Debate: 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

YES

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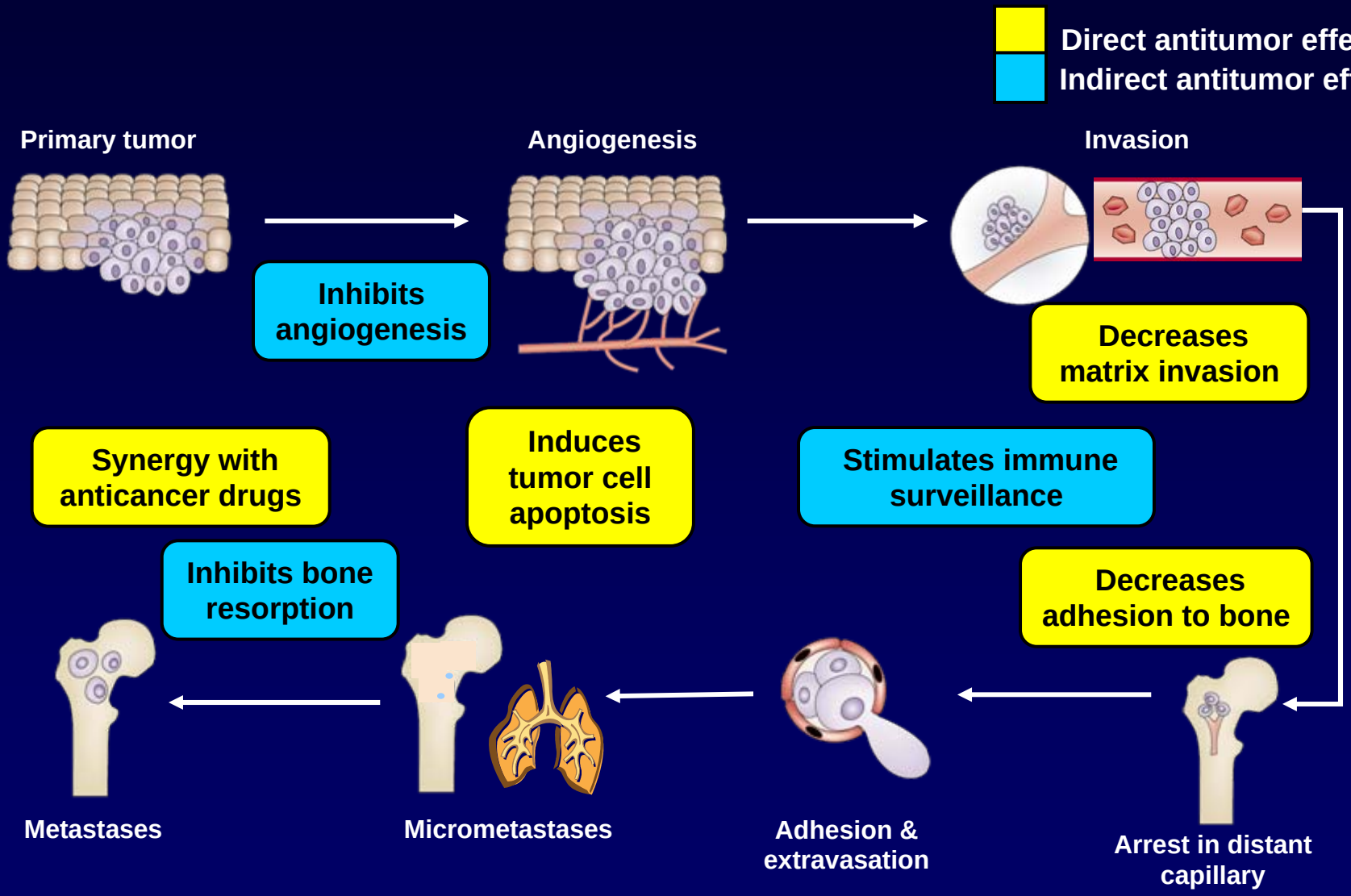
Bisphosphonates Can Inhibit the Metastatic Process at Several Key Steps



Breast Cancer: Adjuvant Clodronate Trials

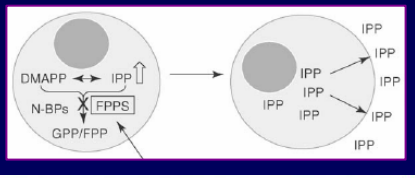
	Diel/Jaschke[1,2]	Powles[3]	Saarto[4]	Paterson[5]
No. of patients	290	1069	299	173
Selection	BM^{+*}	Stage I-III	LN^{+}	BM^{+}
Treatment length (yr)	2	2	3	3
Follow-up time (yr)	8.5	5/10	10	3
Skeletal effect	NS	+	NS	+
Extraskeletal effects	NS	NS	–	NS
Disease-free survival	NS	NS	– (ER^{-})	NS
Overall survival	+	+	NS	NS

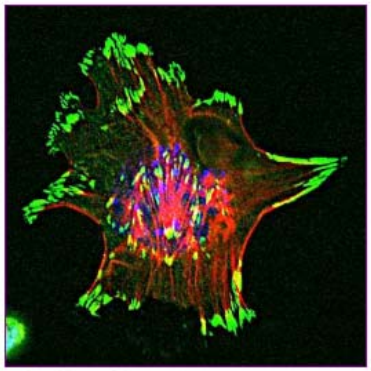
BM = bone metastases; LN = lymph node; NS = not significant; ER = estrogen receptor; + = better than competitor; – = worse than competitor; * Primary breast cancer patients (T1 to T4 and N0 to N2) with micrometastases in the bone marrow.

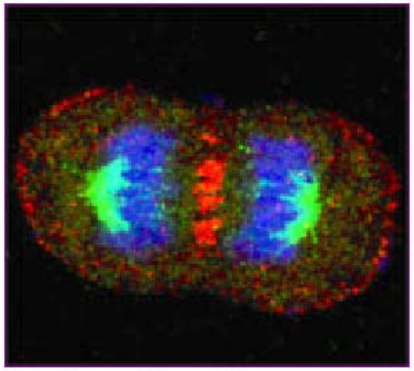
1. Diel IJ, et al. *N Engl J Med*. 1998;339(6):357-363. 2. Jaschke A, et al. *J Clin Oncol*. 2004;22(14S): Abstract 529. 3. Powles TJ, et al. *Breast Cancer Res.* 2006;8:R13. 4. Saarto T, et al. *Acta Oncol.* 2004;43(7):650-656. 5. Paterson AH, et al. *J Clin Oncol*. 1993;11(1):59-65.

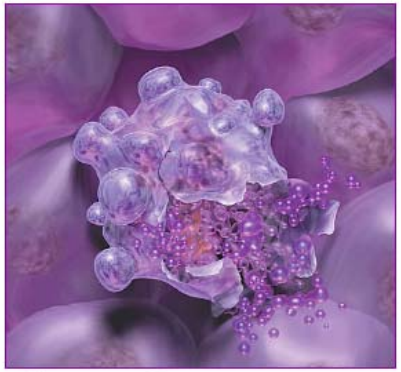
In Vitro Antitumor Activity of Zoledronate

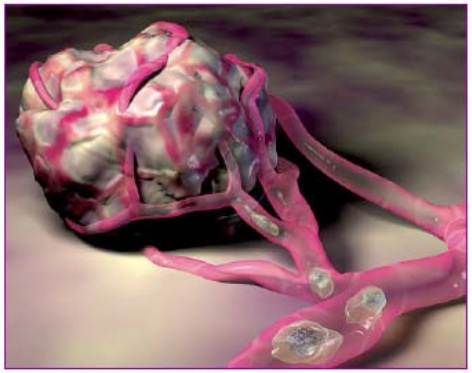
- **Inhibition of cancer cell adhesion to extracellular matrix proteins**
  (van der Pluijm G, et al. *J Clin Invest*. 1996;98(3):698-705. Boissier S, et al. *Cancer Res*. 1997;57(18):3890-3894. and others…)
- **Inhibition of cancer cell proliferation and induction of apoptosis**
  (Shipman CM, et al. *Br J Haematol.* 1997;98(3):665-672. and others…)
- **Inhibition of cancer cell migration and invasion**
  (Boissier S, et al. *Cancer Res*. 2000;60(11):2949-2954. and others…)
- **Inhibition of angiogenesis**
  (Fournier P, et al. *Cancer Res*. 2002;62(22):6538-6544. Wood J, et al. *J Pharmacol Exp Ther*. 2002;302(3):1055-1061. and others…)
- **Stimulation of the expansion of human γδT cells**
  (Kunzmann V, et al. *Blood*. 2000;96(2):384-392. and others…)




Cell adhesion

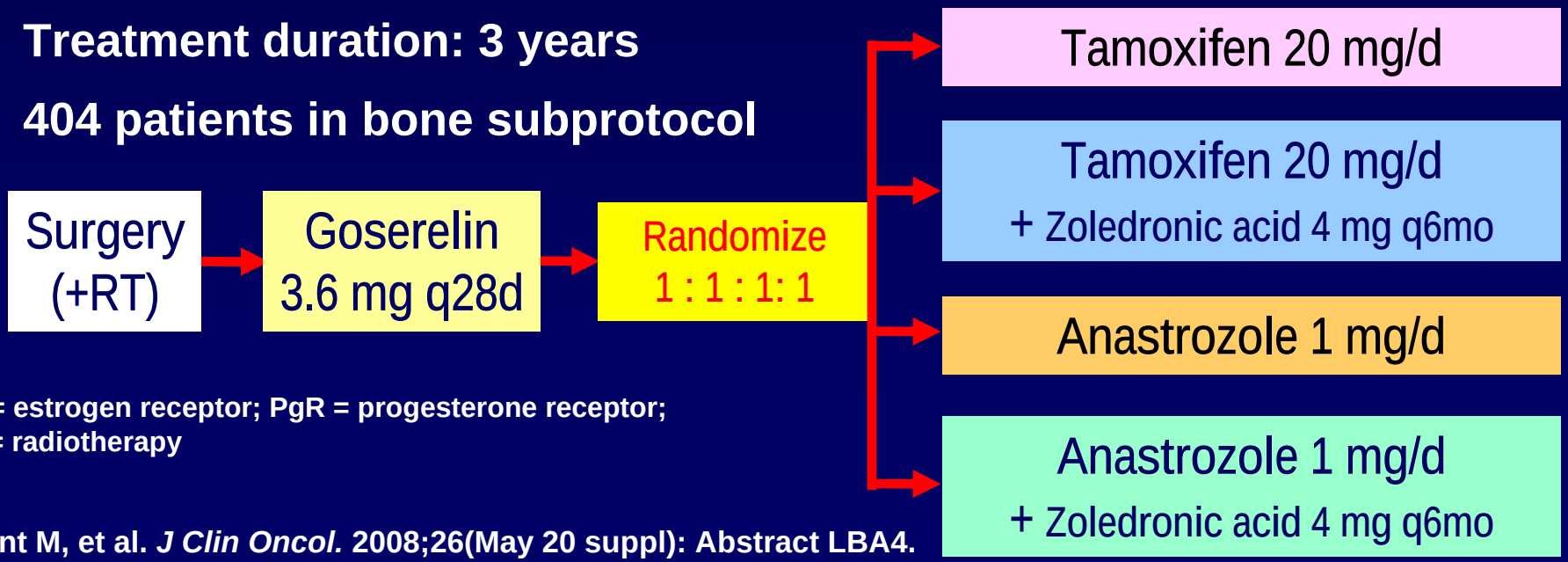

Cell proliferation


Apoptosis


Angiogenesis

ABCSG-12 Trial Design

- Accrual 1999 - 2006
- 1803 premenopausal patients with breast cancer
- Endocrine-responsive (ER^+ and/or PgR^+)
- Stage I and II, <10 positive nodes
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years
- 404 patients in bone subprotocol



ER = estrogen receptor; PgR = progesterone receptor; RT = radiotherapy

Gnant M, et al. *J Clin Oncol.* 2008;26(May 20 suppl): Abstract LBA4.

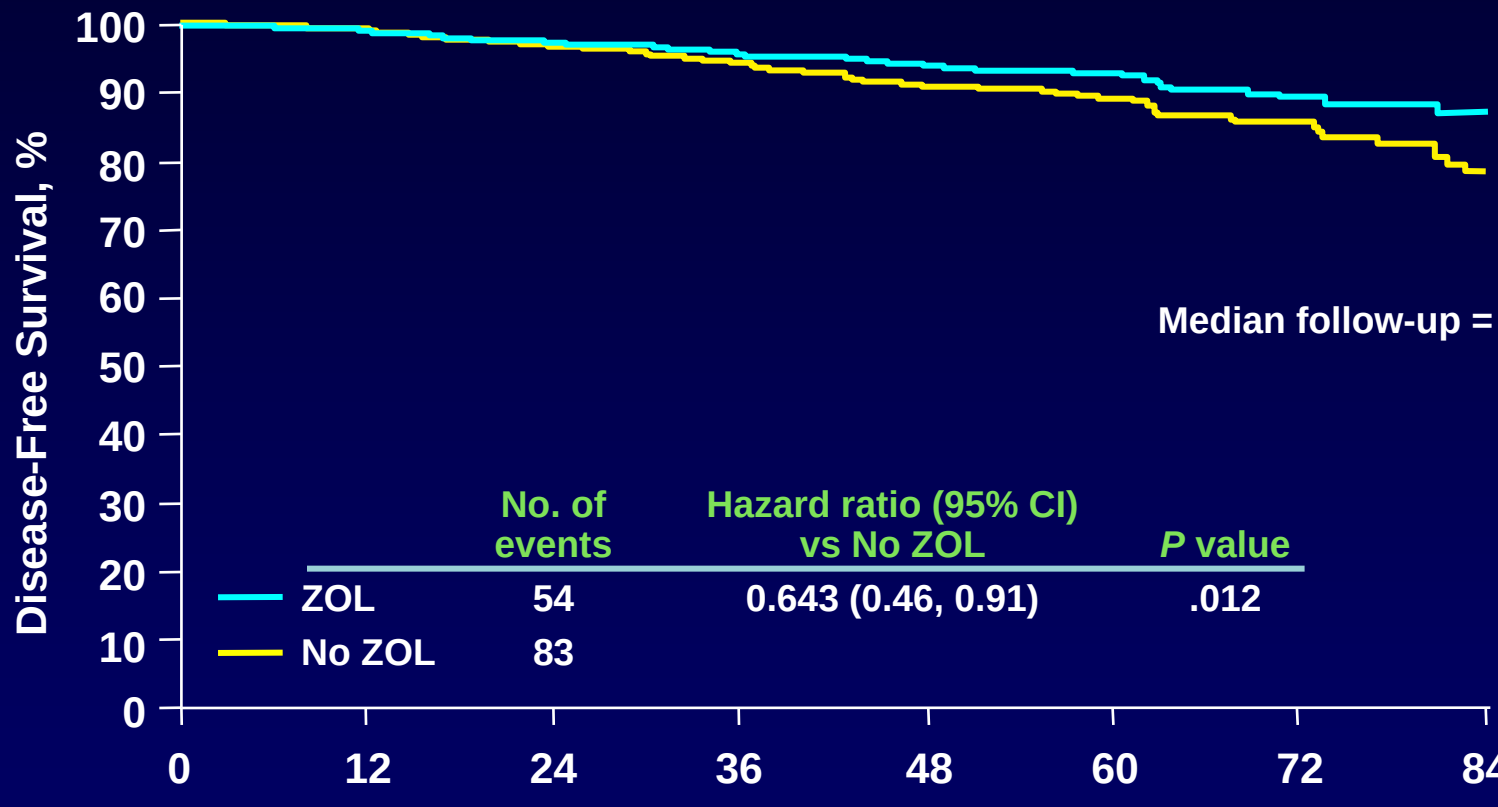
ABCSG-12 Baseline Demographics and Disease Characteristics

n, (%)	TAM (n = 451)	TAM + ZOL (n = 449)	ANA (n = 453)	ANA + ZOL (n = 450)
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)
$ER^{+/2+}$	217 (48.1)	210 (46.8)	221 (48.8)	211 (46.9)
ER^{3+}	204 (45.2)	204 (45.4)	206 (45.5)	210 (46.7)
$PgR^{+/2+}$	212 (47.0)	206 (45.9)	217 (47.9)	190 (42.2)
PgR^{3+}	185 (41.0)	195 (43.4)	200 (44.2)	212 (47.1)
Histologic grade 3	93 (20.7)	89 (19.0)	97 (21.5)	98 (21.0)
Neoadj. chemo	24 (5.3)	23 (5.1)	24 (5.3)	26 (5.8)

TAM = tamoxifen; ZOL = zoledronic acid; ANA = anastrozole; ER = estrogen receptor; PgR = progesterone receptor

Update of Gnant M, et al. *J Clin Oncol.* 2008;26(May 20 suppl): Abstract LBA4.

ZOL Significantly Improves DFS Compared With Endocrine Therapy Alone



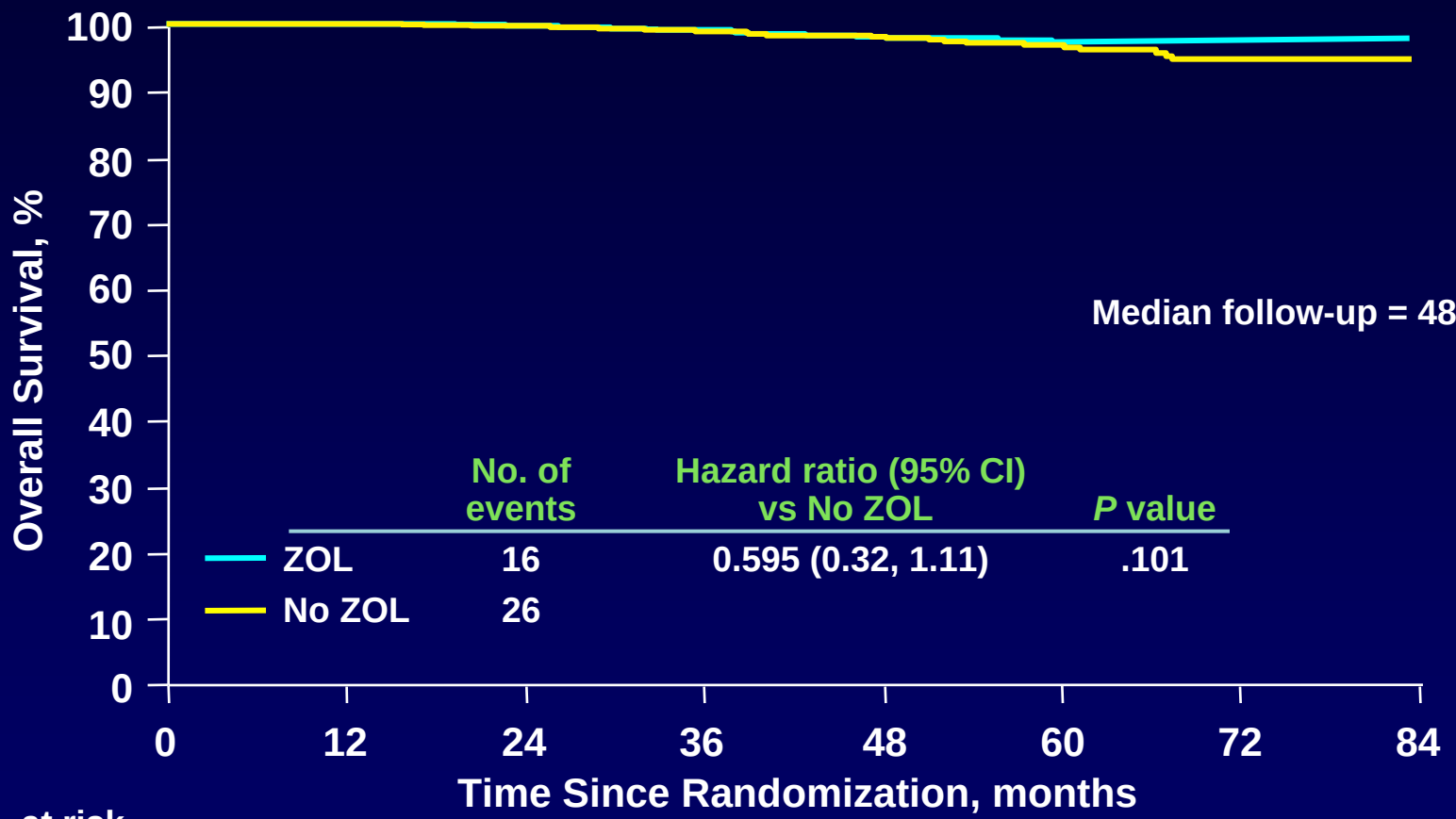
No. at risk

No ZOL	904	832	713	537	407	241	145	47
ZOL	899	846	730	555	414	257	123	54

ZOL = zoledronic acid; DFS = disease-free survival; CI = confidence interval

Update of Gnant M, et al. *J Clin Oncol.* 2008;26(May 20 suppl): Abstract LBA4.

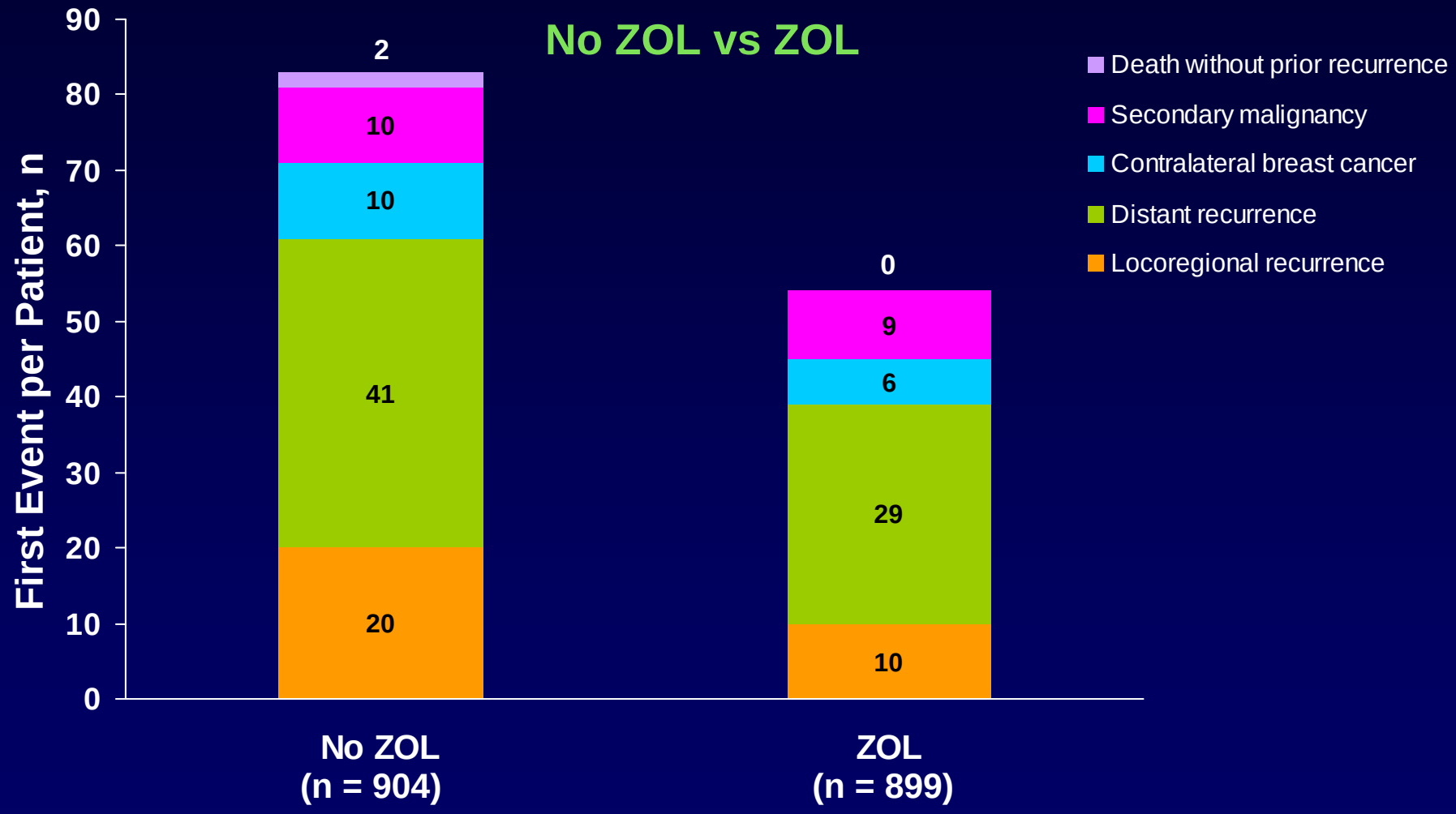
ZOL-Treated Patients Showed a Nonsignificant Trend Toward Improved OS



ZOL = zoledronic acid; OS = overall survival; CI = confidence interval

Update of Gnant M, et al. *J Clin Oncol.* 2008;26(May 20 suppl): Abstract LBA4.

ZOL Reduced Recurrence at All Sites



ZOL = zoledronic acid; DFS = disease-free survival; ITT = intent-to-treat

Gnant M, et al. *J Clin Oncol*. 2008;26(May 20 suppl): Abstract LBA4.

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
AE, n (%)					
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[a]	5 (1.1)	3 (0.7)	0 (0.0)	6 (1.3)	.054
SAE, n (%)					
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[a]	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.
[a] No confirmed cases of osteonecrosis of the jaw.

Gnant M, et al. *J Clin Oncol*. 2008;26(May 20 suppl): Abstract LBA4.

ABCSG-12: Summary of ZOL Versus No ZOL

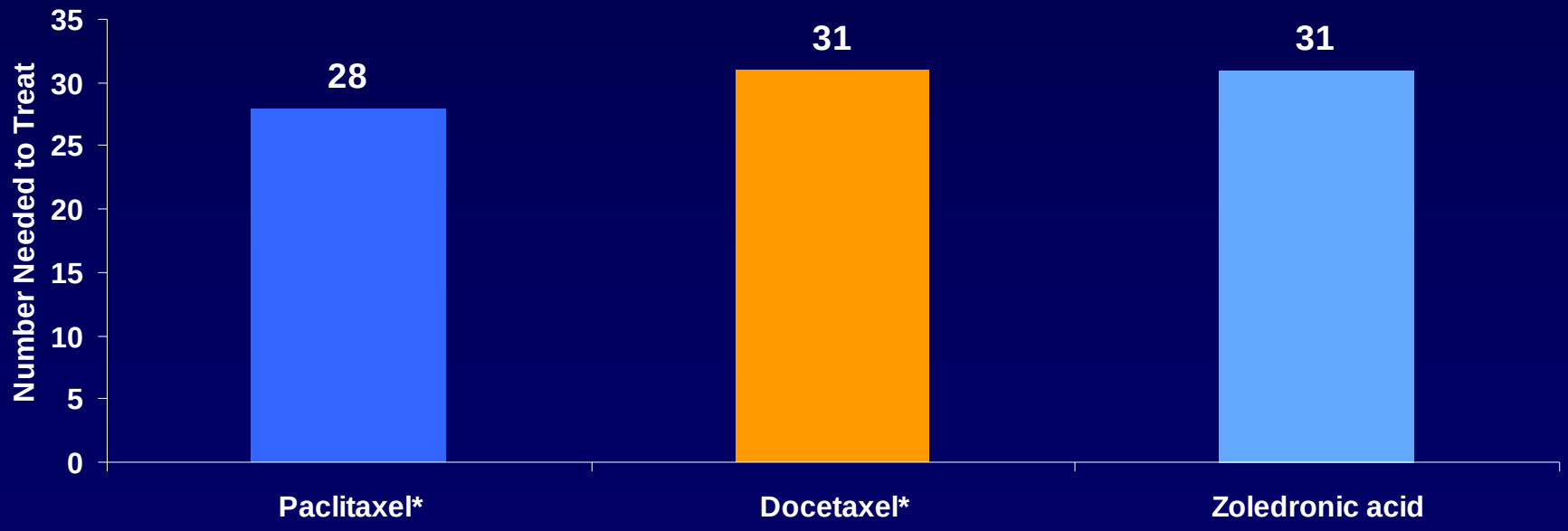
- Adding ZOL to endocrine therapy significantly improved DFS and RFS vs endocrine therapy alone
  - Trend toward improved OS
  - Fewer patients with bone metastases: 16 ZOL vs 23 No ZOL
- Addition of ZOL significantly
  - ⬇ Contralateral breast cancer
  - ⬇ Locoregional recurrence
  - ⬇ Distant recurrence (in bone and in other sites)
- Combination of ZOL and endocrine therapy was generally well tolerated

ZOL = zoledronic acid; DFS = disease-free survival; RFS = recurrence-free survival; OS = overall survival.

Gnant M, et al. *J Clin Oncol.* 2008;26(May 20 suppl): Abstract LBA4.

Estimation of the Number Needed to Treat

- Number of patients needed to treat for 1 patient to gain disease-free survival (DFS) clinical benefit
  - NNT = 1 / Absolute risk reduction
- Zoledronic acid has similar DFS efficacy to other paradigm-changing cancer therapies (ie, taxanes)



*Bria E, et al. *Cancer*. 2006;106(11):2337-2344.

ABCSG-12 Results Reinforce the 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."

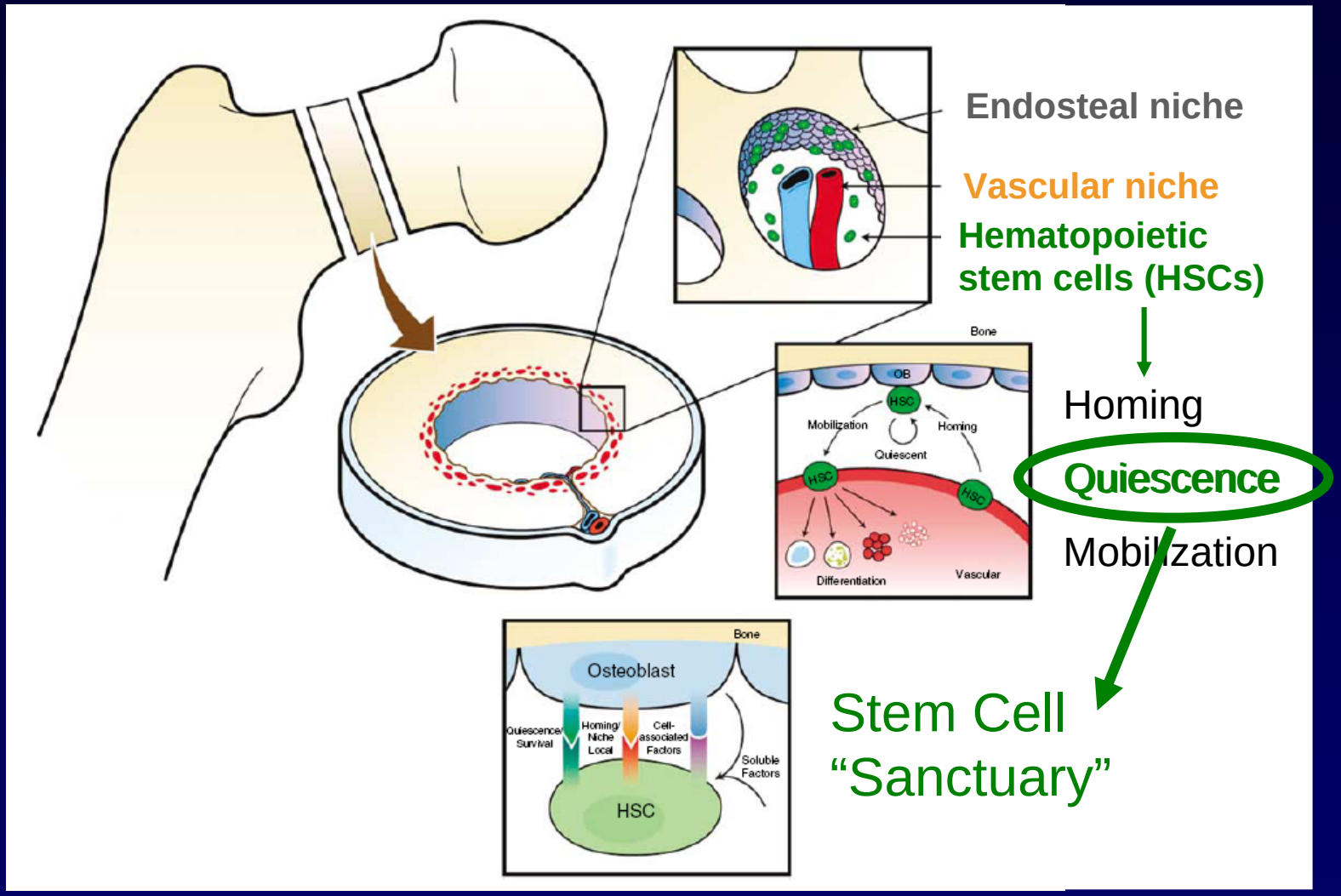
The Distribution of Secondary Growths in Cancer of the Breast
The Lancet, 1889

The evidence seems to me irresistible that in cancer of the breast the bones suffer in a special way, which cannot be explained by any theory of embolism alone. Some bones suffer more than others; the disease has its "seats of election." The same thing is seen much more clearly in those

All reasoning from statistics is liable to many errors. But the analogy from other diseases seems to support what these records have suggested. The eruptions of the specific fevers and of syphilis, the inflammations after typhoid, the lesions of tuberculosis, all show the dependence of the seed upon the soil. The best work in the pathology of cancer is now done by those who, like Mr. Ballance and Mr. Shattock, are studying the nature of the seed. They are like scientific botanists; and he who turns over the records of cases of cancer is only a ploughman, but his observation of the properties of the soil may also be useful.

The Lancet, 1889

Metastatic Niches in Bone Marrow

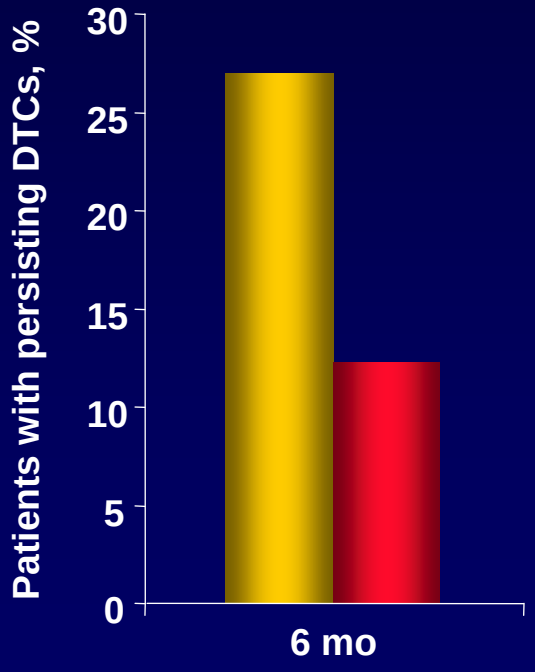


Shiozawa Y, et al. *Leukemia*. 2008;22(5):941-950.

ZOL Reduced Residual Cancer Burden in 3 Clinical Trials in Early Breast Cancer

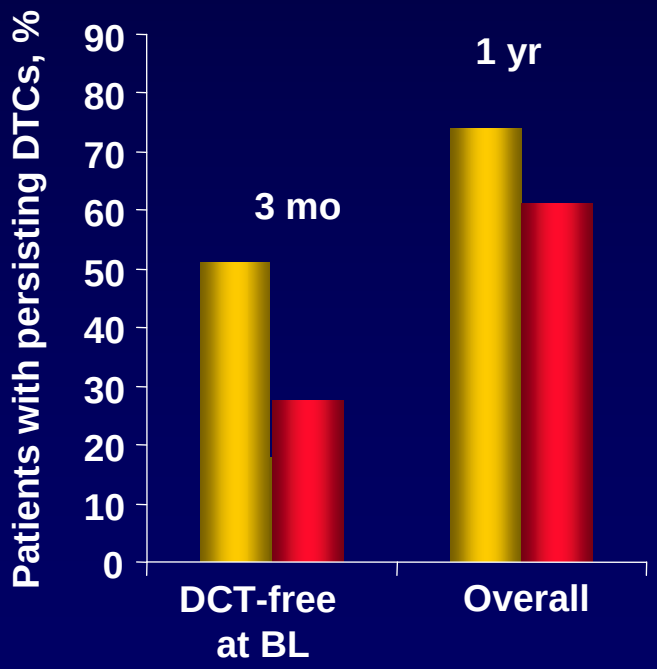
Rack et al[1] (N = 172)
- ZOL q4wk vs
- No ZOL for 6 mo

ZOL ↑ DTC clearance



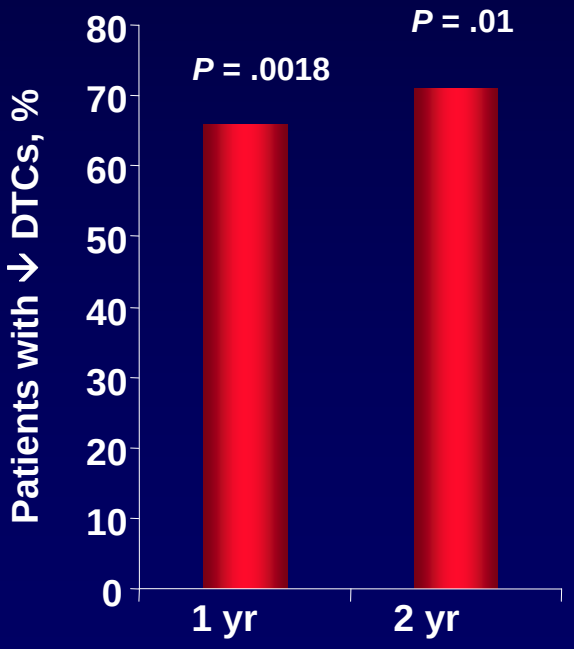
Aft et al[2] (N = 120)
- ZOL q3wk vs
- No ZOL for 1 yr (w/Chx)

ZOL keeps patients DTC-free



Lin et al[3,4] (N = 45)
ZOL q4wk (vs BL) for 2 yr

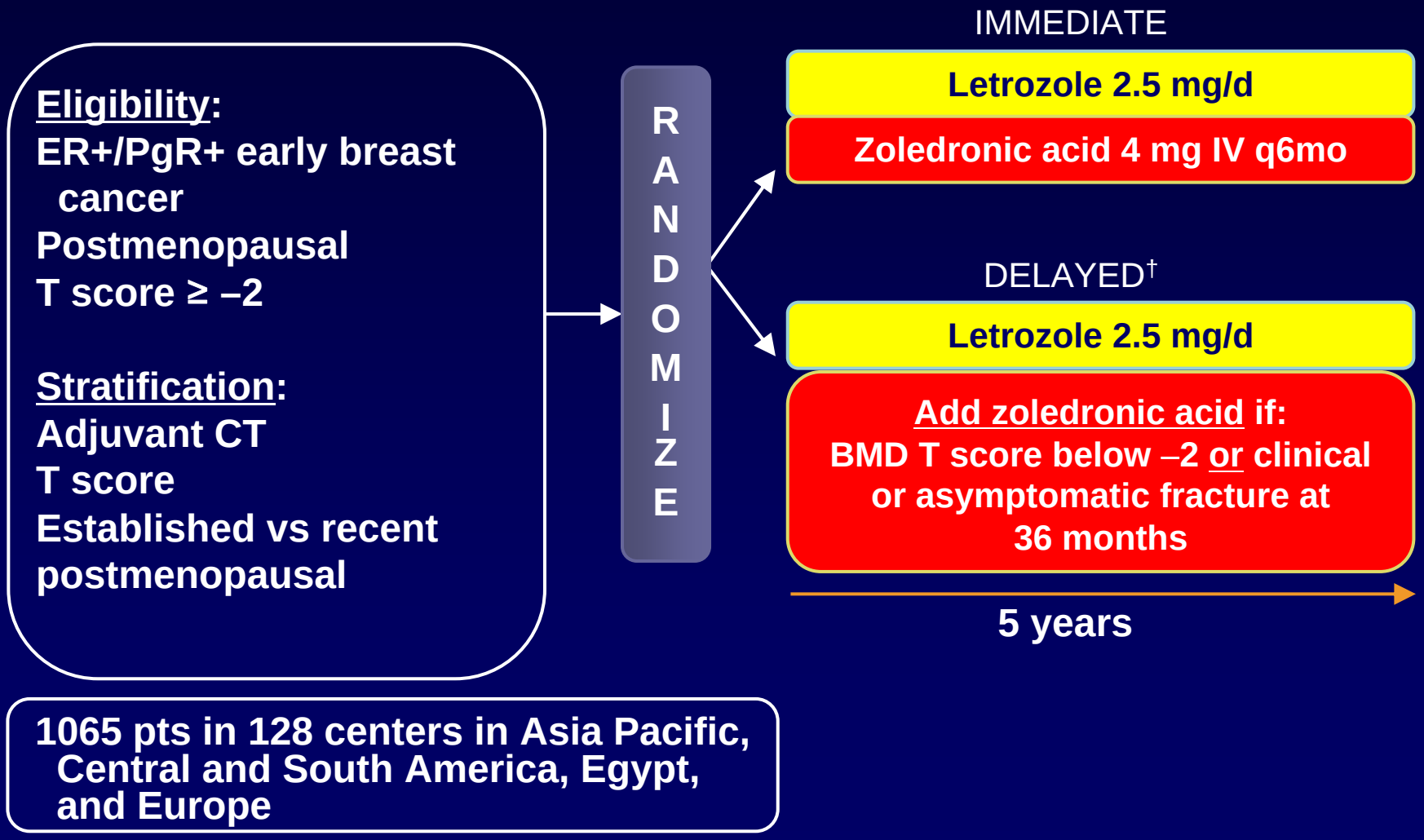
ZOL consistently ↓ DTCs over time



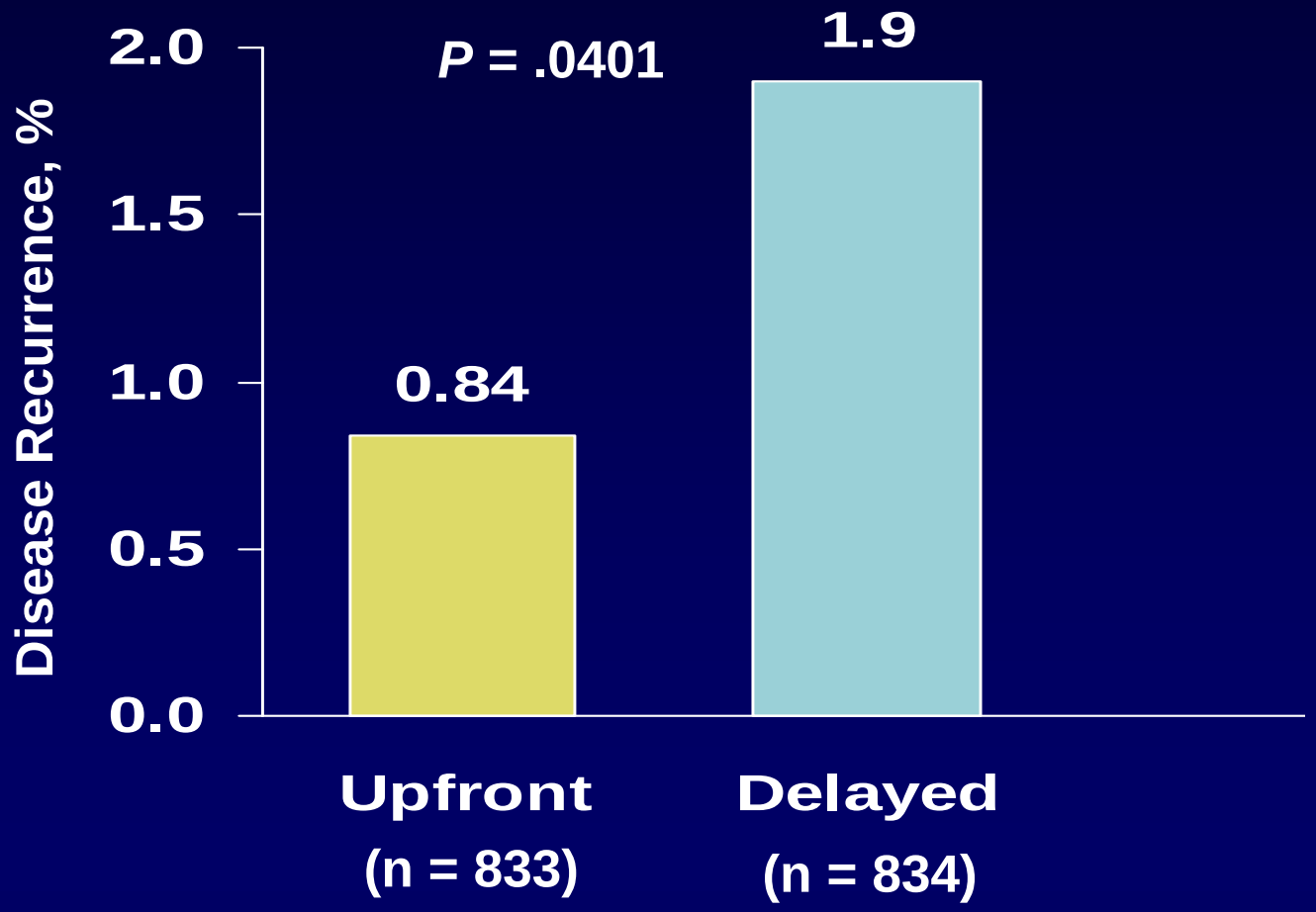
ZOL = zoledronic acid; DTC = disseminated tumor cells; BL = baseline; Chx = chemotherapy.

1. Rack B, et al. *Dtsch Med Wochenschr.* 2008;133(7):285-289. 2. Aft R, et al. *J Clin Oncol*. 2008;26(May 20 suppl): Abstract 1021; 3. Lin A, et al. *Breast Cancer Res Treat.* 2007;106(suppl 1): Abstract 510; 4. Lin A, et al. *J Clin Oncol*. 2008;26(May 20 suppl): Abstract 559.

ZO-FAST Design

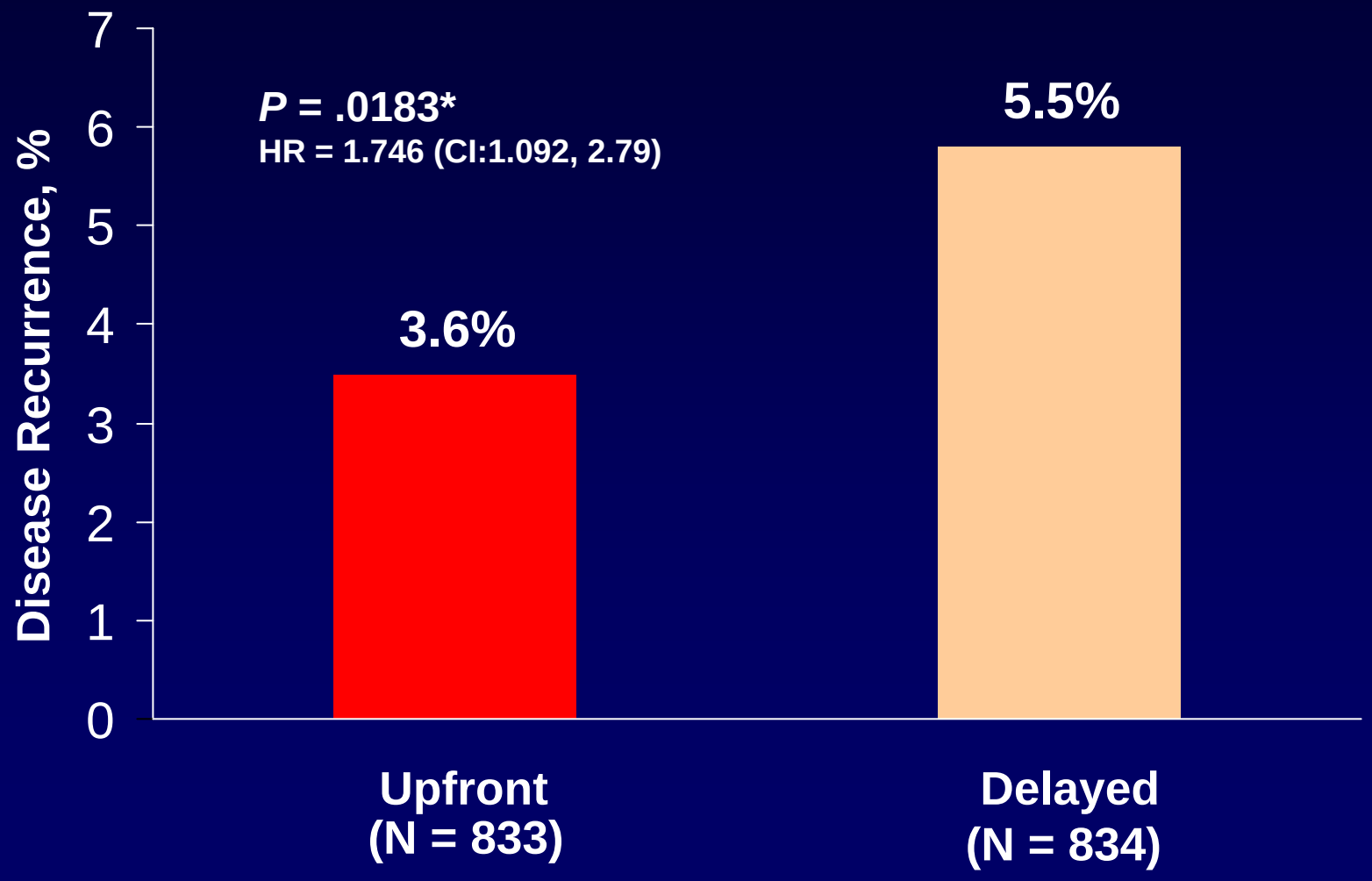


Zoledronic Acid Reduces Disease Recurrence: Z-FAST/ZO-FAST Integrated Analysis (12 Months)



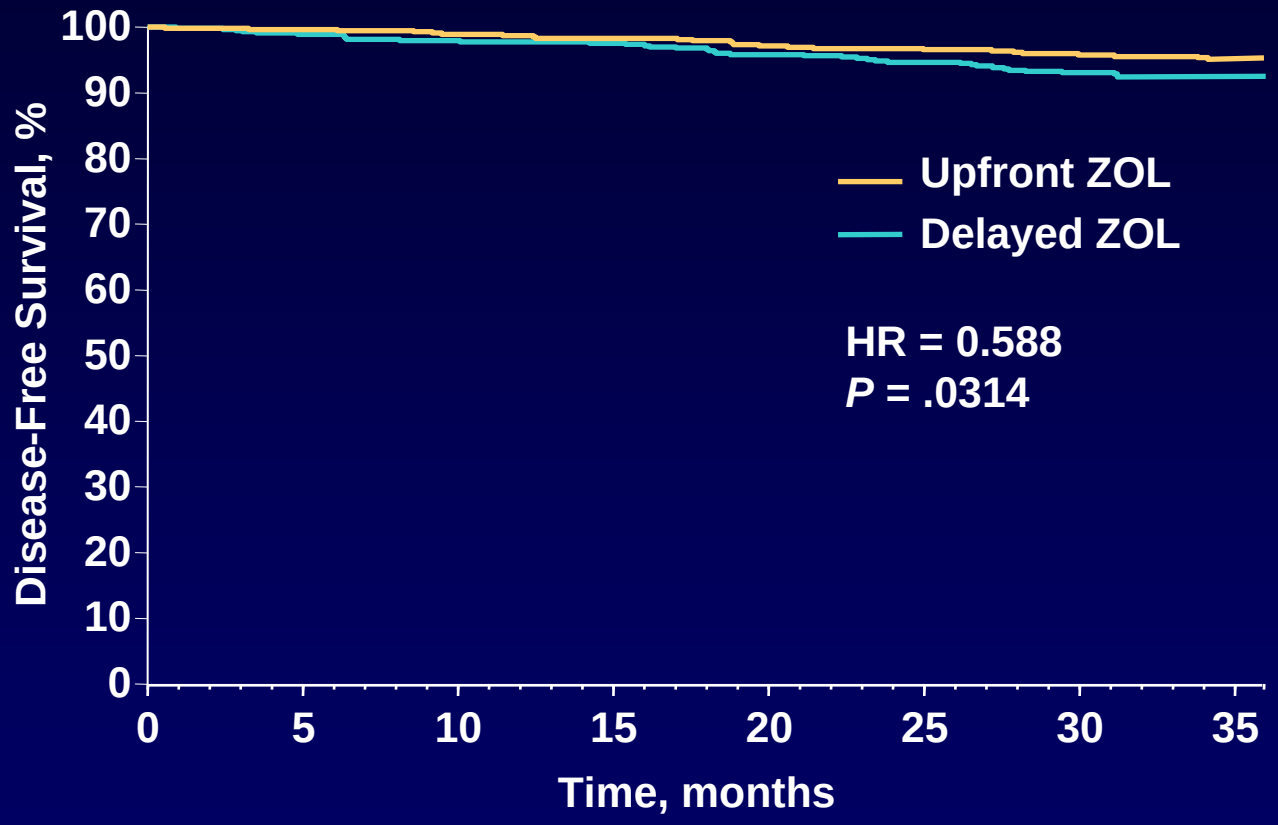
Brufsky A, et al. *Oncologist.* 2008;13(5):503-514.

Zoledronic Acid Reduces Disease Recurrence in Postmenopausal BC (24 Months)



*Frassoldati A, et al. (ESMO 2008, abstract #185).

ZO-FAST 36-Month Analysis: Disease-Free Survival

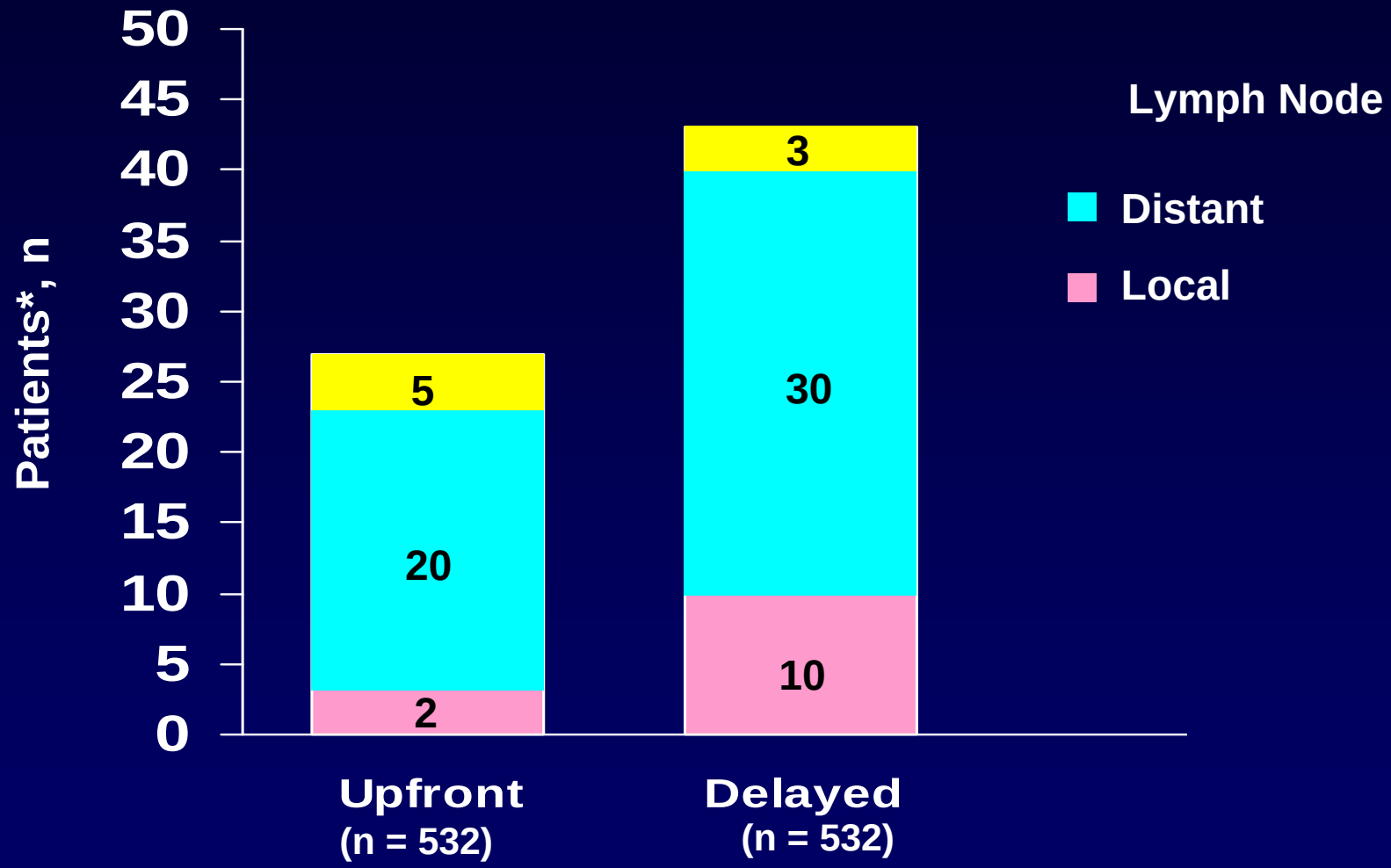


Upfront ZOL significantly decreased the risk of DFS events by 41%

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

Eidtmann H, et al. *Cancer Res.* 2009;69(suppl 2): Abstract 44.

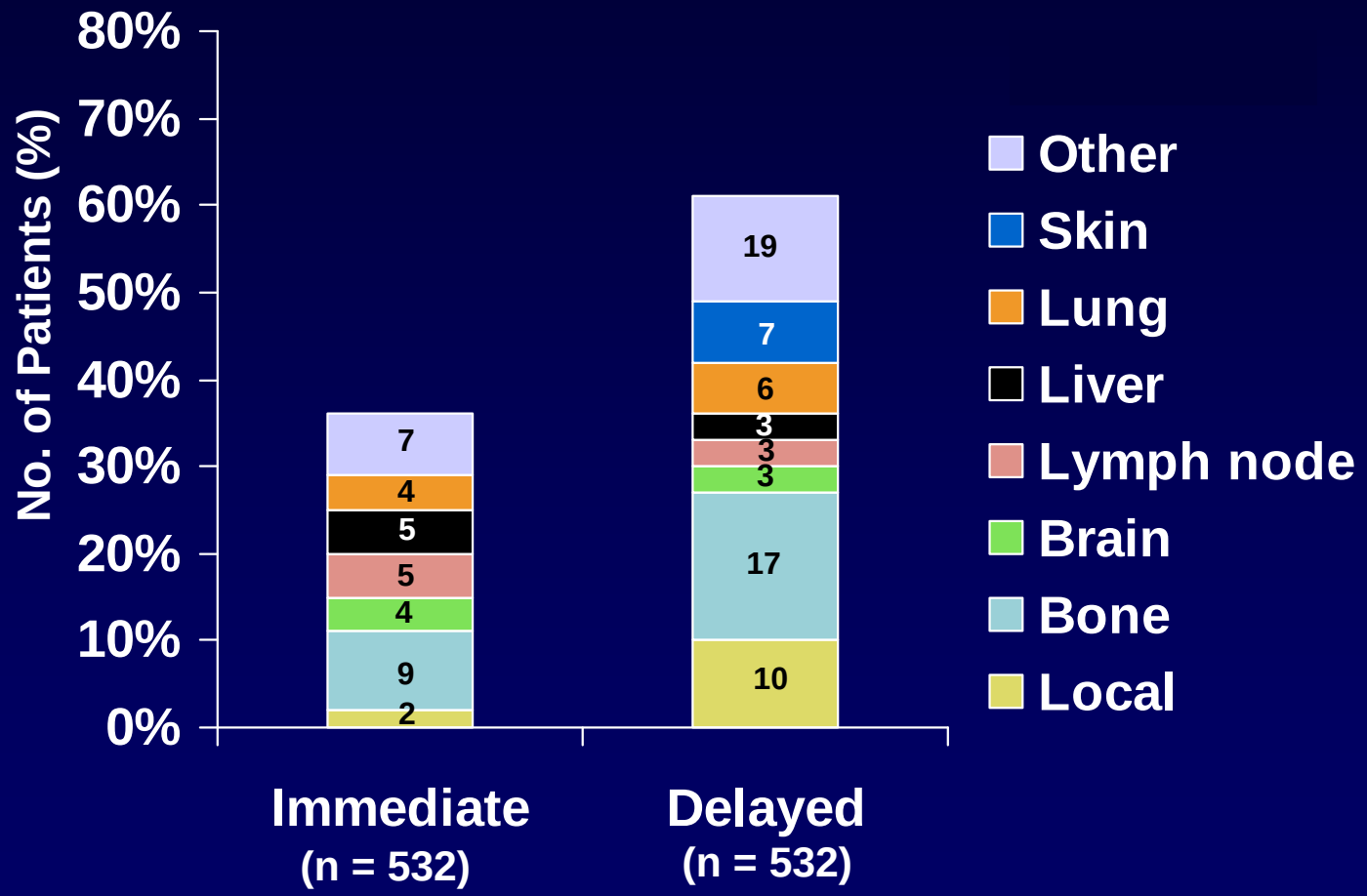
ZO-FAST 36-Month Analysis: Disease Recurrence



ZOL = Zoledronic acid
*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.

Eidtmann H, et al. *Cancer Res.* 2009;69(supp12): Abstract 44.

ZO-FAST (36 Month): Sites of Disease Recurrences



Eidtmann H, et al. *Cancer Res.* 2009;69(supp12): Abstract 44.

Antitumor Effects of Zoledronic Acid in the Bone Microenvironment

- ZOL creates a “less fertile soil” in the bone microenvironment
  - ↓ Osteoclast-mediated osteolysis
  - ↓ Release of growth factors from the bone matrix
  - ↓ Cancer cell survival and tumor growth

Conclusions and Perspective

- **Addition of zoledronic acid to adjuvant endocrine therapy improves disease-free survival compared with endocrine therapy alone**
  - **Zoledronic acid ⬇ disease recurrence in bone and in other sites**
- **Ongoing trials will further address the potential for improving disease outcomes with bisphosphonates**
  - **Optimal dosage and regimen**
  - **Long-term safety and efficacy**
- **Yes, in the near future, we will use zoledronic acid in the adjuvant treatment of breast cancer**