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Pre-clinical Evaluation of Alpha-particle Radiotherapy Targeting CXCR4 in Small Cell Lung Cancer

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BACKGROUND: Small cell lung cancer (SCLC) is currently incurable, accounting for 15% of lung carcinoma. There is thus critical needs for new diagnostic and therapeutic strategies. Chemokine receptor 4 (CXCR4), is known to drive proliferation and metastases in multiple types of cancer. We have demonstrated high CXCR4 expression in SCLC cell lines, as well as specific receptor-mediated tumor targeting by 68Ga-Pentixafor PET imaging in mice. Alpha-particles, with high linear energy transfer have potential for effective cell-killing and low off-target radiation exposure. Therefore, targeted _-therapy is estimated to be 100-500 fold more potent than _-particle therapy. We hypothesize that 212Pb-Pentixather would be an effective radiopharmaceutical in controlling SCLC expressing CXCR4. We evaluated the efficacy and toxicity of 212Pb-Pentixather in vitro and in animal model.

METHODS: 212Pb-Pentixather was successfully labeled and tested for stability by RTLC and HPLC. In vitro cytotoxicity of 212Pb-Pentixather was evaluated by alamar blue assay. 212Pb-Pentixather therapy efficacy, renal, hematological and bone marrow toxicity was evaluated in nu/nu mice bearing DMS273 tumor xenografts.

RESULTS: 212Pb-Pentixather was stable for 40 hours in mouse serum at 37°C and was 98% radiochemical pure by HPLC chromatogram at 48 hours in solution without serum. 212Pb-Pentixather demonstrated dose-, time-dependent cytotoxicity to typical lung carcinoid and SCLC cell lines. Moreover, single iv administration of 212Pb-Pentixather (1 µCi/g BW) effectively inhibited DMS273 progression and significantly extended the overall survival (P= 0.01), without body weight loss. There was no significant kidney injury by Q-PCR of NGAL and

KIM1 expression. And there were no significant bone marrow toxicity by flow cytometry assay.

CONCLUSION: 212Pb-Pentixather has demonstrated significant radiotherapeutic effect with little renal or bone marrow toxicity in mice bearing SCLC xenografts. Future experiments will explore dose optimization with and without thioredoxin reductase inhibitors to improve therapeutic efficacy and to further reduce renal and bone marrow toxicity.

ABSTRACT ID: 34