

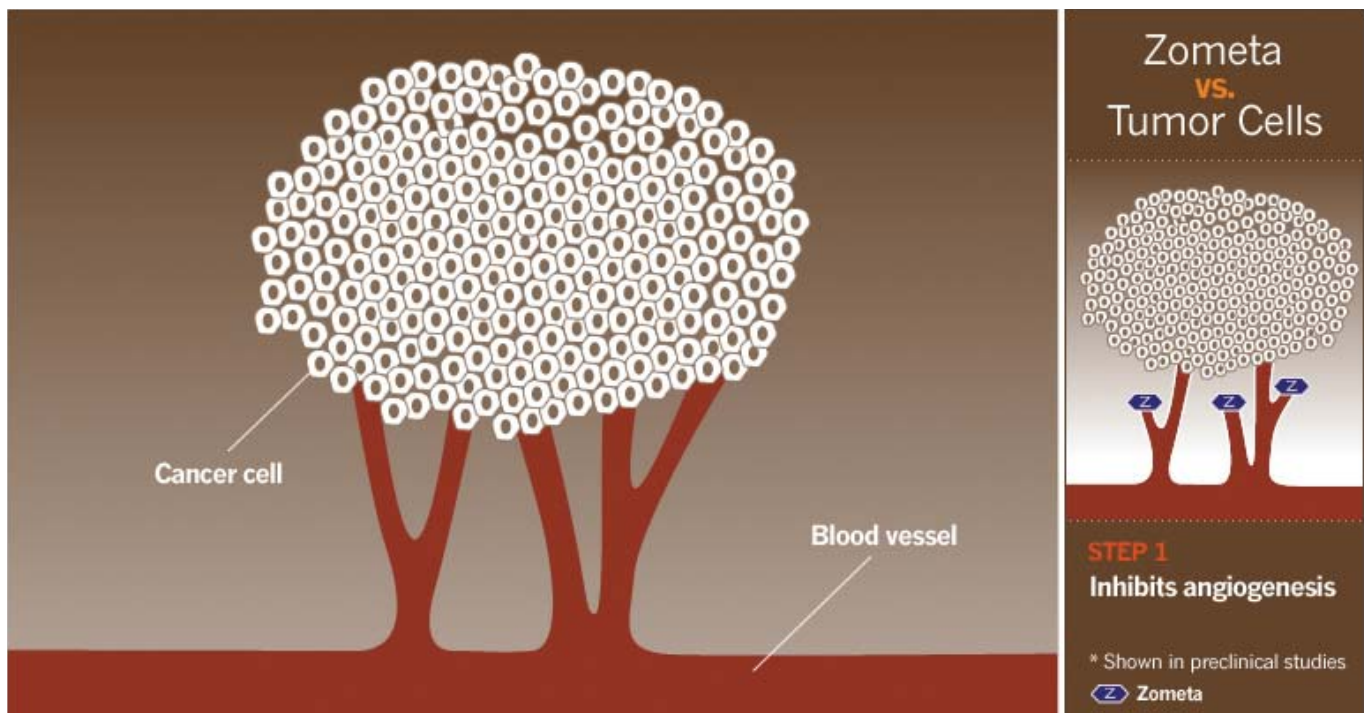
Zometa® vs. Tumor Cells – Targeting the Seeds of Cancer Recurrence

Zometa® (zoledronic acid) injection has transformed the treatment of patients with bone metastases by reducing and delaying bone complications, such as fractures, one of the most painful and debilitating complications of advanced cancer, and helping people with bone metastases maintain their functional independence.

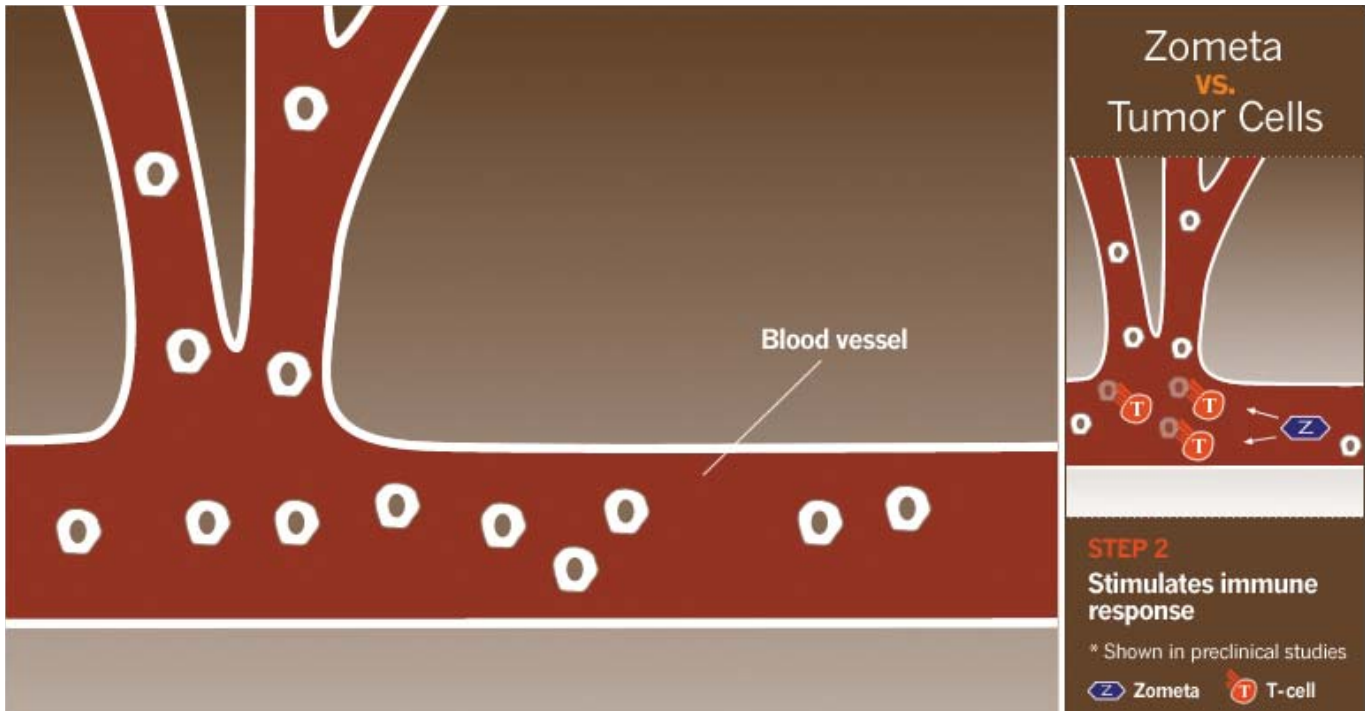
Laboratory research has suggested that Zometa may also have anticancer effects, helping protect against the return

and spread of cancer before it reaches an advanced stage. A growing number of clinical studies are examining this anticancer effect of Zometa.

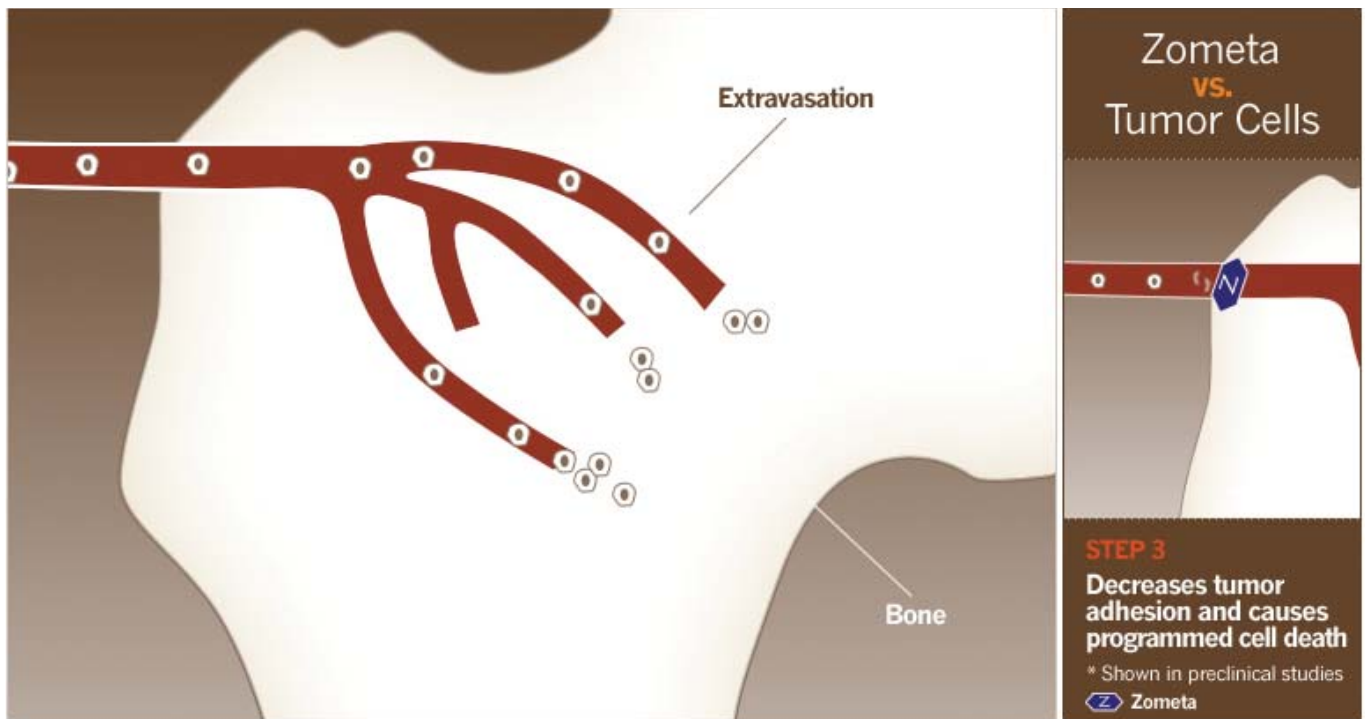
A tumor passes through six stages on its path to spreading or metastasizing. In the laboratory, Zometa has been shown to make the passage through several key steps of this process much more difficult.



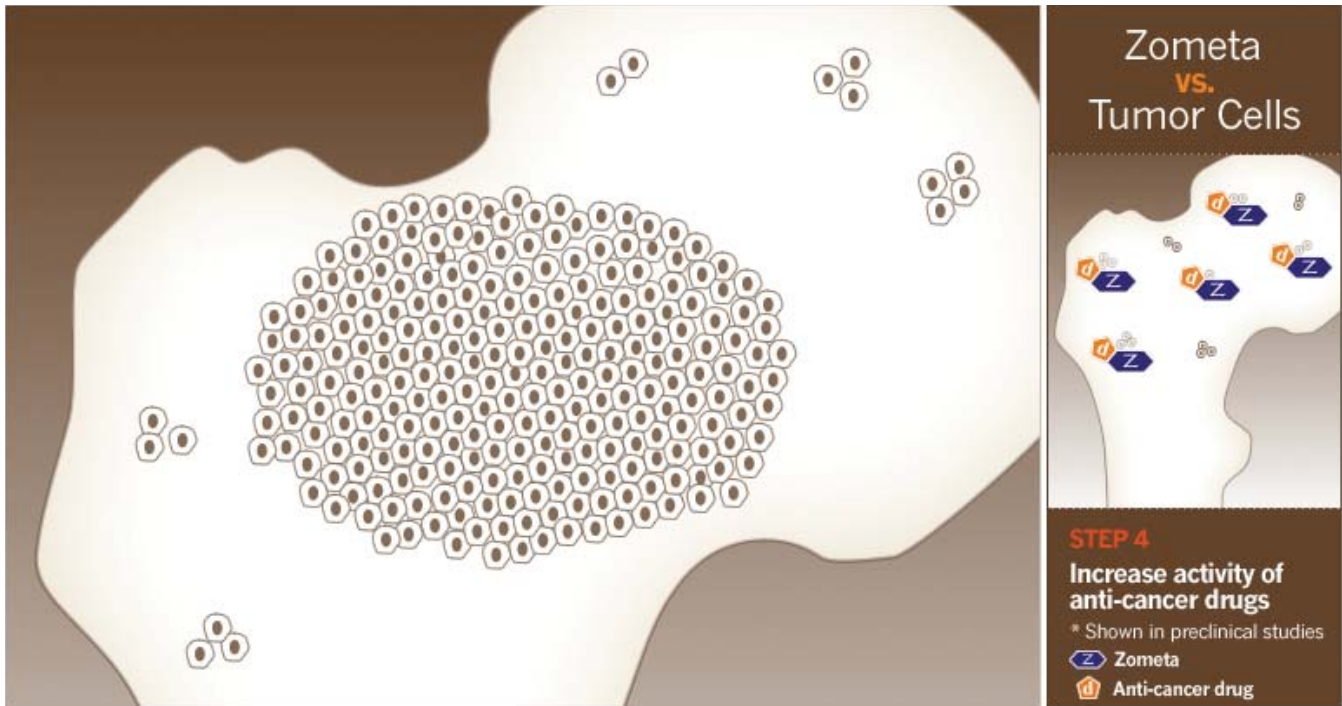
[1] As tumors grow in size, they need to develop new blood vessels to support their growth. At this stage, Zometa can inhibit the tumor's ability to recruit new blood vessels, a process called angiogenesis.



[2] Even in early-stage cancer, some individual tumor cells can break off from the primary tumor and enter the blood circulation. Zometa helps to stimulate the immune system to produce cancer-fighting T cells.



[3] Tumor cells that evade the immune system can accumulate in the vessel system of certain sites, such as bone. Zometa can interfere with passage through the vessel by decreasing tumor cells' ability to adhere and by directly causing the death of tumor cells.



[4] Tumor cells can either grow further directly in the site, or leave the vessel system of the site in a process called extravasation. These cells move into the circulation and then lodge in other distant metastatic sites, forming a small cluster, or micrometastases, undetectable by standard diagnostic tests. These micrometastases then must develop a blood supply in order to undergo significant growth. Zometa has been shown preclinically to increase the activity of anticancer drugs that target the ability of micrometastases to proliferate and form secondary and metastatic tumors.

About Zometa

Zometa is indicated for patients with multiple myeloma and documented bone metastases from solid tumors in conjunction with standard antineoplastic therapy; prostate cancer should have progressed after treatment with at least one hormonal therapy.

Important Safety Information

Zometa is contraindicated in patients with hypersensitivity to zoledronic acid or other bisphosphonates, or any of the excipients in the formulation of Zometa. Hypersensitivity reactions, including rare cases of urticaria and angioedema and very rare cases of anaphylactic reaction/shock, have been reported.

Due to the risk of clinically significant deterioration in renal function, which may progress to renal failure, single doses of Zometa should not exceed 4 mg, and the duration of infusion should be no less than 15 minutes. Risk factors for the deterioration of renal function include impaired baseline renal function and multiple cycles of bisphosphonate treatment.

Zometa is not recommended in patients with bone metastases with severe renal impairment. In patients with mild to moderate renal impairment at baseline, lower doses of Zometa are recommended based on calculated creatinine clearance. Before each Zometa dose, serum creatinine should be measured and treatment should be withheld for renal deterioration until serum creatinine has returned to within 10% of the baseline value.

Zometa should not be used during pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus.

Osteonecrosis of the jaw (ONJ) has been reported predominantly in cancer patients treated with intravenous bisphosphonates, including Zometa. Many of these patients were also receiving chemotherapy and corticosteroids, which may be risk factors for ONJ. Postmarketing experience and the literature suggest a greater frequency of reports of ONJ based on tumor type (advanced breast cancer, multiple myeloma) and dental status (dental extraction, periodontal disease, local trauma, including poorly fitting dentures). Many reports of ONJ involved patients with signs of local infection, including osteomyelitis. Cancer patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates. While on treatment, these patients should avoid invasive dental procedures, if possible. No data are available as to whether discontinuation of bisphosphonate therapy reduces the risk of ONJ in patients requiring dental procedures. A causal relationship between bisphosphonate use and ONJ has not been established. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

In postmarketing experience, severe and occasionally incapacitating bone, joint and/or muscle pain has been reported infrequently in patients taking bisphosphonates

The most common adverse events ($\geq 15\%$) in bone metastases clinical trials, regardless of causality, with Zometa 4 mg (n=1031) were as follows: bone pain (55%), nausea (46%), fatigue (39%), anemia (33%), pyrexia (32%), vomiting (32%), constipation (31%), dyspnea (27%), diarrhea (24%), weakness (24%), myalgia (23%), anorexia (22%), cough (22%), arthralgia (21%), lower-limb edema (21%), malignant neoplasm aggravated (20%), headache (19%), dizziness (excluding vertigo) (18%), insomnia (16%), decreased weight (16%), back pain (15%), and paresthesia (15%).

Caution is advised when bisphosphonates are administered with aminoglycosides, loop diuretics and potentially nephrotoxic drugs.

Zometa contains the same active ingredient as found in Reclast® (zoledronic acid). Patients being treated with Zometa should not be treated with Reclast.

Patients should be administered an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of vitamin D daily.

Please see full Prescribing Information.