Introduction

Bone metastases count 30-80% of metastases in the most common cancers including breast, prostate, lung and bladder cancer, and multiple myeloma. Despite recent progress in cancer therapy, metastatic bone disease remains incurable. However, novel therapies including immunotherapies have the potential to treat bone metastatic disease.

The aim of this study was to establish syngeneic models with a focus on bone metastasis that could be used in preclinical efficacy studies.

Materials and Methods

Syngeneic models were established for breast (4T1-GFP, ATCC), bladder (MBT-2, Riken) and lung cancer (KLN-205, Riken), and multiple myeloma (STG1M, University of Texas Health Science Center at San Antonio) in female BALB/c, C3H, DBA and BalbRJ mice, respectively (all mice from Envigo). The cells were inoculated into systemic circulation (4T1 intracardially or STG1M into the tail vein) or into the bone marrow (MBT-2 and KLN-205). In the 4T1 model, tumor burden was determined by GFP imaging (Lightrhs Research) ex vivo and in the STG1M model by measuring serum IgG2b paraprotein levels (Bethyl Laboratories Inc.). Tumor-induced bone changes were followed by X-ray imaging (Faxitron) in all models. At sacrifice, hind limbs were collected and analyzed by histology. Tumor-infiltrating lymphocytes (TILs); CD3; CD4; CD8; CD19, CD20 and CD56 were analyzed by immunohistochemistry (IHC). The effects of standard-of-care (SOC) compounds were assessed in the 4T1 (cyclophosphamide, 100 mg/kg; Bayer AG, Pharmaceuticals, Berlin, Germany) and KLN-205 (bortezomib, 1 mg/kg; Q1W, Harmlen Pharmaceuticals) models. The effects of anti-PD-1 therapy (200 µg/dose, Q3D, BioXCell) was evaluated in the MBT-2 model.

Conclusion

A high incidence of bone metastases was achieved in all models. The use of systemic models allows studying the efficacy of test compounds in prevention or treatment of metastases. Intratibial models can be used when the primary interest is in cancer-induced changes or tumor growth in bone. Mimicking the clinical situation, none of the tested SOC compounds could prevent tumor growth completely, and therefore combination therapies are warranted for better overall efficacy.