Published in final edited form as:

Eur Urol. 2014 September ; 66(3): 502–509. doi:10.1016/j.eururo.2014.02.040.

Prognostic significance of bone metastases and bisphosphonate therapy in patients with renal cell carcinoma

Rana R. McKay, MD¹, Xun Lin, PhD², Julia J. Perkins, MD², Daniel Y. C. Heng, MD³, Ronit Simantov, MD², and Toni K. Choueiri, MD¹

¹Dana-Farber Cancer Institute, Boston, United States

²Pfizer Oncology, New York, United States

³Tom Baker Cancer Center, Calgary, Canada

Abstract

Background—Bone metastases (BMs) are frequently present in patients with metastatic renal cell carcinoma (mRCC) and cause significant morbidity.

Objective—The purpose of this analysis was to assess the impact of BMs and bisphosphonate therapy (BT) on outcomes in mRCC.

Design, Settings, and Participants—We conducted a pooled analysis of patients with mRCC treated from 2003–2011 on phase II and III trials.

Outcome Measurements and Statistical Analysis—Statistical analyses were performed using Cox regression and the Kaplan-Meier method.

Results and Limitations—We identified 2,749 patients treated with sunitinib (n=1,059), sorafenib (n=355), axitinib (n=359), temsirolimus (n=208), temsirolimus + interferon-alpha (IFN- α) (n=208), or IFN- α (n=560), with 28% (n=781) having BMs. 285 patients (10.4%) received BT. The presence of BMs was associated with shorter overall survival (OS) (13.2 versus 20.2 months, $p<0.0001$) and progression-free survival (PFS) (5.1 versus 6.7 months, $p<0.0008$) when compared to those without BMs. When stratified by risk groups, the presence of BMs was associated with shorter OS in all risk groups. Overall, the use of BT in patients with BMs was not associated with improved OS (13.3 versus 13.1 months, $p=0.3801$) or PFS (5.1 versus 4.9 months, $p=0.1785$) compared to patients who did not receive BT. Bisphosphonate users with BMs did not have a decreased rate of skeletal-related events compared to non-users (8.6% versus 5.8%, $p=0.191$). Additionally, BT was associated with increased rates of hypocalcemia, renal insufficiency, and osteonecrosis of the jaw ($p<0.0001$). Data was analyzed retrospectively.

Corresponding Author: Toni K. Choueiri, MD Dana-Farber Cancer Institute/ Brigham and Women's Hospital/Harvard Medical School 450 Brookline Avenue Boston, MA 02215 Phone: (617) 632-5456 Fax: (617) 632-2165 toni_choueiri@DFCI.harvard.edu.

Disclosures: Toni K. Choueiri has received research funding from Pfizer and has an advisory role at Aveo, Pfizer, Novartis, GlaxoSmithKline, Genentech, and Bayer and Onyx. Daniel Y.C. Heng has an advisory role at Aveo, Pfizer, Novartis, and Bayer. Xun Lin, Julia J. Perkins, and Ronit Simantov are employees at Pfizer.

Take Home Message (27 words, maximum 40): Bone metastases have a negative impact on survival in patients with metastatic renal cell carcinoma. Bisphosphonate therapy did not impact the rate of skeletal-related events or survival.

Conclusions—We confirm that the presence of BMs is associated with shorter survival in mRCC. BT did not impact survival or SRE prevention and was associated with increased toxicity.

Patient Summary—In this analysis, we demonstrate that BMs are associated with shorter survival in patient with mRCC. Additionally, we call into question the utility of BT in this population.

Keywords

Bisphosphonates; Bone metastases; mTOR inhibitors; Renal cell carcinoma; VEGF targeted therapy

Introduction

Approximately 30% of patients with metastatic renal cell carcinoma (mRCC) have bone metastases (BMs).⁽¹⁾ Patients with BMs are vulnerable to significant skeletal morbidity, which can lead to quality of life deterioration. Additionally, these patients are at risk of skeletal-related events (SREs); including pain requiring radiation, pathologic fractures, spinal cord compression, surgery to bone, and occasionally hypercalcemia.

Skeletal lesions from mRCC are typically osteolytic on imaging. The mechanism by which mRCC induces osteolytic bone changes is unclear. In normal bone, structural integrity is maintained via a process of bone resorption and formation.⁽²⁾ It is proposed that dysregulation of this process results in a vicious cycle of bone destruction and tumor growth.⁽²⁾ Integral to the interaction of tumor cells with the bone microenvironment is the release by osteoblasts of receptor activator of nuclear factor kappa β ligand (RANKL), a cytokine critical in osteoclast differentiation and survival.⁽²⁾

Osteoclast-targeted agents are used to prevent skeletal complications related to BMs and do not appear to impact survival. Bisphosphonates bind to bone and have a direct inhibitory effect on osteoclasts.⁽³⁾ Zoledronic acid, a potent bisphosphonate, was approved for SRE prevention in 2002, corresponding with the cytokine era of mRCC.⁽³⁾ Denosumab, a monoclonal antibody against RANKL, prevents osteoclast differentiation and survival.⁽⁴⁾ It was approved for SRE prevention in 2010. Compared to other cancers, there are limited prospective data on the role of osteoclast-targeted therapy in mRCC.

Outcomes of patients with mRCC have improved dramatically since 2005 when agents targeting the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways were introduced. Despite improvements in survival, there is increasing evidence that BMs in mRCC are associated with worse outcomes.^(5, 6) Understanding the prognostic impact of BMs on outcomes is critical for personalizing treatment for patients with mRCC. Additionally, it is important to understand the role of osteoclast-targeted agents in patients with BMs. In this study, we utilized a clinical trials database of patients with mRCC to characterize BMs, evaluate their impact on survival, and investigate the role of bisphosphonate therapy (BT).

Patient and Methods

Study Design

We conducted a post hoc analysis of pooled prospective data of patients with mRCC treated on phase II (NCT00054886, NCT00077974, NCT00267748, NCT00338884, NCT00137423) and III (NCT00083889, NCT00065468, NCT00678392) trials conducted by Pfizer Oncology. We identified 2,749 patients treated for mRCC between January 2003 and November 2011.

Baseline demographic, clinical, and laboratory data were collected. Data regarding osteoclast-targeted therapy were collected. Users of osteoclast-targeted therapy were defined as those receiving a bisphosphonate or denosumab at baseline or during the study period. The decision to start an osteoclast-targeted agent and management of patients while on therapy was at the discretion of the treating physician. SREs of pathologic fractures and spinal cord compression were captured from the adverse event database. All studies in the database used Common Terminology Criteria for Adverse Events, Version 3.0, which did not include a category to record bone radiotherapy or surgery to the bone. Data regarding adverse events including hypocalcemia, renal insufficiency, and osteonecrosis of the jaw (ONJ) were collected. Survival data was collected for all patients.

Statistical Methods

The primary outcome was to assess overall survival (OS) and progression-free survival (PFS) of patients with BMs compared to those without BMs. The secondary outcome was to assess OS and PFS of patients with BMs treated with BT compared to those not receiving BT. OS was defined as the time from initiation of therapy to death from any cause. PFS was defined as the time from initiation of therapy to date of progression or death from any cause, whichever came first. Distributions of OS and PFS were calculated using the Kaplan-Meier method. Median OS and PFS along with 95% confidence intervals (CI) were reported. Associations between OS and PFS were assessed using the log-rank test in univariate analysis or Wald-chi square test from Cox regression in multivariable analysis, adjusted for age, sex, race, Memorial Sloan-Kettering Cancer Center (MSKCC) and the International mRCC Database Consortium (IMDC) risk groups.⁽⁷⁾ Subgroup efficacy analyses were performed in the following groups: 1) MSKCC risk groups, 2) IMDC risk groups, and 3) therapy type.

Results

Patient and disease characteristics

Most patients were less than 65 years of age, men, with good performance status, and clear-cell histology (Table 1). Patients received treatment with sunitinib (n=1,059), sorafenib (n=355), axitinib (n=359), temsirolimus (n=208), temsirolimus + interferon-alpha (IFN- α) (n=208), and IFN- α (n=560), of which 1,759 received first-line therapy. The presence of baseline lung, liver and BMs was 77%, 28%, and 28%, respectively. With regard to risk groups, more patients with BMs had poor-risk disease compared to those without BMs.

Bisphosphonate therapy and skeletal-related events

Of the 2,749 patients in the cohort, 285 (10.4%) patients received BT (zoledronic acid n=233, pamidronate n=57, unspecified n=1), three of whom received more than one agent sequentially. No patient received denosumab. All 285 patients were receiving BT at baseline and the majority continued therapy during the study period (n=272, 95.4%). Of the 285 BT users, 23 (8.1%) were on calcium supplementation and four (1.4%) were on vitamin D supplementation at baseline. Of the 781 patients with BMs, 162 (20.7%) received BT. Indications for BT in patients without documented BMs (n=123/1968) included hypercalcemia (53%), osteoporosis or prophylaxis (13%), no reason given (11%), or pain (5%). In 23 patients, BMs were recorded as the indication for BT, although BMs were not documented as a site of involvement.

Rates of hypocalcemia, renal insufficiency, and ONJ were higher for patients receiving BT compared to those not receiving BT ($p<0.0001$) (Table 2). Seven patients had ONJ, all of whom were treated with sunitinib; six had baseline BMs, and six were treated with BT.

Of the 781 patients with BMs, 6.4% (n=50) experienced SREs. Of the patients with BM and SREs, 28% (n=14/50) were on BT, while 72% (n=36/50) did not receive BT. Most SREs were skeletal fractures (n=41). In the 781 patients with BMs, the rate of SREs in patients receiving BT was 8.6% (n=14/162) compared to 5.8% (n=36/619) in patients not receiving BT ($p=0.191$, Odds Ratio 1.532 95% CI 0.805-2.914).

Clinical outcomes for the entire cohort

The median OS and PFS for the entire cohort were 17.4 and 6.4 months, respectively. When stratified by MSKCC risk groups, median OS was 37.8, 19.3, and 8.4 months for the favorable, intermediate, and poor-risk groups, respectively. The median PFS was higher in patients with MSKCC favorable and intermediate-risk disease compared to poor-risk disease (median PFS 11.0, 6.6, and 3.6 months for the MSKCC favorable, intermediate, and poor-risk groups, respectively). A similar trend was observed for OS and PFS stratified by IMDC risk groups (median OS was 42.4, 20.7, and 7.6 months and PFS was 11.1, 7.4, and 3.2 months for the favorable, intermediate, and poor-risk groups, respectively).

Impact of bone metastases on clinical outcomes

The presence of BMs was associated with shorter OS (13.2 versus 20.2 months, $p<0.0001$) and PFS (5.1 versus 6.7 months, $p=0.0008$) when compared to those without BMs (Table 3, Figure 1). When stratified by MSKCC risk groups, the presence of BMs was associated with shorter OS in each MSKCC risk group, though this was not statistically significant for the poor-risk group. An equivalent pattern was observed for OS stratified by IMDC risk groups and PFS stratified by MSKCC and IMDC risk groups (Table 3).

Furthermore, the presence of BMs was an independent factor for worse OS in patients treated with IFN- α or targeted therapy; a similar but less pronounced trend was observed for PFS (Table 3). In patients with BMs, the median OS and PFS were similar for patients with or without SREs (median OS 15.1 versus 13.1 months, $p=0.901$, hazard ratio (HR) 1.023,

95% CI 0.713-1.458, and PFS 6.6 versus 5.0 months, $p=0.689$, HR 1.074, 95% CI 0.758-1.522, for patients with or without SREs, respectively).

Impact of bisphosphonate therapy on clinical outcomes

When evaluating patients with BMs, BT was not associated with improved OS (13.3 versus 13.1 months, $p=0.3801$) or PFS (5.1 versus 4.9 months, $p=0.1785$) when compared to patients who did not receive BT (Table 4, Figure 1). Additionally, when stratified by MSKCC risk groups, IMDC risk groups or therapy type, BT was not associated with a difference in OS or PFS compared to non-users (Table 4).

Discussion

This is the first and largest clinical trials database evaluating the impact of BMs and BT in patients with mRCC. This database provides a powerful tool for analysis of patient characteristics and outcomes given prospective data collection. Additionally, this database contains patients treated with a broad range of therapies on clinical trials in the modern era.

In this analysis, the presence of baseline BMs was 28%, consistent with rates previously described.⁽¹⁾ The rate of SREs in patients with BMs was 6.4%, lower than previously reported rates. In the cytokine era, when therapies for mRCC were limited, rates of SREs in patients with BMs were upwards of 74%.⁽⁸⁾ The SRE rate in patients with BMs secondary to mRCC in the targeted era is largely unknown. The lower rate of SREs documented in this analysis could be explained by the improved efficacy of targeted agents. Maita *et al* demonstrated that sunitinib prevented the growth of RCC cells in a bone metastatic mouse model and caused significant declines in bone turnover markers in patients treated with sunitinib.⁽⁹⁾ Additionally, the lower rate of SREs could reflect an underestimation of actual events given that the database was not designed to capture SREs and adverse event monitoring occurred only during the period for which patients were on the clinical trial. We did not observe a correlation between SRE rate and survival. This is the first study exploring the prognostic significance of SREs in patients with mRCC. In prostate and breast cancer, the presence of SREs has been associated with a negative impact on survival in some retrospective analyses.^(10, 11)

Of patients with baseline BMs, 21% ($n=162$) received BT, highlighting that use of BT is not common in patients with mRCC with BMs, similar to prior data. In a study of 6,347 patients with genitourinary malignancies with BMs, including 941 with mRCC, 23% received zoledronic acid.⁽¹²⁾ This could be related to physician preference, increased renal insufficiency in mRCC patients, and/or toxicity when combined with VEGF-targeted therapy. In this cohort, no patient received denosumab, a more potent osteoclast-targeting agent, shown to be superior to zoledronic acid in preventing SREs in advanced cancer patients based on data from three phase III trials.⁽¹³⁻¹⁵⁾ The role of denosumab in mRCC needs to be further explored.

In this series, we were unable to demonstrate a benefit of BT with regard to SRE prevention in patients with BMs, likely a reflection of the small number of SREs in this cohort. A subgroup analysis of patients with mRCC ($n=74$) on a phase III trial conducted during the

cytokine era showed that zoledronic acid significantly prevented SREs (37% versus 74%, $p=0.015$) compared to placebo.⁽⁸⁾ The role of BT in SRE prevention during the targeted era remains unknown.

Despite the potential benefit, BT can be associated with side effects. In this series, BT was associated with increased rates of hypocalcemia, renal insufficiency, and ONJ. Additionally, hypocalcemia and renal insufficiency were higher among bisphosphonate users receiving non-VEGF targeted therapy as compared to VEGF-targeted therapy. This could be secondary to increased poor-risk patients in this group, who may experience more toxicity from BT. Additionally, hypocalcemia may be related to underutilization of calcium supplementation in patients receiving BT. The incidence of ONJ in cancer patients receiving BT ranges from 1.5-6.1%.^(16, 17) Risk factors for developing ONJ include drug potency, therapy duration, oral disease, and invasive dental procedures.⁽¹⁷⁾ Additionally, there exists the potential for increased toxicity in patients receiving VEGF-targeted therapy with BT. In this series, all patients who developed ONJ received VEGF-targeted therapy. In a study of 46 patients with mRCC and BMs treated with zoledronic acid and targeted therapy, the rate of ONJ was 29% and was only seen in patients treated with sunitinib.⁽¹⁸⁾ After implementation of mandatory oral examinations prior to BT use, rates decreased to 11%. It is possible that the potent antiangiogenic activity of VEGF-targeting agents may inhibit bone remodeling and potentiate ONJ development.

In this analysis, we confirm that the presence of BMs is associated with shorter PFS and OS in mRCC, consistent with growing data in the field.^(5, 6, 19-23) In an analysis from the IMDC of 2,027 patients with mRCC treated with targeted therapy, patients with BMs had a shorter median OS (14.9 versus 25.1 months, $p<0.0001$) compared to patients without BMs.⁽⁶⁾ Additionally, inclusion of BMs in the IMDC prognostic model was found to enhance the prediction performance of the model, suggesting that BMs can be used as an additional prognostic factor in this model.⁽⁶⁾ This data demonstrate that BMs are an independent risk factor for worse prognosis in mRCC and raise the question of whether they should be considered as a stratification factor when designing future prospective studies.

Additionally, this analysis demonstrates that BT did not have a significant impact on survival in mRCC. This is consistent with larger prospective studies in breast, prostate, and other solid malignancies which have failed to demonstrate a survival advantage to BT, however in contrast to small studies in mRCC which have suggested that BT may be associated with improved survival (Table 5). The lack of clinical efficacy of BT in terms of survival may be related to the improved efficacy of targeted therapy. Additionally, prior studies documenting a survival benefit with BT were retrospective and possibly subject to selection bias given imbalances in the treatment arms.

Though this analysis utilized prospectively collected data from a clinical trials database, there are several limitations. Data collection was not designed to examine BMs, SREs, and bisphosphonate use specifically. Additionally, all patients in this database were enrolled on clinical trials, which could lead to selection bias. In these studies, response was assessed radiologically by Response Evaluation Criteria In Solid Tumors (RECIST) criteria. BMs were recorded as non-measurable lesions using RECIST criteria and thus were not

measured. Given that eligibility required patients to have measurable disease, patients with bone-only metastases were excluded. Management of BMs was at the discretion of the treating physician including need for BT, dosage and schedule of BT, need for dose modification given renal insufficiency, need for supplemental calcium or vitamin D, and oral examination. Information is lacking regarding dosing and schedule of BT.

Conclusions

In this analysis, we confirm that BMs are an adverse risk factor for survival in mRCC and should be considered in the design of future trials in mRCC. In patients with BMs, BT did not impact SRE rate or survival and was associated with adverse events including hypocalcemia, renal insufficiency, and ONJ. Though data regarding BT are limited given the post hoc nature of this analysis, these findings are hypothesis-generating and warrant further investigation. Larger prospective studies are needed to better define the potential benefit and toxicity of BT. This will be instrumental in guiding the future clinical management of patients with mRCC with BMs.

Acknowledgments

This study was funded by Pfizer, Inc. Additionally, this research is supported in part by the Trust Family and the Michael Brigham Funds for Kidney Cancer Research for Dr. Choueiri.

References

1. Bianchi M, Sun M, Jeldres C, et al. Distribution of metastatic sites in renal cell carcinoma: a population-based analysis. *Ann Oncol.* 2012; 23(4):973–80. [PubMed: 21890909]
2. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med.* 2004; 350(16):1655–64. [PubMed: 15084698]
3. 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(16):3150–7. [PubMed: 12915606]
4. Lacey DL, Boyle WJ, Simonet WS, et al. Bench to bedside: elucidation of the OPG-RANK-RANKL pathway and the development of denosumab. *Nat Rev Drug Discov.* 2012; 11(5):401–19. [PubMed: 22543469]
5. Beuselinck B, Oudard S, Rixe O, et al. Negative impact of bone metastasis on outcome in clear-cell renal cell carcinoma treated with sunitinib. *Ann Oncol.* 2011; 22(4):794–800. [PubMed: 20937648]
6. McKay RR, Kroeger N, Xie W, et al. Impact of Bone and Liver Metastases on Patients with Renal Cell Carcinoma Treated with Targeted Therapy. *Eur Urol.* 2013
7. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol.* 1999; 17(8):2530–40. [PubMed: 10561319]
8. 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(5): 962–9. [PubMed: 12942563]
9. Maita S, Yuasa T, Tsuchiya N, et al. Antitumor effect of sunitinib against skeletal metastatic renal cell carcinoma through inhibition of osteoclast function. *Int J Cancer.* 2012; 130(3):677–84. [PubMed: 21387300]
10. Sathiakumar N, Delzell E, Morrissey MA, et al. Mortality following bone metastasis and skeletal-related events among women with breast cancer: a population-based analysis of U.S. Medicare beneficiaries, 1999–2006. *Breast Cancer Res Treat.* 2012; 131(1):231–8. [PubMed: 21842243]

11. Sathiakumar N, Delzell E, Morrissey MA, et al. Mortality following bone metastasis and skeletal-related events among men with prostate cancer: a population-based analysis of US Medicare beneficiaries, 1999-2006. *Prostate Cancer Prostatic Dis.* 2011; 14(2):177–83. [PubMed: 21403668]
12. Henk HJ, Kaura S. Assessment of zoledronic acid treatment patterns and clinical outcomes in patients with bone metastases from genitourinary cancers. *J Med Econ.* 2012; 15(1):185–94. [PubMed: 22168786]
13. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet.* 2011; 377(9768):813–22. [PubMed: 21353695]
14. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol.* 2011; 29(9):1125–32. [PubMed: 21343556]
15. Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol.* 2010; 28(35):5132–9. [PubMed: 21060033]
16. Migliorati CA, Woo SB, Hewson I, et al. A systematic review of bisphosphonate osteonecrosis (BON) in cancer. *Support Care Cancer.* 2010; 18(8):1099–106. [PubMed: 20411279]
17. Saad F, Brown JE, Van Poznak C, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. *Ann Oncol.* 2012; 23(5):1341–7. [PubMed: 21986094]
18. Smidt-Hansen T, Folkmar TB, Fode K, Agerbaek M, Donskov F. Combination of zoledronic Acid and targeted therapy is active but may induce osteonecrosis of the jaw in patients with metastatic renal cell carcinoma. *J Oral Maxillofac Surg.* 2013; 71(9):1532–40. [PubMed: 23642545]
19. Choueiri TK, Garcia JA, Elson P, et al. Clinical factors associated with outcome in patients with metastatic clear-cell renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. *Cancer.* 2007; 110(3):543–50. [PubMed: 17577222]
20. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. *Cancer.* 2010; 116(18):4256–65. [PubMed: 20549832]
21. Patil S, Figlin RA, Hutson TE, et al. Prognostic factors for progression-free and overall survival with sunitinib targeted therapy and with cytokine as first-line therapy in patients with metastatic renal cell carcinoma. *Ann Oncol.* 2011; 22(2):295–300. [PubMed: 20657034]
22. Riechelmann RP, Chin S, Wang L, et al. Sorafenib for metastatic renal cancer: the Princess Margaret experience. *Am J Clin Oncol.* 2008; 31(2):182–7. [PubMed: 18391604]
23. Vrdoljak E, Szczylik C, Mardiak J, et al. Use of bisphosphonates in combination with sunitinib in renal cell cancer patients with bone metastases from the expanded access study. *European Cancer Congress.* 2013 Abstract 2756.
24. Keizman D, Ish-Shalom M, Pili R, et al. Bisphosphonates combined with sunitinib may improve the response rate, progression free survival and overall survival of patients with bone metastases from renal cell carcinoma. *Eur J Cancer.* 2012; 48(7):1031–7. [PubMed: 22409947]
25. Beuselinck B, Wolter P, Karadimou A, et al. Concomitant oral tyrosine kinase inhibitors and bisphosphonates in advanced renal cell carcinoma with bone metastases. *Br J Cancer.* 2012; 107(10):1665–71. [PubMed: 23132391]
26. Yuasa T, Urakami S, Yamamoto S, et al. Treatment outcome and prognostic factors in renal cell cancer patients with bone metastasis. *Clin Exp Metastasis.* 2011; 28(4):405–11. [PubMed: 21365325]
27. Broom RJ, Hinder V, Sharples K, et al. RAD001 and zoledronic acid in patients with renal cell carcinoma with bone metastases (RAZOR): A randomized phase II trial. *ASCO Meeting Abstracts.* 2013; 31(6_suppl):402.

Figure 1.

Kaplan-Meier curves of (A) PFS and (B) OS based on presence or absence of baseline BMs. The presence of BMs was associated with shorter PFS and OS when compared to those without BMs. Kaplan-Meier curves of (C) PFS and (D) OS in patients with BMs treated versus not treated with BT. BT was not associated with improved PFS or OS in patients with baseline BMs.

Table 1

Baseline patient and disease characteristics.

Characteristic n (%)	Patients with BMs n=781	Patients without BMs n=1968	Patients Receiving BT n=285	Patient not Receiving BT n=2,464	Total Cohort n=2749
Age at initiation of therapy					
< 65 years	547 (70.0%)	1,281 (65.1%)	212 (74.4%)	1616 (65.6%)	1,828 (66.5%)
65 years	234 (30.0%)	687 (34.9%)	73 (25.6%)	848 (34.4%)	921 (33.5%)
Sex					
Male	574 (73.5%)	1,370 (69.6%)	205 (71.9%)	1739 (70.6%)	1,944 (70.7%)
Female	207 (26.5%)	598 (30.4%)	80 (28.1%)	725 (29.4%)	805 (29.3%)
Region					
US	247 (31.6%)	862 (43.8%)	190 (66.7%)	919 (37.3%)	1109 (40.3%)
Outside US	534 (68.4%)	1106 (56.2%)	95 (33.3%)	1545 (62.7%)	1640 (59.7%)
ECOG Performance Status					
0	247 (31.6%)	1,035 (52.6%)	85 (29.8%)	1197 (48.6%)	1,282 (46.6%)
1	508 (65.0%)	879 (44.7%)	186 (65.3%)	1201 (48.7%)	1,387 (50.5%)
2	21 (1.9%)	37 (1.9%)	11 (3.9%)	47 (1.9%)	58 (2.1%)
Unknown	5 (0.6%)	17 (0.9%)	3 (1.1%)	19 (0.8%)	22 (0.8%)
Pathology					
Clear cell	704 (90.1%)	1,746 (88.7%)	242 (84.9%)	2208 (89.6%)	2,450 (89.1%)
Non-clear cell	41 (5.2%)	99 (5.0%)	16 (5.6%)	124 (5.0%)	140 (5.1%)
Unknown	36 (4.6%)	123 (6.3%)	27 (9.5%)	132 (5.4%)	159 (5.8%)
Baseline metastatic site					
Bone	781 (100.0%)	0(0.0%)	162 (56.8%)	619 (25.1%)	781 (28.4%)
Lung	616 (78.9%)	1,508 (76.6%)	222 (77.9%)	1902 (77.2%)	2,124 (77.3%)
Liver	225 (28.8%)	541 (27.5%)	88 (30.9%)	678 (27.5%)	766 (27.9%)
Brain	1 (<1%)	1(<1%)	0 (0%)	2 (<1%)	2 (<1%)
Other*	691 (88.5%)	1,525 (77.5%)	242 (84.9%)	1974 (80.1%)	2,216 (80.6%)
Previous nephrectomy					
Yes	622 (79.6%)	1,675 (85.1%)	216 (75.8%)	2081 (84.5%)	2,297 (83.6%)
No	80 (10.2%)	168 (8.5%)	35 (12.3%)	213 (8.6%)	248 (9.0%)
Unknown	79 (10.1%)	125 (6.4%)	34 (11.9%)	170 (6.9%)	204 (7.4%)
Prior type of therapy					
Any prior therapy	376 (48.1%)	893 (45.4%)	92 (32.3%)	1177 (47.8%)	1,269 (46.2%)
Cytokine therapy	160 (20.5%)	411 (20.9%)	43 (15.1%)	528 (21.4%)	571 (20.8%)
Targeted therapy	155 (19.8%)	327 (16.6%)	29 (10.2%)	453 (18.4%)	482 (17.5%)
MSKCC risk group					
Favorable	124 (15.9%)	461 (23.4%)	42 (14.7%)	543 (22.0%)	585 (21.3%)
Intermediate	308 (39.4%)	796 (40.4%)	111 (38.9%)	993 (40.3%)	1,104 (40.2%)
Poor	267 (34.2%)	509 (25.9%)	109 (38.2%)	667 (27.1%)	776 (28.2%)
Unknown	82 (10.5%)	202 (10.3%)	23 (8.1%)	261 (10.6%)	284 (10.3%)
IMDC risk group					

Characteristic n (%)	Patients with BMs n=781	Patients without BMs n=1968	Patients Receiving BT n=285	Patient not Receiving BT n=2,464	Total Cohort n=2749
Favorable	94 (12.0%)	377 (19.2%)	29 (10.2%)	442 (17.9%)	471 (17.1%)
Intermediate	367 (47.0%)	923 (46.9%)	107 (37.5%)	1183 (48.0%)	1,290 (46.9%)
Poor	284 (36.4%)	550 (27.9%)	129 (45.3%)	705 (28.6%)	834 (30.3%)
Unknown	36 (4.6%)	118 (6%)	20 (7.0%)	134 (5.4%)	154 (5.6%)

* Other is defined as any other metastases excluding bone, lung, liver, and brain. BM = bone metastases, BT = bisphosphonate therapy, ECOG = Eastern Cooperative Oncology Group, IMDC = International mRCC Database Consortium, MSKCC = Memorial Sloan-Kettering Cancer Center, US = United States.

Table 2

Adverse events associated with BT.

	N	Hypocalcemia	Renal Insufficiency	ONJ	P-Value
Overall Cohort					
BT Yes	285	21 (7.4%)	14 (4.9%)	6 (2.1%)	P<0.0001
BT No	2,464	75 (3.0%)	62 (2.5%)	1 (<1%)	
BM Patients					
BT Yes	162	18 (11.1%)	6 (3.7%)	5 (3.1%)	P<0.0001
BT No	619	20 (3.2%)	11 (1.8%)	1 (<1%)	
BM Patients Treated with BT					
VEFG Therapy	82	1 (1.2%)	1 (1.2%)	5 (6.1%)	P=0.0025
Non-VEGF Therapy	80	17 (21.3%)	5 (6.3%)	0	

ONJ = osteonecrosis of the jaw, BM = bone metastases, BT = bisphosphonate therapy, VEGF = vascular endothelial growth factor.

Table 3

Impact of BMs on OS and PFS.

	N	Median (months)	OS		Median (months)	PFS	
			P-Value	HR (95% CI)		P-Value	HR (95% CI)
Overall Cohort							
BM Yes	781	13.3	<0.0001	0.774	5.1	0.0008	0.837
BM No	1,968	20.2		(0.687-0.873)	6.7		(0.752-0.929)
MSKCC Risk Groups							
Favorable							
BM Yes	124	27.0	0.0136	0.605	10.6	0.0493	0.764
BM No	461	45.1		(0.406-0.902)	11.3		(0.583-0.999)
Intermediate							
BM Yes	308	16.1	0.0236	0.797	5.8	0.0316	0.832
BM No	796	21.9		(0.654-0.970)	7.2		(0.704-0.984)
Poor							
BM Yes	267	7.8	0.0378	0.827	3.0	0.1138	0.872
BM No	509	8.6		(0.691-0.989)	3.7		(0.735-1.033)
IMDC Risk Groups							
Favorable							
BM Yes	94	32.0	0.0370	0.627	10.8	0.0038	0.662
BM No	377	45.1		(0.405-0.972)	12.0		(0.501-0.875)
Intermediate							
BM Yes	367	17.0	<0.0001	0.698	6.5	0.0133	0.828
BM No	923	23.6		(0.586-0.832)	7.8		(0.713-0.961)
Poor							
BM Yes	284	7.16	0.1443	0.884	2.9	0.3868	0.931
BM No	550	7.82		(0.749-1.043)	3.5		(0.793-1.094)
Type of Therapy							
IFN- α							
BM Yes	181	12.2	0.0313	0.779	2.6	0.2033	0.871
BM No	379	17.4		(0.620-0.978)	3.8		(0.703-1.078)
Targeted Therapy							
BM Yes	600	13.4	0.0001	0.761	5.6	0.0017	0.825
BM No	1,589	20.7		(0.662-0.875)	7.8		(0.731-0.931)

BM = bone metastases, CI = confidence interval, HR = hazard ratio, IMDC = International mRCC Database Consortium, IFN- α = interferon alpha, MSKCC = Memorial Sloan-Kettering Cancer Center, OS = overall survival, PFS = progression-free survival.

Table 4

Impact of BT on OS and PFS in patients with BMs.

	OS				PFS		
	N	Median (months)	P-Value	HR (95% CI)	Median (months)	P-Value	HR (95% CI)
Overall Cohort							
BT Yes	162	13.3	0.3801	1.106	5.1	0.1785	1.154
BT No	619	13.1		(0.883-1.385)	4.9		(0.937-1.470)
MSKCC Risk Groups							
Favorable							
BT Yes	24	37.5	0.6076	1.220	10.7	0.7120	1.117
BT No	100	27.0		(0.571-2.606)	10.5		(0.620-2.015)
Intermediate							
BT Yes	73	16.8	0.5607	1.111	5.8	0.6228	1.085
BT No	235	15.7		(0.780-1.581)	6.3		(0.784-1.503)
Poor							
BT Yes	56	8.0	0.7118	1.067	3.7	0.2232	1.236
BT No	211	7.8		(0.758-1.501)	3.0		(0.879-1.738)
IMDC Risk Groups							
Favorable							
BT Yes	15	32.0	0.6311	1.252	12.3	0.2968	1.406
BT No	79	28.1		(0.500-3.133)	9.8		(0.741-2.665)
Intermediate							
BT Yes	74	20.6	0.0592	1.384	8.1	0.0722	1.319
BT No	293	16.3		(0.987-1.939)	6.5		(0.975-1.785)
Poor							
BT Yes	65	6.4	0.6785	0.937	2.5	0.3897	1.146
BT No	219	7.3		(0.689-1.275)	2.9		(0.840-1.564)
Type of Therapy							
IFN-α							
BT Yes	44	14.6	0.5200	1.149	2.3	0.4464	0.847
BT No	137	10.7		(0.752-1.757)	3.1		(0.553-1.298)
Targeted Therapy							
BT Yes	118	13.2	0.5345	1.087	6.5	0.0144	1.349
BT No	482	13.5		(0.835-1.417)	5.5		(1.062-1.714)

BT = bisphosphonate therapy, CI = confidence interval, HR = hazard ratio, IMDC = International mRCC Database Consortium, IFN- α = interferon alpha, MSKCC = Memorial Sloan-Kettering Cancer Center, OS = overall survival, PFS = progression-free survival.

Table 5

Summary of studies describing the impact of BT in mRCC.

Study	Design	Patients	Therapy	Bisphosphonate	Outcome
Keizman <i>et al</i> (2012) ⁽²⁴⁾	Retrospective	n=76 *Patients in the bisphosphonate arm were more likely to have prior nephrectomy, clear-cell histology, excellent performance status and less likely to have liver metastases and 2 sites of disease	First-line sunitinib +/- bisphosphonate	Zoledronic acid (n=29), Pamidronate (n=6)	Bisphosphonate arm associated with improved median PFS (15 versus 5 months, p<0.0001) and OS (not reached at 45 months versus 14 months, p=0.029)
Beuselinck <i>et al</i> (2012) ⁽²⁵⁾	Retrospective	n=76 *Patients in the bisphosphonate arm were younger, more likely to have prior nephrectomy, clear-cell histology, excellent performance status, and less number of sites of metastasis	First-line sunitinib (n=57) or sorafenib (n=19) +/- bisphosphonate	Zoledronic acid (n=47), Pamidronate (n=1), ibandronate (n=1)	Bisphosphonate arm associated with improved median PFS (7.0 versus 4.0 months, p=0.0011) and OS (17.0 versus 7.0 months, p=0.022)
Yasuda <i>et al</i> (2012) ⁽²⁶⁾	Retrospective	n=45 MSKCC intermediate-risk patients *Patients in the bisphosphonate arm were likely to receive targeted therapy and had improved performance status, which was statistically significant	First-line immunotherapy (n=32) and/or targeted therapy (n=10) +/- bisphosphonate	Zoledronic acid	Zoledronic acid arm associated with improved median OS (not reached at 25 month follow up versus 13.4 months, p=0.0034)
Broom <i>et al</i> (2013) ⁽²⁷⁾	Prospective	n=30 *Patients in the bisphosphonate arm were more likely to have favorable risk disease by IMDC criteria	Randomized to first-line everolimus + zoledronic acid versus everolimus	Zoledronic acid	Zoledronic acid arm had improved median PFS (7.5 versus 4.6 months, p=0.03)

IMDC = International mRCC Database Consortium, MSKCC = Memorial Sloan-Kettering Cancer Center, OS = overall survival, PFS = progression-free survival.