Renal cell carcinoma bone metastases: clinical advances

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***Abstract*:** Bone is a common site of metastatic spread in patients with advanced renal cell carcinoma (RCC) occurring in around one-third of patients enrolled in clinical trials evaluating modern systemic therapies for this disease. Until recently, limited systemic therapeutic options were available for advanced RCC. Nowadays, a quiver of agents have demonstrated activity, including compounds targeting the vascular endothelial growth factor (VEGF) axis and those targeting the mammalian target of rapamycin (mTOR). Despite a detailed biological understanding of how these drugs work, their effect on bony metastases is less clear. Data suggesting that bisphosphonates (namely zoledronic acid) benefit patients with bone metastases from advanced RCC was gathered prior to the targeted therapy era; therefore, there is some uncertainty about their role in patients on modern RCC therapies. This review summarizes the current targeted therapies registered for use in advanced RCC and postulates how some of them might affect the behavior of bone metastases. It also explores the data available on the role of bisphosphonates for bone metastases from RCC, describes methods of assessing response to therapy for bone metastases and delineates future expectations for the treatment of bone metastases from advanced RCC.

***Keywords*:** bisphosphonates, bone metastases, bone pain scales, renal cell carcinoma, targeted therapy, urinary N-telopeptide

Introduction

Renal cell carcinoma (RCC) is the most common malignancy of the kidney. In 2007, just under 58,000 people in the United States developed RCC and 12,980 died from the disease [Jemal *et al*. 2009]. The incidence of RCC has been increasing by about 3% per year in North Americans, with the highest rates now seen among African Americans [McLaughlin and Lipworth, 2000]. Almost 30% of patients with RCC present with metastatic disease, and furthermore, about 40% of patients who undergo resection of their primary with curative intent will relapse with disseminated disease [Motzer *et al*. 1996].

Bone is the second most common site of distant metastatic spread (following lung) in patients with advanced RCC. About one-third of patients in modern randomized trials of targeted therapies for advanced RCC have bone metastases [Rini *et al*. 2008; Motzer *et al*. 2007, 2008]. Furthermore, when patients progress on first-line therapy, the prevalence of bone metastases seems to increase, raising the possibility of the bones being a poorly controlled site of spread in this disease [Patil *et al*. 2009]. In one series of 103 patients with advanced RCC, of those with bone metastases, the most common sites of boney involvement were the pelvis and ribs (48%), followed by the spine (42%), then the long bones and skull [Zekri *et al*. 2001].

The mechanisms responsible for tumor growth in bone are complex and involve tumor driven stimulation of the osteoclasts, osteoblasts and other components of the bone microenvironment. Contrary to the pattern in some other tumor types such as prostate cancer, bone metastases from RCC are predominantly osteolytic and associated with bone destruction. In the aforementioned series, 71% of bone lesions evaluable by radiologic assessment were osteolytic with the remainder being either osteoblastic or mixed [Zekri *et al*. 2001].

Metastatic bone disease causes significant morbidity through skeletal related events (SREs),

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defined as a pathological fracture; surgical intervention (to treat or prevent an impending fracture); requirement for palliative radiotherapy to bone; spinal cord compression; or hypercalcemia of malignancy. In the series from Zekri and colleagues, palliative radiotherapy to bone was required in more than 80% of patients with bone metastases, and long-bone fractures occurred in at least 40% of patients. Therefore, bone metastases from RCC can be responsible for some of the most devastating complications in the advanced stage of this malignancy.

A retrospective review of 58 patients with advanced RCC receiving first-line systemic therapy with sorafenib showed that patients with bone metastases had a poorer prognosis than those patients without bone disease. The median progression free survival (PFS) was 11.2 months (95% confidence interval [CI] 7.4–13.2) for patients without bone metastases ($n = 36$) at the time of commencing treatment *versus* 4.7 months (95% CI 3.6–7.4) among patients with bone metastases ($n = 22$, log rank test $p = 0.002$). Cox regression proved that the presence of bone metastases was associated with shorter PFS after adjusting for other prognostic factors ($p = 0.02$) [Riechelmann *et al*. 2008]. A recent analysis of variables among RCC patients receiving first-line therapy with either sunitinib or interferon-alpha in a randomized trial [Patil *et al*. 2009] also confirmed that the presence of bone metastases was a poor prognostic feature in addition to those previously described [Motzer *et al.* 1999].

Current systemic therapy for RCC

Until recently, the main treatment options for patients with advanced RCC were interleukin (IL)-2 and interferon-alpha, which have somewhat limited efficacy in this disease. High-dose IL-2 therapy can rarely induce a durable complete response and interferon-alpha provides only a modest survival advantage in patients with RCC. Prior to the targeted therapy era, there were no other viable systemic treatment options for patients who were ineligible for, or unable to tolerate these cytokines [Negrier *et al.* 1998; Fyfe *et al.* 1995].

The targeted therapy era has revolutionized the systemic approach to the treatment of advanced RCC. The following agents have been registered for the treatment of patients with advanced RCC by the United States Food and Drug Administration (FDA). A summary is presented in Table 1.

Sunitinib

Sunitinib is an orally administered tyrosine kinase inhibitor (TKI) for a number of receptors including vascular endothelial growth factor receptor (VEGFR) types 1–3, platelet-derived growth factor receptor (PDGFR), stem cell factor receptor (KIT), FMS-like tyrosine kinase 3 (Flt-3), colony stimulating factor receptor type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). FDA approval of sunitinib followed the results of a phase III trial which randomized 750 treatment-naive patients with advanced RCC to either sunitinib or interferon-alpha. The median PFS was more than doubled in the sunitinib arm (11 months *versus* 5 months, $p < 0.001$) [Motzer *et al.* 2007]. Final overall survival (OS) data has subsequently been published [Motzer *et al.* 2009]. On the intention-to-treat analysis the median OS was 26.4 *versus* 21.8 months ($p = 0.013$ per unstratified Wilcoxon test) favouring sunitinib. When patients who received post-study treatments were excluded from the analysis (56% of patients on the sunitinib arm and 59% of patients on the interferon-alpha arm received post-study treatment), the median OS difference appeared to be pronounced (28.1 months *versus* 14.1 months, $p = 0.003$).

Sorafenib

Sorafenib is also an orally administered multi-TKI, which differs from sunitinib in that it also inhibits Raf kinase. Its registration followed the results of a phase III trial which randomized 903 patients with metastatic RCC, who had progressed on immunotherapy, to either sorafenib or placebo. The median PFS was almost doubled in the treatment arm (5.5 *versus* 2.8 months) [Escudier *et al.* 2007a]. In an analysis of this trial, which censored patients who crossed over from placebo to sorafenib, the median OS for patients receiving sorafenib was 17.8 *versus* 14.3 months for placebo (hazard ratio [HR] 0.78, $p = 0.0287$) [Bukowski *et al.* 2007].

Bevacizumab

Bevacizumab (an intravenously administered anti-VEGF antibody) has demonstrated benefit in a phase III trial which randomized 649 treatment naïve patients with advanced RCC to either interferon-alpha alone or interferon-alpha plus bevacizumab. The median PFS was almost doubled in the combination arm (10.2 *versus* 5.4 months, $p = 0.0001$) [Escudier *et al.* 2007b]. Another similarly designed phase III trial

Table 1. Summary of phase III randomized trials of targeted therapy in patients with advanced renal cell carcinoma (RCC).

	Sunitinib	Sorafenib	Bevacizumab	Temsirolimus	Everolimus
Study arms	Sunitinib (50 mg PO OD 4 weeks on, 2 weeks off) *versus* INF-α (9 MU SC thrice weekly)	Sorafenib (400 mg BID) *versus* placebo	Bevacizumab (10 mg/kg IV every 2 weeks) plus INF-α (9 MU SC thrice weekly) *versus* INF-α alone	Temsirolimus (25 mg IV weekly) *versus* INF-α (3 MU SC thrice weekly, ↑ to 18 MU) *versus* temsirolimus (15 mg IV weekly) plus INF-α (6 MU SC thrice weekly)	Everolimus (10 mg OD) *versus* placebo
Patient population	Treatment naïve metastatic RCC	Metastatic RCC following failure of one line of immunotherapy	Treatment naïve metastatic RCC	Treatment naïve metastatic RCC with poor-prognosis features	Metastatic RCC following failure of sunitinib, sorafenib or both
Median PFS	11 mo *versus* 5 mo ($p < 0.001$)	5.5 mo *versus* 2.8 mo ($p < 0.000001$)	10.2 mo *versus* 5.4 mo ($p = 0.0001$) and 8.5 mo *versus* 5.2 mo ($p < 0.0001$)	5.5 mo *versus* 3.1 mo *versus* 4.7 mo ($p =$ NA)	4 mo *versus* 1.9 mo ($p < 0.001$)
Median OS (ITT)	26.4 mo *versus* 21.8 mo ($p = 0.013$)*	17.8 mo *versus* 15.2 mo ($p = 0.146$)	23.3 mo *versus* 21.3 mo ($p = 0.1291$) and 18.3 mo *versus* 17.4 mo ($p = 0.097$)	10.9 mo *versus* 7.3 mo ($p < 0.01$) *versus* 8.4 mo	NA

BID, twice daily; INF-α, interferon alpha; ITT, intention-to-treat analysis; IV, intravenous; mo, months; MU, million units; NA, not available; NS, not significant; OD, once daily; OS, overall survival; PFS, progression-free survival; PO, orally; RCC, renal cell carcinoma; SC, subcutaneous.
*unstratified Wilcoxon test.

randomized 732 treatment naïve patients to receive either of the aforementioned treatment regimens. The combination therapy arm with bevacizumab had a higher median PFS (8.5 *versus* 5.2 months, $p < 0.0001$) when compared to the interferon monotherapy arm [Rini *et al.* 2008].

Temsirolimus

Temsirolimus is an intravenously administered mammalian target of rapamycin (mTOR) inhibitor. Its registration trial was a phase III trial of 626 patients with metastatic RCC with poor to intermediate prognostic characteristics who were randomized to either temsirolimus or interferon-alpha or the combination of both. The temsirolimus-alone arm was associated with an improved OS compared to interferon-alpha alone (HR 0.73, 95% CI 0.58–0.92; $p = 0.008$) [Hudes *et al.* 2007].

Everolimus

RAD001 (Everolimus) is an orally available mTOR inhibitor and the most recent agent to be FDA registered. It was evaluated in a phase III placebo-controlled trial with patients who had progressed following treatment with either sunitinib, sorafenib or both. Results following early termination of the trial showed a significant median PFS difference favoring the everolimus arm (4.0 *versus* 1.9 months, $p < 0.001$) [Motzer *et al.* 2008]. It is therefore the only agent with phase III trial evidence of activity in the second-line setting following treatment with an anti-VEGFR multi-TKI.

Trial limitations

In all of the aforementioned randomized trials, patients were required to have measurable disease in order to be eligible. Bone metastases are not considered to be measurable by RECIST criteria and in fact are difficult lesions to assess response

to therapy by imaging, as they tend to change in radiological appearance rather than in size [Clamp *et al*. 2004]. We therefore do not have specific data from the above-mentioned trials directly looking at how bone metastases respond to these new targeted therapies.

Bisphosphonates for bone metastases from RCC

Bisphosphonates have radically altered the management of bone metastases from a variety of malignancies by reducing or significantly delaying the occurrence of SREs. Bisphosphonates bind selectively to bone at sites of active mineral deposition and, once incorporated into bone mineral, act as specific inhibitors of osteoclast-mediated bone resorption [Fleisch, 2002].

The most convincing data in the RCC population comes from a subset analysis of a randomized trial which enrolled patients with bone metastasis from solid tumors other than breast or prostate cancer [Rosen *et al*. 2003]. There were 773 such patients randomized to receive either zoledronic acid or placebo via a 15-minute infusion every 3 weeks for a total of 9 months. Of these, 74 had advanced RCC. Initial randomization included two zoledronic acid dosing groups of either 4 or 8 mg but then because of nephrotoxicity concerns the 8 mg group was switched to 4 mg dosing. In the RCC subset, the proportion of patients randomized to the placebo group who experienced an SRE was higher than for patients with other malignancies, further exemplifying the aggressiveness of bone metastases from RCC. Over the total trial duration, 74% of RCC patients in the placebo arm experienced an SRE compared to only 44% in the total trial population.

Specific results from the subset of RCC patients in this trial have been published separately [Lipton *et al*. 2004]. There were 46 RCC patients treated with either 4 mg of zoledronic acid ($n = 27$) or placebo ($n = 19$). Over the course of the 9-month trial the proportion of these patients who suffered an SRE was reduced by 50% in the treatment arm (37% *versus* 74% with placebo, $p = 0.015$). Zoledronic acid also significantly prolonged the time to first SRE (median not reached at 9 months *versus* 72 days for placebo, $p = 0.006$). Furthermore, zoledronic acid significantly reduced the annual incidence of SREs by 21% (mean 2.68 *versus* 3.38 events per year for placebo, $p = 0.014$) and significantly reduced the risk of developing a SRE by 61% compared with placebo by multiple event analysis (risk ratio = 0.394, $p = 0.008$). Finally, the median time to progression of bone lesions was also significantly extended with zoledronic acid treatment ($p = 0.014$). Zoledronic acid is therefore the first bisphosphonate to significantly diminish skeletal morbidity and delay the progression of bone lesions in patients with advanced RCC. Provisional results from a 21-month extension phase of the above trial confirmed the benefit of zoledronic acid in this population and show that the median time to first SRE in the 4 mg zoledronic acid arm was 442 days (compared to 72 days for placebo, $p = 0.007$) [Lipton *et al*. 2004].

Provisional results have recently been presented on a series of 51 patients with advanced RCC and bone metastases who were all treated with zoledronic acid (4 mg) every 3 weeks and followed for 54 weeks. Thirteen (26%) of these patients suffered a SRE [Tunn *et al*. 2009]. Although the above data strongly suggest that benefit can be conferred to patients with advanced RCC and bone metastasis by the administration of bisphosphonates, we must remember that the randomized data are only a subset analysis and the patient numbers studied are relatively small. For this reason, bisphosphonate funding for these patients has lagged behind the funding of these drugs for patients with other malignancies, such as breast and prostate cancer, in many countries. Furthermore, the data on bisphosphonates in this condition come from the era prior to the widespread use of targeted therapies. The role of bisphosphonates in the modern era of targeted therapy for advanced RCC and bone metastases is therefore somewhat unclear.

Rationale for activity on bone metastases of targeted therapy in use for RCC

Many of the targeted therapies in use or development for advanced RCC inhibit either VEGF or its receptor function. There is some biological rationale for the use of these drugs specifically to control bone metastases. One study has investigated the *in vitro* inhibitory effects of sunitinib against CSF-1R phosphorylation as well as osteoclast formation and function in tumor-bearing mice [Murray *et al*. 2003]. CSF-1R is thought to potentiate invasion of malignant tumours [Wrobel *et al*. 2004]. In this study, phosphorylation of CSF-1R was indeed inhibited by sunitinib. Inhibition of osteolysis was confirmed by significant lowering of serum pyridinoline

levels following sunitinib treatment and bone tumor growth was stunted as evidenced by bioluminescence imaging. While VEGF has been demonstrated to be over-expressed in actual bone metastases from breast cancer patients [Ooi *et al.* 2007], this does not seem to be a prominent feature of RCC bone metastases. In fact, one series of 20 cases showed that VEGFR-2 protein expression fell from 35% in the primary specimen to 10% in the bone metastases suggesting a phenotypic change during progression to the bones [Badalian *et al.* 2007]. Several other receptors have been implicated in mediating the activity of bone metastases in advanced RCC, namely transforming growth factor-beta 1 (TGF-beta 1) and epidermal growth factor receptor (EGFR) [Weber *et al.* 2007; Kominsky *et al.* 2007]. The chemokine macrophage inflammatory protein-1 delta (MIP-1 delta) was found to be increased in RCC bone metastases compared to patient-matched primary RCC tissue and this protein has been shown to stimulate osteoclast precursor cell types and enhance osteoclast activity as well as cause bone resorption in murine models [Kominsky *et al.* 2008]. Therefore, there may be a number of pathways involved in the activity of bone metastases from RCC that are not affected by any of the anti-VEGF targeted therapies currently in use.

There are some preclinical data to suggest that everolimus may have some activity in the bones. This comes from the study of the administration of everolimus in an ovariectomized rat model which seemed to prevent the loss of cancellous bone in association with decreased osteoclast-mediated bone resorption [Kneissel *et al.* 2004]. Further evaluation of the potential bone effects of the m-TOR inhibitors in humans is planned.

Assessing the response of bone metastases to therapy

As mentioned above, the radiological assessment of the response to treatment of bone metastases from any malignancy is difficult. Furthermore, because the hard endpoint of SREs requires following large numbers of patients for a long period of time in order to gather meaningful results, there has been considerable interest in surrogate markers that can predict for SREs. Urinary N-telopeptide (uNTX) is a peptide fragment of the N-terminus of type I collagen, which is predominant in bone and is correlated with the presence of metastatic disease. Its measurement has assumed a role as such a marker [Broom *et al.* 2007].

In one study of 121 patients with bone metastases from various malignancies, patients with uNTX levels higher than 100 nmol/mmol creatinine before initiation of bisphosphonate therapy had a 19-fold increase in the relative risk of a SRE during the first 3 months of therapy compared to those patients with lower uNTX (<100 nmol/mmol) [Brown *et al.* 2003]. Logistic regression analyses demonstrated that 84% of the SREs that occurred in the first 3 months of treatment could be predicted by uNTX measurements.

In a retrospective analysis of 1824 patients with bone metastases from a variety of malignancies who were receiving bisphosphonate therapy in three randomized trials, uNTX levels and subsequent risk of SREs were assessed [Coleman *et al.* 2005]. Most of these patients were receiving zoledronic acid. Patients receiving zoledronic acid with uNTX higher than 100 nmol/mmol creatinine had a 2–3 times greater risk of experiencing an SRE when compared to those with levels less than 50 nmol/mmol. The risk of SREs associated with moderately elevated uNTX levels (50–99 nmol/mmol) was also significantly higher across all disease groups when compared to patients with uNTX below 50 nmol/mmol. In this analysis, there was also a significant correlation between high uNTX levels and the relative risk of death across all solid tumor groups.

Thus, a significant correlation exists between uNTX and subsequent risk of SREs in a number of solid tumors and because of this uNTX is used as an endpoint in many studies that are designed to assess the effectiveness of bone-specific antineoplastic therapies.

A prospective pilot study specifically designed to assess the effect of the anti-VEGFR multi-TKIs has recently been presented [Sahi *et al.* 2009]. In patients with bone metastases from RCC and at least moderately elevated uNTX levels prior to treatment with sunitinib or sorafenib, there was significant trend to decrease uNTX levels during 12 weeks of therapy, but the fall was not as quick nor as marked as typically seen with bone-specific therapies such as bisphosphonates [Sahi *et al.* 2009].

As well as through causing SREs, bone metastases cause considerable morbidity through debilitating pain. Bone pain from metastases seems unique in several ways. It has common clinical features, such as a predilection to flare when

weight is placed on the affected area, therefore impacting on some aspects of daily function. Bone pain may also affect how patients view their disease, with new or increasing pain often inciting anxiety about disease progression. The Functional Assessment of Cancer Therapy — Bone Pain (FACT-BP) is a 16-item brief scale developed to assess cancer-related bone pain and its effects on quality of life (QL); the higher the aggregate score, the less the bone pain and/or the better the QL. It has been prospectively validated in a group of 61 patients (from two similarly designed trials) with metastatic breast cancer and bone metastases, who switched bisphosphonate therapies upon progression of their bony disease [Broom *et al*. 2009].

Future directions in the treatment of bone metastases from RCC

Radiation is a common therapeutic modality used for alleviating pain and other problems from symptomatic bone metastases. There are early emerging data examining the safety of concurrent administration of multi-TKIs with radiotherapy. One series of 12 patients treated with full-dose sunitinib (50 mg daily) together with high-dose radiotherapy to various sites (including the spine), suggests that such a combination may be relatively safe [Staehler *et al*. 2009]. Further research examining such combined modality therapy is underway. The safety and activity of the combination of sorafenib and palliative radiotherapy is being assessed in a phase I/II study in this patient population. It is designed to examine the reduction in pain from bone lesions and check for toxicity.

There are also several novel classes of agents that are undergoing clinical trial evaluation as bone-specific antineoplastic therapies and therefore these may have a role in the future management of patients with RCC and bone metastases. These include the RANK ligand inhibitors, cathepsin K inhibitors and the Src kinase inhibitors.

Denosumab

Denosumab is a fully human monoclonal antibody to receptor activator of nuclear factor-kappa B ligand (RANKL). RANKL is an integral mediator of osteoclast differentiation and function. Cancer cells secrete a variety of cytokines such as parathyroid hormone-related protein, IL-6 and tumor necrosis factor-α that all promote bone resorption in culture. The secretion of these factors into the bone microenvironment has been shown to enhance the production of RANKL via their action on the surface of stromal osteoblasts [Wittrant *et al*. 2004]. RANKL can also be produced directly by tumour cells and is a member of the TNF ligand family which binds to its receptor, RANK, present at the surface of osteoclast precursors and mature osteoclasts, inducing osteoclast differentiation and activation [Nakagawa *et al*. 1998]. RANKL is the protein denosumab binds to and inhibits, thereby inhibiting the excessive osteoclastic activity associated with bone metastases. Denosumab is currently being evaluated in a phase III double-blind, placebo-controlled trial which randomizes patients with advanced cancer and bone metastases to either subcutaneous denosumab or intravenous zoledronic acid every 4 weeks. Patients with RCC are eligible for this trial but not patients with breast or prostate cancer as they are being assessed in two separate identically designed studies.

Odanacatib

Odanacatib is a selective inhibitor of cathepsin K, a lysosomal cysteine protease that is highly expressed in osteoclasts. Cathepsin K inhibition is known to suppress osteolysis in preclinical models of metastatic bone disease. A double-blind randomized controlled trial (oral odanacatib 5 mg daily for 4 weeks *versus* intravenous zoledronic acid 4 mg given once at study initiation) assessing the safety and effectiveness of odanacatib in reducing markers of bone remodeling in women with breast cancer having bone metastases is currently being done. Preliminary results from this study show that markers of bone resorption (uNTX) were similarly suppressed after 4 weeks of treatment in both arms (77% change with odanacatib *versus* 73% change with zoledronic acid) [Jensen *et al*. 2008].

Dasatinib

Dasatinib is a molecule which inhibits Src kinase and is also known to inhibit bone resorption *in vitro* and in rat models. Src kinases are known to play a major role in osteoclast function. A correlative study of bone metabolism on a subset of patients enrolled in a phase II trial of dasatinib in relapsed multiple myeloma has been performed. Results from this small subset (seven patients) showed that therapy with dasatinib in such patients was associated with decreased osteoclast function and no change in osteoblast function (mean decrease in uNTX = 34.4% after one cycle). No patient achieved an objective

paraprotein response to dasatinib which suggests it directly inhibits osteoclasts [Wildes *et al.* 2009]. There are also other Src kinase inhibitors being studied in clinical trials.

Ongoing evaluation

Therefore, as well as the bisphosphonates, there are a number of agents in varying stages of clinical development that could potentially have a role in the future management of this patient population. However, prior to their trialing in combination with the targeted therapies already in widespread use for advanced RCC, we need to further evaluate the effects on bone metastases of these already registered agents alone. Research of this nature will help clarify the need for bone-specific therapies in the modern targeted therapy era.

Conclusions

The widespread use of targeted therapies has revolutionized the treatment of metastatic RCC. For bone metastases from RCC specifically, the third-generation bisphosphonate, zoledronic acid, is the only drug to date that has demonstrated an ability to significantly delay or prevent skeletal complications in these patients. However, there is a paucity of data on bisphosphonates in RCC compared with other malignancies where the development of bone metastases is common (ie breast or prostate cancer). Furthermore, the data on zoledronic acid were obtained prior to the era of targeted therapies, which may themselves transpire to have some effect on bone metastases. This is currently being studied and depending on the findings of this ongoing research, further evaluation of bisphosphonates (or other novel bone-specific therapies) in combination with the already registered targeted therapies may be required in this malignancy which commonly causes catastrophic skeletal complications. We also await with interest the results of the trial comparing zoledronic acid with denosumab in patients with bone metastases, specifically as to whether or not there is information embedded in this data that is directly applicable to RCC patients. Further data from other novel agents undergoing clinical evaluation (Src kinase and cathepsin K inhibitors) are also awaited.

Conflict of interest statement

None declared.

References

Badalian, G., Derecskei, K., Szendroi, A., Szendroi, M. and Timar, J. (2007) EGRF and VEGFR2 protein expressions in bone metastases of clear cell renal cancer. *Anticancer Res* 27: 889–894.

Broom, R., Simmons, C., Clemons, M. and Cole, D. (2007) The role of urinary n-telopeptides in evaluating the palliative benefit of bisphosphonates in metastatic breast cancer. *Prog Pall Care* 15: 1–5.

Broom, R., Du, H., Clemons, M., Eton, D., Dranitsaris, G., Simmons, C. *et al.* (2009) Switching breast cancer patients with progressive bone metastases to third-generation bisphosphonates: measuring impact using the Functional Assessment of Cancer Therapy — Bone Pain. *J Pain Symptom Manage* 38: 244–257.

Brown, E., Thomson, C.S., Ellis, S.P., Gutcher, S.A., Purohit, O.P. and Coleman, R.E. (2003) Bone resorption predicts for skeletal complications in metastatic bone disease. *Br J Cancer* 89: 2031–2037.

Bukowski, R.M., Eisen, T., Szczylik, C., Stadler, W.M., Simantov, R., Shan, M. *et al.* (2007) Final results of the randomized phase III trial of sorafenib in advanced renal cell carcinoma: survival and biomarker analysis. *J Clin Oncol* 25(18S): abstr 5023.

Clamp, A., Danson, S., Nguyen, H., Cole, D. and Clemons, M. (2004) Assessment of therapeutic response in patients with metastatic bone disease. *Lancet Oncol* 5: 607–616.

Coleman, R.E., Major, P., Lipton, A., Brown, J.E., Lee, K.A., Smith, M. *et al.* (2005) Predictive value of bone resporption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. *J Clin Oncol* 23: 4925–4935.

Escudier, B., Eisen, T., Stadler, W.M., Szczylik, C., Oudard, S., Siebels, M. *et al.* (2007a) Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 356: 125–134.

Escudier, B., Pluzanska, A., Koralewski, P., Ravaud, A., Bracarda, S., Szczylik, C. *et al.* (2007b) Bevacizumab plus interferon alpha-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 370: 2103–2111.

Fleisch, H. (2002) The role of bisphosphonates in breast cancer: development of bisphosphonates. *Breast Cancer Res* 4: 30–34.

Fyfe, G., Fisher, R.I., Rosenberg, S.A., Sznol, M., Parkinson, D.R. and Louie, A.C. (1995) Results of treatment of 255 pateints with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J Clin Oncol* 13: 688–696.

Hudes, G., Carducci, M., Tomczak, P., Dutcher, J., Figlin, R., Kapoor, A. *et al.* (2007) Temsirolimus, interferon-alpha or both for advanced renal-cell carcinoma. *N Engl J Med* 356: 2271–2281.

Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J. and Thun, M.J. (2009) Cancer statistics. *CA Cancer J Clin* 59: 225–249.

Jensen, A.B., Olmeo, N., Wynne, C., Ramirez, G., Lebrecht, A., Mehta, A. *et al.* (2008) Effect of cathepsin k inhibition on suppression of bone resorption in women with breast cancer and established bone metastases in a 4-week, double-blind, randomized controlled trial. *J Clin Oncol* 26(15S): abstr 1023.

Kneissel, M., Luong-Nguyen, N.H., Baptist, M., Cortesi, R., Zumstein-Mecker, S., Kossida, S. *et al.* (2004) Everolimus suppresses cancellous bone loss, bone resorption, and cathepsin K expression by osteoclasts. *Bone* 35: 1144–1156.

Kominsky, S.L., Doucet, M., Brady, K. and Weber, K.L. (2007) TGF-beta promotes the establishment of renal cell carcinoma bone metastasis. *J Bone Miner Res* 22: 37–44.

Kominsky, S.L., Abdelmagid, S.M., Doucet, M., Brady, K. and Weber, K.L. (2008) Macrophage inflammatory protein-1 delta: a novel osteoclast stimulating factor secreted by renal cell carcinoma bone metastasis. *Cancer Res* 68: 1261–1266.

Lipton, A., Colombo-Berra, A., Bukowski, R.M., Rosen, L., Zheng, M. and Urbanowitz, G. (2004) Skeletal complications in patients with bone metastases from renal cell carcinoma and therapeutic benefits of zoledronic acid. *Clin Cancer Res* 10: 6397S–6403S.

McLaughlin, J.K. and Lipworth, L. (2000) Epidemiological aspects of renal cell cancer. *Semin Oncol* 27: 115–123.

Motzer, R.J., Bander, N.H. and Nanus, D.M. (1996) Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *N Engl J Med* 335: 865–875.

Motzer, R.J., Mazumdar, M., Bacik, J., Berg, W., Amsterdam, A. and Ferrara, J. (1999) Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol* 17: 2530–2540.

Motzer, R.J., Hutson, T.E., Tomczak, P., Michaelson, M.D., Bukowski, R.M., Rixe, O. *et al.* (2007) Sunitinib versus interferon alpha in metastatic renal-cell carcinoma. *N Engl J Med* 356: 115–124.

Motzer, R.J., Escudier, B., Oudard, S., Hutson, T.E., Porta, C., Bracarda, S. *et al.* (2008) Efficacy of everolimus in advanced renal cell carcinoma: a double blinded, randomised, placebo-controlled phase III trial. *Lancet* 372: 449–456.

Motzer, R.J., Hutson, T.E., Tomczak, P., Michaelson, M.D., Bukowski, R.M., Oudard, S. *et al.* (2009) Overall survival and updated results for sunitinib compared with interferon alpha in patients with metastatic renal cell carcinoma. *J Clin Oncol* 27: 3584–3590.

Murray, L.J., Abrams, T.J., Long, K.R., Ngai, T.J., Olson, L.M., Hong, W. *et al.* (2003) SU11248 inhibits tumor growth and CSF-1R dependant osteolysis in an experimental breast cancer bone metastasis model. *Clin Exp Metast* 20: 757–766.

Nakagawa, N., Kinosaki, M., Yamaguchi, K., Shima, N., Yasuda, H., Yano, K. *et al.* (1998) RANK is the essential signaling receptor for osteoclast differentiation factor in osteoclastogenesis. *Biochem Biophys Res Commun* 253: 395–400.

Negrier, S., Escudier, B., Lasset, C., Douillard, J.Y., Savary, J., Chevreau, C. *et al.* (1998) Recombinant human interleukin-2, recombinant human interferon alpha-2a, or both in metastatic renal-cell carcinoma. *N Engl J Med* 338: 1272–1278.

Ooi, W.S., Popovic, S., Kalina, M., Kahn, H., Singh, G., Gainford, M.C. *et al.* (2007) Mechanisms of bone metastasis (BM) growth in patients with metastatic breast cancer (MBC): an exploratory study. *J Clin Oncol* 25(18S): abstr 1102.

Patil, S., Figlin, R.A., Hutson, T.E., Michaelson, M.D., Negrier, S., Kim, S.T. *et al.* (2009) Prognostic factors for overall survival with sunitinib as first-line therapy in patients with metastatic renal cell carcinoma (mRCC). *J Clin Oncol* 27(15S): abstr 5042.

Riechelmann, R.P., Chin, S., Wang, L., Tannock, I.F., Berthold, D.R., Moore, M.J. *et al.* (2008) Sorafenib for metastatic renal cancer: the Princess Margaret Experience. *Am J Clin Oncol* 31: 182–187.

Rini, B.I., Halabi, S., Rosenberg, J.E., Stadler, W.M., Vaena, D.A., Ou, S.S. *et al.* (2008) Bevacizumab plus interferon alpha compared with interferon alpha monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol* 26: 5422–5428.

Rosen, L.S., Gordon, D., Tchekmedyian, S., Yanagihara, R., Hirsh, V., Krzakowski, M. *et al.* (2003) 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 Tumor Study Group. *J Clin Oncol* 21: 3150–3157.

Sahi, C., Knox, J.J., Hinder, V., Deva, S., Cole, D., Clemons, M. *et al.* (2009) The effects of sorafenib and sunitinib on bone turnover markers in patients with bone metastases from renal cell carcinoma. *J Clin Oncol* 27(suppl): abstr e16145.

Staehler, M., Haseke, N., Stadler, T., Steif, C.G. and Wilkowski, R. (2009) Effectivity of simultaneous radiation therapy and multi-kinase inhibition with sunitinib in progressive metastatic renal cell cancer. *Proc Am Soc Clin Oncol, Genitourinary Cancer Symposium* [abstract 334].

Tunn, U., Stenzl, A., Kindler, M., Strauss, A., Miller, K., Reubel, A. *et al.* (2009) The effect of zoledronic acid on bone metastasis in patients suffering from renal cell cancer (RCC): a German prospective single-arm clinical trial. *J Clin Oncol* 27(15S): abstr 5107.

Weber, K., Doucet, M. and Kominsky, S. (2007) Renal cell carcinoma bone metastasis — elucidating the molecular targets. *Cancer Metastasis Rev* 26: 691–704.

Wildes, T.M., Procknow, E., Gao, F., Dipersio, J.F. and Vij, R. (2009) Dasatinib in relapsed or plateau-phase multiple myeloma. *Leuk Lymphoma* 50: 137–140.

Wittrant, Y., Theoleyre, S., Chipoy, C., Padrines, M., Blanchard, F., Heymann, D. *et al.* (2004) RANKL/RANK/OPG: new therapeutic targets in bone tumors and associated osteolysis. *Biochim Biophys Acta* 1704: 49–57.

Wrobel, C.N., Debnath, J., Lin, E., Beausoleil, S., Roussel, M.F. and Brugge, J.S. (2004) Autocrine CSF-1R activation promotes Src-dependant disruption of mammary epithelial architecture. *J Cell Biol* 165: 263–273.

Zekri, J., Ahmed, N., Coleman, R.E. and Hancock, B.W. (2001) The skeletal metastatic complications of renal cell carcinoma. *Int J Oncol* 19: 379–382.