


Updates in Survival in patients with Lung Cancer using Bisphosphonate Therapy


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Metastatic Bone Disease Is Prevalent

	5-year world prevalence, thousands ¹	Incidence of bone metastases in cancers ²	Median survival, months ²⁻³
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



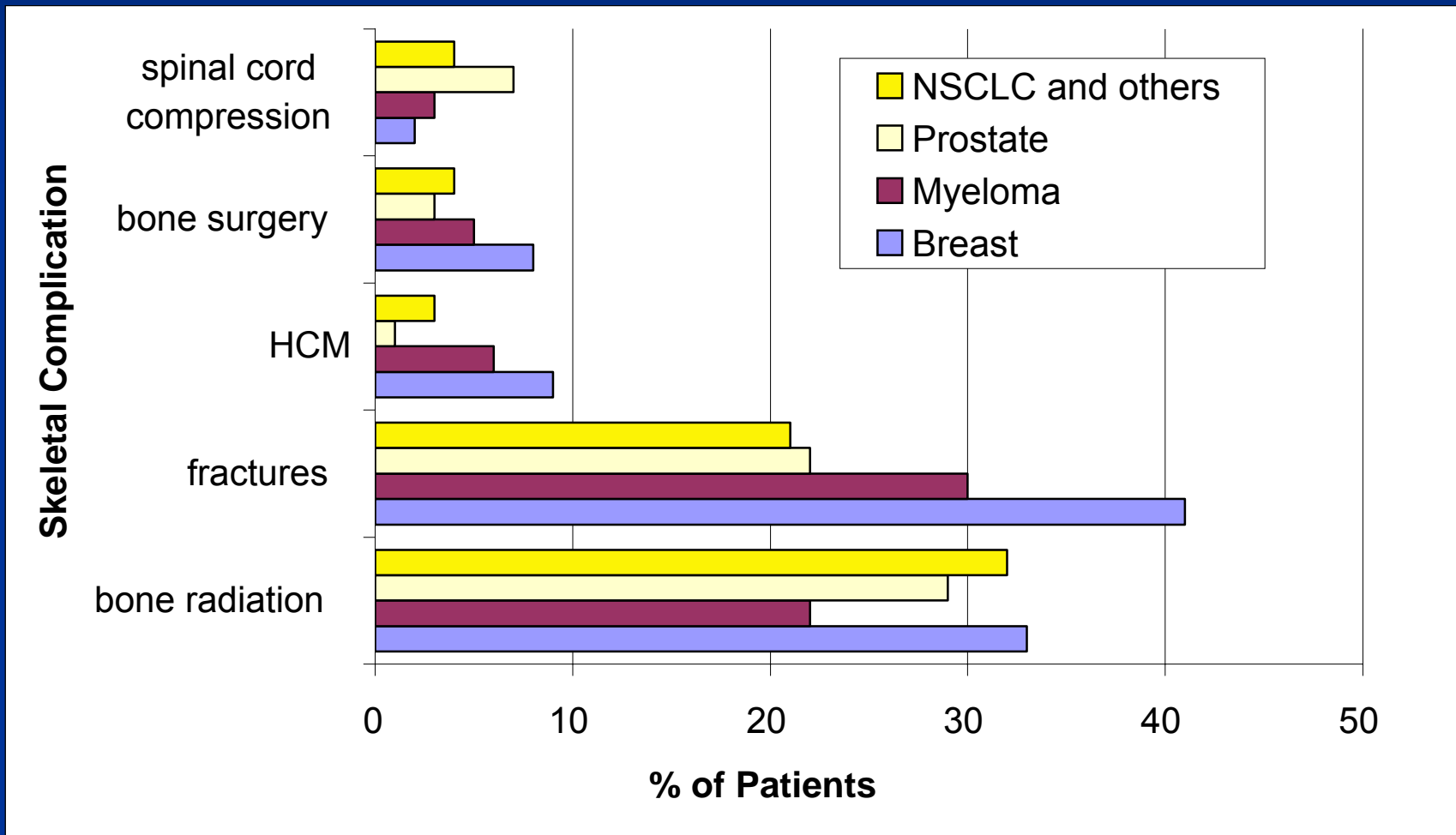


1. Ferlay J et al. IARC Globocon 2000. Cancer Incidence, Mortality, and Prevalence.

2. Coleman RE. *Cancer Treat Rev.* 2001;27:165-176.

3. Coleman RE. *Cancer.* 1997;80:1588-1594.

Frequency of Skeletal Complications in Metastatic Bone Disease



Annual incidence in the absence of bisphosphonates

Consequences of Bone Metastases

- Bone Pain
- Fractures
- Spinal Cord Compression
- Hypercalcemia
- Other Symptoms

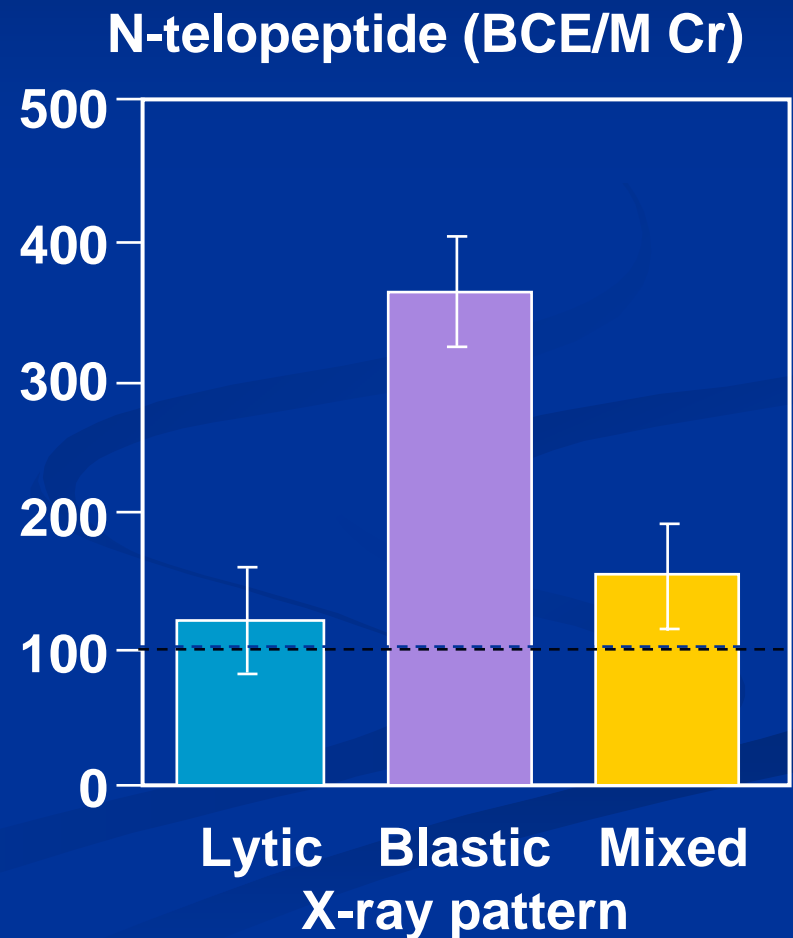
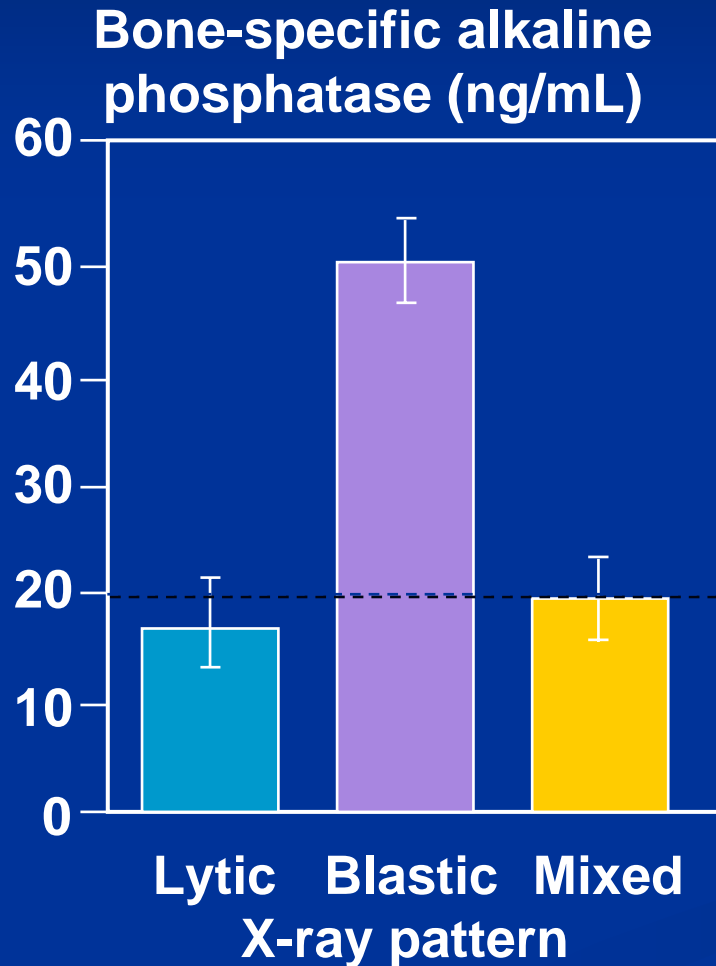
Hypercalcemia of Malignancy

- Most common metabolic complication of cancer
 - Frequency falling in breast cancer and myeloma
 - Incidence highest in squamous carcinomas
- Skeletal and renal components
 - Osteoclastic bone resorption
 - Bone metastases
 - PTHrP
 - Renal reabsorption of calcium
 - PTHrP
 - Renal impairment
 - Reduced GFR due to dehydration
 - Bence Jones protein deposition

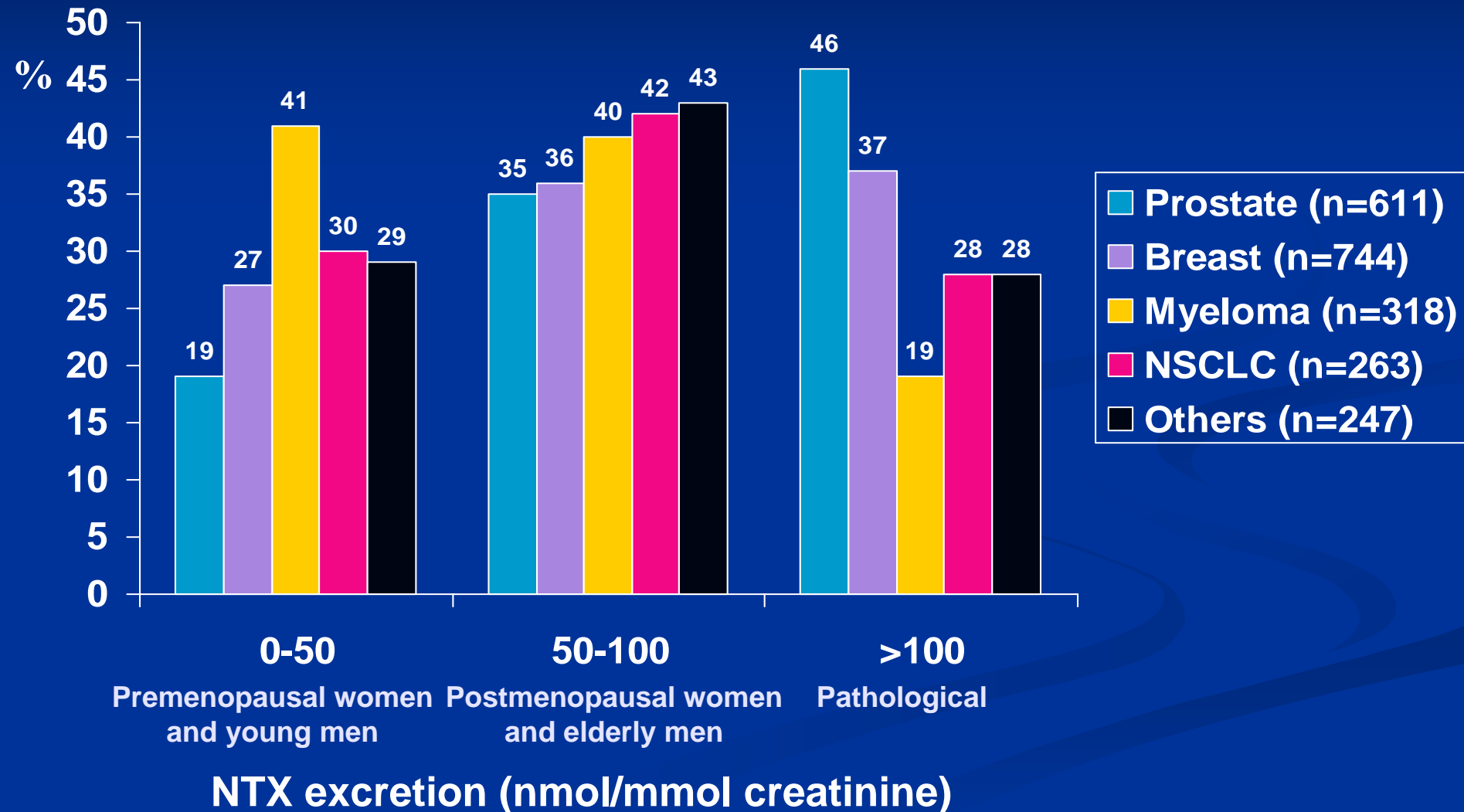
Markers for Assessing Bone Turnover

Bone Formation Markers	
Bone alkaline phosphatase (ALP)	Serum
Osteocalcin (OC)	Serum
Bone Resorption Markers	
C-telopeptides of type I collagen (CTX)	Urine
Deoxypyridinoline (D-Pyr)	Urine
N-telopeptides of type I collagen (NTx)	Urine
Pyridinoline (Pyr)	Urine

Bone Markers in Osteolytic and Osteosclerotic Disease



Bone Resorption Rates in Metastatic Bone Disease*



NTX excretion (nmol/mmol creatinine)

*Prior to bisphosphonate treatment

Influence of Accelerated Bone Resorption on Outcome in Solid Tumors, Including Lung Cancer (n=238)

NTX > 100 v < 100 nmol/mmol creatinine	Relative Risk*	95% CI	P value
All SREs	3.25	2.26 - 4.68	<.001
First SRE	3.05	1.96 - 4.72	<.001
Prog Disease	2.02	1.48 - 2.74	<.001
Death	4.59	2.82 - 7.46	<.001

Treatment Strategies

- Radiotherapy and/or radionuclides
- NSAIDS and opioids
- Bisphosphonates

Bisphosphonates for Bone Metastases

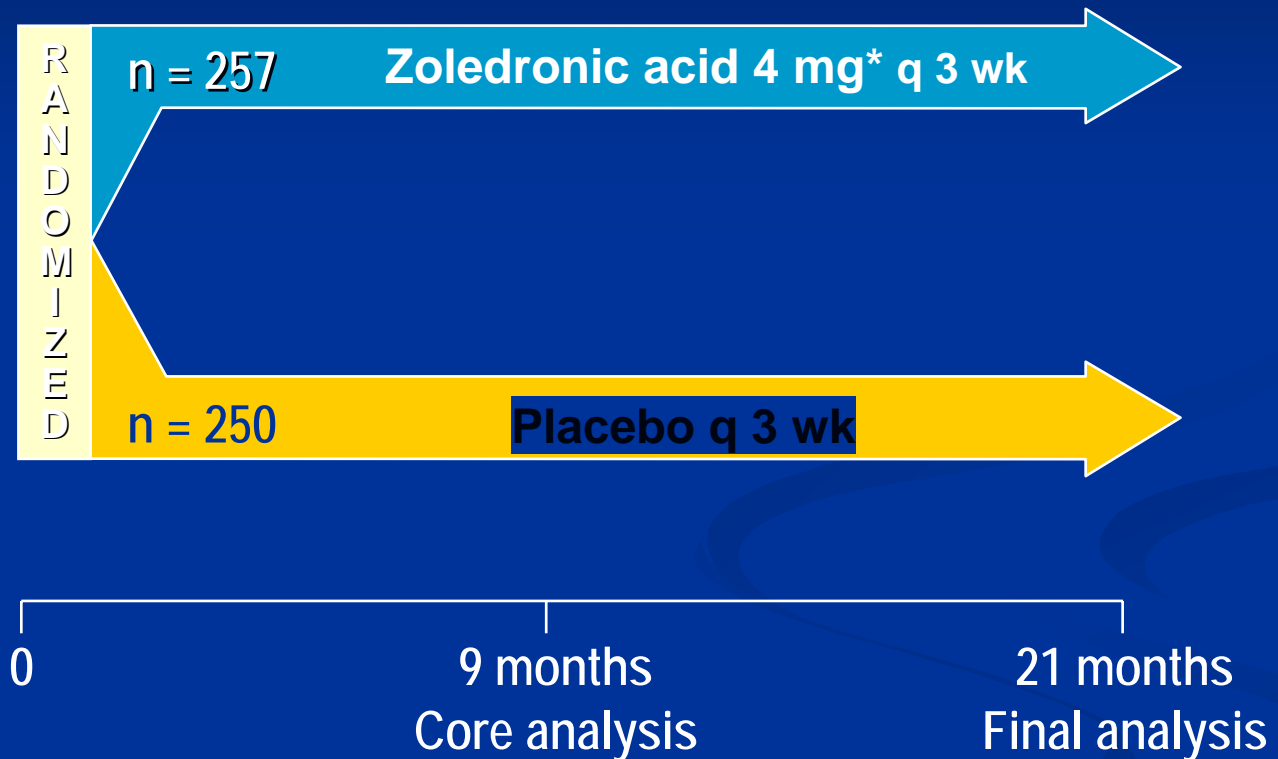
- Inhibit **osteoclast** function & bone resorption
- **Nitrogen**-containing BP have anti-cancer affects
(*Cancer Treatment Reviews* 31:S1, 2005)

Relative In Vivo Potencies

Etidronate (Didronel)	1	1st generation
Pamidronate (Aredia)	100 *	
Alendronate (Fosamax)	1000*	} 2nd generation
Ibandronate (Boniva)	10,000*	
Zoledronic acid (Zometa)	100,000	} 3rd generation
*Nitrogen-containing BP	<i>(J Bone Miner Res</i> 9:745, 1994)	

- Oral bioavailability low & **excreted renally**
(eg, 23 to 55% of zoledronate excreted unchanged within 24 hr)
- Zoledronic acid (4 mg) reduces the inc. **of SRE by 31%** (HR 0.693, $P = .003$) in NSCLS (*Cancer*. 2004;100:2613.)

Effect of Zoledronic Acid on Solid Tumors Trial Design



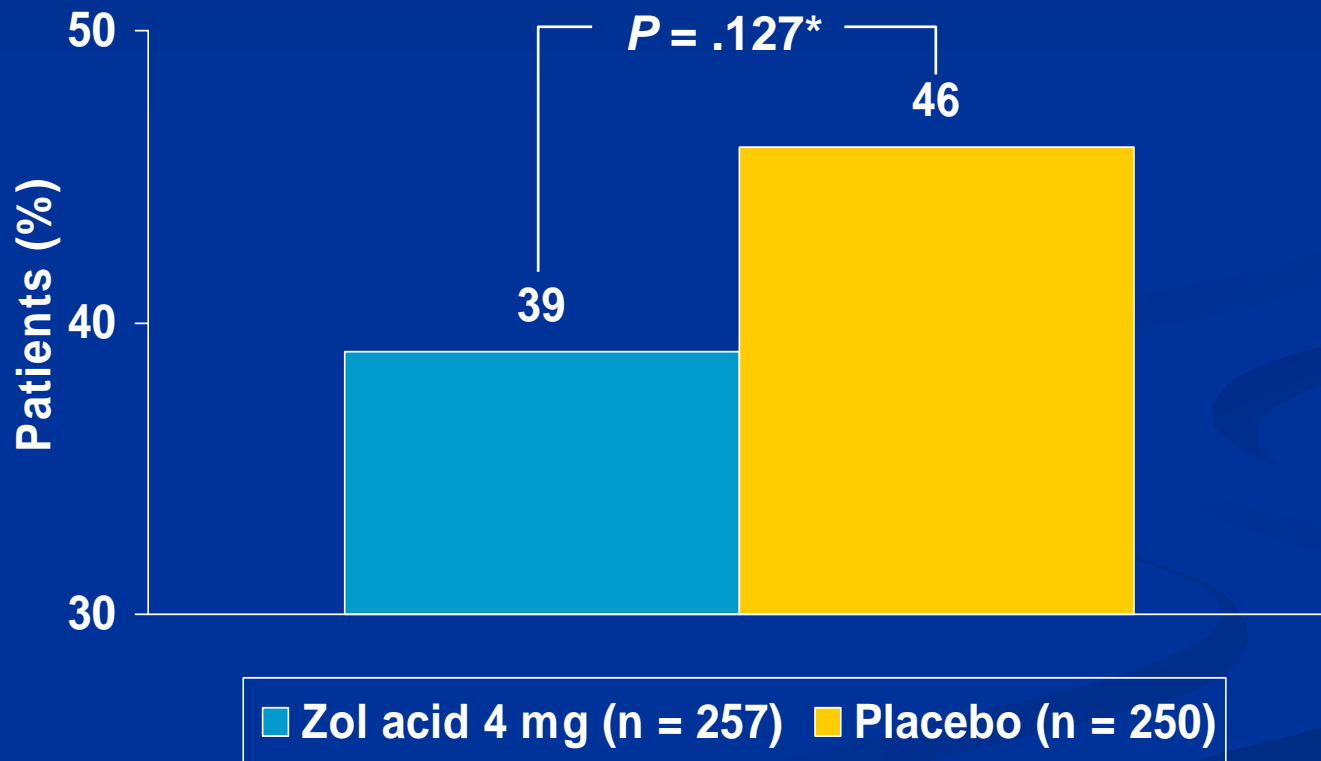
Stratification based on NSCLC versus other solid tumors

***266 patients were randomized to receive zoledronic acid 8 mg and then reduced to 4 mg; no efficacy conclusions drawn from 8/4 mg group**

Solid Tumors

Percentage of Patients With an SRE

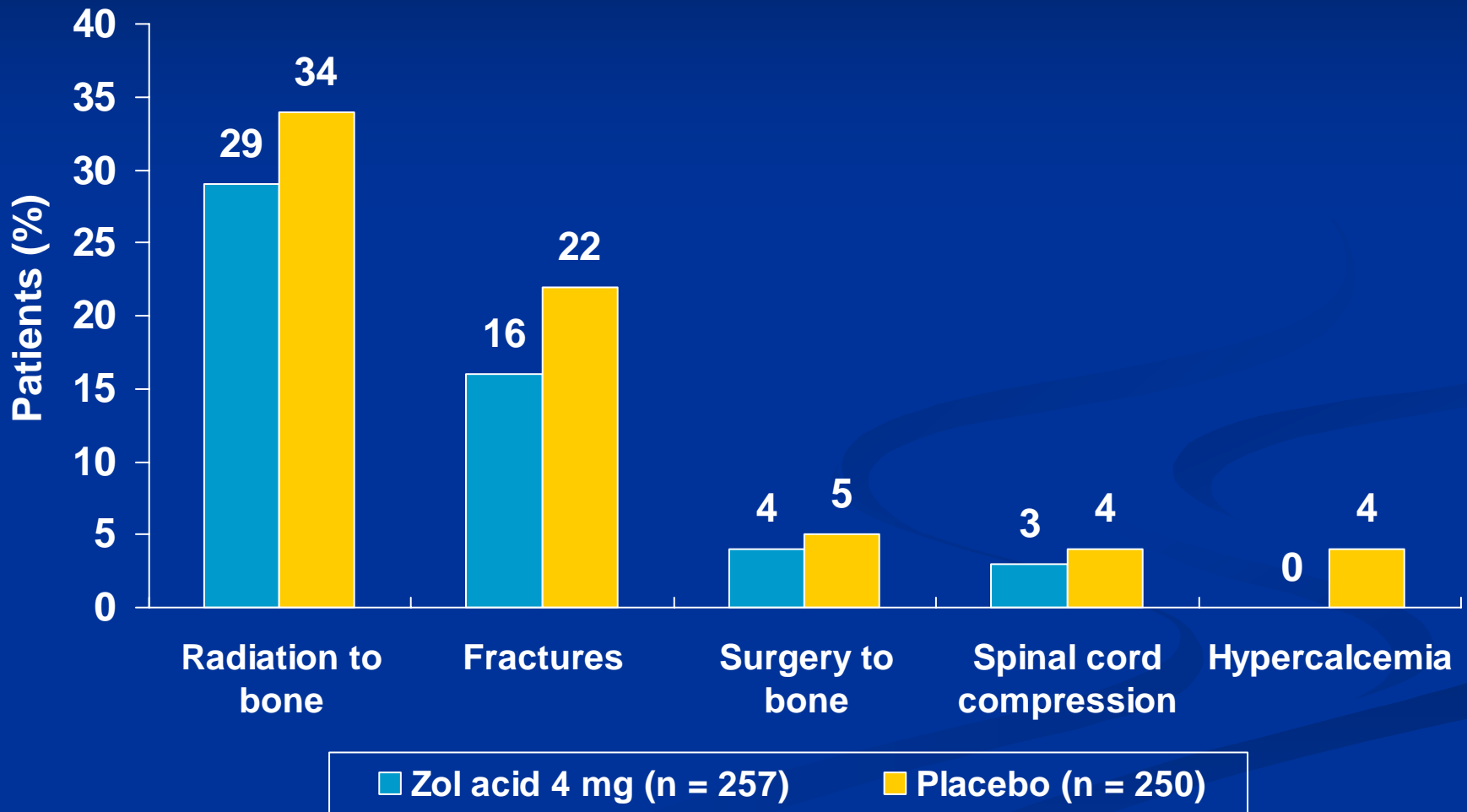
Substantially fewer patients experienced an SRE with treatment



* + HCM $P < .05$ for zoledronic acid 4 mg.

Solid Tumors

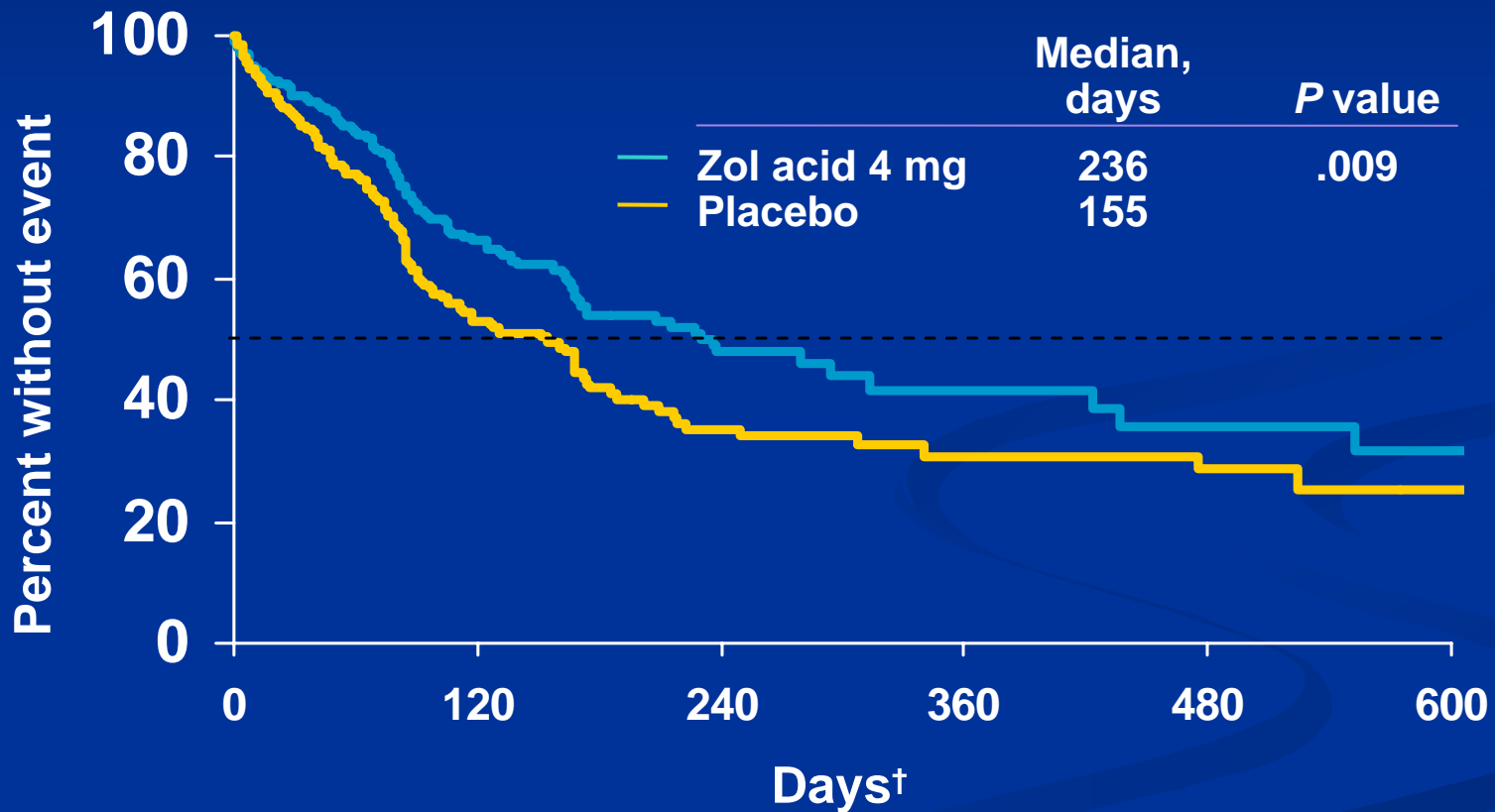
Percentage of Patients With Each SRE



Solid Tumors

Time to First SRE

Zoledronic acid delays the onset of skeletal complications by >2 months



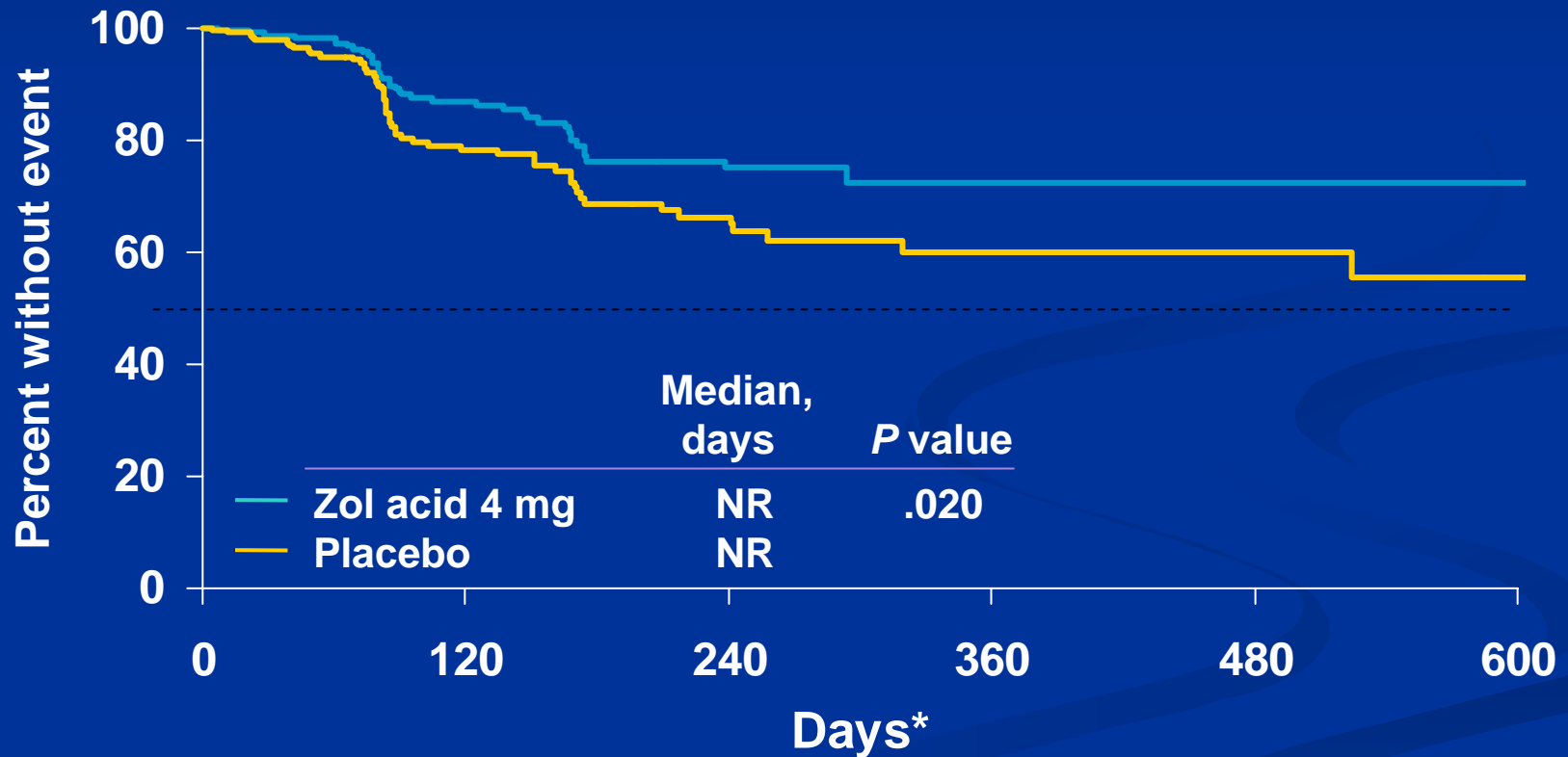
*Hypercalcemia of malignancy is included as a skeletal-related event.

†After start of study drug.

Solid Tumors

Time to First Pathologic Fracture

Zoledronic acid significantly delays the onset of fractures

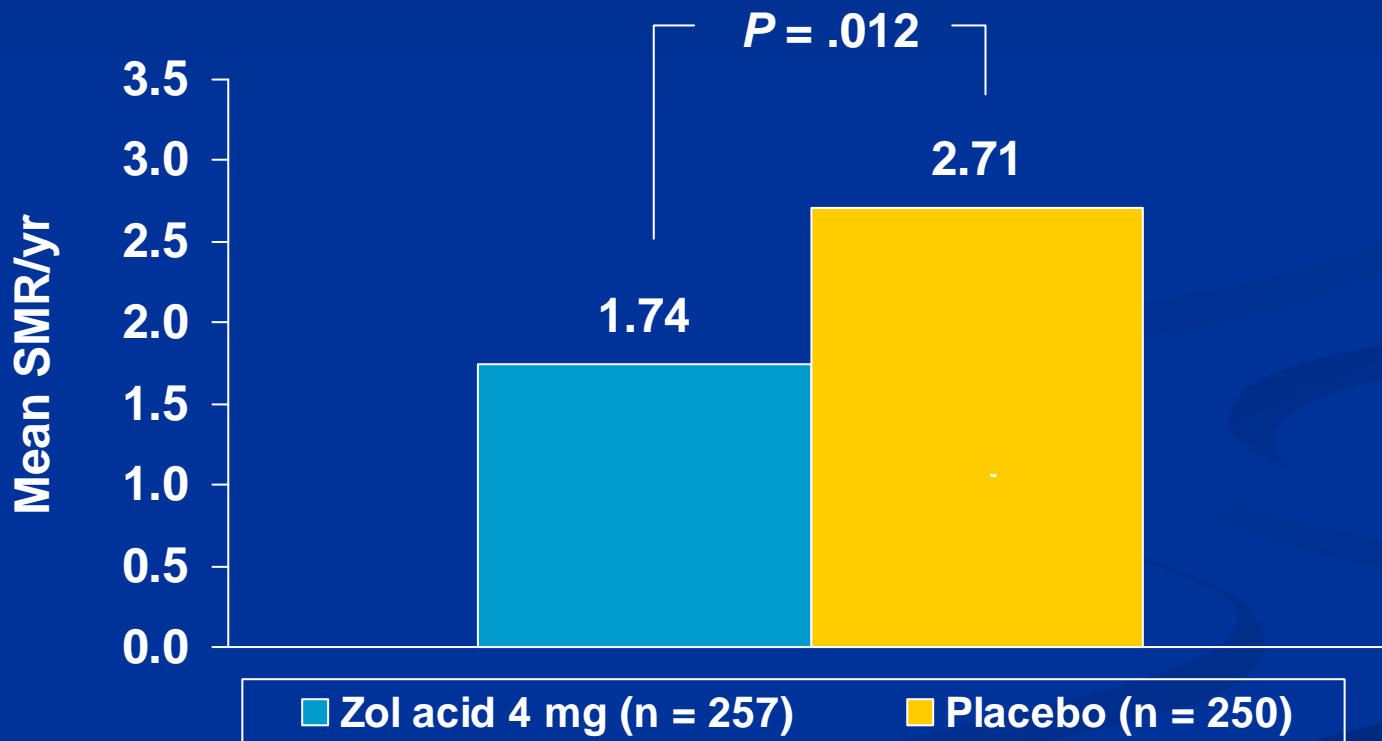


*After start of study drug.

Solid Tumors

Skeletal Morbidity Rate*

Zoledronic acid significantly reduces the number of skeletal complications a patient experiences in a year

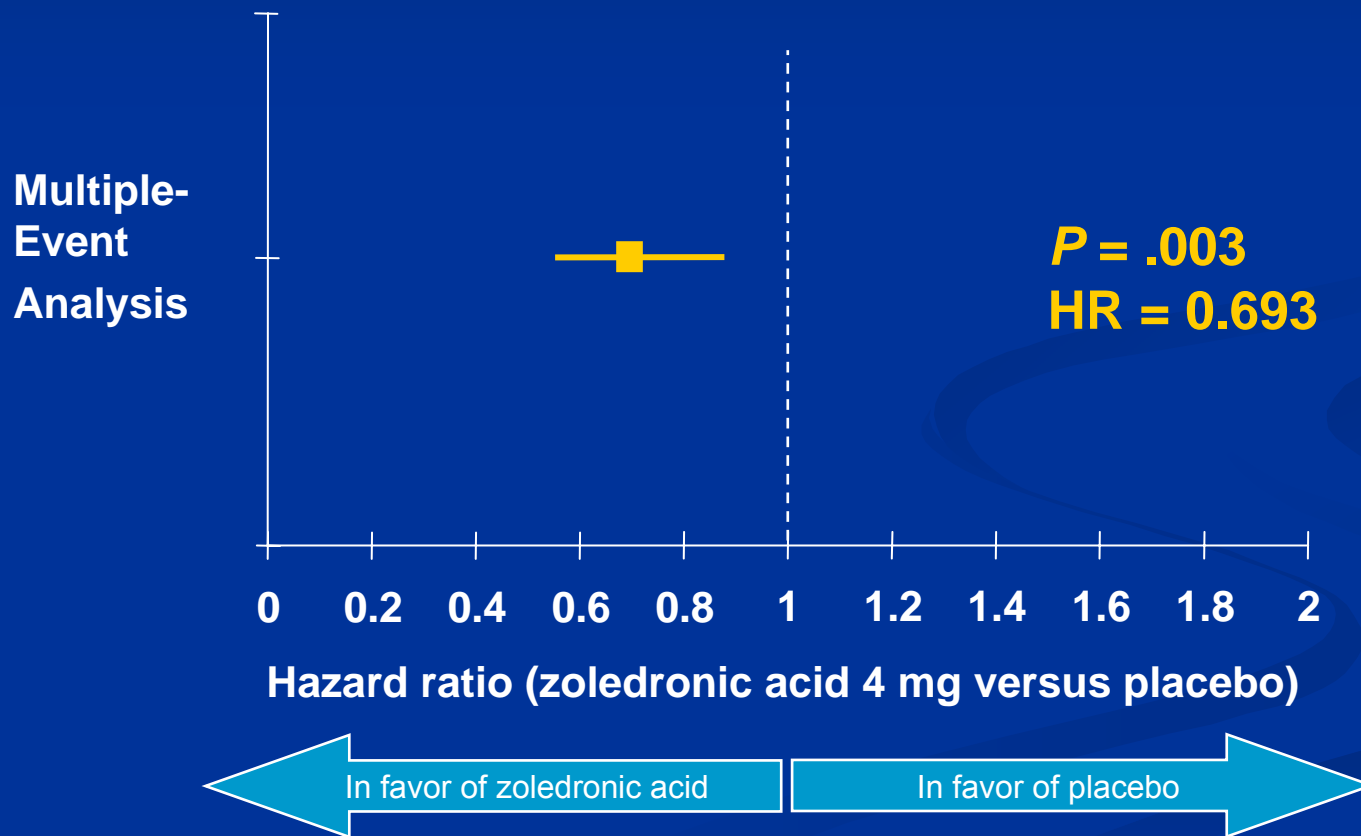


*Hypercalcemia of malignancy is included as a skeletal-related event.

Solid Tumors

Multiple-Event Analysis

Zoledronic acid significantly decreases the risk of developing skeletal complications by 31%



*Hypercalcemia of malignancy is included as a skeletal-related event.

IV Bisphosphonate Pain Management

- **Acute phase reaction (1%-18%)**
 - Self-limiting flu-like symptoms
 - Fever
 - Arthralgia/myalgia
 - Bone pain
 - Onset <24 hrs
 - Duration \leq 48 hr
 - Less with \geq 2 cycles
- **Management**: Acetaminophen and oral fluids

Infusion Time and IV Bisphosphonate Toxicity Profile

- Renal Dysfunction (\uparrow Scr)* - Class Effect - Time/Dose-Dependent

BP	Dose (mg)	Infusion vol (mL)	Infusion time (min)
Pamidronate	90	500	≥ 120
Ibandronate	2-6	250-500	≥ 120
Zol acid	4	100	≥ 15

- Proximal convoluted tubule injury
(*Basic Clin Pharm Toxicol.* 2005;97:374.)
- Incidence for Zoledronic acid (ZA) in NSCLC: ZA 10.9% vs 6.7%, $P = .23$
(*Cancer.* 2004;100:2613.)

Renal Monitoring Guidelines for Zoledronic Acid

*Serum Creatine (Scr) **PRIOR** (7-10 days) to each dose

- Baseline Scr <1.4 mg/dL & increase Scr \geq 0.5 mg/dL
- Baseline Scr >1.4 mg/dL & increase Scr \geq 1.0 mg/dL
- Doubling of baseline Scr

*Dose delay until Scr no higher than 10% above baseline value (increase infusion time, 15 to 30 mins?)

*Discontinue BP if Scr elevation does not resolve with 4-8 wks

*Avoid nephrotoxic agents (NSAIDs, radio contrast dyes, cisplatin) administer \geq 24 hrs post-zoledronic acid

Patients Receiving NSAIDs

Recommendation: Patients with mild/moderate renal insufficiency avoid NSAIDs with short $t_{1/2}$ 2 days prior to and 2 days following zoledronic acid (NSAIDs with long $t_{1/2}$ at least 5 days)

NSAIDs	$t_{1/2}$ (hr)
Ibuprofen (various)	3-4
Ectodolac (Lodine)	7
Ketoprofen (Orudis)	2-3
Diclofenac (Voltaren)	2
Oxaprozin (Daypro)	50
Piroxicam (Feldene)	45
Nabumetone (Relafen)	30
Sulindac (Clinoril)	17
Naproxen Na (various)	13

Administration of Zoledronic Acid in Renal Impairment

Creatine Clearance*	Zoledronic Dose†
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>60 mL/min	4.0 mg
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50-60 mL/min	3.5 mg
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40-49 mL/min	3.3 mg
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30-39 mL/min	3 mg
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<30	treatment not recommended
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*Cockcroft-Gault formula

†Calculated AUC for CRCL 75 mL/min

Zoledronic Acid

Administration & Monitoring Guidelines

- Medication review & dental history (exam)
- Evaluate Scr, serum electrolytes (Ca, Mg, PO₄), prior to dose (serum NTx?)
- Calcium (500 mg) and vit D (400 IU) supplementation
- Insure adequate hydration
- Advise patient of acute phase reactions and management
- Zoledronic acid ___ mg IV over NO LESS than 15 min
- Document cumulative cycles

ASCO 2006 Updates

Abstract 7228—General Poster Session

Presenter: Matczak (Major) —Poster W13

Effects of zoledronic acid on survival in patients with lung cancer and high baseline N-telopeptide (NTX) levels: stratified by baseline bone alkaline phosphatase (BALP)

Study design

- Retrospective analysis of patients with lung cancer and high NTX levels in Study 011
- Patients were stratified by baseline BALP levels
 - Normal (< 146 IU/L)
 - Elevated (≥ 146 IU/L)
- Cox regression models were used to assess correlations between high baseline NTX levels and survival, stratified by baseline BALP levels

Abstract 7228—General Poster Session

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- 144 lung cancer patients with bone metastases and high NTX levels were included in this analysis

Table 1. Patient Demographics and Baseline Disease Characteristics

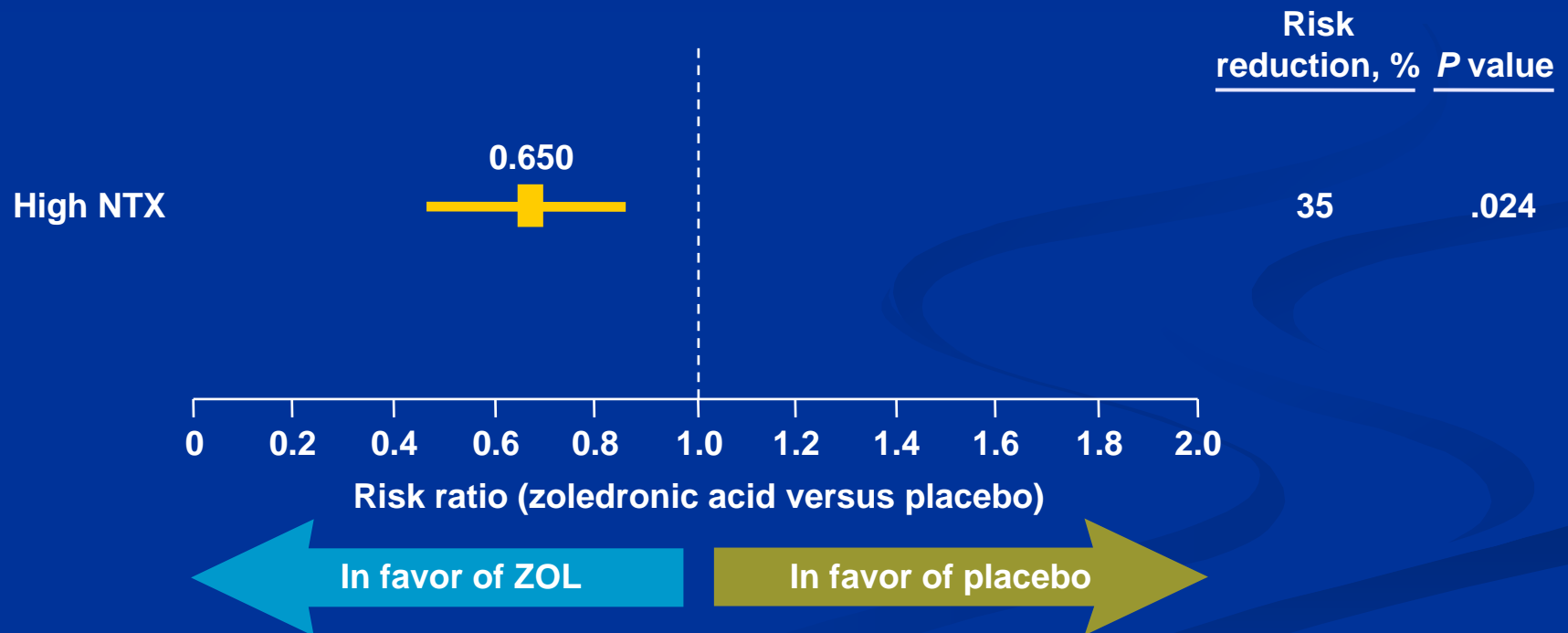
Characteristic	Patients with lung cancer (n = 144)
Median age, years (range)	64 (37 - 88)
Gender, n (%)	
Men	94 (65)
Women	50 (35)
ECOG performance status, n (%)	
0 to 1	122 (85)
≥ 2	22 (15)
Baseline NTX level, nmol/mmol creatinine, mean ± SE	115.9 ± 67.2
Serum creatinine, mg/dL, mean ± SE	0.96 ± 0.22

ECOG = Eastern Cooperative Oncology Group; NTX = N-telopeptide; SE = Standard error.

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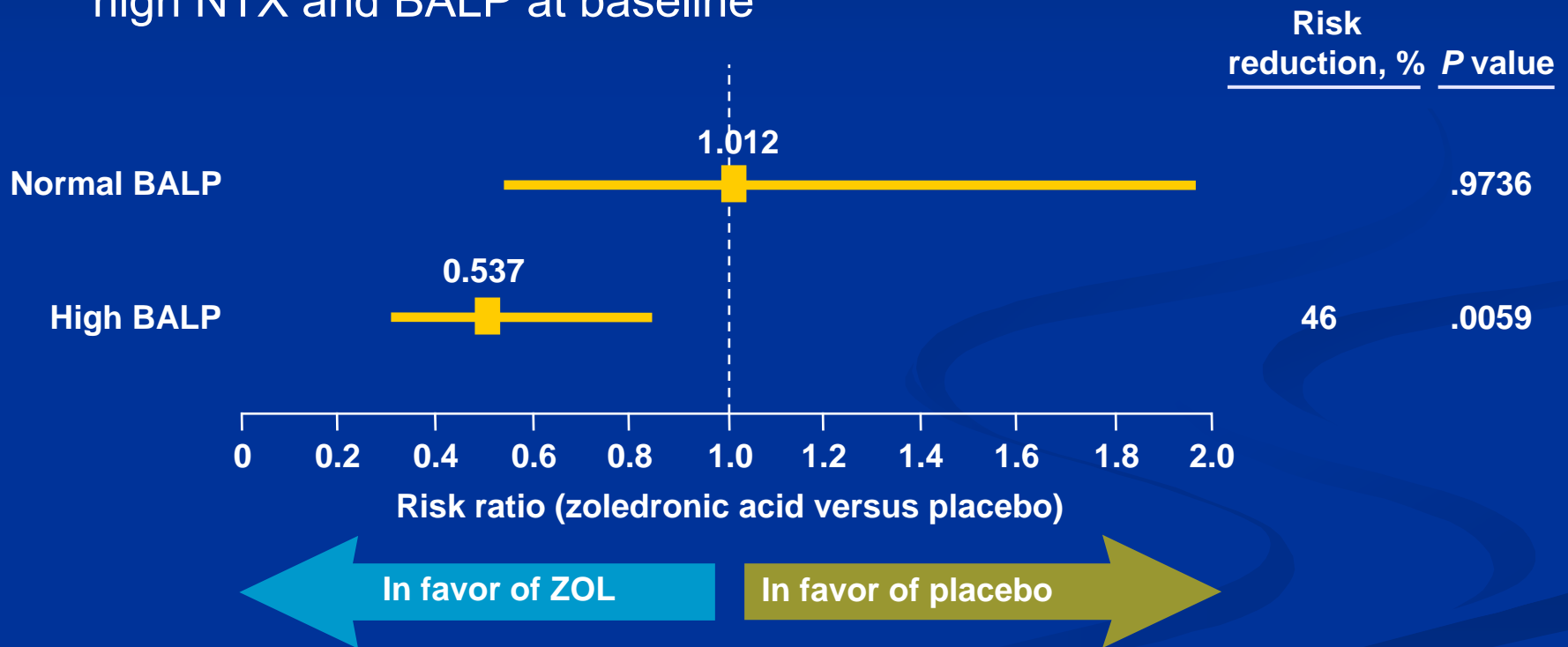
- Zoledronic acid 4 mg produced a significant 35% reduction in the risk of death on-study compared with placebo in patients with lung cancer and high NTX at baseline



Abstract 7228—General Poster Session

Presenter: Matczak (Major) —Poster W13

- The reduction in risk of on-study death for zoledronic acid compared with placebo was because of a significant benefit among patients with high NTX and BALP at baseline



Abstract 7228—General Poster Session

Presenter: Matczak (Major)—Poster W13

Effects of zoledronic acid on survival in patients with lung cancer and high baseline N-telopeptide (NTX) levels: stratified by baseline bone alkaline phosphatase (BALP)

Conclusions

- This exploratory analysis is the first to demonstrate that zoledronic acid may improve survival in a subgroup of lung cancer patients
 - Zoledronic acid may improve survival compared with placebo in patients with lung cancer who have high levels of bone metabolism
 - These patients may have more aggressive metastatic disease

Abstract 8529—Poster Discussion

Presenter: Chen—Poster 18

Effect of the number of bone lesions on efficacy of zoledronic acid for prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors

- Exploratory analysis by number of bone lesions in 3 randomized, controlled trials in patients with breast cancer (n = 739), prostate cancer (n = 397), or lung cancer (n = 480) treated with zoledronic acid 4 mg, pamidronate 90 mg, or placebo
- Zoledronic acid significantly reduced the mean skeletal morbidity rate (SMR) compared with placebo in the lung cancer or other solid tumors (LC/OST) and prostate cancer (PC) studies; benefits were most profound in patients with > 3 bone lesions ($P = .008$ and $P = .035$ for LC/OST and PC, respectively)
 - In breast cancer patients, the mean SMR was lower in the zoledronic acid versus pamidronate groups
- Zoledronic acid reduced SREs, regardless of the number of bone lesions, and the benefits were greater for patients with > 3 bone lesions

Abstract 18541—Publication Only

Presenter: Ucar

Effect of zoledronic acid (ZOL) compared with placebo on overall disease and bone lesion progression in patients with bone metastases from certain solid tumors: stratification by baseline characteristics

Study Design

- Retrospective analysis of patients with bone metastases from lung cancer or other solid tumors who were treated with ZOL or placebo (Study 011) and had baseline disease characteristics more severe than the median BPI, duration of disease, and time to diagnosis of bone metastases
 - BPI score ≥ 2.75 (n = 236)
 - Cancer duration < 15 months (n = 193)
 - Patients who developed bone metastases < 8.5 months from initial cancer diagnosis (n = 193)

Abstract 18541—Publication Only

Presenter: Ucar

Results

- Zoledronic acid 4 mg (ZOL) produced significant reductions in the risk of disease progression compared with placebo in patient subsets
 - For baseline BPI score ≥ 2.7 , ZOL significantly reduced the relative risk of disease progression and bone lesion progression by 34% ($P = .014$) and 32% ($P = .028$), respectively, compared with placebo
 - For cancer duration < 15 months ($n = 193$), ZOL significantly reduced the relative risk of disease progression and bone lesion progression by 45% ($P = .002$) and 40% ($P = .016$), respectively, compared with placebo
 - For bone metastases diagnosed < 8.5 months from initial cancer diagnosis ($n = 193$), ZOL significantly reduced the relative risk of disease progression and bone lesion progression by 39% ($P = .009$) and 48% ($P = .004$), respectively compared with placebo
- ZOL provides significant benefits, and benefits may be more profound in patients with more aggressive disease

Abstract 7049—Poster Discussion

Presenter: Scagliotti—Poster 18

Bone sialoprotein is predictive of bone metastases in resectable non-small cell lung carcinoma a case-control study and prevalence data

Study design

- Primary tumor samples were analyzed for markers of bone resorption
 - 30 NSCLC that metastasized to bone (group A)
 - 30 NSCLC without any metastases (group B)
 - 26 NSCLC with non-bone metastases (group C)

Abstract 7049—Poster Discussion

Presenter: Scagliotti—Poster 18

Bone sialoprotein is predictive of bone metastases in resectable non-small cell lung carcinoma a case-control study and prevalence data

Conclusions

- Bone sialoprotein (BSP) was strongly associated with bone dissemination ($P < .001$) and with poor outcome ($P = .02$)
 - None of the other markers tested was differentially expressed within the groups or demonstrated a prognostic impact
- Bone sialoprotein expression in resected NSCLC may predict bone dissemination, and may be useful in selecting patients for treatments targeted to inhibit the spread of bone metastases

BSP may be useful to identify patients who are likely to develop bone metastases, and may therefore benefit from treatment with ZOL to prevent disease progression