

**Title:**

**A pilot study of the efficacy and safety of the sclerostin-inhibitor romosozumab as a bone-modifying agent for patients with metastatic breast cancer to bones, and osteoporosis or osteopenia with high risk of fracture.**

In a healthy bone, there is a balance between bone formation by the “bone-forming” cells osteoblasts, and bone destruction by the “bone-resorbing” cells osteoclasts. When tumor cells are present in the bones, such as in metastatic disease, there is an imbalance that results in accelerated bone destruction; this can cause pain, fractures, and other complications that can significantly affect functional status as well as quality of life of cancer patients.

Breast cancer cells frequently metastasize to the bone: about 70% of breast cancer patients with advanced disease develop osteolytic bone metastases. Bone metastases often cause “skeletal-related events”, including pathological fractures, hypercalcemia, and pain, that require interventions and severely compromise quality of life. Destruction of the bone tissue in breast cancer metastases occurs due to an increased number and activity of osteoclasts due to the presence of tumor cells.

Currently, treatment of metastatic bone disease for breast cancer patients entails the use of drugs such as zoledronic acid and denosumab: these drugs block the activity of osteoclasts, and therefore reduce bone destruction. However, there is no treatment that actually targets osteoblasts, and therefore possibly promotes “healing” of the metastatic bony lesions. Romosozumab is an anti-sclerostin monoclonal antibody that can both increase bone formation and decrease bone resorption. It is FDA-approved for the treatment of osteoporosis in postmenopausal women. It has not yet been studied for the treatment of bone metastases from breast cancer.

Sclerostin is a glycoprotein that has been found in 50-60% of breast cancer tumor tissue and cell lines. Pre-clinical data support the rationale of targeting sclerostin and enhancing osteoblasts activity in the treatment of bone metastases. The use of anti-sclerostin antibody in mice models with breast cancer bone metastases reduced bone metastatic burden, muscle weakness and prolonged survival time, suggesting potential anticancer activity of sclerostin inhibition.

This study will be the first to study romosozumab for patients with metastatic breast cancer to bones: 25 patients will receive romosozumab as a bone-modifying agent for 12 months, in conjunction with their anti-cancer treatment; afterwards they will be treated with standard bone-modifying agents such as zoledronic acid or denosumab.

The goal of this study will be to assess the efficacy and safety of this novel drug in patients with metastatic breast cancer to bones. Activity will be measured by bone turn-over markers, as well as radiological assessments with PET scans. Additionally, bone density and sarcopenia (loss of muscle mass and strength, common in patients with metastatic cancer) will be evaluated.

This trial could be the foundation for a larger future trial of romosozumab in patients with bone metastases and could potentially identify a new treatment option for women with this disease, which will positively impact their outcome and quality of life.