

Review

## Prostate Spinal Metastasis: An Update and Review

Neha Rao<sup>1</sup>, Abhiraj D. Bhimani<sup>1</sup>, Steven T. Papastefan<sup>1</sup>, Pouyan Kheirkhah<sup>1</sup>, Gregory D. Arnone<sup>1</sup>, and Ankit I. Mehta<sup>1</sup>

<sup>1</sup>Department of Neurosurgery, University of Illinois at Chicago

**\*Corresponding author:** Ankit I. Mehta, M.D. Assistant Professor and Assistant Program Director, Director of Spinal Oncology, Adjunct Professor Orthopedic Surgery and Chemical Engineering, Department of Neurosurgery, University of Illinois at Chicago. 912 S. Wood Street, 4N NPI, Chicago, IL 60612. Email: [ankitm@uic.edu](mailto:ankitm@uic.edu)

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### Abstract:

Advanced prostate metastasis causes significant morbidity and mortality on the adult male population. This paper reviews the evidence regarding the efficacy of various treatment options currently present for patients with metastatic castration-resistant prostate cancer (mCRPC) to the spine. Treatment approaches for prostate spinal metastasis involves a multidisciplinary team. This paper is a review of all the viable treatment options available to patients who present with spinal mCRPC, including discussion on gaps in care and emerging treatments that may both address symptoms as well as facilitate local disease control. Despite multiple modalities of treatment, there is limited data to support a treatment paradigm that provides the most efficacious sequence of approved treatments for individual patients. Future studies that analyze these algorithms are needed to improve prostate metastatic care.

**Keywords** prostate cancer, spinal metastasis, metastatic castration-resistant prostate cancer, stereotactic radiosurgery, radium-223, Androgen-Deprivation Therapy

### Introduction

Globally, prostate cancer is the second most frequently diagnosed cancer and the fifth leading cause of death in males (1). In 2012, it accounted for an estimated 1.1 million new cases diagnosed and 307,000 deaths (2). Patients who develop advanced prostate cancer initially undergo surgical or medical castration, which suppresses testosterone levels. Despite this treatment, a majority of the cancers in these patients will advance to become castration-resistant prostate cancer (CRPC) (3). CRPC is particularly debilitating disease characterized by

skeletal-related events (SREs) such as bone pain, fractures, spinal cord compression and vertebral collapse (4). The majority of prostate cancer-related deaths can be attributed to this metastatic castration-resistant prostate cancer (mCRPC), when disease progression occurs despite testosterone suppression (5). CRPC is associated with metastasis in >80% of the cases, with the spine being the most common osseous site of metastasis. About a third of these spinal lesions will present with neurological deficits, intractable pain, and/or mechanical instability, sometimes

requiring surgical treatment (6). Because the prognosis of patients with mCRPC is strongly correlated with spinal metastasis, treatment of spinal metastases is a critical component of care for this patient population (7).

Treatment options for patients with spinal mCRPC must be a multidisciplinary approach that includes the use of analgesia, radiotherapy to dominant sites of bone pain, surgery in selected cases, cytotoxic chemotherapy, hormone treatment, and radioisotopes. Treatment with bisphosphonates is used to reduce skeletal related events (SREs) and narcotic analgesics are used as pain palliatives. Glucocorticoids such as prednisone or hydrocortisone may also be prescribed to reduce the symptoms associated with spinal metastases and cord compression (7). This paper is a review of all the viable treatment options available to patients who present with spinal mCRPC, including a discussion on gaps in care and emerging treatments that may both address symptoms, as well as facilitate local disease control.

### **Treatment Modalities:**

#### **Stereotactic radiosurgery**

If a patient is experiencing localized constant pain despite analgesia, recurrent pathological fractures and spinal cord compression despite surgical fixation, or inoperable pathological fractures, then radiotherapy is indicated.

Advancements in frameless radiosurgical technology have paved the way for the application of radiosurgery to the spine. Stereotactic radiosurgery (SRS) is an emerging form of radiation therapy for the treatment of spinal mCRPC. The goals of radiation therapy in the treatment of spinal tumors have included alleviation of pain, prevention of pathologic fractures, and stopping or reversing the progression of neurologic damage (8). Despite the connotation conveyed in the name, this form of therapy is non-surgical, entirely noninvasive, and comes with less side effects than conventional radiation therapy or brachytherapy (9). Conventional external beam radiotherapy is inferior to SRS in that it lacks the precision required to allow the delivery of large doses of radiation near radiosensitive structures such as the spinal cord (10). Unlike

brachytherapy, stereotactic radiosurgery does not involve the insertion of needles nor does it carry risks of bleeding, risk of infection, general anesthesia, hospital stays, or urinary catheter-related complications. Rapid recovery and symptomatic response are both associated with SRS. While conventionally fractionated radiation requires 40-45 treatment sessions, Stereotactic Body Radiation Therapy (SBRT) requires 3-5 sessions over the course of five to ten days (11). Additionally, there is sparing of the bladder and the rectum that occurs to a greater degree in comparison to the sparing observed in brachytherapy. Hence, this therapeutic technique offers durable pain relief and maintenance of quality of life for medically inoperable patients with spinal mCRPC, including those with recurrent episodes of spinal cord compression. Currently, stereotactic radiosurgery is used as treatment for patients with metastatic spine disease who have pain related to a specific involved vertebral body and as adjuvant therapy for patients who have had open surgical procedure. However, it has been proven to be effective as either primary or adjunctive treatment of metastatic tumors of the spine (12). It has been hypothesized that spinal radiosurgery is likely to become an essential part of any neurosurgical spine center that treats a large number of patients with spinal metastases.

#### **Radium-223**

Radium-223 dichloride (Xofigo), an alpha-emitting radiopharmaceutical antineoplastic agent, is another newly emerging form of treatment that specifically targets bone metastases in metastatic CRPC. Bone targeting radiopharmaceuticals act by binding to hydroxyapatite, the main component of inorganic matrix in bone that is linked with cancer cells found in osteoblastic lesions (13). They are currently used for palliative treatment of bone metastases in patients with metastatic CRPC (14). Alpha-emitters have a relatively short path compared to beta-emitters, which minimizes their toxic effect on adjacent healthy stroma (15, 16). Radium-223 is the only alpha-emitting bone targeted radioisotope available as a treatment modality (14). It is calcium mimetic and able to localize to bone metastases and form complexes with

hydroxyapatite (15). As it decays, Radium-223 creates double-strand DNA breaks due to high linear energy transfer facilitated by its alpha emission, which causes a cytotoxic effect on bone metastatic cancer cells through induction of apoptosis (14, 15). Radium-223 has displayed the ability to prolong life, delay SRE's and improve quality of life (14). Along with having a beneficial therapeutic effect on patients, Radium-223 has shown to have good tolerance and low rates of myelotoxicity. Even though Radium-223 has not been associated with greater pain relief, patients are encouraged to continue use with adjustments to pain medications dosages as needed. About 50% of patients respond favorably to this treatment. Adverse side effects of these pharmaceuticals include damage to surrounding tissues and bone marrow toxicity.

SRE's from mCRPC metastasis to the bone include spontaneous fracture and spinal cord compression, which can result in decreased quality of life (17, 18). With that said, Ra-223 is currently the only bone-targeted drug that has been associated with improved survival, resulting in 30% reduction in the mortality when compared to placebo in castration-resistant prostate cancer and bone metastasis (15). In 2014, the ALSYMPCA trial, a phase-3 double-blind RCT showed that radium-223 treatment improves survival in patients with or without previous docetaxel use (19). However, radium-223 reduced time-to-first SRE in patients with previous docetaxel use, but the difference was not significant in patients without previous docetaxel use (19). While Radium-223 is currently the only bone-targeted radiopharmaceutical to show improved survival in prostate cancer, beta emitters' rhenium-186, rhenium-188, samarium-153, and strontium-89 have all shown to have pain palliative effects. Studies have yet to prove their efficacy and their myelosuppressive effects (17, 18).

### **Surgery**

Vigorous surgical procedures are often pursued following diagnosis of spinal mCRPC. Upon spinal metastases, spinal cord compression develops and becomes the most common complication. Radiotherapy and decompressive surgery remain the frontrunners in the treatment of neurological complications from osseous metastases. More

specifically, surgical decompression succeeded by radiotherapy is the predominant treatment modality for spinal cord compression, and this is because surgery has been associated with a greater probability of recovery than radiation alone. Health-related quality of life has been shown to improve significantly when surgical decompression and spinal stabilization are conducted in conjunction with radiation therapy (20). In order to determine if a patient is a good candidate for surgery, factors such as expected duration of survival, potential of rehabilitation, overall medical condition and type of intervention required need to be evaluated. One study showed that patients with hormone-naïve disease and those with CRPC with good performance status and no visceral metastases were the patients who benefitted the most from surgery for metastatic spinal cord compression (21). Because surgical interventions have only shown to be suitable for patients with a good performance status, a survival prognosis of more than 3 months, and involvement of only one spinal segment, which account for only about 10% of all metastatic spinal cord compression (MSCC) patients, radiotherapy alone is still an important treatment for MSCC (22). In fact, prostate cancer patients, and myeloma patients developing MSCC may live for several years after radiotherapy.

### **Androgen-Deprivation Therapy in Hormone-Sensitive Prostate Cancer**

The prostate is an androgen-dependent organ expressing the androgen receptor (AR), a hormone activated transcription factor and drug target for all stages of prostate cancer. Androgens, such as testosterone and dihydrotestosterone, usually bind to this receptor to initiate a cascade of events beginning with the conformational change and nuclear translocation of the receptor. In prostate cancer, the androgen receptor is primarily involved with the synthesis of PSA and regulation of lipid metabolism. Additionally, in prostate cancer it acquires the ability to promote growth. Hence, androgen deprivation therapy (ADT) remains the gold standard treatment for metastatic prostate cancer (23). According to the EAU 2016 Guidelines on Prostate Cancer, patients with impending spinal cord compression should be treated

with an LHRH antagonist or bilateral orchiectomy. Otherwise, any form of ADT is considered first-line for metastatic prostate cancer to the spine (23). Additionally, consideration of the volume of metastasis is important in determining the appropriate use of ADT. In 2015, the E3805 study by the Eastern Cooperative Oncology Group (ECOG) showed that the median overall survival for patients with metastatic hormone-sensitive prostate cancer with high-volume metastasis was 17 months longer (49.2 months vs. 32.2 months) for patients treated with ADT plus docetaxel compared to ADT alone (24). High-volume disease was defined as the presence of visceral metastases or  $\geq 4$  bone lesions with  $\geq 1$  outside the vertebral bodies and pelvis, a classification based on previous studies (24).

Unfortunately, this treatment modality is not curative due to opposing secondary effects such as amplification of the *AR* gene, increased AR protein expression resulting in hypersensitivity to low levels of androgens, and increased growth factor receptor expression (ie. HER2 and ERBB3) that promote increased PSA production and AR stability (25). Additionally, ADT results in upregulation of glucocorticoid receptors that modify androgen target genes, resulting in refractory treatment response to ADT (26). Consequently, prostate cancer will progress to become castration-resistant, giving rise to mCRPC.

### Androgen-Deprivation Therapy in mCRPC

Several drugs have been proposed to directly and indirectly combat the androgen hypersensitivity found in mCRPC. Enzalutamide (MDV3100) is an androgen receptor antagonist that has been shown to have improved overall survival, radiographic progression-free survival, and prolonged the time to skeletal related events (SRE) (27, 28). It is a diarylthiohydantoin that acts by inhibiting the translocation of AR into nucleus as well as by reducing transcriptional activity of AR gene (28). The improvement was shown in AFFIRM study, an international phase-3 double-blind randomized controlled trial (RCT) (29). Out of 1199 patients, 800 received enzalutamide and 399 received placebo. The higher median survival rate of enzalutamide (18.4 months) compared to placebo (13.6 months) was statistically significant. Moreover,

the PREVAIL study was done with 1717 patients with 872 in the enzalutamide group and 845 in the placebo group (30). The study showed 65% radiographic progression-free survival for enzalutamide group compared to 14% in the placebo group, prompting the study to be stopped early due to the demonstrated benefit (30). In response to this study, the National Comprehensive Cancer Network (NCCN) recommends enzalutamide as an effective treatment in mCRPC before and after docetaxel treatment (31). Adverse effects of enzalutamide are limited compared to alternate chemotherapy regimens, but include (in order of prevalence) fatigue, diarrhea, hot flashes, headaches, and rarely seizures (32, 33).

Abiraterone acetate is a drug that inhibits cytochrome P450 17A1 (CYP17A1) (29, 34). CYP17A1 is necessary for the conversion of mineralocorticoids to glucocorticoids and androgens (29). More specifically, it is involved in testosterone synthesis in the testis and the adrenal glands and is active within tumor cells. Abiraterone acetate has shown to improve survival in mCRPC patients (34). However, the mineralocorticoid excess resulting from CYP17A1 suppression has the potential to cause hypertension, hypokalemia, and fluid retention (34). Adding prednisone to the treatment can help correct the side effect of mineralocorticoid excess (29). Other adverse effects of abiraterone include anemia, GI upset, arthralgias, and increased risk of urinary tract infection (35). The assessment of COU-AA-301 study of 1195 mCRPC patients showed that patients treated with abiraterone + prednisone had significantly longer time (25 months) before the occurrence of first skeletal event when compared to prednisone treatment alone (20.3 months) (30). More specifically, the occurrence of spinal cord compression was 7.3% of the abiraterone + prednisone patients compared to 14.0% in the placebo group (prednisone only) (29, 36).

### Chemotherapy

Mitoxantrone was a common chemotherapeutic drug used in the palliative care of mCRPC patients despite any evidence of an overall survival improvement (37). An RCT of 161 patients showed that even though mitoxantrone showed no significant improvement in

patient survival, the frequency and severity of pain was significantly improved by mitoxantrone use (37, 38). There was a 29% palliative response rate with mitoxantrone + prednisone compared to 12% in prednisone alone (38).

Docetaxel was the first chemotherapeutic drug to show an overall survival benefit in TAX-327 and SWOG 99-16 studies (7, 38, 39). The TAX-327 study compared docetaxel + prednisone to mitoxantrone + prednisone and showed a significant benefit in overall survival with the administration of docetaxel every three weeks along with prednisone (7, 37). The SWOG 99-16 trial compared the effect of docetaxel + estramustine administration to mitoxantrone + prednisone administration. The patients with docetaxel + estramustine treatment had a statistically significant overall survival improvement (37, 39). However, there is no available data in the studies on improvement in SREs including spinal cord compression. The 2015 American Urological Association (AUA) Guidelines recommend docetaxel as one of three first-line treatments (along with enzalutamide or abiraterone + prednisone) for patients with symptomatic mCRPC with good performance status, however it is not recommended in patients with poor performance status (23).

Cabazitaxel is shown to be efficacious in docetaxel-resistant prostate tumors and mCRPC in general by a phase 3 clinical trial (40). Of the 755 men in the trial, 377 were administered mitoxantrone and 378 were administered cabazitaxel. According to the data, cabazitaxel group had a longer median survival (15.1 months) compared to mitoxantrone group (12.7 months). However, compared to the mitoxantrone group, the cabazitaxel group had an increased incidence of neutropenia (58% vs 82%) and diarrhea (1% vs 6%) (40). Despite the increased side effects, the significant improvement of overall survival in cabazitaxel makes it an important chemotherapeutic agent against mCRPC.

### Alternative treatments

Sipuleucel-T is the first therapeutic cancer vaccine approved by US FDA and is an extremely costly mCRPC treatment (41, 42). The treatment removes the patient's leukocytes through leukapheresis, followed

by an ex vivo activation of the autologous peripheral-blood mononuclear cells using a prostate antigen. The cells are then injected back into the patient (41, 43). An improvement in patient survival is shown in an integrated analysis of 2 randomized, double-blind, phase 3 clinical trials (43). The analysis demonstrated a survival benefit for mCRPC patients treated with Sipuleucel-T (23.2 months survival) compared to the ones treated with placebo (18.9 months survival) (41, 43).

Cabozantinib (CBZ) is an oral tyrosine kinase inhibitor that blocks MET, a receptor tyrosine kinase, vascular endothelial growth factor receptor 2 (VEGFR-2), and other tyrosine kinases involved in tumor pathobiology. VEGFR-2 and MET mediate tumor survival, metastasis, and angiogenesis and are expressed by a number of cell types in bone (44). Preclinical models of prostate cancer have shown that cabozantinib targets not only prostate cancer cells, but also cells of the bone microenvironment (including osteoblasts and osteoclasts), thus inhibiting tumor growth and tumor-induced bone changes (45). Because effective suppression of bone metastasis requires targeting the tumor and the bone microenvironment, agents like CBZ prove to be instrumental in improving outcome for patients with skeletal metastases. Pre-clinical studies have shown a decrease in tumor size, necrosis, and growth upon exposure to CBZ treatment (46). Most patients with advanced castration-resistant prostate cancer CRPC develop bone metastases frequently associated with debilitating pain that is itself associated with shorter survival (47). These pain symptoms are rarely relieved with the treatment of narcotic analgesics alone. Results from a phase-II randomized discontinuation trial in patients with advanced prostate cancer demonstrated that CBZ treatment led to pain relief in more than 60% of evaluable patients (48). This palliative effect may be related to CBZ's effects on the cells of the bone microenvironment and the cancer cells themselves (48).

### Bone-Targeted Agents

Skeletal-related events are bone complications such as pathologic fracture, vertebral collapse, and spinal cord compression. SREs are associated with an increased

mortality rate and have a detrimental impact on patient functionality (8). The current treatment paradigm for the prevention of SREs in CRPC patients with osseous metastases includes bisphosphonates and the RANKL antibody denosumab (49).

According to a theory proposed by Mundy and Guise, cancer cells cause bone destruction by stimulating osteoclast activity (50). The humoral factors released from bone resorption provide a nourishing microenvironment in which cancer cells thrive (51). Bisphosphonates play a key role management of malignant bone disease, and more recently in the treatment and prevention of SREs in prostate cancer. Bisphosphonates are synthetic pyrophosphate analogues that selectively inhibit farnesyl pyrophosphate synthase in areas of active remodeling, stimulating osteoblasts and inhibiting osteoclasts (52, 53). Zoledronic acid (ZA) is the most commonly used bisphosphonate for the management of SREs in mCRPC. A 15-month analysis of a clinical trial employing 4-mg dose of ZA demonstrated a statistically significant decrease in the incidence of skeletal-related events (SREs) and delayed the onset of SREs, but no difference in survival, disease progression, quality of life, or performance status (51). Current evidence suggests that the benefits of ZA last for as long as the treatment is given. However, with ZA, dose reductions are required for reduced kidney function, and it is contraindicated in patients with a glomerular filtration rate (GFR) < 35 mL/min. Common side effects include a flu-like reaction to first-time infusion and hypocalcemia, and in 1% of patients, life-threatening osteonecrosis of the jaw (54).

Denosumab, a monoclonal antibody that neutralizes RANKL and inhibits osteoclast function, is a bone-targeted agent (BTA) that decreases the incidence of skeletal related events such as pathologic fractures and spinal cord compression. Additionally, it reduces the need for radiation and surgical interventions (18). In fact, Denosumab has proved to be more efficacious in terms of delaying the time to first and subsequent SREs in patients with bone metastatic disease from prostate cancer. Denosumab is also superior to ZA in that its subcutaneous method of injection that can be administered quickly compared to zoledronic acid, which has to be given as an IV infusion for 30 minutes (18).

It is important to note that neither denosumab nor zoledronic acid has shown to have any anti-neoplastic properties. Accordingly, these agents should be used in combination with an antineoplastic agent, such as sipuleucel-T, enzalutamide, abiraterone, docetaxel, cabazitaxel, or radium-223. However, no prospective study has examined the use of these drugs in combination to determine the efficacy of these combinations.

### **Focused Ultrasound**

Another option available for prostate cancer patients is focused ultrasound. This non-invasive, radiation-free method employs real time images that help the physician aim a focused beam of ultrasound energy to a selected volume in targeted bone and bone-tissue interface (55). This beam of acoustic energy causes a remarkable rise in temperature leading to thermal coagulation of the periosteal membrane surrounding the targeted bone (56). Additionally, high intensity focused ultrasound (HIFU) may even directly lead to damage of tumors residing in the targeted areas (57). It's a method of pain palliation for it causes the destruction of the periosteum, which contains the pain-reporting nerve fibers (58). While it can be an option for patients who are not candidates for radical surgery, HIFU is not suitable for every patient (55). HIFU offers a quick and painless solution for bone metastasis pain and a single therapy session has shown to have significant symptomatic improvement (58). Repeat procedures are possible with HIFU owing to the low rate of complications and it is especially recommended for patients who have maximized their doses for radiation. Nonetheless, it is also possible to combine radiotherapy for the primary tumor alongside HIFU to the bone metastasis without creating local overdose.

### **Gaps in care**

Despite the existence of the plentiful treatment modalities available for metastatic castration resistant prostate cancer, there is limited data to support a treatment paradigm that provides the most efficacious sequence of approved treatments for individual patients. While abiraterone and

enzalutamide are currently in use for CRPC patients, these treatments also eventually fall short in the face of secondary resistance mechanisms that involves the ligand-binding domain of the AR. There is currently no effective treatment modality that combats tumor escape mechanisms, and therefore, spinal mCRPC remains a morbid disease. Clinical trials of succeeding therapies or combination therapies with contrasting mechanisms that are directed at resistance mechanisms, including those that target resistance mechanisms, are currently in the trial phase in the hope to provide maximize efficiency and improve outcome and prognosis.

For example, N-terminal domain (NTD) inhibition is an innovative concept in the field of AR-directed therapies for prostate cancer (57). The first clinical trials of N-terminal domain inhibitors, which have the intention of inhibiting all forms of AR-mediated transcriptional activity, are underway (57). As are clinical trials for Apalutamide, an anti-androgen that is fully antagonistic to AR overexpression and does not induce AR nuclear translocation or DNA binding (57). ODM-201 is an anti-androgen undergoing clinical trials that carries a much higher-grade potency than enzalutamide and apalutamide (57). Seviteronel is proving in clinical trials to have the effect of 17,20-lyase inhibition, thus leading to a reduction of androgen levels but the maintenancy of other steroid hormone levels (57).

Similar to Cabozantinib, Dasatinib is an oral tyrosine kinase inhibitor that functions as an antimetastatic agent, suppressing processes involved in cell proliferation, migration, adhesion, and invasion (59). It's method of action is the inhibition several tyrosine kinases, including including ephrin type-A receptor 2 (EPHA2), activated Cdc42-associated kinase (ACK1), platelet-derived growth factor receptor (PDGFR), c-FMS, and SRC family kinases (SRC, LCK, HCK, FYN, YES, FGR, BLK, LYN, and FRK) (60). Dasatinib is currently being investigated in combination with docetaxel in phase III trials (NCT00744497, NCT01188187), as it has shown promise during phase II trials in terms of safety and efficacy (57). Phase III data from the READY and SYNERGY will determine if dasatinib should be used in combination with docetaxel for the treatment of mCRPC.

While there have been improvements in the area of therapeutic modalities combating spinal mCRPC, gaps in care still remain. Ongoing research and trials are working to elucidate of the mechanisms of resistance and to fabricate new agents to bypass these mechanisms.

### **Multidisciplinary Approach to Care**

The decision of how and when to treat metastatic prostate cancer requires an individualized approach that factors in patient preference with evidence-based medicine. Prostate cancer treatment is multifaceted, and therefore requires a multidisciplinary team approach that utilizes many different medical specialists. A team of medical oncologists, urologists, radiation oncologists, radiologists, neurosurgeons, pathologists, and palliative care specialists should be assembled depending on the specific therapy indicated for the patient (61). Additionally, patient representatives, nurses, social workers and psychologists are often essential for the assessment of patient goals of care and compliance with treatment (61). Both the AUA and EAU recognized the importance of multidisciplinary care in their prostate cancer treatment guidelines, as the future management of metastatic prostate cancer will rely on the proper integration of treatment modalities to maximize survival and quality of life for the patient (17, 23, 61).

### **Abbreviation**

ADT: androgen deprivation therapy  
 AR: Androgen receptor  
 AUA: American Urological Association  
 BTA: bone-targeted agent  
 CBZ: Cabozantinib  
 CRPC: castration-resistant prostate cancer  
 ECOG: Eastern Cooperative Oncology Group  
 HIFU: High Intensity Focused Ultrasound  
 mCRPC: Metastatic Castration-Resistant Prostate Cancer  
 NCCN: National Comprehensive Cancer Network  
 NTD: N-terminal domain  
 MSCC: metastatic spinal cord compression  
 SBRT: Stereotactic Body Radiation Therapy

SRE: skeletal related event

SRS: stereotactic radiosurgery

RCT: randomized control trial

VEGFR-2: vascular endothelial growth factor receptor  
2

ZA: Zoledronic acid

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