Aim: Based on anti-tumour effect of zoledronate in vitro and in experimental models of rat osteosarcoma, we assessed whether zoledronate (Z) in combination with chemotherapy and surgery improved Event-Free Survival (EFS) in children and adult patients (pts) with osteosarcoma.

Methods: Experimental treatment consisted of 10 Z-injections (4 pre and 6 postoperative), 4 mg/injection in adults, 0.05 mg/kg/injection in younger pts. Chemotherapy included methotrexate-etoposide-ifosfamide +/-adriamycine-cisplatin in children/adolescents, and doxorubicin-ifosfamide/doxorubicin-ifosfamide-cisplatinum in adults. Balanced randomisation between Z+arm and Z-arm was stratified by center, age, chemotherapy type and risk group (localised resectable disease versus unresectable primary and/or metastases). The study was planned as an open-label superiority trial, with 3 interim analyses (early stopping for efficacy or harm) disclosed to an independent safety monitoring board (DSMB). 470 pts (170 events) were required to achieve an 80%-power to detect a 13%-improvement of 3-year EFS (H1: 55% versus 68%, HR(event)=0.65) with zoledronate (2-sided alpha=0.05).

Results: A second interim analysis was performed after 318 pts (82% with a localised and resectable tumour) have been recruited between April 2007 and February 2014: 158 Z- and 160 Z+. No significant increase in toxicity was found in Z+, except expected hypocalcemia grade 2-4 (p<0.0001). With a median follow-up of 3.1 years, 106 events and 58 deaths were reported, including one treatment-related death. The risk of treatment failure was not reduced in Z+ compared to Z: HR(event)=1.31 [0.79–2.18], p=0.17; HR(death)=1.42 [0.70–2.88], p=0.21. Results were similar after exclusion of eight Z+patients who had received 0 or 1 zoledronate injection, and were homogeneous across the randomisation strata. Futility analysis, performed on DSMB request, showed that the probability of demonstrating a benefit for Z+ was <0.0001. Following DSMB recommendation, the trial steering committee decided to stop accrual in the trial.

Conclusions: With current follow-up, the addition of zoledronate to chemotherapy did not reduce the risk of failure in osteosarcoma patients.

Disclosure: All authors have declared no conflicts of interest.