A42 **PROTEASOME INHIBITION AGGRAVATES TUMOUR
NECROSIS FACTOR-MEDIATED BONE RESORPTION**

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Methods Heterozygous human tumour necrosis factor α transgenic (hTNF α tg) mice and wild-type littermates were intravenously injected with 0.75 mg/kg bortezomib or phosphate buffered saline twice a week. Mice were weekly assessed for clinical signs of arthritis. After 6 weeks of treatment the mice were analysed for synovial inflammation, cartilage damage, bone erosions and systemic bone turnover. Osteoclast precursors from hTNF α tg mice were obtained from bone marrow and treated with different concentrations of bortezomib. In addition, osteoclasts were analysed by western blot analysis and real-time PCR in more detail.

Results Bortezomib-treated hTNF α tg mice showed moderately increased inflammatory activity and dramatically enhanced bone erosions correlating with a significant increase of synovial osteoclasts. Interestingly, bortezomib did not alter systemic bone turnover in TNF α tg or in wild-type mice. In vitro, therapeutically relevant concentrations of bortezomib resulted in an increased differentiation of monocytes into osteoclasts. Consequently, bortezomib-treated osteoclasts caused resorption pits of higher extent than untreated osteoclasts. Molecularly, bortezomib increased the expression of TRAF6, c-fos and NFAT-c1.

Conclusion In TNF-mediated bone destruction, bortezomib increases synovial osteoclastogenesis and bone destruction. Bortezomib might therefore have a direct osteodestructive effect via stimulation of osteoclastogenesis as well as a more indirect osteoprotective effect—for instance, by killing myeloma cells.