Abstract #126939

Prevention of symptomatic skeletal events with denosumab administered every 4 weeks versus every 12 weeks – a non-inferiority phase III trial (SAKK 96/12, REDUSE).

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Abstract Text:

Background: Denosumab, a monoclonal antibody against RANK-Ligand has been shown to be superior to zoledronic acid in delaying time to a first on-study skeletal-related event (SRE) in patients with solid tumors, with no effects on disease progression or survival (Stopeck et al. JCO 2010, Fizazi et al. Lancet 2011). Many SREs were silent compression fractures found only because of scheduled imaging. The approved dose of denosumab is 120mg sc every 4 weeks (q4w). Although generally well tolerated, there is a dose-dependent increase in osteonecrosis of the jaw in up to 8% of patients (Fizazi et al, ESMO 2012, 937P). Cases of fatal hypocalcaemia were observed during post marketing surveillance. In a study of 255 women with breast cancer and bone metastases randomized to 1 of 5 blinded denosumab cohorts (30mg q4w, 120 mg q4w, 180 mg q4w, 60mg q12w, 180mg q12w) or an open-label iv bisphosphonate, a similar degree of creatinine-corrected urinary N-telopeptide (uNTx/Cr) suppression at weeks 13 and 25 was observed in all cohorts (Lipton et al. CCR 2008). The optimal dose and schedule of denosumab is unknown. Denosumab is associated with considerable costs and adds toxicity; thus a study of de-escalation is warranted. Methods: The aim of the present trial is to test the hypothesis that the benefit of denosumab is maintained if administered 120mg q12w as compared to 120mg q4w. The primary endpoint of this open-label randomized phase III non-inferiority trial is time to first on-trial symptomatic skeletal events (SSE; clinically significant pathological fracture, radiation therapy to bone, surgery to bone or spinal cord compression). With a non-inferiority margin of 1.2 for the hazard ratio, power 80% and type I error 5%, the total sample size is 1380. Secondary endpoints include safety, time to subsequent on-trial SSE, quality of life, health economic outcomes, and change in bone turnover markers. Patients with breast or prostate cancer with bone metastases and adequate organ function are eligible. This trial is open for international collaboration. ClinicalTrials.gov identifier: NCT02051218.
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