This House Believes Bisphosphonates Should be Standard of Care for Early Breast Cancer

Rob Coleman

Sheffield

Rob Coleman and All Reasonable Clinicians Believe Bisphosphonates Should be Standard of Care for Early Breast Cancer

Rob Coleman

Sheffield

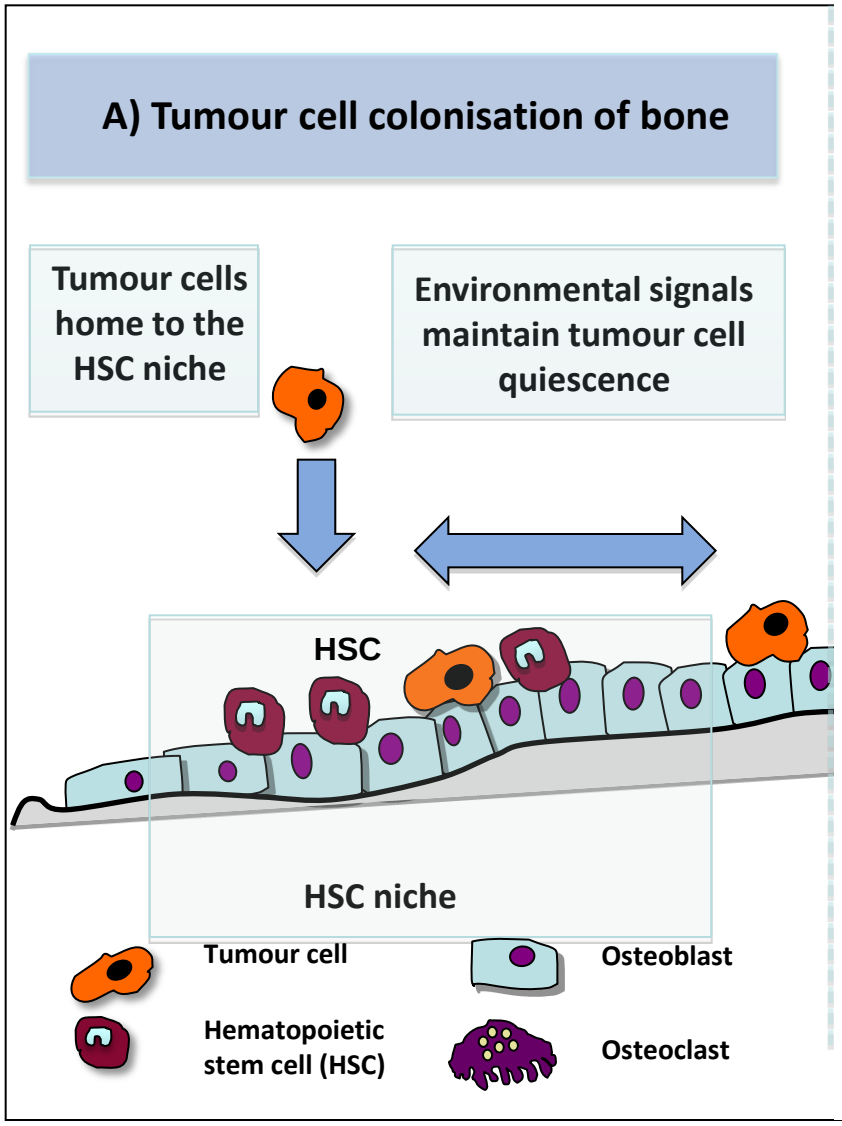
Requirements For a New Treatment in Early Breast Cancer

The University Of Sheffield.

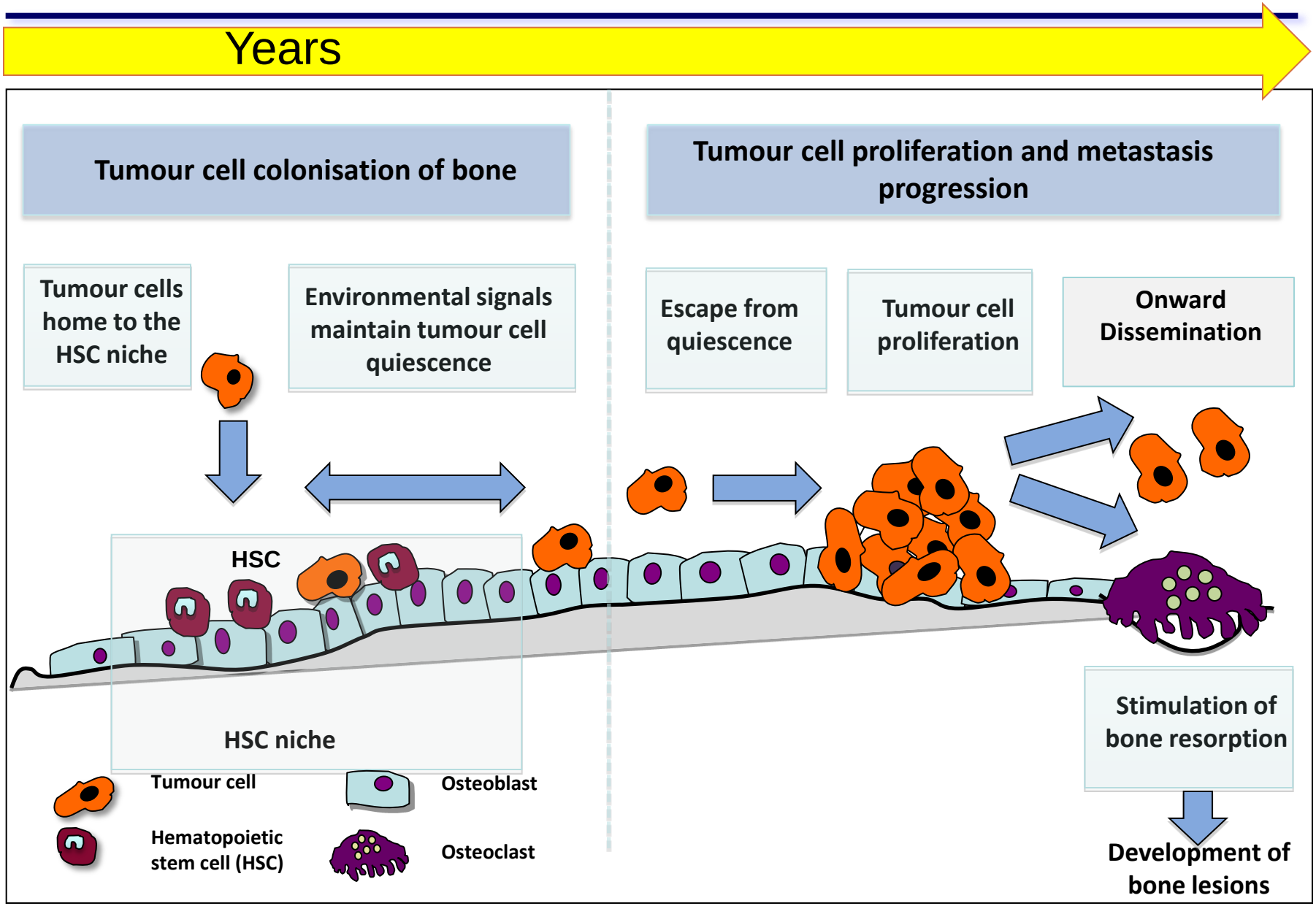
- Biologically plausible
- Multiple supportive clinical trials
- Meaningful benefit
- Compatible with current standard treatment
- Well tolerated
- Cost effective
- (Regulatory approval)

Professor David Dodwell?

Phases of Bone "Metastasis"



Breast Cancer Metastasis



Research is Full of Surprises

The University Of Sheffield.

Late 1990s/2000s
Early Prevention Studies—Clodronate

The University Of Sheffield.

Available online http://breast-cancer-research.com/content/8/2/R13

Research article

Open Access

Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer [ISRCTN83688026]

Trevor Powles[1], Alexander Paterson[2], Eugene McCloskey[3], Phil Schein[4], Bobbi Scheffler[5], Alwynne Tidy[6], Sue Ashley[6], Ian Smith[6], Lars Ottestad[7] and John Kanis[3]

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Breast Cancer Research 2006, 8:R13 (doi:10.1186/bcr1384)
This article is online at: http://breast-cancer-research.com/content/8/2/R1

Abstract

Introduction Experimental and clinical data show that the oral

original article

Annals of Oncology 19: 2007–2011, 2008
doi:10.1093/annonc/mdn429
Published online 29 July 2008

Adjuvant oral clodronate improves the overall survival of primary breast cancer patients with micrometastases to the bone marrow—a long-term follow-up

I. J. Diel[1,2]*, A. Jaschke[1], E. F. Solomayer[3], C. Gollan[1], G. Bastert[1], C. Sohn[1] & F. Schuetz[1]

[1]Department of Gynecology and Obstetrics, University of Heidelberg, Heidelberg, Germany; [2]Institute for Gynecological Oncology, Mannheim, Germany; [3]Department of Obstetrics and Gynecology, University of Tübingen, Germany

Received 27 April 2008; revised 10 June 2008; accepted 19 June 2008

Background: Adding oral clodronate to postoperative adjuvant breast cancer
free survival (DFS) and overall survival (OS). Long-term follow-up data from t
study are reported.
Patients and methods: Patients with primary breast cancer received cloc
treatment along with standard adjuvant breast cancer treatment.
Results: Analysis of 299 of 302 patients demonstrated that a significant imp
clodronate group at a median follow-up of 103 ± 12 months; 20.4% of patient
of control group patients ($P = 0.04$) died during the 8.5 years following primary
in the incidence of bony and visceral metastases and improvement in duration
periods were no longer seen with clodronate.
Conclusion: These long-term survival data extend the survival advantage re
clodronate in breast cancer.
Key words: adjuvant therapy, bisphosphonate, breast neoplasm, clodronat

ORIGINAL ARTICLE

Ten-year Follow-up of a Rand
Adjuvant Clodronate Treatme
Cancer Patients

Tiina Saarto, Leena Vehmanen, Pekka Virkkun

From the Department of Oncology, Helsinki University Ce
Department of Oncology, Uppsala University, Sweden, the
Hospital, Finland (C. Blomqvist), and the Department of R
(P. Virkkunen)

Correspondence to: Tiina Saarto, Department of Oncolog
FIN-00029 HUS, Helsinki, Finland. Tel: +358-9-4711. Fax:

Acta Oncologica Vol. 43, No. 7, pp. 650–656, 2004

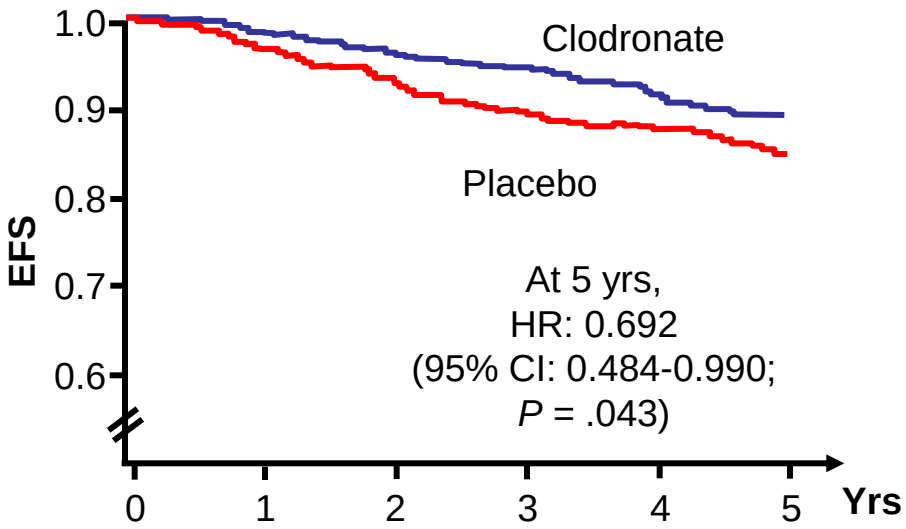
Ten-year follow-up results are presented of an adjuvant clodronate trial in patients with primary breast cancer. Between 1990 and 1993, 299 women with primary node positive breast cancer were randomized to oral clodronate 1600 mg daily (149) or controls (150) for 3 years. All patients received adjuvant chemo- or endocrine therapy. Within 10 years bone metastases were detected at the same frequency in the clodronate and control groups: 44 (32%) vs. 42 (29%), respectively, (p = 0.35). The frequency of non-skeletal recurrences (visceral and local) was significantly higher in the clodronate group 69 (50%) as compared with the controls 51 (36%) (p = 0.005). Ten-year disease-free survival (DFS) remained significantly lower in the clodronate group (45% vs. 58%, p = 0.01, respectively). This was especially seen in oestrogen receptor negative patients (25% vs. 58%, p = 0.004, respectively). No significant overall survival difference was found between the groups. As

Diel IJ, et al. *Ann Oncol*. 2008;19(12):2007-2011; Powles T, et al. *Breast Cancer Res*. 2006;8(2):R13; Saarto T, et al. *Acta Oncol*. 2004;43(7):650-656.

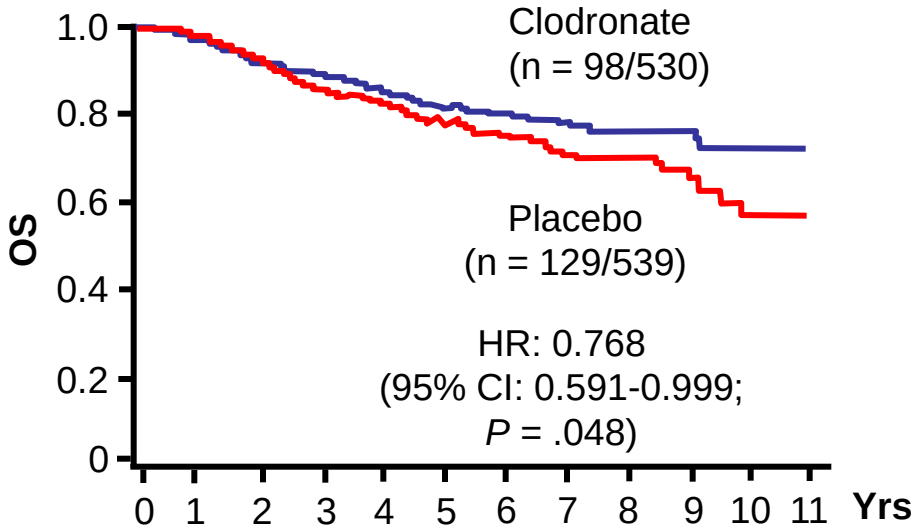
ClodroPlac: Oral Clodronate for Adjuvant Treatment of Stage I-III Breast Cancer (N=1069)

The University Of Sheffield.

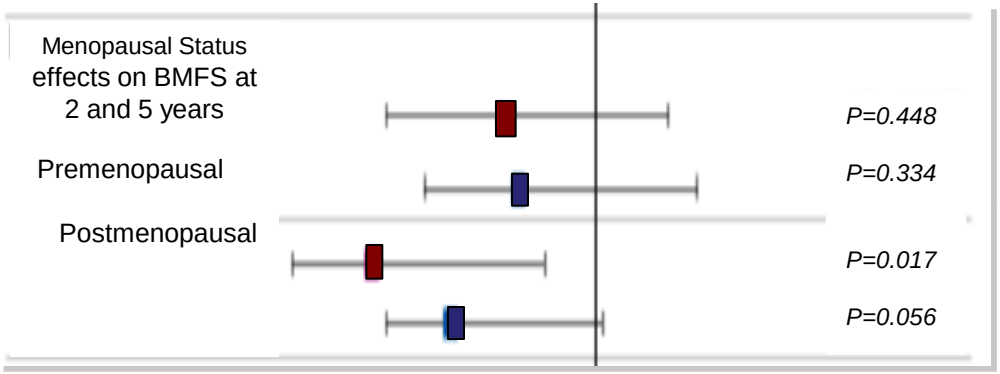
BONE METASTASIS FREE SURVIVAL ITT



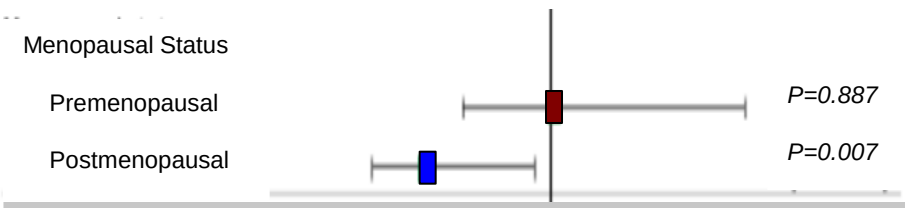
OVERALL SURVIVAL ITT



BONE METASTASIS FREE SURVIVAL - POSTMENOPAUSAL PATIENTS



OVERALL SURVIVAL - POSTMENOPAUSAL PATIENTS

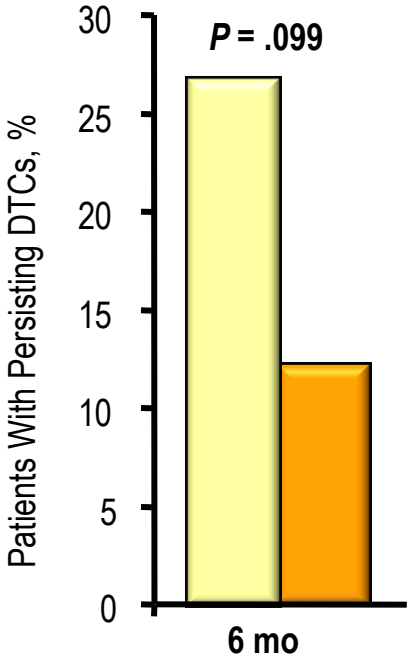


Powles T, et al. Breast Cancer Res. 2006;8:R13. and ASCO Proceedings 2004, Abs 528

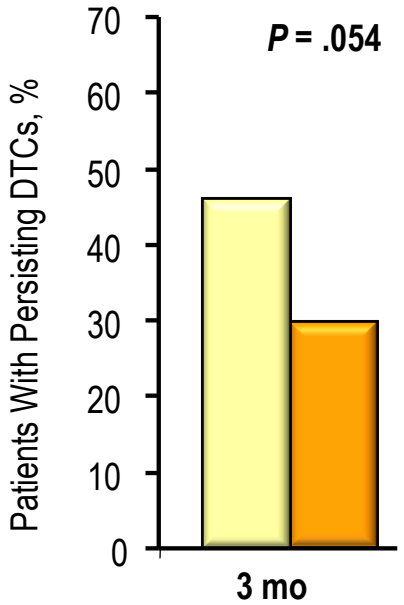
Bone Marrow Tumour Cells Reduced With Zoledronic Acid in Early Adjuvant Breast Cancer

The University Of Sheffield.

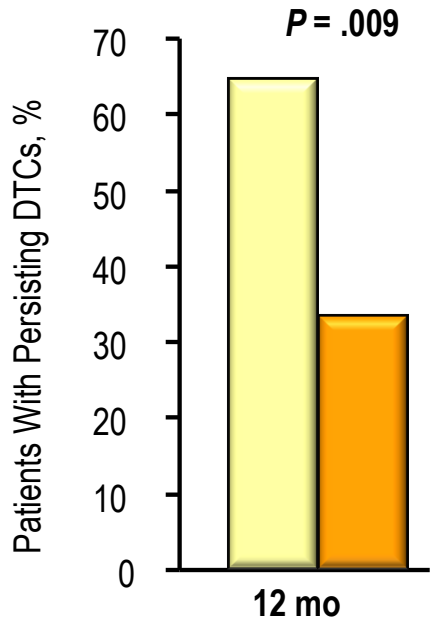
Rack et al[1] (N = 172)
- ZOL q 4 weekk (n = 31) vs
- no ZOL for 6 months (n = 141



Aft et al[2] (N = 120)
- ZOL q 3 weekly vs
- no ZOL for 1 yr (w/Chx)



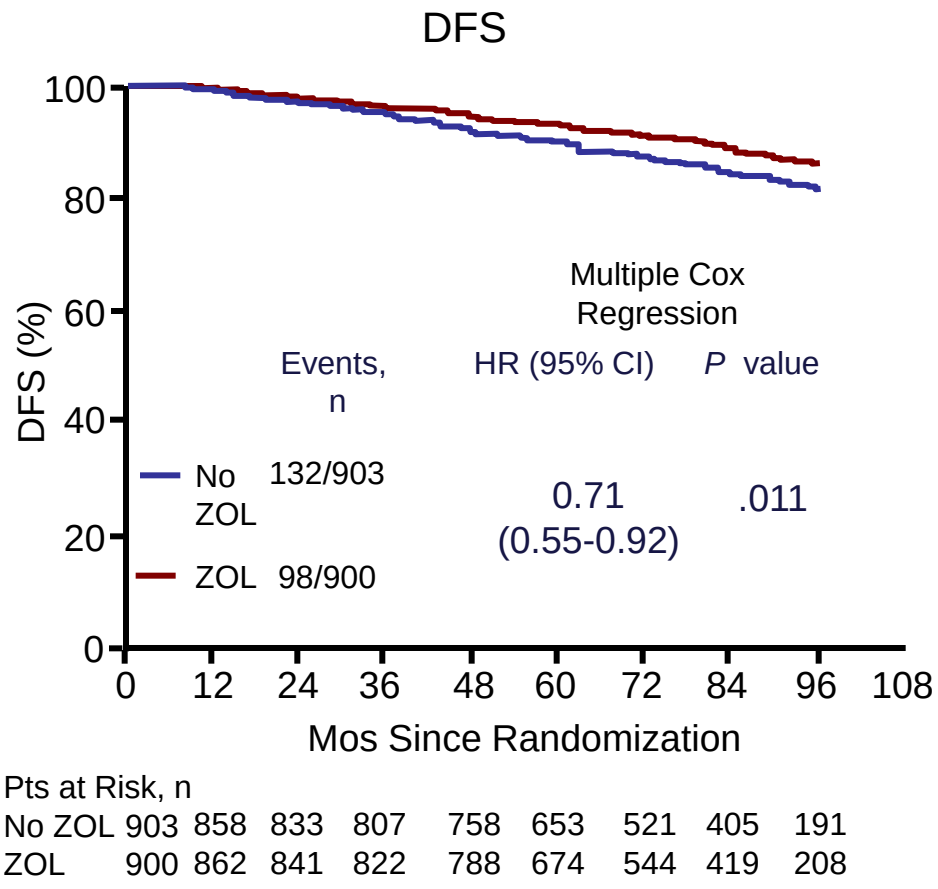
Solomayer et al[3] (N = 96)
- ZOL q 4 weeks (n = 44) vs
- no ZOL for 2 year (+ Adj Rx; n = 52)



Abbreviations: Chx, chemotherapy; DTC, disseminated tumour cell; ZOL, zoledronic acid.

1. Rack B, et al. *Anticancer Res.* 2010;30(5):1807-1813;
2. Aft R, et al. *Lancet Oncol*. 2010;11(5):421-428.;
3. Solomayer EF, et al. *Ann Oncol* 2012; 23(9):2271-7.

ABCSG-12 (84 Months): Efficacy



Pts at Risk, n

No ZOL	903	858	833	807	758	653	521	405	191
ZOL	900	862	841	822	788	674	544	419	208

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Endocrine Therapy plus Zoledronic Acid in Premenopausal Breast Cancer

Michael Gnant, M.D., Brigitte Mlineritsch, M.D., Walter Schippinger, M.D., Gero Luschin-Ebengreuth, M.D., Sabine Pöstlberger, M.D., Christian Menzel, M.D., Raimund Jakesz, M.D., Michael Seifert, M.D., Michael Hubalek, M.D., Vesna Bjelic-Radisic, M.D., Hellmut Samonigg, M.D., Christoph Tausch, M.D., Holger Eidtmann, M.D., Günther Steger, M.D., Werner Kwasny, M.D., Peter Dubsky, M.D., Michael Fridrik, M.D., Florian Fitzal, M.D., Michael Stierer, M.D., Ernst Rücklinger, Ph.D., and Richard Greil, M.D., for the ABCSG-12 Trial Investigators*

ABSTRACT

BACKGROUND

Ovarian suppression plus tamoxifen is a standard adjuvant treatment in premenopausal women with endocrine-responsive breast cancer. Aromatase inhibitors are superior to tamoxifen in postmenopausal patients, and preclinical data suggest that zoledronic acid has antitumor properties.

METHODS

We examined the effect of adding zoledronic acid to a combination of either goserelin and tamoxifen or goserelin and anastrozole in premenopausal women with endocrine-responsive early breast cancer. We randomly assigned 1803 patients to receive goserelin (3.6 mg given subcutaneously every 28 days) plus tamoxifen (20 mg per day given orally) or anastrozole (1 mg per day given orally) with or without zoledronic acid (4 mg given intravenously every 6 months) for 3 years. The primary end point was disease-free survival; recurrence-free survival and overall survival were secondary end points.

RESULTS

After a median follow-up of 47.8 months, 137 events had occurred, with disease-free survival rates of 92.8% in the tamoxifen group, 92.0% in the anastrozole group, 90.8% in the group that received endocrine therapy alone, and 94.0% in the group that received endocrine therapy with zoledronic acid. There was no significant difference in disease-free survival between the anastrozole and tamoxifen groups (hazard ratio for disease progression in the anastrozole group, 1.10; 95% confidence interval [CI], 0.78 to 1.53; P=0.59). The addition of zoledronic acid to endocrine therapy, as compared with endocrine therapy without zoledronic acid, resulted in an absolute reduction of 3.2 percentage points and a relative reduction of 36% in the risk of disease progression (hazard ratio, 0.64; 95% CI, 0.46 to 0.91; P=0.01); the addition of zoledronic acid did not significantly reduce the risk of death (hazard ratio, 0.60; 95% CI, 0.32 to 1.11; P=0.11). Adverse events were consistent with known drug-safety profiles.

CONCLUSIONS

The addition of zoledronic acid to adjuvant endocrine therapy improves disease-free survival in premenopausal patients with estrogen-responsive early breast cancer. (ClinicalTrials.gov number, NCT00295646.)

From the Medical University of Vienna (M.G., R.J., M. Seifert, G.S., P.D., F.F.), Hanusch Hospital (M. Stierer), and the Austrian Breast and Colorectal Cancer Study Group (E.R.) — all in Vienna; Paracelsus Medical University Salzburg, Salzburg (B.M., C.M., R.G.); Medical University of Graz, Graz (W.S., G.L.-E., V.B.-R., H.S.); Hospital of the Sisters of Mercy (S.P., C.T.) and General Hospital Linz (M.F.) — both in Linz; Medical University of Innsbruck, Innsbruck (M.H.); and Wiener Neustadt Hospital, Wiener Neustadt (W.K.) — all in Austria; and the University of Schleswig-Holstein, Kiel, Germany (H.E.). Address reprint requests to Dr. Gnant at the Medical University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria, or at michael.gnant@meduniwien.ac.at.

*The investigators participating in the Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12) are listed in the Appendix.

N Engl J Med 2009;360:679-91.

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N ENGL J MED 360;7 NEJM.ORG FEBRUARY 12, 2009

679

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Gnant M. et al. SABCC 2011. Abstract S1-2

AZURE: Study Design

The University Of Sheffield.

Accrual September 2003 - February 2006

3,360 Breast Cancer Patients
Stage II/III

R

Standard therapy

Standard therapy + Zoledronic acid 4 mg

6 doses Q3-4 weeks	8 doses Q 3 months	5 doses Q 6 months

Months 6 30 60

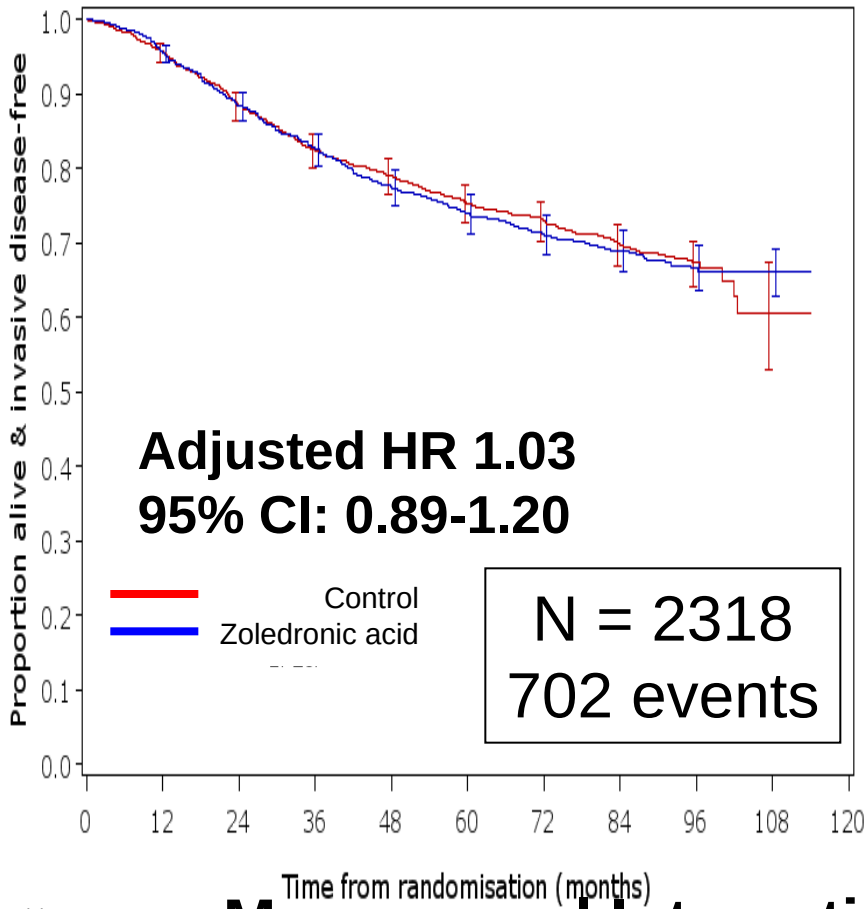
Zoledronic acid treatment duration 5 years

Countries	Centres	Patients
UK	123	2710
Eire	10	247
Australia	28	226
Spain	8	107
Portugal	1	32
Thailand	2	25
Taiwan	2	13

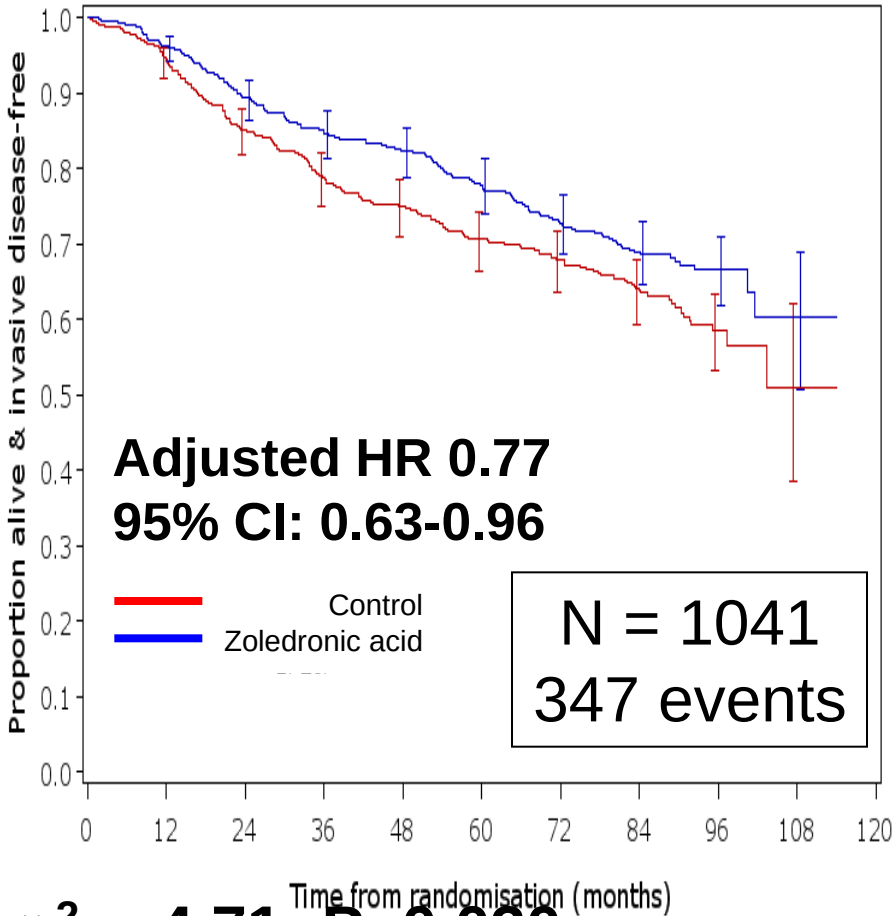
AZURE: Invasive DFS by Menopausal Status (Median follow up 84 months)

The University Of Sheffield.

Pre, peri and unknown menopausal status



>5 years post-menopausal



Menopausal Interaction: χ^2_1 =4.71; P=0.030

Coleman et al Eur J Cancer 2013;49(3)LBA9,S5

Time to Bone Metastasis

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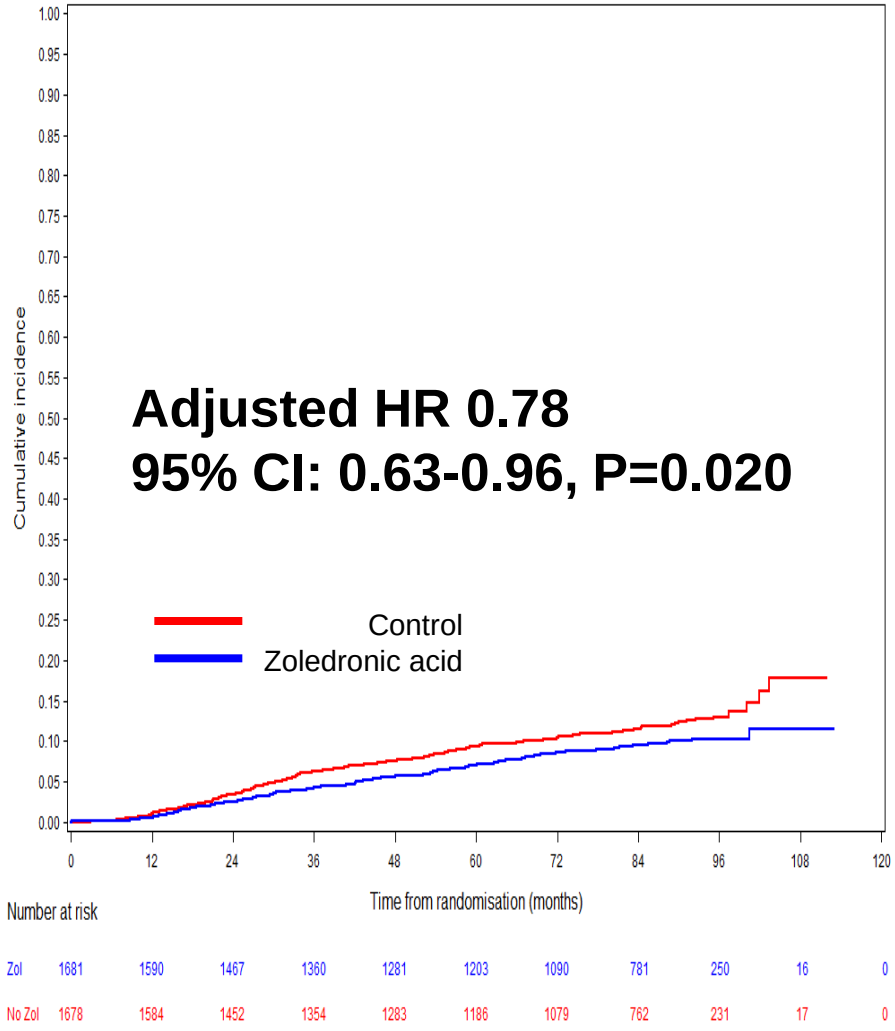
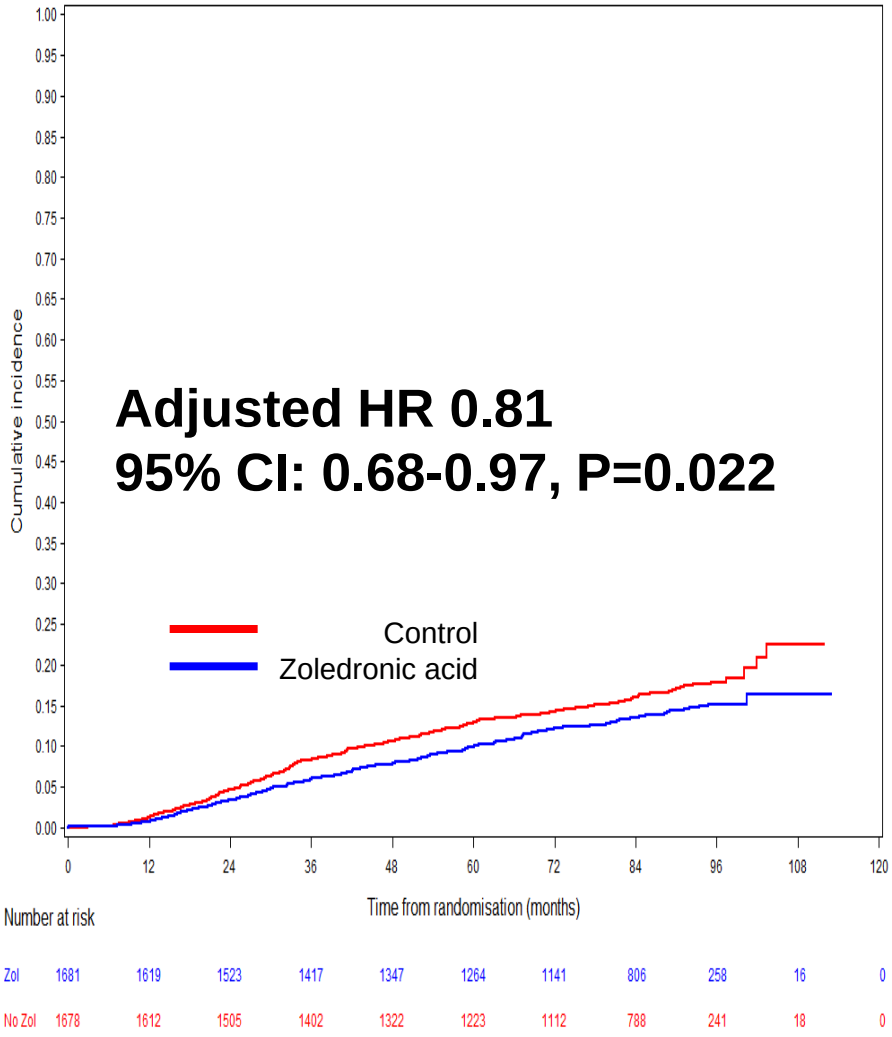
Bone metastasis as first recurrence

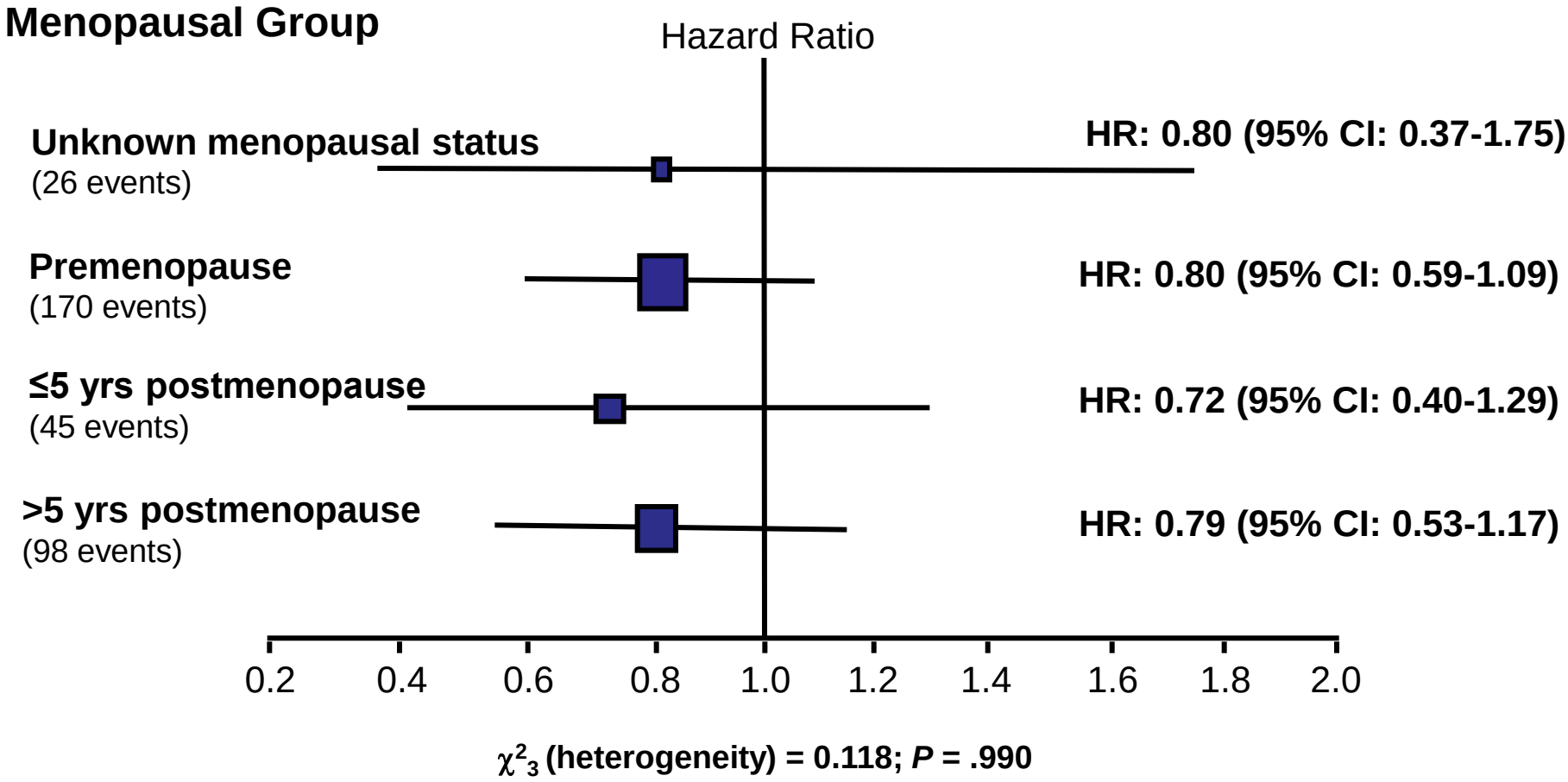


Bone metastasis at any time



Coleman et al Eur J Cancer 2013;49(3)LBA9,S5

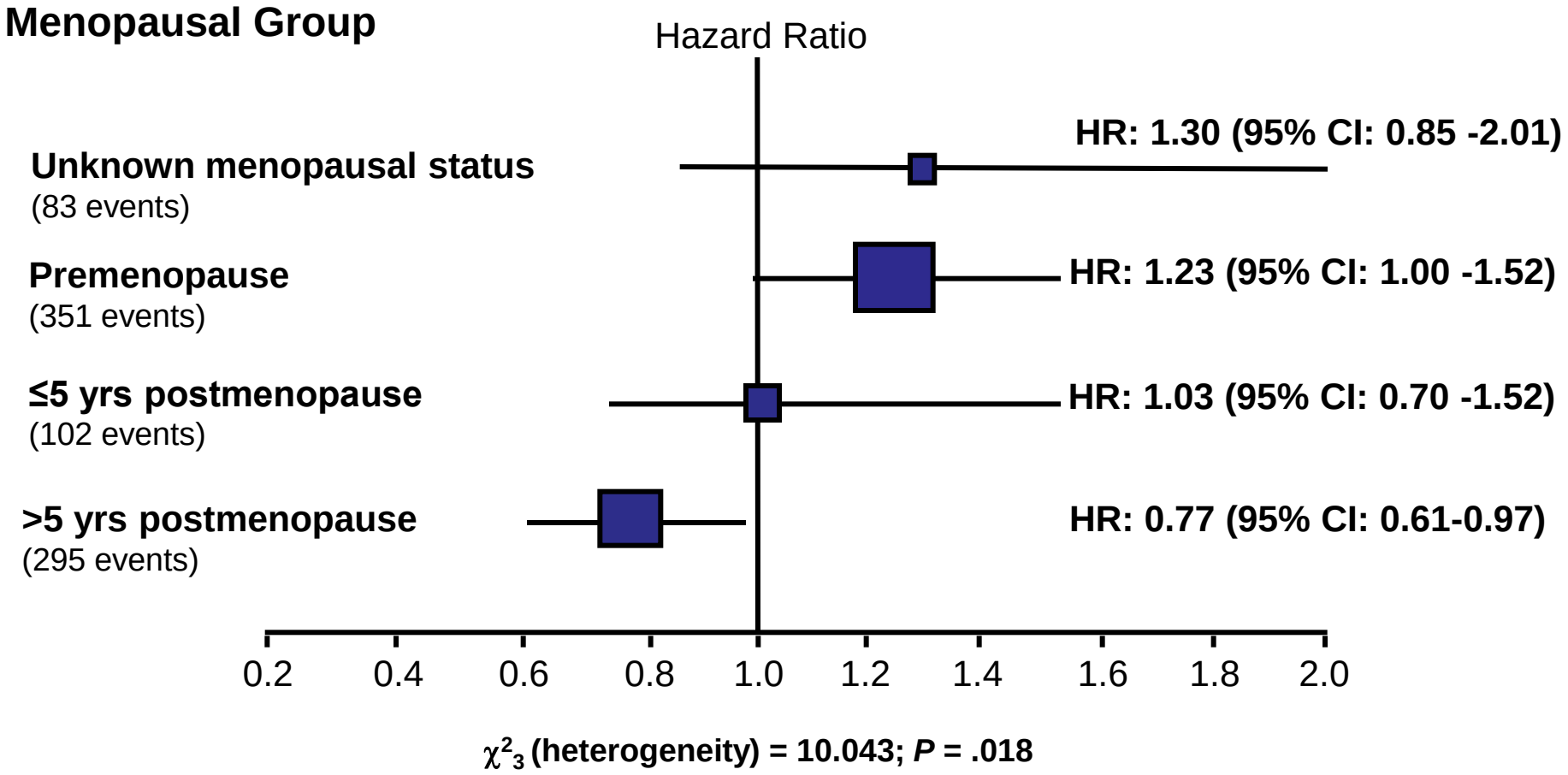
AZURE: Treatment Effects on Bone Metastasis as First IDFS Event by Menopausal Status



Adjusted for imbalances in ER, lymph node status, T stage and neo-adjuvant therapy.

No differences in effects on bone IDFS events by menopausal status

Impact of Menopausal Status on First IDFS Event Outside Bone



Adjusted for imbalances in ER, lymph node status, T stage and neo-adjuvant therapy.

Significant differences in extraskeletal IDFS events by menopausal status

Coleman et al Eur J Cancer 2013;49(3)LBA9,S5

Consistent Beneficial Effects in Postmenopausal Breast Cancer

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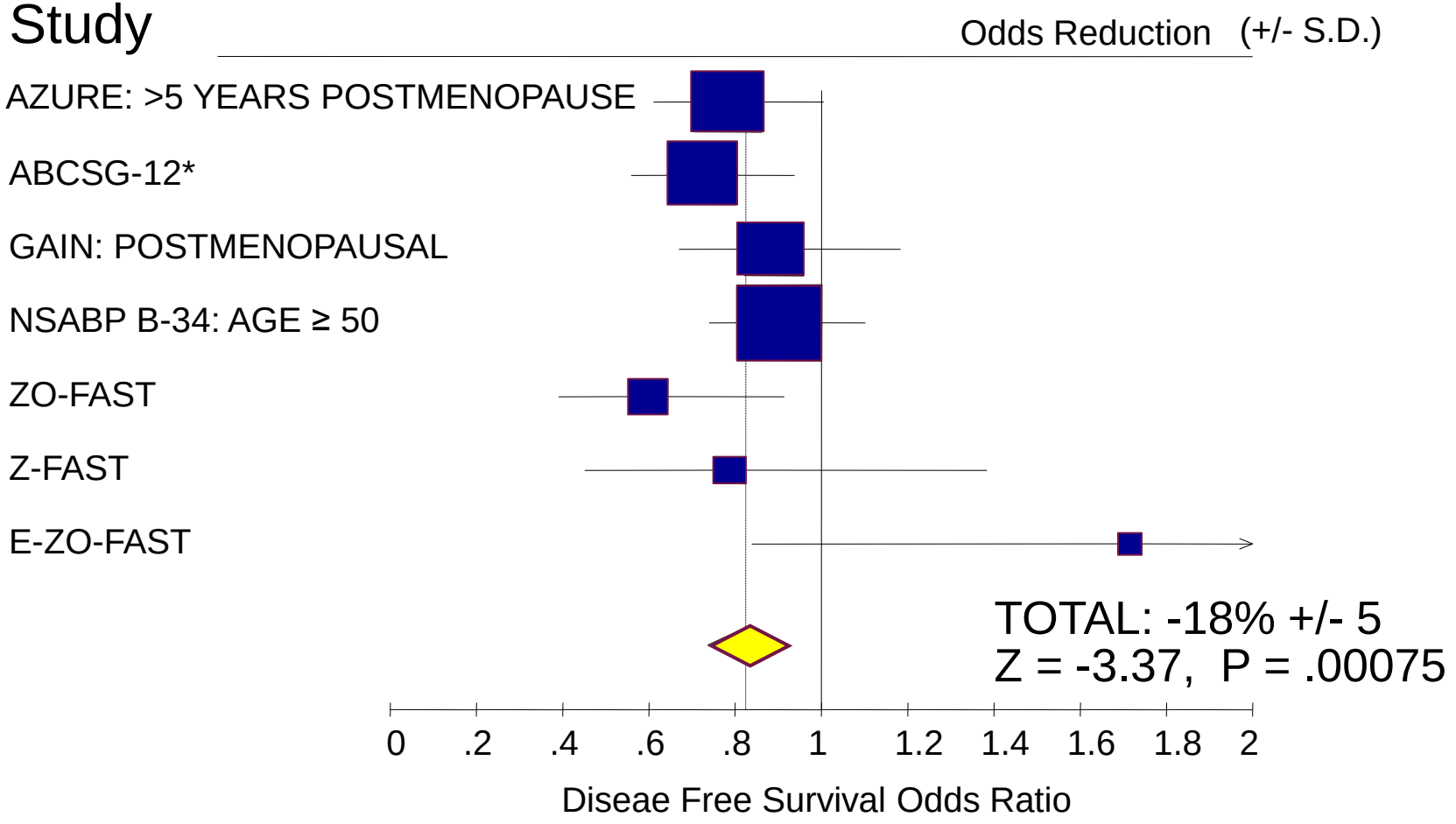


X^2_6(heterogeneity) = 8.46 P = .21

*** Induced menopause**

Gregory W. et al. ASCO 2012, Abs 513.

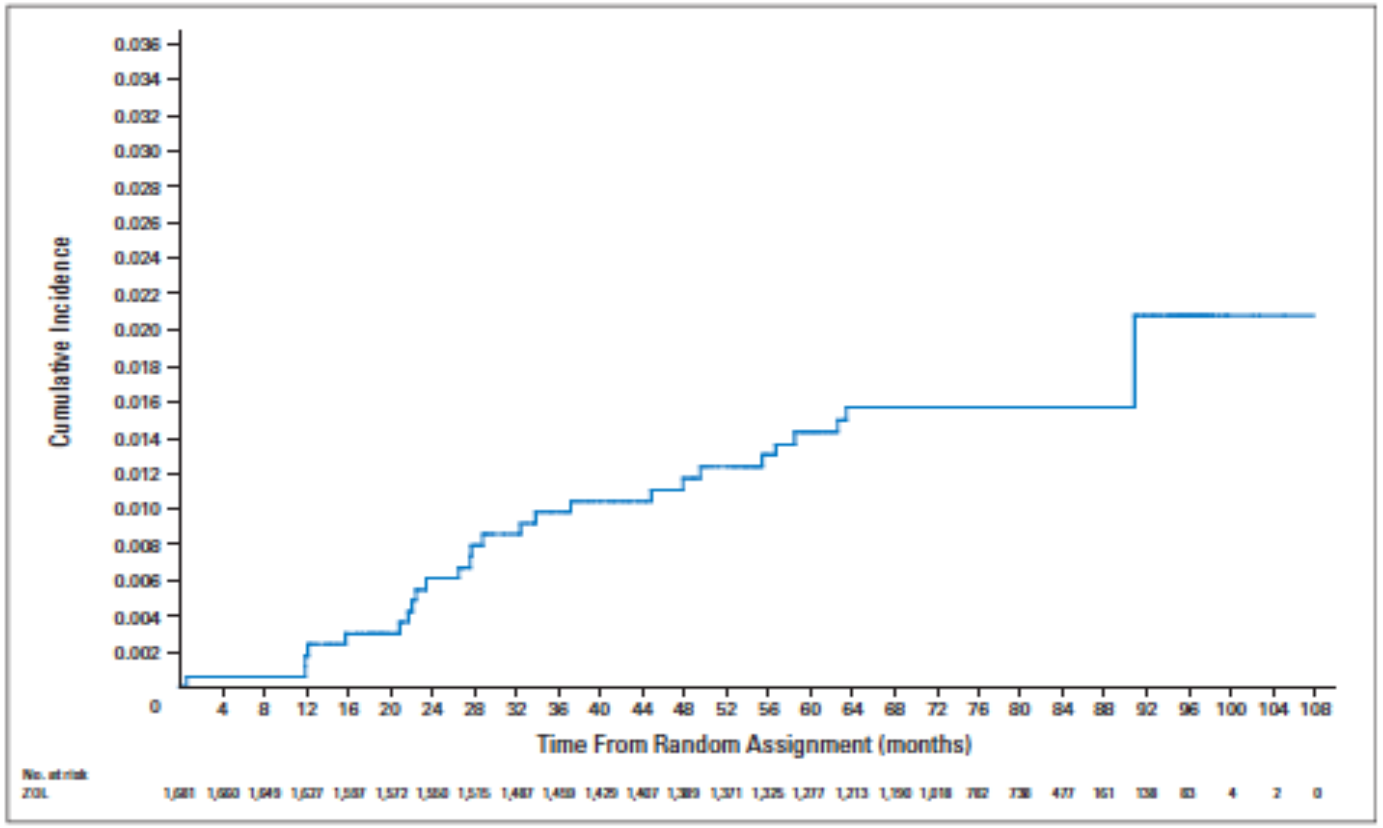
Achieving Meaningful Benefit

The University Of Sheffield.

Intervention	Comparator	Study population	5 year risk reduction
Adjuvant tamoxifen	Nil	ER+	39%
Aromatase inhibitors	Tamoxifen	ER+ Postmen	24%
Adjuvant CMF	Nil	“Most”	14%
Adjuvant anthracyclines	CMF	“Most”	17%
Adjuvant taxanes	Anthracyclines	All “high risk”	16%
Trastuzumab	Nil	Her2+	35%
Bisphosphonates	Nil	Postmen	18%

ONJ is Uncommon in the Adjuvant Setting

Cumulative incidence rate at 7 years = 2.1% (95%CI 0.9%-3.3%)
>50% resolved



Rathbone E et al J Clin Oncol 2013; 31:2685-2692

Oral Health Related QOL is Unaffected by Zoledronic Acid

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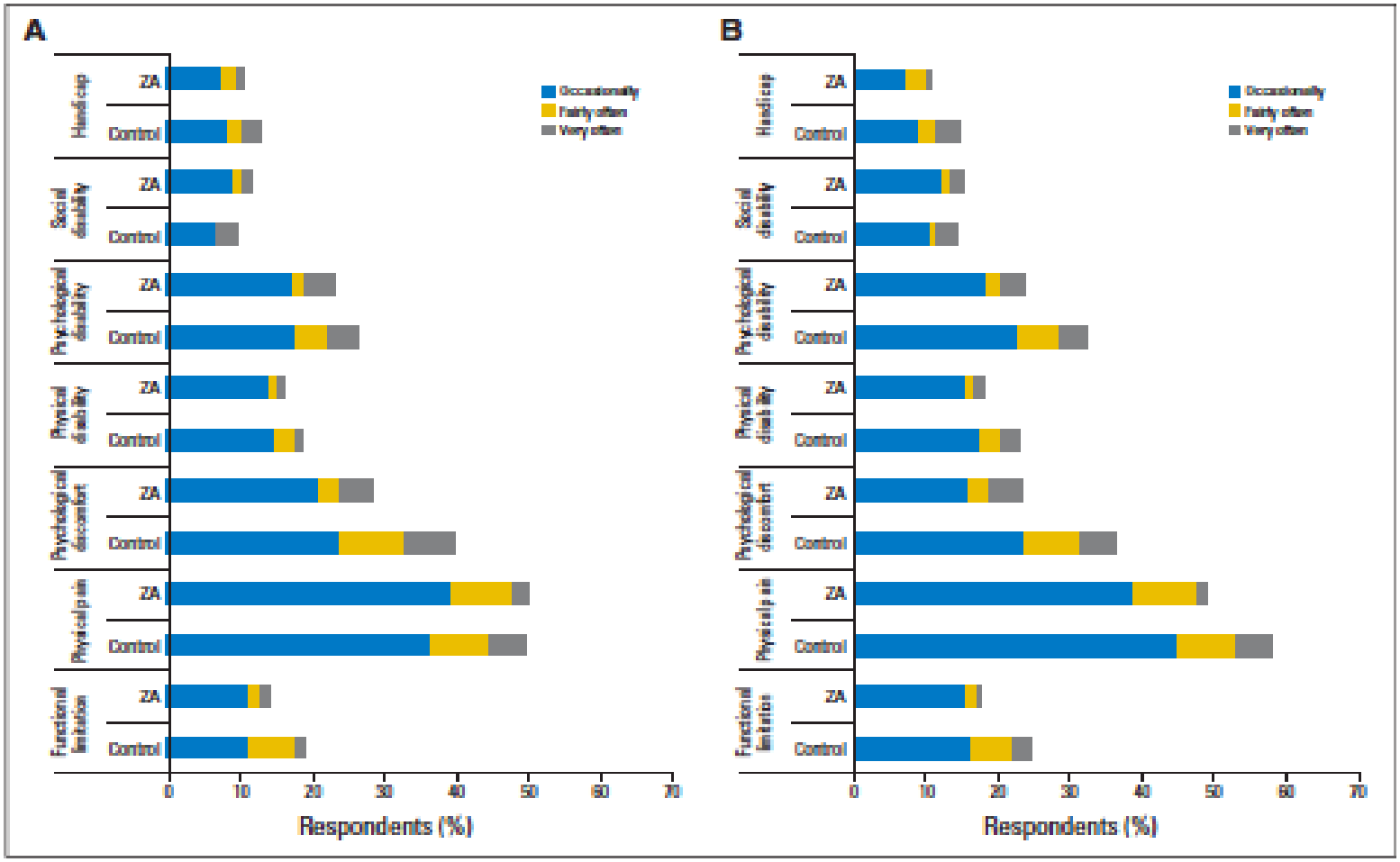
Oral HR-QOL in Last month

Oral HR-QOL Over 5 Years



Rathbone E et al J Clin Oncol 2013; 31:2685-2692

Cost-Effectiveness

The University Of Sheffield.

- Drug costs
  - Zoledronic acid - £4 - £30 for 4mg
- Clinical review and administration costs
  - Day case cost - Around £120
- Monitoring costs
  - Renal function £5

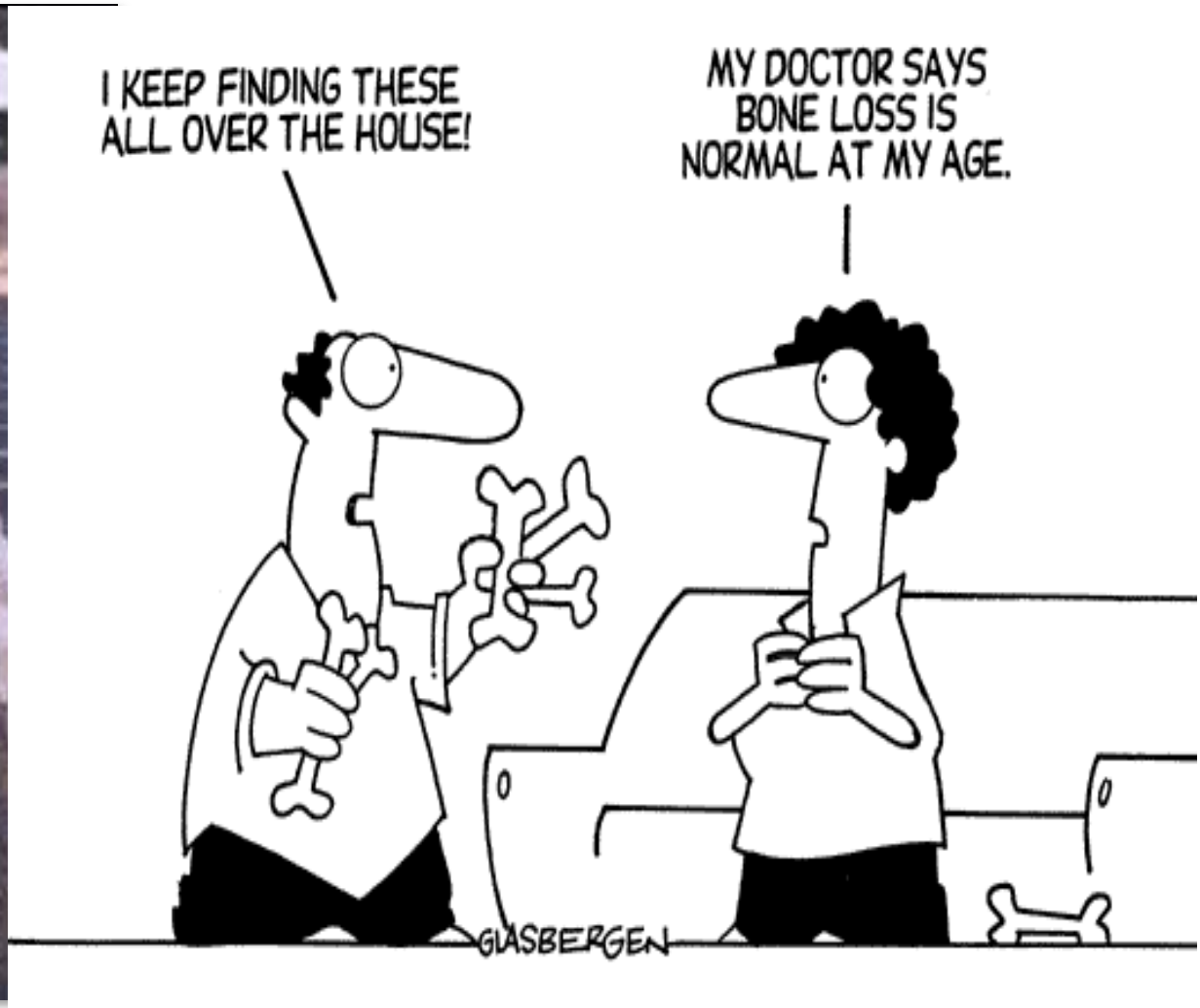
7-19 treatments = £910 - £2850

Today's Bonus Ball!

The University Of Sheffield.

Preservation of Normal Bone Health

The University Of Sheffield.



Requirements For a New Treatment in Early Breast Cancer

The University Of Sheffield.

- Biologically plausible ✓
- Multiple supportive clinical trials ✓
- Meaningful benefit ✓
- Compatible with current standard treatment ✓
- Well tolerated ✓
- Cost effective ✓
- (Regulatory approval)

Don’t Ignore the Evidence?

The Answer Must Be “YES!”