Metastatic bone disease has a major impact on both morbidity and mortality of breast cancer patients. Alterations in mTOR signaling are involved both in cancer progression and in osteoclasts differentiation. The aim of this study is to highlight the role of the mtor inhibitor Everolimus on osteoclastogenesis induced by growth factors or by cancer cells. To this end, we have developed an in vitro human model of osteoclastogenesis from peripheral blood monocytes. We used the conditioned media of the osteotropic human breast cancer cell line SCP2 to induce osteoclast differentiation. Everolimus was tested at an early step of osteoclastogenesis (5°-7° days) and later at 10°-12° days of differentiation. Osteoclastogenesis was detected by trap assay at day 14. SCP2 conditioned media (CM) was found to significantly induce osteoclastogenesis respect to control media. Furthermore the osteoclast number observed were similar to that obtained with growth factors RANKL and MCSF (differential medium: DM). Everolimus significantly decreased osteoclastogenesis in the presence of both CM and DM. Interestingly, the effect of Everolimus was much higher if administered to cells early. In this case the inhibition of osteoclastogenesis reached almost the 70%. In conclusion, with this study we develop an in vitro model that reproduce the interactions between breast cancer cells and the bone microenvironment. In particular we found a different effect on breast cancer-induced osteoclastogenesis according to the timing of Everolimus administration. Our model may represent a valid platform for preclinical trials of bone targeted drugs and for the study of the molecular mechanisms beyond breast cancer interplay with bone cells. In the future great importance will be also given to test drugs combinations.