Background: Treatment-induced bone loss is a risk factor for skeletal morbidity in cancer patients. Despite the widespread use of immune checkpoint inhibitors (ICIs) their impact on bone health is still poorly defined. Here, we prospectively analyzed bone turnover markers (BTM) in patients receiving single-agent PD1 or PD-L1 inhibitors and we evaluated direct effects of ICI on bone cell homeostasis in vitro.

Methods: Patients with advanced cancer and no evidence of bone metastases assessed per bone scan or PET-CT were enrolled. Serum markers of bone resorption (C-terminal telopeptide (CTX)) and bone formation (osteocalcin (OCN) and procollagen type I N-propeptide (PINP)) were measured before each ICI application, as well as parameters of bone metabolism. Dose-dependent effects of PD1 and PD-L1 inhibitors on osteoclast and osteoblast differentiation in vitro were evaluated by morphological and functional assays.

Results: A total of 53 samples were collected from 10 patients receiving PD1 (n=5) and PD-L1 (n=5) inhibitors for a median of 15 weeks (range 7 to 31). 80% of the patients were male, median age was 71 years (range 58-77). Three weeks after the first ICI application we observed a significant decrease in CTX levels (mean CTX 0.51 ng/ml ± 0.42 at baseline to 0.42 ± 0.37 at week 3; p = 0.017), which remained below baseline at 15 weeks (mean 0.36 ng/ml ± 0.25, p= NS). No significant changes in OCN, PINP and parameters of bone metabolism were detected. Interestingly, changes in CTX at 3 weeks correlated with treatment response and a decrease above 20% was associated with a longer progression-free survival (PFS) (median PFS 68.7 months vs 15.8 months, p < 0.003). In vitro studies confirmed inhibition of osteoclast differentiation (OC number decreased to 26% and 18% of control in the presence of 1000 ng/ml PD-L1 and PD1 inhibitors, respectively) as well as function (resorbed area 8% in the control vs < 0.2%) in the presence of ICI. In contrast, no direct effect of ICI was observed on osteoblasts.

Conclusions: Despite the small number of patients included, our study demonstrates for the first time that ICIs inhibit bone resorption in cancer patients by directly impairing osteoclastogenesis. Further analyses are ongoing to elucidate the molecular mechanisms responsible for the anti-catabolic effects ICIs.

Ethics Approval: Ethic: GS4-EK-4/606-2019, NÖ Ethikkommission