



I BIFOSFONATI NEL PAZIENTE ONCOLOGICO ED EMATOLOGICO

Alessandria, mercoledì 14 maggio 2008

Improving survival?

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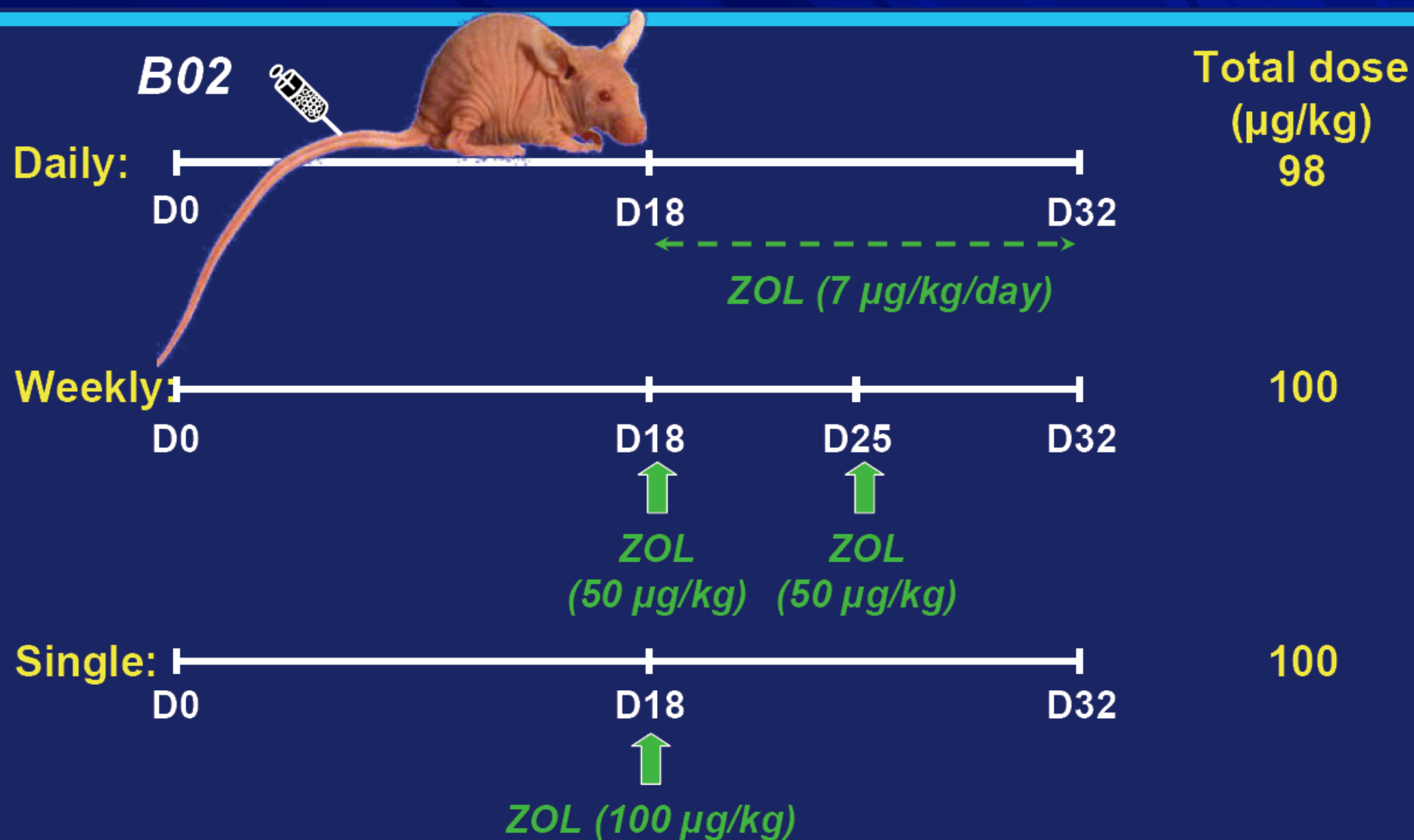


Bisphosphonates in Pre-clinical Models of Cancer

Doses of bisphosphonates used in animal studies are 10 to 40 times higher than the dosing regimens that have been approved for the treatment of cancer patients with skeletal metastases.....

.... But !!!

Effects of clinical dosing regimens of zoledronic acid on experimental breast cancer bone metastasis



ZOL: Total cumulative dose calculated equivalent to the monthly 4-mg intravenous dose given to patients.

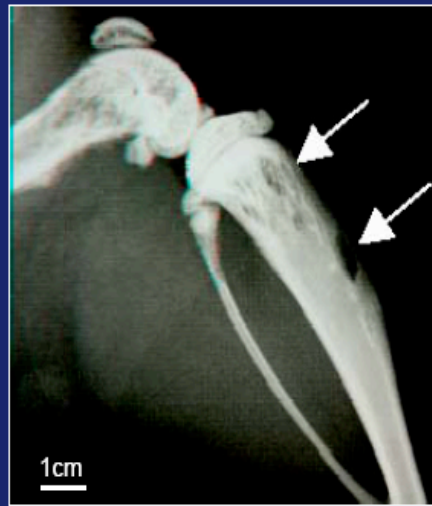
Daubiné F. et al. JNCI, 2007

Zoledronic Acid Therapy With a Frequent Dosing Interval Affects Skeletal Tumour Burden

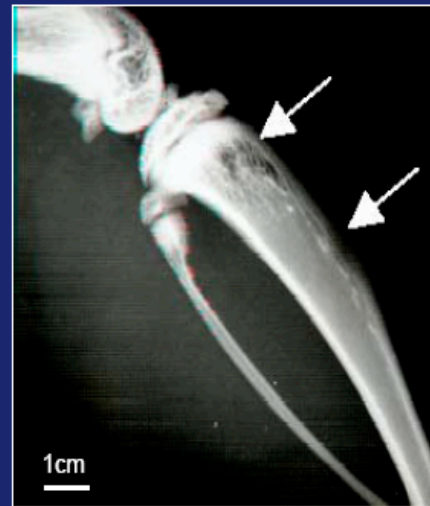
Vehicle



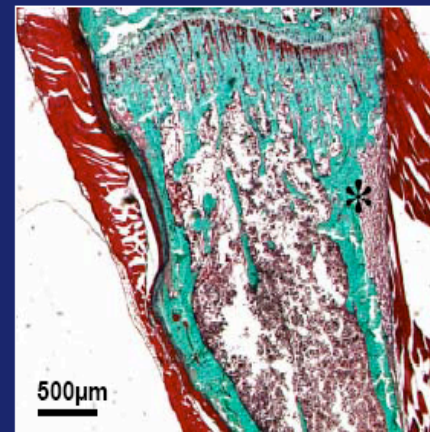
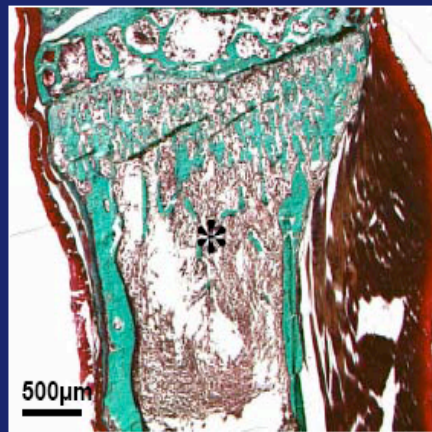
ZOL (single)



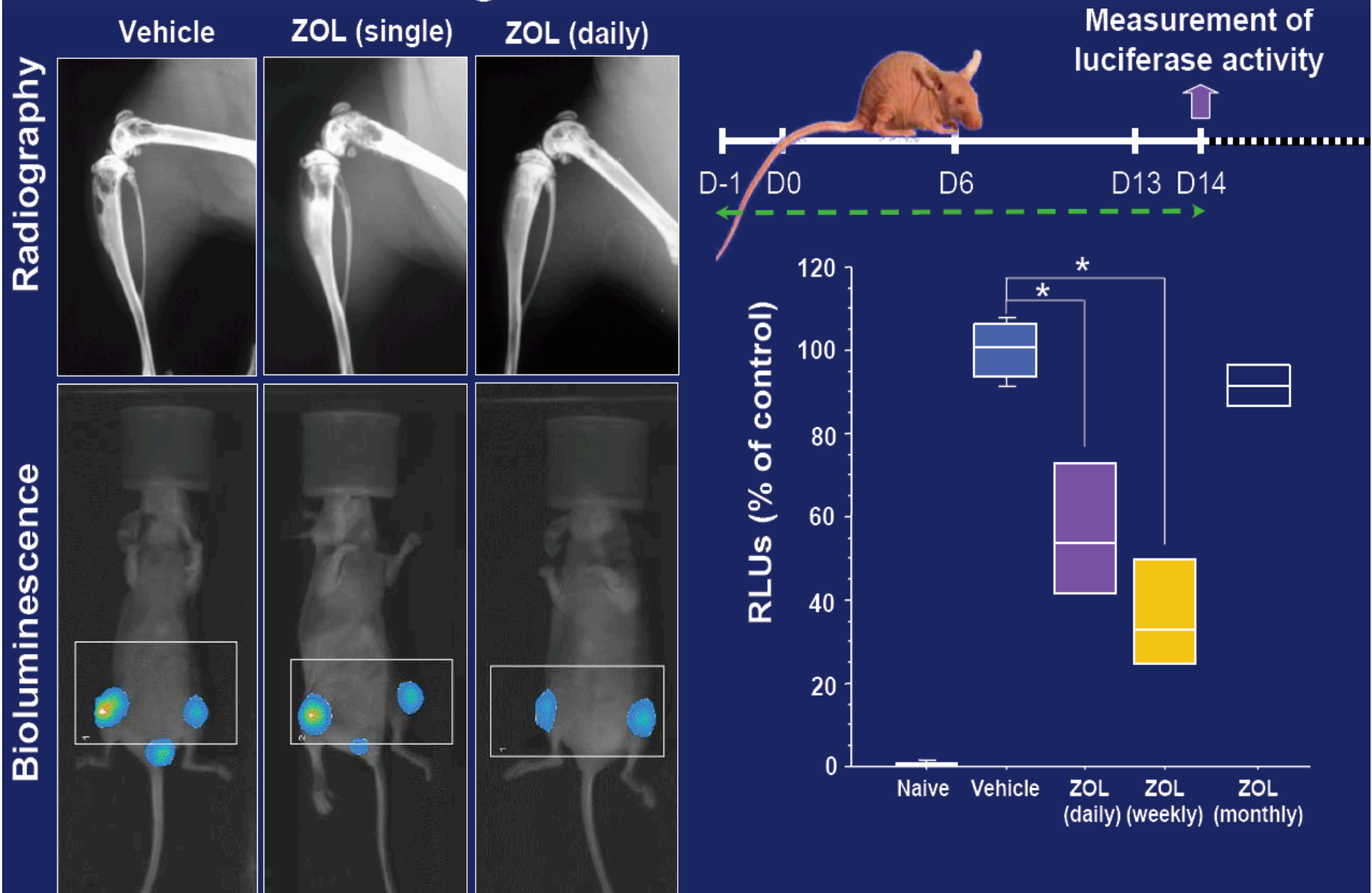
ZOL (daily)



ZOL (weekly)



A Daily or Weekly Preventive Regimen of Zoledronic Acid Reduces the Homing of Tumour Cells to Bone



Do bisphosphonate increase survival in cancer patients?

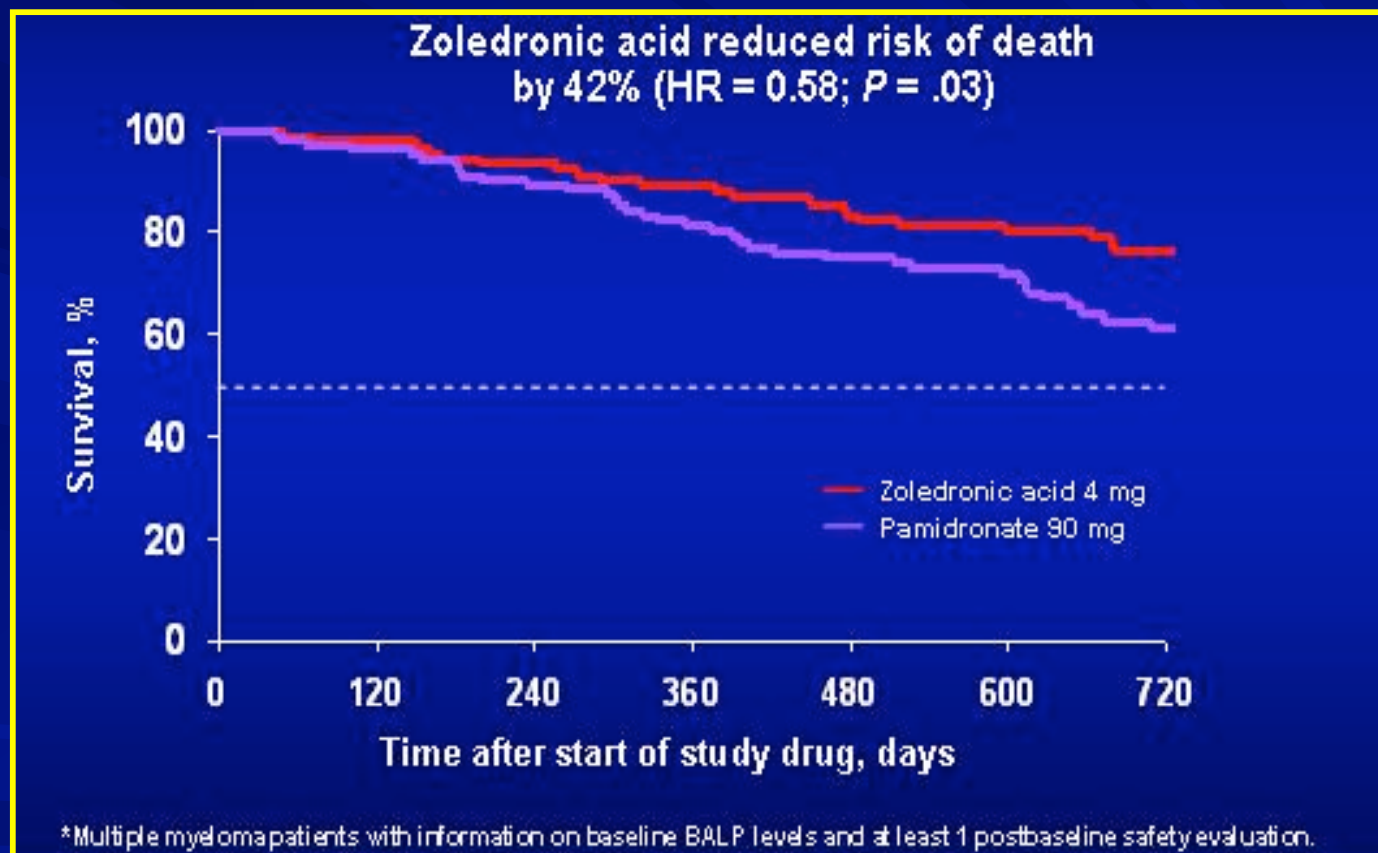
Clinical evidences related to
retrospective analyses from
randomized prospectives studies

Santini D et al. Ann Oncology, 2007

James Berenson, ASCO 2006



Kaplan-Meier Estimates of Time to Death by Treatment Group Stratum: High BALP



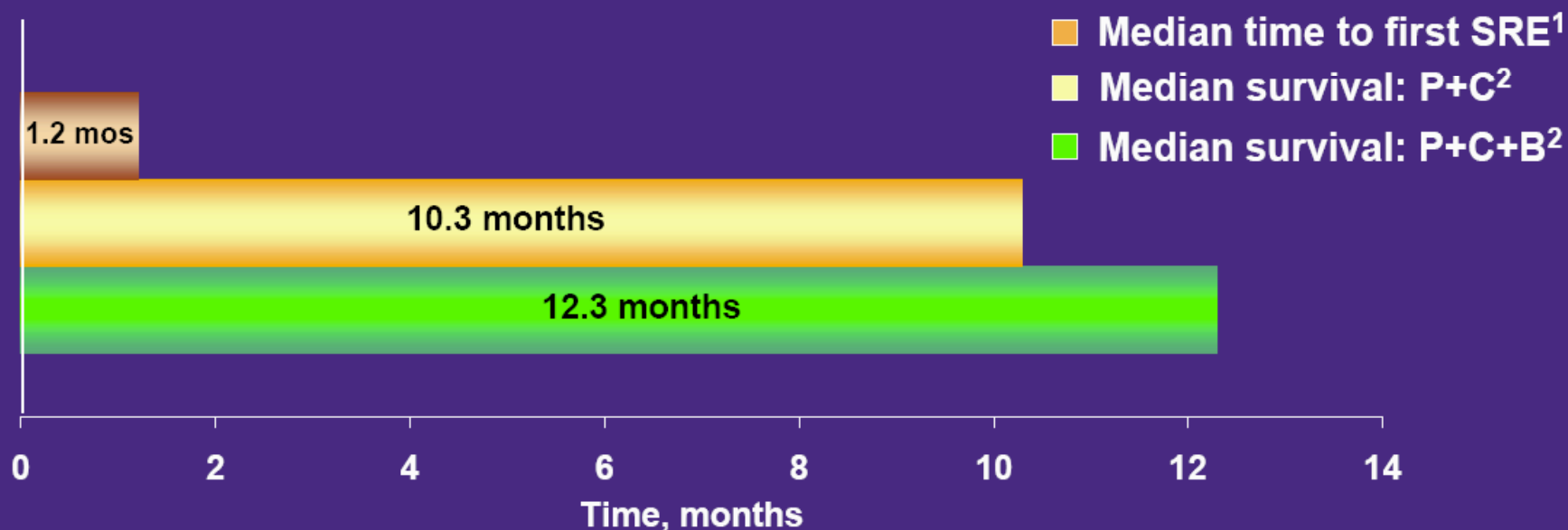
Effects of Zoledronic Acid on Survival in Patients With Lung Cancer and High Baseline N-telopeptide Levels: Stratified by Baseline Bone-Specific Alkaline Phosphatase

**P Major,¹ V Hirsh,² A Lipton,³
RJ Cook,⁴ C Langer,⁵ Y-J Hei⁶**

¹Juravinski Cancer Centre, Hamilton, Ontario, Canada; ²McGill University Health Centre, Montreal, Quebec, Canada; ³M.S. Hershey Medical Center, Hershey, Pennsylvania, USA; ⁴University of Waterloo, Waterloo, Ontario, Canada; ⁵Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA; ⁶Novartis Pharmaceuticals Corp, East Hanover, New Jersey, USA

Bone Metastases Are a Growing Concern in the Lung Cancer Field

- Recent advances in treatment have extended the **survival** of advanced LC pts to **approximately 1 year**
 - Pts are living long enough for the effects of tumor on bone to manifest in skeletal complications



LC = Lung cancer; P = Paclitaxel; C = Carboplatin; B = Bevacizumab.

1. Delea TE, et al. *Oncology* 2004;67:390-396; 2. Sandler A, et al. *N Engl J Med*. 2006;14:2542-2550.

Consequences of SREs in Patients With Lung Cancer

- 50% of patients with bone mets experience ≥ 1 SRE each year¹
- In patients with an SRE, median survival = **4 months**²
- In a recent chart review of patients with bone mets from lung cancer (N = 70), patients with SREs had **~50% shorter survival** versus patients without SREs³
- A history of SREs is associated with a significant **41% increased risk** of experiencing **additional SREs** compared with patients with no prior SRE ($P = .036$)⁴

SRE = Skeletal-related event.

1. Rosen LS, et al. *Cancer*. 2004;100:2613-2621.

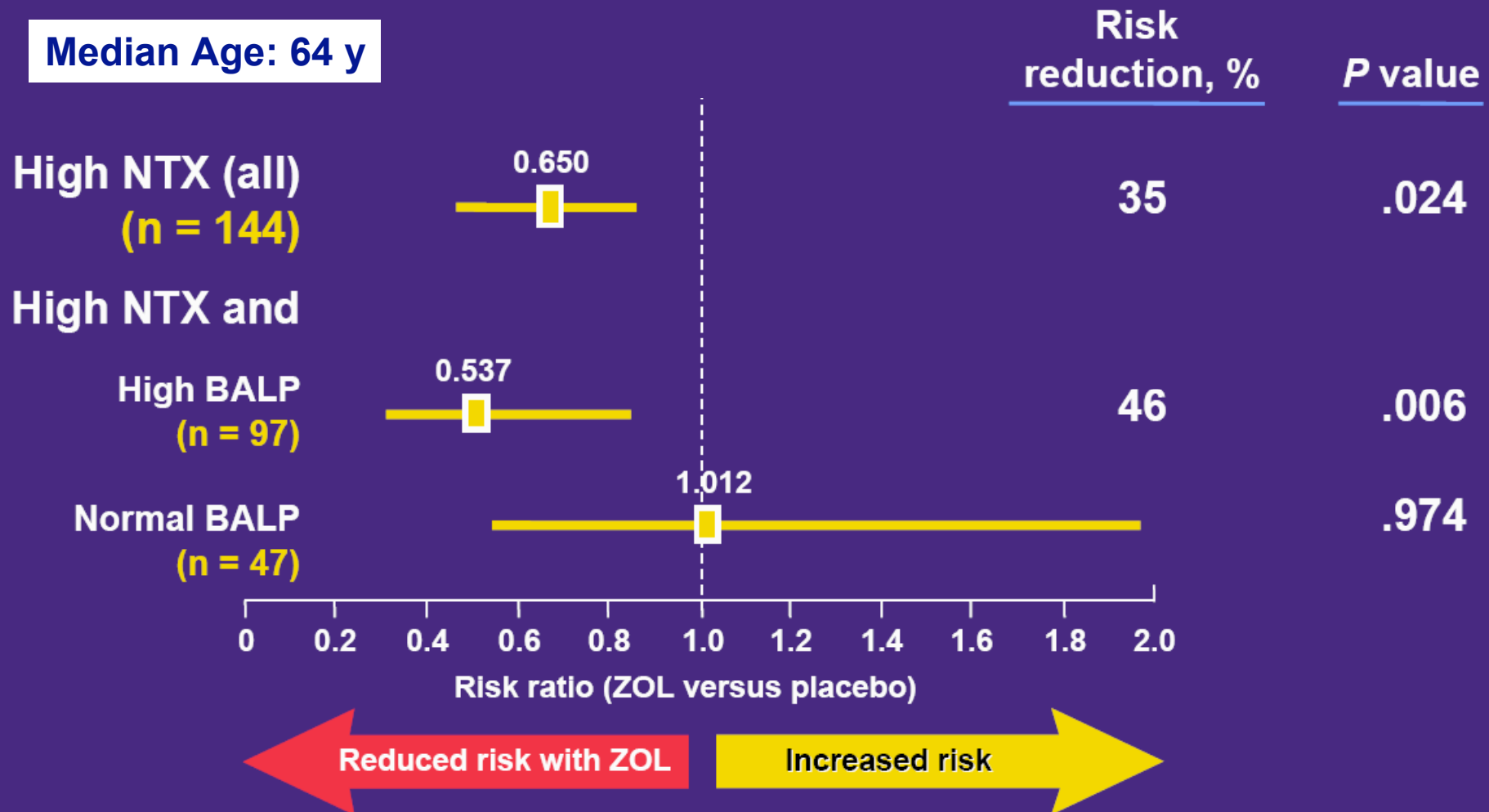
2. Delea TE, et al. *J Thorac Oncol*. 2006;1:571-576.

3. Tsuya A, et al. *Lung Cancer*. 2007;57:229-232.

4. Hirsh V, et al. *Clin Lung Cancer*. 2004;6:170-174.

ZOL Increased Survival Compared With Placebo in Patients With NSCLC and High NTX and BALP

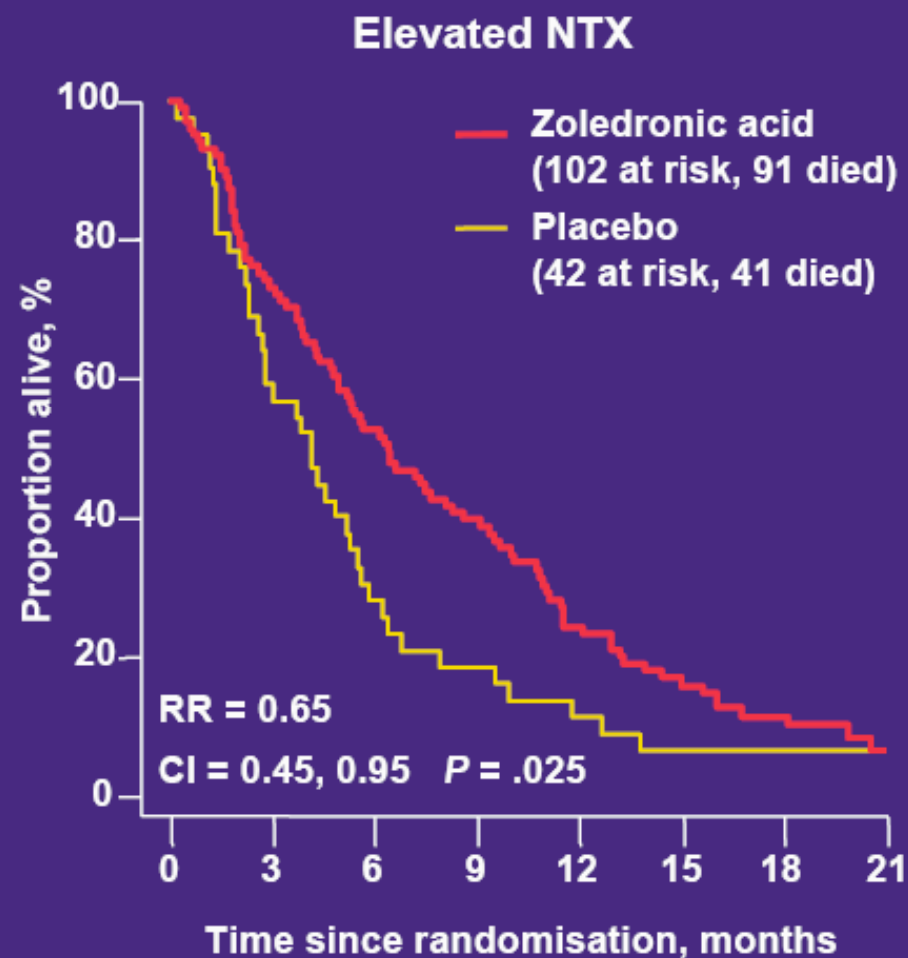
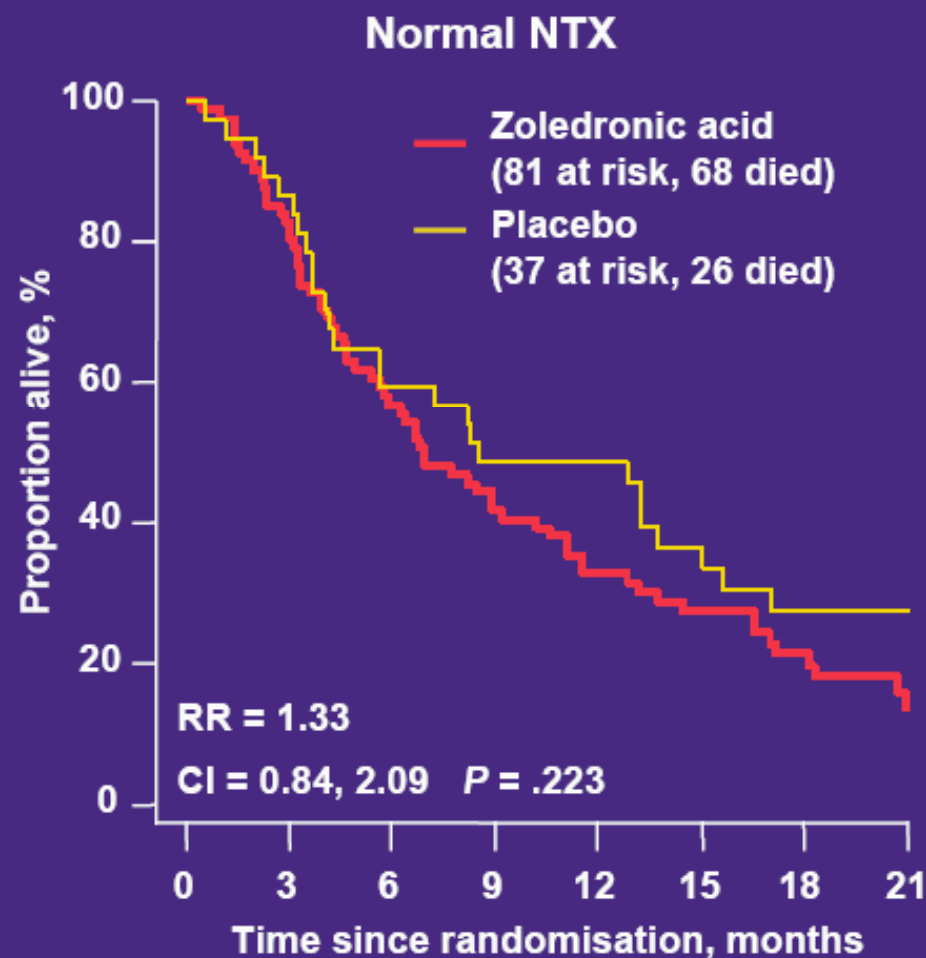
Median Age: 64 y



ZOL = Zoledronic acid; NSCLC = Non-small cell lung cancer; NTX = N-telopeptide of type I collagen; BALP = Bone-specific alkaline phosphatase.

Matczak E, et al. Presented at: ASCO 42nd Annual Meeting; June 2-6, 2006; Atlanta, GA. Abstract 7228.

Survival Among Patients Stratified by Baseline NTX Levels (NSCLC)



NSCLC = Non-small cell lung cancer; NTX = N-telopeptide of type I collagen.
Adapted from Hirsh V, et al. *J Thorac Oncol*. In press.

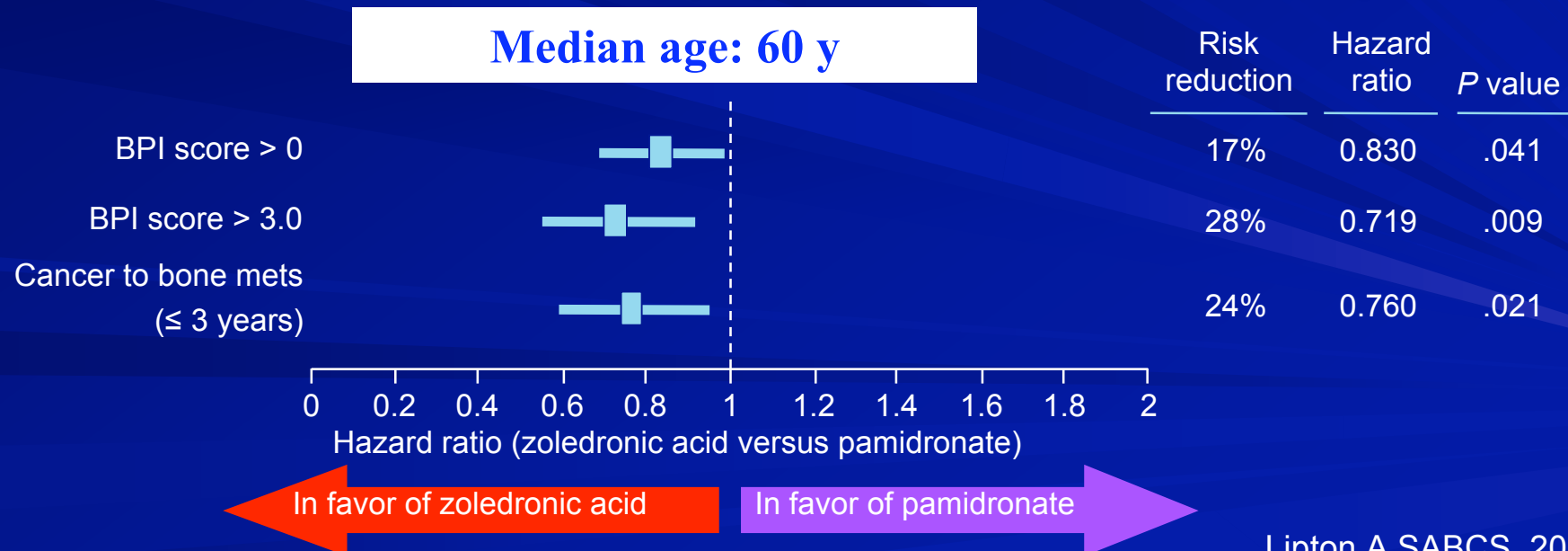
Zoledronic Acid Reduced Risk of Disease Progression in a subset Breast Cancer Patients with Bone Mets

■ Methods

- Retrospective analysis of patients with bone mets from BC treated with ZOL or PAM, stratified by baseline characteristics: BPI and time to from initial diagnosis to Bone Met

■ Results

- Reduced Risk of overall disease progression compared with PAM
 - ~24% (HR = 0.760; P = .021) in pts who developed bone mets ≤ 3 years from initial diagnosis
 - 28% (HR = 0.719; P = .009) in pts with a baseline BPI score > 3.0 (n = 317)



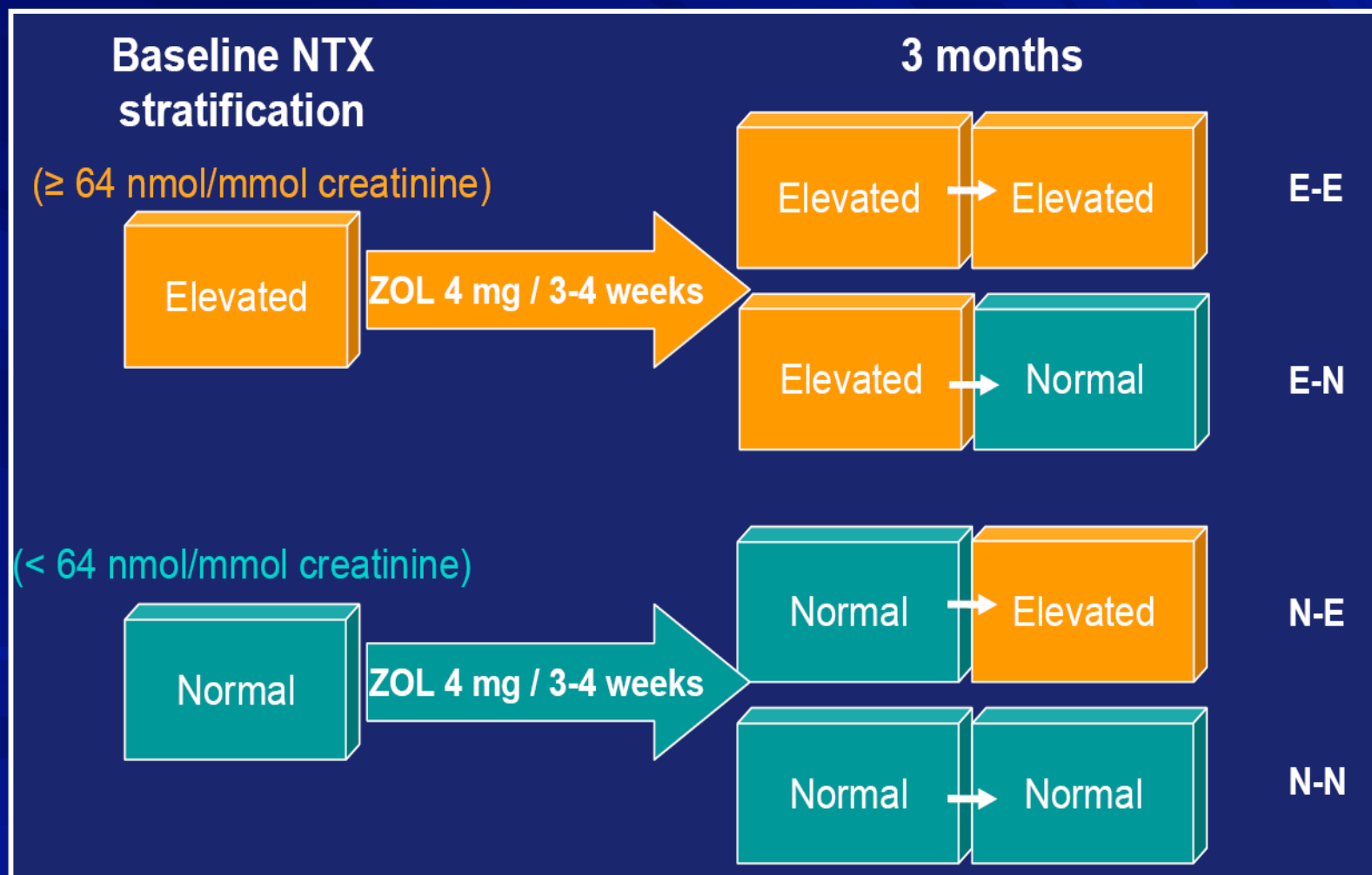
Normalization of Bone Markers and Improved Survival During Zoledronic Acid Therapy

Lipton et al, presented at ASCO 07 and ECCO 07

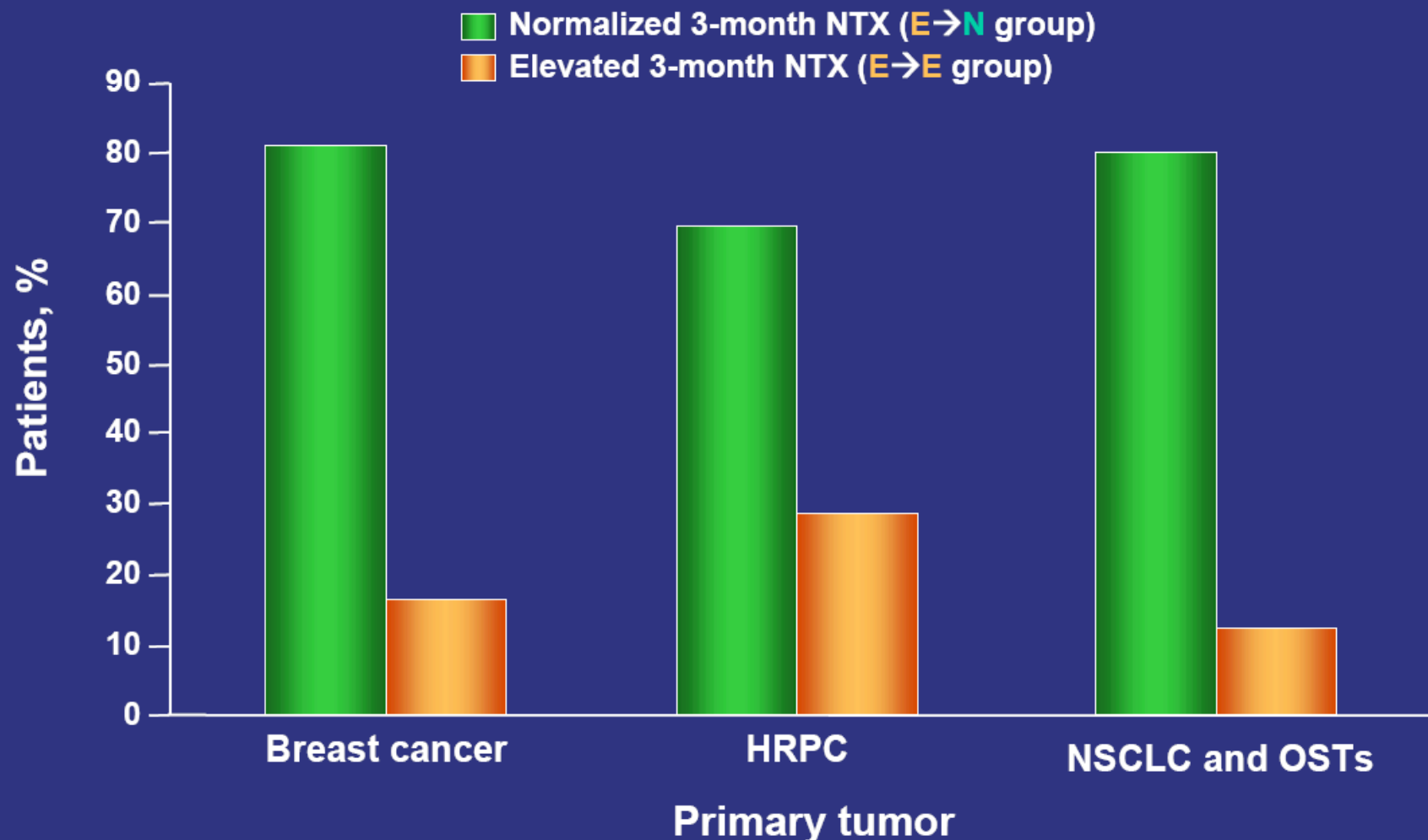
- Retrospective analysis of phase III zoledronic acid bone metastasis trials
 - 897 patients
 - Hormone Refractory Prostate cancer (Placebo controlled) (n = 314)
 - Lung cancer/other solid tumours (Placebo controlled) (n = 204)
 - Breast cancer (Pamidronate controlled) (n = 379)
- Only patients with baseline and 3-month NTX assessments were included in the analysis

Study Design

BC, PC, NSCLC, OST



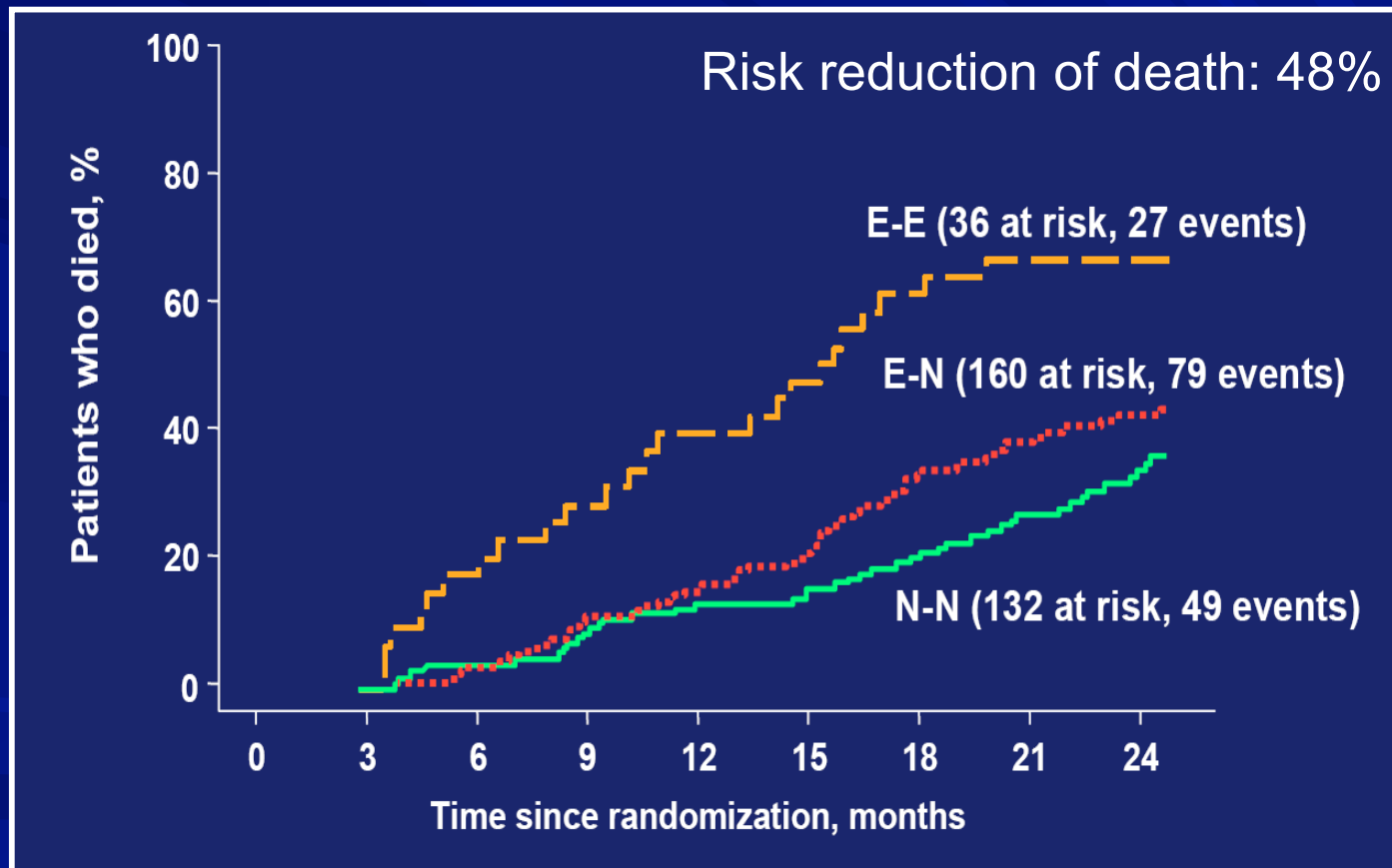
Zoledronic Acid Normalized NTX Levels Within 3 Months in the Majority of Patients



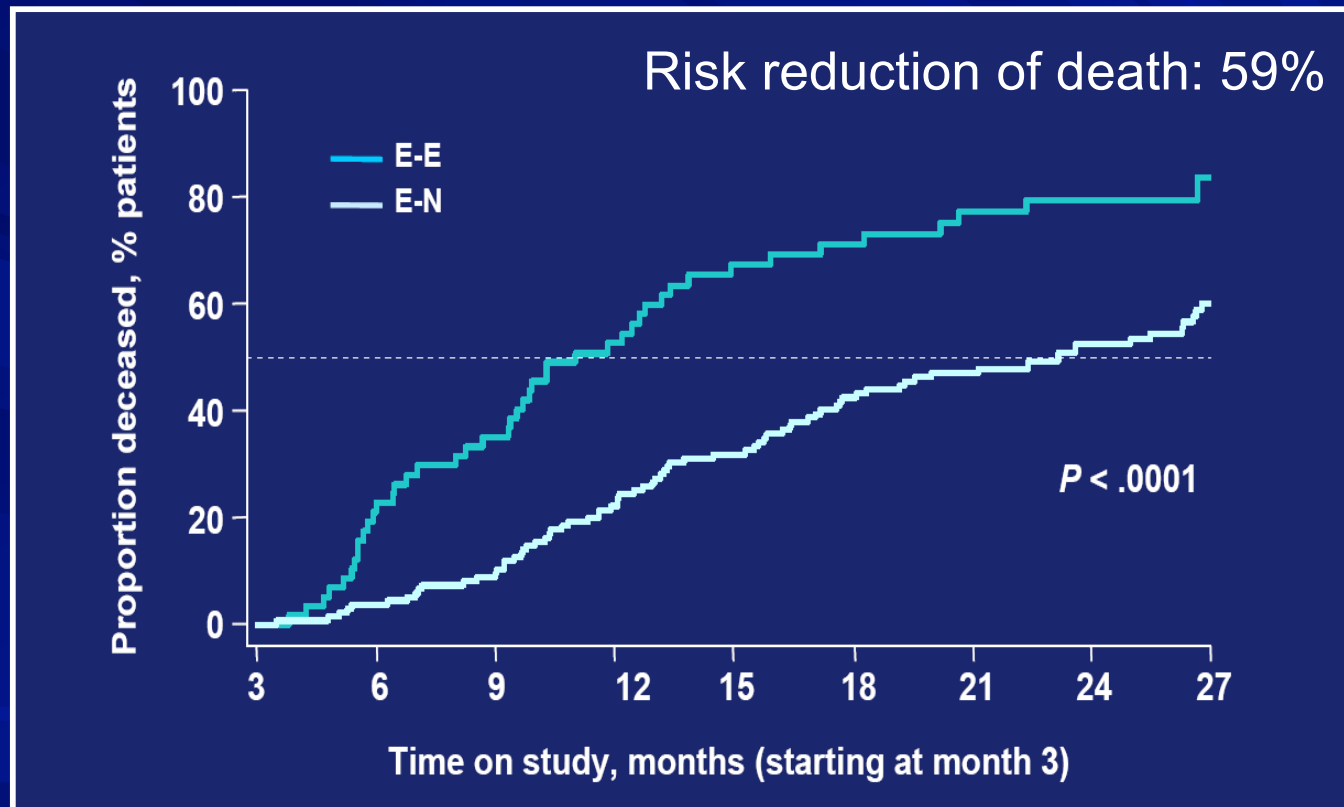
NTX = N-telopeptide of type I collagen; HRPC = Hormone-refractory prostate cancer; NSCLC = Non-small cell lung cancer; OST = Other solid tumors.

Lipton A, et al. Presented at: ECCO 2007. Abstract 304.

Normalization of NTX (3 months) Correlates with Survival Similar to That for Normal Baseline NTX Breast Cancer

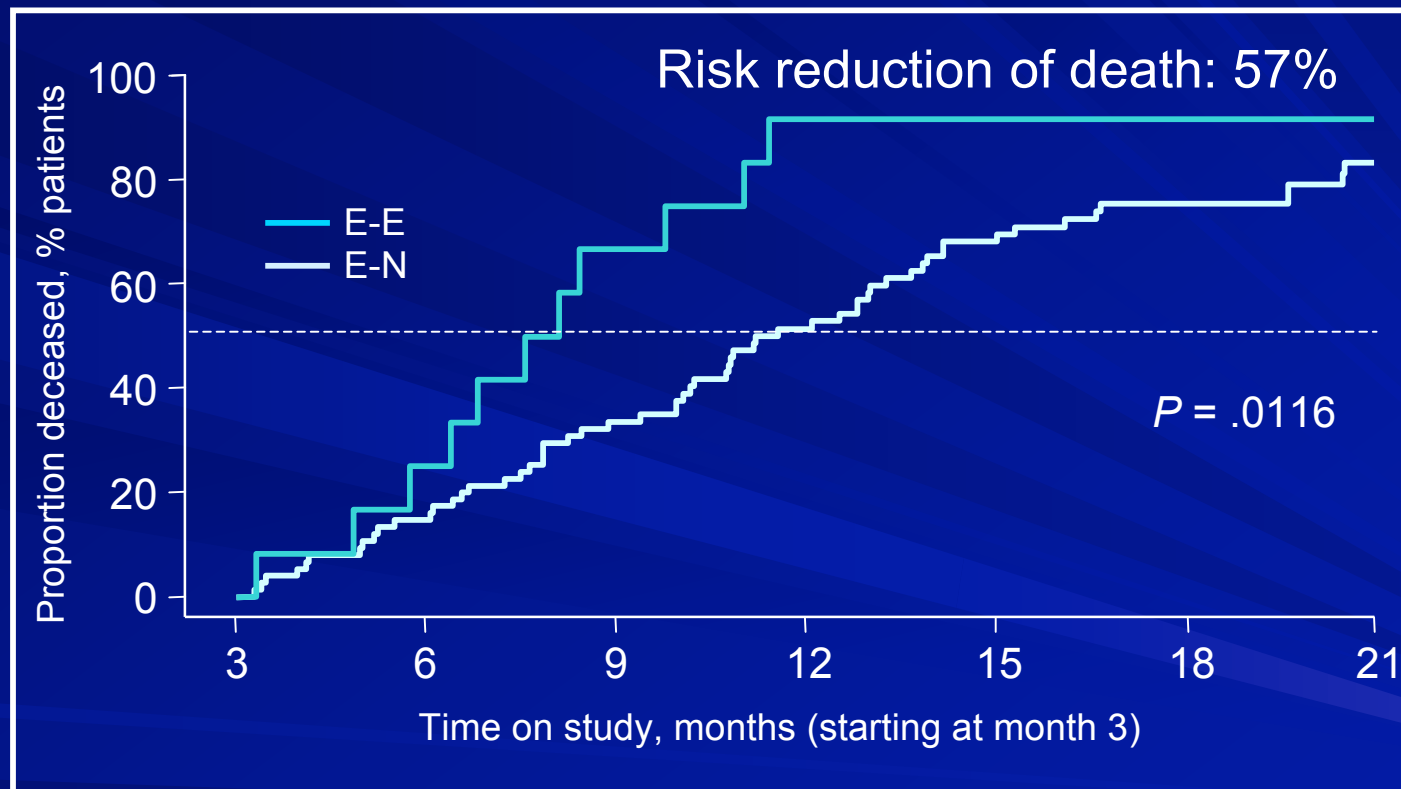


Normalization of NTX (3 months) Correlates with Survival Prostate Cancer



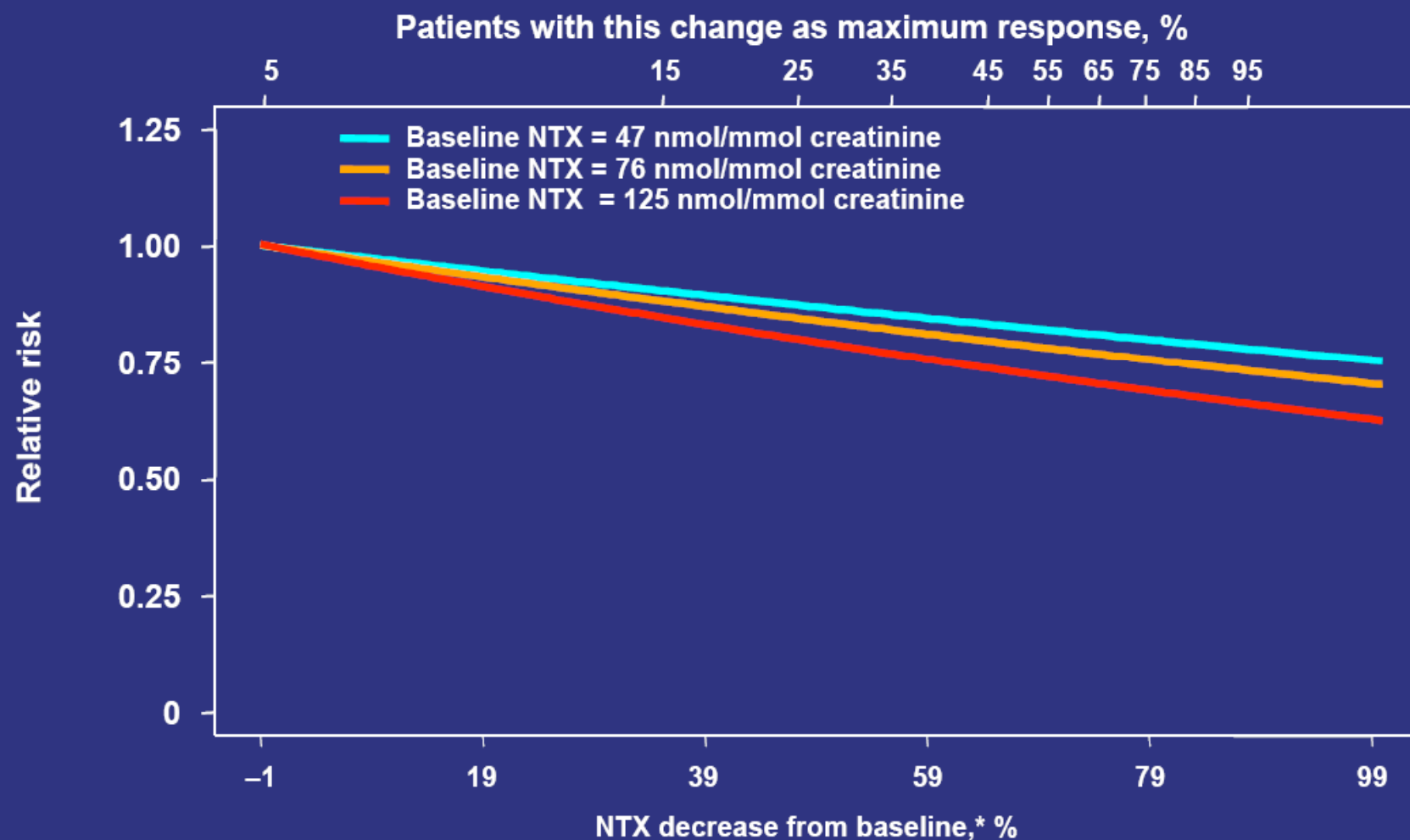
NTX: N-Telopeptide of type I collagen; **E-E:** Patients whose NTX levels remained elevated at 3 months; **E-N:** Patients whose NTX levels normalized at 3 months from elevated baseline levels

Normalization of NTX (3 months) Correlates with Survival NSLC and OST



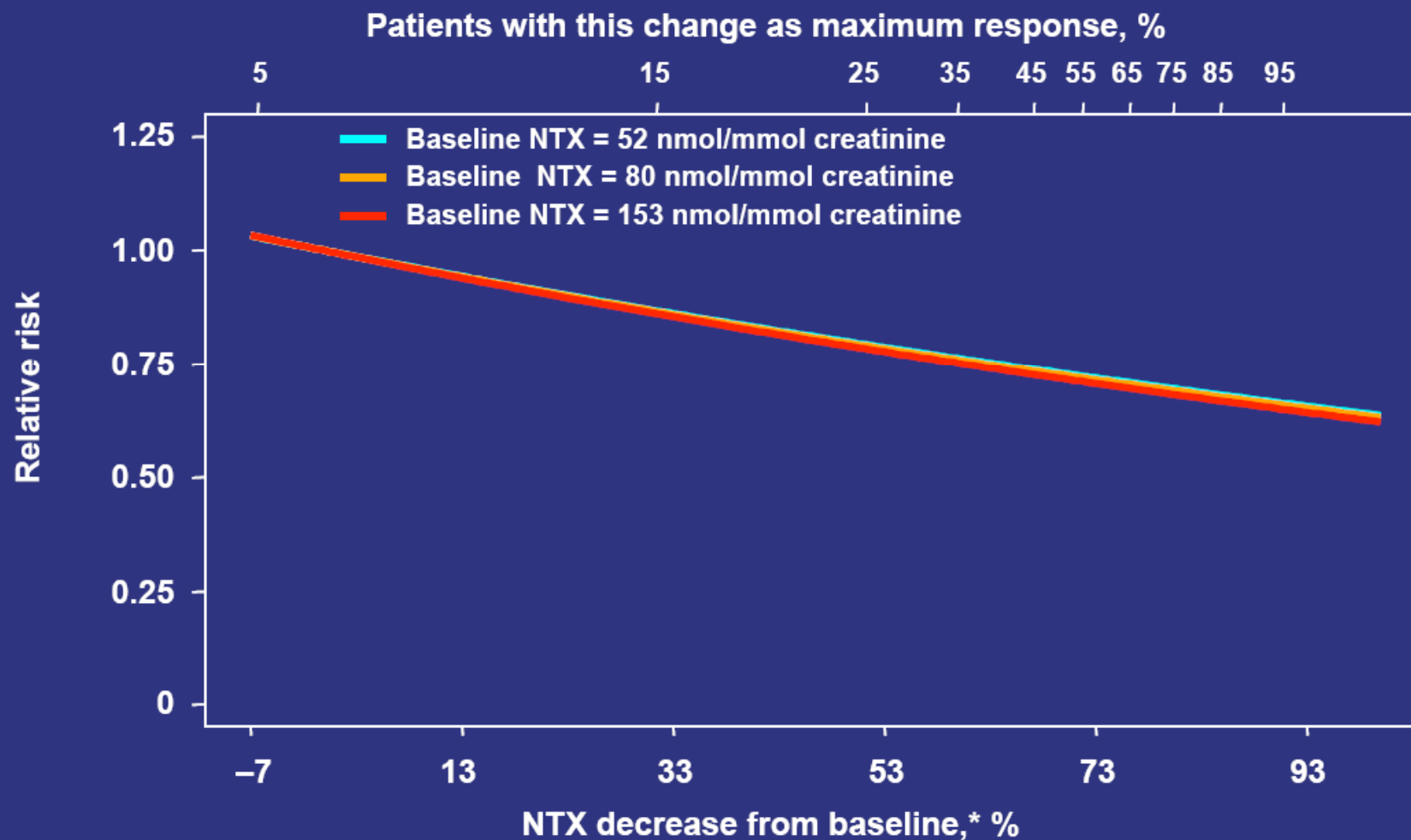
NTX: N-Telopeptide of type I collagen; **E-E:** Patients whose NTX levels remained elevated at 3 months; **E-N:** Patients whose NTX levels normalized at 3 months from elevated baseline levels

NTX Decreases Provided a Continuum of Survival Benefits in Patients With Breast Cancer



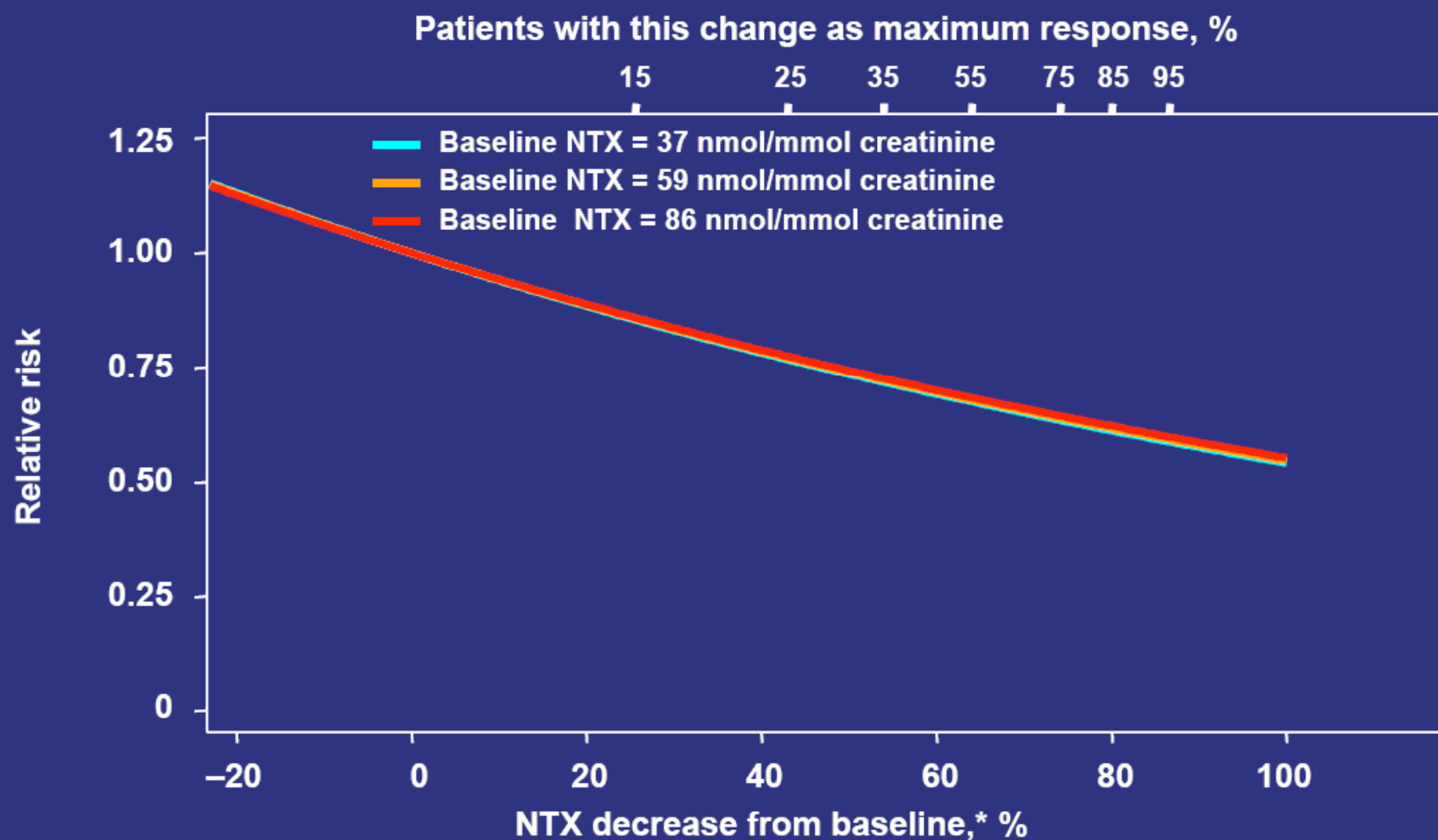
*Calculated as $([\text{Baseline NTX} \text{ minus } 3\text{-month NTX}] \div \text{baseline NTX}) \text{ times } 100$.

NTX Decreases Provided a Continuum of Survival Benefits in Patients With HRPC



*Calculated as $([\text{Baseline NTX} \text{ minus } 3\text{-month NTX}] \div \text{baseline NTX}) \text{ times } 100$.

NTX Decreases Provided a Continuum of Survival Benefits in Patients With Lung Cancer



*Calculated as $([\text{Baseline NTX} - \text{3-month NTX}] \div \text{baseline NTX}) \times 100$.

Do bisphosphonate increase survival in cancer patients?

First clinical evidences from
prospective studies

Santini D et al. Ann Oncology, 2007

Zoledronic Acid Eliminated Residual Isolated Breast Cancer Cells in the Bone Marrow

STUDY 1¹

- 31 patients received ZOL q 4 weeks for 6 months
 - 4 (13%) had persisting tumour cells
- Compared with 141 patients who did not receive ZOL
 - 38 (27%) patients had persisting tumour cells

STUDY 2²

- 45 patients received zoledronic acid q 4 weeks for 2 years²
 - At 1 year, in 32 evaluable patients, mean OTC had decreased from 25.4 to 8 OTC/mL (P = .02)

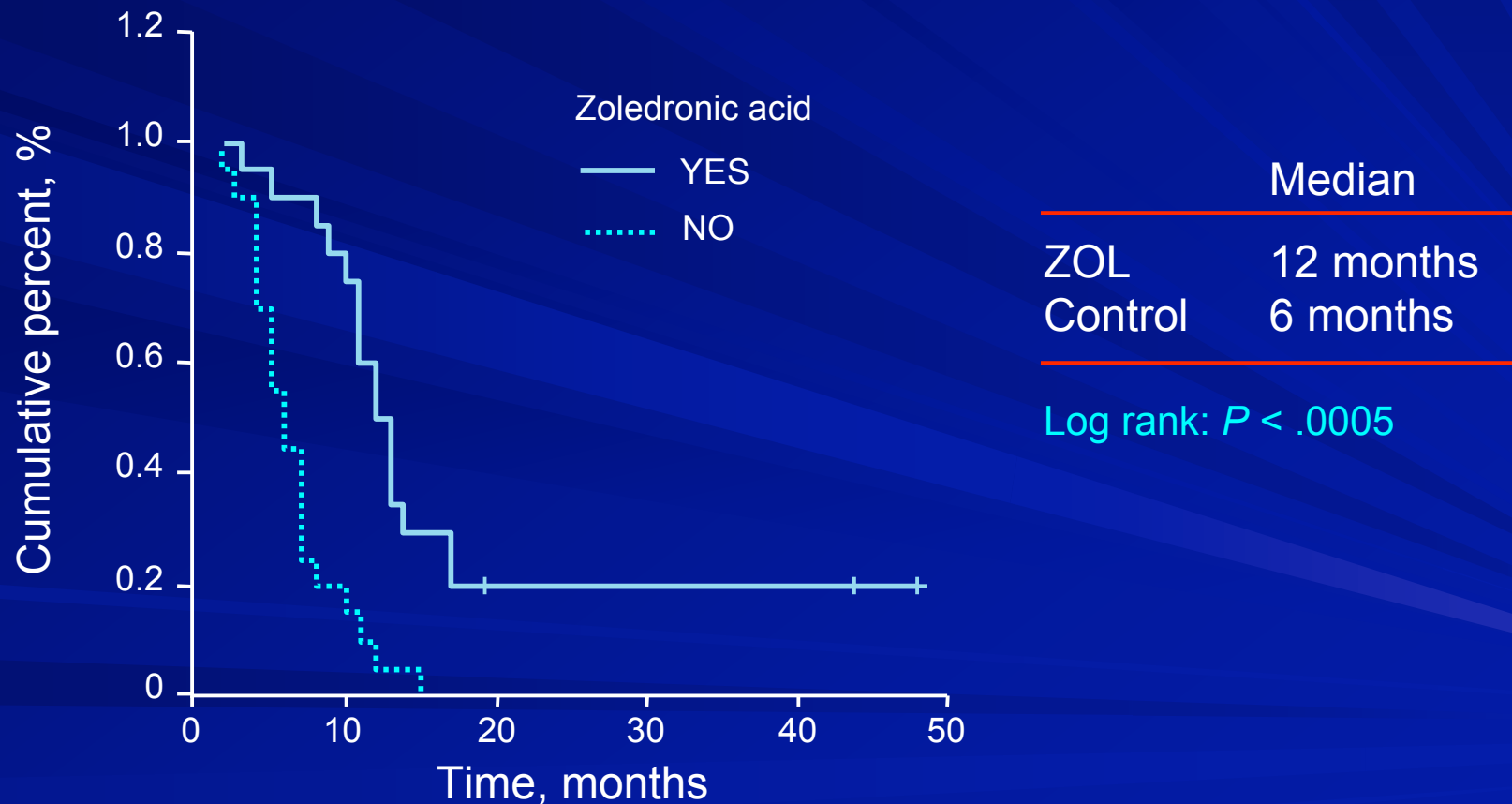
1. Rack BK, et al. *Breast Cancer Res Treat.* 2007;106:S40. Abstract 511;

2. Lin A, et al. *Breast Cancer Res Treat.* 2007;106:S40. Abstract 510.

OTC = occult tumour cell

Zoledronic Acid Significantly Prolonged Bone-Metastasis-Free Survival

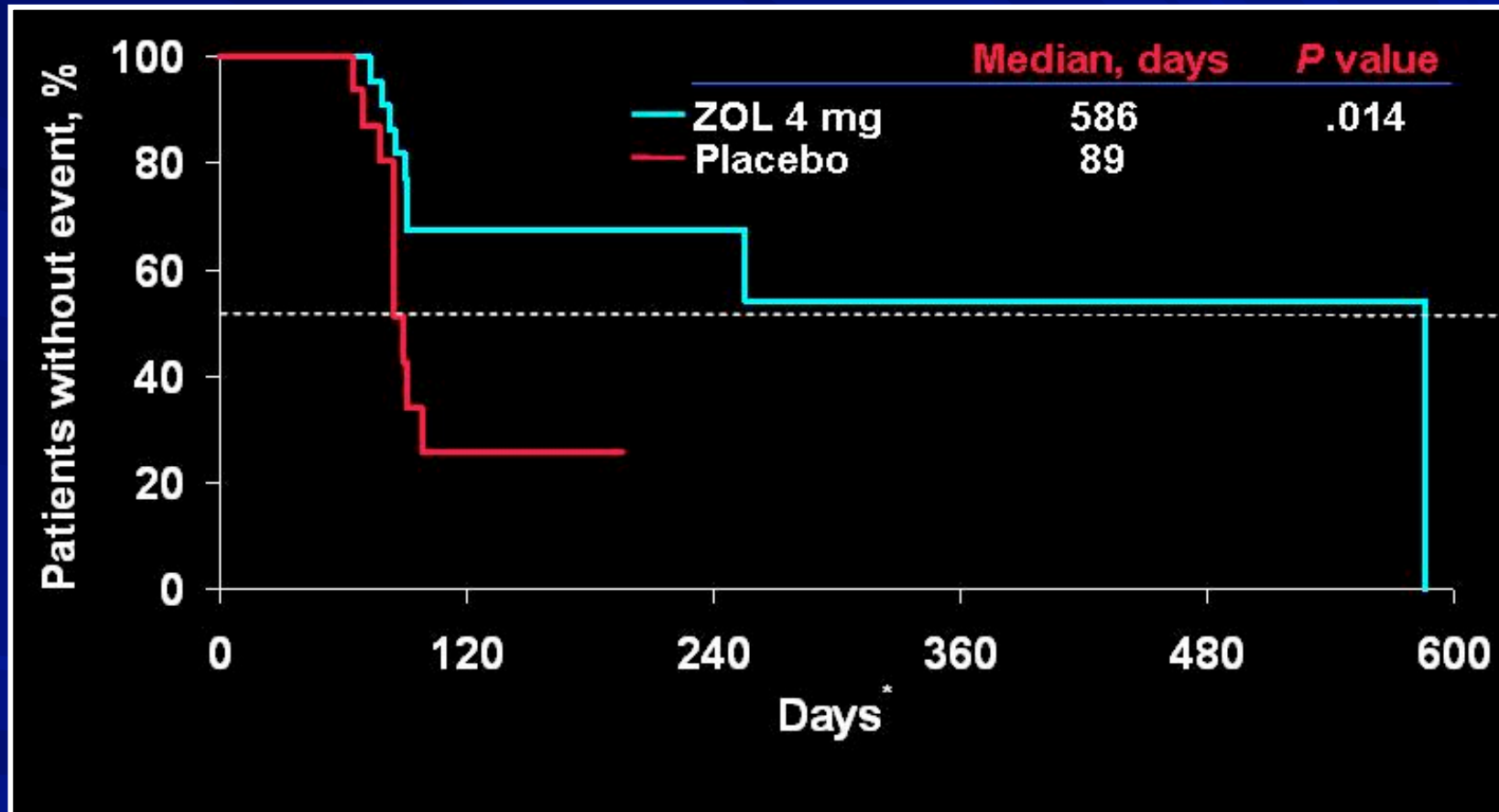
Bone-metastasis-free interval (18-month analysis)



Bisphosphonates and survival in prostate cancer

... And recent exploratory analyses demonstrated that the death rate was slightly lower for patients treated with zoledronic acid compared with placebo (66% versus 73%, respectively)

Zoledronic Acid Significantly Extends the Time to Bone Progression in Patients With Renal Cell Carcinoma

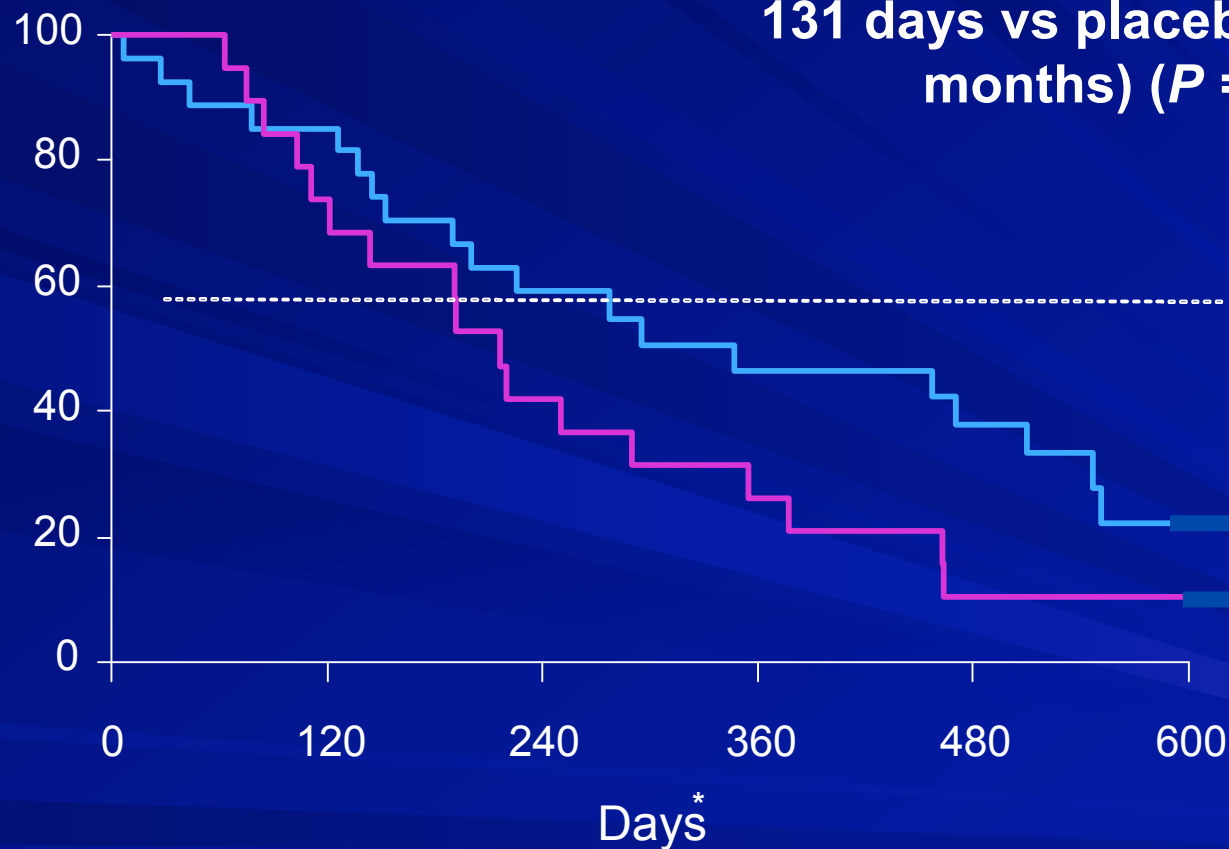


*After start of study drug.

Reprinted with permission. Lipton A, et al. Cancer. 2003;98:962-969.

Zoledronic Acid and RCC Survival

**ZA increases median survival of
131 days vs placebo (11.5 vs 7.2
months) ($P = 0.104$)**



Zol 4 mg	27	23	15	11	8	2
Placebo	19	14	8	5	2	1

Reprinted with permission. Lipton A, et al. Cancer. 2003;98:962-969.

Z-FAST, ZO-FAST, E-ZO-FAST Trials— Disease Recurrence at 12 Months

Z-FAST/ZO-FAST/E-ZO-FAST pooled exploratory analysis

Upfront group
(n = 1,096)

Delayed group
(n = 1,097)

Disease recurrence at month 12,
no. of patients (%)

17 (1.5)

23 (2.1)

Local

5 (0.5)

6 (0.5)

Distant

11 (1.0)

17 (1.6)

Z-FAST/ZO-FAST integrated analysis

Upfront group
(n = 833)

Delayed group
(n = 834)

Median time to disease
recurrence, months (range)

8.6 (3.3 - 11.5)

6.4 (1.0 - 10.8)

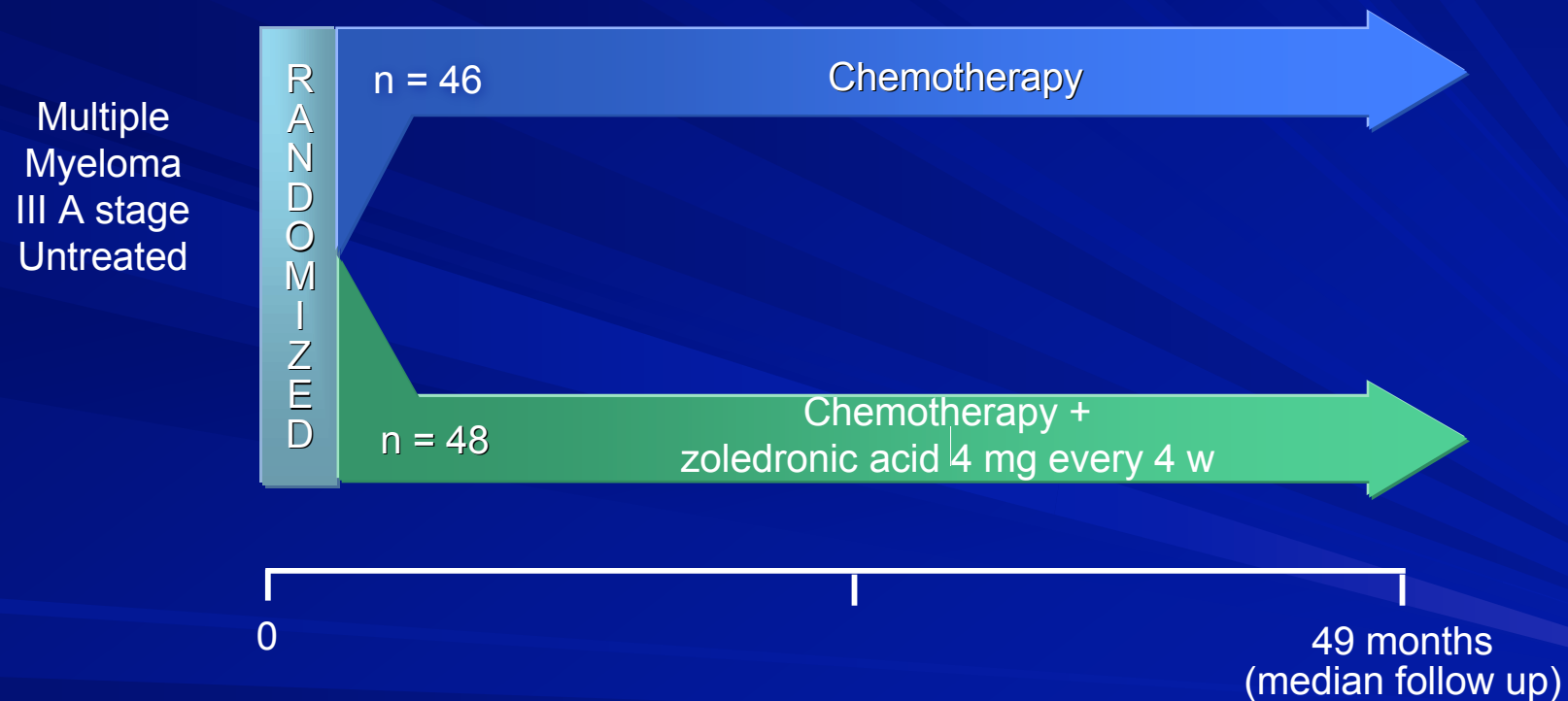
Z-FAST Trial: Effect of Zoledronic Acid on Disease Recurrence

	Patients, n (%)	
	Upfront group	Delayed group
Month 12 ¹	1 (0.3)	6 (2.0)
Month 24 ²	7 (2.3)	12 (4.0)
Month 36 ³	9 (3.0)	14 (4.7)

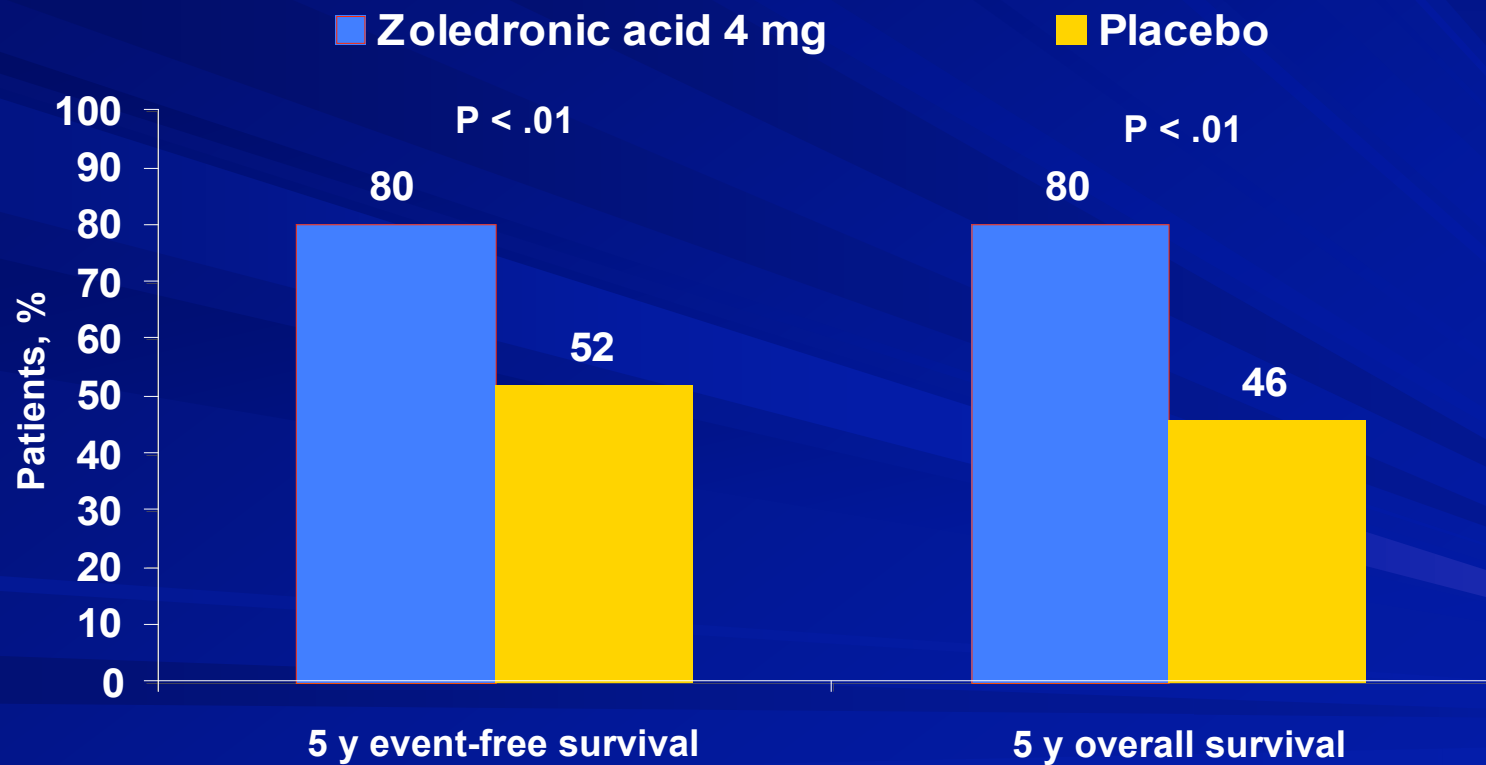
1. Novartis, data on file; 2. Brufsky A, et al. Presented at SABCS 2006. Abstract 5060;

3. Brufsky A, et al. Presented at SABCS 2007. Abstract 27.

Antitumor Effect of Zoledronic Acid in Previously Untreated Patients with Multiple Myeloma



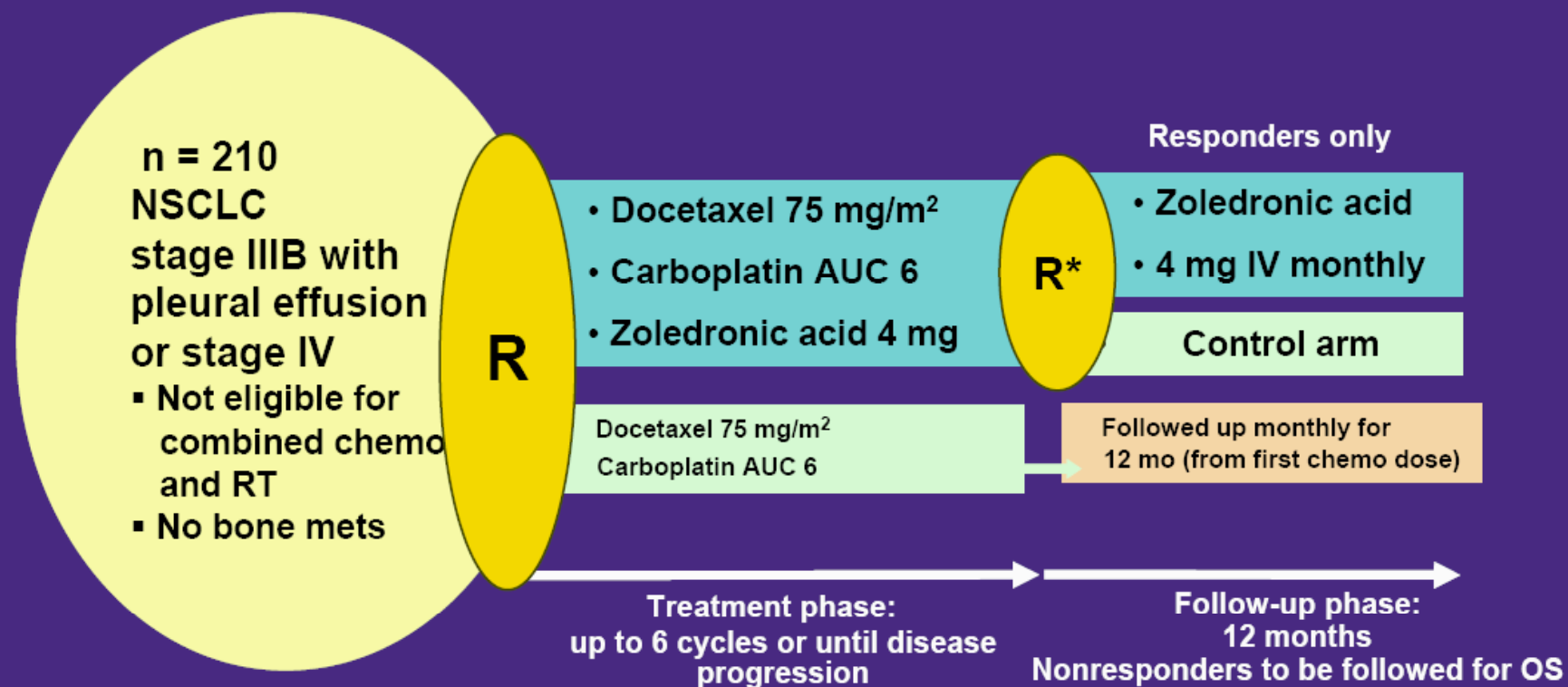
Antitumor Effect of Zoledronic Acid in Previously Untreated Patients with Multiple Myeloma



Exploratory/Antitumor Study in Patients With NSCLC: Z-PACT

Key Endpoints

Proportion of patients with no disease progression, TTP, RR, TTP in bone, OS, safety



- **Complete enrollment: planned = 210; enrolled = 153**

NSCLC = Non-small cell lung cancer; TTP = Time to progression; RR = Response rate; OS = Overall survival.

*Responders only.

Do adjuvant bisphosphonates reduce the risk of disease relapse?

Randomized prospective
adjuvant studies

Santini D et al. Ann Oncology, 2007

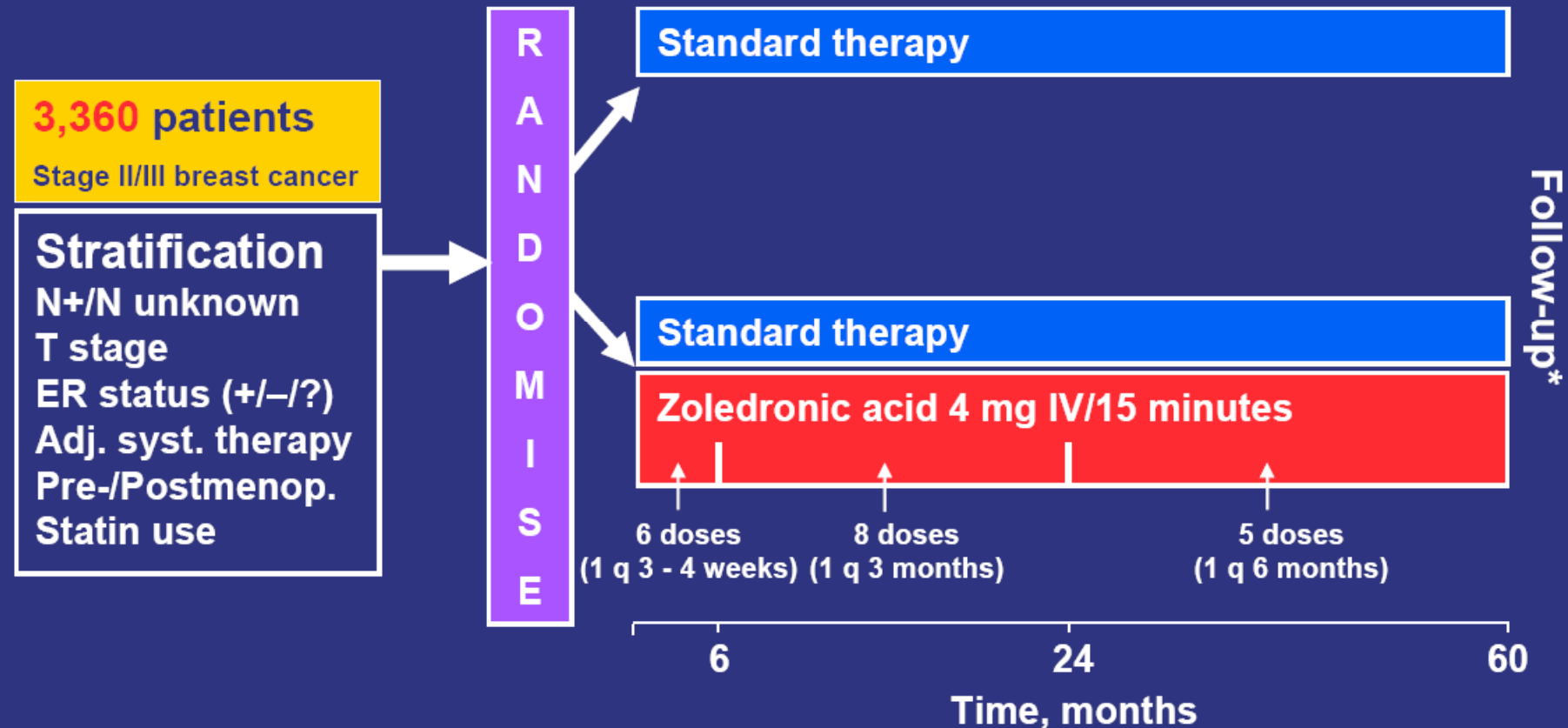
Ongoing Studies for the Prevention of Bone Metastasis

Cancer type	Study	Treatment	Enrollment enrolled/planned
Breast	AZURE	Standard treatment ± zoledronic acid	3,360
	NSABP-B-34		3,400 planned
	Intergroup S0307	Zoledronic acid vs clodronate vs ibandronate	6,000 planned
	SUCCESS	Zoledronic acid 2 years vs 5 years	3,754 / 3,658
Prostate	ZEUS	Zoledronic acid vs control group	1,385 / 1,420
Lung	2419	Zoledronic acid vs control group	292 / 446

First interim analysis expected 2008-2009

Zoledronic Acid for the Prevention of Bone Metastases in Breast Cancer (AZURE)

Study design



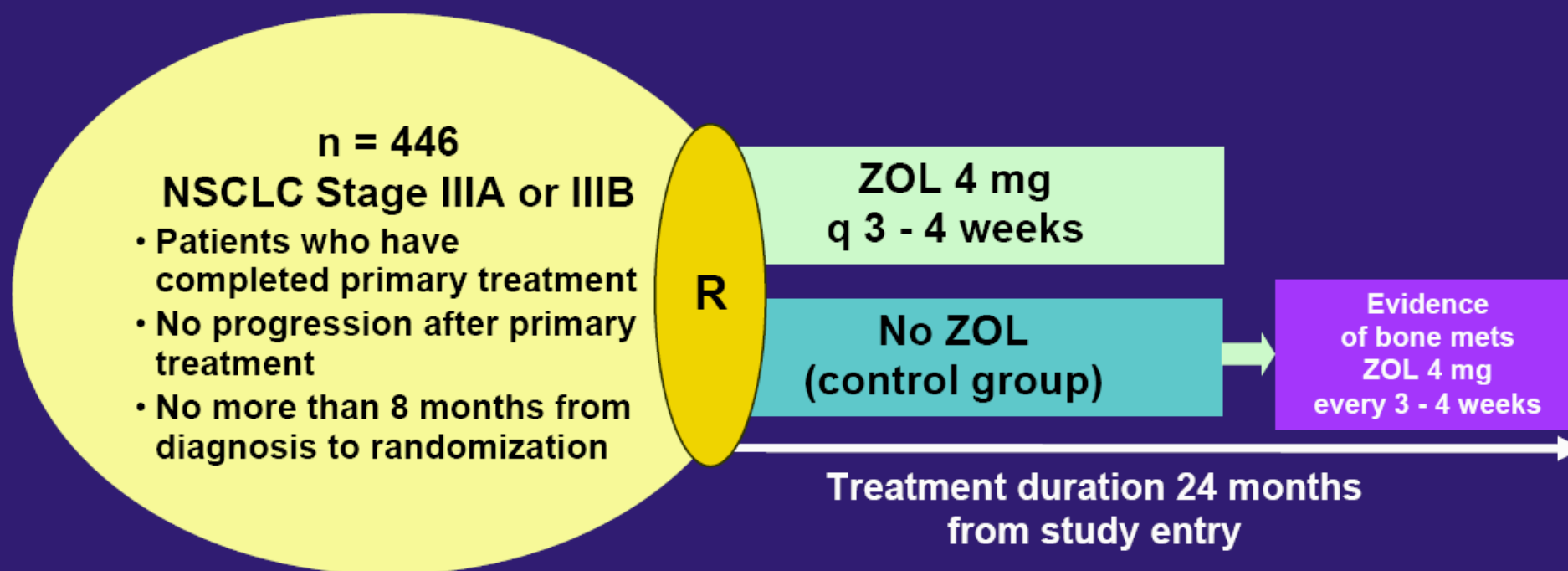
PI: R. Coleman

*Follow-up: 10 years for recurrence and survival.

Prevention of Bone Metastases in Patients With NSCLC: Study 2419

Key Endpoints

Time to occurrence of bone mets; rate of bone mets at 6, 12, 18, and 24 months; TTP; rate and risk of SREs; time to first SRE; OS at 12 and 24 months; BSP expression in primary tumor (substudy)



- **Active enrollment: planned = 446; enrolled = 330***

*As of November 30, 2007.

NSCLC = Non-small cell lung cancer; TTP = Time to disease progression; SRE = Skeletal-related event; OS = Overall survival; BSP = Bone sialoprotein; ZOL = Zoledronic acid.

Principle investigator: G. Scagliotti, University of Torino.

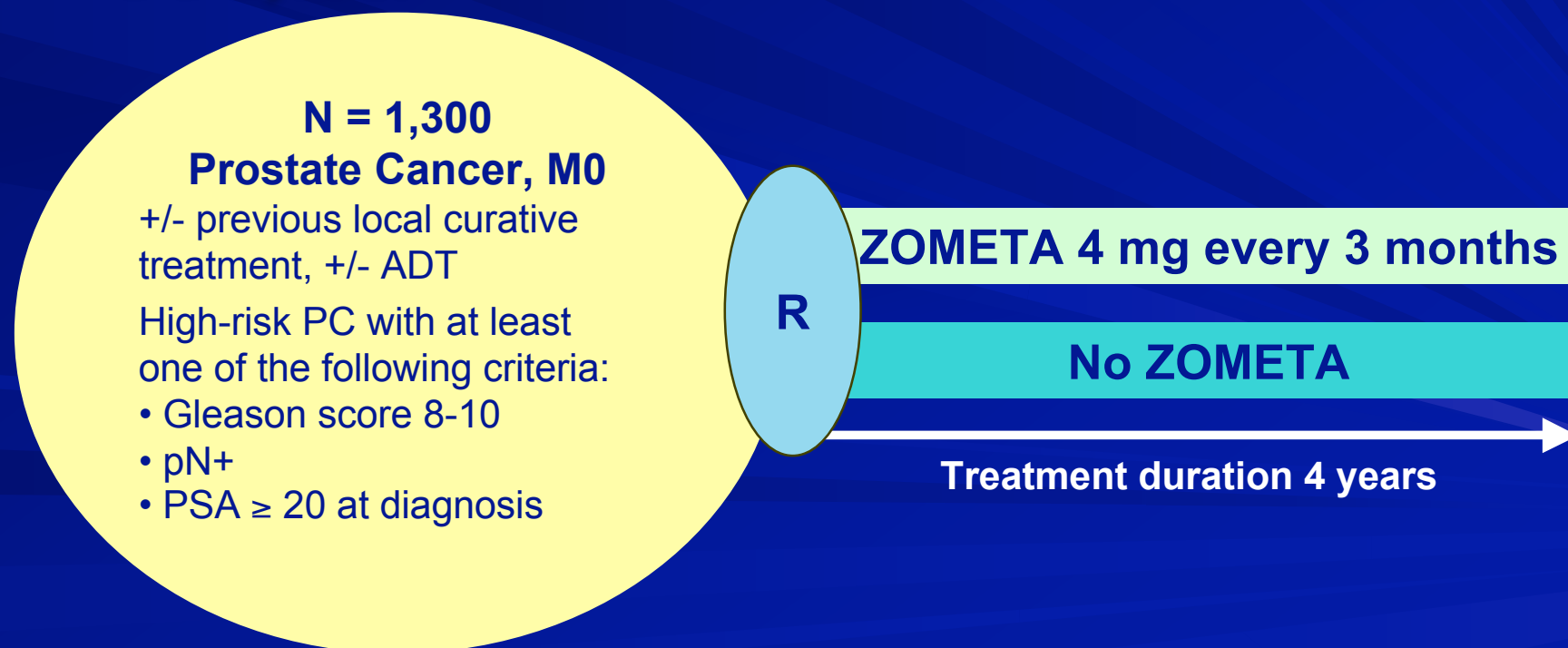
Prostate Cancer: ZEUS study

■ Key endpoints

Proportion of patients with bone metastasis at 48 mo, time to bone mets, overall survival, PSA doubling time, substudies on bone markers and BMD

■ Status

681 patients enrolled, interim analysis expected in 2008/2009,
Final analysis 2011

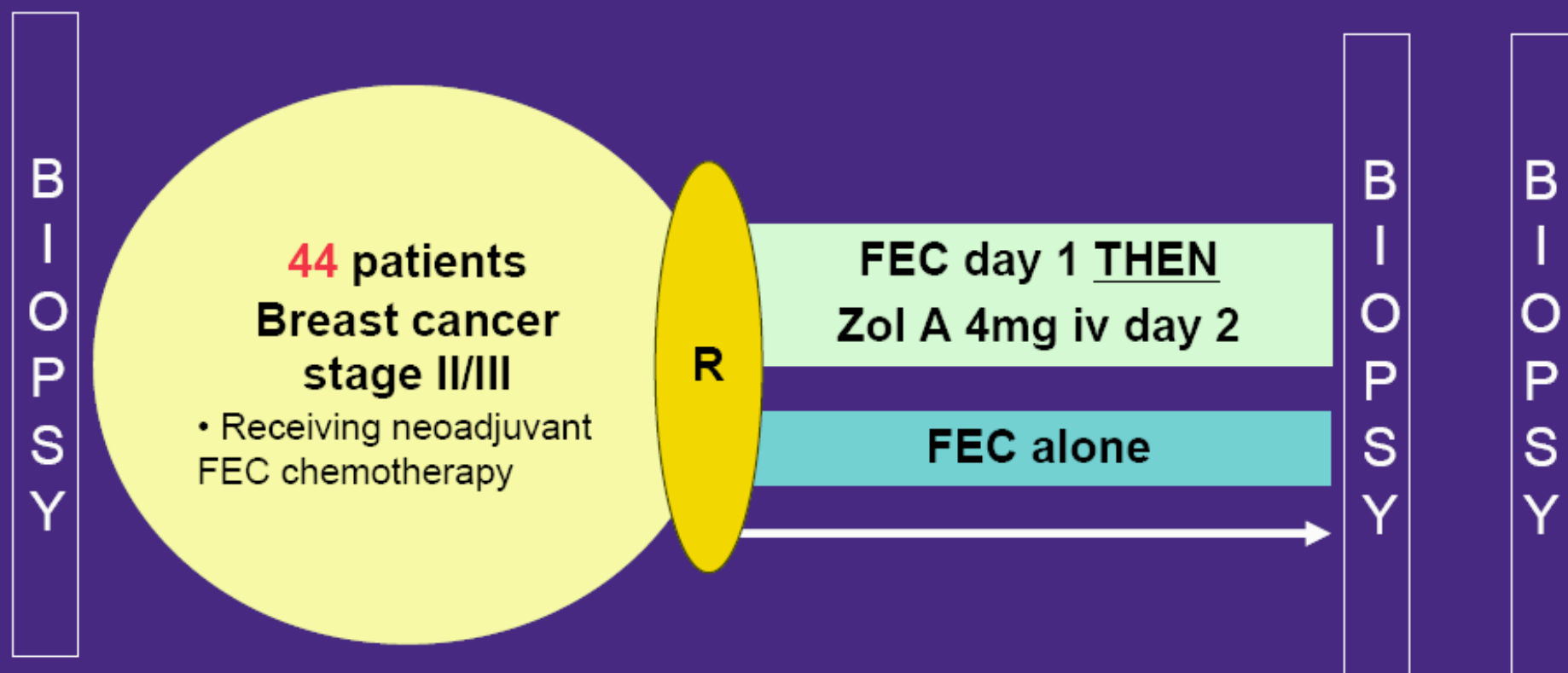


ANZAC: Randomised Phase II Biomarker Study of Neoadjuvant Zoledronic Acid in Breast Cancer

- **Primary endpoint:** Changes in apoptosis and proliferation markers

Diagnosis

Day 4 Day 21



Current accrual: 9 patients



**Thank you very much
for the attention**

... lo so non ce la fate più !!!