

Breast Cancer Bone Metastases: Treatment Options

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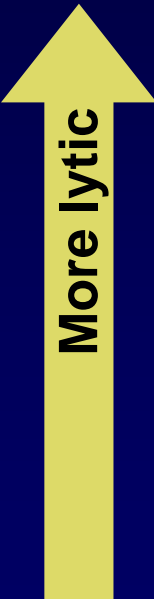
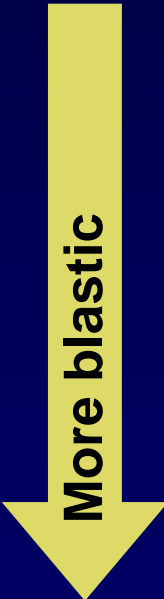
Case Summary

- 67-year-old postmenopausal women, highly hormone-responsive breast cancer, T3N1
- Neoadjuvant HT with letrozole for 6 months → a partial response in right breast
- SURGERY: Breast conserving surgery and axillary dissection
- PATHOLOGY: Highly hormone receptor–positive residual tumor of 2.8 cm, HER2 negative, 2/20 lymph nodes positive
- ADJUVANT THERAPY: Continued letrozole
- IRRADIATION to right breast
- COURSE OF DISEASE: She did fine for 3 years when she developed pain in lumbar spine (VAS 7/10). Bone scintigraphy shows hot spots in thoracolumbar spine and in right pelvis, additional imaging confirms bone metastases only. Her laboratory tests are all normal however creatinine is at upper normal level.
- TREATMENT PLAN: Tamoxifen, irradiation to lumbar spine, and bone targeted agent

Why Bone Targeted Therapy?

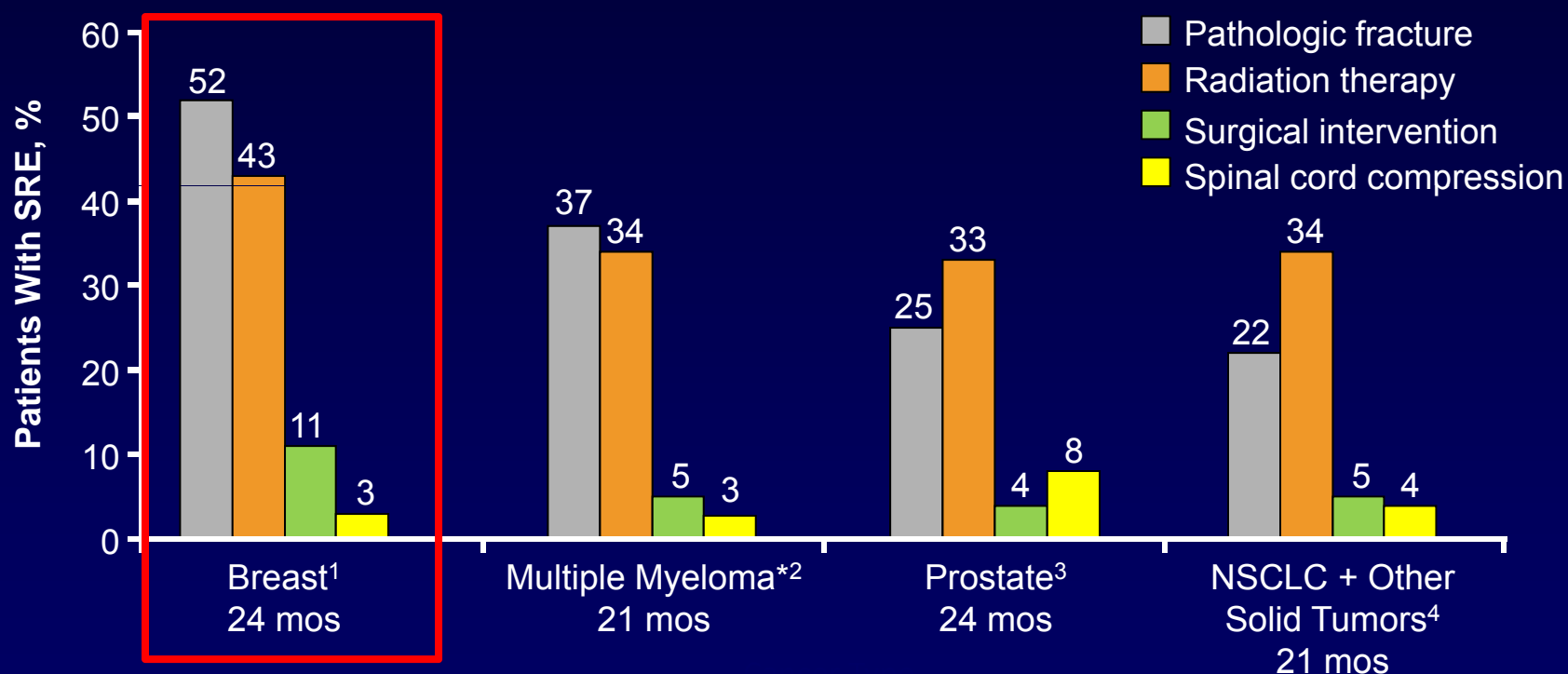
Cancer Bone Disease Is Prevalent

	5-Yr World Prevalence, Thousands ¹	Incidence of Bone Metastases in Cancers, % ²	Median Survival, Months ²⁻⁴
Myeloma	144	70-95	6-54
Renal	480	20-25	12
Melanoma	533	14-45	6
Bladder	1000	40	6-9
Thyroid	475	60	48
Lung	1394	30-40	6-7
Breast	3860	65-75	19-25
Prostate	1555	65-75	12-53


More lytic

More blastic

1. Ferlay J, et al. IARC Globocan 2000. Cancer incidence, mortality, and prevalence, version 1.0. IARC Cancer Base No. 5. Lyon: IARC, 2001. 2. Coleman RE. *Cancer Treat Rev.* 2001;27(3):165-176. 3. Coleman RE. *Cancer.* 1997;80(8 Suppl):1588-1594. 4. Zekri J, et al. *Int J Oncol.* 2001;19(2):379-382.

Skeletal Complications in Large, Randomized Trials: Placebo Arms



*21-month data except for surgical intervention and spinal cord compression, for which only 9-month data are available.

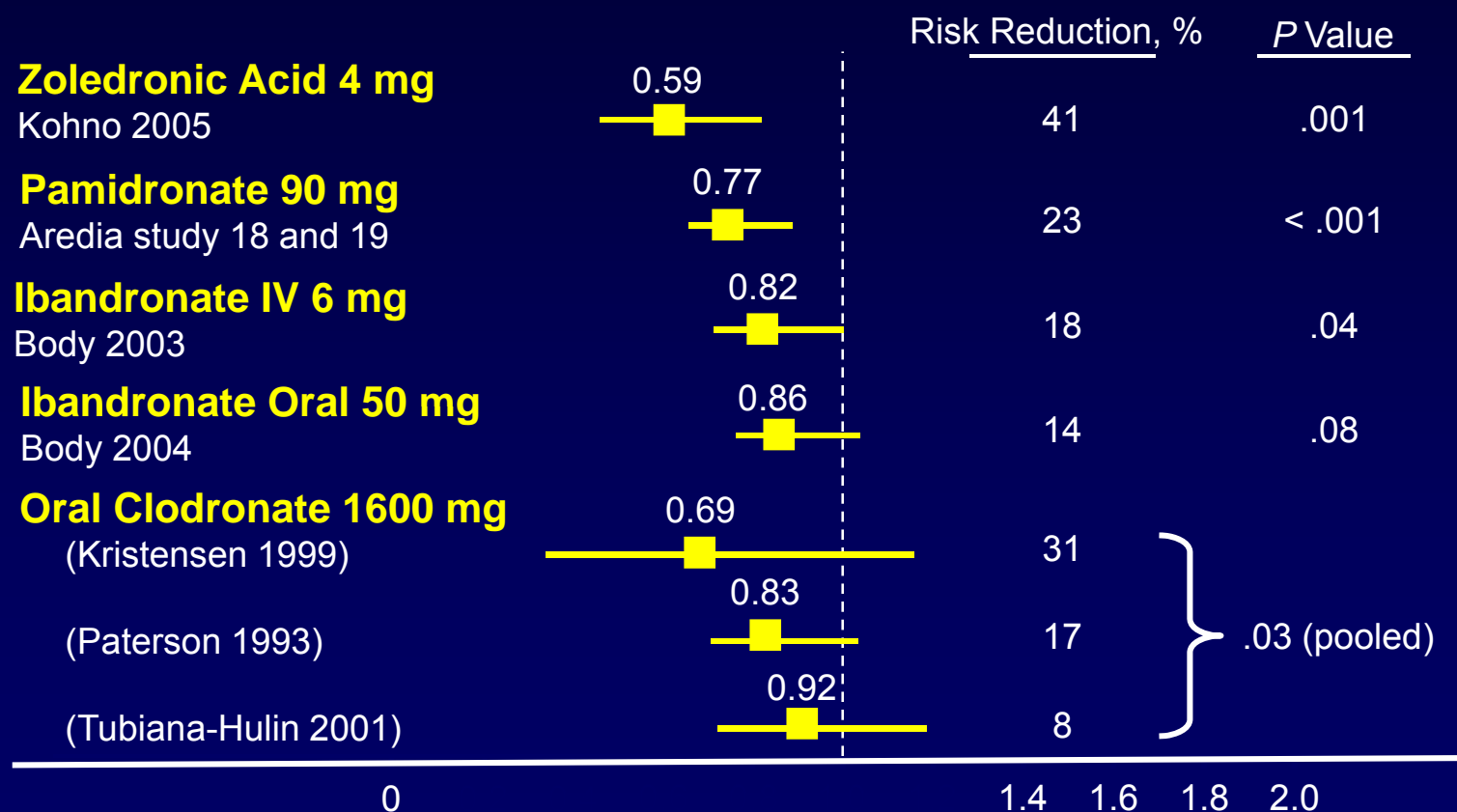
1. Lipton A, et al. *Cancer*. 2000;88(5):1082-1090. 2. Berenson JR, et al. *J Clin Oncol*. 1998;16(2):593-602. 3. Saad F, et al. Presented at the 2003 Annual Meeting of the American Urological Association; April 26 – May 1, 2003: Chicago, Illinois. Abstract 1472. 4. Rosen LS, et al. *Cancer*. 2004;100:2613-2621.

Which Bone Targeted Therapy?

Bisphosphonates

- All bisphosphonates decrease skeletal complications (compared to no treatment)
- Zoledronic acid is better than pamidronate (24-month trial)¹
- Oral ibandronic acid is equal to zoledronic acid (3-month trial with osteolysis markers)²

Bisphosphonates vs Placebo Meta-Analysis Skeletal Related Events (SRE) Risk Reduction in Breast Cancer

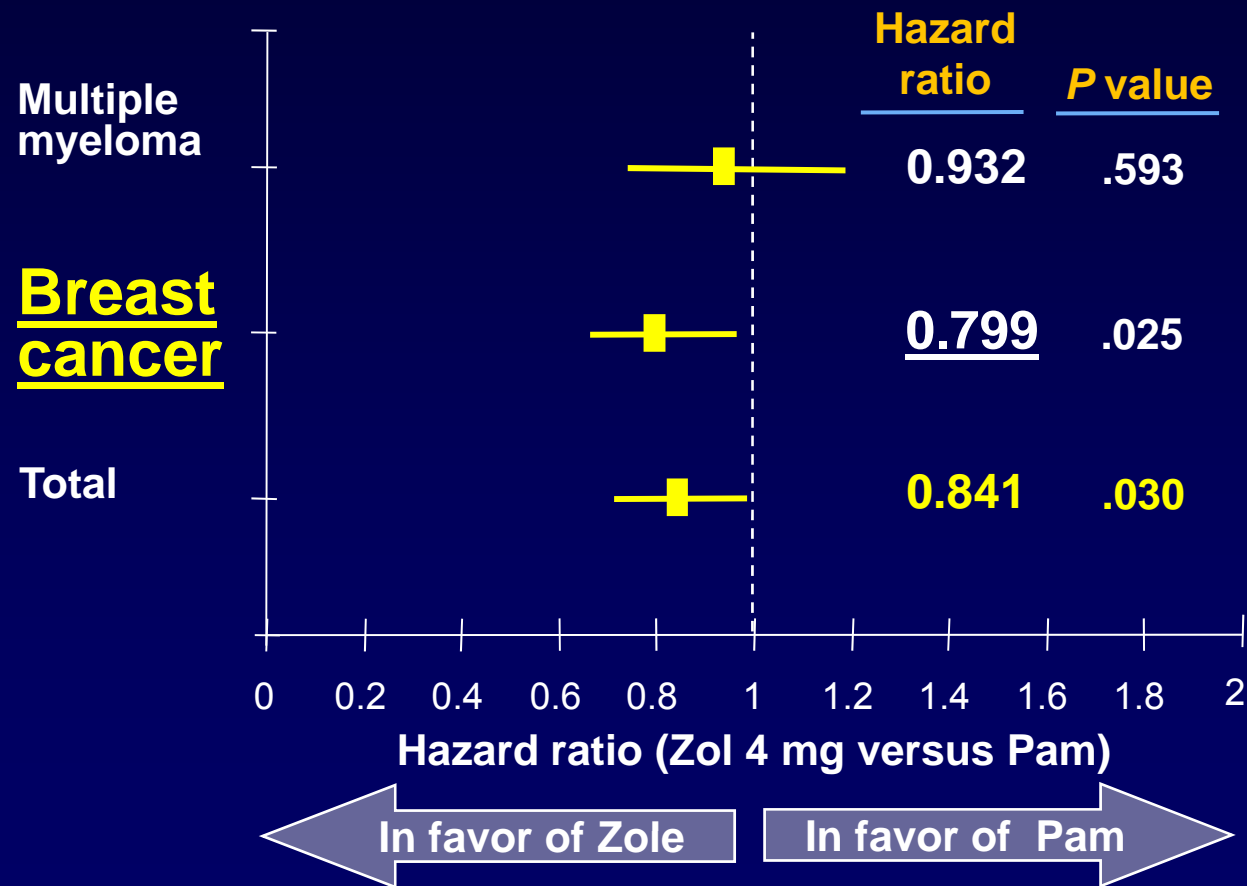


Cochrane database comparing placebo-controlled trials in breast cancer setting.

Adapted from Pavlakis N, et al. *Cochrane Database Syst Rev.* 2005:CD003474.

Zoledronic Acid Is Better than Pamidronate

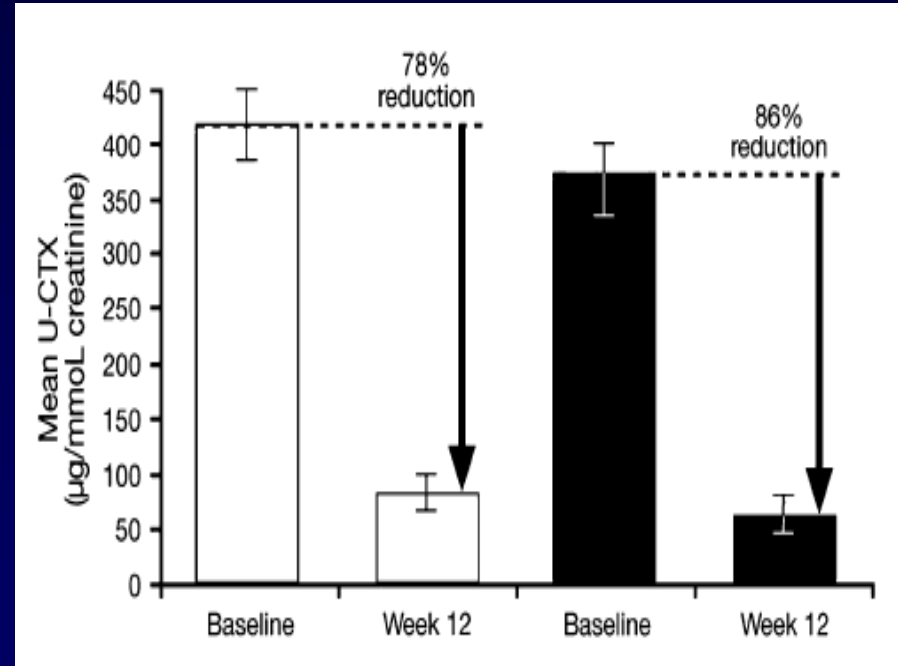
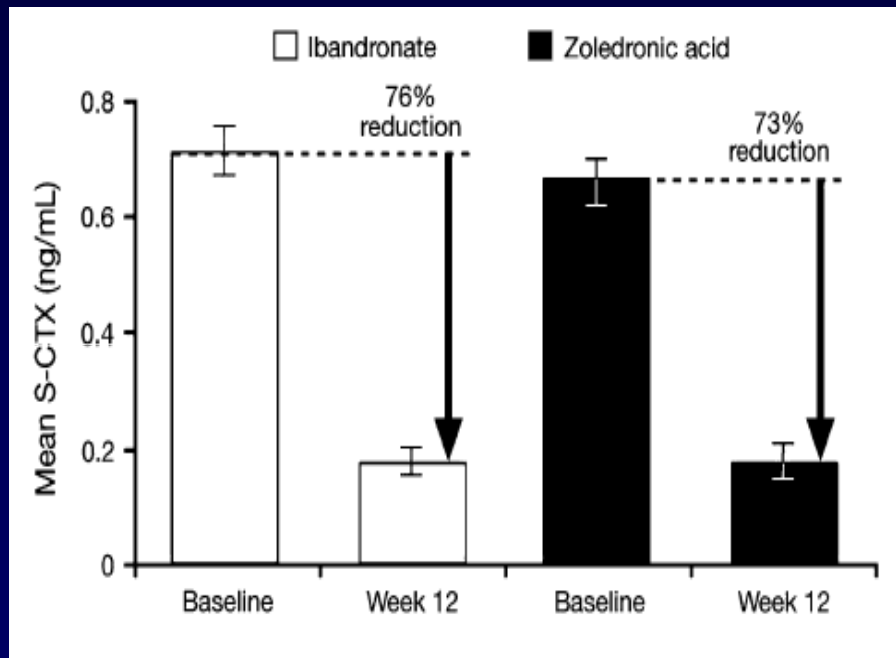
Zoledronic acid 4 mg significantly decreases the risk of developing a skeletal complication (16% reduction) compared to pamidronate



*Hypercalcemia of malignancy is included as an SRE.

Rosen LS, et al. *Cancer*. 2003;98(8):1735-1744.

Oral Ibandronate Is as Active as Intravenous Zoledronic Acid for Reducing Bone Turnover Markers in Women With Breast Cancer and Bone Metastases



Why Oral Ibandronic Acid?

- **Oral formulation**
 - Patients with nonaggressive course of metastatic breast cancer, eg, patient with bone metastases receiving oral hormonal therapy
- **No renal toxicity**
 - An option for patients with renal comorbidity

Ongoing Comparative Trials of Bisphosphonates in Metastatic Breast Cancer

SWOG S0308-USA

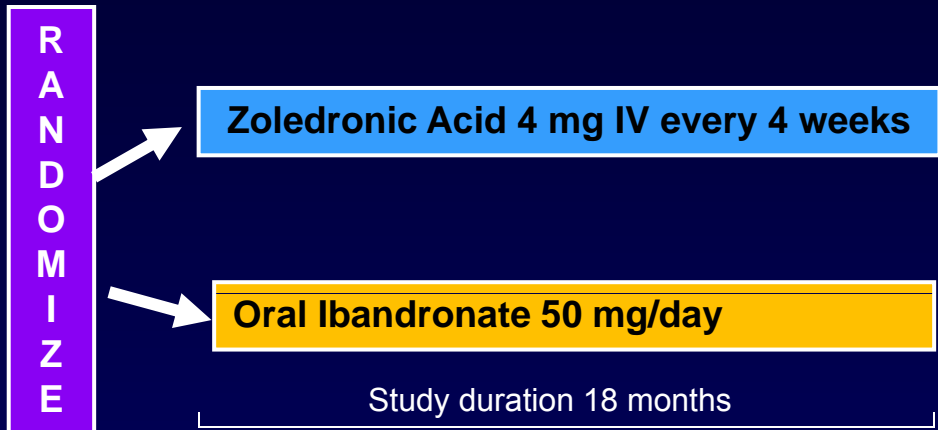
N = 488

Primary endpoint:

- New skeletal related event-SRE

Secondary endpoints:

- Time to first SRE
- Quality of life



ZICE Trial-UK

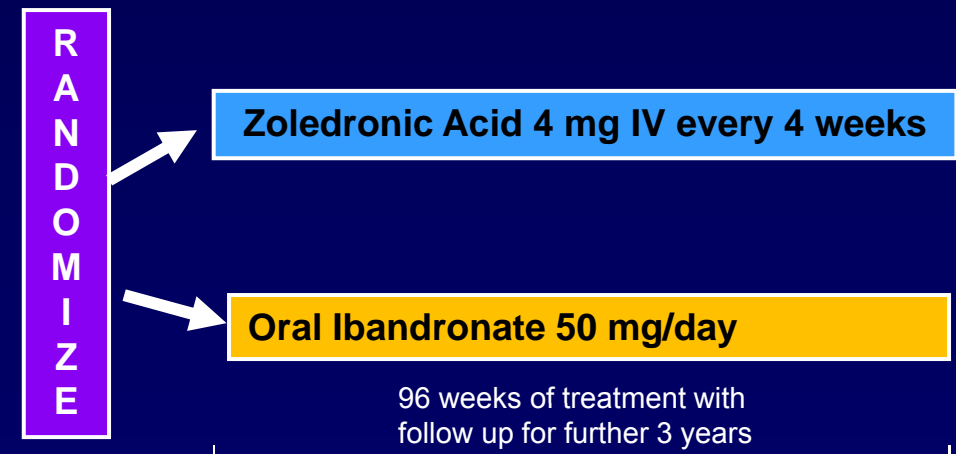
N = 1400

Primary endpoint:

- Multiple event analysis-SREs

Secondary endpoints:

- Proportion of patients experiencing new SRE
- Time to first event



Role of Biochemical Markers of Bone Resorption

- Up to now under investigations

But

- Number of trials with zoledronic acid, ibandronic acid, denosumab had as efficacy criteria suppression of markers of bone resorption¹⁻³

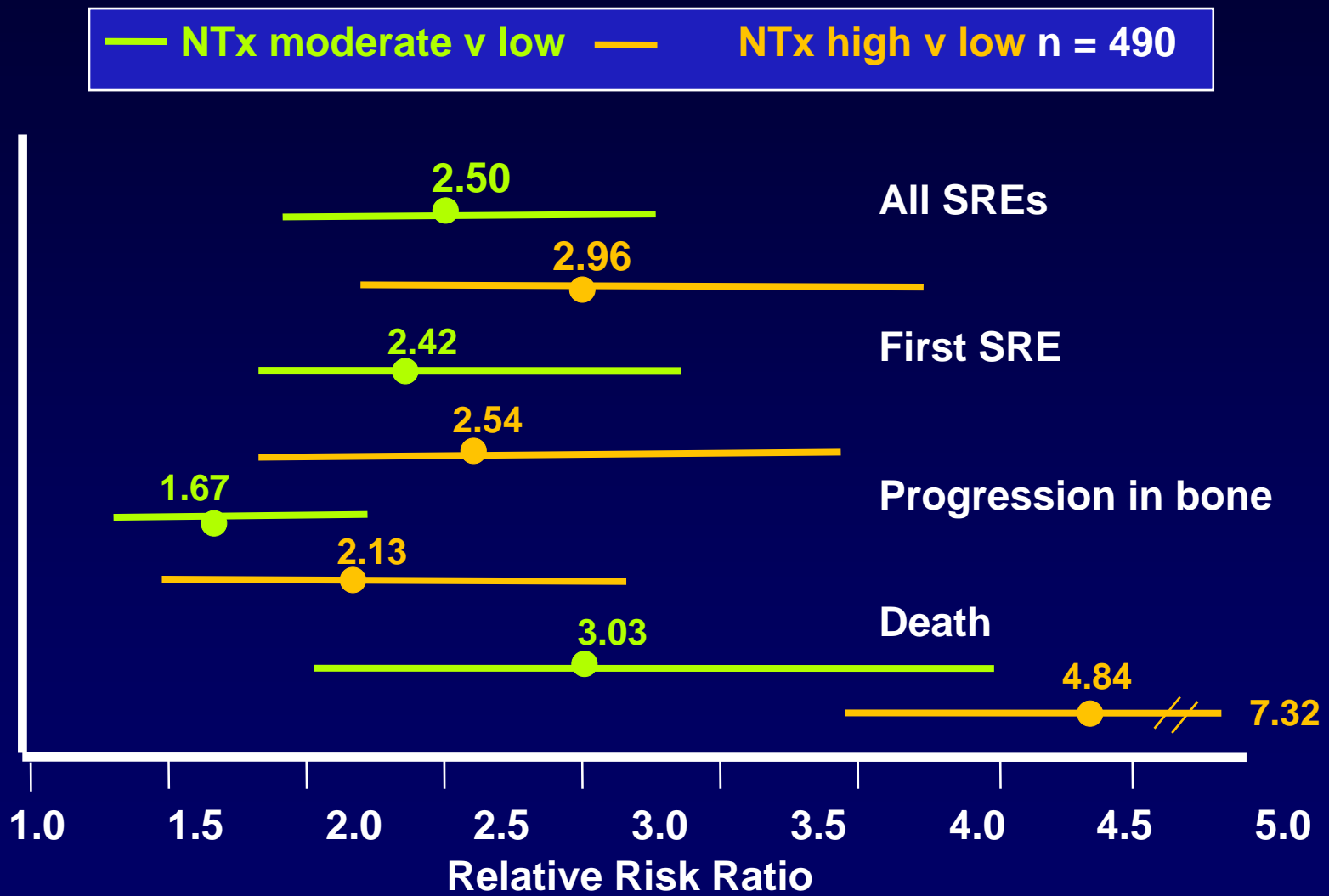
1. Body JJ, et al. *Ann Oncol*. 2007;18(7):1165-1171. 2. Lipton A, et al. *Clin Cancer Res*. 2008;14(20):6690-6696.
3. Fizazi K, et al. *J Clin Oncol*. 2009;27(10):1564-1571.

Analysis of Urinary NTx in Breast Cancer

Normal at baseline and normalized at 3 months level of uNTx predict

- Lower rate of skeletal complications**
- Lower rate of bone metastases progression**
- Increasing of overall survival**

Analysis of Urinary NTx in Patients with Breast Cancer

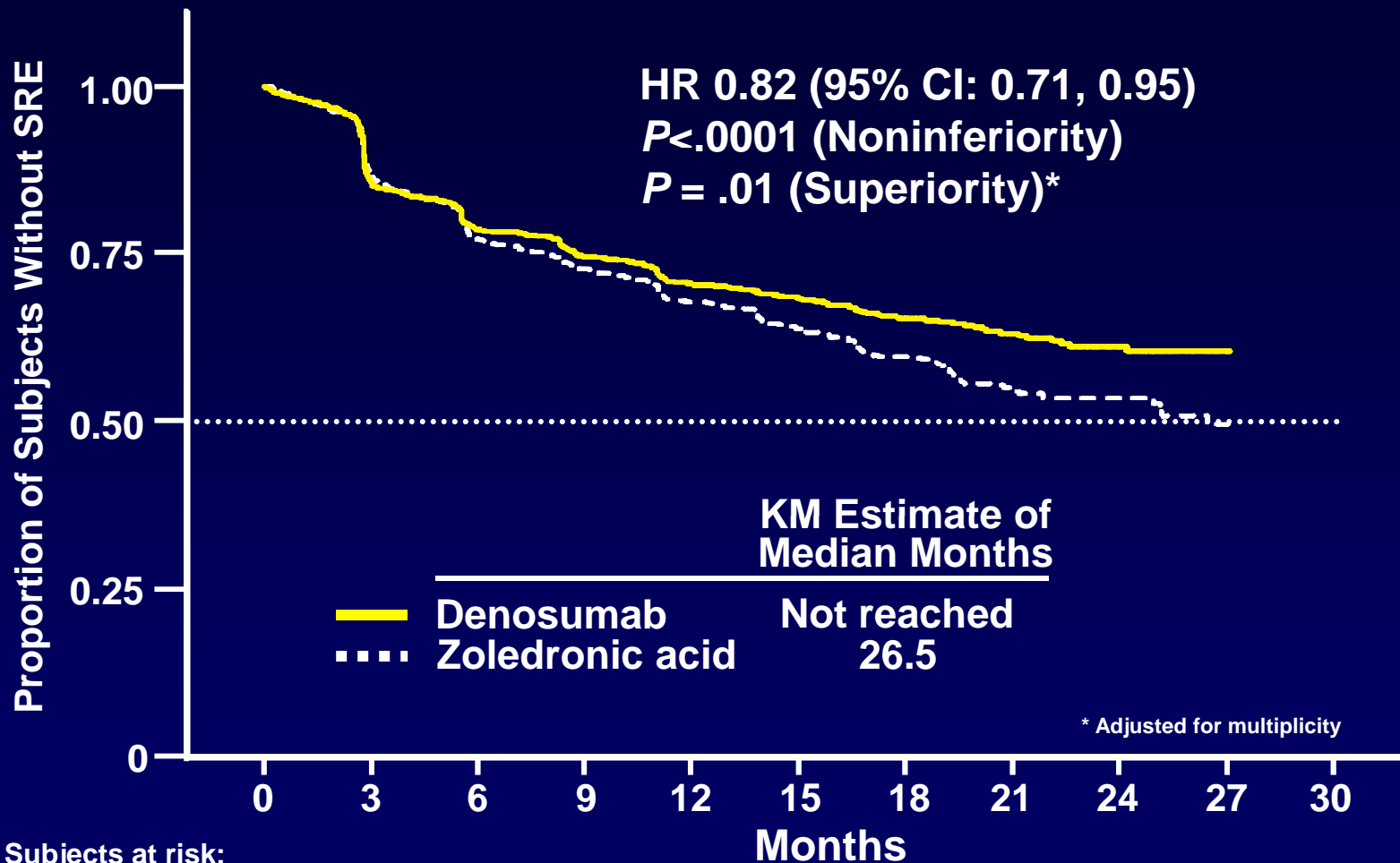


Denosumab: Promising New Bone Targeted Agent

- Human monoclonal antibody
- High affinity & specificity → RANK ligand
- No neutralising antibodies detected in clinical trials
- Delivered subcutaneously



Denosumab vs Zoledronic Acid Phase III Study—Time to First On-Study SRE



Subjects at risk:

	0	3	6	9	12	15	18	21	24	27	30
Zoledronic Acid	1020	829	676	584	498	427	296	191	94	29	
Denosumab	1026	839	697	602	514	437	306	189	99	26	

Stopeck A, et al. *Eur J Can Suppl.* 2009;7(2): Abstract 2LBA and oral presentation.

Stopeck A, et al. *Cancer Res.* 2009;69(24 Suppl): Abstract 22.

My Opinion

Ibandronic acid 50 mg/day, oral

Reason

Data of similar efficacy

Route of administration

Safety data

