR (95% CI)
Disease-free survival			
TAM (n = 450; 450)	92%	88%	0.67 (0.44, 1.03)
ANA (n = 450; 453)	91%	87%	0.68 (0.45, 1.02)

Gnant M et al. *Proc SABCS* 2010;Abstract P5-11-02.

Adverse Events

Event	TAM alone (n = 450)	TAM + ZOL (n = 450)	ANA alone (n = 453)	ANA + ZOL (n = 450)	*p*-value*
Arthralgia	7.8%	9.3%	19.0%	22.9%	<0.001
Bone pain	22.7%	32.7%	33.1%	44.9%	<0.001
Pyrexia	2.0%	8.2%	2.6%	10.7%	<0.001

* *p*-values are for a four-group comparison.

Gnant M et al. *Proc SABCS* 2010;Abstract P5-11-02.

Serious Adverse Events

	T alone (n = 450)	TAM + ZOL (n = 450)	ANA alone (n = 453)	ANA + ZOL (n = 450)	*p*-value*
Fracture	1.8%	0.9%	1.5%	1.3%	0.73
Thrombosis	0.2%	1.1%	0	0	0.01
Uterine polyps	6.4%	7.8%	0.2%	0.7%	<0.001
Endometrial hyperplasia	6.0%	7.3%	2.0%	0.7%	<0.001
Osteonecrosis of the jaw	0	0	0	0	—

* *p*-values are for a four-group comparison.

Gnant M et al. *Proc SABCS* 2010;Abstract P5-11-02.

Conclusions

- The addition of ZOL to endocrine therapy for 3 years was associated with a durable benefit in disease-free survival in the ANA and TAM groups.
- At 62 months, the benefits of ZOL were decreased bone metastases, decreased contralateral breast cancer, decreased locoregional and distant metastases and improved disease-free survival.
- ZOL did not increase the incidence of serious adverse events compared with endocrine therapy alone.
- ESMO 2010 guidelines now recommend that ZOL may be appropriate for premenopausal women receiving aromatase inhibitor therapy (*Ann Oncol* 2010;21[suppl 5]:v9-14).

Gnant M et al. *Proc SABCS* 2010;Abstract P5-11-02.

Ongoing Adjuvant Bisphosphonate Trials in Breast Cancer

Study	Phase	Target Accrual	Arms	Study Endpoints
SWOG-S0307	III	5,400 (closed)	Zoledronic acid Clodronate Ibandronate	Disease recurrence Disease-free survival Overall survival
NSABP-B-34	III	3,323 (closed)	Clodronate Placebo	Disease-free survival Skeletal metastasis Overall survival
NCT00196872 (German Breast Group)	III	3,000 (open)	Ibandronate Observation	Disease-free survival Overall survival
NCT00196859 (ICE)	III	1,500 (open)	Ibandronate Ibandronate + capecitabine	Local/distant relapse Deaths Bone fracture/surgery

www.ClinicalTrials.gov, January 2011.

Investigator Commentary: Carry-Over Effect of Adjuvant Zoledronic Acid in ABCSG-12

ABCSG-12 was an adjuvant study in younger women who received ovarian suppression with either tamoxifen or an aromatase inhibitor with a second randomization to zoledronic acid or not, which attempted to define the benefits of bisphosphonates in the adjuvant setting.

The study previously reported that adjuvant zoledronic acid prevented loss of bone mineral density, and a provocative finding indicated that patients who received zoledronic acid had an improvement in disease-free survival. In this report, the investigators updated their data and no major difference was evident in the safety or event profile compared to previous reports. They continued to show that zoledronic acid was associated with preservation of bone density and a small improvement in the rate of breast cancer-related events.

Since the larger and more compelling AZURE trial was completely negative, I believe most clinicians will be looking to that study to guide their treatment recommendations.

Interview with Harold J Burstein, MD, PhD, December 22, 2010

The Effect of Zoledronic Acid (ZOL) on Aromatase Inhibitor-Associated Bone Loss in Postmenopausal Women with Early Breast Cancer Receiving Adjuvant Letrozole: The ZO-FAST Study 5-Year Final Follow-Up

de Boer R et al.

Proc SABCS 2010;Abstract P5-11-01.

Endpoints

- Primary: Percent change in lumbar spine (L2-L4) bone mineral density (BMD) at 12 months in the immediate- and delayed-treatment groups
- Secondary:
  - Lumbar spine BMD assessments at 2, 3, 4, and 5 years
  - Percentage change in total hip BMD at each assessment
  - Fractures over 3 years
  - Time to recurrence
  - Overall survival (OS)
  - Safety

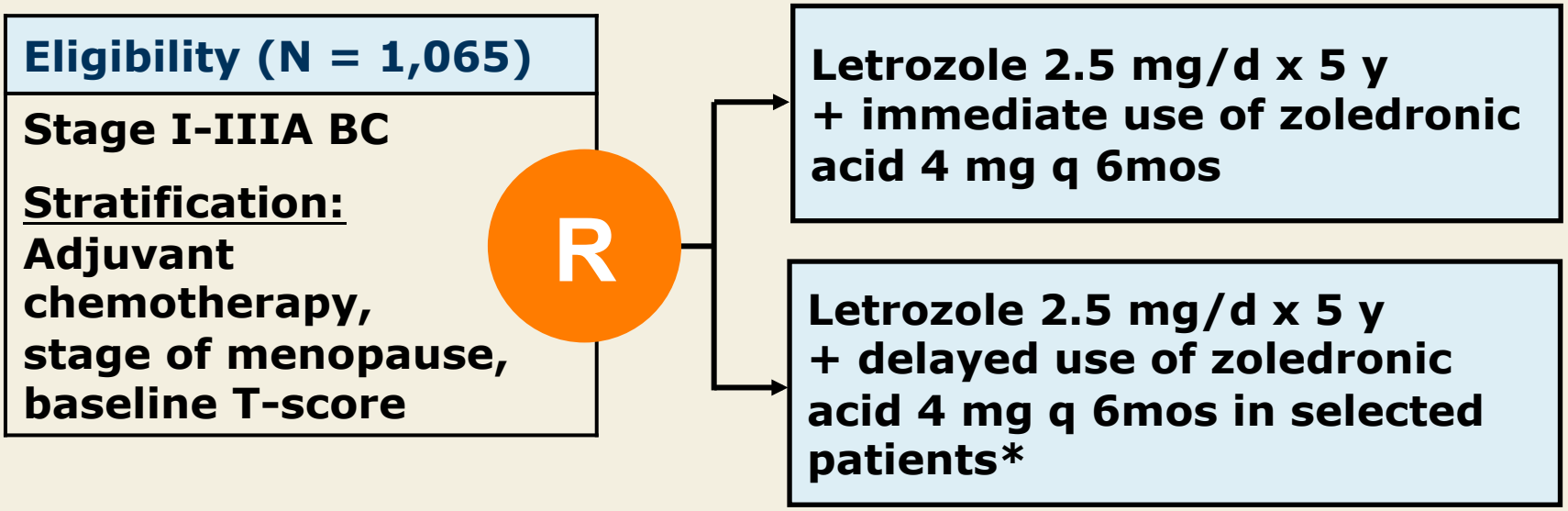
de Boer R et al. *Proc SABCS* 2010;Abstract P5-11-01.

Eligibility

- Post-menopausal women with ER+ and/or PR+ Stage I, II, or IIIA early breast cancer (BC)
- ECOG PS ≤ 2
- Baseline lumbar-spine and total-hip T-scores ≥ -2
- Completed surgical resection
- No residual disease after completion of chemotherapy followed by radiation therapy ≤12 weeks prior
- No clinical or radiologic evidence of distant metastases
- No existing lumbar-spine or hip fracture or a history of low-intensity fractures
- No diseases known to affect bone density

de Boer R et al. *Proc SABCS* 2010;Abstract P5-11-01.

Phase III Study Schema

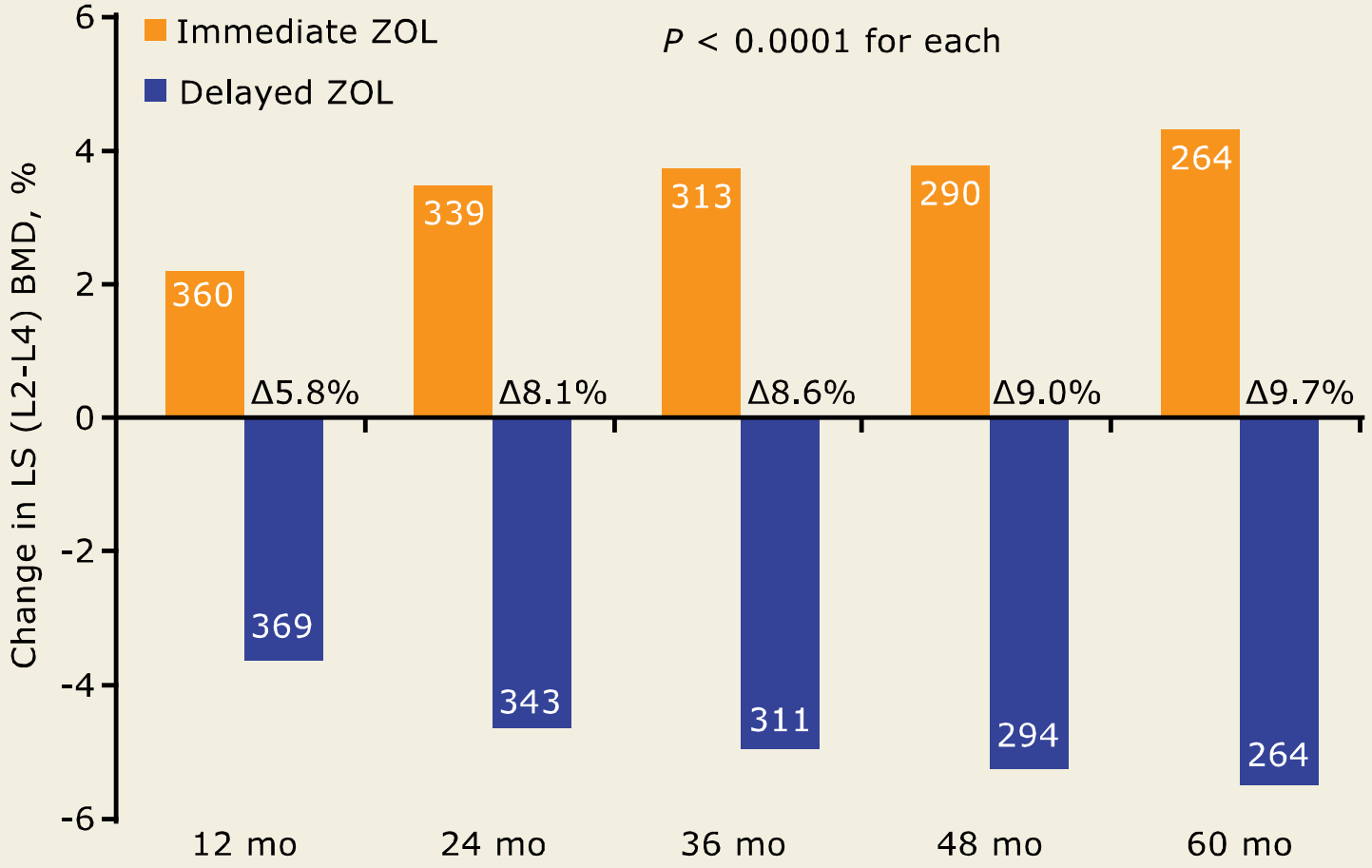


* In patients with BMD T-score < –2.0; a clinical fracture; asymptomatic fracture at 36 mos

All patients also received calcium and vitamin D supplements.

de Boer R et al. *Proc SABCS* 2010;Abstract P5-11-01.

Efficacy Results: Change in BMD



BMD = bone mineral density; LS = lumbar spine; ZOL = zoledronic acid (4 mg q 6 months)

With permission from de Boer R et al. *Proc SABCS* 2010;Abstract P5-11-01.

Efficacy Results: DFS and Recurrence

	Immediate ZOL (n = 532)	Delayed ZOL (n = 533)	HR (*p*-value)
Disease-free survival	91.9%	88.3%	0.66 (0.0375)
Disease recurrence			
Distant	5.5%	8.8%	—
Local	0.94%	2.3%	
Total	6.4%	9.9%	

de Boer R et al. *Proc SABCS* 2010;Abstract P5-11-01.

Adverse Events (AEs)*

	Immediate ZOL n = 525	Delayed ZOL n = 535
Arthralgia	49.0%	46.9%
Hot flush	29.0%	30.5%
Bone pain	18.5%	12.1%
Fatigue	17.7%	17.8%
Pyrexia	15.2%	3.6%
Back pain	15.0%	15.1%
Headache	14.5%	12.0%

* AE in >10% of patients in the overall safety population by treatment received; few fracture events reported, statistically similar in both arms (7.8%, immediate ZOL versus 7.1%, delayed ZOL)

de Boer R et al. *Proc SABCS* 2010;Abstract P5-11-01.

Adverse Events (cont'd)

	Immediate ZOL n = 525	Delayed ZOL n = 535
Pain in extremity	13.3%	15.1%
Myalgia	13.0%	13.3%
Musculoskeletal pain	11.0%	8.6%
Hypercholesterolemia	11.0%	11.2%
Weight increase	10.9%	10.7%
Hypertension	10.5%	11.2%
Nausea	10.3%	10.3%

de Boer R et al. *Proc SABCS* 2010;Abstract P5-11-01.

Conclusions

- The use of immediate ZOL plus letrozole significantly reduced the rate of disease recurrence and DFS and improved BMD compared with delayed ZOL plus letrozole.
  - Mean change in lumbar spine BMD, +4.3% vs -5.4% at 5 years ($P < 0.0001$)
  - DFS, 91.9% vs 88.3% at 5 years ($P = 0.0375$)
- The differences in BMD between the immediate and delayed treatment groups were maintained over time.
- These 5-year data confirm the benefits of immediate ZOL on BMD shown at earlier time points.
- The immediate use of ZOL plus adjuvant letrozole was generally well tolerated.

de Boer R et al. *Proc SABCS* 2010;Abstract P5-11-01.

Investigator Commentary: Zoledronic Acid to Prevent Bone Loss in Patients Receiving an Adjuvant AI in ZO-FAST

ZO-FAST is a randomized study evaluating whether the early use of zoledronic acid versus its later use when patients became osteopenic would help prevent bone mineral density loss in women who were receiving adjuvant letrozole. In this updated analysis, the results were similar to previous reports in that the early use of zoledronic acid is associated with a greater likelihood of maintaining bone density. However, no difference was observed in the incidence of bone fracture between the early and delayed use of zoledronic acid, which is a more important endpoint for most patients. For most clinicians, the standard recommendation is to follow the WHO guidelines for the management of osteoporosis. We screen patients who are receiving aromatase inhibitors, and if the patients become osteopenic or osteoporotic then we institute effective therapy with bisphosphonates.

The ZO-FAST investigators continue to observe a small difference favoring the use of early bisphosphonate therapy in preventing breast cancer events. This observation is part of provocative literature that predated the AZURE trial, the results of which make it difficult to impart much clinical significance to this finding.

Interview with Harold J Burstein, MD, PhD, December 22, 2010

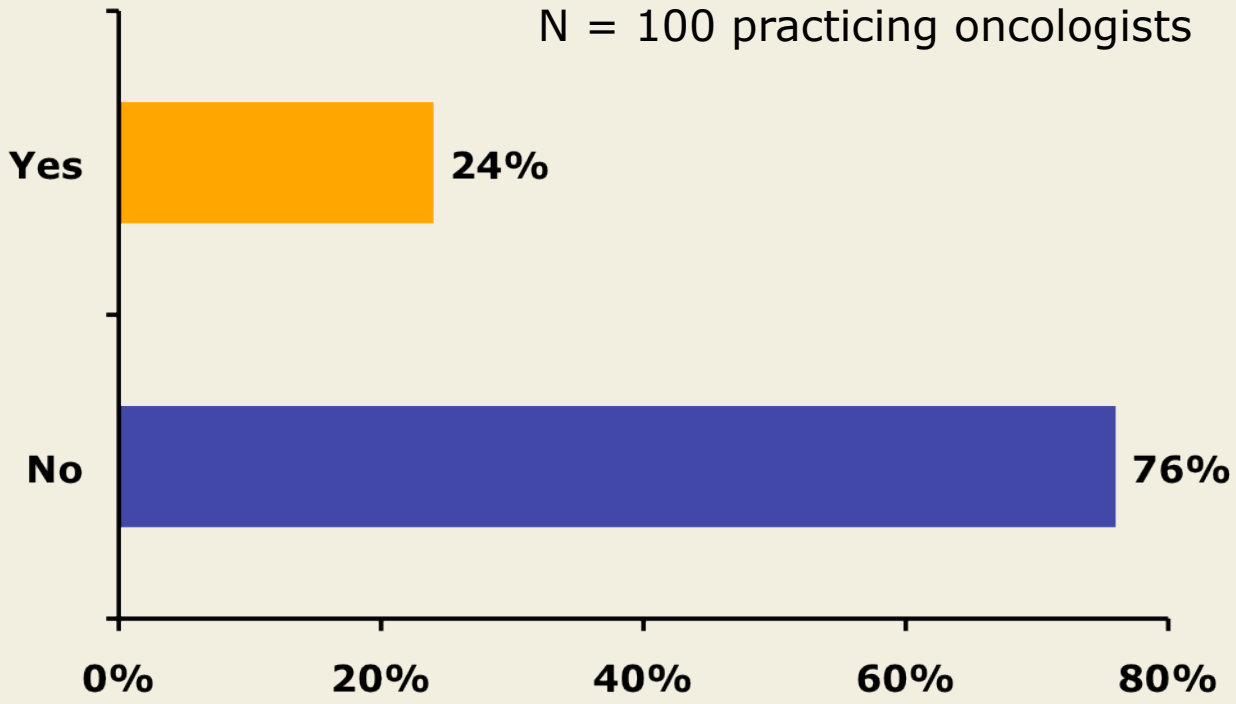
National Patterns of Care Study in Breast Cancer

- Launched October 29, 2009
- 100 US-based community oncologists surveyed
- Completed November 2009

Research To Practice. Patterns of Care in Breast Cancer Survey, 2009.

A 41-YO Premenopausal Woman with a 3.0-cm ER-Pos, HER2-Neg IDC Positive for BRCA2 Mutation

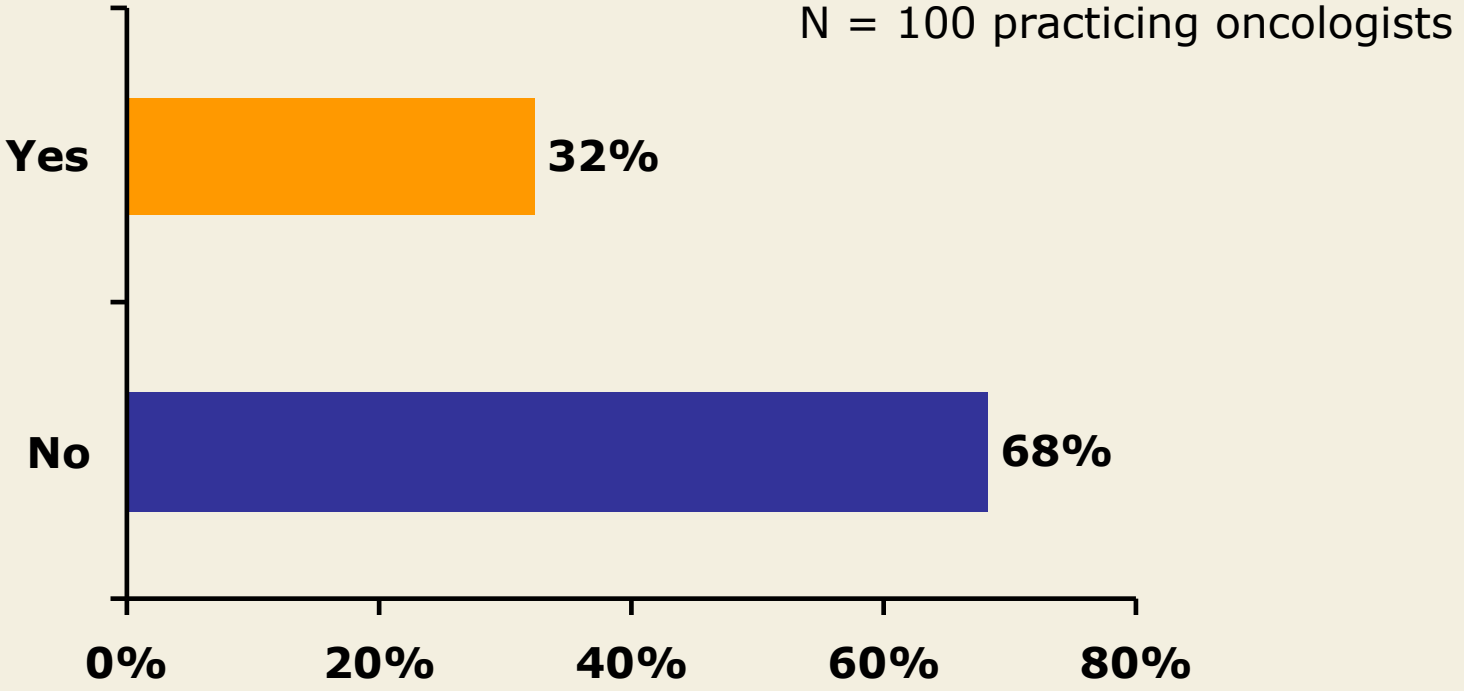
Would you recommend a bisphosphonate for this patient?



Research To Practice. Patterns of Care in Breast Cancer Survey, 2009.

A 59-Year-Old Woman with a 2.5-cm Grade II, ER-Positive, HER2-Negative, Node-Negative IDC

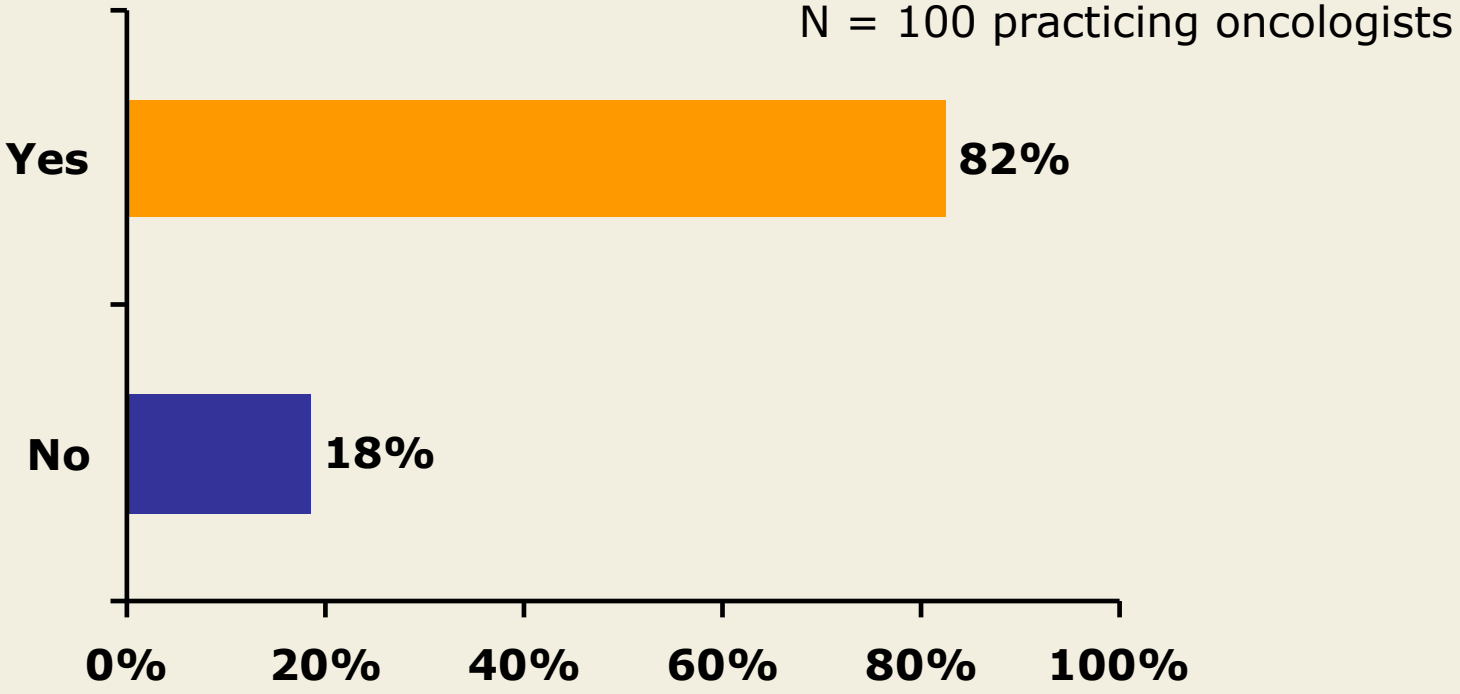
Would you recommend a bisphosphonate for this patient?



Research To Practice. Patterns of Care in Breast Cancer Survey, 2009.

A 59-Year-Old Woman with a 2.5-cm Grade II, ER-Positive, HER2-Negative, Node-Negative IDC

If the patient were eligible, would you recommend participation in the Phase III SWOG-S0307 bisphosphonate trial (zoledronic acid vs clodronate vs ibandronate)?



Research To Practice. Patterns of Care in Breast Cancer Survey, 2009.