# Zoledronic Acid Reduces Long-term Risk of Skeletal Complications in Patients With Advanced Renal Cell Carcinoma or Bladder Cancer

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Abstract xxxx

## Abstract*

**Introduction and Objective**: Patients with bone metastases from renal cell carcinoma (RCC) or bladder cancer are at high risk for skeletal complications including pathologic fracture, spinal cord compression, bone pain, and surgery or radiotherapy to bone. Therefore, an exploratory analysis of a 21-month zoledronic acid study was performed in a subset of patients with RCC or bladder cancer.

**Methods:** Patients with bone metastases secondary to RCC or bladder cancer (n = 72) were randomized to treatment with either zoledronic acid (4 mg) or placebo. Patients were monitored for skeletal-related events (SREs: pathologic fractures, palliative radiotherapy to bone, orthopedic surgery to prevent or treat a pathologic fracture, spinal cord compression, or hypercalcemia of malignancy) and time to first SRE.

**Results:** The proportion of patients with RCC or bladder cancer who experienced 1 or more SREs was lower in the zoledronic acid group compared with the placebo group (39% versus 61%, respectively; $P = .061$), and this reduction was significant in the subset of patients with RCC ($P = .011$). Treatment with zoledronic acid significantly delayed the median time to first SRE (424 versus 72 days, respectively; $P = .007$) and bone lesion progression (586 versus 89 days, respectively; $P = .014$) compared with placebo in patients with RCC. A similar trend was observed in patients with bladder cancer, although the difference was not statistically significant. Zoledronic acid also delayed the time to death in patients with RCC or bladder cancer. Treatment was generally well tolerated.

**Conclusions:** This subset analysis demonstrated that in some subsets of patients with RCC or bladder cancer, 4 mg zoledronic acid reduced the proportion of patients experiencing an SRE and delayed the time to first SRE, bone lesion progression, and death compared with placebo. The results support treatment with zoledronic acid for the prevention of SREs in this patient population.

*Data presented in this poster represent an important update of results published in the abstract.

## Introduction

- Approximately 25% of patients with advanced renal cell carcinoma (RCC) and 40% of patients with advanced bladder cancer will develop bone metastases during the course of their disease[1]
  - Bone metastases can result in debilitating skeletal-related events (SREs) including pathologic fracture, spinal cord compression, the need for palliative radiotherapy or surgery to bone, and hypercalcemia of malignancy (HCM)[2]
- Bisphosphonates have been used extensively to reduce the incidence and delay the onset of SREs in patients with bone metastases from solid tumors including breast cancer, lung cancer, and prostate cancer
  - Zoledronic acid (4 mg via 15-minute infusion) is approved for the treatment of bone metastases secondary to solid tumors[3]
- Data from a phase III, placebo-controlled trial of patients with solid tumors demonstrated the efficacy of zoledronic acid in patients with a variety of solid tumors including lung cancer, RCC, and bladder cancer[4,5]
  - In the overall patient population, zoledronic acid prolonged the time to first SRE by almost 3 months ($P = .009$) and reduced the proportion of patients who experienced any SRE (including HCM; $P = .039$)
  - Zoledronic acid (4 mg) was reported to provide significant benefits in the RCC subset in the 9-month analysis[6]
- Exploratory analyses of the completed trial (21-month) data for patients with RCC or bladder cancer were performed to determine the efficacy of zoledronic acid in this patient population

## Methods

**Study Design**

- Retrospective exploratory analysis of clinical outcomes in patients with bone metastases from RCC or bladder cancer who were enrolled in a phase III, placebo-controlled study[4-6]
  - Patients were treated with zoledronic acid or placebo via 15-minute infusion every 3 weeks for up to 21 months
    - Study medication was initially administered via 5-minute infusion, which was amended to 15 minutes to ensure renal safety after the trial was initiated
  - Patients who were randomized to zoledronic acid 4 mg or placebo every 3 weeks were included in these exploratory analyses

## Methods (continued)

- Inclusion criteria for patients with solid tumors other than breast and prostate cancer
  - ≥ 1 bone metastasis
  - Appropriate antineoplastic therapy at study entry
  - Serum creatinine ≤ 3.0 mg/dL
  - Eastern Cooperative Oncology Group performance status ≤ 2

**Statistical Analyses**

- Time to event analyses were estimated by the Kaplan-Meier method

## Results

**Patients**

- A total of 72 patients with RCC or bladder cancer were included in the analysis
  - Patient demographics and baseline disease characteristics were well balanced between treatment groups (**Table 1**)

**Table 1. Demographics and Baseline Disease Characteristics of Patients With Renal Cell Carcinoma or Bladder Cancer**

| | Zoledronic acid (n = 36) | Placebo (n = 36) |
|---|---|---|
| Mean age, years | 62.6 | 63.1 |
| Sex, male % | 72.2 | 88.9 |
| Mean weight, kg | 81.1 | 78.7 |
| Race | | |
| White, % | 88.9 | 88.9 |
| Black, % | 11.1 | 8.3 |
| Primary cancer, n (%) | | |
| Renal cell carcinoma | 27 (75) | 19 (53) |
| Bladder cancer | 9 (25) | 17 (47) |
| ECOG PS 0 - 1, % | 80.6 | 86.1 |
| Prior SRE, % | 69.4 | 86.1 |
| Prior chemotherapy, % | 72.2 | 69.4 |
| Median time from diagnosis to Visit 2, months | 22.1 | 25.6 |
| Baseline serum creatinine < 1.4 mg/dL, % | 72.2 | 63.9 |

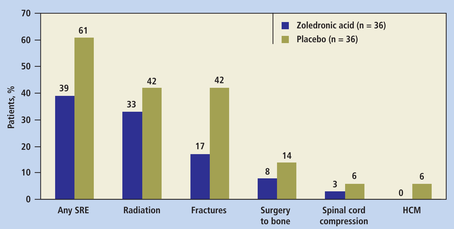
ECOG = Eastern Cooperative Oncology Group; PS = Performance status; SRE = Skeletal-related event.

**Efficacy**

*Skeletal-Related Events*

- Treatment with 4 mg zoledronic acid consistently reduced all types of SREs, including radiation to bone, pathologic fractures, surgery to bone, spinal cord compression, and HCM (**Figure 1A**)
  - The reduction in proportion of patients with any SRE was significant for patients with RCC treated with zoledronic acid compared with placebo ($P = .011$; **Figure 1B**)
  - Zoledronic acid reduced the proportion of patients with any SRE in patients with bladder cancer, although the reduction did not reach statistical significance

Figure 1A




## Results (continued)

Figure 1B

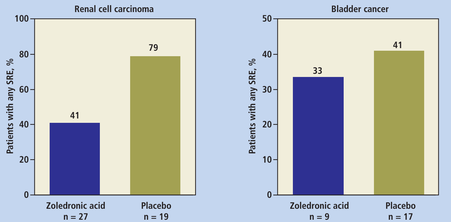



**Figure 1.—Treatment with zoledronic acid reduced the proportion of patients with any SRE.**
(A) Zoledronic acid reduced all types of skeletal-related events (SREs) in patients with renal cell carcinoma (RCC) or bladder cancer. (B) Zoledronic acid reduced the proportion of patients with any SRE in patients with RCC or bladder cancer. This reduction was significant for the RCC patient subset.
HCM = Hypercalcemia of malignancy.

**Time to Event Analyses**

*Renal Cell Carcinoma*

- Zoledronic acid significantly delayed the median time to first SRE and bone lesion progression in patients with RCC (**Table 2**)
  - Zoledronic acid delayed the median time to first SRE by almost 1 year compared with placebo (352 days; $P = .007$)
  - Zoledronic acid delayed the median time to bone lesion progression by 497 days compared with placebo ($P = .014$)
  - Zoledronic acid produced a trend toward increased time to death in patients with RCC compared with placebo

**Table 2. Time to Event Analyses in Patients With Renal Cell Carcinoma**

| | Median time to event, days | | | |
|---|---|---|---|---|
| | Placebo (n = 19) | Zoledronic acid (n = 27) | Zoledronic acid benefit, days | *P* value |
| First SRE | 72 | 424 | 352 | .007 |
| Bone lesion progression | 89 | 586 | 497 | .014 |
| Death | 216 | 347 | 131 | .104 |

SRE = Skeletal-related event.

*Bladder Cancer*

- Zoledronic acid delayed the median time to first SRE, bone lesion progression, and death in patients with bladder cancer (**Table 3**)
  - Although a trend in delayed time to event was observed in patients with bladder cancer treated with zoledronic acid, small patient numbers precluded these analyses from reaching statistical significance

**Table 3. Time to Event Analyses in Patients With Bladder Cancer**

| | Median time to event, days | | | |
|---|---|---|---|---|
| | Placebo (n = 17) | Zoledronic acid (n = 9) | Zoledronic acid benefit, days | *P* value |
| First SRE | 217 | 227 | 10 | .543 |
| Bone lesion progression | 101 | 178 | 77 | .438 |
| Death | 213 | 228 | 15 | .687 |

SRE = Skeletal-related event.

## Results (continued)

**Safety**

- The overall safety profile of zoledronic acid was comparable with that of placebo
- Zoledronic acid demonstrated an acceptable renal safety profile compared with placebo in patients with RCC or bladder cancer (**Table 4**)
  - The proportion of patients who reported a renal-related adverse event was 27.8% of patients treated with zoledronic acid compared with 38.9% of patients who received placebo
  - Only 1 case of renal failure occurred in the zoledronic acid group after the 15-minute infusion amendment was implemented. This event was in a patient with RCC

**Table 4. Renal-Related Adverse Events in Patients With Renal Cell Carcinoma or Bladder Cancer**

| | Patients, n (%)* | |
|---|---|---|
| | Zoledronic acid (n = 36) | Placebo (n = 36) |
| Hematuria | 5 (13.9) | 4 (11.1) |
| Dysuria | 3 (8.3) | 4 (11.1) |
| Renal failure | 2 (5.6)† | 0 |
| Difficulty in micturition | 0 | 1 (2.8) |
| Oliguria | 1 (2.8) | 2 (5.6) |
| **Total** | **10 (27.8)** | **14 (38.9)** |

*Safety-evaluable population
†One patient with bladder cancer received zoledronic acid via 5-minute infusion, and the second patient with renal cell carcinoma received zoledronic acid after the protocol amendment that extended the infusion duration to 15 minutes to ensure renal safety.

## Conclusions

- Zoledronic acid was effective in patients with bone metastases from RCC or bladder cancer
- Significant benefits of zoledronic acid in some patient subsets included
  - Reduced proportion of patients who developed an SRE
  - Delayed time to first SRE
  - Delayed time to progression of bone disease
- Zoledronic acid (4 mg via 15-minute infusion) has a renal safety profile comparable with that of placebo
- Prospective trials are warranted to further assess the benefits of zoledronic acid treatment in patients with bone metastases secondary to RCC or bladder cancer

## References

1. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev.* 2001;27:165-176.
2. Coleman RE. Skeletal complications of malignancy. *Cancer.* 1997;80(suppl):1588-1594.
3. Zometa® (zoledronic acid) injection [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2005.
4. Rosen LS, Gordon D, Tchekmedyian S, et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial—the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol.* 2003;21:3150-3157.
5. Rosen LS, Gordon D, Tchekmedyian NS, et al. 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. *Cancer.* 2004;100:2613-2621.
6. Lipton A, Zheng M, Seaman J. Zoledronic acid delays the onset of skeletal-related events and progression of skeletal disease in patients with advanced renal cell carcinoma. *Cancer.* 2003;98:962-969.