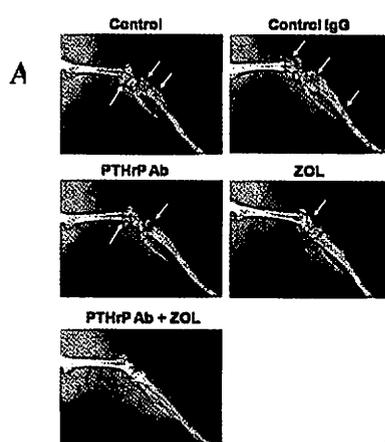


## Intensification therapy with anti-parathyroid hormone-related protein antibody plus zoledronic acid for bone metastases of small cell lung cancer cells in severe combined immunodeficient mice.

Yamada T, Muguruma H, Yano S, Ikuta K, Ogino H, Kakiuchi S, Hanibuchi M, Uehara H, Nishioka Y, Sone S.

Bone metastases occur in more than one-third of patients with advanced lung cancer and are difficult to treat. We showed previously the therapeutic effect of a third-generation bisphosphonate, minodronate, and anti-parathyroid hormone-related protein (PTHrP) neutralizing antibody on bone metastases induced by the human small cell lung cancer cell line, SBC-5, in natural killer cell-depleted severe combined immunodeficient mice. The purpose of our current study was to examine the effect of the combination of PTHrP antibody and zoledronic acid, which has been approved to treat bone metastases, against bone metastases produced by SBC-5 cells expressing PTHrP. Treatment with PTHrP antibody and/or zoledronic acid did not affect the proliferation of SBC-5 cells *in vitro*. Repeated treatments with either PTHrP antibody or zoledronic acid inhibited the formation of osteolytic bone metastases of SBC-5 cells but had no effect on metastases to visceral organs. Importantly, combined treatment with PTHrP antibody and zoledronic acid further inhibited the formation of bone metastases. Histologic assays showed that, compared with either PTHrP antibody or zoledronic acid alone, their combination decreased the number of tumor-associated osteoclasts and increased the number of apoptotic tumor cells. These findings suggest that this novel dual-targeting therapy may be useful for controlling bone metastases in a subpopulation of small cell lung cancer patients.



**A. Inhibition of bone metastasis by treatment with PTHrP antibody and/or zoledronic acid in NK cell-depleted SCID mice.**