



## I BIFOSFONATI

NEL PAZIENTE  
ONCOLOGICO ED  
EMATOLOGICO

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# METASTASI SCHELETRICHE da TUMORI SOLIDI

Altre neoplasie

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# Metastasi ossee e carcinoma polmonare

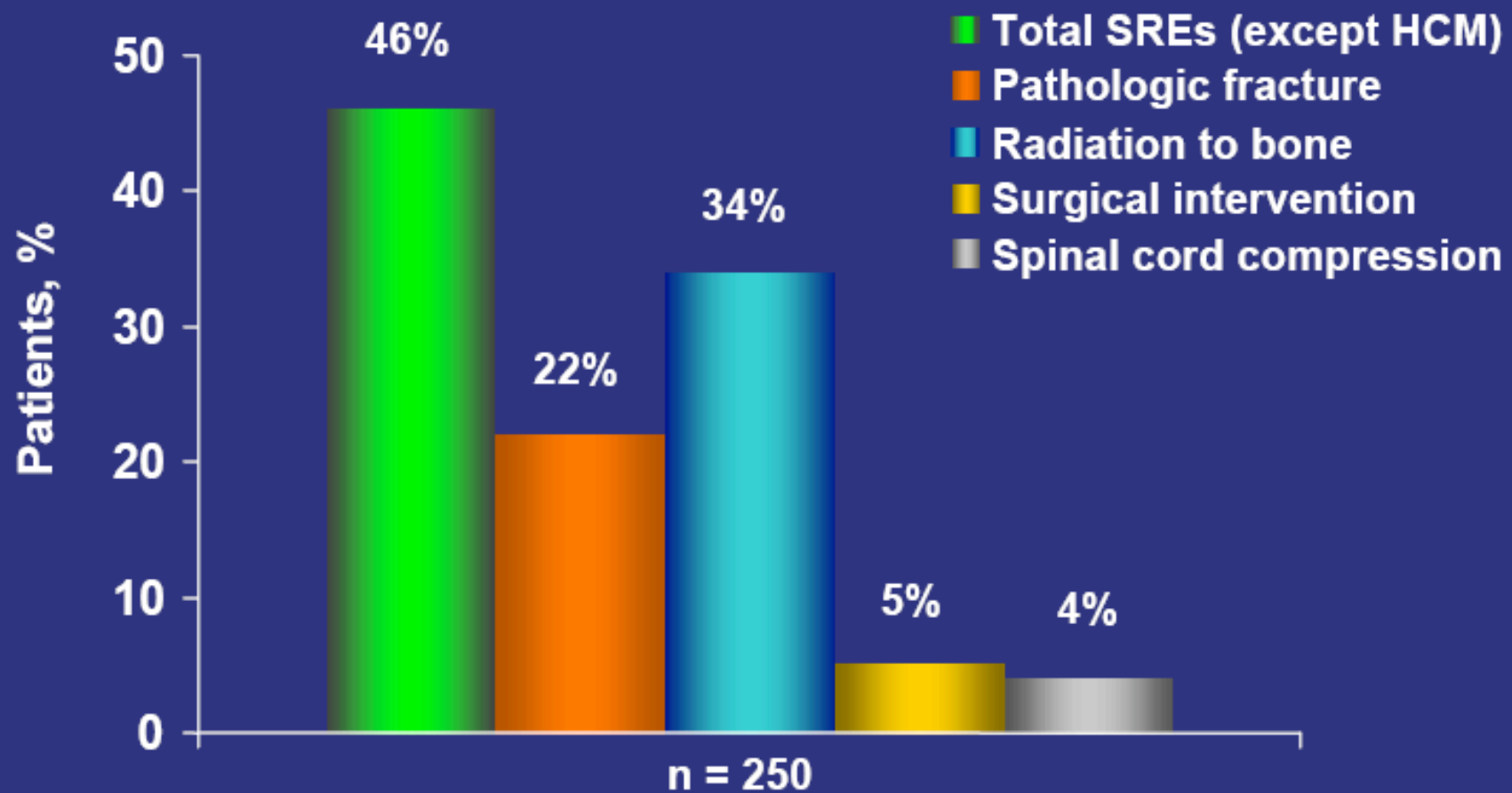
- Lesioni ossee si manifestano nella storia naturale della malattia in circa il 40% dei pazienti
- La sopravvivenza mediana dalla diagnosi di mts ossee è inferiore ai 6 mesi
- In genere le lesioni sono litiche ma i neuroendocrini (SCLC) hanno una tendenza a produrre lesioni addensanti
- La radioterapia esterna e i radioisotopi a scopo palliativo pare siano meno efficaci rispetto ad altre neoplasie

# Metastasi ossee e carcinoma renale

- Lesioni ossee si manifestano nella storia naturale della malattia nel 25-40% dei pazienti
- La sopravvivenza mediana dalla diagnosi di mts ossee può arrivare a 12 mesi
- Le lesioni sono litiche con pattern di sede particolare (scapola)
- La radioterapia esterna probabilmente necessita di dosi più elevate ma è efficace nella palliazione

## SREs Are a Serious Threat to Patients With NSCLC or Other Solid Tumors if Bone Metastases Are Untreated

21-month data from placebo arm of randomized study



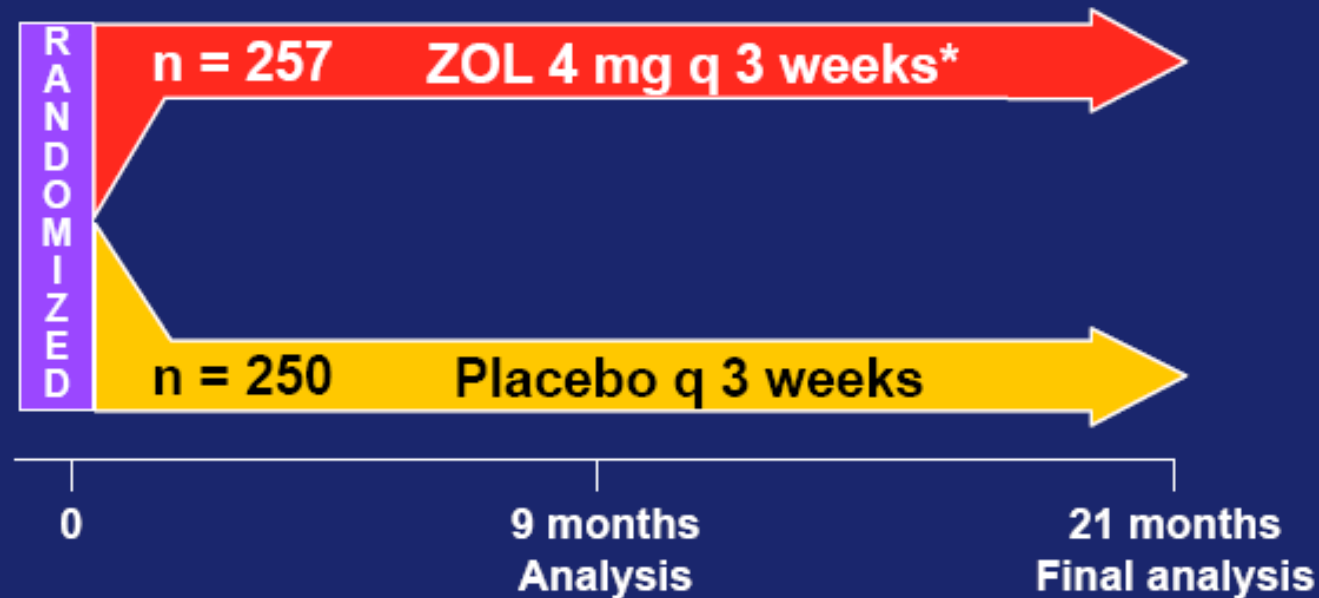
SRE = Skeletal-related event; NSCLC = Non-small cell lung cancer; HCM = Hypercalcemia of malignancy.  
Rosen LS, et al. *Cancer*. 2004;100:2613-2621.

## **Long-Term Efficacy and Safety of Zoledronic Acid in the Treatment of Skeletal Metastases in Patients with Nonsmall Cell Lung Carcinoma and Other Solid Tumors**

*A Randomized, Phase III, Double-Blind, Placebo-Controlled Trial*

- Doppio cieco vs placebo
- Circa 2/3 dei pazienti avevano manifestato un evento scheletrico prima dell'arruolamento
- Tiroide 11 pazienti, testa collo 17, rene 74, primitività occulta 51, altri 177
- Circa il 25% completa i 9 mesi di trattamento
- La durata mediana del trattamento è di 4 mesi
- La sopravvivenza mediana è di 6 mesi

# Clinical Trial of ZOL in Patients With Bone Metastases From NSCLC and Other Solid Tumors



- Stratification based on NSCLC versus other solid tumors
  - ~50% of patients had NSCLC
  - ~7% of patients had SCLC; ~43% of patients had other solid tumors

All patients received daily oral vitamin D 400 IU and calcium 500 mg.

ZOL = Zoledronic acid; NSCLC = Non-small cell lung cancer; SCLC = Small cell lung cancer.

\*Patients were also randomized to 8 mg ZOL, but this dose was discontinued.

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

## Long-Term Efficacy and Safety of Zoledronic Acid in the Treatment of Skeletal Metastases in Patients with Nonsmall Cell Lung Carcinoma and Other Solid Tumors

*A Randomized, Phase III, Double-Blind, Placebo-Controlled Trial*

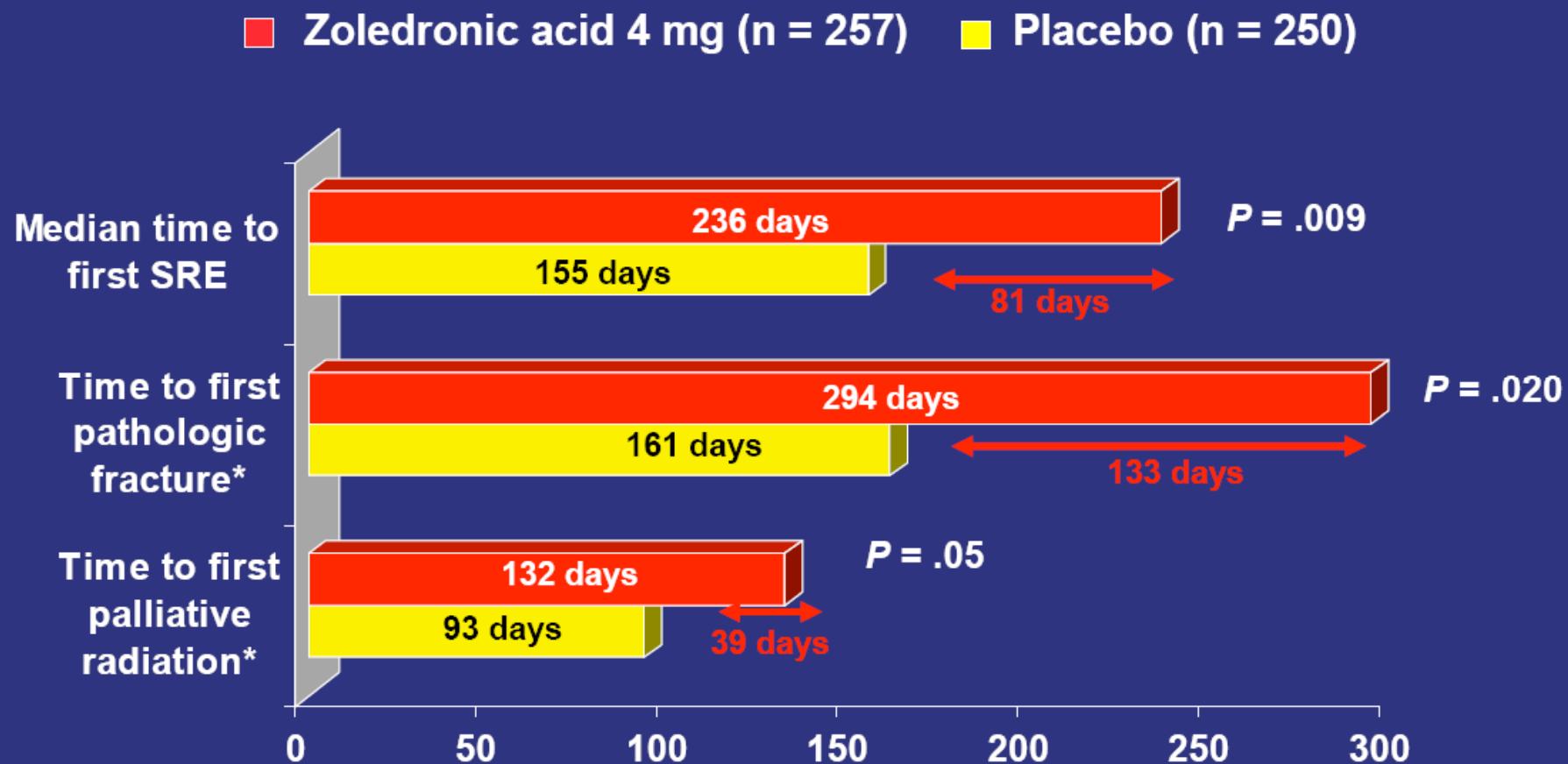
**TABLE 2**  
**Incidence of Skeletal Complications by Treatment Group**

Skeletal complication	Patients, no. (%)		
	Zoledronic acid, 4 mg ( <i>n</i> = 257)	Zoledronic acid, 8/4 mg ( <i>n</i> = 266)	Placebo ( <i>n</i> = 250)
Any SRE (– HCM)	100 (39)	95 (36) <sup>a</sup>	114 (46)
Any SRE (+HCM)	100 (39) <sup>a</sup>	96 (36) <sup>a</sup>	120 (48)
Radiation to bone	74 (29)	73 (27)	86 (34)
Pathologic fractures	40 (16)	32 (12) <sup>a</sup>	55 (22)
Surgery to bone	11 (4)	14 (5)	13 (5)
Spinal cord compression	8 (3)	7 (3)	10 (4)
HCM	0 (0) <sup>a</sup>	3 (1)	9 (4)

SRE: skeletal-related event; HCM: hypercalcemia of malignancy.

<sup>a</sup> *P* < 0.05 versus placebo.

# Zoledronic Acid Delayed Time to SREs in Patients With NSCLC and OSTs

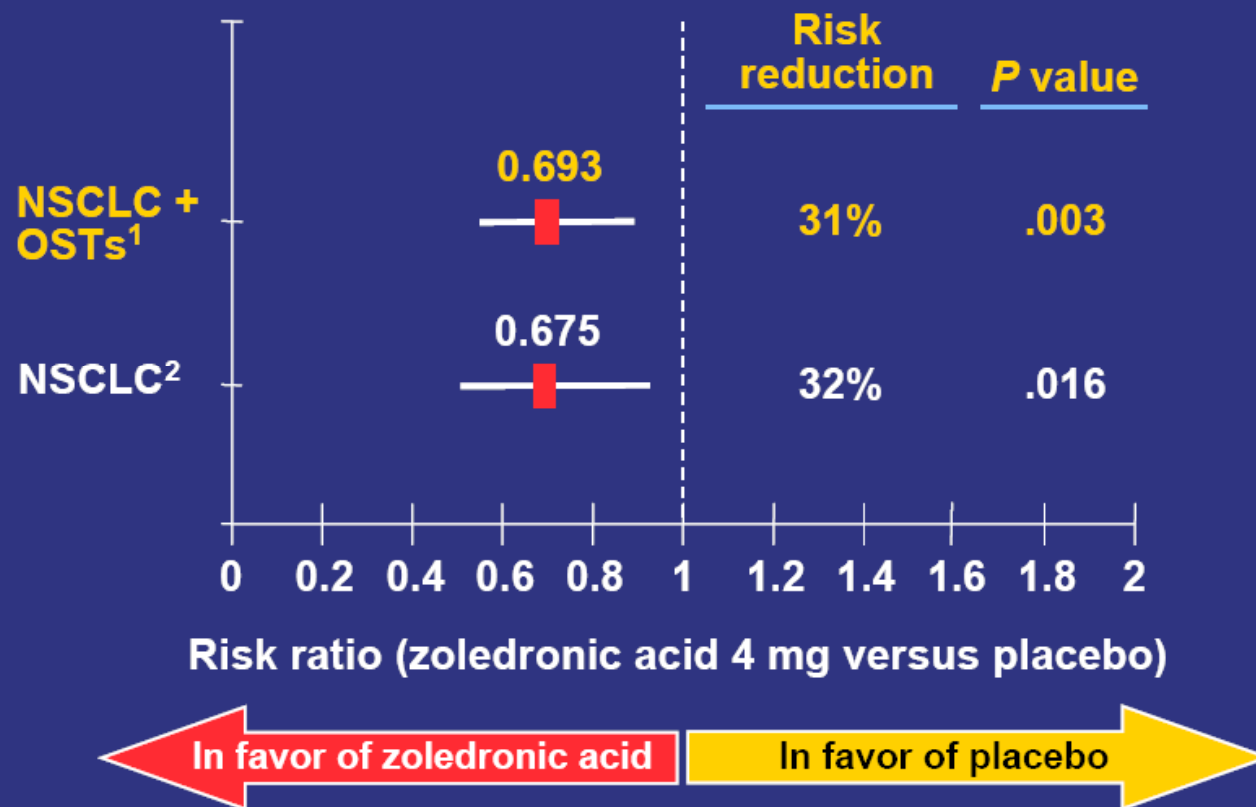


SRE = Skeletal-related event; NSCLC = Non-small cell lung cancer; OST = Other solid tumors.

\*Medians not reached. Values given are for the respective 25% quartiles.



# Zoledronic Acid Reduced the Risk of Developing an SRE



SRE = Skeletal-related event; NSCLC = Non-small cell lung cancer; OST = Other solid tumors.

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

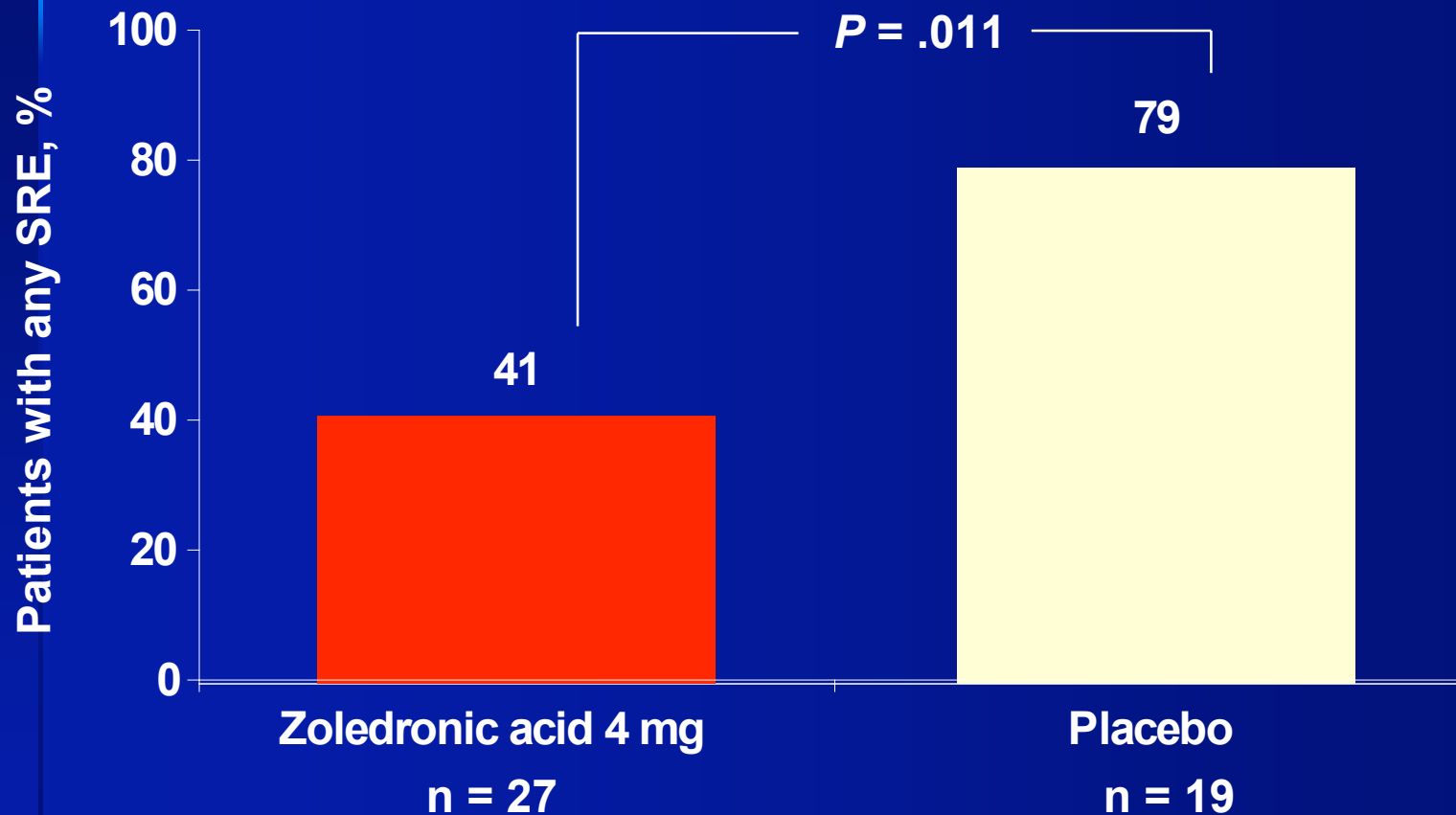
2. Belch A, et al. *Proc Am Clin Oncol*. 2003;22:761. Abstract 3058.

# Advanced Renal Cell Carcinoma (Protocol 011 – Subset analysis)

Variable	Zoledronic acid 4 mg	Placebo
N	27	19
Median age, years	64	65
Sex, %		
Male	18 (67)	17 (89)
Female	9 (33)	2 (11)
Primary therapy, n (%)		
Immunotherapy†	17 (63)	9 (47)
Hormonal therapy	1 (4)	1 (5)
Median time from initial diagnosis to study entry, months§	25.5	21.2
ECOG performance status, n (%)		
≤1	21 (78)	18 (95)
≥2	5 (19)	1 (5)
No. of lesions at study entry, n (%)		
Unknown	1 (4)	1 (5)
1–3	21 (78)	12 (63)
4–6	4 (15)	4 (21)
7–9	1 (4)	2 (11)
Previous SRE, n (%)		
Yes	22 (81)	18 (95)
No	5 (19)	1 (5)

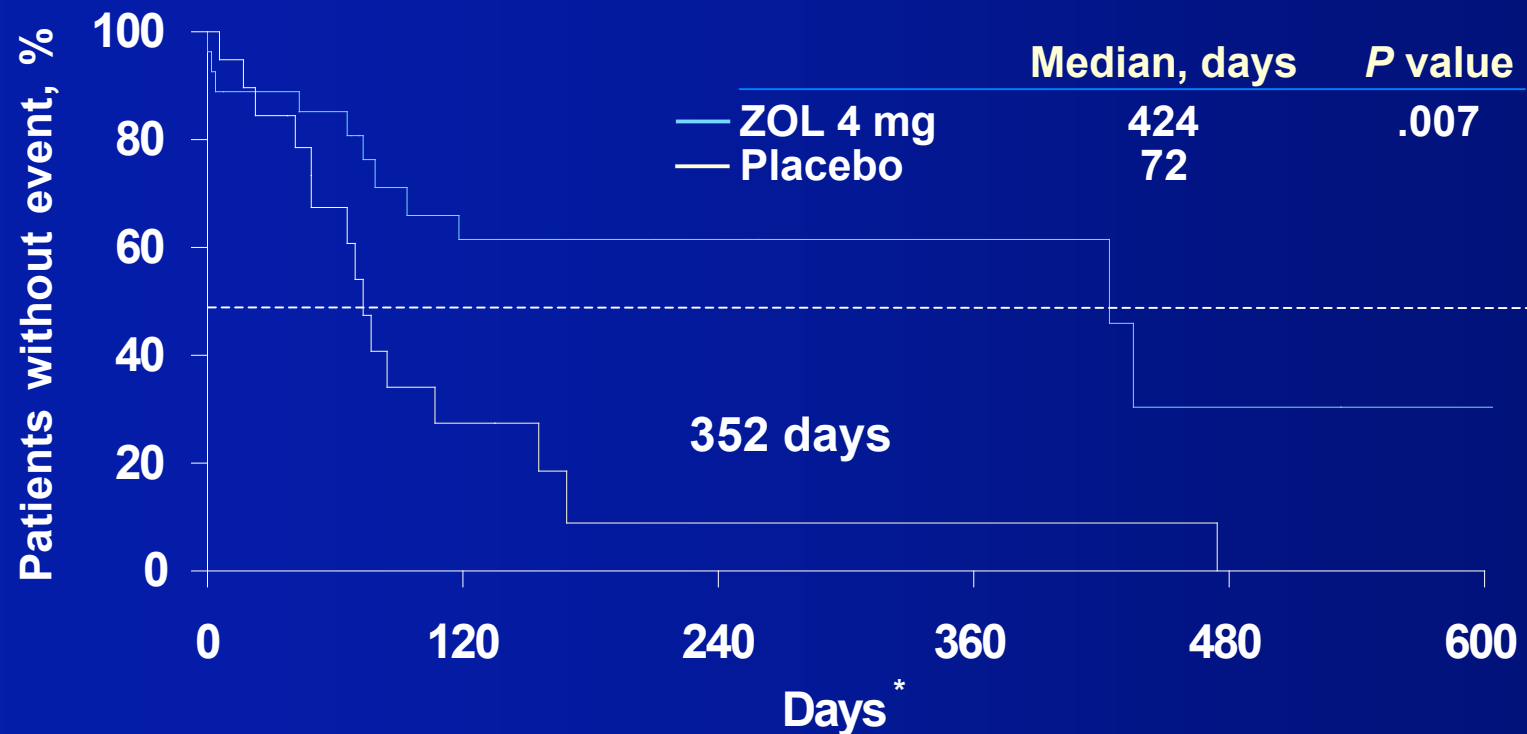
# Advanced Renal Cell Carcinoma (Protocol 011 – Subset analysis a 21 mesi)

Percentuale di pazienti con  $\geq 1$  SRE



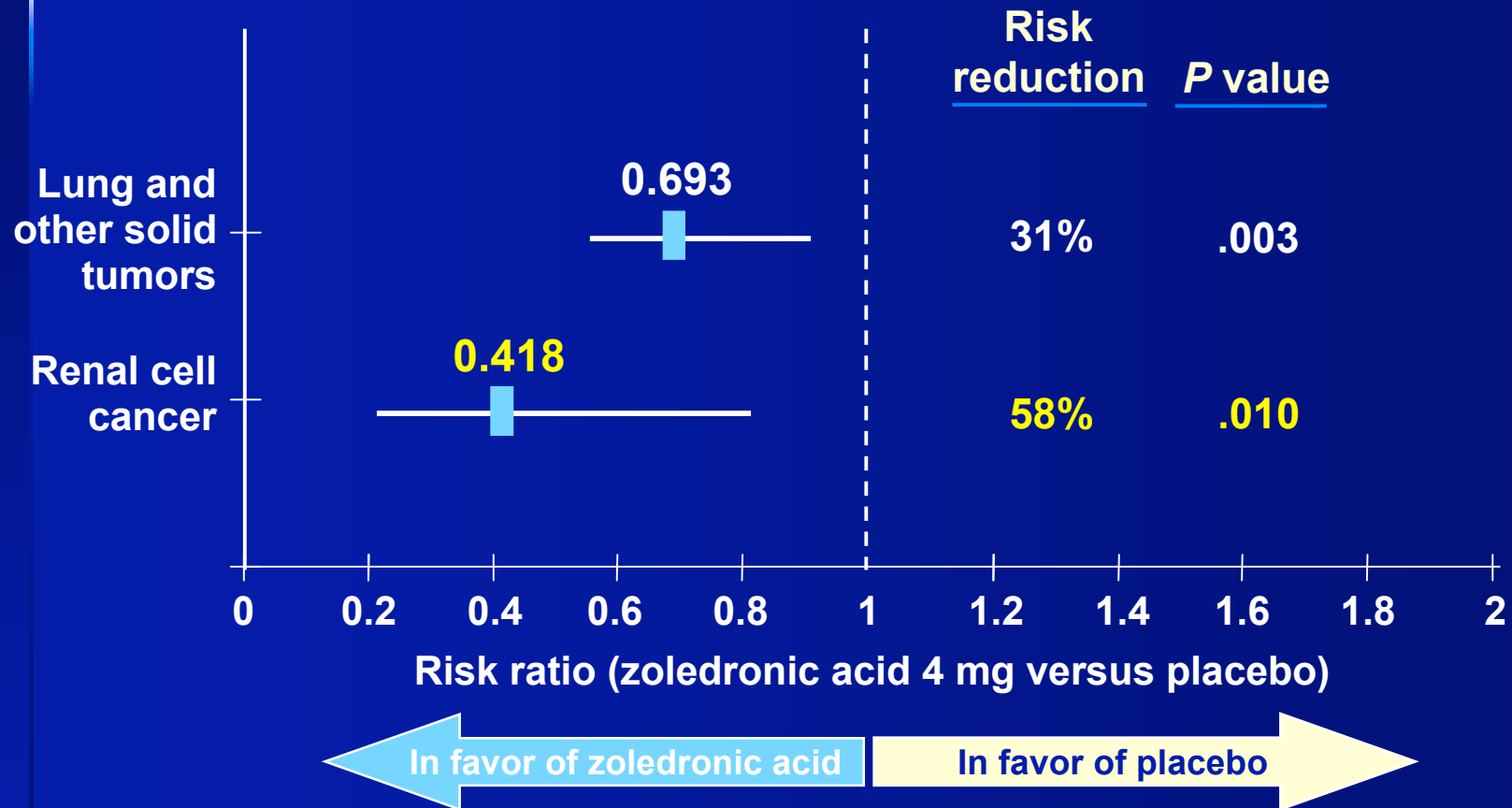
# Advanced Renal Cell Carcinoma (Protocol 011 – Subset analysis a 21 mesi)

Tempo di comparsa del primo SRE



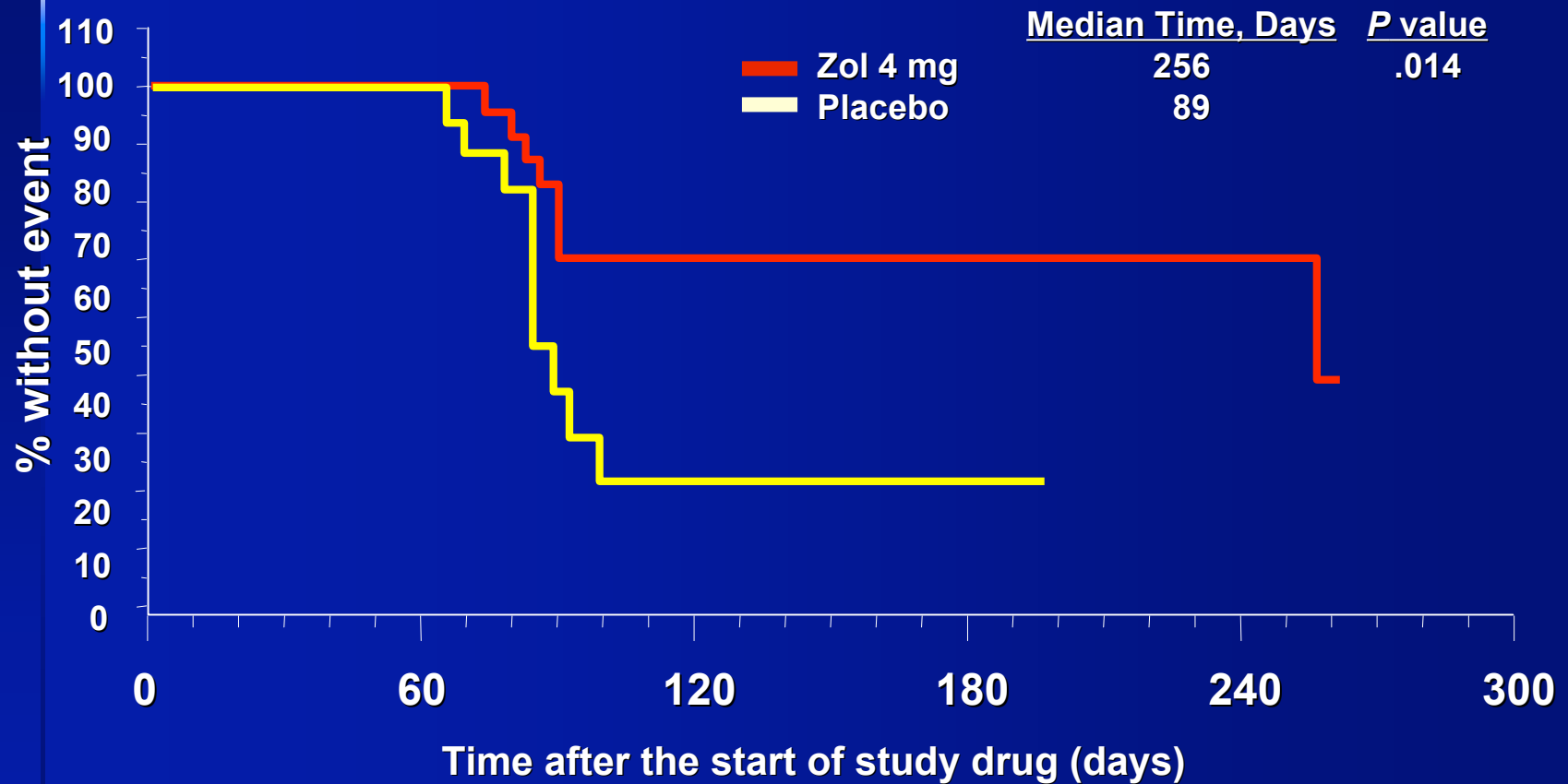
# Advanced Renal Cell Carcinoma (Protocol 011 – Subset analysis a 21 mesi)

Andersen-Gill multiple-event analysis

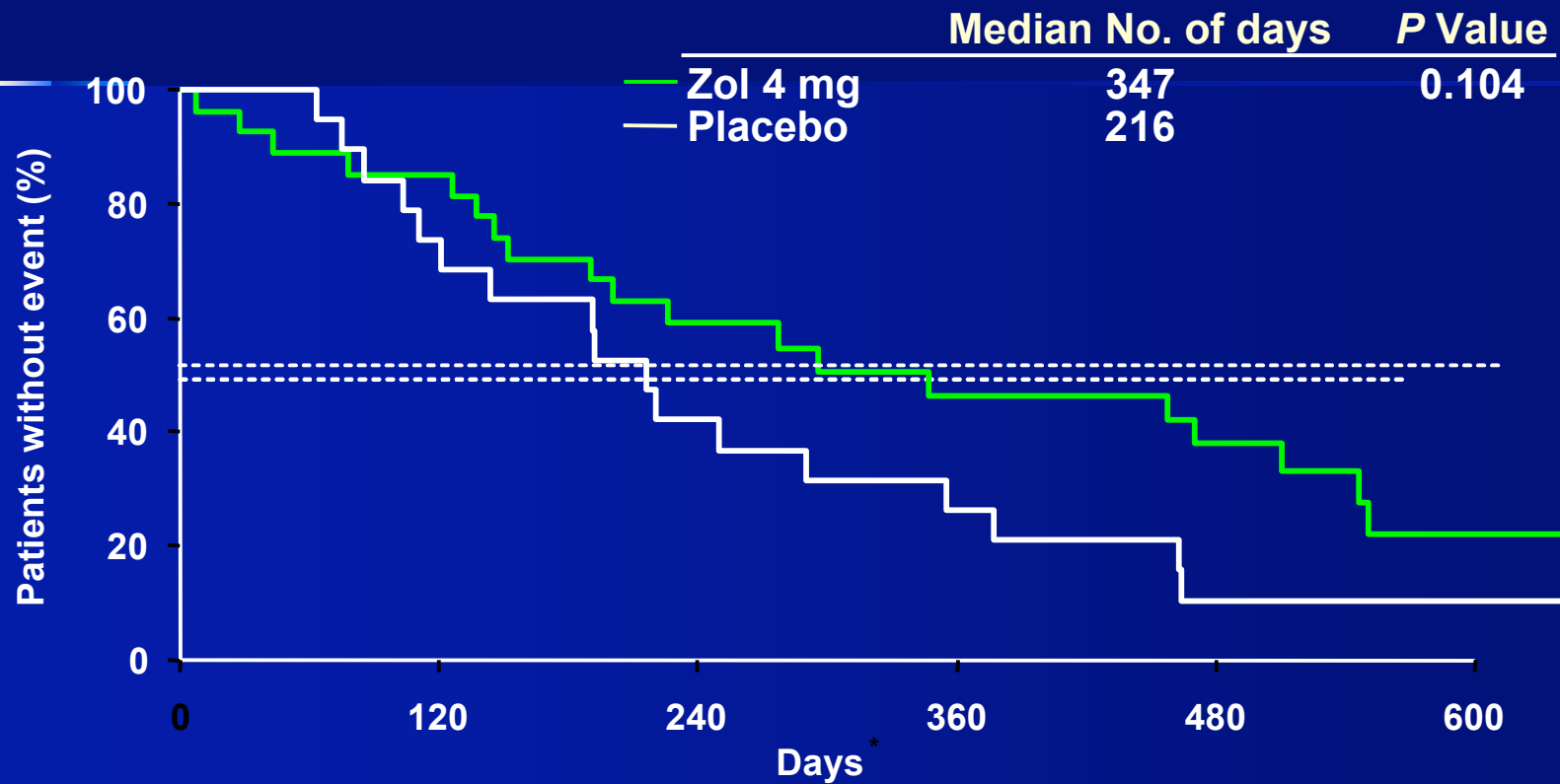


# Carcinoma renale

## tempo alla prima progressione delle metastasi



# RCC : Survival



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

\*After start of study drug.

## Exploratory Bone Marker Analyses Suggest Potential Survival Benefits With Zoledronic Acid

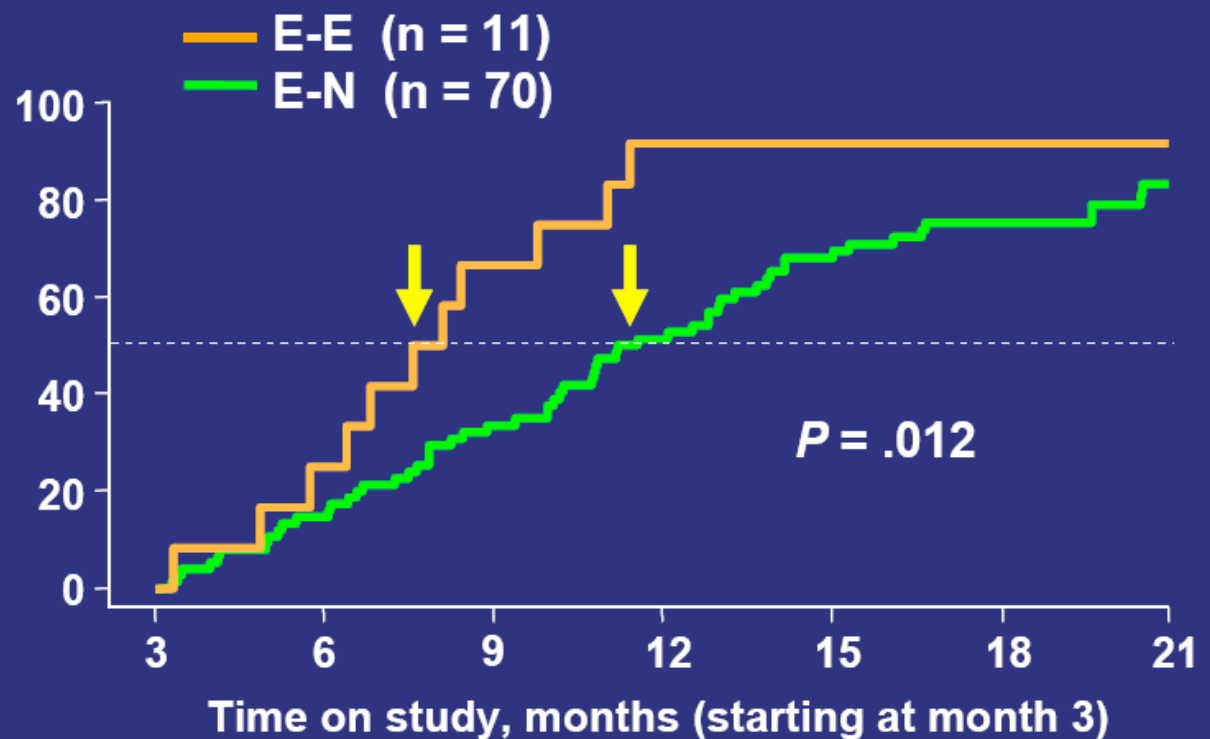
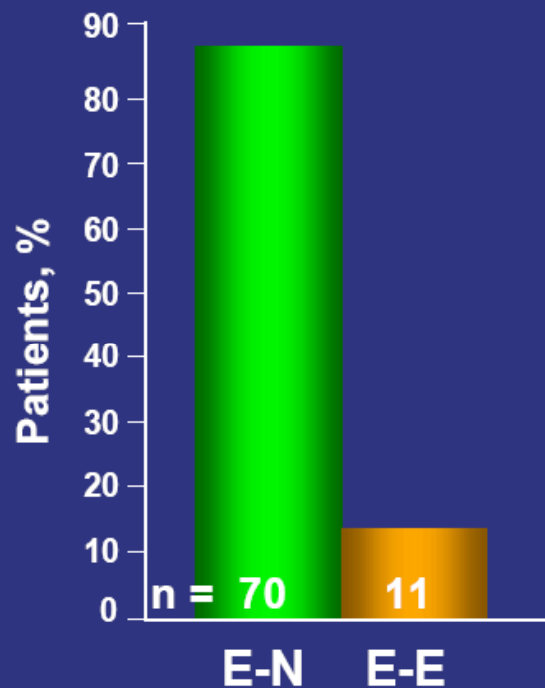
- Elevated levels of bone turnover markers are predictive of negative outcomes in patients with breast, prostate, and lung cancer, or other solid tumors<sup>1,2</sup>
- Zoledronic acid treatment has been reported to significantly reduce NTX and BALP levels in patients with bone metastases
  - Reduction correlates with improved long-term clinical outcomes<sup>3,4,5</sup>

NTX = N-telopeptide of type I collagen; BALP = Bone-specific alkaline phosphatase.

1. Brown JE, et al. *J Natl Cancer Inst.* 2005;97:59-69; 2. Lipton A, et al. *Eur J Cancer.* 2005;3:121. Abstract 431; 3. Lipton A, et al. *J Clin Oncol.* 2007;25:496s. Abstract 9013; 4. Pectasides D, et al. *Anticancer Res.* 2005;25:1457-1463; 5. Coleman RE, et al. *J Clin Oncol.* 2005;23:4925-4935.

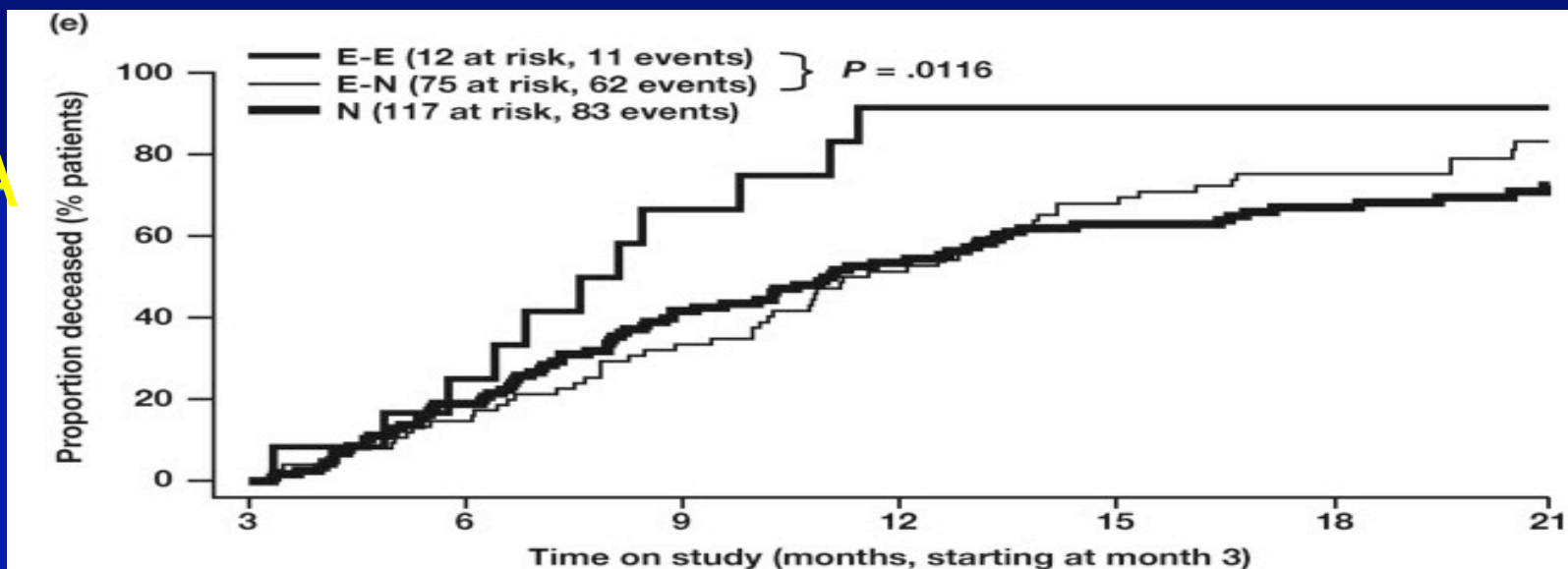


## Zoledronic Acid-Mediated Normalization of NTX Levels Prolonged Survival in Patients With NSCLC or OSTs

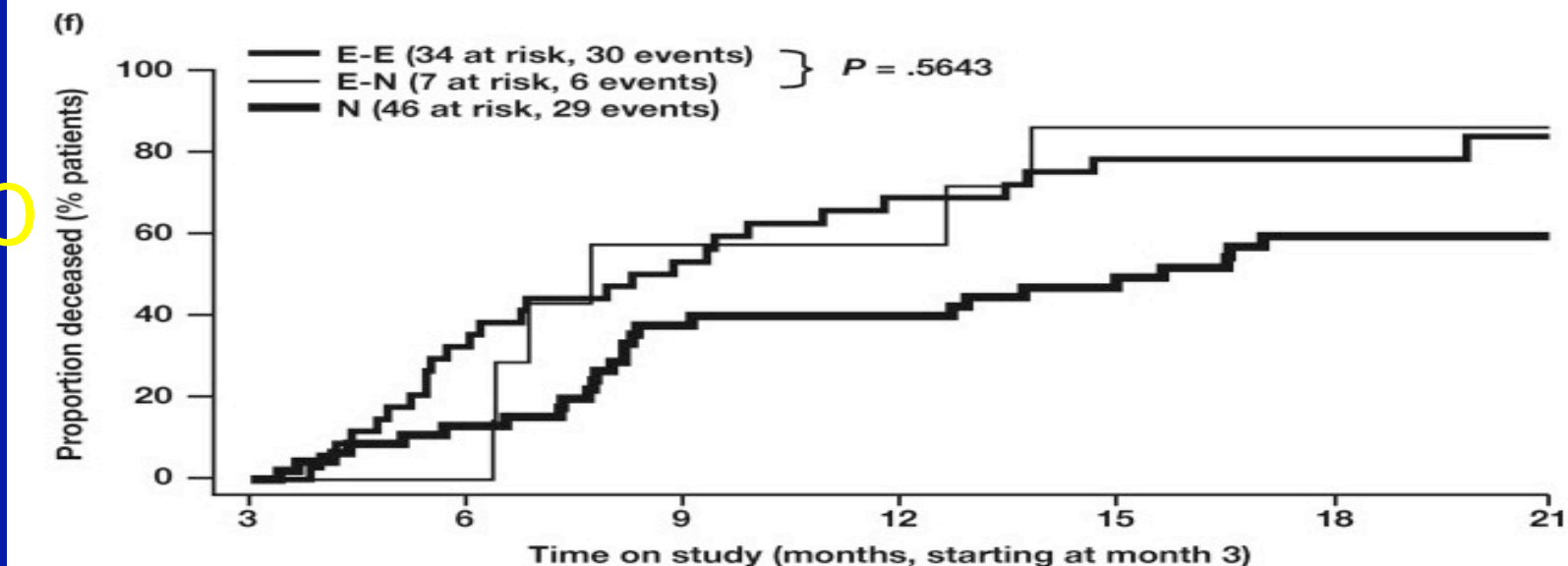


# Normalization of bone markers is associated with improved survival in patients with bone metastases from solid tumors and elevated bone resorption receiving zoledronic acid

ZOMETETA



PLACEBO



# CONCLUSIONI

- Gli eventi scheletrici sono ridotti nel numero e/o ritardati nel tempo nei tumori polmonari e renali in modo clinicamente significativo
- L'acido zoledronico è il primo ed il solo bisfosfonato utile a questo scopo
- La tossicità è del tutto accettabile
- I dati sulla sopravvivenza in relazione ai marker di turnover osseo suggeriscono un effetto rilevante su di essa da parte dell'acido zoledronico
- L'utilizzo dell'NTX nell'indirizzare il trattamento potrebbe rendere "targeted" la terapia con acido zoledronico

# CONCLUSIONI

- ABC
- ABC
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