

Answer Key to eAJKD's [Nephrology Jumble Bumble: Hypercalcemia of Malignancy](#)**1. BREAST**

One of the mechanisms of hypercalcemia in solid tumors is local osteolysis by metastatic tumor cells. Breast cancer is the most common solid tumor that causes hypercalcemia by this mechanism. The metastatic cells in the bone release local PTHrP leading to excessive bone resorption and hypercalcemia.

2. OSTEOPROTEGERIN

Receptor activator of nuclear factor kappa B ligand (RANKL) is a surface-protein found on osteoblasts that interact with receptor activator of nuclear factor kappa B (RANK) on osteoclast precursors to activate maturation of osteoclasts, leading to bone resorption. Osteoprotegerin is a competitive inhibitor of RANKL. Inhibition of osteoprotegerin by PTH and PTHrP stimulates osteoclastic activity.

3. HUMORAL

Patients with non-metastatic solid tumors as well as some hematologic cancers may develop hypercalcemia through release of a soluble molecule, parathyroid hormone-related protein (PTHrP). This condition is termed as “humoral hypercalcemia of malignancy.” It is the most common mechanism of hypercalcemia in patients with malignancy (up to 80%). Although PTHrP and PTH act on the same PTH-1 receptor, PTHrP does not increase intestinal calcium absorption and has minimal effect on 1,25 dihydroxyvitamin D synthesis.

4. ZOLENDRONATE

Bisphosphonates are the mainstay of therapy in the management of patients with bony metastasis. Zoledronate and pamidronate are the FDA-approved bisphosphonate for treatment of hypercalcemia of malignancy. In randomized controlled [trials](#), zoledronate has been shown to be more potent than pamidronate, with an additional advantage of longer duration of response.

Bonus Answer:**DENOSUMAB**

Denosumab is a monoclonal antibody that targets RANKL, and has been shown effective in the treatment of hypercalcemia from metastatic malignancies (breast and prostate cancers) and multiple myeloma. Trials have demonstrated either [superiority](#) or [non-inferiority](#) of denosumab to zoledronic acid in preventing or delaying skeletal-related events.