FC-162

L-MTP-PE and zoledronic acid association in osteosarcoma: preclinical evidence of positive therapeutic combination for clinical transfer

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Background: Zoledronic Acid (ZA, zometa(r)), a potent inhibitor of bone resorption is currently evaluated in phase III clinical trials in Europe for the treatment of malignant primary bone tumors. The beneficial effect of the liposomal form of MuramylTriPeptide-Phosphatidyl Ethanolamine (MTP-PE, MEPACT(r)), activating the macrophage population in tumors, has also proved its efficacy in osteosarcoma. The objective of our study was to evaluate the safety of the combination of zoledronic acid and liposomal mifamurtide in pre-clinical models of osteosarcoma before transfer to patients.

Methods: Two protocols were developed in mouse syngenic models of osteosarcoma: (1) 1 or 2.5 mg/kg MEPACT alone in primary tumor progression and pulmonary metastasis dissemination (experimental model induced by paratibial injection of murine osteosarcoma cells), (2) the potential interference of MEPACT on ZA (100microg/kg) induced effect on osteosarcoma. These effects were evaluated at clinical, radiological (bone microarchitecture by microCT analysis), biological and histological levels.

Results: MEPACT alone induced slight but not significant inhibitory effect on primary osteosarcoma growth. However, it significantly inhibits spontaneous (lung metastasis dissemination from primary bone tumor) and experimental (lung colonization after intraveinous injection of osteosarcoma cells) metastases at pulmonary site. ZA alone protected against tumor-associated bone lesions. Surprizingly, combination of both drugs induced significant inhibition of primary bone growth.

Conclusions: In mouse, MEPACT alone has a potent inhibitory effect on lung metastasis development, probably due to high macrophage infiltration in the lung parenchyma. Preliminary data did not evidence any interference of MEPACT with ZA potential therapeutic activity in preclinical models of osteosarcoma. In addition, combinatory drugs inhibit primary osteosarcoma development.