

The Role of Bisphosphonates in RCC

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Bone Metastasis in Renal Cell Cancer Background

- **More than 100,000 deaths per year worldwide**
 - **Incidence is increasing**
- **A substantial number of patients will have metastatic disease at time of initial diagnosis**
 - **Hematogenic: Lung >> Bone >> Liver >> Brain**
- **Up to 35% of patients with renal cell cancer will develop bone metastases**
- **Bone metastases is a bad prognostic sign poorly responding to systemic therapy**

Skeletal Morbidity Rate in RCC Is Similar to Breast Cancer or Multiple Myeloma

- RCC patients develop 2.5 to 4.0 SREs/patient/year

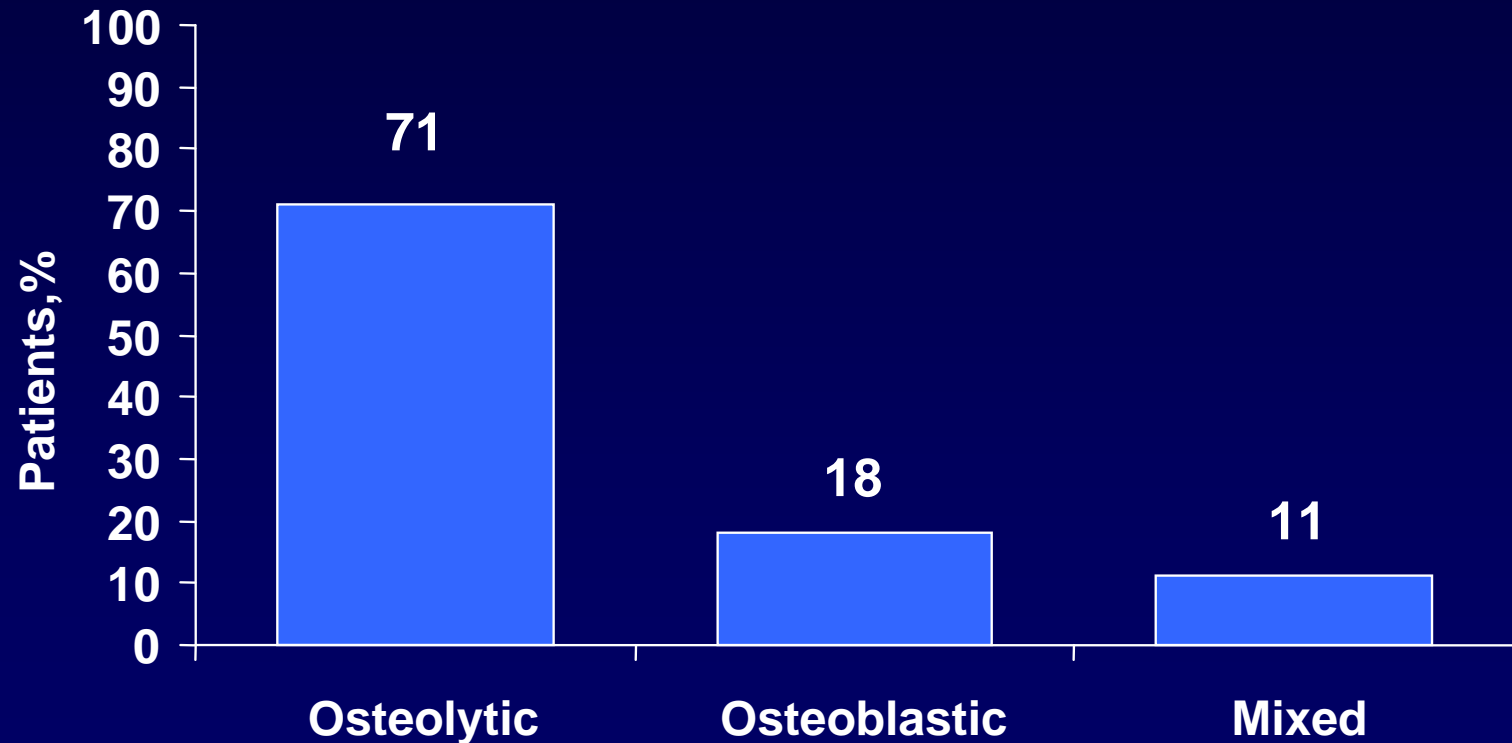
Patients, n (%)

SRE	(n=103)	Events, n
Radiotherapy	25 (81)	37
Long-bone fractures	13 (42)	15
Hypercalcemia of malignancy	9 (29)*	16
Orthopedic surgery	9 (29)	12
Spinal cord compression	4 (13)	4

*An additional 32 patients developed hypercalcemia of malignancy without evidence of metastatic bone disease on imaging tests.

Radiologic Appearance of Bone Lesions in Renal Cell Cancer

- Among 28 patients* with bone lesions, the majority of lesions were osteolytic



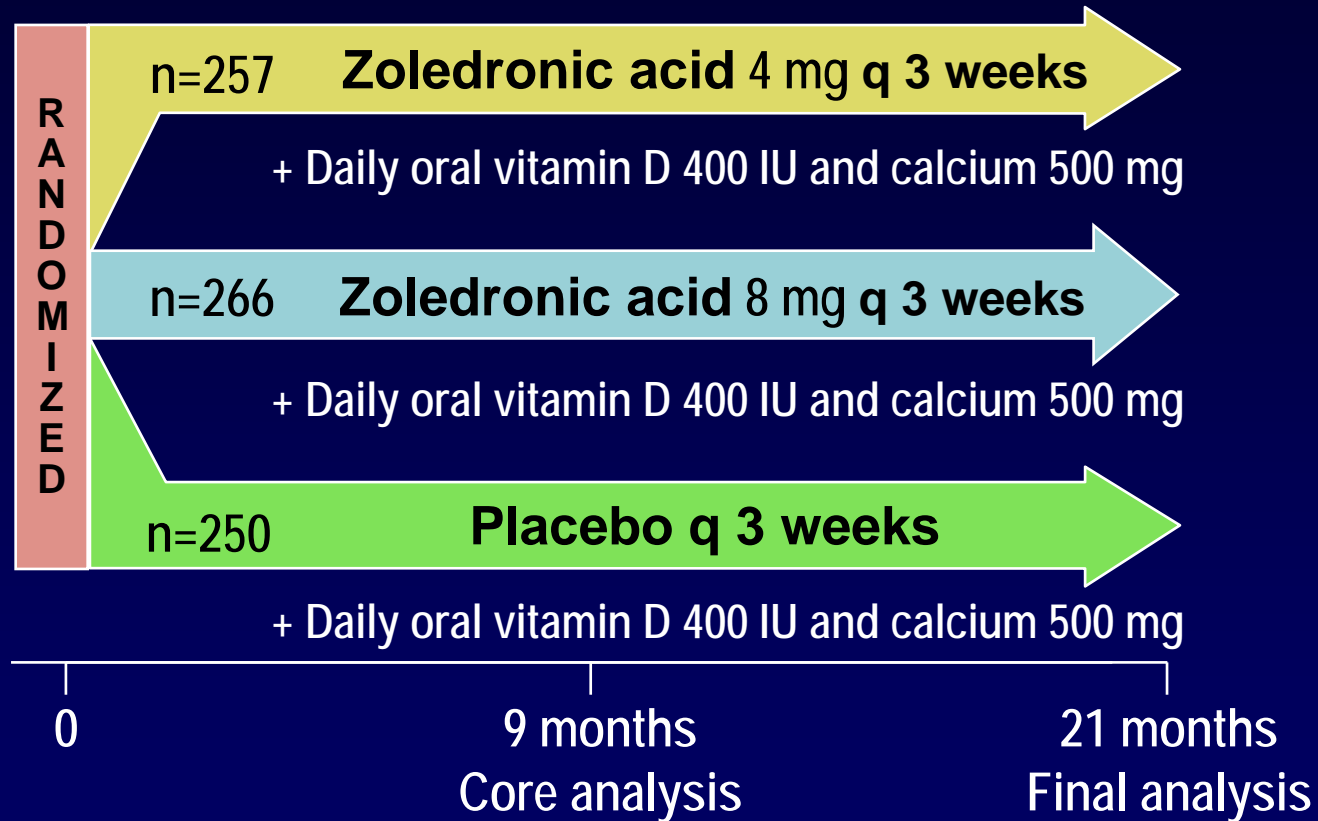
*Radiographs were not available to classify type of bone metastasis for 3 patients.
Zekri J, et al. *Int J Oncol.* 2001;19:379-382.

Zoledronic Acid (ZOMETA®) in Patients With Renal Cancer

Double-Blind, Placebo-Controlled Trial Design

- **Solid tumors other than prostate and breast cancer**
 - ≥ 1 bone metastasis
- **Appropriate antineoplastic therapy at study entry**
- **Serum creatinine 3.0 mg/dL (265 μ mol/L)**
- **ECOG performance status of 0, 1, or 2**
- **Stratification**
 - **Non-small cell lung cancer (NSCLC)**
 - **Other solid tumors**

Lung Cancer and Solid Tumors Trial Design

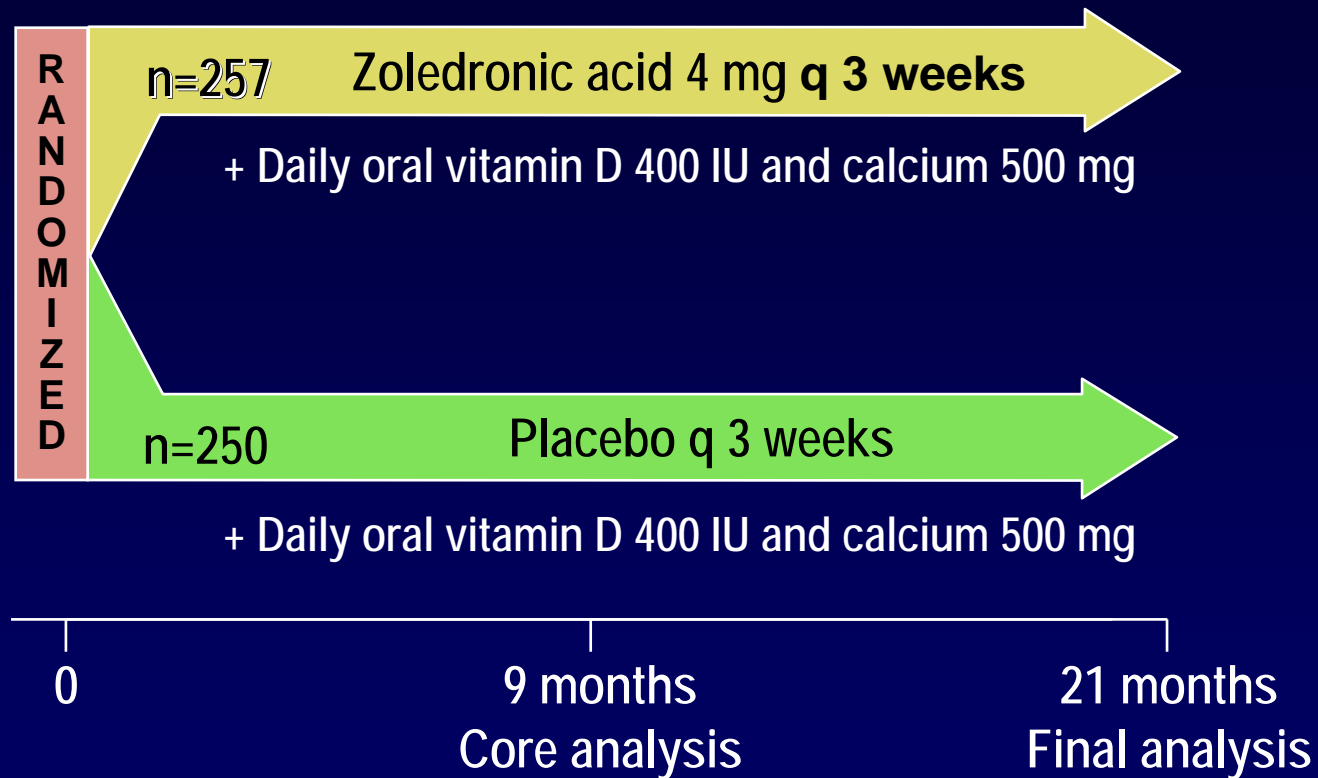


- **Included 74 patients with RCC (n=46 for Zol 4 mg and placebo)**

Dose Amendments

- **Amendment 3 (June 1999)**
 - Infusion time increased from 5 to 15 minutes
 - Infusate volume increased from 50 to 100 mL
- **Amendment 5 (June 2000)**
 - Zoledronic acid 8 mg dose reduced to 4 mg (zoledronic acid 8/4 mg)

Lung Cancer and Solid Tumors Trial Design



- **Included 74 patients with RCC (n=46 for Zol 4 mg and placebo)**

Tumor Types

Tumor type	Patients	
	n	%
NSCLC	378	49
Renal cell carcinoma	74*	10
SCLC	58	8
Colon/rectum/intestine	55	7
Cancer unknown primary	51	7
Bladder	32	4
Esophagus/gastroesophageal	17	2
Head and neck	17	2
Melanoma	16	2
Thyroid	11	1
Other tumor types (n=11)	57	7

*Zoledronic acid 4-mg group and placebo, n=46.

Study Endpoints

- **Primary efficacy endpoint**
 - Proportion of patients with ≥ 1 SRE
- **Secondary endpoints**
 - Time to first SRE
 - Skeletal morbidity rate (SMR)*
 - Multiple-event analysis*
 - Pain/analgesic scores
 - Bone lesion response
 - Time to progression of disease
 - Safety (including survival)

*21-day window: events occurring with 21 days of a counted event were excluded.

Skeletal-Related Events

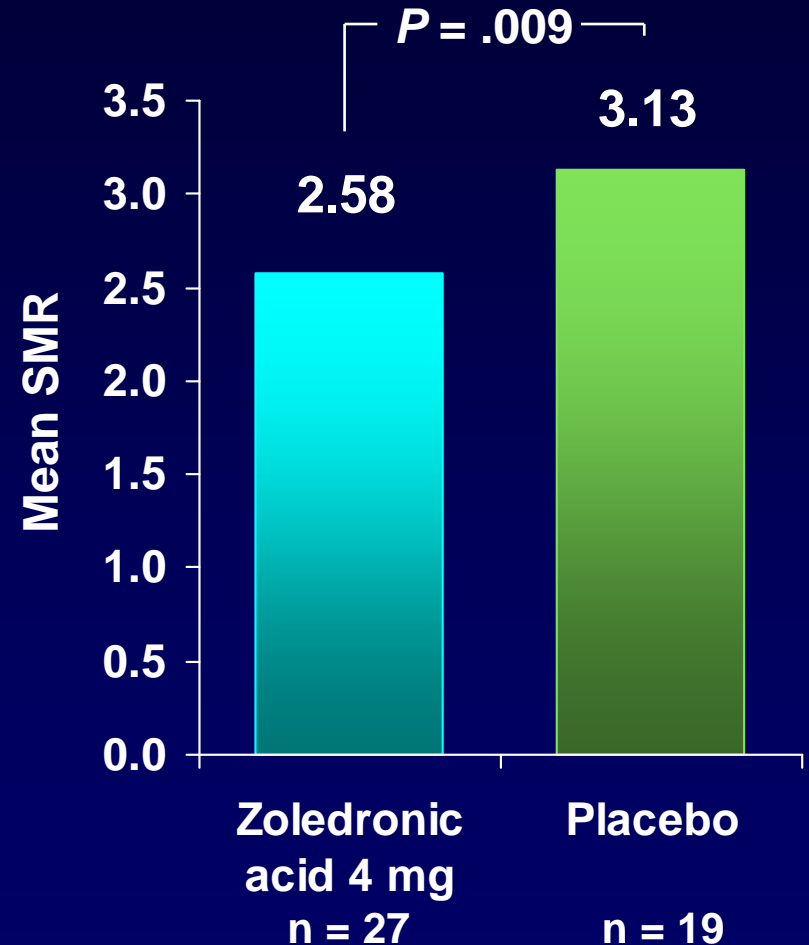
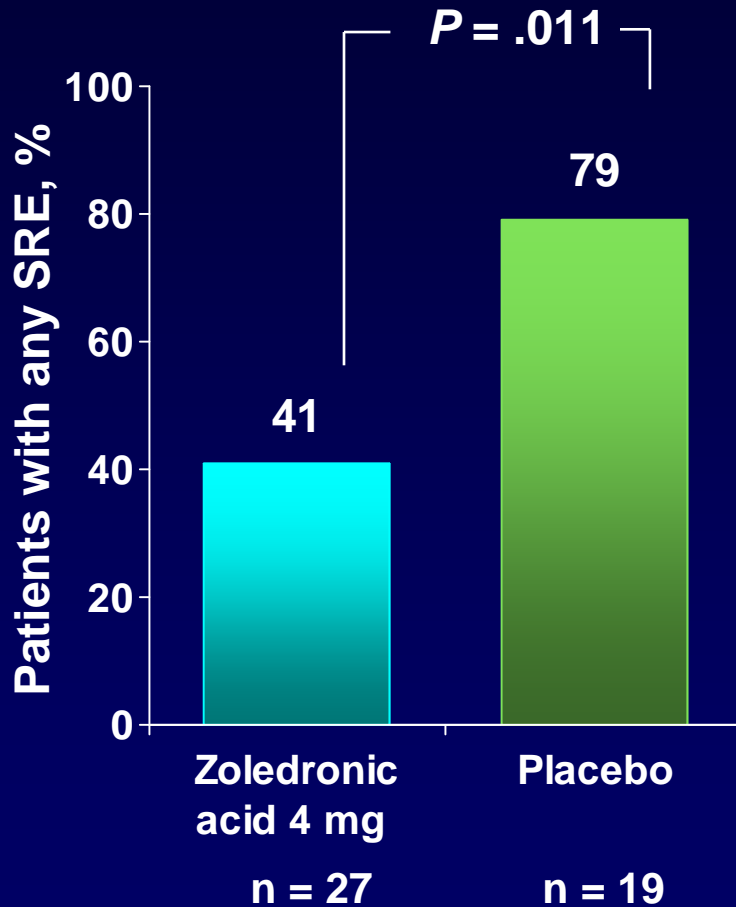
- **SREs are objective measures of skeletal morbidity**
 - Pathologic bone fracture
 - Radiation therapy to bone
 - Spinal cord compression
 - Surgery to bone

Baseline Characteristics

	Zoledronic acid 4 mg (n=27)	Placebo (n=19)
Median age, years	64	65
Primary therapy, n (%)		
Immunotherapy	17 (63)	17 (61)
Hormonal therapy	1 (4)	1 (5)
Previous SRE, n (%)	22 (81)	18 (82)
Baseline serum creatinine, n (%)		
Normal (< 1.4 mg/dL)	17 (63)	16 (57)
ECOG ≤ 1, n (%)	21 (78)	18 (95)
Number of lesions at 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)

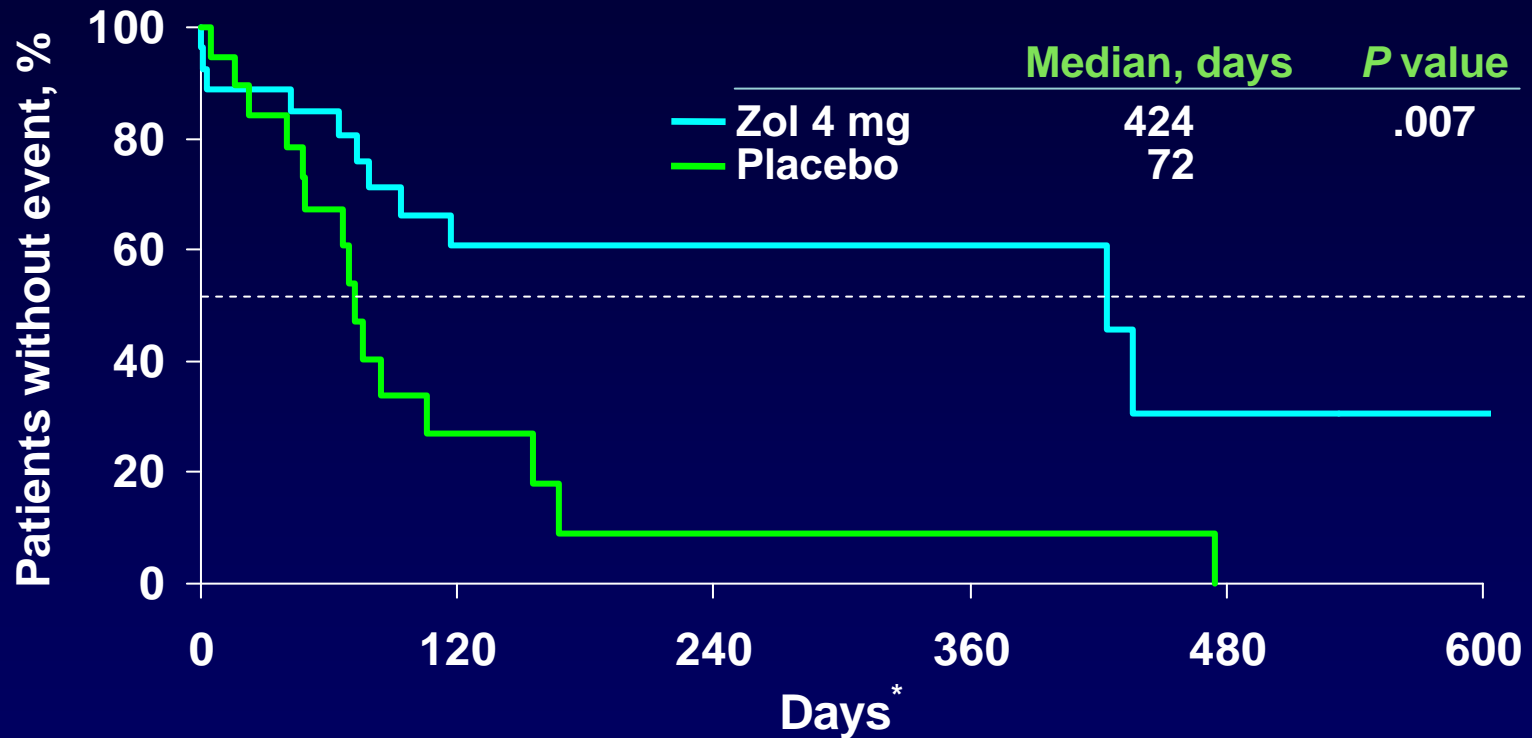
*Safety-evaluable population.

Percent of Patients With Any SRE and SMR



SMR = Skeletal morbidity rate, in events per year.

Time to First SRE

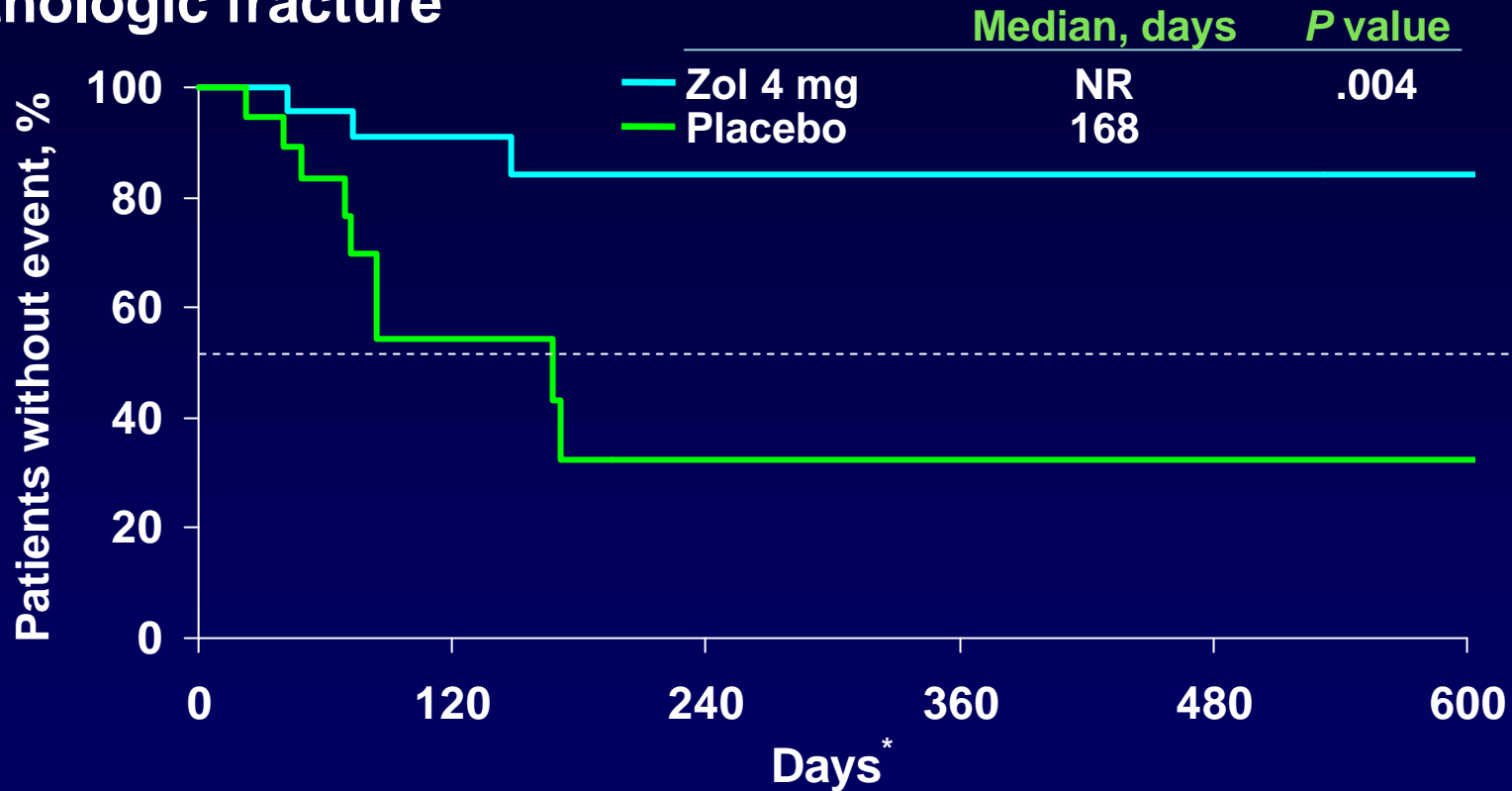


Zol 4 mg	27	12	7	4	2	1
Placebo	19	4	1	1	0	0

*After start of study drug.

Time to First Pathologic Fracture

Zoledronic acid significantly extends time to first pathologic fracture

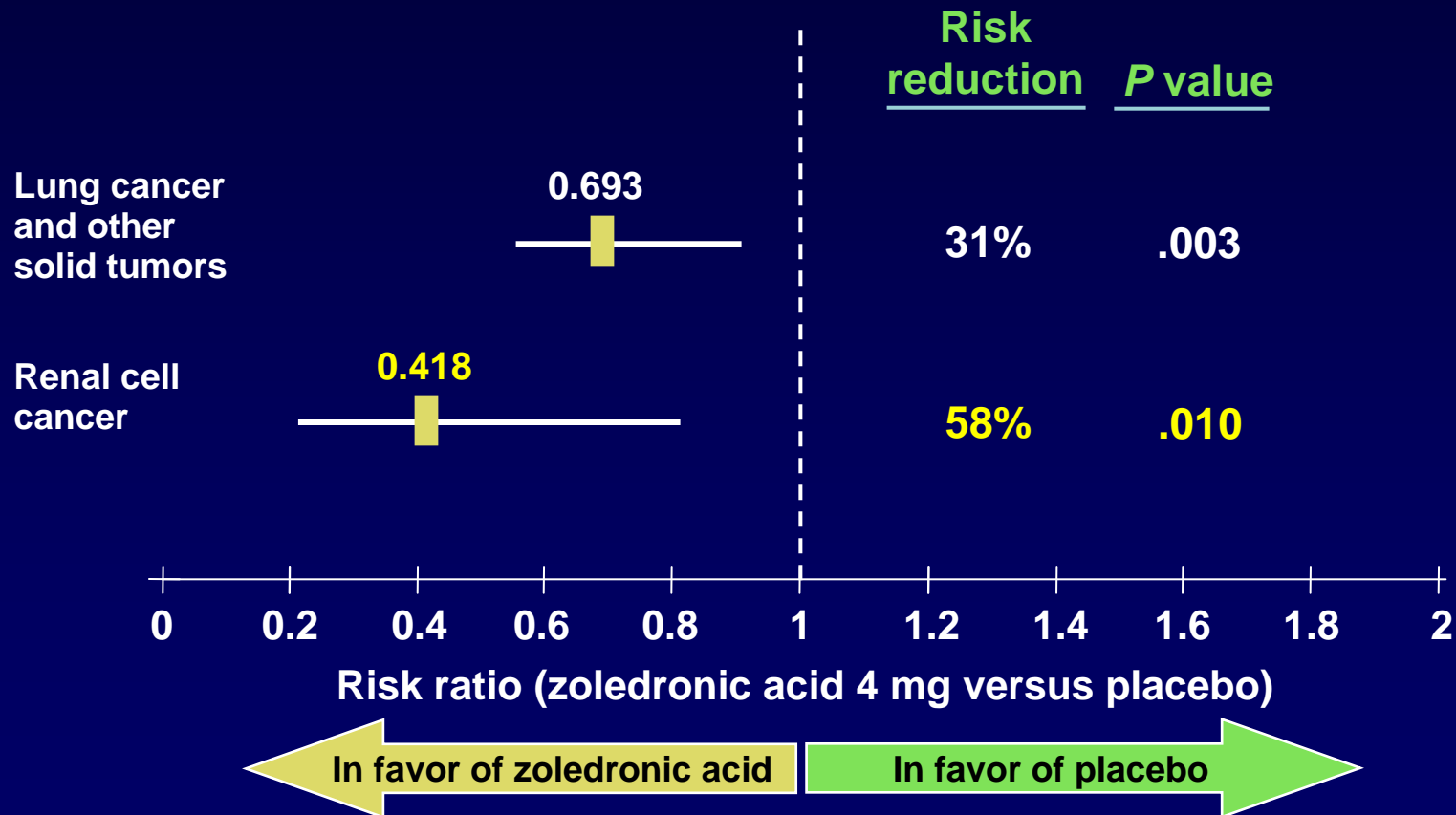


Zol 4 mg	27	17	9	5	4	2
Placebo	19	6	1	1	1	1

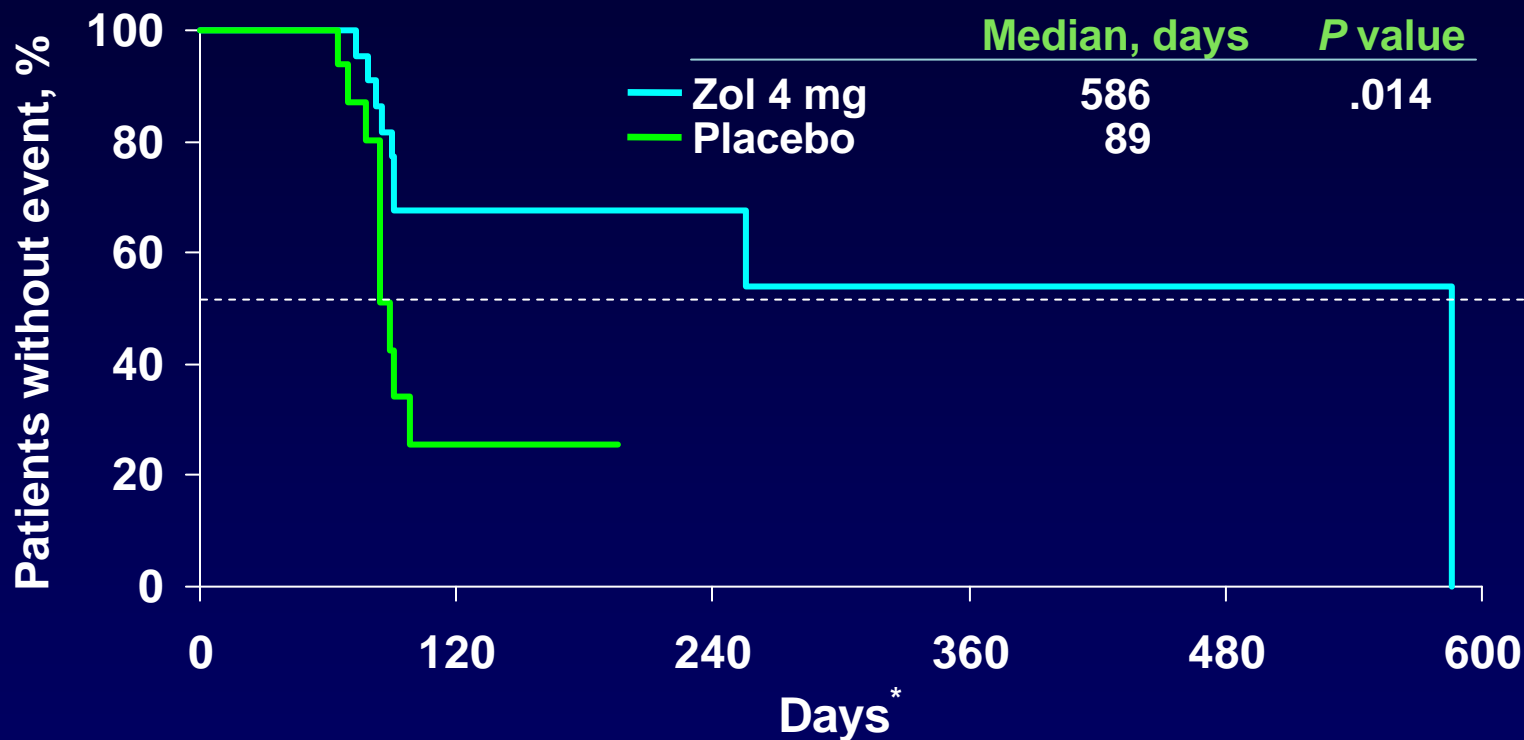
*After start of study drug.

Multiple Event Analysis (Andersen-Gill Method)

58% reduction in the risk of developing an SRE for RCC patients receiving zoledronic acid compared with placebo



Time to Progression of Bone Lesions



Zol 4 mg	27	13	7	3	2	0
Placebo	19	3	0	0	0	0

*After start of study drug.

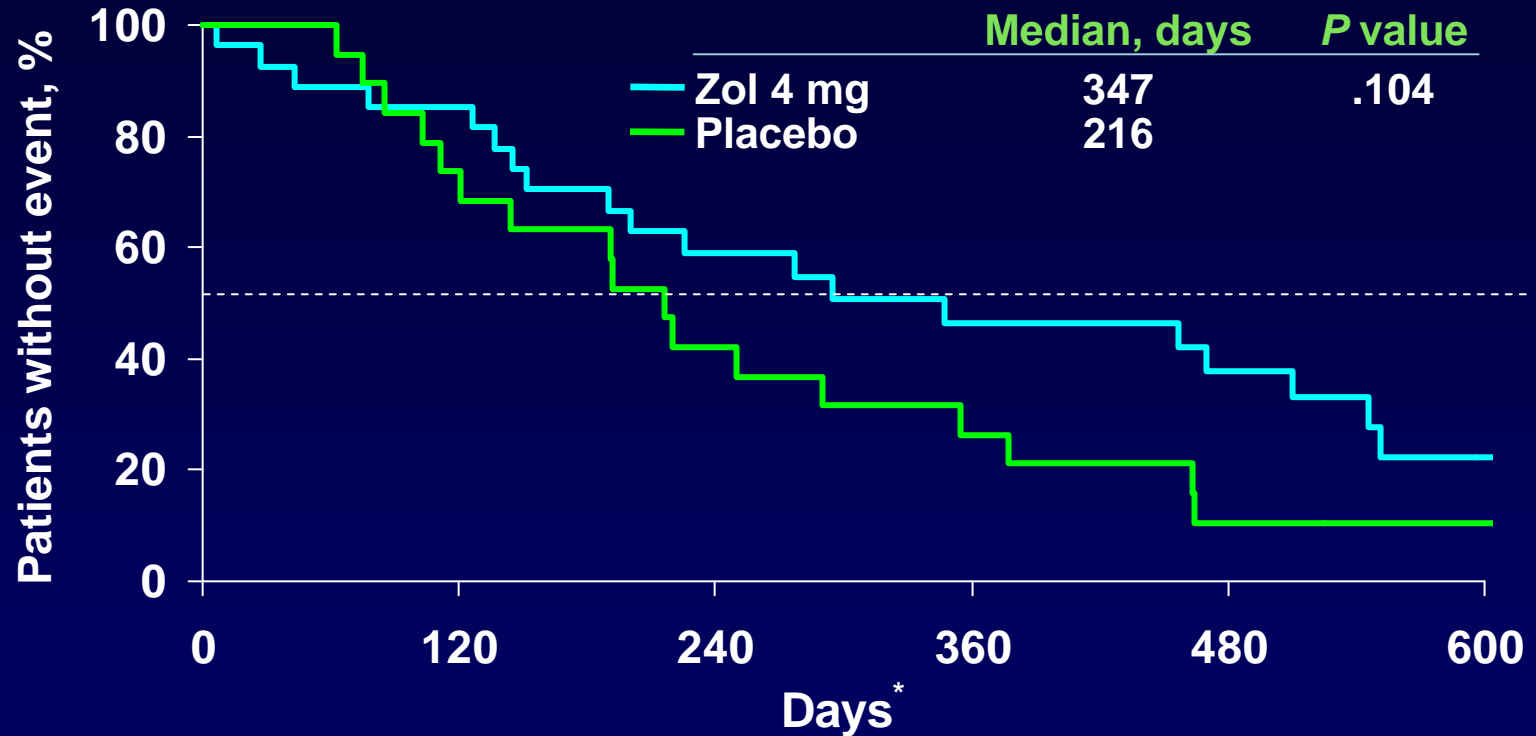
Renal-Related Adverse Events

	Patients, n (%) [*]	
	Zoledronic acid 4 mg [†] (n = 27)	Placebo (n = 19)
Hematuria	2 (11.1)	1 (6.7)
Hyperuricemia	1 (5.6)	0 (0.0)
Renal failure	1 (5.6)	0 (0.0)
Difficulty in micturition	0 (0.0)	1 (6.7)
Oliguria	0 (0.0)	1 (6.7)
Total	4 (22.2)	3 (20.0)

*Safety-evaluable population.

[†]Via 15-minute infusion.

Survival



	0	120	240	360	480	600
Zol 4 mg	27	23	15	11	8	2
Placebo	19	14	8	5	2	1

*After start of study drug.

Conclusions

- **Zoledronic acid was effective in patients with bone metastasis from RCC**
 - **Reduced risk of developing an SRE**
 - **Delayed time to first SRE**
 - **Delayed time to progression of bone disease**
- **Patients treated with zoledronic acid 4 mg had renal safety profile comparable with placebo**